

# 00-4 Planning Report

## The Economic Impacts of NIST Cholesterol Standards Program

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for

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Economic Analysis Group

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# **The Economic Impacts of NIST'S Cholesterol Standards Program**

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Prepared for:

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## EXECUTIVE SUMMARY

The National Institute of Standards and Technology (NIST) develops and maintains national standards, certifies standard reference materials (SRMs), and offers a wide variety of calibration services that are used to assure the quality of clinical laboratory processes. The purpose of this case study is to assess the economic impacts of cholesterol-related standard reference materials (SRMs) from NIST's Clinical Standards Program.

Cardiovascular disease is a major health hazard in the U.S. The control of blood levels of cholesterol, especially the constituent known as “bad” cholesterol, is regarded by the medical community as essential to good health. Accurate measurement of cholesterol and its constituents, therefore, is important to minimizing cardiovascular disease.

A national quality control system, the National Reference System for Clinical Laboratories (NRSCL), has evolved within the U.S. medical community and its supporting industries to assure accurate measurement of cholesterol and other medically significant constituents of blood. NIST has played an important part in that system by developing basic measurement methods and standards as well as providing highly accurate reference materials to assure the accuracy of cholesterol tests.

The measurement technologies developed by NIST are highly accurate, complex, and expensive compared to the measurement technologies typically used in high-volume cholesterol-testing laboratories. Assuring access to the most accurate measurement technologies across the supply chain—from measurement system manufacturers, to clinical laboratories, to medical service providers—is essential for controlling the disparities in measurement accuracy among laboratories. In the absence of public sector efforts to make these measurement technologies widely available, it is unlikely that the private sector would have undertaken a similar investment. Even in the late 70's, more than 10 years after the release of the first NIST cholesterol standard, industry still faced a wide array of analysis methods that could be implemented in instrumentation and laboratory analysis processes. Within the private sector, incentives to share information about the relative attributes of these measurement technologies

were low. Where such incentives existed—for example between measurement system suppliers and potential clinical laboratory customers—the cost of comparing and verifying such information was high.

The economic consequences of NIST’s Cholesterol Standards Program are experienced at four levels in the supply chain that ultimately delivers medical services to the consumer. First, due to the availability of highly accurate cholesterol reference materials, manufacturers of cholesterol measurement systems (including measurement instruments and the complementary diagnostic chemicals used with them) experience lower production costs than they would if SRMs were not available from NIST. Second, in their interactions with measurement system users (clinical laboratories) concerning the quality and accuracy of their products, measurement system manufacturers face significantly lower transactions costs than they would if the accuracy of their products was not “anchored” to nationally-recognized standards. Third, clinical laboratories experience lower cost in maintaining their quality control and assurance systems. Finally, consumers of medical services receive higher quality medical services in the form of more accurate test results, because inaccurate cholesterol tests can lead to unnecessary medical expenses and health risks.

Conservative estimates of the economic impact of NIST’s investments on the first three levels of the supply chain are shown in Table ES-1.

**Table ES-1—Economic Impact of NIST’s Cholesterol Standards Program**

<b>Performance Metric</b>	<b>Lower-Bound Estimate</b>
<b>Net Present Value (1999 dollars)</b>	\$3,573,812
<b>Social Rate of Return</b>	154%
<b>Benefit-to-Cost Ratio (1999 dollars)</b>	4.47

The benefits to industry resulting from NIST’s investments have changed over the more than three decades in which NIST’s has been involved in cholesterol measurement. Technological and other economic trends have biased the reported benefits in a downward

direction. Among the most significant of these trends are the movement to “closed” automated measurement systems, and the change in the composition of knowledge and skill levels within clinical laboratories that has come about as a result of cost-cutting trends in the medical community.

The study timeframe for this analysis (1986-1999) covers only a part of the program’s life cycle. This biases the measured impacts downward because the benefits enjoyed by respondents have declined relative to the earlier phase of the program’s history. Another source of downward bias in the impact calculations was the choice not to scale respondent’s estimates to reflect benefits of their industry as a whole. The structure of the industry in question was not well enough understood to justify such a procedure.

Nevertheless, the results indicate that NIST has played an important economic role in support of a national effort to monitor, measure, and control cholesterol levels, thereby contributing to reduced levels of cardiovascular disease.

# **The Economic Impacts of NIST's Cholesterol Standards Program**

## **1. INTRODUCTION**

The focus of this economic impact assessment is NIST's Clinical Standards Program, the cholesterol family of Standard Reference Materials (SRMs), and associated measurement methodologies, in particular. NIST has developed accurate and precise analytical methods ("definitive methods") for measuring the purity and concentration of various chemical compositions (commonly referred to as "analytes") in human specimens. These methodologies provide the foundation for a nation-wide system assuring the accuracy of health-related testing. NIST also procures vials of chemical materials, verifies the assay and the purity or concentrations of these materials using its definitive method, and distributes these materials through its Standard Reference Materials Program.

Every day, in hundreds of thousands of physician's offices and hospitals across the nation, tests of human specimen are performed to diagnose, monitor, or treat health problems. NIST cholesterol-related SRMs are used throughout the clinical laboratory supply chain—from instrument manufacturers to hospital laboratories—to assure the accuracy of cholesterol measurement. The accuracy of these clinical testing procedures has been the subject of public concern and regulation for over a decade. Current guidance by public health organizations suggests that adults at low risk for cardiovascular disease have cholesterol tests repeated every 5 years. If the original screening results misclassify a person with abnormal values into the acceptable range, the excess risk may go undetected for an extended period of time.<sup>1</sup>

To assure the accuracy of various diagnostic tests, a regimen of standard quality assurance practices has evolved within the health care community. This National Reference System for Clinical Laboratories (NRSCL) is an evolving system of private, public, and academic institutions that seek to promote consistency of laboratory results within all clinical laboratory

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<sup>1</sup> M. Dominiczak and J. McNamara, "The System of Cardiovascular Prevention," in Nader Rifai, et al., *Handbook*

disciplines. The goal of the NRSCL is the harmonization of clinical laboratory measurement so that the clinically significant characteristics of an analyte are equivalent among all medical institutions.<sup>2</sup>

In the case of cholesterol measurement, NIST plays an important role in this national reference system, primarily by providing standards for cholesterol of known assay and purity to manufacturers of cholesterol-testing products and to the clinical laboratories that utilize cholesterol-testing products.<sup>3</sup>

The Clinical Standards Program is part of a much larger effort by NIST's Chemical Science and Technology Laboratory (CSTL) to help the U.S. chemical manufacturing, energy, health care, biotechnology, food processing, and materials processing industries to meet the broad range of international measurement requirements and compete in global markets. CSTL is one of seven operating units in NIST's Measurement and Standards Laboratories (MSL). It performs leading-edge research in measurement science; develops and maintains measurement methods, standards, and reference data; and develops models for chemical, biochemical, and physical properties and processes.

CSTL's Analytical Chemistry Division engages in the development and evaluation of measurement methods of known accuracy, precision, sensitivity, and selectivity. The resulting reference methodologies provide the foundation for the certification of chemical composition in more than 850 Standard Reference Materials important to U.S. industry, government agencies, and educational institutions. The Division's cholesterol-related activities are central to its Clinical Standards Program.

This report assesses the economic impacts of NIST's cholesterol SRMs at three of four levels in the medical services supply chain: in the development of cholesterol measurement

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*of Lipoprotein Testing*, AACC Press, 1997, pp. 60-74.

<sup>2</sup> *The Reference System for the Clinical Laboratory: Criteria for Development and Credentialing of Methods and Material for Harmonization of Results; Proposed Guideline*, NRSCL 13-P, Vol. 15, No. 12, December 1995, p. ix.

<sup>3</sup> An "assay" is defined by the National Council of Clinical Laboratory Standards (NCCLS) as the quantitative determination of the amount, activity, or potency of a constituent. (See, NCCLS, (NRSCL 8-P3) October 17, 1996.)

system products; in the clinical laboratories' cost of quality; and in the transactions and communications between manufacturers and clinical labs.

In Chapter 2, we discuss the economic importance of accurately measuring cholesterol and the sources of cholesterol measurement inaccuracy; the evolution of a national infrastructure to assure traceability to national standards of measurement accuracy, and NIST's role in the national infrastructure dedicated to cholesterol measurement. Chapter 3 describes the industry supply chain and discusses some of the trends that have caused relations between suppliers of measurement technologies and their users to change over time. In Chapter 4, the approach to measuring the impacts of the cholesterol SRMs program is described and hypothesized outcomes are discussed. Chapter 5 presents the quantitative and qualitative findings of the study survey. Finally, the quantitative analysis of the economic impact of NIST's investments is presented in Chapter 6.

## 2. THE ECONOMIC IMPORTANCE OF ACCURATE CHOLESTEROL MEASUREMENT

### 2.1 CHOLESTEROL AND HEALTH

Proper health care for all Americans is both a policy objective of the U.S. government and an important foundation for continued prosperity.<sup>4</sup> Poor health care costs lives and affects economic growth. Cardiovascular disease (CVD) includes heart disease and stroke. In 1997, heart disease in the U.S. was responsible for the deaths of 725,000 persons over the age of 22. Heart disease is the leading cause of death for persons 65 and over. It is the second leading cause of death for persons 45 and over.<sup>5</sup> The cost of heart disease in the United States in 1999 was estimated at \$215 billion.<sup>6</sup>

One of the most important means of minimizing the risks of heart attacks and heart disease is maintaining desirable cholesterol levels in the bloodstream. Medical experts consider the provision of precise and accurate measurement of cholesterol, “an essential component of a cardiovascular disease prevention system.”<sup>7</sup> Some believe that national and international efforts to contain cardiovascular disease, through the development and enforcement of measurement standards over the past three-to-four decades, may be regarded as one of clinical chemistry’s greatest contribution to public health.<sup>8</sup>

To assure the accuracy of various diagnostic tests, a regimen of standard quality assurance practices has been developed by the health care community. Under the sponsorship of the National Council of Clinical Laboratory Standards (NCCLS), a National Reference System for

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<sup>4</sup> “Investing in people” (education and health care) is one of three crucial elements of the Clinton Administration’s economic strategy. See *Economic Report of the President*, February 1998, pp. 3-5.

<sup>5</sup> CDC, National Vital Statistics Reports, Vol. 48, Table 33, “Leading causes of death and numbers of deaths, according to age: United States, 1980 and 1997.”

<sup>6</sup> This figure includes health expenditures (direct costs, which include the cost of physicians and other professionals, hospital and nursing home services, the cost of medications, home health and other medical durables) and lost productivity resulting from morbidity and mortality (indirect costs). *2000 Heart and Stroke Statistical Update*, American Heart Association, <http://www.americanheart.org/statistics/index.html> (July 20, 2000)

<sup>7</sup> M. Dominiczak and J. McNamara, “The System of Cardiovascular Prevention,” in Nader Rifai, et al., *Handbook of Lipoprotein Testing*, AACC Press, 1997, pp. 60-74.

<sup>8</sup> Nader Rifai, et al., *Handbook of Lipoprotein Testing*, AACC Press, 1997, pp. xxi.

Clinical Laboratories (NRSCL) has evolved.<sup>9</sup> The NRSCL is a system of private, public, and academic institutions that seek to promote consistency of laboratory results within all clinical laboratory disciplines. The goal of the NRSCL is the harmonization of clinical laboratory measurement so that the clinically significant characteristics of an analyte are equivalent among all medical institutions.

In 1985, the National Institutes of Health (NIH) launched the National Cholesterol Education Program (NCEP) and the NCCLS established that National Reference System for Cholesterol (NRS/CHOL) in support of efforts of the NCEP. The NRS/CHOL is one facet of the NRSCL. It is comprised of the NIST definitive method (the isotope dilution mass spectrometric procedure (IDMS)), a CDC reference method (a modified Abell-Kendell method), a NIST-certified pure cholesterol reference material (SRM 911), and NIST-certified serum-based secondary reference materials (e.g., SRM 909, SRM 1951 and SRM 1952).<sup>10</sup>

NIST's development and distribution of widely accepted reference materials (NIST's so-called standard reference materials or SRMs) have made a significant contribution to these developments. These reference materials are used by manufacturers and clinical laboratories to gauge their measurement systems to a substance of known and extremely high purity or to known and accurate concentrations.

## 2.2 SOURCES OF CHOLESTEROL MEASUREMENT INACCURACY<sup>11</sup>

There are multiple sources of error in the measurement of cholesterol. The reliability of cholesterol measurement depends on how well potential sources of error are controlled, beginning with factors that occur before samples are taken and laboratory analysis is undertaken.

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<sup>9</sup> The NCCLS is an international, interdisciplinary, nonprofit, standards-developing and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community.

<sup>10</sup> *Recommendations for Improving Cholesterol Measurement (A Report from the Laboratory Standardization Panel of the National Cholesterol Education Program)*, U.S. Department of Health and Human Services, National Institutes of Health, NIH Publication No. 93-2964, January 1993, p. 21.

<sup>11</sup> Unless otherwise noted, the material in this section is based on, *Recommendations for Improving Cholesterol Measurement (A Report from the Laboratory Standardization Panel of the National Cholesterol Education Program)*, U.S. Department of Health and Human Services, National Institutes of Health, NIH Publication No. 93-2964, January 1993.

“Error” refers to the factors that can alter a measurement such that it does not reflect a patient’s usual cholesterol level or normal metabolic state. There are two broad categories of error: pre-analytic and analytic error.

### **2.2.1 Pre-analytical Issues**

Pre-analytic error is the primary cause of error in cholesterol measurement but it is not the easiest to control. Pre-analytic factors include: intra-individual biological variation, pregnancy, trauma, surgery, acute illness, chronic diseases, diet, acute exercise, and medication as well as the conditions of patient preparation, sample collection, sample handling, storage, and shipment to the laboratory. Factors that contribute to the patients usual cholesterol levels include age, sex, and body weight; behavioral factors such as diet, alcohol use and exercise; genetic factors and chronic medical disorders.

### **2.2.2 Analytical Issues**

Analytical variation, or “laboratory error,” refers to errors associated with cholesterol measurement procedures themselves. National efforts to standardize cholesterol have focused on improving the analytical accuracy of laboratories and minimizing inter-laboratory variations. The major components of a clinical laboratory’s analytic system are as follows:

- Method or sequence of chemical reactions
- Reagent
- Measurement instrument
- Approach to calibration.

Each of these components is discussed in turn.

By the early 1990s, enzymatic methods had replaced “wet chemistry” methods in most clinical laboratories.<sup>12</sup> These enzymatic methods are less corrosive than wet chemistry methods

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<sup>12</sup> This implies a degree of homogeneity among clinical laboratory practices that was not always the case. When NIST first became involved in cholesterol measurement standardization, the situation regarding methods was characterized as chaotic by one observer. See, B. Zak, “Cholesterol Methodologies: A Review,” *Clinical*

and thus do not tend to degrade the performance of the instrument as previous methods did. The specific enzymatic method has unique characteristics that interact with the analyte or other aspects of the specimen to influence measurement results. The microbial source of the enzyme, as well as the concentrations of other chemicals in the specimen matrix, can also affect the accuracy of cholesterol measurement.

The reagents are highly complex mixtures. Their design is affected by considerations other than accuracy, such as cost and convenience. Reagents can also be a source of analytical error in cholesterol measurement. Instability, chemical or biological contamination, changing composition of purchased reagents and improper storage of reagents can affect accuracy.

A wide variety of instruments are used in clinical laboratories. They are comprised of sophisticated mechanical, optical, and electronic subsystems. Inherent errors in these subsystems can cause variation in the measurements reported by different instruments. The nature of the pipetting device used in sample preparation; the consistency of temperature control; the characteristics of the spectrophotometer; the approach to isolating particular wavelengths; and the sophistication of microprocessors in controlling and monitoring various instrument functions can all influence the accuracy and precision of instrumentation.

As late as 1993, the NCEP reported that accurate calibration remained a major problem in clinical laboratories. The approach to calibration is a major factor in determining the overall accuracy of a system. It is essential that manufacturers link the accuracy of their systems to the accuracy base of the NRS/CHOL. NIST's SRMs are typically used by manufacturers (and clinical laboratories) to assign (or check) concentration values in the calibrators they sell to calibrate the instruments and reagents and, thereby, to assure they are performing accurately (i.e., that they are maintaining a linear relationship between response and concentration).

## 2.3 NIST'S ROLE IN CHOLESTEROL MEASUREMENT STANDARDIZATION

### 2.3.1 Chronology of Significant Events

NIST engages in the development of materials and methodologies that are used by clinical testing facilities across the United States—indeed, throughout the world—to assure accurate medical testing and evaluation. One critical area in which NIST has made important contributions to advances in measurement and reliability is that of cholesterol testing. NIST has made contributions in several respects, including the development of the definitive method, a highly specialized analytical method with a comprehensive accuracy assessment, and the development and sale of a family of cholesterol standard reference materials tied to the definitive method. The SRMs have been widely used for assuring the accuracy of manufacturer's cholesterol testing systems, specifically for assigning cholesterol concentration values to commercially marketed “calibrators” that accompany an instrument, providing the user with a traceable measurement system. These calibrators are designed to calibrate the reagents used in measurement instruments.<sup>13</sup> In addition to assuring the accuracy of the values assigned to NIST's SRMs, the definitive method is the ultimate source of accuracy and reliability in national clinical laboratory blood sample assays.<sup>14</sup>

As indicated in Table 1, NIST's involvement with cholesterol begins in the mid-1960s. At that time, the clinical chemistry community had expressed the need to formulate specifications for a standard to be used for conducting cholesterol assays. NIST cooperated with the American Society of Clinical Pathology and the American Association for Clinical Chemists.

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<sup>13</sup> To use a mechanical analogy, these chemical calibrators serve the same function that a precision metal cube (standard) serves for the user of a micrometer. The linear measurement of the standard is assigned by the manufacture of the micrometer. To assure that the micrometer is measuring properly it is applied to the “known” length of the metal standard. If the reading on the micrometer is not the same as the known value of the standard, the micrometer scales are re-adjusted accordingly. The calibrator, in a chemical measurement system, serves the same function except that rather than assuring a true measure of “length” the calibrator provides a true (“definitive”) measure of the concentration of cholesterol in a matrix solution. That value assigned to the calibrator (a “secondary” reference material) is assigned on the basis of the NIST primary standard, also known as a Standard Reference material (SRM).

<sup>14</sup> In cooperation with the Centers for Disease Control (CDC), a network of clinical reference laboratories (known as the Cholesterol Reference Method Laboratory Network—CRMLN) periodically assesses the cholesterol content of fresh patient blood samples and checks these against more sophisticated and accurate assessments made by the CDC. The CDC's “reference method” is calibrated to NIST's “definitive method.”

**Table 1—Timeline of Significant Events in the Development of Cholesterol-related SRMs and the Definitive Method<sup>15</sup>**

<b>Date</b>	<b>Event</b>
1966	NIST participates with the American Society of Clinical Pathology (ASCP) and the American Association of Clinical Chemists (AACC) in specifying a standard for serum cholesterol assays.
1966-67	NIST contracts for production of pure cholesterol specifying “Fieser’s Method.”
1967	NIST issues SRM 911 (99.4% ± 0.3% pure).
1969	National Institutes of Health (NIH) funds NIST to development of a wide range standard analytes for the purpose of improving clinical diagnosis.
	NIST begins development of an atomic absorption spectroscopic (AAS) procedure as a “referee method” for the determination of calcium in human serum. An isotope dilution mass spectrometric (IDMS) procedure, for calcium determinations, was developed at the same time as “an independent method of known accuracy” as required by the NIST certification process for SRMs. This IDMS method developed for calcium is known as a definitive method. A NIST special publication was released in 1972. NIST then began the development of IDMS definitive methods for the determination of glucose in serum, an organic analyte in an organic matrix.
1974	Food & Drug Administration (FDA) funds development of NIST’s IDMS capability as a definitive method for several analytes viewed as critical to improving the evaluation of clinical measurements.
1979-80	First organic IDMS method published.
1980	NIST uses its IDMS definitive method to assign 8 (of 17) analytes in human serum (SRM 909).
1982	Centers for Disease Control & Prevention (CDC) adopts the Abell-Kendall procedure as its reference method because its values for cholesterol concentrations in serum differed only slightly from those of the definitive method.
1986	The NIST DM is modified to incorporate new technology. <sup>16</sup>
1987	NIST-CDC cooperate in the development of SRM 1951 (cholesterol in human serum-frozen) and assign DM and RM values for total cholesterol.
1990	NIST-CAP cooperate in development of SRM 1952a (cholesterol in human serum- freeze dried) and assign DM values for total cholesterol
1991	NIST assigns 11 analytes to SRM 909a (human serum-freeze dried) using its IDMS/DM.
1996	NIST assigns 13 analytes to SRM 909b (freeze-dried human serum) using definitive methods.
1997	NIST certifies cholesterol in SRM 1951a (lipids in fresh-frozen human serum), developed through a subcommittee project of NCCLS, involving NIST, CDC, CAP, and the clinical instrument manufacturers.

<sup>15</sup> Robert Schaffer, et al., “History of NIST’s Contribution to Development of Standard Reference Materials and Reference and Definitive Methods for Clinical Chemistry,” *Clinical Chemistry*, Vol. 41, No. 9, 1995.

<sup>16</sup> P. Ellerbe, et al., “A Comparison of Results for Cholesterol in Human Serum Obtained by the Reference Method and by the Definitive Method of the National Reference System for Cholesterol,” *Clinical Chemistry*, Vol. 36, No. 2, 1990, p. 370. The DM was modified, in part, by replacing packed columns in the gas chromatograph with capillary columns and updating the mass spectrometer with improved technology. The procedure modification is described in, P. Ellerbe, et al., “Determination of Serum Cholesterol by a Modification of the Isotope Dilution Mass Spectrometric Definitive Method,” *Analytical Chemistry*, Vol. 61, pp 1718-23.

Chemistry in developing such specifications. NIST arranged for the manufacture of pure cholesterol, produced according to a specified process (the so-called “Fieser method”); assessed the purity of the material; and issued the cholesterol as SRM 911 in 1967. The success of this effort led the clinical chemistry community to fund NIST’s development of a number of reference materials for other analytes considered important to practicing clinical chemists.

In cooperation with the Centers for Disease Control (CDC) and the College of American Pathologists (CAP), NIST became further involved in the development of reference methods and definitive methods for the accurate assessment of health-related analytes and the chemical composition of materials that contain them. NIST developed additional cholesterol SRMs in recognition of shortcomings of cholesterol measurement nationally and of efforts to establish better traceability for clinical laboratories making these measurements.

NIST’s efforts during the 1980s paralleled a growing national awareness of both the health hazards associated with cardiovascular disease and the need to address clinical diagnostic practices at the national level. A report by NIH/NCEP’s Laboratory Standardization Panel in 1988 concluded that “considerable inaccuracy” in cholesterol testing existed in the United States. Estimates from various testing and monitoring organizations suggested that the range of inaccuracy at the time could have been as high as 25 percent. The NCEP recommended attaining higher accuracy levels by 1992.

The Clinical Laboratory Improvement Act (CLIA) of 1988 established standards designed to improve quality of clinical laboratory testing in U.S. laboratories that conduct tests on human specimens for health assessment or for diagnosis, prevention, or treatment of disease. CLIA mandates proficiency testing as a means to externally validate the quality of a laboratory’s performance. Each laboratory is challenged in three testing events annually. Several initiatives have been instituted to support this proficiency testing and as a result a national reference system as emerged to provide clinical laboratories and their suppliers with traceability to NIST’s definitive methodology.

Since 1988, accuracy and consistency have improved. The U.S. General Accounting Office (GAO) concluded in a 1994 report that under controlled conditions, research facilities,

clinical laboratories and hospital laboratories generally had “reasonably accurate and precise” measurement of cholesterol levels in test samples. In 1995, the NCEP issued national performance criteria for components of cholesterol measurement: Triglycerides, HDL and LDL. NIST’s Cholesterol Standards Program has continued to develop SRMs to meet the increasingly demanding metrological challenges of the clinical laboratory community.

### 2.3.2 Clinical Laboratory Traceability for Cholesterol

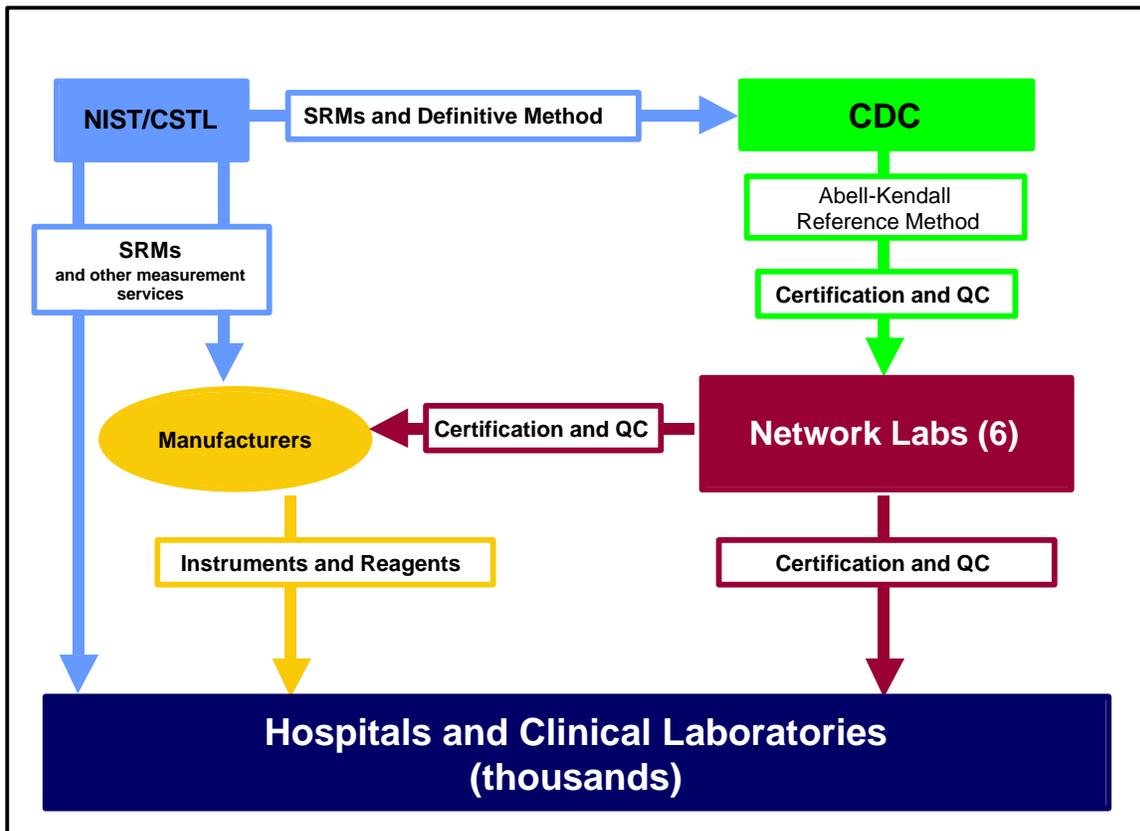
As depicted in Figure 1, NIST’s SRMs and the definitive method constitute the “accuracy base” of a system of traceability that runs from NIST; to cholesterol system manufacturers and public organizations, like the Centers for Disease Control and Prevention (CDC), and the and quasi-public College of American Pathologists (CAP, an industry association of medical pathologists<sup>17</sup>); and, ultimately, to the hospitals, physician offices, and independent laboratories where cholesterol tests are actually performed. Traceability is very important to those engaged in any kind of demanding measurement process. Traceability means that the standard used to set values of purity or concentration can be traced back to a recognized and well-established standard of high purity or accuracy.

The cornerstone of cholesterol traceability is NIST’s definitive method. For a method to be considered definitive it must have been subjected to an extensive investigation and evaluation for sources of inaccuracy. The sources of inaccuracy and their range must be documented. The mean value of the definitive method is considered to be the “true value.” The definitive method developed for cholesterol determinations, as well as other clinically important analytes is *Isotope Dilution Mass Spectrometry (IDMS)*. Typically, IDMS is labor intensive, expensive, and requires highly specialized instrumentation and analysis. Its costs are prohibitive and its methods too time consuming to be used in a clinical setting.<sup>18</sup>

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<sup>17</sup> Pathologists are medical doctors who specialize in laboratory medicine. They are experts in the use of laboratory tests to diagnose and treat disease. Pathologists, as the directors of medical laboratories, are responsible for sophisticated laboratory tests on samples of tissues or fluids, and the quality and accuracy of the results.

<sup>18</sup> The NIST definitive method involves a very precise technique that specifically measures cholesterol concentrations. It is very costly in terms of time and skill level as well as in the instrumentation required. Most clinical laboratories do not have the instrumentation, the highly skilled scientists, or the time to perform this definitive method.



**Figure 1—Traceability to NIST’s Cholesterol Accuracy Base**

NIST’s role in the national reference system of clinical laboratories is two-fold. First, NIST’s definitive method is used to anchor the results of collective quality control and assurance efforts such as proficiency tests required of clinical laboratory systems by Federal law.<sup>19</sup> The Clinical Laboratory Improvement Act of 1988 (commonly referred to in the medical industry as “CLIA”), directs the U.S. Department of Health and Human Services (HHS) to adopt standards under which clinical laboratories subject to CLIA ‘88 will operate. According to clinical laboratory experts:

[CLIA] established standards designed to improve the quality of clinical laboratory testing in U.S. laboratories that conduct testing on human specimens for health assessment or for the diagnosis, prevention, or treatment of disease. CLIA mandates proficiency testing as a means to externally validate the quality of a laboratory’s performance. Each participating laboratory is challenged in

<sup>19</sup> The Clinical Laboratory Improvement Act of 1988, Pub.L.No. 100-578, codified at 42 U.S.C. 263a (CLIA '88).

three testing events annually. In each test event, 5 unknown samples of each analyte or test are provided.<sup>20</sup>

NIST's definitive method plays an important part in the national proficiency program for clinical laboratories mandated by CLIA. Some 15 public and private laboratories and organizations are authorized to administer CLIA-approved testing programs. The College of American Pathologists (CAP) is one such organization. CAP administers the Laboratory Accreditation Program which examines all aspects of quality assurance in the laboratory, including methodology, reagents, control media, equipment, specimen handling, procedure manuals, reports and proficiency testing, personnel, safety, and the overall management principles that distinguish a quality laboratory.<sup>21</sup> Upon successful completion of the inspection process, the laboratory is awarded CAP accreditation. CAP's proficiency tests for cholesterol are anchored to the NIST definitive method.

NIST's definitive method also provides the accuracy base for CDC's cholesterol measurement system certification program (the Cholesterol Reference Method Laboratory Network, or CRMLN).<sup>22</sup> The CRMLN, in turn, assures that manufacturers are transferring the accuracy base to their "calibrators" and that reagents used in measurement instruments are calibrated properly. In other words, CRMLN assures that the reagents, and the instrument systems of which they are a part, are accurately "reading" the cholesterol concentrations of samples.

NIST's other important role in the national reference system is to organize the production, assessment, and quality assurance of primary and secondary reference materials.<sup>23</sup>

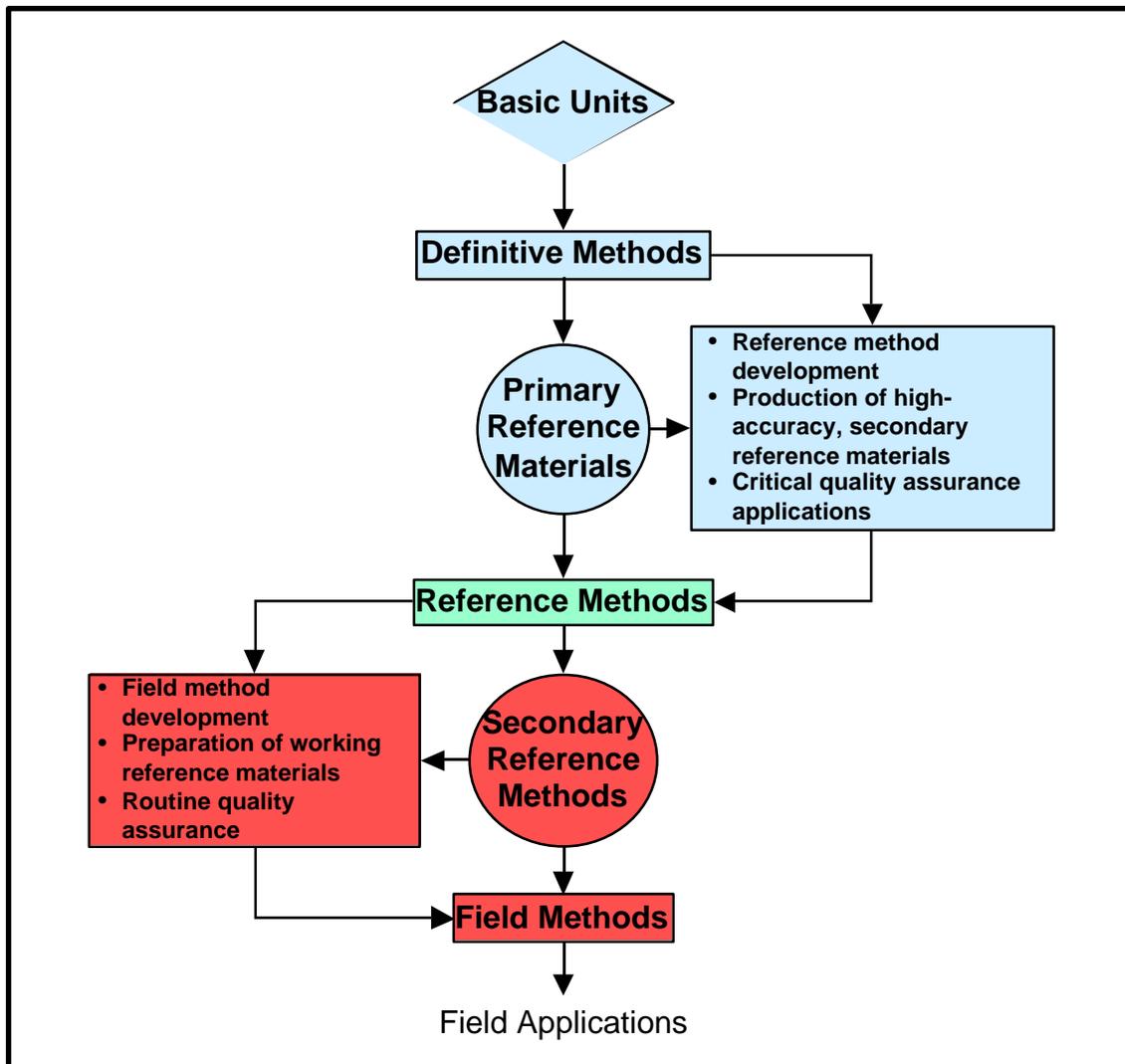
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<sup>20</sup> G. Myers, et al., "Standardization of Lipid and Lipoprotein Measurements," in Nader Rifai, et al., *Handbook of Lipoprotein Testing*, AACC Press, 1997, p. 239-40.

<sup>21</sup> College of American Pathologists, [www.cap.org](http://www.cap.org)

<sup>22</sup> There are 6 labs in the CRMLN: University of Wisconsin (State Laboratory of Hygiene); Northwest Lipid Research Laboratories (Seattle); Wadsworth Center for Laboratories and Research (New York State Department of Health); Washington University School of Medicine; Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University; Pacific Biometrics Research Foundation. See, G. Meyer, "Standardization of Lipid and Lipoprotein Measurement," in Rifai, et al, (ed.) *Handbook of Lipoprotein Testing* (1997), page 237.

<sup>23</sup> By definition, a "reference material" is a material or substance, one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials. A "certified reference material" (CRM) is a reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for



**Figure 2—Traceability Hierarchy of Measurement Methods**

NIST reference materials are trademarked as “standard reference materials” (SRMs). Figure 2 shows the relationship between the definitive method for measuring cholesterol concentration and all other applied methods and “standards.”

NIST SRMs are used by cholesterol measurement system manufacturers for both internal and external quality assurance. Internally, the company uses SRMs to assign cholesterol concentration values to its calibrators to eliminate bias and to ensure that readings which users obtain are accurate and traceable to NIST. A company also uses SRMs externally with its

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which each certified value is accompanied by an uncertainty at a stated level of confidence. The term “standard reference material” (SRM) is the Trademark name of a certified reference material that has been certified and is

customers as part of a quality assurance function. In this role, the company interacts with users in performing “trouble-shooting” and dispute resolution arising, for example, from a rigorous proficiency test requirement to which many clinical laboratories are subject under (CLIA).

Of primary concern to this study are NIST’s cholesterol reference material (99.9percent pure cholesterol—SRM 911) and NIST’s human serum reference materials (various analytes of known concentration, including cholesterol, in frozen and freeze-dried human blood—SRMs 909, 1951, and 1952).<sup>24</sup> Manufacturers utilize NIST SRMs primarily in the development, production, and quality assurance of calibrators, one of the three classes of the diagnostic chemicals used to support cholesterol measurement instruments.<sup>25</sup>

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distributed by the NIST.

<sup>24</sup> The terms “reference material,” “calibration material,” and “calibrator,” are equivalent terms. “Primary standard,” “secondary standard,” are the international terms for what the NCCLS, the national clinical laboratory standards body, calls “calibration material.” See, NCCLS, (NRSCL 8-P3) October 17, 1996.

For the purposes of this report, we will use the term “reference material” followed by some organizational or functional information that allows the reader to assess “distance” from the NIST accuracy base. An important distinction will be between commercial “calibrators” (formally “secondary calibrators,” defined by NCCLS as, a substance or device that is based on a reference preparation, or in which the analyte concentration or other quality has been determined by a formal analytical procedure of stated reliability) and those available from public or quasi-public organizations, such as industry and professional associations.

<sup>25</sup> The dominant instrument manufacturers produce a measurement device that measures multiple analytes, cholesterol being just one of these. Instrument manufacturers also typically produce the diagnostic chemicals with which the instrument “reads” analyte qualities (reagents), such as concentration, and with which the machine’s accuracy (calibrators) and total analysis process (controls) are monitored for stability and accuracy. Reagents tend to be analyte-specific. Calibrators and controls are not analyte-specific.

### 3. INDUSTRY SUPPLY CHAIN

Figure 3 identifies three levels of the industry supply chain that are affected by NIST's clinical standards programs: diagnostic chemical manufacturers; instrument system manufacturers; and clinical laboratories (the latter consisting of three distinct sub-sectors).<sup>26</sup> Based on a review of SRM sales data, we estimate that chemical manufacturers and instrument manufacturers purchase roughly one third of the cholesterol family of SRMs. Another large fraction appears to have been purchased by independent and hospital-based clinical laboratories.<sup>27</sup>

#### 3.1 CLINICAL LABORATORIES<sup>28</sup>

There are more than 171,000 clinical laboratories in the U.S.<sup>29</sup> The clinical laboratory industry is comprised of three major types of laboratories:

- Hospital laboratories
- Independent laboratories
- Physician's office laboratories (POLs).

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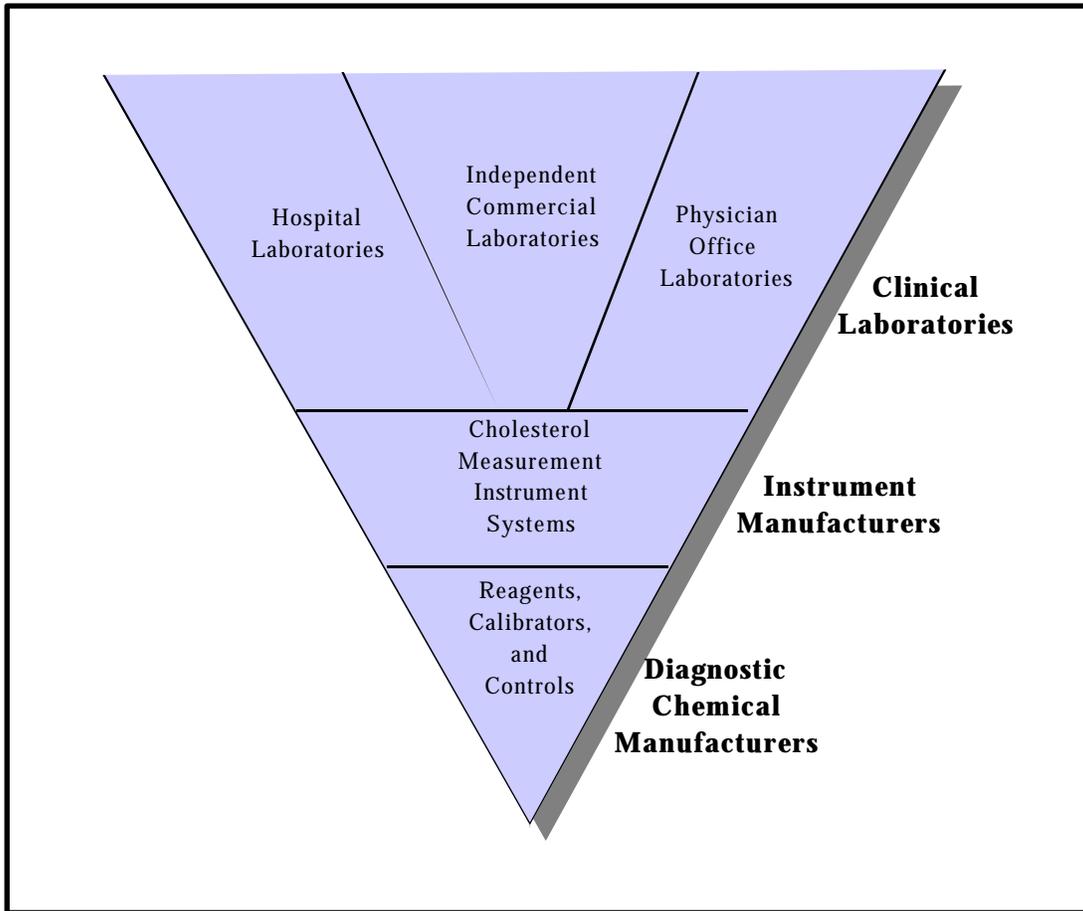
<sup>26</sup> It was anticipated that program impacts on a fourth tier of the supply chain—recipients of cholesterol testing services (patients)—would be assessed. Survey participants were unable to provide estimates of trends in misclassifications that result in duplicate testing costs. Cholesterol measurement experts were unable to identify studies that related improvements in cholesterol measurement to misclassification trends.

<sup>27</sup> The fraction purchased by clinical laboratories is difficult to estimate for three reasons. First, the number of organizations is very large and there is not a standard list that would allow the identification of all clinical laboratories. Even if this were the case, buying organizations purchase under multiple names making an accurate matching of names to purchasing organizations unreliable. Second, due to extensive consolidation in the independent clinical laboratory segment of the clinical laboratory industry, organizational names appear to have changed considerably. Third, hospital laboratories are only occasionally identified as such. Many are associated with universities. We assume that many university purchasers are hospitals but certainly university researchers also purchase cholesterol-related SRMs for a number of reasons.

<sup>28</sup> Unless otherwise indicated, the source of information on the clinical laboratory industry is, Thomas Hoerger, et al., Background Report on the Clinical Laboratory Industry, Research Triangle Institute, Oct. 1996.

<sup>29</sup> Health Care Finance Administration (HCFA), Oscar Database, July 21, 2000.

**Figure 3—The Relevant Supply Chain for Cholesterol SRMs**



Hospital laboratories provide laboratory services to hospital in-patients and out-patients. Independent laboratories process specimens on referral from physicians and transport them to central facilities for batch processing. POLs typically service their owners' medical practices, providing quick test results for low complexity tests. More complex tests are typically referred to hospital or independent laboratories.<sup>30</sup>

<sup>30</sup> The clinical laboratory industry is comprised of elements of the Medical Laboratories industry (SIC 8071) as defined in the Standard Industrial Classification system.

There are over 8,000 CLIA-certified hospital laboratories in the country; almost 90,000 certified POLs; and over 5,000 certified independent laboratories. Among the independent laboratories, LabCorp, Quest Diagnostics, and SmithKline-Beecham are believed to control almost 60 percent of the national independent laboratory market.<sup>31</sup> Annual revenues of the clinical laboratory industry have been estimated at \$30-35B (1995) with approximately 50 percent going to hospitals; 26 percent to independent labs and ~24 percent going to POLS.

### 3.2 INSTRUMENT MANUFACTURERS

The term “measurement system” refers to the hardware and software that comprise a measurement instrument and the complementary diagnostic chemicals (reagents, calibrators, and controls) that allow the instrument to “read” the attributes of the target sample. The system’s suite of diagnostic chemical are also used to assess the accuracy of the instrument as well as the larger measurement procedure of which the instrument is a part.

Cholesterol measurement systems belong to a class of measurement instrument commonly referred to within the industry as “general chemistry” instruments. General chemistry instruments are increasingly automated, offer an ever-widening array of tests, and the technology is changing more rapidly than ever before.<sup>32</sup> Manufacturers compete to provide clinical users with measurement instruments that perform a wide range of analytical tests rapidly and that eliminate as much preparatory and post-processing expense as possible. (Examples of such pre- and post-processing expense include the elimination of time-consuming and error-prone steps for reconstituting reagents to make solutions, or to prepare dilutions from more concentrated solutions; minimization of reagent waste; reagent storage; and specimen identification, labeling,

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<sup>31</sup> As of 1996, these three independent laboratories controlled a number of well-known independent clinical laboratories. Corning Life Science controlled: MetPath, Damon, Nichols Institute, Clinical Pathology Facility, DeYor CPF, Associated Clinical, Clinical Labs of Lincoln, and Pharmaceutical Laboratory Services. LabCorp controlled: National Health Laboratories, Allied Clinical Labs, Roche Biomedical Labs, Reference Pathology Laboratory, Physician Clinical Laboratories, Sierra Nevada Laboratories, and Suburban Pathology Laboratories. During the course of this study, consolidation among the large independent laboratories continued: Corning and SmithKline-Beecham were purchased by Quest Diagnostics in 1999.

<sup>32</sup> M. Dominiczak and J. McNamara, “The System of Cardiovascular Prevention,” in Nader Rifai, et al., *Handbook of Lipoprotein Testing*, AACC Press, 1997, pp. 60-74; Carl A. Burtis, “Converging Technologies and Their Impact on the Clinical Lab,” *Clinical Chemistry*, Vol. 42, No. 11, 1996, pp. 1735-1749.

handling, delivery, transport, storage, retrieval).<sup>33</sup> In the face of rapid technological change, some observers believe that an emphasis on quality control is increasingly important.<sup>34</sup>

### **3.3 THE MARKET FOR CHOLESTEROL DIAGNOSTICS**

The market for cholesterol measurement systems is complex and fragmented. Instrument manufacturers also produce (or distribute under proprietary label) the diagnostic chemicals required to calibrate, operate, and perform quality control on their instruments. Some instrument manufacturers have designed “open” systems, capable of utilizing the diagnostic chemicals of competing instrument manufacturers or of diagnostic chemical vendors. Others maintain “closed” systems.<sup>35</sup>

While the instruments themselves are multifunctional, the diagnostic chemicals or reagents are analyte-specific. According to industry representatives, calibrators, and controls typically are applicable to a number of different analytes.

Industry representatives estimate that in 1997 the worldwide market for diagnostic chemicals (reagents, calibrators and controls) was approximately \$4.3 billion. The U.S. market is estimated to constitute some 40 percent of that total, or \$1.7 billion. Industry representatives estimate that the value of the cholesterol-related diagnostic chemical market alone is approximately \$100 million a year, 95 percent of which is estimated to be reagents, with calibrators and controls comprising the remaining 5 percent. Some 75 percent of the diagnostic chemical market is believed to be controlled by instrument manufacturers. Diagnostic chemical vendors control the remaining 25 percent.

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<sup>33</sup> C. A. Burtis, “Converging technologies and their impact on the clinical lab,” *Clinical Chemistry*, Vol. 42, No. 11, 1996, pp. 1735-1749; and “Advanced Technology and Its Impact on the Clinical Laboratory,” *Clinical Chemistry*, Vol. 33, No. 3, 1987.

<sup>34</sup> Alejandro Macias and Lynne Garcia, “Progress in Clinical Laboratories,” *Review of Clinical Investigations*, Vol. 47, No. 5, September-October 1995.

<sup>35</sup> Among the leading cholesterol measurement system manufacturers, Dade Diagnostics, and Ortho Clinical have

Table 2 identifies the major cholesterol measurement instrument manufacturers and diagnostic chemical vendors.<sup>36</sup>

**Table 2—Major Chemistry Instrument & Diagnostic Chemical Manufacturers**

<b>Instrument Manufacturers<sup>37</sup></b>	<b>Diagnostic Chemical Vendors</b>
Abbott Laboratories	Bio-Rad Laboratories, Inc
Bayer Corporation	Diagnostic Chemicals Limited
Beckman Coulter, Inc.	Daiichi Pure Chemicals Co., Limited
Roche Diagnostics/Boehringer Mannheim	International Reagent Corporation
Dade International, Inc.	King Diagnostics, Inc.
Olympus Optical Company	New England Diagnostics
Ortho-Clinical Diagnostic Company	Reagent Applications, Inc. (Raichem)
Pacific Biometrics, Inc.	Shino-Test Co.
	Sigma Chemical Company
	Trace America, Inc.
	Wako Pure Chemical Industries, Inc.

Table 3 provides estimates of the market shares of the dominant manufacturers of blood chemistry measurement systems.

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closed systems.

<sup>36</sup> Instrument manufacturers produce both cholesterol-specific measurement instruments and multi-analyte instruments. As discussed in the text, most instrument manufacturers also produce and/or market the diagnostic chemicals that accompany their instruments. No attempt was made to identify the product models associated with each manufacturer and the shares of these instruments command for each of the three distinct market niches (hospital labs, physician office laboratories, and independent labs). Instruments and their related diagnostic chemicals are complementary.

<sup>37</sup> Instrument manufacturers also manufacture and/or market the complementary diagnostic chemicals (reagents, calibrators, and controls) utilized in their instruments.

**Table 3—Chemistry Instrument Installed Base: Hospital & Commercial Labs<sup>38</sup>**

<b>Instrument Manufacturers</b>	<b>1995</b>	<b>1997</b>
Dade International, Inc.	22%	26%
Beckman Coulter, Inc.	20%	22%
Roche Diagnostics/Boehringer Mannheim	20%	18%
Ortho-Clinical Diagnostic Company	15%	18%
Abbott Laboratories	7%	5%
Bayer Corporation	4%	3%
Others (including Olympus)	12%	8%
Total Market	100%	100%

### **3.4 CHANGES IN BUYER SUPPLIER RELATIONS: IMPLICATIONS FOR THE UTILITY OF NIST SRMs**

By 1993, a well-defined and developed national system existed for assuring the standardized measurement of cholesterol. The major features of this system were discussed above. This section highlights some of the trends that have affected manufacturers and users of cholesterol measurement systems over the years during which standardization emerged.

As this national system matured with its proficiency testing program successfully in place, commercially-provided secondary standards became more widely used by those

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<sup>38</sup> These data were provided by IMV Limited. There is no public source of statistics on the structure of the market for cholesterol-related measurement systems or cholesterol-related diagnostic chemicals. The installed base estimates provided by IMV Limited are poor indicators of the cholesterol-related measurement systems that are the specific focus of this impact assessment. First, cholesterol analysis is only a subset of chemistry analysis. Typically chemistry analyzers are multifunctional, multi-analyte instruments so these estimates are indicative of a much more broadly defined market. Second, the installed base estimates provided by IMV Limited do not include the installed base of a very large segment of the market—independent-testing laboratories. Third, the installed base of instruments does not accurately reflect test volume (because different machines have very different throughput capabilities) or, relatedly, the shares of diagnostic chemical sales controlled by manufacturers. Independent corroboration by a number of industry representatives and analysts suggest that while the share may be somewhat inaccurate indicator of the cholesterol measurement system market, the dominant firms in the target industry are represented in the table.

performing clinical testing. NIST SRMs were reserved for use at the highest level of the traceability chain. The net result was that the routine use of SRMs declined. As discussed in detail in Chapter 4, the timeframe selected for this economic impact assessment is one in which the widespread use of NIST's cholesterol SRMs was in decline.

In 1949, a national survey on total cholesterol measurement among clinical laboratories showed an inter-laboratory comparability of approximately 24 percent, reflecting a large variability of measured cholesterol values from one institution to the next. By 1969 this variability had decreased to 18.5 percent, and by 1983, to 6.4 percent. By the early 1990s, inter-laboratory comparability ranged from 5.5 –7.2 percent, showing stability over the intervening decade.

When NIST became involved in the standardization of cholesterol measurement, no consensus existed as to what analytic method most accurately measured cholesterol. In 1977, clinical laboratories still faced a “quandary” when choosing among a variety of complex measurement methods.<sup>39</sup> The wide variety of analysis methods, in itself, would have been sufficient to cause high variability in accuracy between clinical laboratories. At that time clinical laboratories were unregulated and far less cost-sensitive than they are today. They maintained in-house capabilities to develop and implement a variety of complex analytic procedures. Many developed their own diagnostic chemicals (reagents, calibrators, and controls) and performed complex and labor intensive analysis functions.

Simultaneously, instrument and chemical manufacturers were striving to incorporate a variety of measurement methods into instrument systems that automated the labor-intensive processes performed in the clinical laboratories. Competition among manufacturers no doubt emphasized the differences among measurement systems adding additional layers of complexity to choices facing clinical laboratories.

In addition to the trend toward standardization, in which NIST has played a prominent part, two other trends have affected the manner in which NIST's contributions to standardization have been realized. First, there was a shift within the community of manufacturers and users

from “wet chemistry” to “dry chemistry” measurement technologies. The wide introduction of enzymatic reagents (dry chemistry) in the late 1960s early 1970s heralded a major change in the “process technologies” with which cholesterol had been measured for 50 years. These dry chemistry technologies had numerous advantages over traditional technologies.<sup>40</sup> The cholesterol measurement methods that became the basis for national traceability in the early 1980s at NIST and CDC are “wet chemistry” methods. While typically more accurate than dry chemistry methods, these wet chemistry (or “strong acid” methods) were too complex and costly for the large volume requirements of the routine laboratory.<sup>41</sup>

With increasing automation and the movement to “closed systems,” in which measurement instrument and related diagnostic chemicals are sold as an integrated system, the wide use of NIST’s SRMs declined. The accuracy of diagnostic test kits that were marketed to clinical laboratories was assessed by the manufacturer (rather than the clinical laboratory) either directly or through the CDC system. In other words, as the Cholesterol SRMs program matured SRMs were increasingly needed only at the highest level to provide traceability of the entire system to NIST.

In retrospect, the technological trends favoring dry chemistry also had ramifications for highly trained analytical chemists that determined the quality assurance practices of clinical laboratories. The exodus of clinical chemists from clinical laboratories to manufacturers was foreseen by one observer:

As regards their analytical role, clinical chemists should continue to perform significant analytical function in the overall practice of laboratory medicine; however, where they apply their analytical expertise may change. If advanced instruments will be completed automated, have built-in quality assurance capabilities, and be able to monitor their own performance and status, highly trained personnel may not be needed in the laboratory to perform these functions. However, these functions will shift to industry, to join method development and evaluation, and will require trained personnel with expertise in research and development. Thus, the clinical chemists of the future will more

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<sup>39</sup> B. Zak, “Cholesterol Methodologies: A Review,” *Clinical Chemistry*, Vol. 23, No. 7, 1977, pp. 1201-1214.

<sup>40</sup> C.A. Brutis, “New Technologies to Improve Laboratory Testing,” in E.W. Bermes (ed.) *The Clinical Laboratory in the New Era*, Washington, D.C., AACC Press, 1985.

<sup>41</sup> B. Zak and J. D. Artiss, “Some Observations on Cholesterol Measurement in the Clinical Laboratory,” *Microchemical Journal*, Vol. 41, 1990, pp. 251-270.

probably be employed in industry than in a hospital. This translocation is already occurring: a recent study by the American Association for Clinical Chemistry found that, in 1976, 57% of new AACC members worked in hospitals and 16% in industry; by 1982 these numbers had changed to 37% (hospitals) and 36% (industry).

A second important trend that has unfolded along with the trend toward cholesterol measurement standardization was an increasing emphasis on cost-control in the health care industry. The health care industry has undergone a dramatic restructuring over the last two decades in large part to contain the high and rising costs of US health care.<sup>42</sup> With technological trends reducing the demand for the expertise of clinical chemists in the laboratory setting, and cost-containment pressures being exerted throughout the healthcare industry, it is to be expected that only the most essential and cost-effective quality practices would be retained in the clinical laboratory environment.

Today, NIST's cholesterol SRMs remain an important part of the traceability chain for clinical laboratories and cholesterol measurement system manufacturers. However, the importance of NIST's cholesterol SRMs is increasingly felt at a distance, through the CDC's manufacturers certification program for measurement system manufacturers. As explained in section 2.3.2, NIST's cholesterol SRM anchors the CRMLN's assessment of cholesterol measurement accuracy to the national standard of cholesterol purity.

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<sup>42</sup> These trends were synthesized from a variety of sources and reported in NIST Planning Report 98-2, *The Economics of a Technology-Based Service Sector*, especially Chapter 7, "Case Study: Barriers to Technology Development and Implementation in the Health Care Industry," pp. 121-141.

## **4. ECONOMIC ASSESSMENT FRAMEWORK**

### **4.1 NIST'S CHOLESTEROL STANDARDS PROGRAM OUTPUTS**

The primary outputs of NIST's Cholesterol Standards Program being evaluated in this report are the following cholesterol-related standard reference materials: SRM 911, SRM 909, SRM 1951, and SRM 1952. NIST's SRMs are widely used throughout the clinical laboratory industry supply chain, primarily to assign cholesterol concentration values to commercial secondary reference materials, also known as commercial calibrators.

This economic impact assessment focuses on the use of these SRMs by manufacturers of cholesterol measurement systems, diagnostic chemical manufacturers, and the clinical laboratories that use NIST SRMs to perform quality control and assurance.

### **4.2 EVALUTION FRAMEWORK AND APPROACH**

#### **4.2.1 Cholesterol SRMs: Mitigation of Market Failures**

The existence of market failures is the chief economic rationale for government involvement in technology development activities.<sup>43</sup> Traditionally, NIST has provided those elements of an industry's technology that must be shared in order to have a significant economic impact. Economists refer to such technologies as "infratechnologies."<sup>44</sup> Because of the "public goods" character of such technology infrastructure (resulting from common use) private firms tend to underinvest in its development. For a private firm, the problem of capturing sufficient returns from investment in such a technology is accentuated by the prospect of several companies developing alternative infratechnologies (different approaches to performing the same test). Only one version, or a hybrid of several versions, is eventually accepted as the industry standard so investments in the other versions have to be written off.

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<sup>43</sup> R. G. Noll, "Economic Perspectives on the Politics of Regulation," in *Handbook of Industrial Organization, Vol. II*, R. Schmalensee and R. Willig (Eds.) Elsevier 1989, pp. 1253-1287

<sup>44</sup> G. Tasse, *The Economics of R&D Policy*, (Quorum Books) 1997.

Table 4 summarizes the market barriers that were at work within clinical laboratories and between clinical laboratories and the manufacturers of the cholesterol measurement systems they utilize. A lack of standardized cholesterol measurement practices was largely responsible for the inadequate state of practice in cholesterol measurement across the nation in the late 1960s and early 1970s. Two principle barriers stood in the way of standardization. First, a wide variety of analysis techniques were available to clinicians and instrument designers and there was little consensus on which would yield the best results, technically and commercially. Second, the incentive to share information across companies in the same industry is typically low. Where the incentive exists, implementation can be difficult because the information provided is often suspect. Suppliers of complex measurement systems, no doubt, had ample incentives to share

**Table 4—Economic Analysis Framework**

<b>Market Barriers</b>	<b>Related NIST Outputs</b>	<b>Hypothesized Outcomes</b>	<b>Beneficiaries</b>	<b>Benefit Measures</b>	<b>Comparison Scenario</b>
<i>Excessive competition among alternative measurement methods and their implementations, leading to higher-cost, lower quality testing services nationwide.</i>	SRMs 909, 911, 1951, and 1952	Laboratory standardization on NIST reference materials (reduced variation in inter-lab accuracy).	Users and manufacturers of cholesterol measurement calibrators (secondary standards)	Cost avoidance in calibrator development, production, and quality control	Development and validation of calibrators w/o NIST traceability
<i>High transaction costs from uncertainty over test information accuracy (information sharing difficulties).</i>	SRMs 909, 911, 1951, and 1952	Transaction costs are lower due to measurement uncertainty reductions from traceability to NIST	Manufacturers of cholesterol measurement systems and clinical users	Cost avoidance in buyer-seller interactions to establish calibrator or measurement system values when systems fail (i.e., “trouble shooting.”)	Process validation w/o NIST traceability
<i>High transaction costs from uncertainty over test information accuracy (leading to repeat testing and incorrect diagnosis).</i>	SRMs 909, 911, 1951, and 1952	Transaction costs are lower due to measurement uncertainty reductions from traceability to NIST	Manufacturers of cholesterol measurement systems and clinical users	Cost avoidance by clinical laboratories due to more efficient/effective quality control	Quality control process costs w/o NIST traceability

information about the quality of their products (vs. those of their rivals) with clinical testing laboratories. But the credibility of information shared would be suspect and the cost of verifying it would be high. Economists refer to these costs as transaction costs.

Because of the lack of standardization, the public health risks of cardiovascular disease were higher than desirable. From an economic perspective, the mitigation of these barriers was the motivation for NIST's involvement and investment in the development and dissemination of cholesterol SRMs. In the absence of NIST's investments, inter-laboratory variation in the accuracy of cholesterol measurements across the nation would have lagged behind what was historically achieved and manufacturers would have born additional private costs in attempting to accurately assign cholesterol concentration levels to calibrators used with their measurement systems. In addition, both cholesterol measurement system manufacturers and clinical laboratories that use their products would have incurred additional costs in resolving disputes with suppliers ("trouble-shooting") concerning the sources of inaccuracies that occur in the regular course of clinical measurement practice.

#### **4.2.2 Comparison Scenario**

Industry representatives perceive NIST as the ultimate basis, "the ground truth," for the levels of accuracy that has been achieved in the measurement of cholesterol. By the same token they recognize that NIST is one facet of the larger national system—the National Reference System for Cholesterol (NRS/CHOL)—that assures the accuracy and traceability of clinical measurements. In the case of cholesterol SRMs, our surveys posited a counterfactual hypothesis whereby the private sector organizations that rely upon NIST cholesterol SRMs were responsible for developing and implementing measurement alternatives to the products and analytical services performed by NIST.

It was difficult for industry representatives to clearly separate one component of the national traceability *system*—the NRS/CHOL—from the whole and therefore to assess the hypothetical cost implications of only one facet of the system being unavailable.

To respond, two counterfactual scenarios were adopted in the course of the survey phase of the assessment:

- NIST ceases to perform its functions in the national traceability chain but all other facets of the NRS/CHOL remained intact
- CDC replicates the functions currently performed by NIST.<sup>45</sup>

The costs estimated in both cases are interpreted to be the cost-avoidance *benefits* that accrue to industry representatives as a result of the NIST program. Since the first of the two hypotheses produced more conservative estimates, this scenario was used to assess the impact of the cholesterol SRMs program.

### 4.2.3 Impact Estimation Timeframe

NIST's involvement in cholesterol standards goes back more than 30 years. In estimating the economic impact of projects with this temporal scope, difficulties are often encountered in obtaining records or recollections of costs and benefits. This is true of both the cost (NIST) and the benefits (industry) sides. Experience suggests that ~10 years from time of study is an outside temporal boundary for estimating costs and benefits unless relevant historical records are available.

In 1986, NIST's definitive method was significantly altered to update the technology. This significant change in the capital stock of the program provided a convenient starting point for the assessment timeframe. All pre-1986 investments are treated as "sunk costs."<sup>46</sup>

Initially, the period from 1986 to the present appeared adequate for estimating the economic impact of the program. Given this start date for the economic impact assessment, the costs of updating the DM; the costs of maintaining the DM and all net costs associated with the

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<sup>45</sup> An estimate of the cost of CDC replacing NIST (a surrogate for social the cost-avoidance benefits) was developed in communications between NIST and CDC. Personal correspondence with Dr. Ellyn Beary (NIST/CSTL), January 11, 2000.

<sup>46</sup> A sunk cost is an investment that produces a stream of benefits over a long period of time but can never be recouped. Because it can never be recouped it has no "economic value"—no alternative employment—and should, therefore, be ignored in our calculations of economic impact.

development, procurement, and maintenance of relevant SRM series could be accounted for.<sup>47</sup> (The relevant SRM series are 911, 909, 1951, and 1952.) There are a number of releases associated with each SRM. For example, 909a and 909b were developed and released following the modification of the definitive method in 1986.) Other organizations (for example, CAP) have also made contributions to the development of some SRMs in the post-1986 timeframe.

It became clear during the survey phase of this study that the timeframe chosen for the assessment biased the reported benefit estimates downward. Given the difficulties associated with assessing NIST programs of long duration, we feel that the choice of timeframes was, nevertheless, reasonable. Furthermore, the sentiment expressed by respondents concerning the life-cycle of the cholesterol program's value assures that the substantial benefit estimates provided by respondents are a conservative assessment of the true value of the program to society.

#### **4.2.4 Hypothesized Outcomes**

In the absence of NIST's cholesterol SRMs, considerable expense would have to be undertaken to replicate the process through which high-accuracy cholesterol calibrators are produced, distributed, and used. It appears likely that the analytical methods developed and utilized by NIST are uneconomical for the private sector to maintain and that many laboratories today lack the capability to implement rigorous measurement methods. In part this is due to the unit cost of highly accurate reference materials, and in part it is due to inherent limitations on the expected demand for reference materials produced and marketed by private sector firms.<sup>48</sup> This aspect of barriers to wider investment in infratechnologies affects both ends of the supply chain: the manufacturers of measurement systems (whose use NIST, or NIST traceable, primary

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<sup>47</sup> The analytical capability represented by the definitive method is utilized to assign values to all organic reference material developed and distributed by NIST. Therefore, a fraction of the total cost associated with the modification and maintenance of the DM for cholesterol was estimated. Similarly, cholesterol is only one of 13 or more assigned analyte values for the SRM 909 series. SRM 911, 1951, and 1952 are constituents of cholesterol only. Only a fraction of the cost for development, maintenance, and distribution of the SRM 909 series was allocated to the Cholesterol Standards Program.

<sup>48</sup> It is believed that a private sector firm would be perceived as too opportunistic to take advantage of NIST's independent "honest broker" status and that NIST's extensive distribution of information concerning the analytic method (the so-called definitive methods) employed by NIST would be curtailed to limit access to what would be proprietary knowledge.

reference materials to assign cholesterol concentration levels to secondary reference materials); and the clinical laboratories that utilize SRMs to assure measurement quality control.

Without NIST standards, and the definitive method that anchors the accuracy of those reference materials, the capacity to perform accurate assignment of concentration values would be diminished and additional quality control steps would be necessary in an attempt to assure confidence in the values assigned. In addition, disputes that arise concerning the source of errors would be more frequent and more costly to resolve because more effort is required to establish the source of the error and to assure that the error is not repeated.

In addition to these intermediate impacts, in the absence of sufficient investment in NIST's infratechnologies patients would be uncertain of their health status and clinical laboratories would be very uncertain about the quality of the measurement systems they employ. For manufacturers, the costs of quality control and quality assurance would be considerably higher without NIST SRMs and the resolution of conflicts surrounding the quality of their products and services would also be higher. In short, NIST's cholesterol standards program appears to substantially lower the cost of information that is critical to the pace and level of cholesterol measurement-related transactions within the health community, especially between clinical laboratories and their industrial suppliers. In the absence of high levels of quality assurance, sales of measurement systems, sales of measurement services, and, ultimately, the health of the population would certainly suffer.

To summarize, the benefits of NIST's Cholesterol Standards Program were formulated in terms of the following hypotheses:

- Availability of SRMs to measurement system manufacturers reduces product formulation and quality control costs, especially the cost of assigning reliable concentration values to commercially-marketed calibrators
- Availability of SRMs reduces the internal cost of quality control and quality assurance for clinical laboratories.
- Use of SRMs (traceability) reduces transaction costs for manufacturers and clinical laboratories, in the form of "trouble shooting" that occurs when products or systems fail to provide expected results.

## 5. SURVEY FINDINGS

### 5.1 THE SURVEY POPULATION

The survey population consists of two groups: manufacturers and clinical laboratory service providers. Representatives of these groups were interviewed informally, by phone, during the fact-gathering phase of the study. This was followed by an electronic mail survey. Follow-up phone interviews and electronic mail exchanges were conducted with selected respondents to clarify or further explore their responses.

Approximately 20 manufacturers of cholesterol measurement instruments and complementary diagnostic chemicals were identified. Seven of the 17 manufacturers contacted provided information on their use of SRMs, the importance of traceability to NIST and the additional costs they would have incurred in the hypothetical absence of NIST's definitive method and the family of cholesterol SRMs.

Three large national independent clinical laboratories provided detailed survey responses. The three organizations responding control scores of individual laboratories across the U.S. and are responsible for a significant fraction of all cholesterol tests performed by independent clinically laboratories annually. Several hospital laboratory directors responded to surveys but since these could not be construed as a representative sample of all hospital laboratories, the quantitative analysis of costs and benefits presented below is not based on their responses.<sup>49</sup>

### 5.2 QUANTITATIVE FINDINGS

Survey respondents provided estimates of internal cost avoidance realized by their organizations due to the traceability of their products and services to the definitive method. Not

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<sup>49</sup> The impact of NIST's cholesterol standards program on POLs was not addressed for two reasons. First, the number of these organizations is very large and no comprehensive list could be identified. Second, in fact-finding interviews, measurement system manufacturers asserted that POL users typically lack the sophistication to adequately address the metrological issues associated with cholesterol testing and would, therefore, be unable to assess the role and impact of NIST's cholesterol SRMs.

all the manufacturing respondents currently use SRMs, but all recognized that in the absence of traceability to NIST they would have to incur additional costs.

The reported cost avoidance is of two kinds: production costs and transaction costs. In the hypothetical absence of NIST, manufacturers and clinical laboratories would incur additional operating costs in assigning, or validating, cholesterol concentration values to secondary or working calibration standards. Dispute resolution costs (transaction costs), born largely, but not solely, by the manufacturers when the measurement processes in clinical laboratory settings get out of control, would be higher if manufacturers could not trace their value assignments to NIST.

The sum of these “costs avoided” are interpreted as the benefits to society of NIST’s investment in the development and maintenance cholesterol SRMs and the definitive method that assures their accuracy.

### **5.3 QUALITATIVE FINDINGS**

Many industry respondents recognize the continuing importance of being traceable to NIST. According to a leading manufacturer,

Traceability to a higher order reference material is a fundamental expectation of customers worldwide. The availability of reference materials directly from NIST, for use in support of product calibration by the manufacturer of an [cholesterol measurement] system, adds a significant dimension of certainty to the process and ultimately to the value of our product. This added dimension of certainty ... facilitates the resolution of numerous potential problems and questions from customers when accuracy may be in question. This provides for more efficient problem resolution where the root causes may be related to operator protocols, or other system failure modes, independent of the underlying calibration.

According to a representative of one of the largest national independent testing laboratories, “standardization is used strategically to attract national contracts. It also enables better purchasing decisions.” While manufacturers and testing laboratories recognize the importance of traceability, relations between clinical laboratories (buyers) and manufacturers (suppliers) appear to have changed in complex ways.

Today not all laboratories have the capability to establish a reference material. Industry respondents point out that automation of the measurement process, as well as the long-term “de-skilling” of the clinical laboratory, has resulted in a situation where only relatively few commercial testing laboratories have the expertise to develop even a secondary reference material in the absence of commercially available standards traceable to NIST. According to one survey respondent, describing the changed environment within clinical laboratories, “we no longer have the time available to perform our own documentation.”

Independent testing laboratories have become “production operations.” While lead laboratories within a commercial laboratory network retain high-level measurement expertise, the experimental and research culture that used to characterize clinical testing is no longer typical. Coupled with the manufacturers’ drive to automate as many of the measurement functions as feasible, this de-skilling of the clinical laboratory appears to have shifted the locus of measurement expertise to the manufacturer.

Nevertheless, the large clinical laboratories have retained market power and use it effectively to influence the manufacturer’s quality control processes and costs. When measurement processes go out of control, clinical laboratories consider it the measurement system manufacturer’s responsibility to identify the problem and expend the resources to solve it. Not surprisingly, clinical laboratory representatives report that a primary criterion for instrument manufacturers is the maintenance of traceability to NIST.

Clinical laboratory representatives report both these trends are increasing laboratory reliance on “closed systems” in which instrument, reagents, calibrators, and controls are sold and assured only as a package or system. While some respondents continue to rely on “open” systems, the trend appears to be in the other direction. Industry representatives report that closed systems tend to obviate the direct need for NIST SRMs. In the words of one survey respondent, “instrument calibration has become more and more difficult for a clinical lab to change.” For these and other reasons, the College of American Pathologists is reported to have decided to discontinue the distribution of traceable cholesterol reference materials. Other survey

respondents describe a trend, here and abroad, away from standard *materials* and toward standard *methods*.

While it is difficult to say with certainty, it appears that the increasing pressure for cost-control in clinical laboratories, and the technological trends favoring “closed” cholesterol measurement systems, created an environment in which the CDC’s CRMLN program (certifying measurement systems against the reference method) has been “selected” (to use an evolutionary metaphor) over the more traditional reference material approach. CRMLN certification has become widely regarded as “good enough.”<sup>50</sup>

Of course this reference method is traceable to a NIST standard reference material and the definitive method. But, where manufacturers use the reference method, they are not relying directly on the NIST’s primary standards and are effectively satisfied with measurement results that are somewhat less accurate. In the words of one manufacturer,

The difference is that, whereas, in the past, we would have purchased the NIST material and standardized our systems ourselves, we now rely on CDC-certified labs to standardize sera for our standardization procedure. In this way, we maintain CDC certification of our systems for our customers to A-K [the Abell-Kendall measurement method — the reference method used by CDC’s CRMLN], but no longer standardize directly to the NIST material.

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<sup>50</sup> A representative of a cholesterol measurement system manufacturer explained that the company was under considerable pressure from the clinical laboratory (customer) community to become certified through the CRMLN even though the company’s technical staff felt that the NIST reference material approach was more appropriate than the reference method.

## 6. QUANTITATIVE ANALYSIS

### 6.1 COST AVOIDANCE BENEFITS

Whether they use SRMs directly or not, survey respondents recognize the value of having products traceable to NIST primary reference materials. They provided point estimates of additional costs that would be incurred in the hypothetical absence of NIST SRMs.<sup>51</sup> These “costs avoided” are of two kinds: internal production and quality control costs, and transaction costs. In Table 5 these two types of benefits are combined and projected back over the span of the study period. Projecting the point estimates of cost avoidance back in time results in a conservative estimate of the program’s impact. As explained above, it is believed that the time

**Table 5—Industry Cost Avoidance Benefits**

Year	Manufacturing Production Cost Avoidance (Current \$)*	Laboratory Operations Cost Avoidance (Current \$)	Transaction Cost Avoidance (Current \$)	Total Industry Benefits (Current \$)
1986	-	-	-	-
1987	-	-	-	-
1988	351,681	84,713	63,372	499,766
1989	366,159	88,200	65,981	520,341
1990	382,506	92,138	68,927	543,570
1991	397,451	95,738	71,620	564,809
1992	408,193	98,325	73,556	580,074
1993	418,935	100,913	75,492	595,339
1994	429,210	103,388	77,343	609,940
1995	439,018	105,750	79,110	623,878
1996	447,424	107,775	80,625	635,825
1997	455,364	109,688	82,056	647,108
1998	460,034	110,813	82,898	653,745
1999	467,040	112,500	84,160	663,700

\*The point estimates from the industry survey were converted into nominal dollars using the GDP Price Index (chain type), with 1999 as the reference year.

period studied is one in which the direct benefits of the cholesterol SRMs to industry has been declining, certainly harder to quantify. In other words, from the perspective of the program’s entire history, it is safe to surmise that these estimates are biased downward. Accordingly, had point estimates been obtained during the earlier part of the study period, and certainly if they had

<sup>51</sup> Respondents provided single point estimates for one year (1999).

been obtained for the preceding era (1967-1986), these estimates would have been higher, perhaps dramatically so.

### **6.1.1 Production Cost Avoidance**

Out of 17 manufacturers surveyed seven responded completely. Only five provided quantitative estimates of counterfactual cost avoidance benefits. The estimates ranged from \$6,500 per year to \$220,000, with a mean cost avoidance benefit of \$66,720. Since all seven respondents recognized NIST's value, the average annual benefit of \$66,720 is assigned to all seven for a total annual benefit of \$467,040.

Three independent national clinical laboratories and several hospital system laboratories were surveyed. Based only on the survey results from independent clinical laboratories the average annual cost avoidance per laboratory system is \$37,500. The annual cost avoidance estimate for the three large independent clinical labs is \$112,500.

### **6.1.2 Transaction Cost Avoidance**

Only one organization provided quantitative data allowing a quantitative estimate of transaction cost savings. Absent NIST traceable standards, according to the respondent, laboratory personnel would spend considerably more time engaged in trouble-shooting activities. The estimated saving per laboratory, per month, between 1990 and 2000 is 2hrs. Based on data provided by respondents we estimate the average hourly burdened rate of a person engaged in trouble-shooting activities between laboratories and manufacturers to be \$21.92. Therefore, the estimated transaction cost savings to a clinical lab is \$43.84 per month or \$526 per year. The independent laboratories surveyed manage approximately 80 laboratories of the type where this kind of trouble-shooting for cholesterol tests would occur. Transaction cost savings due to the availability of NIST traceable standards is therefore estimated to be \$42,080 per year for the three independent laboratory systems surveyed. Doubling this figure to account for similar savings on the manufacturers' side of the trouble-shooting transaction results in a total annual transaction cost savings attributable to NIST traceability of \$84,160.

The total estimated annual counterfactual cost saving (benefits) attributable to NIST traceability is \$663,700.<sup>52</sup> We project the benefits back to 1988 which was the year of the first sale of an SRM series (the SRM 911b series) certified by means of the upgraded IDMS system. The reader will recall that it was the investment of substantial fixed costs in the upgrading of NIST's mass spectrometer apparatus that determined the start date (1986) for this impact assessment. Cholesterol SRMs have been available since 1967.

## 6.2 NIST EXPENDITURES

The costs associated with the development and distribution of the cholesterol SRMs that are the focus of this impact assessment were derived from data provided by CSTL concerning SRM sales and their distribution over time, as well as one-time equipment costs, incurred when NIST renovated the IDSM process in, as well "other agency" cost incurred by the College of American Pathologists (CAP) in support of the certification of some of the SRMs as several investments made by according to procedures developed by NIST's Program Office, Strategic Planning and Economic Analysis Group. Table 6 presents these costs over the course of the study period.

These costs are comprised of development costs, production costs, and overhead costs. They are derived from SRM unit price and yearly sales data except where organizations outside NIST contributed resources. For several years the CAP-funded NIST's SRM development and production activities. These costs are included in the costs represented in Table 6.<sup>53</sup>

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<sup>52</sup> \$467,040 (manufacturers internal process cost avoidance) + \$112,500 (dominant independent clinical labs' internal process cost avoidance) + \$84,160 (transaction cost savings to independent labs and their measurement system suppliers).

<sup>53</sup> While the detail is not shown here, no production or overhead costs were recorded prior to 1989. Production costs for 1986 and 1987 are excluded because certification of the SRMs placed in inventory in those years occurred prior to 1986. No overhead costs are shown for 1986 and 1987 since the SRMs sold in those years were developed prior to 1986. The College of American Pathologists contributed ~\$150,000 (FY1999) over the course of the study period for the development and production of SRMs: \$70,000 (1986); and \$20,000 per year (1988, 1990, 1995, and 1996).

**Table 6—Cholesterol SRM Program Costs**

Year	NIST Costs (Current \$)
1986	101,000
1987	-
1988	80,600
1989	70,600
1990	79,900
1991	127,000
1992	119,800
1993	77,200
1994	134,777
1995	155,575
1996	351,752
1997	132,700
1998	40,247
1999	52,249

**6.3 MEASURES OF ECONOMIC IMPACT**

Table 7 transforms the “current” costs and benefits reported in Tables 5 and 6 into a time series of constant 1999 dollars that provides the basis for the summary economic impact

**Table 7—Constant 1999 Dollar Benefits and Costs (1986-1999) \***

Year	Benefits (Constant 1999 Dollars)	Costs (Constant 1999 Dollars)	Net Benefits (Constant 1999 Dollars)
1986	-	143,466	(143,466)
1987	-	0	0
1988	663,700	106,976	556,724
1989	663,700	90,095	573,605
1990	663,700	97,546	566,154
1991	663,700	149,196	514,504
1992	663,700	137,063	526,637
1993	663,700	86,115	577,585
1994	663,700	146,656	517,044
1995	663,700	165,505	498,195
1996	663,700	367,173	296,527
1997	663,700	136,103	527,597
1998	663,700	40,860	622,840
1999	663,700	52,249	611,451

\* The deflator used to convert current to constant dollars is the Gross Domestic Product Price Index (chain-type).

estimates reported below: social rate of return (SRR), net present value (NPV) and, and benefit-to-cost ratio (B/C).<sup>54</sup> (For a discussion of these metrics see Appendix B.)

Estimates of economic impact metrics for NIST's cholesterol standard reference material program are displayed in Table 8. They are characterized as "lower-bound" estimates because they have a conservative, downward bias. There are two primary reasons for this bias. First, the time period studied appears to be one in which NIST's role had begun to change such that fewer users purchased SRMs directly. They increasingly relied, instead, on the NIST-anchored CDC laboratory network program. The absence of appropriate historical records and the limited memories of participants make it difficult to assess programs with histories stretching back more than 30 years. Second, no attempt was made to scale the survey results to the entire population of beneficiaries because the information concerning the structure of the population of clinical laboratories — especially hospital clinical laboratories and physician office laboratories — could not be ascertained within the resources available.

**Table 8—Lower-Bound Estimates of Economic Impact (1986–1999)**

Performance Metric	Lower-Bound Estimate
Net Present Value (1999 dollars)	\$3,570,000
Social Rate of Return	154%
Benefit-to-Cost Ratio (1999 dollars)	4.47

Despite methodological choices that bias the economic impact metrics in a downward direction, the results of the preceding analysis indicate that NIST has played an important and appropriate economic role in supporting the national effort to monitor, measure, and control cholesterol levels. The reported SRR is very close to the average return (159%) estimated for all other quantitative assessments of NIST infratechnology programs.<sup>55</sup>

<sup>54</sup> The deflator used to convert current to constant dollars is the Gross Domestic Product Price Index (chain-type).

<sup>55</sup> This average is based on 19 impact assessments. See, <http://www.nist.gov/director/planning/studies.htm>, August 1, 2000.

## APPENDIX A: WHAT IS CHOLESTEROL?<sup>56</sup>

Cholesterol is a soft, waxy substance found in the bloodstream and in all the body's cells. It is an important part of a healthy body because it is used to form cell membranes, some hormones and other needed tissues. But a high level of cholesterol in the blood—hypercholesterolemia—presents a major risk factor for heart attacks and strokes (cardiovascular disease—CVD).

Cholesterol comes from two sources. It is produced by the body, mostly in the liver (about 1,000 milligrams a day). It is also found in foods that come from animals, such as meats, poultry, fish, seafood and dairy products. Foods from plants (fruits, vegetables, grains, nuts and seeds) do not contain cholesterol.

Cholesterol and other fats cannot dissolve in the blood. They have to be transported to and from the cells by special carriers of lipids and proteins called lipoproteins. There are three classes of these lipoproteins: low-density lipoproteins (LDLs), very low-density lipoproteins (VLDLs), and high-density lipoproteins (HDLs). Cholesterol is a constituent of each of these classes of lipoprotein and is chemically “available,” i.e., measurable, differently for each. LDLs and HDLs are our chief concerns.

LDL is the major cholesterol carrier in the blood. When a person has too much LDL cholesterol circulating in the blood, it can slowly build up within the walls of the arteries feeding the heart and brain. Together with other substances it can form plaque, a thick, hard deposit that can clog those arteries. This condition is known as atherosclerosis. The formation of a clot (or thrombus) in the region of this plaque can block the flow of blood to part of the heart muscle and cause a heart attack. If a clot blocks the flow of blood to part of the brain, the result is a stroke. A high level of LDL cholesterol reflects an increased risk of heart disease. That is why LDL cholesterol is often called "bad" cholesterol.

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<sup>56</sup> American Heart Association; [http://www.amhrt.org/Heart\\_and\\_Stroke\\_A\\_Z\\_Guide/ncep.html](http://www.amhrt.org/Heart_and_Stroke_A_Z_Guide/ncep.html)

About one-third to one-fourth of blood cholesterol is carried by HDLs. Medical experts think HDL tends to carry cholesterol away from the arteries and back to the liver, where it is passed from the body. Some experts believe HDL removes excess cholesterol from atherosclerotic plaques and thus slows their growth. HDL is known as "good" cholesterol because a high level of HDL seems to protect against heart attack. The opposite is also true: a low HDL level indicates a greater risk.

One of the most important means of minimizing the risks of heart attacks and heart disease is maintaining desirable cholesterol levels in the bloodstream, as shown in Table A-1.<sup>57</sup> Typically, a healthy adult should attempt to maintain cholesterol levels less than 200 mg/dL (milligrams per deciliter) through proper diet, regular exercise and, if necessary, prescription treatment. A cholesterol level of 200-239 is generally considered to be worthy of monitoring. While not in a high-risk zone, it approaches what most physicians consider worrisome levels. Individuals with cholesterol levels above 240 generally have a higher risk of heart attack or heart disease.

**Table A-1—Cholesterol Blood Level Thresholds**

<b>Cholesterol Type</b>	<b>Desirable</b>	<b>Borderline High Risk for CVD</b>	<b>High Risk for CVD</b>
<b>Total Cholesterol</b>	< 200 mg/dL	200-239 mg/dL	240 mg/dL
<b>LDL Cholesterol</b>	< 130 mg/dL	130-159 mg/dL	160 mg/dL
<b>HDL Cholesterol</b>	> 60 mg/dL	-	< 35 mg/dL

<sup>57</sup> Ernst Schaefer and Judith McNamara, "Overview of the Diagnosis and Treatment of Lipid Disorders," in Nader Rifai, et al., *Handbook of Lipoprotein Testing*, AACC Press, 1997, p. 29.

## APPENDIX B: MEASURES OF ECONOMIC IMPACT<sup>58</sup>

Economists and business analysts use a number of measures to estimate the economic impact of science and technology projects. The most accurate employ the “net present value” concept whereby the value of a times series of net benefits (benefits minus cost) from an investment project (projected or realized) are adjusted to their “present” value by means of a “discount” rate.<sup>59</sup> The three metrics used to characterize the economic impact of NIST’s investments in this report are: net present value (NPV), social rate of return (SRR), and benefit-to-cost ratio (B/C).

**Net Present Value (NPV).** NPV is the value of projected or realized series of net benefits stated in “present” or “current” dollars. The adjustment of the net benefits for each period in a time series is accomplished by a discount rate reflecting the return that could have been earned on the money invested the project being evaluated. Mathematically,

$$NPV = \sum_{t=0}^{t=n} (B_t - C_t) / (1 + i)^t$$

where  $(B_t - C_t)$  represents the net benefits associated with the project in year  $t$  and “ $i$ ” is the value of the discount rate.

**Social rate of return (SRR)** SRR is the value of the discount rate,  $i$ , that equates the net present value (NPV) of a stream of net benefits associated with a research project to zero. Mathematically,

$$NPV = [(B_0 - C_0) / (1 + i)^0] + \dots + [(B_n - C_n) / (1 + i)^n] = 0$$

where  $(B_t - C_t)$  represents the net benefits associated with the project in year  $t$ , and  $n$  represents the number of time periods (years in most cases) being considered in the evaluation.

This measure is more commonly referred to as the internal rate of return (IRR) and used to measure relative impact of a private firm’s investment projects. Because the benefits of

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<sup>58</sup> Unless otherwise indicated, the following characterization of economic impact metrics follows closely the discussion of Albert N. Link and John T. Scott, *Public Accountability: Evaluating Technology-Based Institutions* (Boston: Kluwer Academic Publishers) 1998.

<sup>59</sup> Gregory Tasse, *Rates of Return from Investments in Technology Infrastructure*, NIST Planning Report 96-3,

NIST's investments accrue to a large number of organizations, and these benefits are used to calculate the economic impact of public investments, this traditional financial metric has been called the social rate of return.<sup>60</sup>

The time series for calculating the SRR runs from the beginning of the research project,  $t = 0$ , to a milestone terminal point,  $t = n$ . Net benefits refer to total benefits (B) less total costs (C) in each time period. For unique solutions of  $i$ , in the equation directly above, the SRR can be compared to a value  $r$  that represents the opportunity cost of funds invested by the technology-based public institution. Thus, if the opportunity cost of funds is less than the internal rate of return, the project was worthwhile from an *ex post* social perspective.

**Benefit-to-cost ratio.** The ratio of benefits-to-costs is the ratio of the present value of all measured benefits to the present value of all costs. Both benefits and costs are referenced to the initial time period,  $t = 0$ , as:

$$B / C = [ \sum_{t=0 \text{ to } t=n} B_t / (1 + r)^t ] / [ \sum_{t=0 \text{ to } t=n} C_t / (1 + r)^t ]$$

A benefit-to-cost ratio of 1 implies that the project is a break-even project. Any project with  $B / C > 1$  is a relatively successful project. Furthermore, the information developed to determine the benefit-to-cost ratio can be used to determine net present value for each of several projects, allowing in principle one means of prioritizing projects *ex post*.

Fundamental to implementing the ratio of benefits-to-costs is a value for the discount rate,  $i$ . The calculated metrics, above, approximate the opportunity cost of public funds by following the guidelines set forth by the Office of Management and Budget (OMB) in Circular Number A-94, which states:

Constant-dollar benefit-cost analyses of proposed investments and regulations should report net present value and other outcomes determined using a real discount rate of 7 percent.

That procedure was followed in developing the economic impact estimates for this report.

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June 1996.  
<sup>60</sup> Gregory Tasse, *Rates of Return From Investments in Technology Infrastructure*, NIST Planning Report 96-3, June 1996.