PERSPECTIVES

Host-Environment Medicine

A Primary Care Model for the Age of Genomics

Peter M. Rabinowitz, MD, MPH, Alex Poljak, MD

Rapid developments in genomic and proteomic testing promise to impact the way in which clinicians assess disease risk and drug selection in their patients. Because most diseases result from host-environment interactions, however, primary care providers will need to avoid the trap of biological determinism by examining the important role of environmental factors in their clinical assessments and interventions. This article discusses the application of host-environment concepts to recent developments in the areas of genomics and proteomics.

KEY WORDS: genomics; environment; primary health care; models, theoretical; risk factors.

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Because of advances in the emerging fields of genomics and proteomics, patients and their health care providers will soon face questions about a wide range of new genetic and metabolic markers. These markers can provide detailed information about disease susceptibility, selection of drugs, and early evidence of disease (Table 1).

These developments, however, raise the concern that both physicians and patients could fall into a trap of biological determinism, believing that one's genetic and metabolic makeup far outweighs the role of environmental factors in disease. Such thinking fails to acknowledge that most health outcomes are the result of interactions between host factors and environmental factors. Therefore, as physicians' sophistication about host factors grows, their knowledge and appreciation of their patients' environments also needs to increase. As Khoury has stated, "The nature versus nurture controversy is being replaced by systematic evaluation of nature-nurture interaction."¹

Definition: Host and Environmental Factors in Health and Disease

For the purposes of this paper, a *host factor* is defined as a person's intrinsic physical or behavioral character-

istics, while *environmental factors* encompass the extrinsic social, chemical, physical, and biological forces acting upon that person. Figure 1 portrays this definition of host and environmental factors. Many conditions, such as cigarette smoking, can involve both host factors (e.g., susceptibility to COPD and cancer as well as limited confidence in ability to quit, or "self-efficacy"²), as well as environmental factors (such as the chemical constituents of the smoke, dietary factors, and the social milieu in which the person smokes or is passively exposed).

Genomics, Pharmacogenomics, and Proteomics

Until recently, medical genetics has focused on highly penetrant disorders such as Huntington Disease, cystic fibrosis, and Duchenne muscular dystrophy.³ Now, however, the emphasis of genetic research is shifting toward understanding of more common, multifactorial diseases, such as cancer and heart disease, as well as individual response to pharmacologic agents. The Human Genome Project has allowed researchers to look for the genetic variants with higher prevalence but lower penetrance known as polymorphisms, which code for proteins determining an individual's metabolic and immunologic status.

While mutations are rare differences occurring in less than 1% of the population, polymorphisms have been defined as variations in which the least common allele is present in 1% or more of the population.⁴ For example, while several genes with dominant transmission for Alzheimer's disease risk have been identified, these account for less than 1% of cases. In contrast, the apolipoprotein E (APOE) polymorphism may explain up to 17% of Alzheimer's disease in the general population.⁵ Indeed, most of the variation in the human DNA sequence appears to be due to the presence or absence of polymorphisms that may differ by a single nucleotide (single nucleotide polymorphism). The Human Genome project will lead to identification of hundreds of thousands of such polymorphisms.⁶

Preliminary research has correlated certain polymorphisms with risk for a wide range of clinical conditions, including ventricular hypertrophy, glaucoma, and colorectal cancer.⁷⁻⁹ Some polymorphisms may increase risk for several disorders; the APOE polymorphism that predicts Alzheimer's risk is an important modulator of lipid metabolism and also increases risk for ischemic heart disease. In contrast to monogenic disorders, the relationship between a

Received from the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.

Address correspondence and requests for reprints to Dr. Rabinowitz: Yale University School of Medicine, Yale Occupational and Environmental Medicine Program, 135 College St., Third Floor, New Haven, CT 06510 (e-mail: Peter.rabinowitz@yale.edu).

Table 1. Emerging Technologies

Term	Technology	Uses
Genomics	DNA genotyping, looking for variants including mutations and SNPs	Predict disease susceptibility
	Microarray gene chips looking for RNA expression of multiple genes	Selection of drugs (pharmacogenomics) Susceptibility to environmental toxins
Proteomics	Characterization of protein patterns	Early diagnosis of medical conditions Selection of drugs Susceptibility and early markers for effects of environmental toxins

SNP, single nucleotide polymorphism.

single polymorphism or a combination of polymorphisms and a disease outcome may be highly variable and dependent on host–environment interactions.

In addition to predicting disease susceptibility, polymorphisms are also central to the expanding field of pharmacogenomics.¹⁰ Polymorphisms coding for a drug receptor or key metabolic enzyme can predict response or toxicity to a certain pharmacologic agent. Genetic variants

in the cytochrome P450 (CYP) family of enzymes influence the metabolism of most drugs currently used in medicine.¹¹ Individuals with the inactive “poor metabolizer” genotype for CYP2D6, constituting up to 6% of the population, cannot convert codeine into its active metabolite, morphine, and therefore derive little analgesic benefit from codeine preparations.⁴ Similarly, persons with the “slow acetylator” genotype for *N*-acetyl transferase (NAT) enzymes are at increased risk of hydralazine-induced lupus, and have greater risk of hepatic toxicity from isoniazid.¹² Glutathione S-transferase (GST) enzymes are an important part of the body’s antioxidant defenses, and GST polymorphism status can predict response and toxicity to chemotherapeutics such as Tacrine.¹³ The effect of diet may also vary by polymorphism; intake of polyunsaturated fats appears to raise high-density lipoprotein levels in individuals with a certain APOA polymorphism, whereas individuals lacking the gene experience an opposite effect on the same diet.¹⁴

Other new technologies may offer even more detailed understanding of an individual’s metabolic and immunologic status. The use of DNA microarrays allows for analysis of gene expression for thousands of genes simultaneously.^{15,16} Since genes are variably expressed, this can provide information complementary to genetic testing. The newly emerging field of proteomics moves

FIGURE 1. Host and environmental factors.

beyond genomics in an attempt to map and catalog every protein in the human body¹⁷ and therefore characterize the state of molecular signaling within the cell and the organism.¹⁸ Using information tools to handle vast amounts of protein analysis data, proteomics can therefore provide a comprehensive “snapshot” in time of the biochemical status of a patient. A recent study used serum proteomic analysis to detect ovarian cancer with a sensitivity of 100% and a positive predictive value of 94%.¹⁹

Genomics and Environmental Susceptibility

It has long been recognized that individual susceptibility to environmental carcinogens and other agents varies greatly, but the basis for such variation has remained poorly understood.²⁰ What is intriguing about genomic and proteomic markers for disease susceptibility and pharmacologic response is that they also appear to correlate with individual susceptibility to environmental exposures. CYP status, in addition to predicting drug metabolism, may also affect risk of cancer due to environmental mutagens²¹ and risk for non-cancer diseases related to occupational exposures.²² NAT slow acetylators may be at increased risk of both drug toxicity as well as bladder and lung cancer due to smoking and other environmental toxins.²³

The effect of a single polymorphism may be subtle, and studies have shown that a combination of several polymorphisms may be more predictive of an individual's response to an exposure. Smokers deficient in both a certain CYP gene as well as a certain GST gene may be at elevated risk of squamous cell lung cancer.²⁴ A combination of polymorphisms affects the risk of immunologic hypersensitivity to beryllium, producing sarcoid-like illness.²⁵ Because of the increasing complexity of such gene-environment interactions, the National Institute for Environmental Health Sciences has initiated the Environmental Genome Project to characterize several hundred genes coding for proteins affecting susceptibility to environmental agents.²⁶

Current Limitations of Genomics and Proteomics

Despite all of the ongoing research and publicity surrounding these new technologies, few studies to date have provided clear evidence that such testing can improve clinical outcomes in a cost-effective manner.²⁷ In a recent review of 100 psychiatric admissions, investigators found that polymorphisms for either poor or ultra-rapid CYP2D6 activity were associated with four to six thousand dollars in yearly additional costs resulting from drug dosing problems. They concluded, however, that studies of at least 1,500 individuals were necessary to clearly establish such an association.²⁷ If such large-scale studies begin to be funded and completed, results from such investigations may lead to rapid changes in clinical protocols involving genomic and proteomic tests.

Host-Environment Medicine: A Primary Care Model

While waiting for better clinical research to determine the appropriate role for genomic testing, clinicians can begin to examine possible host-environment interactions in their patients. It seems likely that just as clinicians may need to tailor a drug regimen to a patient's particular genomic status, some patients may need other environmental modifications based on their host status. As our understanding of host-environment interactions grows, the responsibility for knowing relevant details of a patient's environment will probably continue to fall on the primary care physician. The practical application of such knowledge is illustrated in the following case example.

Case Example: Host-Environment Medicine

John G. comes to his physician with several complaints. He is a 55-year-old factory worker with adult onset diabetes who has been bothered by painful neuropathy in his legs. At his visit, he reports that the tricyclic antidepressant that had recently been prescribed for chronic pain control was not working, so he stopped taking the medication. He is also concerned about a raised skin lesion on his neck that has been bothering him lately. Despite counseling about his risk for cancer and cardiovascular disease, he continues to smoke, expressing low confidence in his ability to quit.

The clinician treating John G. wonders if there is a unifying explanation for the tricyclic ineffectiveness and the new skin lesion. As an avid reader of the emerging pharmacogenomics literature, the clinician realizes that individuals who are genetically polymorphic for CYP2D6 ultra-rapid metabolism (UM) may require higher doses of tricyclics and have also been reported to be at increased risk for basal cell carcinoma.²⁸ Beginning to think in a host-environment manner, the clinician considers what medication “environment” would best fit this particular “host,” and beyond drug therapy, what other host-environment interactions might be relevant. Table 2 lists some of these interactions. The goal of a host-environment assessment is to identify the most important host-environment interactions and set priorities for either improving host status, reducing environmental stressors, enhancing environmental supports, or some combination of all three.²⁹

The knowledge that the patient may be at increased risk for basal cell carcinoma leads the clinician not only to arrange a skin biopsy of the suspicious lesion, but also to spend extra effort counseling about the use of sunscreen and avoiding excess sun exposure. After reviewing the medical literature further, the clinician finds reports of both increased tobacco addiction and increased susceptibility to lung and bladder cancer in smokers with the CYP2D6 UM polymorphism,^{30–32} and resolves to invite John's wife to the next visit in order to

Table 2. Host-Environment Interactions for Case Example

Host-Environment Interaction	Intervention
1. CYP2D6 rapid metabolizer, poor self-efficacy $\leftrightarrow$ smoking, toxins in factory	Environment: enlist family to help with cessation, reduce work exposures Host: counseling re increased risk of cancer, self efficacy, enhanced screening for early cancer
2. CYP2D6 rapid metabolizer, neuropathy $\leftrightarrow$ tricyclic medication	Environment: change medication to one that fits metabolic profile
3. CYP2D6 rapid metabolizer, skin lesion $\leftrightarrow$ sunlight	Environment: avoid UV exposure, arrange skin biopsy

discuss ways to improve John's home environment in order to encourage smoking cessation. The clinician also makes inquiries about whether John's factory job exposes him to potential bladder carcinogens to which, with his particular "host factors," he is particularly susceptible. While aware that polymorphism testing for CYP2D6 has not yet been studied in randomized controlled trials to determine if it could lead to better patient outcomes, the clinician begins to consider whether the test³³ could be of use in selected patients who present with particular constellations of medical conditions.

In the future, the clinician may be able to order a DNA chip polymorphism screen on John G's blood sample as well as a targeted proteomic analysis. The DNA chip analysis would allow for identification of multiple polymorphisms that could interact in significant ways. A statistical analysis could compare John G's polymorphism pattern to results from studies of large populations³⁴ to predict probabilities of clinically significant risks. The proteomic analysis could include biomarker testing to look for early evidence of lung or bladder cancer. The results of these genomic and proteomic tests could be merged with computerized medication and environmental risk information about the patient³⁵ in order to help the clinician identify other important host-environment interactions.

Environmental Modifications

Increased understanding of host-environment effects will help clinicians determine which environmental factors are most important and modifiable for an individual patient. Environmental modifications generally fall into 3 categories already familiar to clinicians: avoidance, protection, and social support. The host-environment assessment involves judging which of these modifications will have the most health impact for an individual.

Avoidance may include dietary specifications, avoiding certain medications, and other modifications in the home and workplace to reduce exposure to certain chemicals or physical factors such as noise. Protection could include supplementary intake of antioxidants, prophylactic medications, or improved use of protective barriers such as sunscreen or personal protective equipment at work. Improving social supports could include involving family members, dealing with job health issues, improving the physician-patient relationship, and improving accommodations for persons with disabilities.

Ethical and Employment Issues

The case example above demonstrates some of the promise and potential pitfalls of obtaining genomic information about individual patients. There are ethical issues surrounding wider applications of genomic and proteomic testing, including risks of discrimination by insurance providers, employers, and others. In the workplace, there is concern that genetic information will be used to discriminate against employees found to be potentially more susceptible to occupational disease. Even though the scientific data on the risk associated with a particular polymorphism may be limited, medical insurers and the legal system may begin using such information to deny insurance or settle lawsuits. Conversely, physicians may find themselves liable for failing to test for a genomic marker to predict drug toxicity or effect prior to starting a new medication. There is a need for clearer guidelines for the ethical and medico-legal use of such information.³⁶ At the same time, testing for gene polymorphisms that have variable penetrance and play a limited role in multifactorial diseases may expose an individual to less risk of discrimination than testing for monogenic disorders with high penetrance.³⁷ The use of proteomic testing rather than gene analysis may further reduce the risk of individual "genetic" discrimination.

Environmental Anxiety

As greater attention in medicine focuses on individual susceptibility to disease and environmental agents, another danger is that patients will become inappropriately concerned about avoiding environmental exposures. In an extreme form, this can lead to "environmental anxiety," where a patient is obsessively worried about risks that are actually not significant.³⁸ Such fear can be very disabling. No environment is free of risk, but the greatest risks continue to be well-recognized hazards such as motor vehicle accidents and smoking. Clinicians working to assimilate an ever-increasing amount of risk information on individual patients will need to become increasingly proficient at communicating the relative importance of such risks in the context of other health priorities.

CONCLUSION

The pace of medical progress makes it probable that genomic and proteomic testing will become part of medical routine within a number of years. Over time, outcomes research on populations will help sort out which molecular markers have real value in the evaluation of individual patients and which do not. Almost certainly, our assessments of individual risk will have to become more sophisticated and will require the use of computer-assisted analysis. The increasing volume of information will increase the potential for breaches of confidentiality and for discrimination by insurance carriers and employers. More than ever, clinicians will need to be advocates for their patients to safeguard against such discrimination. All of these barriers will be worth overcoming if the reward is improved opportunities for prevention and treatment of disease. The strength of a host-environment approach to clinical care lies in the fact that unlike many host factors, environmental factors for the most part are modifiable. In the future, clinicians may use sophisticated genomic and proteomic analysis not only to tailor drug therapy to the individual "host" but also to help patients improve multiple aspects of their home and work environments.

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