Opinion

Prospective health care: the second transformation of medicine

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Abstract

Emerging scientific technologies provide rich sources of predictive biomarkers, which could transform health care. Identification of causal biomarkers will enable the development of tools to quantify risk and anticipate disease. Accurate health risk analysis is rapidly becoming feasible, so health care can become rational, preventive and personalized.

Evolution of health care

At the beginning of the 20th century, the emerging sciences of physiology, pathology, chemistry, biochemistry, microbiology and radiology had the potential to change medicine from a practice based on mythology and anecdotal observations to one grounded in experimental science. Particularly powerful was the development of the germ theory, which identified microorganisms as the cause of many diseases prevalent at that time. The medical profession did not, however, easily incorporate science into practice until several decades later, when the development of academic medical centers enabled a science-based approach and the first major transformation of medical practice.

The impact of science on medicine has been striking. The strengths of the reductionist method, which simplifies the concept of pathogenesis to the smallest number of causal factors, are shown by the burgeoning understanding, at a molecular level, of human biology and the underlying causes of many diseases. Spectacular medical therapies abound, and new technology has continued to enhance the capabilities of medicine. Nonetheless, the weaknesses of the reductionist scientific approach are also reflected in our health-care system in which complex chronic diseases account for most of the health-care expenditures. We have created a model that focuses on acute treatment instead of on the prevention of chronic disease (Figure 1).

The reductionist focus on specific and single etiological causes of disease is a useful strategy to understanding pathogenesis, but is limited in truly explaining disease. Even for a microbial disease for which an etiological agent is known, the outcome of infection is highly dependent on the state of the host's immune system and their general health status. In genetic diseases resulting from well understood molecular mechanisms, such as sickle-cell disease, there is a highly variable course: some individuals have severe unremitting crises leading to death by their early twenties, whereas others live well beyond their fifties.

Chronic diseases develop as a consequence of an individual's baseline susceptibility coupled with their exposure to environmental factors (Figure 2a). These may trigger initiating events, leading to the accumulation of pathological changes and the onset and progression of chronic disease (Figure 2b). Today, most health-care expenditure is focused on the later stages of this process, long after the development of many underlying pathological changes. Until recently, it could be argued that the focus on treating disease was justified because the ability to predict, track, and prevent its onset was not technically feasible. This is no longer the case, and the emerging sciences of genomics, proteomics, metabolomics, medical technologies and informatics are revolutionizing the capability to predict events and enable intervention before damage occurs. Personalized risk prediction

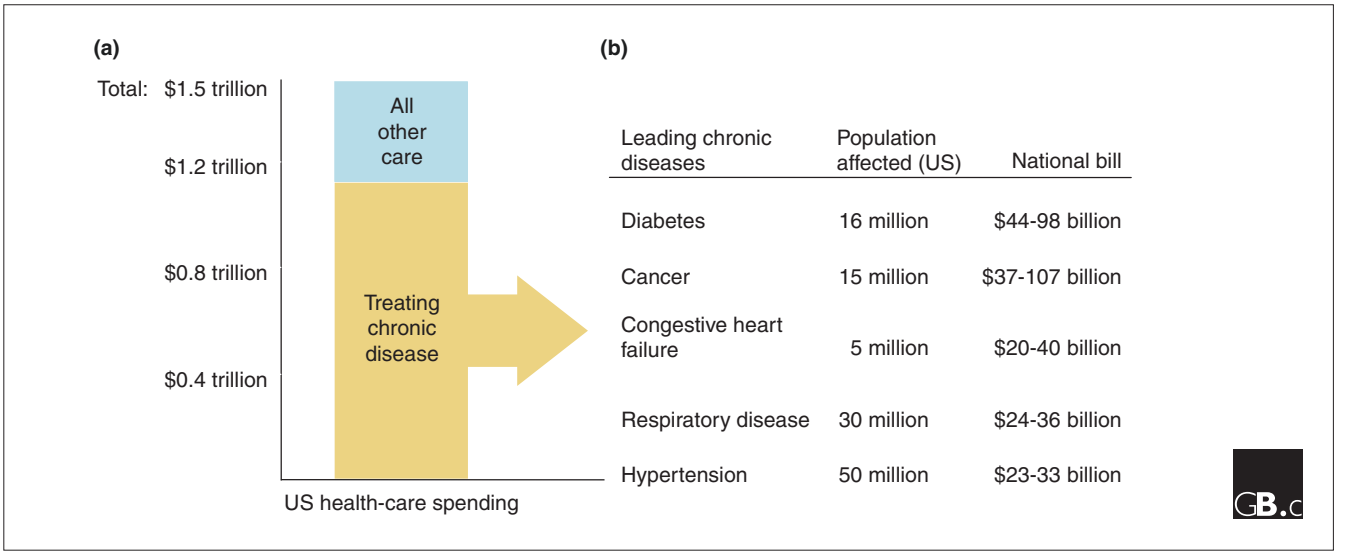

Figure 1
The consequences of reactive health care. **(a)** A graph of US health-care spending shows that nearly three-quarters of a total of $1.5 trillion is committed to the treatment of chronic disease. Little is spent on prevention. **(b)** The most common chronic diseases and the US national expenditure on treating them are indicated. Sources: American Heart Association, American Cancer Society, American Lung Association, and National Institute of Diabetes and Digestive and Kidney Diseases.

and strategic health-care planning will facilitate a new form of care, which we have called 'prospective health care' [1].

The current approach to health care is well demonstrated by the structure of the current medical record in the USA (Figure 3). The medical record is the documentation of the physician's interaction with the patient on any given visit. It begins with a notation of the 'chief complaint', the reason for the patient's visit to the physician; this already presumes that it is a problem that is bringing the patient to see their doctor. What follows is a logical 'work up' of the problem. The present medical record outlines a proven approach to identifying disease and to developing a plan to mitigate against it.

Prospective health care is a new approach that incorporates all the power of current disease-oriented medicine but is based on the concept of strategic health planning, a proactive, prospective approach to care. In this system, individuals will be evaluated to determine their baseline risk for various diseases, their current health status, and the likelihood of their developing specific clinical problems given their risks. In order to provide an individual with their personalized health plan (as part of their prospective personal health record), new capabilities and tools are needed. For example, knowledge and tactics are needed to measure an individual's baseline risk for major chronic diseases. Predictive biomarkers - measurable biological factors that predict disease development, such as low-density lipoprotein (LDL) for cardiovascular disease - need to be identified and tracked over time to determine whether the individual's likelihood of developing any particular disease is increasing or decreasing [2]. In addition, tools are needed to anticipate the development of specific clinical events associated with the chronic disease (for example, myocardial infarct as a consequence of coronary artery disease) and to support appropriate therapeutics based on the individual's needs [3].

Facilitating accurate risk assessment and evidence-based support

The key elements of all risk-prediction tools, from baseline risk assessment to analysis of appropriate therapeutics, will benefit from the molecular understanding of the pathogenesis of disease, along with the identification of predictive factors, particularly biomarkers that anticipate or quantify the pathogenic process. Such factors may be determined in part through the analysis of currently available clinical data, including family history, clinical examination, and conventional laboratory analyses. Analysis of such information already provides valuable insight into the likelihood of an individual developing a disease. The power of such information, however, is rarely - if ever - sufficient to predict accurately the precise timing of an event or the best therapeutic options (Figure 4). This type of prediction will require additional tools and better predictive biomarkers, which are emerging.

Be it disease events and their timing, adverse outcomes of treatment, weather forecasting, or the orbit path of a satellite, prediction requires a mathematical equation, distribution or rule that is a statistical representation of the measured outcome of many past events. The predictive model is composed of predictor variables gathered from

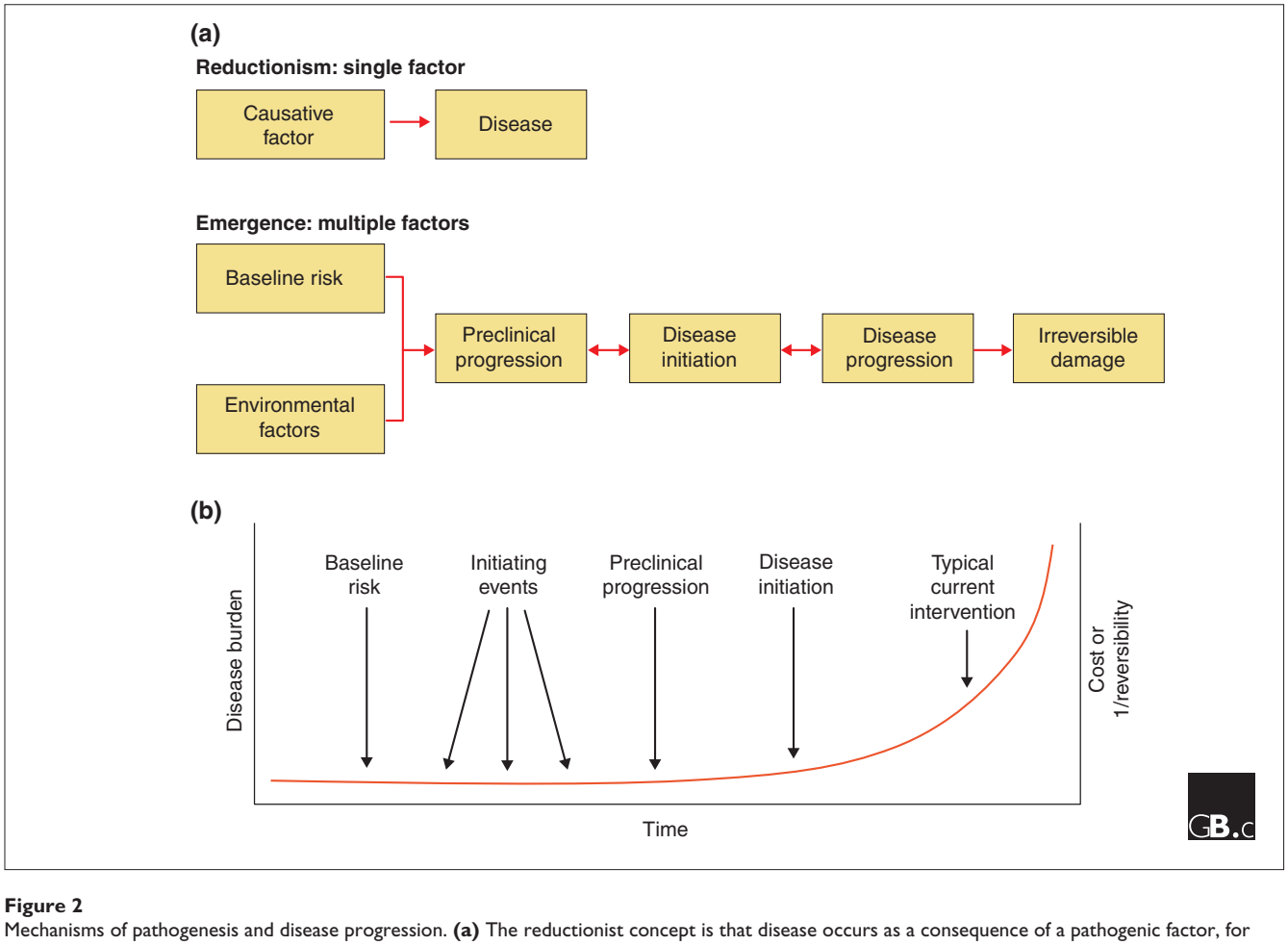

Figure 2
Mechanisms of pathogenesis and disease progression. **(a)** The reductionist concept is that disease occurs as a consequence of a pathogenic factor, for example a microbe (top). This is overly simplistic. Disease is a consequence of susceptibility to pathogenic factors as well as exposure to them (bottom). The emergence concept provides important opportunities for better understanding disease risks, tracking pathogenesis and earlier intervention [42]. **(b)** Disease progression is shown from baseline risk to irreversibility. Diseases develop as a consequence of inherited susceptibilities and environmental exposure. Over time, pathology increases, reversibility decreases and costs increase (red line). Earlier intervention could clearly reduce the costs and the disease burden [42].

studied cohorts - the particular factors that are likely to influence the future outcome. Predictive modeling encompasses various procedures for creating models - from regression to neural networks - that distinguish predictors from many other factors that are not as valuable for anticipating the outcome [4-7]. In marketing, for example, a customer's income, age, sex, and purchase history might predict the likelihood of a future sale, but their place of birth might be an irrelevant variable.

Physicians use a cognitive predictive modeling process, built on experience with numerous patients, lectures, literature reading, and so on, to build internal heuristics for rapidly anticipating or ascertaining problems on the basis of what they judge to be the most salient factors. A key feature of mathematical predictive models that sets them apart from human heuristics is that the data input can be more comprehensive, and the uncertainty of the predictions can be quantified as a result of a confidence interval used with standard regression methods or a high probability density used in Bayesian statistical methods [8,9]. Therefore, with mathematical models, the inputs are more comprehensive and the outputs are more objective. Ultimate decision-making by physicians is critical, however, as humans are more flexible in appreciating outlying issues for which a model might be unable to account. Thus, mathematical models can serve as guidelines and default options to raise the overall standard of care, but not to determine the final diagnosis or treatment plan. An ideal scenario for the practice of health risk assessment is to take advantage of highly accurate predictive models as guidelines to help standardize the quality of care while still giving physicians full flexibility to use good clinical judgment to consider variables not accounted for by a model.

Predictive models have been used for risk assessment related to very clearly defined clinical problems, such as recurrence

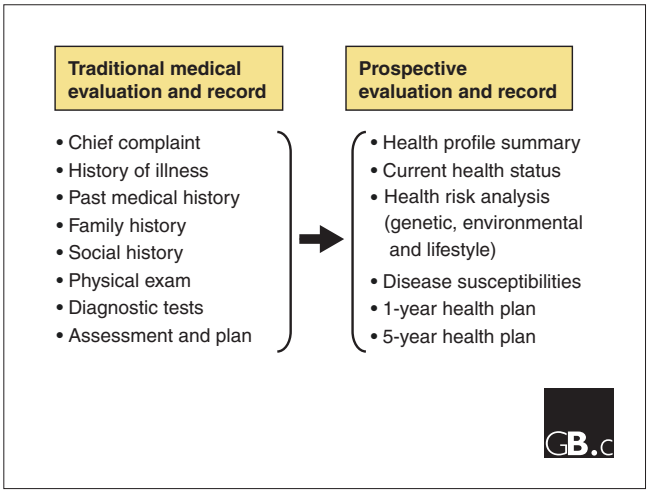

Figure 3
The traditional medical record compared with the prospective approach. Physicians are currently trained to evaluate patients using the approach on the left. This clearly demonstrates a focus on identifying and rectifying disease. The process can be broadened to include strategic health planning, as demonstrated by the prospective evaluation and record on the right.

and survival time, to guide difficult treatment choices for various cancers, and to recommend disease-management choices for patients with heart failure [10-12]. Nonetheless, unlike in other industries, there has not been widespread or standardized use of predictive models in clinical practice. Part of the reason for this is that predictive models created from randomized clinical trials or from prospective data cohorts like the Framingham Heart Study (a population-based study initiated in 1948 with the aim of identifying major risk factors associated with heart disease) were originally based on a limited range of clinical and demographic data from narrow populations, for which results could not be easily generalized [13,14]. Furthermore, when predicting dichotomous outcomes (for example, heart attack or no heart attack over a given time-frame), such models often have a concordance index (a measure of classification accuracy) under 90%, leaving concerns that too many false predictions could be made. Thus, predicting the likelihood of the risk of a heart attack over ten years represents a useful guide for physicians in identifying patients at risk, but to be more useful, clinical medicine requires predictive models that can predict events accurately over far shorter time-frames. To achieve this, more relevant and specific data will need to be collected for analysis (Figure 5).

Genomic research drives the discovery of predictive factors and personalized medicine

Among the most important contributions that genomic research will make to clinical medicine will be to provide a source of relevant predictive biomarkers for use in the development of specific risk assessments, including baseline risk evaluation, disease progression tracking, disease event prediction, and therapeutic support tools. When accurately measured, genomic factors that lie in the causal pathway of disease or therapeutic response, or factors such as single-nucleotide polymorphisms (SNPs) that are highly associated with causal genes, will serve as better predictors of adverse outcomes than much of the data now being collected. Stable DNA gene predictors will enhance baseline clinical risk assessment and primary prevention, and dynamic mRNA, protein and metabolic factors will enhance refined risk assessments to track disease progression, predict events, and guide therapeutic choices.

Demographic, clinical, and family-history predictors that are relatively easy and cost-effective to collect will probably retain their value. But such information alone is associated with many false-positive and false-negative predictions for any given individual. Furthermore, there is an upper limit to the predictive value of many current basic clinical and laboratory tests in anticipating disease pathogeneses well before they occur. Disease genes or SNPs linked to these causal genes, discovered through biological studies, will serve as more accurate markers of disease susceptibility. Depending on the complexity of the disease pathogenesis, such genes may account for a very small to a very large amount of the variation seen in the natural history of a disease. Even in the most complex cases, however, a collection of interrelated genes or SNPs, along with a comprehensive family-history assessment, can serve as a stable baseline of risk assessment that can guide the use of more refined risk assessments - ones that incorporate dynamic molecular factors, reflecting the interaction between the individual's stable genome and the changing environment.

The advantage of genotypic data for baseline prediction is that it can be collected at birth. Baseline risk assessments using basic family and demographic data or static genomic information will probably have lower specificity (a higher number of false positives) than molecular measures that are dynamic and change with someone's environment and development. Nonetheless, baseline assessments will effectively identify the people who require further evaluation using molecular information that reflects disease development. These general concepts also hold true for secondary prevention (for example, heart attack in an individual with diabetes), but the use of stable genomic data may be less valuable when dynamic indicators have already manifested and are part of the same pathway of disease as the gene predictors. In the long term, the decreasing cost of genotyping may facilitate the use of DNA information for a more rational and standardized approach to baseline risk assessment.

Identifying the appropriate disease genes and predictors for baseline risk assessment will be further facilitated by new clinical research and the HapMap project. The International HapMap Consortium is characterizing common patterns of

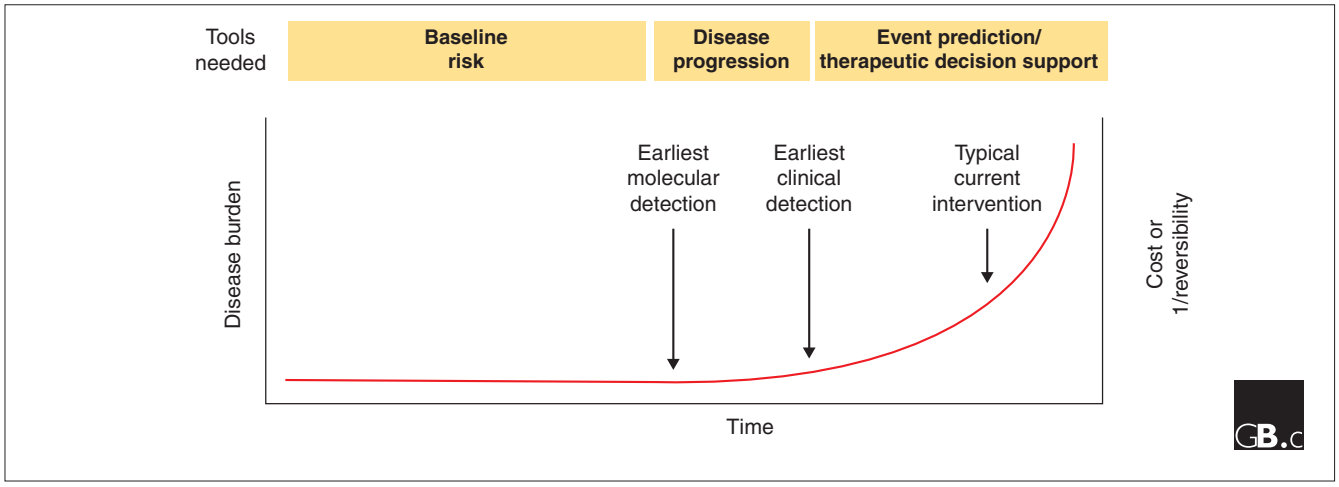

Figure 4
Towards focused prevention and effective intervention. As shown in Figure 2b, the typical time of intervention currently occurs after the disease burden has started to increase. Emerging health risk assessment and evaluation tools will permit early detection (using either clinical observations or molecular biomarkers) and will facilitate prevention and early intervention. Intervention before disease is detected may enable the damage to be prevented.

DNA sequence variation and the extent of linkage disequilibrium in the human genome. This will facilitate the characterization of genotypes and identification of key SNPs related to chronic disease; traditional and advanced association algorithms will allow the analysis of the HapMap [15-19]. Online Mendelian Inheritance in Man (OMIM), a database of disease risk genes, already reveals an increasing number of disease-related stable genomic factors that could be useful in predictive risk assessment [20]. Furthermore, the role of an individual's gene variants in altering the metabolism and efficacy of drugs they take is already proving critical in drug development and in certain areas of clinical practice, such as oncology [21].

For individuals whom genes, SNPs, family history, or clinical information identify as high risk for a particular disease, comprehensive surveillance will be needed to track possible disease progression and to provide therapeutic support. Such tracking will include the measurement of dynamic factors, including gene-expression, proteomics and metabolomic assessments. The use of such analyses to track disease development is still rudimentary but can be expected to be incorporated into personalized health plans in the future. For example, children with a family history of type 1 diabetes can have a baseline risk assessment that considers various SNPs as predictors of developing the disease. Children at enhanced risk could undergo a comprehensive surveillance protocol, tracking their levels of factors that destroy pancreatic β-cells and that produce changes in insulin secretion [22,23]. This process could be used to guide clinical research on preventive interventions for type 1 diabetes. When effective therapies are found, the same types of analyses could guide identification of patients at risk and appropriate intervention.

Initial applications of technologies such as these are being developed to predict outcomes in established conditions. For example, gene-expression microarray tests and proteomic techniques show promise for identifying the aggressiveness of cancer, allowing the creation of predictive models for likely survival time with and without treatment [24-27]. Moreover, gene expression in circulating mononuclear cells is being used to predict organ rejection in patients with heart transplants, obviating the need for myocardial biopsy in some conditions [28].

These examples highlight the need for predictive tools in the selection of treatment options. By including potential therapies in these models, physicians can assess therapeutic options to select their risk/benefit ratios. The highest possible predictive accuracy will be necessary for such screening and decision support to be clinically useful. For example, coronary artery bypass grafting supported by cardiopulmonary bypass on pump is associated with a number of serious adverse outcomes, including stroke. Current predictive models for stroke as a result of 'on-pump' coronary artery bypass grafting, a surgery in which blood is pumped by a machine while the heart is being operated on, have a relatively low sensitivity and specificity; none of the models currently has an overall concordance index over 80%. New SNPs and proteomic quantification of coagulation factors, cytokines and C-reactive protein, which may be causally related to susceptibility to stroke after bypass, may, however, increase the accuracy of future models enough to make them useful in improving therapeutic decision-making - in this case whether to prescribe standard cardiopulmonary bypass, or the more difficult but stroke-lessening off-pump bypass approach, or other therapies [29].

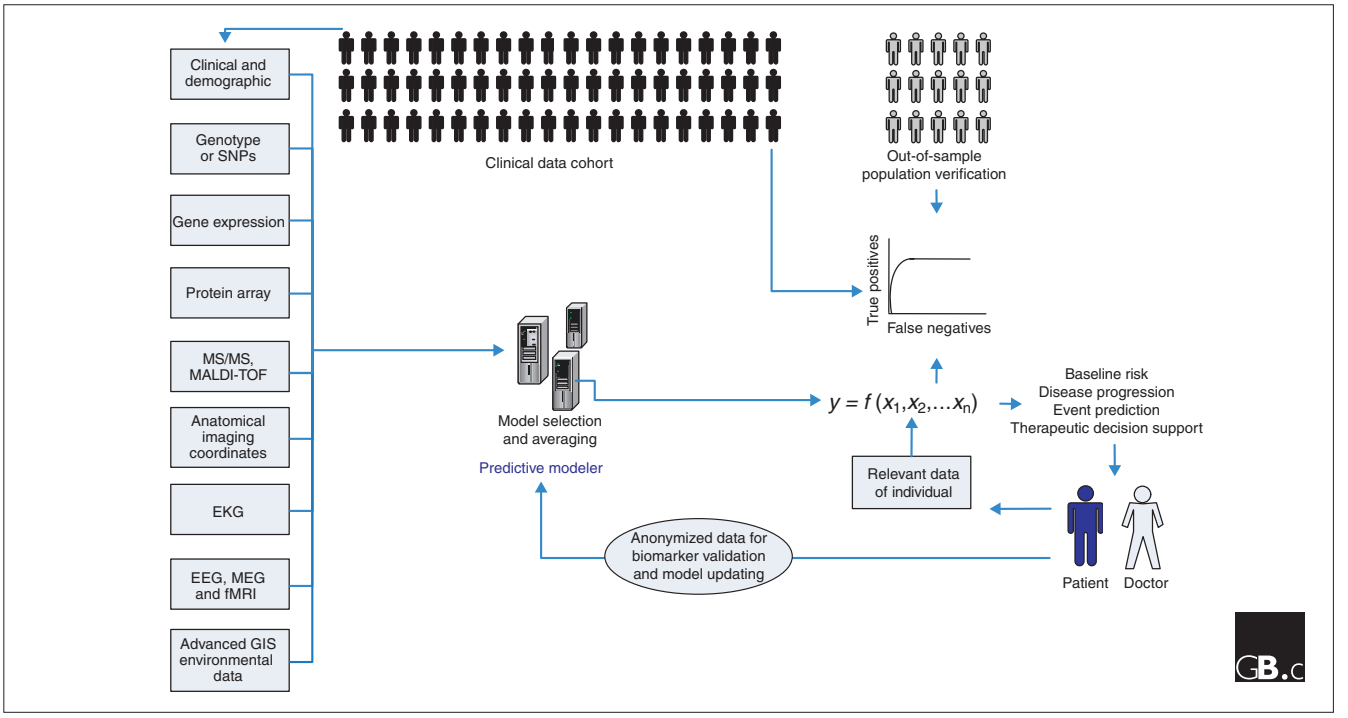

Figure 5
Facilitating risk assessment by linking a dynamic predictive modeling system to clinical decision support. Clinical data and the results of biomarker analyses (left) are collected from a cohort of people (top) and stored in disease model libraries, and models are developed from them (middle). Other populations can be used to verify the data (top right). The models can be used to identify risk prediction factors for particular diseases or events and can be compared against an individual's profile to determine their risk, or to diagnose disease progression (right). Data from each patient can then be fed back into the model, in order to improve it. Abbreviations: EEG, electroencephalogram; EKG, electrocardiogram; fMRI, functional magnetic resonance imaging; GIS, geographic information systems; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; MEG, magnetoencephalogram; MS/MS, tandem mass spectrometry; SNPs, single-nucleotide polymorphisms.

Risk assessment for breast cancer

Breast cancer provides a useful example of how genomic research and predictive models can improve clinical care. For personalized prevention and early intervention, it is necessary to predict baseline risks, provide surveillance for early detection, and facilitate optimal individualized therapy if disease develops. For baseline risk measurement, a tool was developed in 1989 to estimate the likelihood that a woman at a given age and defined risk factors will develop breast cancer over a specified time. The model to do this, termed the Gail breast cancer model, aids physicians in developing a personalized strategy for further screening and treatment. This model was constructed from case-control data of the Breast Cancer Detection Demonstration Project (BCDDP) and included age at menarche, age at first live birth, number of previous biopsies, and number of first-degree relatives with breast cancer as indicators [30].

Newer predictive models include as predictors more robust family history (for example, in the so-called Claus model) and causal disease genotypes such as *BRCA1* or *BRCA2* (for example, in the BRCAPRO model), and these have advantages in predicting breast cancer compared with the original Gail model. Whereas the Gail model is a logistic regression, the Claus model uses a genetic modeling approach to determine age-specific breast cancer development probabilities from family history. BRCAPRO, a Bayesian model, is focused on *BRCA1* and *BRCA2* and the risk of breast cancer. Many of these newer baseline risk models for breast cancer can be accessed through a tool called CancerGene [31]. A current challenge is determining optimal ways to use these models in conjunction with one another, or designing ways to combine clinical information, and genetic and family history data into a single predictive model.

More work is necessary to facilitate accurate prediction of breast cancer. The incorporation of *BRCA1* and *BRCA2* disease alleles as predictors does aid in risk assessment of cancer but does not predict most forms of breast cancer in the population. Breast cancer is a feature of many other syndromes with known genetic mutations, for example Li-Fraumeni syndrome (caused by a germline *p53* mutation), Cowden syndrome (a *PTEN* mutation), and Peutz-Jegher syndrome (an *STK11* mutation) [32,33]. Other genotypes associated with increased risk of breast cancer are located in several genes, including *BRCATA* on 11q, *BRCA3* on 13q21,

RB1CC1 on 8q11, *BWSCRIA* on 11p15.5, and *BRIP1* on 17q22 [34]. Tools have not yet been developed to be used effectively in primary care screening for cancer risk, but it can be assumed that with further research, useful baseline screening tools will become available [35].

A validated 'SNP chip' to test for the presence of disease genotypes for multiple alleles should help improve the sensitivity of the test for use in baseline risk assessment in the broader population [36]. When they become cost-effective, early screening of a broader range of relevant genotypes could be incorporated into personal health plans. Because genotype data are static, a one-time screen has lifelong benefit by determining whether or not the patient should be entered into a more comprehensive breast-cancer surveillance program. Although no high-throughput genotyping tool is currently available for breast-cancer onset prediction, Genomic Health, Inc. has commercialized its Oncotype Dx 21-gene predictor of breast cancer recurrence [37], and Veridex, LLC has published research on its gene-expression tests, reporting improvements in the accuracy of predicting cancer prognosis [38]. These enhancements are based on molecular tumor analysis; the Oncotype Dx test has already been used to enhance Adjuvant Online!, a predictive model for cancer recurrence and survival [39,40]. Such tools, as well as those described earlier, provide evidence that clinical-genomic predictive models may soon have utility in clinical practice.

Future clinical research and/or other means of monitoring clinical information will be vital to validate and add additional discoveries in genome biology for application to clinical care. Bioinformatics tools can help cull the literature for factors that may have an association with a particular adverse outcome, and clinical experts can identify the factors that should be evaluated as risk factors in prospective patient cohorts. To support increasingly accurate risk assessments, we envisage a process in which the validation of new genomic biomarkers by biostatistical means will be coupled to the use of current best practice. Over time, improving development of accurate predictive models will become an output of clinical practice.

The application of these new technologies to health care will not only provide a far more detailed understanding of health and its evolution toward disease, but will also support the ability to predict events and anticipate appropriate interventions. Highly accurate risk assessment is an important component of a shift to prospective health care. Causal genomic factors and their products will play key roles as predictors of disease in tools used for clinical decision support. Clinical research is necessary to validate the accuracy of newly developed predictive models and the relative usefulness of new biomarkers. The creation of systems to facilitate this type of information gathering, as well as the use of model-based clinical decision support, is critical for enabling us to provide prospective health care.

Just as a century ago the emerging sciences transformed medicine, the new sciences of the early 21st century will again transform health care. Whereas a century ago microbiology and biochemistry drove fundamental change, the current drivers will include the emerging technologies of genomics, proteomics and metabolomics, coupled with bioinformatics, medical informatics, biostatistics, data mining and decision sciences [41,42].

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