Transformation of MS care in the 21st Century
How NARCRMS will change the way we practice

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North American Registry for Care and Research in MS (NARCRMS)

Outline
- Primer on ADNI
- Overview of NARCRMS
- Example of how this will change clinical trials
- Example of how it will change the way we practice as physicians
- Example of how patients will look at their disease and treatment

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

Origin of ADNI
- Neil S. Buckholtz
  - Chief of the Dementias of Aging branch of NIA
- William Potter
  - Chief Scientist at Eli Lilly
- Richard J. Hodes
  - Director, NIA
  - Foundation of NIH
- Steven M. Paul
  - Scientific Director, NIMH
  - Chief CNS Research, Eli Lilly

Collaboration commenced in 2003
ADNI

Landmark milestones
October 2004 - ADNI was formed
• Focus on PET and MRI
June 2009 to 2011 – ADNI GO was formed
• Established various diagnostic criteria for different stages of AD
• 200 early patients entered into a longitudinal cohort
2011 to present. ADNI 2 Established
• Biomarkers evaluated

Funding
• Pharmaceutical Industry
  – $20 million
• National Institute of Aging
  – $20 million
• National Institute of Bioimaging and Bioengineering
  – $20 million
• VA Office of R&D, Federal Stimulus Package
  – $24 million
  – $70 million
ADNI

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) unites researchers with study data as they work to define the progression of Alzheimer’s disease. ADNI researchers collect, validate and utilise data such as MRI and PET images, genetic, cognitive tests, CSF and blood biomarkers as predictors for the disease. Data from the North American ADNI’s study participants, including Alzheimer’s disease patients, mild cognitive impairment subjects and elderly controls, are available from this site.

ADNI Funding - Industry

National Institute on Aging

National Institute of Biomedical Imaging and Bioengineering

Benevolence

Genentech

Ingenomics

IXICO

Janssen

Merck

NeuroRx

Pfizer

Synarc

Takeda

Takeda Canada

Adler Neuroimaging

Alzheimer's Association

Canadian Institutes of Health Research

Institut de recherche Armand-Frappier
ADNI – BioPharma Partners

Private Partner Scientific Board
The ADNI Private Partner Scientific Board (PPSB), convened by the Foundation for the National Institutes of Health, serves as a forum for open dialogue as it relates to the project’s progress and new trends in research and development as it relates to the field of Alzheimer’s disease. If you have any questions about the PPSB or how to become a member, please contact Julie Wolf-Kodda at jwolfo@nia.nih.gov. Current PPSB partners include:

- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation
- Amgen Life Science Ltd.
- BioClinica
- Biogen Idec
- Bristol-Myers Squibb
- Canadian Institutes of Health Research
- Eisai Inc.
- Elan Pharmaceuticals
- Eli Lilly and Company
- F. Hoffman-La Roche Ltd.
- GE Healthcare
- Genentech
- Invogenetix
- IXICO Ltd. Institut de Recherches Internationales Servier
- Janssen Alzheimer Immunotherapy
- Johnson & Johnson
- Medpace
- Merck & Co.
- Meso-Scale Diagnostics
- NeuroRx Research
- Novartis Pharmaceuticals Corporation
- Pfizer, Inc.
- Piramal Imaging
- Sanochemia
- Takeda

FNIH
Partners for Innovation, Discovery, Health

Wei Li, Ph.D. — 2013 Sayer Vision Research Lecturer
Wei Li, Ph.D., is the first recipient of an award in recognition of his role in Vision Research. He has received the award for his work on the structure of the eye and the way it is affected by diseases. (12)

The 2011 Lasker Award in the Biomedical Sciences Nomination is Now Open

 verschlagwörter

- Disease Research Mayo
- The Edward J. Seif Family Foundation
- Combined Patient Campaign Mayo

Click here to learn more >>

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The Biomarkers Consortium Neuroscience Steering Committee is pleased to sponsor a DSP Phenomena Workshop. Visit >>

Click here to learn more >>
Alzheimers Disease Neuroimaging Initiative (ADNI)

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<td>Coordination Center</td>
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<td>Acquisition Sites</td>
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ADNI Program Leadership
- Michael W. Weiner, MD, UCSF

Biomarker Core
- John Q. Trojanowski, MD, PhD, UPenn

Biostatistics Core
- Laurel Beckett, PhD, UCDavis

Clinical Core
- Paul Aisen, MD, UCSD
- Ronald Peterson, MD, Mayo Clinic, Rochester, MN

Genetics Core
- Andrew Saykin, Psy.D, Indiana University

Image Analysis and Modeling Center
- Arthur W. Toga, PhD, USC

MRI Core
- Clifford Jack, MD, Mayo Clinic, Rochester, MN

Neuropathology and brain Banking Core
- John C. Morris, MD, Washington Univ. St. Louis, MO

PET Core
- William Jagust, MD, UC Berkley
ADNI
Summary

• The database is not owned by any one participating entity but is collectively owned by ADNI.
• Database is open to all stakeholders with all patient protection / privacies in place
• Cores are located at sites that have exhibited excellence in the services that they provide

PATIENT CENTERED OUTCOME RESEARCH

Patient reported data

Physician reported data

NARCOMS

Longitudinal Integrated Data

NARCRMS

Patients

4P
Patient Physician Partnership Program

Patient Education
Empower patients to take charge of their MS

Professional Education
Understand Multiple Sclerosis in all its manifestations
North American Registry for Care and Research in MS

NARCRMS

- Collaboration of Industry and MS Centers to create an “Open Source” database in MS, available in real time to patients, physicians, and industry
- Participation by Insurance Industry is being explored
- Patient identifiers are preserved at sites where patients are cared for
- The same information is available to all other participants in a de-identified format
- The database will be updated in real-time on a daily basis

NARCRMS

Serves two functions

1. Registry function – All participating sites will report all confirmed MS patients to NARCRMS. Just demographic information will be collected
2. Database function
   - Entry point is through NARCOMS.
   - Informed consent – Sign on at the web-site & at the institution
   - Patients have to self-register and receive a unique identifier number. That number will not be duplicated so no two patients will ever have the same number
   - Unique identifiers prevent patient duplication when movements between centers occur
   - The unique identifier is required to enter NARCRMS
   - Once patients complete the registration they have no further access to enter any information in NARCRMS
NARCRMS

• Data Collection – Routine visit
  – Visit information from EMR during routine visits
  – Laboratory information from EMR collected during routine visits
  – Routine MRI images
• Data Collection – Annual visit (Birth month)
  – Standardized testing
  – Standardized MRI
  – Biomarkers collection

What are the advantages of using REDCap?

• This tool is useful for small to medium sized studies to support effective data capture.
• Up-front cost: $0.00
• Easy and intuitive to design, develop, and use data collection forms/screens.
• Screen layouts are clear and simple to navigate.
• Interactive editing includes range checks, data type checks, valid date checks, and branching logic.
• REDCap provides audit trails for tracking the history of data entry and revision.
• REDCap permits downloads of data to Excel, PDF, SAS, SPSS, Stata and R.
• REDCap is being used extensively by other CTSAs, including Vanderbilt, Mayo Clinic, and Harvard.
• REDCap software includes models for a number of standard data collection instruments (e.g., RAND SF-36, many others, see http://www.project-redcap.org/library/index.php).
• REDCap permits double-data-entry.
• There are many training videos available on the UMN REDCap website.
• REDCap supports web-based randomization.
• REDCap’s Data Quality module supports reporting on problems with data consistency within and across forms.
NARCOMS
Cloud Computing

Cloud Computing
• HIPAA compliant
• Title 21 CFR part 11 compliant
• EU Safe harbor compliant
Steering Committee

Steering Committee
- Stephen Hauser, MD – Chair
- Howard Weiner, MD
- Michael Weiner, MD
- Michael Racke, MD
- Barbara Teter, RN
- Stanley Cohan, MD
- Anthony Traboulsee, MD
- David Li, MD
- Kottill Rammohan, MD
- Anne Cross, MD
- Aaron Miller, MD

Consortium of MS Centers
- June Halper
- Corey Ford
- Robert Lisak
- Colleen Harris

National MS Society
- Nicholas LaRocca

North American Research Committee on MS (NARCOMS)
- Gary Cutter

CMS / Insurance Industry
- CDC
- FDA
North American Registry for Care and Research in MS
NARCRMS

• Every member of CMSC can participate. Includes academia and private practice.
• Every patient in the US is eligible to participate
• A patient has to enroll in NARCOMS before they can be available in NARCRMS
• Every patient will be assigned a unique identifier to avoid duplication when they move to another center
• Every patient will be included in the registry but participation in the database will require informed consent

North American Registry for Care and Research in MS
NARCRMS

• Minorities and patients from lower socioeconomic classes will be recruited into the database
  – Offer a Spanish version of data entry / testing
  – Create apps for mobile devices especially smartphones
Why Should You participate?

• If you enjoy participating in a clinical trial, you will enjoy participating in this program.
• You will be reimbursed for services like in a clinical trial for data entered.
• You can do simple studies yourself, or do complex studies by linking with Centers around the country
• You can care for your patients better since they will come with better information about themselves.

Why should a Patient Participate?

• In addition to routine care related information, participating patients will also receive information about their disease status
• Annual metrics not usually collected in day-to-day care such as EDSS, MSFC, cognitive status, and standardized MRI will be done
• They can compare themselves to other patients on similar treatment regarding relapse rate, progression and changes in MRI; at their center, regionally or nationally.
• For outliers one should consider early intervention in change of DMT
Why should Industry Care?

- Designing clinical trials should be easier when one uses real-world data regarding exacerbation and progression rates from the population used for recruiting rather than a best-guess estimate.
- Pre-entry disease course in subjects will be better defined
- Recruited subjects may be more aligned to the inclusion / exclusion criteria.
- Smaller sample sizes may be possible with better defined populations
- Recruiting for clinical trials will be easier
- Phase 4 data after release of drug to the market is best obtained on the basis of this database.

Why should a patient participate in the program?

- How am I doing with my treatment now?
- How is my disease course clinically, for relapses and progression, and by MRI?
- Am I an outlier? If so does it warrant a change in strategy now?
How can A longitudinal database change my Practice?

Case.
• A 22 year old AA male is seen with evidence of a sensory thoracic myelopathy. MRI of the spine shows patchy lesions from C2 to T10.
• Lesions not longitudinally extended.
• Brain shows moderate disease burden with enhancing lesions.
• CSF shows elevated IgG index with OCBs.
• Receives 5 days of IV Steroids. Recovery is complete.
• EDSS = 0.
• Long-term Management:
  — Standard therapy or aggressive therapy?

How can A longitudinal database change my Practice?

• A new agent is released for clinical use
• A known side effect of the drug is occurrence of a certain type of leukemia thought to be rare
• You notice a case from your practice.
• You query the database and find more cases than what was expected
• You may choose or not choose to write about it but bring it to the attention of regulatory authorities who also has the same information
• Your decision to use or not use this agent may antecede any decision by regulatory authorities based on your collective experience.
Designing the Perfect Progressive MS Clinical Trial

Lessons from EDMUS

EDMUS Database
Relapse and Disability in MS

EDMUS Database
Relapse and Disability in MS


EDMUS Database
Relapse and Disability in MS

How can information from a database change recruitment to a Clinical Trials?

- Recruitment of patients into Progressive MS clinical Trial
  - Inclusion criteria is EDSS 3 to 6.5
- Scenario 1. Most recruited patients are skewed towards the higher disability scores – The study is doomed to fail
- Scenario 2. Most patients are around EDSS =3. The study may show a benefit if the test –drug has a beneficial effect

EDSS 4.5 to 6.0 is the same duration for all patients regardless of how long it took an individual patient to reach EDSS 4.5

Transition of RRMS to SPMS
Processes From Within: Progression

- Secondary Progressive MS
- Primary Progressive MS
- Benign MS
- Normal Aging

Processes From Without: Exacerbation

- Secondary Progressive MS
- Primary Progressive MS
- Normal Aging
- RRMS
Brain Parenchymal Fraction


Baseline Year 1 Year 2

Placebo Patients (n=72)

Healthy Controls (n=16)

0.871 ±0.008

0.83 (z=-5.2)

0.824 (z=-6.0)

0.820 (z=-6.5)

Normalized Brain and Cortical Volumes are Significantly Affected in RIS patients

How can information from a database change recruitment to a Clinical Trials?

Recruitment of patients into Progressive MS clinical Trial
- Inclusion criteria is EDSS 0 to 3.5

AND
- Rate of brain atrophy in the upper quartile

- Sample Size needed for the trial may be modest since the choice of the patient is favored for progression

This approach may also permit the possibility of doing a phase 2 trial to see if DMTs influence the progressive component of this disorder
Proposed Time line

<table>
<thead>
<tr>
<th>Incorporate and establish Charter</th>
<th>2014</th>
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<tr>
<td>Phase 1 Cores:</td>
<td>2015</td>
</tr>
<tr>
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<td>Phase 4 Cores</td>
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<tr>
<td>• Health Care Economics</td>
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NARCOMS

Novartis Pharmaceuticals
- Allitia Di Bernardo (now with GSK)
- Kerri Wyse
- Russell Seay
- Cathryn Clary
- Ralph Kern
- Rahul Sasane
- Dean Hakanson
- Lou Barbato
- Shreeram Aradhye
NARCOMS

Biogen Idec
• John Richert
• Mike Yeh
• Stefan Lanker

NARCOMS

Roche / Genentech
• Bruno Musch
• Donna Masterson
• William Evans
• Charles Barr
NARCRMS

TEVA Pharma
• John Congleton
• Scott Kolodny
• Joan Brooks

Norman Schatz, MD
Philip Frost, MD

Thank You!
• Raw data is available to all stakeholders
• Subcommittees will decide availability of biologic samples to investigators
• Investigators are required to post on eBulletin Boards studies in progress
• Investigators may join other groups or work on the same data on their own
• NARCRMS will not police publications which will be decided by journal peer-review
• NARCRMS should be acknowledged in ALL publications that have used data from this database
• Intellectual property rights will be co-shared by investigators and NARCRMS if such property was developed using NARCRMS

Accelerated Cure Project

Previously The Boston Cure for MS
Databases currently in use

- New York State Consortium
- CLIMB / SUMMIT / EPIC
- Accelerated Cure Project
- MS Base
- EDMUS
- Oregon State MS Database
- Sonya Slifka Study
- Sylvia Lowry Database
- NARCOMS
### Health Care Economics

What are some of the issues?

- How many MS patients are there in this country? How many MS patients do you have in your practice?
- What is the spread according to disease types
- What is the impact of current therapies
- Have we improved the quality of life of our patients
- Is the high cost of MS care worth the returns? Less unemployment, improved mobility, less disability?
- Is the burden to society less?
- Is the burden to health care cost better?

### Biomarkers

- What is the long-term disease course in the disease modifying era?
- Can we develop biomarkers that predict future disability?
- Can we identify up front, patients who need aggressive care?
- Can we develop markers that allow us to use health-care resources wisely?
Databases currently in use

MS Base

Databases currently in use

MS Base

Patient Enrollments

Patient Enrollments By Date

Patient Enrollments By Country
Databases currently in use

Worldwide Data on MS

• Jan Hillert (Jan.Hillert@ki.se): Swedish
• Helmut Butzkoeven (butz@unimelb.edu.au): MS Base
• Michel Clanet (michel.clanet@inserm.fr): EDMUS
• Maria Troiano (maria.troiano@uniba.it): Italian
• Per Soelberg Sørensen (Per.Soelberg.Soerensen@regionh.dk): Danish