this depth and sensitivity applies not only to the detection of rare, novel pathogens in a sea of host signal but also to the identification of heterogeneous pathogen subpopulations in a single host that may differ, for example, in drug resistance profiles or pathogenesis determinants. Future studies will be needed to elucidate the clinical significance of these variable subpopulations, even as deep sequencing is now providing unprecedented levels of detail about majority and minority members of this population.

HOST-BASED DIAGNOSTICS

While pathogen-based diagnostics continue to be the mainstay for diagnosing infection, serologic testing has long been the basis of a strategy to diagnose infection by measuring host responses. Here, too, the application of genomics is now being explored to improve upon this approach, given the previously described limitations of serologic testing. Rather than using antibody responses as a retrospective biomarker for infection, recent efforts have focused on transcriptomic analysis of the host response as a new direction with diagnostic implications for human disease. For instance, while pathogen-based diagnostic tests to distinguish active from latent tuberculosis infection have proved elusive, recent work shows that the transcriptional profile of circulating white blood cells exhibits a differential pattern of expression of nearly 400 transcripts that distinguish active from latent tuberculosis; this expression pattern is driven in part by changes in interferon-inducible genes in the myeloid lineage. In a validation cohort, this transcriptional signature was able to distinguish patients with active versus latent disease, to distinguish tuberculosis infection from other pulmonary inflammatory states or infections, and to track responses to treatment in as little as 2 weeks, with normalization of expression toward that of patients without active disease over 6 months of effective therapy. Such a test could play an important role not only in the management of patients but also as a marker of efficacy in clinical trials of new therapeutic agents. Similarly, other investigators have been trying to identify host transcriptional signatures in circulating blood cells that are distinct in influenza A infection from those in upper respiratory infections caused by certain other viruses or bacteria. These signatures also varied with phase of infection and showed promise in distinguishing exposed subjects who will become symptomatic from those who will not. These results suggest that profiling of host transcriptional dynamics could augment the information obtained from studies of pathogens, both enhancing diagnosis and monitoring the progression of illness and the response to therapy.

In this era of genome-wide association studies and attempts to move toward personalized medicine, genomic approaches are also being applied to the identification of host genetic loci and factors that contribute to infection susceptibility. Such loci will have undergone strong selection among populations in which the disease is endemic. By identifying the beneficial genetic alleles among individuals who survive in such settings, markers for susceptibility or resistance are being discovered; these markers can be translated into diagnostic tests to identify susceptible individuals in order to implement preventive or prophylactic interventions. Further, such studies may offer mechanistic insight into the pathogenesis of infection and inform new methods of therapeutic intervention. Such beneficial genetic associations were recognized long before the advent of genomics, as in the protective effects of the negative Duffy blood group or heterozygous hemoglobin abnormalities against *Plasmodium* infection. Genomic methods enable more systematic and widespread investigations of the host to identify not only people with altered susceptibility to numerous diseases (e.g., HIV infection, tuberculosis, and cholera) but also host factors that contribute to and thus might predict the severity of disease.

THERAPEUTICS

Genomics has the potential to impact infectious disease therapeutics in two ways. By transforming the speed of diagnostic information acquisition or the type of diagnostic information that can be attained, it can influence therapeutic decision-making. Alternatively, by opening up new avenues to understanding pathogenesis, providing new ways to disrupt infection, and delineating new approaches to antibiotic discovery, it can facilitate the development of new therapeutic agents.

GENOMIC DIAGNOSTICS INFORMING THERAPEUTICS

Efforts at antibiotic discovery are declining, with few new agents in the pipeline and even fewer entering the market. This phenomenon is due in part to the lack of economic incentives for the private sector; however, it is also attributable in part to the enormous challenges involved in the discovery and development of antibiotics. For obvious market-related reasons, nearly all efforts have focused on broad-spectrum antibiotics; the development of a chemical entity that works across an extremely diverse set of organisms (i.e., more divergent from each other than a human is from an amoeba) is far more challenging than the development of an agent that is designed to target a single bacterial species. Nevertheless, the concept of narrow-spectrum antibiotics has heretofore been rejected because of the lack of early diagnostic information that would guide the selection of such agents. Thus, rapid diagnostics providing antibiotic susceptibility information that can guide antibiotic selection in real time have the potential to alter and simplify antibiotic strategies by allowing a paradigm shift away from broad-spectrum drugs and toward narrow-spectrum agents. Such a paradigm shift clearly would have additional implications for the current escalation of antibiotic resistance.

In yet another diagnostic paradigm with the potential to impact therapeutic interventions, genomics is opening new avenues to a better understanding not only of different host susceptibilities to infection but also of different host responses to therapy. In a sense, the promise of "personalized medicine" has been a tantalizing holy grail. Some signs now point to the realization of this goal. For example, the role of glucocorticoids in tuberculous meningitis has been long debated. Recently, polymorphisms in the human genetic locus *LTA4H*, which encodes a leukotriene-modifying enzyme, were found to modulate the inflammatory response to tuberculosis. Patients with tuberculous meningitis who were homozygous for the proinflammatory *LTA4H* allele were most helped by adjunctive glucocorticoid treatment, while those who were homozygous for the anti-inflammatory allele were negatively affected by steroid treatment. This anti-inflammatory adjunct has become the standard of care in tuberculous meningitis, but this study suggests that perhaps only a subset of patients benefit and further suggests a genetic means of prospectively identifying this subset. Thus, genomic diagnostic tests may eventually inform diagnosis, prognosis, and treatment decisions by revealing the pathogenic potential of the microbe and detecting host responses to both infection and therapy.

GENOMICS IN DRUG AND VACCINE DEVELOPMENT

Genomic technologies are already dramatically changing research on host–pathogen interactions, with a goal of increasingly influencing the process of therapeutic discovery and development. Sequencing offers several possible avenues into antimicrobial therapeutic discovery. First, genomic-scale molecular methods have paved the way for comprehensive identification of all essential genes encoded within a pathogen's genome, with consequent systematic identification of all possible vulnerabilities within a pathogen that could be targeted therapeutically. Second, transcriptional profiling can offer insights into mechanisms of action of new candidate drugs that emerge from screens. For instance, the transcriptional signature of cell wall disruptors (e.g., β-lactams) is distinct from that of DNA-damaging agents (e.g., fluoroquinolones) or protein synthesis inhibitors (e.g., aminoglycosides). Thus, transcriptional analysis of a pathogen's response to a new antibiotic can either suggest a mechanism of action or flag compounds for prioritization because of a potentially novel activity. In an alternative genomic strategy for determining mechanisms of action, an RNA interference approach followed by targeted sequencing has been used to identify genes required for antitrypanosomal drug efficacy. This approach provided new insights into the mechanism of action of drugs that have been in use for decades for human African trypanosomiasis. Third, sequencing can readily identify the most conserved regions of a pathogen's genomes and corresponding gene products; this information is invaluable in narrowing antigen candidates for vaccine development. These surface