A Look Toward the Future

Moderator:
Timothy O’Leary, MD, PhD
Deputy Chief Research and Development Officer
• 10.7% of people over 20 years of age have diabetes mellitus (DM).

• 23.1% of people over 60 years of age have DM.

• 68% of people with DM have heart disease on death certificates.

• 16% of people with DM have stroke on death certificates.

• 75% of people with DM have hypertension
Total Diabetes Burden in U.S. in 2007

- Diabetes is the leading cause of new blindness and of kidney failure in adults.
- 60-70% of people with DM have nerve damage.
- Over 60% of non-traumatic amputations occur in diabetes.

**Cost of DM**
- $174 billion (CDC)
- Over $200 billion (ADA)
Design

• VA diabetes trial

• 20 Centers, 1791 patients

• Prospective, randomized study of Intensive vs Standard glycemic treatment on CV events in patients with Type 2 DM with sub-optimal response to maximum oral agents or insulin.

• Blood pressure, lipids, diet and lifestyle treated identically in both arms.

Veterans Affairs Diabetes Trial

Veterans Affairs Diabetes Trial

A Primary Outcome

HR (CI) 0.88 (0.74, 1.05)
P = 0.14

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<th>Years</th>
<th>Standard therapy</th>
<th>Intensive therapy</th>
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<tr>
<td></td>
<td>No. at Risk</td>
<td>No. at Risk</td>
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<td>892</td>
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Results and Conclusions from the VADT

- BP, lipids, and glucose can be controlled in VA patients.
- With good risk factor control, intensive glucose control does not decrease CV events.
- Early intensive glucose control (before 15 years) may be beneficial.
- Late intensive glucose control (after 20 years) may be harmful.
- Severe hypoglycemia is associated with increased CV events.
Comparative Effectiveness Research and Hypertension

William C. Cushman, MD
Chief, Preventive Medicine
Memphis VA Medical Center
In the 1960s Edward D. Freis lead the first double-blind, multi-institutional controlled clinical trial of cardiovascular drugs, the Veterans Administration Cooperative Study on Antihypertensive Agents.

This landmark study showed that treating high blood pressure with medications dramatically reduced disability and death from stroke, congestive heart failure, and other cardiovascular diseases.

A number of VA Cooperative Studies in hypertension followed this trial.
• Dr. Cushman chaired the PATHS trial.
• PATHS tested whether veterans who drank an average of 6 alcohol drinks per day and who had high blood pressure or prehypertension could reduce their alcohol intake to less than 2 drinks per day, and whether this would lower BP or prevent hypertension in a randomized clinical trial.
• More than 600 Veterans participated – both groups lowered their drinking and BP.
  • Although the intensive intervention group lowered their drinking and BP more, the difference in blood pressure was not statistically significant.
  • The results were consistent with other trials testing the effect of alcohol intake reduction on BP.
ALLHAT: Antihypertensive and Lipid-Lowering for the Prevention of Heart Attack Trial

- Sponsored by National Heart Lung and Blood Institute (NHLBI) in collaboration with VA.
- Over 42,000 participants from more than 600 clinical sites in North America.
- Dr. Cushman chaired the VA participation: approximately 7,000 Veterans from 70 VA medical center sites.
- Demonstrated that newer antihypertensive drugs were not better than a thiazide-type diuretic in preventing cardiovascular events (such as heart attacks, stroke, heart failure), but the diuretic was better in preventing heart failure or stroke compared with each of the 3 newer drugs.
ACCORD Trial: Action to Control Cardiovascular Risk in Diabetes

- Sponsored by NHLBI with VA participation lead by Dr. Cushman
  - More than 10,000 participants, 1,500 of whom were from 11 VA Medical Centers

- Tested whether more intensive treatment of blood sugar, blood pressure and blood fats would lower cardiovascular events compared with accepted standard treatment in people with diabetes mellitus.
Dr. Cushman lead the ACCORD BP Trial oversight committee.
The ACCORD BP Trial compared the effect on cardiovascular outcomes of targeting a systolic BP less than 120 mm Hg (intensive therapy) vs. a systolic BP less than 140 mm Hg (standard therapy) in 4733 participants with diabetes and elevated BP.
BP averaged 119/64 mm Hg in the intensive therapy group and 134/71 mm Hg in the standard therapy group through most of the trial.
ACCORD BP Trial

- The results showed that there was not an important difference in the occurrence of cardiovascular events between the two groups of participants.
- Although strokes were not very common, the risk of stroke was about 40% lower in the intensive group.
  - Since stroke was not the main outcome and didn’t make the main outcome significantly lower, the trial did not prove that intensive therapy was better.
- There were more hospitalizations seen in the intensive group (vs. standard group) for side effects due to BP medications.
- The intensive group reported no more dizziness or kidney failure than the standard participants.
• Targeting near normal systolic BP (less than 120 mm Hg) did not reduce the combined numbers of heart attacks, strokes and heart disease deaths more than targeting a systolic BP less than 140 mm Hg.

• Participants in the standard therapy group fared very well, with only about half as many strokes, heart attacks or heart disease deaths as expected, emphasizing the value of treating systolic pressures to less than 140 mm Hg.

• Diet and exercise are still recommended for persons with diabetes to help lower heart disease risk and help with BP, blood fats, and blood sugar control.
Importance to Veterans

- Of the approximately 5.5 million Veterans treated in VAs nationally:
  - About half have high BP
  - About a quarter have diabetes mellitus
  - About 2/3 of those with diabetes have high BP

- These clinical trials show that:
  - Treating high BP markedly reduces cardiovascular events
  - Thiazide-type diuretics lower BP very well, are well tolerated are the best BP lowering drug class for reducing cardiovascular events
  - Intensively lowering BP in diabetes is not necessary for reducing most cardiovascular events

- The SPRINT trial, beginning this fall, will test whether intensive treatment of BP will benefit other groups of patients. Almost 2000 Veterans will participate in this NHLBI trial of almost 10,000 participants.
85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT

For Veterans

VETERANS AFFAIRS RESEARCH & DEVELOPMENT
VA Genomic Medicine Program:
Million Veteran Program

J. Michael Gaziano, MD, MPH
Director, MAVERIC
Epidemiology: Types of Studies

- Experimental
  - Randomized intervention
  - Non-Randomized intervention

- Observational
  - Descriptive
  - Analytic
    - Case-control
    - Cohort
Evolution of Epidemiology

- Descriptive studies
- Early analytics
- Case-control studies
- Cohort studies
- Mega-cohort/biobank

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Death before old age is not.

Richard Doll

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Lung Cancer
No Smoking

Smoking
Lung Cancer
No Lung Cancer

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The Black Death

Bruegel’s
Triumph of Death
c. 1556
### Current Large-Scale Biobanks

**Europe**
- Icelandic Biobank and deCODE
- UK Biobank
- Banco Nacional de ADN [Spain]
- GenomEUtwin
- Finnish biobank
- Swedish biobank
- German biobank, KORA
- UK DNA Banking Network & British biobank
- Estonian biobank:
  - Family-based collections [Nordic]
  - Generation Scotland
  - HUNT (cardiovascular)& Biohealth [Norway]
  - EPIC, European (cancer)
  - Danubian Biobank Consortium
  - GATiB Genome Austria Tissue Bank
  - Biobank Hungary

**North America**
- Canadian Consortium [Canada]
- dbGaP, NIH [US]
- National Children's Study [US]
- Marshfield Clinic [US]
- National Health and Nutrition Examinations Surveys [US]
- Kaiser Permanente Northern CA [US]
- Vanderbilt University
- Howard University African Diaspora [US]
- Mayo Clinic
- ACS
Genetic Research in the VA

• VA is an ideal setting for a large 21\textsuperscript{st} century mega-cohort/biobank
  - National pool of willing participants
  - Outstanding electronic medical record
  - Diverse expertise
  - Research infrastructure
Create national resource for current and future genomic research initiatives to improve healthcare to Veterans

**VA Genomic Medicine Program**

Primary (direct) recruitment:

- Million Veteran Program

Secondary recruitment:

- VA studies (CSP/ERIC)
Million Veteran Program

• Enroll up to 1 million users of the VHA into an observational cohort
  ▪ Collect health and lifestyle information
  ▪ Blood collection for storage in biorepository
  ▪ Access to electronic medical record
MVP Infrastructure

- VA Central Office
  Genomic Medicine Program

- Genomic Medicine Coordinating Centers:
  MAVERIC, Boston / CERC, West Haven

- Biospecimen Repository:
  MAVERIC Core Laboratory

- Bioinformatics Platform:
  GenISIS

- Participating VAMCs
Recruitment and Scheduling

- Coordinated centrally by MAVERIC and CERC
  - Mail, call, data processing centers; biorepository
- Invitational mailing
  - Includes invitational letter and brief survey
- Study visit scheduling
Study Visit

- Procedures
  - Informed consent/HIPAA
  - Blood collection (10 mL EDTA)
- Optional Lifestyle Survey
Dear MVP Member,

We thank you for your participation in this exciting research program!

We are asking for your help in completing the optional Lifestyle Survey that asks additional questions to help us to better understand your health and lifestyle habits. Your answers will provide us with more detailed information about your health and family history, exercise, activity and dietary habits, occupational and community exposures, and mental and social health. The more information you provide to us, the more researchers will be able to learn about genes and health.

Any information you provide will about you or your family members will be kept confidential and secure according to VA policy. Once you have completed the questions, please return the survey in the stamped return envelope.

If you have any questions, please contact MVP Call Center staff toll-free at 888-441-6075.

Sincerely,

J. Michael研究生, MD
Principal Investigator, MVP
VA Boston Healthcare System

John Russo, MD, MPH
Principal Investigator, MVP
VA Connecticut Healthcare System
MAVERIC Core Library

- New laboratory to house biospecimens from MVP and other CSP studies
- Standard protocol for processing and storage of genetic samples
- Automation of extraction and storage procedures
• Provide integrated system for multiple users
• Manage recruitment and enrollment centrally and by site staff
• Interface with call center, mail center and scheduling application
• Store genetic and clinical data
• Host platform for scientific analysis
The Genomic Information System for Integrated Science (GenISIS)
Timeline

Start-up

Year 1
- Infrastructure, Launch sites
- Recruit 50K

Year 2
- Recruit 100K
- Expansion
  - Recruit 200K

Year 3
- Recruit 225K

Year 4
- Recruit 225K
- Recruit 225K

Year 5
- Recruit 200K

1 Million Enrolled!
New Genomic Technology for the Study of Amyotrophic Lateral Sclerosis (ALS)

Steven A. Schichman, M.D., Ph.D.
Director, Pharmacogenomics Analysis Laboratory
Central Arkansas Veterans Healthcare System, Little Rock, AR

Durham VAMC and Duke University Medical Center, NC: Eugene Z. Oddone, M.D., M.H.S.; Silke Schmidt, Ph.D.; Dawn Provenzale, M.D., M.S.; Michael A. Hauser, Ph.D.

Boston MAVERIC and Tissue Core Biorepository, MA: Mary Brophy, M.D.; Donald E. Humphries, Ph.D.
What is ALS?

• Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig’s disease, is a progressive neurodegenerative disease leading to muscle paralysis and death.

Incidence and Mortality of ALS

- Incidence
- Mortality

![Incidence and Mortality Chart]

Per 100,000 individuals

- General Population
- All Veterans
Bench to Bedside

• Identify genes associated with ALS using state-of-the-art genomic technology.

• Identify additional genetic and environmental risk factors.

• Identify potential drug targets to improve survival rates.
Project Summary

Microarray Image  Laser Scanner  Microarrays

DNA  DNA Extraction
Status of Project

Data Analysis Ongoing

Durham VA Medical Center
North Carolina

Project Completion

*2.1 Billion Results from 1,765 DNAs
Acknowledgements

- National Registry of Veterans with ALS Study, funded by US Department of Veterans Affairs
- Genes and Environmental Exposures in Veterans with ALS (GENEVA) Study, funded by NIEHS
- ALS Association Study, conducted at Duke University Medical Center and Durham VAMC
- Veterans with ALS and Lead Exposure Study, funded by NIEHS
- Thank you, Veterans, for your participation!
Genetics of Functional Disability in Schizophrenia and Bipolar Illness: Background and Rationale for CSP 572

Philip D. Harvey, PhD
Atlanta VAMC
Professor of Psychiatry, Emory University School of Medicine
Prevalence of Schizophrenia and Bipolar illness

• These are very common illnesses among Veterans
• They are associated with considerable cost and functional impairment
• 92,000 Veterans received treatment for schizophrenia in FY 2008
• 79,000 Veterans received treatment for bipolar disorder
• Of these patients, over 58,000 receive service connected disability of 70% or more
• 90% fall into eligibility criterion A, which means either 100% service connected or low income veterans
Genetics of Severe Mental Illness

- Heritability estimates for both of these illnesses are quite high.
- Heritability of schizophrenia appears to be about 80% and about 75% for bipolar illnesses.
- Further, components of the illness appear to be heritable as well.
- For instance, impairments in certain aspects of cognitive functioning appear quite substantial.
Rates of Real-World Functional Milestones in Schizophrenia and Bipolar Disorder

From Huxley and Baldessarini, 2007; Leung et al., 2008; Harvey et al., 2009
Cognition and Disability

• The single largest predictor of functional disability appears to be cognitive functioning
• Correlations between disability and cognitive functioning are moderate, but quite consistent across studies.
Genetics of Cognitive Functioning

- Individual aspects of cognitive functioning appear quite heritable in families of people with schizophrenia and bipolar illness

- Here are some examples:
  - Episodic memory: .56
  - Vigilance: .60
  - Executive Functions: .50
  - Working memory: .54
Disability as a Central Illness Feature

• Disability is a highly heritable trait
  ▪ Kendler et al., 1995
  ▪ McGrath et al., 2009

• In fact, it was more heritable than cognition, other symptoms, and poor social adjustment prior to onset

• Cognitive impairment is heritable as well

• Is disability heritable because of cognition or skills deficits?

• Are skills deficits central features of the illness?
85 Years of Discovery, Innovation, & Advancement

For Veterans

Veterans Affairs Research & Development