

# Aging of the Cardiovascular System

## *Implications for Gero-Cardio-Oncology management*

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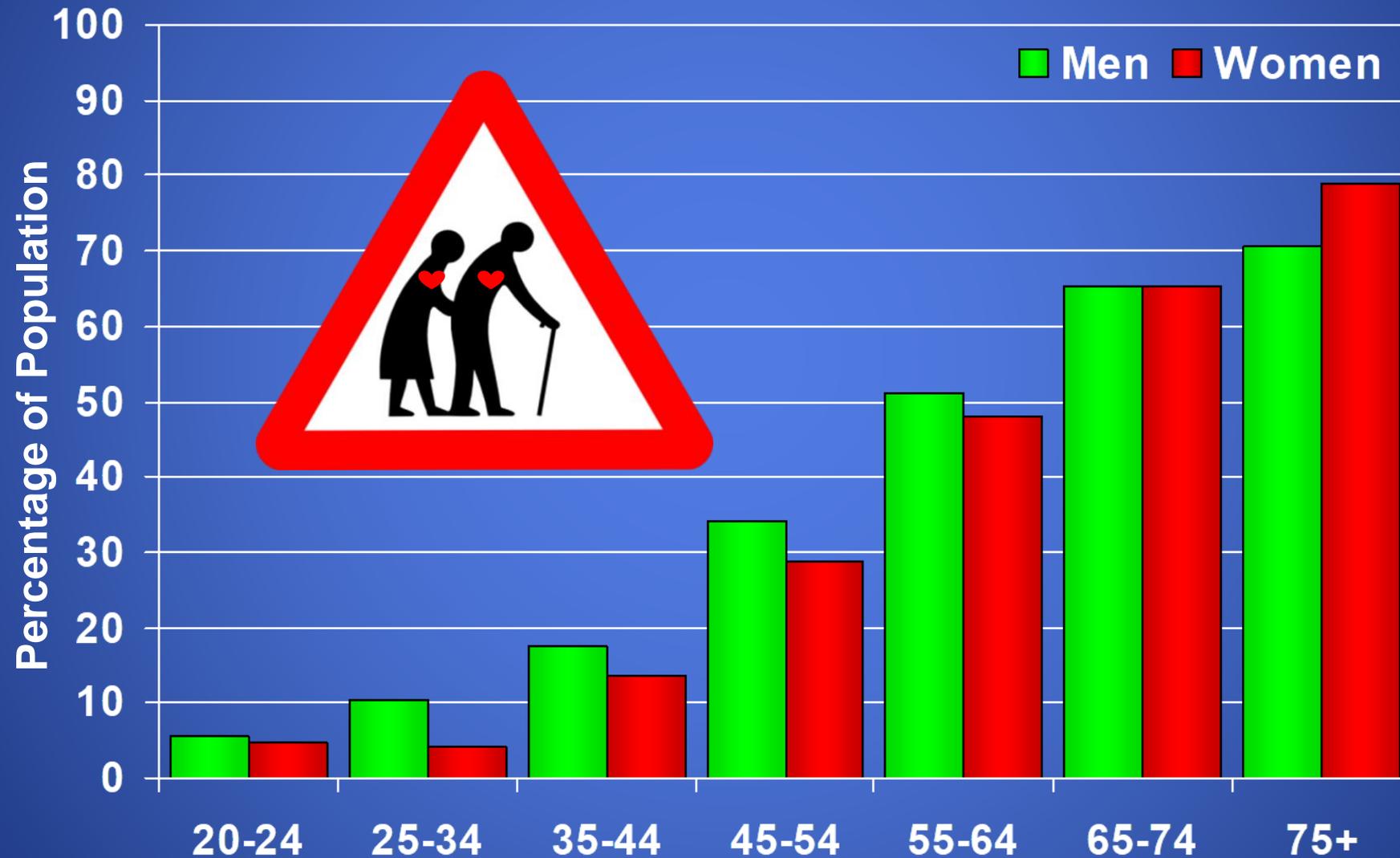
Associate Director for Clinical Translation and Director of Emerging Therapeutics, Aging Institute, University of Pittsburgh

Director, Transitional Care (Cardiac Rehabilitation, GeroFit, C-TraC, COMPASS), VA Pittsburgh Healthcare System

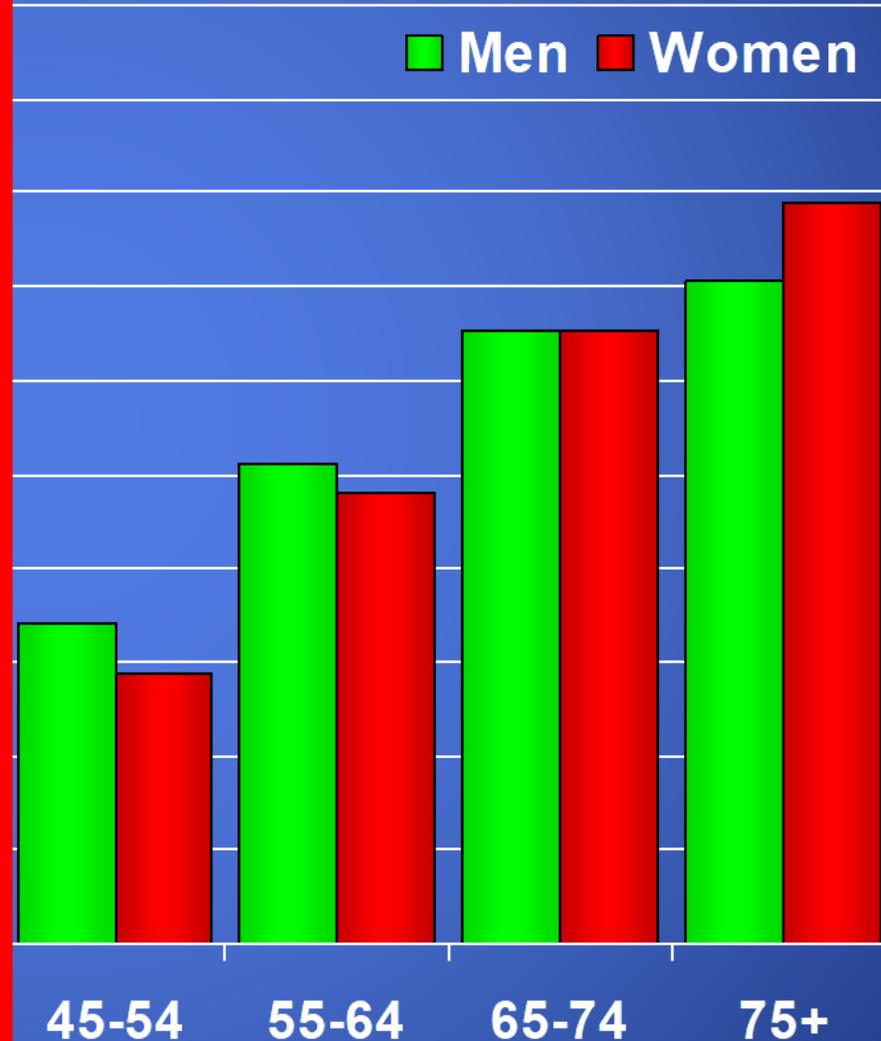


- No disclosures

# ↑ CVD with Aging



# ↑ CVD with Age: Driven by Biological Changes



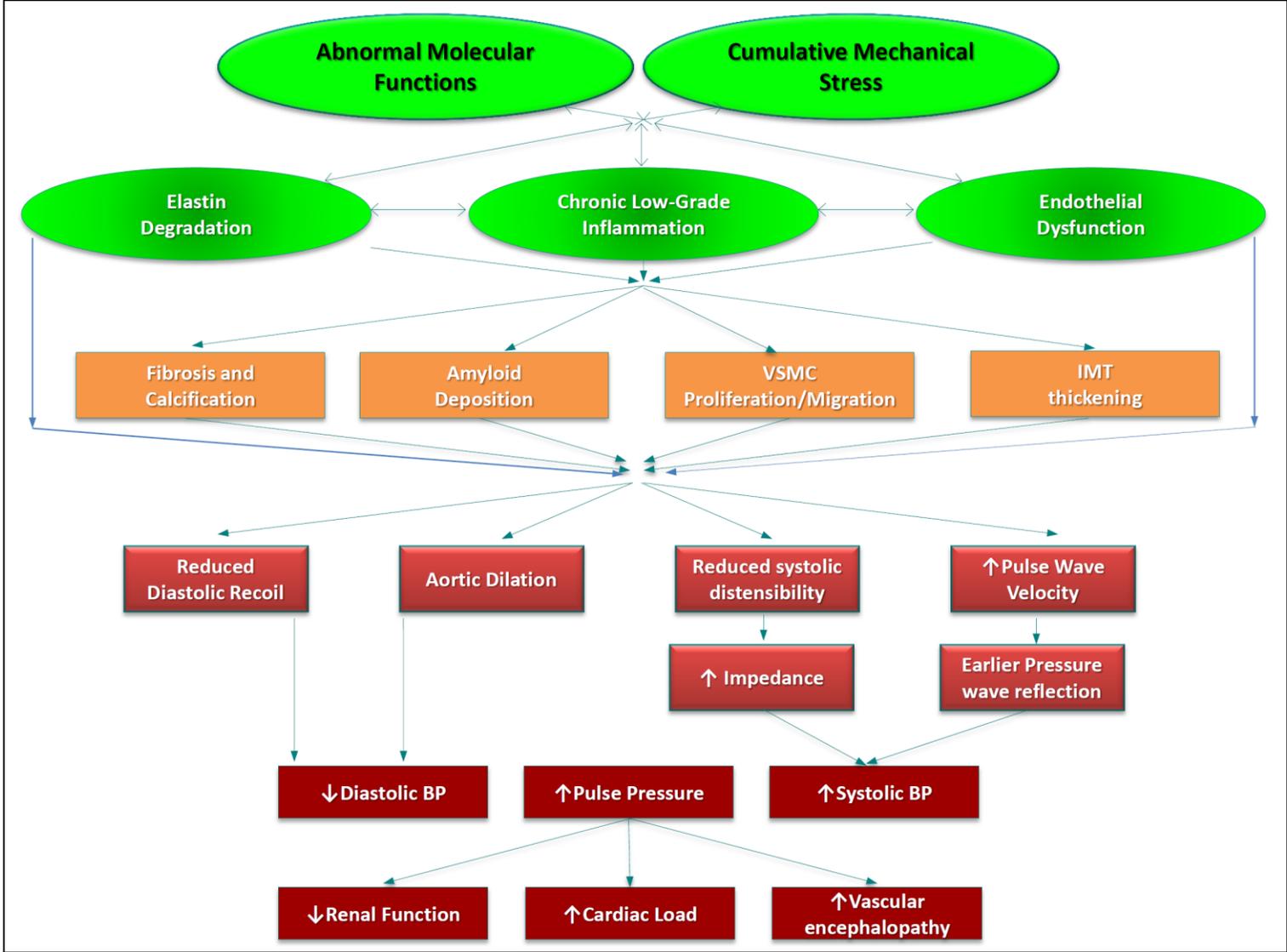




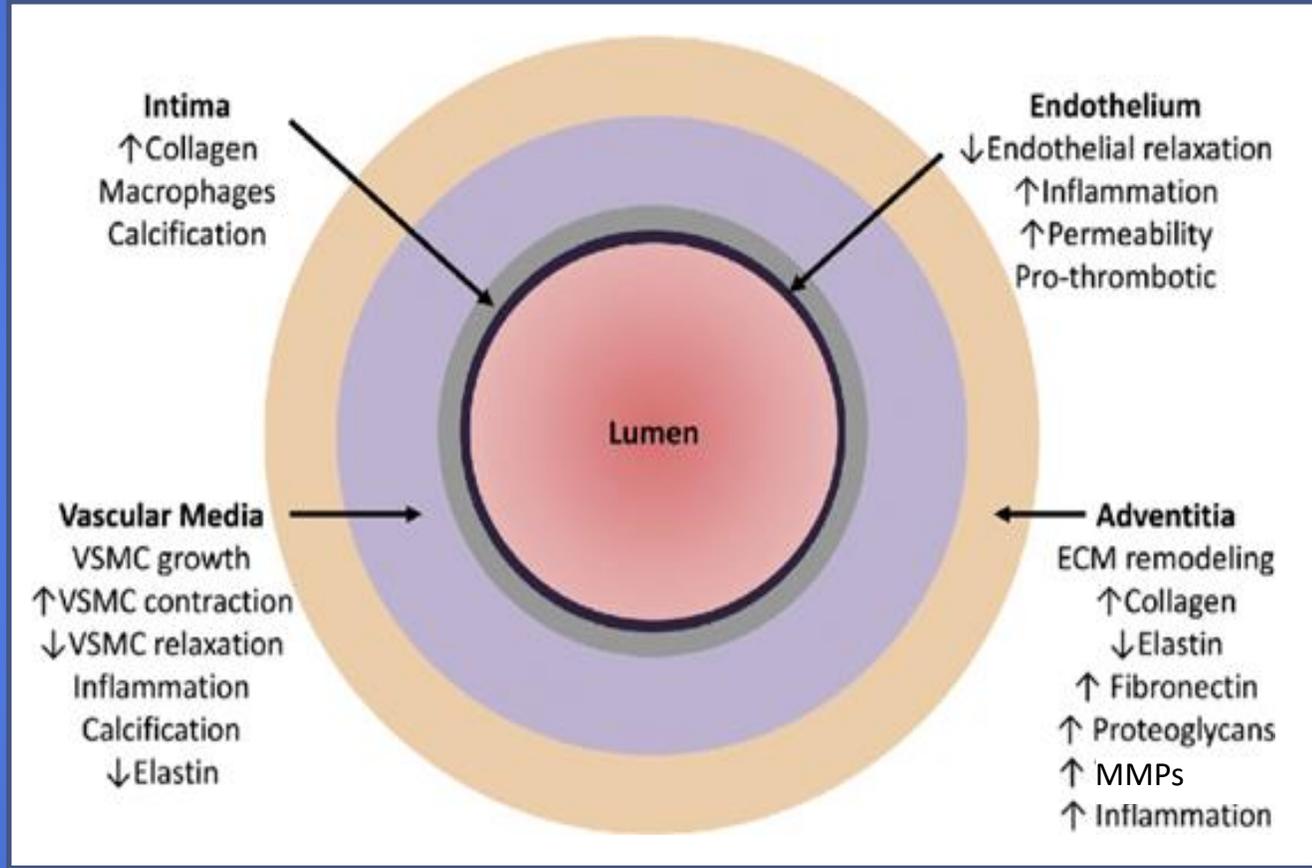
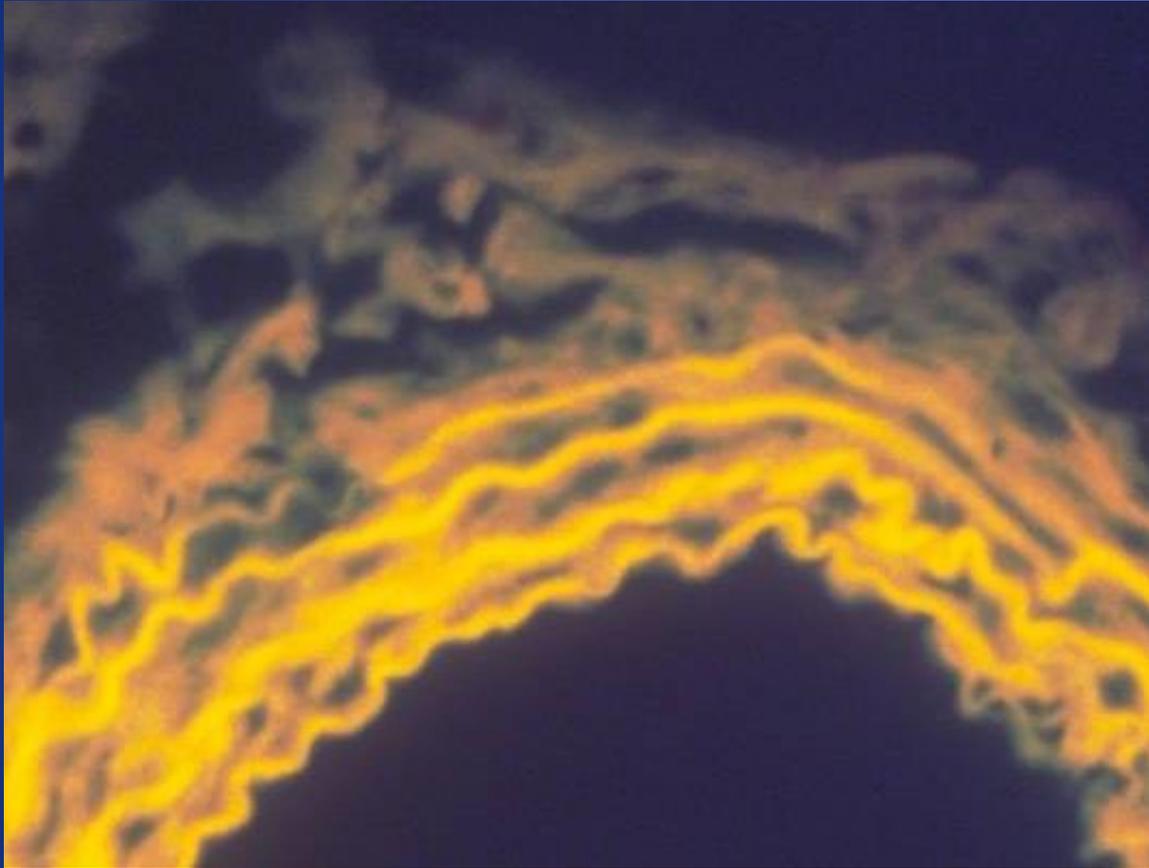
Myocardial ischemia  
 • Diminished perfusion



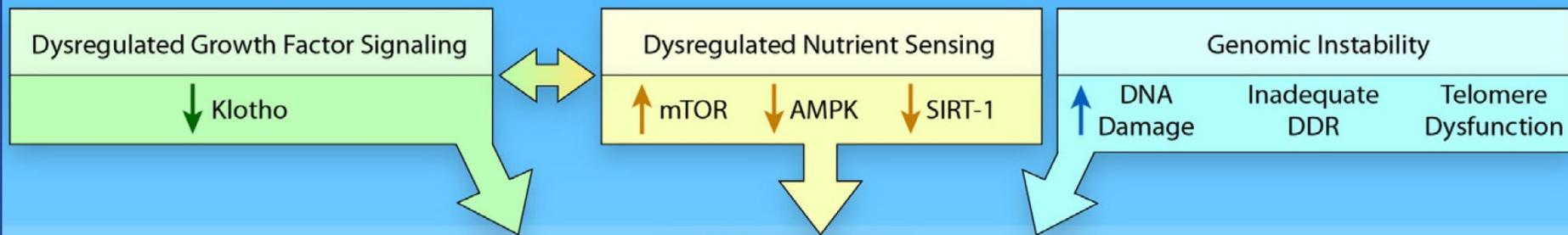
Myocardial ischemia  
 • Diminished perfusion



Myocardial ischemia  
 • Diminished perfusion



## Signaling Pathways and Genetic Factors



## Cellular Processes

**Cellular Senescence &  
Dysregulated Autophagy**

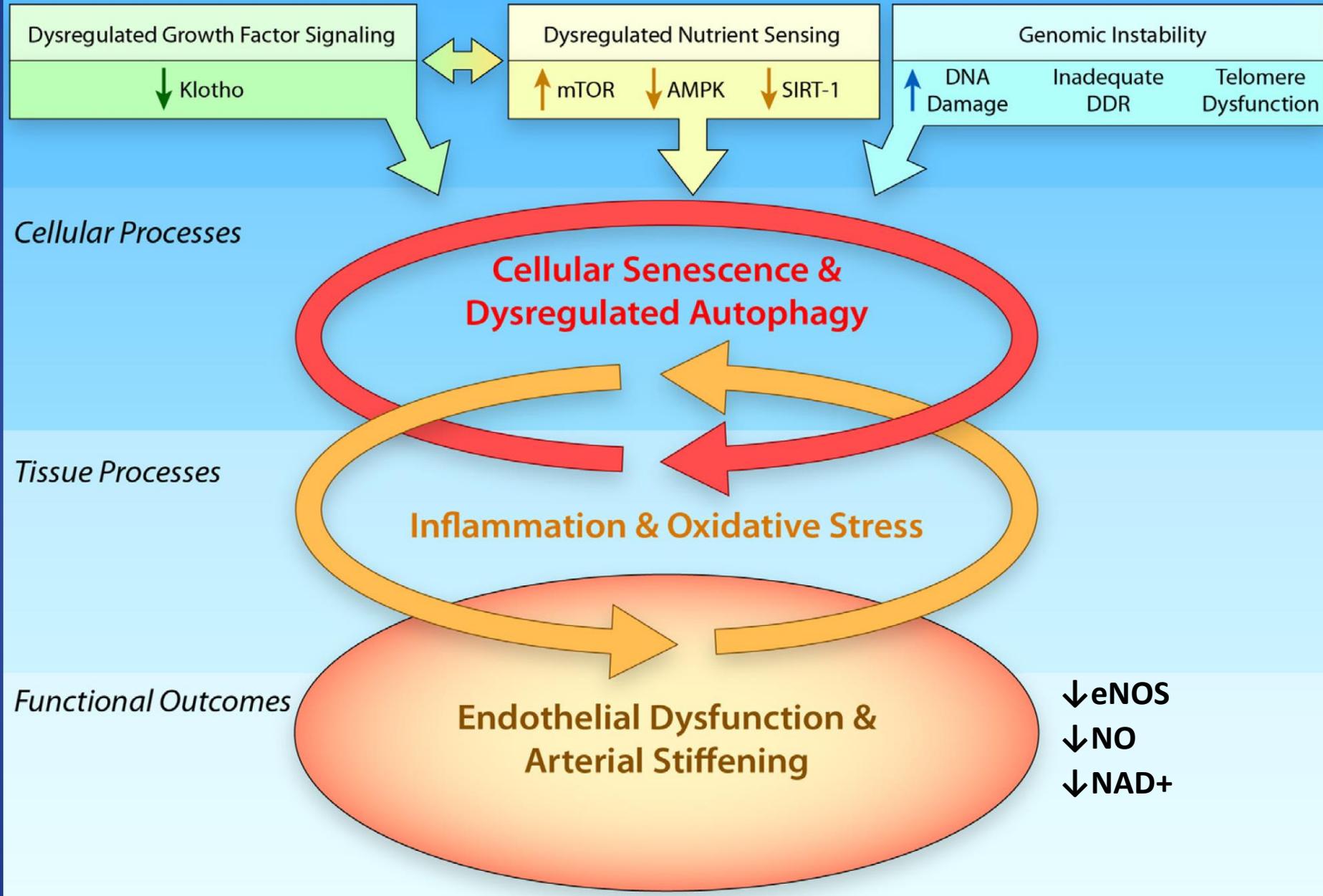
## Tissue Processes

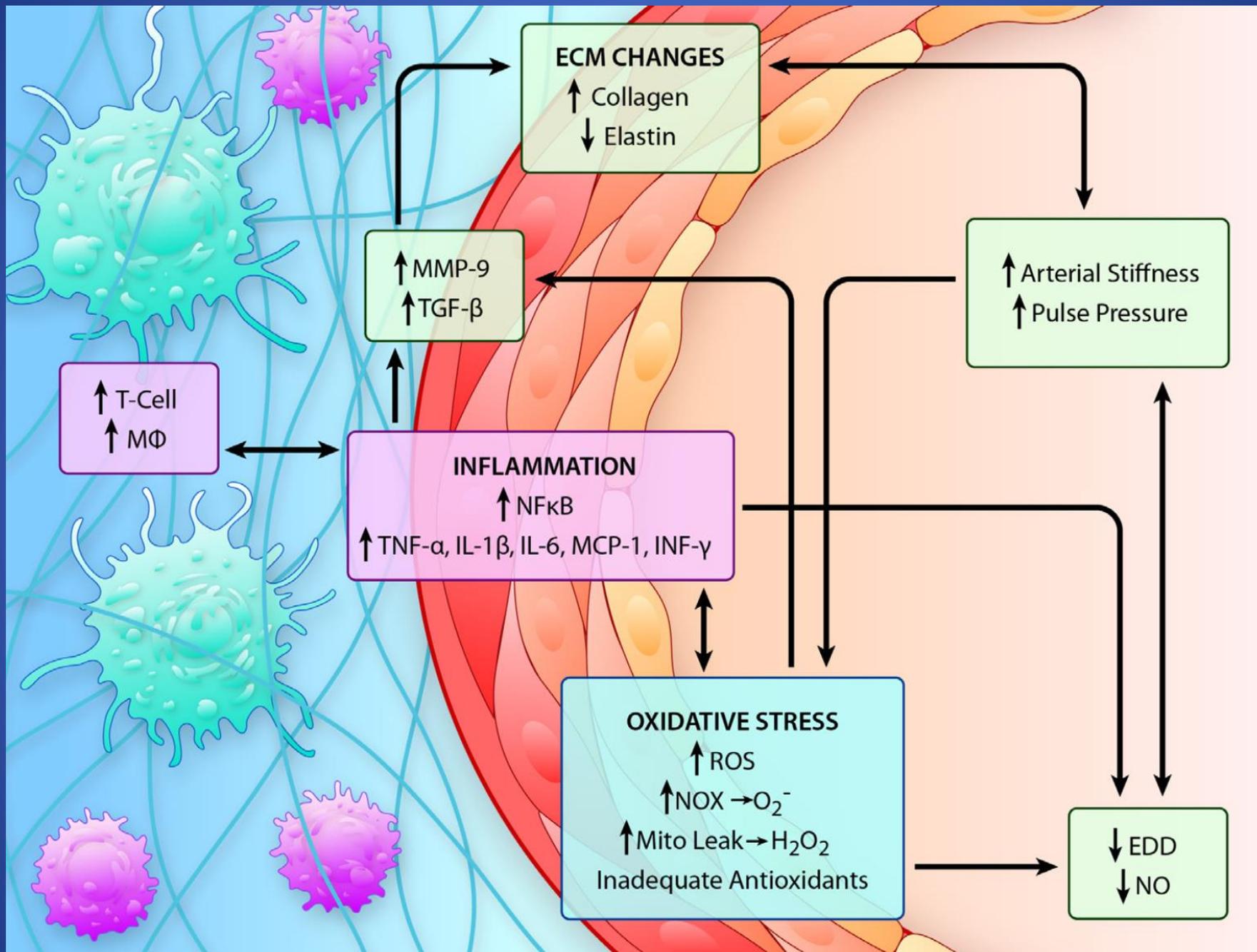
**Inflammation & Oxidative Stress**

## Functional Outcomes

**Endothelial Dysfunction &  
Arterial Stiffening**

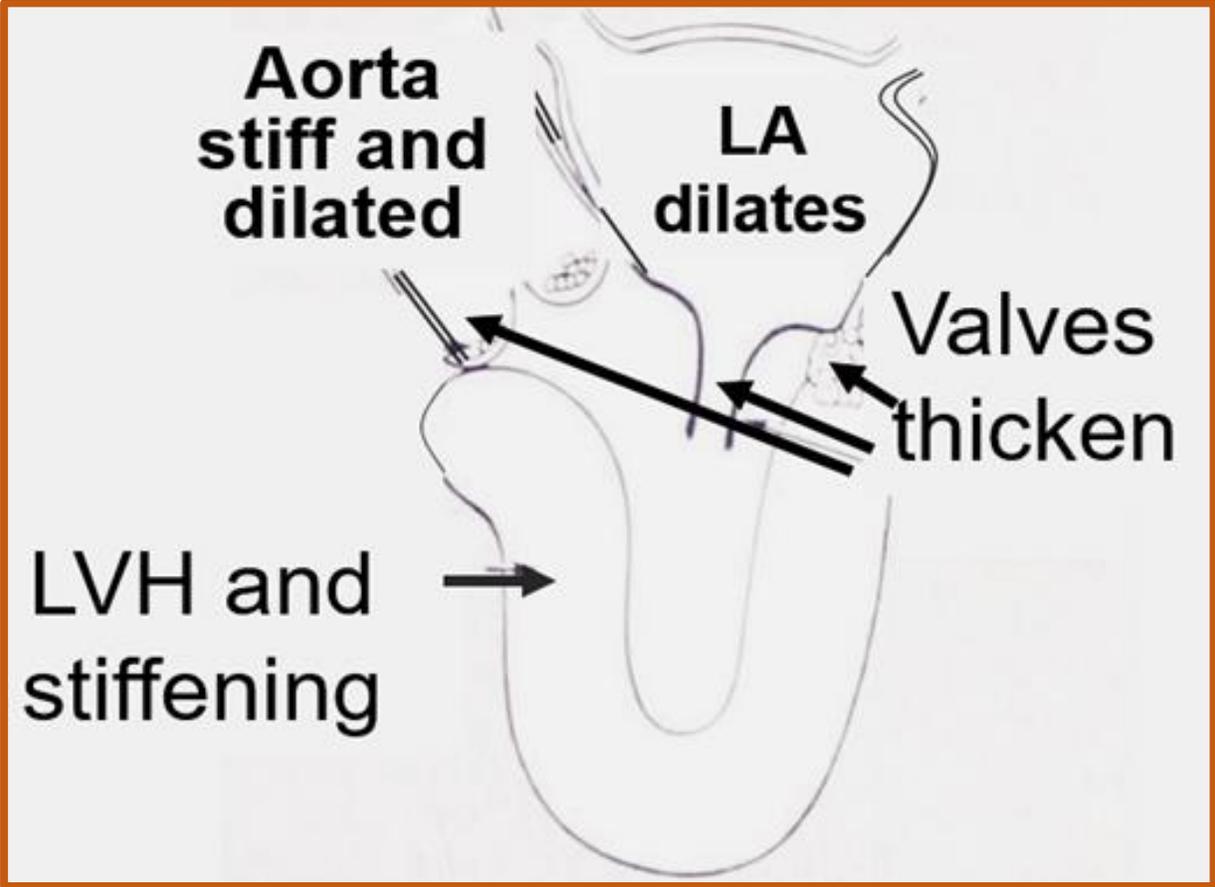
# Signaling Pathways and Genetic Factors







# Cardiovascular Coupling



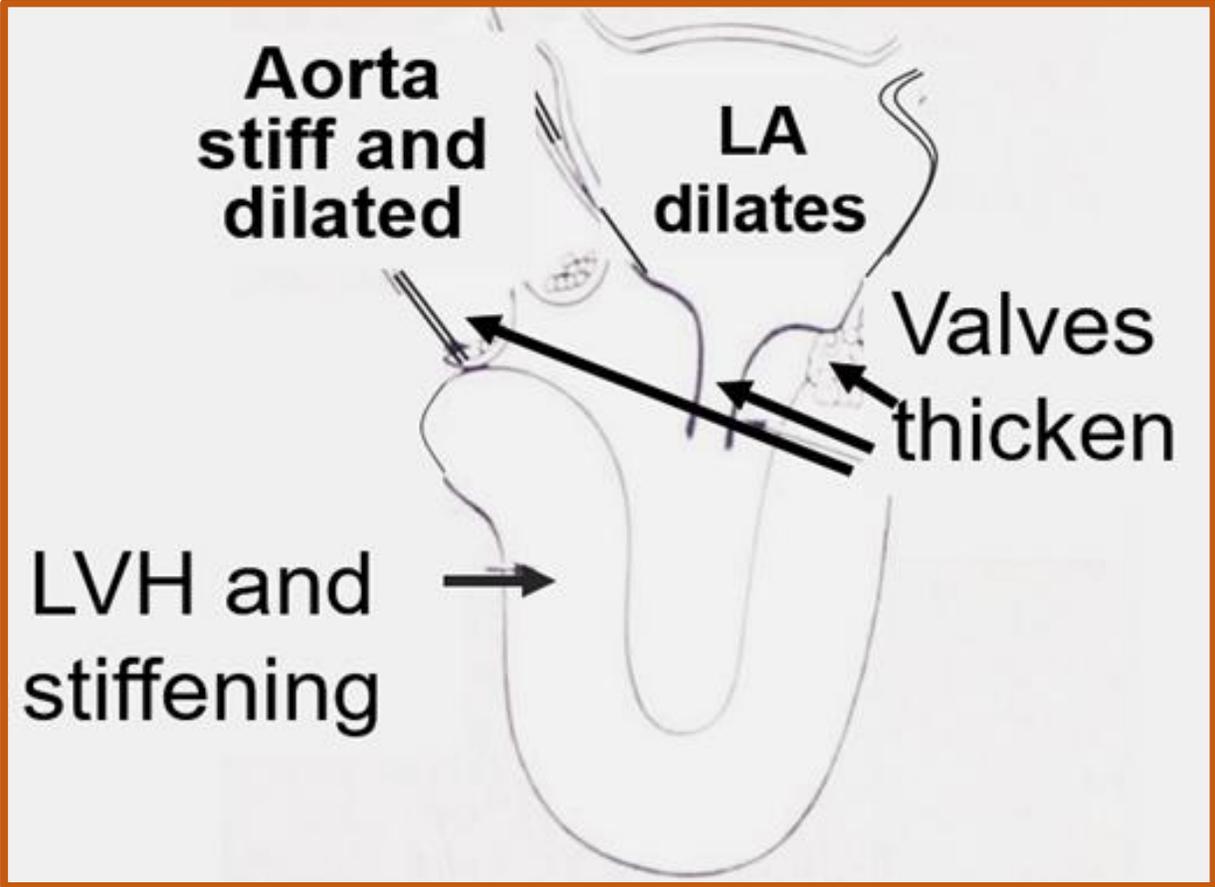
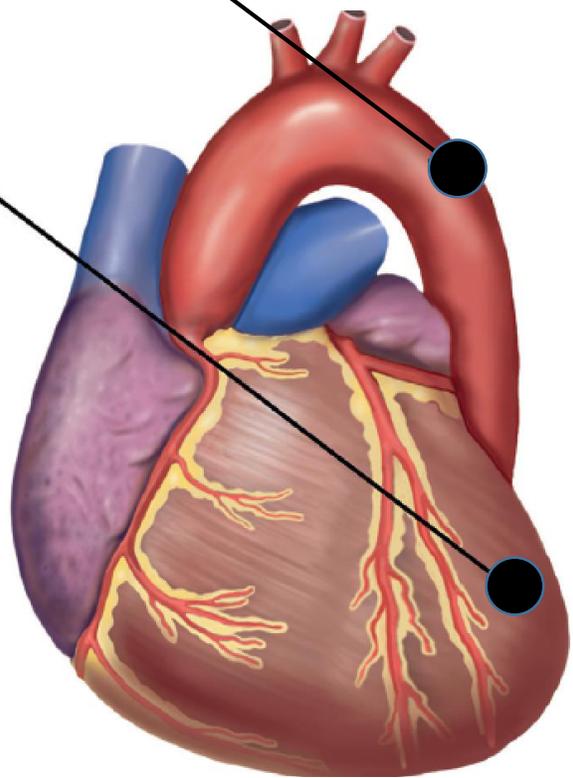
# Cardiovascular Coupling

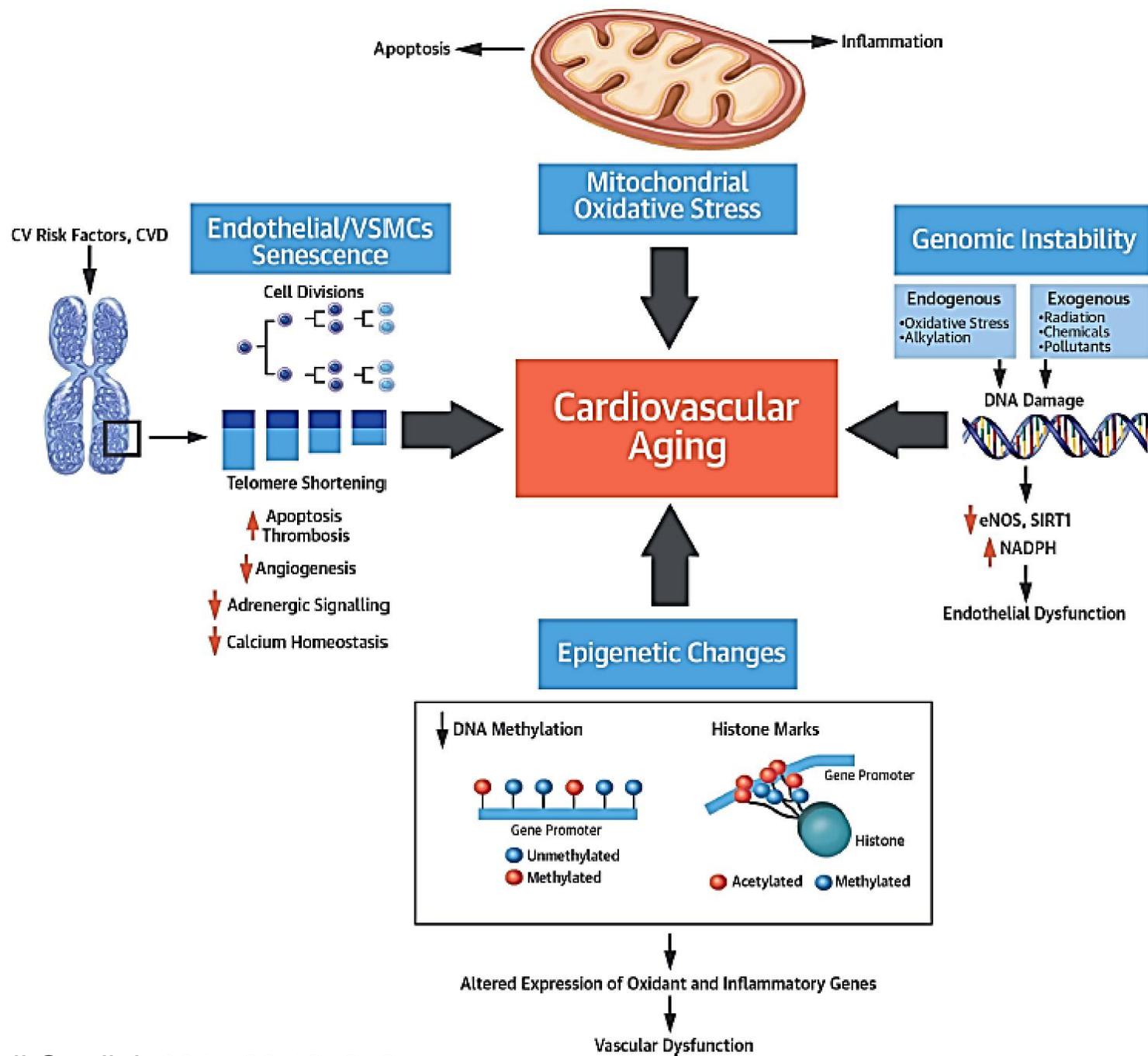
## Stiff Aorta

↑ Collagen      ↑ TGFβ  
 ↓ Elastin      ↓ Elastases  
                  MMPs 9 and 12  
                  Cathepsins S,K,L  
                  Neutrophil Elastase

## Left Ventricle

↑ Afterload      } ↑ MVO<sub>2</sub>  
 ↓ Coronary Perfusion } ↑ Ischemic Potential  
  
 Hypertrophy      } TGFβ  
 Fibrosis            } ANG II  
                           } Aldosterone  
                           ↓  
                           HFpEF  
                           HFrfEF





# Cardiac structure and function

## Physiologic Changes

### LV composition and mass

- ↓↓ numbers of myocytes
- ↑↑ myocyte hypertrophy
- ↑ deposition of collagen, fibrous tissue, amyloid, and lipofuscin within connective tissue

### LV wall thickness, cavity size, and shape

- ↑↑ myocardial thickness
- ↑↑ concentric LVH
- ↑ interventricular wall thickness
- ↑ spherical LV shape

### Left Heart Valves

- ↑ calcium deposition & collagen infiltration
- ↑ myxomatous degeneration
- ↑ fixation of valvular leaflets

### LV function

- ↓ early diastolic peak filling
- ↑ LV filling facilitated by atrial contraction
- ↑ late LV filling
- ↑ LVEDP during exercise

## Clinical Implications

### Left Ventricle

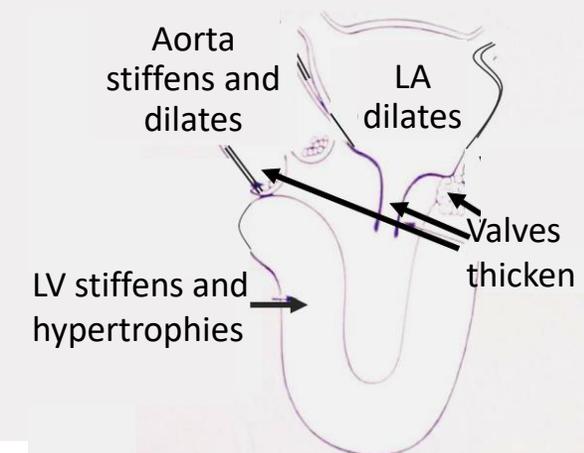
- ↑ LV stiffness and fibrosis
- ↑ LV hypertrophy and diastolic volume
- ↑↑ susceptibility to myocardial ischemia
- ↑↑ LV dysfunction and heart failure
- ↑ susceptibility to ventricular ectopy

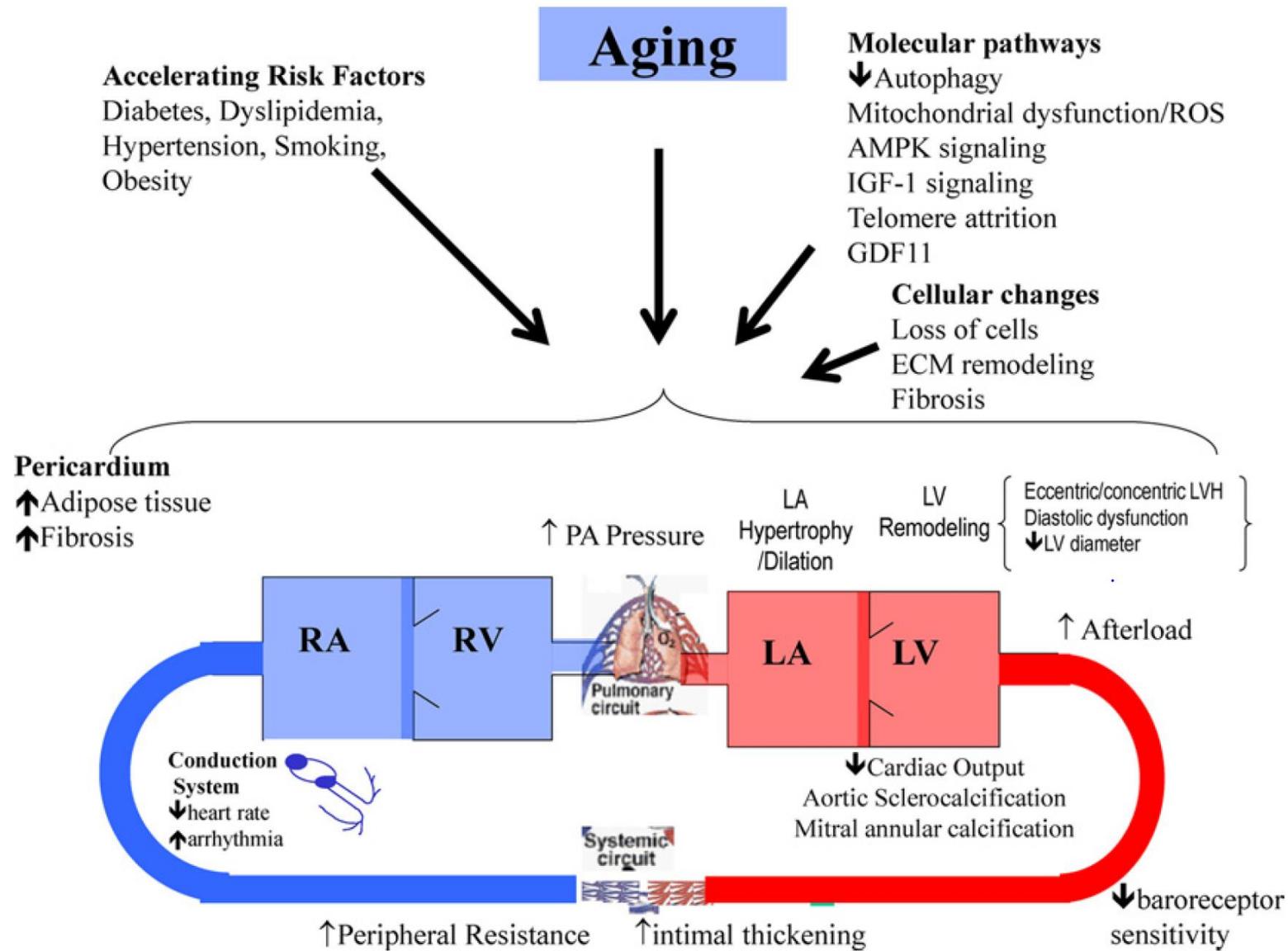
### Left Atrium

- ↑ susceptibility to atrial fibrillation

### Left Heart Valves

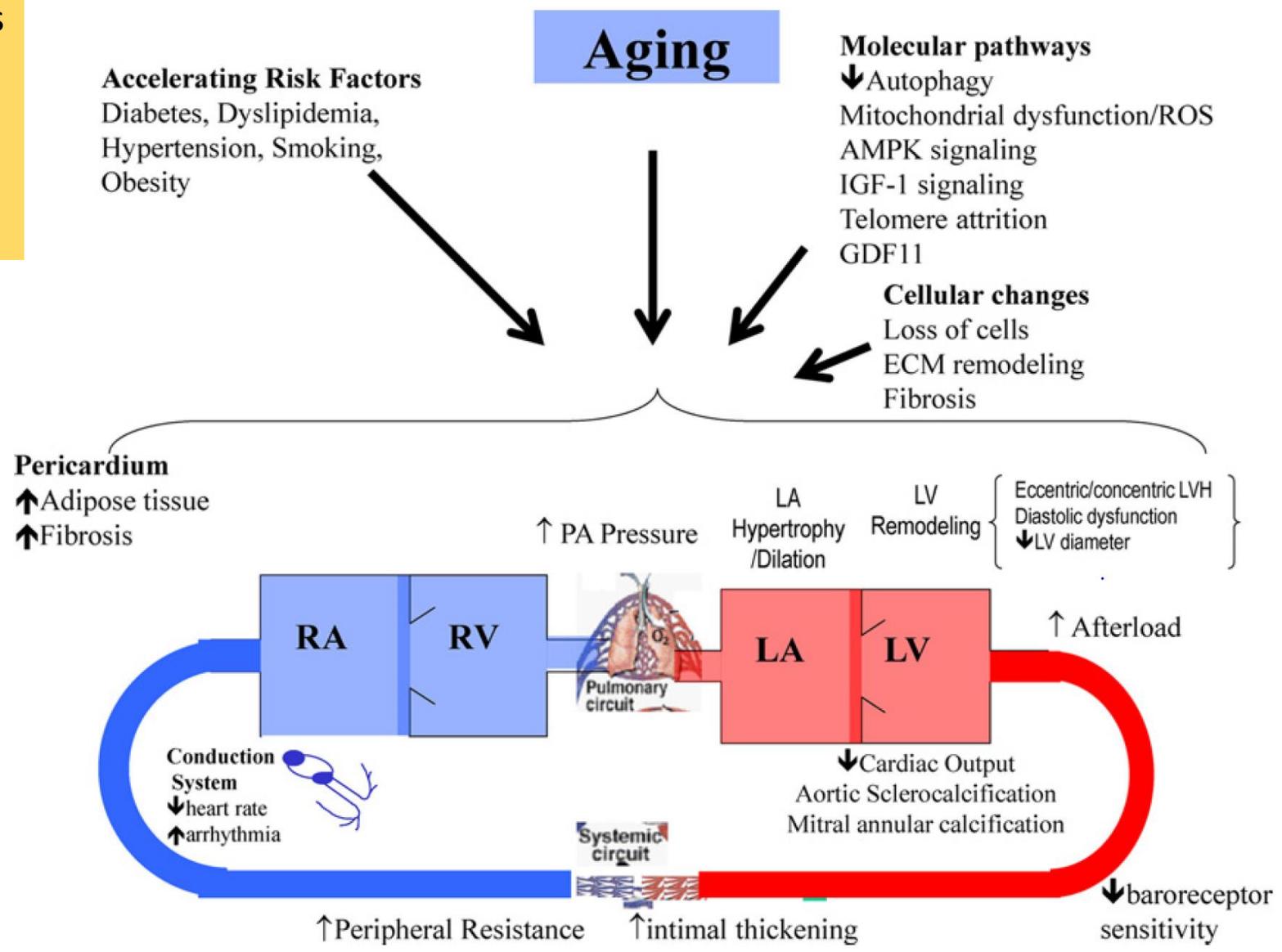
- ↑ aortic sclerosis and stenosis
- ↑ mitral annular calcification
- ↑ mitral and aortic regurgitation





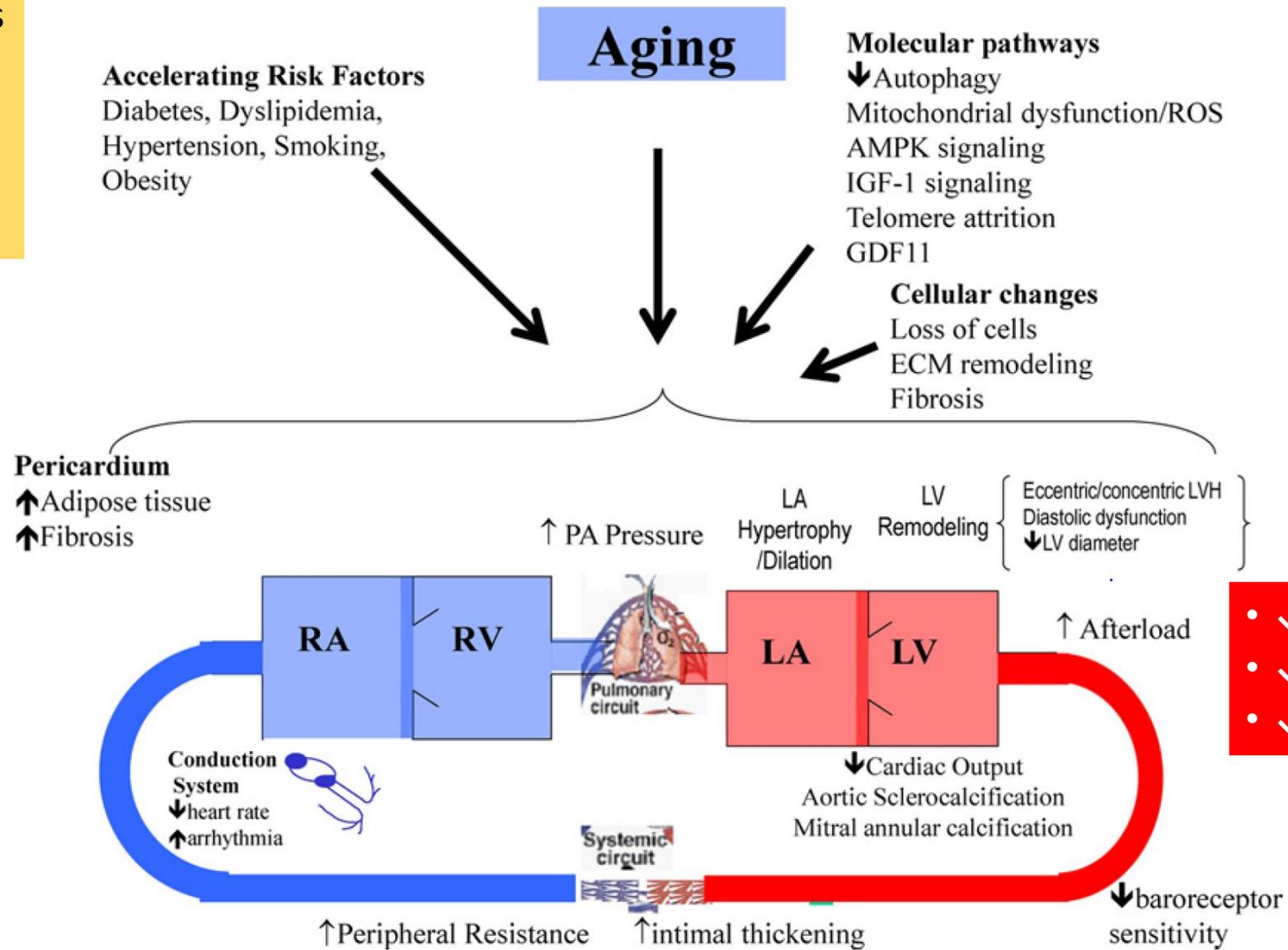
- Environmental Stress – Pollution
- Sedentariness
- Social Determinants of Health

- Inflammation
- Senescence
- Genetics
- Epigenetics
- Proteostasis



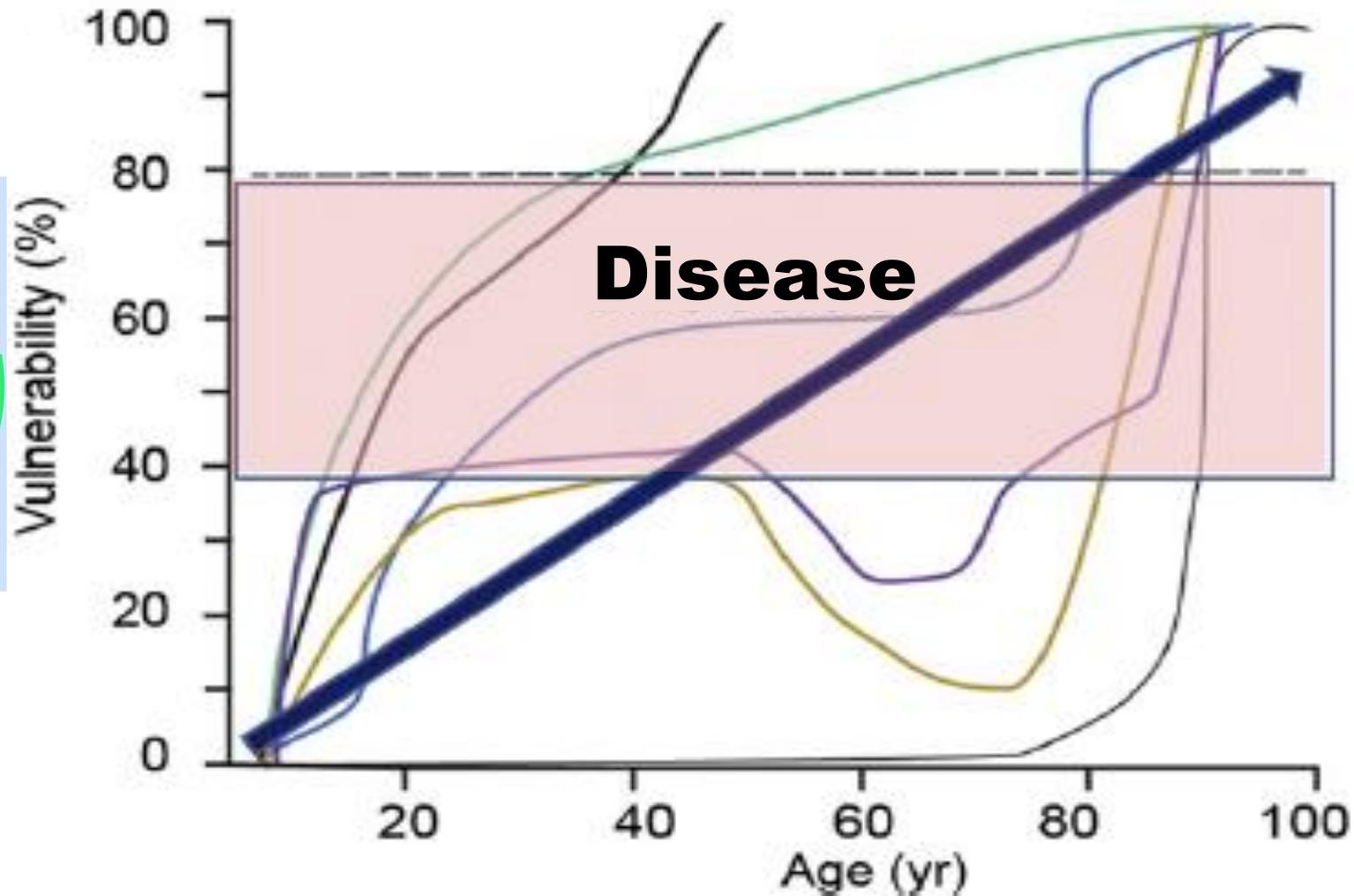
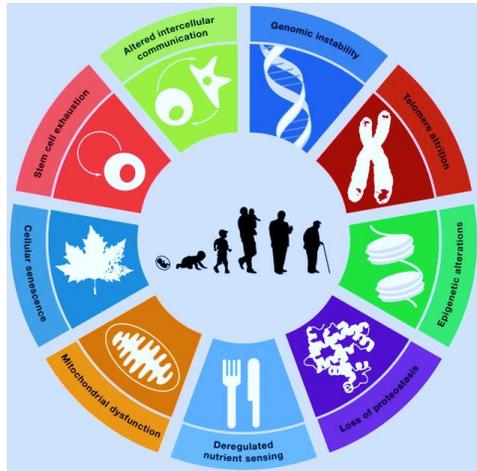
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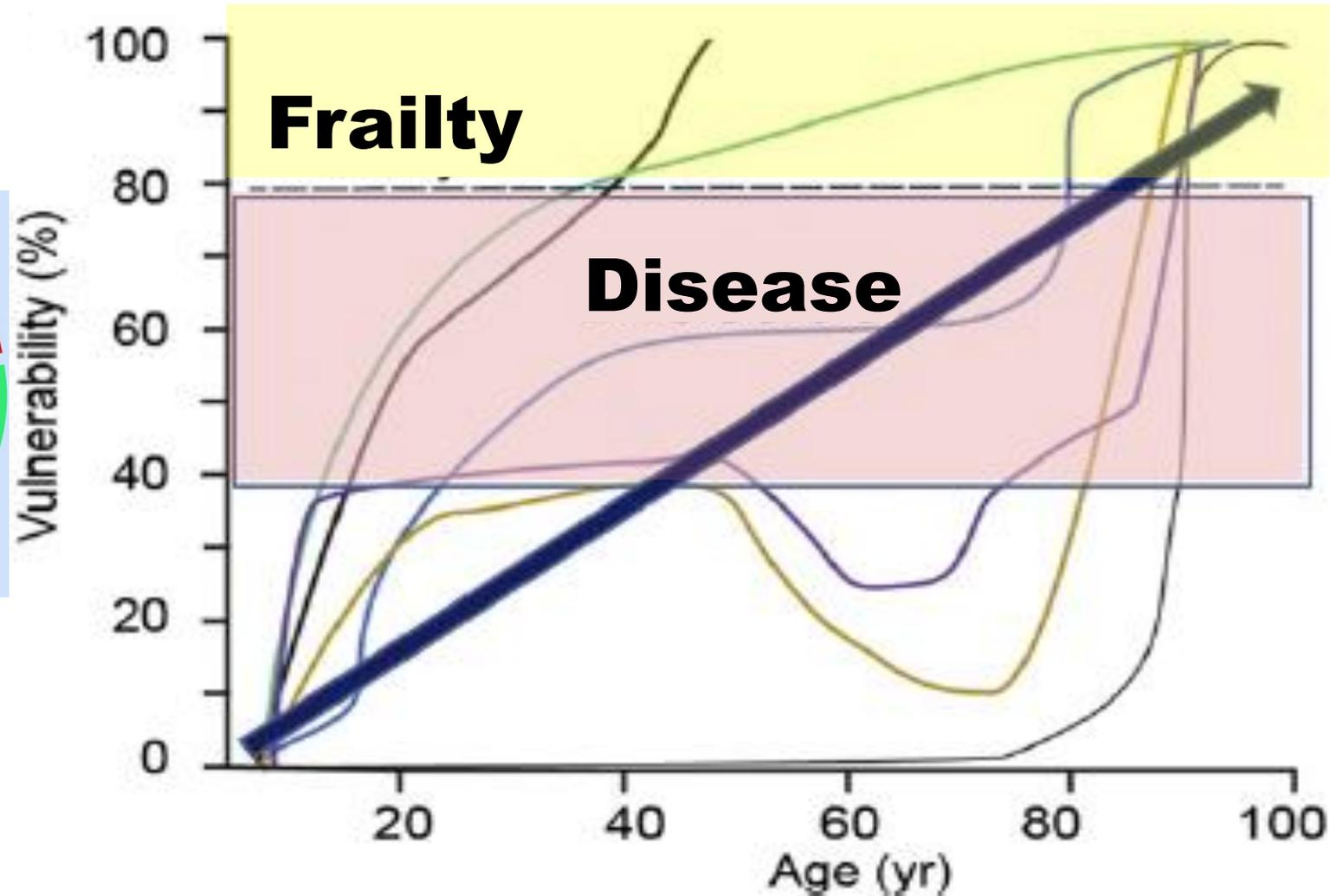
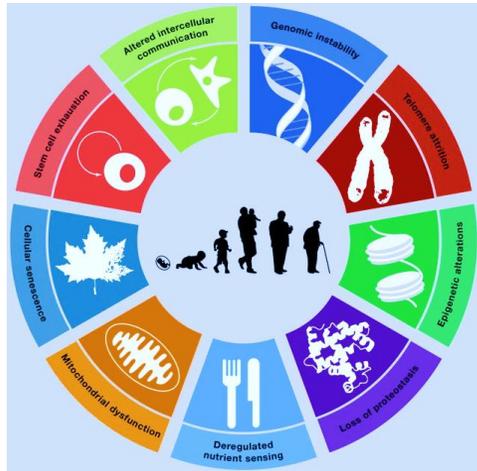


- ↓ Renal function
- ↓ Pulmonary function
- ↓ Autonomic function

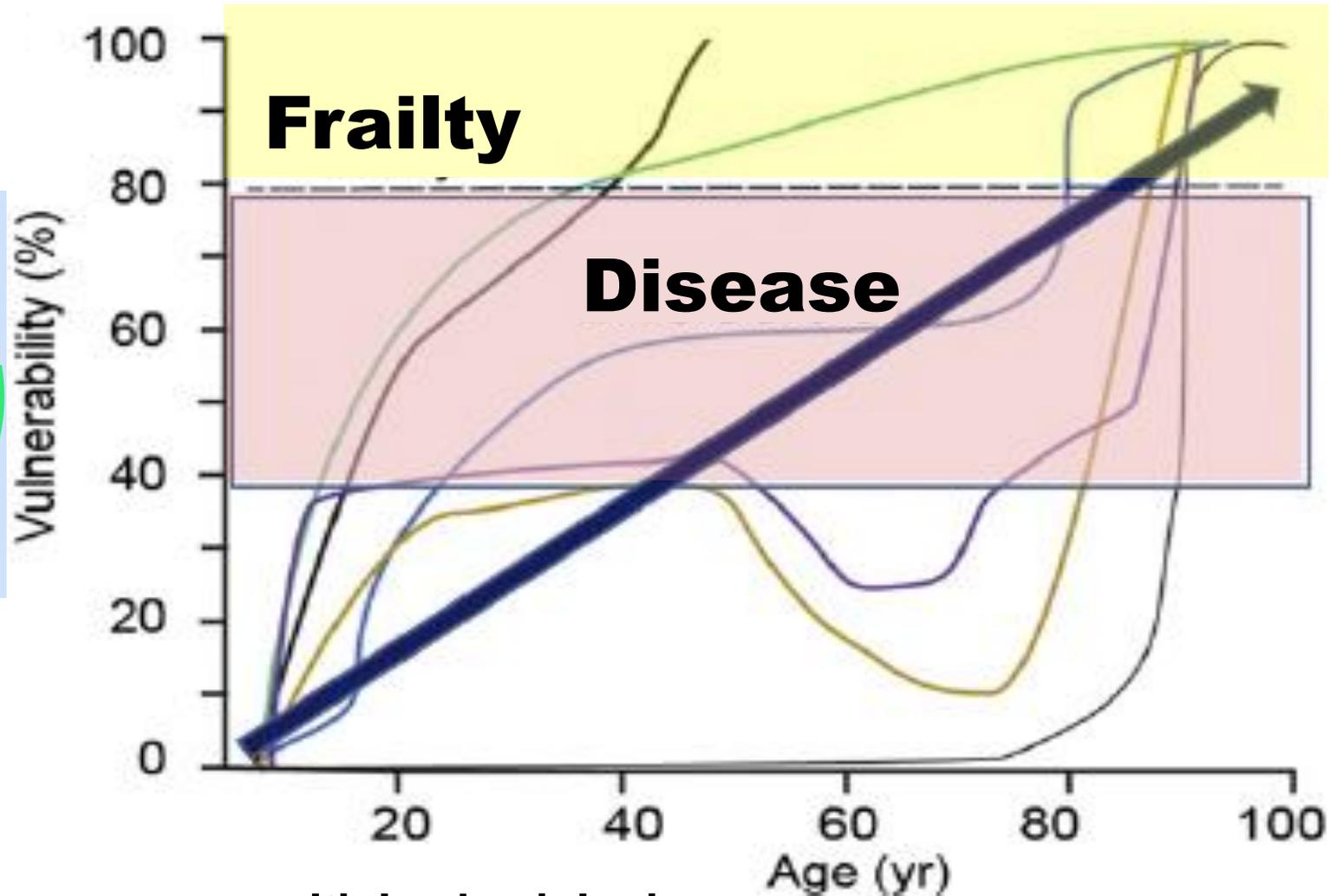
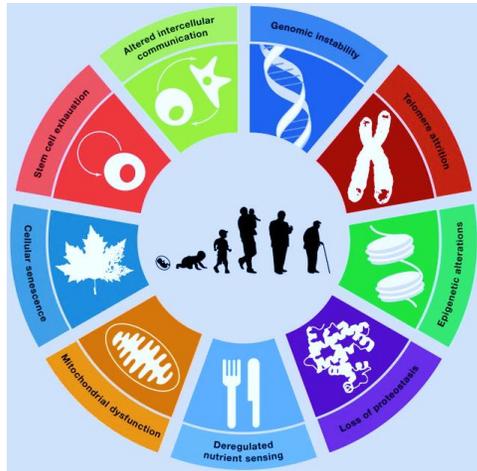
# Age: CVD with Cumulative Disease and Vulnerability



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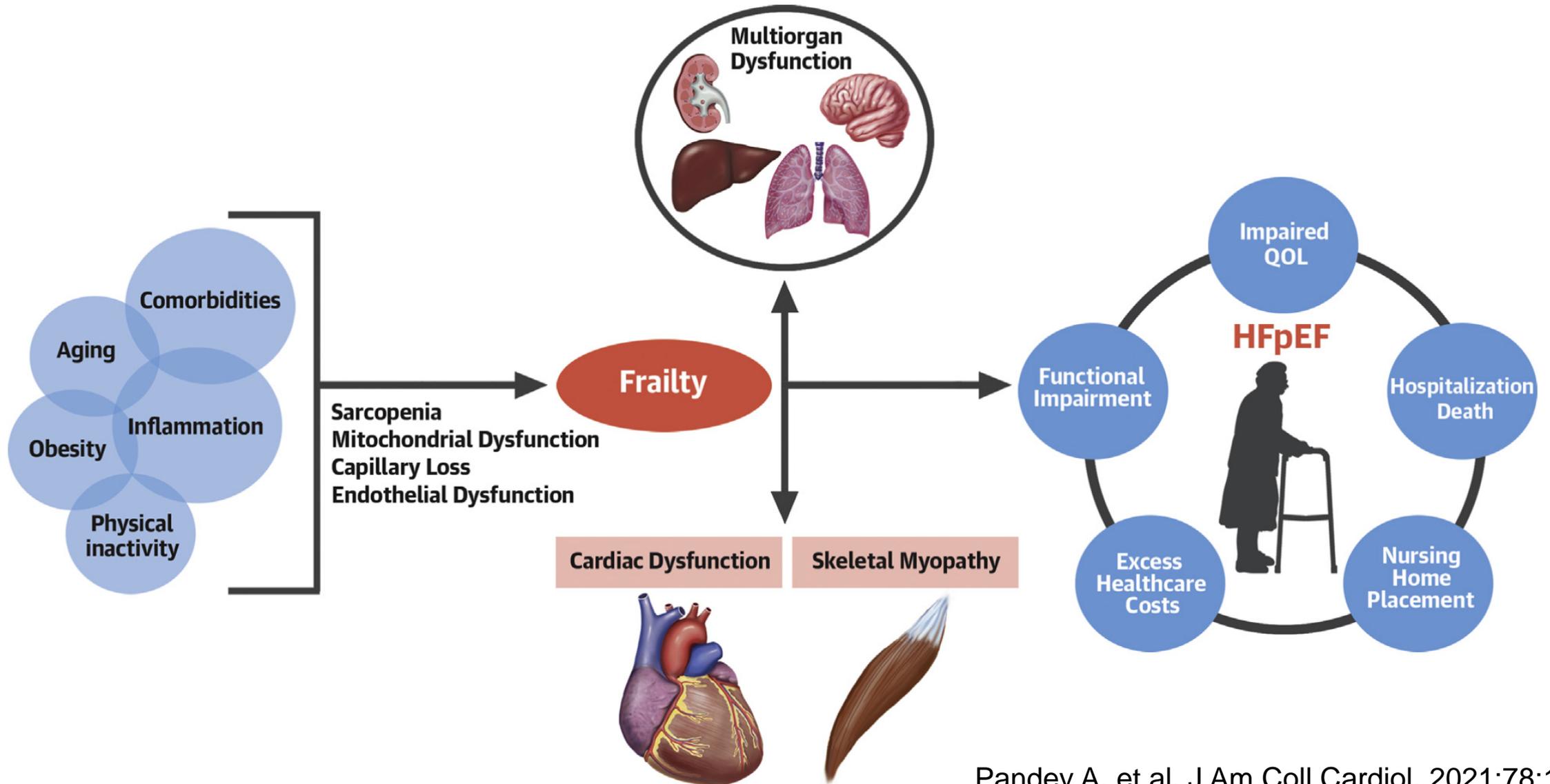
# Age: CVD with Cumulative Disease and Vulnerability



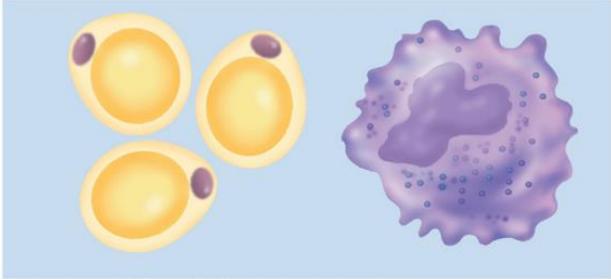
Cumulative declines across multiple physiologic systems: ↓ Reserve to tolerate stressors

	Physiologic Changes	Clinical Implications
<b>Compounding physiological changes</b>	<ul style="list-style-type: none"><li>• ↓Cardiovascular reserves</li><li>• ↓Function compounded by multimorbidity</li><li>• ↑Polypharmacy</li><li>• ↑Sarcopenia</li><li>• ↑Changes in fat distribution</li><li>• ↑Intramuscular fat</li><li>• ↓Cardiorespiratory fitness (peak oxygen uptake[VO<sub>2</sub>])</li></ul>	<ul style="list-style-type: none"><li>• ↓Muscle function</li><li>• ↑Exercise intolerance</li><li>• ↑Fatigue</li><li>• ↓Activity</li><li>• ↓Functional independence</li><li>• ↓Quality of life</li><li>• ↑Frailty</li><li>• ↑Disability</li></ul>

# Distinctive Age-Related Vulnerabilities to Cardiac Pathophysiology

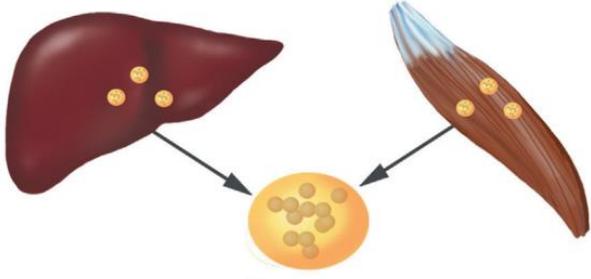


**Adipose Tissue** **Ectopic Lipids**

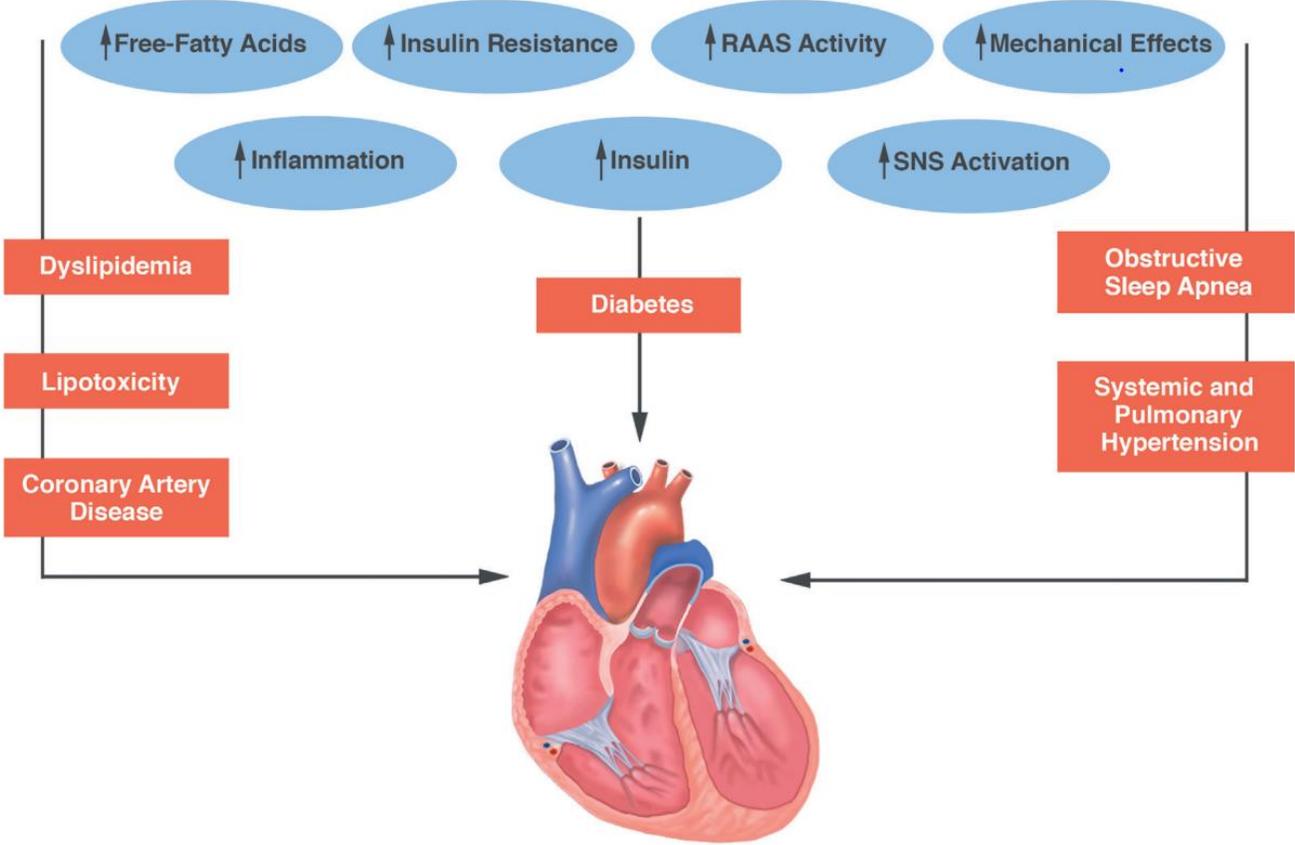


Fat Cells

Macrophage

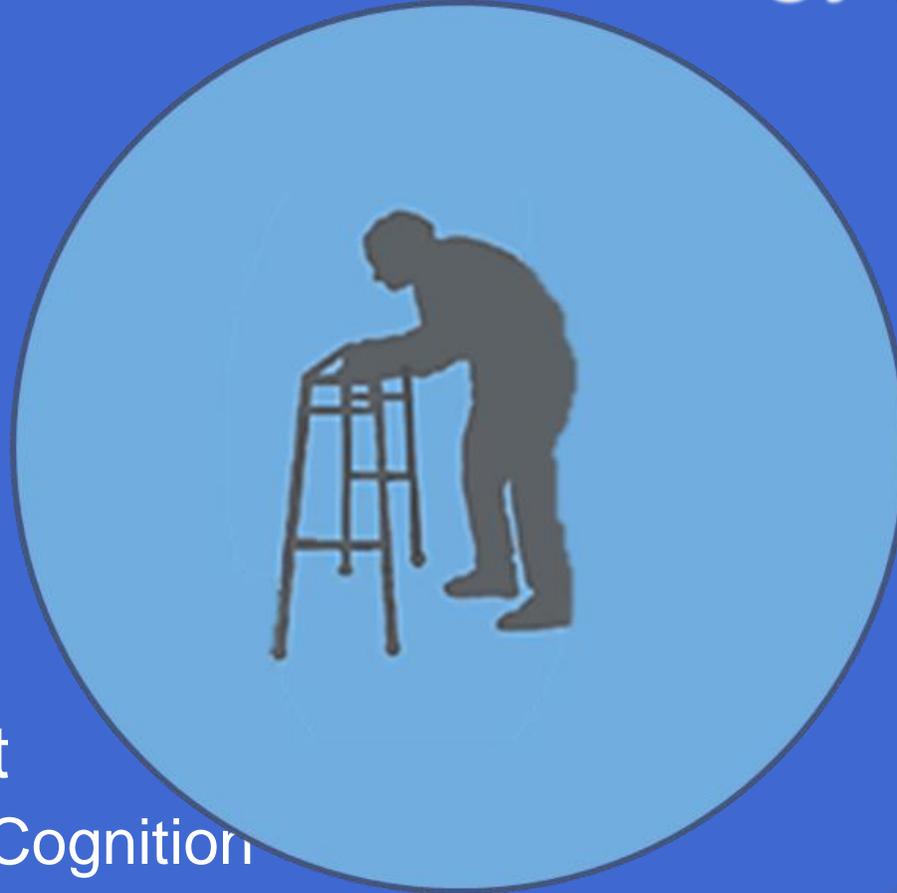


Liposomes



**Heart Failure**

# Geriatric Cardiology



- Diagnosis
  - Multimorbidity
- Risk Assessment
  - Multimorbidity
  - Frailty
  - Cognition
  - Biological
- Disease Management
  - Multimorbidity, Frailty, Cognition
  - Pharmacology
  - Function, Falls
  - Quality of life

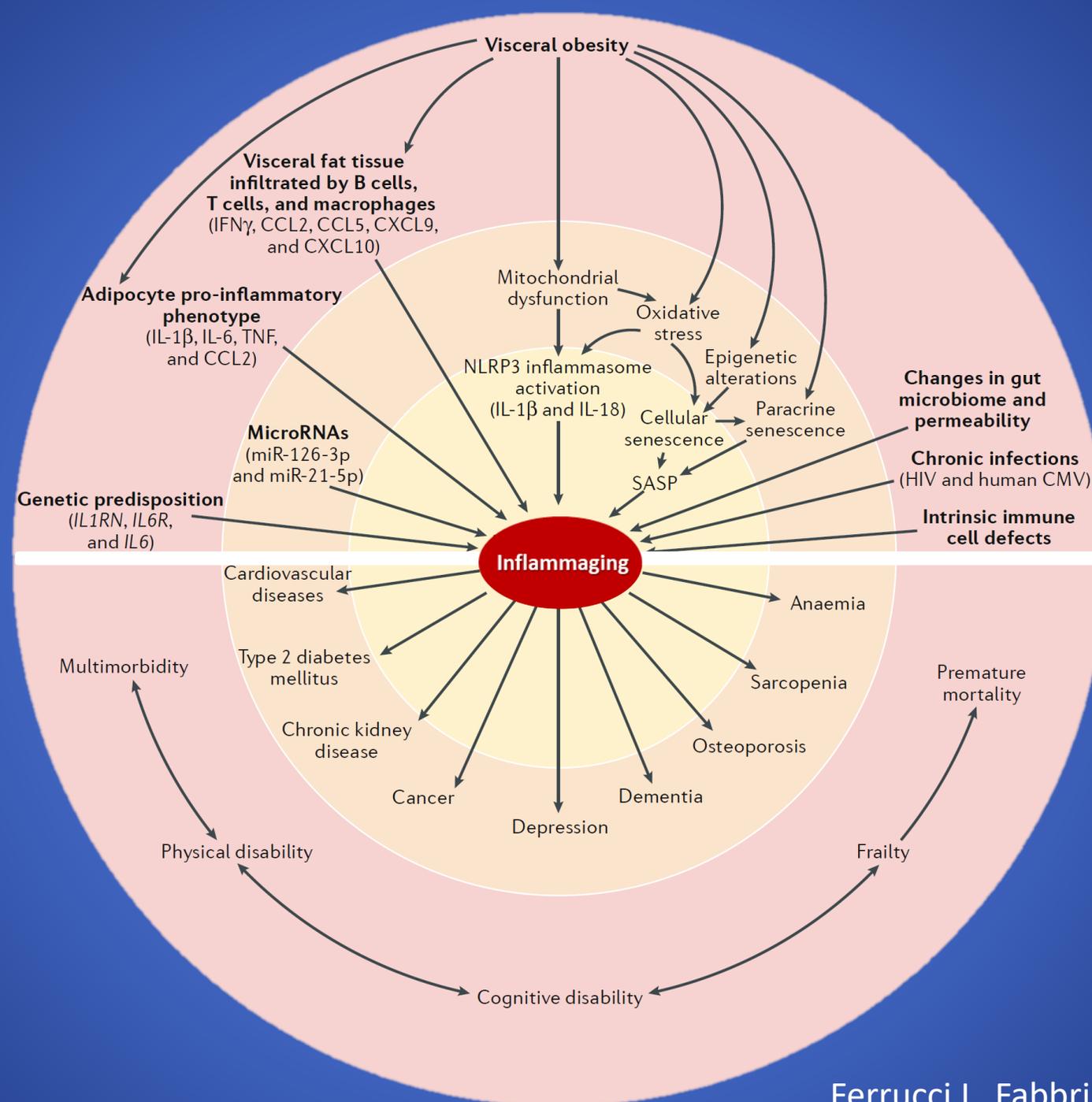
- Process of care
  - Shared Decision Making
  - Transfers
  - Independence
  - Access
  - Palliative Care
- Psychosocial
  - Health Literacy
  - Disparities

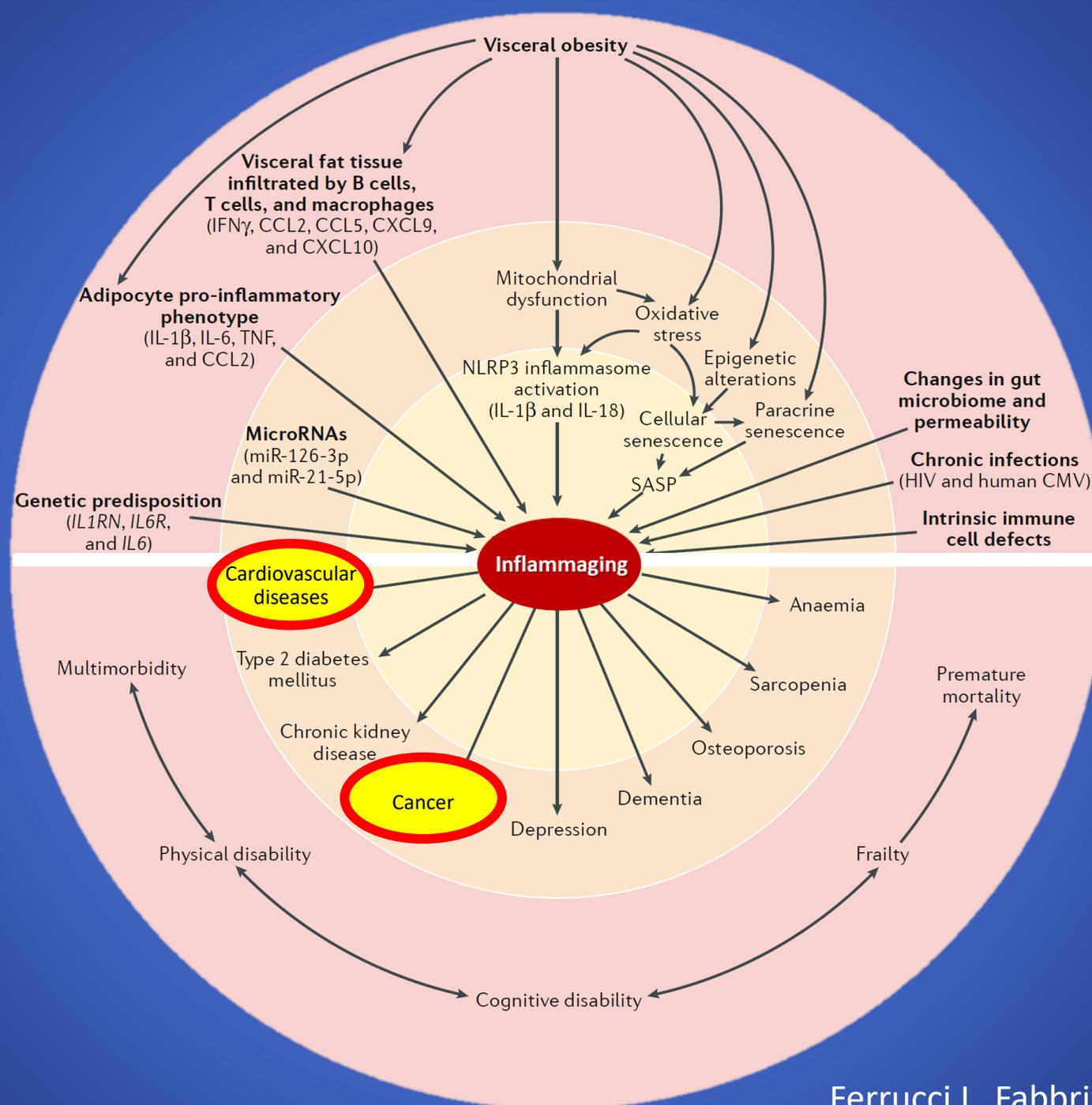
# Geriatric Cardiology

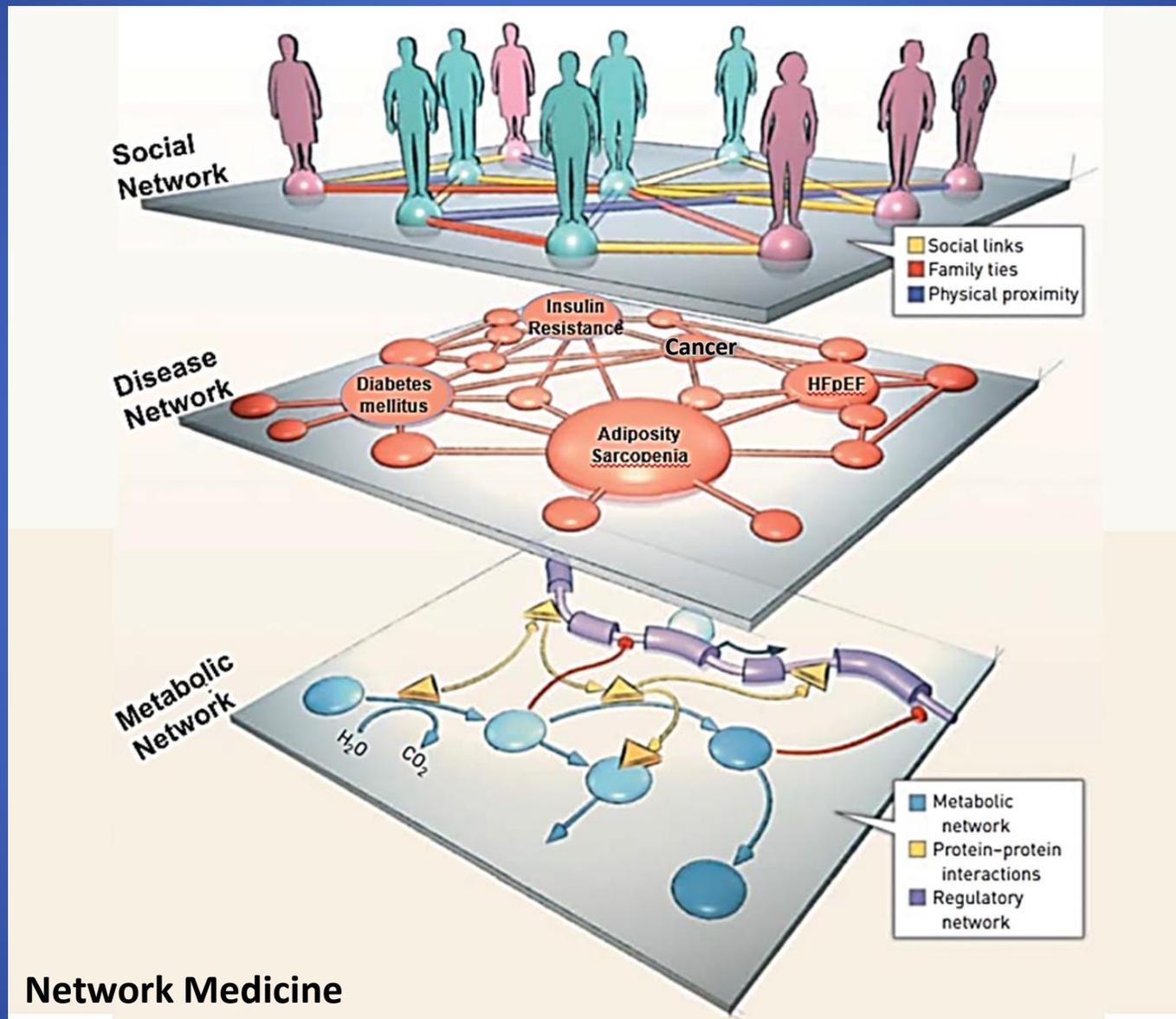
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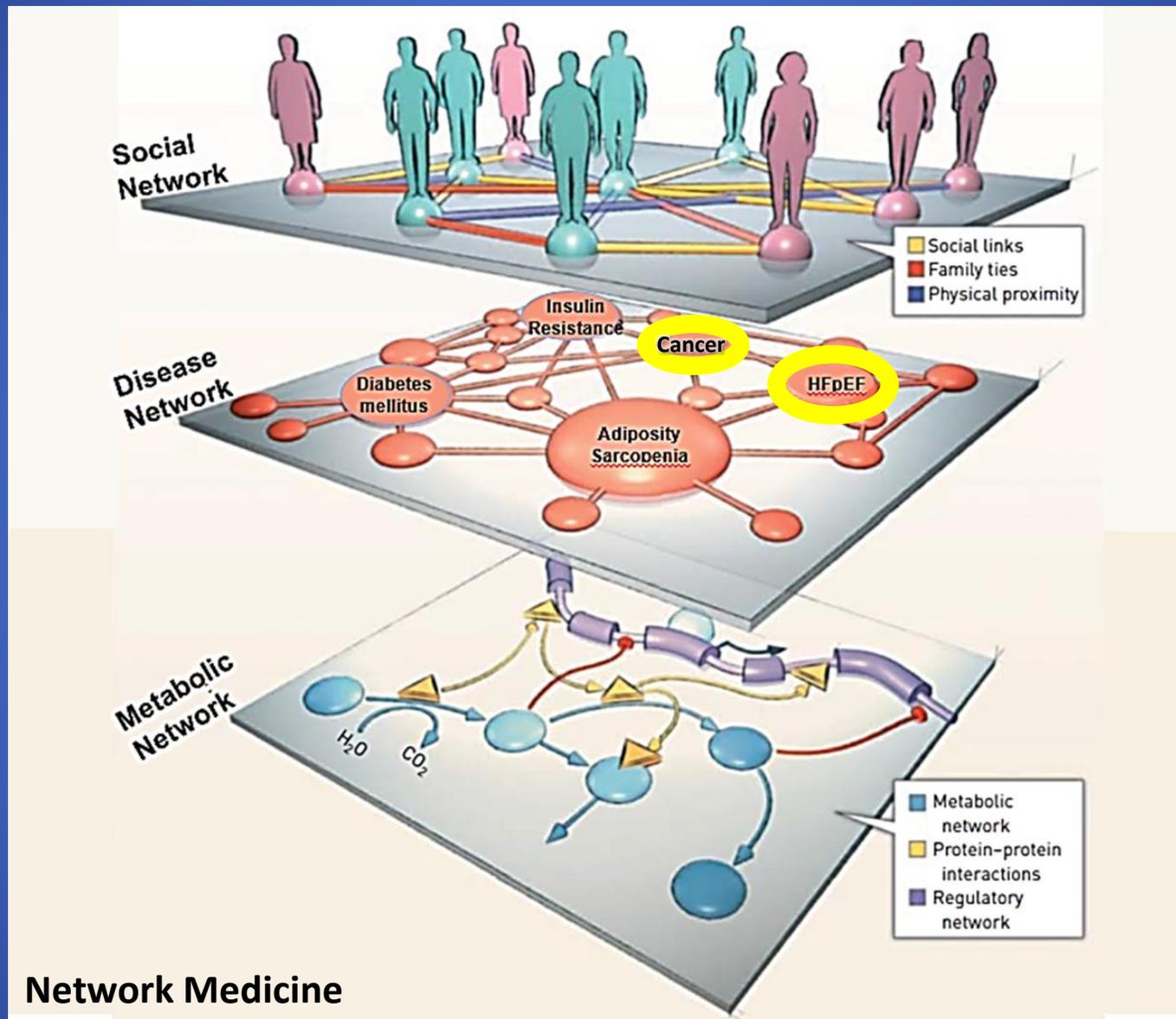


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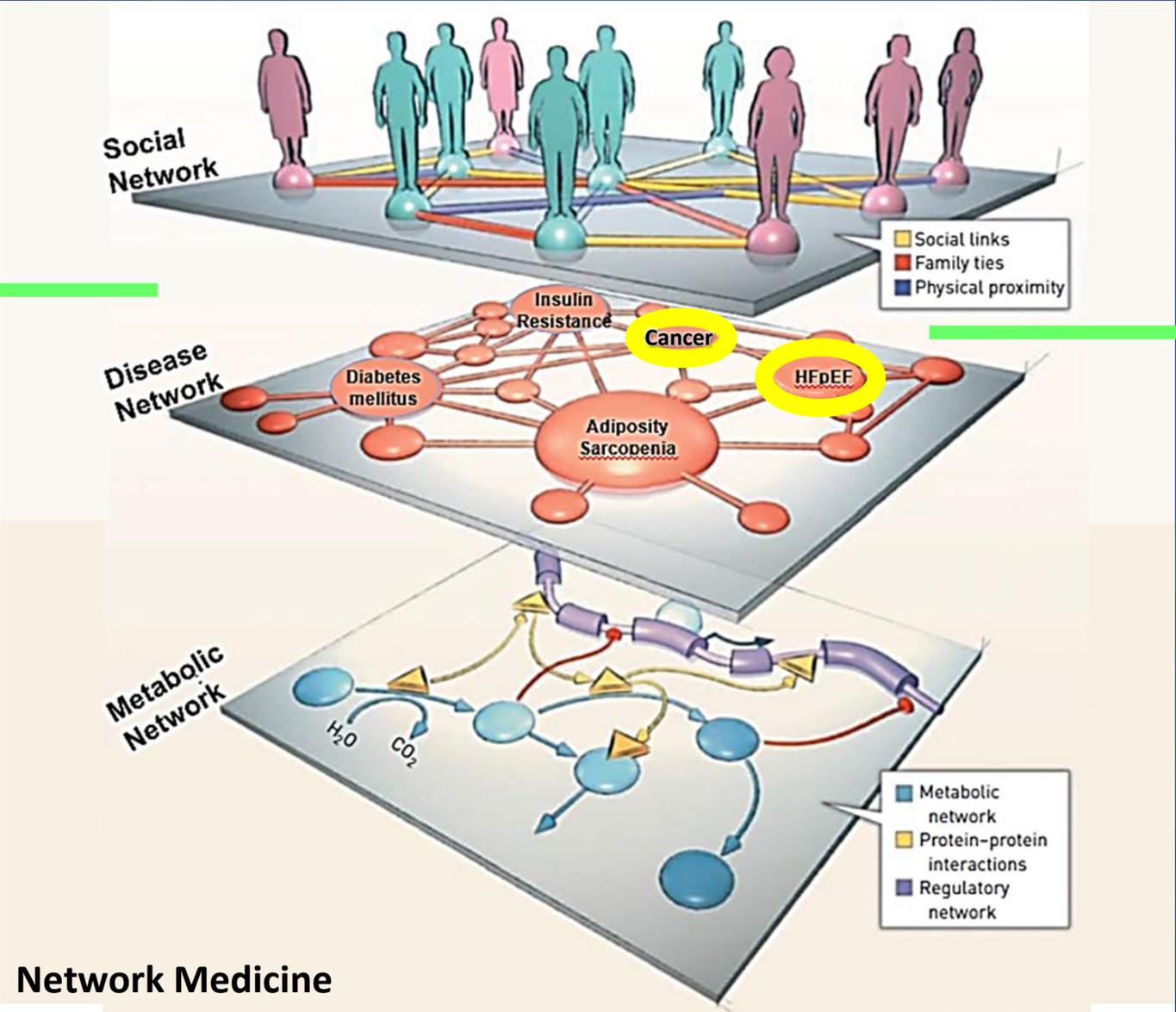






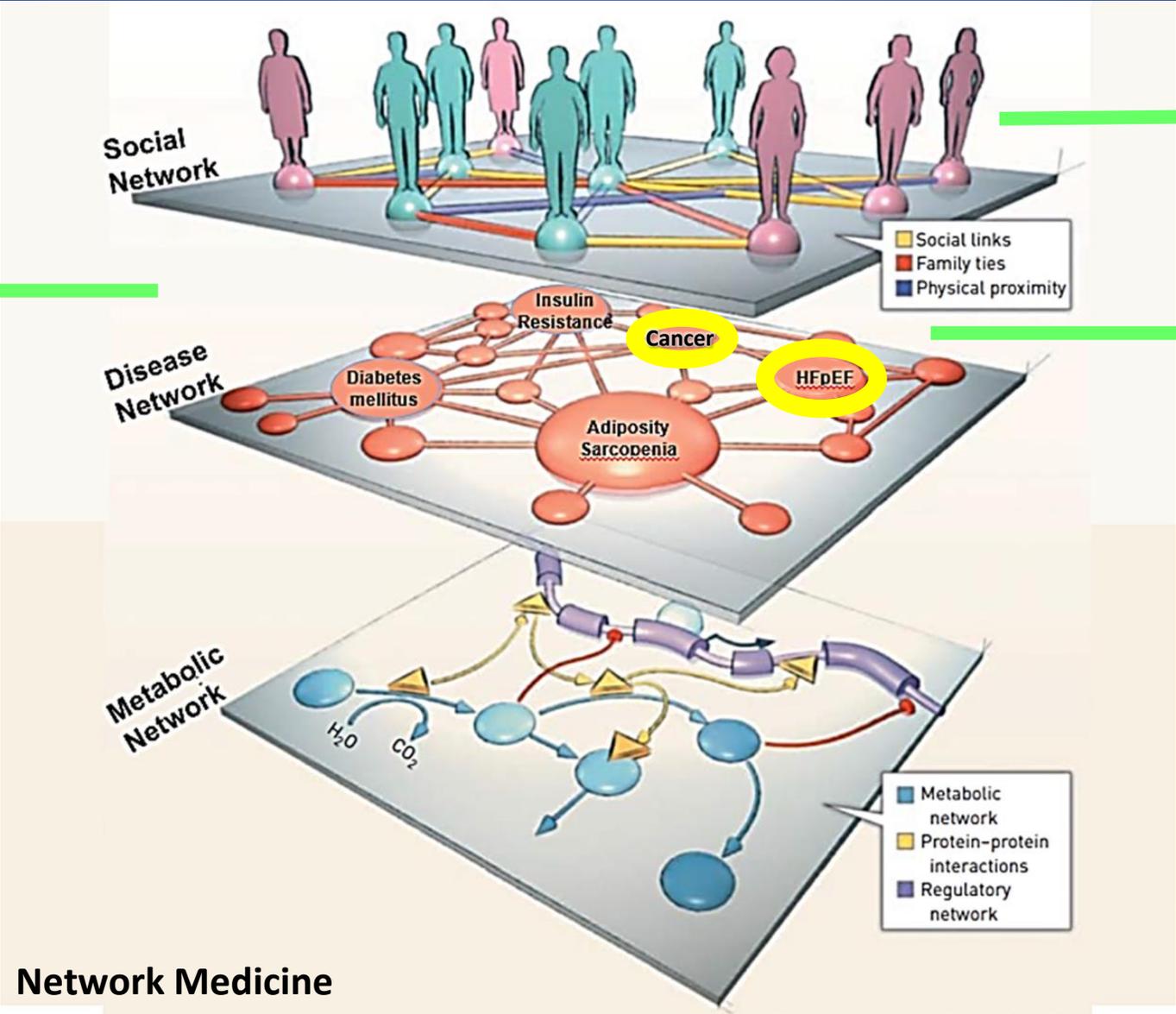


- Frailty
- Cognitive Decline
- Functional decline
- Falls



Diminished cardiovascular reserves

- Frailty
- Cognitive Decline
- Functional decline
- Falls

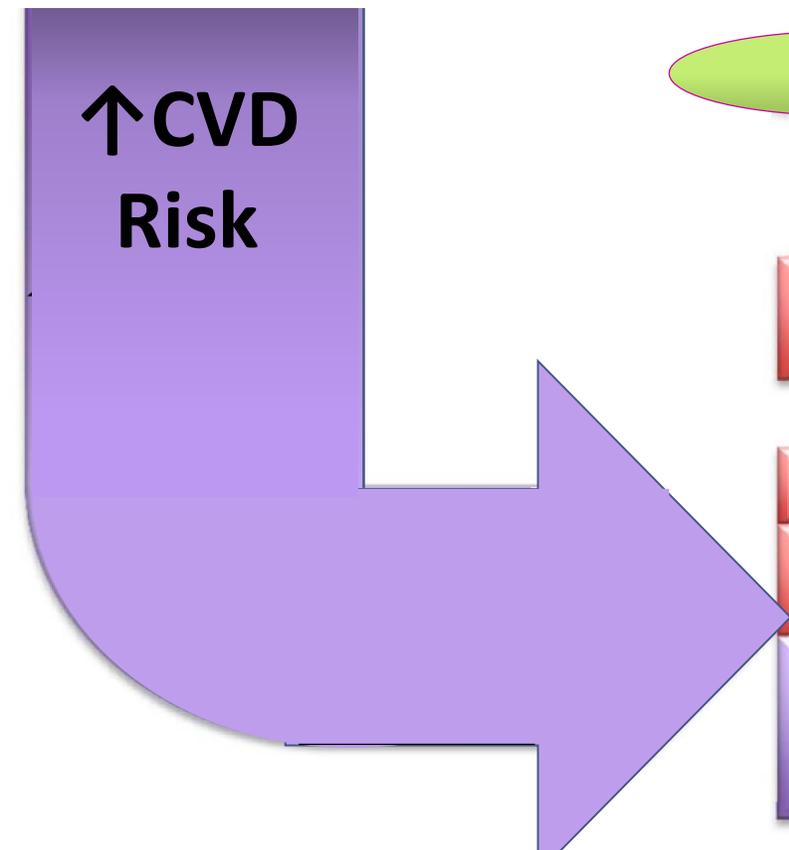
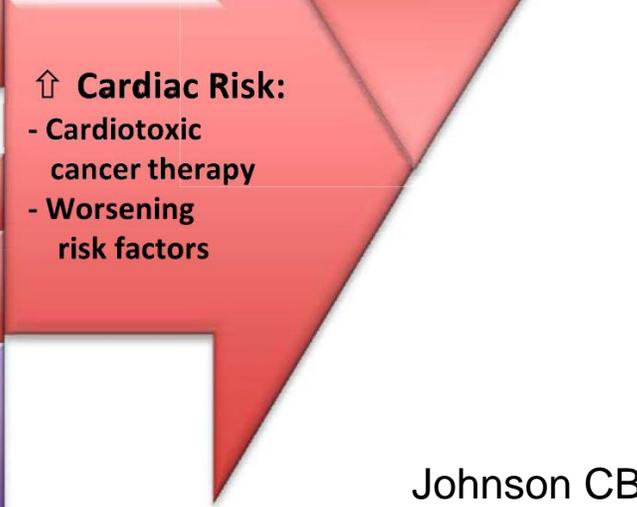


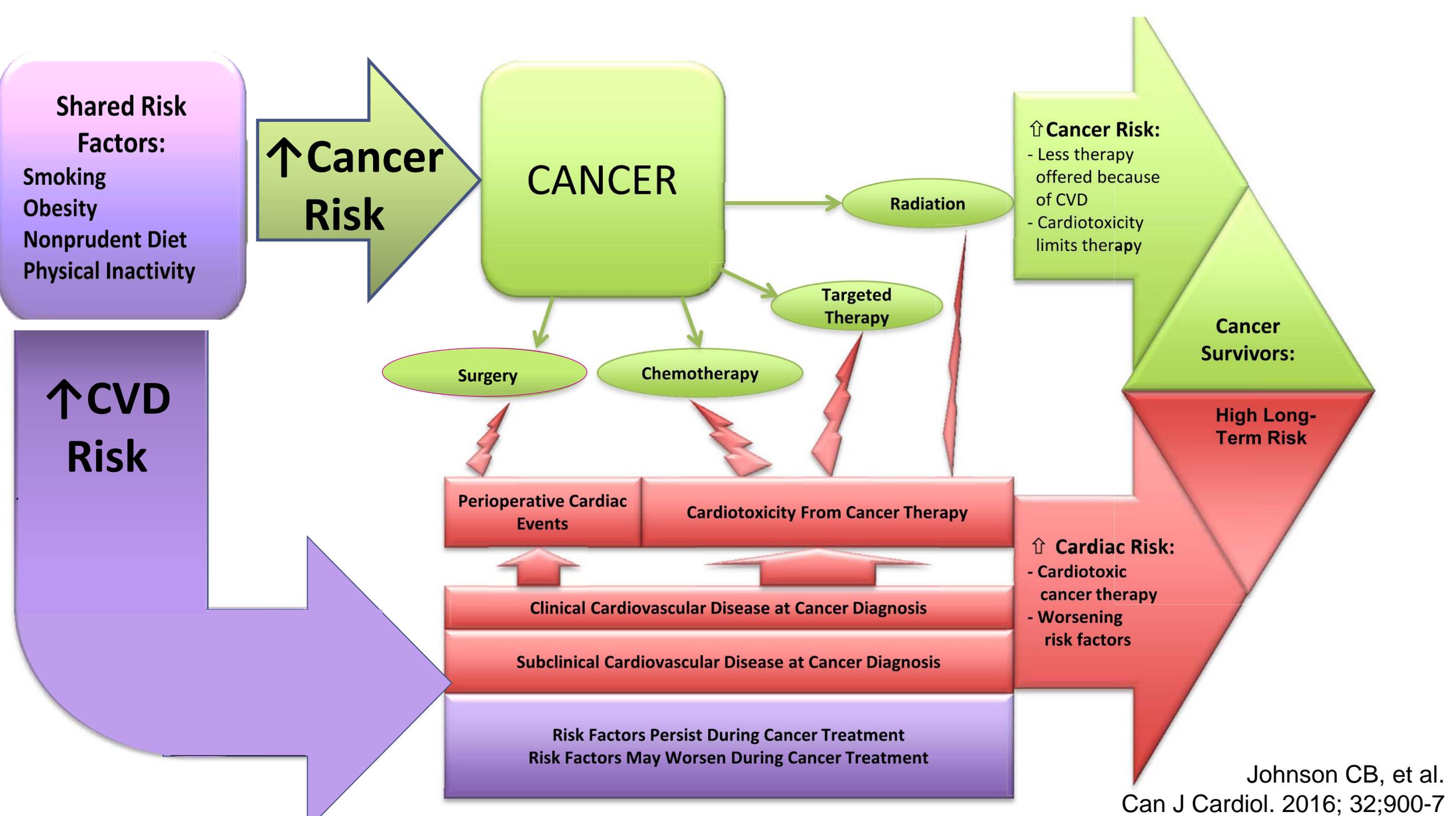
Multiple clinicians and providers, each with their own priorities of care

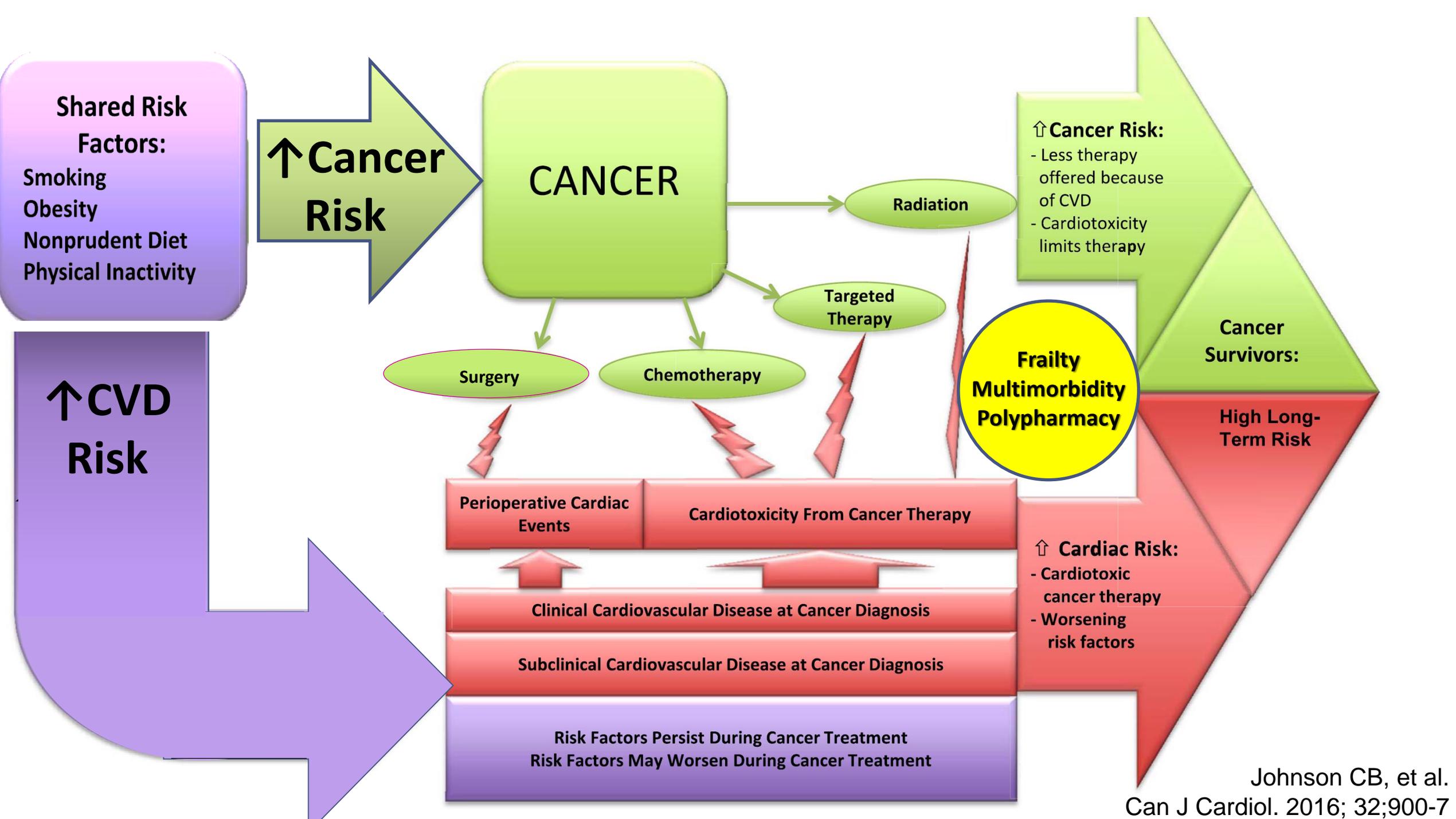
Diminished cardiovascular reserves

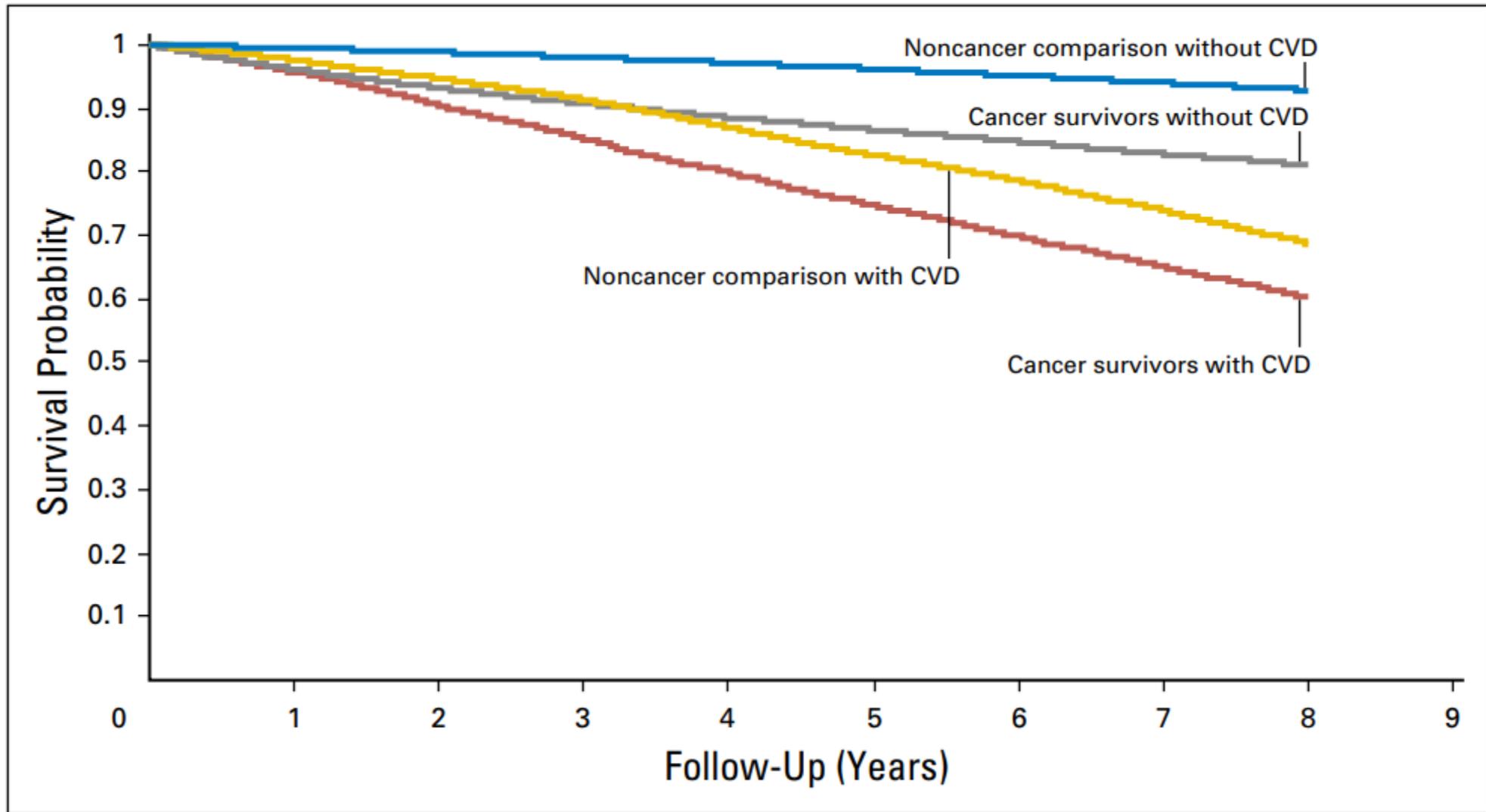
Network Medicine

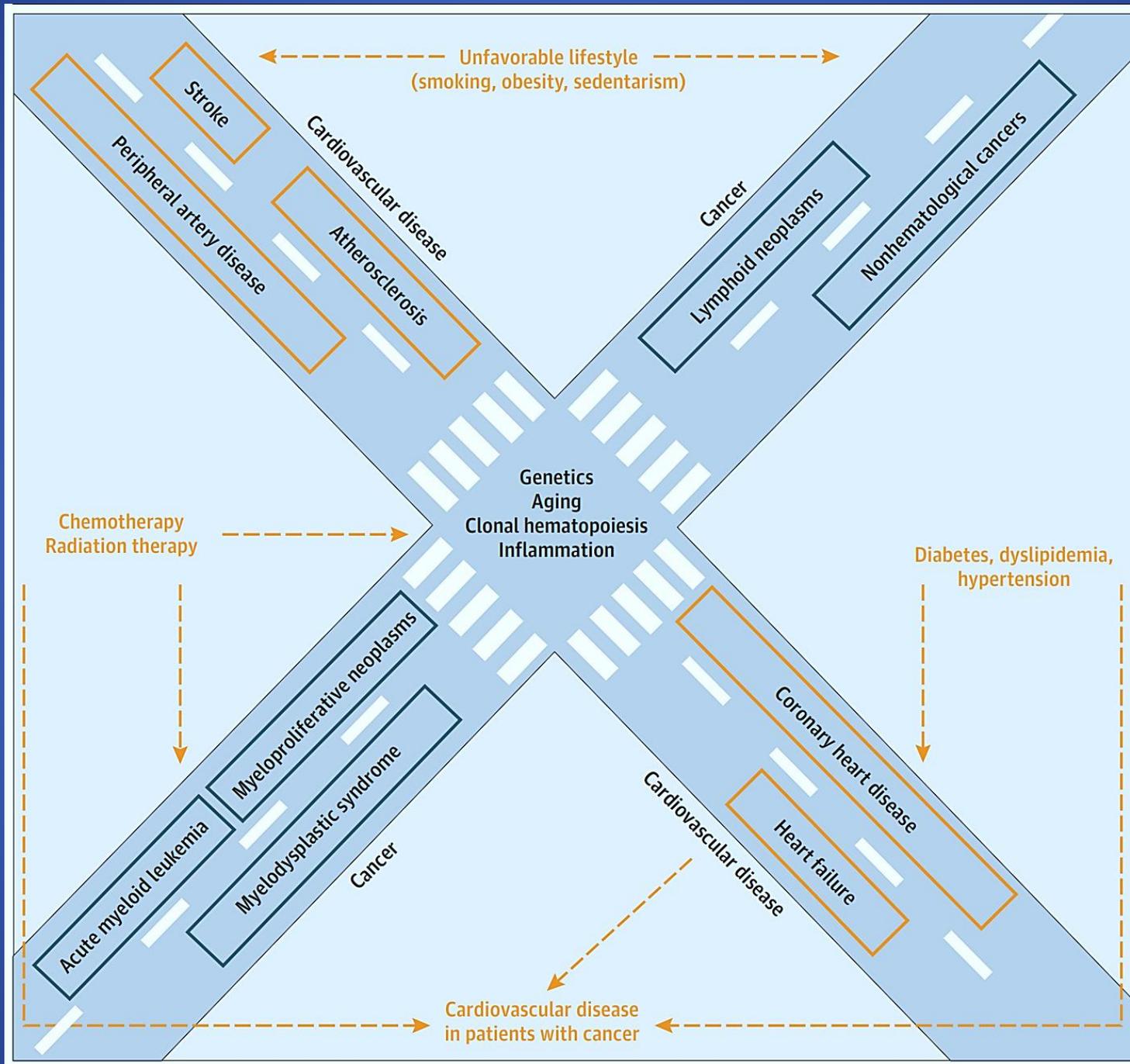
Adapted from Barabasi AL. N Engl J Med. 2007;357:404-7





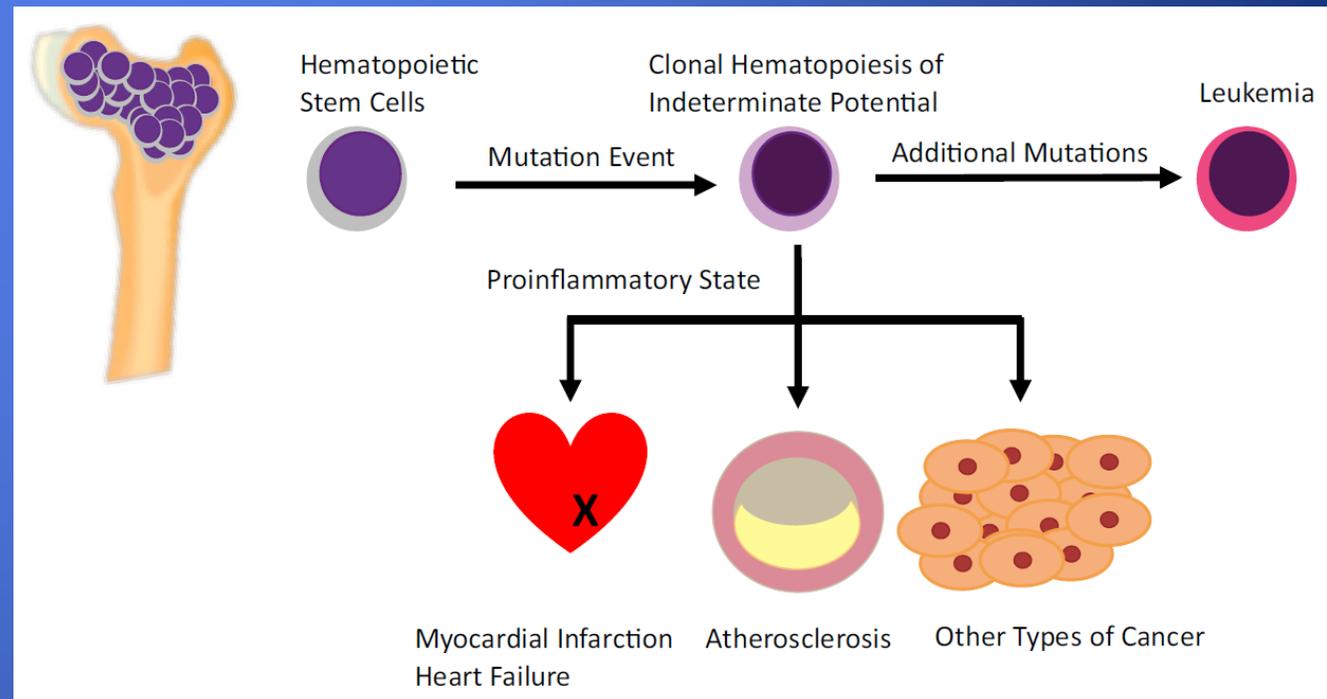






# Reverse Cardio-Oncology: *Cancer provoking CVD*

- Higher prevalence of cancer incidence in those with CVD
  - HTN: kidney, colorectal, breast, prostate CA
  - Stroke and AF: thromboembolism
- Mechanisms:
  - Inflammation
  - Clonal Hematopoiesis
  - Hypoxia
  - Circulating Factors
    - Cardiokines
    - MicroRNA
    - Exosomes
    - Microvesicles



## Cancer

### Major drivers

- Mutation(s)
- Age
- Environmental mutagens (e.g. smoking)
- Impaired DNA repair

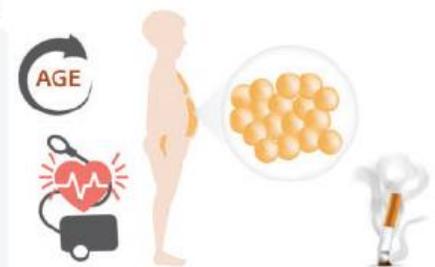


# Mechanisms and Mediators Common to Cancer and Atherosclerosis

## Atherosclerosis

### Major drivers

- Risk factors:
- Age
  - LDL
  - HBP
  - DM
  - Smoking
  - Obesity
  - etc.



## Cancer

Epithelial-mesenchymal transition



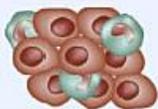
Cancer and stromal cell proliferation



Dysregulated cell death



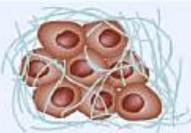
Leukocyte infiltration: innate and adaptive



Tumor angiogenesis, defective endothelial barrier function



Extracellular matrix remodeling (tumor expansion)



Invasion and metastasis



## Examples of putative mediators

TGF- $\beta$ , FGF withdrawal, VEGF

Oncogenes, proto-oncogenes (e.g. c-sis/PDGF), and dysregulated tumor suppressors

Bcl-2, NFkB, Mertk, CD47

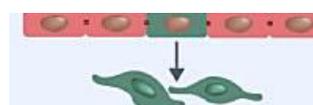
Cytokines  $\rightarrow$  adhesion molecules, chemokines

Vascular endothelial growth factor

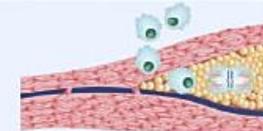
Interstitial collagenases (e.g. MMPs -1, 8, 13), Elastases (e.g. MMP-12, Cathepsins S, L, K)

Type IV collagenases (e.g. MMP-2), Interstitial collagenases (e.g. MMPs-1,8,13)

## CVD



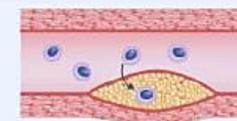
Endothelial-mesenchymal transition



Smooth muscle cell and macrophage proliferation



Dysregulated cell death, defective efferocytosis



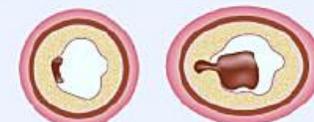
Leukocyte infiltration: innate and adaptive



Plaque angiogenesis, defective endothelial barrier function



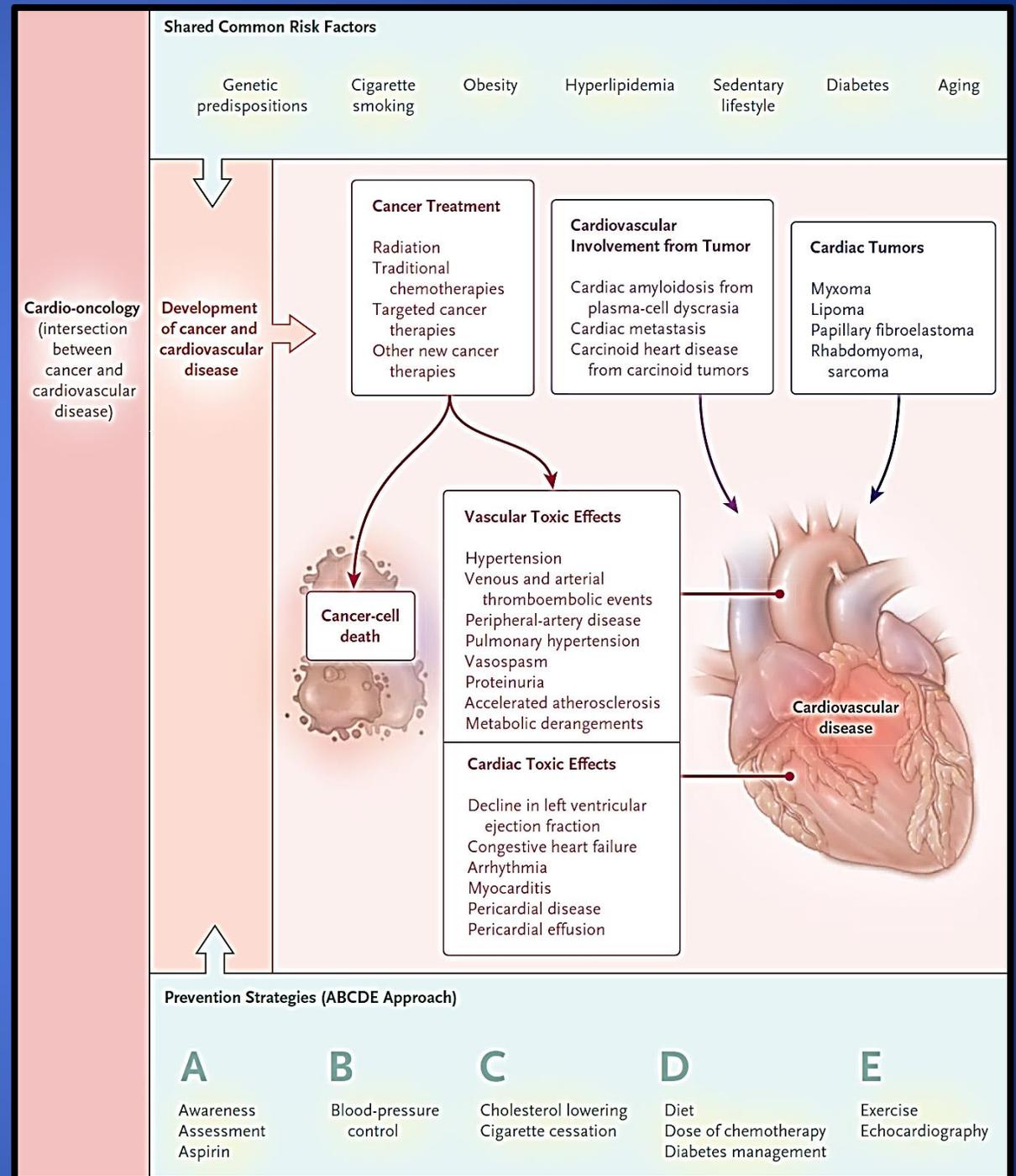
Extracellular matrix remodeling (compensatory enlargement)



Rupture and erosion

# Cardiovascular Toxic Effects of Targeted Cancer Therapies

Javid J. Moslehi, M.D.

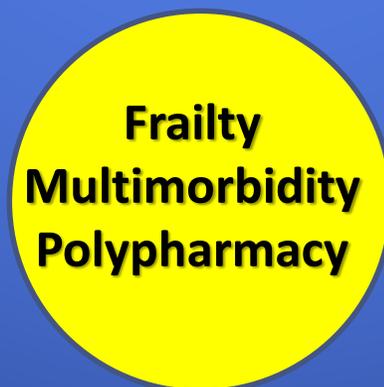


# Predictable incidence of CVD for patients with cancer

- Heart failure
  - HFpEF and HFrEF
- Arrhythmia
  - Supraventricular and Ventricular
- Ischemia
  - Supply and Demand
- Pericardial Disease
- Thromboembolic Disease
  - AF
  - HF
  - Sedentariness
  - Central catheters
  - Volume depletion
  - Remodeling
  - CA Rx (hormonal Rx, immunomodulatory Rx, blood products)

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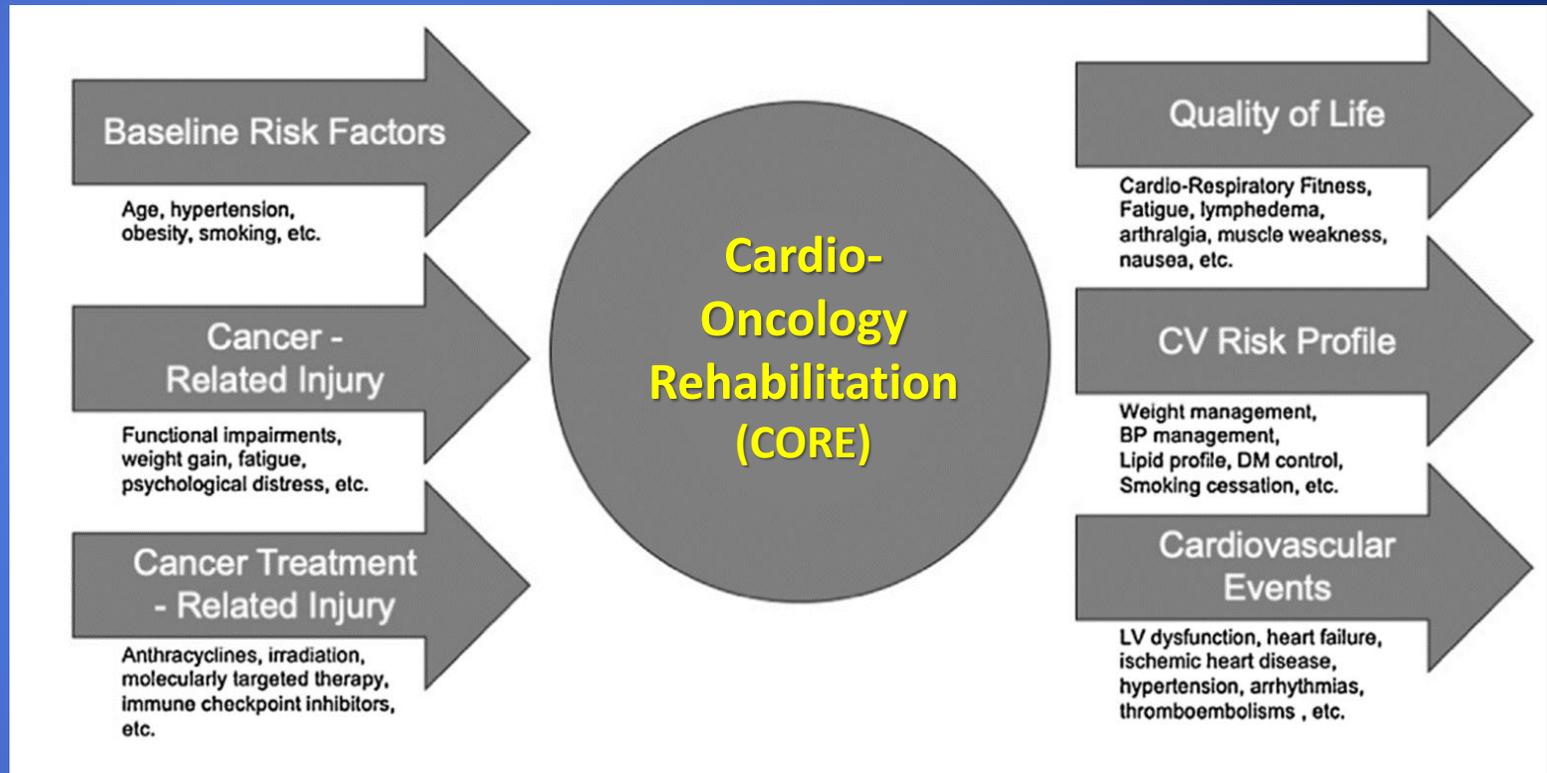
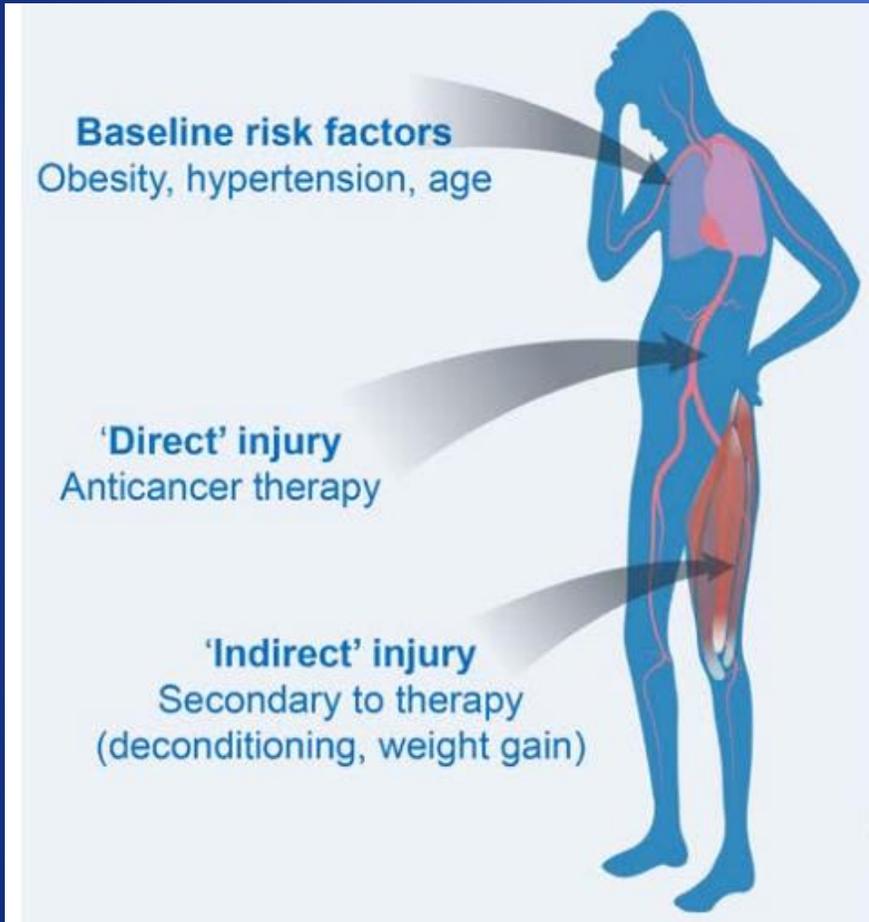
# Managing older CA patients with integrated care

- Value of team-based approach, including cardiologist, oncologist and geriatrician
- Relevance of Comorbidity
- Value of surveillance and relevance of biomarkers
  - Traditional (Troponin, BNP), ECG, Echocardiography (strain imaging), Other (Clonal hematopoiesis)
  - Lipids, thyroid, glucose
- Value of preventive care with ACE-inhibitor, beta-blockers, aldosterone-blockers, anti-coagulation, tobacco cessation
- Urgency of worsening HF, arrhythmia, HTN
- Careful management of fluids
- Value of sleep, nutrition, and broad approach to wellness
  - Consideration of cardiac rehabilitation
  - Consideration of palliative care
- Dyspnea, Fatigue and other symptoms may have multiple etiologies
  - *Broaden differential to include CVD, comorbidities, and geriatric syndromes*

# Managing older CA patients with integrated care

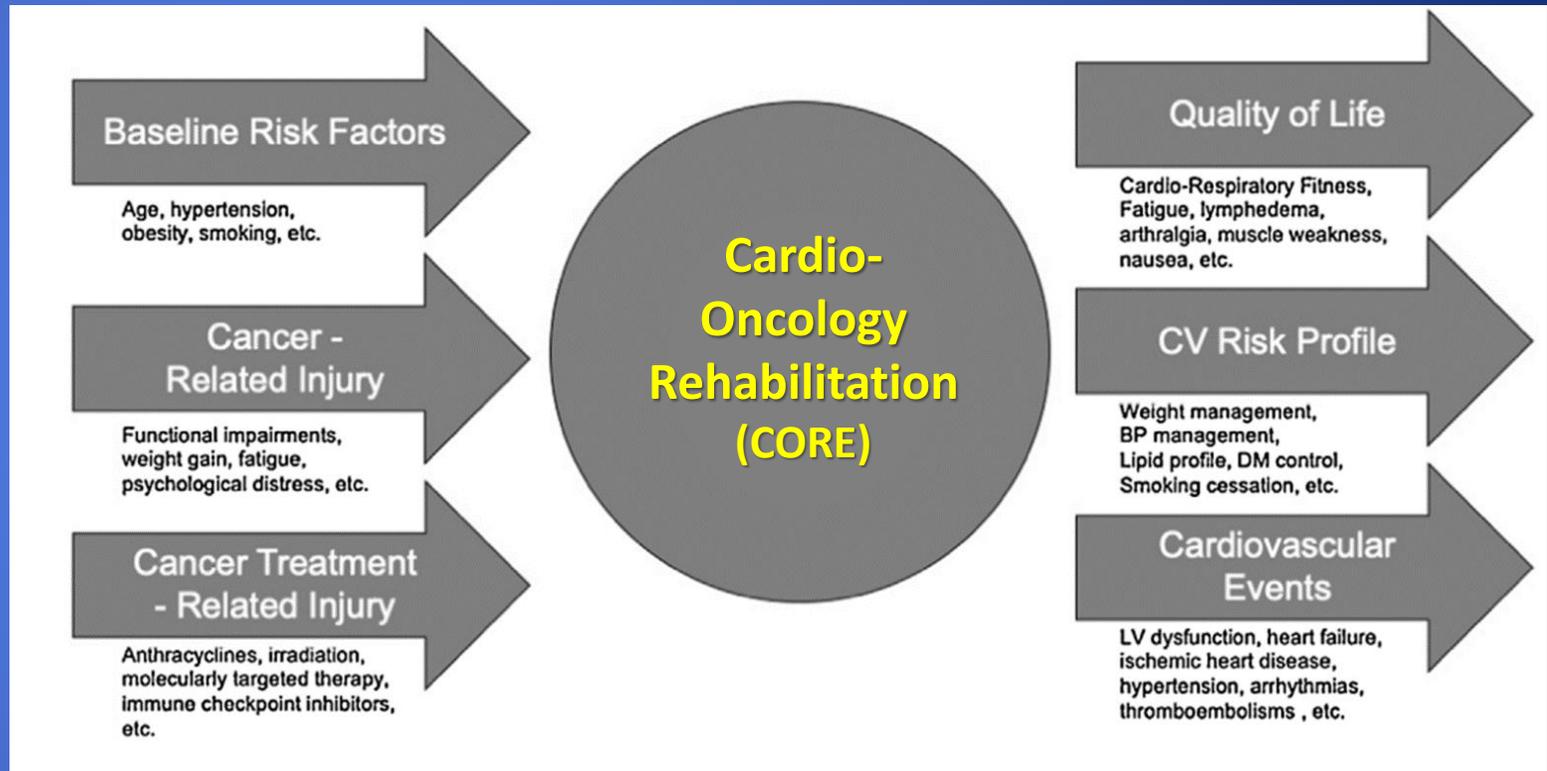
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# CVD is predictable in older adults with Cancer



Sase JM et al. J of Cardiol. 2020;76:559-76

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Sase JM et al. J of Cardiol. 2020;76:559-76



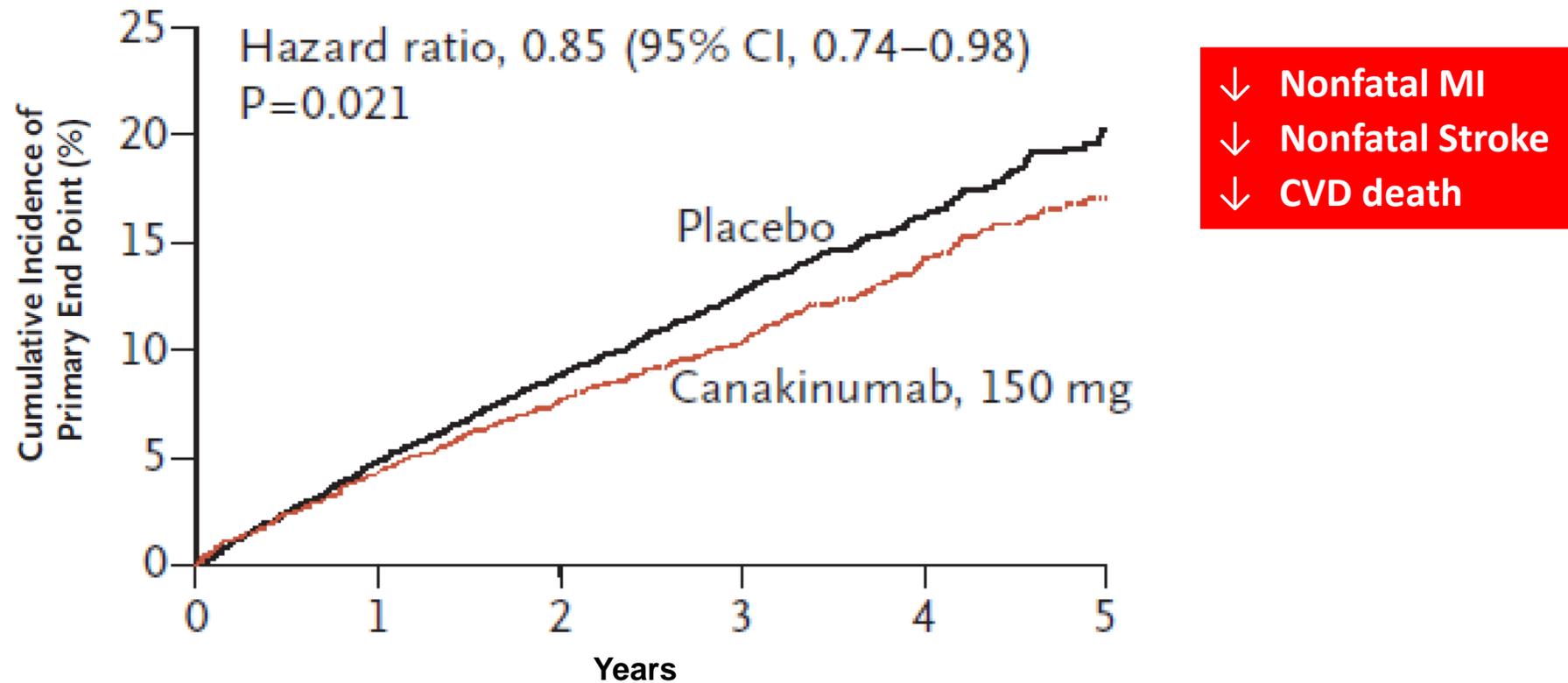
## Modified Application of Cardiac Rehabilitation

- Expanding the concept of risk:
  - *Cardiac, comorbidity, frailty, psychosocial*
- Expanding models of process:
  - *Site-, home-, and hybrid-based models*

# Inflammation → ↓ CVD Events

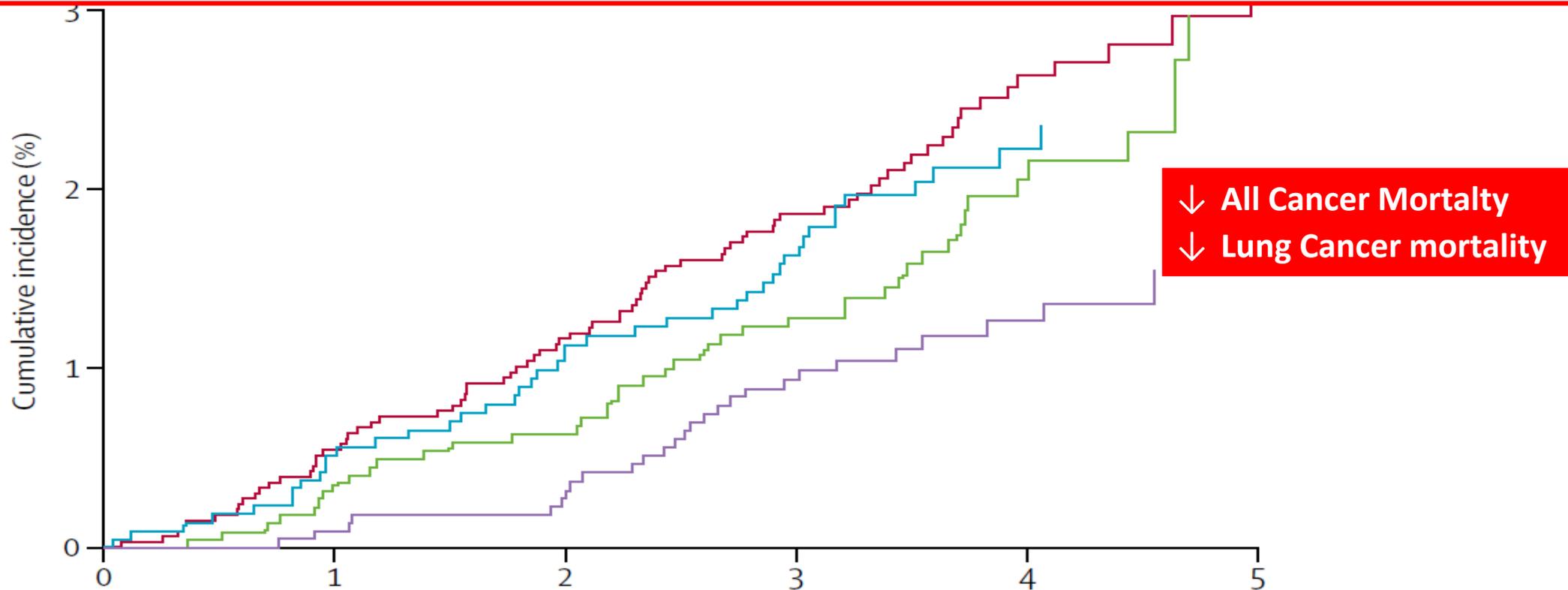
## Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

N = 10,061 stable post MI patients; CRP ≥2mg/L



# Inflammation → ↓ Lung Cancer

- Baseline hsCRP (6.0 mg/L vs 4.2 mg/L;  $p < 0.0001$ ) and IL-6 (3.2 vs 2.6 ng/L;  $p < 0.0001$ ) significantly higher among participants diagnosed with lung cancer than among those not diagnosed with cancer.
- Canakinumab associated with dose-dependent reductions of Lung CA incidence and mortality

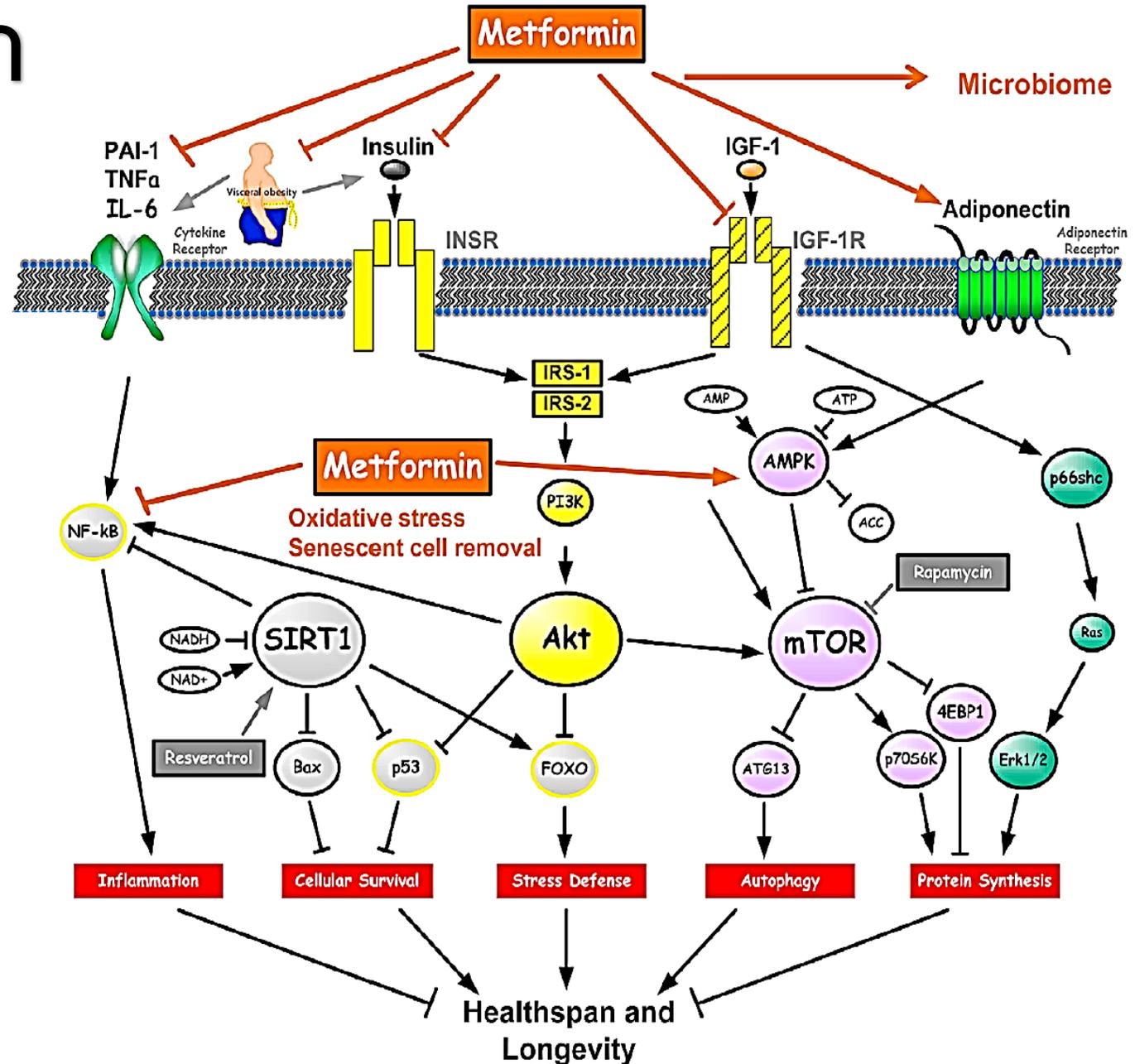


N = 10,061 stable post MI patients; CRP  $\geq 2$ mg/L; No prior CA

# Targeting Aging with Metformin (TAME)

## Metformin

- Most widely prescribed oral medication for type 2 DM worldwide
  - ↓ Cancer incidence and mortality



*MI, HF, Stroke, CA, MCI/Dementia and death*

# Summary

- Aging biologically drives vulnerabilities to intrinsic physiological changes and a continuum to CVD in a context of aggregate complexity
- CVD and Cancer stem from same underlying molecular and environmental risks, and mounting age is a driver to both
- CVD and Cancer each exacerbate incidence and management complexity of each other
- Therapeutics and Prevention (aging and disease) are rising areas of opportunity, both in respect to physiological and subcellular mechanisms of Aging, CVD and Cancer

# Thank you

- National Institute on Aging
  - R01 AG060499-01: Modified Application of Cardiac Rehabilitation for Older Adults (MACRO)
  - R01 AG058883: Nitrite therapy to improve mitochondrial bioenergetics and physical activity in older adults (NO-Frail)
  - U19 AG065188: PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults (PREVENTABLE) Study
  - P30AG024827: Pittsburgh Claude D. Pepper Older Americans Independence Center
- Geriatrics, Research, Education and Clinical Care (GRECC), VA Pittsburgh Healthcare System
- Aging Institute, University of Pittsburgh