Cancer and the Aging Body

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No Disclosures

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.

Multiple Hit-Induced Multisystem Toxicity

Baseline risk factors

SMOKING, HYPERTENSION, AGE

‘Direct’ hit

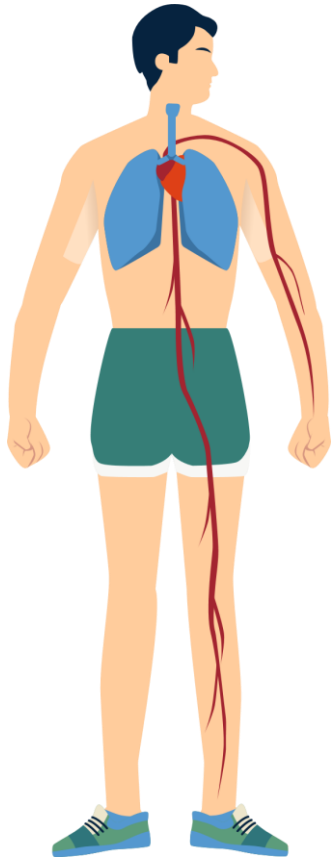
CANCER / SURGERY / THERAPY

‘Indirect’ hit

SECONDARY TO CANCER / SURGERY/ THERAPY

(E.G., DECONDITIONING)

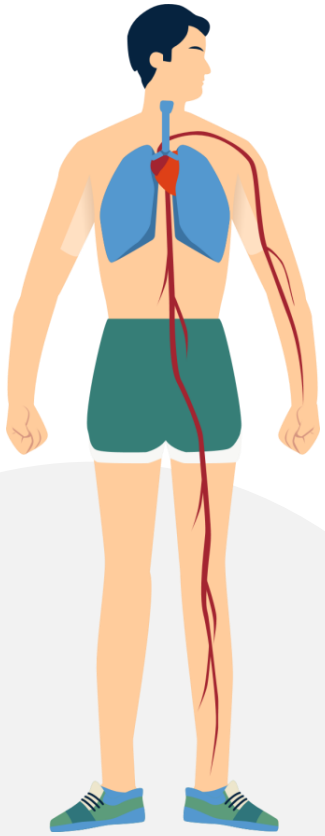
CANCER PATIENT



- COGNITIVE IMPAIRMENTS
- IMMUNE DYSFUNCTION
- CARDIAC ATROPHY
- ANEMIA
- GASTROINTESTINAL EVENTS
- EXERCISE INTOLERANCE
- SKELETAL MUSCLE ATROPHY
- BONE DEMINERALIZATION

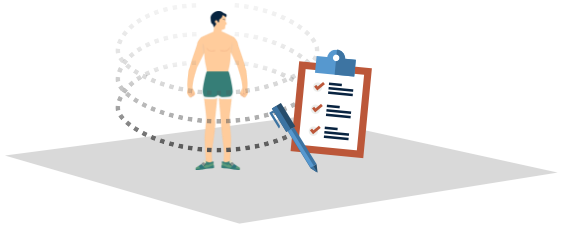
Current Assessments

ASSESSMENT ACROSS THE CANCER CONTINUUM

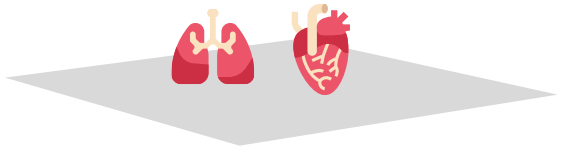


PRE-THERAPY

PERFORMANCE STATUS, CHRONOLOGICAL AGE

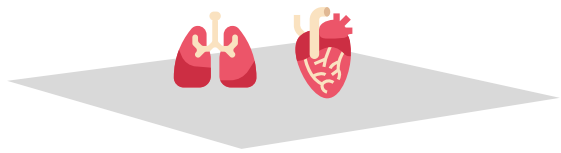


CARDIAC, PULMONARY FUNCTION



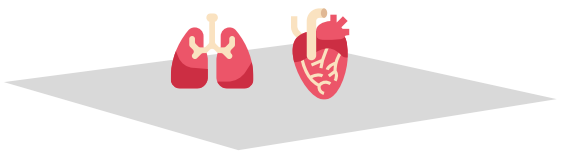
DURING THERAPY

CARDIAC, PULMONARY FUNCTION



POST-THERAPY

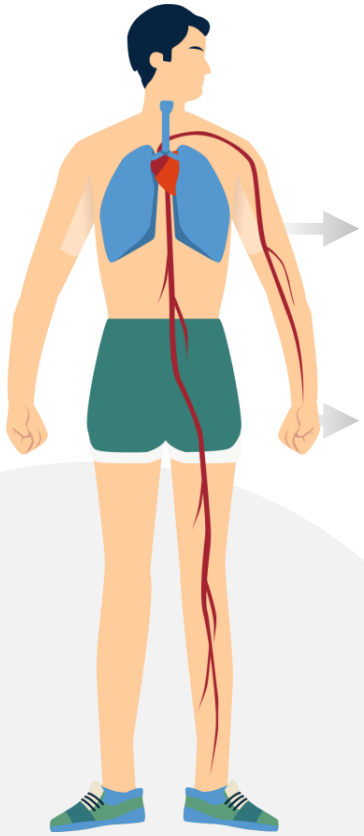
CARDIAC, PULMONARY FUNCTION



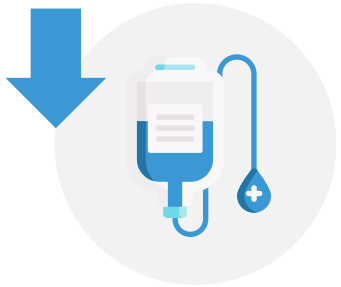
SCOTT ET AL. J CLIN ONCOL, 2020

Current Management

PHARMACOLOGY ACROSS THE CANCER CONTINUUM



PRE-THERAPY



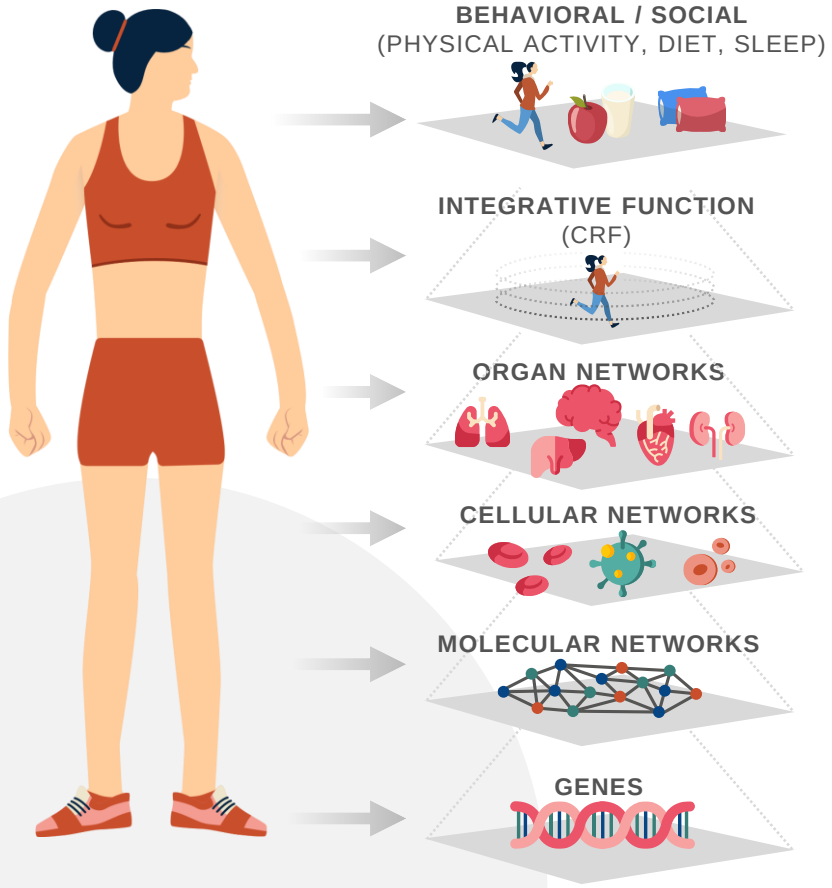
DURING THERAPY

POST-THERAPY

SCOTT ET AL. J CLIN ONCOL, 2020

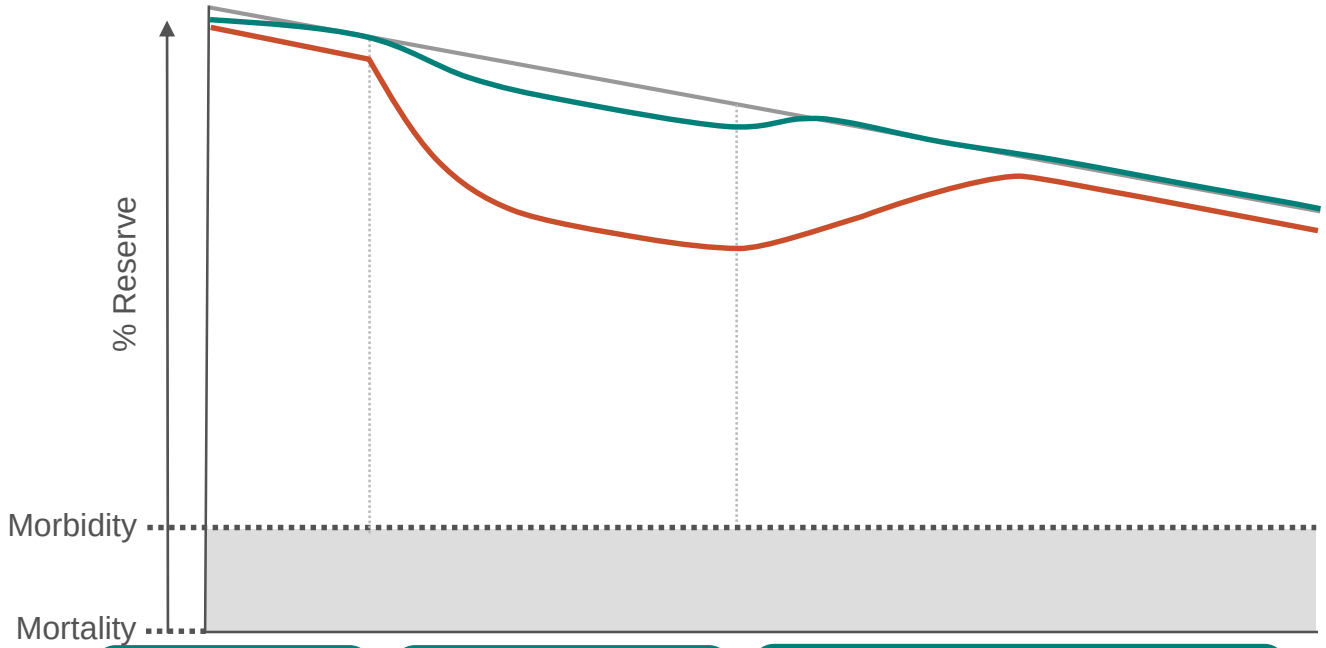
Multisystem Countermeasures Program

PHENOTYPING



SCOTT ET AL. CELL, 2019

INTERVENTIONS ACROSS THE CANCER CONTINUUM



AT DIAGNOSIS
To augment reserve

DURING THERAPY
To mitigate decline

POST-THERAPY
To return to baseline levels

Phenotyping

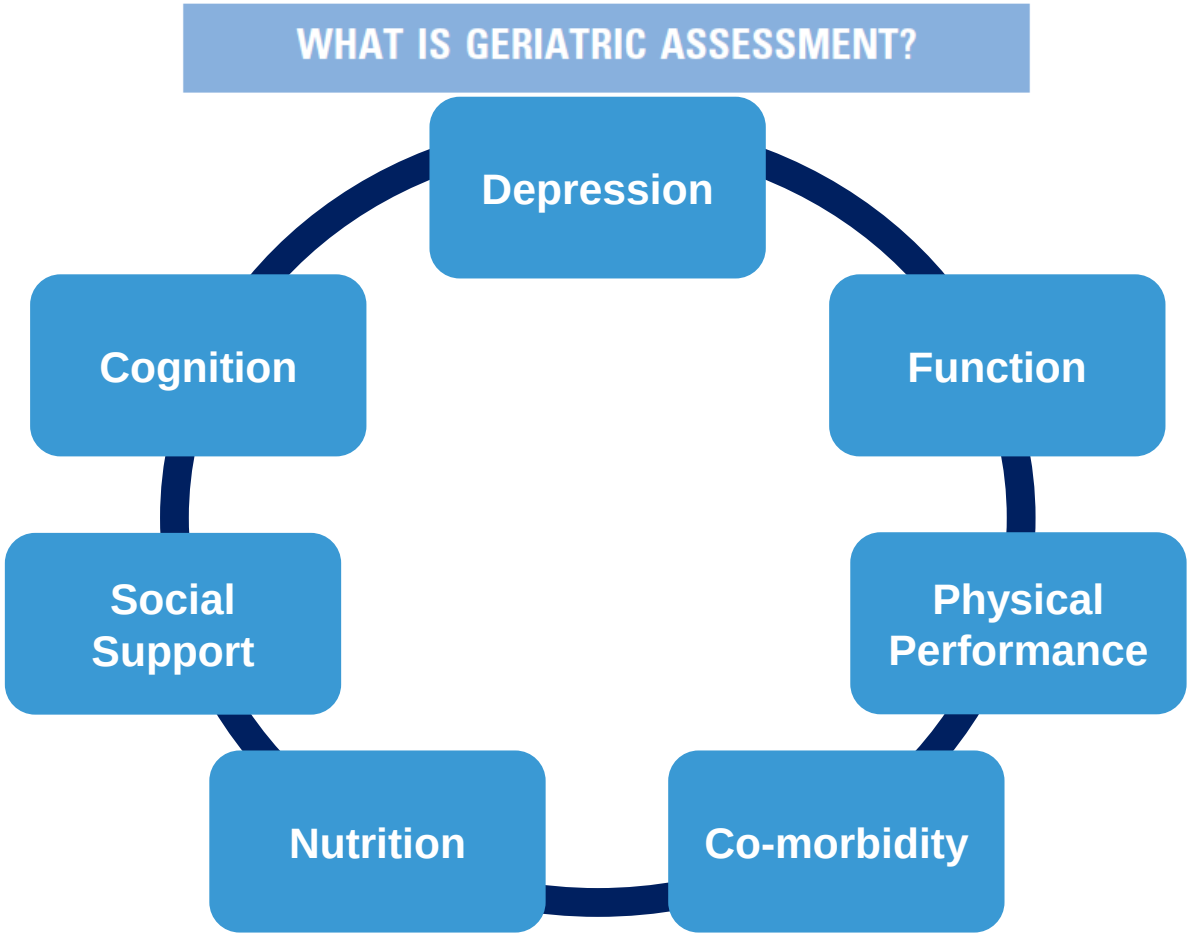
Integrative: Geriatric Assessment

VOLUME 25 · NUMBER 14 · MAY 10 2007

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

A Practical Approach to Geriatric Assessment in Oncology

Miriam B. Rodin and Supriya G. Mohile



FEASIBILITY

HURRIA ET AL. J CLIN ONCOL, 2011

PROGNOSTICATION

HURRIA ET AL. J CLIN ONCOL, 2011
EXTERMANN ET AL. CANCER, 2012

GA-GUIDED CLINICAL CARE

HURRIA ET AL. J CLIN ONCOL, 2016
CORRE ET AL. J CLIN ONCOL, 2016

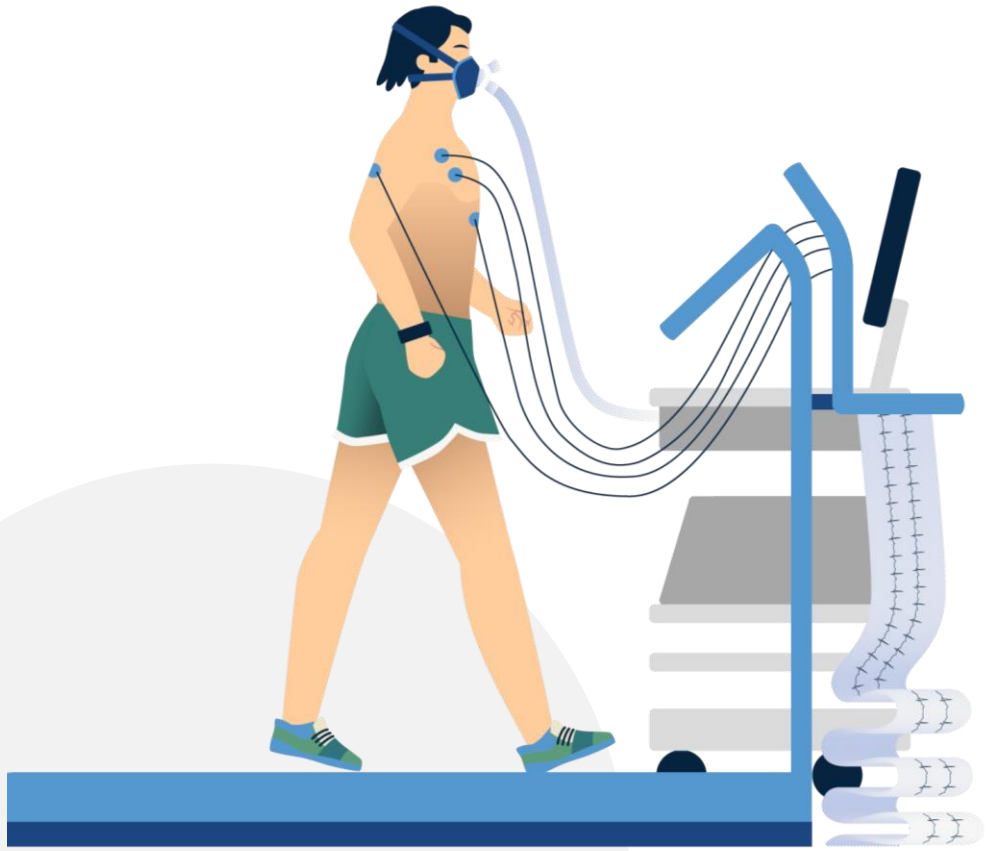
GA-GUIDED INTERVENTIONS

NADARAJA ET AL. J GERIATR ONCOL, 2020
DERMAN ET AL. J GERIATR ONCOL, 2021
LI ET AL. JAMA ONC, 2021

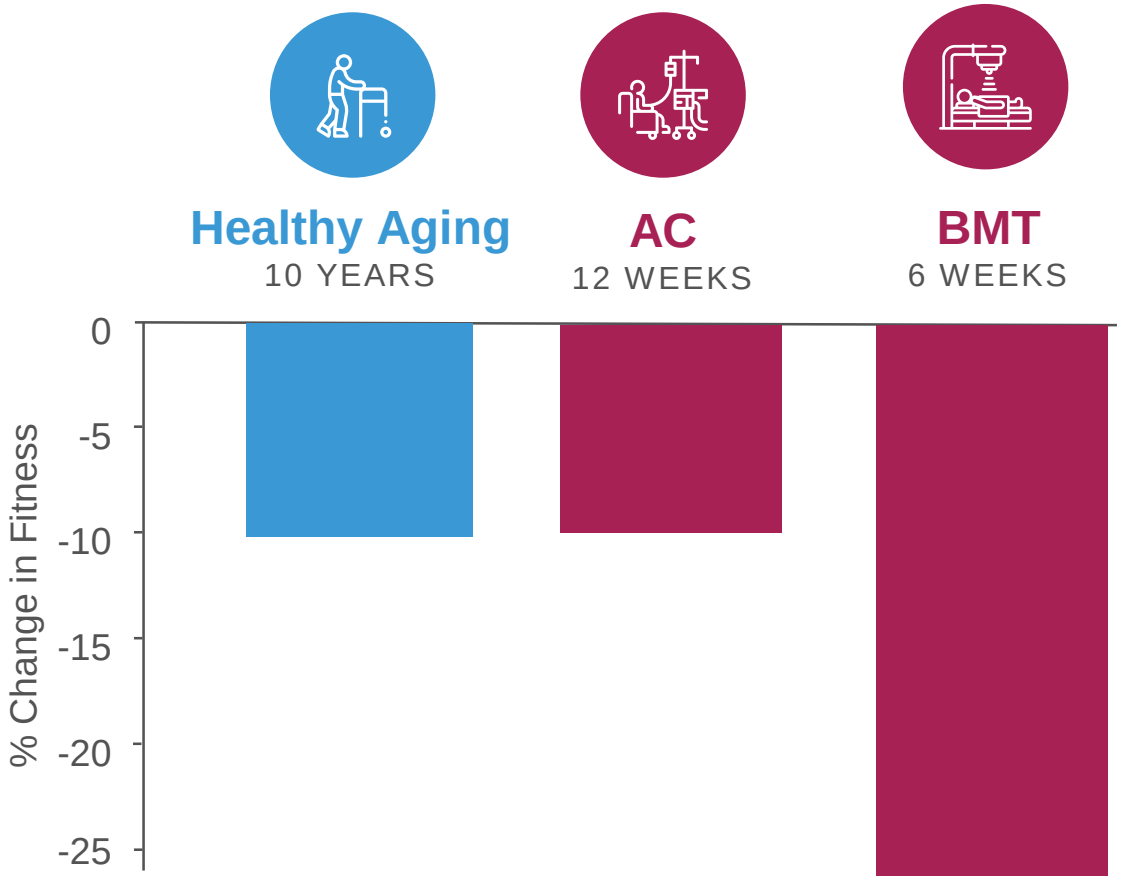
Integrative Physiological Function: Cardiorespiratory Fitness

Cardiopulmonary Exercise Test (CPET)

- Symptom limited cardiopulmonary exercise test
- Cardiorespiratory fitness (VO_2peak – $mL.kg^{-1}min^{-1}$)



Therapy-induced accelerated physiological aging



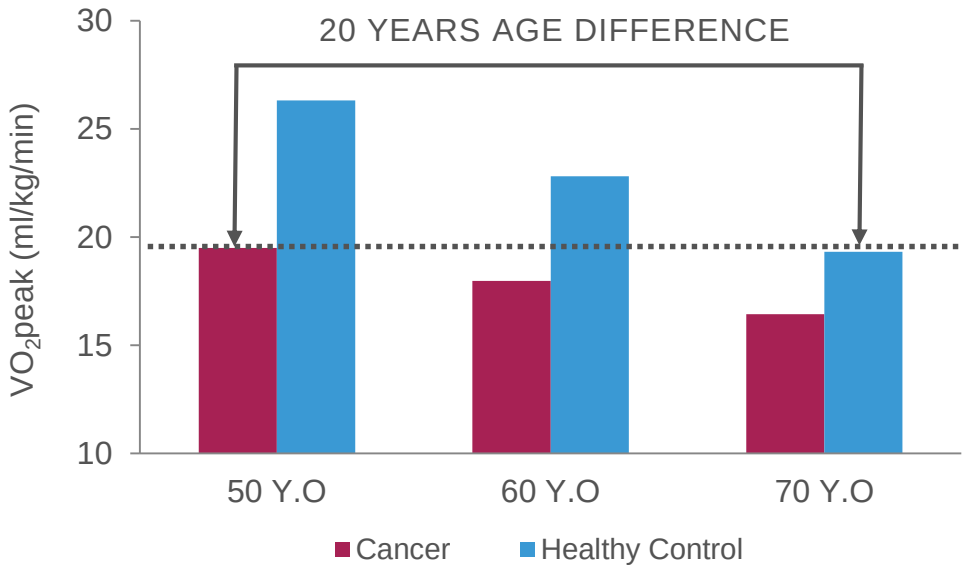
HORNSBY ET AL. ACTA ONCOL, 2014
JARDEN ET AL. BMT, 2009

Integrative Physiological Function: Cardiorespiratory Fitness

STUDY #1:

Persistent Impairment

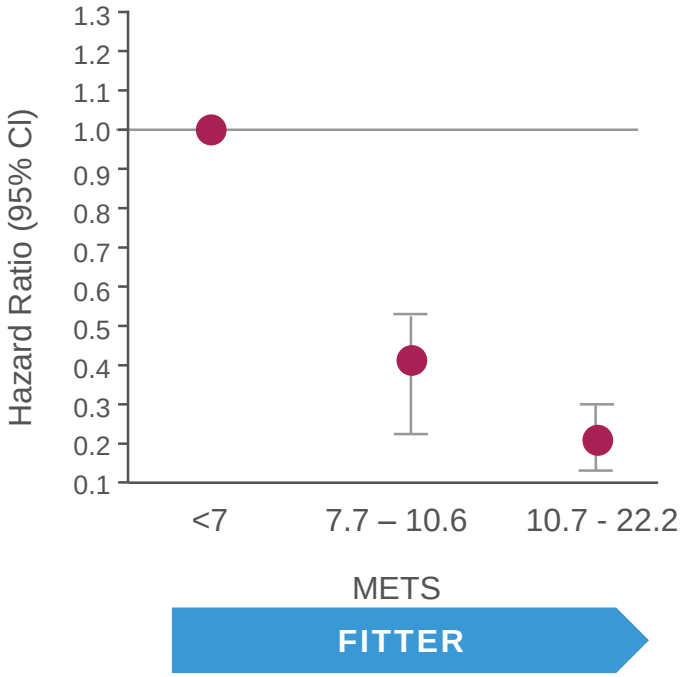
- Breast cancer (n=140)
- Healthy age-matched (n=107)
- 3 years post-therapy



STUDY #2:

Prognostic Importance

- Various Cancers (n=1,632)
- 5-year follow-up



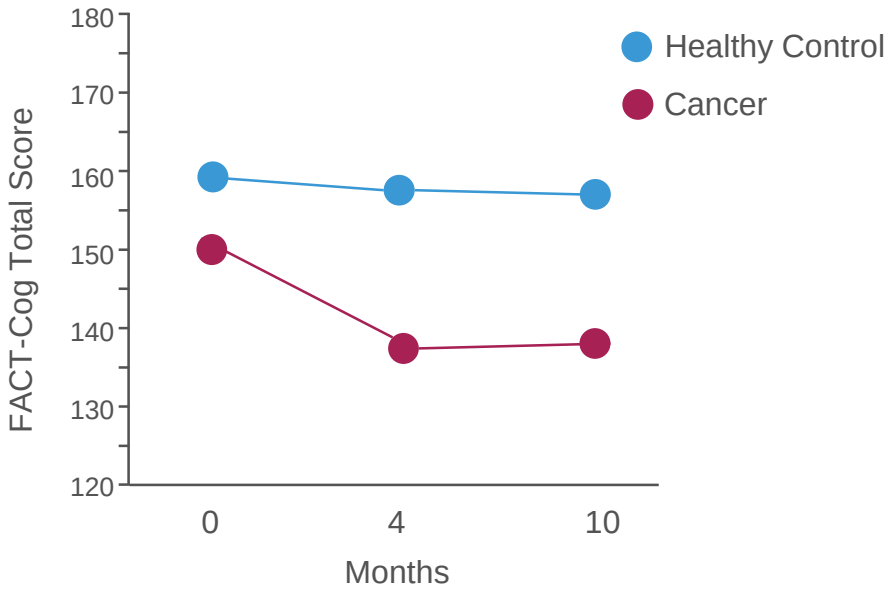
JONES ET AL. J CLIN ONCOL, 2012
GROARKE ET AL. EUR HEART J QUAL CARE CLIN OUTCOMES, 2020

Organ-Level Assessments

STUDY #1:

Cognitive Function

- Lymphoma (n=248)
- Healthy age-matched (n=212)
- Pre chemotherapy; at chemotherapy completion; 6 mo post chemotherapy

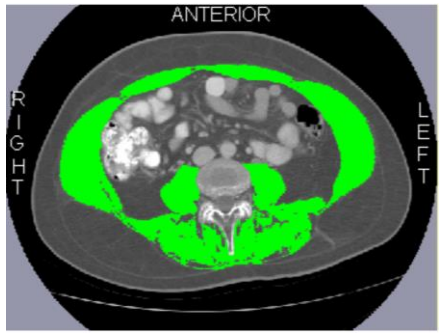


STUDY #2:

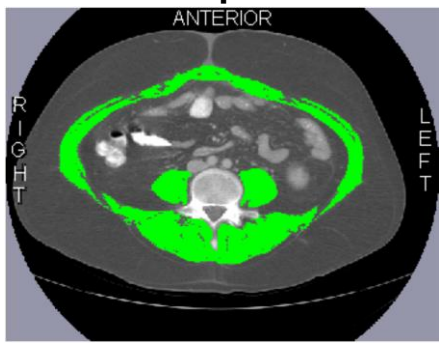
Pre-HCT Muscle

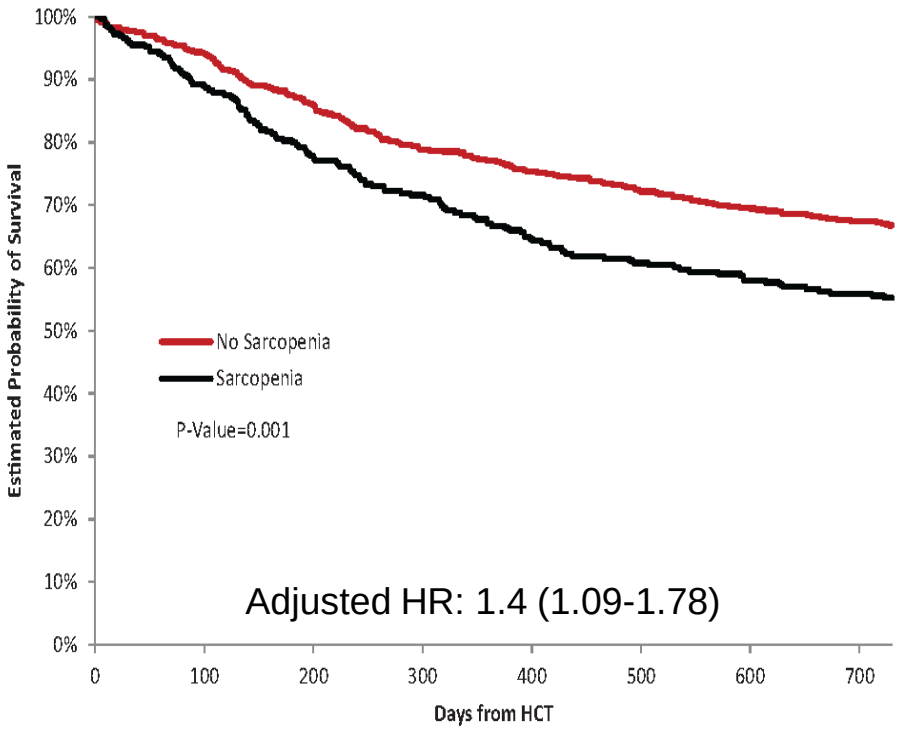
- Leukemia / MDS (n=859)
- 2-year follow-up

Non-Sarcopenic



Sarcopenic





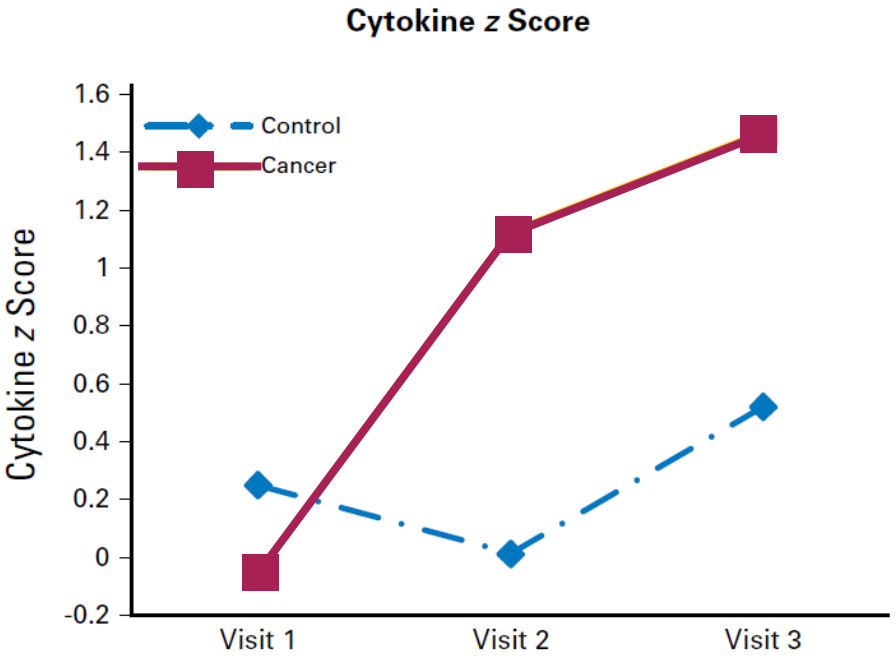
JANELSINS ET AL. J NATL CANCER INST, 2021
ARMENIAN ET AL. J NATL CANCER INST, 2019

Blood-Based Biomarkers

STUDY #1:

Inflammatory Markers

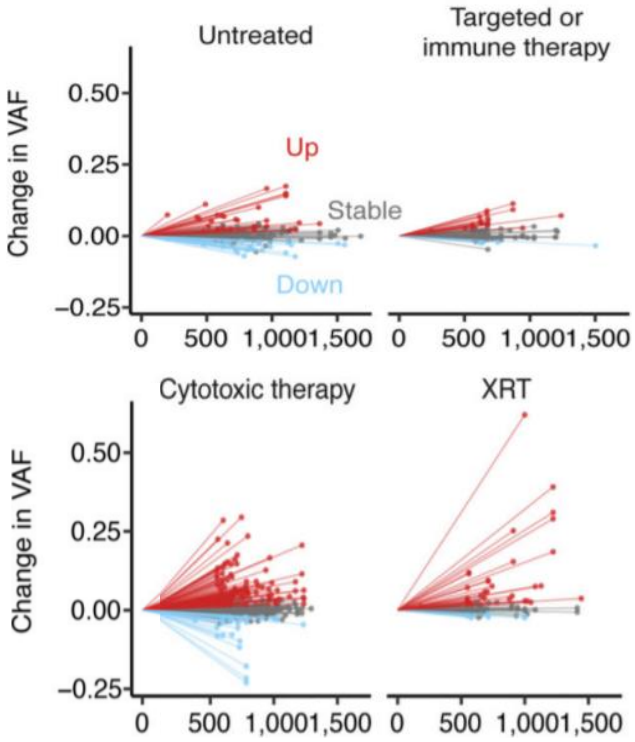
- Breast cancer (n=248)
- Healthy age-matched (n=106)
- Pre chemotherapy; 6 mo post chemotherapy; 18 mo post chemotherapy



STUDY #2:

Clonal Hematopoiesis

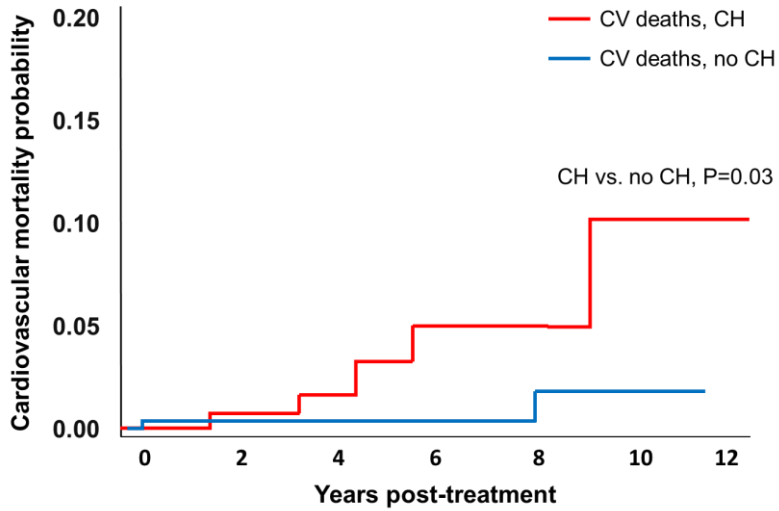
- Adult cancers (n=10,138)
- Cancer therapy exposed (n=5,978)
- Cancer therapy naïve (n=4,160)



STUDY #3:

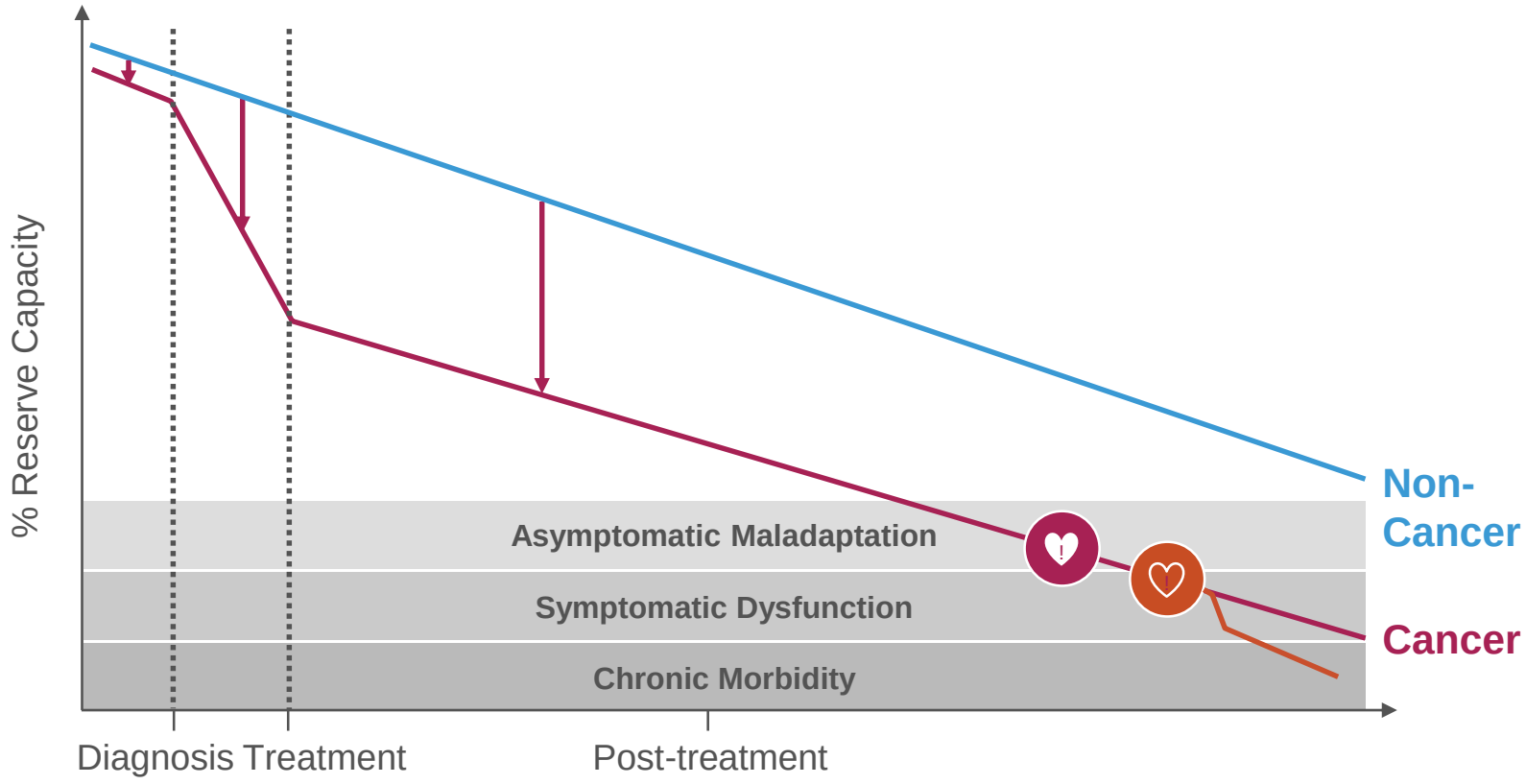
Clonal Hematopoiesis

- Non-Hodgkin lymphoma (n=401)
- With CH (n=120)
- Non-CH (n=281)



ALFANO ET AL. J CLIN ONCOL, 2017
BOLTON ET AL. NAT GENET, 2020
GIBSON ET AL. J CLIN ONCOL, 2017

Summary: Aging Across the Cancer Continuum



Pre Treatment

~17% lower

During Treatment

⬇ 10%-20%

Acute Post Treatment

~ 30% lower

Chronic Post Treatment

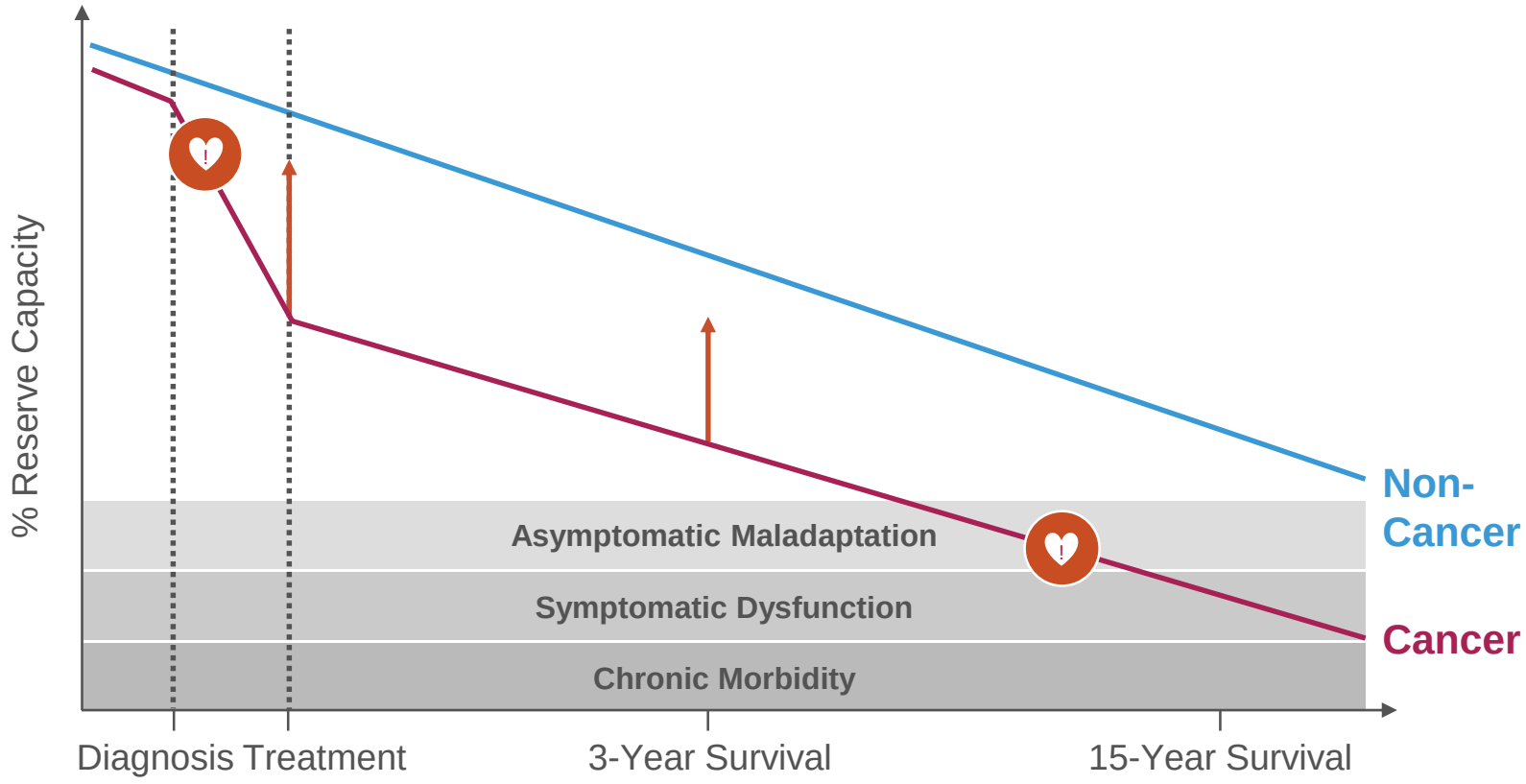
⬆ 20%-50%
IN EVENTS

High Risk at Diagnosis

⬇ Reserve

Interventions

Exercise Training Across the Cancer Continuum



Pre Surgical

↓ ~40%

POST-OP EVENTS RISK

During Treatment

↑ 5%-10%

VO2 PEAK

Acute Post Treatment

↑ 10%-20%

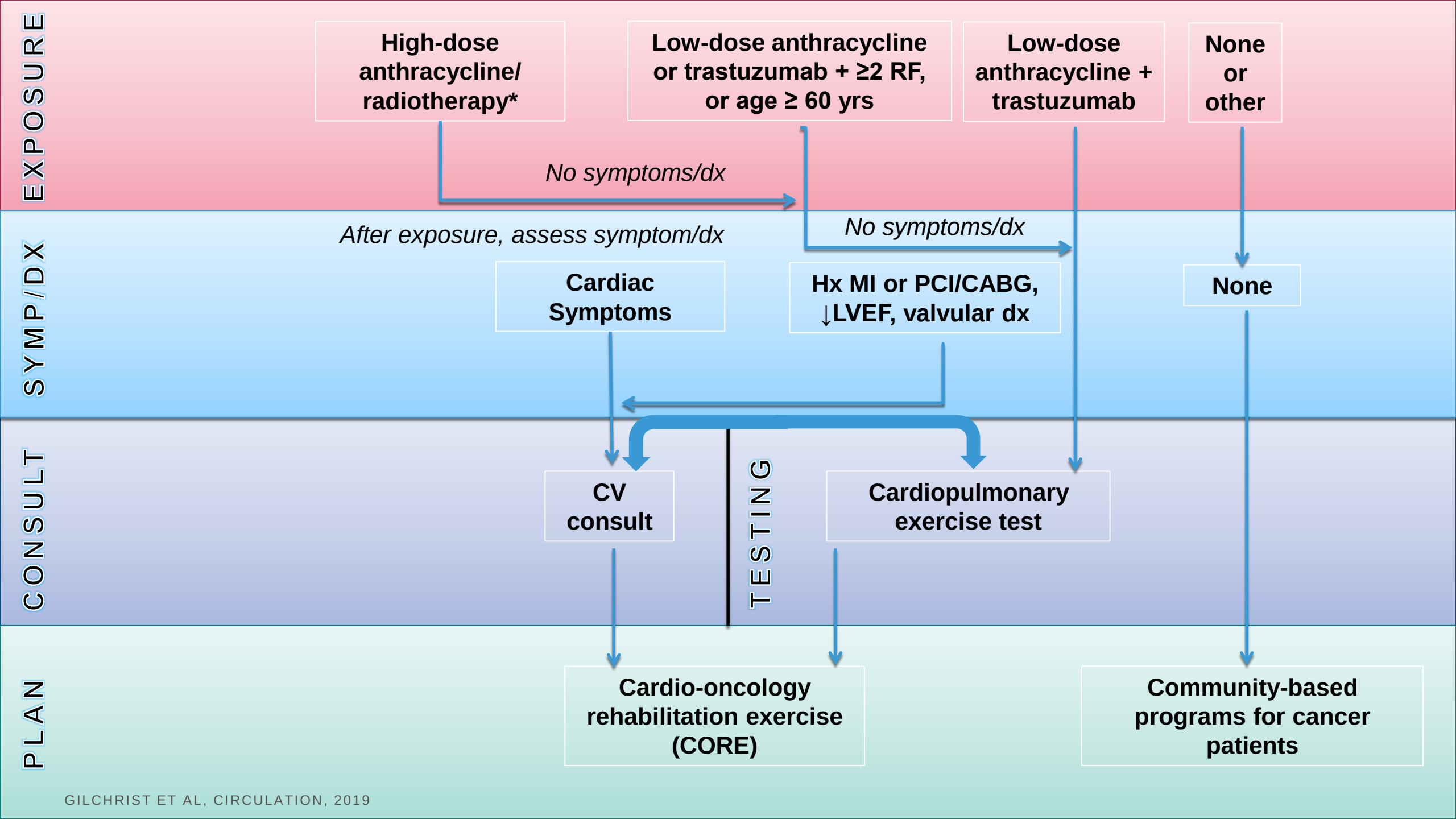
VO2 PEAK

Chronic Post Treatment

↓ 20%-40%

CVD EVENTS RISK

SCOTT ET AL. JAMA ONCOL, 2018
SCOTT ET AL., J CLIN ONCOL. 2018



GILCHRIST ET AL, CIRCULATION, 2019

Randomized Exercise Trial in Chronologically Older Breast Cancer Survivors

Stretching vs. Resistance and Aerobic Exercise

- n=114 breast cancer survivors
- >2 years post-therapy
- Mean age: 71 years (64-87 years)

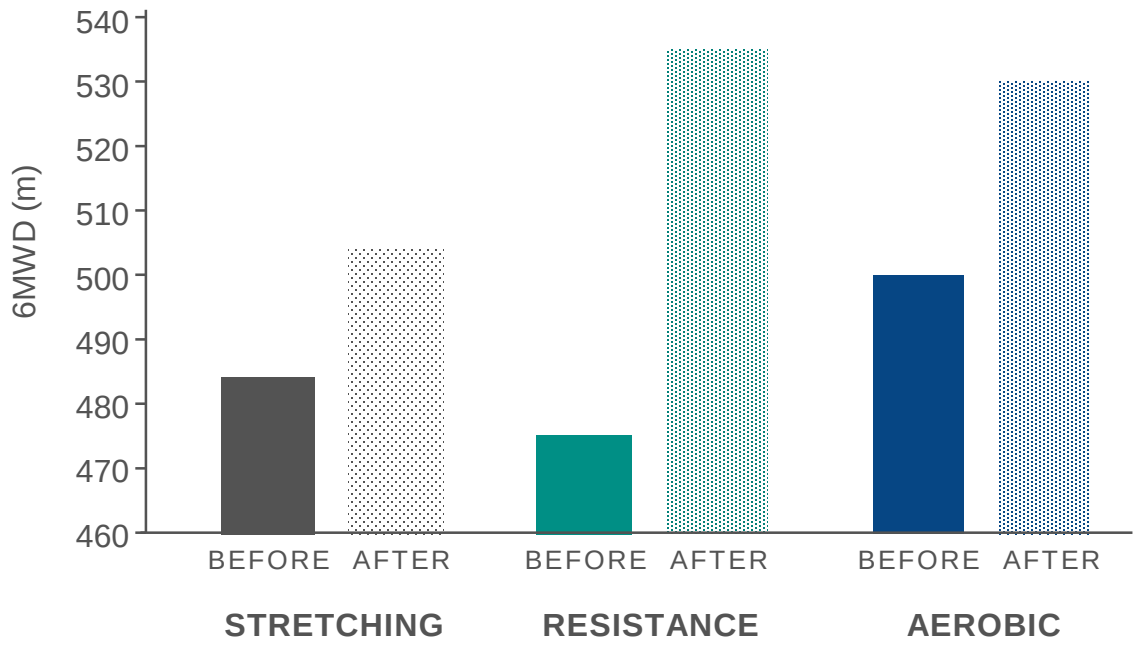
Randomized to 12 months supervised + 6 months unsupervised of:

STRETCHING CONTROL (N=38)

RESISTANCE EXERCISE (N=39)

AEROBIC EXERCISE (N=37)

Study results



Randomized Exercise Trial in Phenotypically Older Breast Cancer Survivors

Stretching vs. Linear and Non-Linear Aerobic Exercise

- n=174 breast cancer survivors
- 1-5 years post-therapy
- Mean chronological age: 58 years
- Mean physiological age: 73 years

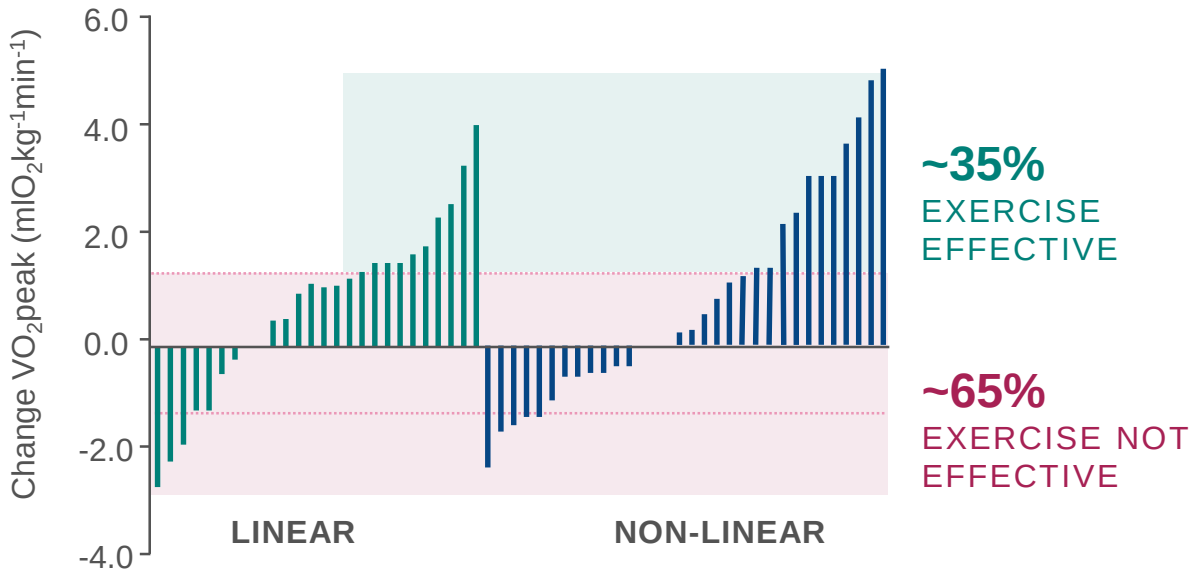
Randomized to 16 weeks of:

STRETCHING CONTROL (N=57)

LINEAR EXERCISE (N=58)

NON-LINEAR EXERCISE (N=59)

Individual Patient Response



SCOTT ET AL., CIRCULATION, 2020

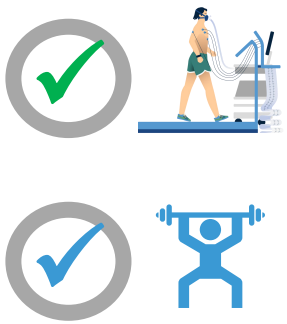
Randomized Exercise Trial in Older Lung Cancer Survivors

Stretching vs. Aerobic, Resistance, and Combined Exercise

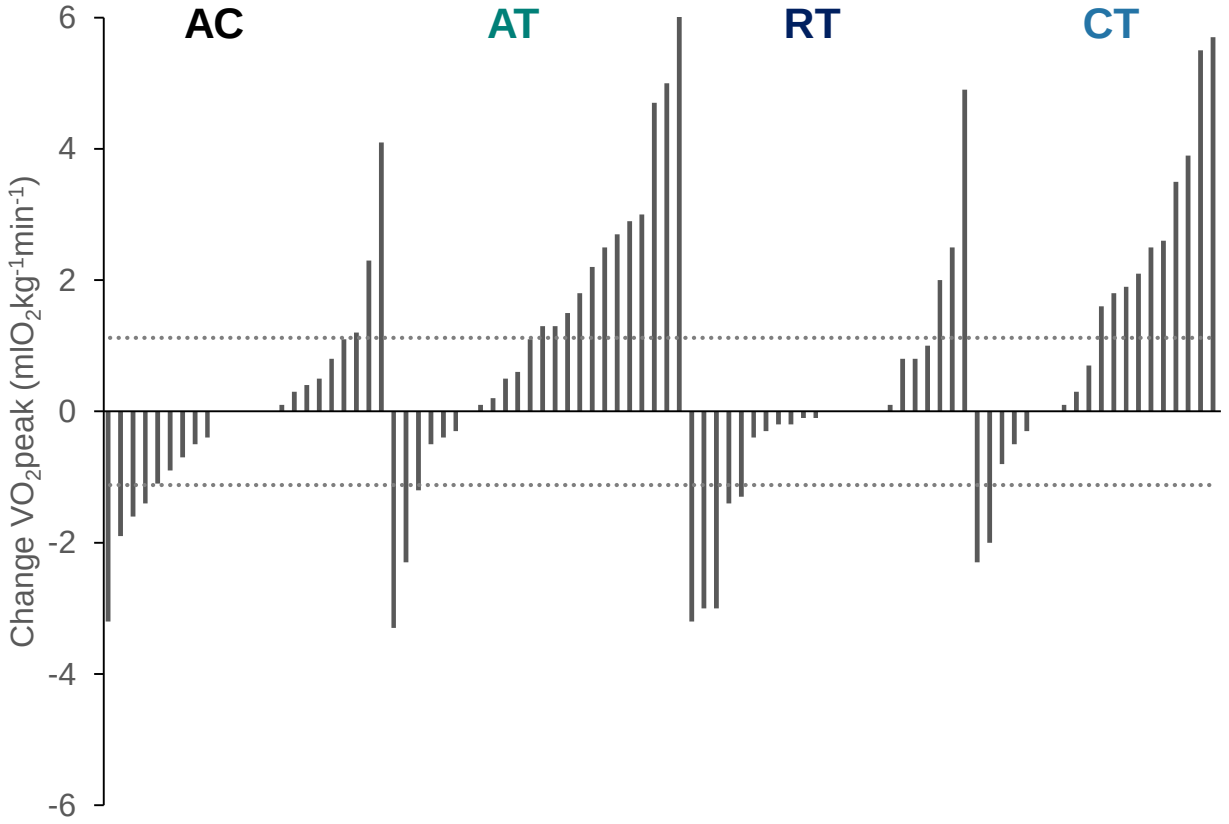
- n=90 lung cancer survivors
- 1-10 years post-therapy
- Mean chronological age: 65 years
- Mean physiological age: >80 years

Randomized to 16 weeks of:

- STRETCHING CONTROL (N=23)
- AEROBIC EXERCISE (N=24)
- RESISTANCE EXERCISE (N=23)
- COMBINED EXERCISE (N=20)



Individual Patient Response



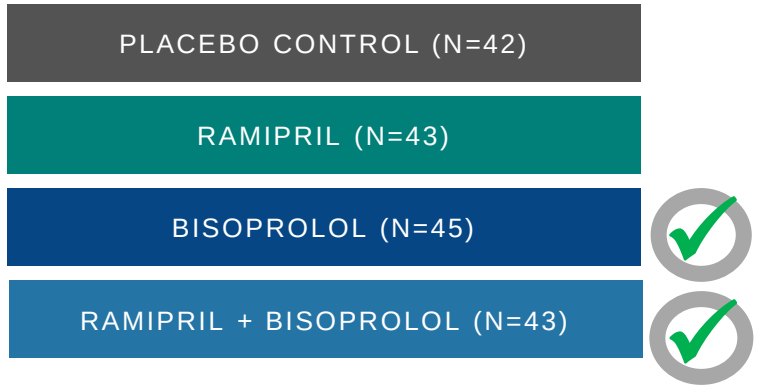
SCOTT ET AL., J CACHEXIA SARCOPENIA MUSCLE, IN PRESS

Randomized Pharmacological Cardioprevention Trial in Breast Cancer

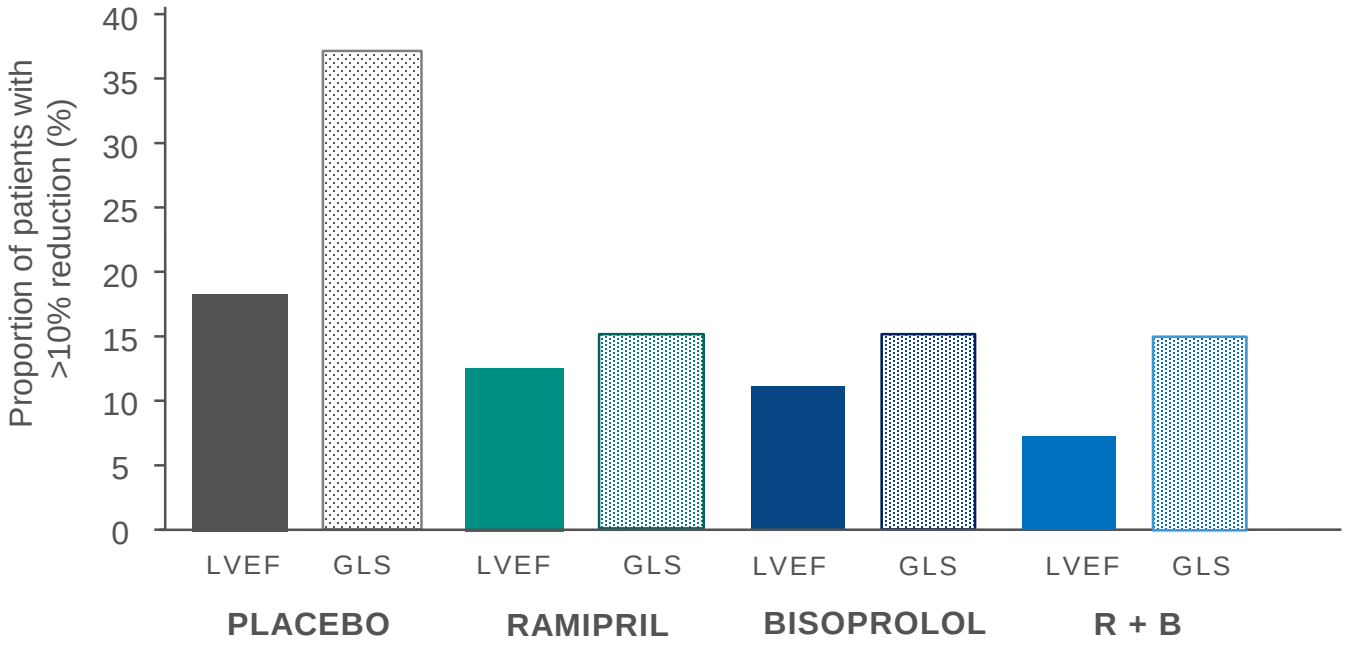
Placebo versus ramipril, bisoprolol, or ramipril plus bisoprolol

- n=174 breast cancer patients
- Initiating anthracyclines +/- trastuzumab
- Mean chronological age: 48 years

Randomized to 1 year of:



Study results



LIVI ET AL., JAMA ONC, 2021

Phase I Senolytics Trial in Diabetic Kidney Disease

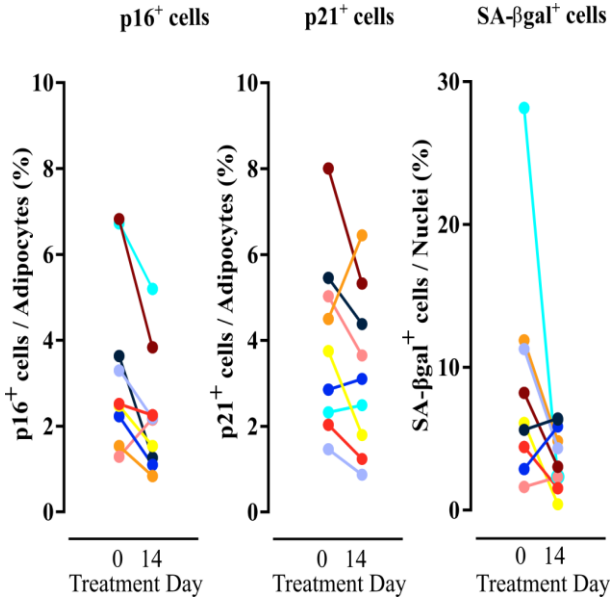
Dasatinib and Quercetin (D + Q)

- n=9 diabetic kidney disease
- Mean chronological age: 68 years

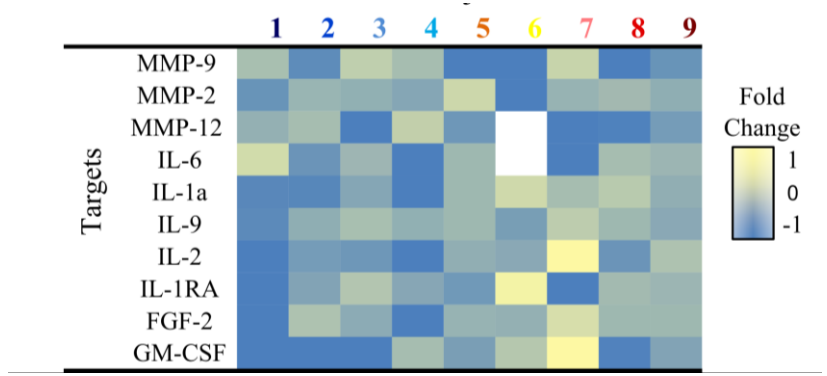
3 days of oral D 100 mg + Q 1000 mg

Adipose tissue, skin biopsies, and blood collected before and 11 days post-treatment

Individual Patient Response



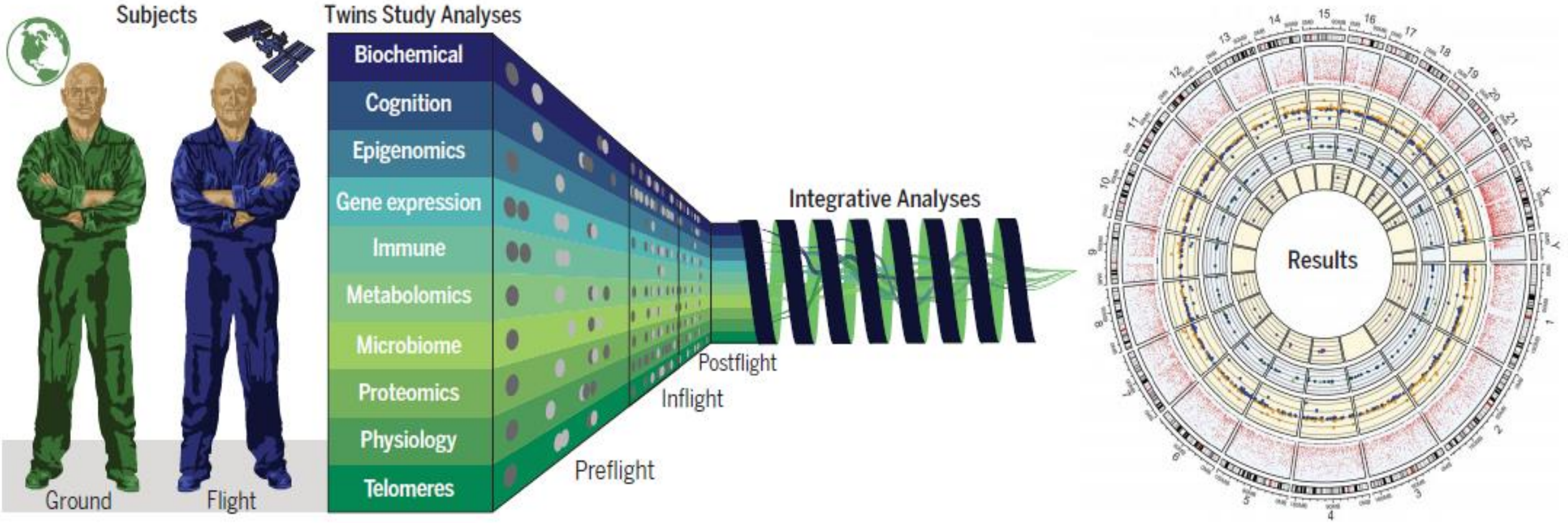
SIGNIFICANT REDUCTION IN ABDOMINAL SUBCUTANEOUS ADIPOSE TISSUE SENESCENT CELLS



SIGNIFICANT REDUCTION IN PLASMA SASP FACTORS

Future Directions

Spaceflight: Dense and Dynamic Phenotyping



Multidimensional, longitudinal assays of the NASA Twins Study. (Left and middle) Genetically identical twin subjects (ground and flight) were characterized across 10 generalized biomedical modalities before (preflight), during (inflight), and after flight (postflight) for a total of 25 months (circles indicate time points at which data were collected). (Right) Data were integrated to guide biomedical metrics across various "-omes" for future missions (concentric circles indicate, from inner to outer, cytokines, proteome, transcriptome, and methylome).

Garrett-Bakelman *et al.*, *Science* **364**, 144 (2019) 12 April 2019

Targeted Intervention Strategies to Optimize Response

Data Driven Approaches

INPUT

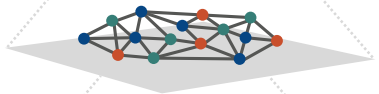
BEHAVIORAL / SOCIAL
(PHYSICAL ACTIVITY, DIET, SLEEP)

INTEGRATIVE FUNCTION
(CRF)

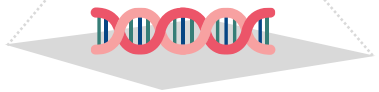
ORGAN NETWORKS

CELLULAR NETWORKS

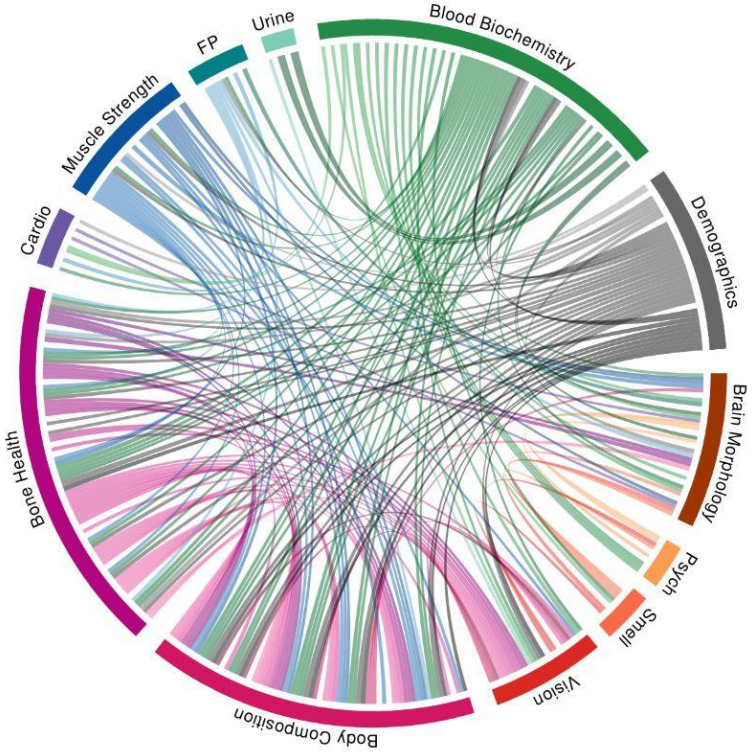
MOLECULAR NETWORKS



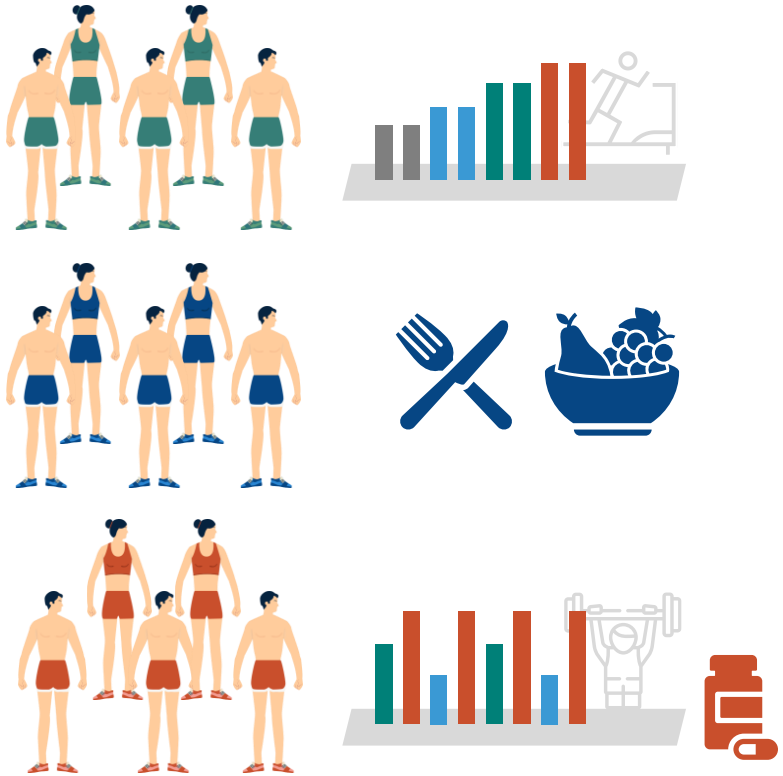
GENES



DATA INTEGRATION / RISK STRATIFICATION



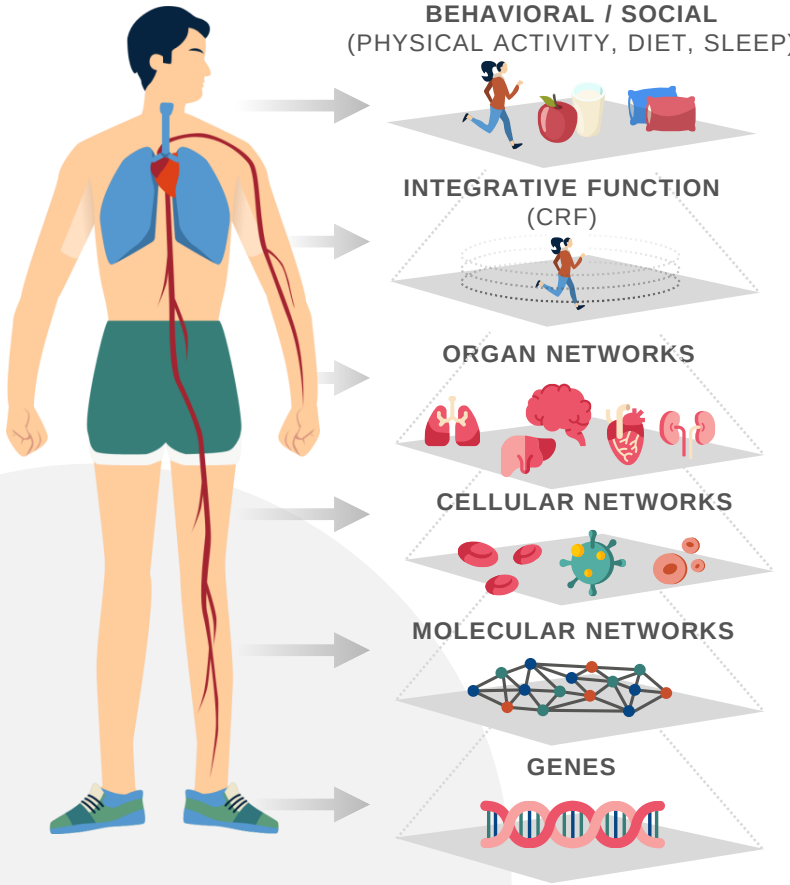
OUTPUT: INTERVENTIONS



SCOTT ET AL., CIRCULATION, 2018

Digital Phenotyping

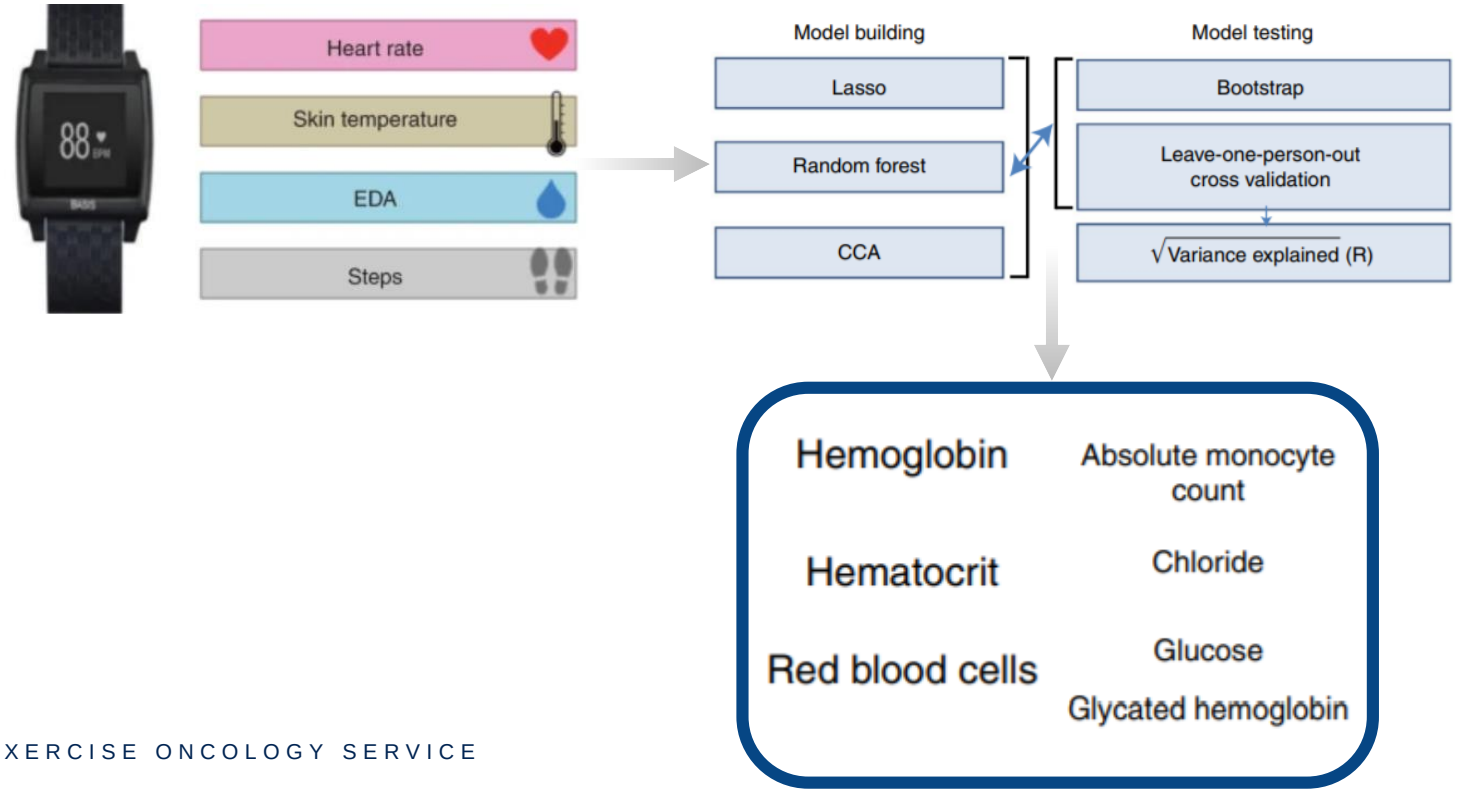
CURRENT PHENOTYPING: CENTER-BASED



NEXT FRONTIER: DIGITAL DYNAMIC PHENOTYPING

nature medicine

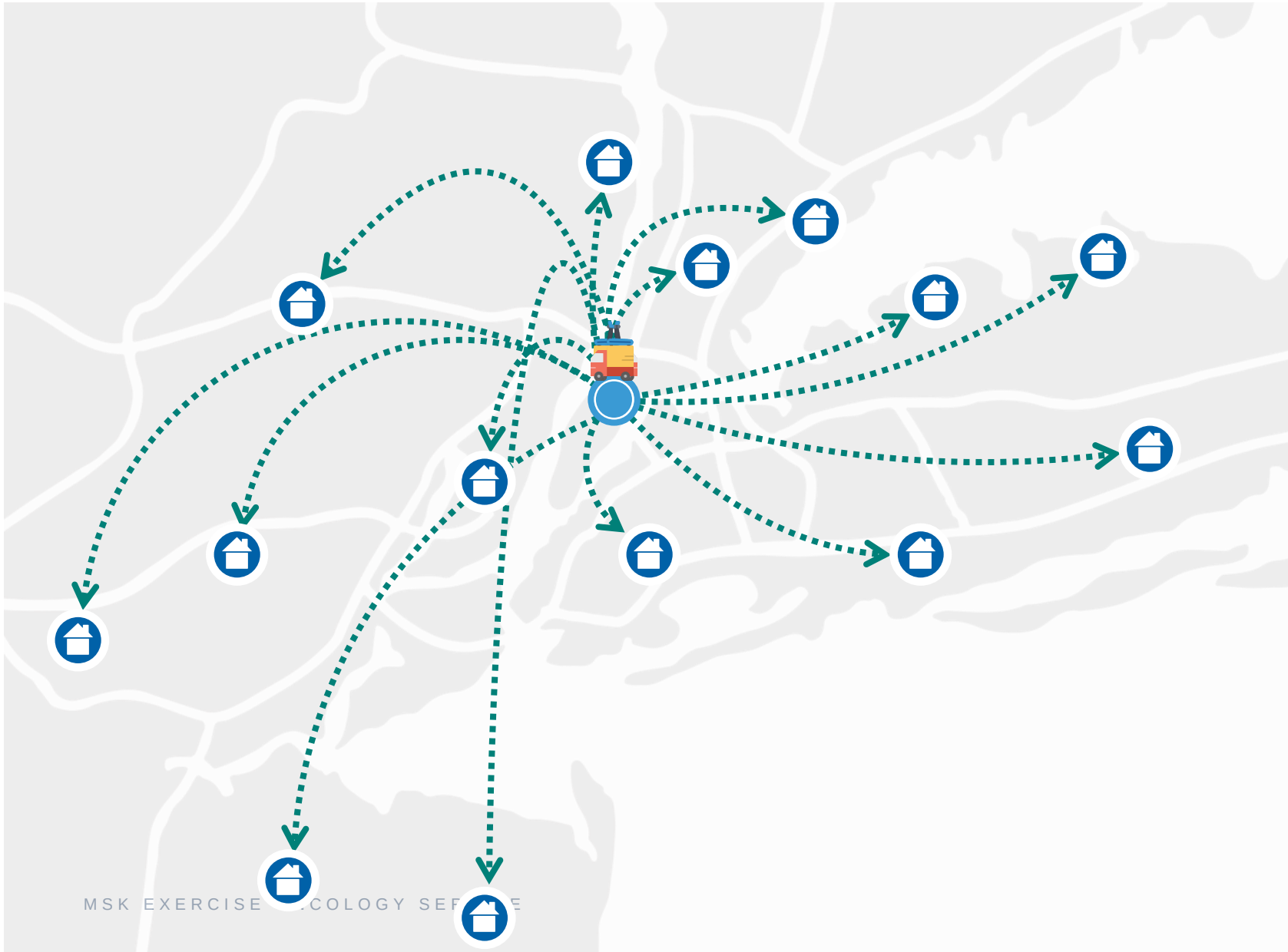
Wearable sensors enable personalized predictions of clinical laboratory measurements



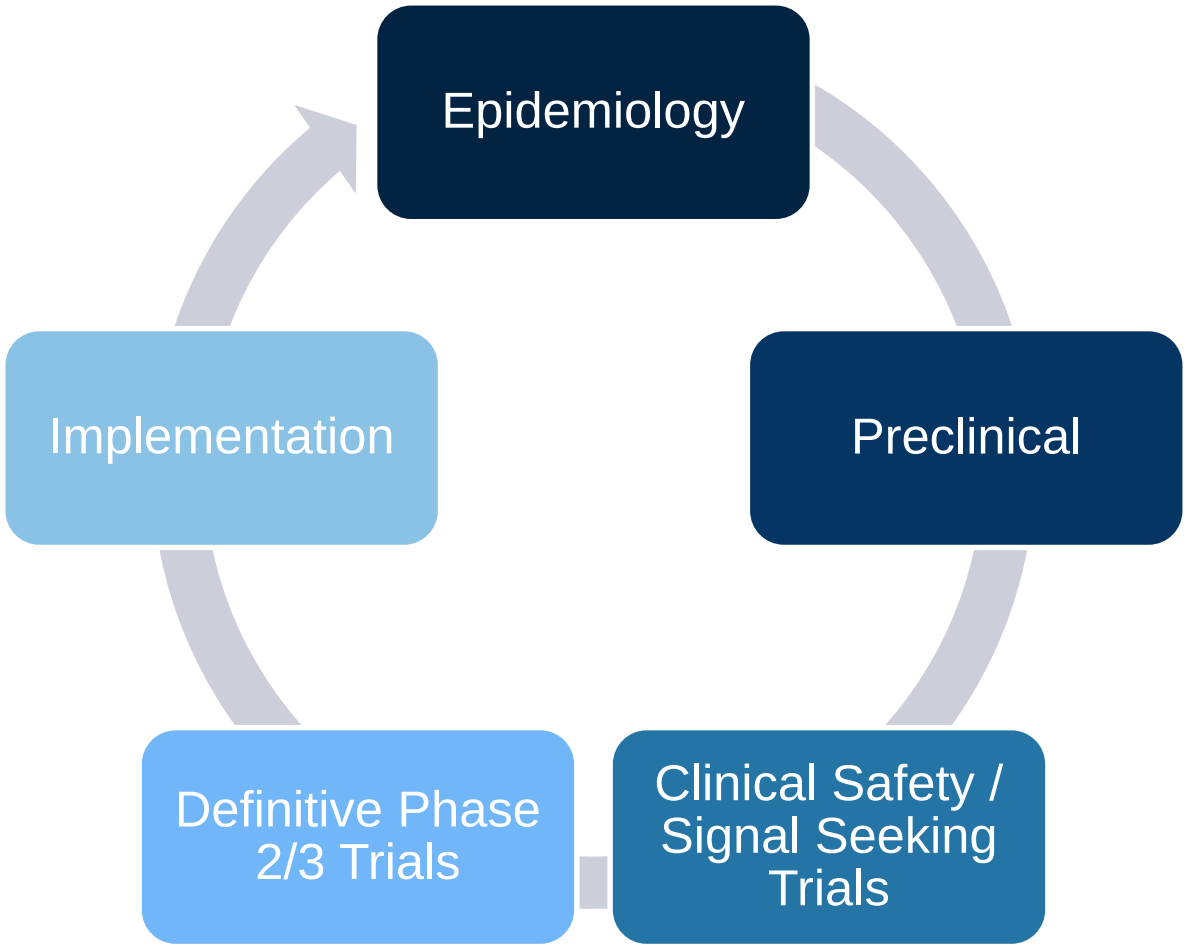
SCOTT ET AL. J CLIN ONCOL, 2020
DUNN ET AL. NAT. MED, 2021

Digital Interventions

TELE-EX SOLUTION



Knowledge Gaps



EPIDEMIOLOGY
- Prognostic importance of biomarkers
- Risk stratification using dense and dynamic phenotyping

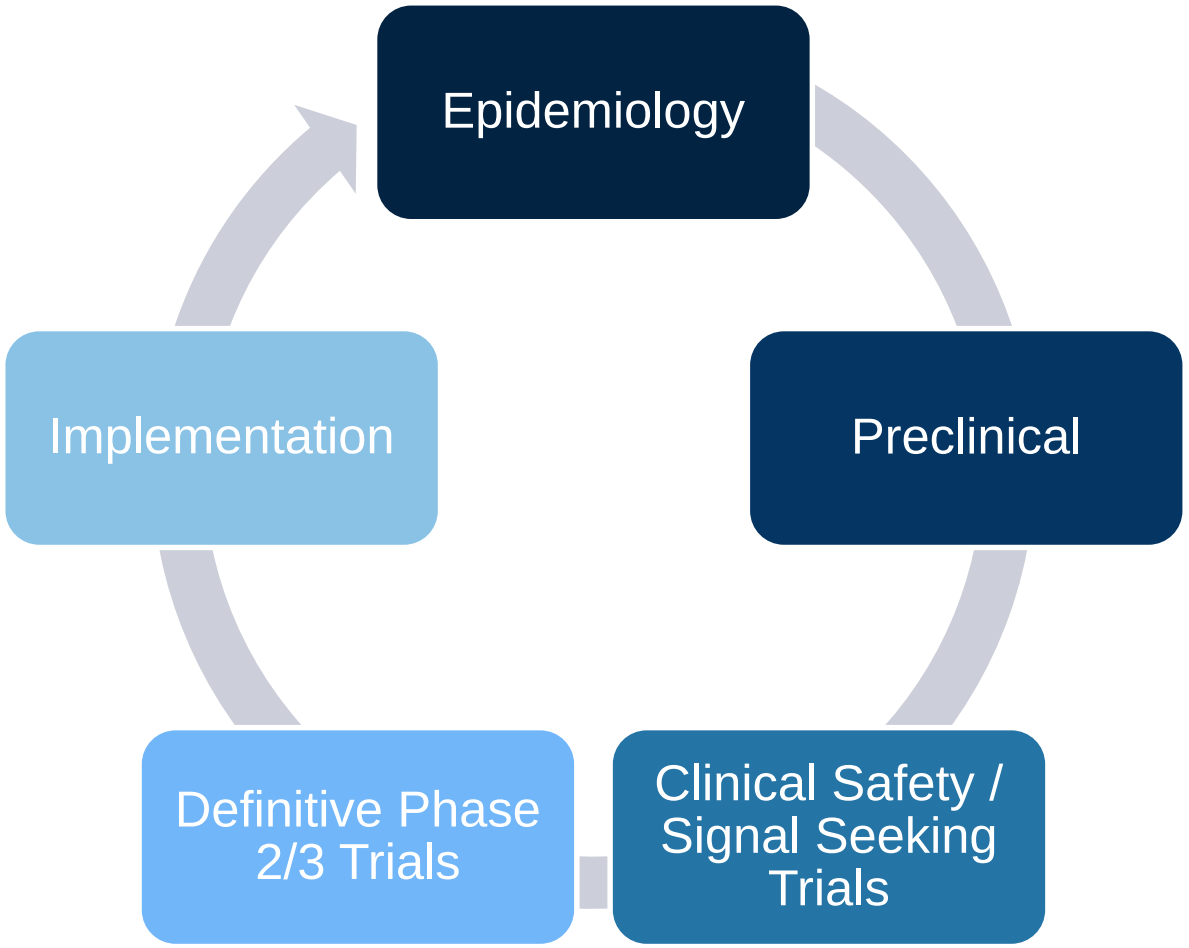
PRECLINICAL
- Mechanisms of multi-disease across the lifespan
- Intervention effects in appropriate models

CLINICAL SAFETY / SIGNAL SEEKING
- Phenotype-guided clinical care / interventions
- Individual patient responses

DEFINITIVE PHASE 2/3
- Effects of interventions on hard endpoints
- Multi-site trials

IMPLEMENTATION
- Patient / Clinician uptake
- Cost

Research Opportunities



EPIDEMIOLOGY
- Leverage existing sources (CCSS, CRDC) for 'systems' epidemiology

PRECLINICAL
- In vitro and in vivo models based on human data
- iPSC, organoids for modeling and interventions

CLINICAL SAFETY / FEASIBILITY
- Sequential multiple assignment randomized trials (SMART)

DEFINITIVE PHASE 2/3
- Leverage clinical trials networks
- Digitized trials with centralized cores

IMPLEMENTATION
- Multiphase optimization strategy (MOST)

Research Gaps

Leverage ongoing trials

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

PAR-21-055:

- **Time-sensitive mechanistic ancillary studies to ongoing clinical projects**
- **Identify novel targets for diagnosis, treatment, and prevention of disease**
- **Collaboration between basic and clinical investigators**
- **Collaborations in which a senior investigator from the parent study supports a junior investigator to serve as PI on an ancillary study are encouraged**

1

Standard measures

Optimized, minimal set of core measures:

- **Costs of standard measures covered**
- **Single data repository**

2

Cross-cutting programs

MoTrPAC
The Molecular Transducers of Physical Activity Consortium

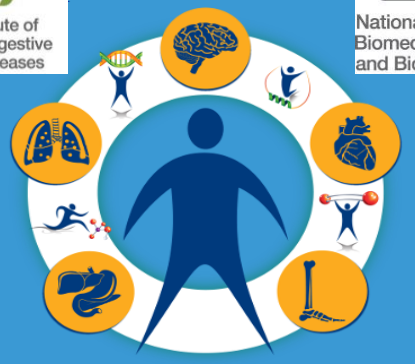
NIH National Institute on Aging

NIH The Common Fund

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Institute of Biomedical Imaging and Bioengineering



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Acknowledgments

MSK Exercise Oncology Team

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