Molecular diagnostics now provides most laboratory tests in infectious disease and genetics, and an increasing number in oncology. Massively parallel methods allow sequencing of entire genomes, and sequence databases within and between species provide the information necessary to develop sensitive and specific diagnostic assays. Indeed, most microorganisms today are classified on the basis of sequence rather than phenotype. If a microbial sequence is present where it should not be, a presumptive diagnosis is made. Modern genetics, empowered by the 3.08 billion–base book of the human genome, has advanced beyond single-gene disorders to gene families, exomes, transcriptomes, and ultimately, the complete genome. Severe challenges in data processing and interpretation remain, but the enormity and potential closure of the undertaking is inspiring. New classes of nucleic acid biomarkers, including long noncoding RNAs and microRNAs, provide a deep well for correlation to disease. If a patient’s sequence variation is consistently associated with disease, a genetic diagnosis is made. Similarly, cancer is caused by genome sequence variations. These variations are typically widespread, with myriad copy number and sequence changes throughout the genome. Some of these variants identify molecular pathways that can be blocked or enhanced by drugs that affect tumor growth.

Molecular diagnostics is empowered by continual advancements in technology. Applications of massively parallel sequencing have exploded, affecting all areas of medicine, including molecular diagnostics. The polymerase chain reaction has evolved from gel analysis to real-time PCR to, most recently, digital PCR, where individual targets are amplified in picoliter to nanoliter volumes and statistics are used to calculate target concentrations instead of standard curves or internal controls. Genome-wide studies are no longer considered fishing expeditions, and disease association studies that use expression, single nucleotide polymorphism, and copy number microarrays have identified useful markers that have been reduced to practical molecular tests. Big data needs have resulted in new bioinformatics tools that continue to evolve rapidly.

But wait, just what is molecular diagnostics? The words, “molecular” and “diagnostics” do not appear together in the scientific literature until the mid-1980s (Fig. 1). Since 1985 (around the time that PCR appeared), these words increasingly cohabit scientific abstracts at an exponential rate, doubling every 6–7 years. “Molecular” came to mean DNA or RNA, unfairly excluding proteins, electrolytes, small molecules, and other polymers.

Substantial growth of molecular diagnostics in clinical laboratories was deferred over 10 years, taking off around 1997 in parallel with the commercial availability of real-time PCR instruments (Fig. 2). The number of tests offered by clinical laboratories rose linearly until 2006 and then assumed a faster, but still linear, rate of growth through 2014. The volume of testing performed over time was...
approximately linear, with a noticeable plateau between 2009 and 2012, perhaps as a result of the Great Recession.

Clinical laboratory use of molecular diagnostics for infectious disease, genetics, and oncology is unique for each specialty (Fig. 3). The greatest workload of patient testing is in infectious disease, although the number of different tests is relatively small. A few popular tests (HIV, hepatitis B and C viruses, and human papilloma virus) command a large volume of testing. Genetics has a greater variety of tests, but the volume is only 20% that of infectious disease testing. Since 2008, the number of different genetic tests has exploded, likely resulting from the proliferation of sequencing technologies, including massively parallel sequencing. In oncology, the number of different tests parallels infectious disease. Oncology test volume is low but exponential, suggesting the most rapid growth rate.

In this issue of Clinical Chemistry, we provide commissioned reviews, commentaries, editorials, opinions, a perspective, reflections, and an interview with Drs. Bert Vogelstein and Kenneth Kinzler to cover the ever-expanding topics and issues encompassed by molecular diagnostics. In addition, 17 investigator-initiated original articles were accepted for this issue. Four and a half times more were rejected, for an acceptance rate of 18%. The accepted articles reflect the current interests of the authors and editors, including 4 articles on massively parallel sequencing, 3 on digital PCR, and 2 each on circulating tumor cells, cell-free nucleic acid, new RNA species, and methylation. We are proud of their quality, thank all authors for their patience with the editorial process, and ask your understanding for those that do not appear in this issue of the journal.

It has been 6 years since molecular diagnostics has been highlighted in a special issue of Clinical Chemistry. In 2009, molecular diagnostics was “at the cutting edge of translational medicine,” and now we suggest “a revolution in progress.” The field is rapidly changing and remains attractive to academics and industry, often mentioned along with personalized medicine as our solution to better health care. The number of targeted cancer therapeutics continues to increase along with companion diagnostics. Noninvasive prenatal diagnostics for trisomy 21 is now clinical reality, enabled by massively parallel sequencing of fetal nucleic acid circulating in the mother’s bloodstream. Recreational genomics, analyzing one’s own genome at millions of sites, is so popular that its wisdom has been questioned by the US Food and Drug Administration (FDA). Gene patents have been ruled unpatentable by the US Supreme Court if they depend only on natural phenomena, including sequences found in nature. Commercial 1-h sample-to-answer molecular diagnostics are now FDA approved for infectious disease applications. These range from single-organism tests for hospital-acquired infections to multiplexed panels that are syndrome focused to identify the causative microbe in infections that may be viral, bacterial, or parasitic. The
Affordable Care Act, proposed regulation of Laboratory Developed Tests, and new taxes on medical device manufacturers are in part government adjustments to the ongoing revolution in molecular diagnostics. What would happen if, say, an Ebola outbreak occurred in West Africa and threatened to become a worldwide epidemic? Can we offer better screening than travel and contact history with body temperature measurements? In this case, the molecular diagnostics industry did work with government agencies to develop and approve molecular diagnostic tests for Ebola by Emergency Use Authorization. These tests can be used locally to detect Ebola with high sensitivity and specificity in about 1 h, perhaps a better solution in uncertain cases than 21-day quarantines and/or transport of infectious fluids to central laboratories.

What will happen next? That is the excitement and uncertainty of a revolution.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:


Consultant or Advisory Role: R.W.K. Chiu, Sequenom, Inc.; Y.M.D. Lo, Sequenom, Inc.


Honoraria: None declared.


Expert Testimony: None declared.


Acknowledgments: We acknowledge the excellent contributions of Dr. Frank Cockerill to this issue and are grateful for his efforts, input, and time.