

# Polishing the Crystal Ball: Emerging Trends in Contemporary Clinical Laboratory Medicine

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For clinical laboratory medicine in the 21st century nothing is so important as strong prediction. Strong in the sense of robust and specific detail of the predicted events and strong in the sense of high likelihood of predicted outcomes. For a discipline that has focused primarily on diagnosis for more than a century, this new ascendancy of prognosis in the application of clinical laboratory data represents a paradigm shift. The value of a laboratory test in the modern era is often measured by the utility of the test result in predicting a future clinical event in the patient's course. In some cases the test result will be useful in predicting relevant events that will occur in the next few minutes or hours and, in other cases, events years and even decades in the future.

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The prevailing diagnostic applications of medical laboratory testing in the 20th century are giving way in the 21st century to prognostic implications for risk stratification, prevention, therapeutic design and timing, and ultimately even for disease definition. In the 20th century the laboratory helped the physician answer the question: Is anything wrong with the patient and if so

what? This paradigm led to a generalized notion that a laboratory result was either normal or abnormal. In the new 21st century paradigm, the role of the laboratory will increasingly be one of helping the physician answer the question: What will happen to this patient and will any of several interventions likely change what will happen in a favorable way? In the new paradigm, significance for laboratory results will increasingly be measured in incremental impact on likelihood of clinically significant events and methods of prevention or mitigation.

This issue of the *North Carolina Medical Journal* examines some of the factors driving this paradigm shift and the implications of increasing prognostic utility for laboratory testing. We explore some innovations that illustrate the trend and the implications

for health care providers and patients alike in commentaries that illustrate emerging technologies, evolving platforms for testing, and new ways of applying the data to shape the interaction of patient and health care provider. For contemporary clinical laboratory medicine, change occurs along 3 principal axes: what we can detect, where the analysis occurs, and how the result is applied in patient management.

What we detect in the modern clinical laboratory changes, as it has for over 150 years, through the power of advances in analytic technology. Today clinical laboratories in most modern hospitals routinely detect analytes down to a level of one part per 10 billion. Not only has the detection level of our assays been improved by several orders of magnitude, but the inventory of analytes with clinical significance has exploded as our more sensitive assays allow researchers to explore in detail the relationships between disease and body chemistry. Dozens of new markers with potential

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clinical significance are introduced every year. Advances in proteomics, nucleic acid amplification, and molecular genetic pathology promise to accelerate the introduction of new tests with clinical significance.

Where we test is undergoing a dramatic shift. The first useful clinical laboratory test was the visual, olfactory, and gustatory analysis of urine. Analysis was often performed at the patient's bedside. In the 20th century, the emergence of more sophisticated testing that required either laboratory expertise or expensive equipment led to centralized laboratories in hospitals or at reference sites. Specimens were obtained from the patient and then transported to the testing laboratory, sometimes in the same building and sometimes thousands of miles away. Most testing moved away from the patient and into the remote laboratory. Then with the introduction of semi-quantitative glucose testing with dipsticks in the early 1960s and true quantitative glucose testing with portable glucometers in the 1970s, analytical chemistry testing began to return to the near patient environment. The trend has only accelerated with the introduction over the past two decades of a variety of point-of-care testing devices that put powerful analytic capabilities into the hands of health care professionals at the bedside, require only minimal expertise for operation, and provide real-time data for clinical management and decision making.

In contemporary clinical laboratory medicine, the site of testing is determined in part by the time frame in which prognostic significance applies. If the results of the test predict clinical events or therapeutic impact that will occur within minutes, the testing is likely to occur in a setting near the patient. For tests with prognostic significance in the hour to 24-hour range, a centralized laboratory remains the most likely venue. Intense clinical management of the patient in either the inpatient or ambulatory setting favors rapid turnaround for even routine tests, and economic pressures for efficient and cost-effective care are driving dramatic changes in the centralized hospital laboratory of the early 21st century.

Already for diabetes, and in the near future for other conditions, the ease of operation and reliability of point-of-care devices will facilitate the migration of traditional laboratory testing not only away from the central laboratory but also out of the hands of health professionals and into the hands of patients. Patients so empowered will be able to participate more effectively in the management of their own disease and in triage decisions that determine if and when intervention by medical professionals will be necessary.

A third area of accelerating change, and perhaps the most intriguing, is how the data generated by clinical laboratory medicine is employed in the management of the patient. Modern medicine and the experimental laboratory were born conjoined twins in the 19th century with the discovery of causal agents for disease, especially micro-organisms. A classification of diseases based on etiology and pathogenesis is still used today and continues to evolve in large measure on the basis of discoveries in the experimental laboratory. Once a causal understanding of the disease is established in the experimental laboratory, the clinical laboratory is positioned to test for the presence of etiological agents or their biochemical or immunological footprints. For the

20th century and the latter 19th century, the role of the clinical laboratory was to support or refute a physician's diagnosis.

While advances in the clinical laboratory continue to support this diagnostic paradigm, increasingly the clinical laboratory produces data with direct prognostic implications. Molecular studies can identify patients with genetic risk for the future development of disease; proteomics offers the promise of detecting patients that are evolving toward a disease state long before the disease is clinically manifest; and immunopathological assays may identify which patients among a group with the same type of tumor will do well on one treatment regimen and which will do better on another. Polymerase chain reaction (PCR) detection of microbials offers the promise of detecting and identifying pathogens in real clinical time instead of the days or weeks required by conventional microbiological assays, and identification of human papillomavirus strains in infected patients now rivals and supplements the value of the tried and proven morphologic pap smear in predicting which patients require intervention to prevent progression to cervical cancer.

## Milestones in the History of the Laboratory Medicine

A cursory outline of milestones in the development of clinical laboratory medicine is helpful in understanding the implications of the rapidly evolving discipline. Examination of urine for prognosis was advocated by Hippocrates as early as 400 BC. Kouba et al recently described the 1100 year evolution of the prognostic application of uroscopy to a diagnostic approach advocated by Theophilus.<sup>1</sup> The objective and systematic use of urine examination by Theophilus became a paradigm for the use of an analytic test to establish diagnosis.<sup>1</sup> By 900 AD, guidelines for the use of urine examination as a diagnostic aide were available, and by 1500 AD, color charts for the interpretation of urine in diagnosis were widespread.<sup>2</sup>

The invention of the microscope in the 17th century greatly extended the power of observation as a tool for diagnostic formulation. The microscopic analysis of urine sediment emerged as an important additional quantitative analysis in the latter half of the 18th century with J. W. Tichy's work.<sup>2</sup> The microscopic recognition of the cellular components of blood by Marcello Malpighi in 1661-1665, and subsequent studies by Antony von Leewenhoek, promoted a second body fluid to importance in laboratory medicine.<sup>3</sup> However, throughout the 17th and 18th century, urine continued to be the sample of choice for medical analysis. The 17th century chemical analysis of blood was significantly advanced by the important work of William Hewson, who first demonstrated the presence of a coagulable substance that could be separated from the cellular component of blood. Hewson's discovery of "coagulable lymph," or fibrinogen, provided the foundation for the laboratory investigation and evaluation of coagulation and disorders of coagulation.<sup>2</sup>

The second century Greek physician Galen is often considered the most influential medical author of all time. Galen taught that illness was a result of imbalance in the 4 fundamental

humors (phlegm, blood, yellow bile, and black bile). This view was unassailed until the mid 18th century when the work of Giovanni Battista Morgagni in the post-mortem laboratory established a systematic correlation between clinical symptoms and anatomical changes in organ structure. Morgagni's seminal work *De Sedibus et Causis Morborum (On the Sites and Causes of Diseases)* became a foundation for the development of the science of pathologic anatomy. Nevertheless, the notion that the anatomical changes were themselves reflective of some imbalance in body humors continued for another hundred years.

The emergence of the germ theory of disease in the late 19th century not only laid to rest the humoral theory of Galen but also forged a relationship between modern medicine and the laboratory that came to dominate western medicine in the 20th century.<sup>5</sup> Physicians and patients had long recognized that outbreaks of epidemic disease implied an element of contagion, but assumed that some ambient and nonliving substance causing an imbalance in humors led to disease. Thus in the great London cholera outbreak of 1854, "miasma," a conjectured, noxious, and airborne substance arising from the decay of organic matter, was proposed by most medical authorities of the time as the cause of the epidemic. Physician John Snow, after a careful study of the patterns of case occurrence, came to the conclusion that the disease was spread by an agent in contaminated water from a particular pump in the city.<sup>6</sup> Snow's work advanced public hygiene and epidemiology and stimulated the search for specific agents for epidemic disease. The work of Snow as well as Semmelweis and Lister, established that at least some diseases were the results of contagious agents and the spread of these agents could be restricted by antiseptic procedures. A search for these contagious agents culminated in the revolutionary laboratory work of Louis Pasteur and Robert Koch that demonstrated the agents to be microbes.<sup>4</sup> The demonstration that living organisms caused disease advanced an approach to classifying disease based on external cause, an approach that persists and dominates our modern view.

A cornerstone in the development of a causal taxonomy of disease was the introduction of Koch's postulates in 1884. The postulates provided criteria for establishing an etiological link between a microbe and a disease. The four postulates in modern form are: (1) the putative causative organism must be found in every patient with the disease, (2) the organism must be isolated from a diseased individual and grown in culture, (3) the organism must produce disease when introduced into a healthy individual (usually an experimental animal), and (4) the organism must be reisolated from the experimentally infected animal.<sup>7</sup> Postulates 3 and 4 fall entirely into the domain of the experimental laboratory. However, the requirements of the first 2 postulates provided great impetus to the emergence of the clinical microbiology laboratory. If Koch's postulates are satisfied and a causal link established between a microbe and a disease, then it should be necessary in a patient with symptoms of that disease to require that the causative agent be recovered from the patient and grown in culture in order to establish a definitive diagnosis. This logic provided a strong tradition for clinical laboratory measures in confirming a

medical diagnosis.

By the end of the 19th century, the clinical laboratory provided the culture of microbial pathogens, hemoglobin estimation, counting of red and white blood cells, microscopic identification of some parasites, clotting time in coagulation disorders, examination of sputum in tuberculosis, simple immunological tests such as agglutination tests for typhoid fever, and the demonstration of amino aciduria in liver disease.<sup>2</sup>

The first half of the 20th century saw an explosion of advances in analytical techniques in clinical chemistry, immunology, and blood banking as well as microbiology. With the exception of the important therapeutic applications of blood banking, the emphasis was almost entirely on the application of the methods of the clinical laboratory in diagnosis. The first textbook of laboratory medicine was edited by James C. Todd and published in 1908 as *A Manual of Clinical Diagnosis*. Ninety-eight years and seven editors later, the 21st edition remains the authoritative reference for clinical pathology under the title, *Henry's Clinical Diagnosis and Management by Laboratory Methods*.<sup>8</sup> The addition of the word management reflects the emerging importance of the laboratory in not only helping make a diagnosis but also in providing data to monitor progression of disease and therapy.

Many diagnostically useful tests in clinical chemistry were developed in the first 50 years of the 20th century: serum phosphorus (1920), serum magnesium (1921), protein electrophoresis (1926), erythrocyte sedimentation rate (1929), alkaline phosphatase (1930), lipase (1932), amylase and acid phosphatase (1938), ammonia (1939), creatinine phosphokinase (1954), lactate dehydrogenase (1955), and alanine aminotransferase (1956).<sup>9</sup> The tests were useful but labor intensive and required manual methods by skilled technologists using sophisticated instrumentation. They were primarily applied in patients only after a physician's thorough evaluation and examination had narrowed the differential diagnosis to a short list of possibilities.

The introduction of the first automated clinical chemistry analyzer by Technicon Corporation in 1959 was a watershed in the application of these clinical analyses.<sup>10</sup> The Technicon Auto-Analyzer and the subsequent development of ever more powerful automated analyzers ushered in an era in which large batteries of laboratory tests could be performed quickly and economically. The ease and economy of performing multiple clinical chemistry tests presented for the first time in laboratory medicine the potential of screening healthy populations with batteries of tests to detect disease early, before pathological damage could occur. In the case of screening neonates for inborn errors of metabolism this strategy has worked exceedingly well. In 2006, the North Carolina Laboratory of Public Health screened 127 175 newborns for 41 genetic disorders. In the well adult population the results have been less satisfactory. For a period of time in the 1970s and 1980s, annual physicals might include batteries of 40 or more laboratory tests; but this approach led to little measurable improvement in outcomes. For most of the analytes in these batteries, there is overlap between values encountered in healthy and diseased populations. The more tests performed, the greater the likelihood that one or

## Prediction and Accuracy

Galen and Gambino and subsequent researchers<sup>a,b</sup> have applied mathematical tools to medical decision making to quantify the justifiable level of confidence a particular test result can offer physicians and patients in predicting the presence or absence of disease. A full understanding of the subject is challenging for many health professionals and formidable for the lay public, however, some generalizations are possible. The overlap in the distribution of values for analytes in diseased and healthy populations means no one test can perfectly discriminate between diseased and healthy individuals.

The *sensitivity* of a test is the probability of getting a positive test result in a diseased patient. The *specificity* of a test is the probability of getting a negative result in a person without the disease. For any given test we can adjust the limit of the reference range to improve sensitivity and capture a greater portion of the diseased population, but in doing so we also increase the number of healthy patients in the test positive group (*false positive*). If we make an adjustment in the reference limit in the other direction, we can exclude more healthy individuals from the test positive population, but we also exclude some diseased individuals (*false negatives*). Tests that have both higher sensitivity and specificity for a certain disease are preferred. We can compare tests by plotting the true positive rate against the false positive rate at all cutoff points for reference range. This curve, called the *receiver operating characteristic curve* (ROC curve), provides a measure of the accuracy of the test for that disease. The test with the bend in the curve that is closest to the upper left hand corner of the graph is the more accurate test.<sup>b</sup>

The clinical laboratory strives to develop tests with optimal sensitivity and specificity. Clinician and patients are most interested in the interpretation of a particular test result for a given patient: the *predictive value*. The *positive predictive value* of a test gives the probability of a disease given a positive test result, whereas the *negative predictive value* gives the probability of no disease given

a negative test result. A counter-intuitive concept is that the predictive value of a test depends not only on the accuracy of the test, but also on the prevalence of disease in the population tested.<sup>a</sup> Therefore, the same test can have different predictive values when applied to different populations with different prevalence of the same disease.

Consider this example. We have a test that returns a positive result 99% of the time in diseased individuals and only 1% of the time in healthy individuals (false positive rate). We apply the test to a group of 200 000 individuals with a disease prevalence of 50%. The test will return a true positive finding in 99 000 of the 100 000 individuals with disease and a false positive finding in 1000 of the 100 000 individuals without the disease. Accordingly, any one individual with a positive test will have a 99% chance of having the disease.

Now we apply the same test to a population in which the prevalence of the disease is only 0.1%. Only 200 patients out of 200 000 have the disease and 198 (99%) will test positive. Of the 199 800 individuals without disease, 1% or 1998 will test positive. We now have 2196 individuals with a positive test result and only 198 with the disease: a predictive value of 9%. Therefore, in different populations the same test has an entirely different significance for a positive result. This is the reason that some tests may be excellent at confirming a suspicion on the part of the physician that a disease is present, but not very good for screening healthy populations with low disease prevalence. By evaluating relevant medical history, symptoms, and risk factors and then choosing tests for diseases that might fit these findings, the physician effectively creates a test population with a much higher prevalence of disease than the general population. Confirmation by laboratory testing will have much greater positive predictive value in such prescreened populations. It is also the reason that screening healthy individuals with large batteries of laboratory tests in the 1970s and 1980s generated so many false positive results.

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more test results will fall outside the reference range, not because the patient has a disease, but simply because of variation in the distribution of values for that analyte in the healthy population. The problem of getting abnormal laboratory results in normal patients led to important advances in the mathematical quantification of predictive value for test results in Galen and Gambino's publication of the landmark 1975 monograph, *Beyond Normality: the Predictive Value and Efficiency of Medical Diagnosis*.<sup>11</sup> Advances in analytical technology have only accelerated at the end of the 20th century with the development of radioimmunoassay

(1950), immunoelectrophoresis (1952), high-performance liquid chromatography (1969), enzymatic immunoassay (1972), and the laser cell sorter (1975).<sup>12</sup>

At the start of the modern medical era, Louis Pasteur advocated for the advancement and expansion of the medical laboratory.<sup>13</sup> By the end of the 20th century western medicine was dominated by this diagnostic laboratory paradigm: in the experimental laboratory, understanding the etiology and pathogenesis of the disease and, in the clinical laboratory, identifying the etiologic agent or the footprints of the pathogenic

process to confirm the diagnosis. Then, from the diagnosis, formulate a prognosis and, if necessary, propose a treatment. The dominance of this paradigm was summarized by Andrew Cunningham and Perry Williams in the opening paragraph of their 1992 monograph, *The Laboratory Revolution in Medicine*.

If you feel unwell and go to see a doctor or are admitted to hospital, the chances are that the physicians will take a sample of your body – generally blood, tissue or urine – and send it away to another place for testing; in such cases the decision as to whether you are ill or not, and if you are, what disease you have, will be primarily taken not by you and not by your doctor but by a laboratory test. If you require treatment, this will probably involve the administration of medicinal substances prepared not by you or your doctor but in a highly specialised factory-like laboratory. If you decide to become a doctor yourself, your formal professional training will begin not with general practice, nor with hospital work, but with study of the medical sciences, in lecture rooms, libraries and laboratories.<sup>5</sup>

Now, at the start of a new century, this diagnostic laboratory paradigm may be undergoing a new revolution.

## The Case of Cardiac Troponin

Cardiovascular disease is the leading cause of death in the United States and has been every year since 1900 except for the pandemic flu year of 1918.<sup>14</sup> More Americans die of cardiovascular disease than of the next 4 leading causes of death combined.<sup>14</sup> Coronary artery disease leading to myocardial ischemia accounts for more than half of deaths due to cardiovascular disease.<sup>14</sup> Despite the importance of this disease, laboratory tests for the diagnosis of myocardial injury due to ischemia lagged the development of tests to detect disease in other organs until the discovery of transaminase elevations following myocardial infarction (MI) in the 1950s.<sup>15</sup> Because glutamate-oxaloacetate transaminase (now aspartate transaminase) and alanine transaminase are also released by damage to other organs such as liver and skeletal muscle, elevations of the transaminases were poor discriminators for injury to cardiac muscle versus other tissue.

A significant advance in the laboratory detection of myocardial injury was the introduction of creatine kinase isoenzyme assay.<sup>16</sup> Creatine kinase (CK) exists in 3 isoforms. One of the isoenzymes, CK-MB, is present in greater concentration in heart muscle than in skeletal muscle. While massive increases of CK can be seen in injury to skeletal muscle, a CK increase with a greater ratio of CK-MB to the other isoforms suggests injury of cardiac muscle. The clinical utility of the assay was initially limited by the need to perform electrophoretic separation of the isoenzymes, so assays could only be performed about once a day. At a time when patients were being admitted to hospitals for several days just to exclude MI, that limitation was acceptable.

With the advent of efficacious therapies for treatment and prevention of MI, the need for rapid laboratory confirmation of MI increased. Direct immunometric assay for CK-MB<sup>17</sup> (CK-MB mass) significantly reduced the time required to perform the test, making stat assays in an hour or less possible. CK-MB mass assay greatly facilitated the laboratory confirmation of a diagnosis of MI. However, since CK-MB is not specific for myocardium, the assay still suffered from low sensitivity for small infarcts and low specificity in the setting of skeletal muscle injury. The initial detection of CK increase in the setting of MI had been possible because of the enzymatic properties of CK.<sup>18</sup> The technology of immunometric assay made possible the detection at low levels of protein markers without enzymatic activity. A search for a protein specific to cardiac muscle culminated in the identification of cardiac troponin subunits I and T (cTnI and cTnT), which are specific to cardiac muscle. Cardiac troponins are released into the circulation following necrosis of myocardial fibers. In the absence of irreversible myocardial damage, the level of cardiac troponin is so low that it is undetectable by most assays. Following myocardial injury, cardiac troponin is released from damaged myocardial fibers and becomes detectable 2 to 4 hours after ischemic onset. Troponin levels rise and peak 24 to 48 hours after the infarct. Elevations of cTnI persist for 5 to 10 days after the infarct.<sup>19</sup>

Because cardiac troponin is only present in heart muscle, its presence in blood is a very sensitive and specific marker for cardiac injury. CK-MB was a significant advance over previous enzyme methods and reached sensitivity levels of 80%. With the most current cTn, assays sensitivity for myocardial injury is 96% to 98%.<sup>19</sup> Because of the greater sensitivity cTn is the preferred marker for detecting and ruling out MI.<sup>19,20,21</sup> The rise in cardiac troponin and CK-MB occurs only 2 to 4 hours after ischemic injury, so samples taken within the first 2 to 3 hours after symptoms may not demonstrate an elevation.<sup>19</sup> Cardiac troponin assay in serial samples taken 1 to 2 hours apart provides the most sensitive means for both detecting and excluding MI. Acute MI can be excluded in those patients with chest pain who, 4 to 6 hours after onset of symptoms, still have nonrising serial cTn levels below the 99% reference cutoff for the assay utilized.<sup>22</sup>

The diagnostic power of current cardiac markers is so strong that in 2000 the American College of Cardiology and the European Society of Cardiology issued a consensus statement redefining MI based on changes in sensitive and specific biomarkers such as cTn and CK-MB. The new clinical definition provides that MI is diagnosed when there is a typical rise and fall of biochemical markers of myocardial necrosis and one of the following: ischemic symptoms, development of pathologic Q waves on the ECG, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention (eg, coronary angioplasty).<sup>23</sup> The one finding that has to be present is the temporal change in a sensitive and specific marker for cardiac necrosis such as cTn or CK-MB.

The troponin story to this point is just another illustration of how a clinical laboratory test can be a powerful aid to diagnosis. The prognostic power of cTn emerged when patients with low

or borderline elevations of cTn were studied. The pathologic definition of MI is the irreversible damage of cardiac muscle due to ischemia. While diagnosing and treating MI is important, it's better to prevent it. When cTn assays were first introduced, many physicians complained that the tests were too sensitive because some patients had elevated levels of troponin but did not have clinical evidence of MI. However, when followed, these patients had a much higher incidence of significant cardiac events and sudden death after discharge than did patients with no cTn elevation.<sup>24</sup> Multiple studies have demonstrated that patients with stable or unstable angina or acute coronary syndrome all have significantly worse prognosis if cTn is elevated.<sup>25,26,27</sup> Moreover, the increase in mortality risk in patients with acute coronary syndrome with increased cTn levels is proportional to the increase in cTn.<sup>26</sup> The prognostic significance of small elevations of cTn, less than the cut-off level for diagnosis, has proven to be so prognostically significant that troponin elevation is a key criterion in the risk stratification and clinical management of patients with unstable angina and acute coronary syndrome.<sup>23,28</sup>

Cardiac troponin has proven to be an exquisitely sensitive marker for myocardial injury arising from any source. Elevations can be seen in cardiotoxicity from drugs, hypothyroidism, sepsis, inflammatory myocarditis, heart failure, and cardiac trauma among others. In these cases the cTn elevation reflects real damage to cardiac fibers. In chronic conditions the cTn tends to be stable and clinical interpretation is necessary to distinguish cTn elevation due to ischemia from elevations due to myocardial injury from other causes. Even in those patients without symptoms or other evidence of cardiac disease, cTn retains prognostic significance. Patients with sepsis, noncardiac patients on critical care units, and emergency department patients without cardiac illness all have increased risk of short-term mortality if cTn is elevated compared to similar patients with normal cTn.<sup>29</sup>

## The Emerging Paradigm

Cardiac troponin is just one of many laboratory assays with strong prognostic significance. Cardiac troponin elevation predicts increased risk for patients with infarction, angina, and acute coronary syndrome, but some patients without elevated cTn still experience significant cardiac events including infarction and sudden cardiac death in the the 60 days following a cTn assay.<sup>19</sup> A search is underway for biomarkers that can predict ischemic events in asymptomatic patients without cTn elevation. No marker with prognostic significance comparable to cTn for this group of patients has yet been identified but several candidates, including C-reactive protein (CRP), sCD40 ligand, matrix metalloproteinases, myeloperoxidase, and ischemia-modified albumin, are being intensely studied.<sup>19</sup> For all of these analytes, prognostic significance is the desired characteristic.

In the case of heart failure, brain-type natriuretic peptide (BNP) is released by myocardium in response to stretch. BNP and its pro peptide NT-proBNP are increased in heart failure and have proved useful in diagnostic triage of patients with dyspnea.<sup>30</sup> High levels of BNP and NT-proBNP indicate poor prognosis

in both heart failure patients and patients with acute coronary syndrome.<sup>31,32</sup>

Biomarkers with prognostic significance for disorders other than cardiovascular disease are also proliferating. Molecular genetics already has wide implications in the diagnosis, prognosis, and therapeutic management of neoplasia.<sup>33</sup> There are currently 17 588 disorders, variations, or protein structural alterations demonstrated to have a genetic basis in humans. While the majority of these are rare or cause minor changes of no clinical significance, some have increased risk of subsequent development of disease ranging from amyotrophic lateral sclerosis to hereditary breast cancer.<sup>33</sup> For many common diseases, genetic predisposition may depend on complex interactions of multiple alleles. The possibility of widespread screening using DNA microarray technology for genetic combinations that predispose to disease has attracted wide commentary.<sup>34</sup> Identifying those at increased risk has the potential to benefit the individual by interventions or lifestyle modifications that prevent or delay the onset of the disease. Identifying those at risk also entails significant ethical and social issues and has the potential to stigmatize and harm individuals.

Not everyone who has a demonstrated genetic predisposition for a certain disease will develop the disease. The relative risk factor may vary substantially and most diseases for which a genetic basis has been demonstrated entail complex interactions between several genes and often environmental agents as well. For diabetes mellitus<sup>35</sup> and some other autoimmune diseases<sup>36</sup> there is promise that autoantibodies that appear years before the onset of the symptoms may help predict which patients will go on to develop the disease. In the case of type 1 diabetes, autoantibodies to insulin, glutamic acid decarboxylase, and islet antigen-2 may appear as early as 10 years before onset of the disease. When one antibody is present a person has a 10% chance of developing type 1 diabetes within 5 years. When 2 antibodies are present the risk increases to 50%, and when all 3 antibodies are present the risk exceeds 60%.<sup>35</sup> Similarly in rheumatoid arthritis an autoantibody to citrulline may appear as early as 10 years before onset of the disease and the appearance of the autoantibody increases the risk of onset of rheumatoid arthritis 15 fold.<sup>36</sup> Finally, mathematical techniques will be increasingly used to predict future clinical events based on combinations of biomarkers independent of a patient's specific diagnosis. In a recent report, Gruenewald used recursive partitioning techniques to identify combinations of 13 biomarkers that conveyed higher risk of mortality in a 12-year study of older adults.<sup>37</sup>

In the 21st century, emphasis in clinical laboratory medicine has shifted from diagnosis to prognosis, risk stratification, treatment selection, and monitoring. If the medical paradigm of the 20th century was: first diagnosis then prognosis and treatment; then the paradigm for this century may be: first assess risk, then suggest risk modification or intervention; next monitor for early predictors of progression and, if detected, intervene; if symptoms appear, stratify for selected treatment based on prognostic tests.

## Rocket Science or Stamp Collecting?

This is an exciting time for clinical laboratory medicine. Rapid advances in science and technology are expanding the role and utility of clinical testing in the central laboratory, at the patient bedside, and in patients' homes. New and more sensitive assays provide valuable information for clinical decision making in real time. It's also an intriguing time as research in scientific laboratories identifies a host of markers that provide, for many patients and healthy individuals alike, powerful predictions of clinical events in the near and distant future. These technologies herald a paradigm shift in the relationship between medicine and the clinical laboratory from diagnosis to greater emphasis on prognosis, prevention and management, and from binary decisions about the patient as "diseased or well" to incremental prediction of risk and potential therapeutic benefit.

There is a significant difference in the predictive power of those sciences in which progress in knowledge is manifest by ever more powerful and elegant mathematical formulas and those descriptive sciences in which progress in knowledge is expressed by ever more complex and arcane taxonomies. The distinction was famously articulated by the early 20th century physicist and Nobel prize winner Ernest Rutherford who quipped, "all science is either physics or stamp collecting."<sup>38</sup> Collectors are students and illustrators of the taxonomies created to describe the objects they collect. In the early 20th century when Rutherford made his remark, many sciences including botany, zoology, geology, and medicine were primarily concerned with classification. From Rutherford's perspective, physicists calculated the formulas that orchestrated the universe, whereas other scientists simply classified. The relationship between the laboratory and medicine throughout the 20th century has been based on a taxonomic approach to disease. We have, from Rutherford's perspective, primarily been stamp collectors.

Despite the disdain in Rutherford's remark, we should not underestimate the important advances made through diagnostic taxonomy. Since the mid-19th century a classification of disease has evolved based on scientific understanding of the dysfunctions in anatomy, physiology, and chemistry that cause illness. This understanding is often founded upon, and evolves through, investigations in the experimental laboratory. The critical first

step in the approach to an ill patient is to diagnose or classify the patient's disorder. Once the classification or diagnosis is established, the physician can answer the patient's question, "Is something wrong with me, and if so, what will happen to me?" Armed with a diagnosis, the physician can make predictions about the patient's likely clinical course. If the course is unfavorable, intervention can be considered and selected.

Making a diagnosis has prognostic and therapeutic significance because we have studied the natural course and response to therapy of other patients that have been assigned to the same diagnostic category. Of course, we know that the patients assigned to these disease categories are never exactly alike, and natural course and response to therapy will vary among patients with the same diagnosis. So our predictions for outcome, response to therapy, and side effects based upon the classification of the patient's disease are too often couched in terms of probabilities that leave the patient and family confused and dissatisfied. For all the progress scientific medicine and the laboratory have made together, we are humbled when we consider the rocket scientist who, armed with the calculus of physics, can hurl an object into space and predict with stunning accuracy when and where the probe will rendezvous with a speeding comet, millions of miles away and months or even years in the future. Beside the predictive power of scientists who calculate, the prognostic skill of the scientist who classifies seems feeble indeed.

The clinical laboratory has been and will continue to be a powerful source of data for classification and diagnosis. The promise of the clinical laboratory in the 21st century will be to increasingly provide data with which the physician can calculate as well as classify. In some cases the calculation will have clinical significance for the patient well before pathologic changes that permit a diagnosis have occurred. In other cases the data may support calculation of a prognosis that is much more specific than could be rendered on the basis of diagnosis alone. There is much speculation that the future of medicine will entail a highly personalized approach to prevention, treatment, and disease management in each patient. With the help of the clinical laboratory, the physician may well be moving toward a fuller implementation of the dictum "treat the patient and not the disease" and in doing so becoming a little more of a rocket scientist and a little less of a stamp collector. **NCMJ**

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