

Initiatives on the Horizon II

Phenotyping



Major Roadmap Initiatives

Programs expected to consist of multiple, coordinated funding initiatives designed to overcome grand challenges in biomedical/health research.

Protein Capture Tools

The Proteome is the complete set of proteins in the body. Efforts in this area would support developing and making available to the scientific community high quality probes specific to every protein in the human and in desired animal models. This would allow the ability to characterize protein function in health and disease and to monitor the markers of a disease in order to deploy early prevention efforts and to identify potential therapeutic targets.

Phenotyping

A human Phenotype is the total physical appearance and constitution of a person, often determined by multiple genes and influenced by environmental interactions. Initiatives in this area would encourage the development of resources to systematically catalog human phenotypes in an effort to characterize complex diseases and disorders.



Phenotyping as an Example of Early-Midstage Concept Development

- Identified by RM process
- Voted "A1" status by the IC Directors
- Undergoing further concept development
- Potentially to be presented to IC Directors in Feb 08
- Asking CoC to advise on concept and further development
- This still would require a successful vote and prioritization by the IC Directors to proceed to RFA

Initiatives on the Horizon II: Phenotyping

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Patient-Reported Outcomes Measurement Information System
Dynamic Tools to Measure Health Outcomes From the Patient Perspective

*Patient-Reported Outcomes
Measurement Information
System (PROMIS): An NIH
Roadmap Initiative*



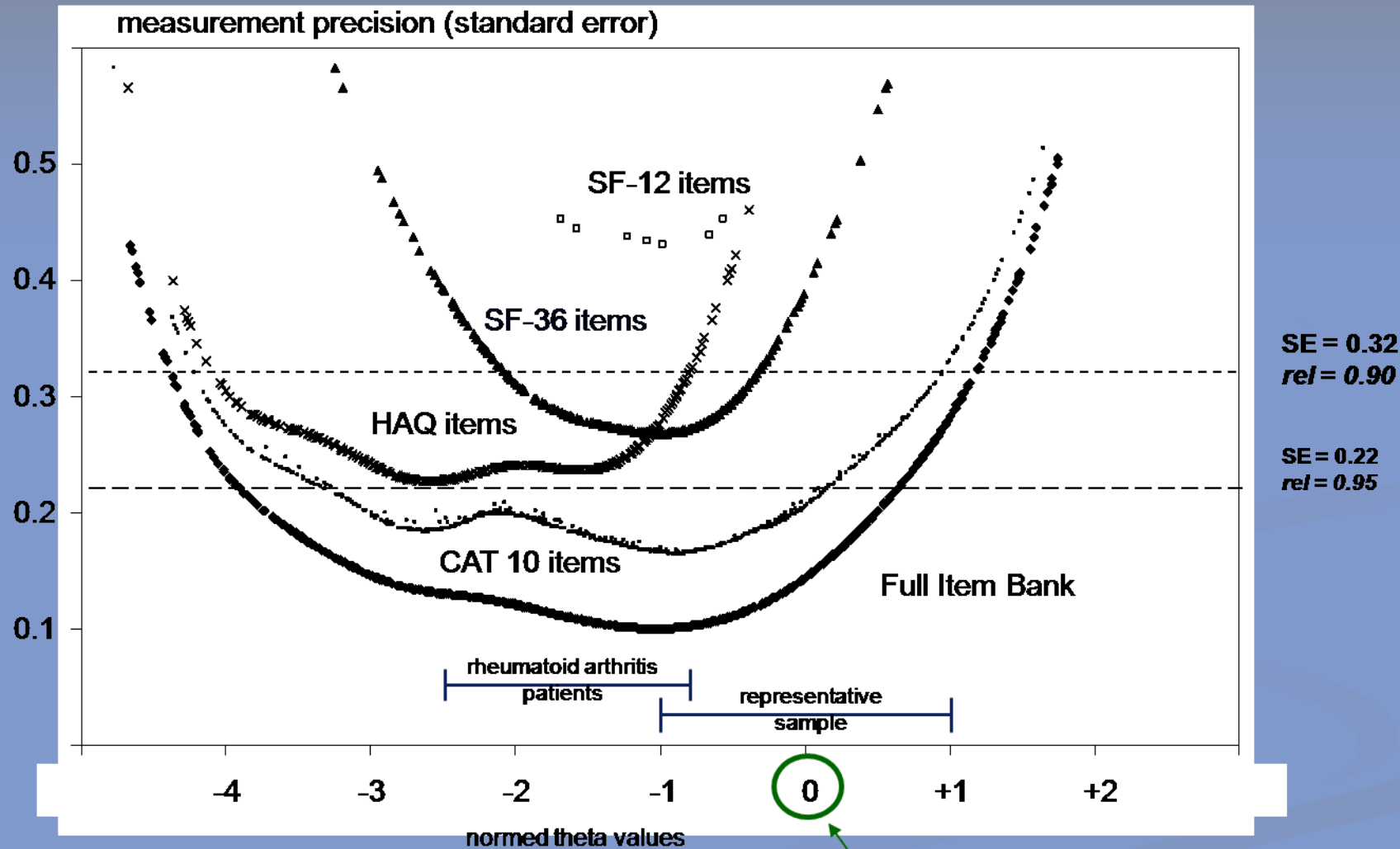
Broad Objectives of PROMIS

RFA-RM-04-011

- Develop and test a large item bank measuring patient-reported outcomes (PROs)
- Create a computerized adaptive testing system that will allow for efficient, psychometrically robust assessment of patient-reported outcomes for a wide range of chronic disease outcome research
- Create a publicly available system that can be added to and modified periodically and that will allow clinical researchers access to a common item repository and to computerized adaptive testing

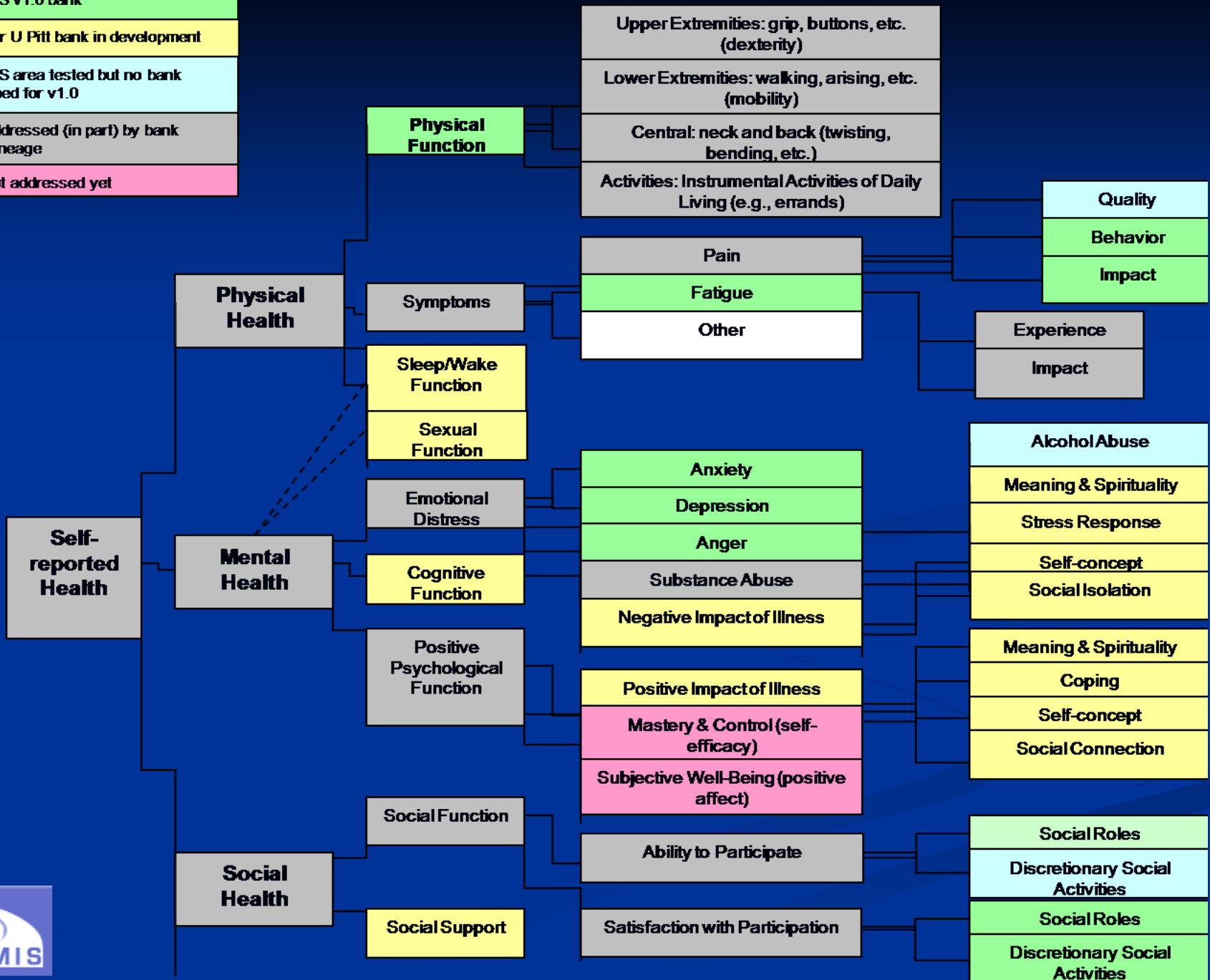


Improved Precision vs. Legacy Measures



US Representative
Sample

PROMIS v1.0 bank
CaPS or U Pitt bank in development
PROMIS area tested but no bank developed for v1.0
Area addressed (in part) by bank within lineage
Area not addressed yet

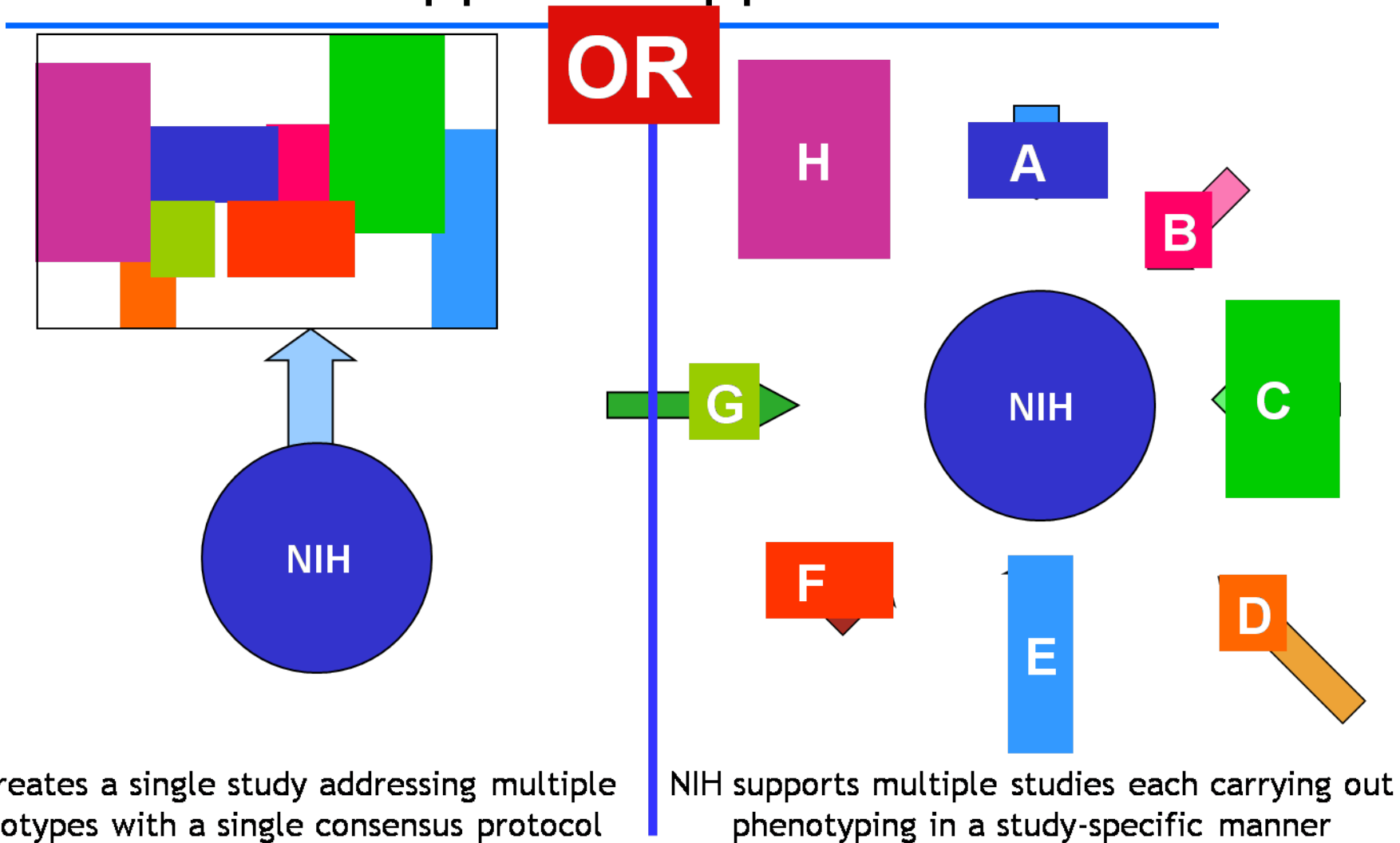


Depression

32 items

ID	Stem
EDDEP03	I felt that I had no energy
EDDEP04	I felt worthless
EDDEP05	I felt that I had nothing to look forward to
EDDEP06	I felt helpless
EDDEP07	I withdrew from other people
EDDEP09	I felt that nothing could cheer me up
EDDEP13	I felt that other people did not understand me
EDDEP14	I felt that I was not as good as other people
EDDEP16	I felt like crying
EDDEP17	I felt sad
EDDEP19	I felt that I wanted to give up on everything
EDDEP21	I felt that I was to blame for things
EDDEP22	I felt like a failure
EDDEP23	I had trouble feeling close to people
EDDEP26	I felt disappointed in myself
EDDEP27	I felt that I was not needed
EDDEP28	I felt lonely
EDDEP29	I felt depressed
EDDEP30	I had trouble making decisions
EDDEP31	I felt discouraged about the future
EDDEP35	I found that things in my life were overwhelming
EDDEP36	I felt unhappy
EDDEP39	I felt I had no reason for living
EDDEP41	I felt hopeless
EDDEP42	I felt ignored by people
EDDEP44	I felt upset for no reason
EDDEP45	I felt that nothing was interesting
EDDEP46	I felt pessimistic
EDDEP48	I felt that my life was empty
EDDEP50	I felt guilty
EDDEP54	I felt emotionally exhausted
EDDEP56	I had trouble enjoying things that I used to enjoy

Phenotyping in clinical studies: two opposite approaches



NIH creates a single study addressing multiple phenotypes with a single consensus protocol

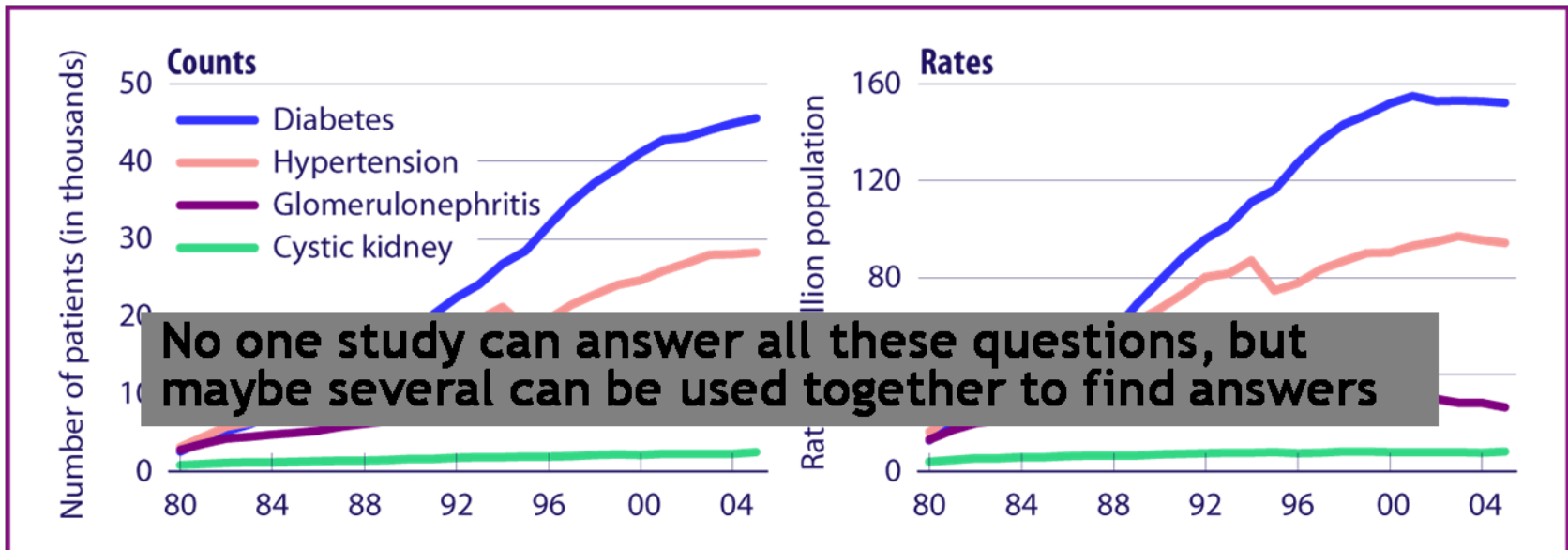
NIH supports multiple studies each carrying out phenotyping in a study-specific manner

Three Genetic Studies of Diabetic Nephropathy - summing the parts

Important disease

AND

Important questions:



GENKID - Genetics of kidneys in Diabetes (type 1 diabetes, case/control and trio recruitment)

ESRD Incidence by Diagnosis

EDIC - Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (type 1 diabetes, DCCT participants plus available family members)

How can these different studies be used for comparison/replication?

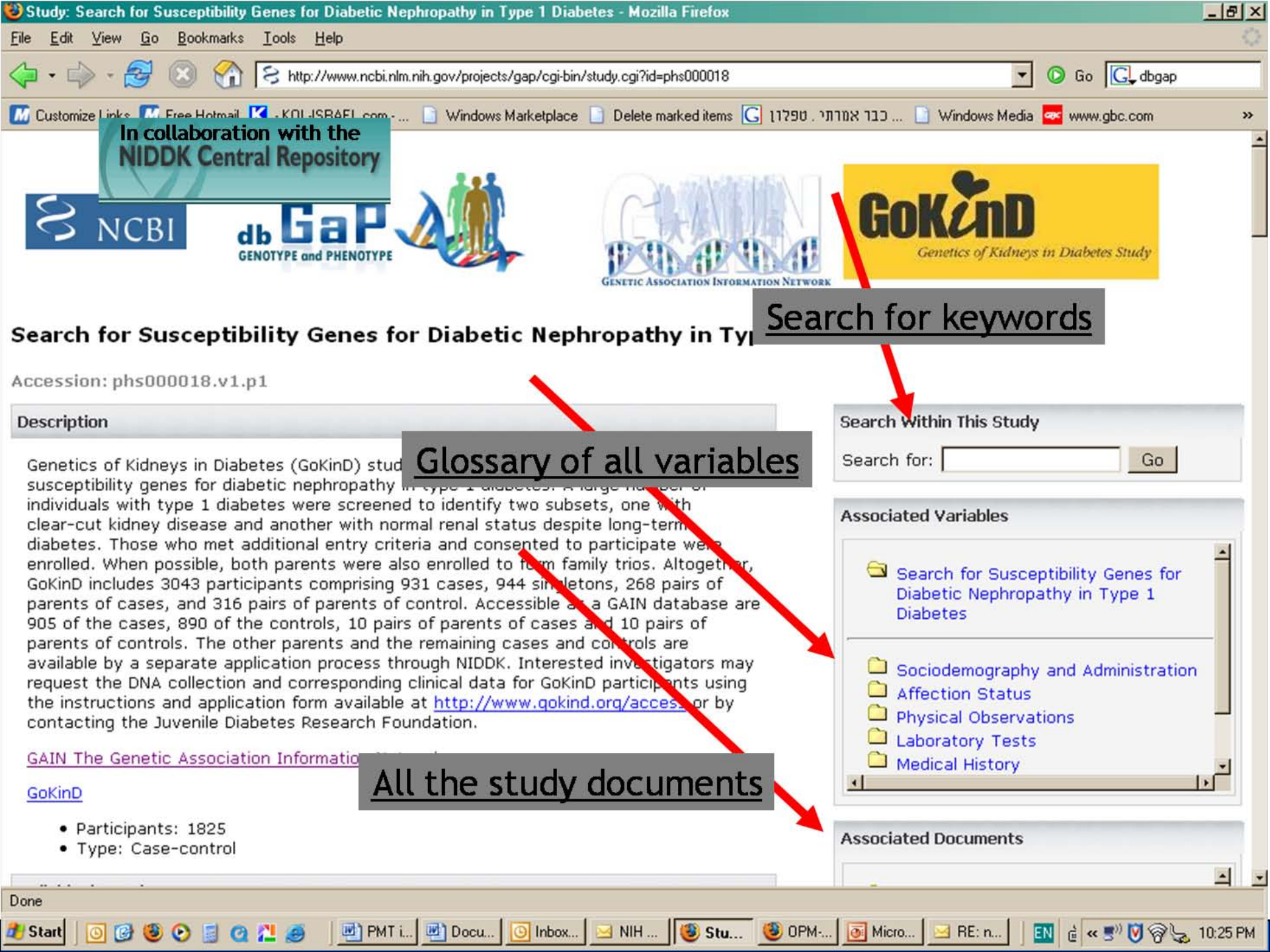
1. Carry out common variables analysis and make it available

Lab Test	FIND	GOKIND	EDIC
AutoAb GAD65	18, 24, 25		
AutoAb IA-2			
Genotyped	9		
HbA1C (%)	27	28,35	(yes)
Serum creatinine (mg/dL)	28	38, 43, 44, 45, 24, 36, 37, 38	yes

[2. Carry out similar genotyping on a similar time line]

3. Support collaborative efforts

4. Make the data and samples available in easily searchable form



In collaboration with the
NIDDK Central Repository



Search for keywords

Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes

Accession: phs000018.v1.p1

Description

Genetics of Kidneys in Diabetes (GoKinD) study identifies susceptibility genes for diabetic nephropathy in type 1 diabetes. A large number of individuals with type 1 diabetes were screened to identify two subsets, one with clear-cut kidney disease and another with normal renal status despite long-term diabetes. Those who met additional entry criteria and consented to participate were enrolled. When possible, both parents were also enrolled to form family trios. Altogether, GoKinD includes 3043 participants comprising 931 cases, 944 singletons, 268 pairs of parents of cases, and 316 pairs of parents of control. Accessible as a GAIN database are 905 of the cases, 890 of the controls, 10 pairs of parents of cases and 10 pairs of parents of controls. The other parents and the remaining cases and controls are available by a separate application process through NIDDK. Interested investigators may request the DNA collection and corresponding clinical data for GoKinD participants using the instructions and application form available at <http://www.qokind.org/access> or by contacting the Juvenile Diabetes Research Foundation.

[GAIN The Genetic Association Information Network](#)

[GoKinD](#)

- Participants: 1825
- Type: Case-control

Glossary of all variables

Search Within This Study

Search for:

- #### Associated Variables
- Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes
 - Sociodemography and Administration
 - Affection Status
 - Physical Observations
 - Laboratory Tests
 - Medical History

All the study documents

Associated Documents

Leveraging Past Investment to Build a Functional Future

- Collect the fruits of investments made.
- Invest a bit more to reveal common features on this base.
- Provide a stable, public base for a functional exploration of emerging phenotype standards.
- Require new studies to adhere to standards proven in the marketplace.
- Collect the fruits of new investments made.

Clinical Studies Have Been Unique

- Framingham Heart Study (NHLBI)
 - Blood pressure resting
 - Blood pressure after exercise
 - Blood pressure over many years and generations
 - Occasional eye exams
- AREDS Macular Degeneration Study (NEI)
 - Retinal images
 - Staging of Macular degeneration progress
 - Cataracts
 - Blood pressure as part of physical exam

The Genome is Common to All

Macular Degeneration



No



No



Yes



No



No

BP Resting



High



Low

dbGaP Captures Existing Phenotype Investment As Is

Study: National Eye Institute (NEI) Age-Related Eye Disease Study (AREDS) - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?id=phs000001

Study: National Eye Institute (NEI) Age-Related Eye...





National Eye Institute (NEI) Age-Related Eye Disease Study (AREDS)

Accession: phs000001.v1.p1

Description

The Age-Related Eye Disease Study (AREDS) was initially designed as a long-term multi-center, prospective study of the clinical course of age-related macular degeneration (AMD) and age-related cataract. In addition to collecting natural history data, AREDS included a clinical trial of high-dose vitamin and mineral supplements for AMD and a clinical trial of high-dose vitamin supplements for cataract. AREDS participants were 55 to 80 years of age at enrollment and had to be free of any illness or condition that would make long-term follow-up or compliance with study medications unlikely or difficult. On the basis of fundus photographs graded by a central reading center, best-corrected visual acuity and ophthalmologic evaluations, over 4,700 participants were enrolled in one of several AMD categories, including persons with no AMD.

The clinical trials for AMD and cataract were conducted concurrently. AREDS participants were followed on the clinical trial for a median time of 6.5 years. Subsequent to the conclusion of the clinical trial, participants were followed for an additional 5 years and natural history data were collected. The AREDS research design is detailed in AREDS Report 1. AREDS Report 8 contains the mainline results from the AMD trial; AREDS Report 9 contains the results of the cataract trial. Blood samples were also collected for genetic research. Genetic samples from 600 AREDS participants were evaluated with a genome-wide scan for inclusion in the dbGaP.

It is hoped that this resource will better help researchers understand two important diseases that affect an aging population. These data may be applied to examination and inference on genetic and genetic-environmental bases for age-related diseases of public health significance and may also help elucidate the clinical course of both conditions, generate hypotheses, and aid in the design of clinical trials of preventive interventions.

[AREDS, The National Eye Institute](#)

[AREDS, The EMMES Corporation](#)

- Subjects: 600

Search Within This Study

Search for:

Associated Analyses

- NEI Age-Related Eye Disease Study (AREDS)
- AMD status

Associated Variables

- Physical Observations
 - Clinical Examination
 - Organ Systems
 - Eye
- rpSCscore
- rpSCbase
- rpSC
- rpSCbase

Associated Documents

- NEI Age-Related Eye Disease Study

Done

Internet | Protected Mode: On

100%

Original Semantics in Protocols and Questionnaires

Chapter 7. EXAMINATION PROCEDURES (dbGaP ID: phd000007) - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetDocument.cgi?id=phd000007

Chapter 7. EXAMINATION PROCEDURES (dbGaP ID: phd000007) - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/pdf/phd000007.pdf

http://www.ncbi.nlm.nih.gov/projects/gap/pdf/... 1 / 36 102% Find

NCBI

NEI Age-Related Eye Disease Study

Chapter 7: EXAMINATION PROCEDURES

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- + 7.3 INTRAOCULAR PRESSURE MEASUREMENT
- 7.4 PUPIL DILATION
- + 7.5 HEIGHT AND WEIGHT MEASUREMENT
- + 7.6 BLOOD PRESSURE MEASUREMENT
- + 7.7 NUTRITION AND SUNLIGHT EXPOSURE QUESTIONNAIRES
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- + 7.22 END-OF-STUDY VISIT
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7.1. INTRODUCTION

NATIONAL INSTITUTES OF HEALTH

NCBI dbGaP Document
NEI Age-Related Eye Disease Study

Chapter 7 EXAMINATION PROCEDURES

7.1 INTRODUCTION

The procedures for carrying out the examinations required in the study are described in this chapter. Required ocular examinations include refraction and visual acuity measurements, intraocular pressure measurement, and ophthalmoscopic examination. General characteristic assessments include measurement of height, weight, and blood pressure and determination of past medical history. Risk factor assessments will require the administration of the food frequency and sunlight exposure questionnaires as well as collection of blood specimens. Procedures for participant identification, masking, distribution and management of the supplementation, adherence assessment, and home visit examination are also described. Procedures for taking photographs of the lens and fundus are described in detail in Chapter 8. The schedule and description of participant visits in Chapter 6 outline the examinations required during each visit.

7.2 REFRACTION AND VISUAL ACUITY

A manifest refraction and visual acuity measurement according to the detailed study protocol must be performed during (a) the Qualifying Visit when the visual acuity score using Chart R is 73 letters or less in at least one eye, (b) the Randomization Visit, (c) Annual Visits, and (d) any Nonannual Visit when the visual acuity score using Chart R has dropped by 10 letters or more compared to the Randomization Visit score for the first time. Participants' pupils should not be dilated at the time of visual acuity testing at any study visit; except they may be dilated during the Qualifying Visit. Pinhole acuity will not be tested as part of AREDS. At the Qualifying Visit, visual acuity may be initially assessed utilizing the participant's current distance glasses. At the Nonannual Visits, visual acuity is initially assessed utilizing the previously obtained manifest refraction. Participants will be asked to read the letters on Chart R only (not Charts 1 or 2), using the equipment described in Section 7.2.1. They will start reading from the top left-most letters—first with the right eye and then with the left eye. A visual acuity score will be calculated as described in Section 7.2.3.3. If at the Qualifying Visit

commented that 2 sets each of 2.5% Neomycin, the ophthalmologist examines the fundus, slit-lamp biomicroscopy. Ocular photography should be performed and the quality of photographs should be documented.

The procedures are set forth below.

Measurements should be recorded with indoor clothing only.

Weight and height measurements should be recorded with weight balances are set at "zero" and the scale should be zeroed in the scale.

Height and hands relaxed and at your side, and your feet should be flat on the scale.

ds).

Done Unknown Zone | Protected Mode: On Internet | Protected Mode: On 100%

Stable Public IDs Provide A Base of Real Data For Standardized Measures

Variable: syst12 - Windows Internet Explorer

Chapter 7. EXAMINATION PROCEDURES (dbGaP ID: phd000007) - Windows Internet Explorer
 http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetDocument.cgi?id=phd000007

7.6. BLOOD PRESSURE MEASUREMENT

Blood pressure measurements will be taken by a certified examiner preparing the participant, using the proper techniques, utilizing equipment provided below. Some institutions have installed electronic automated standard mercury units are the instruments of choice; however it is

7.6.1. Participant Preparation

- The participant should be seated with feet flat and on the floor positioned at heart level and should not have smoked, eaten, 30 minutes prior to the measurement. The participant should measurement, and requested not to talk while blood pressure
- Choose appropriate cuff size for arm to be tested. The rubber is too narrow, the blood pressure reading will be erroneously 1 cm wide is satisfactory for the average adult arm.

7.6.2. Technique

- Use a standard mercury sphygmomanometer to measure the to avoid loss of mercury. The level of mercury in the tube should necessary, mercury should be added to the reservoir to bring column of the usual desk or wall manometer must be vertical manometers are designed to be read at a reclined angle and instrument be used with the tube and its scale in the correct inspected regularly for dirt or sign of oxidation. Clogging in the mercury column to respond sluggishly to declining pressure in the vent should be serviced at least annually to ensure conti
- Place lower edge of cuff with its tubing connections approximat (2.5 cm above antecubital space).
- Wrap cuff snugly about arm with inflatable inner bladder cent
- Be sure that the connecting tube attached to the mercury cuff attached to the inflating bulb is close to the participant's body locking fabric fastener over the area where it is applied to the
- Attach the cuff connection and inflate the cuff while palpating

BASELINE INTERVIEW — PHASE II (dbGaP ID: phd000020) - Windows Internet Explorer
 http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetDocument.cgi?id=phd000020#V11

I would like to take your blood pressure now and again later during this interview.

8. Sitting blood pressure. (Participant must have been seated and quiet for at least 5 minutes prior to the measurement. See Section 7.6 of the Manual of Operations.):

- Systolic (mmHg)
- Diastolic (mmHg)
- Certification number of blood pressure examiner:

9. Have you ever smoked cigarettes for a total of 6 months or more?

no
 yes

If no, skip to 10

- How old were you when you first started smoking?
- Over your lifetime of smoking, on the average, how many packs per day have you smoked?
 - ≤ ½ pack
 - > ½, ≤ 1 pack
 - > 1, ≤ 2 packs
 - > 2 packs
- Do you smoke cigarettes at present?
 - no
 - yes

If no, skip to e

d. If you currently smoke, how many cigarettes a day do you smoke?

Skip to 10

e. If you do not smoke currently, how old were you when you last quit smoking?

10. Have you ever smoked cigars, a pipe, or chewed tobacco for a total of 6 months or more?

no
 yes

Done

Internet | Protected Mode: On 100%

Standards Emerge from Utility

Variable: syst12 - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/variable.cgi?id=phv0000094

syst12

Accession: phv0000094.v1.p1

>> [NEI Age-Related Eye Disease Study \(AREDS\)](#) >> [syst12](#)

Description

Sitting systolic blood pressure (at follow-up year 12)

Done

Variable: L_ANKLE - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/variable.cgi?id=phv00021576

L_ANKLE

Accession: phv00021576.v1.p1

>> [Framingham SHARE](#) >> [Framingham SHARE Ankle Arm BP](#) >> [L_ANKLE](#)

Description

SYSTOLIC BLOOD PRESSURE BY DOPPLER IN LEFT ANKLE

Variable: SYSBP - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/variable.cgi?id=phv00019997

SYSBP

Accession: phv00019997.v1.p1

>> [Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes](#) >> [SYSBP](#)

Description

Systolic blood pressure (mmHg)

Done

Standards Emerge from Utility

Recommendations for Blood Pressure Measurement in Humans and Experimental Animals: Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals From the Subcommittee of Professional and Clinical Guidelines of the American Heart Association

Hypertension

Hypertension. 2005;45:142-161. Published online before print December 20, 2004. doi: 10.1161/01.HYP.0000150859.47929.8e

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Blood pressure measurement - Ward and Langton 7 (4): 122 - Continuing Education in Anaesthesia, Critical Care & Pain

Blood pressure measurement

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syst12

Accession: gpl000000004.v1.p1

>> NEI Age-Related Eye Disease Study (AREDS) - syst12

Description

Sitting systolic blood pressure (at follow-up year 12)

L_ANKLE

Accession: gpl000000004.v1.p1

>> Framingham Study - Framingham Study, Ankle Arm BP - L_ANKLE

Description

SYSTOLIC BLOOD PRESSURE BY DOPPLER IN LEFT ANKLE

SYSBP

Accession: gpl000000004.v1.p1

>> Search for Similarity Series for Subject: Systolic Blood Pressure >> E1700

Description

Systolic blood pressure (mmHg)

Leveraging Past Investment to Build a Functional Future

- Collect the fruits of investments made.
- Invest a bit more to reveal common features on this base.
- Provide a stable, public base for a functional exploration of emerging phenotype standards.
- Require new studies to adhere to standards proven in the marketplace.
- Collect the fruits of new investments made.

Studies scheduled for dbGaP submission 2007-2008

Projected Availability	Study Name / Disease Focus	Sponsor	Type	Number of Participants
Nov-06	AREDS	NEI	Case-Control GWAS	600
Nov-06	Parkinsonism	NINDS/NIA	Case-Control GWAS	2,573
Jun-07	ADHD	GAIN	Trio GWAS	2,874
Aug-07	Diabetic Nephropathy	GAIN	Case-Control GWAS	1,835
Sep-07	GeneLink	NHLBI	Multipoint linkage analyses	n.d.
Sep-07	Stroke	NINDS	Case-Control GWAS	1,555
Sep-07	Motor Neuron Disease/ALS	NINDS	Case-Control GWAS	1,876
Sep-07	LEAPS	MJFF	Tiered case-control GWAS	886
Sep-07	Major Depression	GAIN	Case-Control GWAS	3,720
Oct-07	Framingham SHARe	NHLBI	Family-Based Longitudinal GWAS	~9,500
Oct-07	Psoriasis	GAIN	Case-Control GWAS	2,898
Nov-07	DCCT/ EDIC	NIDDK	Longitudinal GWAS	
Dec-07	Schizophrenia	GAIN	Case-Control GWAS	2,909
Dec-07	Bipolar Disorder	GAIN	Case-Control GWAS	2,400
Early 2008	Alzheimers	NIA	Case-Control GWAS	10,000
Late 2008	8 GEI Studies	NHGRI	TBD	>30,000
Late 2008	Medical Resequencing, phase 1	NHGRI	TBD	~15,000
Late 2008	MESA SHARe	NHLBI	Longitudinal GWAS	8,000
				99,636



The National Children's Study: A possible model for the Phenotype Initiative

Peter Scheidt, MD, MPH

National Institute of Child Health

and Human Development,

Department of Health and Human Services



The National Children's Study

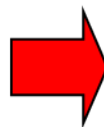
- Largest long-term study of children's health and development ever to be conducted in the U.S.
- Longitudinal study of children, their families, and their environment (over 21 years or longer, from before birth)
- Approximately 100,000 children included to study important but less common outcomes
- Environment & genetic expression
- Hypothesis driven and national resource for future studies



Priority Health Outcome & Exposure Data



Priority Exposures	Examples
Physical Environment	Housing quality, neighborhood
Chemical Exposures	Pesticides, phthalates, heavy metals
Biologic Environment	Infectious agents, endotoxins, diet
Genetics	Interaction between environmental factors and genes
Psychosocial milieu	Families, SES, institutions, social networks



Priority Health Outcomes	Examples
Pregnancy Outcomes	Preterm, Birth defects
Neurodevelopment & Behavior	Autism, schizophrenia, learning disabilities
Injury	Head trauma, Injuries requiring hospitalizations
Asthma	Asthma incidence and exacerbation
Obesity & Physical Development	Obesity, Diabetes, altered puberty



Study Participation

- Contact by telephone, computer, and mail-in questionnaires every 3 months until child is 5 years of age; annually thereafter
- Collection of biological samples from mother, father, child, and air, water, soil, and dust from child's environment
- Collection of environmental data from schools and childcare facilities of participants
- Health event data collection – PHR's, electronic health records when available

