Chaire d'innovation technologique
Liliane Bettencourt

Grandes tendances en recherche biomédicale

Elias Zerhouni

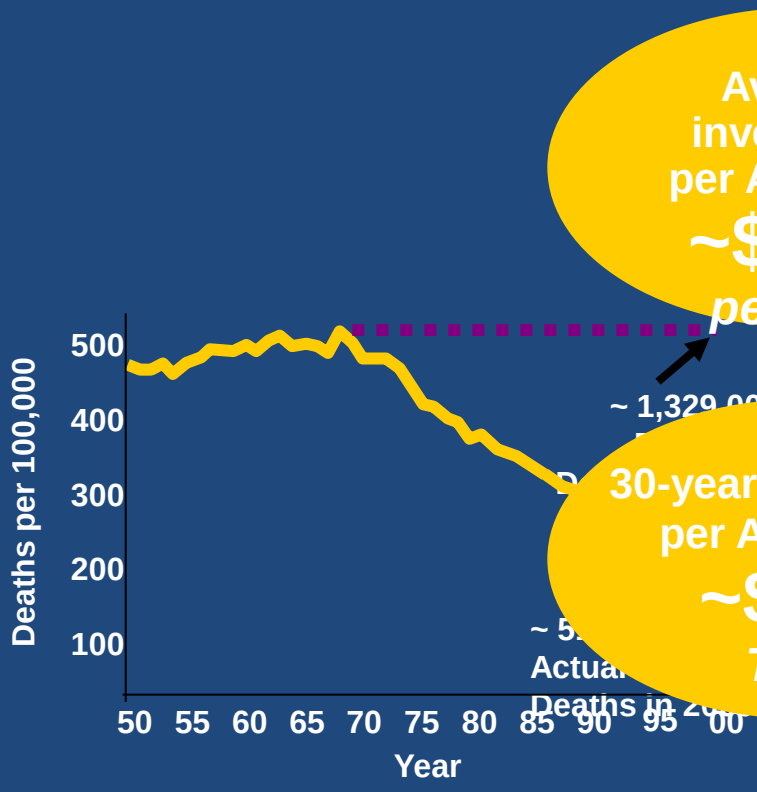
24 Janvier 2011

COLLÈGE DE FRANCE
1530

MEDECINE ET SANTE PUBLIQUE

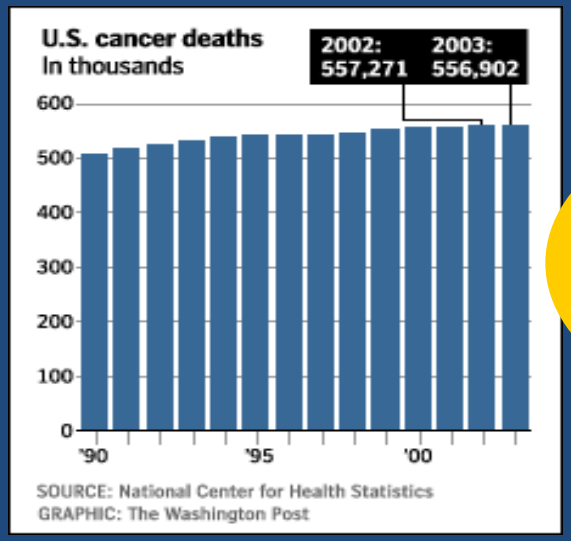
Les Grandes Tendances
et Défis Actuels

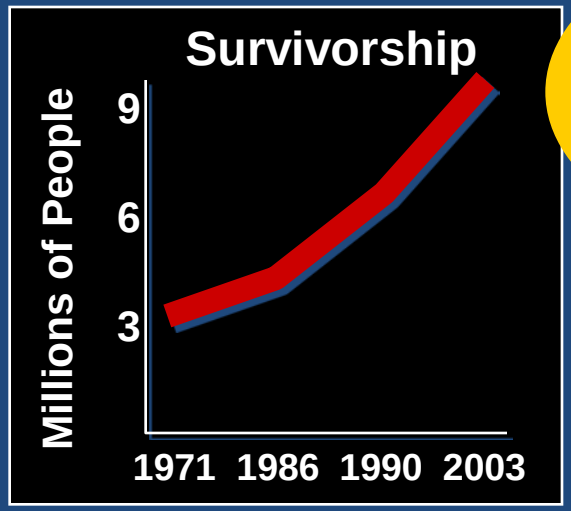
Coronary Heart Disease



- 63% decrease in ortality
- million early aths averted per year
- $2.6 trillion in nomic return
- w, effective treatments and prevention strategies
- New discoveries being developed with industry

Cancer





- For the first time in recorded history, annual cancer deaths [in the] United States have fallen
  - [...]rvivors
- Improved effectiveness of early detection and screening
  - [...], minimally [in]vasive treatments for cancer
- New drugs developed for cancer

Average investment per American
~$8.60
per year

30-year investment per American:
~$260
Total

America Is Living Longer
And Healthier

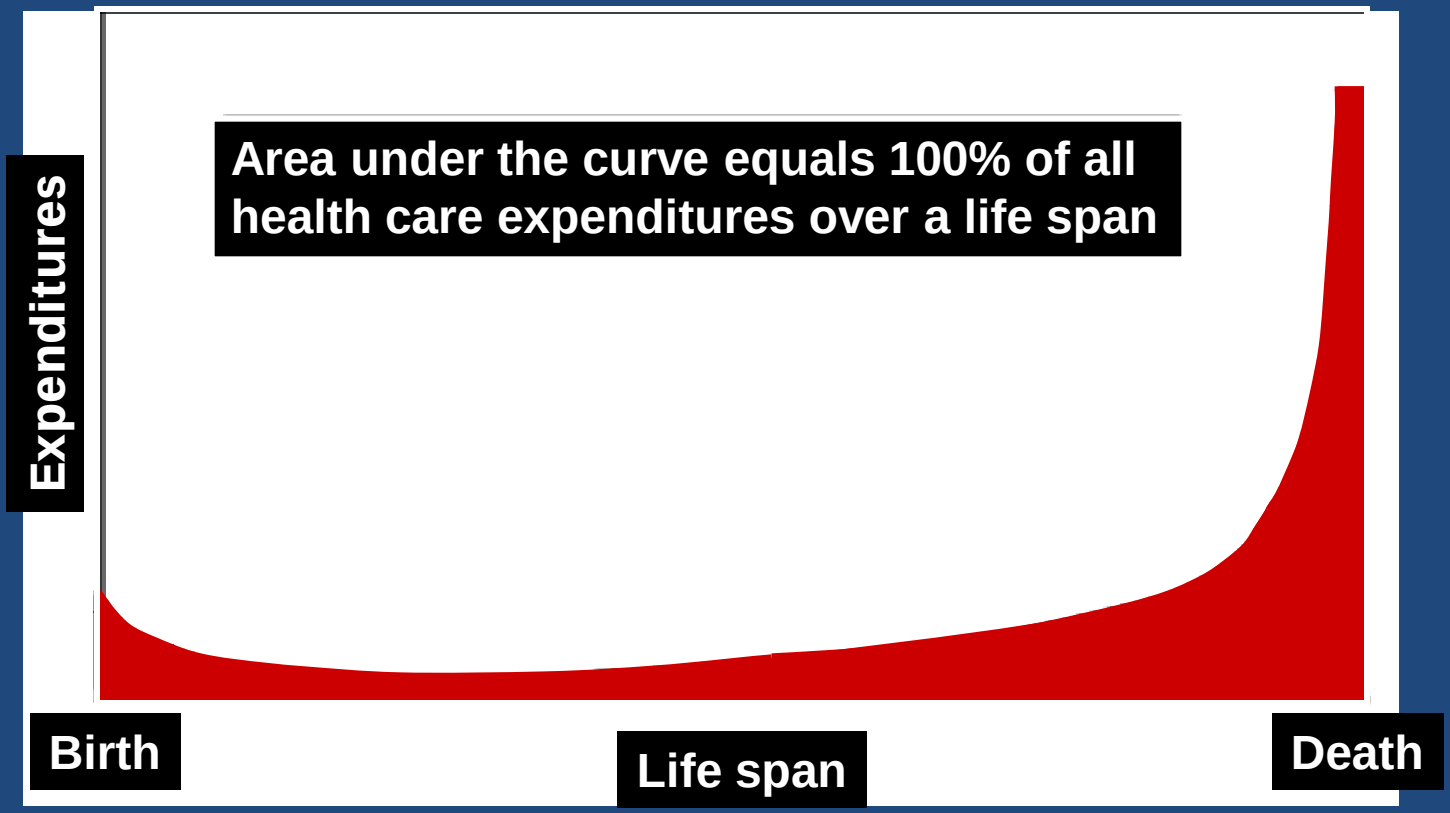
Since 1982, disability rate for elderly Americans declined by 30%

In past 30 years, American life expectancy increased by ~6 years

- **Improvements in:**
  - Recovery from heart ease, stroke
  - ness
  - ion impairment
  - Osteoporosis
  - **e and joint health**
  - more effective ses of drugs for thritis
  - Improvements in joint replacement technology

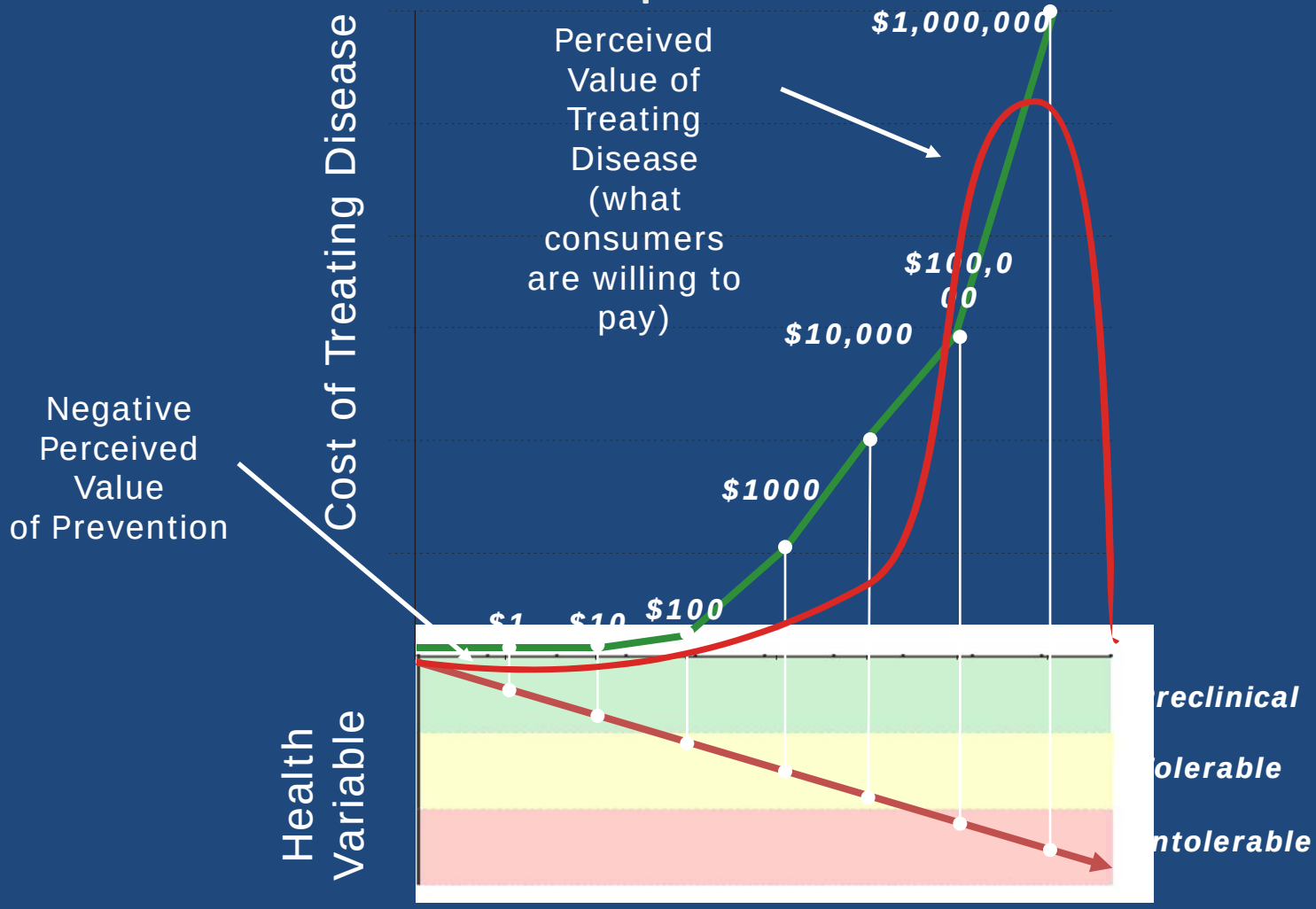
Last-year-of-life expenses constituted 22 percent of all medical, 26 percent of Medicare, 18 percent of all non-Medicare expenditures, and 25 percent of Medicaid expenditures

Hoover DR et al., *Health Serv Res*. 37,1625 (2002).

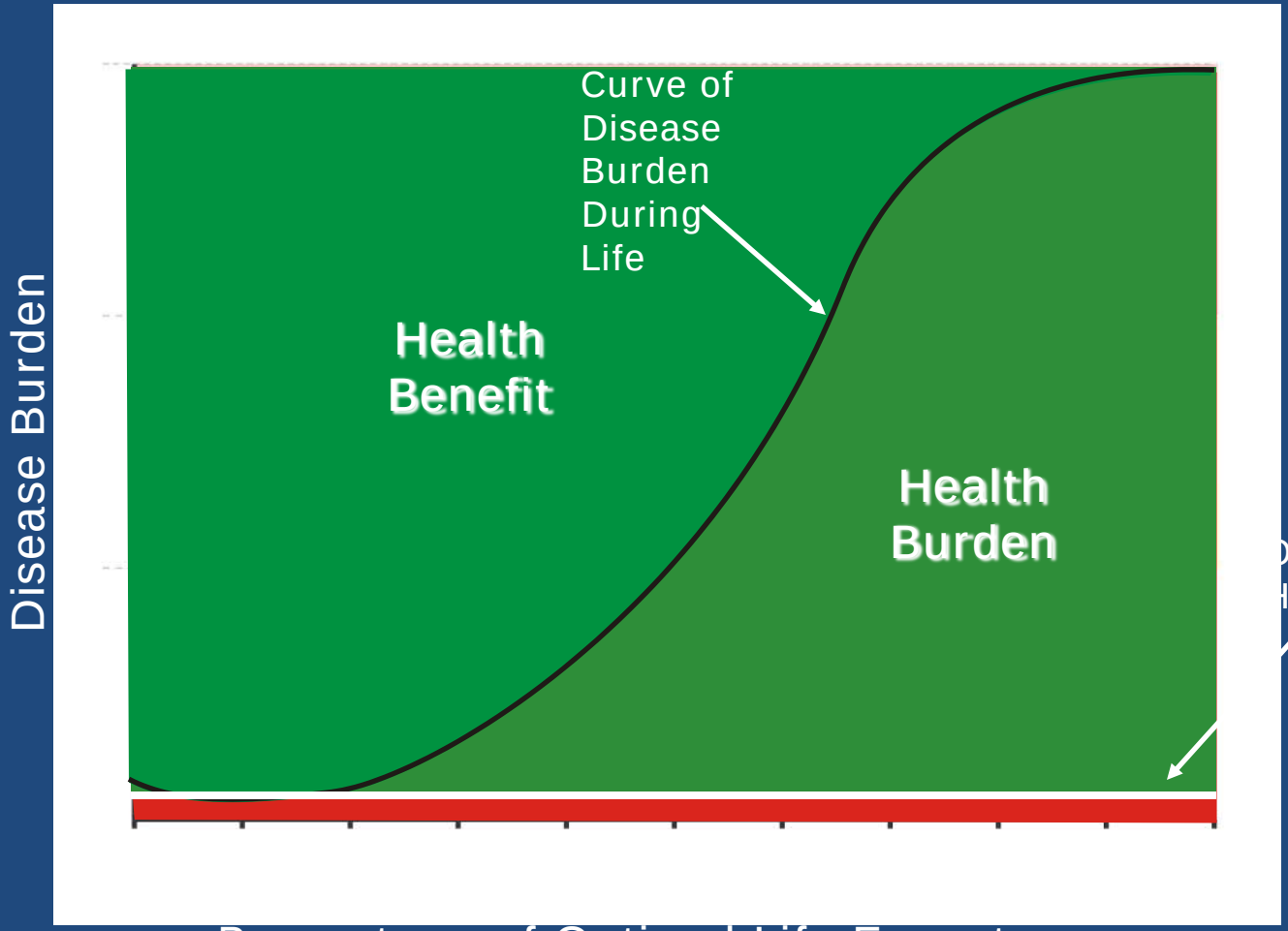


J Lynn, DM Adamson Rand Health White Paper WP-137 (2003)

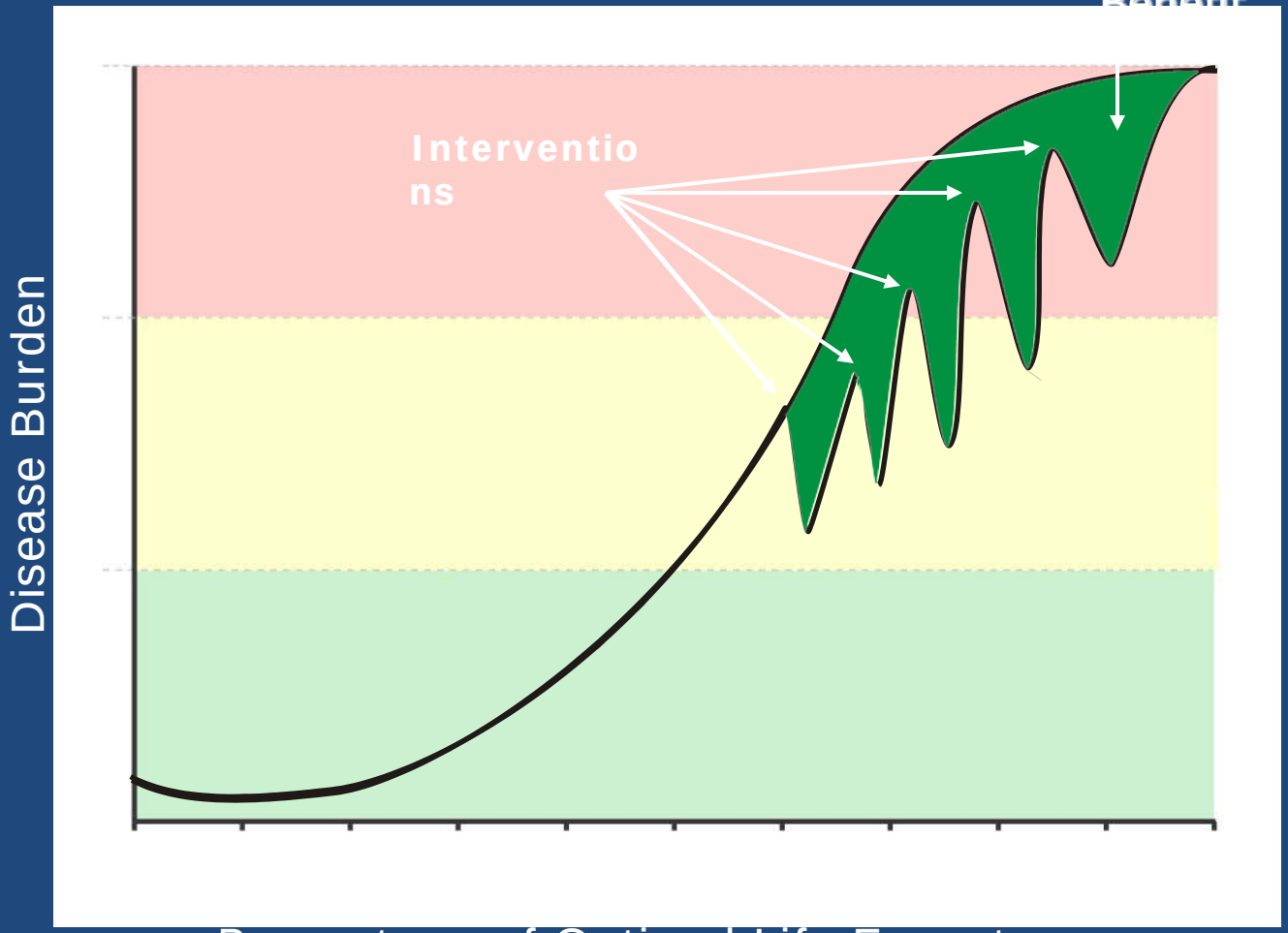
Relationship of stage of intervention to healthcare costs
An empirical view



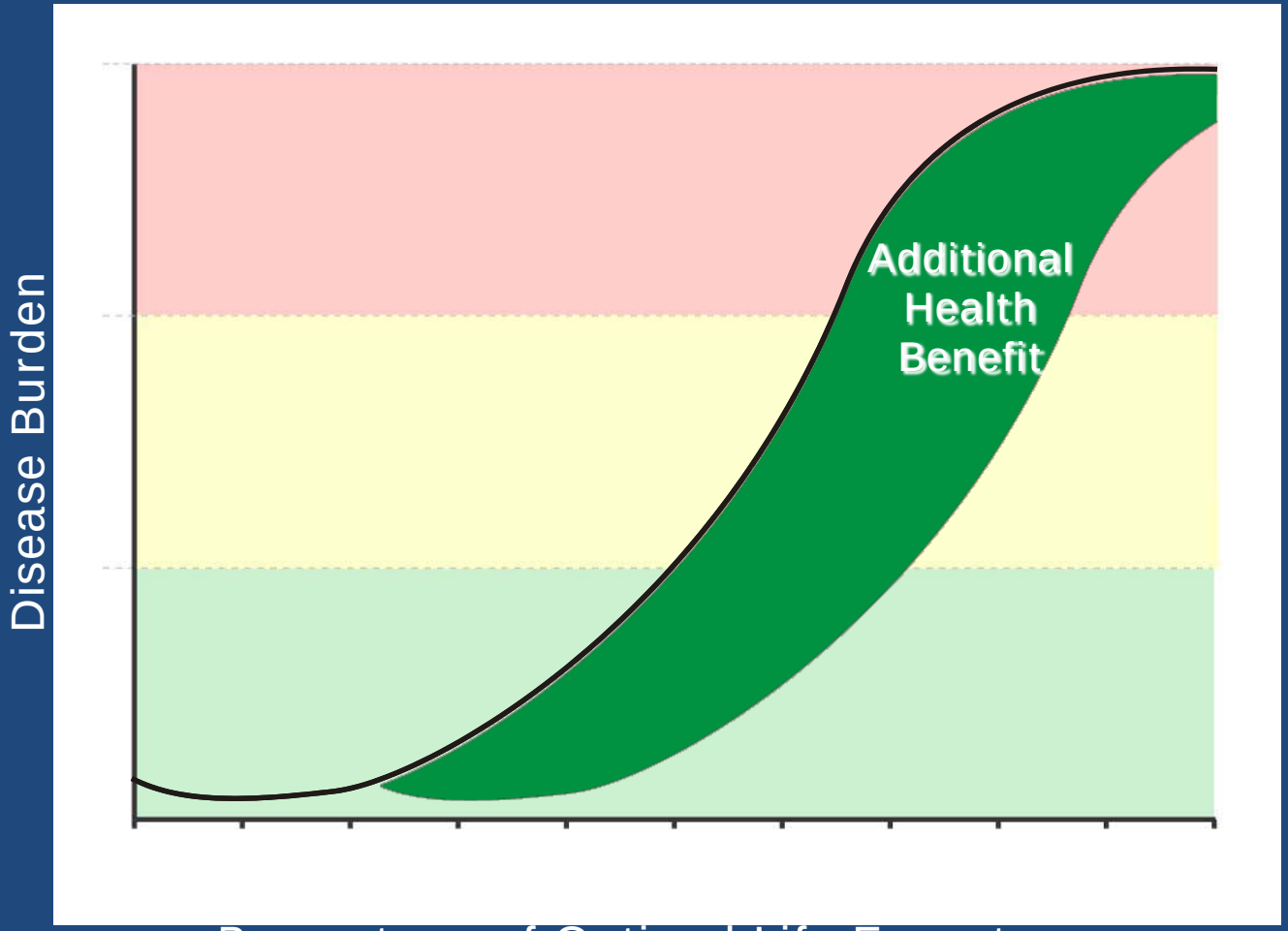
NEED FOR MULTIPRONGED STRATEGIES



Treat Disease with Multiple Interventions



Delay Onset of Disease

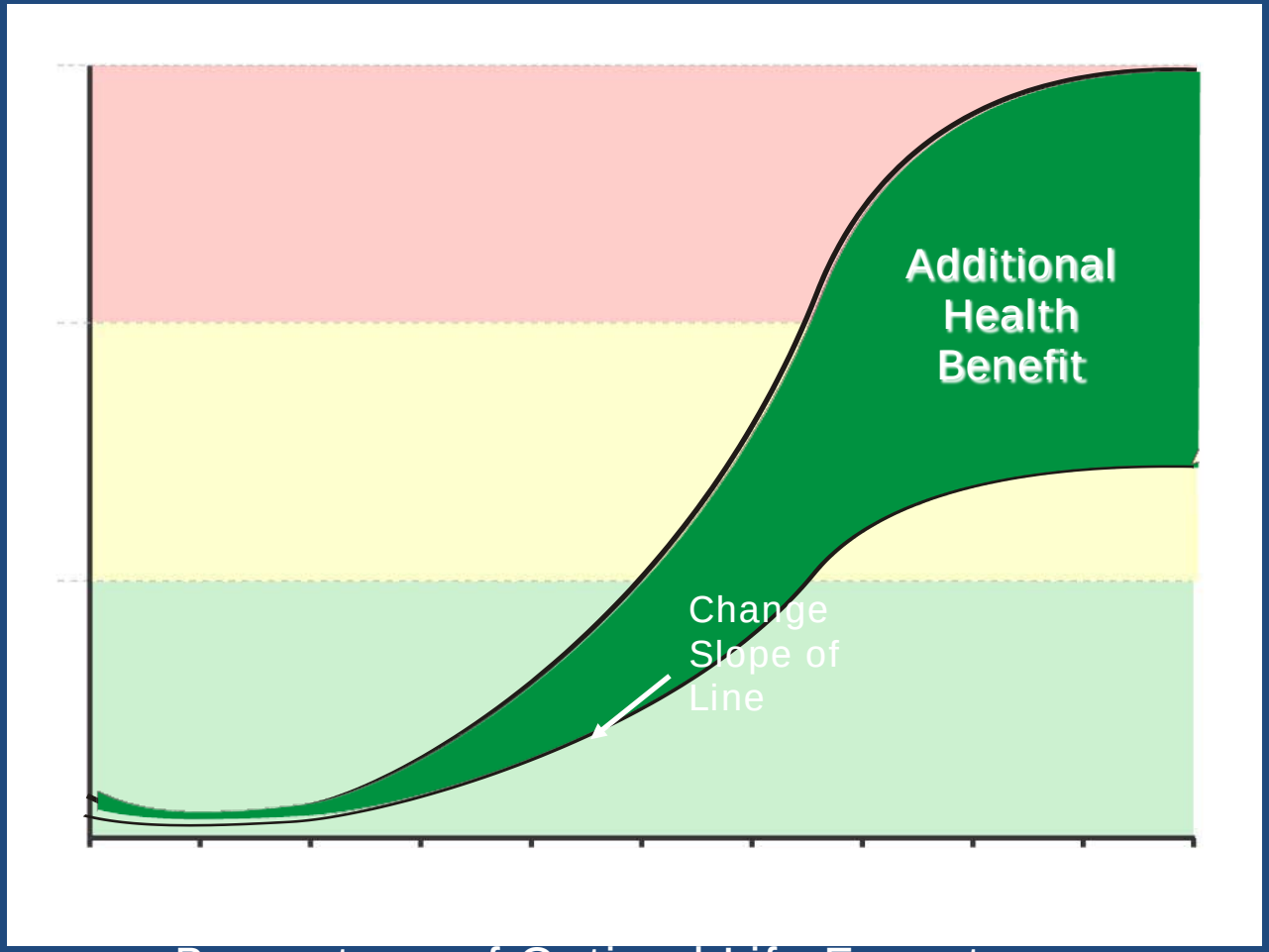


Delay Onset of Disease: Alzheimer disease

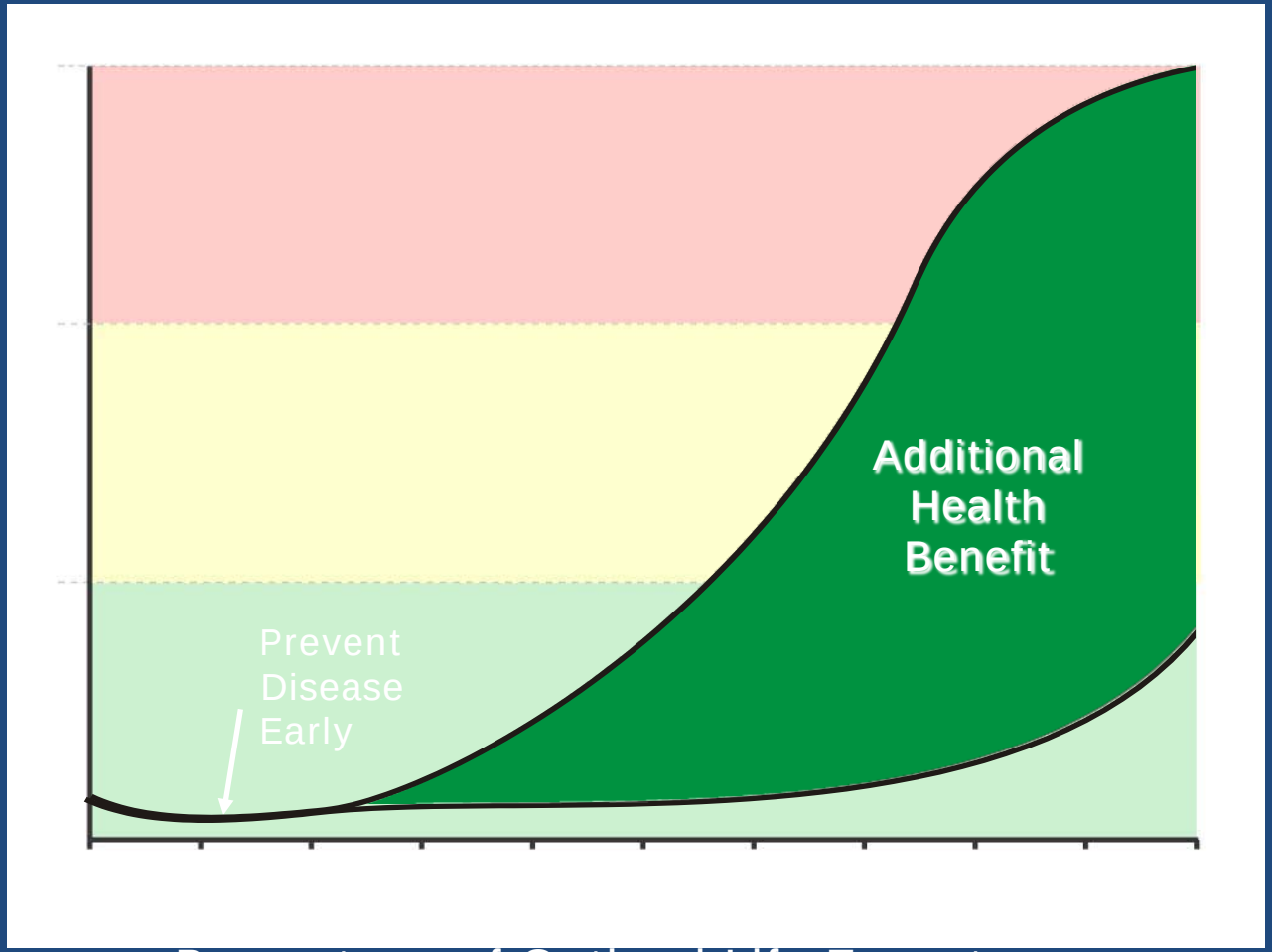
- it may be possible to reduce the current morbidity from Alzheimer disease by 50% if onset can be postponed by only 5 years

Breitner JC Clinical genetics and genetic counseling in Alzheimer disease Ann Intern Med. 1991 Oct 15;115(8):601-6

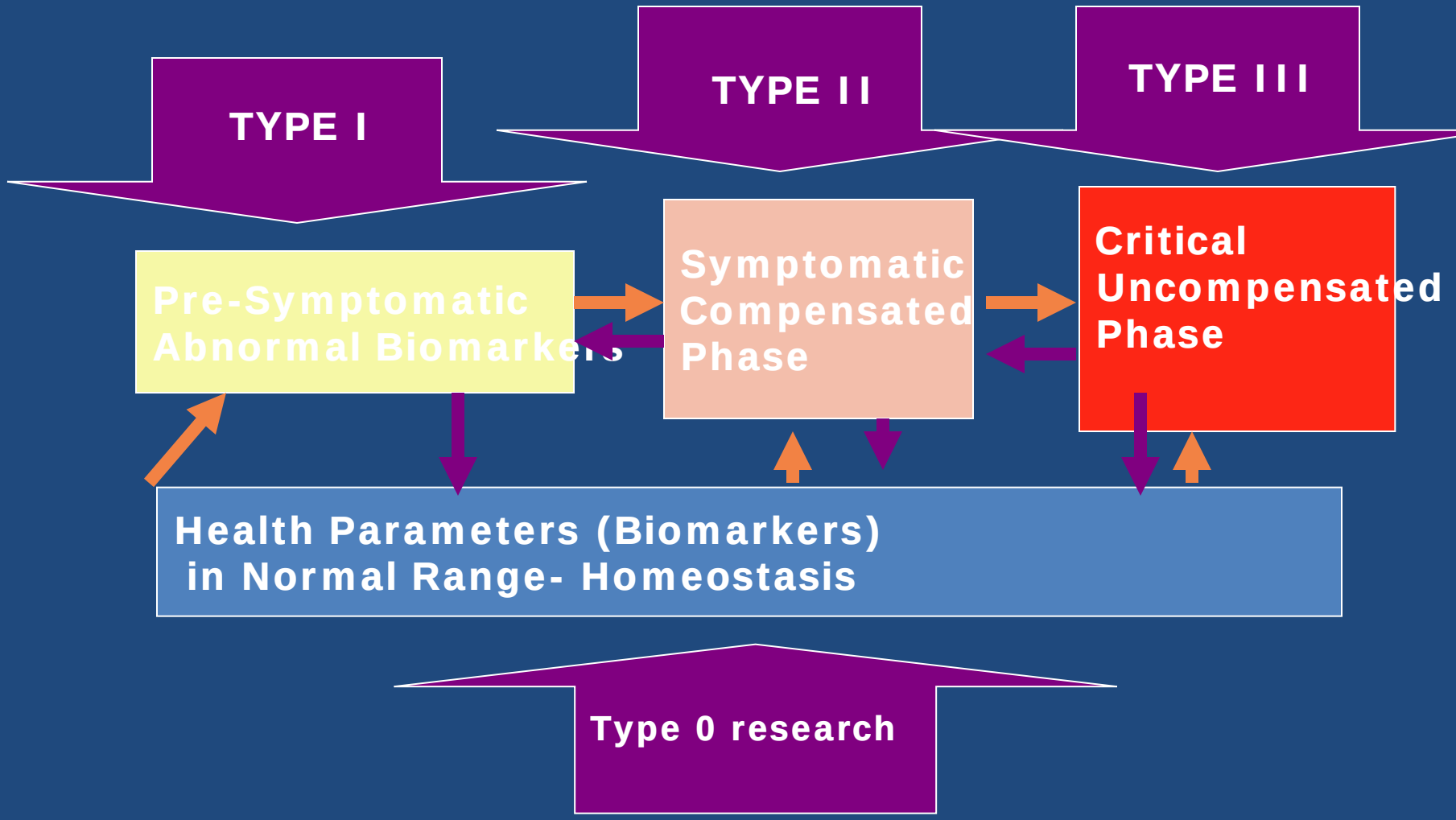
Reduce Severity of Disease



Early Preemption/Prevention of Disease



A Total Disease Cycle Research Approach

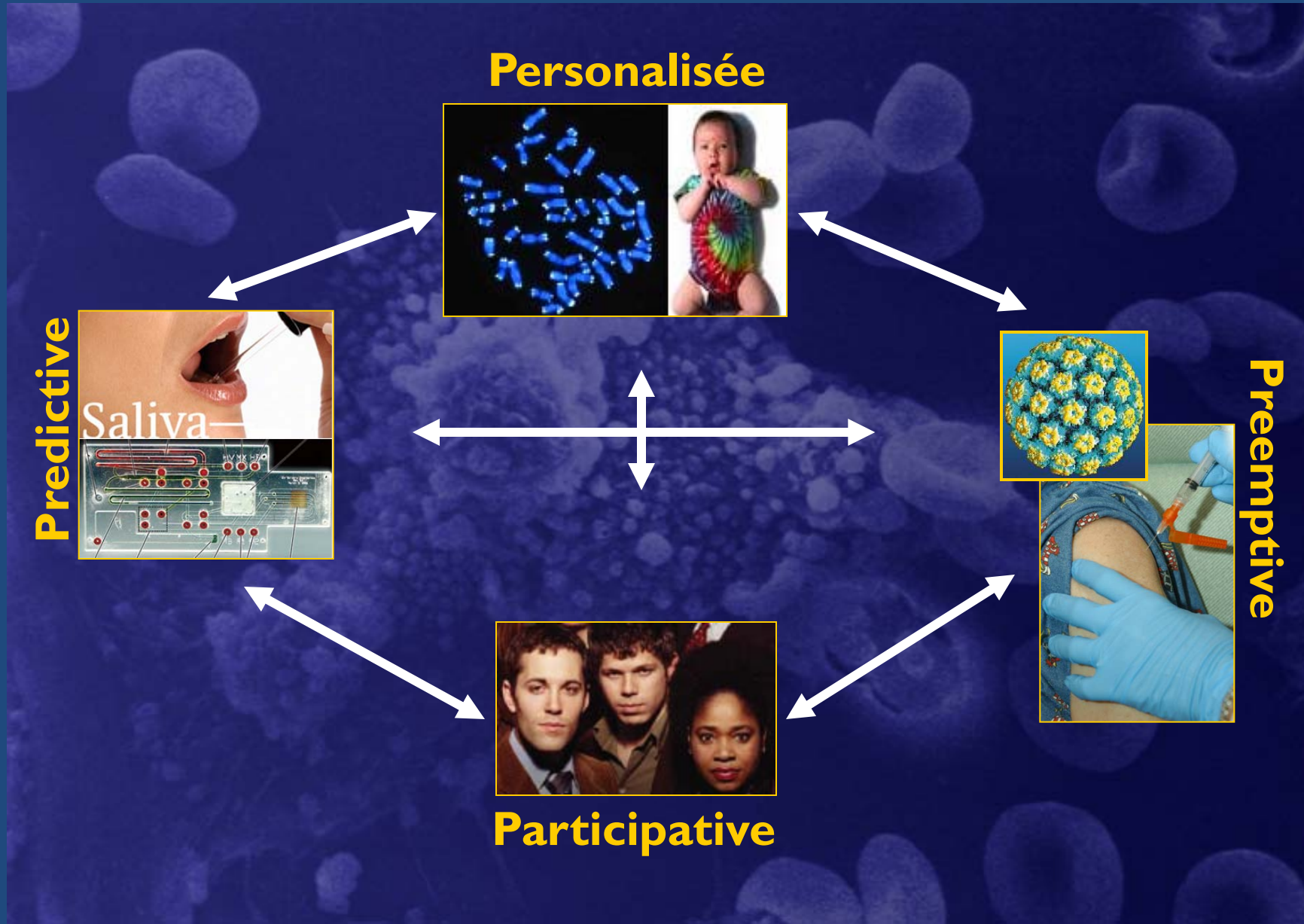


Need To Transform Medical Research in the 21st Century

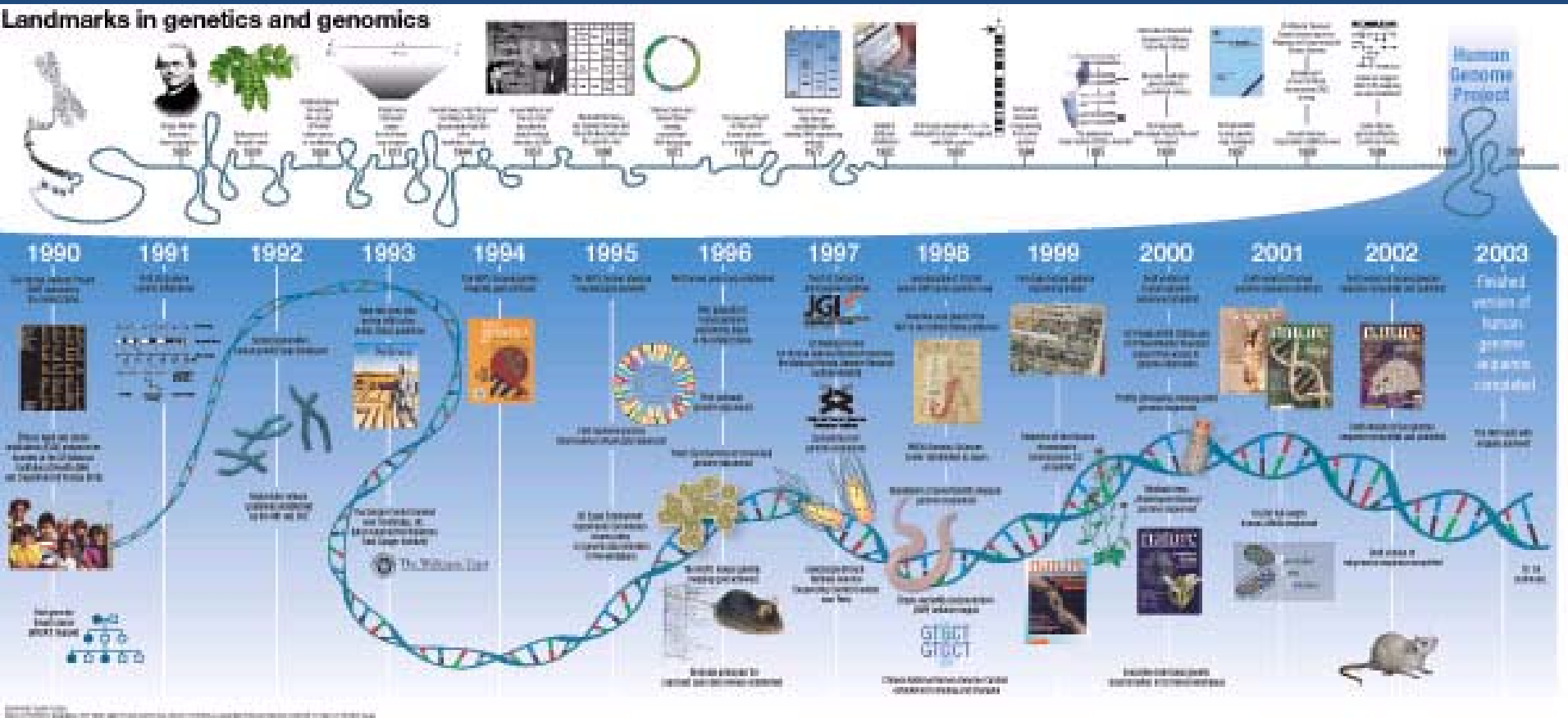
20th Century	21st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
We did not understand the molecular and cellular events leading to disease	Understanding of preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

Les quatre piliers de la medecine future

D'une medecine curative à une medecine preemptive

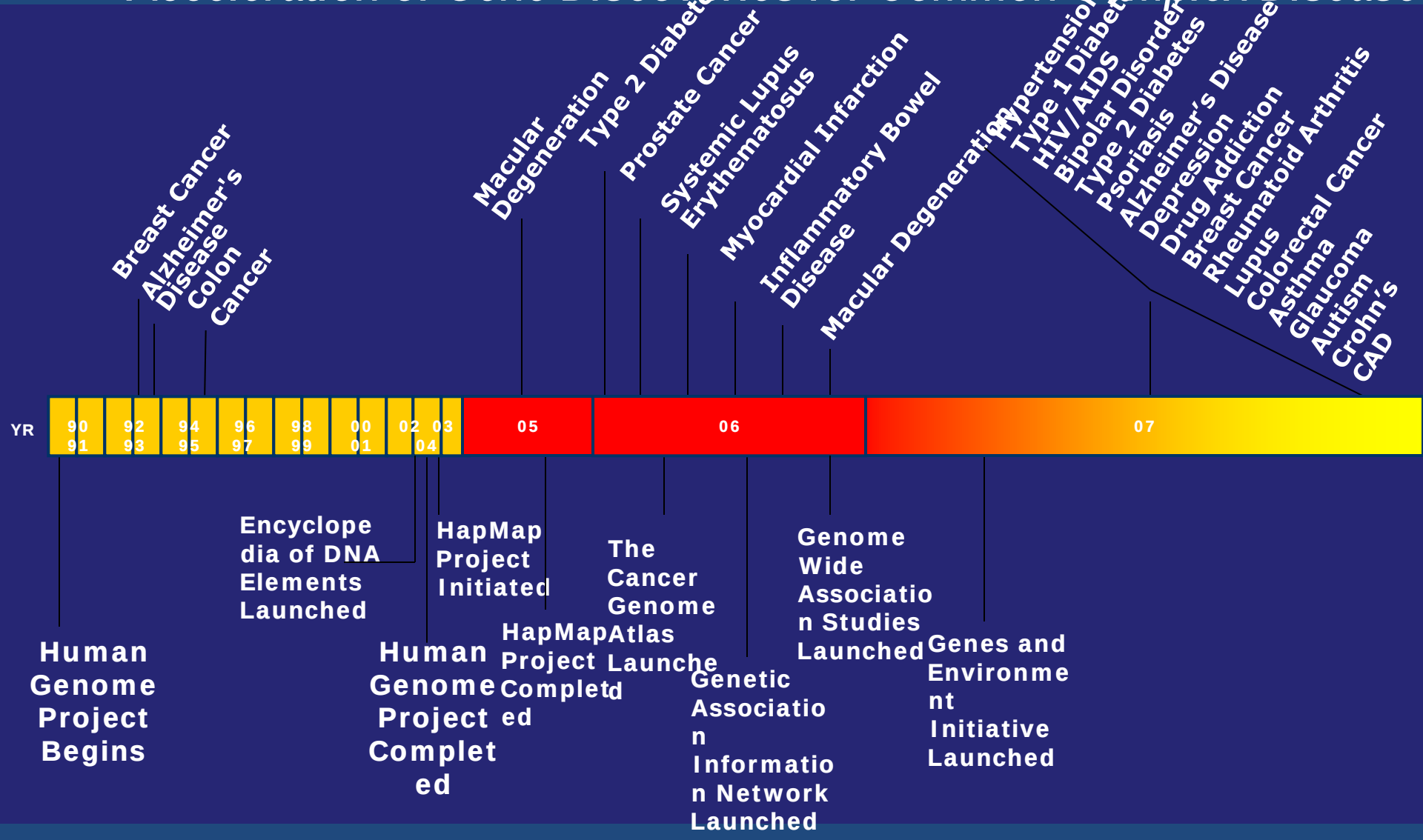


Central roles of molecular biology, genetics and genomics



Exciting Times:

Acceleration of Gene Discoveries for Common Complex Diseases



NIH Research Initiatives

Genetics of Age-related Macular Degeneration (AMD)

- A Common Variant of the Complement Factor H gene (*CFH*) on human Chromosome 1q31
  - Identified as a risk factor for developing AMD by three independent groups:
    - Klein *et al*. Science **308**, 385 (2005)
    - Haines *et al*. Science **308**, 419 (2005)
    - Edwards *et al*. Science **308**, 421 (2005)
  - Results from long-term NIH investments in genomics and genetics initiatives (Human Genome Project, Age-Related Eye Diseases Study)

GWAS Consortium: Predictive

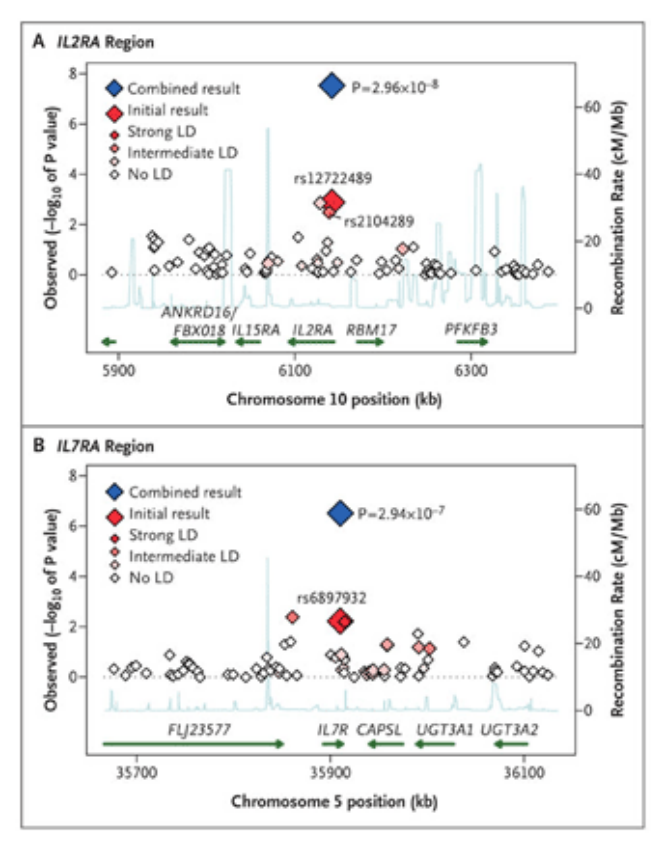
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2007 VOL. 357 NO. 9

Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study

The International Multiple Sclerosis Genetics Consortium*

- First genes associated with MS since HLA in the 1970s
- Both encode interleukin receptors (IL-Rs), validating immunomodulatory treatments
- IL-Rs and related genes link a growing number of autoimmune diseases



GWAS: Toward Predictive Medicine

A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

A Whole-Genome Association Study of Major Determinants for Host Control of HIV-1

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene

Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes

Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study

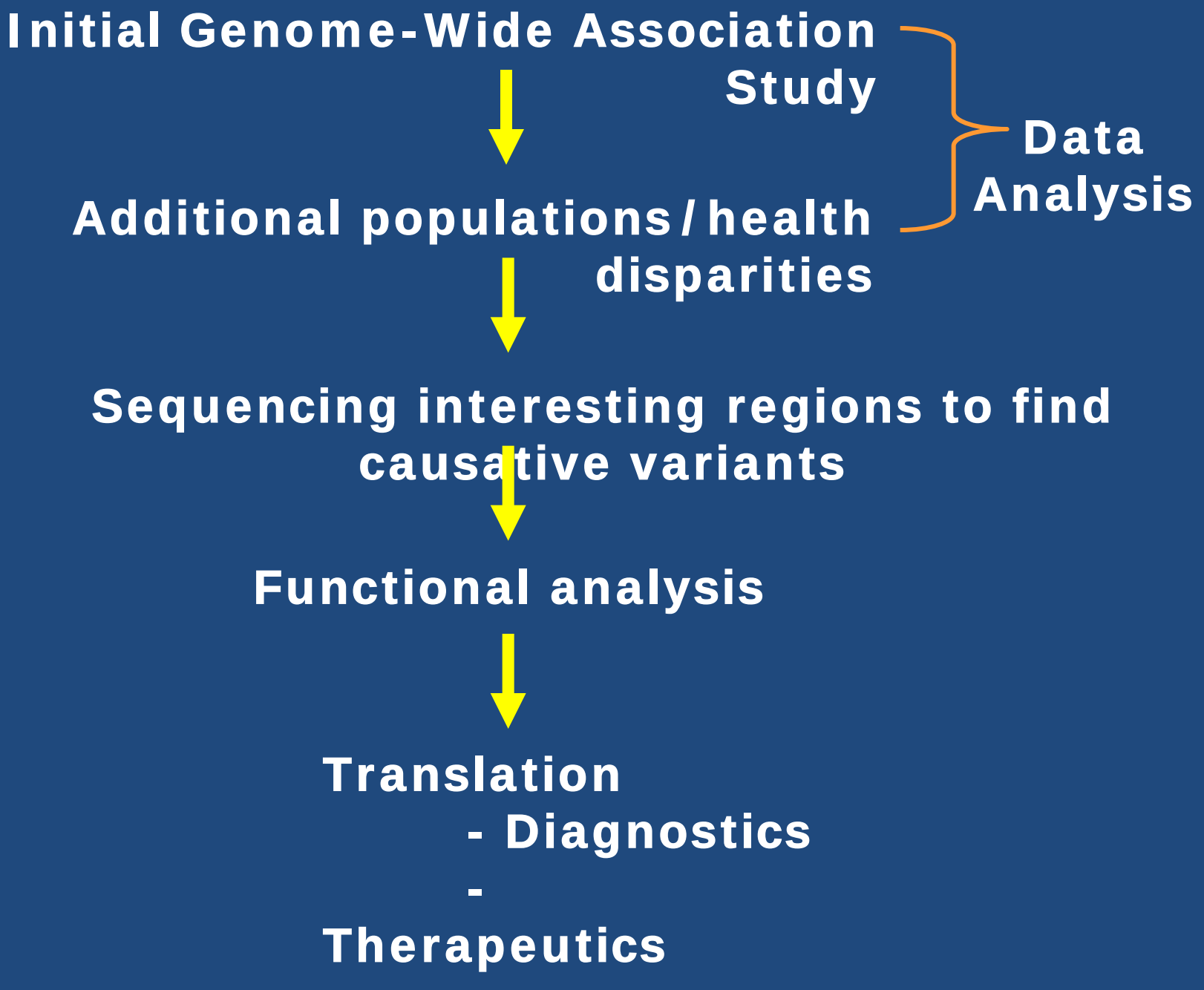
A common variant associated with prostate cancer in European and African populations

Genome-wide association study identifies novel breast cancer susceptibility loci

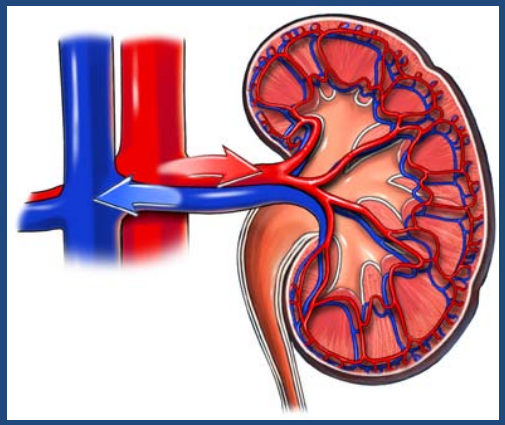
From New SNP to New Therapy

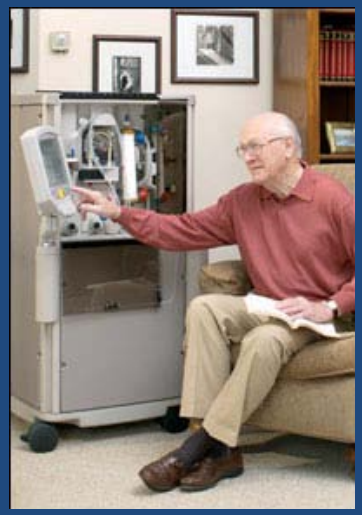
"A long and treacherous road!"

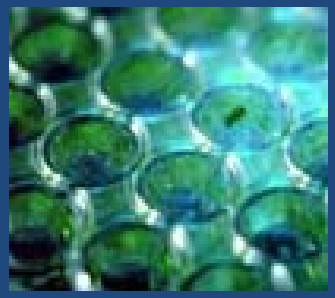
- Initial steps: Replication, sequencing, functional studies
- First order translation: Stratification to maximize therapeutic response and minimize adverse effects
- Second order translation: Develop therapeutic or preventive interventions based on GWAS-guided identification of targets
- Requires new Toolkit for functional studies of the whole pathway and not just the discovered target!
  - siRNA for knock down
  - vectors for delivery
  - Molecular libraries for small molecule probes


Initial Genome-Wide Association Study
Additional populations / health disparities
Data Analysis
Sequencing interesting regions to find causative variants
Functional analysis
Translation
- Diagnostics
-
Therapeutics

Predictive: End Stage Renal Disease

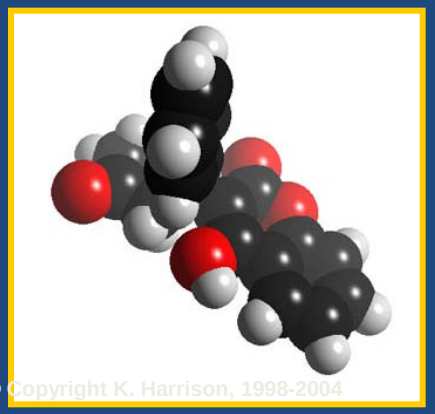


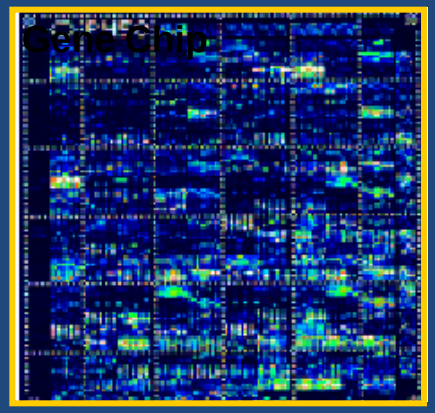




- **End-stage Renal Disease:**
  - **$22.8 billion in U.S. public and private spending (2001)**
  - **In the past decade, the absolute number of ESRD patients more than doubled and the incidence rate doubled**
  - **More than 85,000 new cases per year**
- **Apolipoprotein E (APOE)**
  - **Variation predicts kidney disease progression**
  - **Prediction independent of diabetes, race, lipid and non-lipid risk factors**

New Discoveries Make it Possible to "Personalize" Cardiovascular Treatment



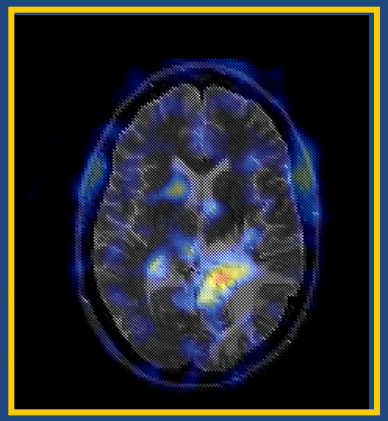


- Warfarin: An anticoagulant drug used to reduce the risk of clots causing strokes or heart attacks
- Effective daily dose ranges from 0.5 mg to 60 mg
- Too little: clots, stroke
- Too much: bleeding/death
- Genomic experiments can test for two different genetic variations that predict best dose

Personalization:
Promises from Cancer Research

Cancer Genome Project

- Pilot project to systematically explore the universe of genomic changes involved in all types of human cancer



Genetic analysis of malignant brain tumors

- Results can predict the tumor's sensitivity to specific drugs
- Allows Doctors to **personalize** more effective treatment

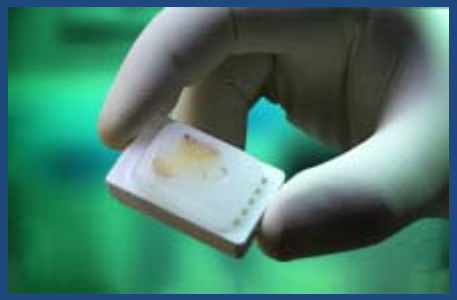
Cancer Treatment Gets Personal: Potential New Model of Cancer Treatment

“Advances in understanding genetic basis of cancer have led to promising new therapies, which have fueled discussions about a future model of cancer care--treatment decisions are guided by the molecular attributes of the individual patient.”

http://www.sciencemag.org/sciext/cancer/

New Discoveries Make it Possible to "Personalize" Cancer Treatment

Identified 16 informative genes



Test tumor samples for mutations in these genes

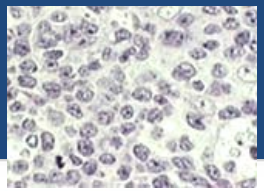
Predict which patients need chemotherapy

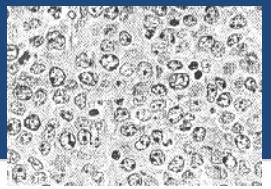
Impact:

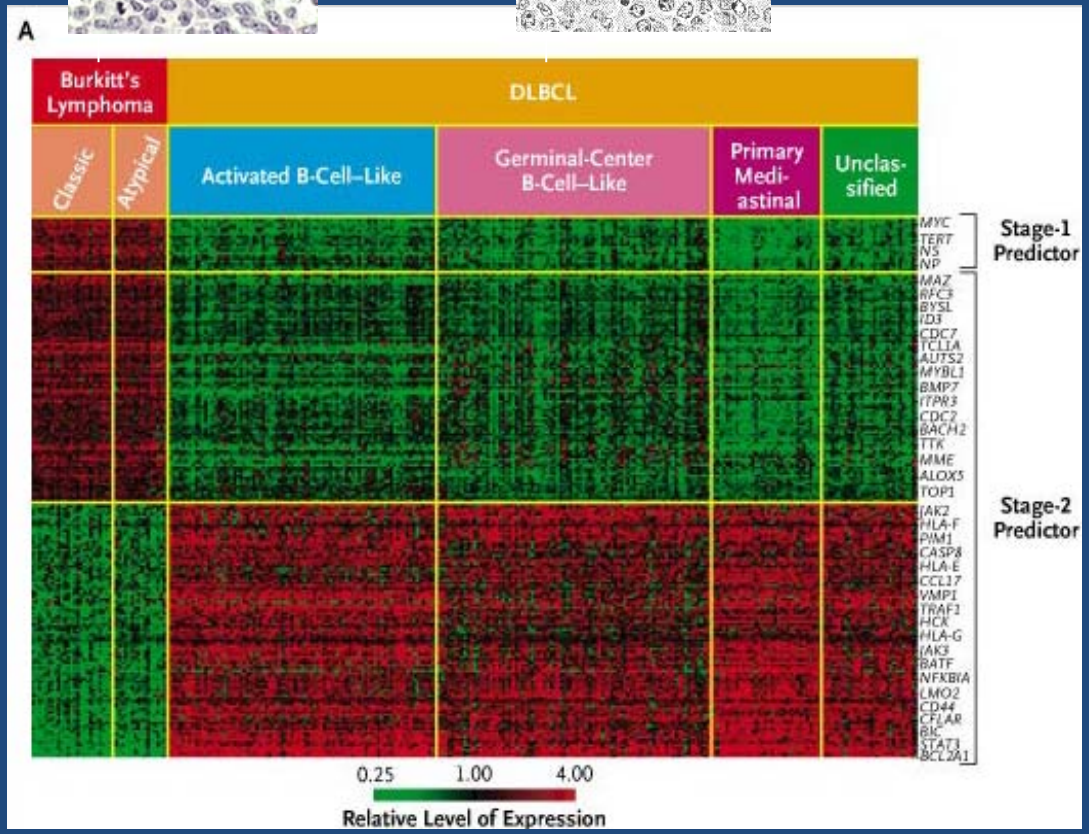
- **100,000 women *each year* can make a more informed choice**
- **70,000 women may not have to undergo chemotherapy**
- **Reduces routine cost of treating these patients**
  - **For each patient year of life gained, we save ~$8,000**

Molecular Profiling and Treatment Decisions

- **Burkitt's lymphoma and diffuse large B-cell lymphoma look alike histopathologically but require *different treatments***
- **Genetic signatures defined for Burkitt's and DLBCL**
- **Expert histopathologists misdiagnosed 17% of cases**
- **Molecular profiling was more accurate for differential diagnosis**

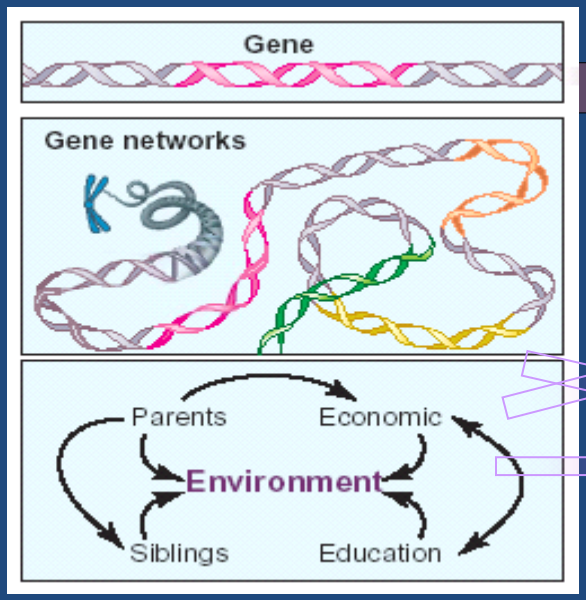




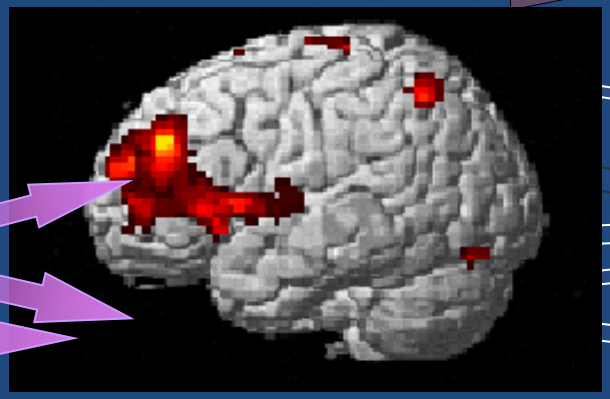


Dave S et al. *N Engl J Med* 2006;354:2431-2442

How Do Genes Influence Behavior?



BRAIN FUNCTION



Behavior*

Protein expression

Neurotransmission

CBF

Metabolism

Electrophysiology

Symptoms

NP function

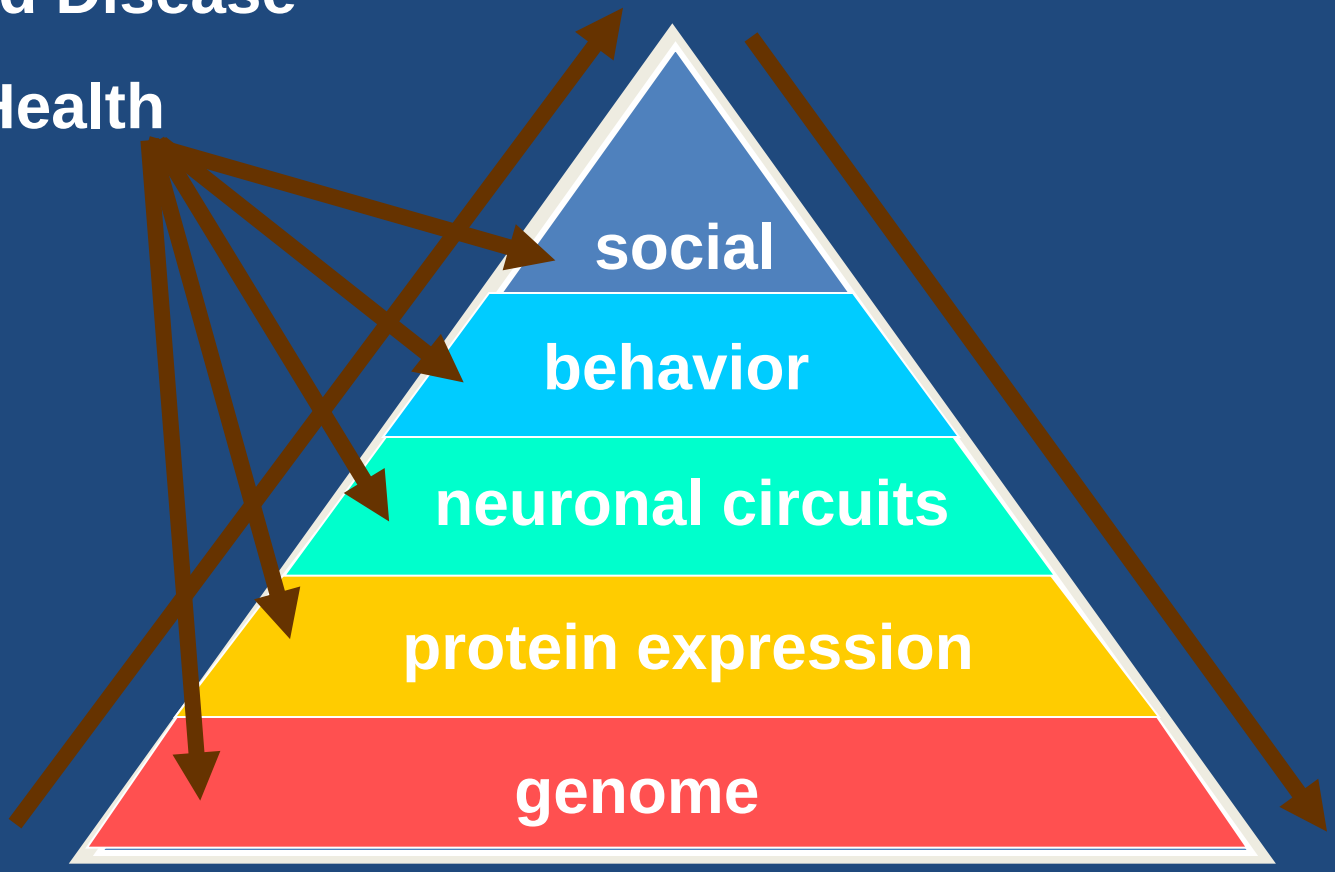
Behavioral test

*Adapted from Hamer, *Science*, 2002; MAO A genotype studies from Caspi et al, *Science*, 2002

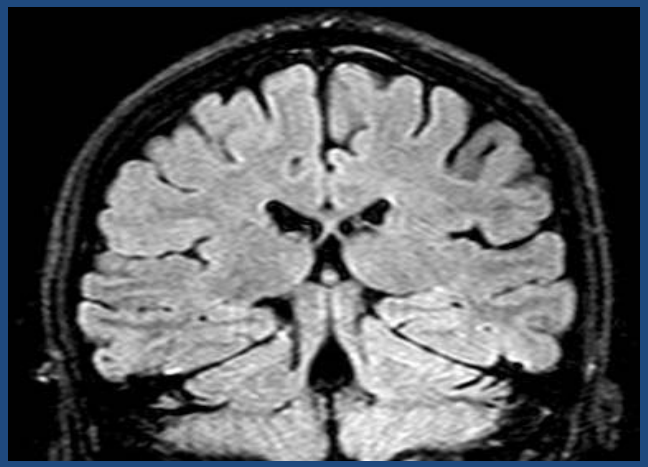
Integration of Knowledge

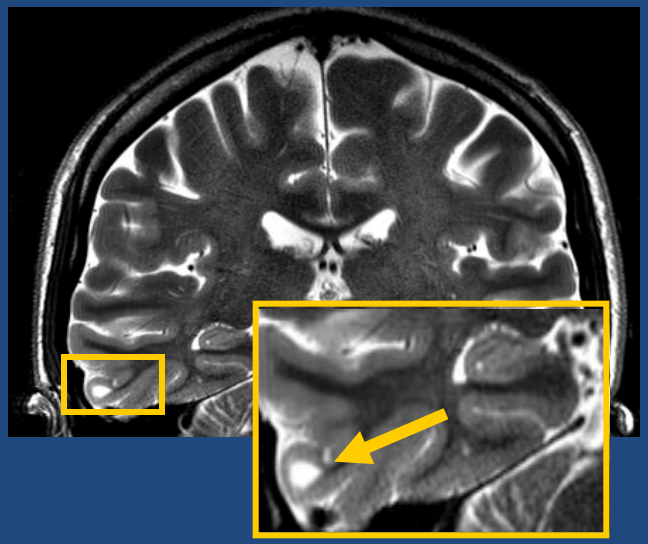
Understand Disease

Optimize Health



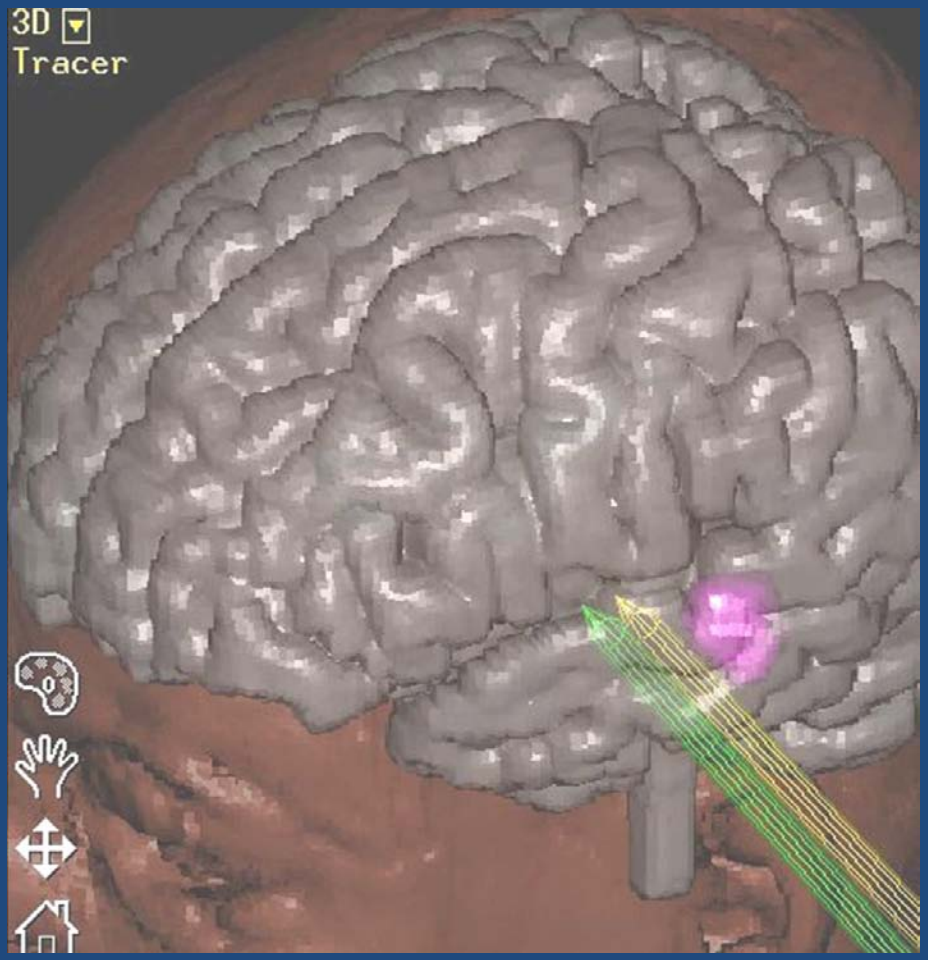
New Advances Make it Possible to “Personalize” Epilepsy Treatment





BWH E. Bromfield, P Black

- Dramatic improvements in Bioimaging technology allows personalized intervention in Neocortical Epilepsy
- Today:
  - 60% Increase in Seizure Foci Identification
  - Successful image-guided epilepsy surgery
  - Reduce or eliminate major post-op neurologic deficits



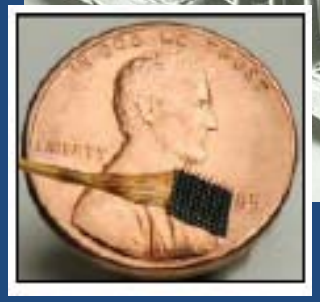
Brain with focus of epileptiform activity from SPECT mapped onto MRI

From Greg Cascino Mayo Clinic Rochester

Cutting Edge Technologies –

Microelectrode Recordings in Human Cortex to better understand, detect and predict seizures

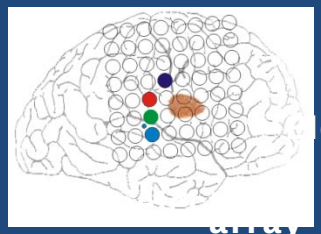
(to be discussed by John Donoghue on Friday afternoon section and some results presented by Sydney Cash at Junior Investigator Program)



Laminar Microelectrode Array developed by Istvan Ulbert and George Karmos and in use by a collaboration led by Eric Halgren and Sydney Cash at UCSD, New York University and Harvard Medical School.

Neuroport® Array developed by Cyberkinetics Neurotechnology Systems Inc. and in use at Columbia Univ. and Harvard Medical School.

Seizure activity recorded on an intracortical grid and laminar microelectrode array showing changing pattern of cortical layers involved in the generation of ictal discharges



Grid electrodes

upper

middle

lower

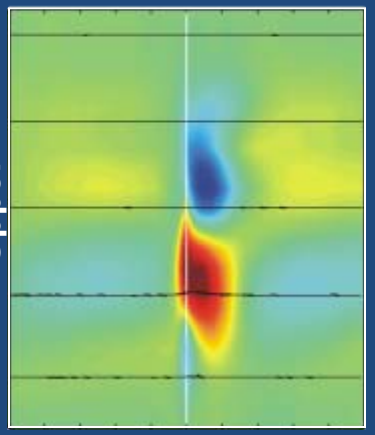
array (subset of channels)

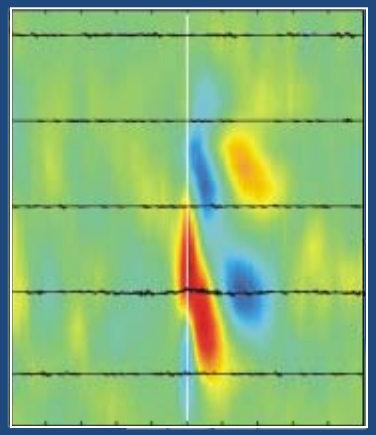
Potential gradient + multi-unit activity

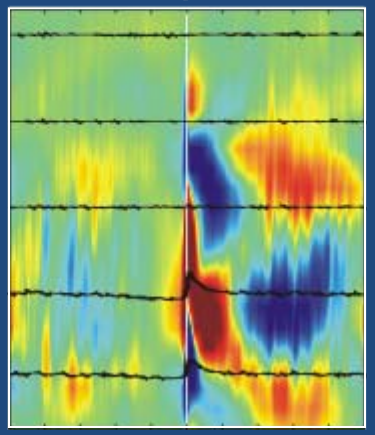
cortex

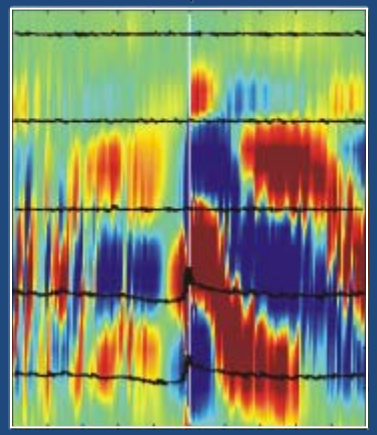
Interictal Spike

60 uv









Cortical Layer

Upper

Lower

-1

1 sec

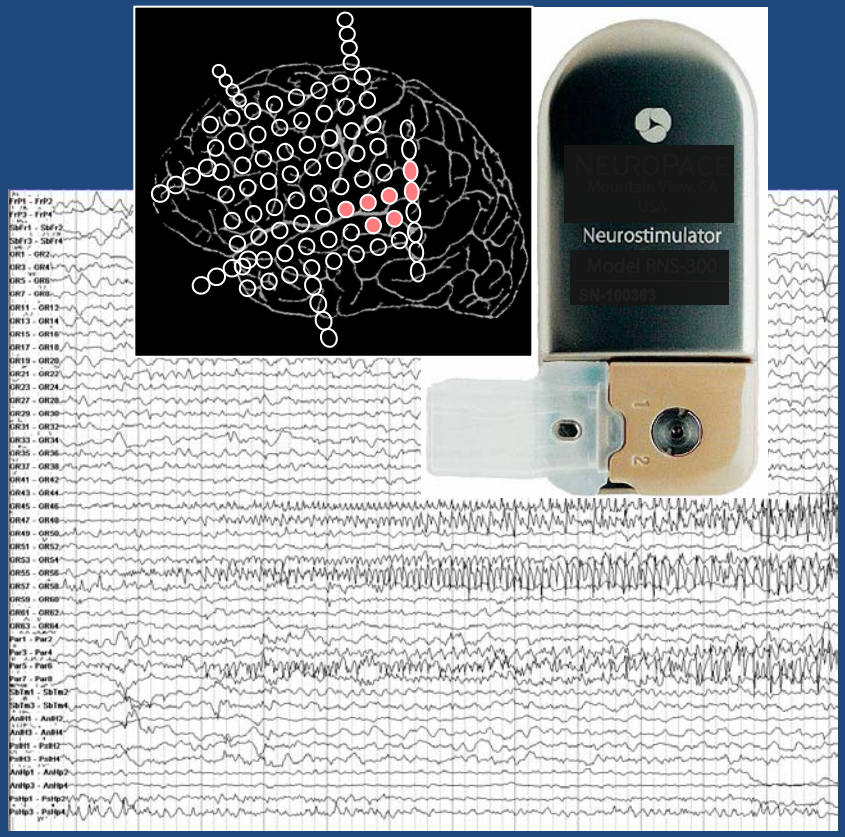
0

Cash / Halgr

Responsive Neurostimulator

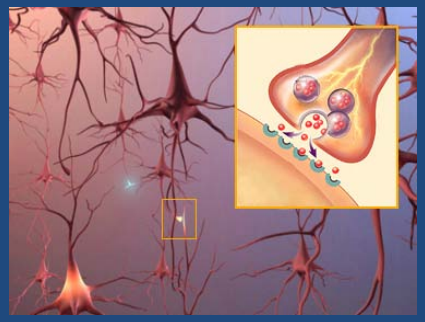
Epilepsy Benchmark (2000): Create a device "that, in at least one type of epilepsy, will detect an oncoming seizure and apply treatment to stop the seizure before it begins"

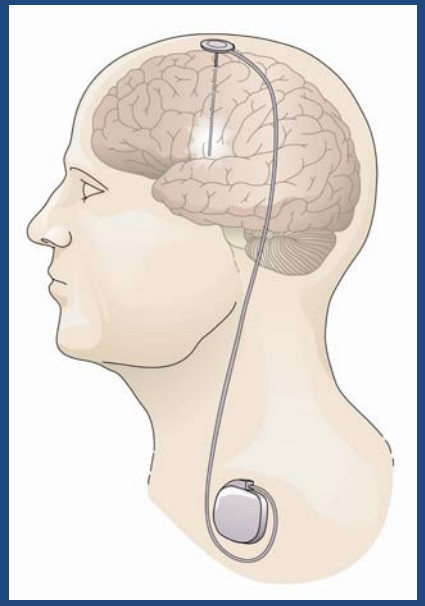
- Responsive neuro-stimulator system now being tested clinically in people with partial seizures
- System includes pacemaker-like device implanted in brain
  - Continuously monitors electrical activity for signs of seizure onset
  - Delivers brief electrical stimulation to suppress seizure



Sydney Cash, Massachusetts General Hospital

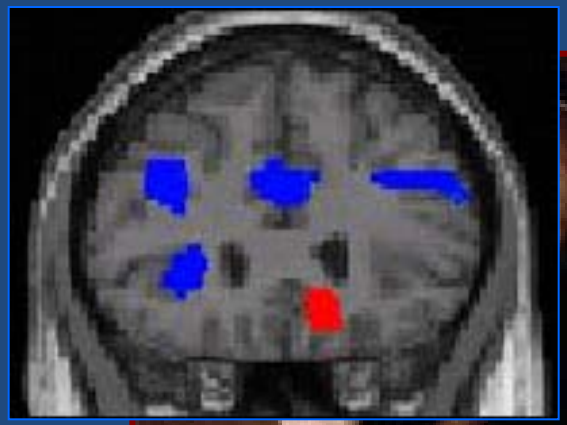
Example of Interdisciplinary Research: *Deep Brain Stimulation Treatment for Parkinson's Disease*

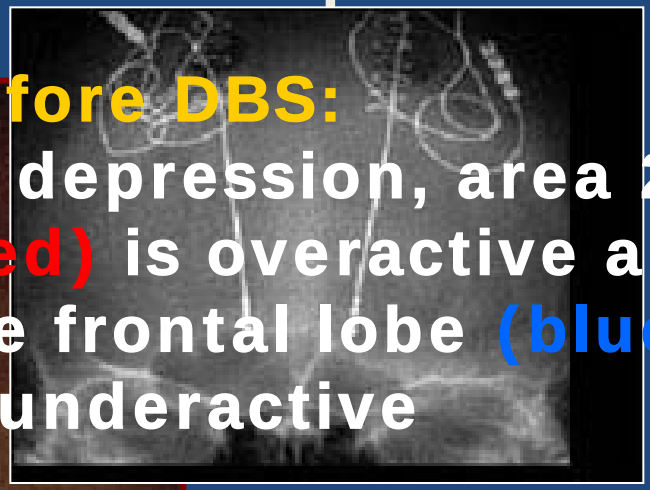




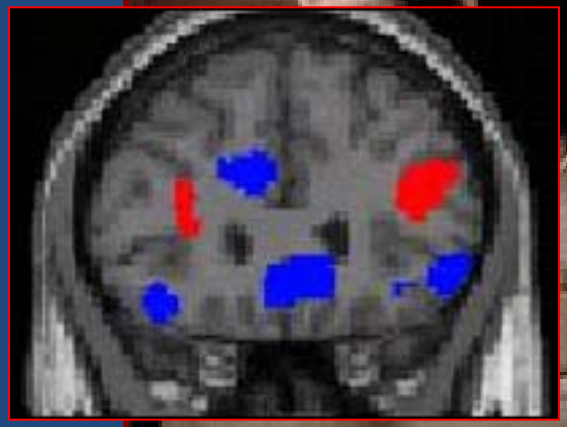
- Basic science investments paved way for clinical success with deep brain stimulation
- Improvements in:
  - Imaging Technology
  - Biomedical materials
  - Basic Neurobiology
- Contributions from industry, international scientific community resulted in treatment development
- Clinical trials in progress

Deep Brain Stimulation for Treatment-Resistant Depression





Before DBS:
In depression, area 25 (red) is overactive and the frontal lobe (blue) is underactive

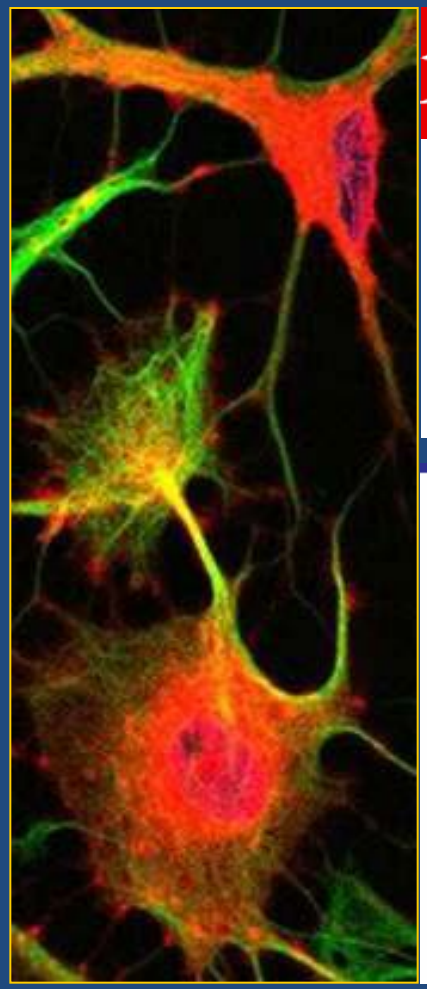


After DBS:
Area 25 activity has decreased and frontal lobe activity has begun to increase

http://www.npr.org/templates/story/story.php?storyId=4627438;
http://news.bbc.co.uk/1/hi/health/4625775.stm

Courtesy Dr. H. Mayberg

2005 Pioneer Award Recipient
Karl Deisseroth, M.D., Ph.D.
Stanford University



nature

ARTICLES

Multimodal fast optical interrogation of neural circuitry

Feng Zhang[1], Li-Ping Wang[1], Martin Brauner[2], Jana F. Liewald[2], Kenneth Kay[1], Natalie Watzke[4], Phillip G. Wood[4], Ernst Bamberg[3,4], Georg Nagel[4,5], Alexander Gottschalk[2] & Karl Deisseroth[1]

What's Light Got To Do

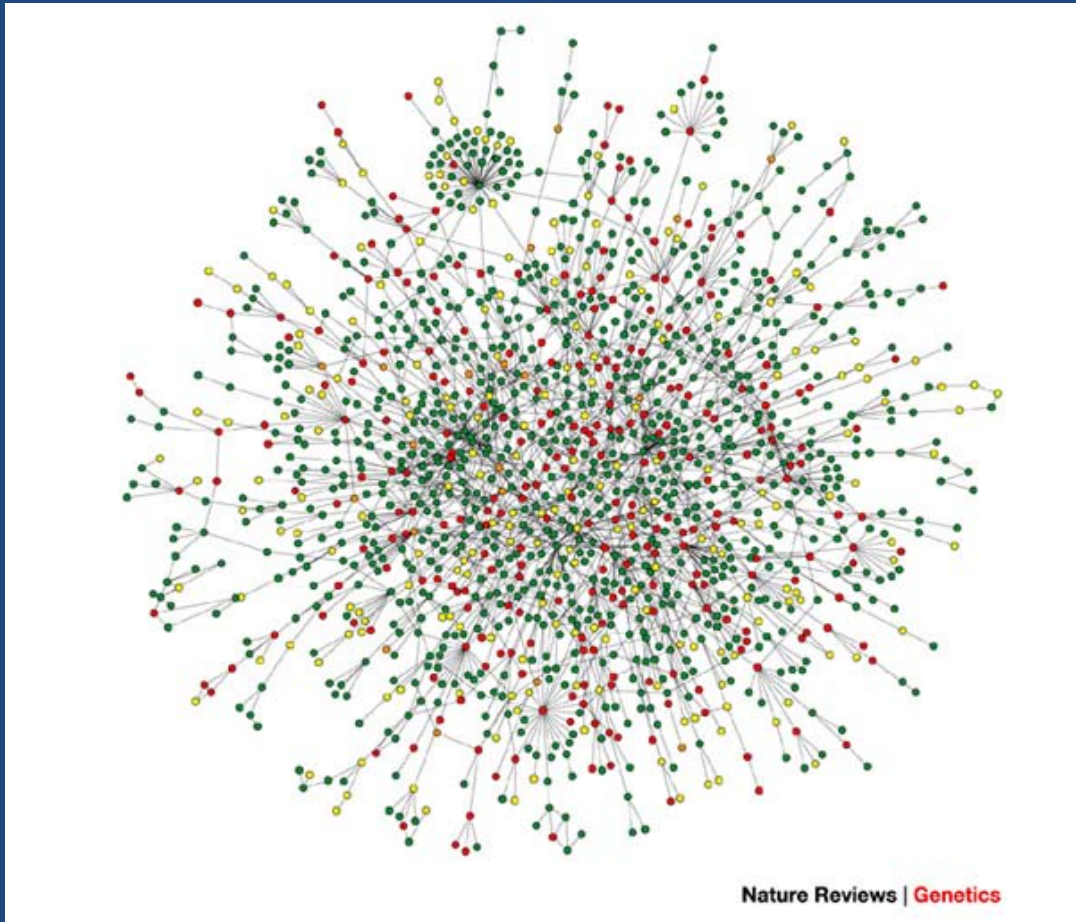
Deisseroth's Optogenetics Targets Brain Circuits

Using light to relieve suffering has a long history. From ancient Egypt to Victorian London, unfiltered sunlight was regarded as a fundamental cure for rashes, rheumatism and rickets.

As scientists discovered that light is not a simple element—that it is both wave and particle, with a spectrum of bandwidths, some invisible to the human eye—they teased out its proper-

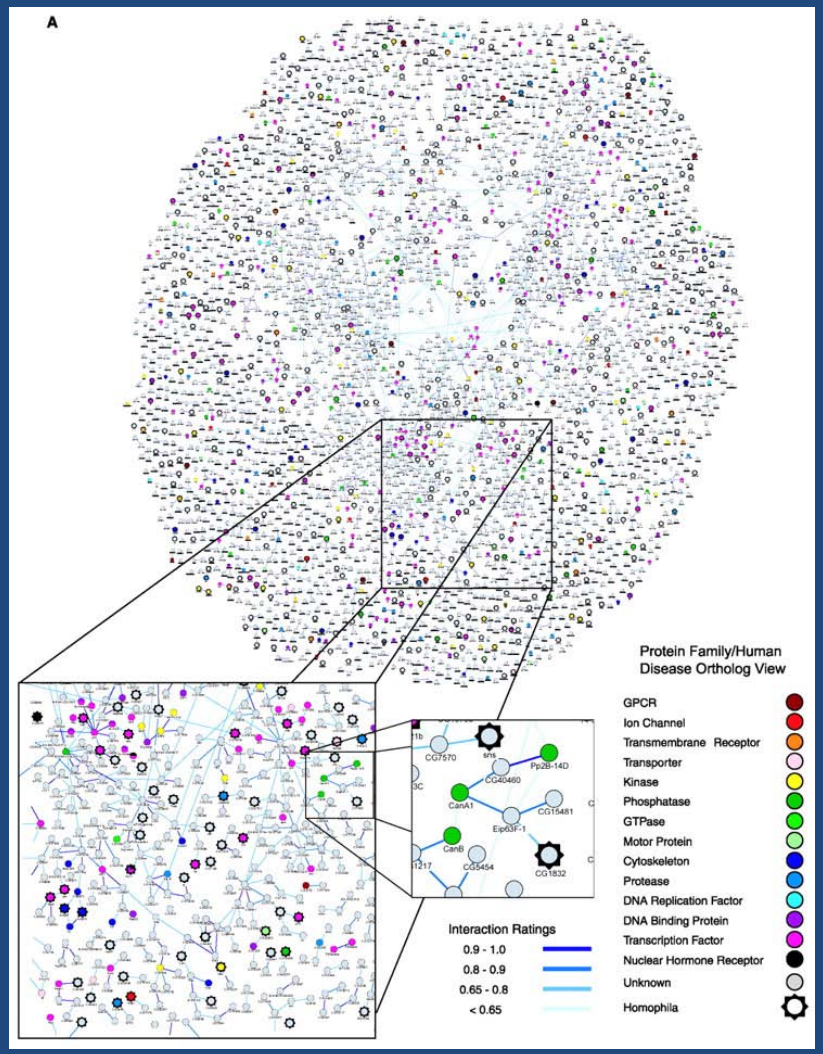
Dr. Karl Deisseroth is bringing his expertise in bioengineering to psychiatry.

Besoin de mieux comprendre la complexite des systemes biologiques



Complexity of Biological Networks

New way of doing cell biology – protein interaction map of the fruit fly



- Beyond scope of an individual researcher
  - Map appeared in *Science* article with 49 authors.
    L. Giot *et al., Science* **302**, 1727 (2003)
- Pathway to potential therapy is clear (but not trivial)
  - relationships involving disease proteins emerge as the map is built.
- Human being can not really "understand" this diagram
  - not like standard textbook pathway diagram of Krebs cycle.
  - Use computer to mine the map, guide thinking about further work.

Elias A. Zerhouni M.D.,
Director, NIH

New Pathways to Discovery

Genomic Era offers unprecedented opportunities

- **Novel Approaches**
  - Building blocks of biology (genes to proteins)
  - Biological pathways and their controls
  - From Reductionist to Integrative biology
- **Innovative Technologies**
  - Bioinformatics and computational biology
  - Molecular libraries
  - Nanomedicine
  - Novel research methodologies

THE CHALLENGE

For 33,000 GENES
ASSUMING ON/OFF
STATES ONLY

33,000x33,000
OR 1 BILLION
CONFIGURATIONS

1 Experiment/hr
8760 hrs/yr

114,000 YEARS!

But if genes are organized in modules of 100 genes each ,
Then only 100,000 configurations are possible (12 years)

HOW CAN COMPLEXITY BE REDUCED?

My combination padlock

9999

(Divide by 2, multiply by 3 remove 1)
6398

4265

2132

0000
Only 3 solutions out of 10,000 possible configurations

NEED TO UNDERSTAND THE QUANTITATIVE RELATIONSHIPS BETWEEN ELEMENTS OF THE SYSTEM

NEED FOR MORE QUANTITATIVE BIOLOGICAL EXPERIMENTAL DATA

Ceci va réclamer un changement radical des caractéristiques des données biologiques

Actuellement	demain
Destructives	Non-Destructives
Qualitatives	Quantitatives
Uni-Dimensionelles	Multi-Dimensional
Basse résolution temporelle	Haute résolution temporelle
Non localisées	Spatially resolved
Basse densité	Haute densité
Normes variables	Normes communes
Non cumulatives	Cumulatives

Bioinformatics and Computational Biology

Deploy a rigorous biomedical computing environment to analyze, model, understand and predict dynamic and complex biomedical systems across scales and to integrate data and knowledge at all levels of organization

Défi scientifique:
Décrypter la complexité biologique

Réponses cellulaires à l'agression

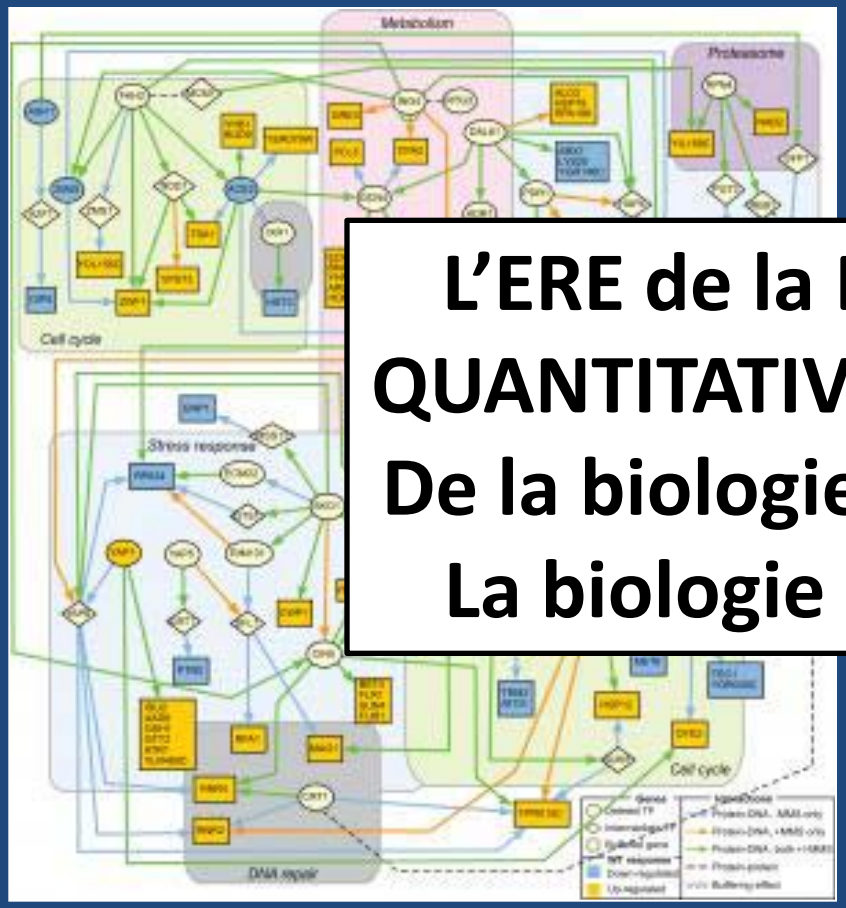
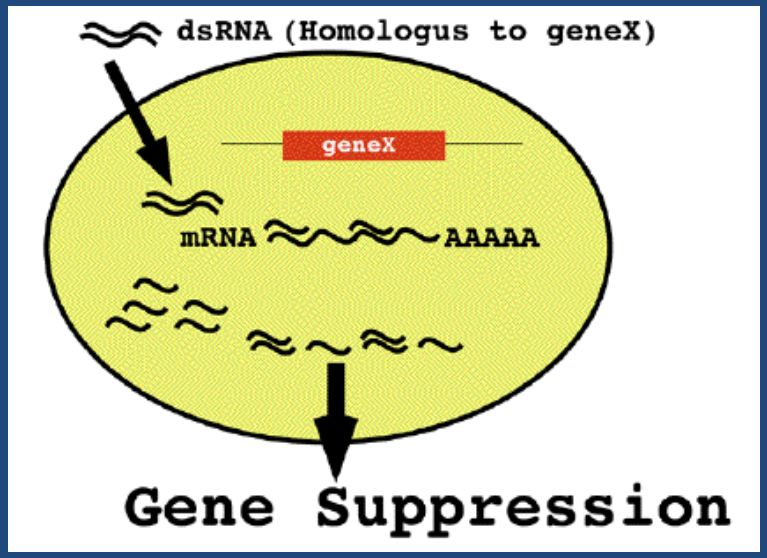


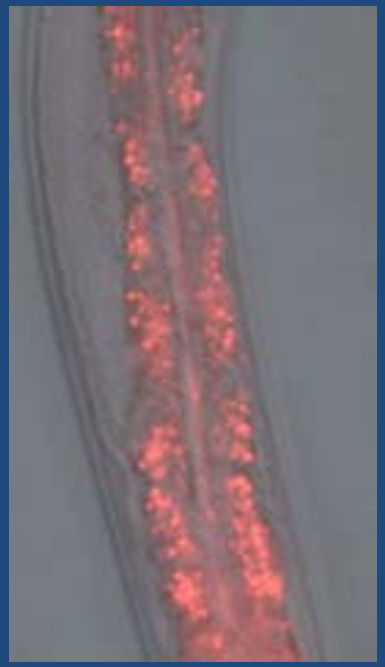
Diagramme électronique

L'ERE de la BIOLOGIQUE QUANTITATIVE des RESEAUX
De la biologie Moleculaire a La biologie MODULAIRE

Source image : UCSD

New Discoveries in Obesity Research Using RNA interference (RNAi)





Normal Worm

305 genes

112 genes

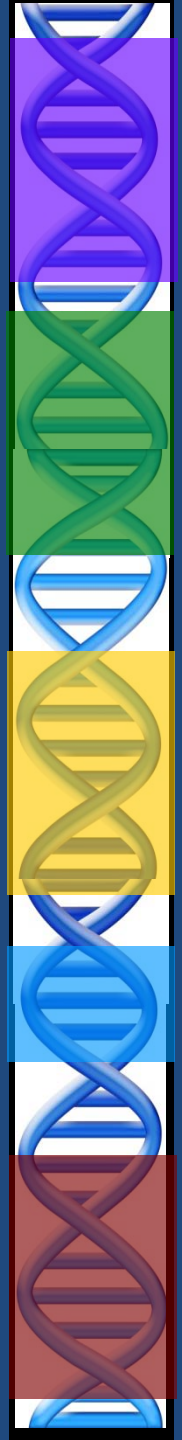
Thin Worm

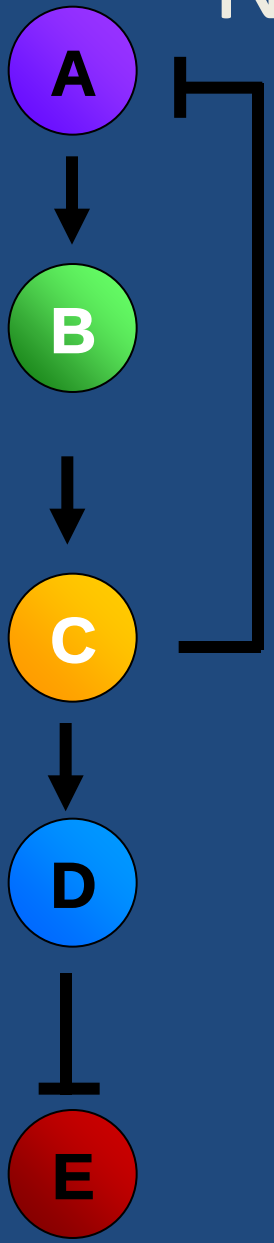
Obese Worm

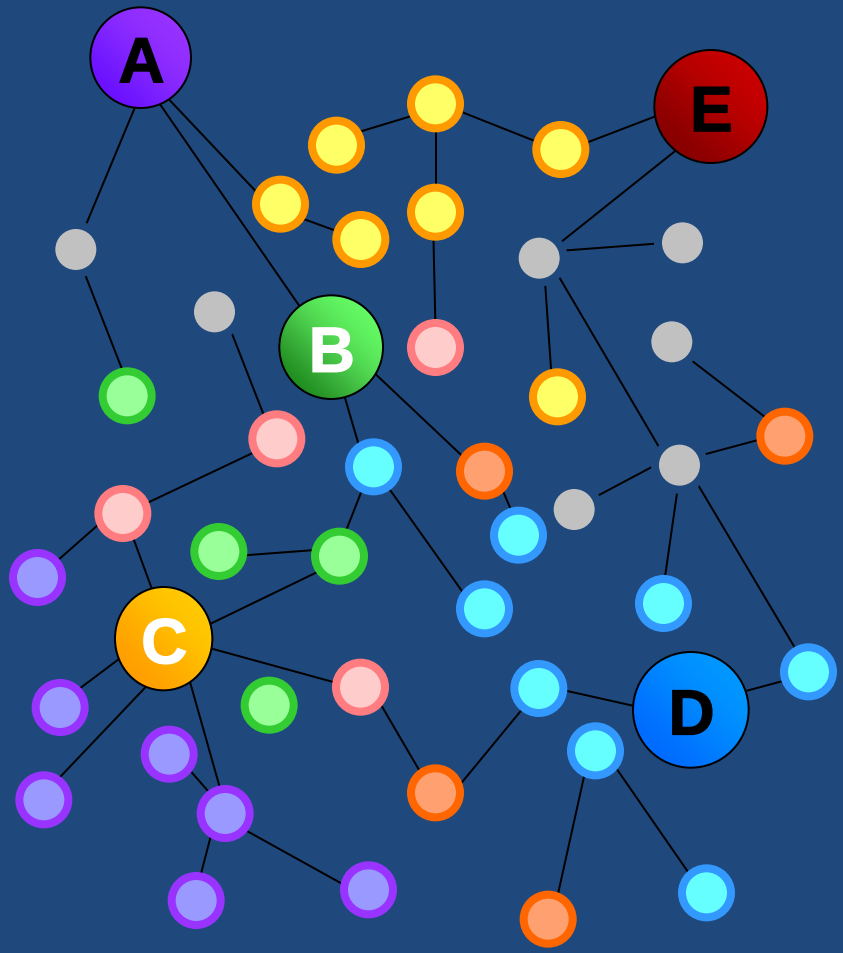
Source: Ashrafi, K., Chang, F.Y., Watts, A.G., Kamath, R.S., Ahringer, J., and Ruvkun, G., "Genome-wide RNAi analysis of Caenorhabditis elegans fat regulatory genes," Nature, Vol. 421, pp. 268-272.

Normal Gene Function

Healthy State

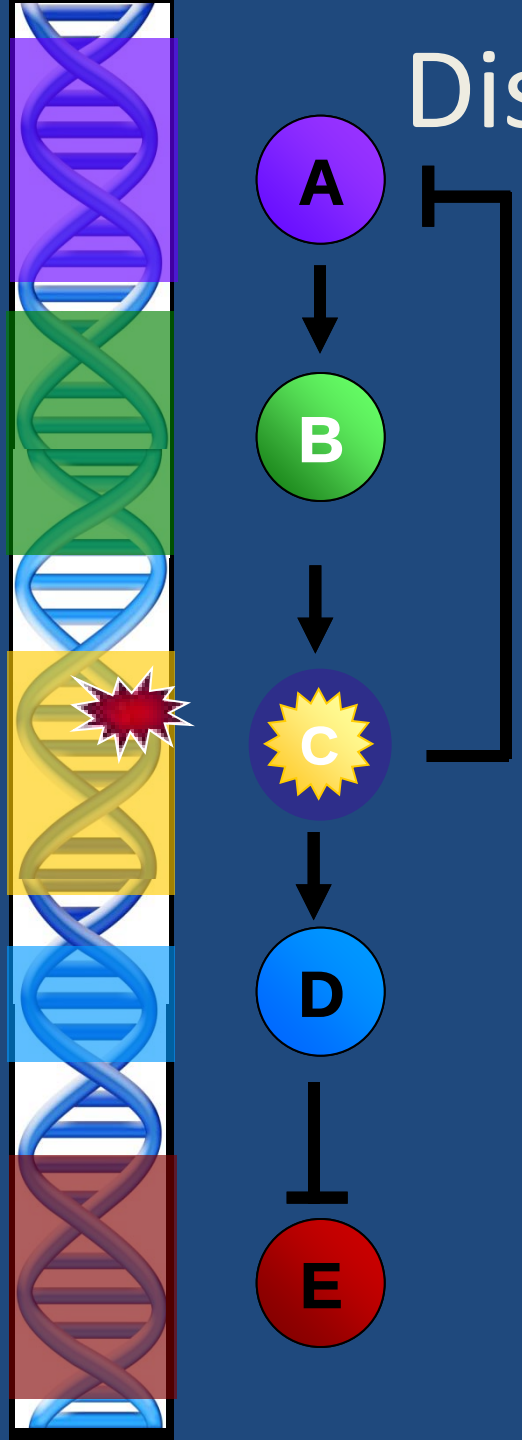


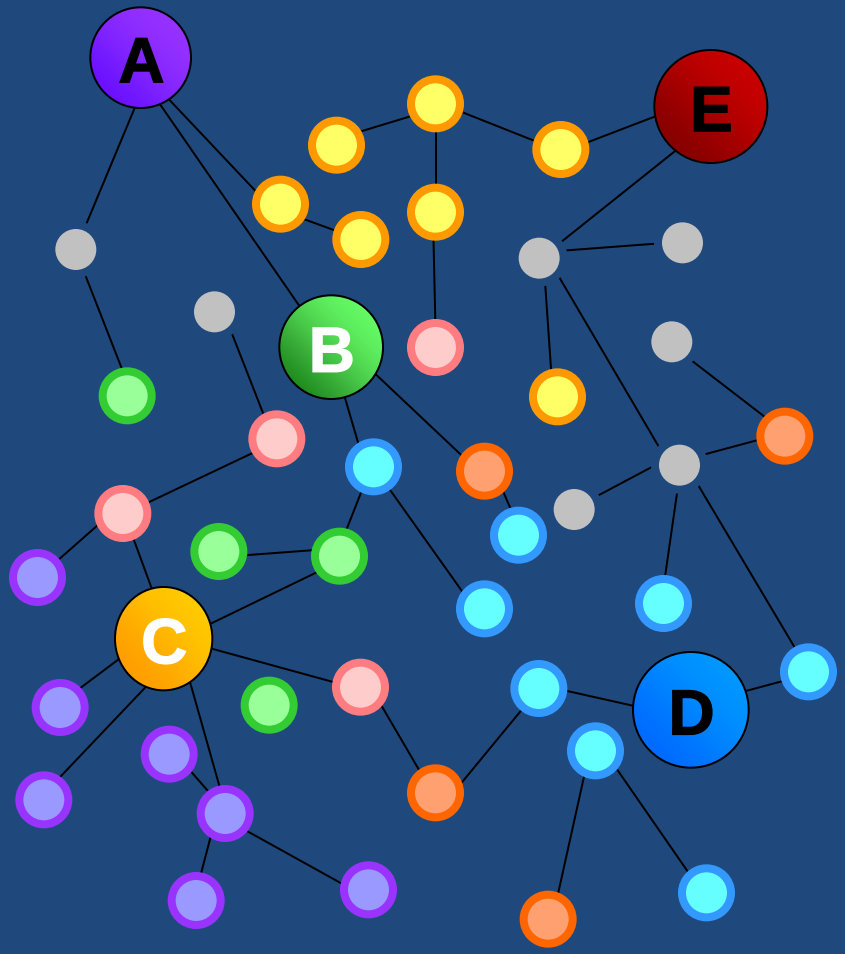




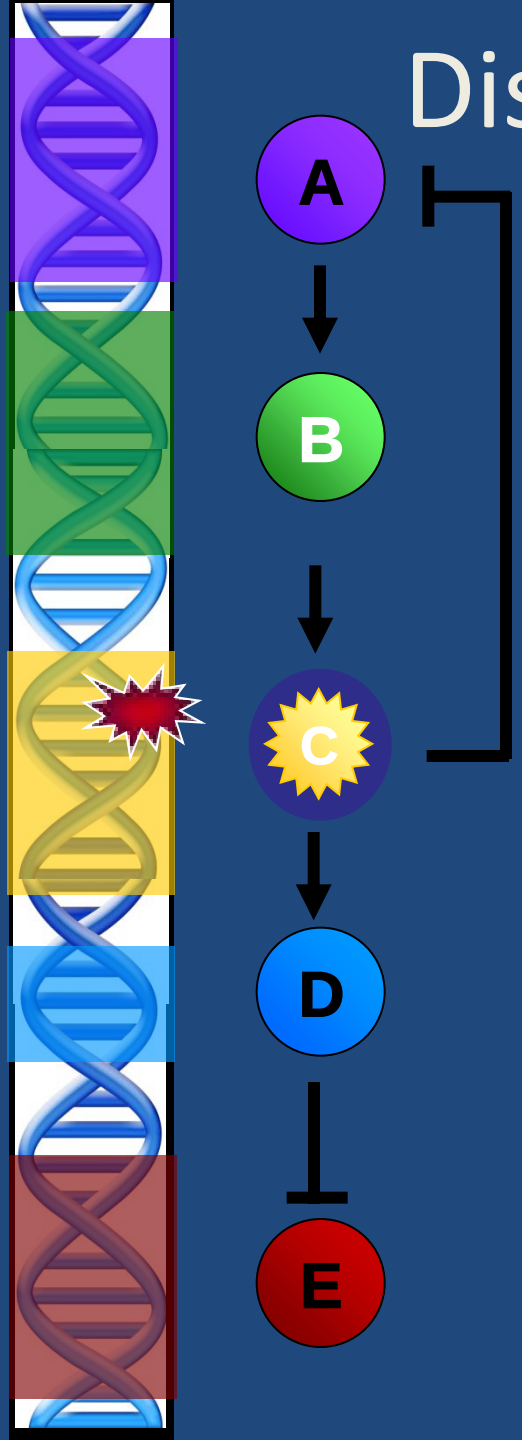
Disrupted Gene Function

Disease State

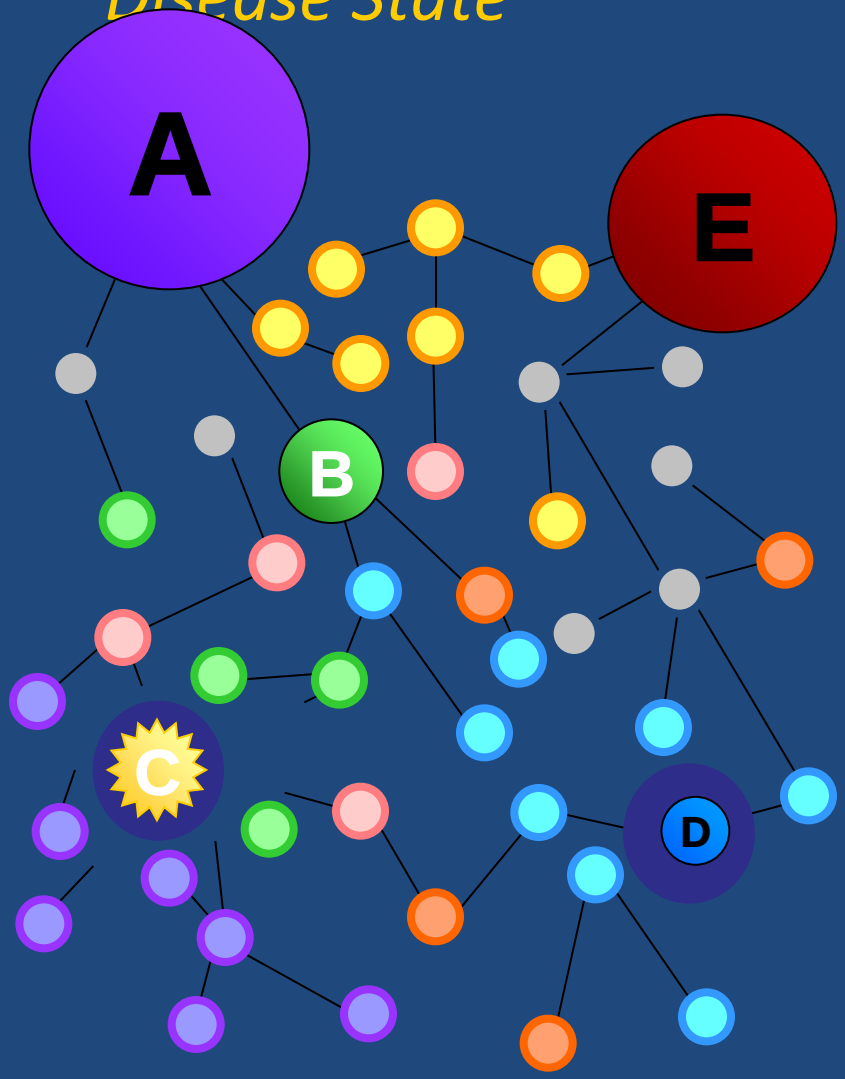




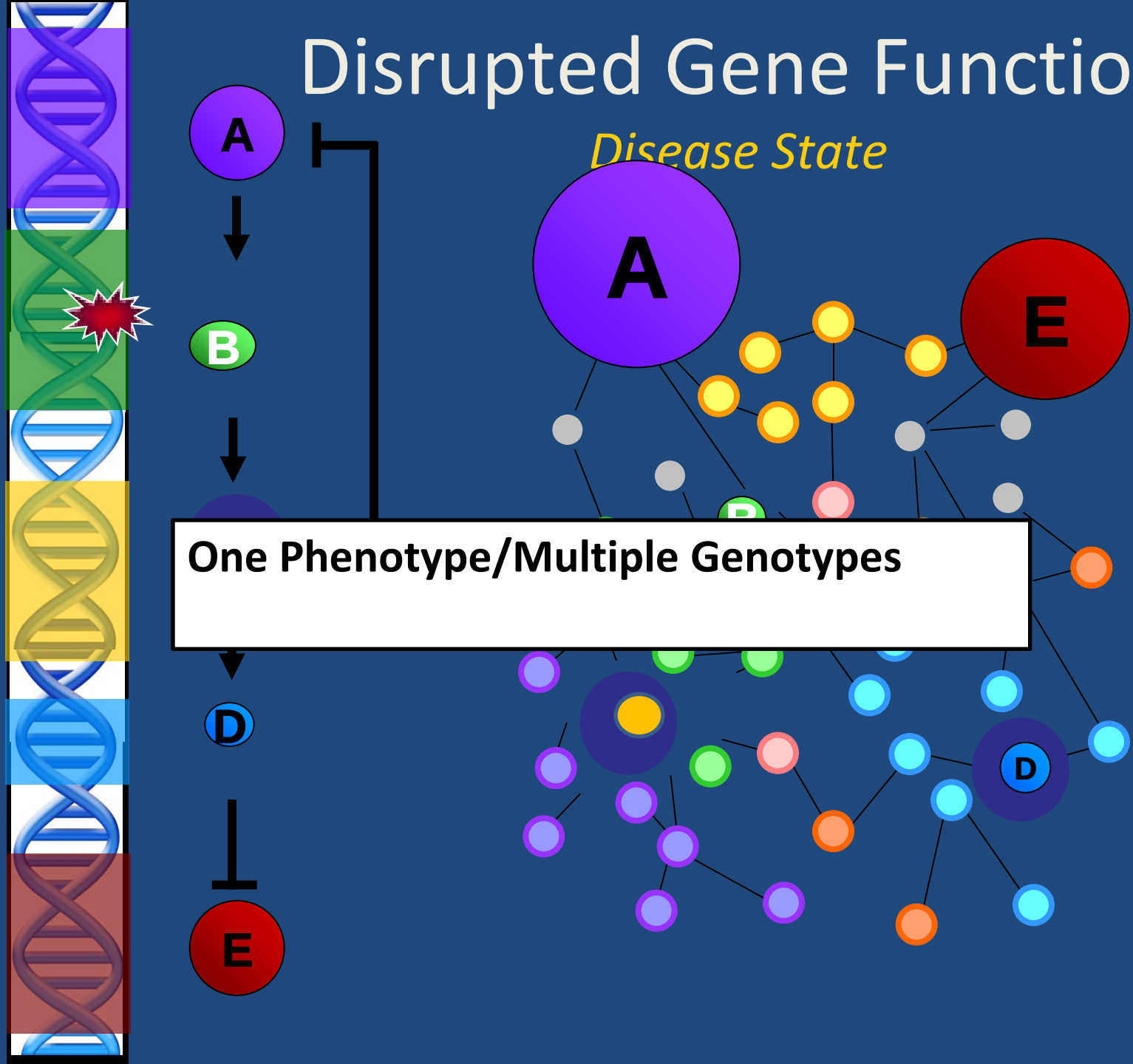
Disrupted Gene Function

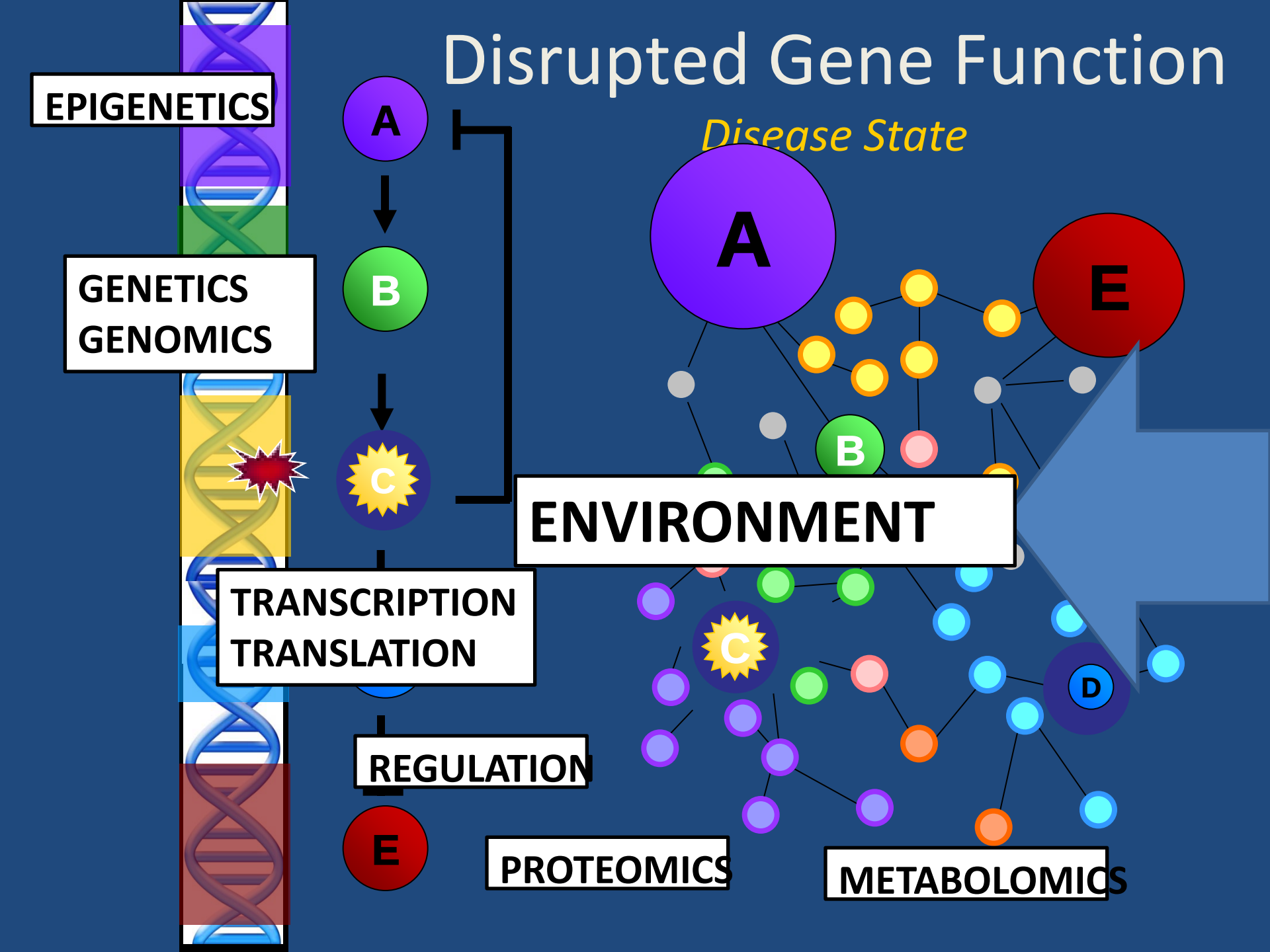


Disease State

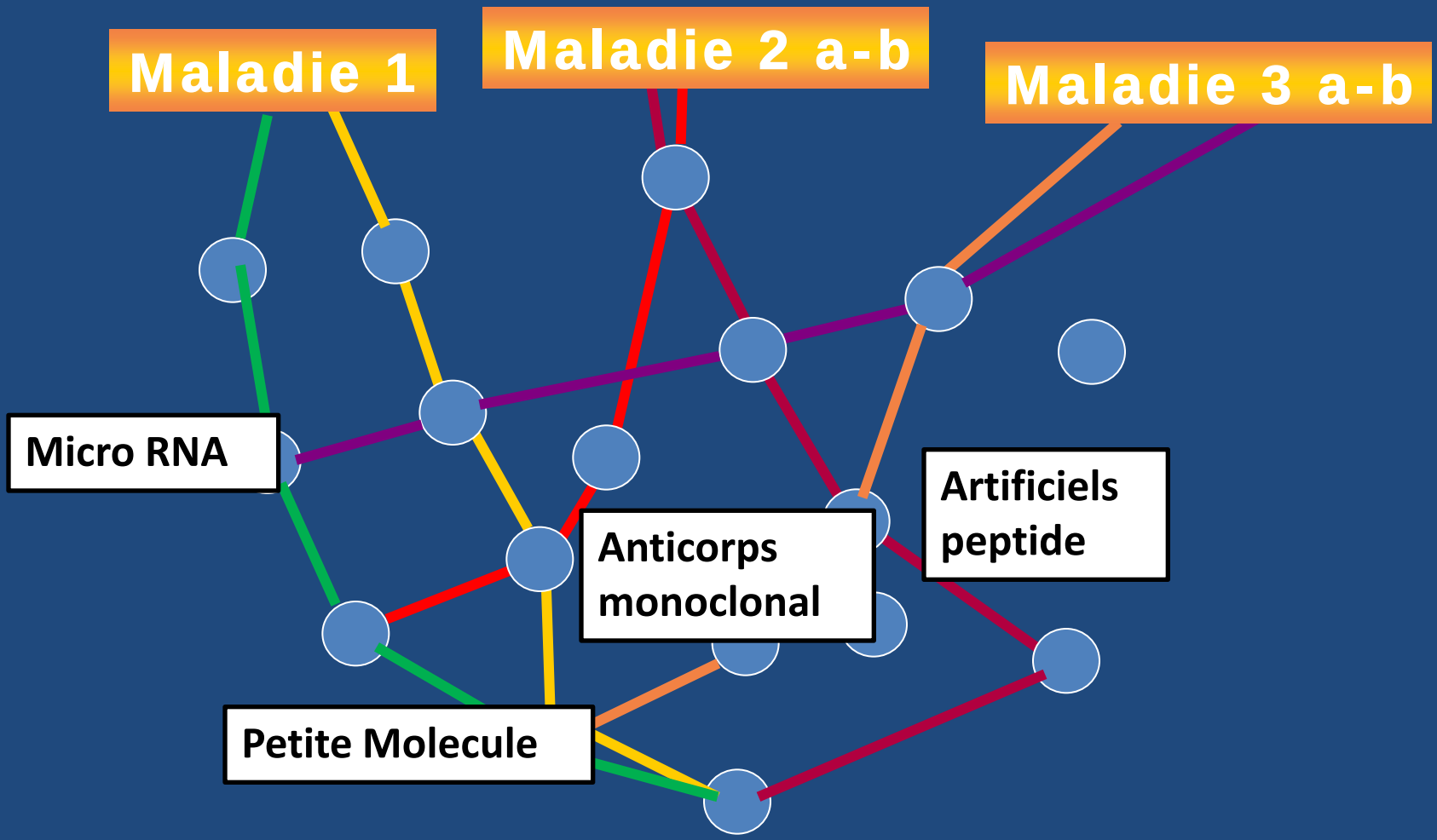


Disrupted Gene Function

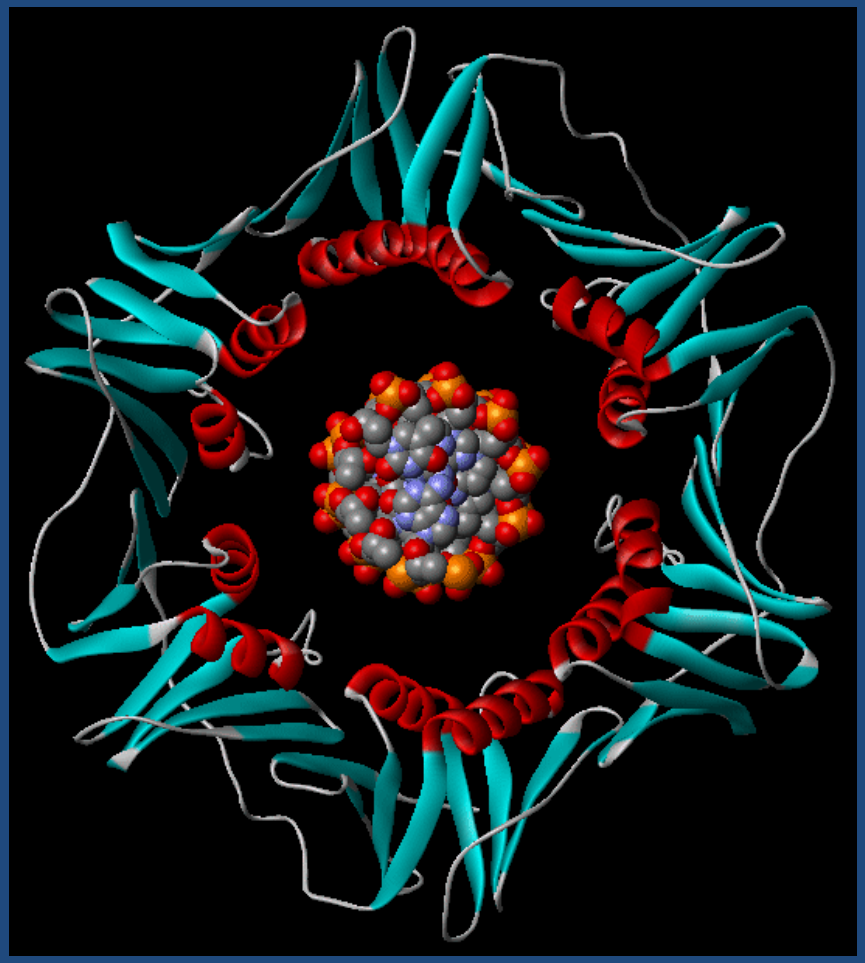



Disrupted Gene Function
Disease State
EPIGENETICS
GENETICS
GENOMICS
TRANSCRIPTION
TRANSLATION
REGULATION
ENVIRONMENT
PROTEOMICS
METABOLOMICS
A
B
C
D
E

Prochaine frontière: le développement de cartes biologiques quantitatives et fonctionnelles



… les médicaments constitueront une part des solutions thérapeutiques



"All molecules are created equal, but some are more equal than others."

Animal Pharm*

*Adapted from George Orwell's Animal Far

From the "*Hardware*" of Life to the "*Software*" of Life

Understanding Molecular Pathways and Their Regulation in Health and Disease

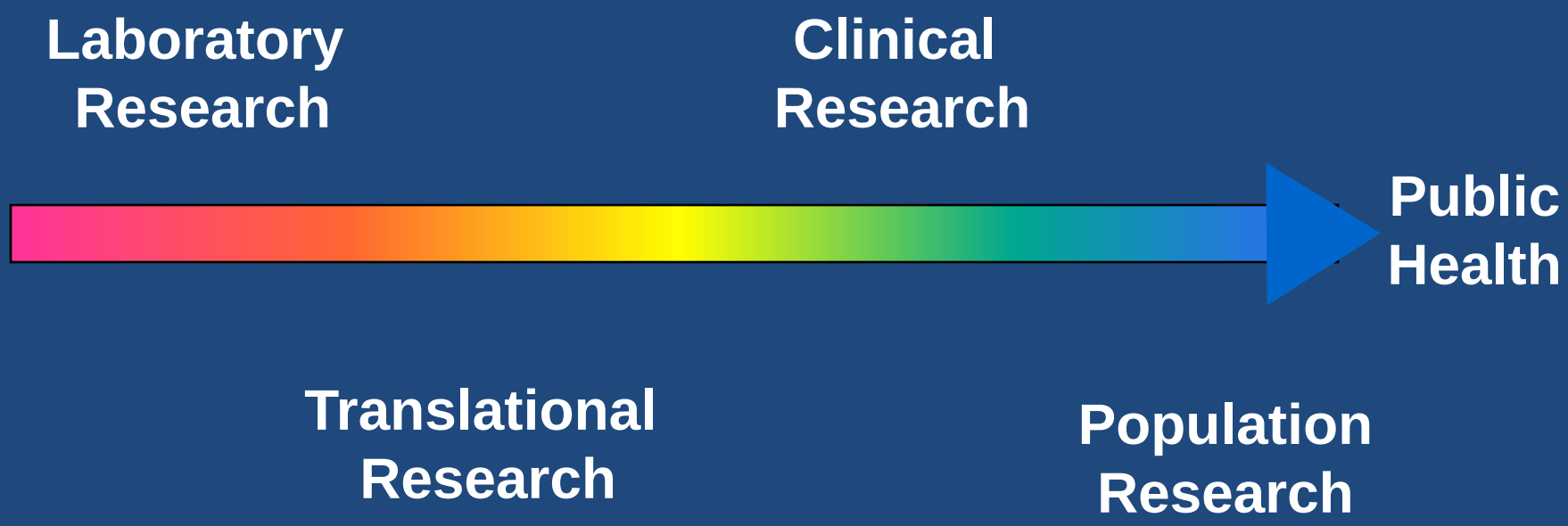
Key to a functional re-classification of diseased based on personal pathways predictive of response to specific therapies

Need for validated Biomarkers !

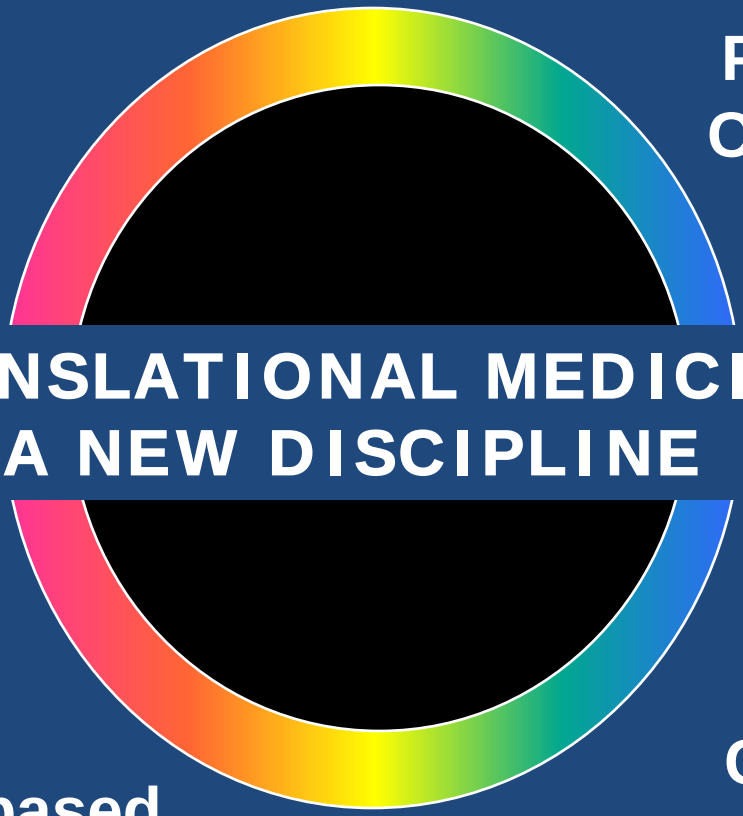
A New Paradigm is Needed: A Systems Based Approach

- Integrated approaches to research and discovery
- Interdisciplinary training
- Translational research as a recognized discipline
- Evolution from departments to interdisciplinary research centers
- Widely shared resources

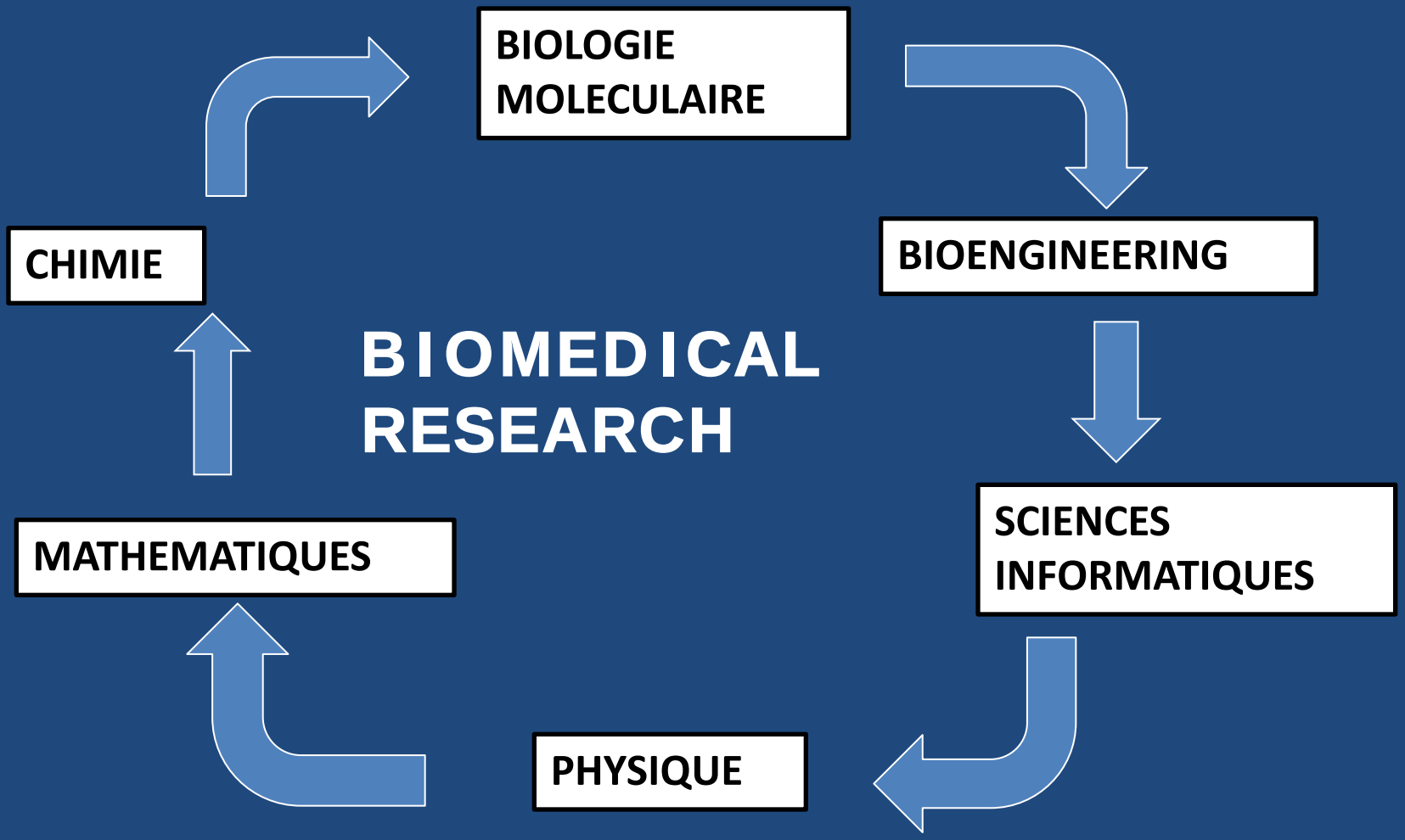
Bridging the translational divide
Standard Model



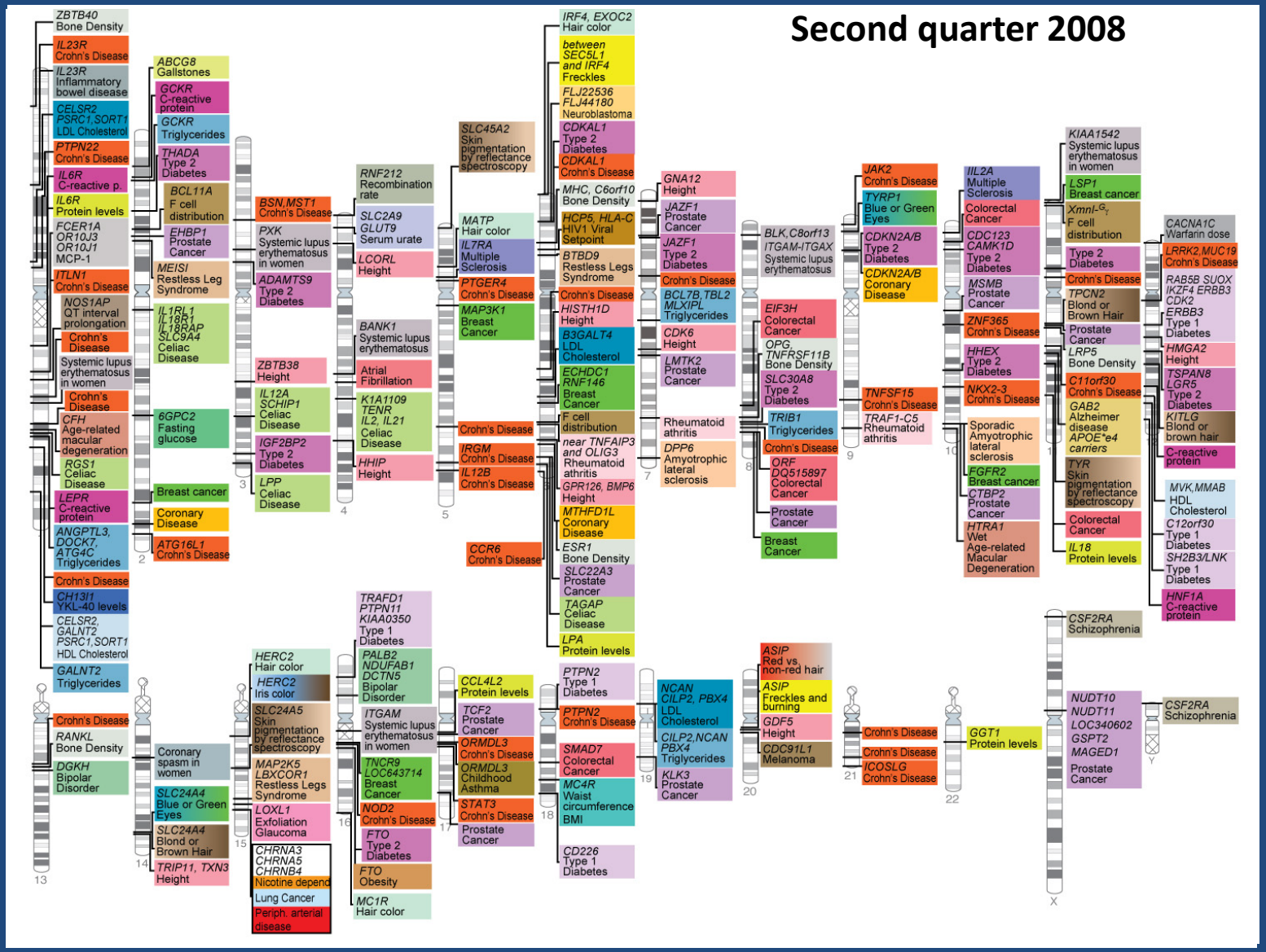
Bridging the translational divide
The Way it Should Work



La recherche biomédicale exige plus de collaborations interdisciplinaires

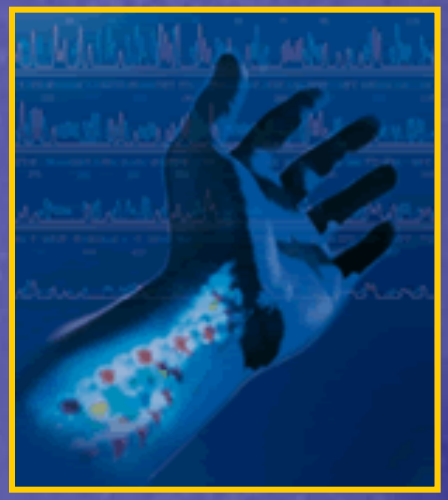


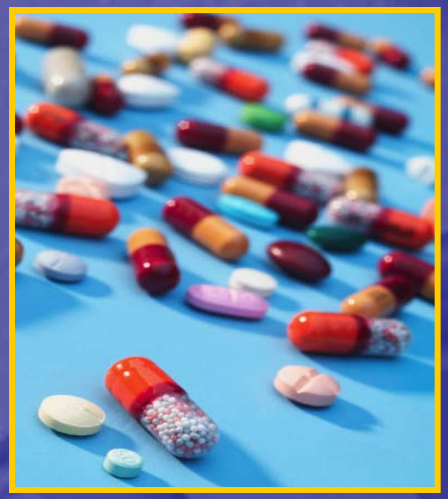
Vers une nouvelle ère en médecine:
Découvertes et Genome-wide Association



Manolio, Brooks, Collins, J Clin Invest 2008; 118:1590-625.

Pharmaco-Genomics: *Managing Human Variability*



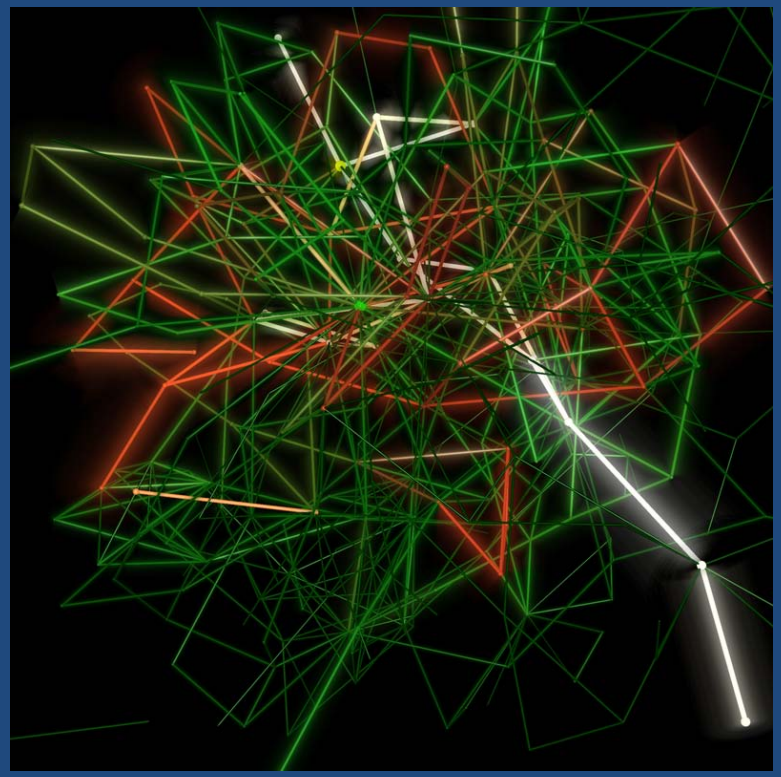


- Pharmaco-Genetics Research Network (PGRN)
  - National collaboration of scientists studying the effect of genes on people's responses to a wide variety of medicines
- Pharmaco-Genetics & Pharmaco-Genomics Knowledge Database (PharmGKB)
  - Integrated knowledge base for pharmacogenetics linking phenotypes and genotypes

http://www.nigms.nih.gov/Initiatives

Mapping Complexity

- **Mathematical model of *E.coli* metabolism**
- **Identifies “busy roads”**
- **Mammalian cells? Organs? Organisms?**



February 20, 2005

Elias A. Zerhouni, M.D., Director, NIH

The Roadmap Epigenome Program: the next step?

- Develop comprehensive epigenome maps from many cell types
- Develop standardized platforms, procedures, and reagents for epigenomics research
- Conduct demonstration projects to evaluate how epigenomes change in disease, with age, or following environmental exposures
- Develop new technologies for single cell epigenomic analysis and in vivo imaging of epigenetic activity
- Create a public data resource to accelerate the application of epigenomics approaches