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From biomedical informatics to translational research

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Outline

- Translational research
- Enabling translational research
- Anatomy of a translational research experiment
- Promising results
- Challenging issues

Translational research

(Translational medicine)

Translational medicine/research

- Definition

  [Butte, JAMIA 2008]

  - Effective transformation of information gained from biomedical research into knowledge that can improve the state of human health and disease

- Goals
  - Turn basic discoveries into clinical applications more rapidly ("bench to bedside")
  - Provide clinical feedback to basic researchers

Combining clinical informatics and bioinformatics

- Associates
  - Clinical informatics
    - Electronic medical records
    - Clinical knowledge bases
  - Common computational resources
    - Biomedical natural language processing
    - Biomedical knowledge engineering
  - Bioinformatics
    - Sequence databases
    - Gene expression
    - Model organism databases

Translational bioinformatics

- *"… the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data into proactive, predictive, preventative, and participatory health.*

  Translational bioinformatics includes research on the development of novel techniques for the integration of biological and clinical data and the evolution of clinical informatics methodology to encompass biological observations.

  The end product of translational bioinformatics is newly found knowledge from these integrative efforts that can be disseminated to a variety of stakeholders, including biomedical scientists, clinicians, and patients."

AMIA strategic plan
http://www.amia.org/inside/stratplan

Aspects of translational research

- Huge volumes of data
- Publicly available repositories
- Publicly available tools
- Data-driven research

Huge volumes of data

- Affordable, high-throughput technologies
  - DNA sequencing
    - Whole genomes
    - Multiple genomes
  - Single nucleotide polymorphism (SNPs) genotyping
    - Millions of allelic variants between individuals
  - Gene expression data from micro-array experiments
  - Text mining
    - Full-text articles
    - Whole MEDLINE
  - Electronic medical records
  - Genome-wide association studies

Publicly available repositories

- DNA sequences
  - GenBank / EMBL / DDBJ
- Gene Expression data
  - GEO, ArrayExpress
- Biomedical literature
  - MEDLINE, PubMedCentral
- Biomedical knowledge
  - OBO ontologies
- Clinical data (genotype and phenotype)
  - dbGaP

Publicly available tools

- DNA sequences
  - BLAST
- Gene Expression data
  - GenePattern, …
- Biomedical literature
  - Entrez, MetaMap
- Biomedical knowledge
  - Protégé

Culture of sharing encouraged by the funding agencies

- Grants for tools and resource development
- Mandatory sharing plan in large NIH grants
- Mandatory sharing of manuscripts in PMC for NIH-funded research

Data-driven research

- Paradigm shift
  - Hypothesis-driven
    - Start from hypothesis
    - Run a specific experiment
    - Collect and analyze data
    - Validate hypothesis (or not)

    Biomedical informatics as a supporting discipline for biology and clinical medicine
  - Data-driven
    - Integrate large amounts of data
    - Identify patterns
    - Generate hypothesis
    - Validate hypothesis (or not) through specific experiments

    Biomedical informatics as a discipline in its own right, addressing important questions in medicine

Translational bioinformatics as a discipline

- *"The availability of substantial public data enables bioinformaticians' roles to change. Instead of just facilitating the questions of biologists, the bioinformatician, adequately prepared in both clinical science and bioinformatics, can ask new and interesting questions that could never have been asked before. […] There is a role for the translational bioinformatician as question-asker, not just as infrastructure-builder or assistant to a biologist."*

[Butte, JAMIA 2008]

Enabling translational research

Clinical Translational Research Awards (CTSA)

Translational research NIH Roadmap

Clinical and Translational Science Awards

- *The purpose of the CTSA Program is to assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to:*
  - *1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams;*
  - *2) create an incubator for innovative research tools and information technologies; and*
  - *3) synergize multi-disciplinary and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care.*

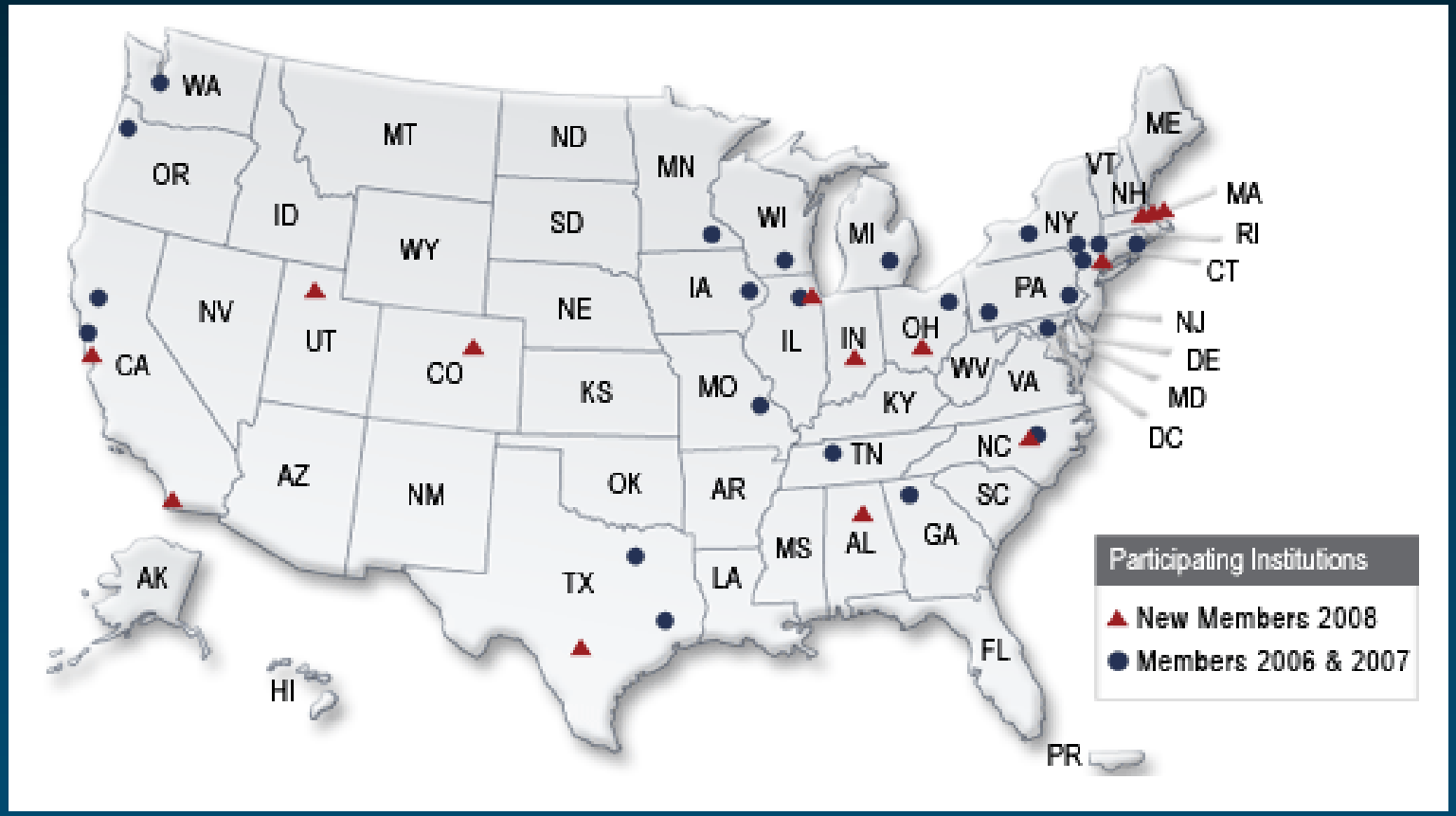
http://nihroadmap.nih.gov/

CTSA program (NCRR)

- 38 academic health centers in 23 states
  - 14 centers added in 2008
  - 60 centers upon completion
- Funding provided for 5 years
- Total annual cost: $500 M
- Annual funding per center: $4-23 M
  - Depending on previous funding

http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/

Clinical and Translational Science Awards

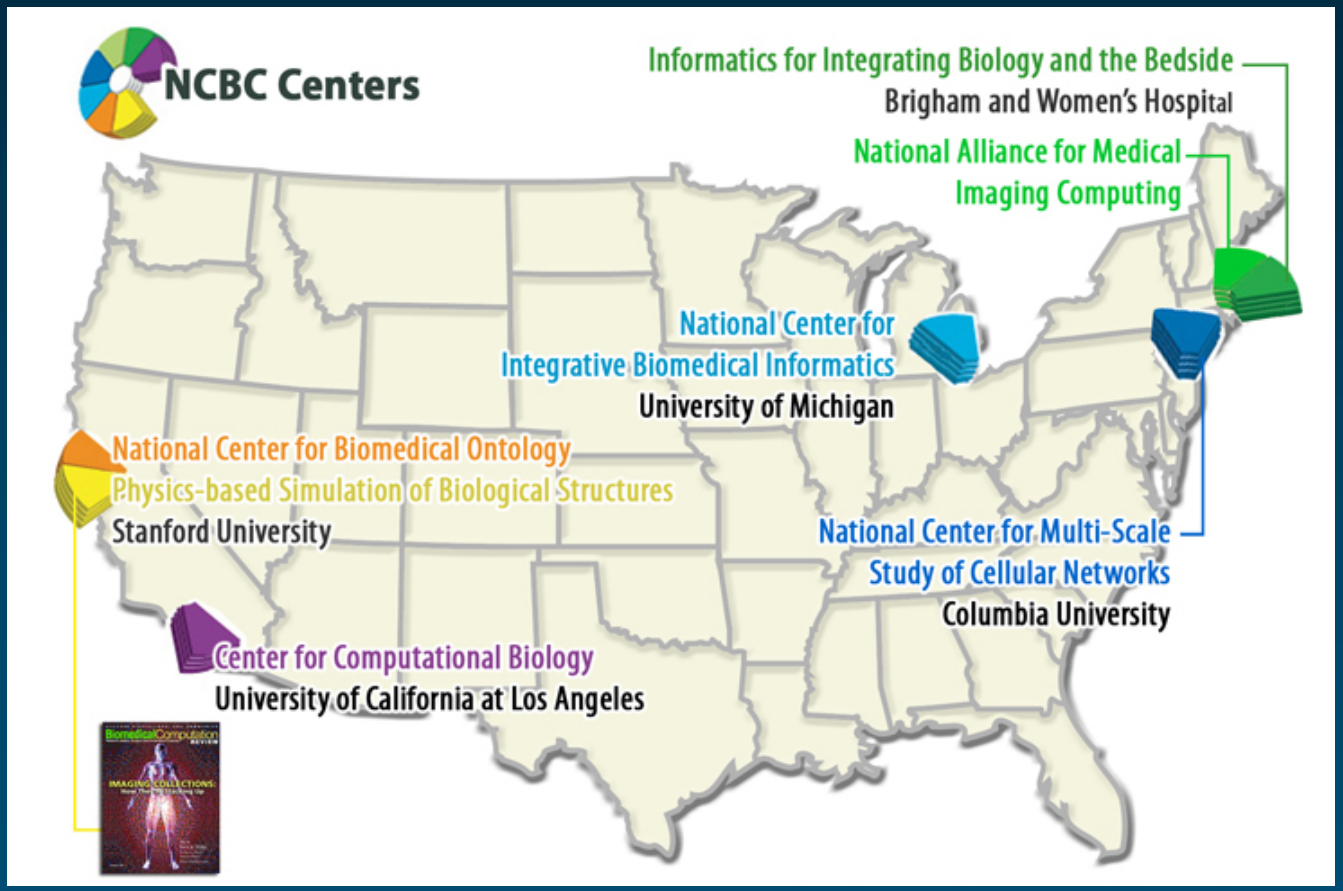


http://www.ctsaweb.org/

Other related programs

- National Centers for Biomedical Computing

"networked national effort to build the computational infrastructure for biomedical computing in the nation"



Other related programs

- Cancer Biomedical Informatics Grid (caBIG)

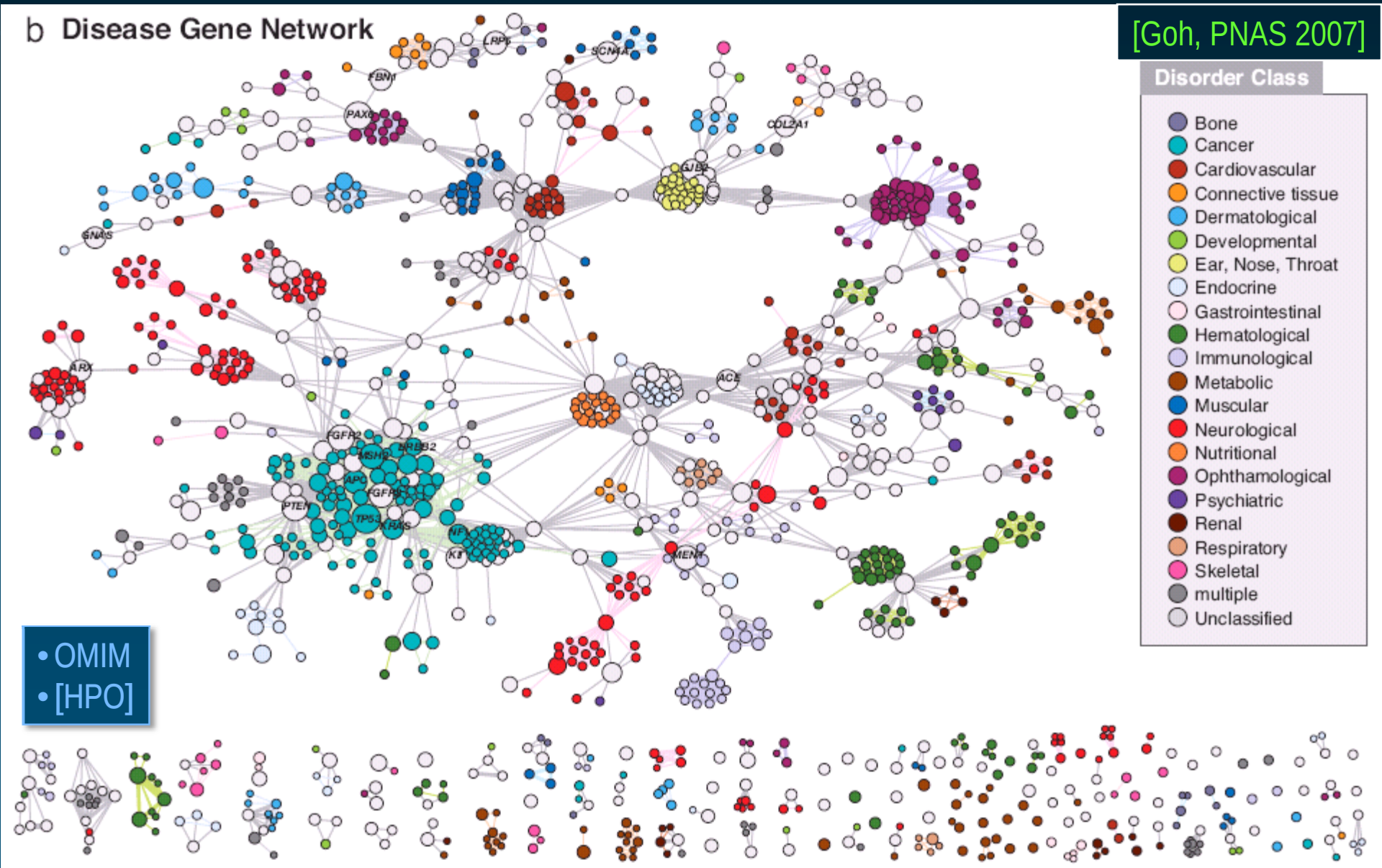
"an information network enabling all constituencies in the cancer community – researchers, physicians, and patients – to share data and knowledge."

  - Key elements
    - Bioinformatics and Biomedical Informatics
    - Community
    - Standards for Semantic Interoperability
    - Grid Computing
  - 1000 participants from 200 organizations
  - Funding: $60 M in the first 3 years (pilot)

https://cabig.nci.nih.gov/

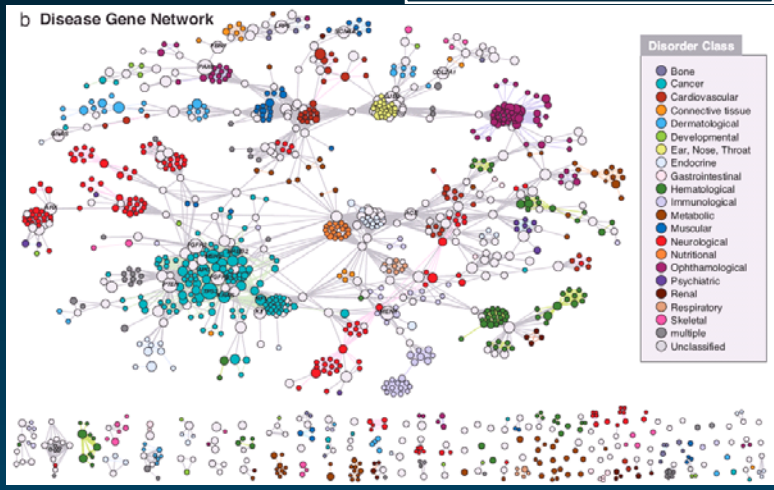
Translational research and data integration

Genotype and phenotype



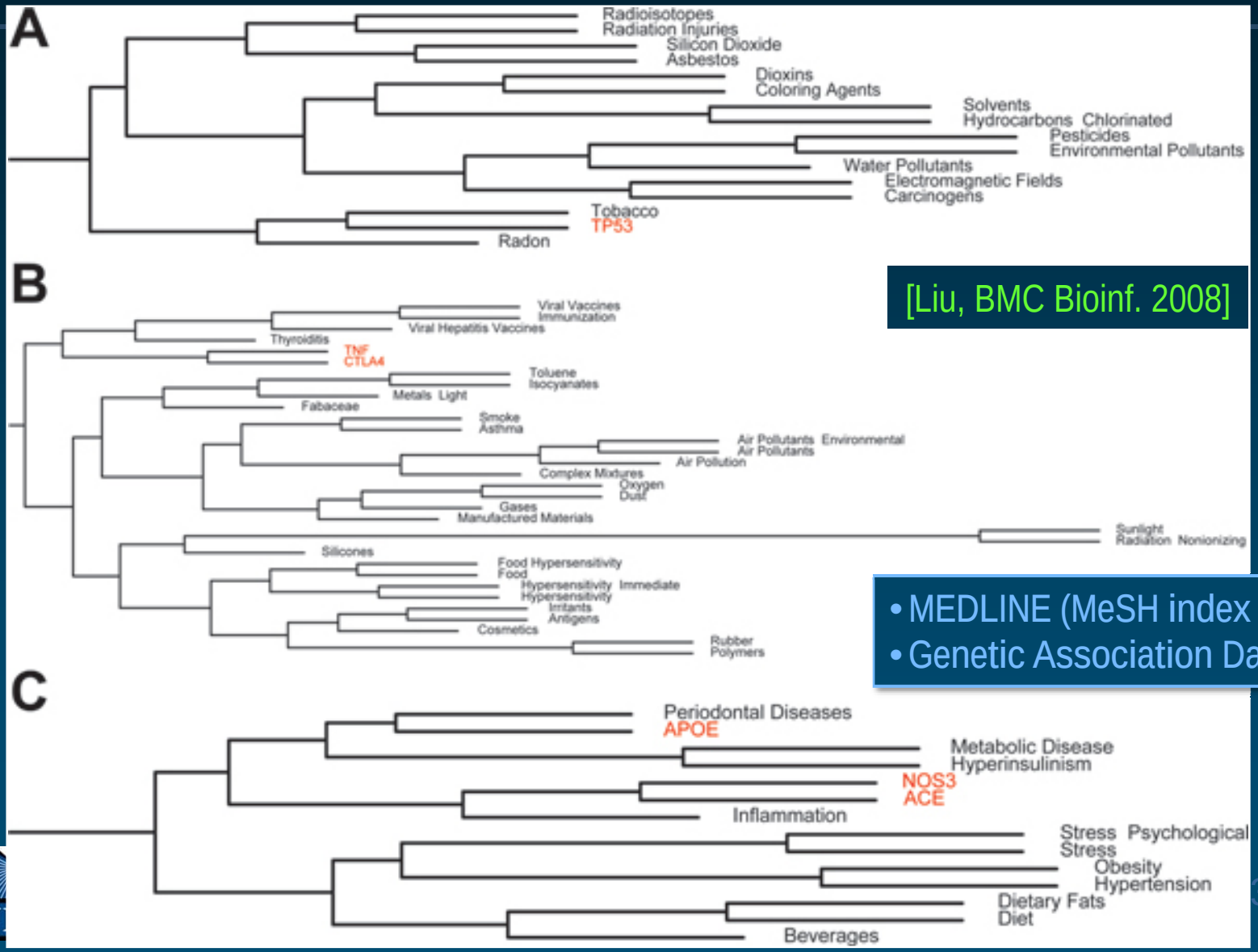
Genotype and phenotype

[Goh, PNAS 2007]



- Publicly available data
  - OMIM
    - 1284 disorders
    - 1777 genes
- No ontology
  - Manual classification of the diseases into 22 classes based on physiological systems
- Analyses supported
  - Genes associated with the same disorders share the same functional annotations

Genes and environmental factors

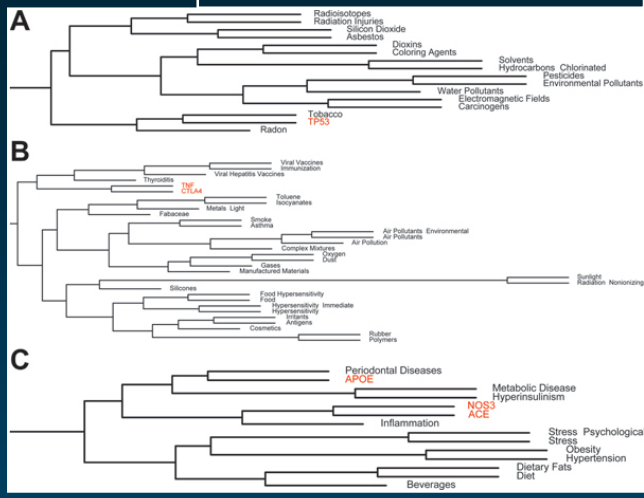


[Liu, BMC Bioinf. 2008]

- MEDLINE (MeSH index terms)
- Genetic Association Database

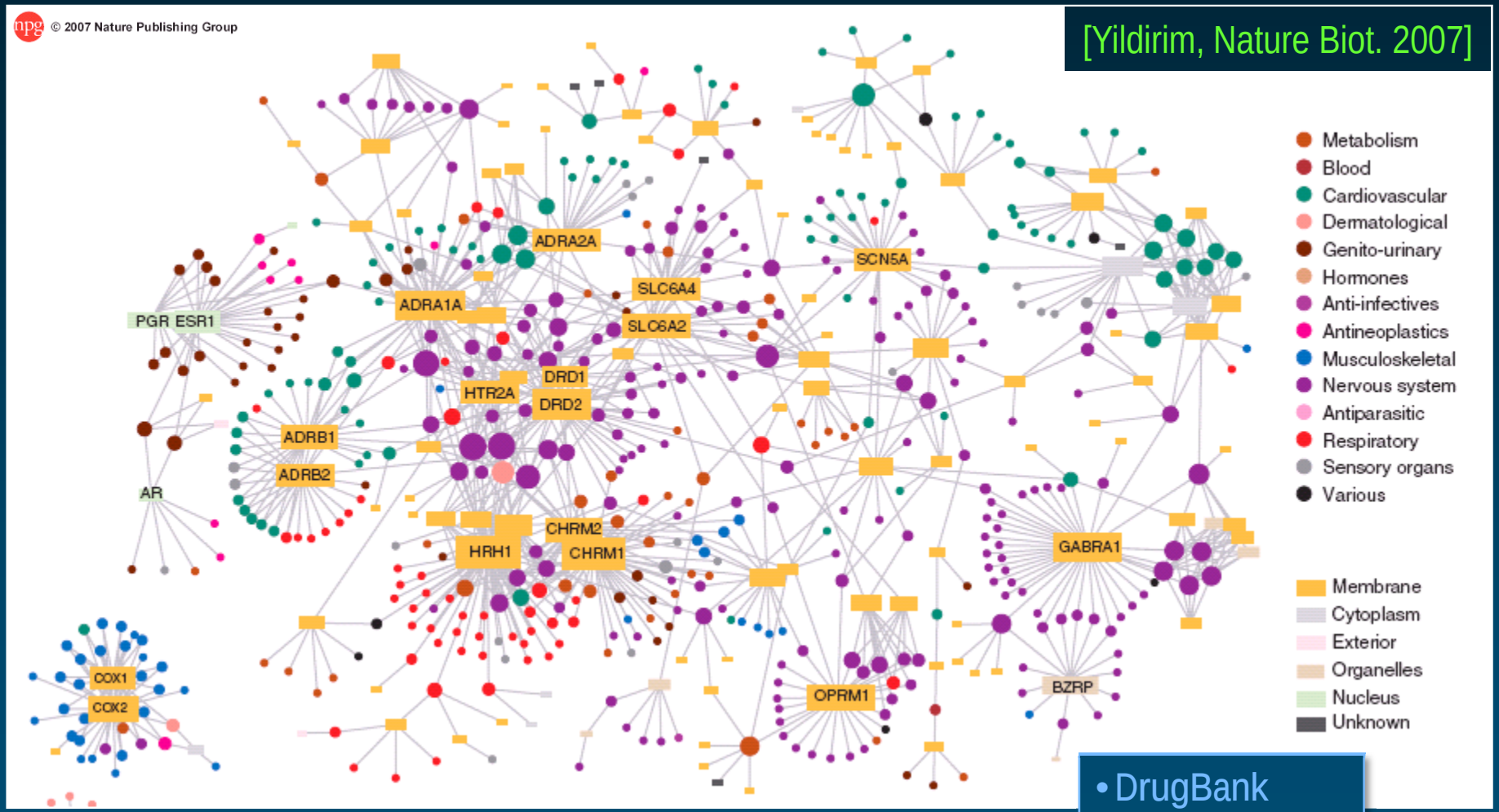
Genes and environmental factors

[Liu, BMC Bioinf. 2008]



- Publicly available data
  - MEDLINE
    - 3342 environmental factors
    - 3159 diseases
  - Genetic Association Database
    - 1100 genes
    - 1034 complex diseases
  - 863 diseases with both
    - Genetic factors
    - Environmental factors
- Analyses supported
  - Proof-of-concept study

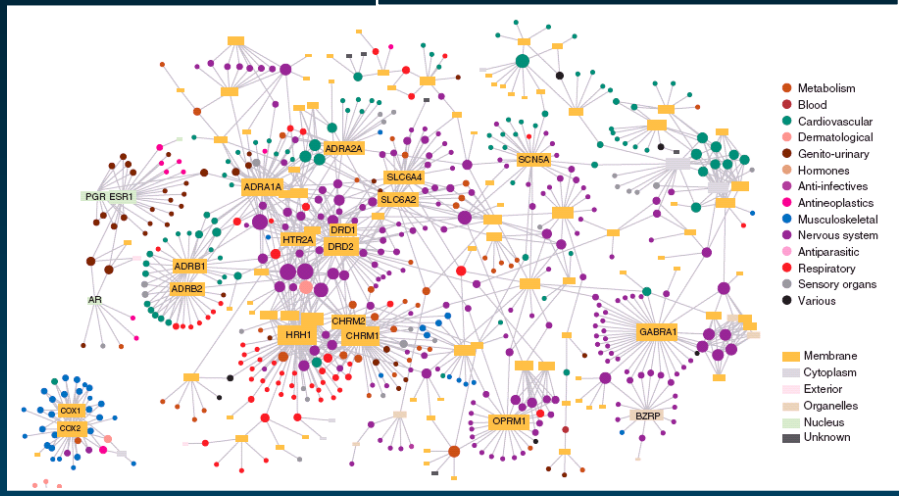
Integrating drugs and targets



- DrugBank
- ATC
- Gene Ontology

Genes and environmental factors

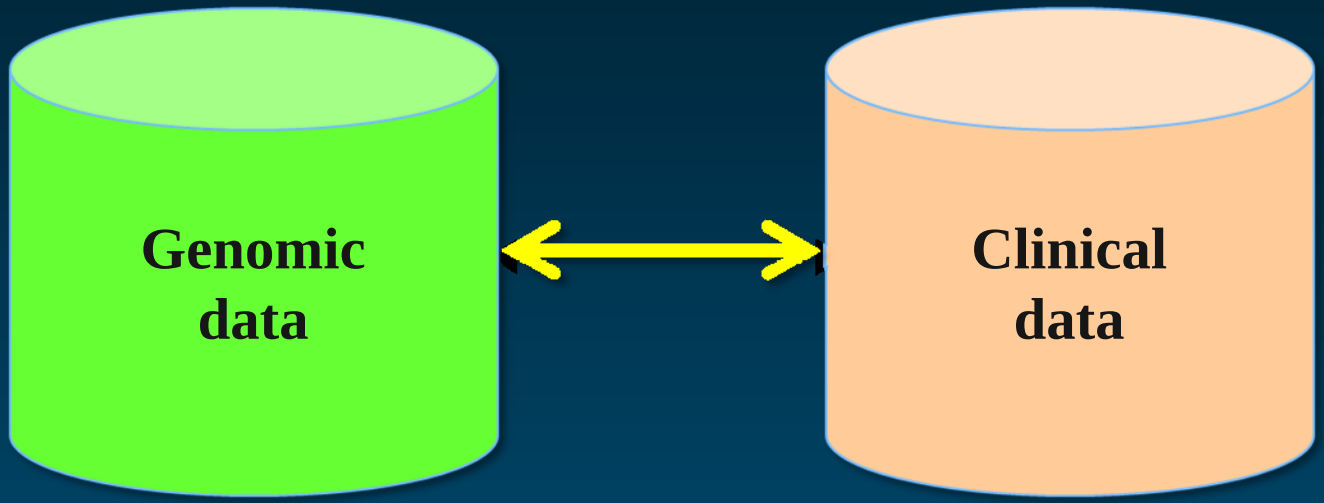
[Yildirim, Nature Biot. 2007]



- Publicly available data
  - DrugBank
    - 4252 drugs
    - 808 experimental drugs associated with at least one protein target
  - ATC
    - Aggregate drugs into classes
  - Gene ontology
    - Aggregate gene products by functional annotations
  - OMIM
    - Gene-disease associations
  - …
- Analyses supported
  - Industry trends
  - Properties of drug targets in the context of cellular networks
  - Relations between drug targets and disease-gene products

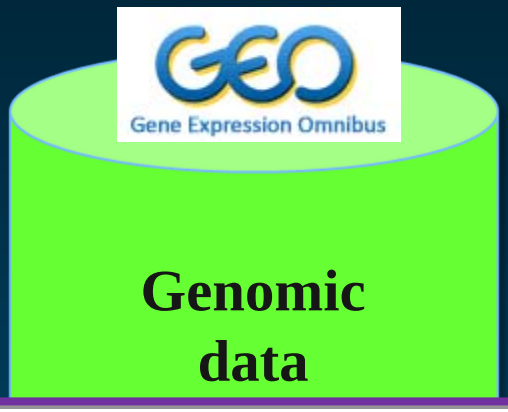
Anatomy of a translational research experiment

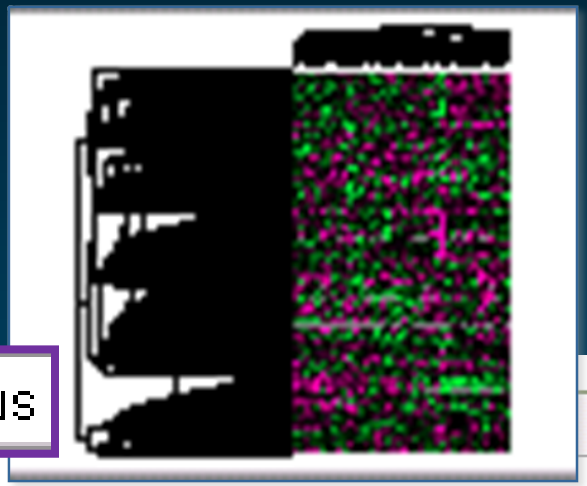
Integrating genomic and clinical data



- No genomic data available for most patients
- No precise clinical data available associated with most genomic data (GWAS excepted)

Integrating genomic and clinical data





Aging and cognitive impairment: hippocampus

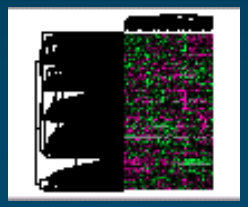
Accession:	GDS2639 ☞ View Expression (GEO profiles)
Title:	Aging and cognitive impairment: hippocampus
DataSet type:	gene expression array-based (RNA / in situ oligonucleotide)
Summary:	Analysis of hippocampi from aged learning-impaired animals on the last day of training in the Morris water maze (MWZ) or 21 days post-training. The MWZ task is a dorsal hippocampal-dependent task. Results provide insight into the molecular basis of aging-related cognitive impairment.
Platform:	GPL341: Affymetrix GeneChip Rat Expression Set 230 Array RAE230A
Citations:	Rowe WB, Blalock EM, Chen KC, Kadish I et al. Hippocampal expression analyses reveal selective association of immediate-early, neuroenergetic, and myelinogenic p… rats. *J Neurosci* 2007 Mar 21;27(12):3098-110. PMID: 17376971

Sample organism:	Rattus norvegicus	**Platform organism:**	
Feature count:	15923	**Value type:**	
Series:	GSE5666	**Series published:**	
Last GDS update:	04/27/2007		

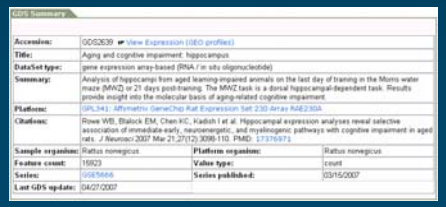
MeSH Terms:

- Age Factors
- Animals
- Cognition Disorders/genetics

Integrating genomic and clinical data

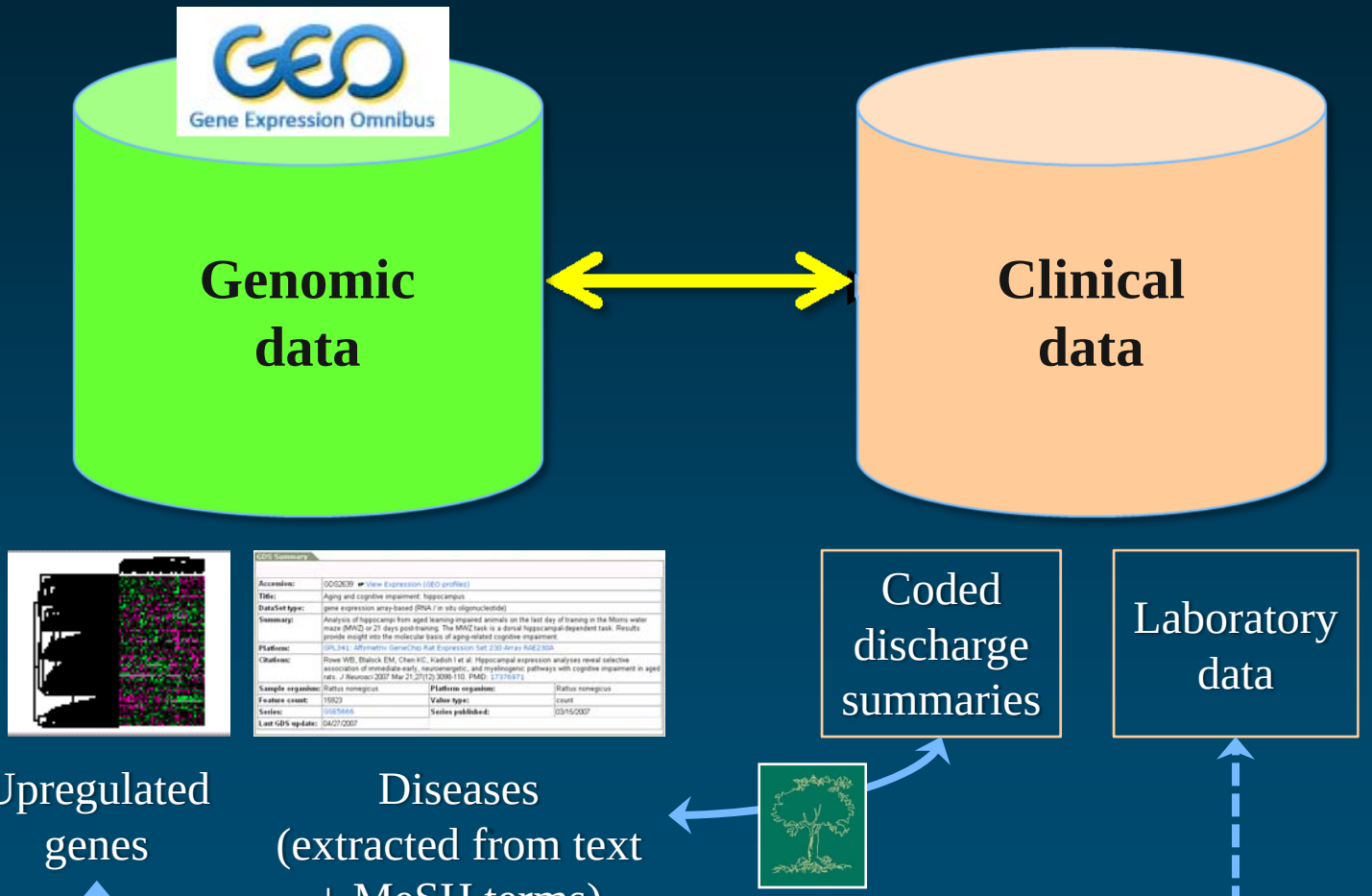


Upregulated genes

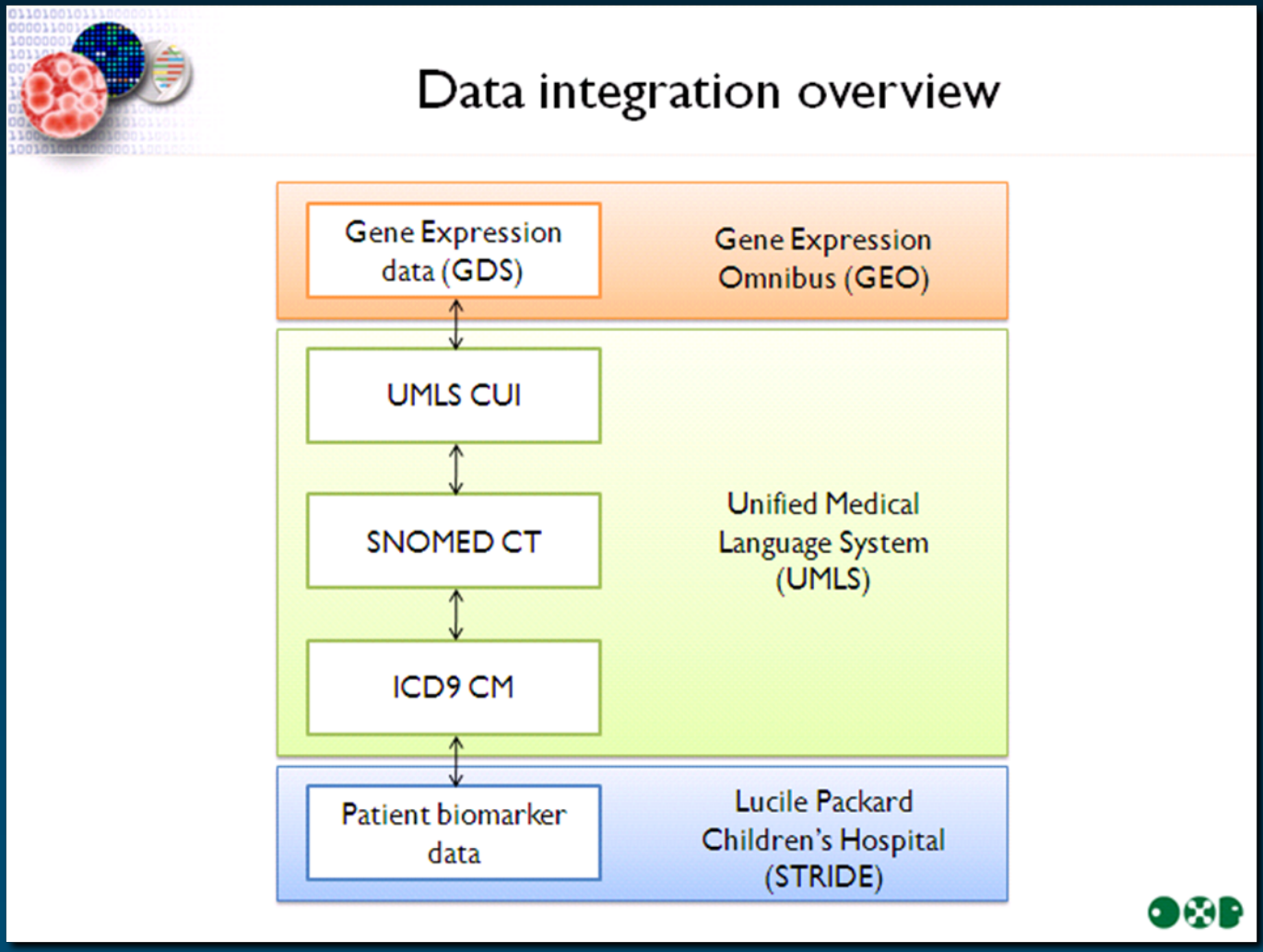


Diseases (extracted from text + MeSH terms)

Integrating genomic and clinical data

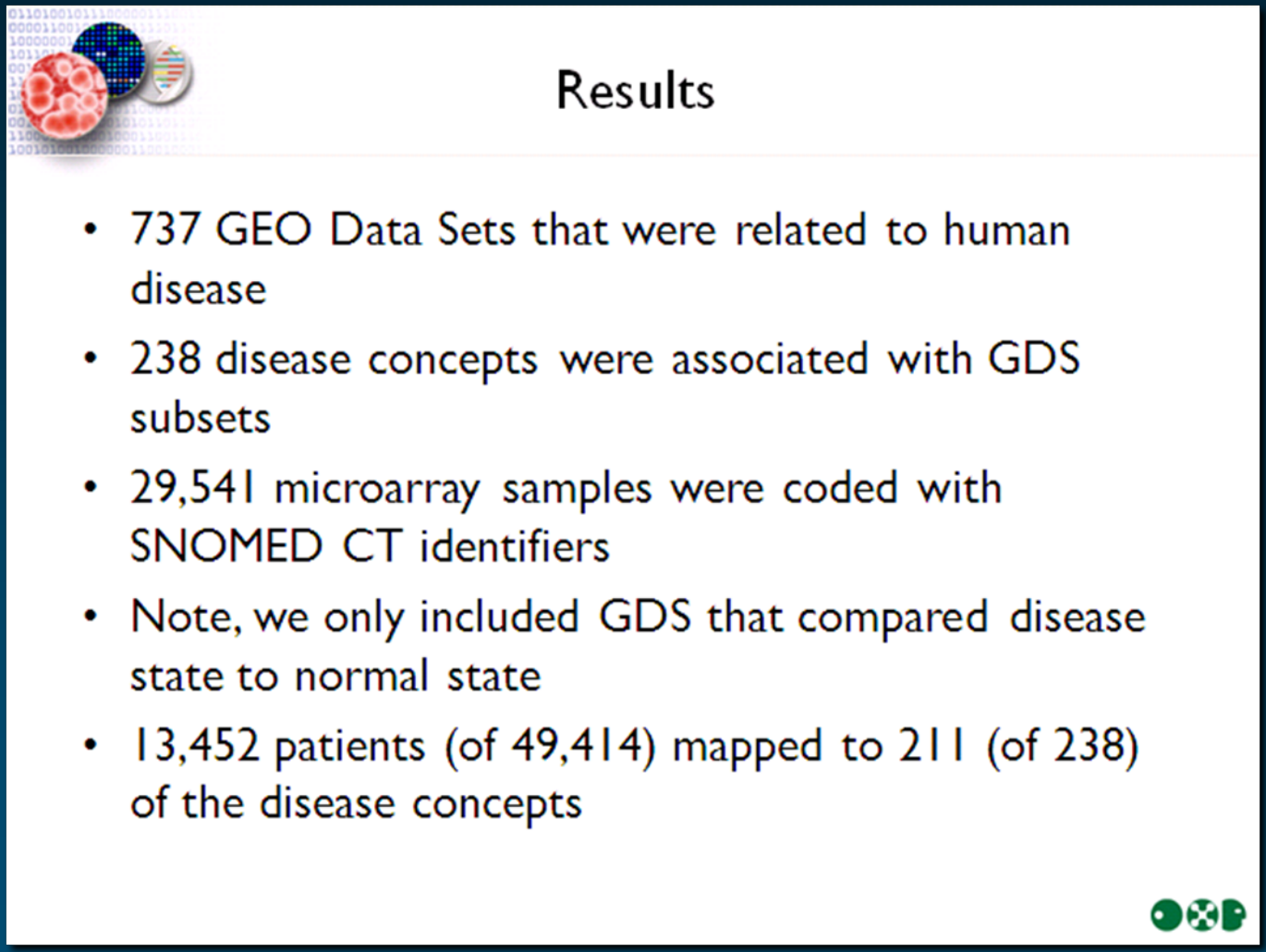


The Butte approach Methods



Courtesy of David Chen, Butte Lab

The Butte approach Results



Courtesy of David Chen, Butte Lab

The Butte approach

- Extremely rough methods
  - No pairing between genomic and clinical data
  - Text mining
  - Mapping between SNOMED CT and ICD 9-CM through UMLS
  - Reuse of ICD 9-CM codes assigned for billing purposes
- Extremely preliminary results
  - Rediscovery more than discovery
- Extremely promising nonetheless

The Butte approach References

- Dudley J, Butte AJ "Enabling integrative genomic analysis of high-impact human diseases through text mining." *Pac Symp Biocomput* 2008; 580-91
- Chen DP, Weber SC, Constantinou PS, Ferris TA, Lowe HJ, Butte AJ "Novel integration of hospital electronic medical records and gene expression measurements to identify genetic markers of maturation." *Pac Symp Biocomput* 2008; 243-54
- Butte AJ, "Medicine. The ultimate model organism." *Science* 2008; 320: 5874: 325-7

Promising results

Pharmacogenomics of warfarin

- Narrow therapeutic range
- Large interindividual variations in dose requirements
- Polymorphism involving two genes
  - CYP2C9
  - VKORC1
- Genetic test available
- Development of models integrating variants of CYP2C9 and VKORC1 for predicting initial dose requirements (ongoing RCTs)
- Step towards personalized medicine

Integration of existing studies/datasets

- 49 experiments in the domain of obesity
  - Rediscovery of known genes
  - Identification of potential new genes

[English, Bioinformatics 2007]

- Analysis of genes potentially associated with nicotine dependence
  - Rediscovery of known findings

[Sahoo, JBI 2008]

- Identification of networks of genes associated with type II diabetes mellitus

[Liu, PLoS 2007; Rasche, MBC Gen. 2008]

Challenging issues

Challenging issues

- Datasets
- Ontologies
- Tools
- Other issues

Challenging issues Datasets

- Lack of annotated datasets
  - Largely text-based (need for text mining)
- Limited availability of clinical data (EHRs, PHRs)
  - Need for deidentification
  - Largely text-based (need for text mining)
- Heterogeneous formats
  - Need for conversion
- Lack of metadata
  - Limited discoverability, limited reuse

Challenging issues Ontologies

- Lack of universal identifiers for biomedical entities
  - Need for normalization through terminology integration systems (e.g., UMLS)
- Lack of standard for identifiers
  - Need for bridging across formats
- Lack of universal formalism
  - Need for conversion between formalisms
- Limited availability of some ontologies
- Delay in adopting standards
  - e.g., SNOMED CT

Challenging issues Tools

- Lack of semantic interoperability
  - Difficult to combine tools/services
- Limited scalability of automatic reasoners
  - Difficult to process large datasets

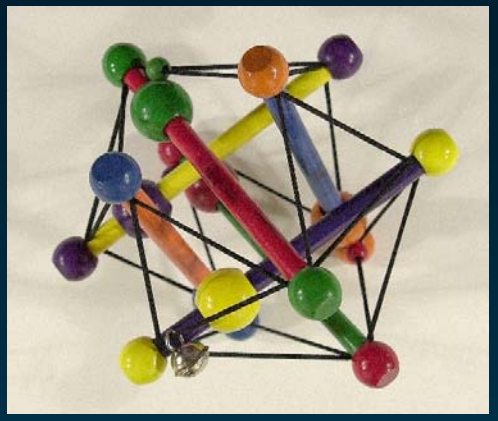
Other challenging issues

- Limited number of researchers "*adequately prepared in both clinical science and bioinformatics*"
- Need for validation of potential *in silico* discoveries through specific experiments
  - Collaboration with (wet lab) biologists
  - Must be factored in in grants

Conclusions

Conclusions

- Translational medicine is an emerging discipline
  - We live in partially unchartered territory
- Biomedical informatics is at the core of translational medicine
  - Strong informatics component to translational medicine
- We live in exciting times
  - New possibilities for biomedical informaticians
  - From service providers…
    …to biomedical researchers



Medical Ontology Research

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