18th Meeting of the Directors of NMIs and Member States Representatives

October 24-25, 2016 *BIPM, France*

Metrological Methodologies in the Health Sector, Chair – Willie E. May

- **Presentations**
  - NIST programs to address next Generation healthcare and forensic science challenges — ***Willie E. May, NIST***
  - Developing chemistry and biology programs in Korea — ***Sang Roul Park, KRISS***
  - Health challenges facing the developing world — ***Dinesh Aswal, NPL (India)***
  - Trace Element Analysis in Food — ***Takashi Usuda, NMIJ***

- **Panel discussion and debate**

NIST Programs to Address Next Generation Healthcare and Forensic Science Challenges

October 25, 2016

Dr. Willie E. May

U.S. Under Secretary of Commerce for Standards and Technology &

Director, National Institute of Standards and Technology

In addition to maintaining the more traditional National Physical Measurement Standards, **we also focus a significant portion of our research and measurement services activities on addressing contemporary societal needs**

NIST has become:

- a key player on the Administration's Innovation Team
- the nation's go-to agency for measurements, standards, and technology in an ever increasing number of areas

1901

Supporting the Industrial Revolution


Interoperability of fire hose screw threads


Light bulb standards


Standards for irons and steels

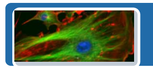

Working with ICC to reduce railway accidents

2016


Advanced communications


Advanced manufacturing


Advanced materials


Bioscience and health

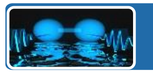

Climate assessment


Cyber-physical systems


Cybersecurity


Disaster resilience


Forensic science


Quantum science

Voting standards

Topics

- **Traditional Clinical Diagnostics Tests**
- **Personalized Medicine/Genetics-Directed Therapy**
- **Measurement Science, Tools, and Standards to Support the Manufacture and Regulatory Approval of Biosimilars**
- **National Head Health Challenge to Stimulate Development of Innovative Energy- Absorbing/Dissipating Materials**
- **Improving the Science that Underpins the Forensic Evidence used in the U.S. Judicial System**

Healthcare reform is a major issue throughout the world

- The rising cost of healthcare and increased prevalence of chronic diseases is having a devastating affect of economic security and quality of life in all parts of the world.
- Major efforts are underway to reform healthcare and reduce spending through increased efficiency and quality, focusing on prevention of disease and creating a healthier population.
- **It is a stated goal of the Obama Administration to improve the quality of U.S. health care while lowering its cost** by computerizing all Americans' medical records. … "this will cut waste, eliminate red tape, and reduce the need to repeat expensive medical tests …. it will save lives by reducing the deadly but preventable medical errors that pervade our health care system".
  - **Need interoperable health IT network** that is **correct, complete, secure, usable, and testable**

Measurements that are comparable over space and time are key to achieving these Global and National Goals

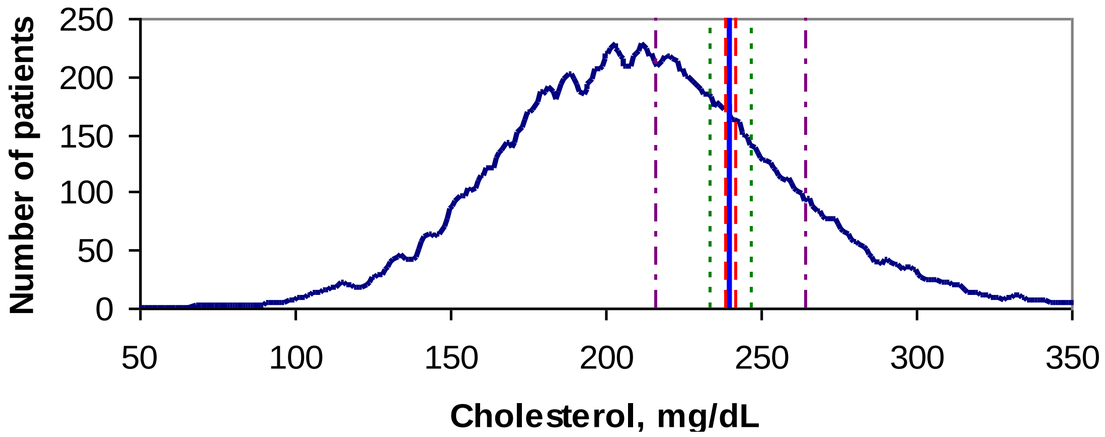
Healthcare reform is a major issue throughout the world

~$3 trillion spent annually in U.S. on healthcare of which 10% -15% is based on measurements

- **70% of healthcare decisions are based on results from clinical laboratory measurements**
- **Bias in measurements affects medical decision-making**

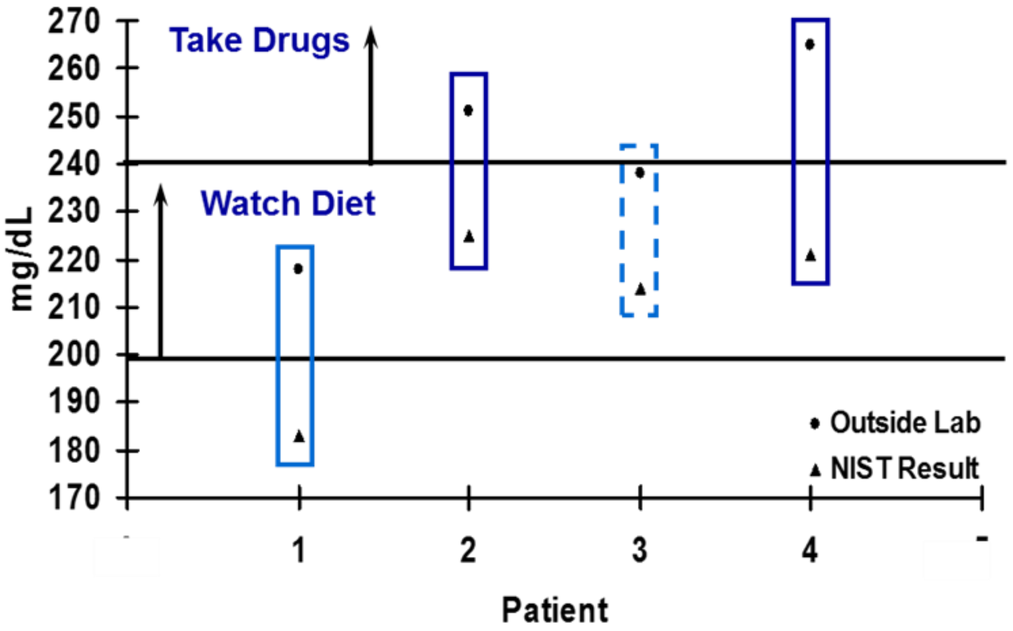
Cholesterol Frequency Distribution of >20,000 Mayo Clinic Patients

(with +1%, +3% and +10% limits around 240 mg/dL criteria point)



If measurement bias were:	Positives (>240 mg/dL) per 1000	Predicted Change in "Positives/1000"
-10% bias	120	-129
-3% bias	203	-46
-1% bias	234	-15
0% bias	249	
+1% bias	263	+14
+3% bias	300	+51
+10% bias	446	+197

NIST Cholesterol-in-Blood Experiment - Impact of Inaccurate Measurements



Lack of Specificity Can Cause Problems

- **Cardiac Troponin I is a heart muscle protein that is observed in the bloodstream after myocardial damage**
- ***Measurement Challenges***:
  - Low levels of detection needed: 0.1 - 20 ng/mL
  - Heterogeneity of troponin forms (phosphorylation, complexation with other troponin subunits, degradation in serum)

Assay Manufacturer	Conc. ng/mL	# Labs
A	19.9	115
B	6.7	489
C	0.85	27

From G. S. Bodor, Denver Health and Hospitals -- personal communication 1997

The Questions are Different for…. Measurements:

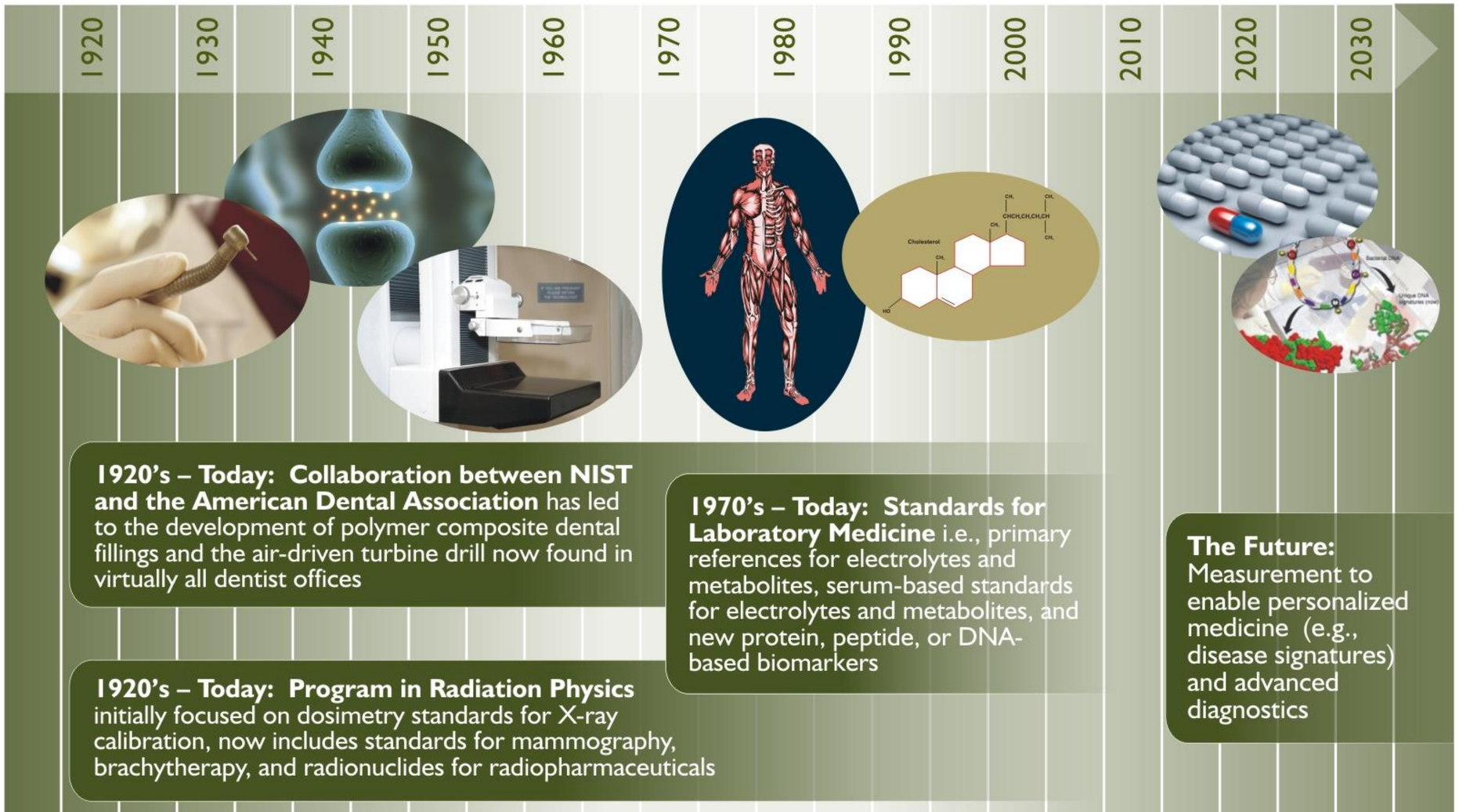
- **>37,000 deaths annually in U.S. from prostate cancer**
- **Blood tests for PSA are used to screen for the likelihood of prostate cancer**
- **PSA is a heterogeneous protein that occurs both free and complexed**
- **Immunoassays are the approach favored for routine measurement of PSA**
- **Wide variability among the results from immunoassays (see below)**
- **High incidence of false positives and false negatives**

# of Labs	- Low -	- Med.-	-High-	-Mean-	- S.D. -	%RSD	95% Confidence Range
2672	10.8	19.4	34.5	19.67	2.14	10.9	15.39-23.95
2653	7.2	9.8	18	9.92	1.11	11.2	7.70-12.14
2689	5.3	7.3	12.8	7.36	0.79	10.7	5.78-8.94
2509	2.1	3	4.7	3.03	0.33	10.8	2.37-3.69
2504	0.6	0.7	1.5	0.73	0.11	14.5	0.51-0.95
2591	0.1	0.2	0.8	0.24	0.1	40.2	0.04-0.44

From: http://www.cooleyville.com/cancer/capsava.htm

NIST has provided Standards for Healthcare Measurements for more than 90 years

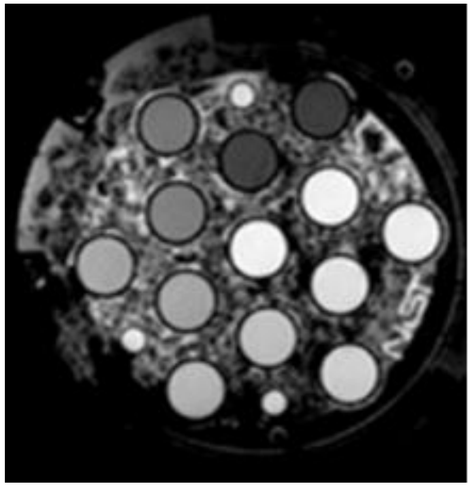
It is congruent with the NIST mission - and indeed our mandate - to address the measurement and standards barriers affecting the cost and quality of healthcare delivery



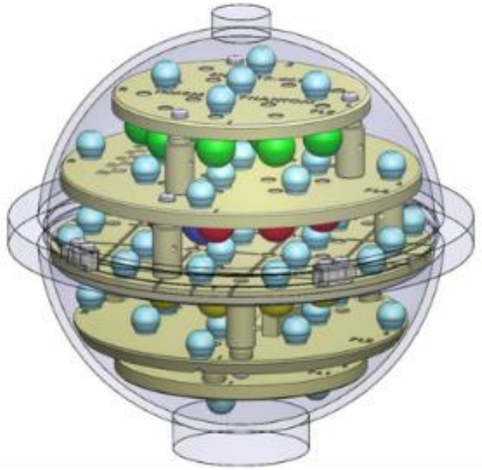
Making Medical Imaging Digital – not Analog

- Standards, phantoms, and improved contrast agents for ionizing and non-ionizing (optical and magnetic) radiation medical imaging technologies to promote reproducibility, reduce uncertainty associated with various imaging modalities.

- First commercially-available traceable **PET phantoms to be shipped with every GE Healthcare PET-MRI scanner.**



NIST MRI Phantoms



Personalized Medicine

*"**Doctors have always recognized that every patient is unique**, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery.* ***What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"*** ***President Obama, January 30, 2015***

Personalized Medicine requires use of information and data from a patient's genotype and phenotype (level of gene expression and/or other clinical information) to:

- stratify disease
- select a medication
- provide a therapy
- initiate a preventative measure that is particularly suited to that patient at the time of administration

Personalized Medicine can address questions of the common man/woman -

- Why do adverse drug reactions and interactions occur in some people and others not?
- Can I be sure that I am getting the right treatment for me
- Can I be sure that the generic protein drug that I get will work the same as the more expensive name brand drug?

Genetics Directed Therapy

"The College of American Pathologists and the American Society of Clinical Oncology have estimated that around 20% of HER-2 testing may be inaccurate"

HER2 Test

180,000/ year

False positive

Up to 36,000 → **Get Herceptin unnecessarily**

- Expensive
- Numerous side effects

False negative

Up to 36,000 → **Herceptin Treatment withheld**

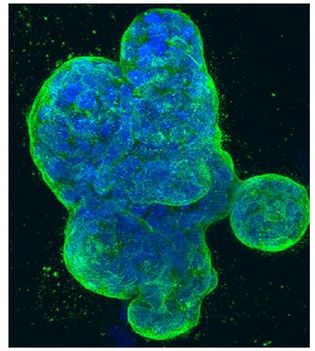
- Inappropriate treatment
- Increased morbidity
- Increased mortality

http://online.wsj.com/article/SB119941325367266813.html

Impact of NIST-developed Certified Reference Material for HER2

In response to the need for better accuracy for HER2 testing

- **NIST developed Standard Reference Material 2373 – "Genomic DNA Standards for HER2 Measurements"**
  - Scientists at the Frederick Cancer Institute evaluated the usefulness of SRM 2373 for ensuring the accuracy of measurements of HER2 gene copy numbers.
  - They reported in the new issue of **the Journal of Molecular Diagnostics,** that the use of SRM 2373 as a QA tool led to increased confidence in HER2 amplification measurements in a clinical setting



Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. The cancer in these cells is driven by the HER2 gene (also known as ErbB2).

Credit: NCI Center for Cancer Research, National Cancer Institute, National Institutes of Health

What's needed to implement personalized medicine more broadly?

Linking outcome of genomics, proteomics, metabolomics, microbiome measurements and imaging data to a specific disease state

Ability to put all of these sources together to determine what are most important factors or combination of factors that link to disease and predict outcome of therapies

Big data analytics, models

Providing Confidence in Genomics Measurements: Genome in a Bottle

NIST led consortium with more than 75 public, private, academic partners

- Developed "**RM 8398 - Human DNA for Whole-Genome Variant Assessment"** to provide quality assurance of whole genome sequencing technologies

- **Use this Standard facilitated FDA approval of results from high-throughput DNA sequencing**

"The federal government opened a new era of genetic medicine on Thursday by introducing a standard way to ensure the accuracy of DNA tests used to tailor treatments for individual patients." *NY Times (5/14/15)*

Biologic Drugs

- **The Cost of Protein therapeutics is one of the fastest growing components to the overall cost of health care in the U.S.**
- The global biologics market is estimated to grow to **~$380 B by 2019 from $200 B in 2013** (BCC Research),
  - These "biologic drugs" are not synthesized chemically, but rather are made in bioreactors using living cells
- These drugs have proven to be **very therapeutic and substantially improve patients' health and quality of life.** However, they are **very expensive and generics are not widely available in the U.S.**
  - Globally, biologics with estimated sales of $100 billion will come off patent protection by 2020

NIST was asked by both FDA and the industry to apply its unique combination of expertise in the physical, chemical, and the biological measurement sciences **to underpin the development and regulatory approval of follow-on biologic/biosimilar drugs**

Atorvastatin (Lipitor)

Small chemical molecule

800-1000 Da

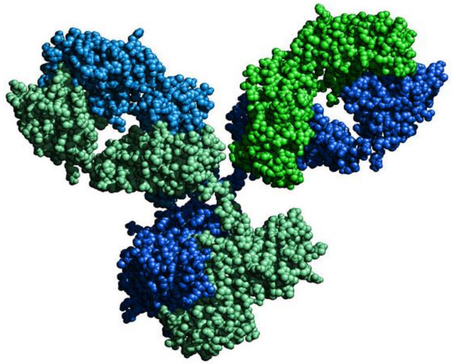
Produced via chemical synthesis

Calcitonin

Simple Biologic

3455 Da, ~32 Amino acids

Produced in yeast, bacteria



Monoclonal Antibody (IgG)

Complex Biologic

150,000 Da, ~1300 Amino acids (with host cell modifications)

Produced in mammalian cells

Note: relative scale is illustrative

Examples of Biologic Drugs and Their Sales

World-wide Biologic Mark estimated to exceed $350B by 2019

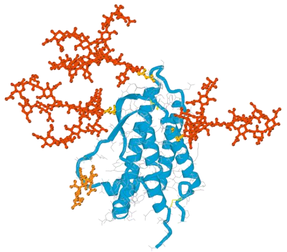
2014 US sales

Humira	rheumatoid arthritis	~$10.7 billion
Lantus	diabetes	~$5.5 billion
Enbrel	rheumatoid arthritis	~$4.4 billion
Remicade	rheumatoid arthritis	~$3.9 billion
Neulasta	chemotherapy infections	~$3.6 billion
Rituxan	cancer	~$3.6 billion
Avastin	cancers	~$2.9 billion
Herceptin	**breast cancer**	**~$2.2 billion**
Epogen	anemia due to chronic kidney disease	~$2.0 billion

http://www.marketwatch.com/story/biosimilarsfollow-on-biologics-market-is-expected-to-reach-35-billion-globally-by-2020-2014-07-21

1. The Economics of Biosimilars by Blackstone and Fuhr (2013) American Health and Drug Benefits. Vol. 6, No 8

Metrology for Biomanufacturing



Measurement science, tools & standards to support manufacturing & regulatory approval of biologic drugs

Program Areas:

1. **Protein structure: higher order structure, post-translational modifications**
   - **“Structural Sameness”** of the manufactured biopharmaceutical

2. **Measurements & standards for protein stability, aggregation, & particles**
   - **Propensity** of the biopharmaceutical **to induce an Immune Response in Patients**

3. **Measurement tools & science to understand production cell variability**
   - **Complex Inner Workings of Cells** used in the production of Biologic Drugs

Congressional Subcommittee Hearing - Need for Measurement Standards to Facilitate R&D of Biologic Drugs, Sept. 2009
(From L to R): ***Dr. Anthony Mire-Sluis (Amgen)***
Dr. Patrick VJJ Vink (Mylan)
Dr. Steven Kozlowski (FDA)
Dr. Willie E. May (NIST)

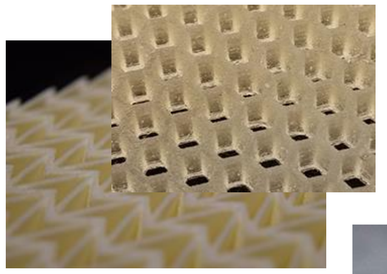
NIST Partnership in Head Health Challenge III

Stimulate development of innovative energy absorbing and dissipating materials

HEAD HEALTH CHALLENGE III

- **$250,000 to 5 finalists** to advance performance of their innovative materials over 2016.
- **Winner will receive $500,000 Grand Prize** in February 2017.

Materials Innovations of Finalists

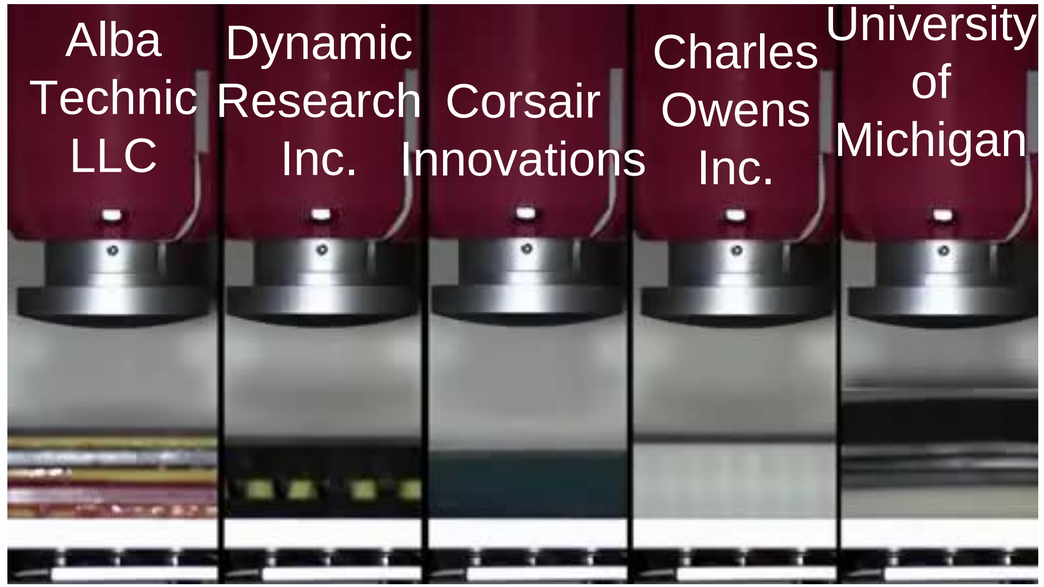


3D printed energy absorbers

Impact absorbing textiles

Designed Multi-layers

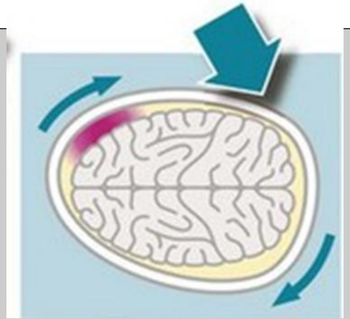
"Architected" Impact Absorbers



NIST testing of finalist materials will help determine the HHCIII Grand Prize Winner

Measurement Challenges Addressed through parallel NIST Research:

- ***Metrology:*** **Materials energy absorption in shear - address brain injuries from rotation**
- ***Modelling:*** **Of the innovative "architected" materials HHCIII finalists produced (w/CHiMAD)**
- ***Standards:*** **Test methods for energy absorbing materials under multiaxial deformation**



First-Round Awardees: Head Health Challenge III - Advanced Materials for Impact Mitigation

- **Alba Technic, LLC** (Winthrop, Maine)
  - patented, shock-absorbent honeycomb material with an outer layer that diverts the energy from a fall or hit.
  - upon impact, the outer layer changes into a hard shell to spread the energy and protect the user from injury.

- **Charles Owen Inc.** (Lincolnton, Ga.)
  - material with a stacked, origami-like design can fold efficiently to optimize energy absorption.
  - material based on originally developed for applications such as solar array packing for space industry.

- **Corsair Innovations** (Plymouth, Mass.)
  - a textile that uses tiny, spring-like fibers to repel rotational and linear impacts,
  - is washable, breathable, wicks sweat and can be easily engineered to meet impact performance requirements.

- **Dynamic Research Inc.** (Torrance, Calif.) and **6D Helmets LLC**
  - 6D's single-impact suspension technology is being evolved for use in repeated impact conditions.
  - 6D's multi-layer, suspended internal liner system allows the outer layer to move independently of the inner layer in order to reduce the effect of both angular and linear impact forces.

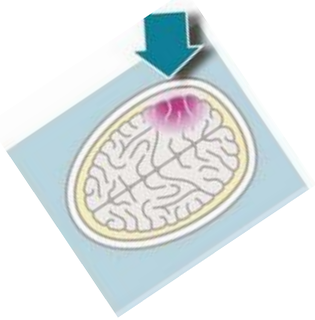
- **University of Michigan** (Ann Arbor, Mich
  - a lightweight, multi-layered composite that includes a viscoelastic material.
  - material can be uniquely utilized to help limit the force of multiple and repeated impact events.

HHCIII Testing Facilities: Linear Impact Tests

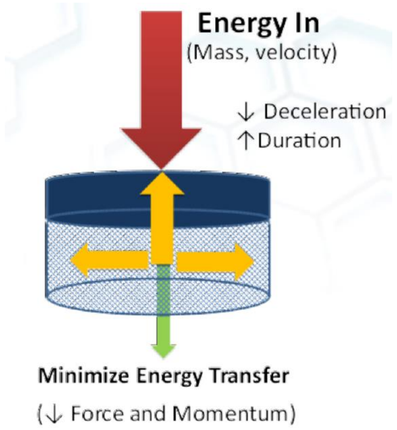
Materials Response to Linear Impact:

- Instrumented drop tower
- Sports-level Impacts: 7.5 J to 75 J range
- Energy/Momentum Transfer through Material

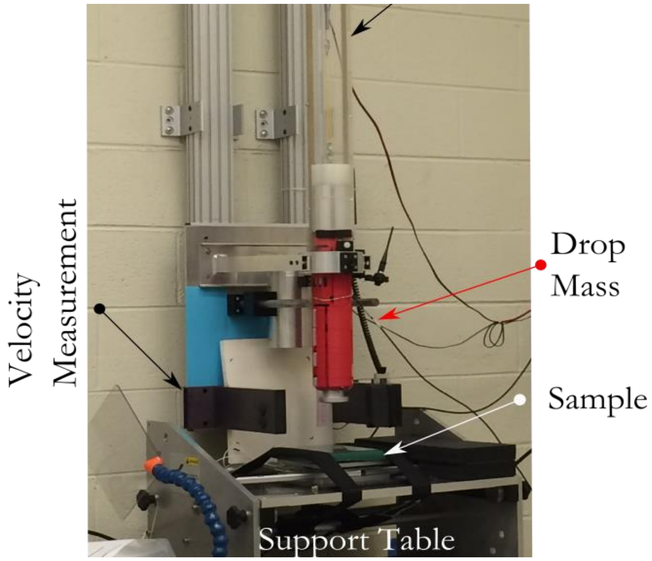
"Direct" Injury



Role of protective material

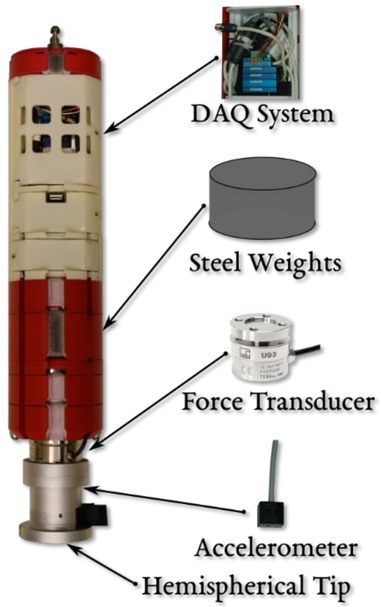


NIST drop tower



Instrumented Drop Mass

- 3.3 kg (tunable)
- 2 triaxial accelerometers
- 127 mm radius Impactor (NOCSAE)
- Force transducer: force transmitted through impactor



HHCIII Materials Test Regimen:

Stepped Impacts with increasing drop height:
- Energy/rate dependence of performance

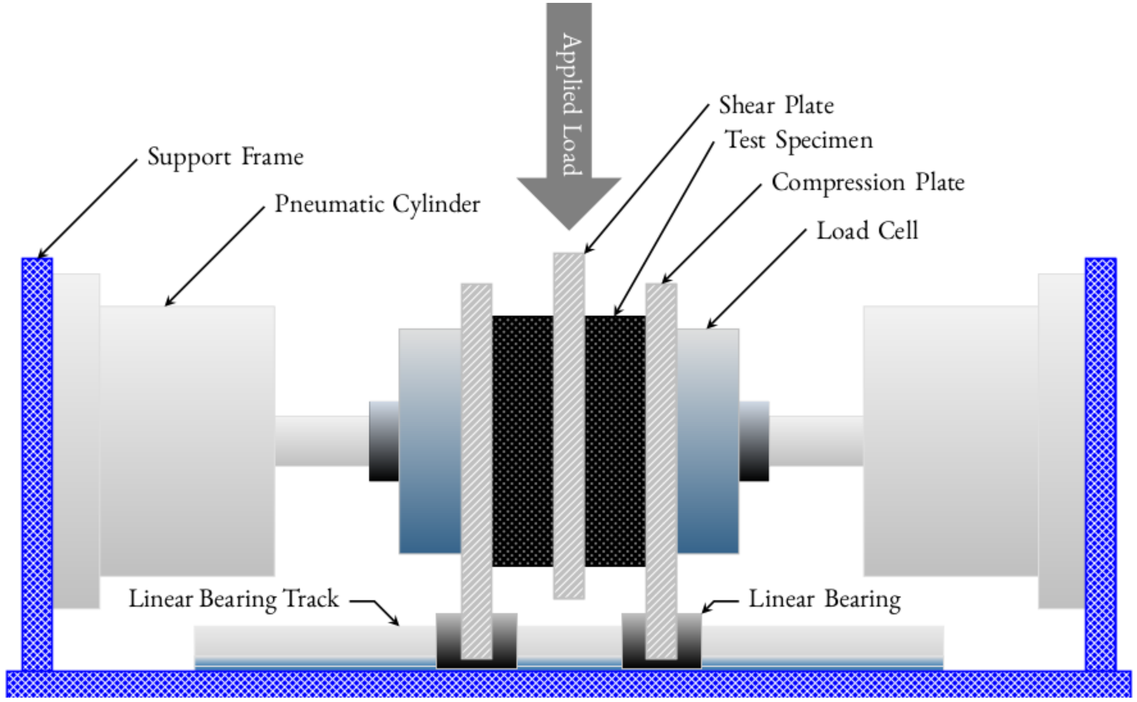
Performance Degradation:
- Multiple impacts @ 60 J, and
- Conditioned with 1200 cycles quasi-static loading

Temperature Dependence
- Conditioned at 0°C & 40°C

New Capability: Shear Impact Test

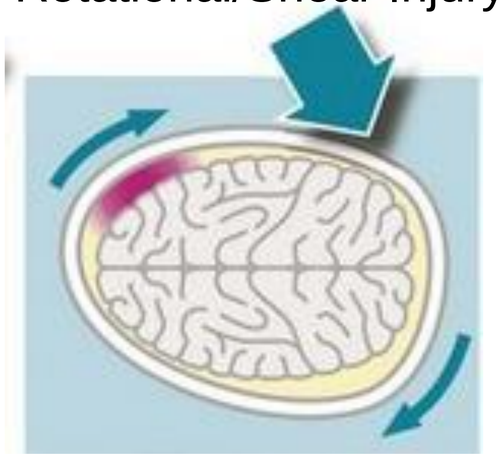
- Material energy absorption under shear impact (w/compression)
- Key to reducing rotational momentum in sports impacts
- First data collected this summer

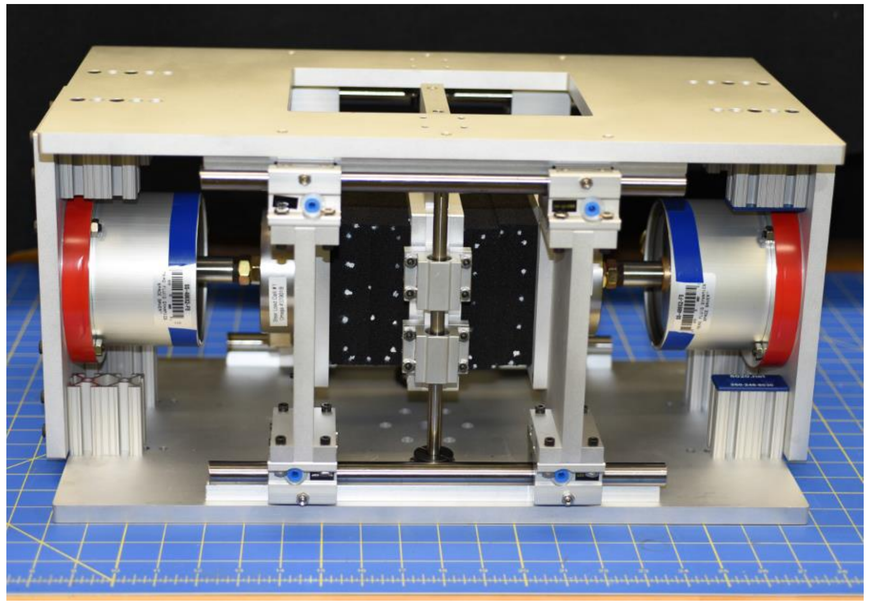
Shear load can be quasi-static or impact



Instrument Design

Rotational/Shear Injury





New NIST instrument

Changes in Needs/Expectations in Rigor for Forensic Evidence

- **Forensic science is in a period of changing expectations and requirements in the U.S.**
  - **There is growing concern about the scientific foundation, measurement rigor, and statistical validity of many forensic analyses** that is leading to renewed attention to how scientific data are presented in evidentiary settings as well as to expectations of forensic science laboratories.

In the News

The Washington Post

National accreditation board suspends all DNA testing at D.C. crime lab

A wake-up call on the junk science infesting our courtrooms

Washington Post, September 20, 2016

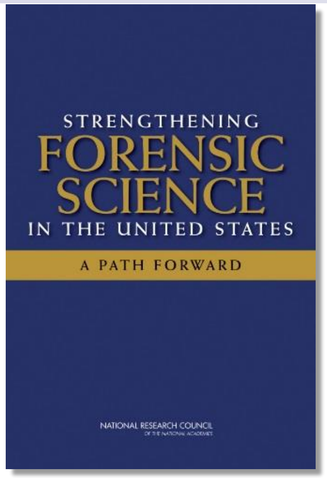
the Atlantic

CSI is a Lie!

The New York Times

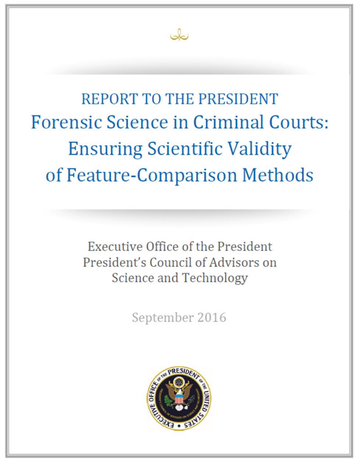
Fix the Flaws in Forensic Science

Status of Forensic Science in U.S.



2009 U.S. National Academy of Science Report

- *"With the exception of nuclear DNA analysis, no forensic method has been rigorously shown to have the capacity to consistently, and with a high degree of certainty, demonstrate a connection between evidence and a specific individual or source." (p.7)*
- [It] also criticized the 21 Scientific Working Groups advising the forensics jurisprudence community as being "too highly fragmented with very different structures and outputs . . .the resulting standards were not enforceable or developed in an open and transparent manner.
  - NIST responded in Feb 2013 with creation of a new entity – the **Organization of Scientific Area Committees (OSAC)**



2016 President's Council of Advisors on Science & Technology (PCAST) Report

- President Obama asked PCAST, in 2015, as to whether there are additional steps on the scientific side, that could help ensure the validity of forensic evidence used in the Nation's legal system
- In Report to the President issued Sep 2016, ***Forensic Science in Criminal Courts: Ensuring Scientific Validity of Feature-Comparison Methods, PCAST identified two important gaps:***
  - *the need for clarity about the scientific standards for the validity and reliability of forensic methods*
  - *the need to evaluate specific forensic measurement methods to determine whether they have been scientifically established to be valid and reliable. The study aimed to help close these gaps for a number of forensic "feature-comparison" methods*

Technical Merit of Forensic Science Methods

PCAST report of Sept 2016 addresses:

- ❑ DNA
- ❑ Bite Marks
- ❑ Footwear
- ❑ Firearms
- ❑ Latent fingerprints

> "NIST should take a leadership role in transforming three important feature-comparison methods that are currently subjective—latent fingerprint analysis, firearms analysis, and, under some circumstances, DNA analysis of complex mixtures—into objective methods"

Initial NIST efforts would look at three examples selected from different areas, as we learn if the approach can be effective:

- DNA Mixtures
- Ballistics and Tool Marks
- Bite Marks

Discussions in progress between PCAST, NIST, and BIPM about having ***Metrologia*** provide Special Issue(s) on "measurement science in forensics"

18th Meeting of the Directors of NMIs and Member States Representatives

October 24-25, 2016 *BIPM, France*

Metrological Methodologies in the Health Sector, Chair – Willie E. May

- **Presentations**

  - NIST programs to address next Generation healthcare and forensic science challenges — ***Willie E. May, NIST***
  - Developing chemistry and biology programs in Korea — ***Sang Roul Park, KRISS***
  - Health challenges facing the developing world — ***Dinesh Aswal, NPL (India)***
  - Trace Element Analysis in Food — ***Takashi Usuda, NMIJ***

- **Panel discussion and debate**