Medicine at a Crossroads: Informatics Driving Discovery and Improving Human Health

Alexa T. McCray, PhD

alexa_mccray@hms.harvard.edu

Society of Neurological Surgeons
June 9, 2013
The Promise of Genomic Medicine

The Promise of Genomic Medicine

Understanding the structure of genomes

1990-2003
Human Genome Project

2004-2010

2011-2020

Beyond 2020

The Promise of Genomic Medicine

Understanding the biology of genomes
Understanding the biology of disease

1990-2003
Human Genome Project

2004-2010

2011-2020

Beyond 2020

Green ED. Nature 2011; 470(10):203-13
The Promise of Genomic Medicine

Advancing the science of medicine

1990-2003
Human Genome Project

2004-2010

2011-2020

Beyond 2020

Green ED. Nature 2011; 470(10):203-13
The Promise of Genomic Medicine

1990-2003
Human Genome Project

2004-2010

2011-2020

Beyond 2020

Improving the effectiveness of healthcare

Green ED. Nature 2011; 470(10):203-13
No longer is data generation the major bottleneck, rather

Computational challenges around

- Data analysis
- Data display
- Data integration
“Biomedical research and the practice of medicine, separately and together are reaching an inflection point: the capacity for description and for collecting data, is expanding dramatically, but the efficiency of compiling, organizing manipulating these data – and extracting true understanding of fundamental biological processes, and insights into human health and disease, from them – has not kept pace.”

Precision Medicine

Toward Precision Medicine
National Research Council, 2011
Precision Medicine

Toward Precision Medicine
National Research Council, 2011
Precision Medicine
Precision Medicine

Toward Precision Medicine
National Research Council, 2011
Precision Medicine

Individual-Centric

Knowledge Network

Taxonomic Classification

Toward Precision Medicine
National Research Council, 2011
A New Taxonomy of Disease

“Could it be that something as fundamental as our current system for classifying diseases is actually inhibiting progress?”

Toward Precision Medicine.
National Research Council, 2011:10
Heterogeneous Data Types

Basic Science Discovery

Text

Laboratory

Varied Methods, Approaches & Tools

Images

Clinical Discovery

Text

Laboratory

Images

Signals

Signals
(BIG) Data Sources

GWAS Data

Variation in level of
Structure
Curation (metadata)

Clinical Systems

Biosensor Data

Social Networking Sites

Public Databases

GWAS Data

Biosensor Data

Social Networking Sites
Terminologies for Curating Biomedical Datasets
**UMLS** (Unified Medical Language System)

**Informatics in Action**

Integrates > 100 existing biomedical terminologies
ClinicalTrials.gov

1997: Congress Passes Law (FDAMA) Requiring Trial Registration

The first U.S. Federal law to require trial registration was the Food and Drug Administration Modernization Act of 1997 (FDAMA) (PDF).

Section 113 of FDAMA required that the National Institutes of Health (NIH) create a public information resource on certain clinical trials regulated by the Food and Drug Administration (FDA). Specifically, FDAMA 113 required that the registry include information about federally or privately funded clinical trials conducted under investigational new drug applications (INDs) to test the effectiveness of experimental drugs for patients with serious or life-threatening diseases or conditions.

The information in the registry was intended for a wide audience, including individuals with serious or life-threatening diseases or conditions, members of the public, health care providers, and researchers.

2004 ICMJE

2007: Congress Passes Law (FDAAA) Expanding ClinicalTrials.gov Submission Requirements

In 2007 the requirements for submission to ClinicalTrials.gov were expanded after Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA) (PDF) Section 801 of FDAAA (FDAAA 801) requires more types of trials to be registered; additional trial registration information; and the submission of summary results, including adverse events, for certain trials. The law also included penalties for noncompliance, such as the withholding of NIH grant funding and civil monetary penalties of up to $10,000 a day.

- ClinicalTrials.gov: See the FDAAA 801 Requirements page
- NIH Office of Extramural Research: Frequently Asked Questions: FDAAA - Further Resources for NIH Grantees

1997 FDMA

2007 FDAAA

Informatics in Action

http://www.icmje.org/publishing_10register.html
International Scope

Types of Studies
- Interventional Trials
  - Drug or Biologic
  - Behavioral
  - Surgical Procedures
- Devices
- Observational Studies
- Device Trials
ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 146,692 studies with locations in all 50 states and in 184 countries.

Locations of Recruiting Studies

- Non-U.S. Only (50%)
- U.S. Only (44%)
- Both U.S. & Non-U.S. (6%)

Total N = 30,211 studies
Data as of June 07, 2013

Learn More
- ClinicalTrials.gov Online Training
- Glossary of common site terms
- For the Press
- Using our RSS Feeds

Search for Studies
Example: "Heart attack" AND "Los Angeles"

Search Help
- How to search
- How to find results of studies
- How to read a study record

For Patients & Families
- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more...

For Researchers
- How to submit studies
- Download content for analysis
- About the results database
- Learn more...

For Study Record Managers
- Why register?
- How to register study records
- FDAAA 801 Requirements
- Learn more...
Several hundred Neurosurgery Studies

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>A Patient Registry at the Neurosurgery Department</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Patients Treated at the Neurosurgery Department</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Procedure: Treatment at the neurosurgery department</td>
</tr>
<tr>
<td>2</td>
<td>Recruiting</td>
<td>Risk Factors of Complications Regarding Patients Undergoing Brain Tumour Neuro-surgery (Cranioscore)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Neuro-surgery, Brain Tumor, Post-operative Complications, Neuro-ICU Stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Other: Collecting pre-operative, per-operative data, neuro-radiological data and post-operative neuro-surgery complications</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td>Comparison of the Effects of Vecuronium and Cisatracurium on Electrophysiologic Monitoring During Neurosurgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Motor Evoked Potential Monitoring, General Anesthesia, Neurosurgery, Brain Tumor, Spine Tumor, Cerebral Aneurysm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Other: MEP monitoring with continuous infusion of vecuronium during general anesthesia, Other: MEP monitoring with continuous infusion of cisatracurium during general anesthesia</td>
</tr>
<tr>
<td>4</td>
<td>Recruiting</td>
<td>Dexmedetomidine on Intraoperative Somatosensory and Motor Evoked Potential Monitoring During Neurosurgery in Pediatric Patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Tethered Spinal Cord, Brain Tumor, Cranio Cervical Compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Other: Isoflurane, Propofol, Dexmedetomidine</td>
</tr>
<tr>
<td>5</td>
<td>Completed</td>
<td>Strategy for Maintaining Partial Neuromuscular Blocking Adequate for Motor Evoked Potential During Neurosurgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Other: TOF count guided adjustment, Other: T1/ T6 guided adjustment, Other: T2/ T6 guided adjustment</td>
</tr>
</tbody>
</table>
UMLS-driven Search
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>Neurotransmitter Measurements Using Wireless Instantaneous Neurotransmitter Concentration System (WINCS) During Deep Brain Stimulation Neurosurgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Essential Tremor; Parkinson's Disease; Dystonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Device: WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System)</td>
</tr>
<tr>
<td>2</td>
<td>Recruiting</td>
<td>Deep Brain Stimulation and Capsulotomy for the Treatment of Refractory Anorexia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Anorexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Procedure: Deep Brain Stimulation (DBS); Procedure: Capsulotomy</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td>Subthalamic Nucleus Stimulation in Parkinson Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Parkinson's Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Procedure: New targeting procedure without electrophysiology; Procedure: Classical neurosurgical procedure</td>
</tr>
<tr>
<td>4</td>
<td>Recruiting</td>
<td>SubGenual CG25 Deep Brain Stimulation in Severe Resistant Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Depression</td>
</tr>
<tr>
<td>5</td>
<td>Recruiting</td>
<td>Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Obsessive-Compulsive Disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Device: Deep brain stimulation (DBS)</td>
</tr>
<tr>
<td>6</td>
<td>Recruiting</td>
<td>Deep Brain Stimulation for the Treatment of Refractory Anorexia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Anorexia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Procedure: Deep Brain Stimulation</td>
</tr>
</tbody>
</table>
Neurotransmitter Measurements Using Wireless Instantaneous Neurotransmitter Concentration System (WINCS) During Deep Brain Stimulation Neurosurgery

Purpose

In this study, the investigators will monitor extracellular neurotransmitter levels using a probe that is able to perform real time electrochemical detection during deep brain stimulation surgery. The overall question this study is designed to answer is: Are there neurotransmitters released during deep brain stimulation?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential Tremor</td>
<td>Device: WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System)</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional

Study Design:
- Endpoint Classification: Efficacy Study
- Intervention Model: Single Group Assignment
- Masking: Open Label
- Primary Purpose: Basic Science

Resource links provided by NLM:

- Genetics Home Reference related topics:  
  - dopa-responsive dystonia  
  - early-onset primary dystonia  
  - essential tremor  
  - Parkinson disease  
  - Perry syndrome

- MedlinePlus related topics:  
  - Dystonia  
  - Parkinson's Disease  
  - Tremor

U.S. FDA Resources

Further study details as provided by Mayo Clinic:

Primary Outcome Measures:
- adenosine release in brain as measured by WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System) recording device  
  - Time Frame: 30 minutes  
  - Designated as safety issue: Yes
  - Pre, during, post DBS (deep brain stimulation)

Secondary Outcome Measures:
- dopamine release in brain as measured by WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System) recording device  
  - Time Frame: 30 minutes  
  - Designated as safety issue: Yes
  - Pre, during, post DBS (deep brain stimulation)

Estimated Enrollment: 45
Study Start Date: January 2010
Estimated Study Completion Date: January 2014
Estimated Primary Completion Date: January 2014 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
</table>
| Experimental: WINCS | Device: WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System)  
  - The experimental protocol will involve, after implantation of the DBS electrodes, the patient will have a single electrochemical recording electrode will be implanted along the same trajectory path as the electrophysiology and the DBS electrode |
| WINCS (Wireless Instantaneous Neurochemical Concentration Sensing System), which is capable of wireless control and data transmission, and in addition is capable of detecting by fast scan cyclic voltammetry (FSCV). |

**Eligibility**

- Ages Eligible for Study: 18 Years to 90 Years
- Genders Eligible for Study: Both
- Accepts Healthy Volunteers: No
- Criteria Inclusion Criteria:
Exclusion Criteria:
- pregnant patients,
- prisoners,
- children (age less than 18), and
- any patients identified as unsuitable for these protocol by the Mayo DBS committee.

**Contacts and Locations**

Please refer to this study by its ClinicalTrials.gov identifier: NCT01705301

**Locations**

United States, Minnesota

Mayo Clinic  
Rochester, Minnesota, United States, 55901
Contact: Debra Gorman, RN  
507-266-3044  
gorman.deborah@mayo.edu
Principal Investigator: Kendall H. Lee, MD, PhD
Principal Investigator: Su-youne Chang, PhD

**Sponsors and Collaborators**

Mayo Clinic

**More Information**

No publications provided

Responsible Party: Su-Youne Chang, PI, Mayo Clinic
ClinicalTrials.gov Identifier: NCT01705301  
History of Changes
Other Study ID Numbers: 09-007441
Study First Received: October 9, 2012
Last Updated: April 26, 2013
Health Authority: United States, Institutional Review Board

Additional relevant MeSH terms:

- **Brain Diseases**
  - Movement Disorders
  - Central Nervous System Diseases
  - Parkinsonian Disorders
  - Basal Ganglia Diseases
  - Neurodegenerative Diseases
  - Neurotransmitter Agents
  - Molecular Mechanisms of Pharmacological Action
  - Pharmacologic Actions
  - Physiological Effects of Drugs

- **Dystonia**
- **Dystonic Disorders**
- **Parkinson Disease**
- **Tremor**
- **Essential Tremor**
- **Dyskinesias**
- **Neurologic Manifestations**
- **Nervous System Diseases**
- **Signs and Symptoms**

ClinicalTrials.gov processed this record on June 06, 2013
Results

- Participant Flow
- Recruitment Details
- Pre-Assignment Details
- Reporting Groups
Baseline Characteristics

1. Primary: Major Adverse Cardiac and Cerebrovascular Events (MACCE) within 30 Days of the Procedure. [Time Frame: Up to 30 days after the procedure was performed]

Outcome Measures

1. Secondary: Device Success [Time Frame: The entire duration of the index procedure]

2. Secondary: Technical Success [Time Frame: The entire duration of the index procedure]

Adverse Events

Results (cont.)

- Baseline Characteristics
- Outcome Measures
- Adverse Events
- More Information
### Serious Adverse Events

**Time Frame**
- Index procedure through the 30 day follow-up visit.

**Additional Description**
- No text entered.

#### Reporting Groups

<table>
<thead>
<tr>
<th>MO.MA Roll-In Cases</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects who were enrolled prior to the pivotal phase of the trial at each US site. All subjects who fulfilled the eligibility criteria and were screened and enrolled to undergo carotid stenting with cerebral protection with the MO.MA proximal flow blockage cerebral protection device.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MO.MA Pivotal Subjects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects who fulfilled the eligibility criteria and were screened and enrolled to undergo carotid stenting with cerebral protection with the MO.MA proximal flow blockage cerebral protection device.</td>
<td></td>
</tr>
</tbody>
</table>

#### Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>MO.MA Roll-In Cases</th>
<th>MO.MA Pivotal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>11/37 (29.73%)</td>
<td>37/225 (16.44%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>0/0 (0.00%)</td>
<td>4/225 (1.70%)</td>
</tr>
<tr>
<td># events</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Coagulopathy *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>0/0 (0.00%)</td>
<td>1/225 (0.44%)</td>
</tr>
<tr>
<td># events</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>1/37 (2.70%)</td>
<td>2/225 (0.89%)</td>
</tr>
<tr>
<td># events</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac failure congestive *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>0/0 (0.00%)</td>
<td>1/225 (0.44%)</td>
</tr>
<tr>
<td># events</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardio-respiratory arrest *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>0/0 (0.00%)</td>
<td>1/225 (0.44%)</td>
</tr>
<tr>
<td># events</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease *</td>
<td></td>
<td></td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td>0/0 (0.00%)</td>
<td>1/225 (0.44%)</td>
</tr>
<tr>
<td># events</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
eMerge Consortium

Informatics in Action

Large-scale genomic data integrated with clinical workflow through EHR systems

http://www.genome.gov/27540473#al-2
Sharing Clinical Data

Informatics in Action

SHRINE (Shared Health Research Information Network)

Query across multiple institutions for research purposes

Objectives

- Increase data set size for analysis and detection of patterns
- Share routine clinical data – not disease specific
- Increase pool of individuals for clinical studies
- Demonstrate cooperation across traditionally competing institutions

http://catalyst.harvard.edu/services/shrine/
SHRINE Query Interface

Query: What is the distribution of individuals with pervasive developmental disorders across 5 collaborating hospitals?
Bayesian model used to predict a patient’s risk of receiving a future diagnosis of abuse, based on the patient’s diagnostic history.

Reis et al. BMJ 2009; Sep;339:b3677
**Medicine at a Crossroads**

- Petabytes of data are being collected
- Data need to be shared
- The data need to be stored, processed, filtered, visualized, integrated, and interpreted
- Social, legal, ethical, and economic issues need to be resolved