Putting a Bug in Your Ear About Genetic Tests

National press attention has recently focused on the dramatic scientific advances in our understanding of the genetics of common chronic disease. These advances have led to the establishment of several high-profile companies that are capitalizing on the windfall of early scientific data by offering testing for the risk of developing multiple disorders like colon cancer, diabetes, and Alzheimer's disease directly to the public. Though of great potential, the immediate relevance and value of this type of testing to the health professions remains to be demonstrated. A more humble area of "genetic" testing with clear immediate relevancy to the care of patients has been making quiet, but increasingly numerous, inroads into clinical medicine: nucleic acid-based testing for microbes.

Many clinicians have used examples of nucleic acid-based testing in the course of their work but probably haven't really given the nature – or increasing prevalence - of the tests much thought. Nucleic acid based tests include assays for detecting disorders like pertussis as well as for genotyping and/or ascertaining viral loads for hepatitis B, C, and HIV. Even more commonly used are the polymerase chain reaction (PCR) based assays for gonorrhea, chlamydia, and human papilloma virus routinely offered as part of well-women care. In most cases these test provide information that can't be easily and/or rapidly obtained by other means and offer sensitive and accurate results of great importance to clinical care. Though clearly not reliant on human genome sequence information, many of these tests have arisen from the explosion of biotechnology spurred on by the Human Genome Project.

In the last few months several new tests have come on line that may be adopted rapidly into the day-to-day practice of primary care. Relevant to the inpatient setting, the FDA has recently approved a test that can be used to diagnose patients with methicillin-resistant Staphylococcus aureus (MRSA) infections in the blood with near 100% sensitivity (FPN Jan. 15, 2008). This test yields a result within a few hours rather than the 48-72 hours it typically takes to culture and screen for MRSA using standard microbiological techniques. At the individual patient level, this offers the potential to rapidly tailor antibiotic choice, thereby avoiding the use of costly and potentially harmful broad spectrum multi-drug regimens. At a public health level, this type of testing could help reduce the prevalence of multi-antibiotic resistant organisms in the environment. There are also indications that nucleic acid-based microbial diagnosis can decrease hospital length of stay. For example, the September 2007 issue of *Pediatrics* included a well-controlled study by King et al. demonstrating a decreased length of stay in infants with meningitis who had a positive enteroviral PCR assay on lumbar puncture.

Relevant to the outpatient setting: how many times has each of you gone through the "it's a viral illness and antibiotics won't help" talk complete with a citation of the guidelines for when antibiotics should be given with a patient with URI symptoms? Recently, the FDA has approved a test that allows you to back up your story with a multiplex PCR assay that detects 12 common respiratory viruses. The list includes: influenza A and B; RSV A and B; human metapneumovirus; parainfluenza virus 1, 2 and 3; rhinovirus; and adenovirus. Depending on sensitivity, specificity, cost and rapidity of turnaround, this

type of testing offers the potential to reduce unneeded outpatient use of antibiotics. Judicious application of this type of testing might even help to determine prospectively whether a doctor's visit is necessary. Properly used, this type of test might meet a lofty goal for any new technology in health care; it could be cost saving.

Another angle on microbial genetics/genomics – which remains in its early stages of development - is the role human genetic variation plays in an individual's interaction with microbes. There is a mounting body of evidence that human genetic variation plays a major role in determining whether and to what extent individuals will be affected by pathogens. For instance, two reports in the January 2008 issue of *The Journal of Infections Disease* by Lim et al. and Kindberg et al. describe studies demonstrating that genetic deficiency of chemokine receptor 5 (CCR5) can help to determine how individuals respond to West Nile virus and tickborne encephalitis virus, respectively. There is cause to be concerned that this type of information might be used in ways that aren't entirely beneficial. For example, one direct to consumer marketing company is offering individuals genetic testing (at less than $100) for rare gene variants thought to be related to less rapid HIV progression. The consequences of such testing could be devastating both for the individual and society if the availability of this test results in less safe sexual practices.

Not that one wants to dwell on this fact much, but in our own bodies microbes outnumber our cells by ten to one. As a species we have co-evolved with these organisms – it seems very likely they have more to do with our well-being (or lack thereof) than meets the eye. The depth, complexity, and importance of the interactions between humans and the microbial world are poorly understood. The NIH has recently launched an initiative to examine the relationship between humans and our small passengers known as the "Human Microbiome Project" (see: http://www.genome.gov/26524200). Over five years, this $115 million dollar project will examine the diversity of species of microbes on and in the human species, and further delineate how these microbes relate to health and disease states. Undoubtedly there will be surprises. Very likely the use of nucleic acid based assays for infectious disease (and maybe tests for "infectious wellness") will become an increasingly common part of the primary care provider's tool kit.