Knowledge Integration in Public Health Genomics: Evaluation of the Epidemiologic Evidence

Muin J. Khoury, MD, Ph.D.

CDC National Office of Public Health Genomics

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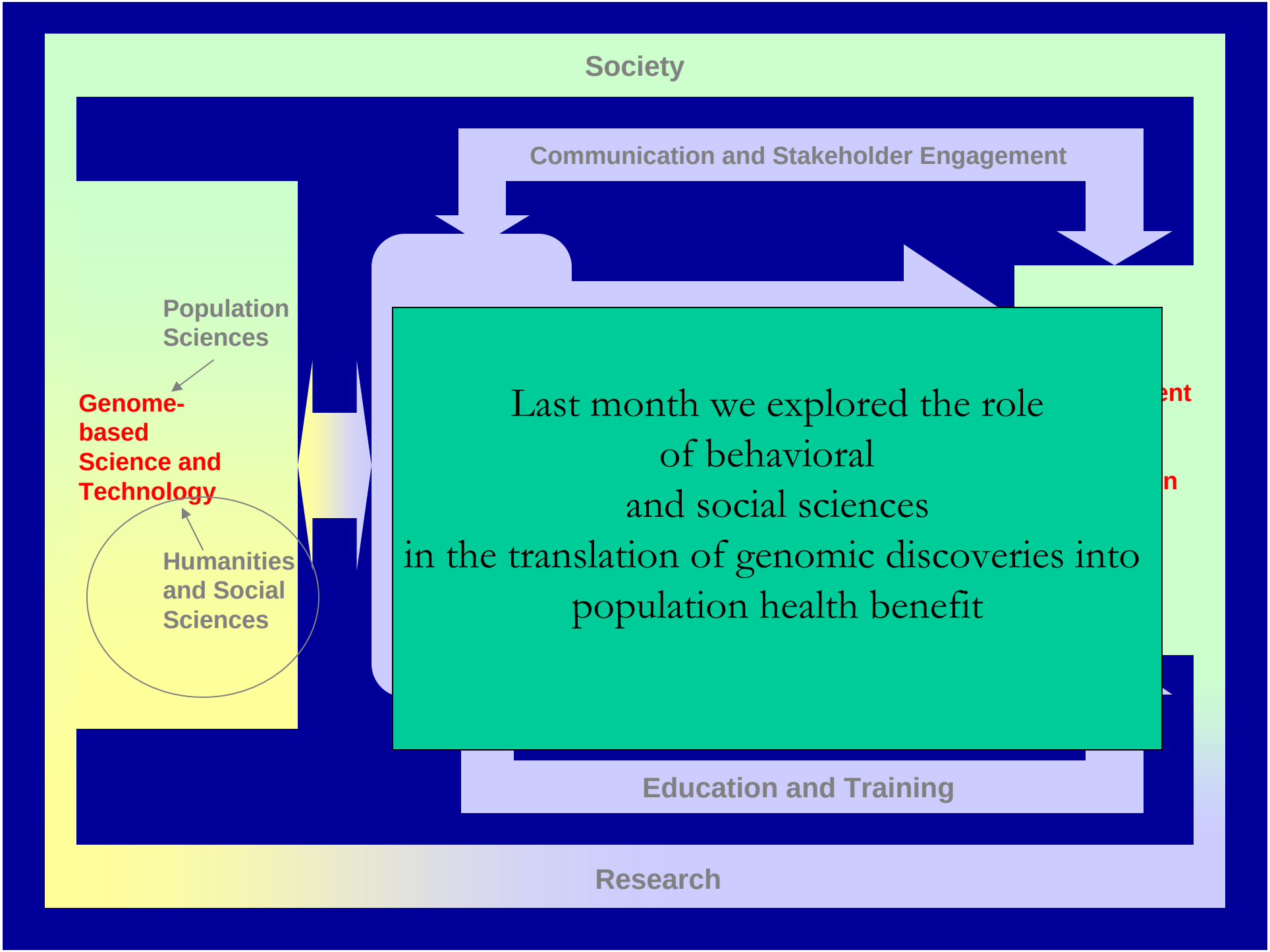
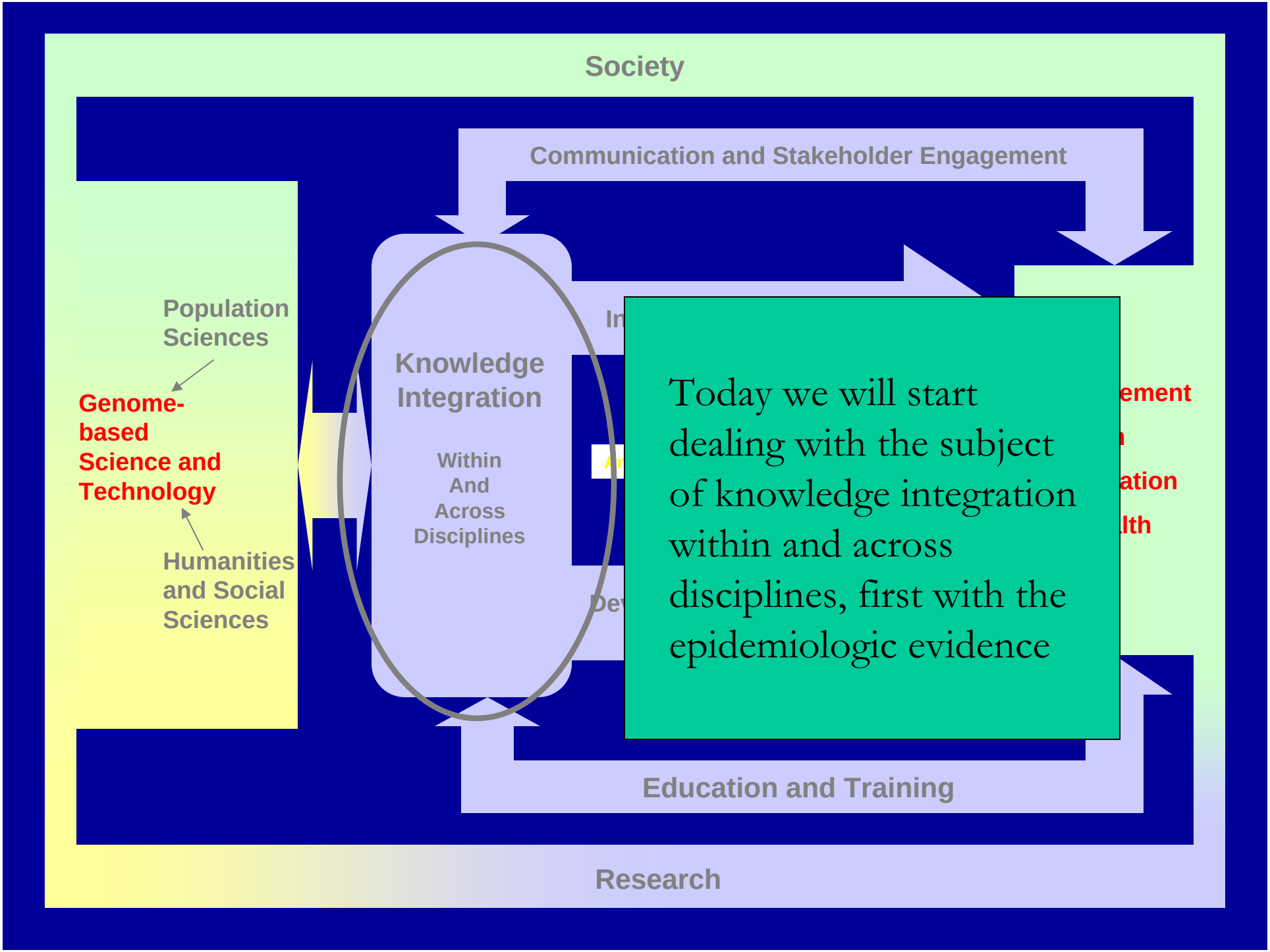

Society
Communication and Stakeholder Engagement
Population Sciences
Genome-based Science and Technology
Humanities and Social Sciences
Last month we explored the role of behavioral and social sciences in the translation of genomic discoveries into population health benefit
Education and Training
Research


Society
Communication and Stakeholder Engagement
Population Sciences
Genome-based Science and Technology
Humanities and Social Sciences
Knowledge Integration
Within And Across Disciplines
Today we will start dealing with the subject of knowledge integration within and across disciplines, first with the epidemiologic evidence
Education and Training
Research

Knowledge Integration

The activity that we call knowledge integration is the driving force or 'engine house' of the enterprise

It is the process of selecting, storing, collating, analysing, integrating and disseminating information both within and across disciplines for the benefit of population health and includes methodological development

It is the means by which information is transformed into knowledge

Interdisciplinarity is a key feature

Outline

- Introduction-Why Integrate?
- HuGENet Road Map
- Literature Scanning, Reporting, Synthesis and Network Collaboration
- Developing the Knowledge Base and Causal Inference

Why Integrate?

ORIGINAL CONTRIBUTION

JAMA April 11, 2007

Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study

Thomas M. Morgan, MD
Harlan M. Krumholz, MD, MS
Richard P. Lifton, MD, PhD
John A. Spertus, MD, MPH

Context Given the numerous, yet inconsistent, reports of genetic variants being associated with acute coronary syndromes (ACS), there is a need for comprehensive validation of ACS susceptibility genotypes.

Objective To perform an extensive validation of putative genetic risk factors for ACS.

Design, Setting, and Participants Through a systematic literature search of articles published before March 10, 2005, we identified genetic variants previously reported as significant susceptibility factors for atherosclerosis or ACS. Restricting our analysis to white patients to reduce confounding from racial admixture, we identifed 811 patients who presented from March 2001 through June 2003 with ACS at 2 Kansas City, Mo, university-affiliated hospitals. During 2005-2006, we genotyped the 811 patients along with 650

COMPELLING EVIDENCE FROM twin and epidemiological studies suggests a genetic basis for atherosclerotic heart

Why Integrate?

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship

Why Integrate?

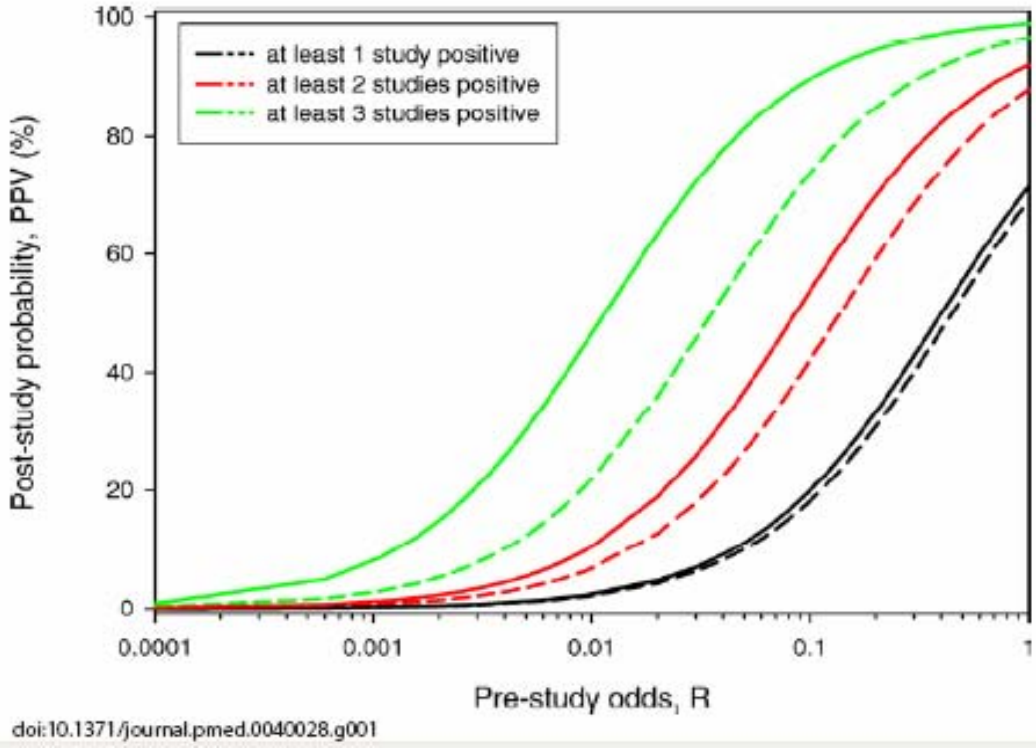
Essay

Most Published Research Findings Are False—But a Little Replication Goes a Long Way

Ramal Moonesinghe*, Muin J. Khoury, A. Cecile J. W. Janssens

We know there is a lot of lack of replication in research findings, most notably in the field of genetic associations [1–3]. For example, a survey of 600 positive associations between gene variants and common diseases showed that out of 166 reported associations studied three or more times, only six were replicated consistently [4]. Lack of replication results from a number of factors such as publication bias, selection bias, Type I errors, population stratification (the mixture of individuals from heterogeneous genetic backgrounds), and lack of statistical power [5].

In a recent article in *PLoS Medicine*, John Ioannidis quantified the theoretical basis for lack of replication by deriving the positive predictive value (PPV) of the truth of a research finding on the basis of a combination of factors. He showed elegantly that

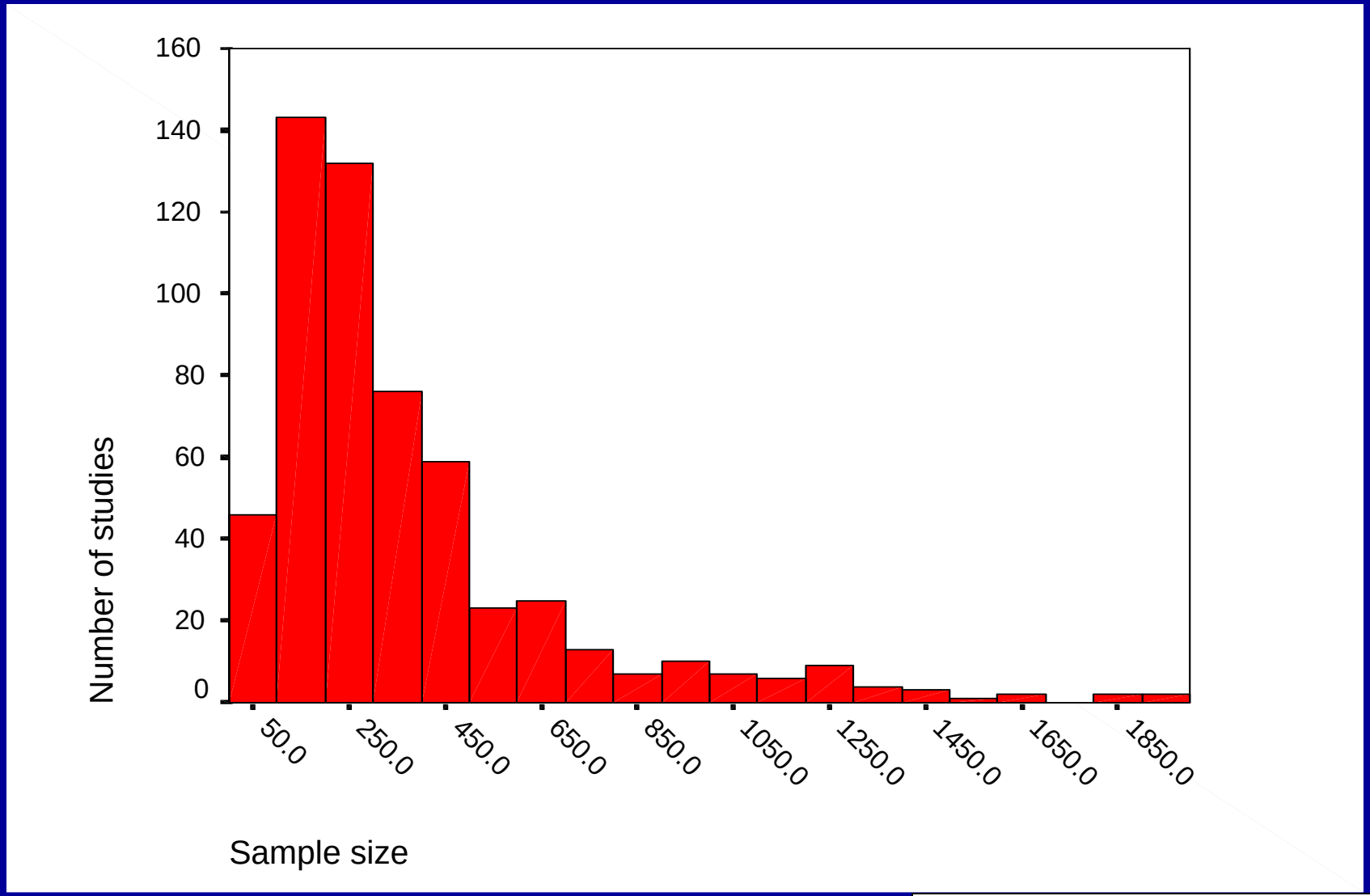


doi:10.1371/journal.pmed.0040028.g001

Why Integrate?

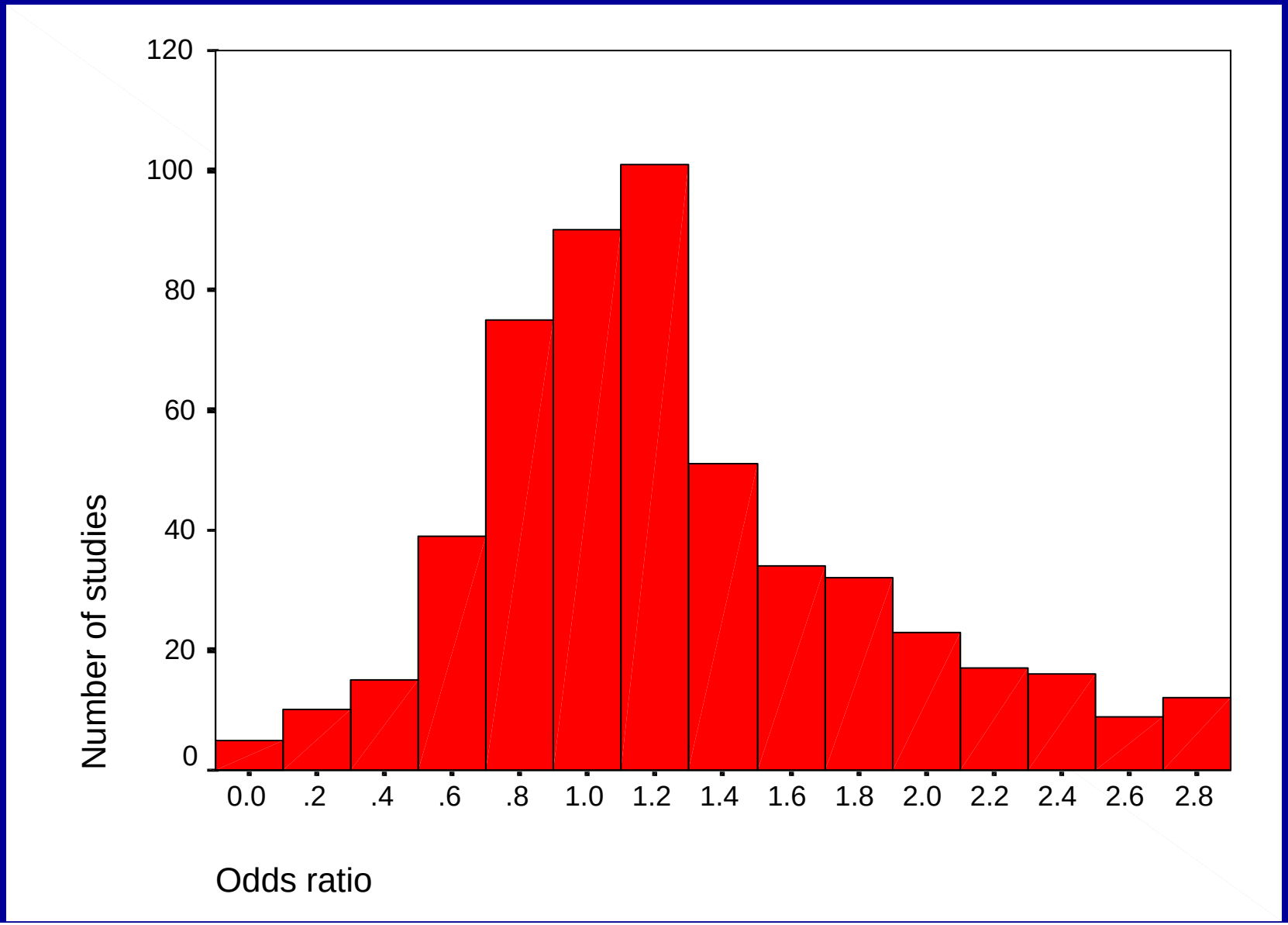
- Unmanageable amounts of emerging information
- Small sample size of individual studies
- Small effect size of individual studies
- Assess replication of associations
- Assess and explain heterogeneity-interactions
- Build the knowledge base: ‘what we know and what we don’t know’
- Produce information needed to calculate risks for use in clinical medicine and public health

Small Sample Sizes of Individual Studies

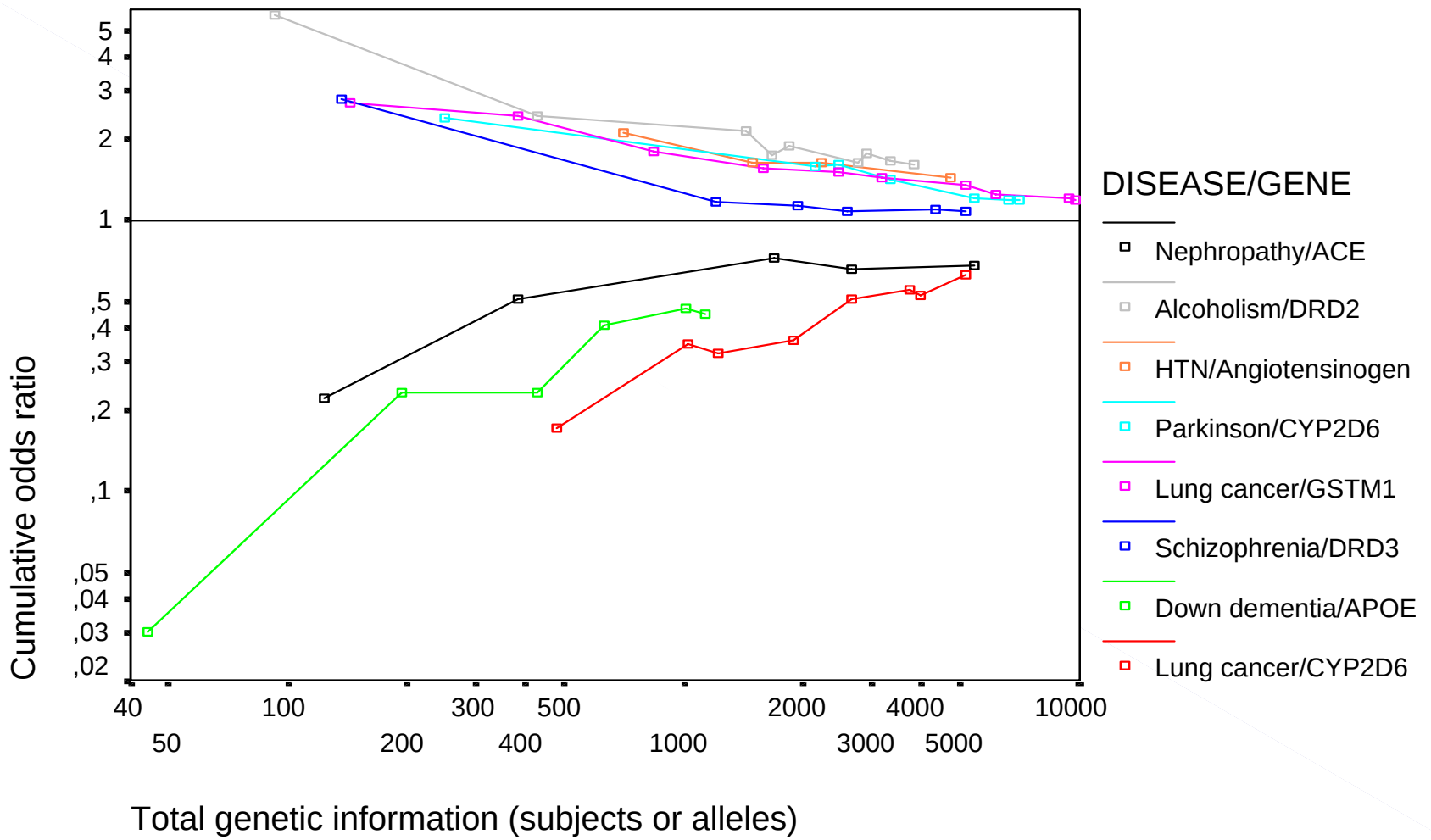


Ioannidis, Trends Mol Med 2003

Small Effect Sizes in Individual Studies



Evolving Genetic Associations: Effects that Diminish Over Time



Ioannidis et al, Nature Genetics 2001

Outline

- Introduction-Why Integrate?
- HuGENet Road Map
- Literature Scanning, Reporting, Synthesis and Network Collaboration
- Developing the Knowledge Base and Causal Inference

Options for Integration of Information

- Single, all-absorbing mega-studies (e.g. proposed US cohort on genes and environment)
- Meta-analyses of group data
- Meta-analyses of individual participant data (pooled analysis)

- All of these designs are unlikely to be successful unless they allow for evolving (often rapidly evolving) evidence

Human Genome Epidemiology Network (HuGENet)

- Global collaboration of individuals and organizations to assess population impact of genomics and how it can be used to improve health and prevent disease
  - 4 coordinating centers
  - Dozens of networks
  - Hundreds of collaborators
  - 10 collaborating journals

Human Genome Epidemiology Network (HuGENet)

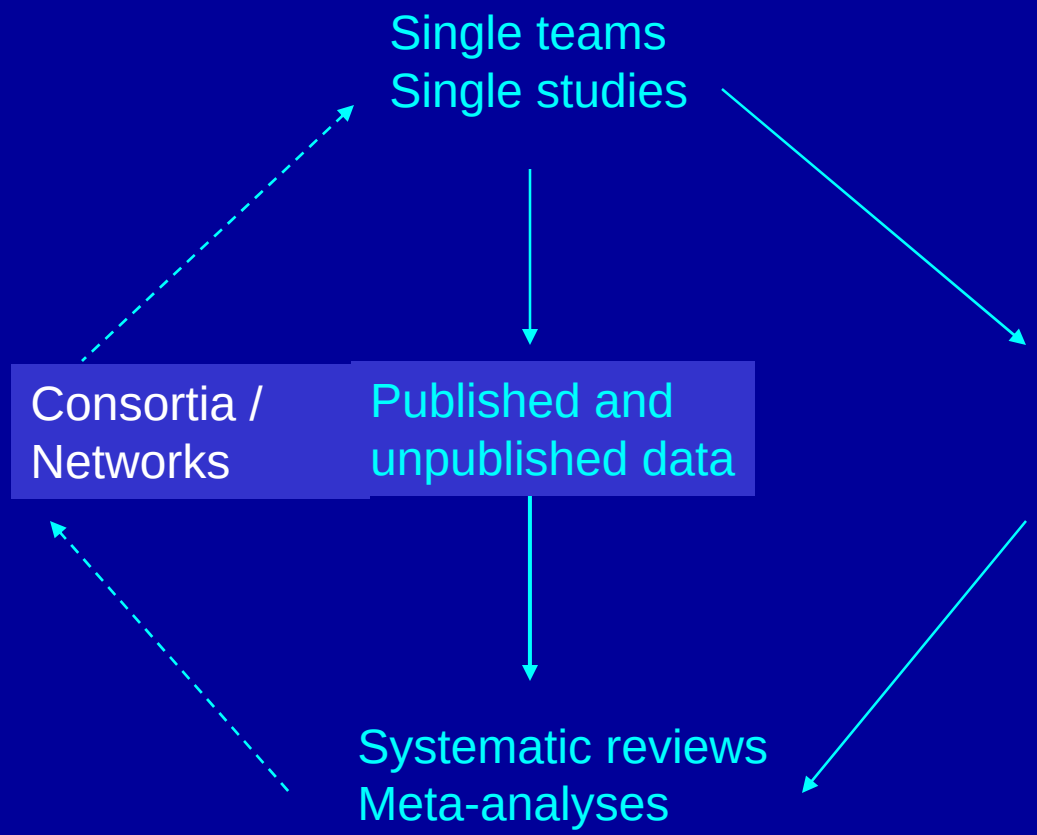
- Published literature scan
- Systematic reviews
- Strengthened reporting
- Network collaboration

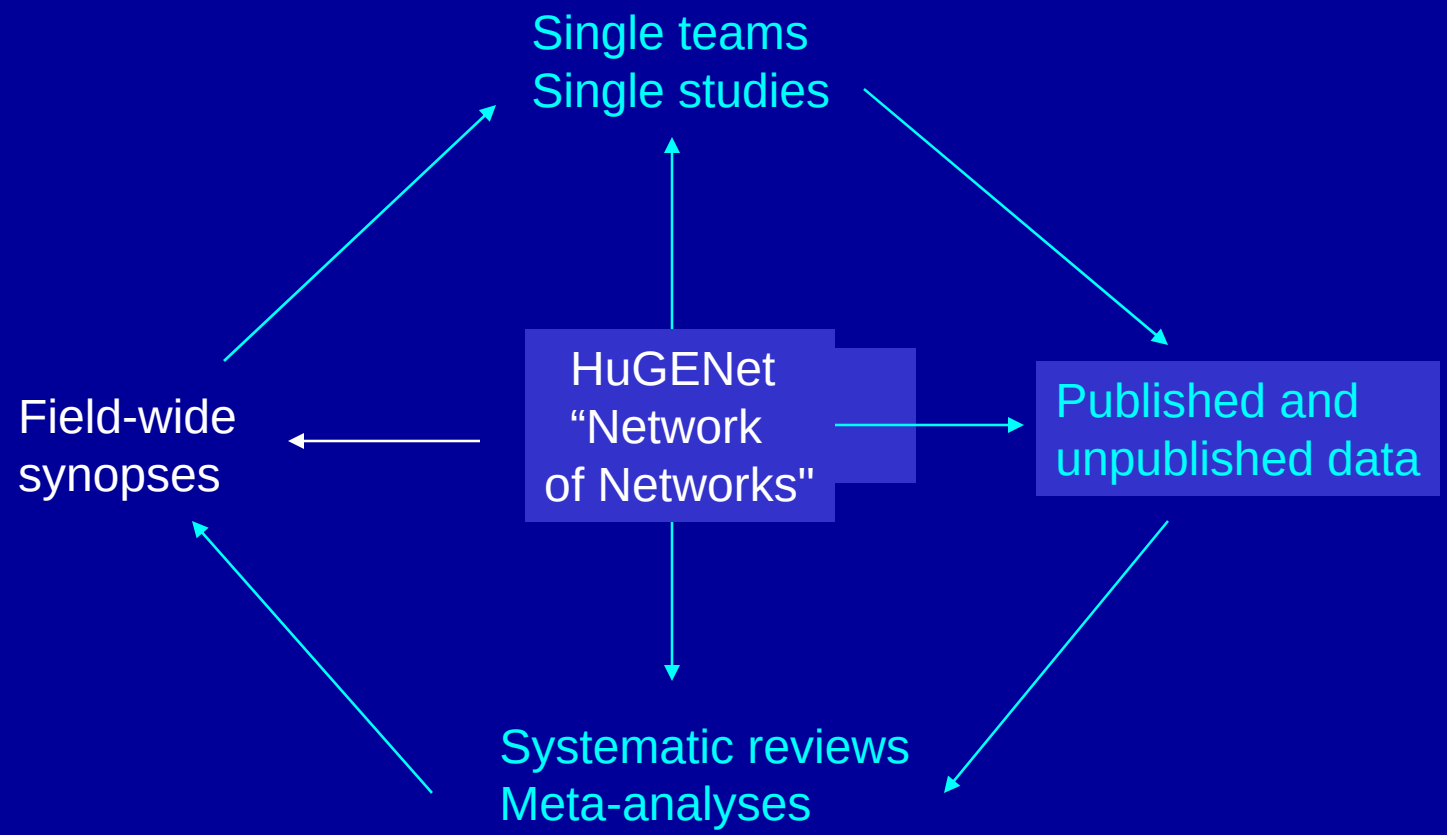
www.cdc.gov/genomics/hugenet

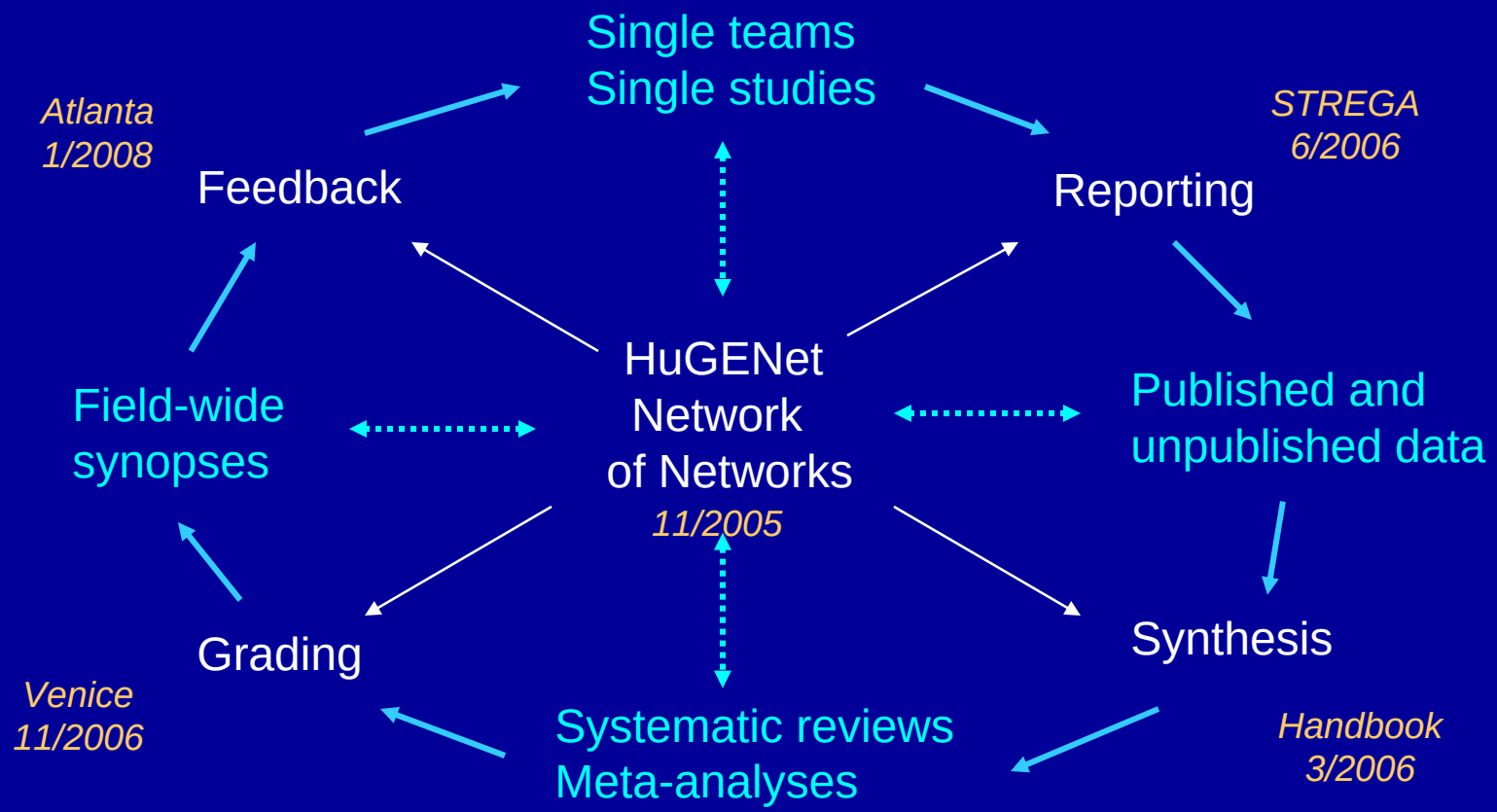
http://www.hugenet.ca **HuGENet Canada**

http://www.hugenet.org.uk UK HuGENet Coordinating Centre

http://www.dhe.med.uoi.gr/hugenet.htm Department of Hygiene and Epidemiology, University of Ioannina School of Medicine


Single teams
Single studies
Consortia /
Networks
Published and
unpublished data
Systematic reviews
Meta-analyses


Single teams
Single studies
HuGENet
"Network
of Networks"
Published and
unpublished data
Field-wide
synopses
Systematic reviews
Meta-analyses



Commentary, *Nature Genetics* 38, 3 - 5 (2006)
A road map for efficient and reliable human genome epidemiology

Examples of Network HuGE Study Platforms

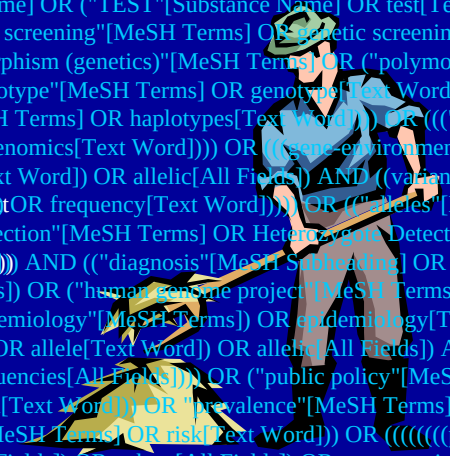
Disease	Consortium	Teams	Subjects
Parkinson	GEO-PD	18	10,000
Osteoporosis	GENOMOS	10	30,000
Preterm birth	PREGENIA	10	20,000
Lymphoma	INTERLYMPH	15	20,000
Lung cancer	ILLCO	30	51,000
Head & Neck	INHANCE	13	28,000
Melanoma	GENOMEL	12	3,000
Pancreatic Ca	PACGENE	10	5,000

From Ioannidis J et al. AJE 2005;162:304

Outline

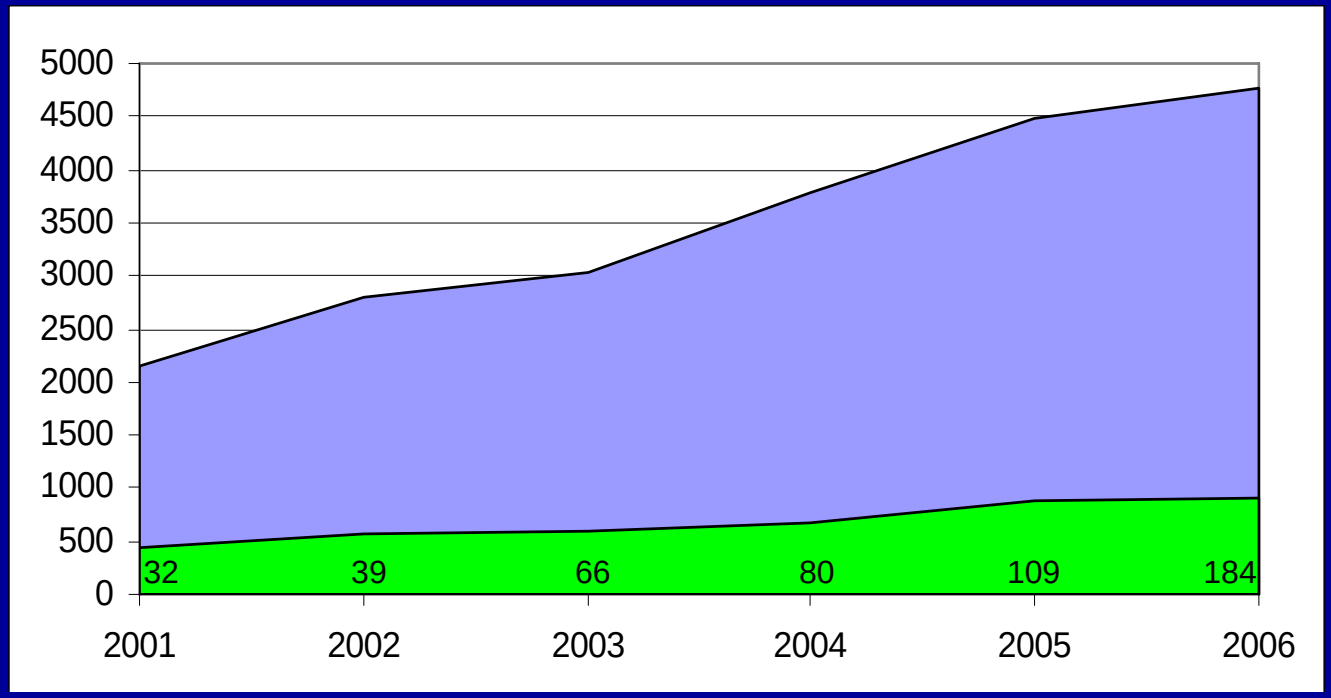
- Introduction-Why Integrate?
- HuGENet Road Map
- Literature Scanning, Reporting, Synthesis and Network Collaboration
- Developing the Knowledge Base and Causal Inference

((((((((((genetic[All Fields] AND ("disease"[MeSH Terms] OR disease[Text Word])) OR ("hereditary diseases"[MeSH Terms] OR genetic disorder[Text Word])) OR (genetic[All Fields] AND ("TEST"[Substance Name] OR test[Text Word]))) OR ("genetic screening"[MeSH Terms] OR genetic screening[Text Word])) OR (genetic[All Fields] AND ("risk"[MeSH Terms] OR risk[Text Word]))) OR ("polymorphism (genetics)"[MeSH Terms] OR genetic polymorphism[Text Word])) OR ("genotype"[MeSH Terms] OR genotype[Text Word])) OR ("genome"[MeSH Terms] OR genome[Text Word])) OR (gene environment interaction[All Fields] OR gene-environment[All Fields])) OR ((genetic[All Fields] OR ("genes"[MeSH Terms] OR gene[Text Word])) AND variant[All Fields])) AND (((((((("epidemiology"[Subheading] OR "epidemiology"[MeSH Terms]) OR epidemiology[Text Word]) OR ("public health"[MeSH Terms] OR public health[Text Word])) OR (("alleles"[MeSH Terms] OR allele[Text Word]) AND (("epidemiology"[Subheading] OR epidemiology"[MeSH Terms]) OR frequency[Text Word]))) OR ("public policy"[MeSH Terms] OR policy[Text Word])) OR (("education"[Subheading] OR education"[MeSH Terms]) OR education[Text Word])) OR ((("epidemiology"[Subheading] OR "prevalence"[MeSH Terms]) OR "epidemiology"[MeSH Terms]) OR prevalence[Text Word])) OR ("prevention and control"[Subheading] OR prevention[Text Word])) OR ("risk"[MeSH Terms] OR risk[Text Word])) OR ((("population"[MeSH Terms] OR population[Text Word]) AND study[All Fields])) NOT ("animals"[MeSH Terms] OR "animal"[MeSH Terms]))



((((((((population[Text Word] OR (a number of) OR genetic[All Fields]) OR comparative[All Fields]) OR prospective[All Fields]) OR cohort[All Fields]) OR cross-section[All Fields]) OR cross-sectional[All Fields]) OR case-control[All Fields]) AND (studies OR study[All Fields]))) OR (clinical trial[All Fields] OR randomized controlled trial[All Fields])) OR (("drug interactions"[MeSH Terms] OR interactions[Text Word]) OR (("interpersonal relations"[MeSH Terms] OR "drug interactions"[MeSH Terms]) OR interaction[Text Word]))) OR ("questionnaires"[MeSH Terms] OR questionnaire[Text Word])) OR (("sensitivity and specificity"[MeSH Terms] OR sensitivity[Text Word]) OR ("sensitivity and specificity"[MeSH Terms] OR specificity[Text Word]))) OR ((((case[All Fields] OR cases[All Fields]) OR ("patients"[MeSH Terms] OR patients[Text Word])) OR (study[All Fields] AND group[All Fields])) OR ((((((("prevention and control"[MeSH Subheading] OR control[Text Word]) OR controls[All Fields]) OR (healthy[All Fields] AND subjects[All Fields])) OR ("child"[MeSH Terms] OR children[Text Word])) OR ("adult"[MeSH Terms] OR adults[Text Word])) OR individuals[All Fields]))) OR ((((("association"[MeSH Terms] OR association[Text Word]) OR ("association"[MeSH Terms] OR associations[Text Word])) OR ("disease"[MeSH Terms] OR disease[Text Word])) AND (("genes"[MeSH Terms] OR gene[Text Word]) OR ("genes"[MeSH Terms] OR genes[Text Word])))) OR oversight[All Fields]) OR ((("genotype"[MeSH Terms] OR genotype[All Fields]) OR allelic[All Fields]) AND distribution[Text Word])) OR ((((("genotype"[MeSH Terms] OR genotype[Text Word]) AND ("phenotype"[MeSH Terms] OR phenotype[Text Word])) OR genotype-phenotype[All Fields]) AND correlation[All Fields])) OR ((positive OR negative) AND predictive value)) OR (odds ratio)) OR (("ethics"[MeSH Terms] OR ethics[Text Word]) OR ethical[All Fields])))) AND "2004/7/7 8.00"[MHDA]:"2004/7/14 8.00"[MHDA])

HuGE Published Literature 2001-2006

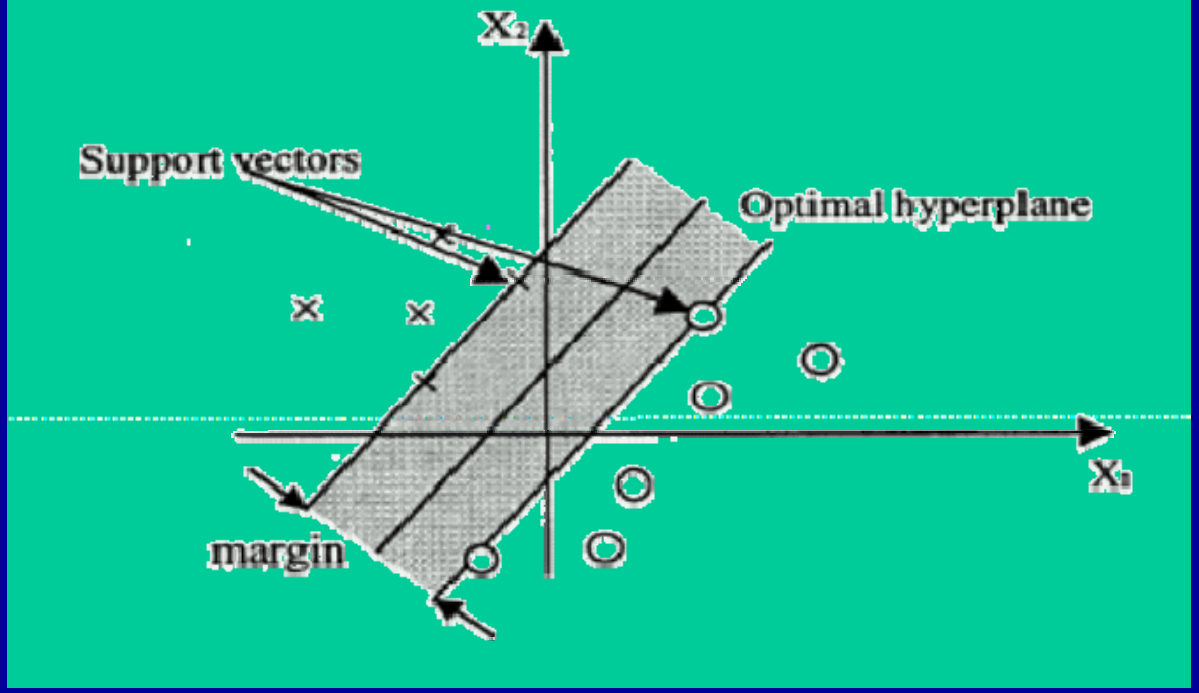


Gene-disease association

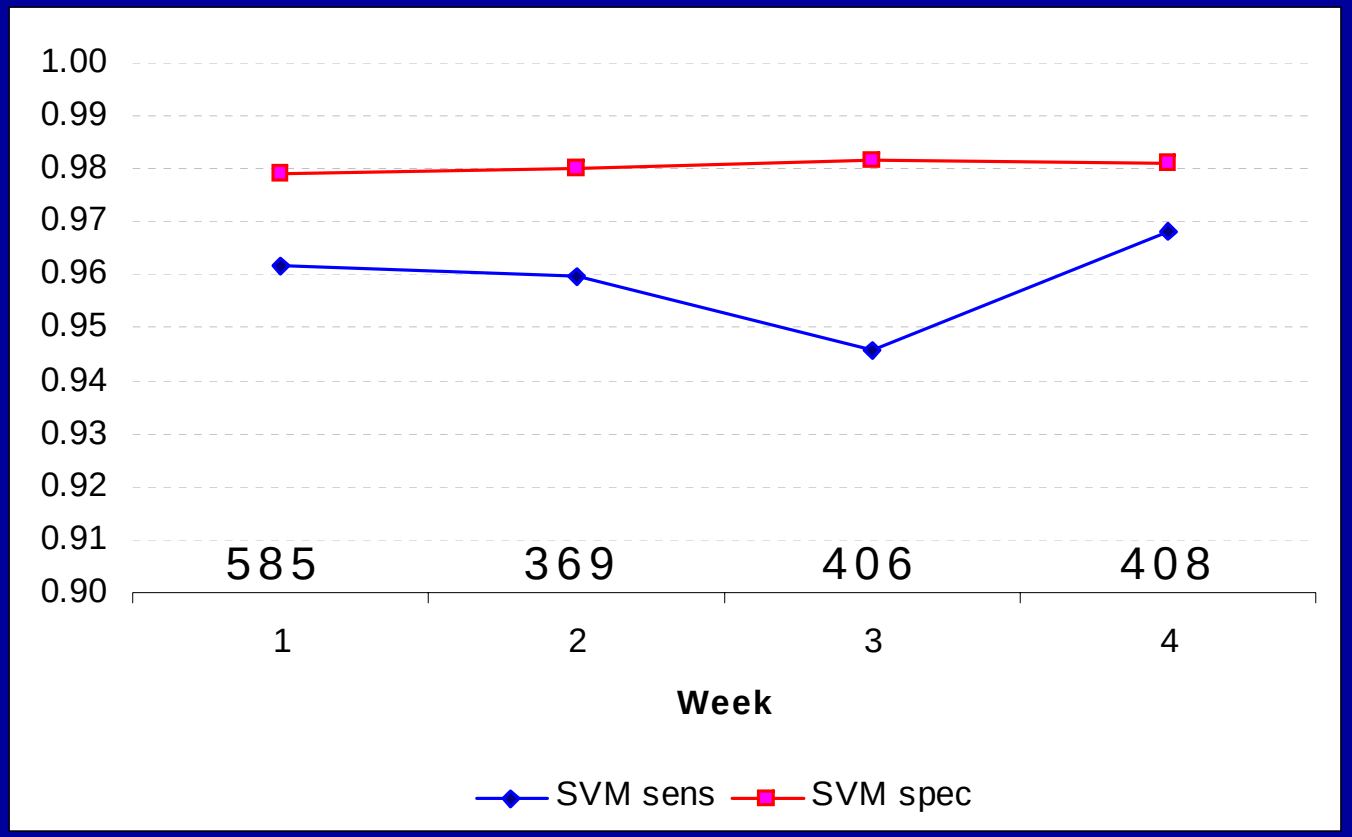
Gene-environment interaction

32 Meta-analysis/HuGE review

HuGE
Classification Problem: Man vs. Machine



Support Vector Machine = SVM



HuGE published literature: SVM model vs human method

Feb-Mar, 2007

Hand searching was reduced by 90%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Public Health Genomics
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LINKS
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HuGE Navigator
HuGE Navigator is a knowledge base that provides integrated information and knowledge in human genome epidemiology (HuGE).
Currently, HuGE Navigator consists of the following applications:
HuGEPedia : an online Human Genome Epidemiology encyclopedia for human diseases.
GeneSelectAssist : a search engine for finding possible candidate genes based on the NCBI Entrez Gene, PubMed and HuGE Pub Lit databases.
HuGE Literature Finder : a search engine for finding PubMed articles related to human genome epidemiology.
HuGE Investigator Browser : a search engine for finding investigators or potential collaborators in a particular HuGE field.
US Genome Variation Database : a collection of genotype prevalence data from CDC NHANES genotying project.
HuGE Reality Checker : a calculator for evaluating the predictive value of genetic markers.

HuGE Investigator Browser

- search HuGE investigators -

Search Investigator for Go Clear First & Last Authors All Authors

- Enter search terms into the text box.
- Search terms can include disease, exposure, gene, author, journal, etc.
- Author options determine the authorship status of investigators of interest.
- Simple Boolean operators are allowed (such as AND or OR).
- Use the Search dropdown list to switch to other HuGE Navigator applications.

HuGE Investigator Browser is a search engine for finding investigators or collaborators in human genome epidemiology based on study interests such disease/condition, environmental risk factors, or gene. Investigator profile information is extracted using an accessory utility that automatically parses the affiliation data provided by PubMed. .

HuGE Investigator Browser

- search HuGE investigators -

HuGE Navigator | Home | About | Search Instructions | FAQs | Contact Us

Search Investigator **for** osteoporosis Go Clear First & Last Authors All Authors

- Enter search terms into the text box.
- Search terms can include disease, exposure, gene, author, journal, etc.
- Author options determine the authorship status of investigators of interest.
- Simple Boolean operators are allowed (such as AND or OR).
- Use the Search dropdown list to switch to other HuGE Navigator applications.

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- search HuGE investigators -
HuGE Navigator | Home | About | Search Instructions | FAQs | Contact Us
Search Investigator for osteoporosis Go Clear First & Last Authors All Authors
Search Criteria: osteoporosis[Query]
Filtered By Country
[Click to re-sort the table base
Investigator N
Deng HW
Ralston SH
Uitterlinden AG
Emi M
Yamada Y
Shimokata H
Chen HY
Langdahl BL
Investigator Information - Microsoft Internet Explorer
Investigator Information
Investigator Name: Deng HW
Query/Domain: osteoporosis
Publications:
All HuGE 32
Query Specific HuGE (all author) 16
Query Specific HuGE (first/last author) 16
All PubMed (query specific) Link
Possible Affiliation Information:
Institute Creighton University
Country United States
Email
Address Osteoporosis Research Center, Creighton University, Omaha, Nebraska 68131, USA

HuGE Investigator Browser

- search HuGE investigators -

Search Investigator for osteoporosis Go Clear First & Last Authors All Authors

Search Criteria: osteoporosis[Query]

Filtered By Country Institute

464 investigators were found.

[Click to re-sort the table based on either investigator names (left icon) or the publication count (right icon)]

Investigator Name	Number of Publications (F/L)
Deng HW	16
Ralston SH	12
Uitterlinden AG	11
Emi M	10
Yamada Y	9
Shimokata H	8
Chen HY	7
Langdahl BL	6

Search Criteria: osteoporosis[Query]>>Deng HW [First/Last Author] **[Query Detail]**

Filtered By Disease Exposure Gene Category StudyType Year Author

Articles 1 - 16 of 16

PubMed It **Display** 25 on Page 1 of 1

1. Tests of linkage and association of PTH/PTHrP receptor type 1 gene with bone mineral density and height in Caucasians. **[Detail]**
Journal of bone and mineral metabolism. 2006 24 (1): 36-41.
Zhang YY, Liu PY, Lu Y, Xiao P, Liu YJ, Long JR, Shen H, Zhao LJ, Elze L, Recker RR, Deng HW

2. Is a gene important for bone resorption a candidate for obesity? An association and linkage study on the RANK (receptor activator of nuclear factor-kappaB) gene in a large Caucasian sample. **[Detail]**
Human genetics 2006 Nov 120 (4): 561-70.
Zhao LJ, Guo YF, Xiong DH, Xiao P, Recker RR, Deng HW

3. Robust and comprehensive analysis of 20 osteoporosis candidate genes by very high-density single-nucleotide polymorphism screen among 405 white nuclear families identified significant association and gene-gene interaction. **[Detail]**
Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2006 Nov 21 (11): 1678-95.
Xiong DH, Shen H, Zhao LJ, Xiao P, Yang TL, Guo Y, Wang W, Guo YF, Liu YJ, Recker RR, Deng HW

4. The human calcium-sensing receptor and interleukin-6 genes are associated with bone mineral density in Chinese. **[Detail]**
Yi chuan xue bao = Acta genetica Sinica. 2006 Oct 33 (10): 870-80.
Wang YB, Guo JJ, Liu YJ, Deng FY, Jiang DK, Deng HW

STrengthening REporting of Genetic Associations (STREGA)

- STROBE: International collaborative initiative for **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology

American Journal of Epidemiology
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DOI: 10.1093/aje/kwf064

Reporting, Appraising, and Integrating Data on Genotype Prevalence and Gene-Disease Associations

Julian Little[1], Linda Bradley[2], Molly S. Bray[3], Mindy Clyne[4], Janice Dorman[5], Darrell L. Ellsworth[6], James Hanson[7], Muin Khoury[4], Joseph Lau[8], Thomas R. O'Brien[7], Nat Rothman[7], Donna Stroup[9], Emanuela Taioli[10], Duncan Thomas[11], Harri Vainio[12], Sholom Wacholder[7], and Clarice Weinberg[13]

[1] Epidemiology Group, Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, Scotland.
[2] Sunrise Medical Laboratory, Hauppauge, NY.
[3] University of Texas Health Science Center at Houston, Houston, TX.
[4] Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, GA.
[5] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA.

STROBE + HuGE= STREGA

STrengthening REporting of Genetic Associations (STREGA)

- STROBE: International collaborative initiative for **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology

STROBE statement: Checklist of essential items Version 2 (April 2005)

	Item #	Cohort	Case-control	Cross-sectional
TITLE & ABSTRACT	1	(a) Identify the article as a cohort study in the title or the abstract.	(a) Identify the article as a case-control study in the title or the abstract.	(a) Identify the article as a cross-sectional study in the title or the abstract.
		(b) The abstract should be a highly informative structured summary of the article, taking account of all issues in the checklist below.		
INTRODUCTION				
Background / Rationale	2	Explain scientific background and rationale for the study.		
Objectives	3	State specific objectives and hypotheses.		
METHODS				
Study design	4	Present key elements of study design. State purpose of original study, if article is one of several from an ongoing study.		
Setting	5	Describe setting, locations and dates defining periods of data collection.		

STROBE + HuGE= STREGA

Reporting Characteristics of 315 HuGE Articles 2001-2003: General

Reporting characteristic	Count	%
Number of study participants		
<100	49	15.6
100-499	190	60.3
500-999	47	14.9
>= 1000	29	9.2
Reported the available power of the study		
No	275	87.3
Yes	40	12.7
Reported that multiple study participant or case or control groups were used		
No	235	74.6
Yes	80	25.4
Provided any information on the origin of the study participants		
No	38	12.1
Yes	277	87.9
Provided any information on the enrollment criteria for the study participants		
No	8	2.5
Yes	307	97.5

Yesupriya et al.

Reporting Characteristics of 315 HuGE Articles 2001-2003: Genotyping

Reporting characteristic	Count	%
Length in pages dedicated to describing genetic testing method		
0	4	1.3
0.01-0.24	184	58.4
0.25-0.49	88	27.9
>0.5	39	12.4
Reference to the genotyping method of another study		
No	62	19.7
Yes	253	80.3
Reported that the genotyping results were validated by using duplicate samples		
No	293	93.0
Yes	22	7.0
Reported that the genotyping results were validated by using a different method		
No	284	90.2
Yes	31	9.8
Reported that the evaluation of the genetic test was blind to the outcomes or phenotypes		
Blind	35	11.1
Unclear	280	88.9
Reported that the evaluation of the outcomes or phenotypes was blind to the genetic test		
Blind	12	3.8
Unclear	303	96.2

Yesupriya et al.

Reporting Characteristics of 315 HuGE Articles 2001-2003: Subject Selection

Reporting characteristic	Count	%
Explicitly stated that all study participants were drawn from the same ethnic population		
Unclear	130	41.3
Stated	185	58.7
Analysis conducted by using different ethnic groups		
No	285	90.5
Yes	30	9.5
If different ethnic groups were included, how was ethnicity treated in the analysis (*n*=30)		
Stratified by or adjusted for ethnic groups	23	76.7
Pooled ethnic groups together	2	6.7
Unclear	5	16.6
Reported that unlinked genetic markers were used to identify population stratification		
No	313	99.4
Yes	2	0.6
Reported that cases and controls were drawn from the same population in regards to geography (*n*=227)		
No	79	34.8
Yes	148	65.2
Reported that cases and controls were drawn from the same population in regards to the clinical population (*n*=227)		
No	180	79.3
Yes	47	20.7

Yesupriya et al.

Reporting Characteristics of 315 HuGE Articles 2001-2003: Analysis

Reported that all genetic variants were examined for Hardy-Weinberg equilibrium		
No	164	52.1
Yes	151	47.9
If Hardy-Weinberg equilibrium was reported, did any polymorphism reportedly fail Hardy-Weinberg equilibrium (*n*=151)		
No	141	93.4
Yes	10	6.6
Sufficient data reported on all genetic variants of interest for all outcomes		
No	41	13.0
Yes	274	87.0
Reported that analyses were conducted by using allele-based genetic contrasts		
No	143	45.4
Yes	172	54.6
Reported that analyses were conducted by using genotype-based genetic contrasts		
No	45	14.3
Yes	270	85.7
If the analyses were conducted by using genotypes, were selected contrasts or all possible contrasts assessed (*n*=270)		
All possible	214	79.3
Selected	56	20.7
Justifications given for the selection of specific genetic contrasts (*n*=56)		
No	33	58.9
Yes	23	41.1

Yesupriya et al.


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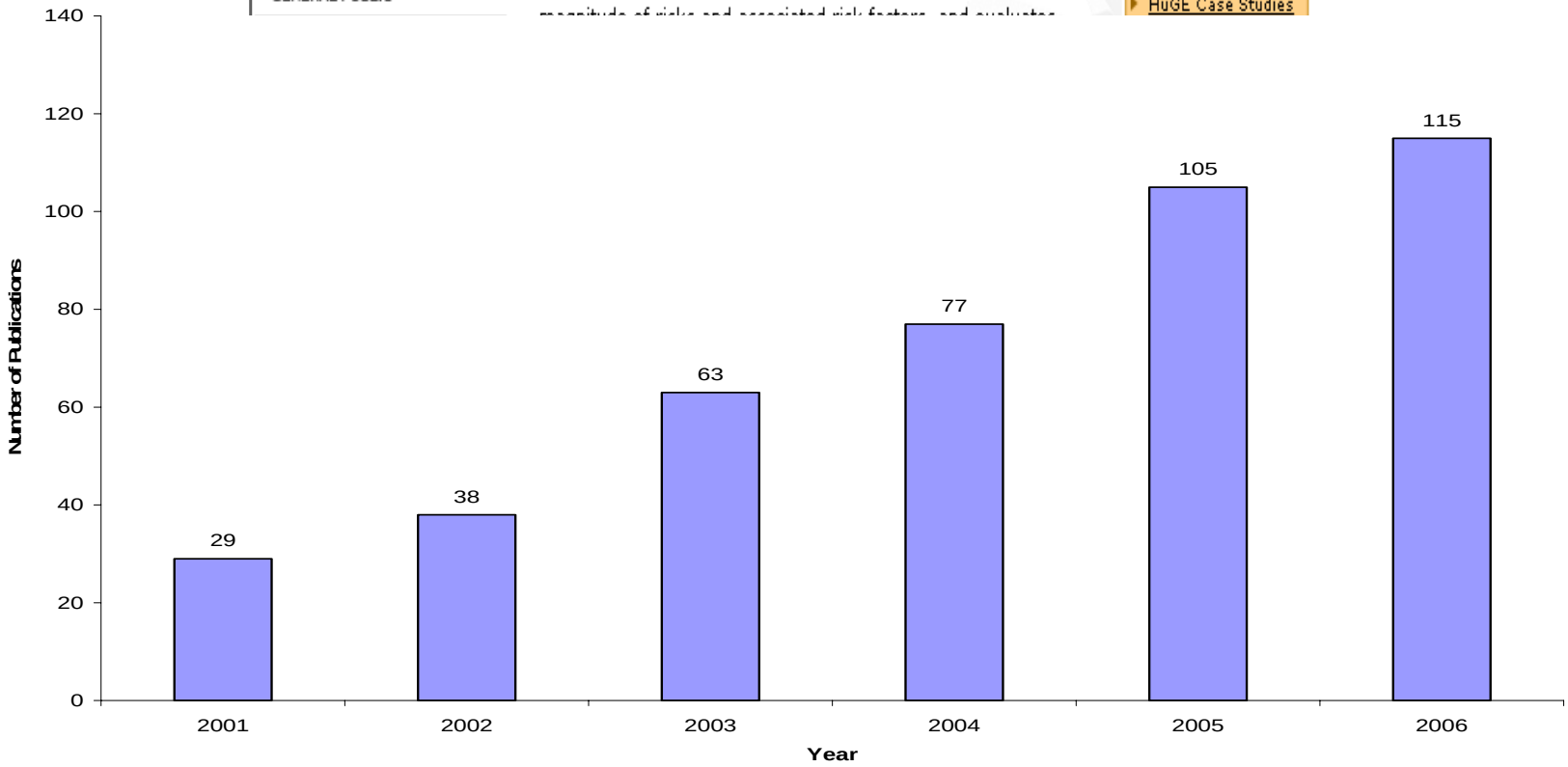
HuGE Book
HuGE Case Studies


Number of Publications
140
120
100
80
60
40
20
0
29
38
63
77
105
115
2001
2002
2003
2004
2005
2006
Year

The HuGENet™ HuGE Review Handbook, version 1.0

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on behalf of the HuGE Net Systematic Review and Meta-Analysis Working Group

American Journal of Epidemiology
Genetics in Medicine
Epidemiologic Reviews
Pediatric Perinatal Epidemiology
International Journal Epidemiology

American J Obs Gyn
Gastroenterology
CEBP
Teratology/Birth Def
Epidemiology

Advantages of MIPD

MIPD* versus MPL*

- Advantages
  - Data
    - More information
    - Inclusion of extended databases from published studies
    - Inclusion of data from unpublished studies
  - Better standardization of information
    - Categorization of eligible participants
    - Outcomes
    - Definition of follow-up period and censoring criteria
  - Analysis
    - Better time-to-event analyses
      - Standardized statistical models
      - Evaluation of time-dependency
  - Better adjusted/multivariate analyses
  - Consistent treatment of loci in linkage disequilibrium
  - Evaluation of dose-response effects for multiple genes or double doses of a single gene
  - Evaluation of subgroup effects, including racial heterogeneity
  - Interpretation
    - Assessment of heterogeneity
    - Assessment of sampling bias in specific studies
  - Other
    - Establishment of international networks of collaborating investigators

Ioannidis et al, Am J Epidemiol 2002

Disadvantages of MIPD

Data

- Data may not be made available from all published studies

Interpretation

- Potential post hoc conflicts with collaborators regarding findings

Resources

- Substantial effort and infrastructure required to:
  - Develop and administer a standardized protocol
  - Collect, manage, and analyze data
  - Communicate with collaborators

Stages in Integrating Evidence

- Formulating the problem
- Identification of studies and publication bias
- Critical appraisal of studies
- Abstraction of data
- Synthesis

Critical Appraisal

- Independent reviewers
- Inclusion/exclusion criteria
- Sequential or multiple publications of analyses of same or overlapping data sets
- Assessment of study quality

Synthesis of the Evidence

- Volume of evidence
- Evidence tables

  - Publication details

  - Study type

  - Factors relating to study quality

  - Measure of association, with indication of its precision

Summary of Studies of Colorectal Cancer & *GSTT1*

Area of study; Recruitment period	Cases Type	N	Controls Type	N	% *GSTT1* null	RR (95% CI) for null *vs* other genotypes	Adjustment	Subgroup analysis reported	Exposure assessment	Reference
Australia, Queensland; period not stated	Patients with *colorectal adenocarcinoma*	125	Unselected subjects (n=94; source not stated) and geriatric (n=54) patients without cancer or a family history of cancer	94 54	19% 9%	0.7 (0.3-1.4) 1.5 (0.6-4.3)	None None	Position of tumour; age	None	Chenevix-Trench et al., 1995 (78)
UK, North Staffordshire Cases & controls 1990-94	Unrelated English "Caucasian" patients with *colorectal cancer* recruited from 1 hospital	211	Hospitalised English "Caucasian" subjects without malignancy or inflammatory pathologies; recruited in same hospital as cases	509	18%	1.9 (1.3-2.7)	None	Position of tumour	None	Deakin et al., 1996 (49)
Japan, Kitakyusko City Cases 1991-95, controls 1993-95	Consecutive patients with *colorectal adenocarcinoma* diagnosed in 2 hospitals and 1 medical centre; 65% male; mean age 64.4 years	103	Subjects who had visited local medical centres for regular health check-ups; no gastrointestinal symptoms and no current or previous diagnosis of cancer; 57% male; mean age 61.9 years	126	44%	1.2 (0.7-2.0)	None	Position of tumour	Medical, residential, occupational and smoking history assessed by interview	Katoh et al., 1996 (14)
Australia, Adelaide; period not stated	White adults with sporadic *colorectal cancer*; source not stated	219	White blood donors	200	19%	3.4 (2.1-5.4)	None	None	None	Butler et al., 1997 (77) (reported in abstract only)
USA (nested case-control study in Physicians Health Study (PHS)); cases 1982-96	Cases with *colorectal cancer* from those randomised in PHS; physicians excluded from randomisation if they had history of myocardial infarction, stroke, transient ischemic attack, cancer, renal or liver disease, peptic ulcer, gout	212	Sample of subjects not diagnosed with colorectal cancer in PHS (same exclusion criteria as listed for cases); matched on year of birth and smoking history	221	23%	0.8 (0.5-1.2)	BMI, physical activity, alcohol use	Position of tumour, age smoking	Smoking history, alcohol intake, diet, frequency of meat intake, physical activity, disease diagnoses	Gertig et al., 1998 (58)
Singapore, period not stated	Chinese *colorectal carcinoma* patients recruited from a surgical department	300	Chinese patients obtained from clinical chemistry department with no history of neoplasms	183	Not stated[TI]	-	-	Position of tumour, tumour histology	None	Lee et al., 1998 (23)

This paper was published with modifications in Am J Epidemiol 2000 May 1;151(9):862-877

PMID: 10791559; UI: 20250198

5, 10-Methylenetetrahydrofolate reductase (*MTHFR*) Gene Variants and Congenital Anomalies

Lorenzo D. Botto and Quanhe Yang

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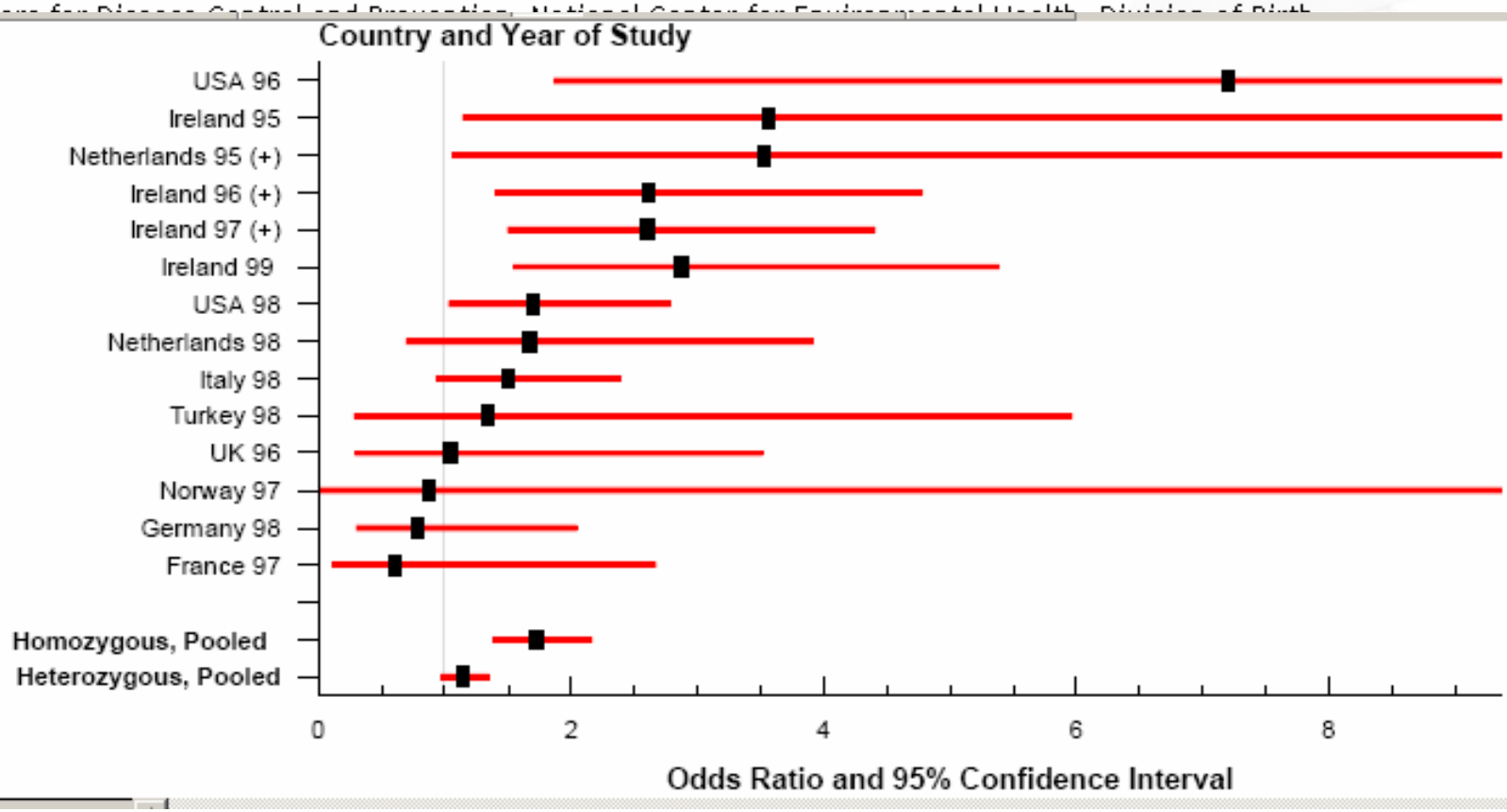
Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Birth



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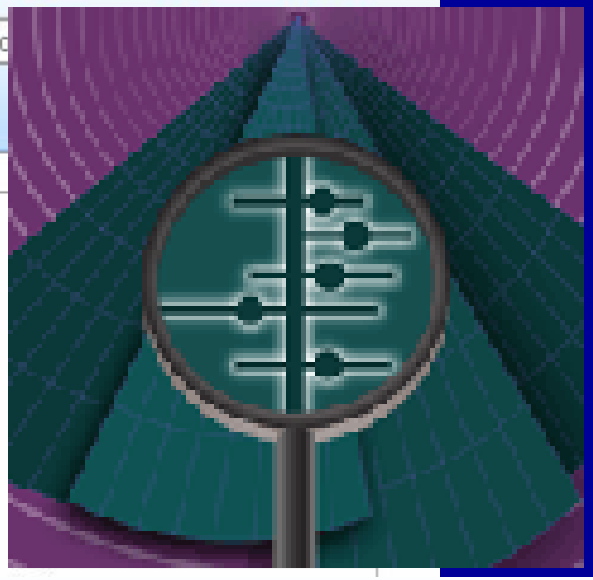

RESEARCH ARTICLE OPEN ACCESS

Epidemiology and Reporting Characteristics of Systematic Reviews

David Moher[1,2,3*], Jennifer Tetzlaff[1], Andrea C. Tricco[1,4], Margaret Sampson[1], Douglas G. Altman[5]

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EDITORIAL OPEN ACCESS

Many Reviews Are Systematic but Some Are More Transparent and Completely Reported than Others

The *PLoS Medicine* Editors

Citation: The *PLoS Medicine* Editors (2007) Many Reviews Are Systematic but Some Are More Transparent

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Citation

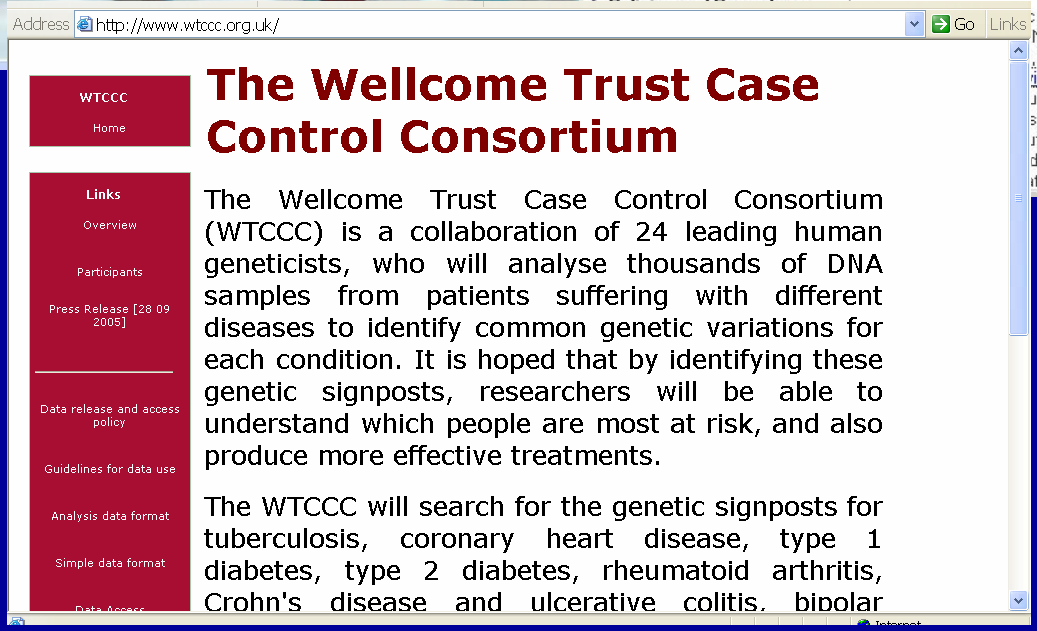
CONTRIBUTE
Write a Response

Methodologic Issues in Meta-Analysis of Gene-Disease Associations

- 37 Meta analyses
- 22% (8) described search terms
- 51% (19) had no inclusion/exclusion criteria
- 76% (28) assessed heterogeneity
- 19% (7) checked for publication bias
- 24% (9) assessed Hardy-Weinberg equilibrium
- 22% (8) had biologic rationale for genetic model

Attia et al, 2003

What about Genome-Wide Association Studies?



Outline

- Introduction-Why integrate?
- The HuGE Net movement
- Collaboration across epidemiologic platforms
- Strengthening the reporting of genetic associations (STREGA)
- Integration across studies-HuGE Reviews
- Developing the knowledge base and causal inference

“Guidelines” for Causal Inference

Consistency

Strength

Dose-response

Biological plausibility

Specificity

Temporality

Experimentation

Coherence

Analogy

(Hill, 1965; US Surgeon General’s Committee, 1964)

The Legend of Biologic Plausibility

- In 2002, studies were published addressing the relationship of the APOE polymorphism with Alzheimer's disease; colorectal cancer; fatty liver; atherosclerosis; hyperlipidemia; acute ischemic stroke; spina bifida; coronary artery disease; normal tension glaucoma; hypertension; Parkinson's disease, diabetic nephropathy; pre-eclampsia; hepatitic C-related liver disease; cerebrovascular disease; coronary artery disease post-renal transplantation; non-specified cognitive impairment; childhood nephrotic syndrome; spontaneous abortion; multiple sclerosis; alcohol withdrawal; cognitive dysfunction after coronary artery surgery; alcoholic chronic pancreatitis; alcoholic cirrhosis; macular toxicity from chloroquine; macular edema; aortic valve stenosis; vascular dementia; type II diabetes mellitus; and migraine.
  - Source. J Ioannidis

Assessment of Cumulative Evidence on Genetic Associations: Interim Guidelines

John P.A. Ioannidis[1-3], Paolo Boffetta[4], Julian Little[5], Thomas R. O'Brien[6], Andre G. Uitterlinden[7], Paolo Vineis[8], David J. Balding[8], Anand Chokkalingam[9], Siobhan Dolan[10], W. Dana Flanders[11], Julian P.T. Higgins[12], Mark I. McCarthy[13,14], David H. McDermott[15], Grier P. Page[16], Timothy R. Rebbeck[17], Daniela Seminara[18], Muin J. Khoury[19]

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Assessing Cumulative Evidence on Genetic Associations (Venice Guidelines)

- Epidemiologic Credibility
- Biology
- Clinical/Public Health Relevance

Amount of evidence	A Large-scale evidence	
	B Moderate amount of evidence	
	C Little evidence	
Replication	A Extensive replication including at least one well-conducted meta-analysis with little between-study inconsistency	
	B Well-conducted meta-analysis with some methodological limitations or moderate between-study inconsistency	
	C No association; no independent replication; failed replication; scattered studies; flawed meta-analysis; or large inconsistency	
Protection from bias	A Bias, if at all present, could affect the magnitude but probably not the presence of the association	
	B No obvious bias that may affect the presence of the association, but there is considerable missing information on the generation and accumulation of evidence	
	C Clear presence of bias that can affect even the presence or not of the association	

Assessing Epidemiologic Credibility of Cumulative Evidence on Genetic Associations- Venice Guidelines

First letter = amount

Second letter = replication

Third letter = protection from bias

AAA	ABA	ACA
AAB	ABB	ACB
AAC	ABC	ACC

BAA	BBA	BCA
BAB	BBB	BCB
BAC	BBC	BCC

CAA	CBA	CCA
CAB	CBB	CCB
CAC	CBC	CCC

Strong evidence

Moderate evidence

Weak evidence

Table 2: Considerations for assessment of clinical and public health relevance and importance of genetic associations

Magnitude of effect	
	Effect size
	Frequency of genetic variant in population
Clinical and public health importance	
	Type of phenotype: biological, endophenoype, hard clinical outcome
	Disease burden; incidence, severity, and mortality
	Interaction with identified modifiable environmental exposures
	Potential to prevent disease through intervention (e.g. through Mendelian randomization insights)

An Online Encyclopedia for Genome Variation and Health?

EDITORIAL

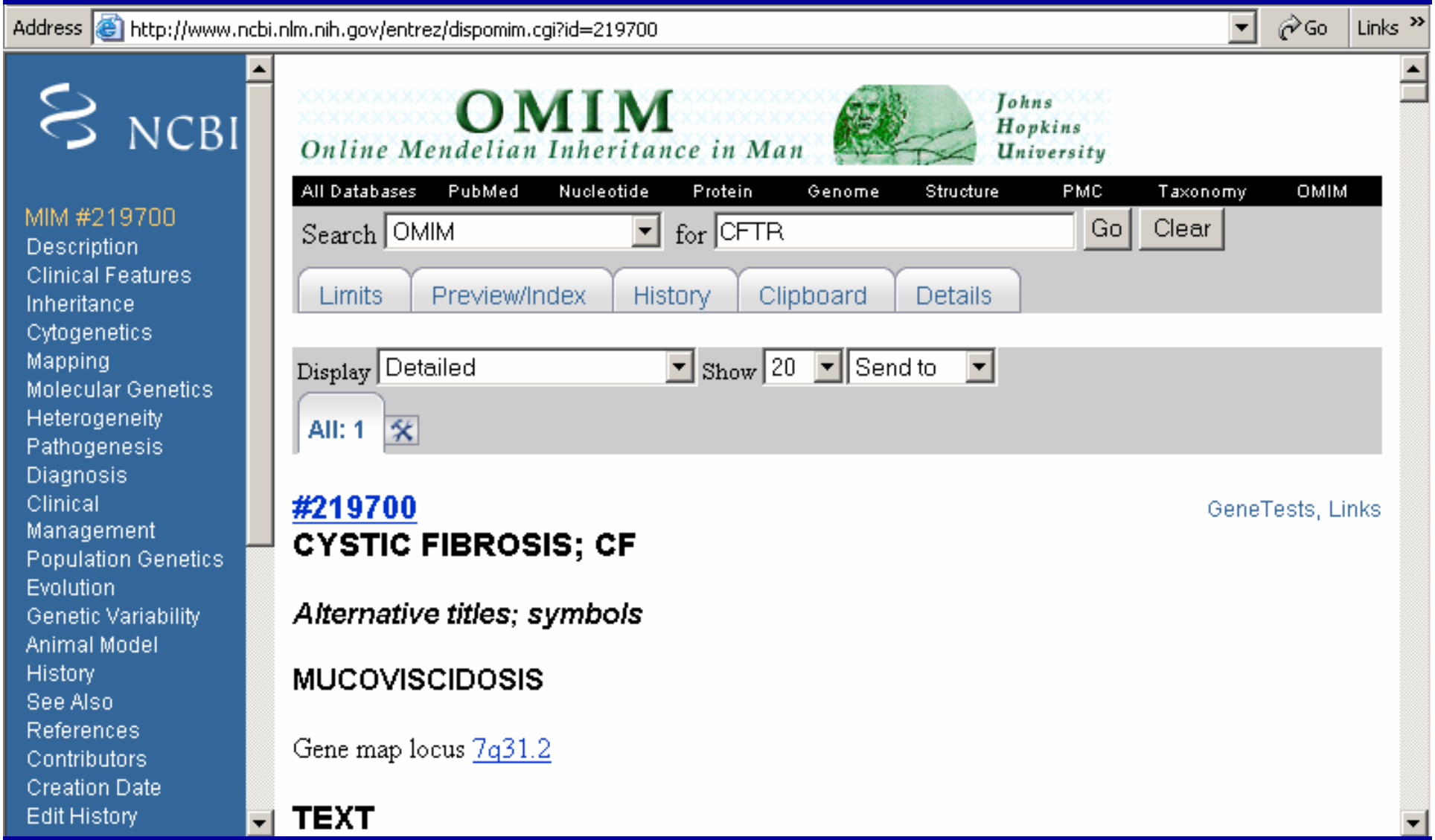
Nature Genetics **38**, 1 (2006)
doi:10.1038/ng0106-1

Embracing risk

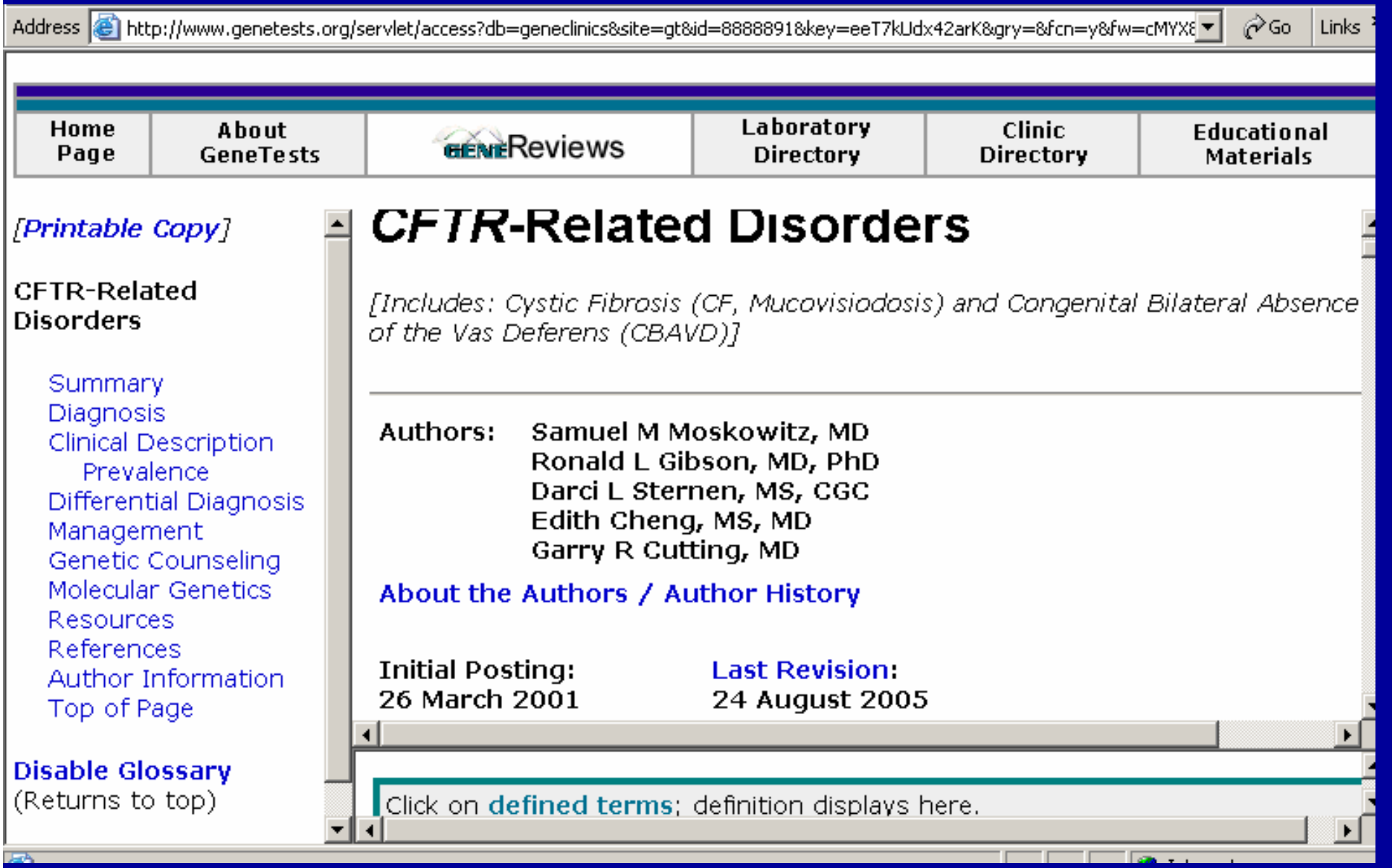
In response to requests from researchers for a way to publish and credit well-executed genetic association studies regardless of the outcome, we offer an experimental solution: the journal will now consider for publication—in Analysis format—annual synopses of all adequate association studies on a particular disease or phenotype. The synopsis may be written by a consortium of the authors of unpublished but publicly deposited studies, and it is hoped that the referees of the synopses will publish their comments as a counterpoint.

Much remains to be done. First, researchers need to decide on minimally acceptable criteria

Models for Online Encyclopedia 1



Models for Online Encyclopedia 2



Models for Online Encyclopedia 3

Address http://en.wikipedia.org/wiki/Main_Page Go Links

WIKIPEDIA
The Free Encyclopedia

Sign in / create account

main page | discussion | view source | history

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- Community Portal
- Featured articles
- Current events
- Recent changes
- Random article
- Help
- Contact Wikipedia
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search

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the free encyclopedia that anyone can edit.

1,461,789 articles in English

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- History
- Society
- Biography
- Mathematics
- Technology
- Geography
- Science
- **All portals**

Overview · Searching · Editing · Questions · Help

Categories · Featured content · A–Z index

Today's featured article

Kochi is a city in the Indian state of Kerala, and one of the principal seaports of the country. Kochi is located in the district of Ernakulam, about 220 km north of the state capital Thiruvananthapuram. The city has an estimated population of 650,000, with an extended metropolitan population of over 1.6 million, making it the largest urban agglomeration and the second largest city in

In the news

- The World Confederation of Labour and the International Confederation of Free Trade Unions merge to form the **International Trade Union Confederation**, representing 166 million members.
- Hassan Nasrallah, the Secretary General of Hezbollah, says negotiations

Outline

- Introduction-Why Integrate?
- HuGENet Road Map
- Literature Scanning, Reporting, Synthesis and Network Collaboration
- Developing the Knowledge Base and Causal Inference