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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PROMIS

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

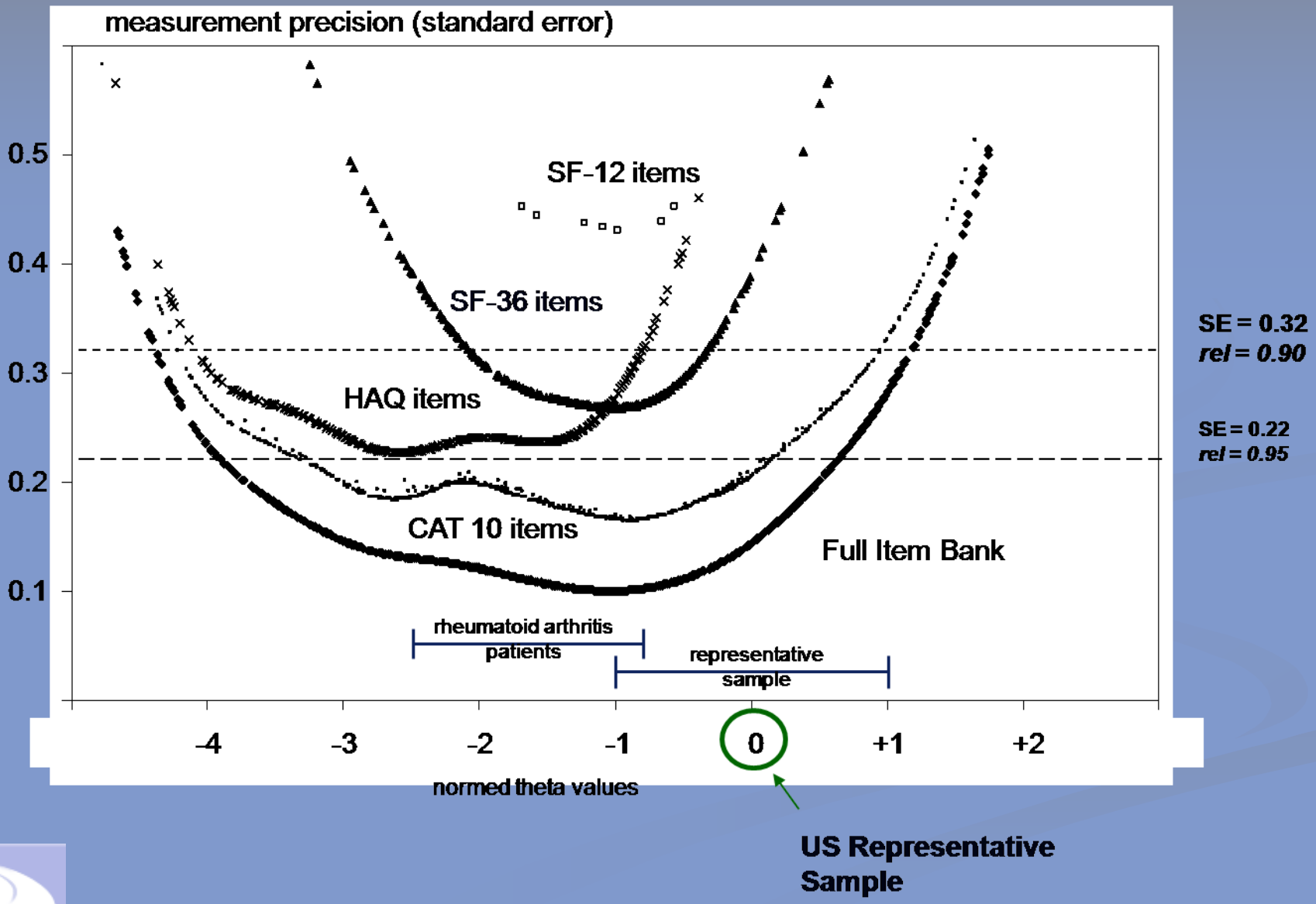
NATIONAL INSTITUTES OF HEALTH

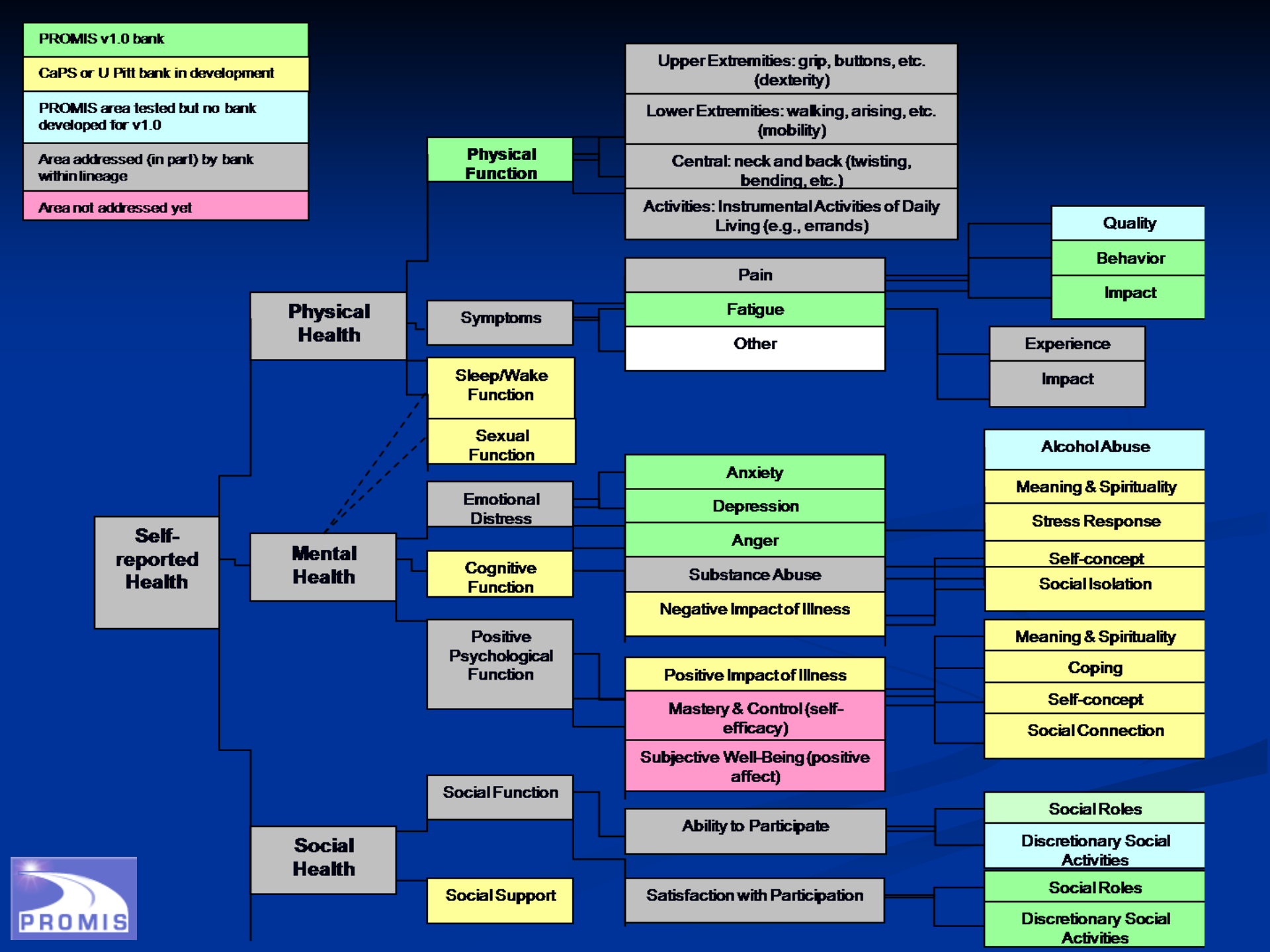
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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




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
Self-reported Health
Physical Health
Mental Health
Social Health
Physical Function
Symptoms
Sleep/Wake Function
Sexual Function
Emotional Distress
Cognitive Function
Positive Psychological Function
Social Function
Social Support
Upper Extremities: grip, buttons, etc. (dexterity)
Lower Extremities: walking, arising, etc. (mobility)
Central: neck and back (twisting, bending, etc.)
Activities: Instrumental Activities of Daily Living (e.g., errands)
Pain
Fatigue
Other
Anxiety
Depression
Anger
Substance Abuse
Negative Impact of Illness
Positive Impact of Illness
Mastery & Control (self-efficacy)
Subjective Well-Being (positive affect)
Ability to Participate
Satisfaction with Participation
Quality
Behavior
Impact
Experience
Impact
Alcohol Abuse
Meaning & Spirituality
Stress Response
Self-concept
Social Isolation
Meaning & Spirituality
Coping
Self-concept
Social Connection
Social Roles
Discretionary Social Activities
Social Roles
Discretionary Social Activities
PROMIS

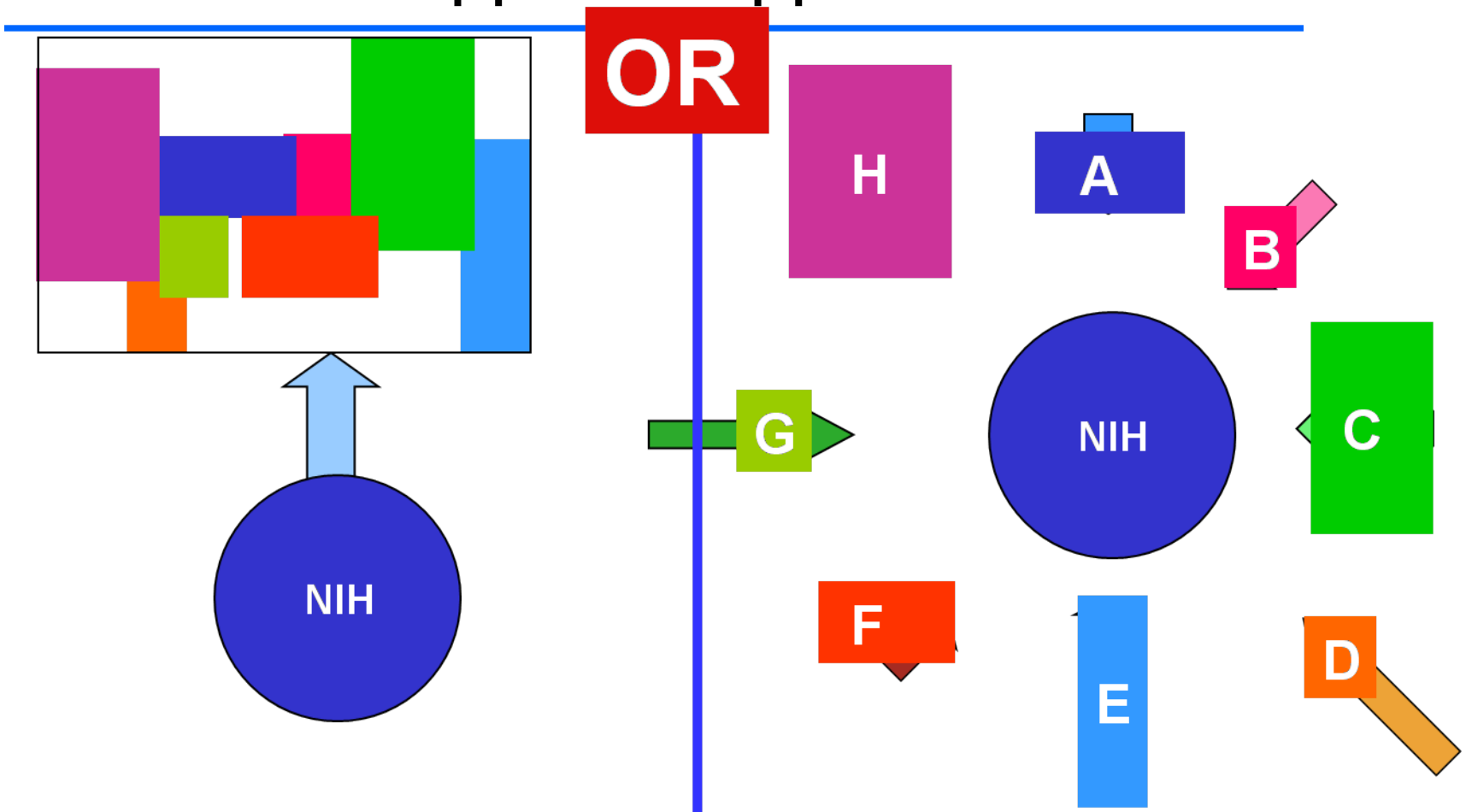
Depression

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

PROMIS

Phenotyping in clinical studies: two opposite approaches

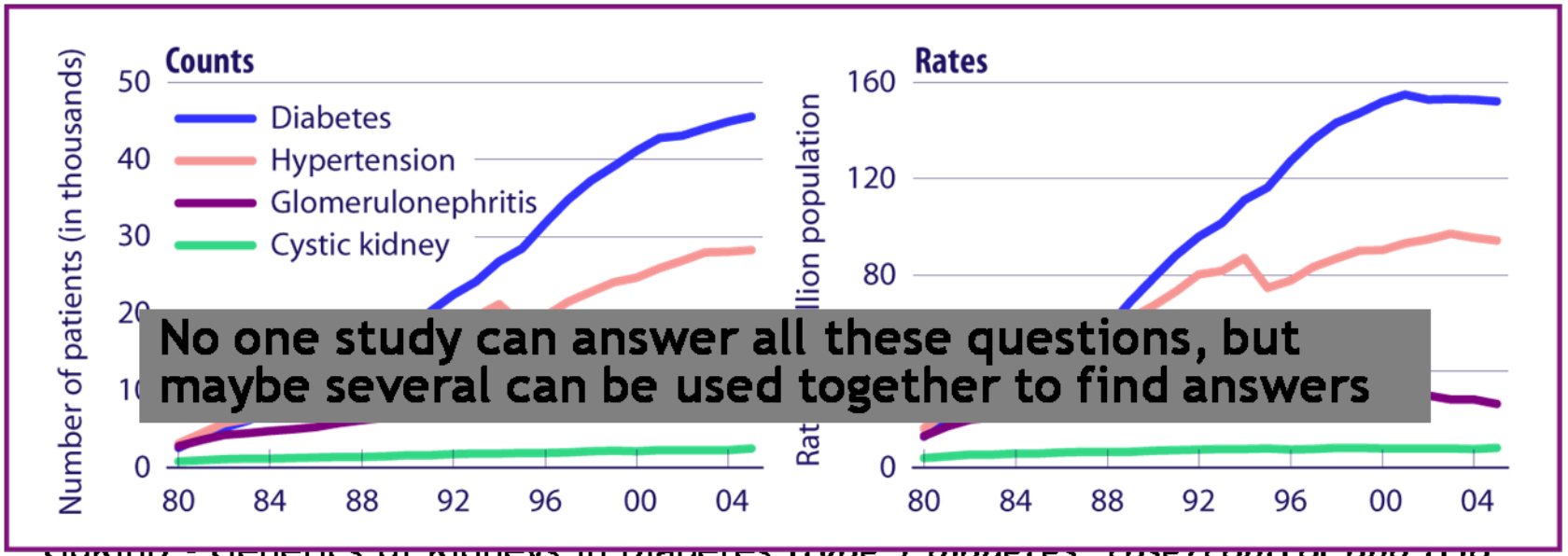


NIH creates a single study addressing multiple phenotypes with a single consensus protocol

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:



No one study can answer all these questions, but maybe several can be used together to find answers

GoKinD - 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?

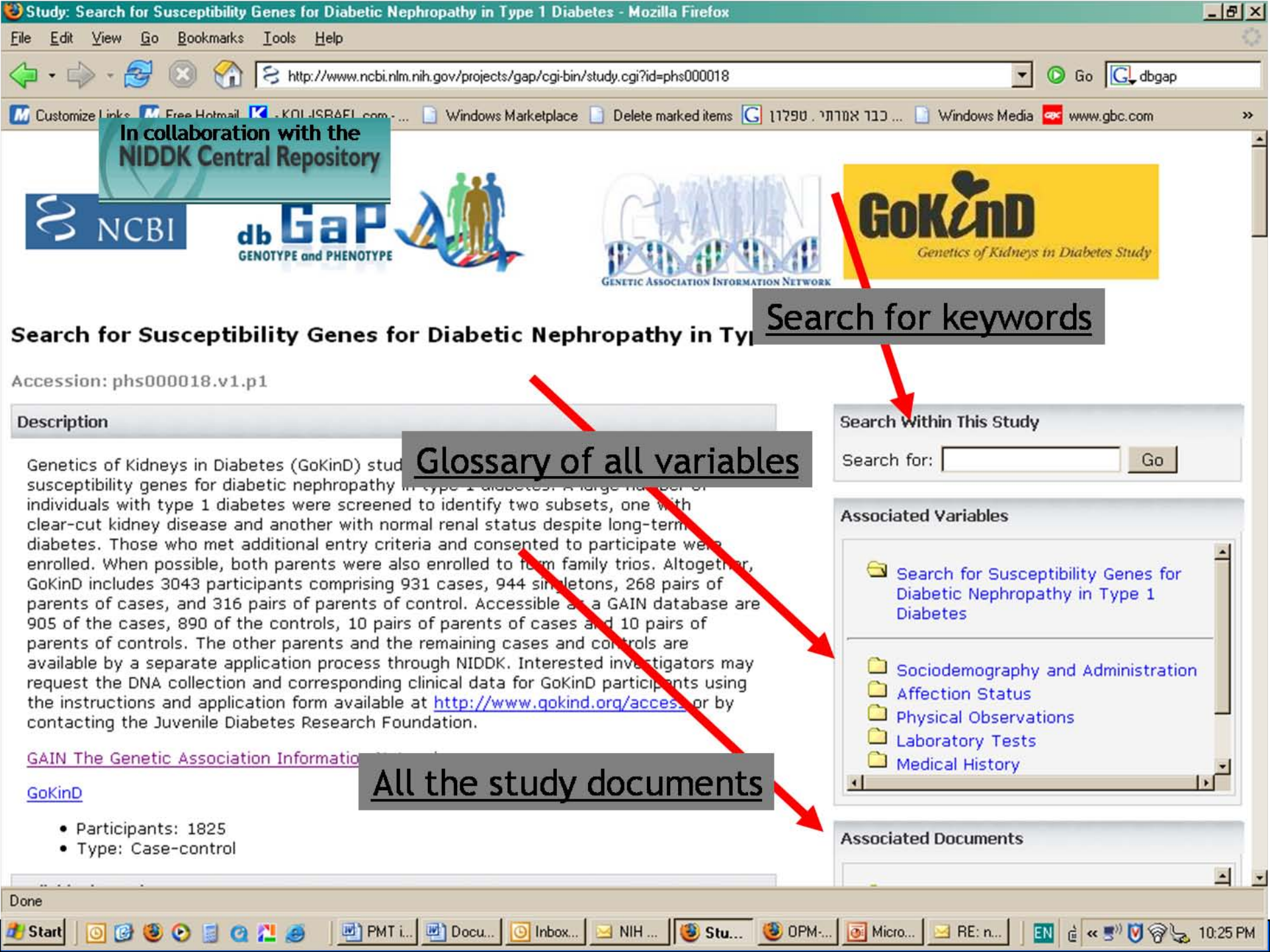
1. Carry out common variables analysis and make it available

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


Study: Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes - Mozilla Firefox
File Edit View Go Bookmarks Tools Help
http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?id=phs000018
Go
dbgap
Customize Links
Free Hotmail
Windows Marketplace
Delete marked items
Windows Media
www.gbc.com
In collaboration with the NIDDK Central Repository
NCBI
db GaP
GENOTYPE and PHENOTYPE
GAIN
GENETIC ASSOCIATION INFORMATION NETWORK
GoKinD
Genetics of Kidneys in Diabetes Study
Search for keywords
Search for Susceptibility Genes for Diabetic Nephropathy in Ty
Accession: phs000018.v1.p1
Description
Glossary of all variables
Genetics of Kidneys in Diabetes (GoKinD) stud
susceptibility genes for diabetic nephropathy
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 at 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.gokind.org/access or by
contacting the Juvenile Diabetes Research Foundation.
GAIN The Genetic Association Informatio
GoKinD
Participants: 1825
Type: Case-control
All the study documents
Search Within This Study
Search for:
Go
Associated Variables
Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes
Sociodemography and Administration
Affection Status
Physical Observations
Laboratory Tests
Medical History
Associated Documents
Done
Start
PMT i...
Docu...
Inbox...
NIH ...
Stu...
OPM-...
Micro...
RE: n...
EN
10:25 PM

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.

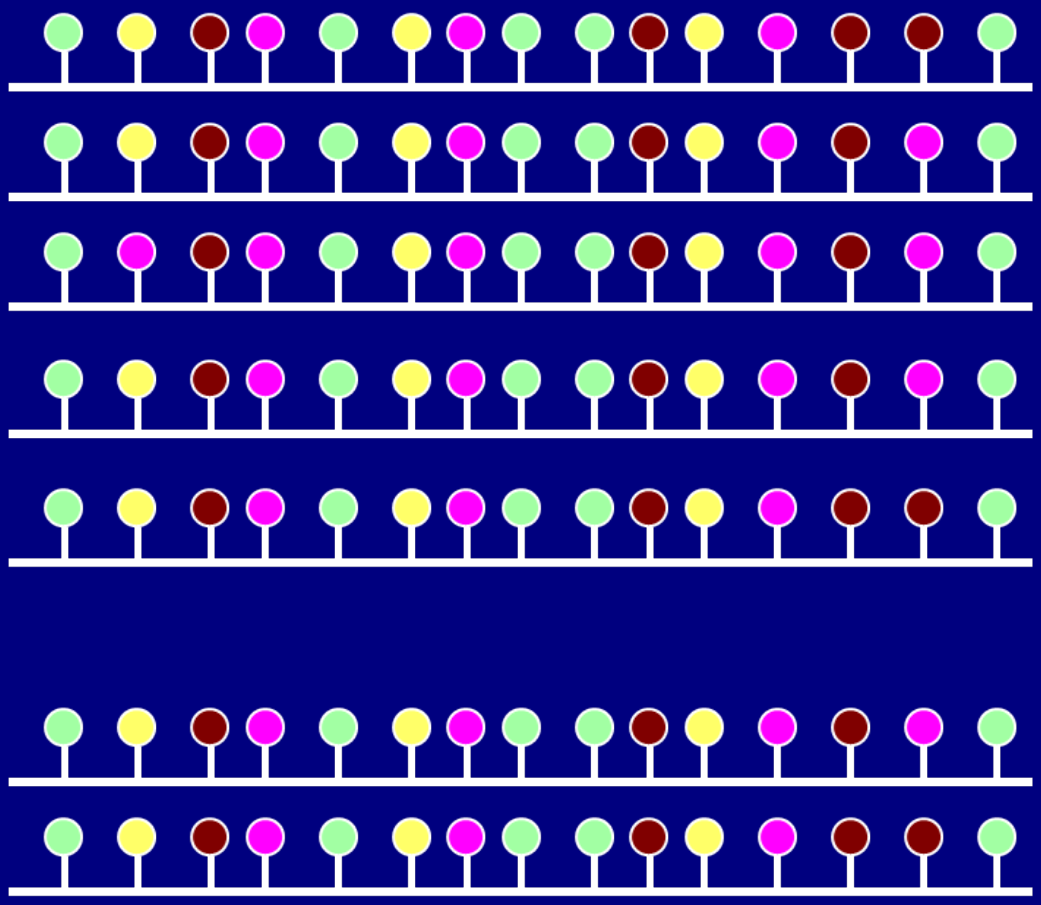
Clinical Studies Have Been Unique

- 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

NCBI

110101

The Genome is Common to All



Macular Degeneration

No

No

Yes

No

No

BP Resting

High

Low

NCBI

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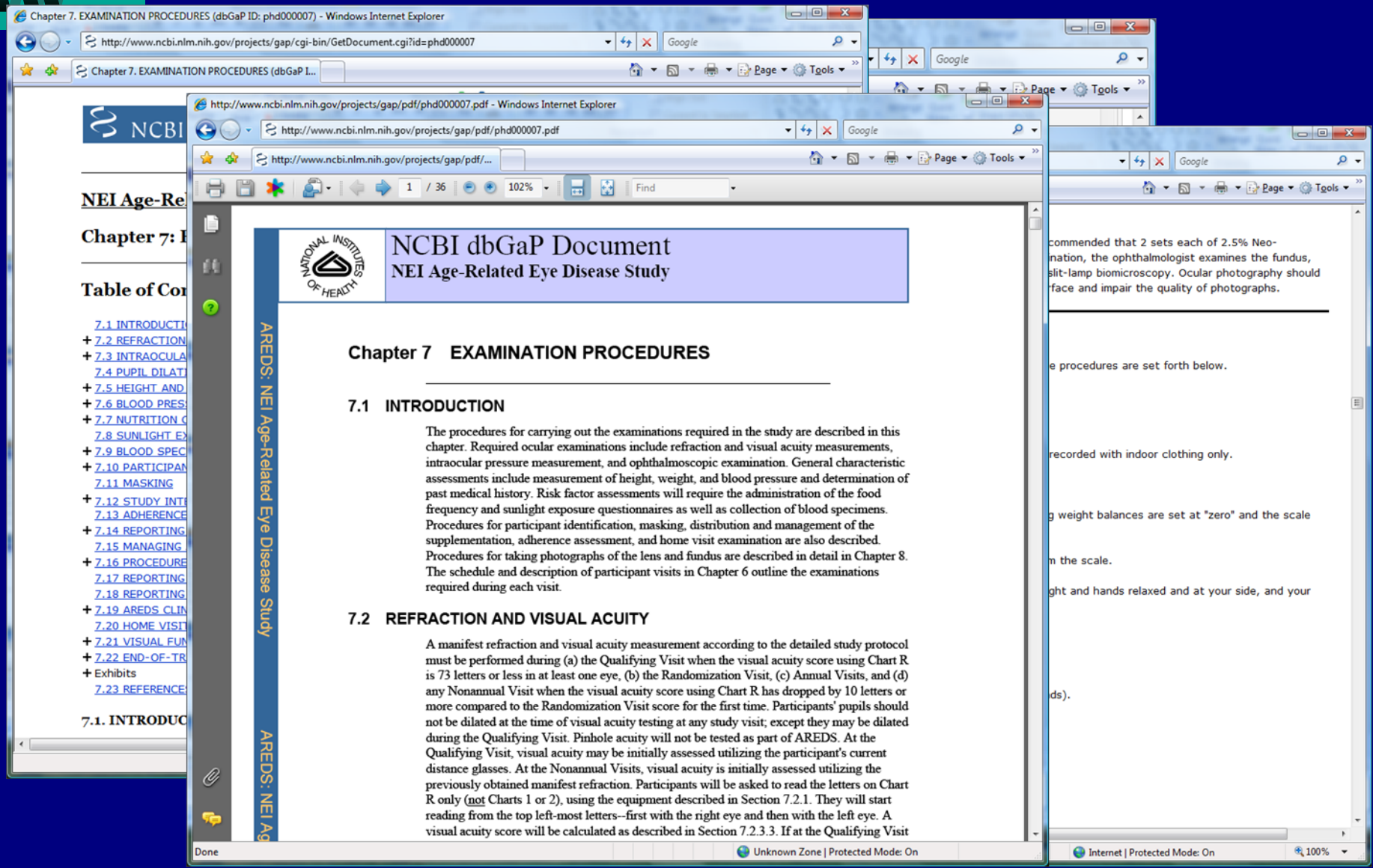
dbGaP Captures Existing Phenotype Investment As Is

NCBI

Original Semantics in Protocols and Questionaires



NCBI

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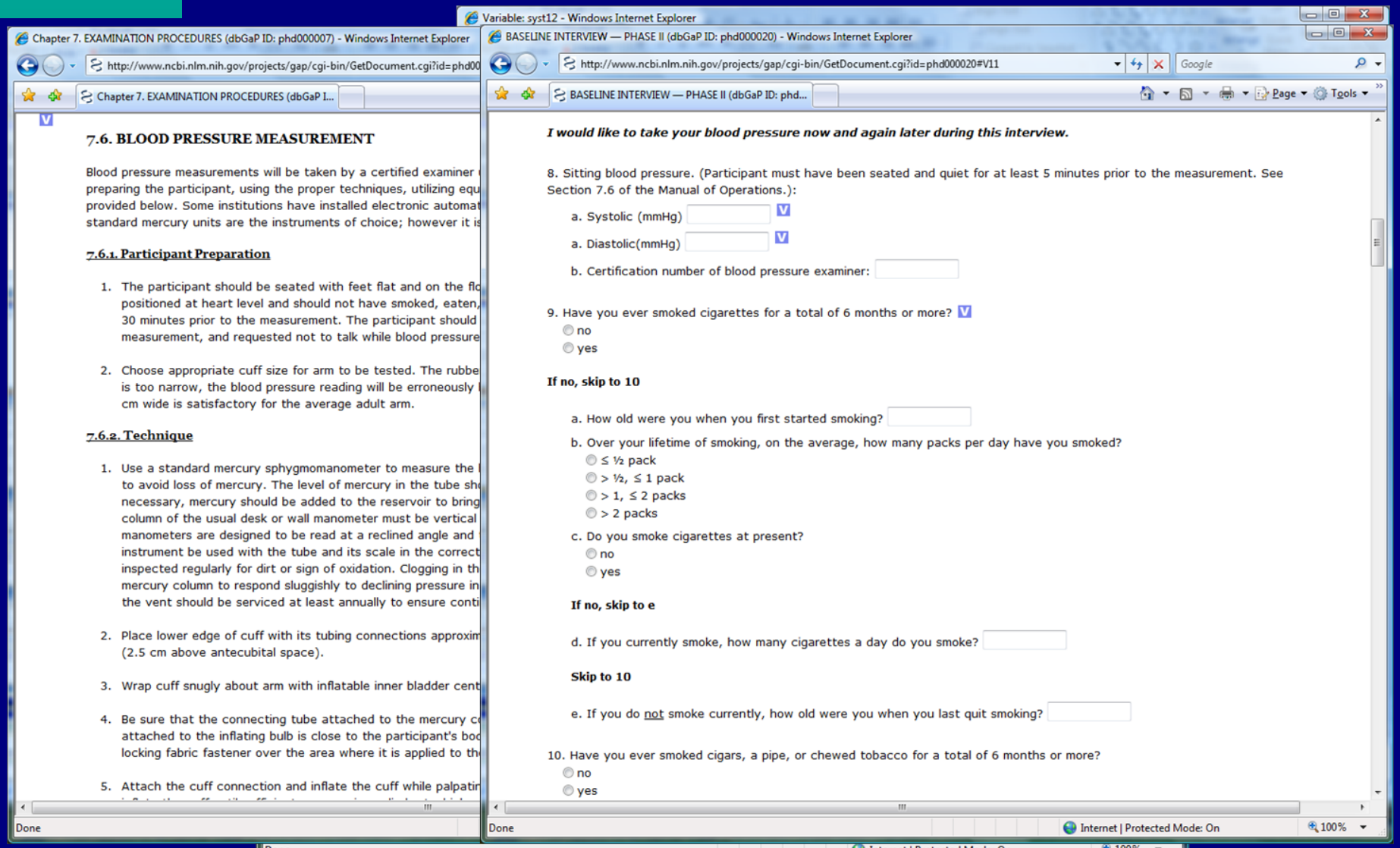
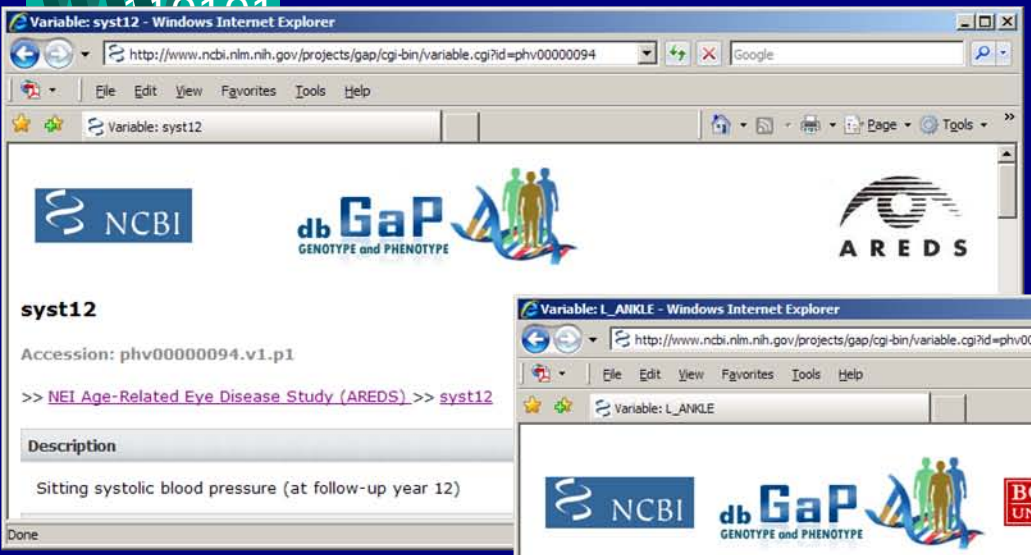
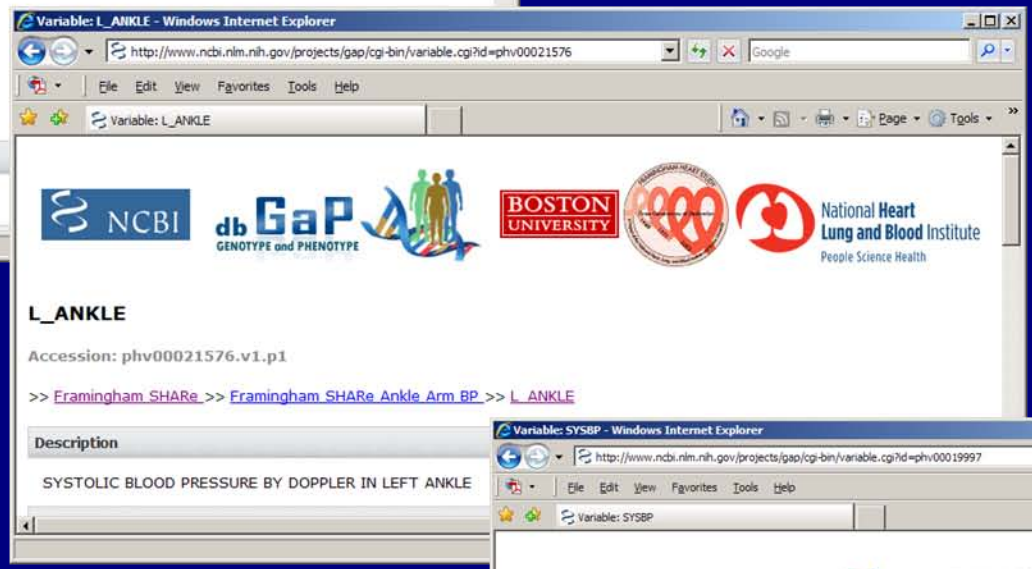
Stable Public IDs Provide A Base of Real Data For Standardized Measures



NCBI

Standards Emerge from Utility





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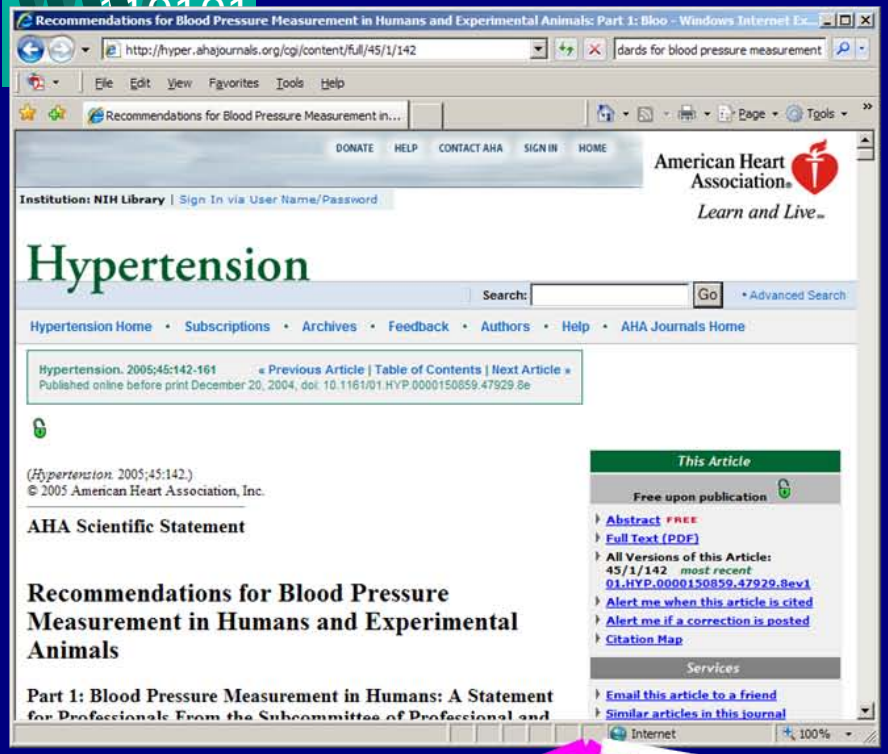
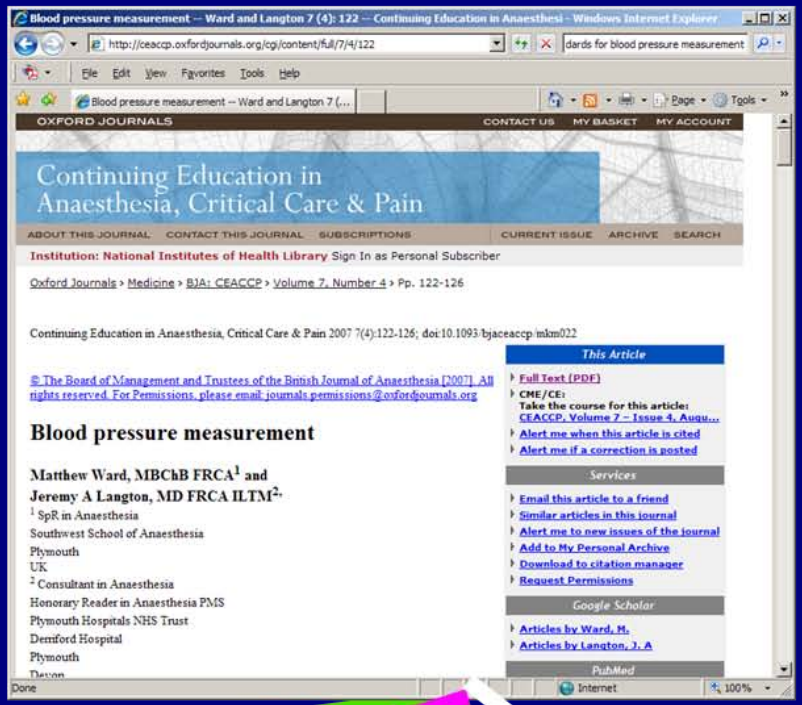
Standards Emerge from Utility





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- 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

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