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**Research & Development**

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# A Look Toward the Future

**Moderator:**

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Deputy Chief Research and Development Officer





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# **VA Diabetes Trial (VADT) Update**

**William C. Duckworth, MD**

**Carlos Abaira, MD**

**Tom Moritz, and VADT Investigators**



# National Diabetes Fact Sheet – 2007 (CDC)



- 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)



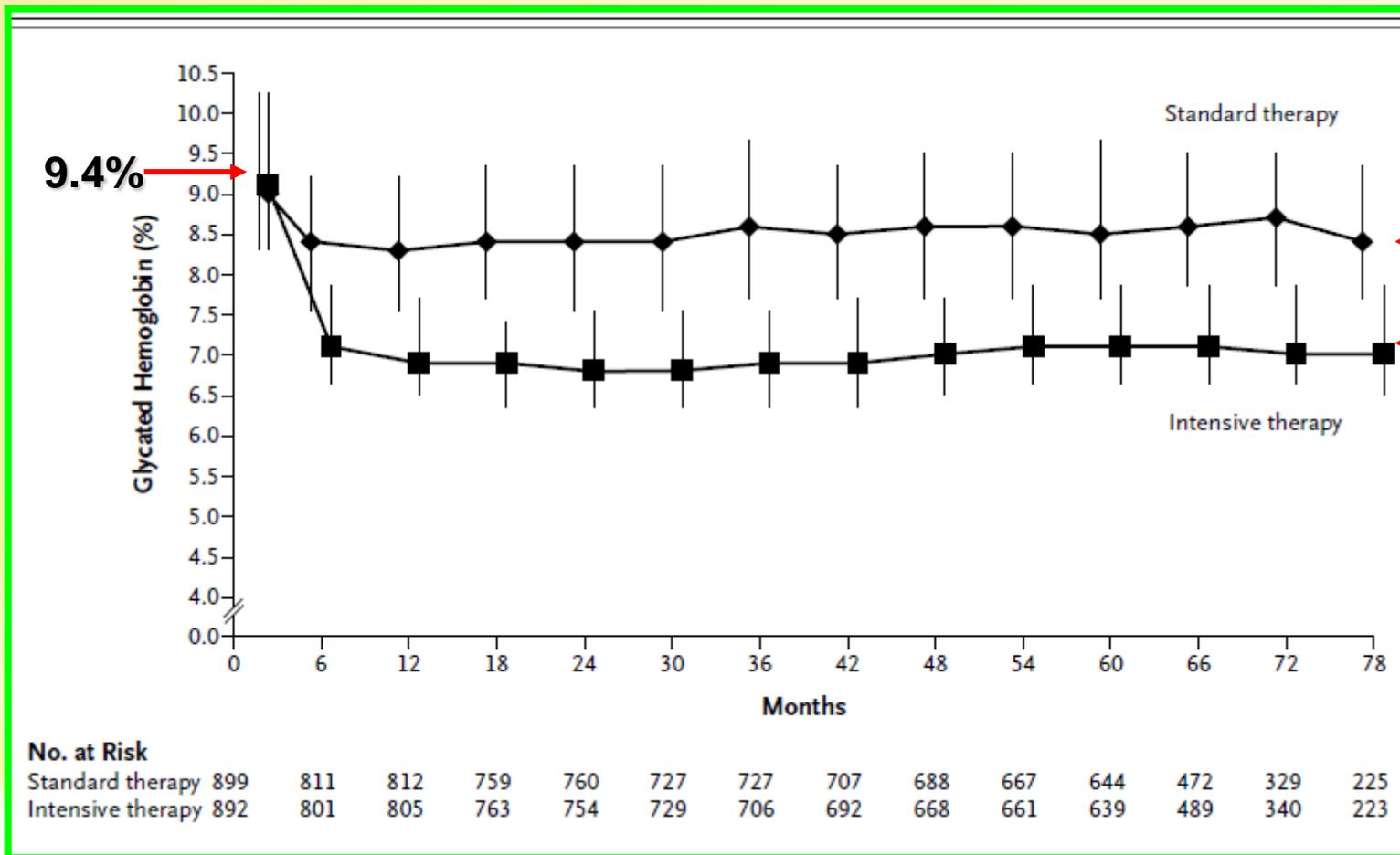
# Design

- 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.

(Abraira C et al. Design of the VADT. J Diab Comp. 2003;17:314-322.)



# Veterans Affairs Diabetes Trial



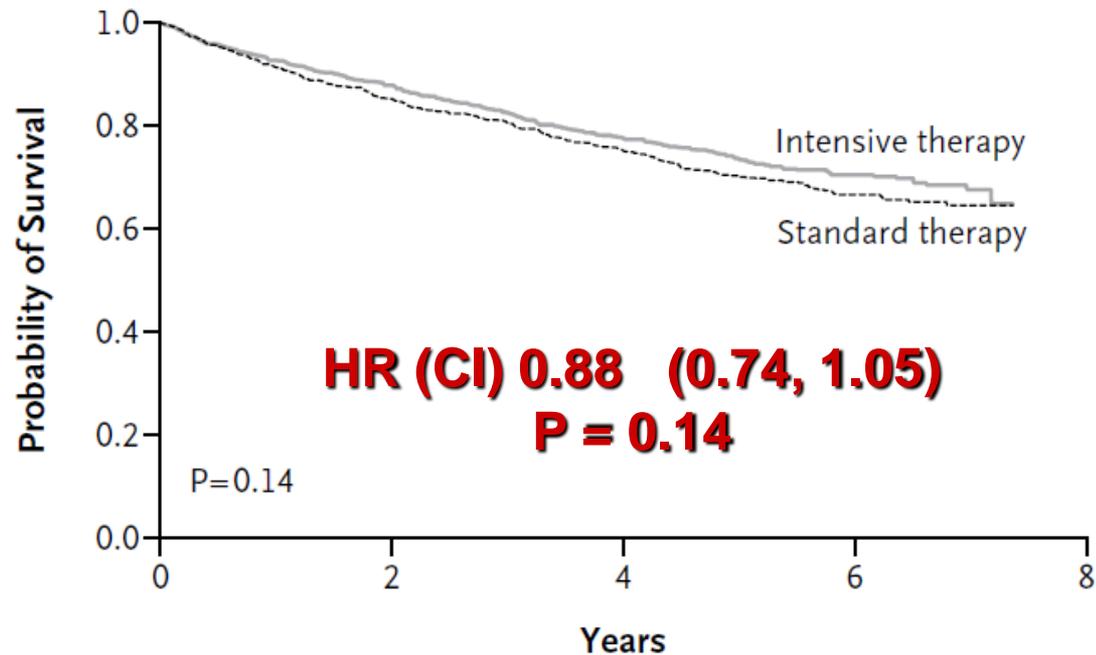
Duckworth W, Abraira C, Moritz T, Reda D *et al* *NEJM* 360: 129-139, 2009



# Veterans Affairs Diabetes Trial



A Primary Outcome



**No. at Risk**

Standard therapy	899	770	693	637	570	471	240	55	0
Intensive therapy	892	774	707	639	582	510	252	62	0



# 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.



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# Comparative Effectiveness Research and Hypertension

**William C. Cushman, MD**  
Chief, Preventive Medicine  
Memphis VA Medical Center



# Hypertension Research in VA



- 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.



# **PATHS: Prevention and Treatment of Hypertension VA Cooperative Study (with NIH)**



- 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.



# ACCORD BP Trial



- 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 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.



# ACCORD BP Trial Conclusions



- 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 and 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.





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# **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

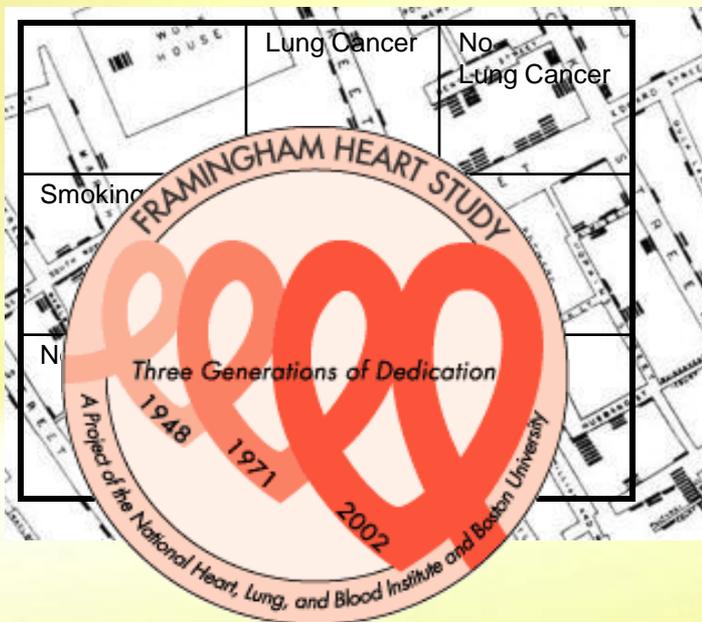
## The Black Death



death before old age is not. — 100 Years

**Richard Doll**

Bruegel's  
Triumph of Death  
c. 1556



# Current Large-Scale Biobanks

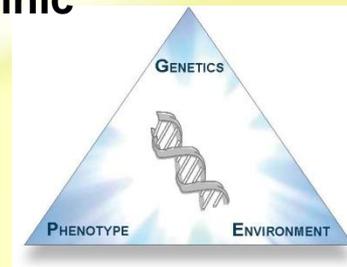


## Europe

- 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<sup>st</sup> century mega-cohort/biobank
  - National pool of willing participants
  - Outstanding electronic medical record
  - Diverse expertise
  - Research infrastructure

The screenshot shows a clinical record interface with the following sections:

- Problems:** Pneumonia, COPD, Essential Hypertension, Peptic Ulcer, Tobacco Abuse, Appendicitis.
- Status:** A, A, A, A, A, I.
- Active Meds:** Enalapril Tab 10mg po q12h, Cimetidine Tab 800mg po qhs, Acetaminophen Capsule 650mg po q6h pm headache, fever, Milk of Magnesia Liquid 30cc po qn constipation, Theophylline Time Release Tab 300mg po q12h, Moxifloxacin Liquid 400cc po prn hearburn, Metoprolerol Sulfate Aerosol 650mcg/inhalation ih q6h.
- Lab Results in Past:** Table with columns for Lab, Date, and Time. Results include CBC w/Diff, Chem 20, and UA.
- Visits:** Table with columns for Date, Time, and Location. Locations include 1A, Gen Medicine, and Cardiology.
- Notifications/Alerts:** New lab results available, Critical Lab Result: GLUCOSE 400 mg/dL, Order released/requires chart signature, Admitted on Dec 12, 1993@10:30.
- Diagnoses/Warnings/Directives:** Environmental.
- Next of Kin:** Jane Doe.
- Allergies:** Cephalosporin, Dairy Products, Strawberries.
- Symptoms:** Thrombocytopenia, Diarrhea, Urticaria, Urticaria.

Navigation tabs at the bottom: Cover, Problems, Meds, Orders, H & P, Notes, Consults, Labs, Xray, Specials, Summ.



# VA Genomic Medicine Program



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



↓  
VA Genomic  
Medicine Program:  
**Million Veteran  
Program**



# 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

	Monday	Tuesday	Wednesday
May 10		11	12
8:20			
8:40			
9:00			
9:20			
9:40			
10:00			
17	18	19	



BARCODE STUDY ID

Dear [Name],

Participate in this program...

I DO NOT WANT TO PARTICIPATE

1. Complete military history and

2. Return

Once we have received your information, we will contact you to schedule your health care visit at the VA. If you have any questions, please call our Call Center staff toll-free at 866-441-1234.

If you do not wish to participate in this program, please return the envelope after checking the "I DO NOT WANT TO PARTICIPATE" box, OR call the MVP Call Center at the number listed above.

Sincerely,

J F V

# Study Visit



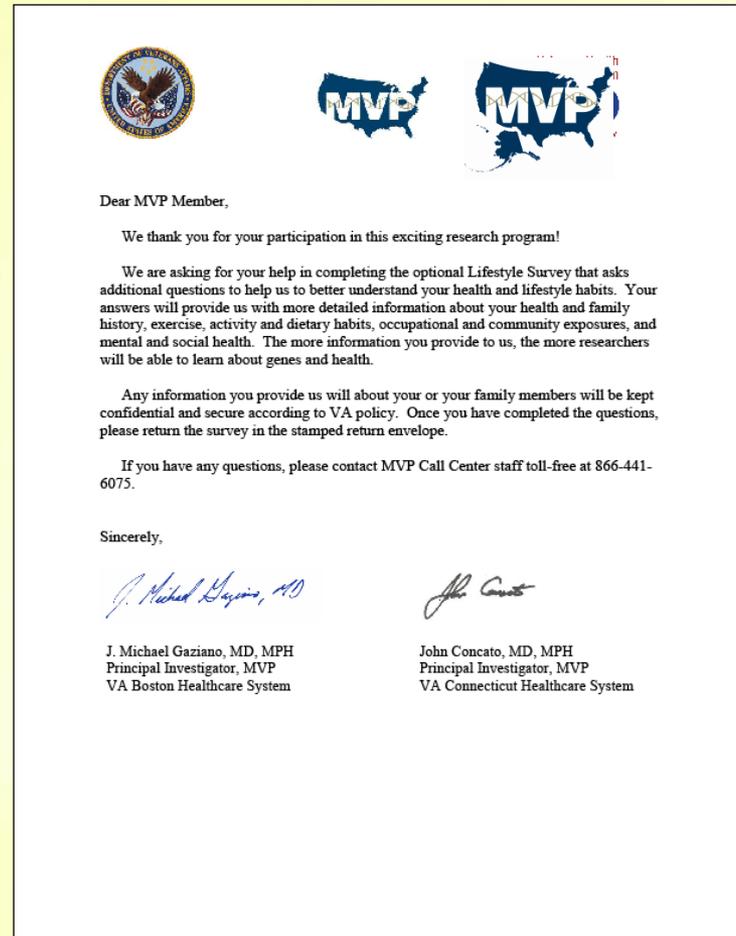
- Procedures
  - Informed consent/HIPAA
  - Blood collection (10 mL EDTA)
- Optional Lifestyle Survey



# Follow-up Contact



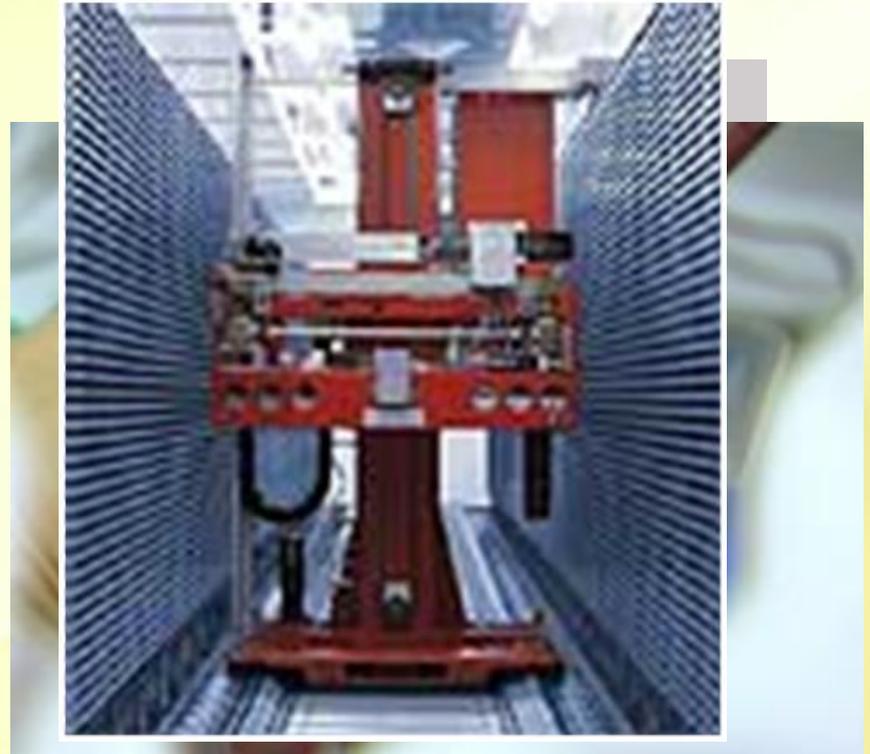
- Thank you letter
- Token of appreciation
- Periodic newsletters
- Possible invitations for future studies



# 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

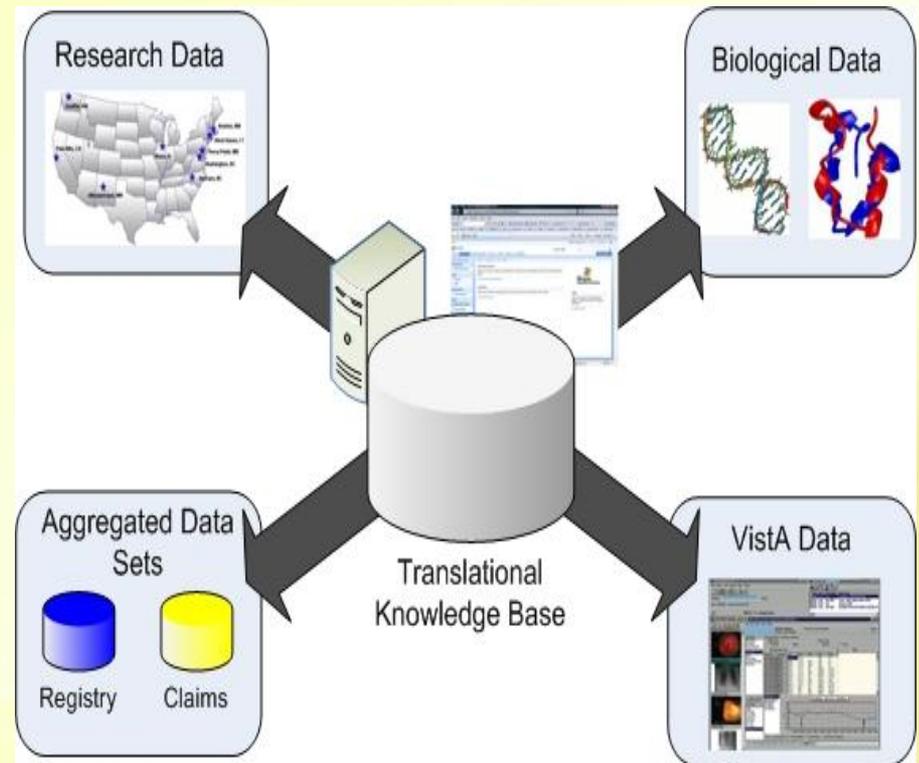


# GenISIS

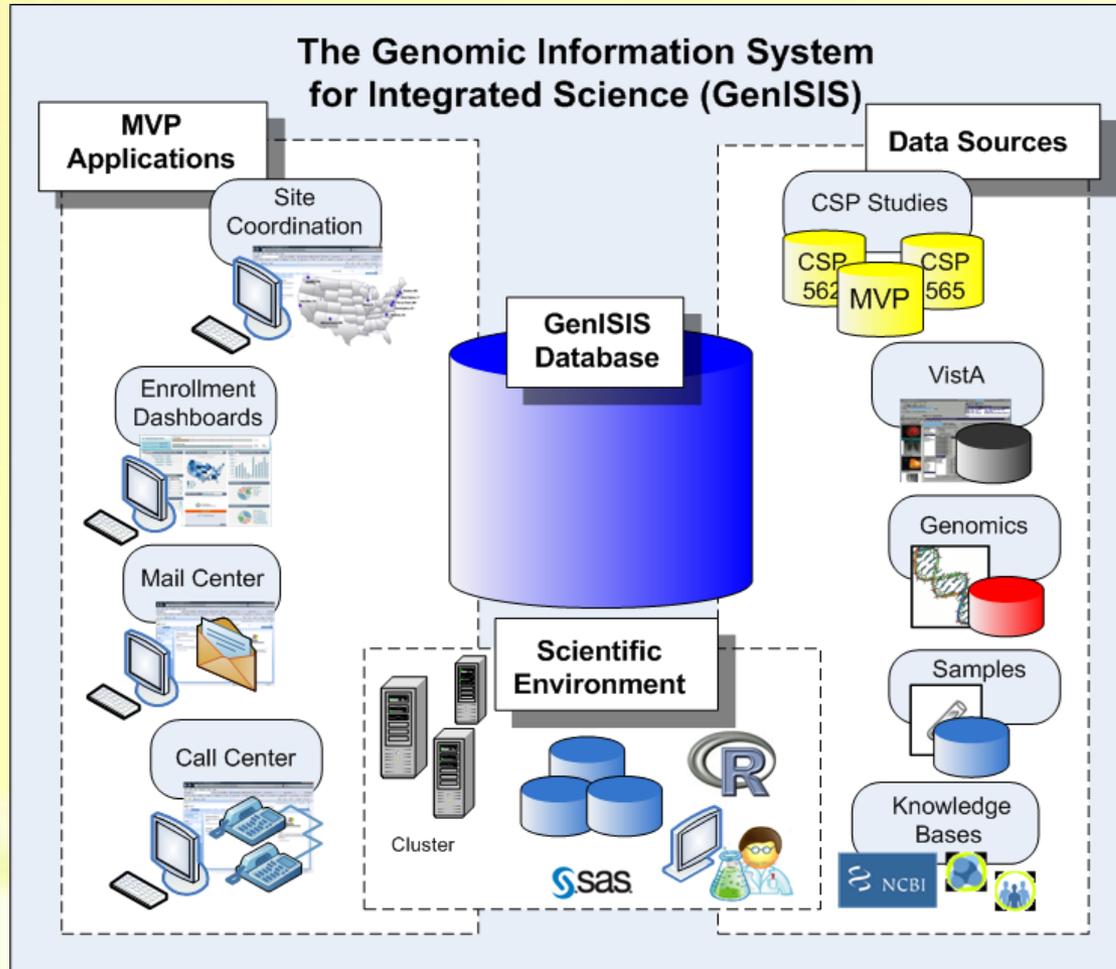
## Genomic Informatics System for Integrative Science



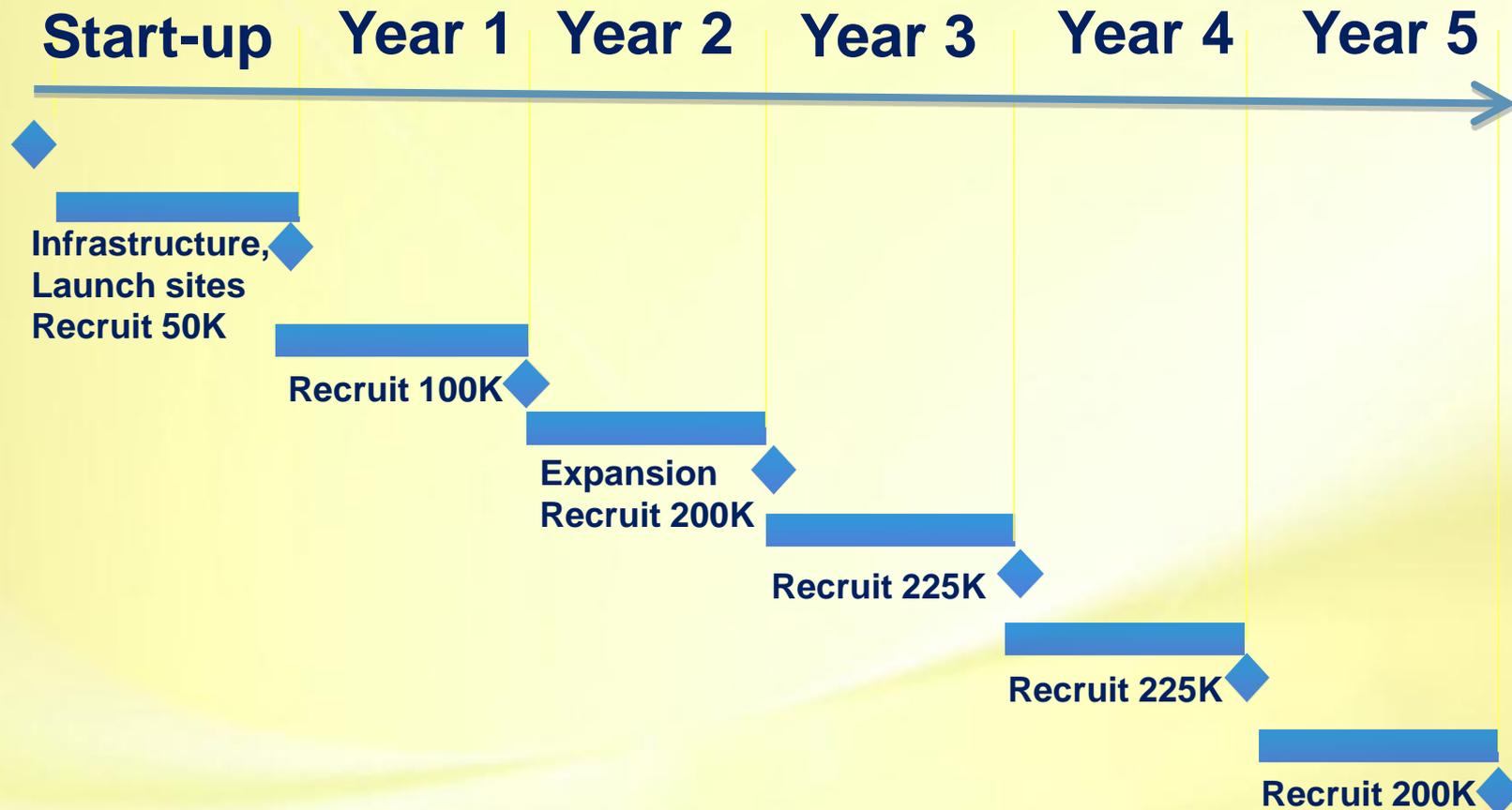
- Provide integrated system for multiple users
- Manage recruitment and enrollment centrally and by site staff
- Interface with call center, mail center and scheduling application
- Store genetic and clinical data
- Host platform for scientific analysis



# GenISIS



# Timeline



# 1 Million Enrolled!





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# **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.

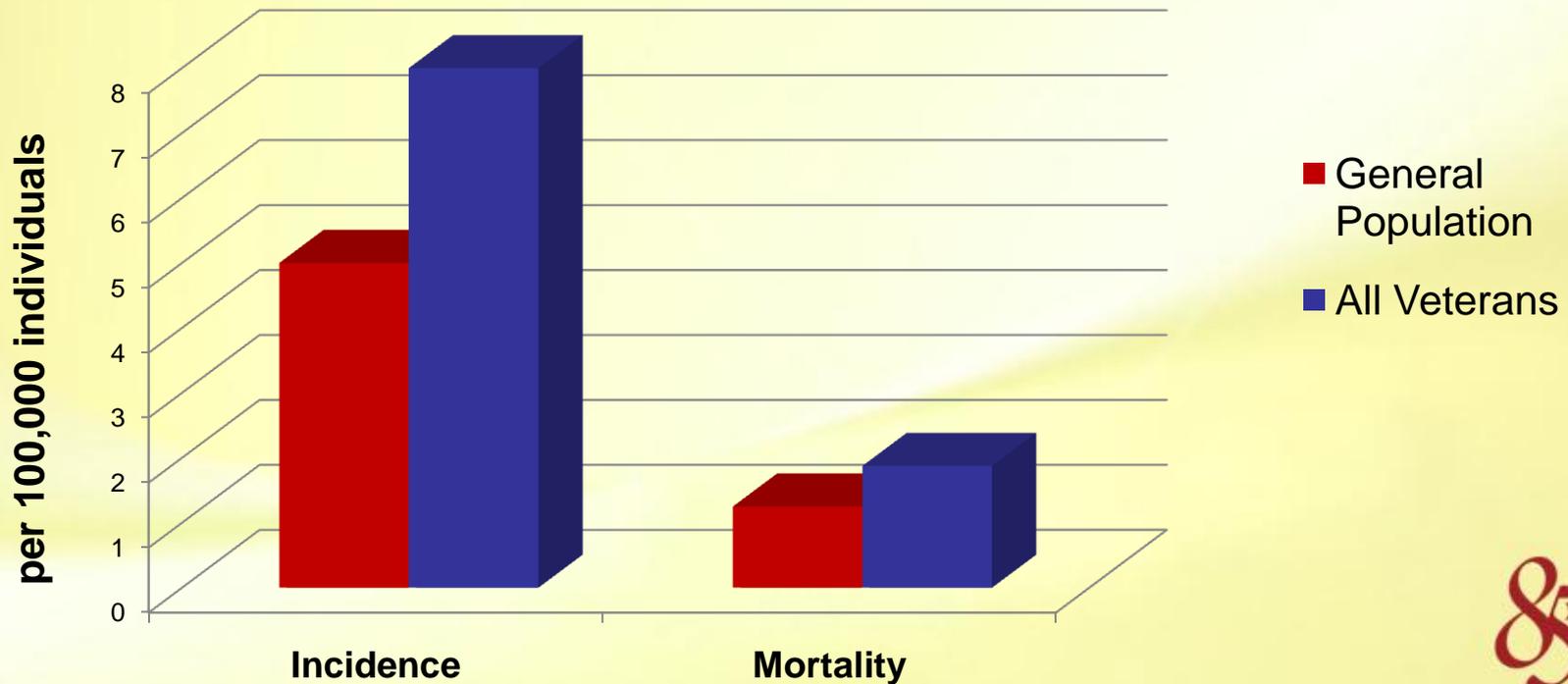


# What is ALS?



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

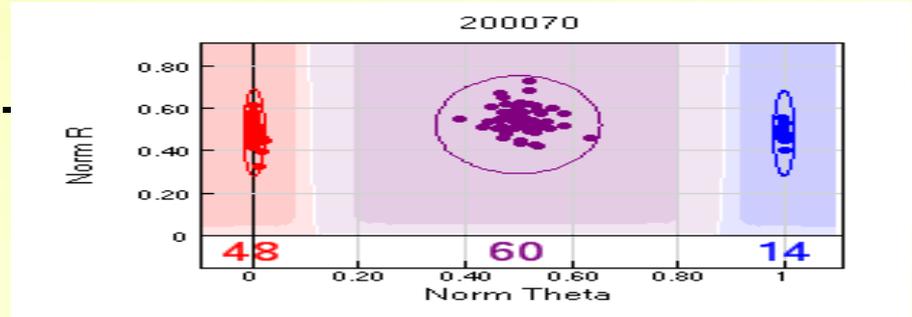
## Incidence and Mortality of ALS



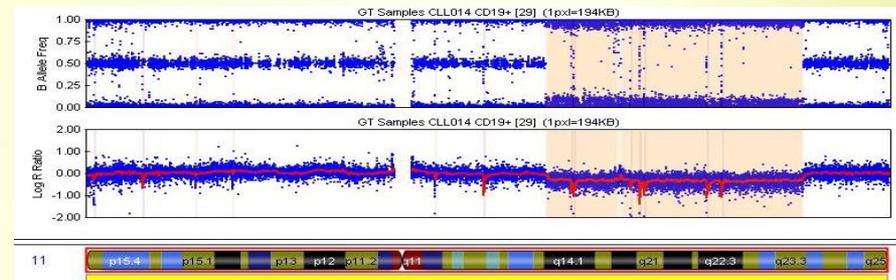
# Bench to Bedside



- 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.



Single Nucleotide Polymorphisms (SNPs)

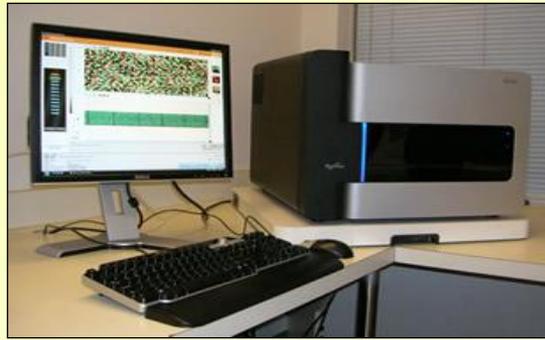


Copy Number Variations (CNVs)

# Project Summary



**Microarray Image**



**Laser Scanner**



**Microarrays**



**DNA**



**DNA Extraction**



# Status of Project

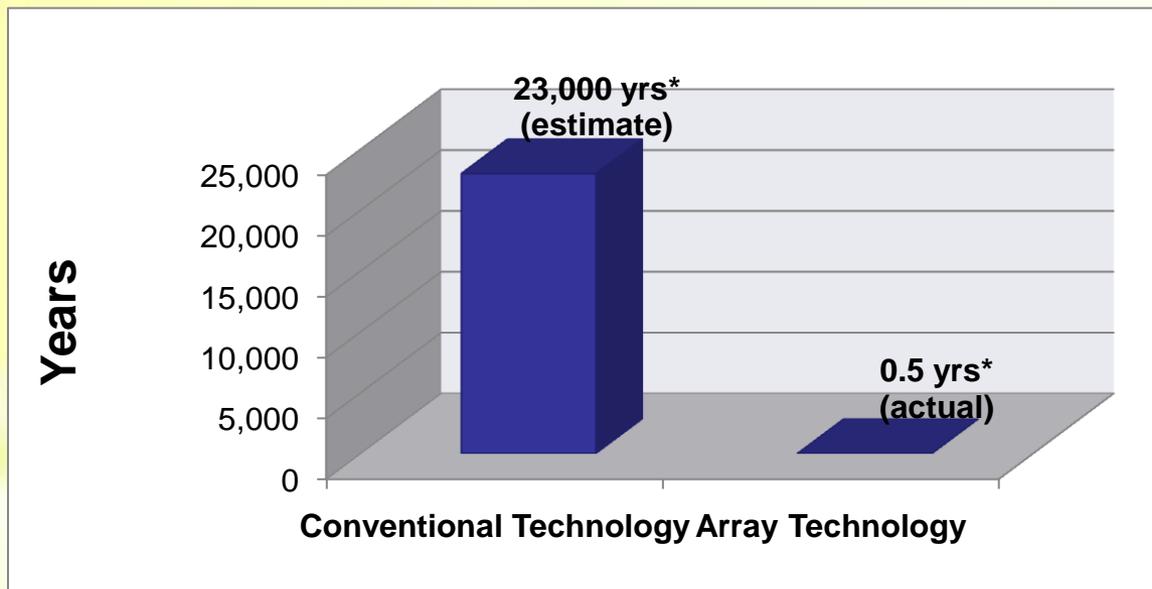
## Data Analysis Ongoing



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!





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# **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

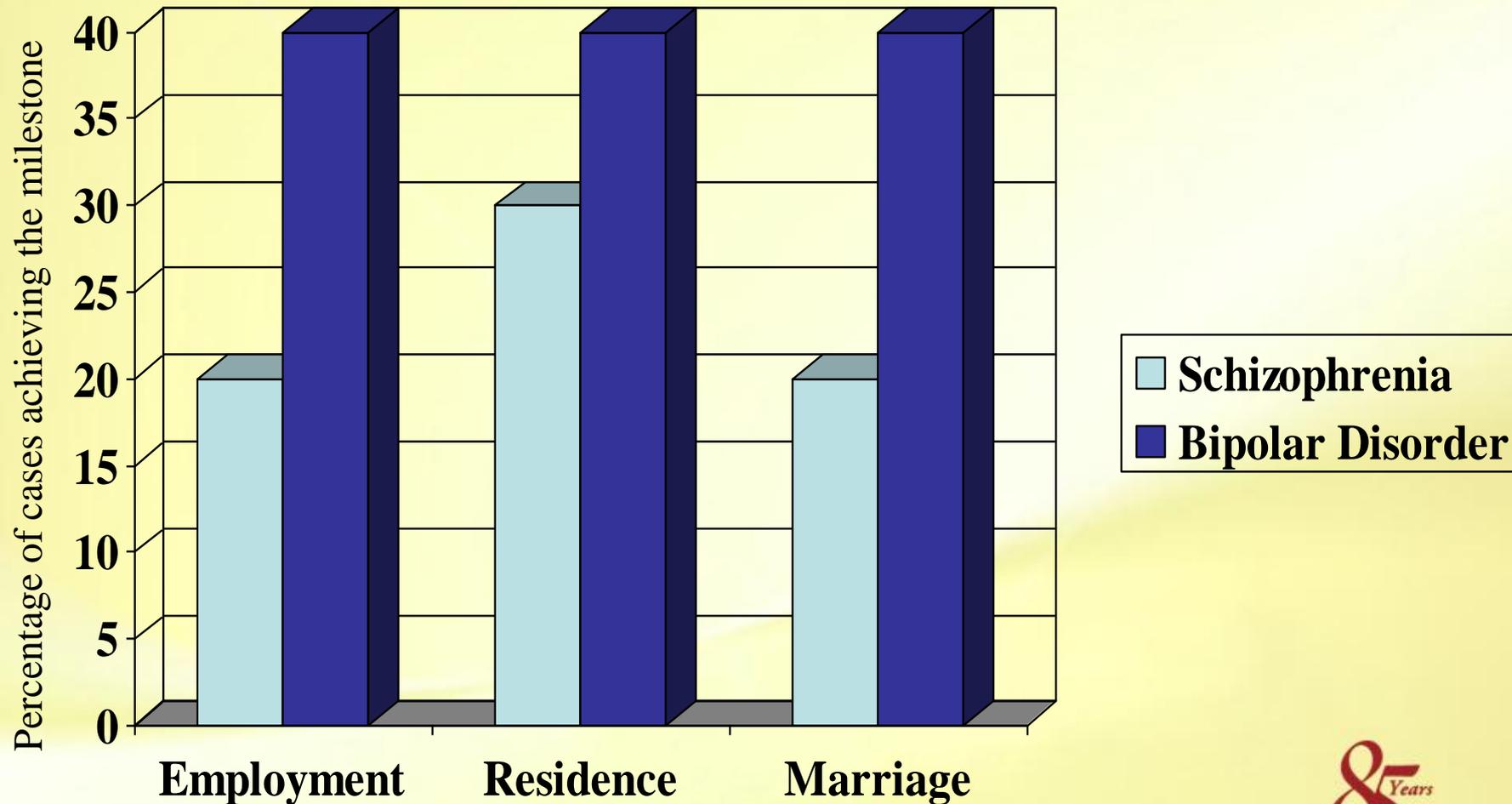


# Genetics of Severe Mental Illness



- 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?



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