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This book is dedicated to the memory of my father, Leon Segal, deprived of formal education by the Holocaust and immigration.

“Put the patient before the disease.”

Sir William Osler

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FOREWORD

Three main ideas, embodied by practical clinical terms, are presented in this book:

A. **True "personalized medicine" should be sought in the realm of internal medicine**, with a clear differentiation from the concept of "precise medicine". **Sarcopenia and frailty assessment are the key to internal medicine's personalization**.

   Introduction*, differentiating personalized and precise medicine, and* ***Chapter 1****, defining sarcopenia, frailty, and means of clinical, laboratory, and imaging assessment.*

B. **Sarcopenia and frailty assessment, as means for personalized medicine, should be implemented in mid-life patients**, aside from their application in the field of geriatric medicine.

   Chapter 2 *includes a tabular description of the existing literature regarding sarcopenia and frailty assessment among non-elderly patients.*

C. **Practical guidelines for patients' management should take into account the extent of mid-life sarcopenia and frailty**. Treatment settings and planning should be guided by such means of medical personalization.

   Chapter 3 *establishes the place for sarcopenia and frailty assessment and the consequent treatment directives for middle-aged patients hospitalized due to acute illness and those treated in an ambulatory setting for chronic diseases.*

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INTRODUCTION

PERSONALIZED VS. PRECISE MEDICINE: PATIENT-ORIENTED VS. DISEASE-CENTERED?

GAD SEGAL, MD

In current medicine, the term "personalized" is frequently used to describe modernism and innovation of clinical practice. Indeed, harnessing the strength of modern technology for better therapy is, and should be, both a desire and a value. The dilemma presented therein regards the question of whether advanced technologies are truly harnessed for the sake of medicine personalization or aiming for higher precision of therapy for certain diseases. Understanding the full scope and answering this question requires better definitions and closer examination of seemingly synonymous and yet different terms: "personalized medicine" vs. "precise medicine".

Disease-oriented diagnosis and therapy, often regarded as personalized medicine, has spread worldwide. The realm of clinical oncology is probably the best example in which the term "personalized medicine" is often confused with the more accurate term "precise medicine". Higher precision undoubtedly enables better diagnosis and therapeutics when focusing on the disease. Nevertheless, it is not "personalized" but rather "precisely" focused on the diseased tissue. The application of PET with fluorodeoxyglucose F18 (^{18}F FDG-PET), for example, in the field of lymphoproliferative diseases enables more precise metabolic mapping of disease (Wright et al. 2017). Unlike Wright et al., who used the term "precise", most authors tend to use the term "personalized" when describing the concept of fitting the diagnostic and therapeutic approaches to the molecular characteristics of the neoplasm. Examples of such ambiguity of terminology can be seen in the case of non-small cell lung cancer—NSCLC (Rocco et al. 2016), small cell lung cancer—SCLC (Schneider and Kalemkerian 2016), liver cancer (Li and Wang 2016) and other cases. In their manuscript heading, Li and Wang include the term

"personalized therapy" while the inner text presents their wish "to execute precision medicine".

Another example of this common contradiction in terms is the frequent use of the ambiguous combination "targeted personalized therapy". This combination is widely used in the oncologic literature, for treatment of colorectal cancer (De Mattia, Cecchin, and Toffoli 2015) and breast cancer (Cox, Alford, and Soliman 2017), and in reviews of advanced anti-cancer therapeutics (Kamel and Al-Amodi 2017). These uses and many others highlight the need to discriminate between "personalized medicine" (not addressed in these publications) and "precise medicine", which is the true value they present.

In a comprehensive review of "personalized medicine in Europe" (Di Paolo et al. 2017), the authors define (and criticize) the concept of personalized medicine as allowing "patients to receive drugs specific to their individual disease" while undermining patients' preferences and beliefs. Nevertheless, an essential component should not be overlooked, one that mitigates the impact of disease and enables patients to survive and express their preferences: the extent to which they are either robust or frail. The concept presented and detailed in the following chapters of this book determines that frailty assessment (mainly by means of sarcopenia assessment) is truly a personalized approach for diagnosis and therapy. Sarcopenia and frailty assessment (presented in their full scope in the following chapters) are the true and valuable embodiment of bringing the "person" into the "personalization" of medicine.

This book should not be regarded as a substitute for whoever wants to specialize in the field of sarcopenia and frailty assessment. Rather, it is specifically for practicing physicians and other health care professionals who would like to integrate the world of sarcopenia investigation and treatment directives into their daily clinical practice.

LIST OF ABBREVIATIONS

ADA, American Diabetes Association

ADL, Activities of daily life

AGE, Advanced glycation end products

ALST, Appendicular lean soft tissue

ALT, Alanine amino transferase

AMI, Acute myocardial infarction

ASA, American Society of Anesthesiologists (score)

AUC, Area under the curve

BIA, Bioelectrical impedance analysis

BIP, Bezafibrate infarction prevention (study)

BMD, Bone mineral density

BMI, Body mass index (kg/m^2)

CCI, Charlson comorbidity index

CCT, Creatinine Clearance

CD, Crohn's disease

CDC, Centers for Disease Control and Prevention

CHD, Coronary heart disease

CHF, Congestive heart failure

CHX, Cardiovascular health study (index)

CI, Confidence interval

CKD, Chronic kidney disease

COPD, Chronic obstructive pulmonary disease

CT, Computerized tomography

DHEA, Dehydroepiandrosterone

DPP4, Dipeptidyl peptidase 4 (inhibitors)

ECOG, Eastern cooperative oncology group (performance status)

ED, Emergency department

ESRD, End stage renal disease

FAM5C, Family with sequence similarity 5, member C

FEV1, Forced expiratory volume in the first second

FI_{34}, Frailty index based on 34 health variables

FI-CGA, Frailty index (derived from) comprehensive geriatric assessment

FIELD, Fenofibrate Intervention and Event Lowering in Diabetes (study)

FIM, Functional Independence Measure

FSST, Four square step test

GFR, Glomerular filtration rate (estimate)

GGT, Gamma-glutamic transferase

GIT, Gastrointestinal tract

GLP1, Glucagon-like peptide-1 (receptor agonists)

GWAS, Genome-wide association studies

HD, Hemodialysis

HER, Human epidermal (growth factor) receptor

HF, Heart failure

HFpEF, Heart failure with preserved ejection fraction

HFrEF, Heart failure with reduced ejection fraction

HGS, Handgrip strength

HOMA-IR, Homeostatic model assessment for insulin resistance

HPA, Hypothalamic-pituitary-testicular axis

HRs, Hazard ratios

HUAC, Hounsfield unit average calculation

IADL, Instrumental activities of daily life

IBD, Inflammatory bowel disease

ICU, Intensive care unit

IGF-1, Insulin-like growth factor 1

IU, International units

L3SMI, L3 (vertebra level) skeletal muscle index

LBM, Lean body mass

LVEF, Left ventricular ejection fraction (percentage)

MAMC, Mid-arm muscle circumference

MD, Mediterranean diet

MEF-2C, Myocyte enhancer factor 2C

mFI, Modified frailty index

MoCA, Montreal cognitive assessment (score)

mTOR, Mammalian target of rapamycin signaling

MUFA, Monounsaturated fatty acids

NAFLD, Non-alcoholic fatty liver disease

NHANES III, the third National Health and Nutrition Examination Survey

NSCLC, Non-small cell lung cancer

NYHA, New York Heart Association (performance status)

OLLP, Offspring of long-lived parents

OSLP, Offspring of short-lived parents

P-5-P; Pyridoxal 5 Phosphate

PD, Parkinson's disease

PGC-1α, Proliferator-activated receptor gamma coactivator 1-alpha

pQCT, Peripheral quantitative CT

PVD, Peripheral vascular disease

RAAS, Renin-angiotensin-aldosterone system

RFS, Recurrence-free survival

ROC curves, Receiver operating characteristic curve

SARMs, Selective steroidal and non-steroidal androgen receptor modulators

SAT, Sub-cutaneous adipose tissue area

SD, Standard deviation

SGLT2, Sodium-dependent glucose cotransporters (inhibitors)

SGPT, Serum glutamic pyruvic transaminase

SHBG, Sex hormone binding globulins

SOF, Study of osteoporotic fractures (index)

TAVI, Transcatheter aortic valve insertion

Tmem119, Transmembrane protein 119

TNFα, Tumor necrosis factor alpha

TPA, Total psoas (muscle) area

TSF, Triceps skin fold

TUG, Timed up-and-go (test)

UC, Ulcerative colitis

ULN, Upper limit of normal

VAT, Visceral adipose tissue area

WC, Waist circumference

Wnt3a, Wingless-type MMTV integration site family, member 3A

CHAPTER ONE

SARCOPENIA AND FRAILTY: DEFINITIONS AND METHODS OF ASSESSMENT

GAD SEGAL, MD

"Each Patient is Different."

Sir William Osler

Upon entering the room, every physician gets a chance for a first look and a first impression of his or her patient. Whether desired or not, this first impression will have a major impact on the ongoing, future patient-doctor relationship. What do we think about this first impression? How prejudiced is it? How precise is it? Is it the beginning of "personalized medicine"? Many such questions will undoubtedly continue to be in the center of clinical medical practice as long as physicians will continue to be human. Since "to err is human", this initial contact, named "eyeballing the patient", along with the conclusions derived from it—especially regarding the extent of a patient's frailty—should be further questioned.

The "eyeball test". Basic, intentional and unintentional, frailty assessment.

In contrast to sarcopenia, which is defined as a too-low muscle volume, frailty, a multi-faceted syndrome rendering the frail patient vulnerable to a myriad of stressors, is both the peak of personalization and abstract at the same time. This has naturally led generations of physicians to evaluate frailty by means of "eyeballing" the patient, determining his or her potential to survive certain diseases or treatments. Eyeballing, being no doubt the best example of personalization rather than precision, lacks standardization and defies all means of objective measurement. Revenig et al. (2015) have shown that during pre-surgical assessment of patients, physicians give too much weight to the patient's age and tend to ignore his

or her functional capacity. By contrast, the patients tended to overestimate their robustness and fitness to withstand the strains of surgery. Therefore, researchers try to replace the eyeball test with other (reliable and measurable) personalization parameters.

One such study was done by Green et al. (2012), who evaluated the impact of frailty in elderly, symptomatic aortic stenosis patients who were undergoing transcatheter aortic valve insertion (TAVI). They devised a frailty score out of the following measurable parameters: Gait speed, grip strength, serum albumin and performance on activities of daily living (ADL). While there was no correlation between the frailty status and procedural outcomes, the frailty score did correlate with these patients' one-year mortality risks. In their editorial comments regarding this study, Rodés-Cabau and Mok (2012) declare that until that time, frailty assessment, based on the traditional "eyeball" test, should have been considered as having an empirical nature, potentially leading to major personal biases, and suffering from low reproducibility and lacking any "scientifically proven methodology". Five years later, Afilalo (2017) called upon cardiologists worldwide to "upgrade their eyeball test" regarding the evaluation process for TAVI, thereby advocating true personalization of cardiovascular medicine, without compromising the objectivity, measurability, and reproducibility of frailty assessment.

Frailty and Sarcopenia Definitions

The origin of the word "sarcopenia" is the combination of the Greek *sarx* or "flesh" and *penia* or "loss"; it was suggested in the year 1989 (Rosenberg 1989) along with the synonymous term "sarcomalacia". Eight years later, Rosenberg defined "sarcopenia" as both the loss of muscle and the related loss of essential body functions (Rosenberg 1997). Many others, later on, defined sarcopenia as a syndrome, with the most common definition stating that sarcopenia is "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, correlated with physical disability, poor quality of life and death" (Santilli et al. 2014; Alfonso J Cruz-Jentoft et al. 2010; Fried et al. 2001). Many authors clearly associate sarcopenia with ageism and gerontology (Fuggle et al. 2017; Marty et al. 2017; Ogawa, Yakabe, and Akishita 2016; Fried et al. 2001), while others note the differences between sarcopenia in old age and during youth. Bijlsma et al. (2014) compared different methods and definitions for such "subtypes" of sarcopenia and, indeed, found that different diagnostics methodologies had totally different clinical

implications for different age groups. In a literature review and meta-analysis, P. Liu et al. (2017) included six studies with a total of 7,367 community-dwelling elderly persons. A pooled hazard ratio analysis showed a significantly increased risk for all-cause mortality among participants with sarcopenia (diagnosed according to different methods of muscle mass quantification): (pooled HR 1.60, 95% CI 1.24–2.06, p = 0.000).

The word "frailty" was been in use for centuries, first dated to the 14th century *(Merriam-Webster* 2018). The medical term "frailty", like sarcopenia, is also defined as a syndrome often, and almost exclusively in the geriatric patient population: "A common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality" (Xue 2011).

Many authors see sarcopenia and frailty as a continuum, or as a cause and outcome. Cederholm even connects this so-called overlapping continuum to mortality, stating that "robustness passes from sarcopenia over frailty to disability leading eventually to a mortal outcome" (2015). Lorenzi et al. defined sarcopenia as the "biologic substrate" of frailty and tried to establish an association between leukocytes telomere length and this continuum (2018). Wilson et al. defined sarcopenia as the "precursor syndrome or the physical manifestation of frailty" (2017).

In the realm of geriatric medicine

Currently, sarcopenia and frailty assessment are a common and consensual part of geriatric medicine (Francesco Landi et al. 2017; Marzetti et al. 2017; Beaudart et al. 2016). It could be stated that in this clinical discipline, indeed, sarcopenia and frailty are already the face of "personalized medicine", being several steps ahead of other, non-geriatric, medical domains. In their study of frail, elderly patients, de Vries and colleagues define a special physical therapy, intended to reduce frailty, as "patient-centered"—only a step from defining this intervention as personalized medicine, as it should be described (de Vries et al. 2016). Studies have already shown that sarcopenia and frailty are widespread in the elderly population—around one-tenth of community-dwelling older individuals (Sánchez-García et al. 2017) and over 40% on admission to geriatric rehabilitation—and this has a potential negative impact on rehabilitation outcomes (Pongpipatpaiboon et al. 2018; Gringauz et al. 2017). Many publications detail the association between sarcopenia and increased risk for all-cause mortality (Liu et al. 2017) and many deal with

the association of, and the impact of, sarcopenia and frailty on patients suffering from diseases that are typically related to aging. Examples of such associations can be found in patients suffering from Parkinson's disease. In PD patients, sarcopenia and frailty were found to be highly prevalent and associated with higher severity of the disease (Vetrano et al. 2018). A much more common chronic disease among elderly persons is arterial hypertension. In hypertensive patients, frailty was found to be associated with increased prevalence of end-organ damage (Tabara et al. 2016). Sarcopenia was found to be associated with higher risk for non-alcoholic liver disease—NAFLD (Hong et al. 2014). In patients with devastating Alzheimer's dementia, it was shown that sarcopenia and frailty are very common and geriatric interventions are recommended to address these diagnoses among Alzheimer's disease patients (Hirose et al. 2016).

Notwithstanding the above, targeting sarcopenia and frailty among patients with advanced dementia should be questioned. Since these patients are known to have a significantly shortened lifespan (Kua et al. 2014), what true impact would such interventions have? Could it be that in such cases straightforward eyeballing of the patient and deciding that he or she is frail would suffice? Since this book focuses on internal medicine patients, such dilemmas relating to clinical geriatric medicine will not be further discussed.

Outside the realm of geriatrics, screening the literature for studies of sarcopenia and/or frailty, limiting the age of involved subjects to the range of 45 to 64 years, yields a very small number of publications. The authors of this book assume that it is only logical to postulate that early sarcopenia detection in mid-life adults would enable prediction and reveal the population that is in a pre-frail state, before frailty makes them the elderly sentenced to shortened lifespans!

Sarcopenia Assessment

A major part of the "sarcopenia" definition, alongside its "syndromic" aspects, is the strict requirement that the patient has a lower-than-normal muscle mass, adjusted for gender and age. As will be detailed later on in this book, it is not only absolute muscle mass that is too low; there is frequently a low muscle mass relative to the fat tissue mass in the body.

There are many quantitative methods and related definitions for sarcopenia assessment and diagnosis (the literature is still poor regarding evidence and high-quality research) (McLean and Kiel 2015; Robinson et al. 2018).

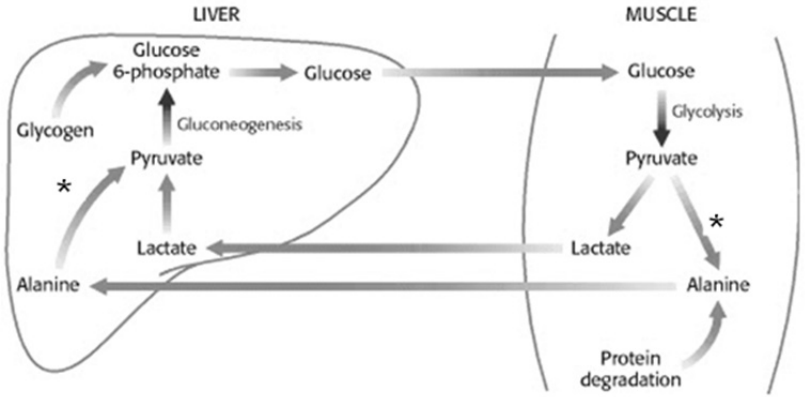
In the following paragraphs, some of these methods will be presented and discussed.

ALT (Alanine amino transferase, SGPT) activity measurement in peripheral blood

Alanine amino transferase (ALT; also known as SGPT, serum glutamic pyruvic transaminase) is the enzyme responsible for reversible transamination between alanine and 2-oxoglutarate to generate pyruvate and glutamate. As such, this fundamental enzyme plays a key role in the intermediary metabolism of glucose and amino acids (Senior 2012; Kim et al. 2008). As detailed in Figure 1, this enzyme catalyzes a bidirectional molecular process in various tissues, including skeletal muscles and the liver. Since ALT activity in the liver is about 3,000 times as high as in the serum, its main purpose in clinical testing is to rule out—and assess, as in the case of hepatitis—hepatocellular injury from various causes. The amount of ALT in tissues other than the liver, like the skeletal muscle tissue, is much lower (Kim et al. 2008). The catalytic activity of ALT (nominally measured in IU, international units) is facilitated by P-5-P, Pyridoxal 5 Phosphate, a metabolic derivative of vitamin B6, acting as the co-factor for this enzyme. Therefore, P-5-P is added to the serum test tubes in order to maximize the catalytic activity of ALT in the blood sample (Marshall 2012).

ALT activity levels are significantly decreased among end stage renal disease (ESRD) patients treated by hemodialysis (Ali Yousif Abd Allah 2016). Also, ALT activity levels are measured as lower in patients who are taking medications that involve/recruit the catalytic activity of P-5-P, thereby lowering ALT activity, dependent of this co-enzyme (such as dopaminergic medications used for Parkinson's disease). The upper limit of normal (ULN) for ALT peripheral blood activity is approximately 40 IU. Above this level of activity in the blood, it is assumed that ALT is pouring out of cellular tissues (mainly liver hepatocytes) and, therefore, ALT levels above 40 IU should not be interpreted in relation to muscle mass, sarcopenia, and frailty. Consequently, patients with such ALT measurements should be evaluated by means other than ALT levels and are usually excluded from clinical studies addressing ALT as a surrogate marker for sarcopenia and frailty.

Figure 1. ALT (SGPT) activity (asterisk) in the liver and skeletal muscle catalyzes the bidirectional transformation of Alanine and Pyruvate.



After preliminary publications associated low ALT levels of activity with lower skeletal muscle mass and increased long-term mortality in the older population (Elinav et al. 2006; Le Couteur et al. 2010), several publications described a more comprehensive association between decreased level of ALT activity in the peripheral blood, sarcopenia, frailty, and increased risk of all-cause mortality in middle-aged, heterogeneous populations. Also, associations were found to exist between low ALT, as a marker for the above parameters, and decreased potential for patients' rehabilitation processes. Earlier publications described such associations in general (Liu et al. 2014), while others investigated the phenomenon more thoroughly.

Le Couteur et al. (2010) investigated the possible relationships between blood tests of liver function and injury (alanine transaminase [ALT], gamma-glutamic transferase, bilirubin, and albumin), on the one hand, and age, frailty, and survival, on the other. They included in their study 1,673 community-dwelling men aged 70 years or older. They found that ALT blood activity was lower in older participants. Those participants with ALT below the median at baseline had their survival reduced (hazard ratio 2.10, 95% confidence interval [CI]: 1.53–2.87) by up to 4.9 years. In addition, they found that low ALT was associated with frailty (odds ratio 3.54, 95% CI 2.45–5.11), and the relationship between ALT and survival disappeared once frailty and age were included in the survival analysis. Their finding, once again, reinforces the idea that low ALT activity is a predictor of reduced survival, associated with frailty and increasing age.