Currently, the practice of pathology is undergoing a transition in which the focus is on individual molecular tests for specific predictive biomarkers for various types of cancers. This current model is predominantly based on single tests for 1 or more biomarkers to predict possible response to 1 or more distinct targeted therapies for a cancer. However, an even more powerful technology looms on the horizon and is expected to eventually replace individual tests as the standard for personalized health care. During the past several years, the ability to map or sequence the entire genome of a cancer in a matter of minutes for a reasonable cost has become an increasingly realistic goal that could make this technology available for routine use in the evaluation of patients’ cancers. Known as whole genome sequencing or analysis or mapping, this global approach would provide a tremendous wealth of information—essentially disclosing the full picture of possible therapeutic targets for a patient’s tumor—in contrast to limited testing for a few separate genes, which might or might not prove of value as targets in a given case.

Today, one might test a sample of a pulmonary adenocarcinoma for epidermal growth factor receptor (EGFR) mutations. Most likely the test would be mutational analysis of the EGFR gene, and, in up to 10% of Western patients, one might find an EGFR mutation that is potentially responsive to anti-EGFR therapy. As part of an algorithm, one might next test for ALK fusion genes using fluorescent in situ hybridization, and, in about 3% to 7% of adenocarcinomas, one might find ALK fusion genes that are potentially responsive to anti-ALK therapy. And so on, for a restricted number of genes. Once the roster of candidate biomarkers has been exhausted, one is left with adenocarcinomas that do not have any of the potential therapeutic targets and, for all cases, one does not know what other targets may be undiscovered in the vast majority of the genome that has not been examined.

In contrast, by mapping the same adenocarcinoma’s entire genome, one can examine not only for EGFR mutations and ALK fusion genes at the same time, but also for other somatic changes throughout the genome, including previously unsuspected new genes, loci, and pathways. This would provide a more complete picture of all possible therapeutic targets with one test.

Of course, the utility of whole genome sequencing is not limited to the therapy of cancer. This technology also has applications for infectious diseases, inherited diseases, and other types of diseases, so that its impact is expected to be felt across the entire spectrum of human disease. Indeed, some have speculated that every person may have his or her genome sequenced at birth to provide a baseline for future prediction/prevention, diagnosis, and treatment throughout the person’s lifetime.

The reason that whole genome sequencing was not previously used for routine clinical practice was the large amount of time and the exorbitant cost of such testing. When the Human Genome Project finished sequencing the first entire human genome in 2003, the project took 13 years and cost nearly $2.7 billion. Not surprisingly, commercial companies have developed new generations of genome sequencing machines that today allow whole genome sequencing at a fraction of the time and cost of earlier sequencers. Companies now talk of sequencing the entire human genome in less than 15 minutes for a cost of $100 per genome. It is the ability to deliver this powerful technology in real time at a practical cost that has led to the expectation that this technology may one day replace the plethora of individual tests now performed in laboratories. Besides clinically acceptable turnaround time and affordable cost, this technology must be suitable for the analysis of routine formalin-fixed, paraffin-embedded specimens.

It seems inevitable that this technology will become routine clinical practice in the future. The pathologist practicing today or in training today will want to know how soon to expect this technology and, of course, what steps he or she should be taking to address it. The answers are complex and challenging. Regarding the latter question, calls to action have recently been published, including, but not limited to, the proceedings of the meeting at the Banbury Conference Center on genome-era pathology and a call for a third track in genomic pathology by James M. Musser, MD, PhD, chair of The Methodist Hospital Department of Pathology and Laboratory Medicine, published in the Archives of Pathology &

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In the future, as the various uses of whole genome sequencing become more commonplace, one should expect significant debate about how to best deal with issues of consent; confidentiality; patents; information control and ownership; appropriate use of genomic information; testing accuracy; disclosure obligations regarding patient, family, insurer, and government (including its use in the criminal justice system); cloning; and genome manipulation.\textsuperscript{16,17}

In conclusion, it seems inevitable that whole genome sequencing will eventually become routine clinical practice, presumably replacing the multiple separate tests for individual genetic anomalies with a single test that allows a very personalized genetic portrait and discovery of information and therapeutic targets that might otherwise go undetected. The implications for medicine are vast, and it is crucial for pathologists to take ownership of whole genomic sequencing in order for our profession to survive. There are a number of practical, economic, and legal issues that must be overcome before genome sequencing is routine practice, and this window provides an opportunity for pathologists to take the steps necessary for their leadership role in this technology.

References


Laboratory Medicine.\textsuperscript{13} The reader is directed to these articles for further discussion of the response of pathology to this technology. There is no doubt that pathologists must embrace whole genome sequencing in order to survive as a profession and that educating our trainees in this field is mandatory.

Regarding how soon to expect genomic pathology as routine practice, there is no doubt that the enthusiasm must be tempered by practical, economic, and legal realities. Although it appears inevitable, it will take a number of years for the further development (including addressing recognized deficiencies), marketing, and finally purchase of sequencers as a capital investment; for training personnel in their use and maintenance; for developing procedures, protocols, and standard reports; and for validating procedures before whole genome sequencing becomes a standard of clinical care in hospitals around the country. Indeed, it is the very fact that whole genome sequencing is only now becoming widely recognized as clinically practical that there is an opportunity during which pathologists can implement the calls to action from the Banbury Conference and Dr Musser before this technology becomes routine practice.\textsuperscript{12,13}

In addition to these usual hurdles that a major innovation must experience before it becomes routine practice, the sequencing of an individual’s entire genome unlocks a glut of legal issues that may also slow implementation. A thorough review of the legal issues surrounding genomic testing is beyond the scope of this editorial; however, clearly a wide variety of medicolegal issues will have to be addressed before examination of a person’s entire genome becomes commonplace. The Human Genome Project, the Human Genome Diversity Project, and the practice of genetic counseling for heritable diseases all have highlighted numerous medicolegal concerns. These medicolegal issues regarding genetic testing, counseling, screening, research, and therapy are complex, and include such diverse issues as privacy and confidentiality; the legal ramifications of applying moral and religious boundaries; ownership and limitation of genetic testing information; the potential misuse of genetic testing, such as determination of sex and “unfair” employment and insurance discrimination; gene patenting; and the appropriate use of forensic genetic databanks. These issues will also arise in some areas of laboratory-developed tests.\textsuperscript{14,15}

Genetic testing technology is rapidly evolving, and the law will continue to struggle to keep pace with the associated medicolegal issues arising in this dynamic environment. The Genetic Information Nondiscrimination Act, enacted in 2008, was a significant attempt to control the use of genetic information. The Genetic Information Nondiscrimination Act prohibits employers and insurers from discriminating on the basis of genetic tests. Issues of patenting, ownership, discrimination, professionalism, and public acceptance promise to encourage more legislative and judicial attempts to provide dependable boundaries for genetic research and the use of genetic information.\textsuperscript{14–17}