NHLBI Strategic Plan: Future Opportunities for Lung Research

Elizabeth G. Nabel, M.D.

Director, National Heart, Lung, and Blood Institute

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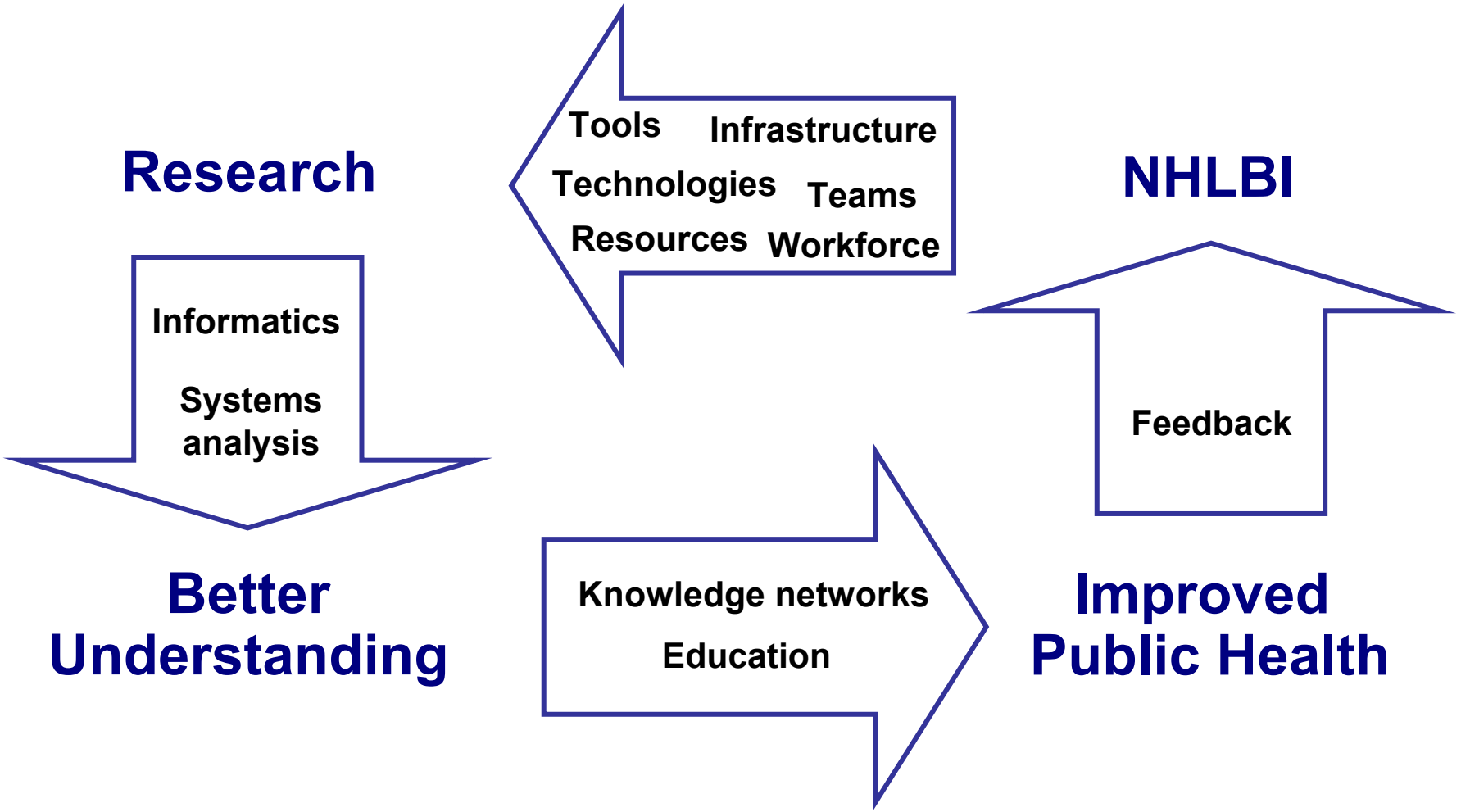
NHLBI's Strategic Plan Promotes Advances in Research Approaches



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Planning Principals

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NHLBI Strategic Plan Objectives

Develop a scientific blueprint for the next decade.

- A living, working plan from an inclusive and participatory process.
- Identify strategic priorities where NHLBI:
  - Initiates – *does not happen unless the Institute takes a lead*
  - Catalyzes – *Institute facilitates the outcome*
  - Supports – *investigator-initiated research*

NHLBI Strategic Plan Goals

Goal 1

Improve understanding of the molecular and physiologic basis of health and disease. Use that understanding to develop improved approaches to disease prevention, diagnosis and treatment. *Form → Function*

Goal 2

To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases. *Function → Cause*

Goal 3

Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery. *Cause → Cures*

NHLBI Strategic Plan Leads Toward Personalized / Pre-emptive Medicine

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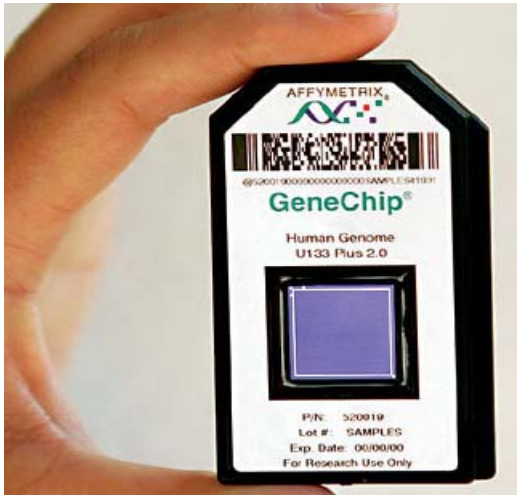
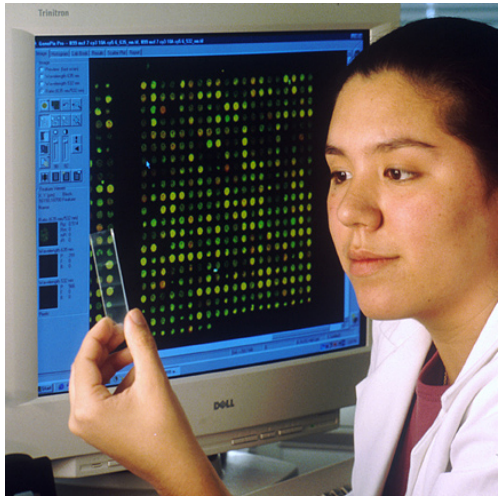
Need to Transform Medical Research in the 21st Century

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
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

The Future Paradigm: Transform Medicine from Curative to Preemptive





Predictive ⟷ Personalized ⟷ Preemptive

Participatory

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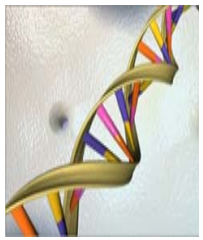
Path to Earlier Diagnosis, Better Prognosis, and Personalized Management

Barrier: Lack of well-defined pre-clinical lung phenotype
Asthma-specific SNP chip, co-developed with Affymetrix, will be validated by screening 5,000 Asthma samples.

Gene Expression Profiling reveals unique patterns which will

- Expedite Diagnosis
- Predict Response to Treatment
- Determine Likelihood of Exacerbation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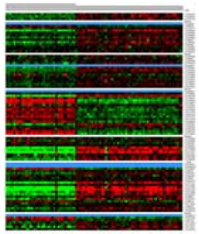
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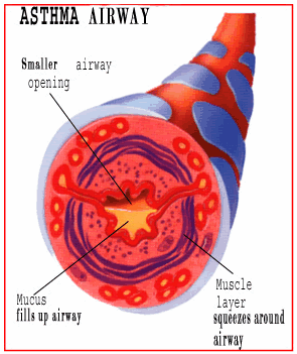

Molecular Phenotype

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Phenotypic Predictors for Prognosis and Choosing Therapies

- Young children with recurrent wheeze are a treatment dilemma
  - Just 1/3 have persistent asthma after age 6
  - Would daily therapy be appropriate for these children?
  - How can you identify and avoid unnecessary treatments for the remaining 2/3?
- API identifies phenotypic characteristics of those at highest risk

Asthma Predictive Index (API)

Identifies high risk children ages 2 & 3:

- **≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)**

PLUS

One major criteria	***OR***	**Two minor criteria**
Parent with asthma		**Food sensitivity**
Atopic dermatitis		**Peripheral eosinophilia (≥4%)**
Aero-allergen sensitivity		**Wheezing not related to infection**

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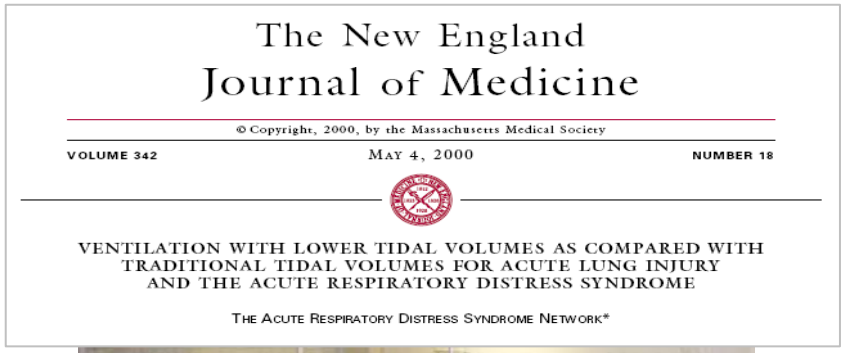
Prevention and Personalized Medicine for ARDS



The New England
Journal of Medicine

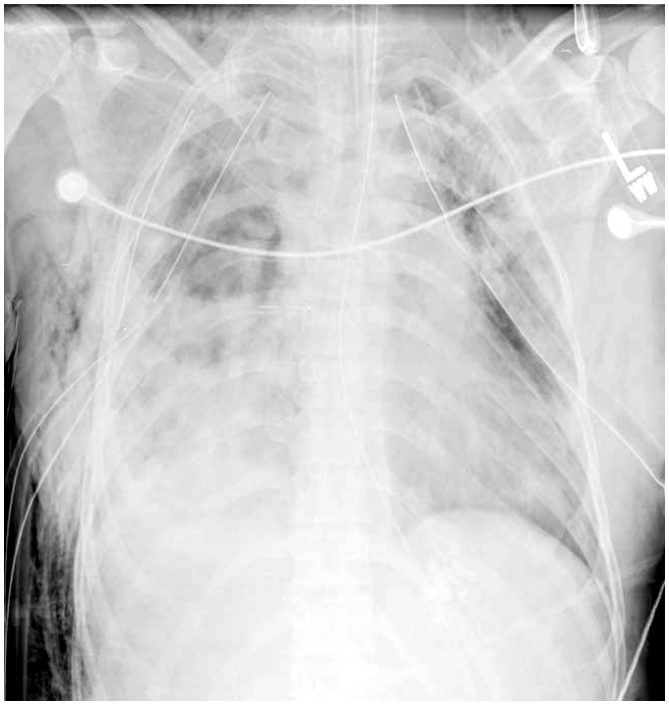
VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

Will earlier alterations in ventilation *prevent* ARDS?

Gajic and colleagues



Can ventilation settings be personalized?

Marini and others

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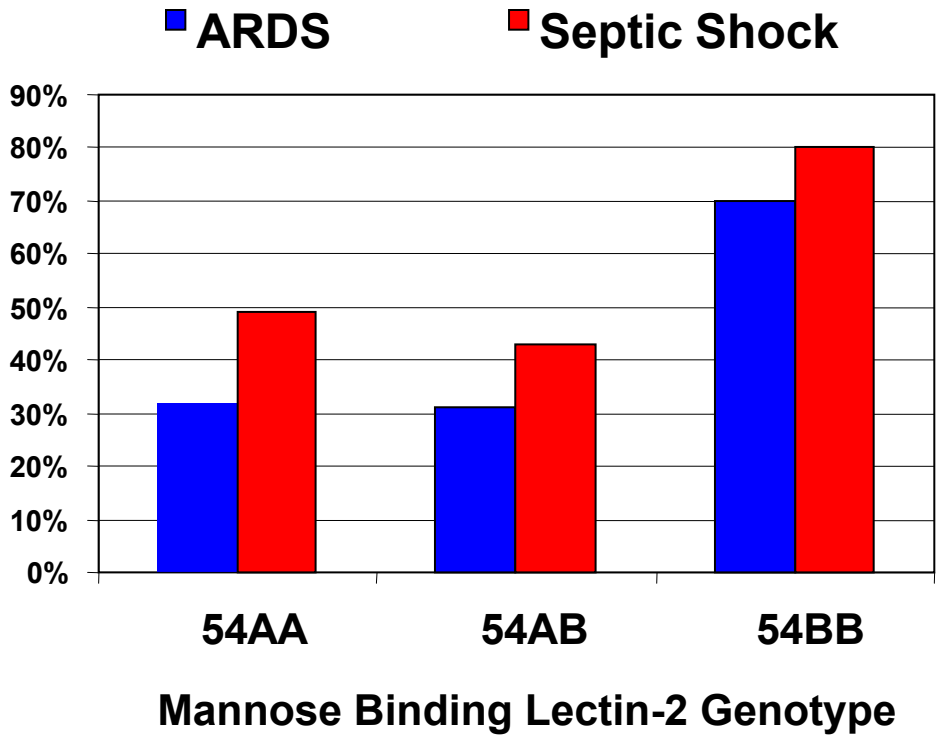
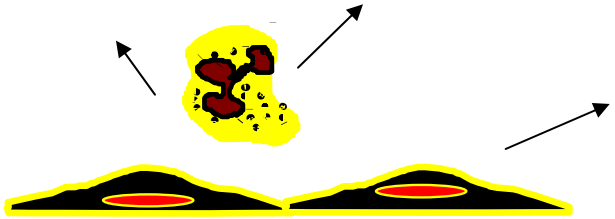
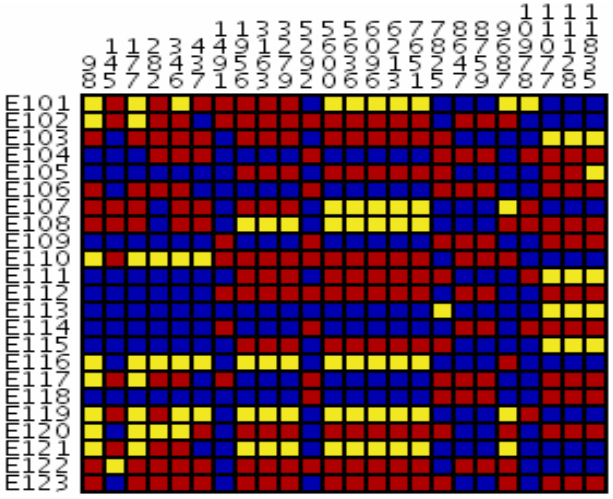
Molecular Prognosis/Diagnosis for ARDS?



Biomarkers



Genomics



Crit Care Med 35: 48, 2007 Gong et al

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Phenotypic Predictors for Disease Diagnosis

SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS)

A planned, multicenter observational study to:

- Phenotype 3000 patients with COPD
- Classify subpopulations by molecular & clinical characteristics
- Validate intermediate outcome measures

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Goal 3

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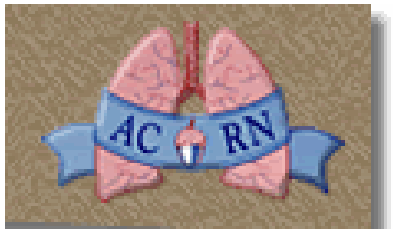
DLD Clinical Research Networks Excel in Translational Research



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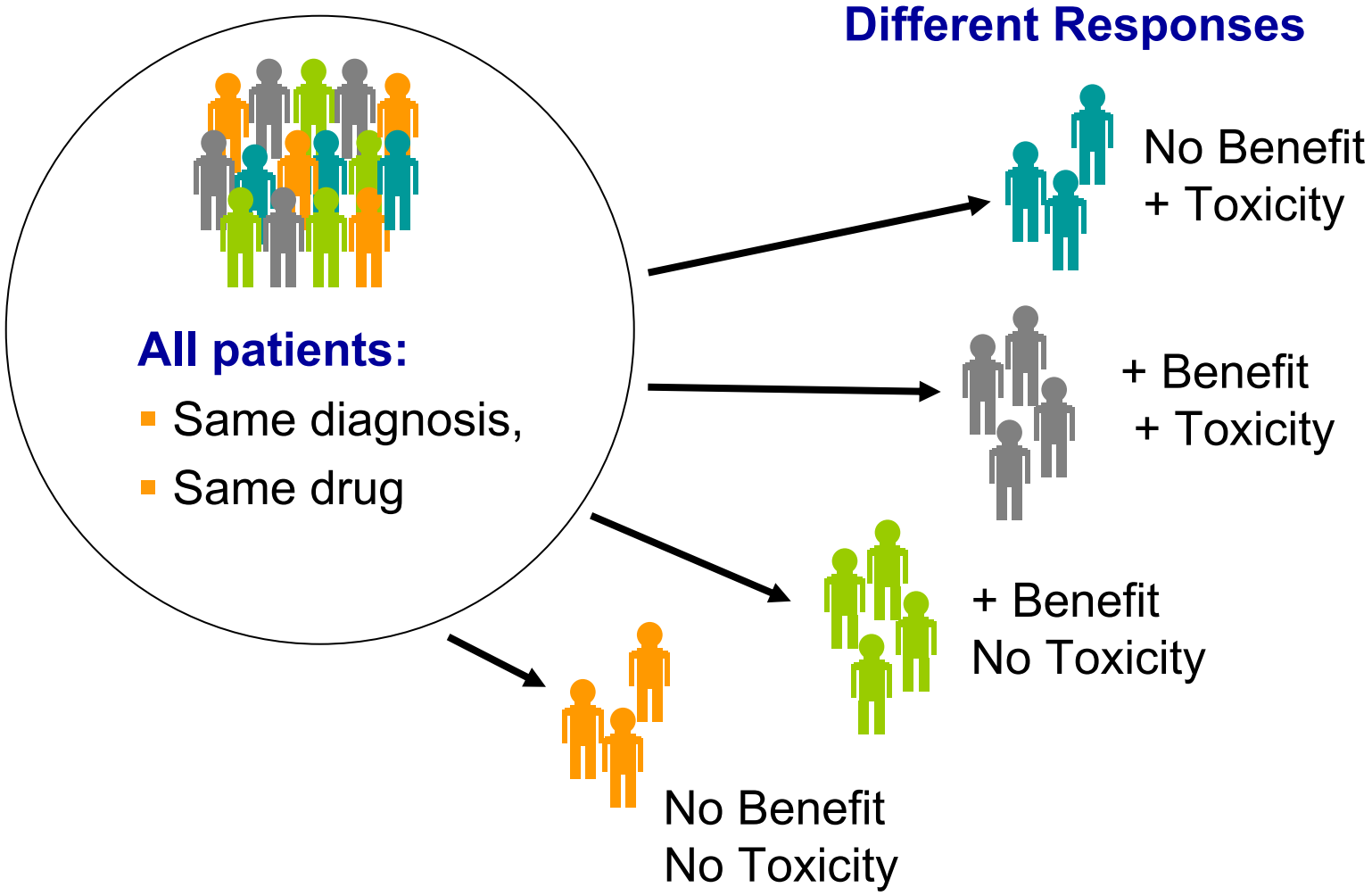
Variations in Drug Response



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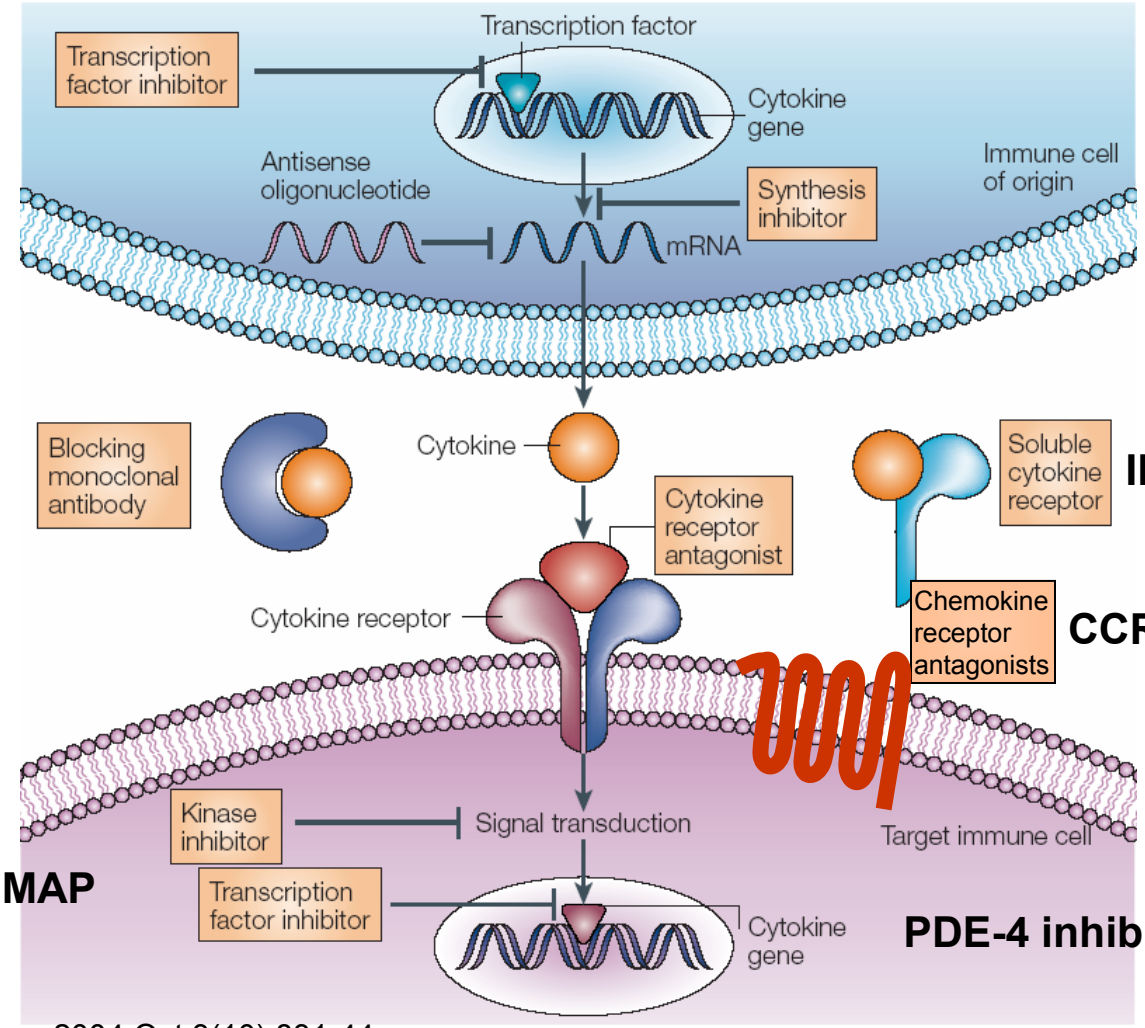
Targeted Drug Strategies to Prevent Disease Progression



Nat Rev Drug Discov. 2004 Oct;3(10):831-44.

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Personalized Medicine: Asthma as a Prototype

- Identification of b-adrenergic receptor polymorphisms
- Demonstration that different haplotype combinations affect agonist response and adverse effects in some patients
- Prospective studies which evaluate treatment response at the genetic level
- Therapeutic regimen based on individual genotype and phenotype

Genetic Predictors of Response

Am J Respir Crit Care Med 2002;162:75-80

The Effect of Polymorphisms of the β_2-Adrenergic Receptor on the Response to Regular Use of Albuterol in Asthma

ELLIOT ISRAEL, JEFFREY M. DRAZEN, STEPHEN B. LIGGETT, HOMER A. BOUSHEY, REUBEN M. CHERNIACK,

Lancet 2004;364:1505-12

Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial

Elliot Israel, Vernon M Chinchilli, Jean G Ford, Homer A Boushey, Reuben Cherniack, Timothy J Craig, Aaron Deykin, Joanne K Fagan, John V Fahy, James Fish, Monica Kraft, Susan J Kunselman, Stephen C Lazarus, Robert F Lemanske Jr, Stephen B Liggett, Richard J Martin, Nandita Mitra, Stephen P Peters, Eric Silverman, Christine A Sorkness, Stanley J Szefler, Michael E Wechsler, Scott T Weiss, Jeffrey M Drazen, for the National

Lancet 2004; 364: 1505–12
See Comment page 1464
Brigham and Women's Hospital

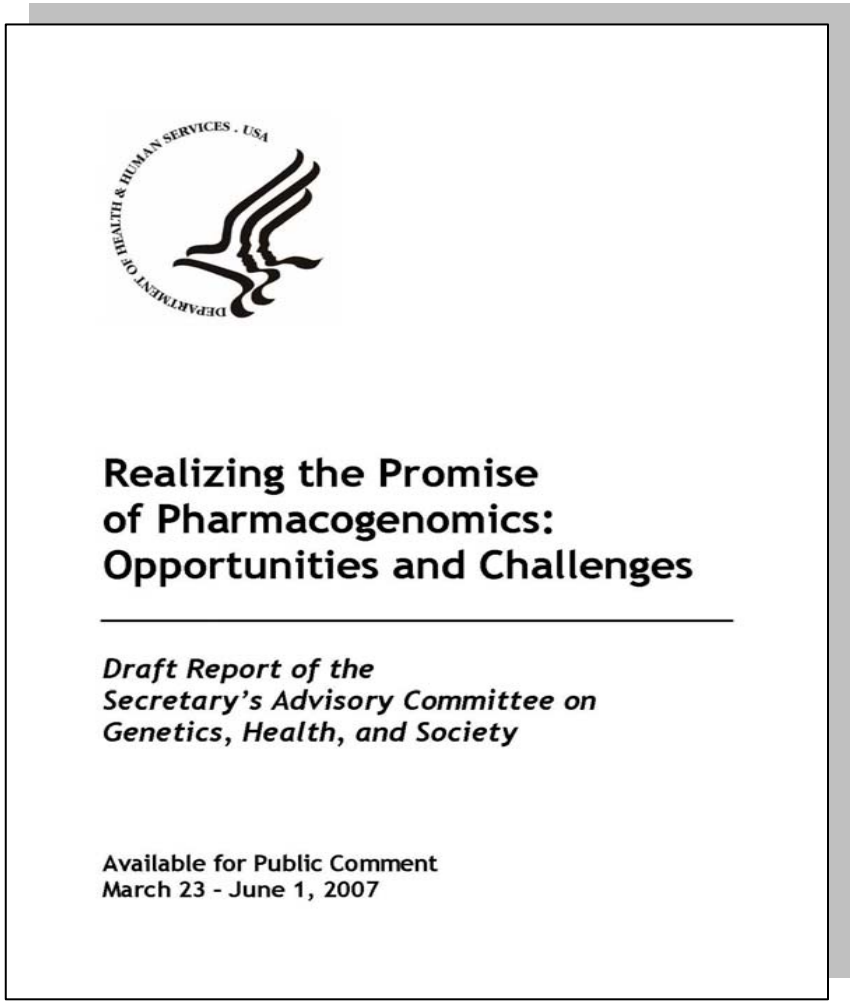
Am J Respir Crit Care Med 2006;173:519-26

β-Adrenergic Receptor Polymorphisms and Response to Salmeterol

Michael E. Wechsler, Erik Lehman, Stephen C. Lazarus, Robert F. Lemanske, Jr., Homer A. Boushey, Aaron Deykin, John V. Fahy, Christine A. Sorkness, Vernon M. Chinchilli, Timothy J. Craig, Emily DiMango, Monica Kraft, Frank Leone, Richard J. Martin, Stephen P. Peters, Stanley J. Szefler, Wenlei Liu, and Elliot Israel, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network

National Heart Lung and Blood Institute

Secretary's Advisory Committee



http://www4.od.nih.gov/oba/SACGHS/public_comments.htm

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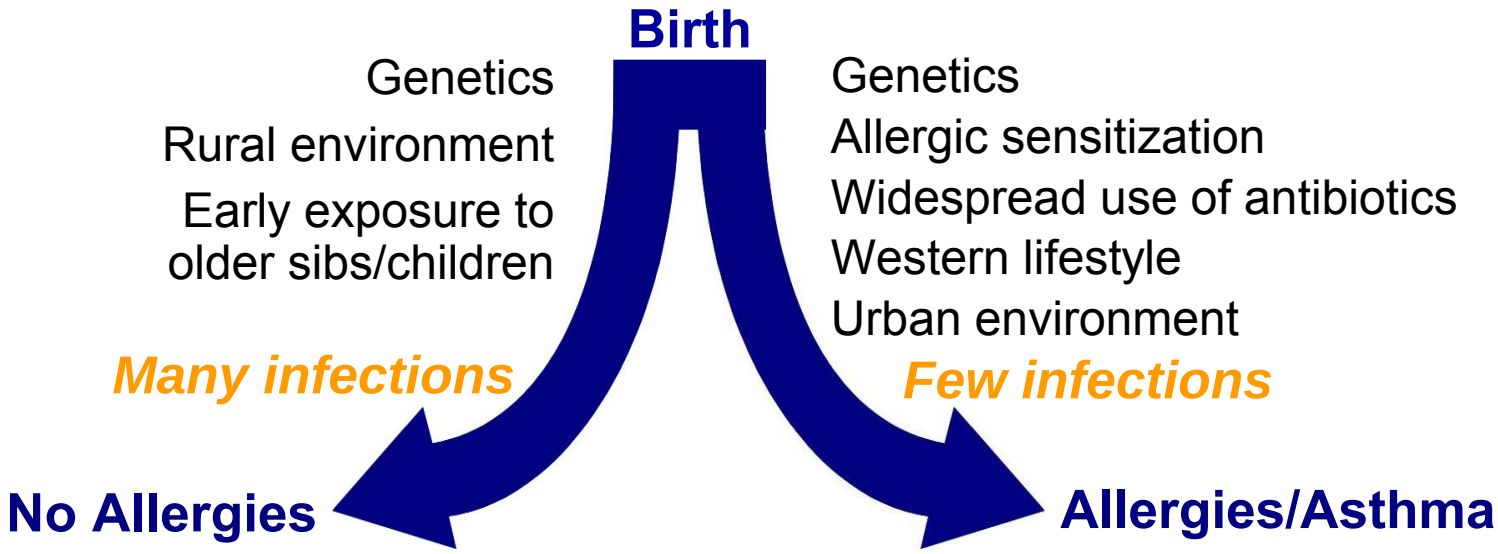
Strategies to Prevent Asthma

Potential Preventive Strategies

- Diet: probiotics
- Pharmacologics: leukotriene modifiers
- Immunomodulators: CpG oligodeoxynucleotides
- Protective exposures: dirt!



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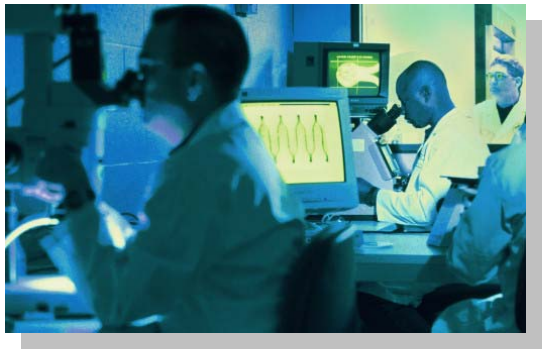
Training of New Clinical Investigators



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Participatory Research

National Asthma Education and Prevention Program

Guidelines Development and Utilization	Partnership Activities	Community Targeted Activities	FLGA Collaborations
▪ Update 2002	▪ Guidelines Implementation Working Group	▪ Asthma Coalitions Contracts	▪ Congressional Report and Inventory
▪ Update 2006	▪ Asthma Managed Care Initiative: Respiratory Therapists	▪ Coalition Outreach and Support	▪ DHHS Action Against Asthma
▪ Pregnancy Guidelines	▪ Emergency Department Approaches to Care	▪ School Based Initiative	▪ Data Fact sheet
▪ HP 2010 Progress Review	▪ MDI Transition Initiative	▪ World Asthma Day	▪ JOSH Special Issue School Lessons Learned
▪ HEDIS	▪ Physician Asthma Care Program	▪ Reducing Asthma Disparities Workshop	▪ Public Housing Initiative HUD/NHLBI
▪ RAND Policy Report	▪ Physician Asthma Care Education Program	▪ AHRQ State Leader Manual	▪ Cross-Agency Collaborations (CDC/NIAID; CMS; HRSA/EPA)
▪ Asthma 2003 Conference	▪ Screening for Asthma in Children Project		
▪ Pt. Education Booklet			

Participatory Research

- Integrate campaign into organizational activities
- Provide distribution vehicle
- Set up Web link
- Offer spokespeople

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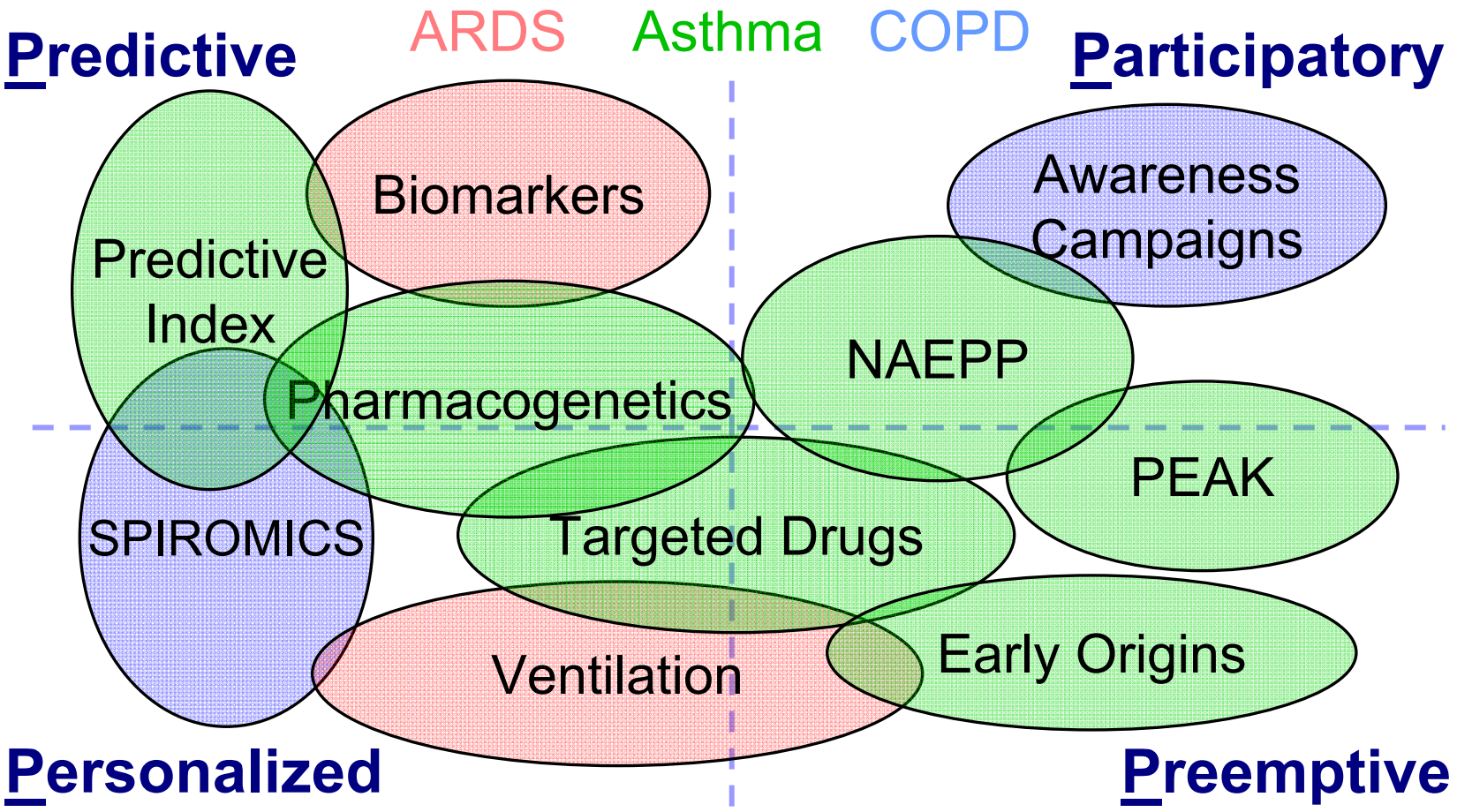
The Strategic Plan and Innovative Lung Research Promote NIH Goals for Transformation of Medicine



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NIH Core Strategic Vision

- Transform medicine and health from a Curative to a Preemptive paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community
- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system

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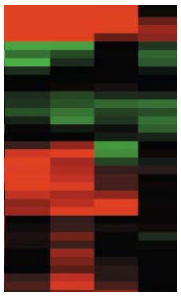
Future Directions

Basic Discovery **Clinical** **Communication**



Genomics

Proteomics

Stem Cell Research
Tissuegenesis

Cell Imaging
Translational

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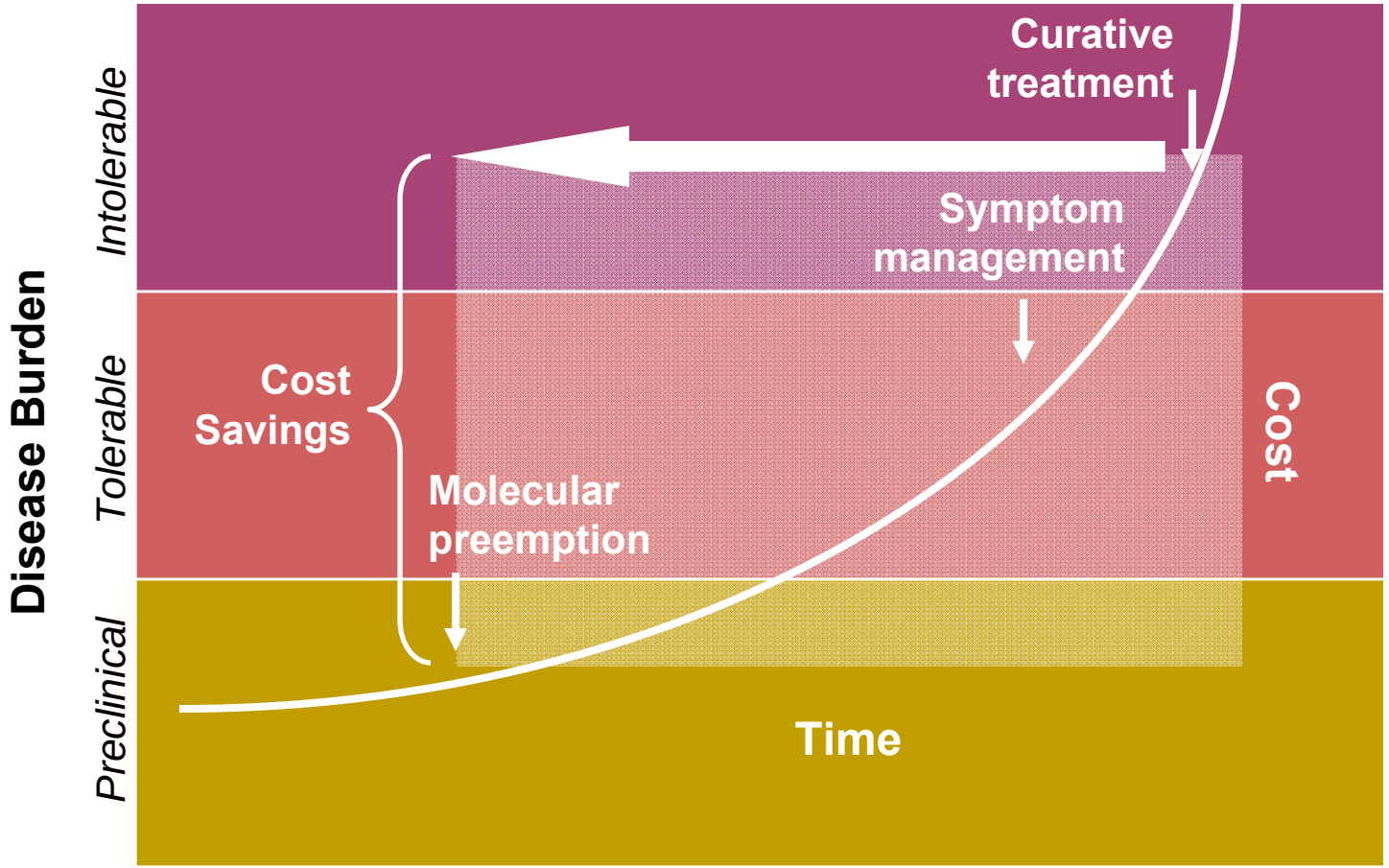
The Future Paradigm: Preempt Disease



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Statewide Program

JOURNAL OF SCHOOL HEALTH
Official Journal of the American School Health Association

Statewide Asthma Training for Minnesota School Personnel

Janet Keysser, Patricia L. Splett, Susan Ross, Erica Fishman

- MN Dept of Health Strategic Plan on Asthma builds on NAEPP Guidelines and CDC State Initiatives
- Healthy Learner's Asthma Initiative creates asthma friendly school policies and education programs

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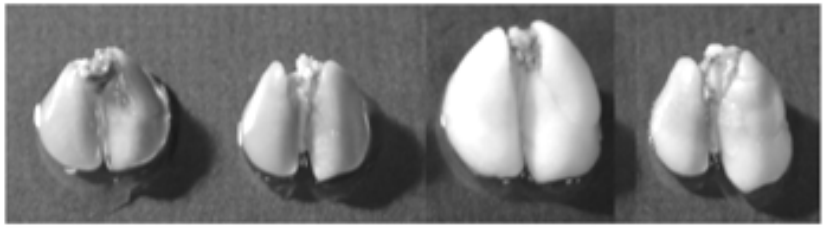
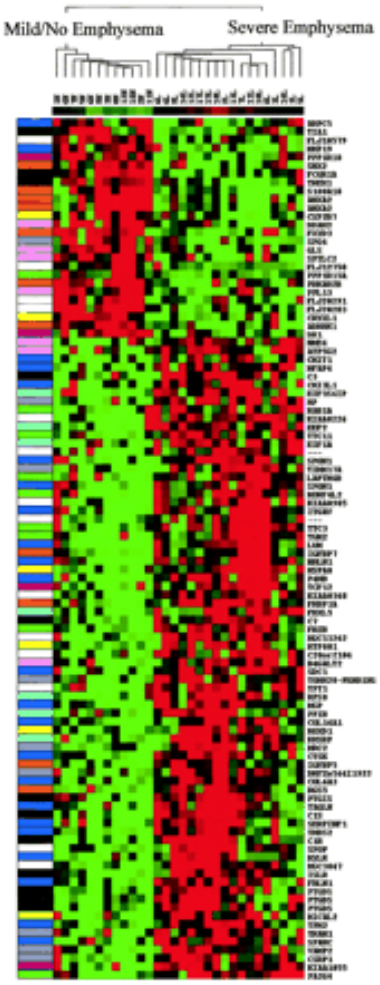
Discovery: COPD Research Is Rapidly Advancing

Challenge is to integrate data from

- Clinical studies
- Biomarker analyses
- Histopathology
- Genomics / Genetics
- Animal models



Lanone, et al., JCI 2002; 110:463.



Spira, et al., AJRCCM 2004; 31:601.

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Goal One: Form to Function

Goal 1: To improve understanding of the molecular and physiological basis of health and disease and use that understanding to develop improved approaches to disease diagnosis, treatment, and prevention.

Challenge 1.1

To delineate mechanisms that relate molecular events to health and disease.

- **1.1.a** Develop a detailed understanding of the molecular, cellular, and physiological mechanisms that maintain health from embryonic development to the end of the human lifespan.
- **1.1.b** Identify intracellular targets of key signaling and transcriptional pathways in normal and pathologic states.
- **1.1.c** Determine key genetic variants that are associated with specific diseases and delineate the molecular mechanisms that account for susceptibility or resistance to disease.
- **1.1.d** Define molecular, cellular, and organ-specific responses to environmental challenges, and the mechanisms by which heritable and non-genetic factors interact in disease initiation and progression and in therapeutic response.
- **1.1.e** Determine the role of systemic pathological processes, such as inflammation, immunity, and infection, in the development and evolution of disease.

Goal One: Form to Function

Challenge 1.2

To discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention, diagnosis – including imaging, and therapy.

1.2.a Identify molecular signatures that allow complex disease phenotypes to be stratified into clinically relevant categories.

1.2.b Develop *in vivo* molecular imaging methods and probes for investigating the biology of disease processes.

Goal Two: Function to Causes

Goal 2: To improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis and treatment.

Challenge 2.1

To accelerate translation of basic research findings into clinical studies and trials and to promote the translation of clinical research findings back to the laboratory.

- **2.1.a** Integrate advances in regenerative biology to develop clinically feasible applications.
- **2.1.b** Apply discoveries in nanotechnology to the development of new diagnostic and therapeutic strategies.
- **2.1.c** Integrate, analyze, and share extant and emerging genotypic and phenotypic data.

Challenge 2.2

To enable early and accurate risk stratification and diagnosis of cardiovascular, lung, and blood disorders.

- **2.2.a** Exploit noninvasive imaging methods to detect and quantify subclinical disease.
- **2.2.b** Apply new discoveries in biomarkers to improve risk assessment, diagnosis, prognosis, and prediction of response to therapy.

Goal Two: Function to Causes

Challenge 2.3

To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.

- **2.3.a** Improve the understanding of the interactions between genetic and environmental factors that influence disease development and progression and response to therapy.
- **2.3.b** Identify and evaluate interventions to promote health and treat disease in genetically defined patient subgroups by altering developmental or environmental exposures including drugs, diet and exercise, sleep duration and quality, and infectious agents and allergens.

Challenge 2.4

To enhance the evidence available to guide the practice of medicine, and improve public health.

Goal Three: Causes to Cures

Goal 3: To generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

Challenge 3.1

To complement bench discoveries and clinical trial results with focused behavioral and social science research.

- **3.1.a** Develop and evaluate new approaches to implement proven preventive and lifestyle interventions.
- **3.1.b** Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support lifestyle changes.
- **3.1.c** Develop and evaluate interventions to improve patient, provider, and health system behavior and performance in order to enhance quality of care and health outcomes.

Goal Three: Causes to Cures

Challenge 3.2

To identify cost-effective approaches for prevention, diagnosis, and treatment.

- **3.2.a** Evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.
- **3.2.b** Develop research designs, outcome measures, and analytical methods to assess prevention and treatment programs in community and health-care settings across populations and lifespan.

Challenge 3.3

To promote the development and implementation of evidence-based guidelines in partnership with individuals, professional and patient communities, and health care systems and to communicate research advances effectively to the public.

- **3.3.a** Establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge.
- **3.3.b** Develop personalized and community- and health care system-oriented approaches to increase the use of evidence-based guidelines by individuals, communities, health care providers, public institutions, and, especially, by populations that experience a disproportionate disease burden.
- **3.3.c** Communicate research advances effectively to the public.

Preventing Early Asthma in Kids

Randomized Trial in Children with Recurrent Wheeze and Positive API

Results:

- Symptoms returned when daily therapy was withdrawn
- Daily inhaled corticosteroids significantly reduced symptom days and need for oral steroids
- Daily therapy did not prevent progression of disease

Conclusions:

- The API is a valuable clinical tool for selecting young wheezers who will benefit from daily therapy
- Research to discover treatments to prevent disease is needed