Genetics and Workplace Issues

PA Schulte, Ph.D.

CDC

NIOSH

- Genetic information could be useful in protecting workers
- However, literature on the role of genetic factors in occupational disease and injuries is relatively sparse
- Use of genetic markers in research and intervention (clinical and regulatory) requires attention to real and perceived social power of the information


Discovery
Validation
Application

- Experimentation
- Observation
- Analysis

- Experimentation
- Observation
- Analysis

- Laboratory Validation
- Population Validation
- ACCE

Model Process for Evaluating Data on Emerging Genetic Tests

Analytical validity

Clinical validity

Clinical utility

ELSI considerations

- 44 target questions aimed at a comprehensive review of a candidate test
- http://www.cdc.gov/genomics/info/perspectives/files/testACCE.htm

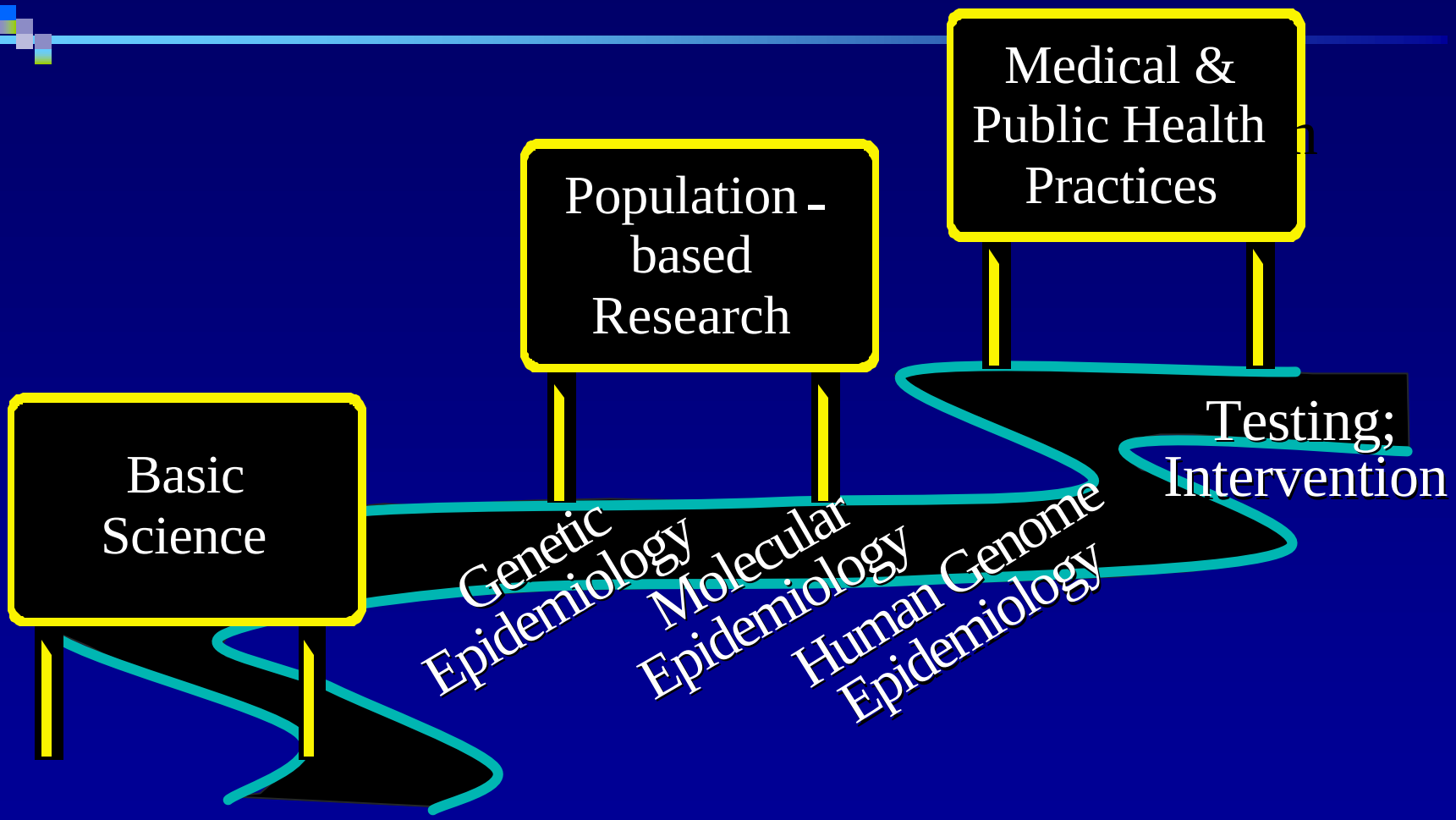
Analytical validity – the ability of the test to measure the genotype accurately and reliably

Clinical validity – ability of test to detect or predict the associated disorder (phenotype)

Clinical utility – risks and benefits associated with introduction of the test into routine clinical practice

ELSI – safeguards and untoward effects or impediments (e.g., stigmatization, discrimination, privacy, informed consent, ownership, results reporting)

Continuum from Basic Science to Medical & Public Health Practice

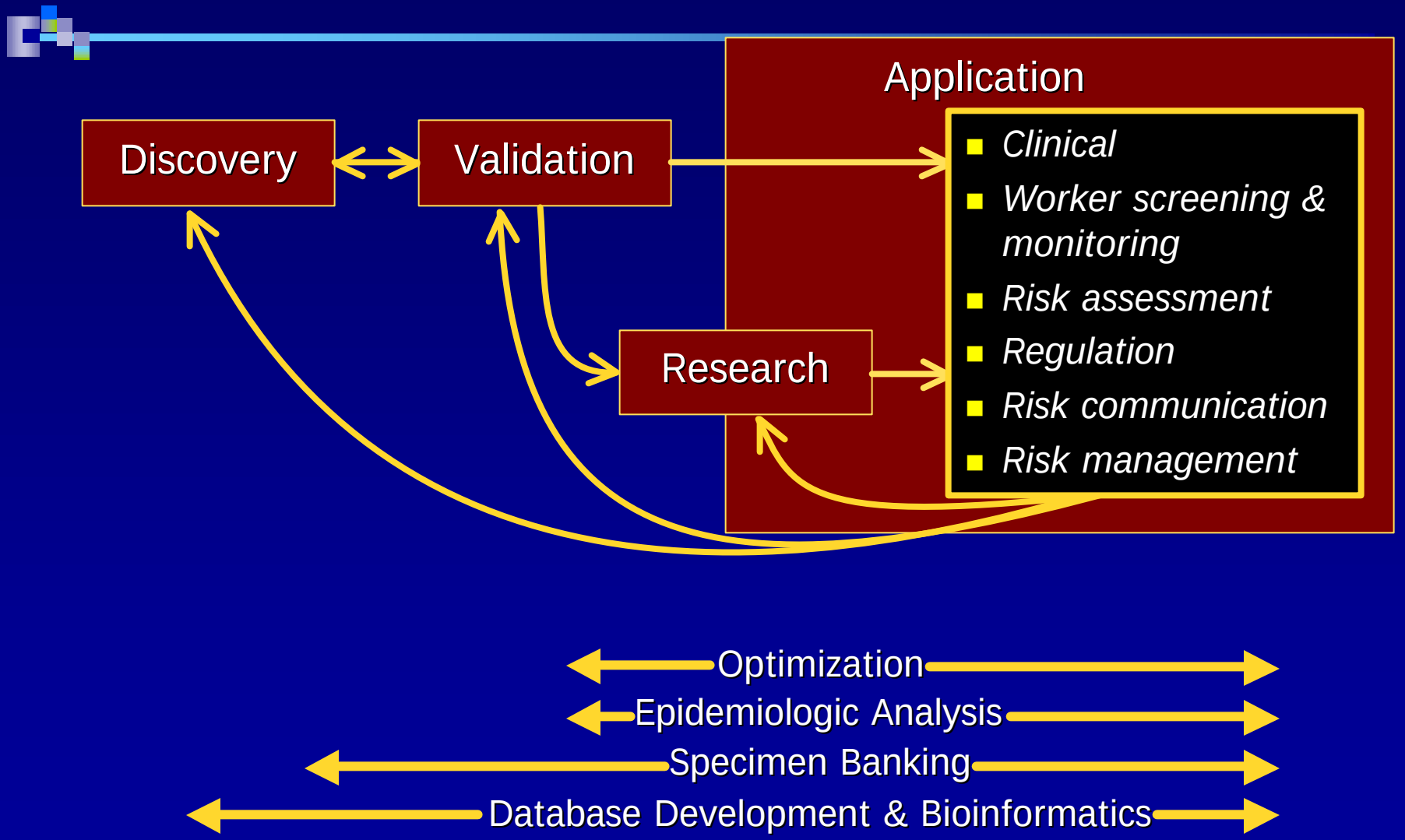


Genetics; Molecular Biology; Biochemistry; Analytical Chemistry

- Experimentation
- Observation
- Analysis

- Laboratory Validation
- Population Validation
- ACCE

- Clinical
- Worker screening & monitoring
- Risk assessment
- Regulation
- Risk communication
- Risk management


Application
Discovery
Validation
Research
Clinical
Worker screening & monitoring
Risk assessment
Regulation
Risk communication
Risk management
Optimization
Epidemiologic Analysis
Specimen Banking
Database Development & Bioinformatics

Strengthen Risk Assessments

- Stratified estimates
- Covariate adjustments
- Modify E – D associations
- Clarify mode of action

GSTTI & Risk Estimates of Methylene Chloride

- Monte-Carlo simulation + PBPK models
- Median estimate 30% higher when GSTTI polymorphism not included

(El-Masri et al., 1999)

Enhance Risk Characterization

- Target subgroups
- Heighten controls

How do you genetically characterize workers?

- Collection of DNA
  - Voluntary or involuntary
- Who owns and controls information?
- What happens to high-risk subgroup?
  - Stigmatization
  - Medical removal
  - Prejudicial actions
- What happens to those not in high-risk group?

Sec 6 (b) 5 of the OSH Act

"... shall set the standard which most adequately assures, to the extent feasible ... that no employee will suffer material impairment of health ... even if the employee has regular exposure to the hazard ..."

Lessons

Relative importance of genetic polymorphism

GSTT1 and ethylene oxide

Utility in job acceptance/placement

Glu 69 and beryllium

Apportionment of Causation

PMP22 and carpal tunnel syndrome

GSTT1 and Ethylene Oxide Exposure

- Ethylene oxide - human carcinogen (IARC)
- 2–fold higher risk of hemoglobin adducts in GSTT1 null genotypes

What to tell participants

- Group risk to individual risk assessment
- *Variables* R^2

GSTT1	4%
Smoking	28%
Ethylene oxide	30%

- Small, transitional study

  “. . . risk uncertain”

Beryllium and HLA DPB1^{E69}

- Risk of CBD with Glu 69 variant; OR = 85 (11-3578) *(Richeldi et al, 1993)*
- Should prospective employees be screened prior to employment

Beryllium and HLA DPB1^{E69}

- Predictive Value 7-9%
- Other Suspected Variants on Ch6
- No curative treatment for CBD
- CBD occurred in relatively well-controlled areas

Carpal Tunnel and PMP 22

- Tested railroad workers with CTS claim or report
- Test not for CTS but for HNPP
- *Test was inappropriate*
  - hereditary factors rare in CTS
  - PMP 22 deletions - rare
  - test not validated

Apportionment of Causality

- Should genetic traits be factored into claims of work-relatedness of disease
- Most workers' comp statutes permit medical testing including genetic testing
- Most U.S. professional organizations do not condone genetic testing without informed consent

Promise:

Understanding disease of genetic and molecular level

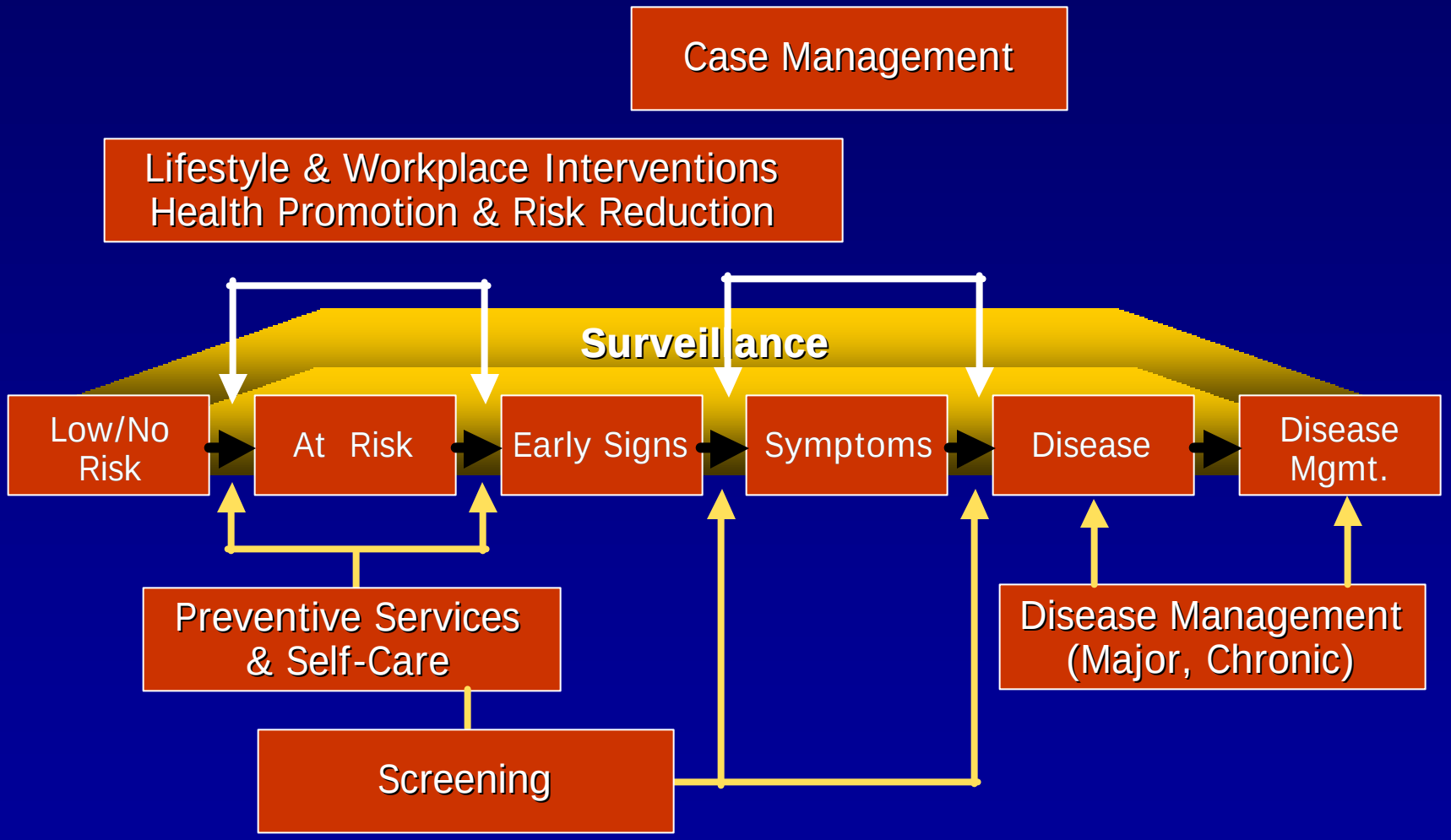
Disease will be subject to truly scientific classification, analysis, and treatment.

Promise is inadequate and misleading

- The presentation of genetic disease and abnormal genetic function is not self-announcing.
- Genes generally do not “cause” disease.
- Moving the level of diagnoses down to the molecular level does not succeed in avoiding the fundamental value judgments defining health and disease.

(Lloyd, 1998)

Framework for Using Biomarkers



(Adapted from Musich et al., 1999)

Extension of Biomedical Paradigm

- Use genetic information like other risk factor information
- Dealing with “worried well”
- Interventions
- Costs

Social Implications

- Reductionism
- Shifts emphasis from environmental control
- Changes focus of public health
- Unequal distributions of benefits and burdens

Is it appropriate to use genetic information to identify individuals with increased risk of occupational disease?

Ultimately for clinical and public health applications there is a need for a *population perspective* on genetic markers

- Prevalence
- Distribution by groups
- Predictive value of tests

Interpretation of Genetic Data for Medical and Public Health Uses

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CDC

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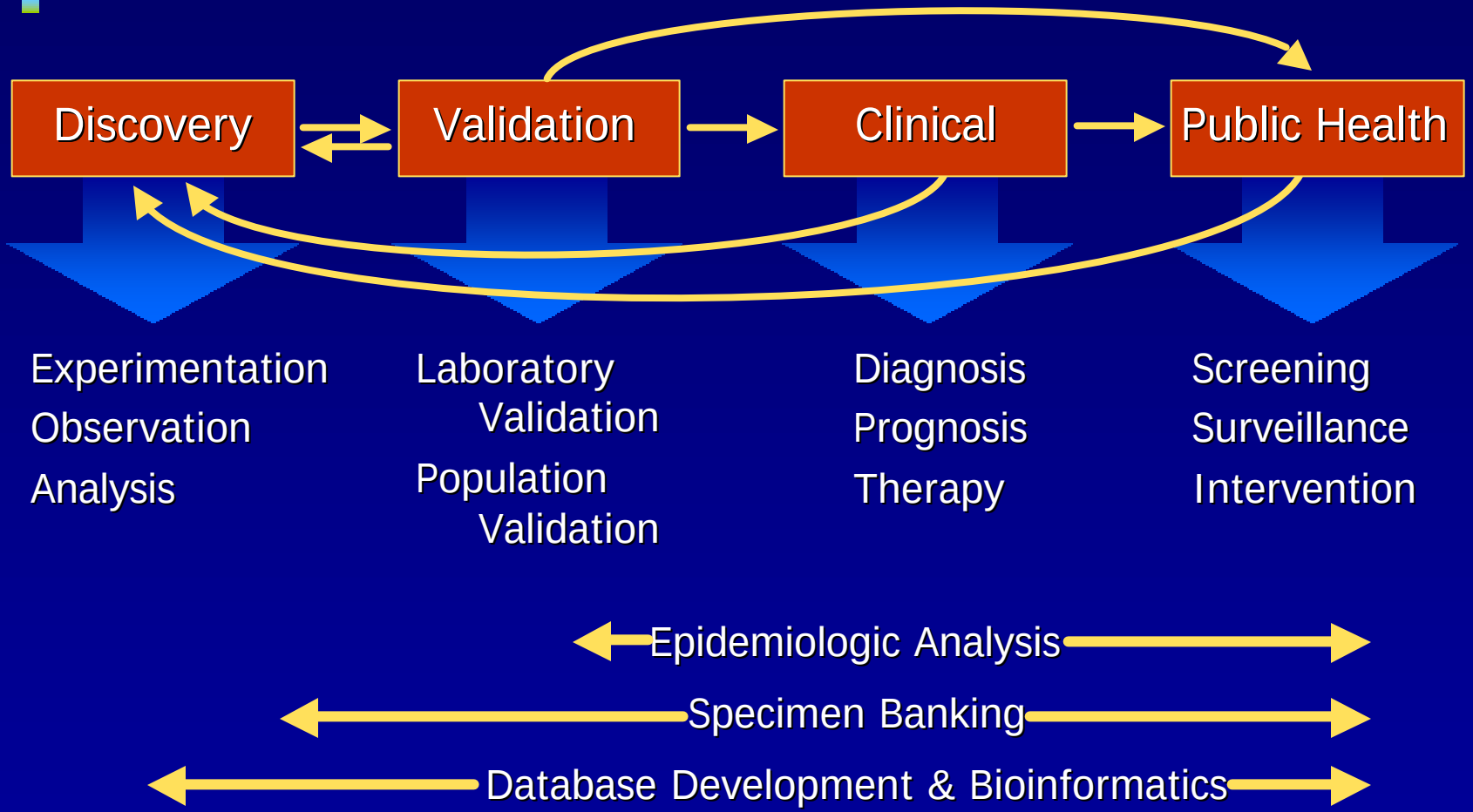
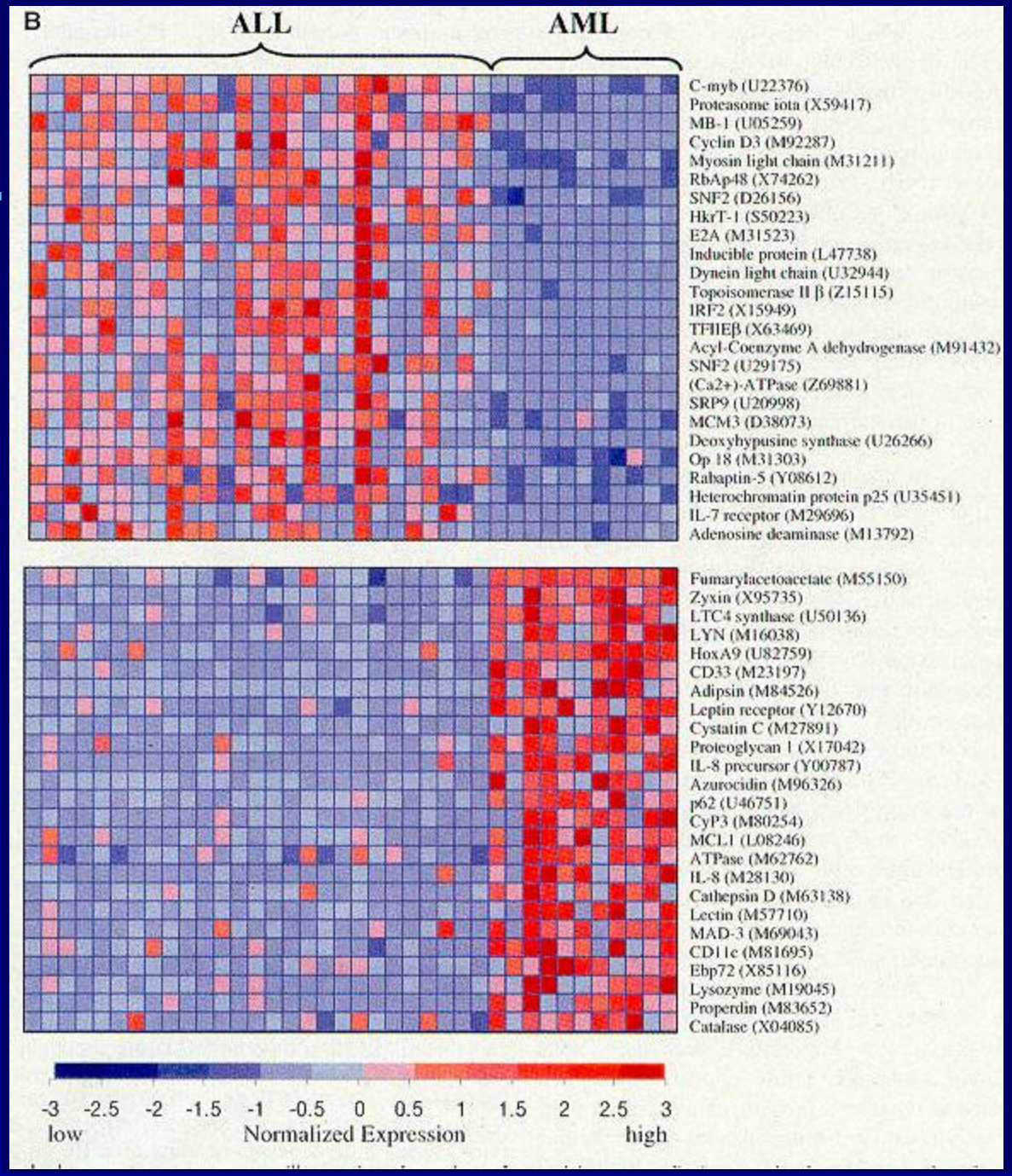
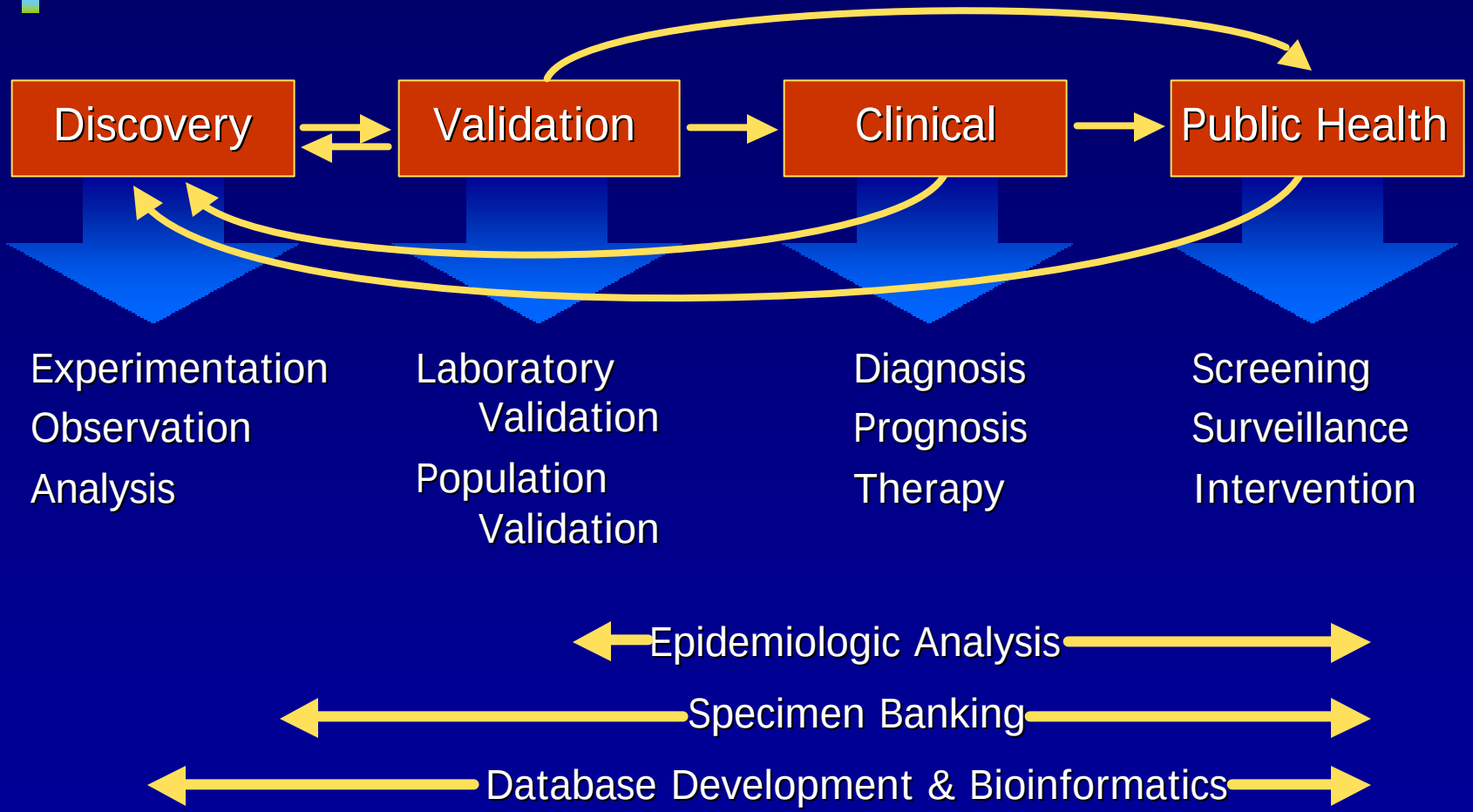
Continuum of Biomarker Development & Use



(Schulte, 2004)


B
ALL
AML
C-myb (U22376)
Proteasome iota (X59417)
MB-1 (U05259)
Cyclin D3 (M92287)
Myosin light chain (M31211)
RbAp48 (X74262)
SNF2 (D26156)
HkrT-1 (S50223)
E2A (M31523)
Inducible protein (L47738)
Dynein light chain (U32944)
Topoisomerase II β (Z15115)
IRF2 (X15949)
TFIIEβ (X63469)
Acyl-Coenzyme A dehydrogenase (M91432)
SNF2 (U29175)
(Ca2+)-ATPase (Z69881)
SRP9 (U20998)
MCM3 (D38073)
Deoxyhypusine synthase (U26266)
Op 18 (M31303)
Rabaptin-5 (Y08612)
Heterochromatin protein p25 (U35451)
IL-7 receptor (M29696)
Adenosine deaminase (M13792)
Fumarylacetoacetate (M55150)
Zyxin (X95735)
LTC4 synthase (U50136)
LYN (M16038)
HoxA9 (U82759)
CD33 (M23197)
Adipsin (M84526)
Leptin receptor (Y12670)
Cystatin C (M27891)
Proteoglycan 1 (X17042)
IL-8 precursor (Y00787)
Azurocidin (M96326)
p62 (U46751)
CyP3 (M80254)
MCL1 (L08246)
ATPase (M62762)
IL-8 (M28130)
Cathepsin D (M63138)
Lectin (M57710)
MAD-3 (M69043)
CD11c (M81695)
Ebp72 (X85116)
Lysozyme (M19045)
Properdin (M83652)
Catalase (X04085)
-3 -2.5 -2 -1.5 -1 -0.5 0 0.5 1 1.5 2 2.5 3
low
Normalized Expression
high

Continuum of Biomarker Development & Use



(Schulte, 2004)

Three Interpretative Issues

- Need for population thinking about genetic information
- Extension of the biomedical paradigm on risk
- Attention to application in qualitative and quantitative risk assessments

Population Thinking

- A way to view variation
- Uniqueness of everything in the natural world
- Contrasted with Essentialism

The uniqueness of biological individuals means we must approach groups of biological individuals in a very different spirit than the way we deal with inorganic entities.

(Mayr, 1982)

Differences in inorganic entities are due to measurement error.

Differences between biological individuals reflect variation.

Need Genetic Data + Population Data to Delineate Variation

Includes:

- Distribution and frequencies of the types of genes, phenotypes, and functions associated with genes.
- Range of environmental variables and parameters of reaction.

(Lloyd, 1998)

Most cases of disease do not arise from the high-risk tail of the risk factor distribution.

Most arise from the mass of the population with risk factor values close to the average.

Continuum of disease risk associated with most exposures. The decision to label a specific exposure level as demarcating low-risk versus high-risk is often arbitrary.

(Rockhill, 2000)

The diversity of theories and models involved in implementing the Human Genome Project provides a unique challenge to both producers and consumers of DNA-sequencing information.

(Lloyd, 1998)

Picture of disease represented by Human Genome Project is over simplified.

Molecular techniques offer an unprecedented amount of social power to label persons as diseased or at risk.

Describing genes as “causing” disease is, on a basic scientific level, to confuse at least two distinct levels of theory and description.

Risk Assessment

Provide society with estimates of the likelihood of illness or injury resulting from exposure to various hazards.

- When social policy decisions are in dispute
- When alternative policies in question are not subject to direct measurement
- When scientific analysis of a hazard is not complete

Risk Assessment

- Group or population level
- Individual level

Goal of Genetic Epidemiology

Extend search for risk factors into the human genome to uncover high-risk individuals who were hitherto hidden with exposures defined by conventional lifestyle or environmental factors.

(Rockhill, 2000)

Risk

Impact on Employers

- Do they focus more on changing the worker instead of the environment?
- Do they have different liability?

Prevention Paradox

A preventive measure that brings large benefits to the community offers little to each participating individual.

(Rose, 1985)

Prevention Paradox

The population strategy offers only a small benefit to each individual since most of them are going to be all right anyway, at least for many years.

(Rose, 1985)

Prevention Paradox

High-risk individual strategy
addresses interventions appropriate to individuals advised to take them

vs.

Population strategy
control determinants of incidence, to lower the mean level of risk, to shift the whole distribution in a favorable direction

Population Thinking and the Role of the Individual

Uniqueness of individuals —

Darwin believed that the struggle for existence due to competition was a phenomenon of individuals, not species.

Issues In Genetic Testing In The Workplace

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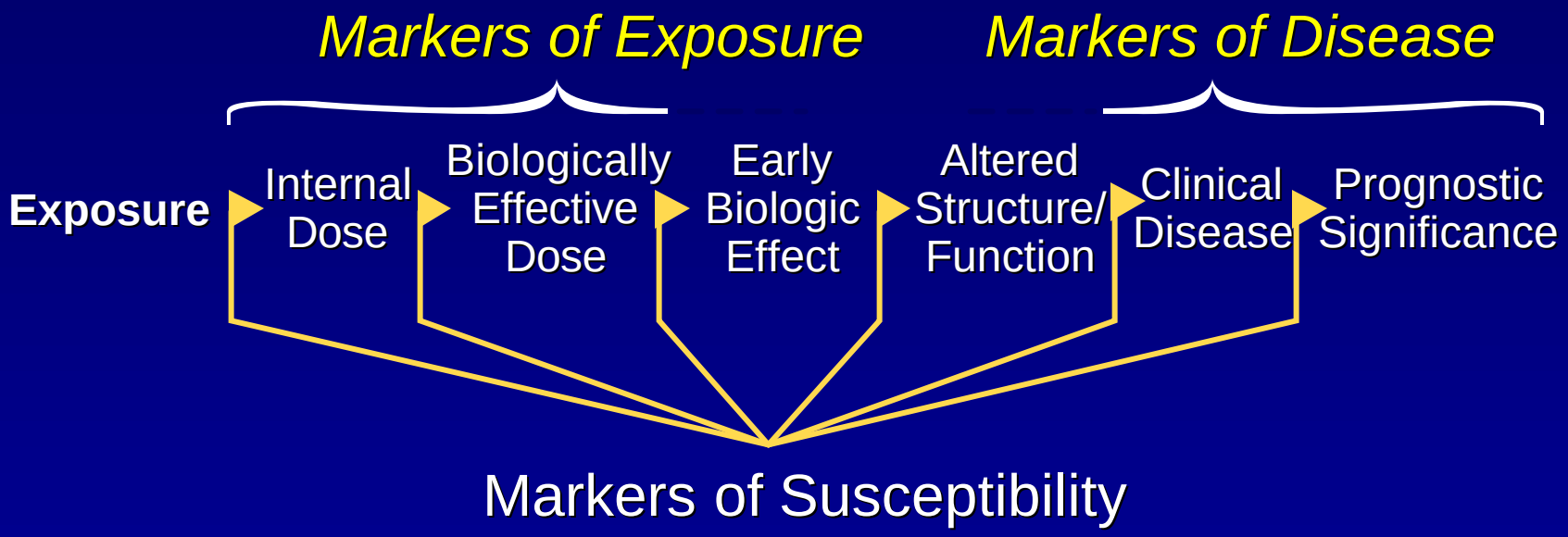
CDC Workplace Safety and Health

NIOSH


Markers of Exposure
Markers of Disease
Exposure
Internal Dose
Biologically Effective Dose
Early Biologic Effect
Altered Structure/ Function
Clinical Disease
Prognostic Significance
Markers of Susceptibility

- Rights Of Participants
- Validity and Clinical Utility
- Actions Resulting from Biomarker Information
- Social Implications

Then

Little guidance on low penetrance gene variants

Now

Beskow et al. (JAMA 2001;10:538-50)

- Inform when clinically relevant
- In workplace: when enabling preventive action

Employer Provided

- Anonymous, voluntary third party testing
- Employee received individual results
- Employer received group results

Issues in Genetic Screening

- Genetic exceptionalism
- How it fits into prevention and detection paradigm
- Not a neutral technology

Should Genetic Traits Be Used To Apportion Causation?

- Beyond worker's control
- Unlikely to find in a small group
- Legal in workers' comp

Microarray Output

- Will amplify issues found with single genes
- Interpretation/factorial fallacy
- Need for standardization, data sorting and reduction
- Need for transitional research
- Departs from traditional laboratory medicine

“Exclusion of workers as a result of genetic testing runs contrary to the spirit & intent of the OSH Act of 1970. It wrongly puts the burden of controlling toxic substances on the worker who is denied employment because of a supposed sensitivity.

Employers should make the workplace safe for all workers, rather than deprive some workers of their livelihood in the name of safety.”

(Bingham, 1980)

If epidemiologists direct their efforts toward a comprehensive search for the genetic underpinnings of every discrete health outcome, and ignore environmental exposures and attributable risk, we will miss an opportunity to prevent disease.

Millikan, 2002

Upholding Principle of Justice

- Hiring on the basis of merit
- Discrimination on genetic factors parallels discrimination on race or ethnicity
- Social construct of the category of “genetic abnormality”
- Judgments about how much of a genetic burden an employer should bear

To Improve Use Of Genetic Information

- Need population thinking
- Extension of traditional biomedical paradigm
- Scientific and social consideration about use in risk assessment

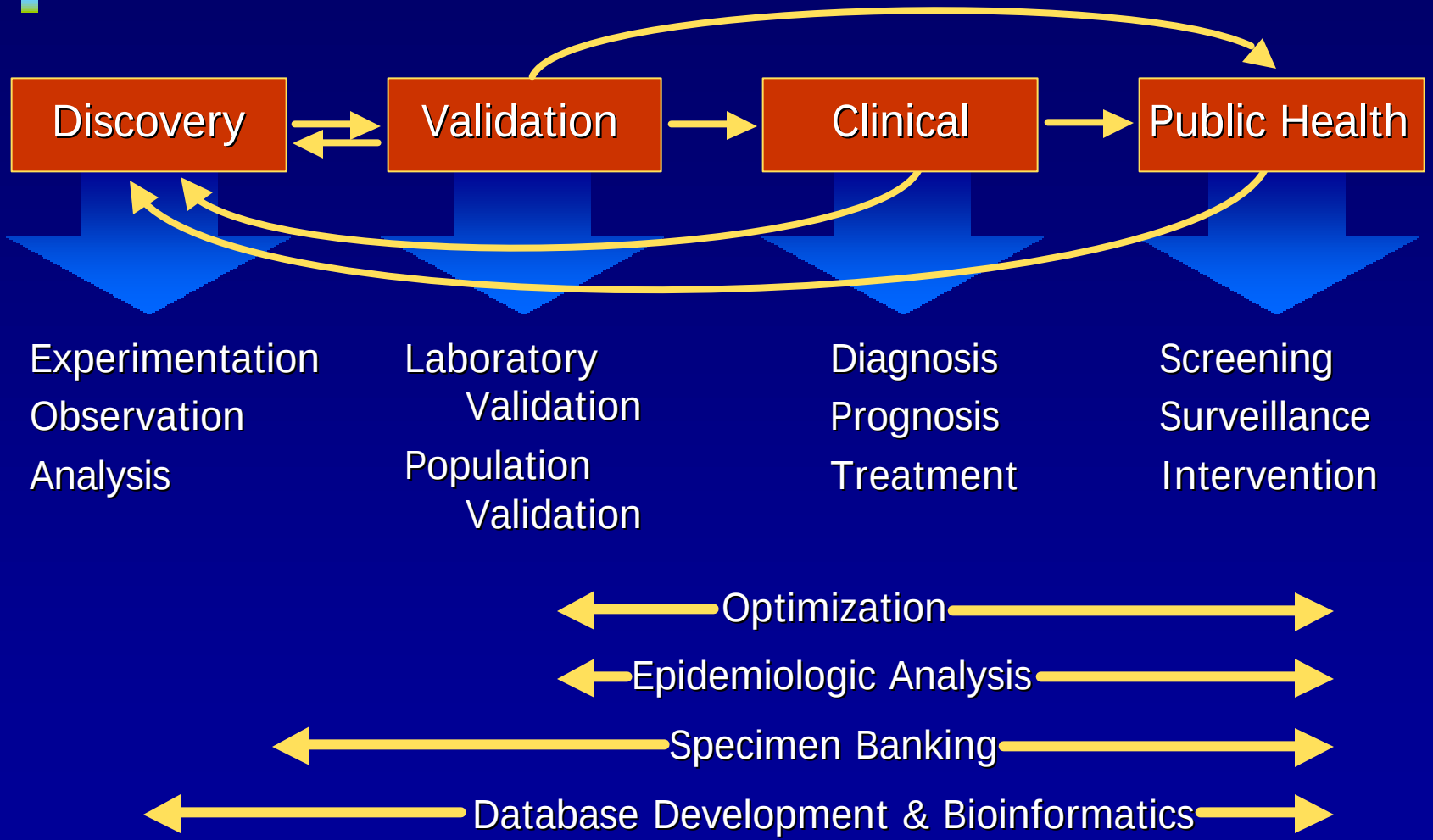
Population Thinking

- Uniqueness of people
- Population sciences variation and abnormality

Risk Assessment

- How to incorporate genetic data in quantitative risk assessments
- How to incorporate information on sensitive populations into laws and regulations
- Impact of such efforts

Continuum of Biomarker Development & Use



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