

Transforming the practice of medicine using genomics

Geoffrey S. Ginsburg
Jeanette J. McCarthy

Duke University, Institute for Genome Sciences & Policy,
 Durham, NC, USA

Address for correspondence:
 Geoffrey S. Ginsburg, M.D., Ph.D.
 Duke Institute for Genome Sciences & Policy
 Box 3382
 Durham, NC 27710, USA
 Ph. 919-668-6210
 Fax 919-668-6202
 E-mail: geoffrey.ginsburg@duke.edu

Summary

Recent studies have demonstrated the use of genomic data, particularly gene expression signatures, as clinical prognostic factors in complex diseases. Such studies herald the future for genomic medicine and the opportunity for personalized prognosis in a variety of clinical contexts that utilize genome-scale molecular information. Several key areas represent logical and critical next steps in the use of complex genomic profiling data towards the goal of personalized medicine. First, analyses should be geared toward the development of molecular profiles that predict future events – such as major clinical events or the response, resistance, or adverse reaction to therapy. Secondly, these must move into actual clinical practice by forming the basis for the next generation of clinical trials that will employ these methodologies to stratify patients. Lastly, there remain formidable challenges in the translation of genomic technologies into clinical medicine that will need to be addressed: professional and public education, health outcomes research, reimbursement, regulatory oversight and privacy protection.

KEY WORDS: genomic medicine, personalized medicine, human genome.

The opportunity to personalize medical treatment

The use of genomic technologies to improve medical decision-making so as to achieve the goal of personalized medicine is poised to transform health care (1). However, despite the vast amount of genomic information now in the scientific literature, the translation of basic scientific findings from the genome to daily use in medical practice has been slow.

New knowledge from the study of the human genome and its RNA, protein, and metabolite by-products now has permitted the development of predictors of disease progression (“who to treat”) and therapeutic response (“how to treat”) in individual patients and thus provides an opportunity to employ these predictors in present day practice. Genome analyses are providing a more detailed understanding of the molecular architecture of disease structure, its likelihood to progress, and of the response of patients to currently available drugs. Genome wide

scans of sequence variation (2), gene expression profiling, proteomics and metabolomics have been used to develop ‘signatures’ that classify disease and that provide the basis for more precise diagnosis and prognosis (3-6). This presents an important and attainable opportunity to employ genomic signatures to transform both the delivery of health care and the development of novel therapeutics as well the appropriate targeting of currently available drugs to the population that will derive the greatest benefit from them.

Personalized cancer treatment today is a spectacularly promising example of the future of genomics-based medical practice. This paradigm of medical care is based on our ability to match accurate prognosis and proper therapy to the molecular characteristics of the individual patient’s tumor. Whole-genome expression data are now being used routinely to identify subtypes of cancer not previously recognized by traditional methods of analysis: profiles and patterns that identify new subclasses of tumors, such as the distinction between acute myeloid leukemia and acute myeloid leukemia (7), or Burkitt’s lymphoma from diffuse B cell lymphomas (8), without prior knowledge of the classes. More recently several genomic signatures that go beyond disease classification have been discovered and validated that predict prognosis and response to therapy for many solid tumors and hematologic malignancies (9, 10).

Last year, oncologists used RNA expression signatures for risk stratification and prognosis in breast cancer for more than 15,000 “treat” vs. “no-treat” decisions (11). A prospective cooperative group clinical trial in Europe (MINDACT) aims to measure the effectiveness of a gene expression predictor of breast cancer prognosis to guiding adjuvant chemotherapy when compared to predictions based solely on the traditional clinical parameters for prognoses (12). An NCI-sponsored study (TailorX) aims to utilize the Oncotype Dx test from Genomic Health, Inc. to identify low risk breast cancer patients unlikely to benefit from chemotherapy (13). For lung cancer a similar opportunity now exists to refine prognosis and redirect treatment in early stage disease (10). Thirty per cent of early stage lung cancers managed with surgical resection and observation – the standard practice – recur and patients die. No clinical markers are capable of identifying which patients will have a recurrence of their disease up front. A genomic signature obtained from a gene expression assay of RNA from a patient’s lung tumor has been reported to predict which patients do so. And a clinical trial has been developed that uses this signature to randomize patients to surgical treatment with or without adjuvant chemotherapy (10). These are clear examples where genomic medicine is redefining disease phenotypes and refining therapeutic strategies.

Of equal if not greater importance in achieving the goal of personalized treatment of cancer patients is an ability to predict response to specified therapies, particularly the standard of care regimens that are part of routine clinical practice today. The selection of therapy for many cancers is still largely empiric and guided by large randomized clinical trials on populations of patients. Estimates of benefits from this approach for individuals are extrapolations from the effects seen in these large trials, and do not necessarily apply to individual patients.

Genomic signatures that predict response and resistance to a spectrum of cytotoxic chemotherapies may now allow assignment of patients to effective treatment regimens best suited to the unique characteristics of their tumor (14). For example, the predictive accuracy in expression results from several sets of samples from patients with breast cancer was > 81% overall. Importantly, in these studies, the overall clinical response rate varied from 25% to 45%. Using the predictors of drug sensitivity essentially increases the 'effective' response rate (the positive predictive value for chemosensitivity for any given drug) to greater than 85%. Thus genomic predictors of chemotherapy response provide an opportunity to determine which drug would be optimal for an individual patient in clinical scenarios for which past studies have not shown a clear superiority for any of the currently available drugs.

The evidence for genomic-based cancer care is now being further built in 'first-of-a-kind' *genomics-guided* clinical trials. A randomized, controlled prospective trial will commence this year to test a strategy in which a genomic signature for response and resistance to docetaxel, adriamycin, and cytoxan will be derived from a diagnostic breast biopsy and will be used to assign women with early stage breast cancer to adriamycin/cytosin vs. docetaxel/cytosin combinations in the neoadjuvant setting (15). This trial, together with the breast cancer and lung cancer prognosis trials, represents the leading edge of the evidence base needed to firmly embed genomics into practice guidelines, reimbursement policy, and health policy.

Beyond cancer, other fields of medicine are also benefiting from whole genome approaches that are defining both susceptibility to complex disease as well as signatures that define disease states and predictive outcomes based on analyses from both disease tissues and from blood (16). Blood based gene expression profiling is particularly important as it presents the opportunity to report on disease processes from remote and often inaccessible sites for direct analyses. Instead of analyzing single genes, global gene expression provides a "molecular signature" that may distinguish between one disease state and another. In addition to identifying signatures or patterns of gene expression that represent a disease state, analyses can be constructed to identify representative pathway genes that might point to novel pathophysiology relevant to the underlying disease state. Peripheral blood gene expression signatures have now been reported in a variety of conditions including rheumatoid arthritis (17, 18), systemic lupus erythematosus (19) multiple sclerosis (20, 21), asthma (22), solid malignancies (23-25), solid organ transplantation (26, 27), as well as environmental exposures (28-30). Many of these conditions have an inflammatory component and thus affect immune cells in the vascular compartment. It is hypothesized that these cellular changes are the basis for the differences in gene expression that is observed in RNA extracted from whole blood specimens or from specific circulating cell types. The greatest potential of this approach would be the enhancement in accurately classifying patients by the type and severity of their disease and to individualize the therapy based on the biology of the disease in an individual patient.

Challenges for clinical adoption of genome based approaches

Despite the optimism from the genome sciences and the need to improve the quality of clinical medicine, the integration of genomics into clinical practice faces challenges that are generally similar to those for the introduction of any other innovative technology (Table I). Aside from the technical hurdles, several public policy issues surrounding the clinical use of genomics

will require dialogue, debate, and resolution. Health care provider and public education, regulatory oversight of new clinical tests, reimbursement, and assurances of privacy and confidentiality are among the issues that must be addressed in order for the use of genomics to become routine.

Table I - Challenges to translating genomics into clinical medicine

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- Professional and public education
 - Health outcomes research
 - Reimbursement: Who will pay? What is the cost?
 - Regulatory issues and clinical guidelines
 - Medical and genetic privacy
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Education. Both the lay public and health care professionals need to better understand genetics and genomics and their potential to impact health and disease. The rapid advancements in genomics research and technologies make it challenging to keep health professionals informed about the benefits, risks, and limitations of new tools as they become available. Although several surveys have documented physician knowledge of genetics (31, 32), none have assessed knowledge of the newer field of genomics. Several papers recognizing the importance of pharmacogenetics have been published (33, 34). Few medical school curricula have been developed in this regard and the same can be said for post graduate educational programs for health professionals.

Cost-effectiveness. Just as with any clinical innovation, the use of genomics in clinical medicine must be evidence based to clinically useful and demonstrated to be cost-effective. At this stage, many genetic and genomic tests lack the clinical data to support health care insurance coverage. Since 1996, about 149 economic analyses of genetic services have been conducted, mostly for adult conditions such as cancer (35). With respect to pharmacogenomics cost-effective studies, most analyses show pharmacogenomic testing to be cost-effective in specific clinical scenarios, although only a handful of studies have been conducted (36). Like an other type of biomarker, the clinical outcome of using the genomic biomarker has to be well-defined for the cost-effectiveness estimate to be accurate.

Regulatory oversight. Currently, most genetic and genomic tests are offered as a clinical laboratory service ("laboratory developed tests") and, therefore, are not subject to regulatory oversight. The extent of regulatory oversight has been an important topic of discussion in recent years resulting in general agreement for the need of enhanced oversight but debate over how that should be implemented. With the current rise in genomics-based tests, regulatory authorities will need to respond to unique issues raised by these new molecular biomarkers and technologies. A delicate balance should be reached where oversight does not discourage innovation but will provide an adequate level of assurance regarding the safety and efficacy of these products.

Privacy. There has been ongoing debate about the uniqueness of genetic information and whether it warrants special protections beyond those in place for standard medical information. The potential for genetic discrimination has been a major concern for researchers, health professionals, patients and the public. In the US, fear of discrimination by employers and health insurers is the main concern, whereas in the UK, use of genetic information by life insurers is the major concern. In order for genomic biomarkers to be integrated into routine clinical practice, associated fears with this type of testing must be put to rest. While the majority of states in the US have enacted leg-

isolation to protect against genetic discrimination by employers and health insurers, national protections are still lacking despite repeated attempts. Legislation may be necessary to ensure that medical privacy rules encompass this new molecular testing and that insurers and employers can never use testing results to discriminate against an individual.

The future of personalized medical care

While the human genome sequence is now available, it is important to acknowledge that our knowledge of the genome and its biological complexity is nowhere near complete, and the use of genomic protocols in standard clinical care faces many challenges. There are a host of clinical, economic, insurance, privacy and commercialization concerns that will need to be addressed and that vary substantially among different countries. We will confront those with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence-based. These issues are being dealt with systematically and the prospects of using genomic information to offer patients health care that is truly personalized in nature is finally within our grasp.

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