17th Meeting of Secretary's Advisory Committee on Genetics, Health and Society December 1, 2008

"Clinical Diagnostics Standards Development at NIST"

Willie E. May, Director
Chemical Science and Technology Laboratory
Leader, Bioscience Strategic Planning Team

Topics

- NBS → NIST
  - Basic Mission and evolving areas of focus
- Why NIST and Biocience and Health?
- Current Portfolio of Activities in Bioscience and Health
- Connections and linkages to the International Measurement Standards Community

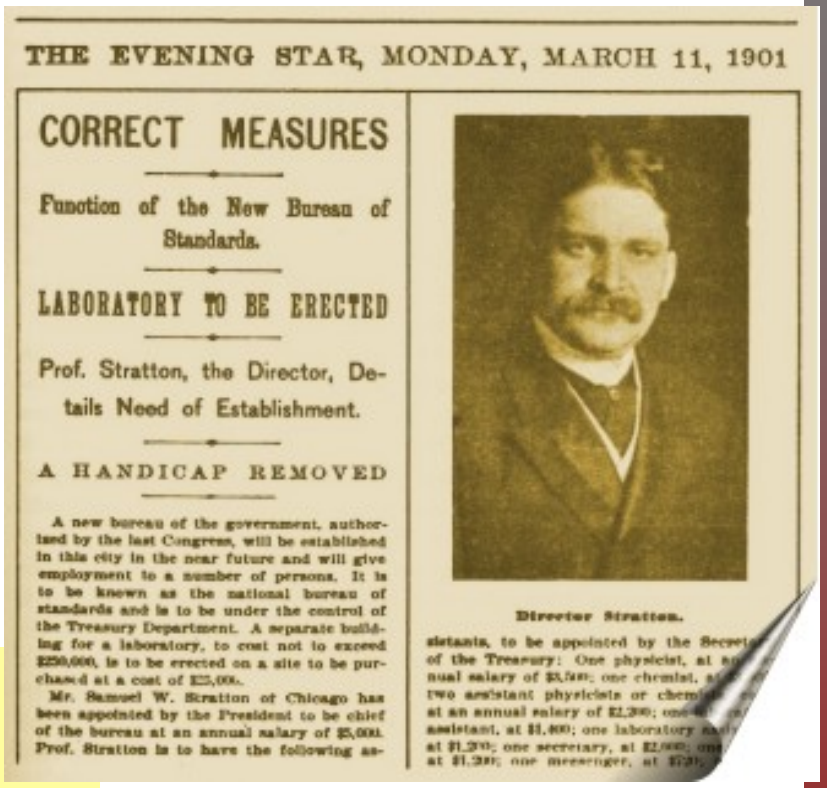
NIST (NBS) established in 1901

"It is therefore the unanimous opinion of your committee that no more essential aid could be given to

- **manufacturing**
- **commerce**
- **the makers of scientific apparatus**
- **the scientific work of Government**
- **schools, colleges, and universities**

than by the establishment of the institution proposed in this bill."

House Committee on Coinage, Weights and Measures ...
May 3, 1900
on the establishment of the National Bureau of Standards (now NIST)



THE EVENING STAR, MONDAY, MARCH 11, 1901

CORRECT MEASURES

Function of the New Bureau of Standards.

LABORATORY TO BE ERECTED

Prof. Stratton, the Director, Details Need of Establishment.

A HANDICAP REMOVED

A new bureau of the government, authorized by the last Congress, will be established in this city in the near future and will give employment to a number of persons. It is to be known as the national bureau of standards and is to be under the control of the Treasury Department. A separate building for a laboratory, to cost not to exceed $250,000, is to be erected on a site to be purchased at a cost of $25,000.

Mr. Samuel W. Stratton of Chicago has been appointed by the President to be chief of the bureau at an annual salary of $5,000. Prof. Stratton is to have the following as-

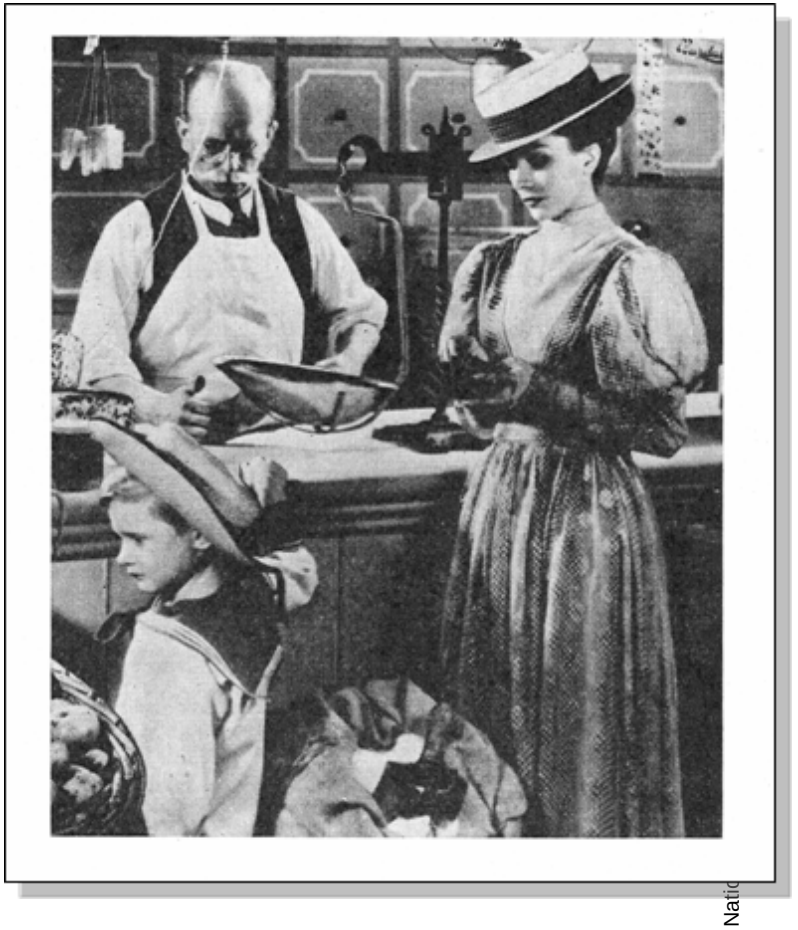
Director Stratton.

sistants, to be appointed by the Secret... of the Treasury: One physicist, at ... nual salary of $3,500; one chemist, a... two assistant physicists or chemi... at an annual salary of $1,200; one ... assistant, at $1,400; one laboratory ... at $1,200; one secretary, at $2,000; one ... at $1,200; one messenger, at $720;

Early Drivers for NBS Activities

Measurements and Standards to support industrial revolution

- construction materials uneven in quality and unreliable
- Eight different “authoritative” values for the gallon
- Nascent electrical industry needed standards
- 50% of scales, 20% of weights, 50% of dry measures, and 25% of liquid measures were in significant error in favor of the shopkeepers.
- Chemical composition standards and dimensional metrology needed to support railway system

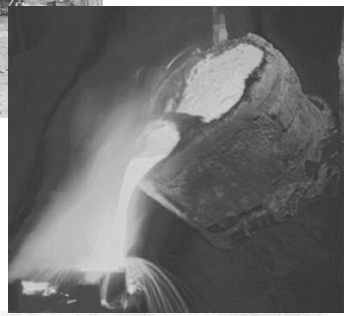


U.S. instruments had to be sent abroad for calibration

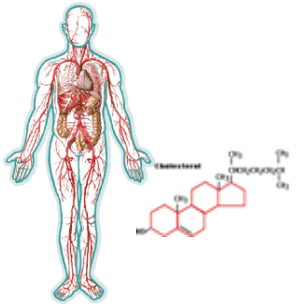
NBS Organic Act of 1901

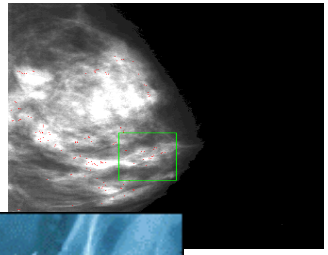
- **Custody of the standards**;
- **Comparison of the standards** used in scientific investigations, engineering, manufacturing, commerce, and educational institutions with the standards adopted by or recognized by the Government;
- **Construction of standards**, their multiples and subdivisions;
- **Testing and calibration** of standard measuring apparatus;
- **Solution of standards problems**; and,
- **Determination of physical constants and the properties of materials,** when such data are of great importance and are not to be obtained of sufficient accuracy elsewhere.

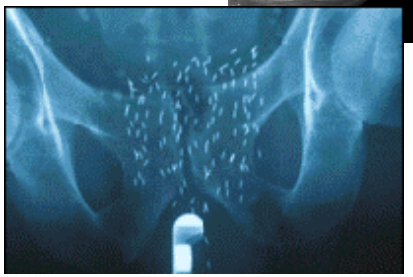
Since its inception NBS/NIST has focused its research and measurement services activities on contemporary societal needs.



1901 2008







NIST Today

Major Assets

- ~ 2,900 employees
- ~ 2600 associates and facilities users
- ~ 1,600 field staff in partner organizations
- ~ 400 NIST staff on about 1,000 national and international standards committees

Courtesy HDR Architecture, Inc./Steve Hall © Hedrich Blessing

Major Programs

- **NIST Laboratories**
- Baldrige National Quality Program
- Hollings Manufacturing Extension Partnership
- Technology Innovation Program

Joint NIST/University Institutes:

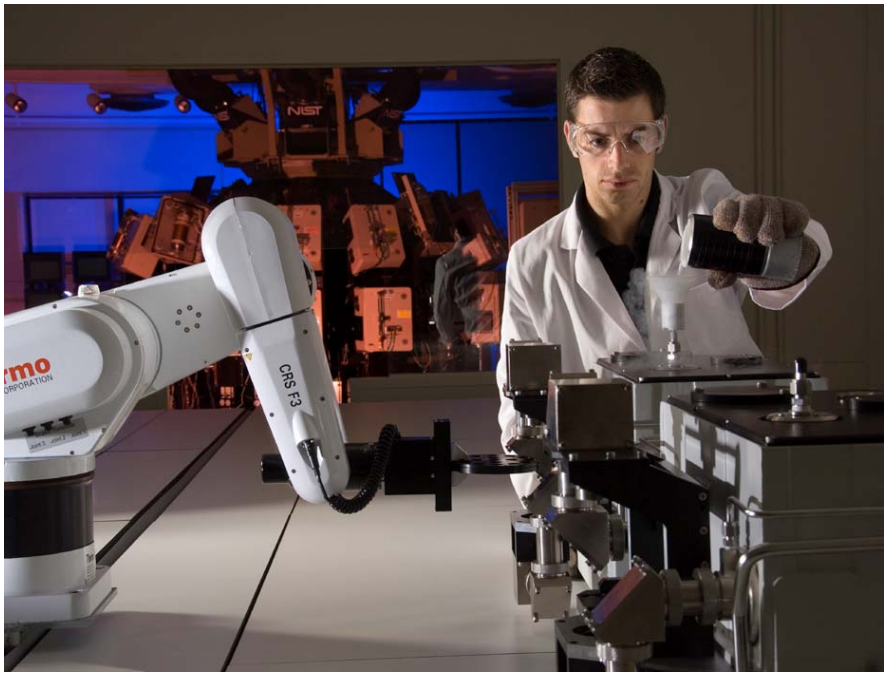
- JILA
- JQI
- CARB
- HML

NIST Mission Today

To promote U.S. innovation and industrial competitiveness by advancing

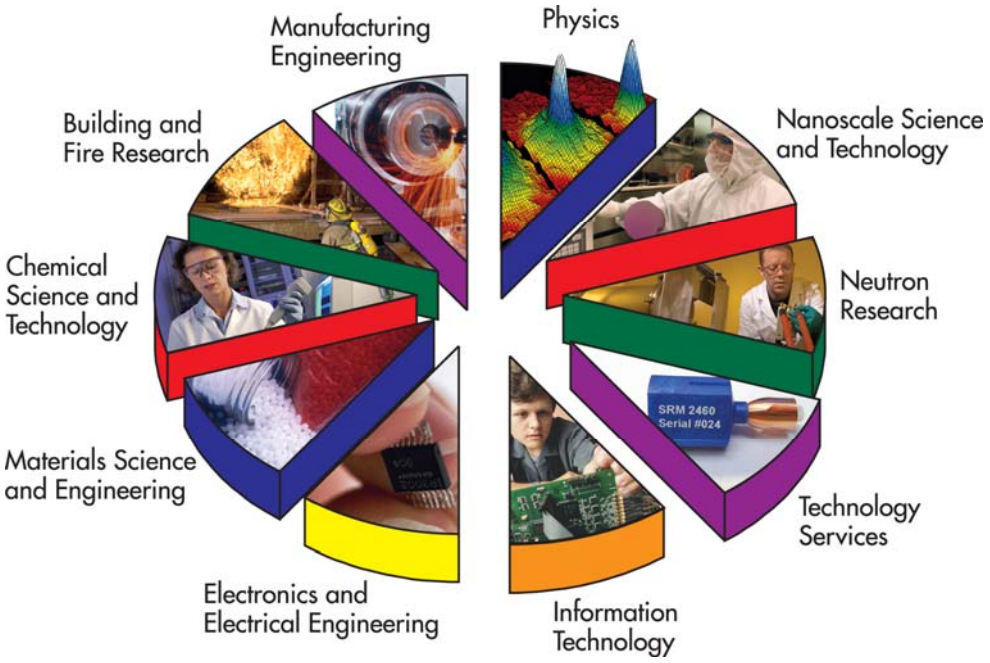
- measurement science,
- standards, and
- technology

in ways that enhance economic security and improve our quality of life



©Robert Rathe

The NIST Laboratories – serve as the ultimate reference point for measurements, standards, and technology research for the U.S. to support industry, science, health, safety, and national defense



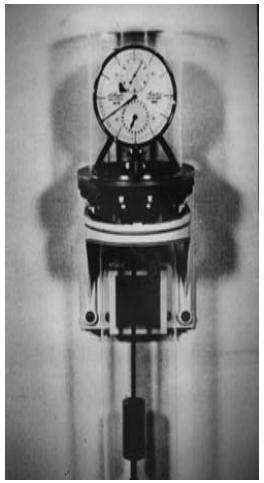
NIST traditionally has focused its research and measurement service activities on the physical science and engineering disciplines

Seven SI base units:

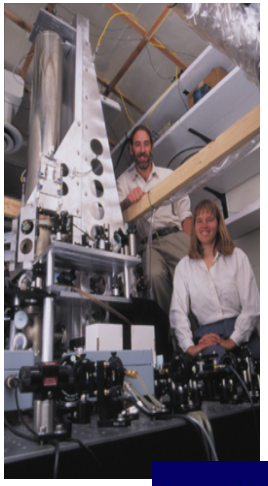
Quantity	*SI Base Unit*	*Definition*
length	meter (m)	distance traveled by light in a vacuum in 1/299792458 of a second
mass	kilogram (kg)	mass of a platinum/iridium cylinder kept in Paris
time	second (s)	time required for 9,192,631,770 cycles of the 3.26 cm microwave line of cesium-133.
temperature	kelvin (K)	273.16 degree K is assigned to the triple point of water (where vapor, liquid, and ice are at equilibrium)
electric current	ampere (A)	amount of current flowing through each of two long parallel wires separated by 1 m that results in a force of 0.2 micronewtons per meter along the wires
luminous intensity	candela (cd)	luminous intensity of 1/600000 m2 of a radiating cavity at the melting point of platinum (2042 K)
amount of substance	mole (mol)	amount of substance that contains the same number of particles as the number of atoms in a sample of pure carbon-12 weighing exactly 12 g

NIST still fulfills the NBS traditional function:
the development & dissemination of primary standards

pendulum clock
1 s in 3 years
(1904)

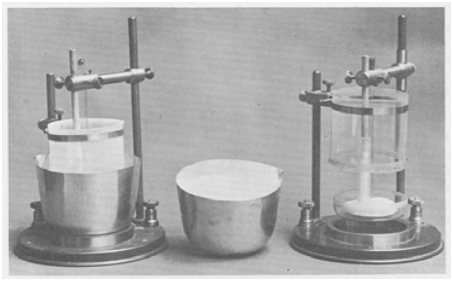


second

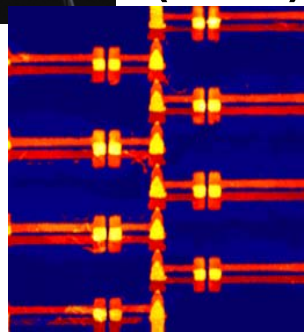


NIST F1
atomic clock
1 s in 30 million
years
(1999)

silver voltameter
current standard
(1910)

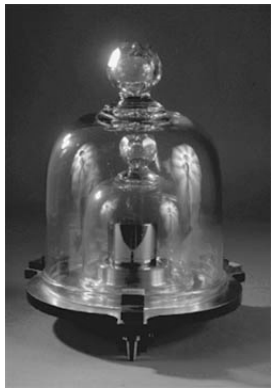


ampere



single
electron
counter
(20xx)

physical artifact
(1889)

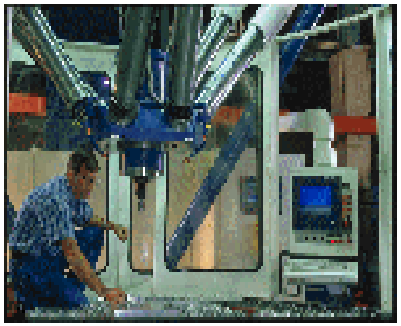


kilogram

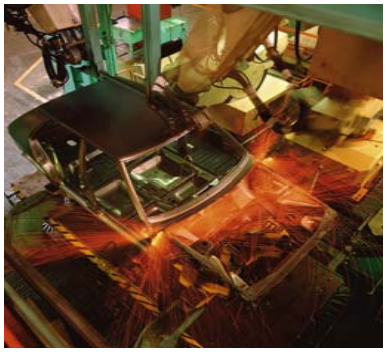
electronic
kilogram
(20xx)

. . . we also serve a much broader customer base …
with constantly changing measurement and standards needs

Environmental Technologies



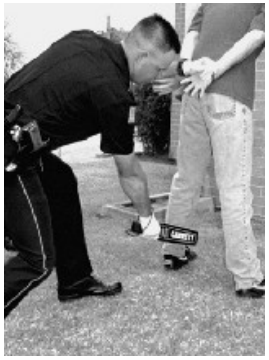
Manufacturing



Transportation

Pharmaceuticals

Food and nutrition



Law enforcement

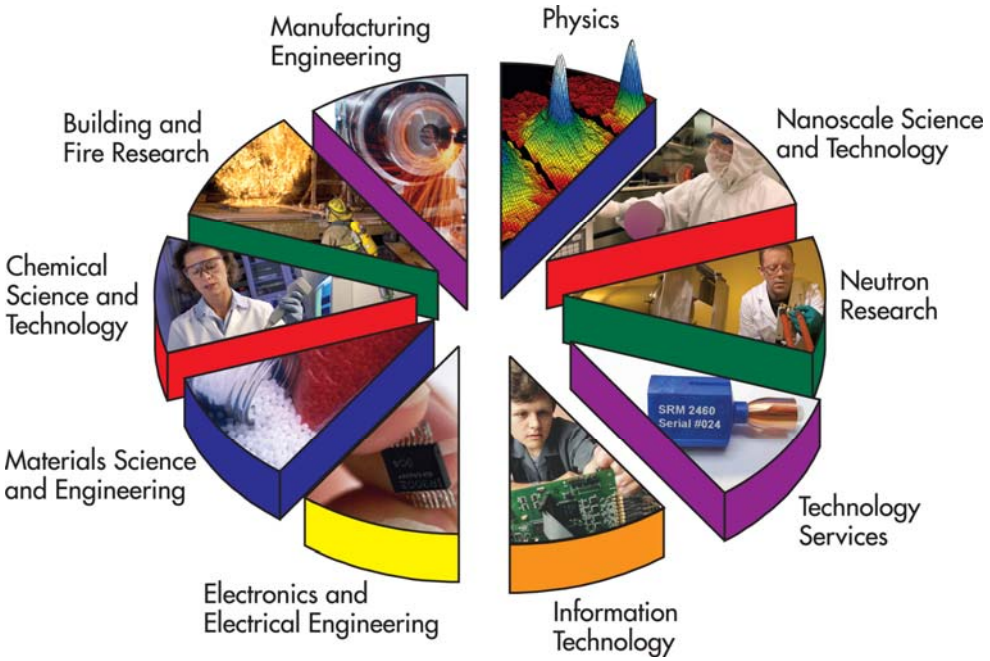
Biotechnology

Computer software and equipment

Construction

Microelectronics

The NIST Laboratories – serve as the ultimate reference point for measurements, standards, and technology research for the U.S. to support industry, science, health, safety, and national defense



NIST traditionally has focused its research and measurement service activities on the physical science and engineering disciplines

"Bioscience and Health" has now been identified as an area for significant emphasis and growth

Why NIST and the Biosciences?

It is **congruent with our mission, and indeed our mandate**, to support U.S. industry and other stakeholders in overcoming measurement and standards-related challenges in the biosciences

by leveraging our vast multidisciplinary expertise in the quantitative physical, chemical and informational sciences

- to provide the measurement infrastructure to provide **confidence in the results from measurements** of complex biological systems

Which will

- **enable** - - and facilitate realization of optimal economic and broad societal benefits from - - new **innovation**s

Why NIST and the Biosciences?

Administration Input

Understanding Complex Biological Systems

*"Agencies should target investments toward the development of a deeper **understanding of complex biological systems** through collaborations among physical, computational, behavioral, social and biological researchers and engineers, who will, among other things, need to develop the data management tools and platforms necessary to facilitate this research."*

John H. Marburger III, Director, Office of Science and Technology Policy

Rob Portman, Director, Office of Management and Budget, June 23, 2006

Other Agency Input

Proteomics Today – The Problem

*"In order for proteomics to be accepted as a valid science in clinical medicine, it is vital that the experimental results be reliable and reproducible within the scientific community. **The absence of these standards… is a barrier to innovation**… and …delays the discovery and transfer of proteomic technologies into clinical applications."*

Anna Barker, Deputy Director, NCI, 2007

Why NIST and the Biosciences?

VCAT Input

"Consider radical changes to how it (NIST) supports the biotechnology and health care industries"

Dr. Thomas M. Baer, Executive Director,
Stanford Photonics Research Center, Stanford University
NIST VCAT Meeting, June, 2006

"Provide measurements and standards to support next-generation clinical diagnostics

- *Technologies for detection organ-specific proteins in blood – e.g., global proteomics, microfluidics, and nanotechnology measurement technologies*
- *Single cell analyses*
- *Technologies for the capture, storage, analysis, integration, and modeling of global data sets"*

Dr. Leroy Hood, President, Institute for Systems Biology
NIST VCAT Meeting, September, 2006

Early Bioscience Activities Focused on Healthcare

1920's – Today: Collaboration between NIST & the American Dental Association

- Led to, among other things, the development of polymer composite dental fillings and the air-driven turbine drill now found in virtually all dentist offices.

1920's – Today: Program in Radiation Physics

- initially focused on dosimetry standards for X-ray calibration
- now includes standards for mammography, brachytherapy, and radionuclides for radiopharmaceuticals

1970's – Today: Standards for Clinical Diagnostics

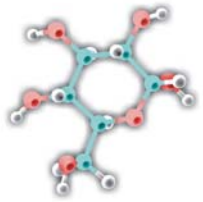
- Primary references for electrolytes and metabolites
- Serum based standards for electrolytes and metabolites
- New protein, peptide or DNA-based biomarkers

NIST has maintained Standards for several Health Status Markers for over 25-years

Reference Systems are Currently in Place for Many Well-Defined Markers that are:

- **Relatively small well-defined molecular or elemental species**
- **Typically, can be determined using well-established ID/MS –based methodology**

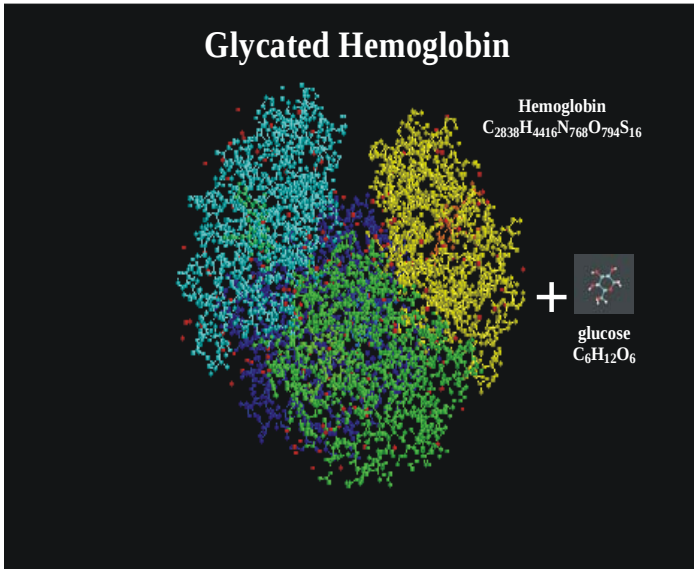
Marker	*Disease State*
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout
Vitamins	Nutrition Status



Glucose

Reference Systems Being Developed for New BioMarkers

Marker	Disease State
Troponin-I	Myocardial Infarction
C-Reactive Protein	Risk of Heart Attack
Homocysteine	Risk of Heart Disease
Glycated Hemoglobin	Diabetes Status
T3, T4 and TSH	Thyroid Function
Speciated Iron	Hemochromatosis
PSA	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Folates	Neural Tube Defects
HER2	Breast Cancer
Fragile X	Mental Retardation



Drivers for NIST Activities:

- Standardization necessary before full medical diagnostic benefit can be realized
- IVD Industry needs
- Well-articulated US "Other-Agency" Needs (FDA, NCI, CDC etc)

Snapshot of NIST's Current Investment in the Biosciences

Includes: appropriated funds, funding from other agencies, reimbursable funds (from provision of Standard Reference Materials, Calibration and Reference Data services), etc.

	Healthcare																
	Diagnostics	Drugs/Pharmaceuticals	Therapeutics (Non-drug)	Medical devices (non-diagnostic)	Bioenergy	Biomanufacturing (non-medical)	Food Safety/ Nutrition/Cosmetics	Environmental	Homeland Security/ Forensics/ Human Identity Testing	Life Sciences Research	Bioinformatics	Nano EHS	Biometrics	Health Care IT	Other bio	NIST Labs Bio Subtotal $K	NIST Labs Subtotal Without Biometrics and HC IT
NIST Laboratories: FY08 Total by Category	**$19,082**	**$2,773**	**$3,696**	**$2,516**	**$2,894**	**$1,234**	**$2,494**	**$3,355**	**$4,682**	**$4,880**	**$1,244**	**$2,604**	**$10,193**	**$3,990**	**$2,704**	***$68,339***	***$54,157***
STRS (appropriated funds)	**14,966**	**1,274**	**1,411**	**2,141**	**2,588**	**1,216**	**446**	**2,648**	**1,215**	**3,999**	**1,244**	**2,519**	1,375	2,022	**2,624**	***41,688***	***38,291***
SRM Production (reimbursable)	654	0	0	0	200	0	174	85	0	0	0	45	0	0	0	***1,158***	***$1,158***
Other Agency/ Non-Fed Govt/CRADA	2,120	1,147	1,708	313	25	0	1,076	352	2,237	157	0	0	8,818	1,967	80	***20,000***	***$9,214***
Other Reimbursable	1,343	352	576	62	81	18	798	270	1,231	7	0	32	0	0	0	***4,769***	***$4,769***
Special Invested Equipment Allocation from Initiative	0	0	0	0	0	0	0	0	0	717	0	8	0	0	0	***725***	***$725***

Health Care

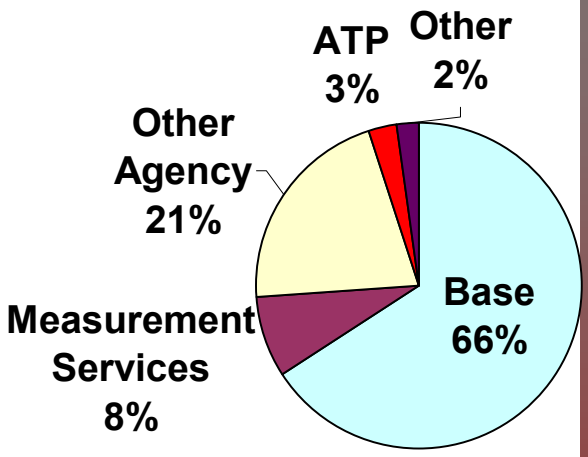
Includes:

Diagnostics and Therapeutics

- **Standards for Clinical Diagnostics**
- Standards for Clinical Proteomics
- Cellular Biometrology
- Metrology for Gene Expression
- Measurements and Standards for Cancer Biomarker Discovery
- DNA Damage and Repair Investigations
- **Standards for Medical Imaging**
- Measurements and Standards for Ionizing Radiation Applications

Drug Development

- Radioactivity Standards and Source Testing
- Ultrafast spectroscopy of proteins



Medical Devices

- Documentary and reference standards for reliability testing of active implantable medical devices and for reduction of uncertainty in bone densitometry.
- Growth and manipulation of nanowires for nanolaser medical applications
- Biological microfluidics;
- Dosimetry Calibration Service

Not totally inclusive of all info in database

The typical role of an NMI is to establish and maintain:

Scientifically-Sound, Metrologically-Based Competencies and Measurement Capabilities that are internationally Vetted and Recognized

To provide calibration and measurement services disseminated to Customers via mechanisms such as:

– Validated Reference Methods
– Certified Reference Materials
– Reference Data
– Value-assignment of customer-provided samples or materials
– Value-assignment of Proficiency Testing samples
– Measurement Services for other Government Agencies
– Etc.

CIPM Mutual Recognition Arrangement

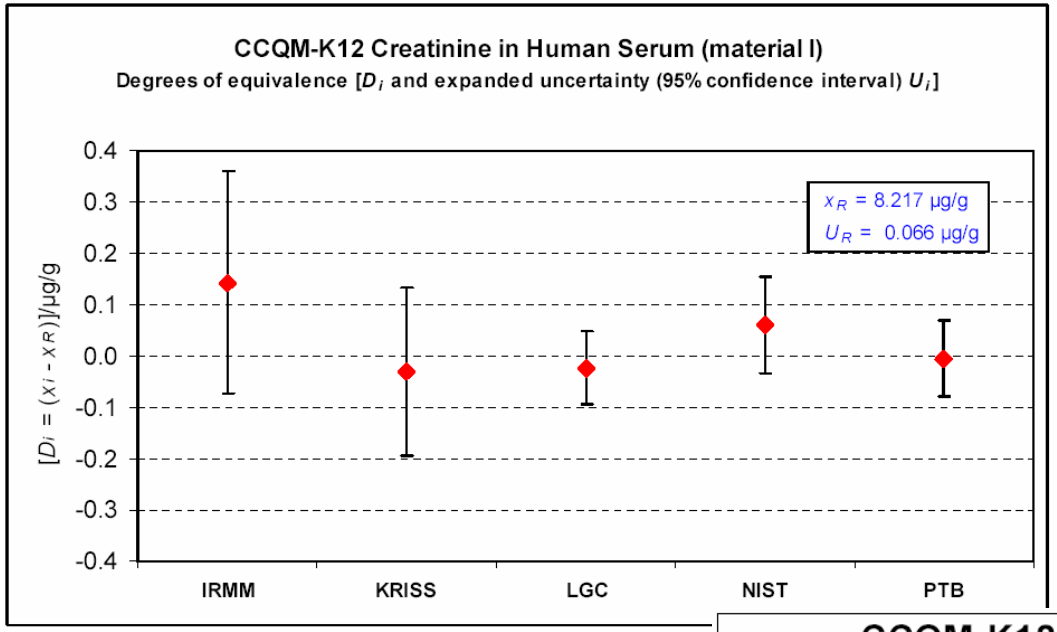
… was established in 1999 in response to a growing need for an open, transparent and comprehensive scheme to give users reliable quantitative information on the comparability of national metrology services and to provide the technical basis for wider agreements negotiated for international trade, commerce and regulatory affairs.

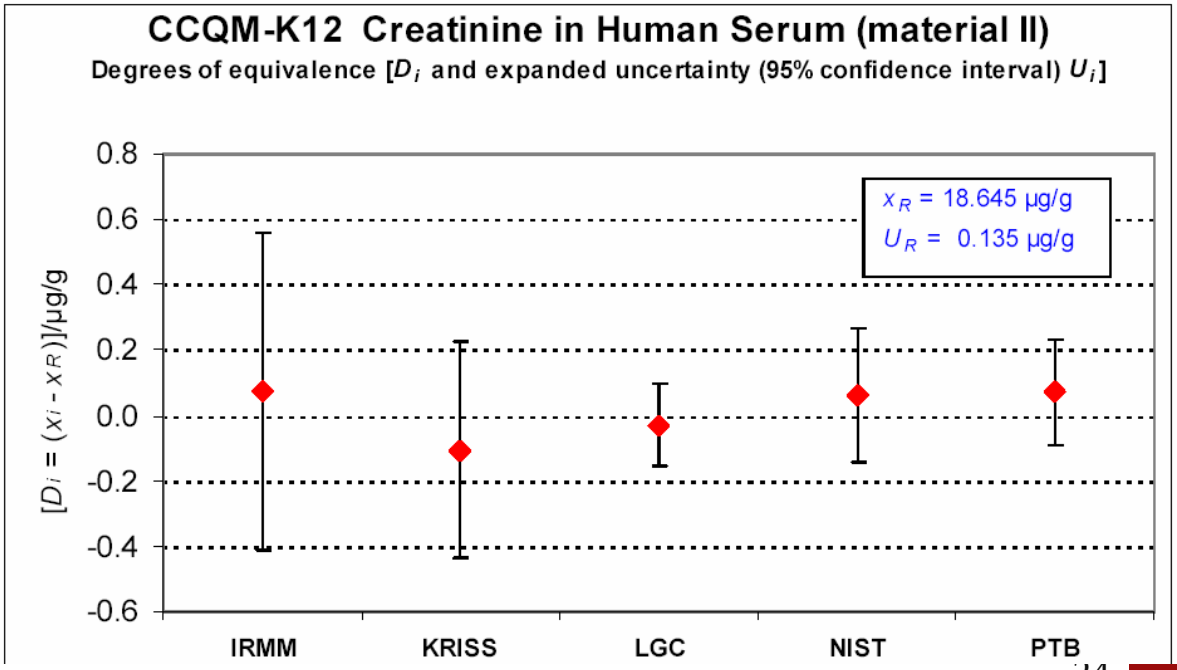
Requires that all Signatories:

1. **Declare and document their calibration and measurement capabilities (CMCs)**
2. **Provide evidence of *successful* participation in formal, *relevant* international comparisons**
3. **Maintain a system for assuring quality of measurement services delivered to customers**

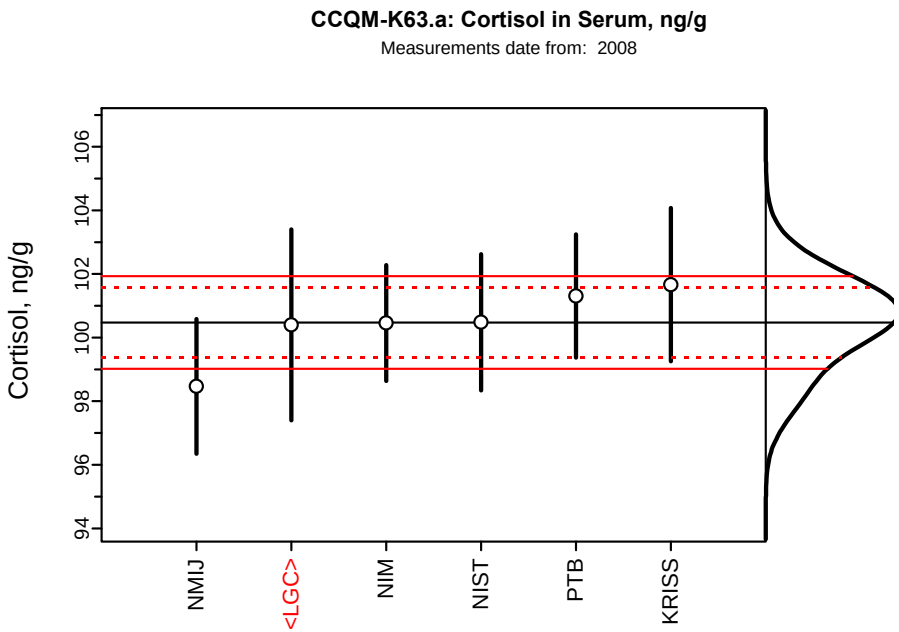
The MRA has now been signed by about 200 NMIs/DIs

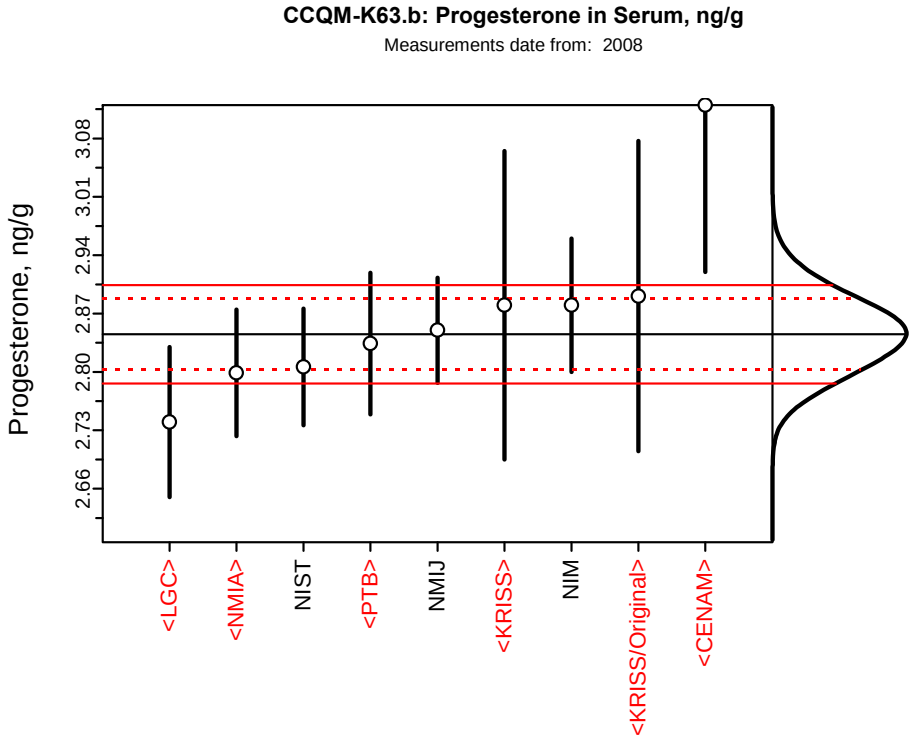
CCQM- K12 Creatinine in Serum Study Period: 2000-2001





CCQM-K63.a,b: Non-Peptide Hormones in Serum: Cortisol and Progesterone





Requirement of EC-IVD Directive Annex 1 (3)

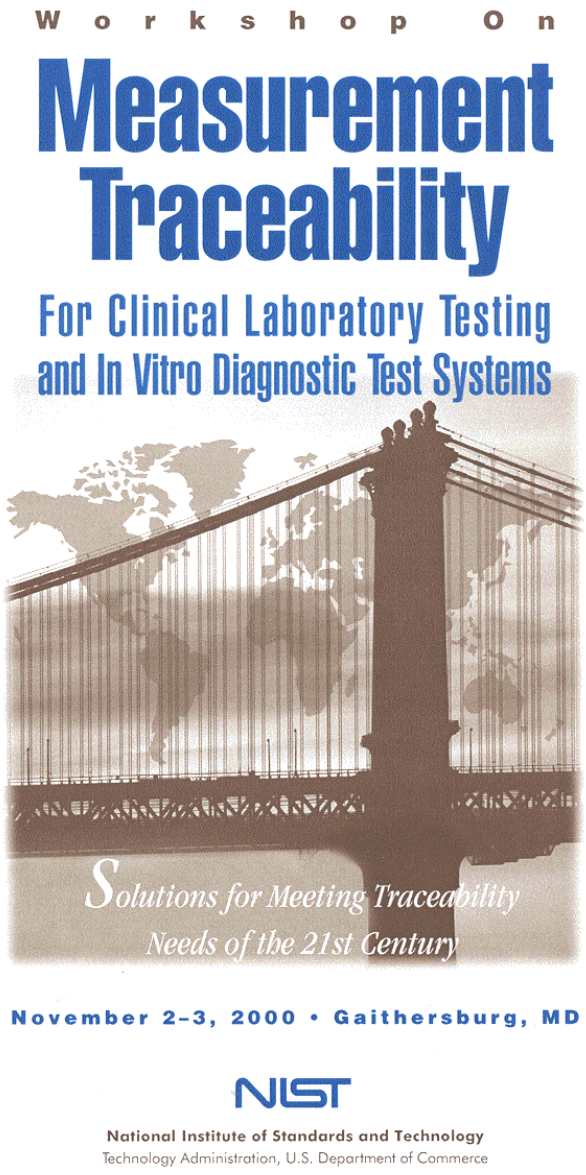
"The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order."

"Aim of the IVD Directive"

"to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels attributed to them by their manufacturer. "

US IVD Manufacturers requested that NIST and other NMIs develop reference materials and measurement procedures to assist them in meeting this new traceability requirement.

First Step Toward a Solution



Attendees included:

- IVD Manufacturers
- Regulatory Agencies and Notified Bodies
- Providers of Proficiency Testing Programs, Laboratory Accreditation, and Measurement Quality assessment Materials
- Laboratory professionals involved in standardization of laboratory methods
- International Standards Laboratories

Recommendations included:

Establishment of a global consortium of IVD manufacturers, professional societies, NMIs, and regulatory bodies to develop an international consensus-based reference system for laboratory medicine.

JOINT COMMITTEE on TRACEABILITY in LABORATORY MEDICINE

That global body was established in Paris on 12 June 2002, to meet the need for a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in Laboratory Medicine and traceability to appropriate measurement standards.

The Declaration of Cooperation was between the International Committee of Weights and Measures **(CIPM),** the International Federation for Clinical Chemistry and Laboratory Medicine **(IFCC),**and the International Laboratory Accreditation Cooperation **(ILAC)**

JCTLM Database: Laboratory medicine and *in vitro* diagnostics

JCTLM

JCTLM-DB

- JCTLM-DB home
- Search form
- Preamble
- Quality manual
- Review Teams
- Nomination forms
- JCTLM

Contact

-JCTLM Secretariat

Useful links

- ILAC
- IFCC
- KCDB
- Metrologia

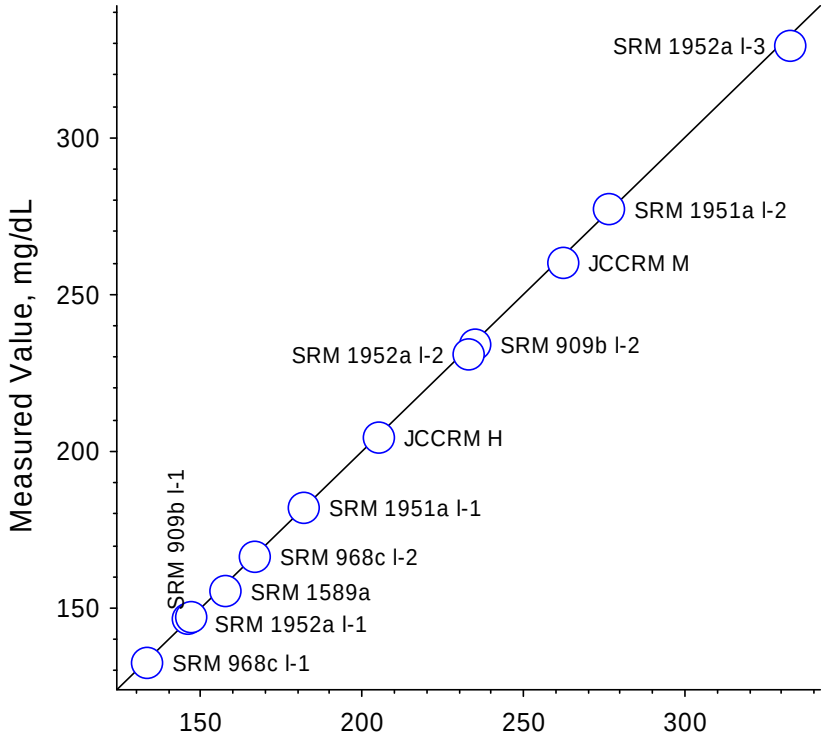
Database of higher-order reference materials and reference measurement procedures

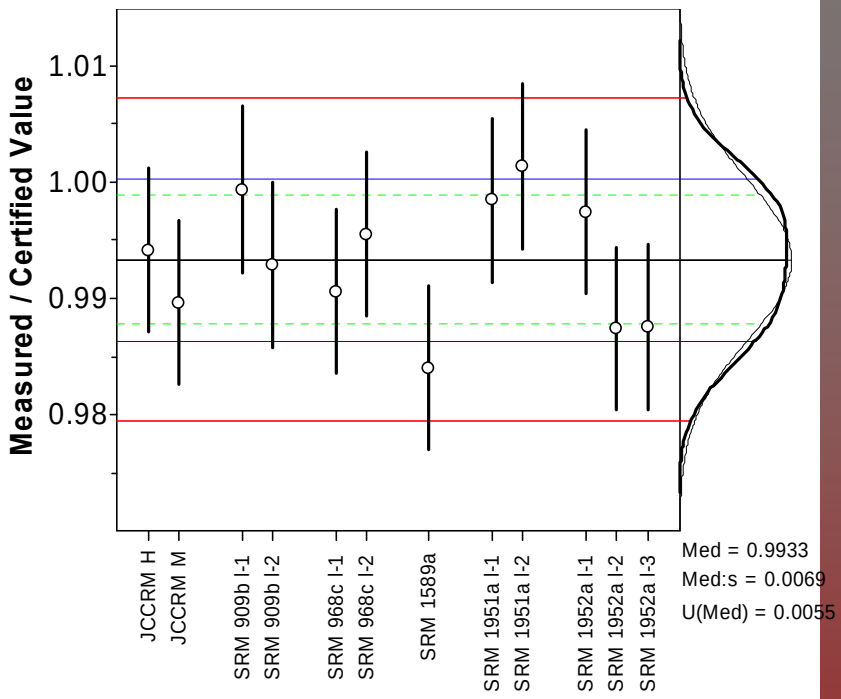
→ **Search the database**

→ **List I : Certified Reference Materials and Reference Measurement Procedures for well-defined chemical entities or internationally recognized reference method-defined measurands.**
Reference Materials and Measurement Procedures included in this category are those that provide values that are traceable to the SI units; e.g., electrolytes, enzymes, drugs, metabolites and substrates, non-peptide hormones and some proteins.

→ **List II: Reference Materials (e.g. reference materials for blood typing, coagulation factors, microbial serology, nucleic acids, and some proteins) that are value-assigned using an internationally agreed upon protocol.**
The values of the measurands in the reference materials on this List are not SI-traceable and/or no internationally-recognized reference measurement procedure exist. List II also contains a group of purified substances that due to the absence of reference measurement procedures should not be directly used for calibration unless commutability is established.

Comparability of Cholesterol in Serum CRMs on JCTLM LIST



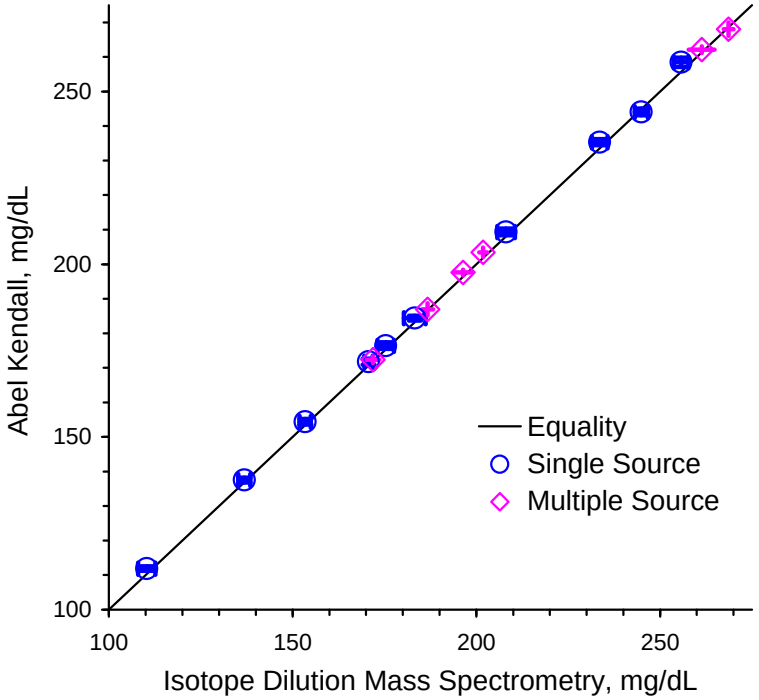


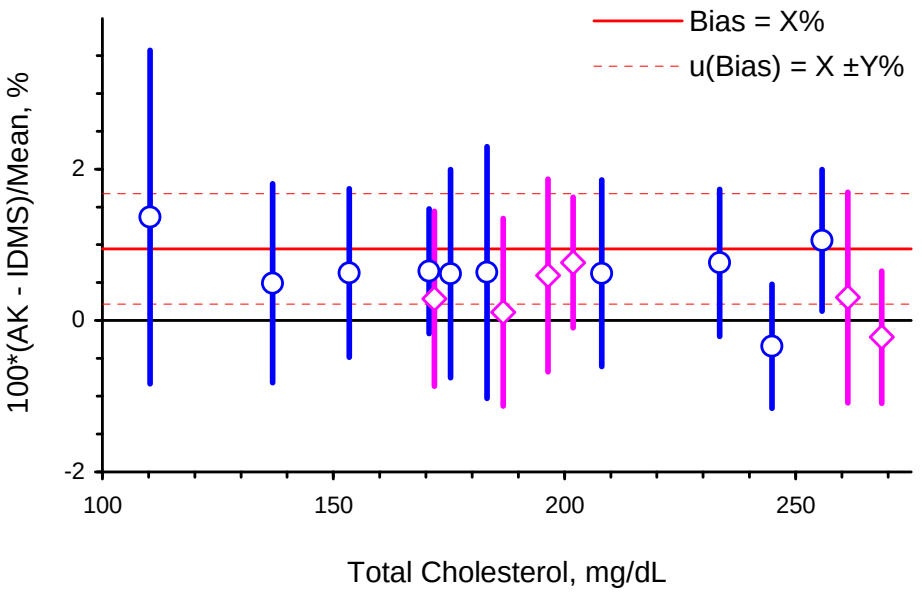
⇨ **CRM comparability independent of analyte level**

The measured/certified ratios for this set of CRMs are:

- ~ normally distributed
- with a standard deviation of ~0.7%

Assessment of Comparability of Two RMPs for Total Cholesterol in Liquid Frozen Serum

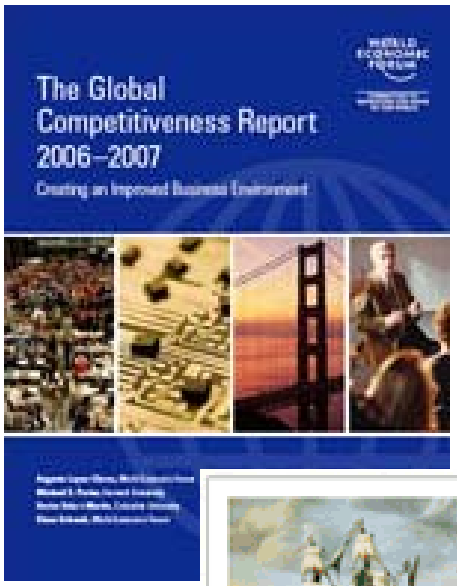


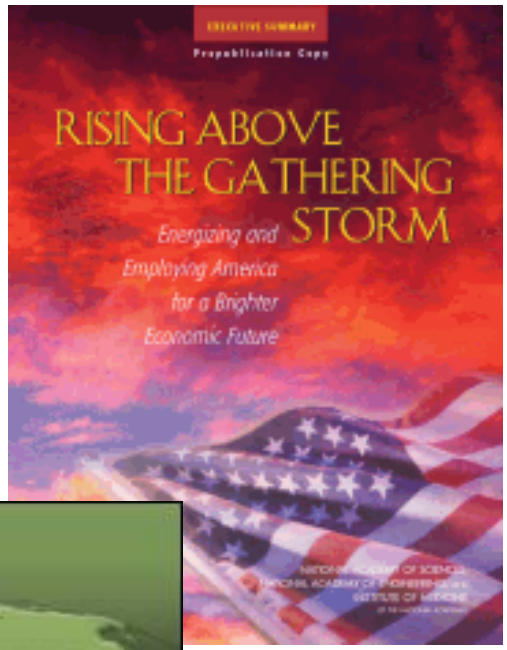


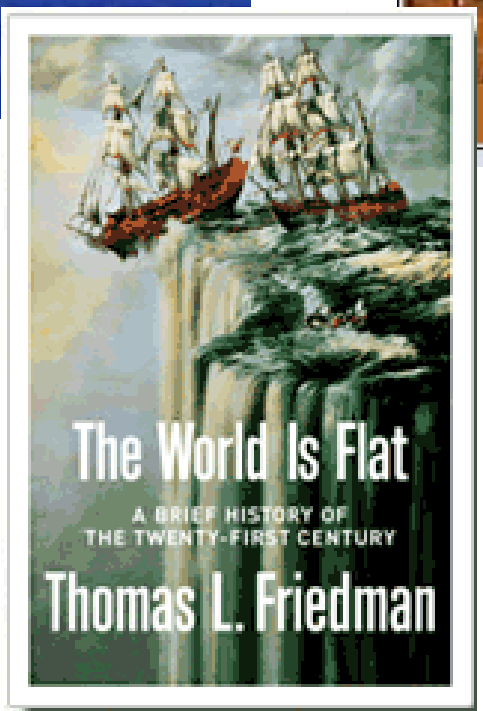
Measurements performed at NIST and CDC; publication to be forthcoming

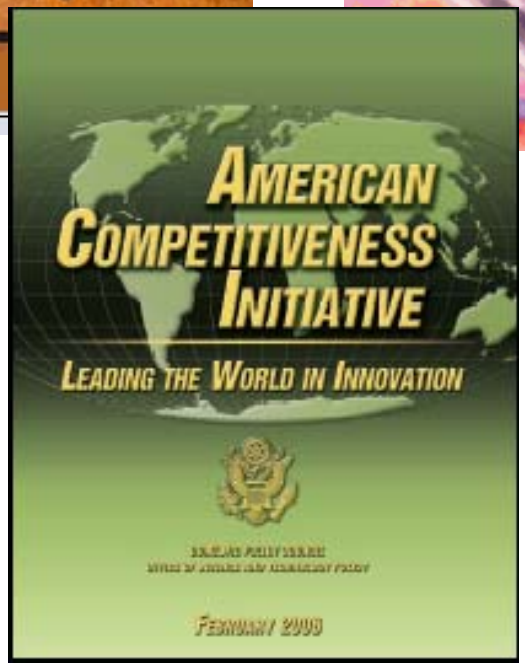
The World is Changing

… and NIST must respond accordingly









Health Care Markets Must Change

Today

HC markets based on numbers of sick people

Metric
Morbidity and mortality rates

Outcome
People suffer and die from chronic and preventable diseases with multiple hospitalizations

Cost
$2 trillion/year in 2005
$4 trillion/year by 2015

NIST Role
Provide measurement science, standards, and technologies to support this transition

Tomorrow

HC markets based on numbers of people with preventable diseases

Metric
Number of people positive for valid predictive biomarkers

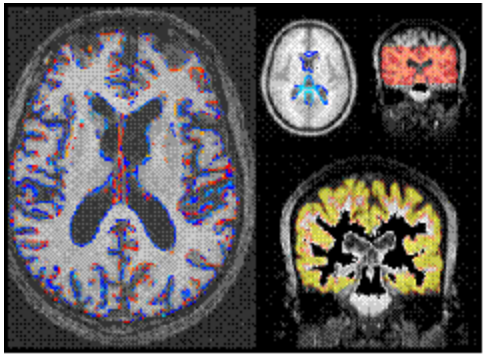
Outcome
Most people will die of old age or trauma with minimal hospitalizations

Cost savings
$50B for diabetes alone

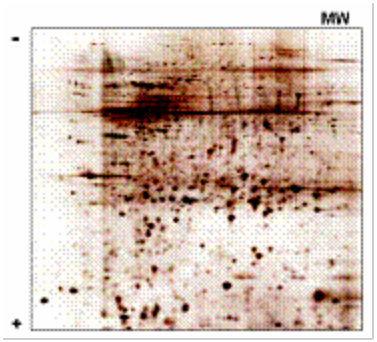
Future Thrust

Tools to Support Visualization of "Disease Signatures"

unique patterns can be used as more definitive indicators of health status



Abnormal Anatomical Features



Abnormal Protein Patterns

A shift from measurement of individual biomarkers to "analysis of disease signatures" would help to enable

- a new comprehensive and integrated approach to wellness that includes prevention of disease, early detection of disease risk and individualized treatment plans for individual patients.
- predictive toxicology for new drug candidates -- ability to predict which individuals will benefit and those who might be most at risk for experiencing serious side-effects

The program has two complementary components

Quantitative Medical Imaging:

1. CT and Spiral CT Imaging Standards
2. PET Imaging Standards
3. MRI Imaging Standards
4. Bone Densitometry Clinical Standards
5. Medical Optical Imaging Standards

Protein Measurement Science:

1. Technologies and Standards for Quantitative Measurements of Proteins
2. Measurement Science and Standards for Determination of Protein Structure
3. Standards for Protein Function Measurements
4. Standards and Technology for Protein Manufacturing Process Monitoring and Control
5. Technologies and Standards to Elucidate the Human Disease Proteome

Thank You for Your Attention

Questions?

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