

a molecular epidemiology...

**Perspective on Tobacco, Genes and
Cancer**

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Cigarettes cause major mortality...

Age 45-85

1 Heart Disease	681,615
2 Cancer	529,999
3 Cerebro-vascular	160,004
4 COPD	121,394
5 Diabetes Mellitus	68,620
6 Influenza & Pneumonia	60,023

Source CDC, 2001 Figures <http://webapp.cdc.gov/cgi-bin/broker.exe>

General inefficacy of solid tumor treatment

NSCLC

avg tumor response rate: 25%

median survival: 25 weeks

one year survival: 20%

Disseminated Cancer

only 11 of roughly 200 known cancers are potentially curable by either chemotherapy (8) or combined (3). e.g., AML 25%, choriocarcinoma 90%, etc.

1.8% of these (50%) can expect 5 year disease free survival

Overview

Hard fought battles over ½ century have resulted in advances in tobacco control in the US/Western Europe with reductions in tobacco related tumors. Unfortunately global increases in per capita tobacco use more than counter these gains.

Conventional treatment of disseminated cancer is inefficacious. Real progress requires focus on molecular targets and pathways critical for development and maintenance of the cancer phenotypes.

Genetics

-3 view of genetics



“ what distinguishes one biological form from another is seldom the presence or absence of a certain genetic template, but rather when and where genes are expressed, how they are modified, into what structural and dynamic relationships their products become embedded.”

-Lenny Moss

1st category

Germline
Population

Some areas of uncertainty in genetics of common cancers....

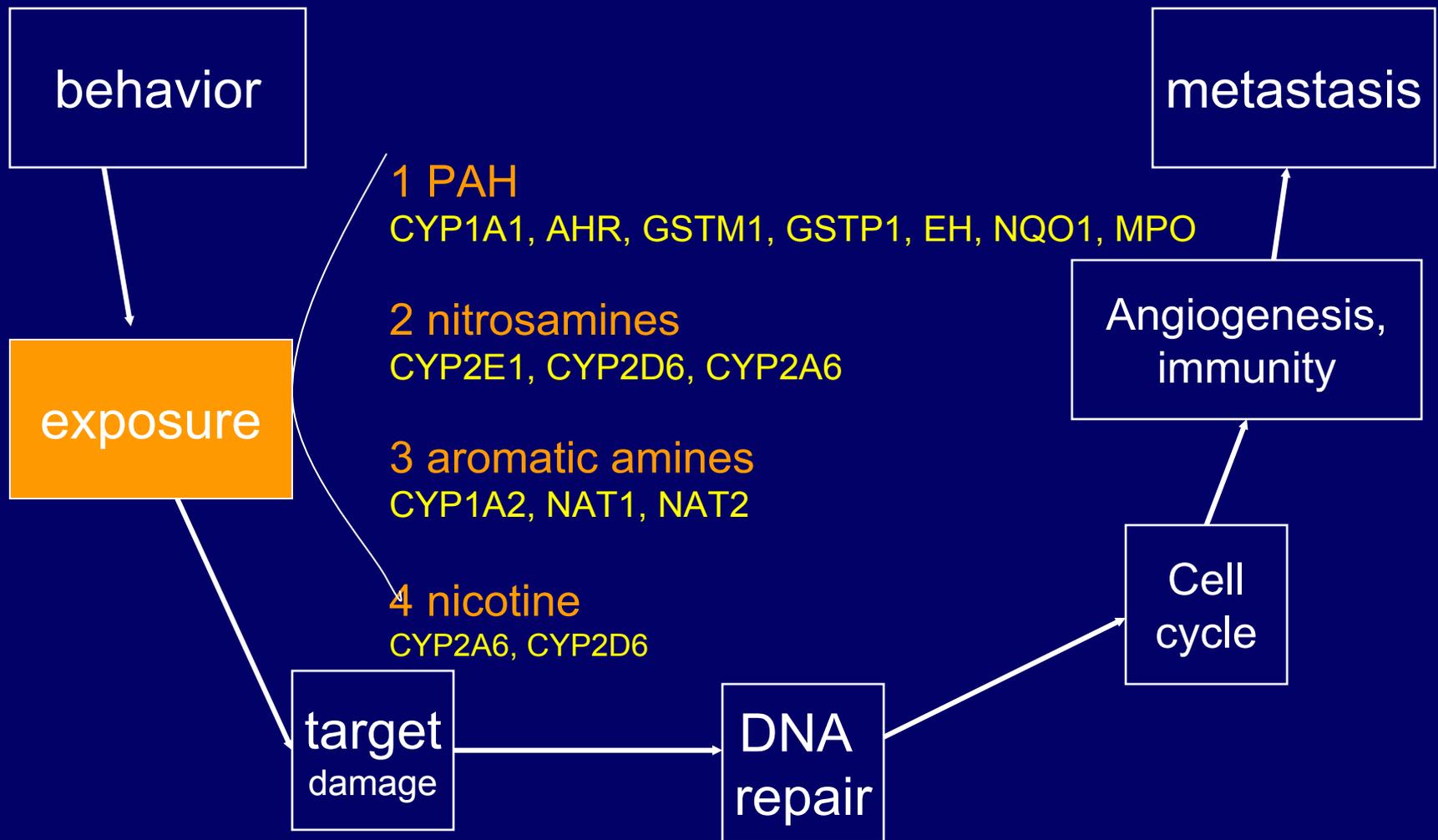
- **Are there established G risk factors?**
- **G vs. G conditional on E/GE vs. GG**
- **complex genetic architecture**
- **does genetic risk reside in pathways**
- **relation to molecular pathology**

Metanalyses: Lung cancer

Gene	studies	OR (95% CI)	author
CYP1A1	22	1.2 (0.9-1.5)	<i>Houlson 2000</i>
	4 MspI	1.7 (1.3-2.3)	<i>d'Errico 1999</i>
	3 exon7	2.3 (1.4-3.7)	<i>d'Errico 1999</i>
CYP2D6	16	1.3 (1.0-1.6)	<i>d'Errico 1999</i>
MPO	* 6	0.7 (0.4-0.8)	<i>Kantarci 2002</i>
GSTM1	23	1.1 (1.0-1.3)	<i>Houlson 1999</i>
	13(C)	1.2 (1.1-1.4)	<i>d'Errico 1999</i>

* 2 recent large studies null

Where genes might operate to influence disease risk...



Challenges in studies of susceptibility genes in lung cancer (and complex disease)

False positives

- Low Prior Probability
- Publication bias
- Poor design
- Population Stratification

False negatives

- Polygenic (power)
- GE/GG
- Unstudied genes
- Phenotype misspecified?
- Wrong or too few SNPs

Wacholder 2000, 2002, Rothman 2001, Caporaso 1999 (2), 2002, 2003

Germline-Population

1. Many population studies of genes-
results still incomplete.....
2. Important to study well-
characterized genes in logical
groups
3. Include intermediate phenotypes
4. Important to power studies to
address GE (GG)

Is it time to consider whole genome approach in lung cancer?

Attractive features of tobacco-related cancers

- cases and controls currently available
- plausible candidates available to include in test regions
- can test cancer and smoking phenotypes in one design

2nd category

Germline
Family

Single and susceptibility genes

	<i>Families</i>	<i>Population</i>
Allele freq	rare	common
# of genes	one/few	many
Gene freq	rare	common
Rel Risk	high	low
Attrib risk	low	high
Role of Env.	low	high
Approach	linkage	association

Point: thousands of mendelian traits mapped in humans using families and linkage approaches

Germline-Family Familial Lung Cancer

Linkage Study	6q23-25 MLOD
52 families	2.79
38 with > 4 affecteds	3.47
23 multigen., > 5 affected	4.36

Bailey-Wilson JE, Amos CI, A major lung cancer susceptibility locus maps to chromosome 6q23-25. *American Journal of Human Genetics*, September 2004

Tobacco

The major cause of morbidity and mortality

Billion deaths projected in this century

Current prevention and treatment ineffective

Lung Cancer

Number one cause of cancer deaths in men and women

Drives overall cancer mortality

Treatment ineffective

Screening controversial

Germline-Family

1. Notable success was a product of GELCC Consortia
2. Further studies high priority:
 - mine region, look for LOH
 - Explore clinical, familial, molecular, exposure features of cases

International Familial CLL Consortium



***1st Meeting
2002***

***2nd Meeting,
2003***



3rd category

Somatic tumor mutations

Somatic-tumor mutations

- Understanding molecular basis of lung cancer is a key gap in crafting more effective interventions including molecular based treatment, prevention, early detection, molecular pathology
- Genetics of LC are complex

Contrast CML and lung cancer

	CML	Lung Cancer
Cytogenetics	t(9;22)	complex and variable
Mol Basis	c-abl/BCL fusion	EGFR (1 of many)
Frequency	95%+	15/58 Japan 1/61 US
Therapy	Gleevec (imatinib)	Iressa (gefitinib)
Epidemiology	-	non-smokers female
Clinical		adenocarcinoma
Response Rate	high	Japan 27% USA 10%

These domains are related

Germline population

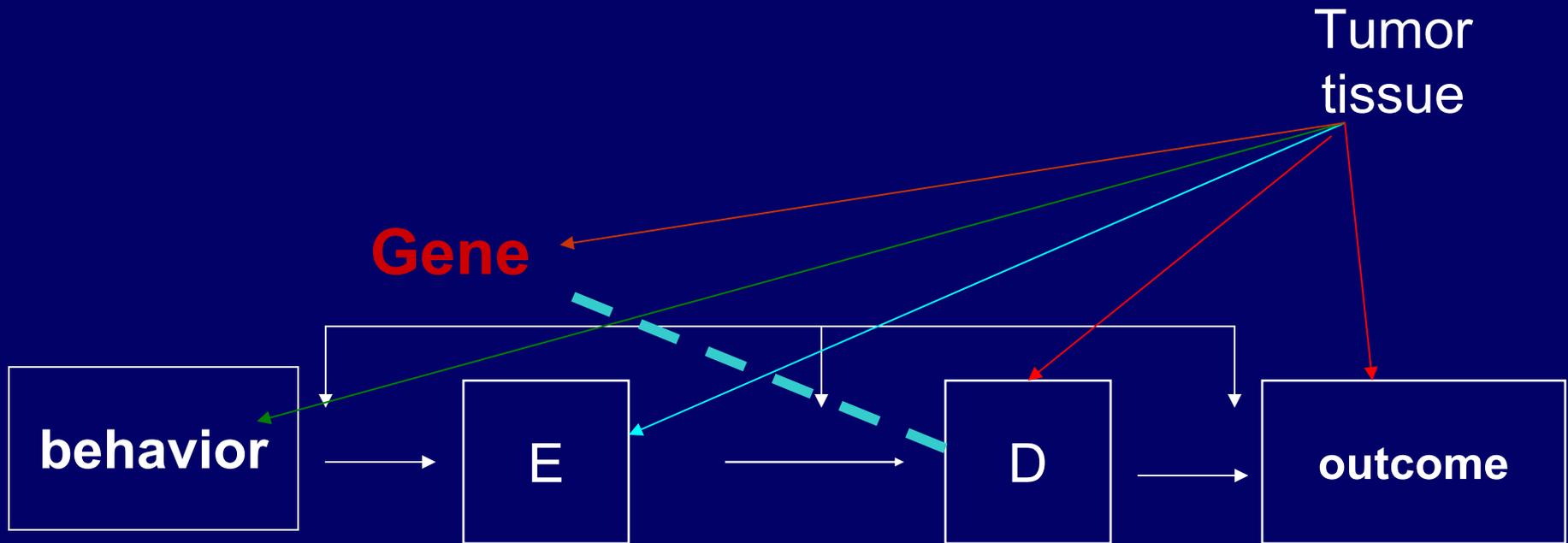
Germline family ————— Somatic

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graph TD; A[Germline population] --- B[Germline family]; A --- C[Somatic]; B --- C;
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Molecular epidemiology

integrative view

MANY NEW CLASSES OF
HYPOTHESES TO TEST



Integrative Molecular Epidemiology

- **interdisciplinary**
- **large study platforms**
- **combine molecular epidemiology and translational medicine goals**
- **advanced technologies**
- **maximize science**
- **cost effective**

Consortia Issues

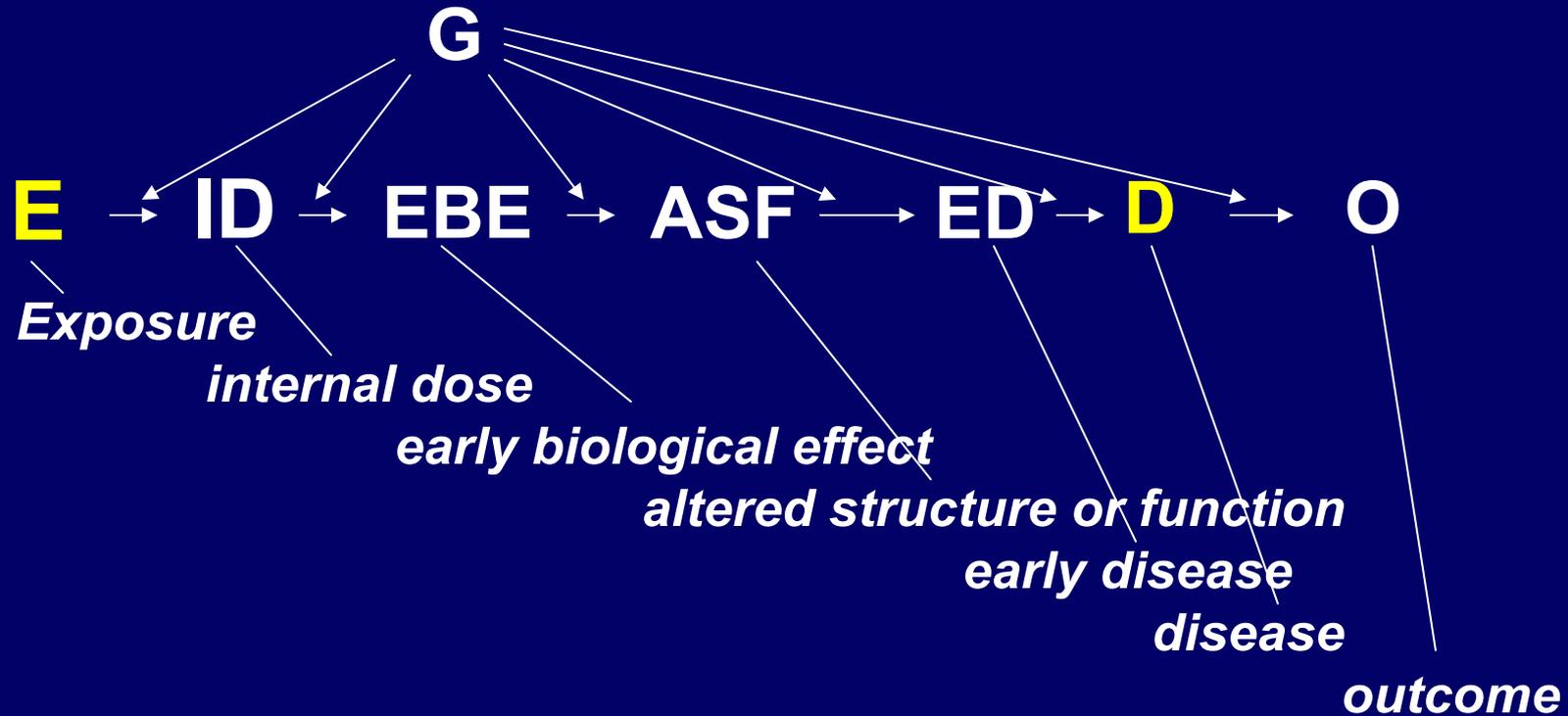
ADVANTAGES

- size (power, subgroups)
- technology
- standardization
- rapid confirmation
- coordination
- pooled resources

DISADVANTAGES

- slow, management difficult, support, apportioning glory
- some weaknesses of metaanalyses

Molecular Epidemiology



Insight from molecular epidemiology:

Adding biospecimen or information to study designs
May efficiently increase scope of questions
that can be addressed

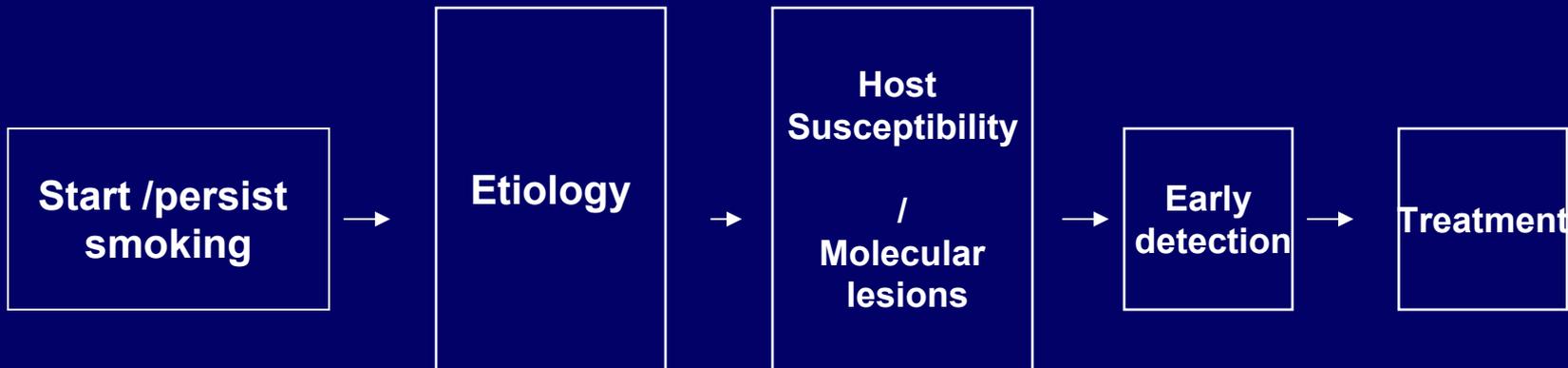
Integrative Approach

Molecular Epidemiology

Translational Medicine



B → **E** → **D** → **O**



Concluding Perspective

Given scientific questions, public health burden, need to integrate new technologies, and substantial but finite budget-

Emphasize larger, integrated studies and consortia.

Challenges and Opportunities Tobacco- Related Cancers

- **genetic studies- whole genome**
- **more dynamic consortia**
- **new technologies**
- **integrated studies**