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# 2004 CARDIOVASCULAR BIOMARKERS AND SURROGATE ENDPOINTS SYMPOSIUM


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2004 CARDIOVASCULAR BIOMARKERS AND SURROGATE ENDPOINTS SYMPOSIUM

# The Need for Biomarkers in Drug Development

Therese M. Heinonen
Montreal Heart Institute

1928
C.S. Keefer and W.H. Resnik

Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium

# 1994 Cardiovascular Biomarkers

**Genetics**
ACE polymorphism
G6PD
Lipid determinants

**Lipids**
lipoproteins
lipoprotein subfractions
Apolipoproteins
Lp(a)
Lipid ratios

**Imaging**
Angiography
Duplex US (PAD, carotid)
IVUS
3D reconstruction IVUS
Ultrafast CT (coronary)
Aortic CT
Scintigraphy (thallium, sestimibe)
Intracoronary endo fct (Ach)
TEE (aortic)
Brachial ultrasound
MRI (carotid, PAD, aortic)
Spiral CT (carotid)
PET
Monoclonal antibody imaging
Pulsatile flow visualization (aorta)
Regional aortic distensibility
Aortic stiffness (Doppler)
Intravascular NMR
Gamma camera cholesterol imaging
Diagonal earlobe crease

**Soluble Markers**
Homocysteine
MCSF
PDGF
Integrins
CD 11. 18. 59
Lysophosphatidyl choline
Lathosterol
C4 binding protein
Complement
CRP
Complement receptors
Serum Amyloid A

# CV Biomarkers Today

**Imaging**
Angiography
IVUS
3D reconstruction IVUS
Ultrafast CT (coronary)
Carotid ultrasound – IMT
MRI (carotid, PAD, aortic)
PET
Aortic CT
Scintigraphy (thallium, sestimibe)
Intracoronary endo fct (Ach)
Brachial ultrasound
Plethysmography
TEE (aortic)
Skin cholesterol
Monoclonal antibody imaging
Pulsatile flow visualization (aorta)
Regional aortic distensibility
Aortic stiffness (Doppler)
Coronary thermography
Coronary elastography
Coronary NIR spectroscopy

**Lipids**
lipoproteins
lipoprotein subfractions
(L1-3, V1-6, H1-5)
Apolipoproteins
(CIII, AII:E, LpB…)
Lp(a)
Lipid ratios

**Inflammation and Proliferation**
CRP
MCSF
PDGF
FDF
FGF
Interleukins (1,6,8,10,12,15)
MMPs (1,2,3,9)
MIP1 (alpha and beta)
TNF alpha
liferating cell nuclear antigen
Hyaluronan receptors
SR-A, SR-B1
TGF
SM myacin heavy chains
CD 11, 18, 36, 40, 68
MCP-1
CCR2
Pentraxin-3
binding protein
kappa B-alpha
otal sialic acid
Osteopontin

**glycoproteins**
ntitrypsin
cid glycoprotein
nacroglobulin
smin
naptoglobin

**Coagulation**
VWF
tPA
PAI-1
PF4
D-dimer
Tissue factor
Fibrinogen
Beta thromboglobulin
Erythrocyte sed. Rate
RBC adhesiveness/aggreg

**sion molecules**
s-ICAM
s-VCAM
P-selectin
E-selectin

**Genetics**
ACE polymorphism
methylenetetrahydrofolate reductase [MTHFR]
apolipoprotein E [apo E]
paraoxonase [PON]

**Immunology**
Anti-oxLDL IgG

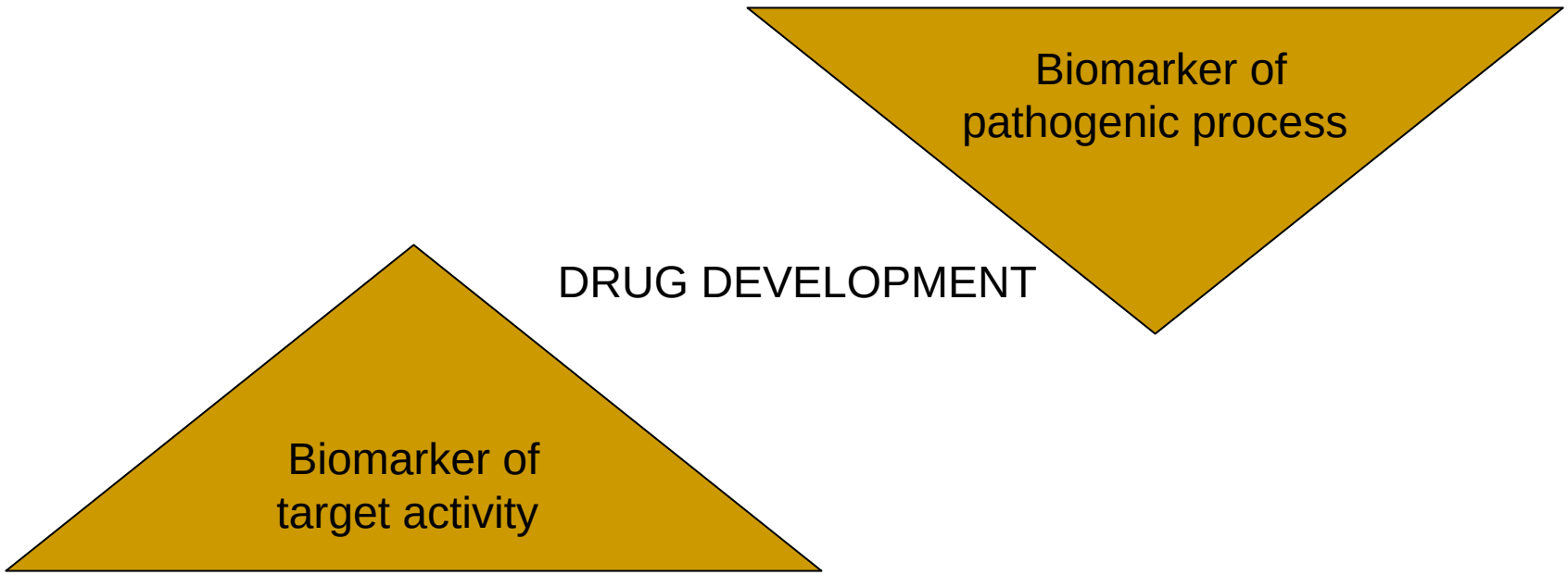
# NIH Biomarkers Definition Working Group (1998)

Biological marker – (biomarker)
a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Surrogate endpoint – a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

Clinical endpoint – a characteristic or variable that reflects how a patient feels, functions or survives.

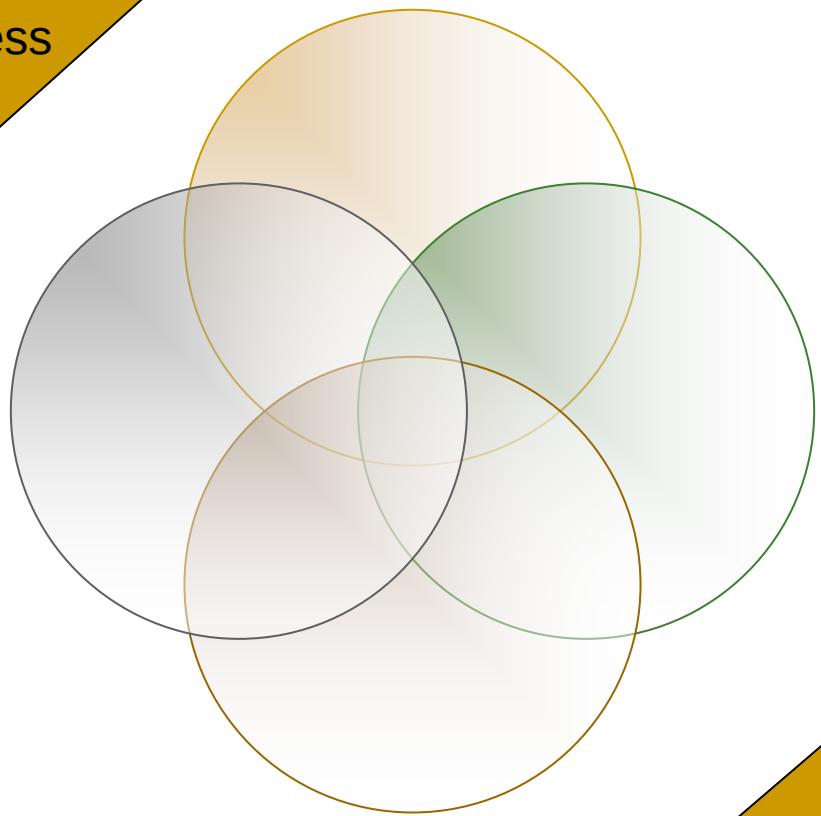
# Types of Biomarkers




Biological marker – (biomarker) a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Clinical Trial Data
(10,000 pts)

Biomarker of
pathogenic process



Epidemiologic Data
(100,000 pts)

Phase I
(100 pts)

Preclinical Data

Biomarker of
target activity

# Atherosclerotic Progression

Lesion prone area of artery

Precursor lesion

Fibrofatty plaque + inflammation (subclinical)

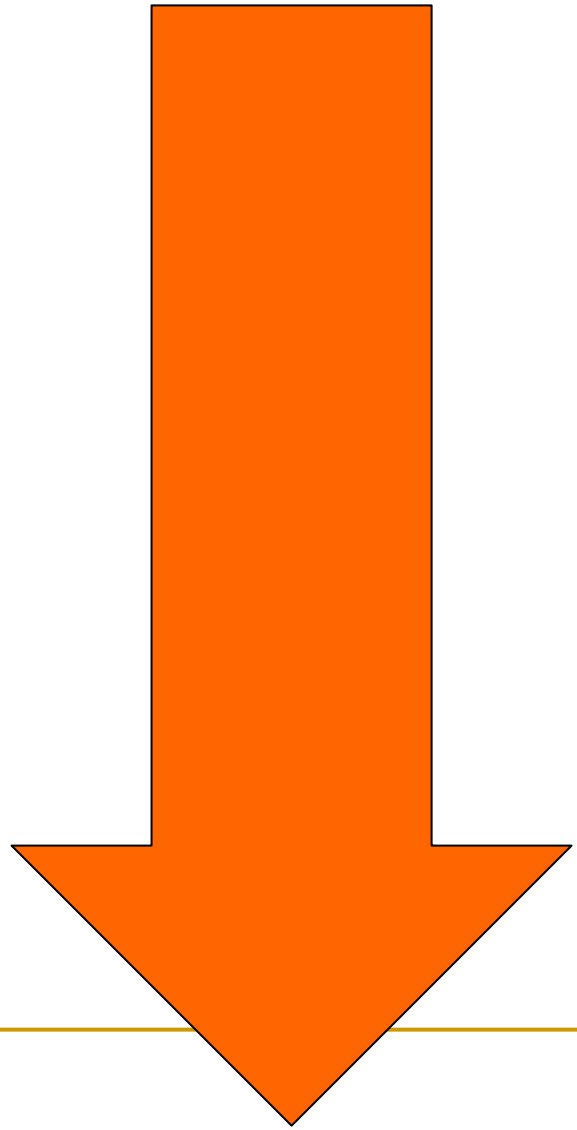
Plaque remodelling  Wall remodelling

Subclinical plaque

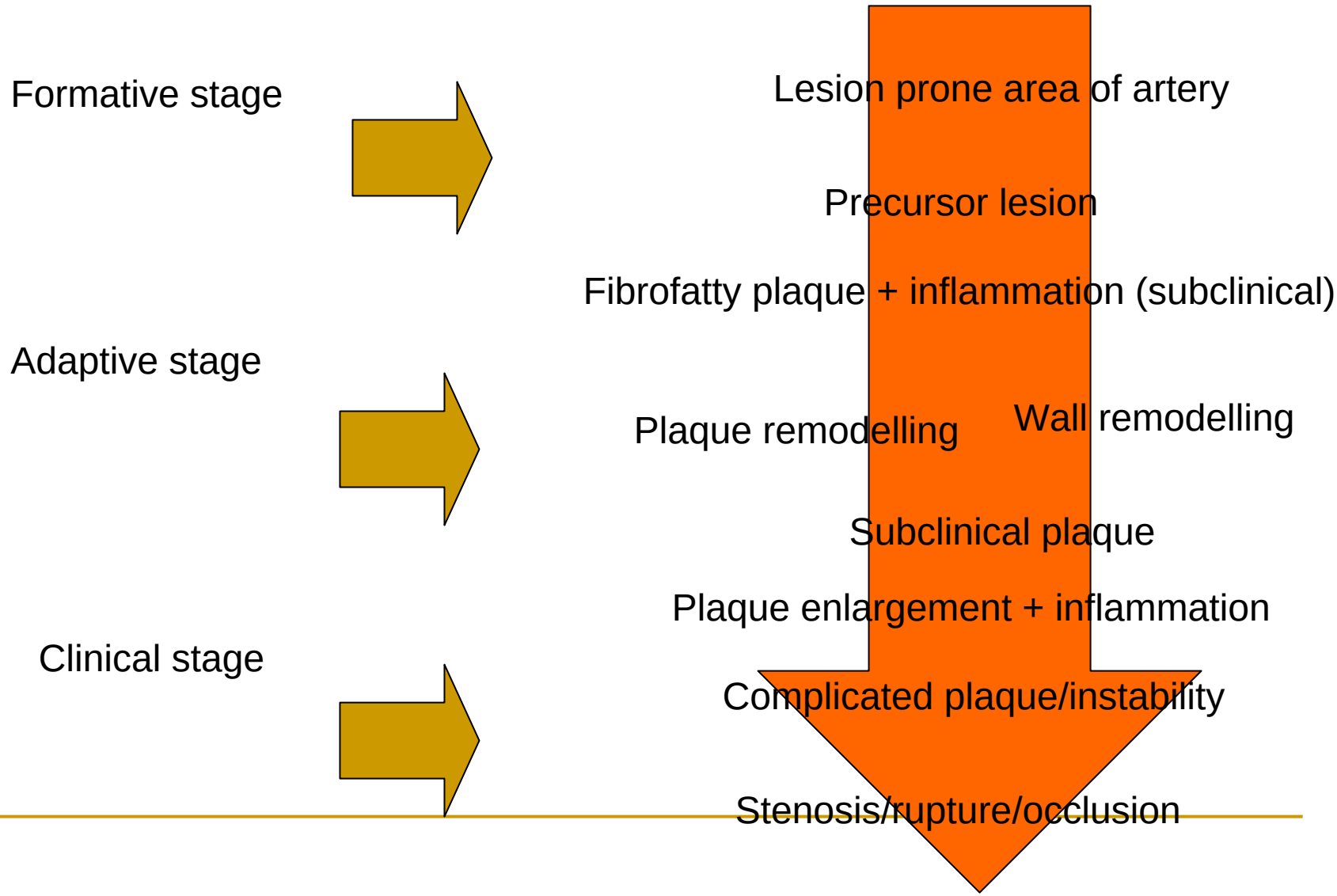
Plaque enlargement + inflammation

Complicated plaque/instability

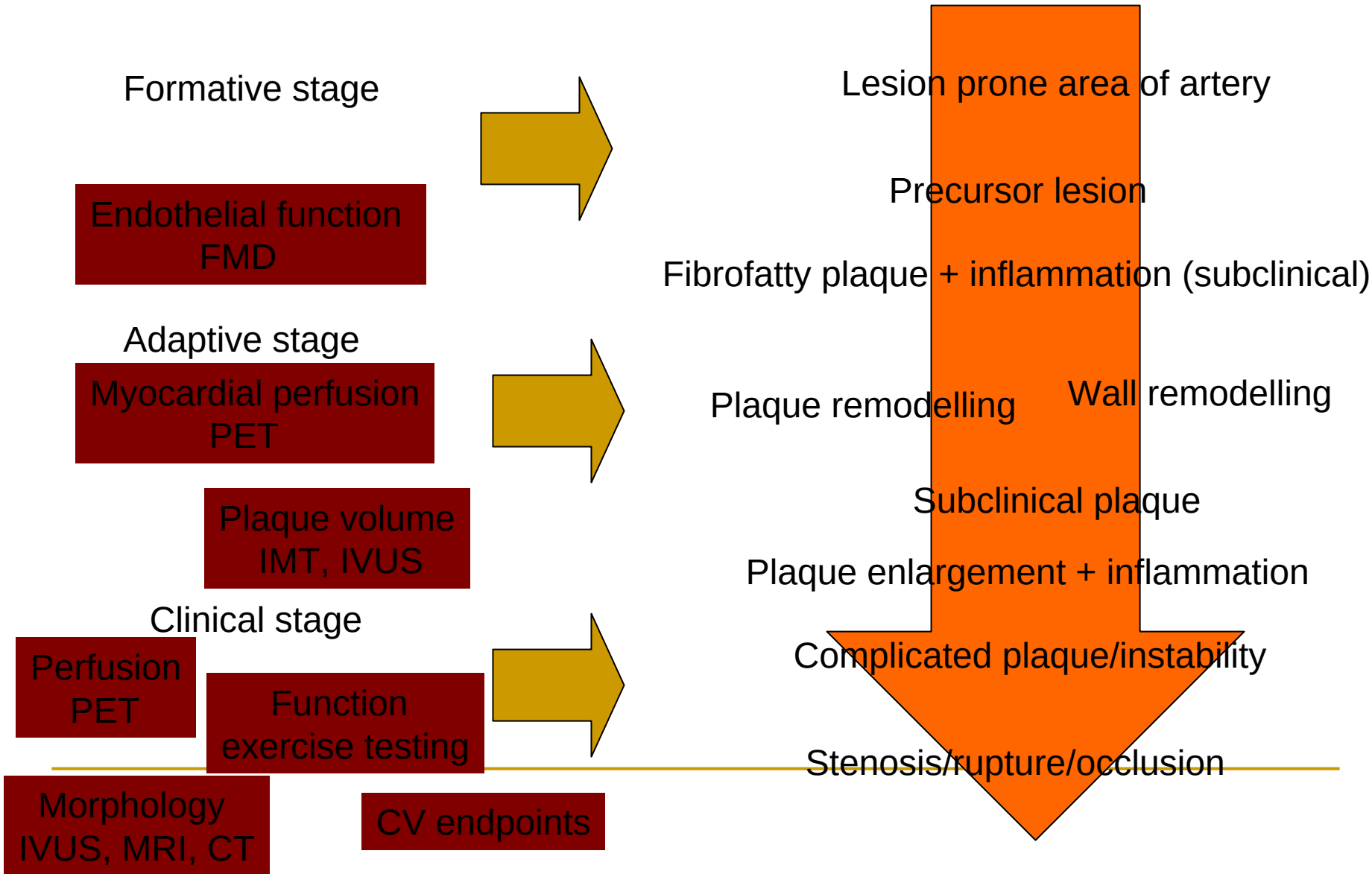
Stenosis/rupture/occlusion



# Targeting stage for modification

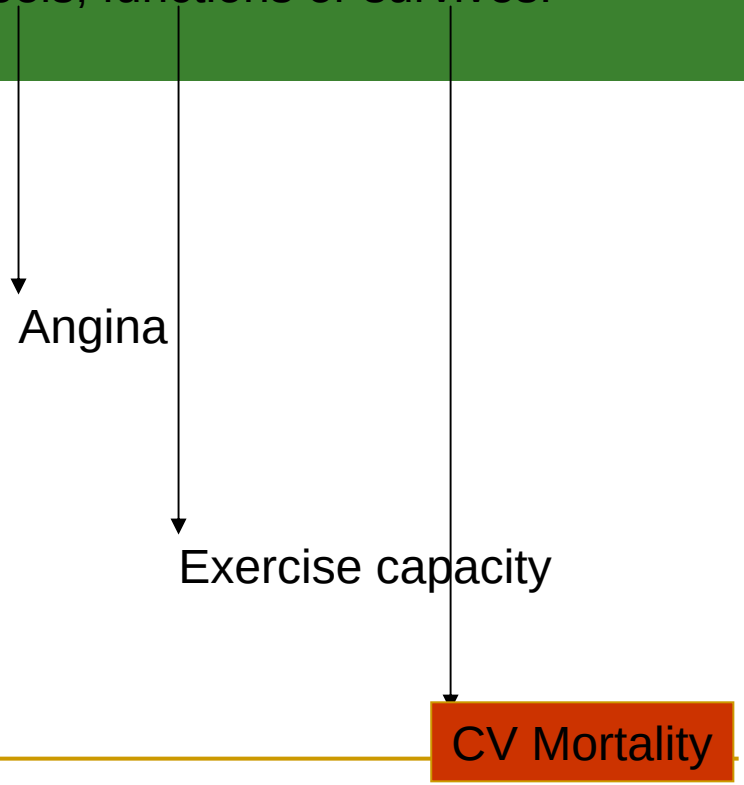


# Selecting technology based on MOA



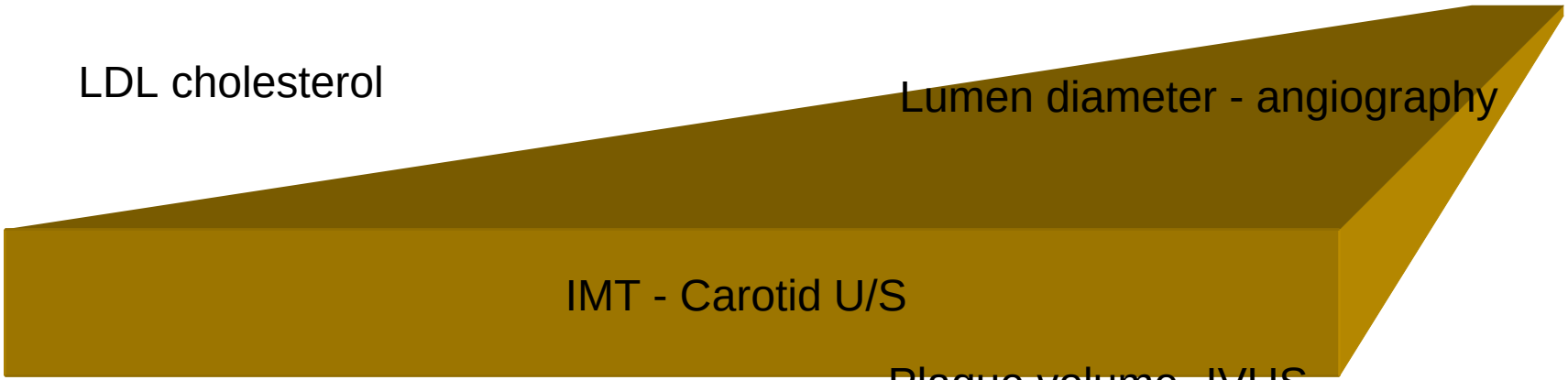
# Surrogate for which clinical endpoint?

Clinical endpoint – a characteristic or variable that reflects how a patient feels, functions or survives.




Surrogate endpoint – a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

# The surrogate "glass ceiling"




Surrogate endpoint – a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

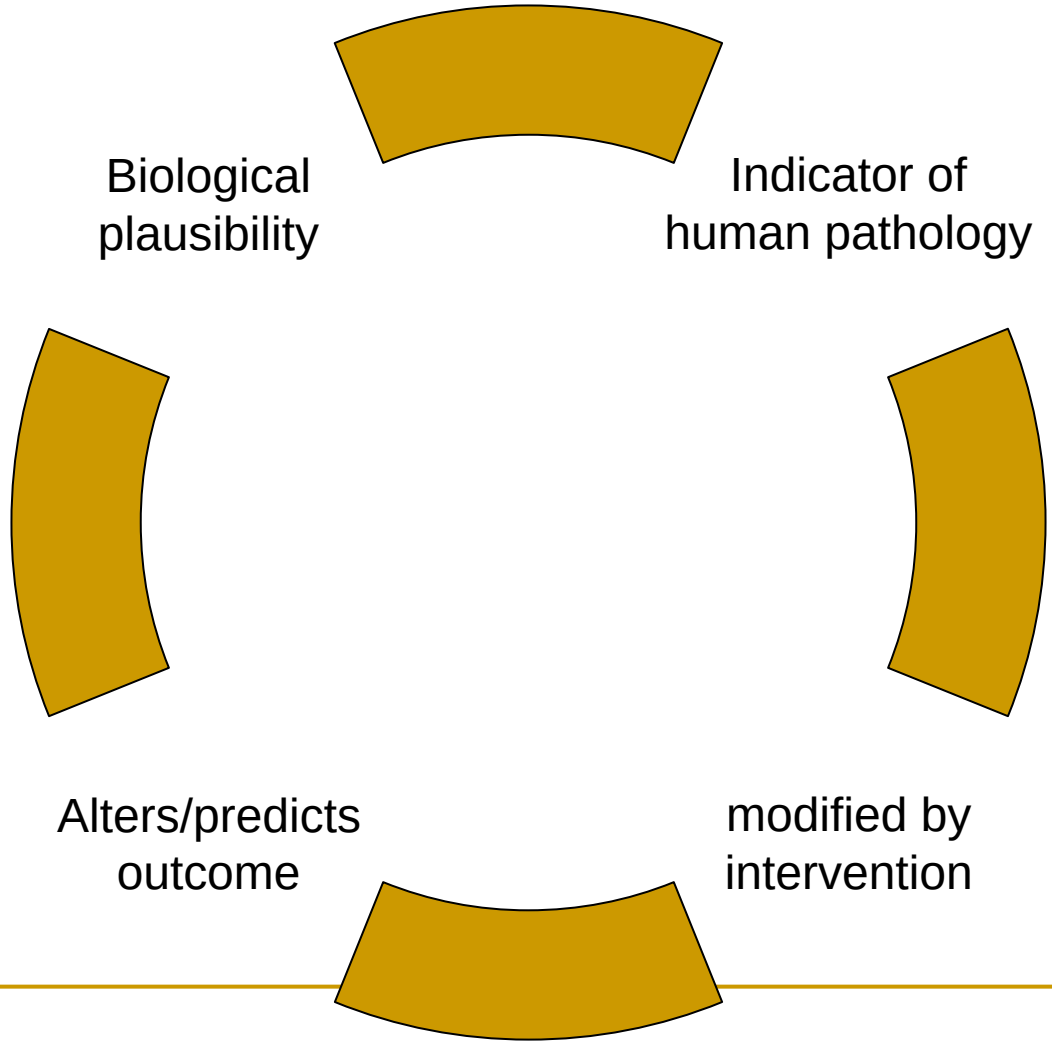
Coronary calcium - CT

Adhesion molecules

apoCIII

Endothelial fct -FMD

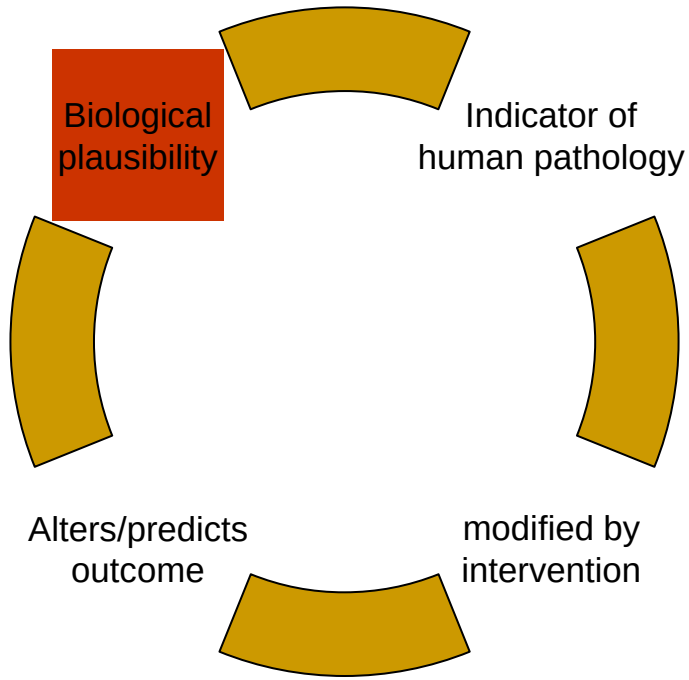
# From Biomarker to Surrogate



# Case Study
# Anginal episodes

Angina = both a biomarker and a clinical endpoint!

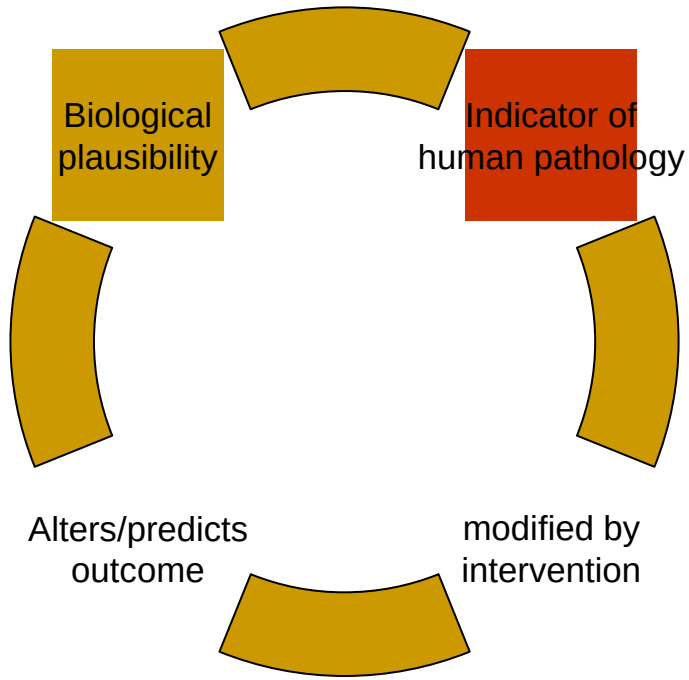
Atherosclerosis = decreased patency = ischemia = anginal symptoms



# Case Study
# Anginal episodes

Correlations between angina and angiographically detected CAD

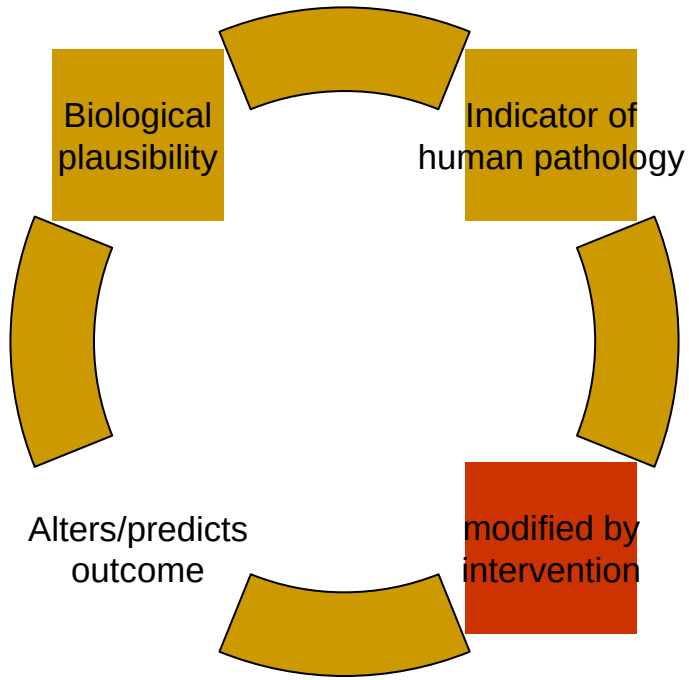
Correlations between angina and clinical events



# Case Study
# Anginal episodes

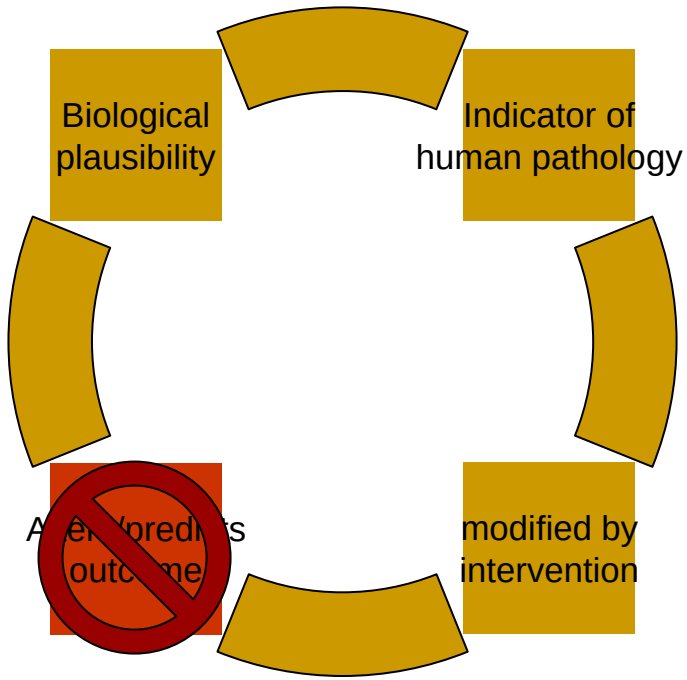
Nitrates, beta blockers and calcium channel blockers all relieve anginal symptoms

Surgical intervention relieves anginal symptoms

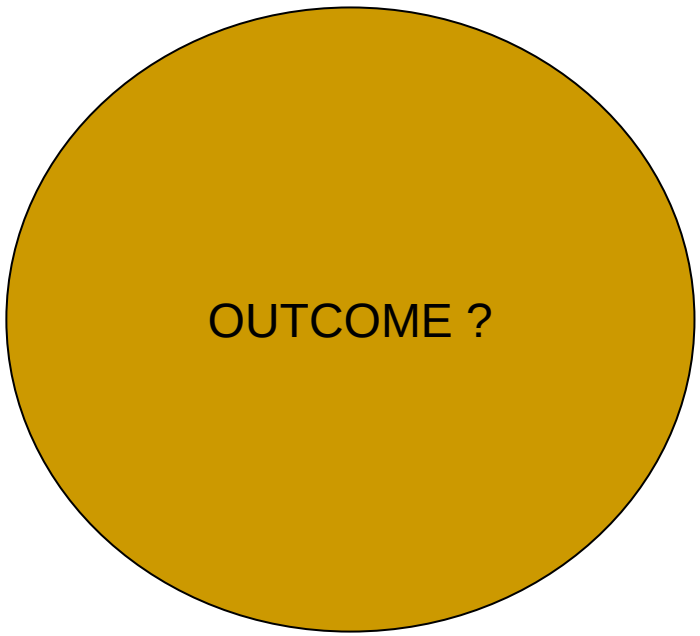


# Case Study
# Anginal episodes

Not all interventions that improve anginal symptoms improve cardiovascular morbidity and mortality



# Case Study
# Anginal episodes




Angina = biomarker for CAD

Angina = clinical endpoint

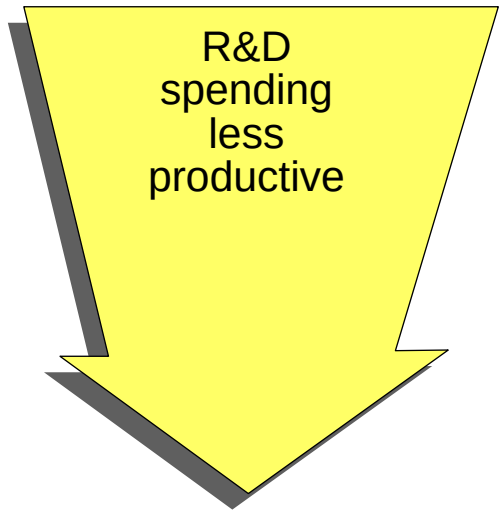
Angina IS NOT a surrogate for
CV morbidity and mortality endpoint

# There is a medical need…

- cardiovascular disease places a great burden on society.
- cardiovascular disease is one of the leading causes of death around the world
- cardiovascular disease has a major impact on an individual's quality of life as a result of chronic pain, activity restriction, unemployment and disability
- In 2002 in the United States alone, > 62 million individuals had one or more type of cardiovascular disease and that the direct and indirect cost of CAD was over $110 billion.

# R&D spending less productive

- 5/5,000 NCEs in preclinical proceed to clinical
- 1/5 in clinical development are approved
- Estimate cost to develop drug –
  - 1976 $54 million, 1987 $231 million
  - 1993 $359 million, 2001 $802 million*
- > $ 26 billion spent on R&D in 2002
- R&D  costs double every 5 years
- Costs increase as compound proceeds through pipeline




*Tufts Center for the Study of Drug Development, Nov 2001

VIABILITY

# Innovation/Stagnation

"Challenge and Opportunity on the Critical Path to New Medical Products"

FDA, March 2004

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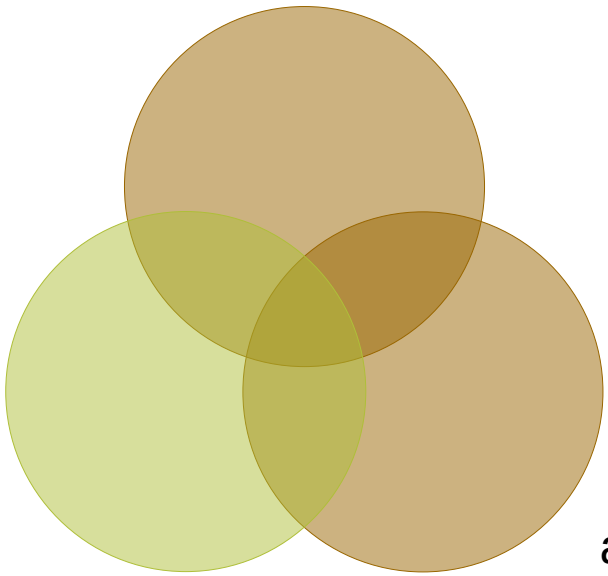

# Summary

- Biomarkers for CV diseases have been used for decades – recent surge in interest and collaborative efforts
- Standard definitions are important components
- A biomarker must meet certain criteria before reaching “surrogate” status
- Biomarkers will help “ better develop the science upon which so many critical public health decisions are based.”