

**Biological Age in Kidney Function Models:
A Framework for Age-Informed Precision Dosing**

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Clinical Pharmacy and Translational Sciences)
in the University of Michigan
2026

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Dedication

In loving memory of my grandparents

Four years, three goodbyes I could not say in person.

*But every page of this work carries your prayers,
your wisdom, and the love that knew no distance.*

*May you see from heaven
what your love helped me accomplish.*

This is for you.

Until we meet again...

Acknowledgements

This dissertation represents not only years of research but also the culmination of a journey made possible by the unwavering support, guidance, and kindness of many remarkable individuals. I am deeply grateful to all who walked alongside me during this transformative chapter of my life.

First and foremost, I extend my deepest gratitude to my dissertation committee. To my advisor, Dr. Amit Pai, thank you for your mentorship, patience, and belief in my potential. Your guidance shaped not only this research but also my growth as a scientist and critical thinker. I am profoundly grateful for the opportunity to learn from you and for the freedom you gave me to explore ideas and develop as an independent researcher. To Dr. Amy Rothberg, Dr. Jasmine Luzum, and Dr. Steven Horbal, thank you for your invaluable insights, thoughtful questions, and constructive feedback that strengthened this work immeasurably. Your expertise and encouragement were instrumental in bringing this dissertation to fruition.

To Dr. Karen Farris, you have been far more than a faculty member to me. You have been a source of maternal warmth and support during some of my most difficult moments. I will never forget the day I called you in tears after losing my grandmother, just before my candidacy exam. Your compassion, understanding, and reassurance carried me through that heartbreak. Thank you for seeing me not just as a student, but as a person, and for offering the kindness I needed when I was so far from home and family.

To Ms. Antoinette Hopper, thank you for your dedication to our professional and career development. The events and opportunities you organized opened doors I never imagined possible. It was through one of these events that I secured my internship at Eli Lilly and Company, an experience that profoundly shaped my career trajectory. Your commitment to preparing us for success beyond academia has made a lasting impact on my professional journey.

To Dr. Levi Hooper, my senior lab colleague and dear friend, thank you for being like a brother to me. Your camaraderie, guidance, and friendship made Ann Arbor feel like home. Whether troubleshooting experiments, sharing ideas, or simply being there during challenging

times, your presence made this journey less lonely and infinitely more meaningful. I am grateful not only for your mentorship but for the genuine friendship we built along the way.

To the exceptional clinical staff at the Michigan Diabetes Research Center Clinical Research Unit (MDRC-CRU), particularly Andrea Waltje, thank you for your professionalism, expertise, and unwavering support throughout the Kidney-PACE study. Andrea, you are the kindest and most compassionate nurse I have ever had the privilege to work with. Your meticulous attention to detail, your patience with participants, and your genuine care for everyone involved made our research possible. Thank you for going above and beyond to ensure the success of our study.

To my CPTS cohort and friends at the College of Pharmacy, thank you for the countless conversations, shared struggles, and moments of laughter that sustained me through the ups and downs of graduate school. Your friendship transformed what could have been an isolating experience into one filled with connection, collaboration, and community. I am fortunate to have shared this journey with such brilliant and compassionate colleagues.

I am deeply grateful to the University of Michigan Rackham Graduate School for awarding me the Doctoral Intern Fellowship, which provided crucial financial support for my tuition during my internship. This fellowship enabled me to pursue invaluable professional experience without interrupting my doctoral progress, and I am honored to have received this recognition and support.

Finally, and most importantly, to my family, words cannot adequately express my gratitude. Mom and Dad, you made the ultimate sacrifice by letting me pursue my dreams thousands of miles away, even as it meant four years of separation, missed celebrations, and bearing unimaginable losses without me by your side. Your unconditional love sustained me through every challenge. Your encouragement lifted me during moments of doubt. Your pride in my accomplishments, celebrated from afar, gave me strength to persevere. Every phone call, every prayer, every word of wisdom carried me forward. This achievement belongs to you as much as it does to me. Thank you for believing in me, for your endless sacrifices, and for being my anchor no matter the distance. I hope this work makes you proud and honors the values you instilled in me.

Table of Contents

Dedication	ii
Acknowledgements	iii
List of Tables	viii
List of Figures	x
Abstract	xii
Chapter 1 Introduction	1
1.1 Methods of Quantifying Biological Age: Epigenetics	2
1.2 Methods of Quantifying Biological Age: Radiomics	6
1.2.1 Radiomic Trends of Age-related Changes in Body Composition	7
1.3 Functional Changes in Kidney Drug Elimination Processes During Aging	16
1.4 Estimated Kidney Function Equations in Older Adults	23
1.5 Vancomycin Clearance Changes Across the Lifespan Through Population-PK Models	28
1.6 A Model of Age-Informed Radiomic Biomarkers as A Covariate of Kidney Function ...	31
1.7 Framing the Dissertation Purpose and Specific Aims	36
Chapter 2 Improving Estimation of Lean Body Weight Using Radiomic-based Skeletal Muscle Biomarkers	39
2.1 Introduction	39
2.2 Materials and Methods	41
2.3 Results	43
2.4 Discussion	49
2.5 Conclusion	53

Chapter 3 Correlating Radiomics-Derived Morphomic Age Against the Models of Kidney Function	54
3.1 Introduction.....	54
3.2 Materials and Methods.....	55
3.3 Results.....	56
3.4 Discussion	61
3.5 Conclusion	65
3.6 Appendix A: Supplemental Materials.....	66
Chapter 4 Investigating Epigenetic Age and Metabolic Age as Potential Biomarkers of Kidney Function	82
4.1 Introduction.....	82
4.2 Methods.....	84
4.2.1 Study Design and Patient Population.....	84
4.2.2 Drug Administration and Pharmacokinetic Sampling	85
4.2.3 Body Composition Assessment Testing and Calculating Metabolic Age	86
4.2.4 Epigenetic Age Sample Collection	89
4.2.5 Quantification of Iohexol in Plasma	89
4.2.6 Population Pharmacokinetic Modeling.....	90
4.3 Results.....	90
4.3.1 Distribution of Measured Glomerular Filtration Rate	94
4.3.2 Univariate and Multivariate Covariate Analysis.....	94
4.3.3 Population Pharmacokinetic Model Development	95
4.3.4 Development of the Metabo-Renal Ratio	97
4.3.5 Preliminary Assessment of BA _{Epi} in the Kidney-PACE Cohort.....	99
4.4 Discussion	101
4.5 Conclusion	105

4.6 Appendix B: Supplemental Materials	107
Chapter 5 Conclusion and Future Directions.....	125
5.1 Summary of Key Findings.....	125
5.2 Future Directions	129
Bibliography	131

List of Tables

Table 1.1 Summarized list of the developed epigenetic clocks to date.	4
Table 1.2 Age-related changes in body composition and involved morphomic covariates.	9
Table 1.3 List of Several High-Risk Renally Eliminated Medications in Geriatric Pharmacotherapy: Adverse Drug Reactions and Relevance to Biological Age-Informed Dosing	20
Table 1.4 Summary of the major equations to estimate kidney function around the globe.	24
Table 1.5 Summary of the population pharmacokinetic (Pop-PK) models of vancomycin clearance in the (older) adult population	29
Table 1.6 Proposed differences between biological morphomic age and chronological age.	35
Table 2.1 Alternate body size descriptors used to define the body size of obese subjects with their expansions	42
Table 2.2 Descriptive statistics of the dataset's patient demographics and morphomic variables	44
Table 2.3 Linear regression model results for DEXA-derived lean body weight against CT morphomic variables, stratified by vertebra number	45
Table 2.4 Linear regression model results for DEXA-derived lean body weight against: 1) alternate body size descriptors and 2) combined standardized 2005 Janmahasatian equation and skeletal muscle area at different vertebra numbers	47
Table 2.5 Summary of prediction error metrics for the proposed models benchmarked against DEXA measurements.....	49
Table 3.1 Descriptive statistics of the dataset's patient demographics and morphomic variables.	57
Table 3.2 Expansion of the models of biological morphomic age.	58
Table 3.3 Complete Pop-PK models of aminoglycoside clearance stratified by the type of age in Monolix.....	59
Table 3.4 List of the morphomic variables and their pragmatic means in the final cohort (n=156).....	66

Table 3.5 List of Potential Morphomic Parameters Extracted by Vertebral Level	68
Table 3.6 Summary of key models leading to selection of the final model, reported based on AIC and software proposal.	71
Table 3.7 Final population PK model parameters for the aminoglycosides stratified by age index.....	77
Table 3.8 Final population PK model parameters for the aminoglycosides built upon age type ONLY.	79
Table 4.1 Expansion of the utilized equations for calculating metabolic age	88
Table 4.2 Descriptive statistics of patient demographics for the Kidney-PACE study.	92
Table 4.3 Summarized statistical comparison of the relevant physiologic and metabolic parameters of the study cohort stratified by sex	94
Table 4.4 Comparison of model performance based upon the metabolic and renal biomarkers..	96
Table 4.5 Final population PK model parameters for iohexol using the metabo-renal ratio.....	97
Table 4.6 Summary results of DNAge in a subset of Kidney-PACE participants.	100
Table 4.7 Complete list of eligibility criteria for the Kidney-PACE study participants.....	107
Table 4.8 Body size descriptors and kidney function estimation equations used in this study ..	108
Table 4.9 Distribution of participants across measured glomerular filtration rate groups, including central tendency and variance of the population to support simulations.....	111
Table 4.10 Univariate analyses to identify significant covariates on CL_{IOH}	112
Table 4.11 Multivariate analyses of age, metabolic, and kidney parameters on CL_{IOH} (mGFR)	114
Table 4.12 Initial Parameter Estimates for the base pharmacokinetic model.....	115
Table 4.13 Parameter estimates of the base pharmacokinetic model	115
Table 4.14 Stepwise population pharmacokinetic model development in Monolix, showing tested covariates on iohexol clearance, corresponding AIC values, change from base model (ΔAIC), and selection rationale.	116
Table 4.15 Complete list of estimated DNAge in all processed samples (n=30) across two parallel clinical studies conducted by our group.....	121

List of Figures

Figure 1.1 Illustration of the hierarchy of deciphering biological age based on molecular approaches, human phenotype, and clinical and laboratory measurements. ALT, alkaline phosphatase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; FEV, forced expiratory volume; LDL, low-density lipoprotein (created with BioRender.com). ..	3
Figure 1.2 Trajectory of changes in body composition measurements by CT scans with aging stratified by sex. (a) Skeletal muscle expanded area and Dorsal muscle group (DMG) muscle expanded area. (b) Visceral fat area (VAT) and Subcutaneous fat area (SAT).Created with BioRender.com.	11
Figure 1.3 Comparison of Bone Mineral Density (BMD) measurement using DEXA versus CT scans in young adults and older adults. Created with BioRender.com.	14
Figure 1.4 Fractional change in kidney function over chronological age with key contemporary kidney function equations. CKD- EPI, Chronic Kidney Disease Epidemiology Collaboration; FAS, Full Age Spectrum; eCler, estimated creatinine clearance; MDRD, Modification of diet in renal disease.	27
Figure 1.5 Schematic model of Morphomic Age as a potential covariate of kidney function. Created with BioRender.com.	34
Figure 2.1 Illustrative comparison of dual-energy x-ray absorptiometry (DEXA) and computed tomography (CT) scan profiles in three individuals with increasing body fat percentage along with an example of the outputs from those imaging modalities. As shown, DEXA does not provide a direct measurement of muscle area (blue shaded region) as is feasible by CT scan (Created with Biorender.com)	41
Figure 2.2 Scatterplot illustrating the correlation between lean body weight measured by dual-energy x-ray absorptiometry (DEXA) with computer tomography (CT)-based skeletal muscle area (SMA), at different vertebral levels	46
Figure 2.3 Scatterplots demonstrating the correlation between the lean body weight measured by dual-energy x-ray absorptiometry (DEXA) and different alternate body size descriptors: a) lean body weight estimated by the Janmahasatian equation published in 2005 (LBW ₂₀₀₅); b) ideal body weight (IBW); c) adjusted body weight (AdjBW); and d) dosing weight (DW). As shown, DEXA-based LBW has the greatest correlation with LBW ₂₀₀₅ (R-squared=0.78)	47
Figure 3.1 Visual predictive check (VPC) plot for the final aminoglycoside clearance model stratified by drug type. The observed data are depicted as dots, with prediction intervals shown	

as shaded areas. Red circles highlight observed data points that deviate from the predicted range, suggesting potential outliers.....	60
Figure 3.2 Schematic of comparing the effectiveness of three proposed BA_{Mor} with chronological age in predicting kidney function. (Made with BioRender.com)	62
Figure 3.3 Observed versus population and individual predicted concentrations for the final model.....	80
Figure 3.4 Distribution of the individual weighted residuals and nonparametric distributional errors for the final model.	81
Figure 4.1 Conceptual framework linking metabolic age, body composition, and kidney function. <i>Created using Claude AI (Anthropic)</i>	84
Figure 4.2 Kidney-PACE study visit timeline showing sequence of procedures and blood sampling schedule following iohexol administration. Created in https://BioRender.com	86
Figure 4.3 Schematic overview of epigenetic age (DNAge) assessment methodology from sample collection through laboratory analysis.....	89
Figure 4.4 Visual predictive check (VPC) plot for the final iohexol clearance model by incorporating the ratio of RMR measured by indirect calorimetry to Serum cystatin C (RMR_IC/CysC). The observed data are depicted as dots, with prediction intervals shown as shaded areas. The red circle highlights an observed data point that deviated from the predicted range, suggesting a potential outlier.	99
Figure 4.5 Observed iohexol concentration–time profile for each study participant.	122
Figure 4.6 Individual observed and model-predicted iohexol concentration-time profiles (outliers proportion: 1.67%).....	123
Figure 4.7 Distribution of the individual weighted residuals and nonparametric distributional errors for the final model.	124

Abstract

Older adults are four to seven times more likely than younger individuals to experience adverse drug events requiring hospitalization, accounting for an estimated 100,000 emergency hospitalizations annually in the United States alone. A key driver of this vulnerability is the reliance on chronological age as the primary determinant of drug dosing, despite substantial interindividual variability in physiological aging that chronological age fails to capture. This dissertation investigated whether biological age biomarkers derived from radiomics, epigenetics, and metabolic rate could improve the prediction of kidney function and drug clearance compared to chronological age, thereby enhancing precision dosing strategies for renally eliminated medications in the aging population.

Three complementary aims were pursued. Aim 1 evaluated whether Computed Tomography (CT)-derived skeletal muscle area (SMA) could improve lean body weight (LBW) estimation in patients with obesity. In 63 participants from the Michigan Weight Management Program, SMA at the L3, L4, and T12 vertebral levels demonstrated strong correlations with Dual Energy X-ray Absorptiometry (DEXA)-measured LBW ($R^2 = 0.76-0.80$). Integration of SMA into the 2005 Janmahasatian equation substantially improved predictive accuracy, increasing R^2 from 0.76-0.78 to 0.84-0.86, with 83-88% of predictions within $\pm 10\%$ of measured values. These findings establish that opportunistic use of existing CT scans can significantly enhance LBW estimation for weight-based dosing.

Aim 2 tested whether composite morphomic age indices could predict renal drug clearance better than chronological age. Using population pharmacokinetic modeling in 156 patients receiving aminoglycosides, three morphomic age indices (BA_{Mor}) were developed from CT-based body composition biomarkers. All three BA_{Mor} -based models demonstrated an improved model fit compared to the chronological age model ($AIC = 2607.38, 2611.90, \text{ and } 2609.25$, respectively, vs. 2618.49). The best-performing index, BA_{Mor_3} , incorporating dorsal muscle group area, bone mineral density, and visceral fat area, yielded the greatest improvement, reducing the AIC by approximately 19 points from the base model (2617.07 to 2598.33).

These findings support the hypothesis that radiomic assessments better capture physiological variability relevant to renal drug elimination.

Aim 3 evaluated metabolic and epigenetic biomarkers as predictors of directly measured kidney function in the Kidney-PACE study. Twenty-four adults (12 diagnosed with type 2 diabetes, 12 controls) underwent gold standard iohexol clearance measurement alongside comprehensive metabolic and epigenetic assessments. Neither chronological age nor metabolic age significantly improved model predictions ($\Delta AIC = +2.1$ and $+1.74$ to $+2.33$, respectively). However, a ratio of resting metabolic rate to cystatin C (RMR/CysC) achieved a ΔAIC of -18.67 in the final model, exceeding the performance of the CKD-EPI 2021 creatinine-cystatin C equation ($\Delta AIC = -8.88$), the current clinical standard. Epigenetic age assessment using Horvath Clock and DunedinPACE showed minimal deviation from chronological age and did not contribute to improved predictions.

Collectively, these findings demonstrate that biological age biomarkers, particularly CT-derived morphomic indices and the RMR/CysC metabo-renal ratio, can enhance precision pharmacotherapy beyond what chronological age alone provides. Traditional metabolic age indices and epigenetic age clocks showed limited utility for pharmacokinetic applications, suggesting that biomarkers reflecting current physiological status are more relevant for drug dosing than those reflecting cumulative aging processes. The practical advantage of radiomic approaches lies in the opportunistic use of existing clinical imaging, requiring no additional scans, contrast administration, or patient procedures. As automated image analysis and metabolic assessment tools become integrated into clinical workflows, these approaches could be implemented at scale to personalize therapy, particularly for renally eliminated medications. If validated in larger clinical studies, this work holds the potential to meaningfully reduce adverse drug reactions in older adults, a population accounting for more than 600,000 emergency department visits annually due to medication harms in the United States, offering a pathway to safer pharmacotherapy that reduces preventable hospitalizations, patient suffering, and the substantial healthcare costs associated with medication-related harm in aging populations.

Chapter 1 Introduction

Aging is a complex and dynamic process associated with various biological, physiological, environmental, psychological, behavioral, and social changes in individuals.¹ These processes manifest through visible physical traits like graying hair to molecular-level changes like telomere length reduction.² The World Health Organization (WHO) expects the global population of older adults (over 65 years) to increase by 400 million individuals by 2030.³ Likewise, about 25% of the US population will consist of older adults by 2060.⁴ This significant increase in older adults is attributed to the aging of the baby boomer generation, public health initiatives, medical innovations, and improvements in healthy lifestyles in the modern era.⁵

Like all biological processes, aging has remarkable interindividual variability that remains difficult to reliably quantify and operationalize in clinical settings. Dose labeling specific to older adults is required by law.⁶ As a consequence, regulatory agencies recognize older adults as a specific population that is pharmacologically vulnerable due to age-related changes in drug absorption, distribution, metabolism, and excretion, warranting dedicated consideration in drug development. However, attention to drug dose considerations in individuals above 80 years is often limited, which leads to drug dosing uncertainty in this emergent population. In this regard, it is important to involve older adults during drug development and clinical trials to evaluate the age-related effects on a drug's risk–benefit ratio.⁷ This is especially true because older adults are often on multiple medications (polypharmacy) and at risk for drug–drug interactions and adverse drug events even with dose adjustments.⁸ According to current estimates, older adults commonly use five or more medications, several of which often require adjustment for kidney function.^{9,10} Attention to this specific population has increased in the past few years, with a focus on approaches to slowing the aging process. Postponing these age-related physiologic changes at the upper end of the lifespan can have pharmacokinetic (PK) consequences that also need further studies.

Aging affects nearly every physiologic process, and countless biomarkers have been proposed to measure it.² Further investigation of these biomarkers may help us find a better understanding of the relationships between an individual's health status and life expectancy. In that context, it may be advantageous to have criteria that can capture the quality of general and organ health on an individual level. This better representation of chronological age is referred to as biological age. By definition, chronological age is the actual time in years from the date of birth to a given date in time. Biological age is a much more complex time variable that incorporates multiple factors that account for cellular and biochemical processes. The quantitative relationship between biological age and drug disposition remains poorly characterized. While chronological age is routinely used as a covariate in pharmacokinetic models, it captures only a fraction of the interindividual variability observed in drug clearance and distribution. Whether biological age can more precisely explain this variability has yet to be systematically evaluated. In recent years, multiple diagnostic tools to quantify biological age have emerged in the United States.¹¹ This remarkable investment in biological age-related research implies that new opportunities exist to improve quantitative systems pharmacology across the lifespan and healthspan.

This chapter provides a comprehensive foundation for the dissertation research. Current methods for quantifying biological age are first reviewed, with emphasis placed on epigenetic aging clocks and radiomic biomarkers derived from medical imaging. Age-related changes in kidney function are then examined, and existing approaches for estimating renal clearance are evaluated, with their limitations in older adults highlighted. Building on these foundations, a novel framework is proposed that integrates radiomic biomarkers with kidney function assessment to improve precision dosing. The chapter concludes by articulating the specific aims through which this framework will be tested and validated.

1.1 Methods of Quantifying Biological Age: Epigenetics

Given the complexity of quantifying biological age, multiple diagnostic approaches have emerged, each capturing different aspects of the aging process. Current biological age diagnostic tools include aging clocks, blood biomarker tests, physical/physicochemical function tests, microbiome tests, bio-imaging tests, and genetic tests. Countless factors inform the evaluation of biological age diagnostics, including clinical effectiveness, cost, accuracy, accessibility,

reproducibility, technical simplicity, breadth of biomarkers measured, etc.¹¹ Biological aging can be estimated based on five fundamental categories that include the evaluation of epigenetics, genetics, proteomics, metabolomics, and composite biomarkers (Figure 1.1).

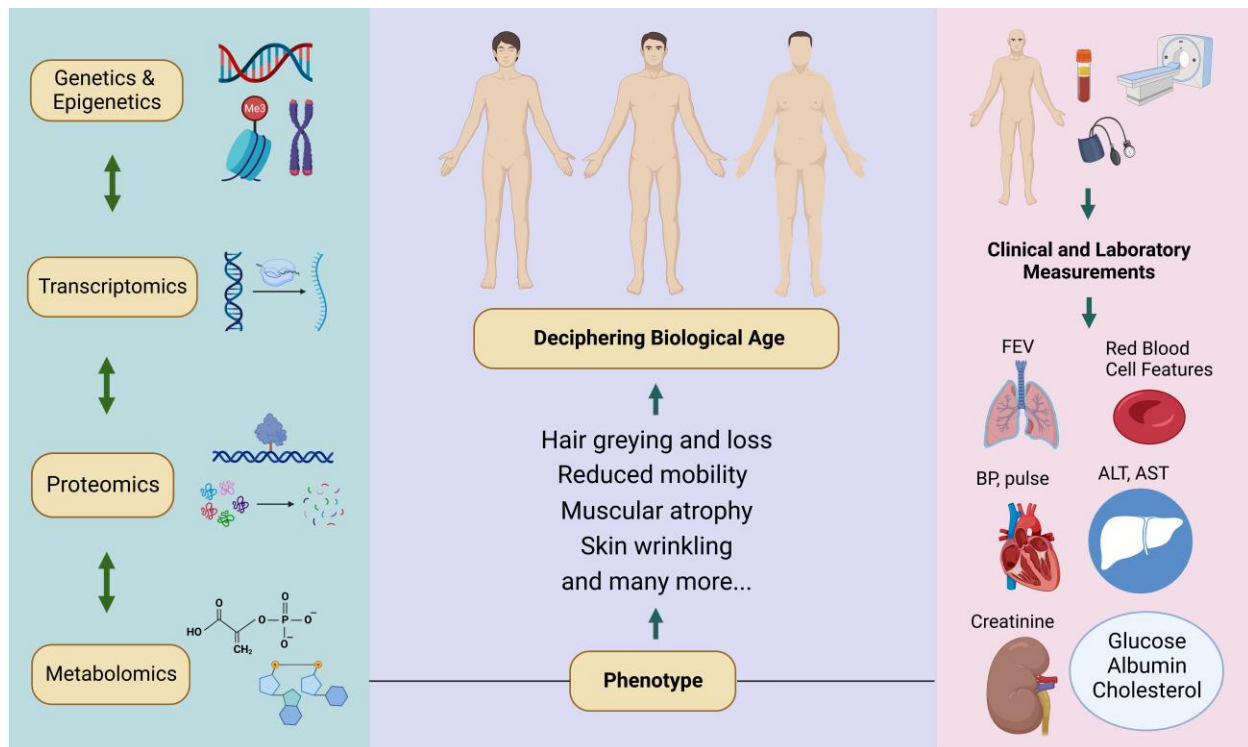


Figure 1.1 Illustration of the hierarchy of deciphering biological age based on molecular approaches, human phenotype, and clinical and laboratory measurements. ALT, alkaline phosphatase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; FEV, forced expiratory volume; LDL, low-density lipoprotein (created with BioRender.com).

Although epigenetics is considered essential, other downstream measurements may offer organ-level specificity. One of the most studied epigenetic biomarkers of aging is DNA methylation (DNAm), which precisely quantifies DNAm at 5'—Cytosine—phosphate—Guanine—3' (CpG) sites. The CpG sites are DNAm regions located at the promoters of genes, enriched by cytosine and guanine base pairs separated by phosphate groups. Gene expression and tissue-specific purposes depend highly on DNAm at CpG sites.¹² Contemporary aging clocks, such as the Horvath, Hannum, GrimAge, PhenoAge, Zhang's epigenetic age, and DunedinPACE clocks, have been designed to estimate biological age using data from different CpG sites (Table 1.1).^{13–17}

Table 1.1 Summarized list of the developed epigenetic clocks to date.

Epigenetic clock	Development	Predictive power
Horvath (2013)	Analysis of 8000 multiple tissue samples; developed to predict chronological age	Compromised cognitive function, grip strength, lung function, Alzheimer's and Parkinson's, osteoarthritis, obesity, metabolic syndrome, and all-cause mortality
Hannum (2013)	Analysis of methylome of over 450,000 CpGs in a diverse group of 656 people; relies exclusively on blood samples to predict chronological age	Motor coordination, cognitive health, immunosenescence, and all-cause mortality
PhenoAge (2018)	Utilizing clinical data from a diverse and nationally representative group comprising 10,000 adults with complete biomarker data; relies on morbidity and mortality data rather than chronological age alone.	One of the stronger predictors of age-related morbidity (Alzheimer's, immunosenescence, frailty, etc.).
GrimAge (2019)	Analysis of over 7000 samples from various data cohorts (including Framingham Heart Study); developed as a composite of 7 surrogate DNA methylation-based markers for plasma proteins, self-reported smoking pack years, gender, and chronological age.	Cardiovascular disease, time to cancer, hypertension, and type 2 diabetes.
Zhang (2019)	Analysis of DNA methylation in more than 13,000 blood samples from 14 data cohorts with a diverse group of individuals	Cardiovascular disease, cancer, and all-cause mortality.
DunedinPACE (2022)	using data from the Dunedin Study 1972–1973 birth cohort tracking a within-individual decline in 19 indicators of organ-system integrity across four-time points spanning two decades to model the Pace of Aging.	Faster aging in young adults with childhood adversity, a blood biomarker of the pace of aging for gerontology and geroscience.

The Horvath clock is a composite score developed based on the methylation levels of 353 CpG sites on the Illumina 27k array. This multi-tissue predictor can estimate the DNAmAge (age of DNA methylation) in numerous cells and tissues. This model reports DNAmAge or the predicted age and includes statistics to inform the user of a potential outlier. In contrast to the Horvath clock, the Hannum clock uses only 71 CpG sites from the Illumina 450k array, and it is another DNAmAge estimator that measures the rate at which an individual's methylome ages. This model uses a regularized multivariate regression method, Elastic Net, combined with a bootstrap approach. This model includes clinical parameters, such as gender and body mass index (BMI) and methylome data – patterns of DNA methylation within the genome – from whole blood samples. The GrimAge is a more recent composite biomarker developed based on seven DNAm surrogates of plasma protein estimators and a DNAm surrogate of smoking pack-years estimator. A 1030 unique CpGs are integrated into the GrimAge model and fewer than 200 CpGs are involved in each of the smoking pack-years biomarkers with seven plasma protein biomarkers. A key feature of the GrimAge model is its predictive ability for time-to-death, age at menopause, and time-to-coronary heart disease.

PhenoAge is a novel composite biomarker of aging that was introduced in 2018. PhenoAge can predict the risks of aging outcomes, such as all-cause mortality, cancers, healthspan, diabetes, and Alzheimer's disease, across diverse cells and tissues by using the collected data from whole blood samples and examining the biology of 513 CpGs involved in the PhenoAge model. PhenoAge provides a more straightforward, closer, and more accurate estimate of the actual health status of individuals compared to other composite biomarkers. A 1-year increase in DNAm PhenoAge is associated with a 4.5% increase in the risk of all-cause mortality.

A more recent DNAm-based biomarker of aging is the DunedinPACE clock, which measures the rate of aging from epigenetic information from 173 CpG sites.¹⁷ This clock helps to better understand how interventions may alter the pace of aging due to its high test–retest reliability. The DunedinPACE is similar to GrimAge but is associated with better prediction of morbidity, disability, mortality, and faster aging in young adults with childhood hardship.¹⁷ Zhang's epigenetic age is another common epigenetic clock that is also known as the “cancer clock.” There is strong evidence that an aging-response relationship exists between DNAm age

and cancer prediction. A 1-year increase in Zhang's epigenetic age resulted in a 6% increase in the risk of developing cancer within 3 years timeframe.¹¹

1.2 Methods of Quantifying Biological Age: Radiomics

Changes in body composition represent some of the most prominent and measurable physical manifestations of aging.¹⁸ Modern radiologic imaging, particularly computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DEXA), enables precise quantification of these age-related structural changes.^{19,20} Unlike anthropometric measures such as weight and waist circumference, these imaging modalities reveal tissue-specific characteristics, including muscle density, fat distribution, bone mineral density, and vascular calcification. The extraction of quantitative features from medical images, termed "radiomics," provides a framework for developing personalized treatment plans and improving diagnostic accuracy.^{21,22} Despite their clinical potential, radiomic biomarkers remain understudied as indicators of biological age and predictors of drug disposition in older adults.

These imaging techniques provide extensive clinical value, revealing patient and disease characteristics not accessible by physical examination.²³ Additionally, chronological age, the traditional measure of aging, cannot precisely distinguish physiological differences among people of the same age group, leading to the introduction of biological age.²⁴ Radiologic imaging biomarkers or "radiomics" representing body composition and aging can shift the paradigm of clinical measures towards personalized treatment plans, improve diagnostic accuracy, and streamline healthcare workflows. Despite their potential, radiomic biomarkers are understudied in the context of human aging and pharmacotherapy in older adults.

Several radiomic markers have been established for different organs and tissues, which can predict organ function or report survival, morbidity, and mortality after a major clinical event or surgery.²⁵⁻²⁷ The kidneys, for example, undergo major changes attributed to aging, and their function is crucial for drug dosing in older adults.²⁸ New age-related radiomic biomarkers of body composition can be used to quantify these changes in kidney function with aging. To validate this approach, pharmacokinetic studies will need to be conducted to confirm the accuracy of approximating kidney function using a combination of biomarkers. This review focuses on conventional body composition measures from an aging perspective and proposes a

model of age-informed body composition biomarkers derived from CT scans (BA_{Mor}) as a factor of kidney function for future dosing optimization and translational studies.

1.2.1 Radiomic Trends of Age-related Changes in Body Composition

The following sections detail the major radiomic biomarkers that track age-related changes in body composition, organized by tissue type. For each tissue, the typical aging trajectory, measurement methodology, and clinical significance are described.

Given the variability in how individuals age, there is an increasing demand for tools that accurately measure biological age to foster and support healthy aging practices.²⁹ The preliminary findings in employing radiomic features for measuring biological age are promising. For instance, one study suggests that radiomic features obtained from MRI scans can estimate the biological age of different cardiac regions, such as left and right ventricles (LV, RV), atria (LA, RA), and the LV myocardium.³⁰ Of the cardiac regions modeled, the LV age model performed the best, whereas the RV model showed the largest discrepancies between estimated BA and CA and the highest errors. Also, the age gap for each cardiac region, determined as the difference between biological and chronological age, was strongly correlated with increased visceral fat and higher bone mineral density (BMD) for larger and smaller age gaps, respectively. These results indicate that different regions of the heart age at different rates. By highlighting the different aging rates in heart regions, these findings underscore the valuable role of radiomic techniques in studying biological aging through body composition.

The opportunities that radiomic techniques provide for studying biological aging with body composition are just as important as their uses in clinical medicine. They can monitor body composition at various spatial scales ranging from the whole body to the cellular level and quantify the geometry of the region of interest in terms of volume, surface area, density, depth, etc.²³ Cross-sectional analyses of body composition with CT and MRI techniques are considered the gold standard methods.³¹ CT scans are generally faster and less expensive than MRI scans but use ionizing radiation.³² This cost-effectiveness can make CT a more feasible option for routine body composition analysis, especially in settings where resources are limited.³³ The annual number of CT scans performed is double that of MRI scans in the United States.^{34,35} Therefore, in this review, our focus is mostly on CT-based markers rather than markers from MRI or other imaging tools.

A summary of the major age-related changes in body composition, their relevant CT biomarker(s), and subsequent clinical implications is provided in Table 1.2. For instance, CT-based skeletal muscle biomarkers are widely used for assessing sarcopenia, a condition characterized by loss of muscle mass, strength, and function in older adults.³⁶ Skeletal muscle area (SMA) represents the skeletal muscle cross-sectional area at a specified vertebral number (typically L3), and skeletal muscle index (SMI) is calculated as SMA at L3 divided by patient height squared.³⁷ More explanations for each body composition component are provided in the next subheadings for better clarity.

The application of cross-sectional CT imaging to assess skeletal muscle and other radiomic biomarkers offers a powerful tool for enhancing clinical measurements, though it comes with significant considerations related to both cost and patient safety due to radiation exposure.³⁸ The average cost of a lumbar spine CT scan, where the psoas muscle is typically measured, is around \$540.³⁹ This cost, alongside other common CT procedures like chest (\$711) and brain (\$446) scans, highlights the financial considerations that must be accounted for in clinical practice.⁴⁰ However, once the CT scan is performed, the remaining workflow, using semi-automated Hounsfield Units (HU) thresholds for image analysis to segment and measure the muscle area, is relatively low-cost, involving mainly the time and expertise of the clinician or researcher.^{41,42} Concerning radiation exposure, a lumbar spine CT scan delivers approximately 6 millisieverts (mSv) of radiation, which remains well within the safety thresholds established by the Radiologic Society of North America, which suggests that the risks at doses below 50 mSv for single procedures or 100 mSv for multiple procedures are minimal or possibly nonexistent.^{43,44} In a similar context, other common CT procedures, such as chest scans (7 mSv), abdominal and pelvic scans (10 mSv), and cardiac scans for calcium scoring (3 mSv), all fall well below the 50 mSv threshold for single procedures, reinforcing the assertion by the Radiologic Society of North America.^{44,45} While the costs and radiation exposure are non-negligible, the precision and reproducibility of CT imaging render it an invaluable resource for assessing body composition.

Table 1.2 Age-related changes in body composition and involved morphomic covariates.

Body composition	Trends with aging	Radiomic biomarker(s)	Clinical implication
<i>Body fat mass</i> Total fat mass Visceral fat Subcutaneous fat	Regional fat redistribution; infiltration into muscle and bone Steadily increase after 30 followed by decrease after 70 Increase Decrease	Total body area; body depth Visceral fat area (VAT); Subcutaneous fat area (SAT)	Insulin resistance; Metabolic syndrome; , Cardiometabolic state
Muscle mass	Decrease	Total psoas area (TPA); Dorsal muscle group (DMG) area	Sarcopenia; Muscle fatty infiltration
Bone density	Decrease	Bone mineral density (BMD)	Osteopenia; Osteoporosis
<i>Organ-specific volumetry</i> Kidney volume Liver volume	Decrease Decrease	Total kidney volume Liver volume	Chronic kidney disease Cirrhosis, hepatomegaly
<i>Miscellaneous</i> Abdominal aortic calcification Fascia thickness	Increase Increase or decrease	Aortic valve calcium score Fascia area	Cardiovascular disease Stiffness, reduced elasticity, and adhesion

1.2.1.1 Muscle

Among body composition changes, skeletal muscle represents one of the most clinically significant and well-studied components of radiometric aging assessment. Aging is associated with a simultaneous decrease in skeletal muscle mass, strength, and quality.⁴⁶ Longitudinal studies have reported an annual 1-2% decline in muscle mass after age 50, leading to up to 40% loss in the seventh decade of life compared to young adults.⁴⁷ The decline in muscle strength is even greater, peaking around 25-35 years and then decreasing at an estimated rate of 1.5% to 3% annually after age 50.⁴⁷ This trajectory of muscle changes over time varies by sex, with men experiencing a higher rate of muscle mass decline and a higher prevalence of sarcopenia.⁴⁸ Race and ancestry also modulate muscle aging. Individuals of African ancestry tend to have 5–8% greater baseline muscle mass than those of European ancestry, and consequently lower rates of sarcopenia by muscle mass criteria,⁴⁹ though functional deficits may still be pronounced, underscoring that muscle quantity and quality do not always decline in parallel across racial groups.⁵⁰ Age-related loss of muscle mass may also be accompanied by increased body fat, resulting in significant weakness even if body weight appears normal.⁵¹

Apart from the SMA and SMI mentioned earlier, single-muscle measures for the psoas muscle are also recognized as biomarkers for sarcopenia. The psoas muscle, a long, ribbon-shaped muscle found on both sides of the spine and the edge of the lower pelvis, is one of the most important muscles covering the vertebral column.⁵² Psoas muscle area (PMA), the cross-sectional bilateral surface area of the psoas muscle, psoas muscle index (PMI), the PMA divided by the patient's height, and psoas muscle density (PMD), the average cross-sectional muscle attenuation in Hounsfield units (HU), are determined to provide information about the muscle status and diagnosis of sarcopenia.⁵³

The psoas muscle can only be measured using abdominal CT or MRI scans. Because of its central location, it is difficult to image with ultrasound, which complicates prospective and repeated data collection. Unlike the psoas muscle, the dorsal muscle group (DMG) is easier to capture using both CT and ultrasound imaging, making it a better option for facilitating prospective studies on sarcopenia.⁵⁴ DMG area refers to any muscles located behind the spine and ribs, extending no farther outwards than the outer edges of the erector spinae muscles.⁵⁴ The cross-sectional area of DMG can be commonly measured using both thoracic and abdominal scans and is reported to be a significant independent predictor of survival and mortality in liver

transplantation recipients.⁵⁴ It has also been used with other CT-based biomarkers (psoas muscle area and subcutaneous fat area) to screen severely malnourished patients.⁵⁵ Using the Reference Analytic Morphomic Population (RAMP) data developed at the University of Michigan from trauma patients across all age groups, the trajectory of changes in skeletal muscle and DMG expanded muscle areas with age shows that these areas peak around age 30 in men and age 20 in women, and then decrease throughout the rest of life (Figure 1.2.A).

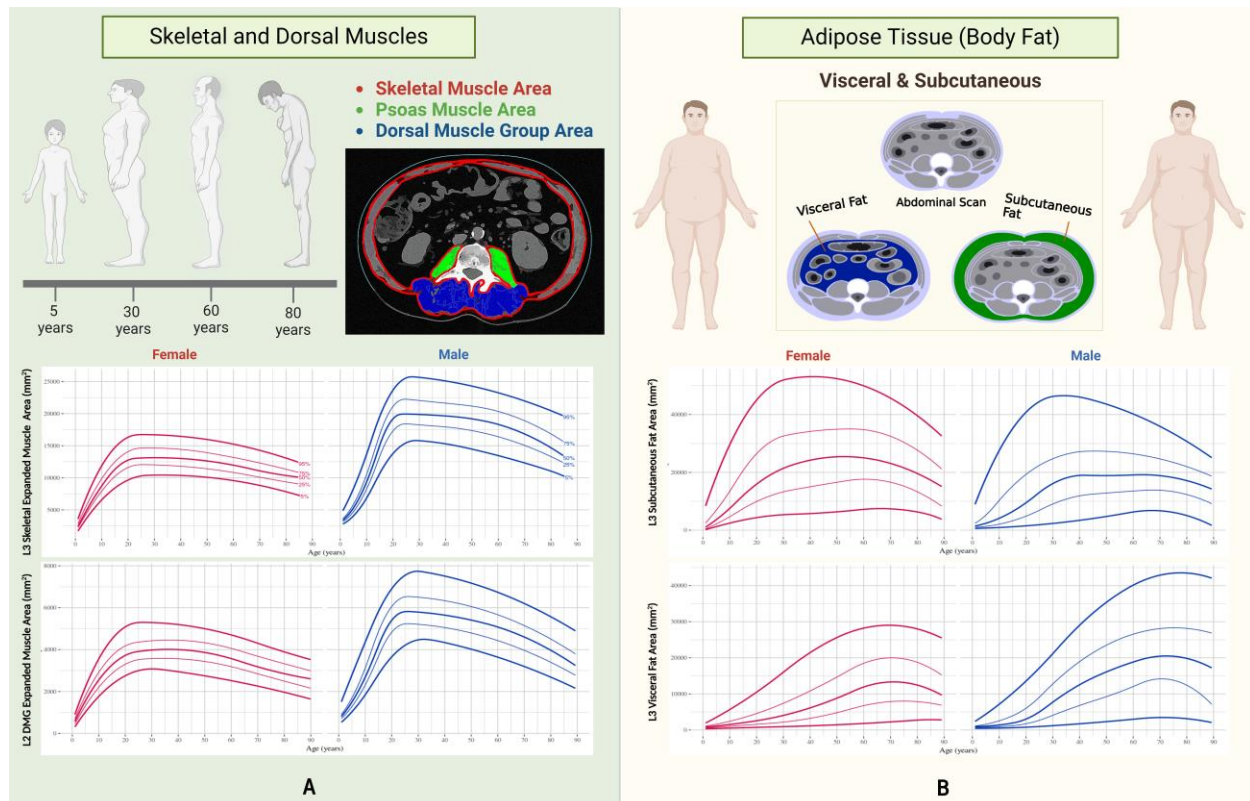


Figure 1.2 Trajectory of changes in body composition measurements by CT scans with aging stratified by sex. (a) Skeletal muscle expanded area and Dorsal muscle group (DMG) muscle expanded area. (b) Visceral fat area (VAT) and Subcutaneous fat area (SAT). Created with BioRender.com.

Aging is also associated with fat infiltration into skeletal muscle, known as myosteatosis.⁵⁶ Given that increased fat reduces the density of muscles, myosteatosis can be characterized as decreased skeletal muscle density. Myosteatosis is associated with several complications, such as inflammation, severe liver disease, insulin resistance, metabolic dysfunction, hip fractures, and mortality in older adult individuals.^{56,57} Myosteatosis is shown to

be correlated with other CT scan measurements such as muscle density, visceral fat, and subcutaneous fat.⁵⁸ Recent findings have highlighted it as a key factor in staging chronic kidney disease (CKD), along with high levels of aortic calcium, which is discussed in the next paragraph.⁵⁹

As people age after 40 years, the likelihood of calcified plaque formation and vessel narrowing increases, leading to atherosclerosis and promoting further plaque formation.^{60,61} Evidence supporting abdominal aortic calcifications (AAC) as a clinical correlate and useful predictor of cardiovascular events is growing.⁶² AAC is commonly seen on CT scans, which can reliably determine the presence and extent of these calcifications. AAC can also serve as an indicator of worsening CKD. The prevalence and progression of aortic calcification increase with more advanced stages of CKD.⁶³ AAC and kidney function are interrelated through shared pathophysiological processes, common risk factors, and their impact on vascular health. Both conditions often coexist in patients with CKD, where factors like hypertension, diabetes, and dyslipidemia contribute to calcification in both the aorta and renal arteries.⁶⁴ Aortic calcification, particularly when leading to aortic stenosis, can impair renal blood flow, increasing vascular resistance and leading to a decline in kidney function.⁶⁵

1.2.1.2 Bone

Concurrent with muscle loss, aging profoundly affects skeletal integrity through progressive bone density decline. At any given age, bone density depends on the maximum bone mass and the subsequent bone loss.⁶⁶ As people age, their bones lose mass and density and contain fewer minerals, making them less strong. Men and women generally reach their highest bone mass by age 30. After this age, men tend to lose about 0.3% of their bone mass annually, while women lose slightly more, about 0.5% per year.⁶⁷ Similar to muscle mass, the average rate of bone loss is reported as 1-2% per year after middle age, with women experiencing a greater decrease of 2-3% per year from 1-3 years pre-menopause until 5-8 years post-menopause, then slowing to 1% per year.^{68,69}

Genetic factors and race, along with controllable lifestyle factors such as diet, physical activity, and optimal body weight are the major determinants of bone health.⁷⁰ BMD is significantly influenced by genetics, with heritability estimates ranging from 50% to 85%.⁷¹ Among the racial groups, in general, increased African genetic admixture is linked to higher

BMD but greater declines in bone strength with aging.⁷¹ Accordingly, black adults typically have the highest BMD and the lowest rates of bone loss compared to Hispanic, Mexican, White, and Asian adults. Asians, on the other hand, often have lower BMD than other racial groups.⁷² Nevertheless, some inconsistencies exist in the reported mean BMD differences among these racial groups. Racial disparities in bone density remain even after controlling for body mass.⁷³ Studies suggest that a 10 percent increase in bone mass may decrease the likelihood of fractures by up to 50 percent.⁷⁴ Traditionally, single- or dual-photon absorptiometry (SPA/DPA) followed by dual-energy X-ray absorptiometry (DEXA) has been employed as the gold standard for measuring BMD, serving as a proxy for bone strength and fracture risk.^{75,76} DEXA offers numerous benefits such as low radiation exposure and scanning skeletal areas most susceptible to osteoporotic fractures. However, DEXA cannot provide a complete assessment of bone size as it does not account for differences in bone depth.⁷⁶ Therefore, researchers have started using HU measurements from CT scans to evaluate BMD in specific chest, abdomen, or spine regions.⁵⁸ CT scans now allow for measuring volumetric BMD and assessing the structural dimensions and internal organization of cortical and trabecular bone, providing estimates of bone strength (Figure 1.3).⁷⁶ Figure 1.3 provides a schematic view of measuring BMD through DEXA or CT scans. While both can measure BMD, only CT scans can provide information on changes in bone dimensions with aging.

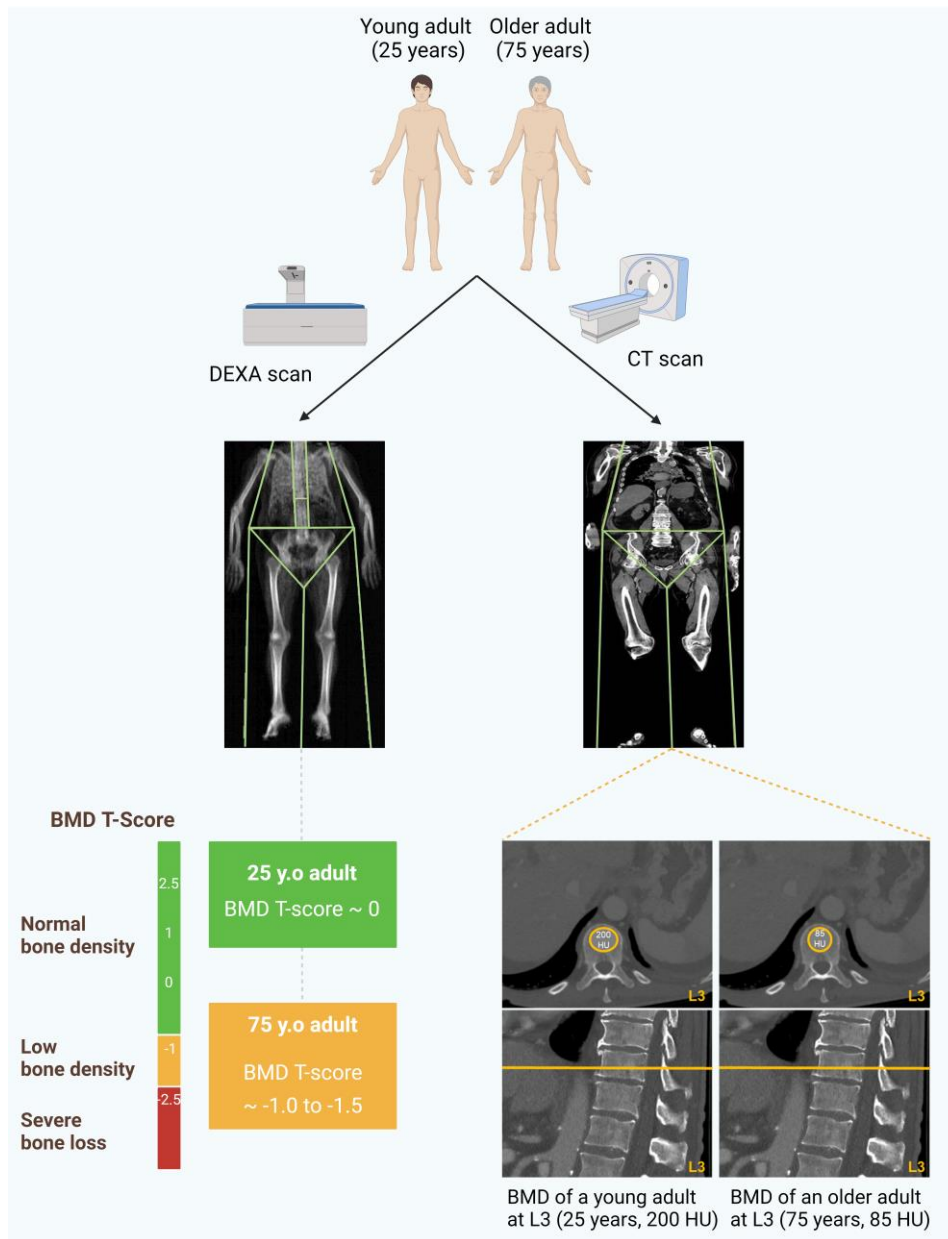


Figure 1.3 Comparison of Bone Mineral Density (BMD) measurement using DEXA versus CT scans in young adults and older adults. Created with BioRender.com.

The BMD HU values in Figure 1.3 are approximated from a study that evaluated BMD distribution at the L1-L5 vertebrae in 296 patients with degenerative lumbar disease using radiologic imaging.⁷⁷ These patients were divided into six age groups (20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years). The study found a decreasing trend in BMD HU values from younger to older patients: the mean BMD was 199.69 HU for patients with an average age of

25.10 years and 85.84 HU for patients with an average age of 73.94 years. Bone density HU values below 100 indicate osteoporosis, values between 100 and 160 suggest osteopenia and values above 160 reflect normal bone mineral density.⁷⁸ On the contrary, DEXA is a real measurement of BMD (g/cm²), which can be influenced by bone size, thickness, and geometry. Larger bones may appear to have higher BMD simply because the area is larger, not necessarily because the bone is denser.⁷⁹ DEXA BMD is often reported using T-scores, which compare a patient's BMD to the average peak BMD of a young, healthy reference population: Normal bone density: T-score ≥ -1 ; Low bone density (Osteopenia): T-score between -1 and -2.5; and Severe bone loss (Osteoporosis): T-score ≤ -2.5 .

1.2.1.3 Adipose Tissue (Body Fat)

While muscle and bone mass typically decrease with age, adipose tissue undergoes redistribution rather than simple loss, with important metabolic consequences. Adipose tissue plays a crucial role in physiology beyond merely storing energy, making its assessment essential in body composition analysis. Therefore, fat quantification should involve compartment-specific analyses, which cannot be provided by BMI.⁸⁰ BMI is likely to misrepresent the risk of obesity-related chronic diseases because it does not accurately reflect body fat and muscle levels, particularly at higher BMI levels.⁸¹ CT is viewed as the gold standard technique for accurately measuring the area of adipose tissue.⁸² It enables the distinct examination of the subcutaneous fat (SAT), known as the fat beneath the skin, and visceral fat (VAT), which is fat stored around intra-abdominal organs.⁸³ Quantifying VAT generally involves segmenting the intra-abdominal compartment and calculating the cross-sectional area of tissue. These measurements are typically taken at abdominal levels ranging from L1 to L4.⁸⁴ Also, subcutaneous fat volume is measured by segmenting the area from the abdominal wall muscles to the skin at a given level. The visceral and subcutaneous fat areas can then be combined to determine the total fat area.^{80,84}

The accumulation and redistribution of adipose tissue in the human body could be affected by aging.⁸⁵ Anatomically, the distribution of adipose tissue is often characterized by sex: Men tend to accumulate more VAT, and women usually have considerably more SAT.⁸⁶ CT assessments of abdominal VAT have confirmed that men accumulate more VAT than women at the same weight (Figure 1.2.B). Additionally, the findings from the RAMP data demonstrate that SAT area measures at L3 peak approximately at age 40 in men and women, while VAT area

measures at L3 are greater in older adulthood than in young adulthood on average. After menopause, women's fat distribution shifts to resemble men's, leading to increased central obesity.^{86,87} Studies have shown a longitudinal association between visceral adipose tissue (VAT) and the development of metabolic syndrome, whereas subcutaneous adipose tissue (SAT) appears to have a protective effect against the incidence of individual components of metabolic syndrome.^{88,89} Greater SAT distribution is correlated with reduced rates of cardiometabolic disorders such as type 2 diabetes (T2DM) and cardiovascular disease (CVD) in both sexes.⁸⁶

Furthermore, the VAT/SAT ratio can be utilized for prognostic purposes. One study showed that an increased VAT/SAT ratio is associated with decreased overall survival in patients with pancreatic cancer.⁹⁰ Another study reported an increased major adverse cardiac event in patients with low BMI having a high VAT/SAT ratio.⁹¹ Finally, patients with gastric cancer who had a higher VAT/SAT ratio were at a greater risk of developing infections at the surgical site after gastrectomy.⁹² Radiologic measurement of SAT and VAT at different vertebra levels can be useful in predicting several clinical outcomes, such as nonmetastatic breast cancer survival, Crohn's disease prognosis, COVID-19 hospitalization, and mortality, and guiding personalized treatment strategies.^{93–95}

1.3 Functional Changes in Kidney Drug Elimination Processes During Aging

Among the physiological systems affected by aging, kidney function merits particular attention in the context of drug dosing. The kidneys serve as the primary route of elimination for many medications, and age-related functional decline directly impacts drug clearance. This decline in function occurs approximately after the chronological age of 40–50 years. On average, kidney function based on the glomerular filtration rate (GFR) declines by 0.75–1 mL/min/year.⁹⁶ Whereas the liver and kidneys are significant routes of drug clearance, kidney function is the quantitative tool used to modify drug dosing in older adults. Therefore, measuring kidney function and following up on these changes as patients age is essential.⁹⁷ In addition to age-related changes to kidney function, poorly managed hypertension, diabetes, and chronic heart disease can accelerate kidney function decline in older adults.⁹

Kidney function is an important surrogate for drug clearance via three independent processes. The three processes of drug elimination via the kidneys include glomerular filtration, proximal tubular secretion, and distal tubular reabsorption.⁹⁸ As people age, kidney blood flow

(about 10% after age 40) and GFR (0.75–1.0 mL/min/1.73 m² per year after age 40) decrease along with increased renal vascular resistance and enhanced filtration fraction.⁹⁹ This increase in the vascular resistance in the efferent arterioles and consequent glomerular pressure enhancement can cause hyperfiltration, which can damage glomerular capillaries and enhance albumin excretion. The amount of albumin excreted in the urine increases with a decline in the quality of the glomerular barrier and might exceed 6.8 µg/min in middle-aged and older adults, often due to comorbid conditions, such as diabetes or cardiovascular diseases.^{100,101} As a person ages, they may experience a decrease in the number of superficial nephrons (glomeruli near the kidney surface), which can result in reduced kidney perfusion. As a result, the capacity for renal autoregulation and the ability to concentrate solutes are impaired following a decrease in medullary osmolality caused by the increased workload on juxtamedullary nephrons (glomeruli near the border of the cortex and the medulla). The glomerular function is generally preserved in older adults without comorbidities, yet the functional reserve declines and limits older adults' adaptation to acute kidney injury or greater demands.¹⁰²

Measurement of GFR is not routine in the clinic and rests principally on measuring serum creatinine (SCr) as a biomarker to estimate GFR. However, despite a decrease in GFR with aging, SCr concentrations often remain within the normal range. This is because older adults generally have less muscle mass, less physical activity than younger adults do, and thus less creatinine production. Maintenance of normal SCr concentrations in older adults does not always equate to normal kidney function in this population.¹⁰³ Davies and Shock were the first to demonstrate the age-dependent decline in kidney function through cross-sectional analyses, which is now corroborated through longitudinal studies.¹⁰⁴ Although it is generally accepted that there is a decrease in GFR of ~1 mL/min/year after age 40, Bolignano et al. have found that the yearly decline rate in GFR varies greatly among adults, ranging from 0.4 to 2.6 mL/min/year.¹⁰⁵ In other words, it could take 100 years to reach mild kidney insufficiency, whereas others suggest it would take half this time if this decline is linear. On average, a drop of 8 mL/min/1.73 m²/decade in GFR is expected after age 40; however, this decrease in GFR will differ from person to person. Given that the individual trajectory is hard to predict, repeated measures of GFR may be necessary to better understand an individual's trajectory in order to define drug dosage adjustments. Unfortunately, few studies have focused on longitudinal GFR measurement as a tool for more optimal drug dosing in older adults.¹⁰⁶

In addition to filtration, many transporters are involved in reabsorption and secretion, contributing to net drug clearance and dosing adjustments. Kidney tubular transporters may also be a source of potential drug–drug interactions between their substrates or/and inhibitors, some of which are summarized by Yin et al.⁹⁸ Age is a likely factor contributing to differences in the expression of these transporters in the human kidneys.¹⁰⁷ Understanding ontogeny and aging-associated alterations in renal transporter expression is necessary to evaluate the effects of drugs or toxicants in specific populations like older adults.¹⁰⁸ A summary of crucial age-related changes to kidney tubule transporters is detailed below.

Numerous transporters are involved in the proximal tubular secretion of drugs. These transporters are mainly distributed on the basolateral and apical membranes of renal proximal tubular cells. In recent years, a significant focus has been directed toward transporters in drug development.¹⁰⁹ Xu et al. were among the first groups profiling the age-associated variations in transporter expression for 12 major proximal tubular transporters.¹⁰⁸ They found a remarkable increase in the mRNA expression levels of these transporters through maturation and adulthood. The levels of mRNA expression continue to remain high during the aging process. Nonetheless, a decrease in mRNA expression levels of specific transporters, such as organic anion transporter 2 (OCT2), organic anion transporter polypeptide 4C1 (OATP4C1), multidrug resistance protein1b – MDR1, namely p-glycoproteins (P-gp) – (Mdr1b), and human multidrug and toxin extrusion 1 (MATE1), was observed with aging.¹⁰⁸ These findings may provide new insights into the renal disposition of drugs.

Like secretion, various transporters are involved in renal reabsorption. Two necessary transporters in this process are the Na⁺/K⁺-ATPase transporter and the K⁺/Cl[–]-symporter, both of which are located on the basolateral membrane of cells and play a pivotal role in the movement of ions like sodium, potassium, chloride, and calcium.¹¹⁰ Few studies have discussed the association between aging and reabsorption transporters, unlike secretion transporters. Frame et al. summarized the age-related alterations in the kidneys' sodium transport system that may contribute to impaired sodium handling and age-related hypertension in different species in their mini review. They found that the activity of the Na⁺/K⁺-ATPase transporter decreased in the distal convoluted tubule and increased in the collecting tubule of Sabra rats with aging.¹¹⁰

As noted, GFR is estimated, but secretion and reabsorption are not in clinical practice. So, an important consideration is whether direct translation of these processes from GFR is

possible.¹¹¹ Again, because these processes are not measured, the general assumption has been that GFR, secretion, and reabsorption decline at similar rates with age. However, the impact of these changes is likely to be dependent on a drug's physicochemical and PK properties, so this remains an open question for future research.

These age-related changes in kidney function have direct implications for drug dosing, particularly for renally eliminated medications. However, accurately quantifying kidney function in older adults remains challenging, as standard biomarkers like serum creatinine can be misleading in this population. Table 1.3, organized alphabetically by therapeutic class, highlights a list of the most clinically significant renally eliminated medications in older adults, illustrating the breadth of drug classes for which imprecise kidney function estimation directly translates to preventable harm.^{112–132}

Table 1.3 List of Several High-Risk Renally Eliminated Medications in Geriatric Pharmacotherapy: Adverse Drug Reactions and Relevance to Biological Age-Informed Dosing

Therapeutic Class	Drug	Renal Elimination	Most Common / Severe ADRs in Older Adults	Renal Dosing Consideration	Relevance to Biological Age Assessment
Antiarrhythmic	Dofetilide Class III antiarrhythmic	~80% unchanged	• Torsades de pointes (TdP), life-threatening polymorphic ventricular tachycardia; incidence 1–3% even with strict monitoring • Sudden cardiac death in patients with ventricular arrhythmias • QTc prolongation, linearly correlated with plasma concentration	Dose determined exclusively by CrCl (Cockcroft-Gault); contraindicated at CrCl <20 mL/min; use of eGFR (MDRD) instead of CrCl in older adults has caused 2-fold overdosing and TdP; mandatory 3-day in-hospital initiation with continuous ECG monitoring	One of the most CrCl-sensitive drugs in clinical use; eGFR overestimation in older adults directly causes life-threatening arrhythmias; biological age-informed CrCl estimation could prevent fatal dosing errors
Antiarrhythmic	Sotalol Class II/III antiarrhythmic	~100% unchanged	• Torsades de pointes, incidence 1–4% in ventricular arrhythmias; associated with sudden death • Bradycardia, heart block, and cardiac asystole with accumulation in renal impairment • Bronchospasm (due to beta-blockade), fatigue, hypotension	100% renally cleared; dose interval extended based on CrCl: every 12h if CrCl >60, every 24h if CrCl 30–60, every 36–48h if CrCl 10–30; contraindicated at CrCl <40 mL/min per some guidelines; requires in-hospital initiation with ECG monitoring	100% renal clearance makes sotalol uniquely sensitive to GFR accuracy; even modest eGFR overestimation causes drug accumulation and arrhythmia; biological age-informed GFR could meaningfully reduce proarrhythmic risk in older adults with AF
Anticoagulant	Dabigatran Direct thrombin inhibitor	~80% unchanged	• Major GI and intracranial bleeding, most renally dependent DOAC • Contraindicated in CrCl <15 mL/min; accumulates rapidly with eGFR decline • No reliable reversal monitoring without specialized assays	Dose reduction at CrCl 15–30; contraindicated below CrCl 15; body weight and renal function must be reassessed regularly in older adults	Most renally sensitive DOAC; eGFR overestimation directly causes drug accumulation and hemorrhage; accurate biological age-informed GFR estimation is critically important
Antimicrobial	Aminoglycosides gentamicin, tobramycin	~95% unchanged	• Irreversible sensorineural hearing loss and vestibular damage • Acute tubular necrosis; nephrotoxicity risk increases with each course • Neuromuscular blockade (rare but life-threatening)	Extended-interval dosing guided by CrCl; lean body weight used for obese patients; CT-derived SMA (Aim 1) improves LBW estimation; TDM mandatory	Central to this dissertation; BA _{Mor} indices (Aim 2) developed using aminoglycoside clearance as GFR surrogate; morphomic age slightly improves clearance prediction over chronological age
Antimicrobial	Vancomycin Glycopeptide antibiotic	>90% unchanged	• Nephrotoxicity, risk compounded with aging-related CKD and NSAIDs • Ototoxicity (hearing loss) at supratherapeutic AUC • Red man syndrome with rapid infusion	AUC/MIC-guided TDM now standard; dose and interval determined by eGFR; total body weight used but lean weight preferred in obesity	Hydrophilic drug; clearance tightly coupled to GFR; morphomic muscle indices improve weight-based dosing in sarcopenic or obese older adults
Cardiovascular	Digoxin Cardiac glycoside	~70% unchanged	• Life-threatening arrhythmias and heart block at toxic levels	Dose must decrease proportionally with GFR decline; lean body weight required for loading dose calculation;	Even modest eGFR overestimation leads to toxic accumulation; CT-derived lean

			• Narrowest therapeutic index of any common cardiac drug • Nausea, visual disturbances (yellow-green halos), confusion	therapeutic range 0.5–0.9 ng/mL in older adults	body weight (Aim 1) could improve initial dose selection and reduce toxicity risk
Chemotherapy	Carboplatin Platinum-based chemotherapy	~65% unchanged	• Severe myelosuppression (thrombocytopenia, neutropenia) — dose-limiting and life-threatening with overdose • Nephrotoxicity with cumulative dosing • Peripheral neuropathy, ototoxicity	Calvert formula uses GFR directly: Dose (mg) = AUC × (GFR + 25); GFR overestimation causes systematic overdosing; body composition critical in sarcopenic obese patients	CT-derived body composition directly embedded in dosing formula; sarcopenic obese patients are overdosed with standard equations; morphomic indices could prevent treatment-related mortality
Diabetes	Metformin Biguanide antidiabetic	>90% unchanged	• Lactic acidosis — rare but mortality >50% when it occurs with severe renal impairment • GI intolerance: nausea, diarrhea, abdominal discomfort • Vitamin B12 deficiency with long-term use	Contraindicated at eGFR <30; dose reduction at eGFR 30–45; requires regular eGFR monitoring; threshold decisions depend entirely on GFR accuracy	A single eGFR miscalculation can mean the difference between safe use and a contraindicated, life-threatening scenario; biological age indices could flag patients near critical thresholds
Diabetes	Insulin All formulations	Partial renal clearance	• Severe hypoglycemia; #2 cause of ADE hospitalization in older adults; hypoglycemia unawareness increases with age • Hypoglycemic coma, cardiac arrhythmias, falls with injury • Weight gain, hypokalemia with intensive regimens	Renal impairment prolongs insulin half-life and reduces clearance; dose reduction required as GFR declines; individualized titration essential in older adults with CKD	RMR-based metabolic biomarkers (Aim 3) directly relevant to insulin sensitivity and glucose homeostasis; metabolic age better reflects glycemic control capacity than chronological age
Neurology/Pain	Gabapentin / Pregabalin Anticonvulsant / neuropathic analgesic	>95% unchanged	• Excessive sedation and respiratory depression, especially dangerous with opioid co-prescribing • Falls and fractures due to dizziness and ataxia in older adults • Peripheral edema, cognitive impairment	Dose reduction required at eGFR <60; significant reduction at eGFR <30; one of the most commonly underdose-adjusted drugs in clinical practice	Widespread use in older adults with chronic pain/neuropathy; eGFR overestimation directly leads to sedation and fall-related injury; accurate GFR is critical for patient safety
Rheumatology	Allopurinol Xanthine oxidase inhibitor	>70% as oxypurinol	• Stevens-Johnson syndrome / toxic epidermal necrolysis; life-threatening; disproportionately occurs when eGFR is overestimated • Allopurinol hypersensitivity syndrome (AHS): fever, rash, multi-organ failure • Oxypurinol accumulation causing bone marrow suppression	Active metabolite oxypurinol accumulates with renal impairment; dose must not exceed 100 mg/day at eGFR <30; HLA-B*5801 testing recommended in high-risk populations	Among the most underappreciated renally sensitive drugs; severe ADRs disproportionately occur in older adults when eGFR is overestimated; biological age-informed GFR could prevent fatal skin reactions

Abbreviations: ADR = adverse drug reaction; ADE = adverse drug event; AF = atrial fibrillation; AUC = area under the curve; CKD = chronic kidney disease; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GI = gastrointestinal; HLA = human leukocyte antigen; LBW = lean body weight; MIC = minimum inhibitory concentration; QTc = corrected QT interval; RMR = resting metabolic rate; SMA = skeletal muscle area; TdP = torsades de pointes; TDM = therapeutic drug monitoring; Vd = volume of distribution.

1.4 Estimated Kidney Function Equations in Older Adults

Conventional methods for estimating kidney function are imprecise and biased by their reliance on endogenous biomarkers. Measurement of creatinine clearance (CrCl) is challenging to carry out due to difficulties with 24-h urine collections.¹³³ Some studies have suggested that shorter collecting times, like 12- and 2-h urine collections, may be comparable to 24-h CrCl measurements.^{134,135} Other variables, such as diet, exercise, and disease conditions, can affect creatinine production, which confounds our interpretation of CrCl. Thus, there is an increasing interest in cystatin C as a potential alternative biomarker of kidney function. Cystatin C has advantages over SCr because it is less affected by age, gender, weight, and muscle mass.¹³⁶ Although cystatin C outperforms serum creatinine, its adoption as a replacement for creatinine as a GFR marker is constrained by factors such as the wide availability of standardized assays, comorbidities like thyroid dysfunction, and interpretation in individuals receiving high doses of glucocorticoids.¹³⁷ Numerous formulas exist to estimate kidney function based on SCr, cystatin C, or a combination of both. Given the plethora of equations used to estimate kidney function, we review the dominant ones in Table 1.4 to explain their similarities and differences when modeling chronological age effects.

Table 1.4 Summary of the major equations to estimate kidney function around the globe.

Equation	Kidney function	Full equation
Cockroft-Gault (1976)	eCl _{cr}	$eCl_{cr} = [(140 - \text{age}) \times \text{body weight} / SCr \times 72] \times 0.85$ [if female]
MDRD (2005)	eGFR _{cr}	$eGFR_{cr} = 175 \times (SCr)^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ [if female] $\times 1.212$ [if Black]
BIS1 (2012)	eGFR _{cr}	$eGFR = 3736 \times (SCr)^{-0.87} \times (\text{age})^{-0.95} \times 0.82$ [if female]
BIS2 (2012)	eGFR _{cr-cys}	$eGFR = 767 \times \text{cystatin C}^{-0.61} \times SCr^{-0.40} \times \text{age}^{-0.57} \times 0.87$ [if female]
FAS (2016)	eGFR _{cr}	$eGFR_{cr} = \frac{107.3}{(SCr/Q)}$ for $2 \leq \text{age} \leq 40$ years $eGFR_{cr} = \frac{107.3}{(SCr/Q)} \times 0.988^{(\text{Age}-40)}$ for age > 40 years
CKD-EPI creatinine (2021)	eGFR _{cr}	$eGFR_{cr} = 142 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.200} \times 0.9938^{\text{age}} \times 1.012$ [if female]
CKD-EPI cystatin (2012)	eGFR _{cys}	$eGFR_{cys} = 133 \times \min(SCys/0.8, 1)^{-0.499} \times \max(SCys/0.8, 1)^{-1.328} \times 0.996^{\text{age}} \times 0.932$ [if female]
CKD-EPI creatinine-cystatin (2021)	eGFR _{cr-cys}	$eGFR_{cr-cys} = 135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.544} \times \min(SCys/0.8, 1)^{-0.323} \times \max(SCys/0.8, 1)^{-0.778} \times 0.9961^{\text{age}} \times 0.963$ [if female]

Abbreviations: eCl_{cr}, estimated creatinine clearance = (mL/min); SCr, serum creatinine; Scys = (mg/dL), serum cystatin C = (mg/L); MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; BIS, berlin initiative study; FAS, full age spectrum; eGFR_{cr}, estimated glomerular filtration rate using creatinine = (mL/min/1.73 m²); eGFR_{cys}, estimated glomerular filtration rate using cystatin C (mL/min/1.73 m²); eGFR_{cr-cys}, estimated glomerular filtration rate using creatinine and cystatin C = (mL/min/1.73 m²).

Units: (mL/min)

The most widely used kidney function equation for drug dosing is the Cockcroft- Gault (CG) equation. The CG equation estimates CrCl, whereas the other equations estimate GFR. Regulatory agencies initially recommended the consideration of eGFR for drug dosing based on the modification of diet in renal disease (MDRD) equation. Because the utility of the MDRD equation is limited to individuals with a GFR less than 60 mL/min/1.73 m², a revision of this formula through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was completed.¹³⁸ The MDRD study was also predominantly based on individuals between 18 and 70 years old. The CKD-EPI equation was introduced in 2009 and, like the MDRD equation, included race as a factor. Three years later, two new CKD-EPI equations were presented; one exchanged creatinine with cystatin C (CKD-EPI_{cys}), and the other integrated both cystatin C and creatinine (CKD-EPI_{cr-cys}) to estimate the GFR. In the 2021 revision of the CKD-EPI equation, the effect of race was removed from both versions because race is considered a social rather than a biological concept, and thus, its inclusion was debated.¹³⁹ Generally, the CKD-EPI equation produces higher GFR estimates and lower CKD prevalence estimates than the MDRD. However, there is a small difference between these two equations in individuals above 70, where CKD-EPI may increase CKD prevalence estimates.¹⁰⁶ The CKD-EPI equation provides a less biased estimate of GFR than MDRD. A large cohort study compared MDRD with CKD-EPI in adults aged 18–107 years.¹⁰⁶ Although CKD-EPI had a significantly higher estimation for GFR than MDRD in this study, the differences between the two equations dropped off with age. Moreover, subjects who were 80 years old and above showed significantly lower CKD-EPI eGFR. Another study compared the GFR calculated by CG and MDRD equations in individuals aged 65–111 years by normalizing CG CrCl to compare to MDRD to help readers recognize this difference better.¹⁴⁰ In this study, the mean GFR calculated by MDRD was much higher than the mean GFR calculated by CG (76.0 ± 24.0 mL/min/1.73 m² vs. 67.9 ± 18.6 mL/min/1.73 m²). There was a strong positive correlation between this variation and age which raises the speculation that CG might be a better choice, especially in the oldest old patients. This variation also showed a negative correlation with BMI and SCr.¹⁰⁶ Accordingly, the precision and accuracy of the MDRD and CG equations should be considered before using them in older adults, as the difference between these two equations increases with age.

Two newer equations developed in Europe include the Berlin Initiative Study 1 and 2 (BIS1 and BIS2) in 2012.¹⁴¹ The BIS equations aimed to improve eGFR accuracy in individuals

over 70 years old using SCr (BIS1) or the combination of SCr and serum cystatin C (SCys; BIS2). This aim has clinical relevance because it reduces the likelihood of misclassifying individuals with a GFR above or below 60 mL/min/1.73 m². Schaeffner et al. found that the new BIS2 equation had the lowest bias, followed by the creatinine-based BIS1 and CG equations. However, all other equations significantly overestimated GFR. The lowest misclassification rate among all equations was observed with the BIS2 equation, but among the creatinine-based equations, the lowest misclassification rate was reported for BIS1.¹⁴¹

Among 610 patients aged 70 years or above, the measured GFR was less than 60 mL/min/1.73 m² in 47.9% of patients. The BIS equations estimated similar proportions of patients with a GFR less than 60 mL/min/1.73 m² (BIS1, 50.4% and BIS2, 47.4%;). Although not substantially different, the authors recommended the BIS2 equation to be the preferred method to estimate GFR in older adults over 70 years old with normal or mild to moderately reduced kidney function. However, in cases where cystatin C is not available, the BIS1 equation can be considered a reliable alternative to BIS2. In another study in patients greater than or equal to 70 years with cardiovascular disease, the BIS1 equation demonstrated a significantly better accuracy in risk stratification of CKD in older adult patients with cardiovascular disease, compared to the CKD-EPI (2012) equation.¹⁴²

As noted, an age-dependent decline in kidney function typically occurs after age 40 years. The Full Age Spectrum (FAS) equation was designed to encompass this principle. Introduced by Pottel et al. in 2016, the FAS equation is a piece-wise equation with a break point at age 40 years.¹⁴³ In addition, SCr is dependent on age and gender, and, as such, the FAS equation normalizes the SCr with Q (SCr/Q), where Q is the mean or median SCr value that accounts for age and sex and its quantities are reported based on a previous SCr reference interval study. The FAS equation has been formulated to encompass the entire age spectrum and can be a powerful alternative to measuring the eGFR in all age groups, even older adults. For example, in a cohort of adult patients with obstructive nephropathy, the FAS equation showed the highest diagnostic accuracy than the MDRD and CKD-EPI (2012) equations, and it seemed closer to ideal for estimating GFR in this population.¹⁴⁴

Figure 1.4 illustrates the fractional change in kidney function with age based on the structural model of the equations in Table 1.4. The purpose of this illustration is to show the reader the differences between these equations rather than suggesting that one is better than the

other. Figure 1.4 shows wide variability in how kidney function decline is expected as a function of age. The CG equation assumes a linear decrease with age, whereas the other equations are modeled as exponential decline functions. The BIS1 and BIS2 equations have faster decline trajectories than the other equations. The CKD-EPI and MDRD predict lower age-related declines (30%–40% loss) than the CG equation (70% loss).

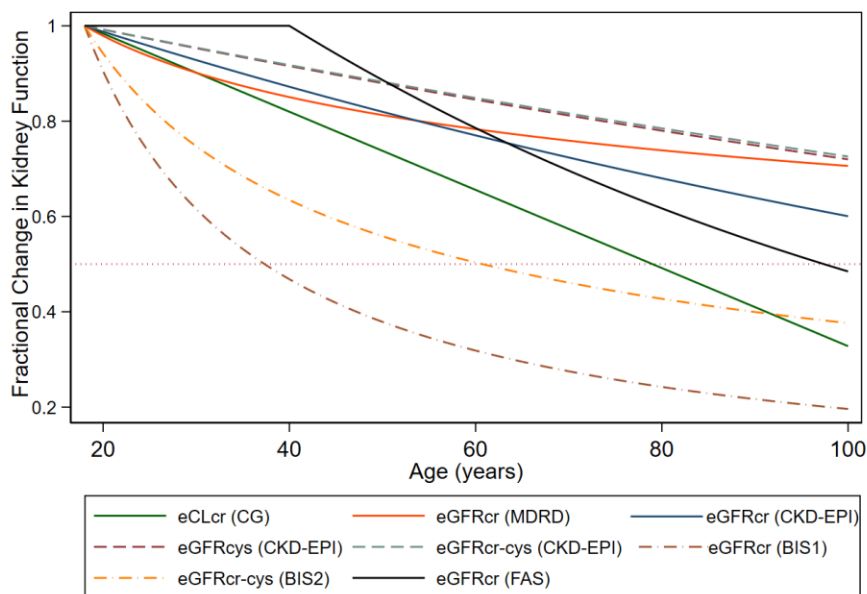


Figure 1.4 Fractional change in kidney function over chronological age with key contemporary kidney function equations. CKD- EPI, Chronic Kidney Disease Epidemiology Collaboration; FAS, Full Age Spectrum; eCLcr, estimated creatinine clearance; MDRD, Modification of diet in renal disease.

In contrast, the FAS equation does not include an age-related decline until age 40 years, followed by an age-related decline that predicts a 50% loss of function between age 40 and 100 years. Although this illustration may suggest that one equation better captures kidney function age-decline trajectories, an important consideration is whether drug clearance reductions follow a similar path. Few population PK studies have compared these eGFR and CrCl equations to determine the optimal equation for predicting drug clearance for drugs primarily eliminated by the kidneys with aging. More work is needed to build consensus around a singular eGFR or eCLcr model that accurately estimates drug clearance and kidney function declines with aging.

These differences in kidney function prediction have real-world consequences for drug dosing. To illustrate this point, we examine vancomycin, a renally eliminated antibiotic commonly used in older adults, as a model compound for understanding how equation choice affects dose predictions.

1.5 Vancomycin Clearance Changes Across the Lifespan Through Population-PK Models

Multiple studies have shown that kidney function does not decline until after age 40 years unless there are non-age-related disease factors. This point is evident in the FAS model for kidney function. Based on Figure 1.4, the CG model projects a 50% decline in kidney function by the time an individual reaches the age of 80 years. With that in mind, we are curious to find out the expected change in drug clearance by these models based on two assumptions: first, a CrCl 120 mL/min or a GFR 120 mL/min/1.73 m² in a 40-year-old patient, and second, a CrCl 60 mL/min or a GFR 60 mL/min/1.73 m² in an 80-year-old patient. To answer this question, we rely on a model substrate vancomycin because it has limited metabolism and is excreted unchanged in the urine. Vancomycin is a glycopeptide antibiotic widely used to treat gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* infections in older adults.

Table 1.5 summarizes some of the previous population-PK studies of vancomycin in adults. As mentioned in Table 1.5 footnotes, the most common model of kidney function used to estimate vancomycin clearance is CG (7 studies). The CrCl guides the dosing adjustment of vancomycin in older adults. Table 1.5 proves this parameter has been consistently repeated in the vancomycin population-PK models for clearance. In all of the summarized population PK models, CrCl was reported as the significant covariate for vancomycin clearance, except for one study in which the cystatin C concentration was the significant covariate. Along with the CrCl, age was also reported as a significant covariate in three models. The mean vancomycin clearance estimate for each summarized model was calculated based on the two assumptions above. Results of this investigation revealed that the median (min, max) vancomycin mean clearance estimate for the assumed 40-year-old man with anormal kidney function was 4.60 (3.30, 6.30), and for the 80-year-old man with a 50% reduction in the kidney function was 2.63 (1.89, 3.56). Additionally, the median percentage reduction in vancomycin clearance was 41.20 (29.94, 51.25).

Table 1.5 Summary of the population pharmacokinetic (Pop-PK) models of vancomycin clearance in the (older) adult population

Author (Year)	Study Sample	Sample size	Age (years)	Vancomycin clearance model	Vancomycin mean CL estimate (L/h)		
					40 years a	80 years b	% Reduction
Sanchez et al. (2010)	Younger adult and older adult patients	141	55 ± 14.58	$Cl (L/h) = 0.157 + 0.563 \times Cl_{cr}$	4.21	2.18	48.22
Tanaka et al. (2010)	Japanese patients with MRSA infections	164	74 (17- 95)	$Cl (L/h) = 0.875 \times eGFR_{cys}$	6.3	3.15	50.00
Purwonugroho et al. (2012)	Thai adult patients	212	66.6 ± 18.4	$Cl (L/h) = 0.044 \times Cl_{cr} (mL/min)$	5.28	2.64	50.00
He et al. (2014)	Chinese patients	260	76.8 ± 11.2	$Cl (L/h) = (1.71 + 8.31 \times (1 - e^{-0.0113(L/h) \times Cl_{cr}})) \times 0.475^{(Age/72)}$	5.21	2.54	51.25
Dedkaew et al. (2015)	Critically ill patients in Thailand	138	65.7 ± 17.6	$tv Cl (L/hr) = 0.27 \times Cl_{cr}^{.63}$	5.51	3.56	35.39
Ji et al. (2018)	Chinese adult patients	160	78 (42- 95)	$Cl (L/h) = 2.829 \times (1 + 0.00842 \times (Cl_{cr} - 80)) \times (\frac{75}{Age})^{0.08143} \times e^{\eta_1}$	3.98	2.34	41.2
Shen et al. (2018)	Chinese adult in-house patients	380	61 (49- 74)	$Cl (L/h) = 3.87 \times (Cl_{cr}/86)^{0.519} \times e^{\eta_{CL}}$	4.60	3.21	30.22
Zhou et al. (2019)	Chinese older adult patients with pulmonary infections	70	78.3 ± 6.96	$Cl (L/h) = 2.45 \times (Cl_{cr}/56.28)^{0.542}$	3.69	2.54	31.16
Kovacevic et al. (2020)	Critically ill septic patients in Bosnia	73	56.9 ± 17.0	$Cl (L/h) = 0.024 \times Cl_{cr} + 1.93$	4.81	3.37	29.94

Zhao et al. (2021)	Chinese patients with augmented renal clearance	209	66.0 ± 16.4	$Cl\ (L/h) = \frac{5.58 \times CG_i^{1.5}}{(93.8^{1.5} + CG_i^{1.5})} \times e^{\eta_1}$	3.30	1.89	42.73
Garreau et al. (2021)	Critically ill patients in France	78	68.9 ± 12.3	$CL_i = 0.79 \times e^{(\frac{Cl_{cr\ i}}{41.4})^{0.5}} \times e^{\eta_{CL_i}}$ with $\eta_{CL_i} \sim N(0, \omega_{CL})$	4.34	2.63	39.40

^a Mean estimates of vancomycin clearance based on a typical patient that is 40 years old with an estimated creatinine clearance or glomerular filtration rate of 120 mL/min or 120 mL/min/1.73 m²

^b Mean estimates of vancomycin clearance based on a typical patient that is 80 years old with an estimated creatinine clearance or glomerular filtration rate of 60 mL/min or 60 mL/min/1.73 m²

† e^{η} = interindividual variations of CL

† Cockcroft-Gault (CG) equation was predominantly used to model vancomycin clearance (7 studies). Equation used to model vancomycin clearance in one study (Tanaka et al.) was Hoek's formula and in three studies was not given (Sanchez et al., He et al., and Shen et al.).

These findings align with our observations in Figure 1.4. As noted in Figure 1.4, a 50% reduction in kidney function at the age of 80 years is predicted by CG, which is close to the median percentage reduction in vancomycin clearance (41.2%). The FAS equation, which considers the age-dependent decline in kidney function after age 40 years, predicts a slower kidney function loss than CG, as the kidney function reaches a 50% reduction around the age of 100 years (Figure 1.4). This prediction becomes even more gradual with the CKD-EPI_{cr} and CKD-EPI_{cr-cys} equations and may require further improvements for the CKD-EPI equations to adjust them for dosing in older adults. Although CG may be better capable of predicting changes in kidney function with aging, this assessment is confounded by the fact that it was the most dominant equation used in these studies. Population PK models that directly compare these alternate equations are necessary to verify these projections.

1.6 A Model of Age-Informed Radiomic Biomarkers as A Covariate of Kidney Function

The preceding sections have established that biological age can be quantified through multiple approaches including epigenetics, radiomics, and metabolism, that kidney function declines with aging but exhibit substantial interindividual variability, and that current kidney function equations rely on traditional covariates that may not fully capture this variability. These observations motivate the central hypothesis of this dissertation: that biological age-related biomarkers of body composition can serve as age-informed predictors of kidney function, potentially improving upon chronological age in pharmacokinetic models. The condition of the kidneys seems to be a key factor in predicting aging.²⁸ As age increases, the kidney's cortex decreases in size, weight, volume, and number of glomeruli.¹⁴⁵ Age-related congestive degeneration and hardening of the glomeruli lead to reduced renal tubule function and decreased glomerular filtration rate (GFR), which determines kidney function and CKD stages.¹⁴⁵ Changes in kidney function with age have profound importance in dosing optimization, especially in older adults.¹⁴⁶ Despite numerous publications improving models for estimating kidney function, we still rely on the primarily originated models (e.g., Cockcroft-Gault) for drug dosing, especially in older adults.¹⁴⁷

As people age, there is a concurrent decline in muscle mass and urinary creatinine clearance (CrCl).¹⁴⁸ Due to increased heterogeneity in muscle mass and creatinine production with aging, CrCl is a less accurate measure of muscle mass and lean body mass in older adults

compared to young adults.¹⁴⁹ Despite the age-related decline in CrCl, plasma creatinine levels do not rise with aging.¹⁵⁰ In healthy older adults, the true GFR measured by inulin clearance is significantly lower than in young adults but remains within the normal range. Inulin is the gold standard marker for evaluating renal clearance and GFR. Both measured CrCl and the Cockcroft-Gault formula underestimates the true GFR.^{147,151} Research continues to find new biomarkers of kidney function to develop better equations.

Apart from filtration, the kidneys also play an important role in the endocrine system by secreting hormones to maintain blood pressure, regulate fluid and salt homeostasis, and promote bone integrity by activating vitamin D₃.^{152,153} The advent of radiomics and the opportunistic screening of radiomic images opened new horizons to finding biomarkers that provide an extensive kidney health and function assessment. Nevertheless, sparse studies have been conducted for this purpose. Among the radiomic techniques, CT scans are the preferred diagnostic tool for CKD since they can provide high-quality images of the renal parenchyma.^{154,155}

The radiomic-based analysis of major body composition components – especially muscles involved in creatinine production – with aging can potentially introduce new biomarkers for kidney function that can be validated against the existing models of kidney function for greater precision. One study demonstrated that patient-specific measures of the skeletal muscle area from their CT scans were strongly correlated with the Cl of aminoglycoside, a surrogate for kidney function, in a retrospective cohort of inpatient adults with a median age of 57 years.¹²¹ Additionally, a recent cross-sectional study of 400 healthy subjects with a mean age of 56.2 years found that adipose tissue and VAT were positively correlated with cystatin C (an endogenous biomarker of kidney function) metabolism, and inversely correlated with eGFR estimated via cystatin C serum concentration (eGFR_{cys}).¹⁵⁶ Furthermore, reduced kidney function with aging can cause lower vitamin D₃ levels, calcium reabsorption, and bone density, which are risk factors for bone pain, muscle twitching, and fragility fractures.¹⁵⁷

The correlations between the covered radiomic biomarkers and kidney function illuminate the potential to refine conventional models of estimating kidney function by replacing body weight-based measures. Each age-informed radiomic biomarker discussed in this dissertation can be evaluated in the population pharmacokinetic (PopPK) models of kidney function surrogates alone or with other covariates (age, sex, Scr, etc.) to determine whether they

can improve the dosing of medications. Given the diversity of the radiomic biomarkers and their personalized identity, it would be advantageous to design a model or index using these biomarkers. This index, derived from radiomics and representing changes in body composition with aging, may be classified as a type of biological age. Efforts in quantifying biological age have dramatically increased in the past decade. Epigenetic clocks and metabolic measurements are trendy examples of quantifying biological age.^{158,159}

Some models of radiomic biological age have been constructed over the past decade to predict essential clinical outcomes. One of the earliest models was introduced by researchers at the Morphomic Analysis Group at the University of Michigan in 2013 to predict postoperative survival.¹⁶⁰ Additionally, Cron et al. introduced a model of morphomic age consisting of visceral fat area, body depth, and total body area as pre-transplant measures predictive of post-kidney transplantation diabetes mellitus in 99 kidney recipients.¹⁶¹ In another study, psoas muscle area, psoas muscle density, and aortic calcification were significantly associated with surgical risk in terms of 1-year post-operative mortality and the length of stay in a cohort of 1,370 patients who underwent general and vascular surgery at the University of Michigan.¹⁸ Nevertheless, a model of morphomic age has not been assessed as a covariate of kidney function. A schematic model for using morphomic age in estimating kidney function is proposed in Figure 1.5. As shown in Figure 1.5, the proposed model built upon the radiomic biomarkers is hypothesized to have a superior association with kidney function than the chronological age. Validation and generalizability of these claims in future work are warranted.

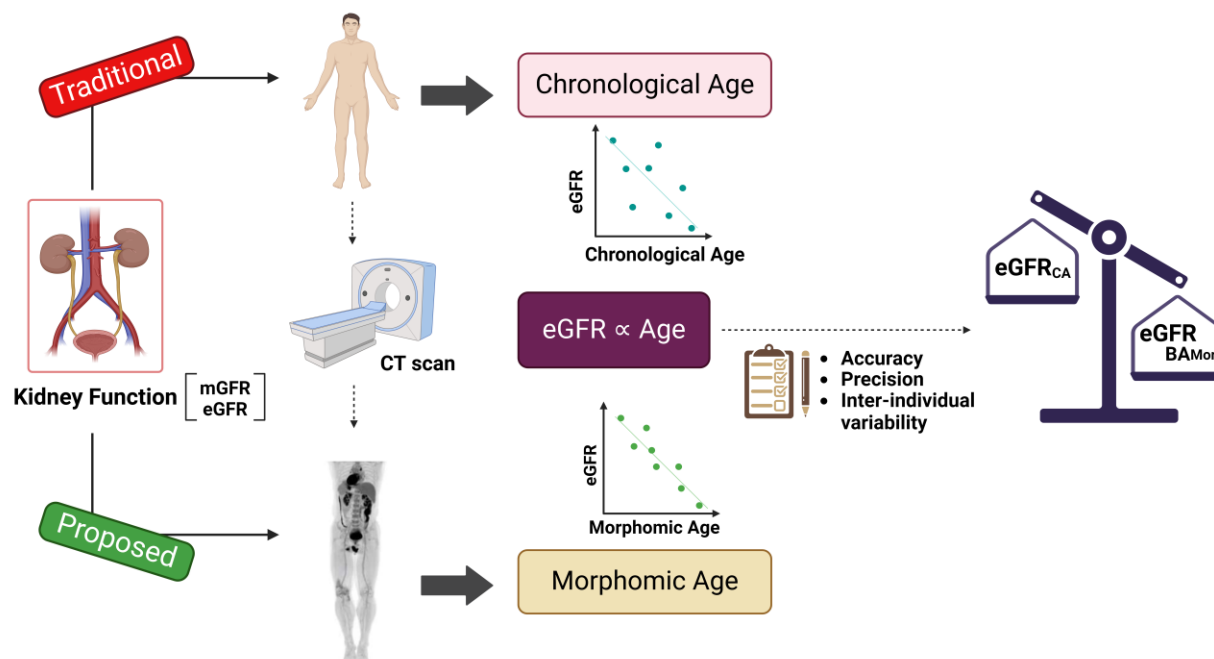


Figure 1.5 Schematic model of Morphomic Age as a potential covariate of kidney function. Created with BioRender.com.

The capability of morphomic age to predict clinical outcomes has led to interest in the potential assessment of the pharmacokinetic changes of drugs. As mentioned earlier, the skeletal muscle area can improve the estimation of aminoglycoside Cl. In a recent study, Pieters et al. developed an automated deep learning-based algorithm for the body composition (muscle and fat) analysis of the abdominal CT scans at the 3rd lumbar vertebra (L3) and introduced two validated equations (CRAFT 1 and CRAFT 2) to estimate the creatinine excretion.¹⁶² CRAFT 1 equation includes CT parameters, age, weight, and stature, whereas CRAFT 2 eliminates weight and stature. These equations demonstrated more accurate results than the CG and Ix equations. These promising results highlight the potential application of CT radiomics as a low-cost, reliable, and safe tool to identify and predict aging consequences on drug pharmacokinetics, organ functions, and clinical outcomes.

Integrating more precise biomarkers of body composition in translational studies can benefit clinicians and patients.¹⁶³ The promise of these biomarkers includes assistance in diagnosing serious complications of aging and providing patient-specific therapeutic and non-therapeutic treatment plans. Patients can also get pragmatic recommendations for healthier aging,

safer medications, and better outcomes. Table 1.6 provides a summarized comparison between biological morphomic age (BA_{Mor}) versus chronological age in terms of the benefits and drawbacks of utilizing each one in clinical studies.

Table 1.6 Proposed differences between biological morphomic age and chronological age.

Criterion	Description	BA _{Mor}	CA
Specificity	Ability to reflect unique biological aging processes	☒	
Age-Informativeness	Capacity to provide information about functional biological age	☒	
Objectivity	Based on quantitative measures rather than subjective estimations	☒	
Predictive of Morbidity	Ability to predict age-related health issues	☒	
Predictive of Mortality	Ability to predict lifespan considering current health status	☒	
Sensitivity to Lifestyle	Reflects the impact of lifestyle on biological age	☒	
Sensitivity to Interventions	Reflects the biological changes after clinical interventions	☒	
Temporal Stability	Reflects aging consistently over time		☒
Accessibility	Ease of measurement		☒
Cost	Expense associated with the measurement		☒
Standardization	Universal application and comparability		☒

We term this integrated radiomic assessment "morphomic age" (BA_{Mor}: Biological Age from Morphomics), a composite index derived from CT-based body composition measurements that reflects an individual's physiological status more accurately than chronological age alone. As discussed in Section 1.2.1, CT-based measurements can quantify multiple aspects of body composition, including skeletal muscle area, muscle density, bone mineral density, and adipose tissue distribution. Emerging evidence suggests these biomarkers correlate with kidney function.

According to Table 1.6, BA_{Mor} excels in specificity and age-informativeness, offering a nuanced picture of an individual's aging process by quantitatively capturing physiological changes like bone density, muscle damage, visceral fat accumulation, vascular calcification, etc.

BA_{Mor}'s effectiveness in predicting morbidity and mortality risks is proven in previous studies. This tailored approach holds the potential to reflect lifestyle influence and the effectiveness of clinical interventions on an individual's biological state more accurately than chronological age.

While chronological age is known as the common measure of time, it is less sensitive to immediate biological shifts but remains consistent over time. The ease of ascertainment, low cost, and widespread standardization render chronological age the solid foundation upon which policies and health system frameworks are built. Its universal applicability, without the need for complex imaging and software-based analysis, facilitates its continued use across human subject studies.

1.7 Framing the Dissertation Purpose and Specific Aims

It is reasonable to assume that a comprehensive biomarker for aging requires a combination of laboratory, epigenetic, non-epigenetic, physical features, organ function biomarkers, and senescence markers. This complexity makes it unlikely to achieve consensus on a single standardized composite aging biomarker in the short term. Determined by numerous sets of variables that change with aging, the composite aging score provides a quantitative approximation of the overall physiological status of individuals. Increasing the number of variables will improve the aging score, but this over-parameterization and complexity may only result in a minor change to the composite aging score. Furthermore, the development of overly complex models of biological age is likely to reduce the probability of clinical implementation. With the advancement of biological age diagnostic tools and particularly the epigenetic clocks, an important research question to address is whether replacing chronological age with biological age will better predict kidney function and drug dosing. If it is shown to be "better," an initial obstacle to implementation will be the cost, which is currently \$300–\$500 per test. If this tool definitively predicts certain health outcomes and better measures of healthspan, then a scale-up of these assays will lower prices over time. At present, these aging clocks are potentially helpful for the evaluation of senolytics or anti-aging drugs. Increased attention to these concepts is necessary for clinical pharmacology as they offer tools that could be exploited to inform sources of interindividual variability in exposure and response to drugs.

Although radiomic data is compelling, blending its depth with the broad applicability of chronological age proposes an elegant symbiosis for future aging research. Integration is likely to

yield more robust aging models and refine our understanding of aging as a multifactorial process. The use of radiomic data in personalizing healthcare, predicting disease onset and progression, and crafting preemptive interventions represents a frontier in pharmacotherapy that harnesses the promise of precision dosing. This integration aligns with the aspiration to craft more deeply informed health strategies that account for the biological uniqueness of individuals as they age. Nevertheless, using cross-sectional imaging for serial assessments of BA_{Mor} presents considerable challenges, particularly in terms of cost, time, and accessibility for patients and clinicians, which currently limits its widespread use. In light of these challenges, prioritizing the use of this approach in patients who could benefit most from precise BA_{Mor} assessments, such as those with advanced CKD or metabolic conditions, would be more beneficial. Ongoing advancements in imaging technology and artificial intelligence hold the potential to streamline these processes, making them more cost-effective and accessible to a broader patient population in the future.

The framework described above requires systematic investigation across multiple dimensions. While promising, the approach faces practical challenges, including cost, accessibility, and the need for validation across diverse populations. Nevertheless, the potential benefits for precision dosing justify focused investigation of key research questions. This dissertation addresses three specific aims that build upon and test the framework described above. Each aim tackles a distinct but complementary aspect of using biological age to improve drug dosing in older adults:

Specific Aim 1: Improving Estimation of Lean Body Weight Using Radiomic-based Skeletal Muscle Biomarkers

Lean body weight (LBW) is a critical covariate in pharmacokinetic models but is challenging to measure accurately. Lean body weight is known to decrease with aging and so may serve as a useful surrogate of biological aging, given that the rate of muscle loss varies considerably among individuals of the same chronological age. This aim investigates whether CT-derived skeletal muscle measurements can improve LBW estimation compared to existing anthropometric equations, with implications for weight-based drug dosing.

Specific Aim 2: Correlating Radiomics-Derived Morphomic Age (BA_{Mor}) Against Models of Aminoglycoside Clearance as Kidney Function Surrogates Building on the framework proposed in Section 1.6, this aim develops composite indices of morphomic age from CT biomarkers and tests whether these indices better predict kidney function, as assessed through aminoglycoside clearance, compared to chronological age in population pharmacokinetic models.

Specific Aim 3: Investigating Epigenetic Age (BA_{Epi}) and Metabolic Age (BA_{Met}) as Biomarkers of Kidney Function This aim complements the radiomic approach by examining epigenetic and metabolic biomarkers of aging, providing a more complete picture of how different biological age assessments relate to kidney function and drug disposition.

Together, these three aims provide convergent evidence for the value of biological age assessment in precision pharmacotherapy for older adults.

Chapter 2 Improving Estimation of Lean Body Weight Using Radiomic-based Skeletal Muscle Biomarkers

2.1 Introduction

The World Obesity Federation estimates that about 1 billion people worldwide were living with obesity in 2020, and that number is expected to nearly double to 2 billion by 2050.¹⁶⁴ This is alarming as obesity is a risk factor for several disease conditions that require short and long-term pharmacotherapies.¹⁶⁵ Drug dose labeling often does not contain guidance for dosing in patients with obesity so the risk of underdosing and overdosing medications remains high in this population, and this applies to both weight-based and fixed-dose medications.¹⁶⁶ It is well established that drug clearance does not scale proportionately with measured weight when scaling information from normal weight to patients with severe obesity.^{167,168} Muscles, organs, and other soft tissues that encompass lean body mass are considered to be the most pharmacologically relevant when predicting drug clearance, though the extent of their importance may vary depending on the specific drug and patient population.^{169,170} Alternate body size descriptors (ABSD) such as ideal body weight (IBW), adjusted body weight (AdjBW), dosing weight (DW), and lean body weight (LBW) are often used as surrogates of lean body mass.^{171,172} However, the value of LBW for predicting drug clearance is subject to ongoing discussion and research. While LBW has shown promise in many studies, its superiority over other measures is not universally established.¹⁷³ Some research suggests that LBW with an allometric exponent of approximately $2/3$ may be most suitable for describing an increase in clearance with body size.¹⁷⁴ However, other studies have found that no single-size descriptor consistently outperforms others for all drugs or age groups.^{169,175}

Throughout this paper, we use the term 'weight' to align with its common usage in pharmacology, rather than 'mass,' which is more commonly used in exercise and fitness science. The aforementioned ABSD are often used interchangeably with preferences based on geography and therapeutic domain but ultimately all these terms rely on height, weight, and sex for their estimation.¹⁷⁶ While these variables are relatively easy to acquire, they cannot consistently

capture the diverse human body phenotypes that exist.¹⁷⁷ For example, age-related skeletal muscle loss with associated adipose weight gain, known as sarcopenic obesity is not captured by these ABSD.^{178–180} Therefore, the inclusion of other measurements that can enhance LBW estimation should improve the precision of the current ABSD.

Dual-energy X-ray absorptiometry (DEXA) imaging is one of the most accurate approaches for measuring LBW.¹⁸¹ DEXA measurements provide specificity of body composition by region such as the arms, legs, and trunk, while also providing cumulative values reported as LBW.¹⁸² DEXA is primarily employed to assess bone mineral density (BMD) at the hip and lumbar spine.¹⁸³ Although DEXA offers detailed body composition assessments, their routine use in clinical medicine is less prevalent than CT scans.¹⁸⁴ For context, an estimated 90 million CT scans are performed in the United States annually, while DEXA scans are recommended in older adults, access and broad use remain limited.^{185,186} Abdominal and thoracic CT scans are the most frequent regions probed for diverse clinical indications.¹⁸⁷

An emerging field of study involves leveraging existing CT scans with morphometric computational tools to evaluate the size, shape, and composition of various body tissues and organs, known as morphomics.¹⁸⁸ These body composition determinations are performed retrospectively and do not require additional patient time or radiation exposure.¹⁸⁹ An unexplored area of research is understanding the extent to which morphomics-derived body composition correlates with the gold standard of DEXA-derived body composition. A schematic illustration of some key outputs of DEXA and CT scan body composition metrics (Figure 2.1) highlights an opportunity to correlate these measurements. Few studies have explored the interchangeability of body composition metrics between CT and DEXA.^{190–192} Therefore, the primary objective of this study is to examine the correlation between CT-related skeletal muscle morphomics and DEXA-measured LBW. The secondary objective was to understand the incremental improvement in the precision of LBW estimation when using existing ABSD along with skeletal muscle morphomic measurements from existing CT scans. Improving the LBW estimation through the opportunistic use of clinical imaging measurements may improve precision dosing considerations across the wide human adult obesity phenotype.

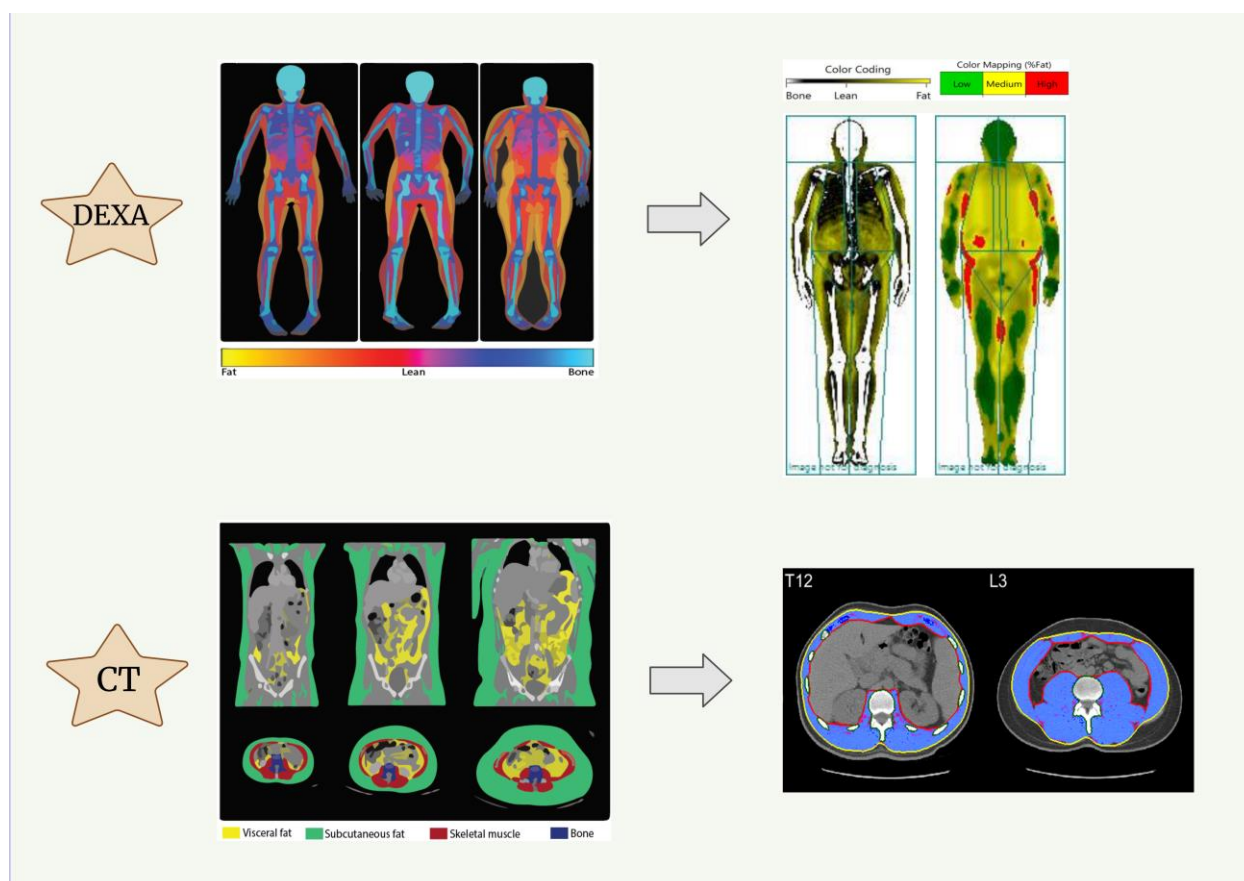


Figure 2.1 Illustrative comparison of dual-energy x-ray absorptiometry (DEXA) and computed tomography (CT) scan profiles in three individuals with increasing body fat percentage along with an example of the outputs from those imaging modalities. As shown, DEXA does not provide a direct measurement of muscle area (blue shaded region) as is feasible by CT scan (Created with Biorender.com)

2.2 Materials and Methods

Patients with obesity participating in the University of Michigan's 2-year Weight Management Program (MWMP) undergo three DEXA scans: at baseline, at 3–6 months, and at the end of the 2 years, to evaluate the impact of weight loss over time.¹⁹³ A database of these patients with available baseline DEXA measurements was compiled and their medical records were retrospectively reviewed using the Picture Archiving and Communication System (PACS) at the University of Michigan Health System to identify individuals who had undergone CT scans at the University's hospital for other purposes within 6 months prior to their DEXA assessments. These CT scans had been performed for various clinical indications as determined

by the treating physicians, including abdominal evaluation due to pelvic pain (29.9%), cancer evaluation (20.9%), cardiopulmonary and pulmonary embolism rule-out (22.4%), post-surgical evaluation (14.9%), and miscellaneous (11.9%). Institutional Review Board (IRB) approval was obtained prior to initiating the study. These records were then linked to form the final dataset, consisting of patients with both DEXA and CT scan data for correlation analysis.

CT-based variables were measured at the thoracic 10 and 12 (T10 and T12) and lumbar 3 and 4 (L3 and L4) vertebra, alongside DEXA-derived variables, for analysis in the study cohort. Among the CT variables, skeletal muscle measurements including skeletal muscle area (SMA), skeletal muscle index standardized by height (SMI_ht), skeletal muscle index standardized by height-squared (SMI_ht²), and skeletal muscle density (SMD) were selected as the independent variables for further analysis. The dependent variable was LBW from the DEXA scan.

Table 2.1 Alternate body size descriptors used to define the body size of obese subjects with their expansions

Body size descriptor	Equation
Total body weight (TBW), Kg	Measured
Ideal body weight (IBW), Kg	<i>Males = 50 + 2.3 × (Ht per inch over 5 ft)</i> <i>Females = 45.5 + 2.3 × (Ht per inch over 5 ft)</i>
Adjusted body weight (AdjBW), Kg	$IBW + 0.4 \times (TBW - IBW)$
Lean body weight (LBW ₂₀₀₅), Kg	<i>Males = $(9270 \times TBW) / (6680 + 216 \times BMI)$</i> <i>Females = $(9270 \times TBW) / (8780 + 244 \times BMI)$</i>
Dosing weight (DW), Kg	<i>Use TBW If $TBW < IBW$</i> <i>Use IBW If $TBW < (1.25 \times IBW)$</i> <i>Use AdjBW If $TBW \geq (1.25 \times IBW)$</i>

Abbreviations: Ht: height; Ft: foot; BMI: body mass index.

Using the equations summarized in Table 2.1, LBW, IBW, and AdjBW were calculated to support our investigation into the correlations between DEXA-measured LBW and other ABSD. LBW was estimated using the Janmahasatian equation (LBW₂₀₀₅), which accounts for height, weight, and sex-specific factors.¹⁹⁴ IBW was calculated using the Devine formula,¹⁹⁵ while AdjBW was determined using the following equation: $AdjBW = IBW + 0.4 \times (\text{actual body weight} - IBW)$.¹⁹⁶ Finally, the common rule referred to as DW applied measured weight, IBW, or

AdjBW, depending on the relationship between the total body weight (TBW) and IBW: TBW is used when it's less than the IBW; if TBW is between IBW and 125% of IBW, then IBW is used; for patients whose TBW is 125% or more of their IBW, AdjBW is used. In fact, the use of different weight measures in this equation reflects the fact that drug distribution and clearance don't always increase linearly with TBW, particularly in obesity.

A univariate linear regression analysis was performed to assess the correlation between four CT-based variables (SMA, SMI_ht, SMI_ht², and SMD) and DEXA-derived LBW. The hypothesis testing was structured with the following assumptions: Null Hypothesis (H₀): $\beta_1 = 0$ (no relationship between the DEXA-derived LBW and CT skeletal muscle variables); Alternative Hypothesis (H₁): $\beta_1 \neq 0$ (a relationship exists between the DEXA-derived LBW and CT skeletal muscle variables). Statistical significance was set a priori at $\alpha = 0.05$. Subsequently, scatterplots were generated, and regression lines were fitted using the “ggplot2” package in R to visually compare these relationships.¹⁹⁷

To assess model accuracy, we calculated the mean percentage error (MPE), mean absolute percentage error (MAPE), root mean square percentage error (RMSPE), and the percentage of predictions within $\pm 5\%$, $\pm 10\%$, and $\pm 20\%$ of DEXA-measured LBW.¹⁹⁸ Bland–Altman analysis was conducted to determine the 95% limits of agreement (LOA) for the MPE. To evaluate internal validity and model robustness, we performed nonparametric bootstrapping (1,000 replicates) to estimate confidence intervals for MAPE and RMSPE. All statistical analyses were done by R Statistical Software version 4.4.1.¹⁹⁹

2.3 Results

We retrieved records from 797 patients in the MWMP with a baseline DEXA Measurement. Of these patients, 63 had a corresponding CT scan available for morphomics analysis. Table 2.2 summarizes the descriptive statistics for patient demographics and the morphomic variables for this study. As shown, the percentage of females was higher than that of males (71.4%), which aligns with the enrollment of patients in the MWMP. The patients had a median age [min, max] of 53.4 [21.2, 70.9] years, weight [min, max] of 104.0 [65.3, 152.4] Kg, and height [min, max] of 166.1 [144.8, 193.0] cm. The patients also had several CT-based morphomic variables (n=13) measured at T10, T12, L3, and L4 vertebra levels and DEXA-derived variables (n=126).

Table 2.2 Descriptive statistics of the dataset's patient demographics and morphomic variables

Characteristic	Data	Range (min, max)
Number of patients	63	
Age, Median (IQR) (Year)	53.4 (13.2)	21.2 – 70.9
Gender		
Female (%)	45 (71.4)	
Weight, mean (SD) (Kg)	103.6 (17.4)	65.3 – 152.4
Height, mean (SD) (cm)	167.1 (10.2)	144.8 – 193
BMI, mean (SD) (Kg/m ²)	36.84 (4.1)	26.81 – 54.26
<i>CT and DEXA Morphomic Variables</i>		
Total lean weight, mean (SD) (Kg)	54.6 (10.7)	36.0 – 78.7
Skeletal muscle area, mean (SD) (mm ²)	10895 (27732.5)	6639 – 18389
Skeletal muscle index_ ht ² , mean (SD) (mm ² /cm ²)	39.0 (7.6)	26.4 – 61.4
Skeletal muscle index_ht, mean (SD) (mm ² /cm)	65.0 (14.5)	42.2 – 106.3
Skeletal muscle density, mean (SD) (HU)	38.0 (7.3)	22.4 – 53.5

Abbreviations: Ht: height; Ht²: height-squared; HU: Hounsfield Unit; SD: standard deviation; BMI: body mass index.

Table 2.3 Linear regression model results for DEXA-derived lean body weight against CT morphomic variables, stratified by vertebra number

DEXA Metric	CT Metric	Vertebra no.	Intercept	Coefficient	p-value	R ²
LBW	SMA	L3	14.9	0.00245	4.12e-9	0.80
		L4	15.5	0.00255	2.09e-8	0.77
		T10	21.8	0.00292	3.29e-9	0.67
		T12	17.1	0.00293	2.91e-10	0.76
LBW	SMI _{ht} ²	L3	14.6	0.702	1.0e-2	0.44
		L4	14.4	0.730	1.55e-2	0.40
		T10	25.4	0.738	1.06e-3	0.42
		T12	18.7	0.817	7.17e-4	0.52
LBW	SMI _{ht}	L3	11.2	0.456	3.91e-4	0.66
		L4	9.89	0.487	6.49e-4	0.64
		T10	23.3	0.471	2.75e-5	0.59
		T12	18.1	0.493	1.77e-5	0.69
LBW	SMD	L3	50.5	0.040	9.06e-1	0.001
		L4	45.0	0.199	5.19e-1	0.019
		T10	49.9	0.105	7.0 e-1	0.005
		T12	50.4	0.102	7.18e-1	0.005

LBW: Lean body weight; SMA: Skeletal muscle area; SMI_{ht}: Skeletal muscle index normalized by height; SMI_{ht}²: Skeletal muscle index normalized by height squared; SMD: Skeletal muscle density; R²: R-squared.

Table 2.3 summarizes the results of the linear regression analysis examining the relationship between DEXA-derived LBW and skeletal muscle morphomic variables. Among the vertebra levels, LBW more strongly correlated with SMA from L3, L4, and T12 compared to T10 (Figure 2.2). Normalization of SMA through SMI did not improve the correlation of these morphomic variables to LBW. No correlation was observed between SMD and LBW. SMA had the highest R-squared values of 0.80, 0.77, and 0.76 related to DEXA-derived LBW at L3, L4, and T12, respectively.

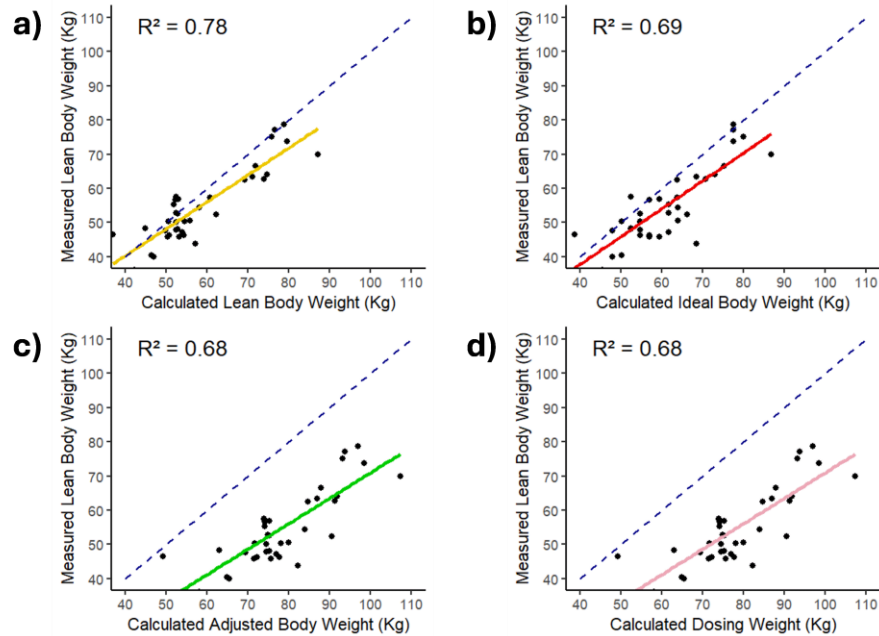


Figure 2.2 Scatterplot illustrating the correlation between lean body weight measured by dual-energy x-ray absorptiometry (DEXA) with computer tomography (CT)-based skeletal muscle area (SMA), at different vertebral levels

After correlating DEXA-based LBW with CT-based muscle morphomics, we then explored whether DEXA-derived LBW correlated with ABSD equations (Table 2.4). Linear regression analyses revealed significant correlations between DEXA-derived LBW and all the tested ABSD (p -value $2.2e-16$ across all models and R -squared between 0.68 to 0.78) with the strongest correlation seen with LBW_{2005} (Table 2.4). The correlations and their corresponding scatterplots are summarized in Figure 2.3.

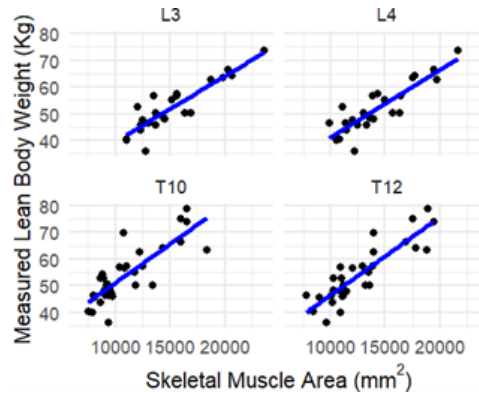


Figure 2.3 Scatterplots demonstrating the correlation between the lean body weight measured by dual-energy x-ray absorptiometry (DEXA) and different alternate body size descriptors: a) lean body weight estimated by the Janmahasatian equation published in 2005 (LBW₂₀₀₅); b) ideal body weight (IBW); c) adjusted body weight (AdjBW); and d) dosing weight (DW). As shown, DEXA-based LBW has the greatest correlation with LBW₂₀₀₅ (R-squared=0.78)

Table 2.4 Linear regression model results for DEXA-derived lean body weight against: 1) alternate body size descriptors and 2) combined standardized 2005 Janmahasatian equation and skeletal muscle area at different vertebra numbers

DEXA Metric	Dependent variable(s)*	Intercept	Coefficient	p-value	R ²
1) DEXA-based LBW ~ Conventional optimal body weight equations					
LBW	Ideal body weight	5.13	0.82	2.2e-16	0.69
	Adjusted Body weight	-3.57	0.74	2.2e-16	0.68
	LBW ₂₀₀₅	8.79	0.79	2.2e-16	0.78
	Dosing weight	3.57	0.74	2.2e-16	0.68
2) DEXA-based LBW ~ CT skeletal muscle area + LBW₂₀₀₅ equation					
LBW	LBW ₂₀₀₅	11.4	15.86	8.75e-2	0.83
	+ SMA at L3		22.35	1.75e-3	
LBW	LBW ₂₀₀₅	10.38	20.32	1.87e-2	0.82
	+ SMA at L4		20.80	2.16e-3	
LBW	LBW ₂₀₀₅	8.86	32.17	2.19e-6	0.84
	+ SMA at T10		16.73	1.91e-3	
LBW	LBW ₂₀₀₅	9.15	26.76	2.61e-4	0.86
	+ SMA at T12		19.84	9.9e-4	

* The dependent variables were a CT scan variable and/or an alternate body size descriptor.

Abbreviations: DEXA: Dual-energy x-ray absorptiometry; LBW: Lean body weight measured by DEXA; LBW₂₀₀₅: Lean body weight estimated by the Janmahasatian equation published in 2005; CT: Computed Tomography; SMA: Skeletal muscle area; SMI_{ht}: Skeletal muscle index normalized by height; SMI_{ht}²: Skeletal muscle index normalized by height squared; SMD: Skeletal muscle density; CT: Computed Tomography; R²: R-squared.

Upon confirming the significant correlation of DEXA-derived LBW with CT skeletal muscle measures and the LBW₂₀₀₅ in separate models, a multivariate analysis was conducted to assess the impact of DEXA in predicting LBW compared to the LBW₂₀₀₅ equation after adding a CT skeletal muscle measurement (Table 2.4). Our findings indicated that incorporating CT-derived SMA into conventional equations relying solely on weight and height substantially improved the R-squared values at all four vertebra numbers (highest at T12 from 0.76 to 0.86). Also, the Akaike Information Criterion (AIC) dropped from 141.3 to 139.8 and from 190.0 to 178.0, with the inclusion of SMA at L3 and T12, respectively. The following equations present an enhanced model of LBW derived from DEXA, incorporating standardized CT-based SMA at T12 or L3 with LBW₂₀₀₅:

$$DEXA\ LBW = 26.76 * (LBW\ 2005\ eq./60) + 19.84 * (CT\ SMA\ at\ T12/13000) + 9.15$$

eq. (1)

$$DEXA\ LBW = 15.86 * (LBW\ 2005\ eq./60) + 22.35 * (CT\ SMA\ at\ L3/13000) + 11.4$$

eq. (2)

To evaluate the accuracy of our models, we compared predicted LBW values using equations (1) and (2) to those measured by DEXA (Table 2.5). Among the 52 patients with available SMA measurements at T12, the MPE was 0.64%, with 95% LOA ranging from -15.42% to 16.71%. For L3 (n = 42), the MPE was 0.63%, with 95% LOA from -15.44% to 16.70%, indicating minimal bias and consistent agreement between LBW predicted by our equations and LBW measured by DEXA. The MAPE was 6.53% at T12 and 6.13% at L3, with corresponding RMSPE of 8.08% and 8.05%, respectively.

To assess internal validity, we performed nonparametric bootstrapping (1,000 resamples) to estimate the uncertainty of these error metrics (Table 2.5). Bootstrapped results confirmed the robustness of the models: MAPE was 6.56% (95% CI: 4.93–8.26%) and RMSPE was 8.07% (95% CI: 6.23–9.87%) at T12; for L3, MAPE was 6.14% (95% CI: 4.15–8.35%) and RMSPE was 7.92% (95% CI: 5.38–10.90%). Regarding clinical relevance, 83.3% of predictions at T12

and 87.5% at L3 were within $\pm 10\%$ of DEXA-measured LBW. Notably, 100% of predictions at T12 and 95.8% at L3 were within $\pm 20\%$ (Table 2.5).

Table 2.5 Summary of prediction error metrics for the proposed models benchmarked against DEXA measurements.

Model	Eq (1)	Eq (2)
Vertebra	T12	L3
MPE (%)	0.64	0.63
95% LOA	-15.42, 16.71	-15.44, 16.70
MAPE	6.53	6.13
RMSPE	8.08	8.05
Within 5%	36.7	41.7
Within 10%	83.3	87.5
Within 20%	100.0	95.8
Bootstrapped MAPE (Mean $\pm$ CI)	6.56 (4.93, 8.26)	6.14 (4.15, 8.35)
Bootstrapped RSMPE (Mean $\pm$ CI)	8.07 (6.23, 9.87)	7.92 (5.38, 10.90)

Eq. (1) – DEXA LBW = $26.76 * (\text{LBW}_{2005} \text{ eq.} / 60) + 19.84 * (\text{CT SMA at T12} / 13000) + 9.15$

Eq. (2) – DEXA LBW = $15.86 * (\text{LBW}_{2005} \text{ eq.} / 60) + 22.35 * (\text{CT SMA at L3} / 13000) + 11.4$

Abbreviations: MPE: Mean percentage error; LOA: Limits of agreement; MAPE: Mean absolute percentage error; RMSPE: Root mean square percentage error; CI: Confidence interval; DEXA: Dual-energy x-ray absorptiometry; LBW: Lean body weight measured by DEXA; LBW_{2005} : Lean body weight estimated by the Janmahasatian equation published in 2005; CT: Computed Tomography; SMA: Skeletal muscle area.

These findings demonstrate that integrating vertebral-level SMA into the traditional 2005 LBW equation can yield highly accurate predictions, with minimal bias and strong agreement with DEXA-derived LBW. While L3 remains the standard site in body composition analyses, the comparable performance of T12 supports its potential utility in contexts where abdominal imaging is unavailable.

2.4 Discussion

In this study, we aimed to investigate the relationship between CT scan-derived muscle morphomics and DEXA-derived LBW in a small cohort of patients with obesity to address the gap in understanding the interchangeability of these two imaging modalities for body

composition assessments. We hypothesized that integrating CT morphometrics, particularly SMA, with existing body composition equations would improve the precision of LBW estimations compared to relying solely on traditional methods like height and weight. The results confirmed our hypothesis, showing that SMA at L3 improves the prediction of DEXA-derived LBW. Furthermore, incorporating CT-derived SMA into the existing LBW₂₀₀₅ equation improved R² values for SMA at L3 and T12. This 5-10% improvement in R² values, compared to the original LBW₂₀₀₅ equation, may be perceived to be small but points to the potential for further improvement with future studies that include larger study sample sizes.¹⁹⁴ Importantly, the use of opportunistic CT data may have some selective advantages over DEXA for LBW measurement. It provides three-dimensional visualization, allowing for precise volume calculations that DEXA cannot match.²⁰⁰ CT also permits detailed regional analysis of body composition, which is particularly useful for assessing LBW distribution. Additionally, CT's cross-sectional images enable more accurate distinction between various tissue types (e.g. muscle), especially in complex anatomical regions²⁰¹. These combined features of CT contribute to a more comprehensive and potentially more accurate assessment of LBW compared to DEXA alone. This approach may offer a more refined and personalized method of estimating LBW, surpassing the limitations of methods such as Bioimpedance Analysis.²⁰²

Incorporating body composition metrics into clinical practice has the potential to refine dosing strategies, reduce the risk of under- or overdosing in patients with obesity. However, the specific body size descriptor is not always clear and the approach is likely to be a lot more nuanced and drug specific.¹⁷³ For drugs where LBW is the clear choice, shifting the current paradigm from conventional weight-based dosing to a more personalized and physiologically accurate methodology may be of value. This is particularly relevant because commonly used ABSD are not interchangeable with LBW. Our results demonstrated that both DW and AdjBW exhibited relatively lower R² values than IBW and the LBW₂₀₀₅ (Table 2.3).

As noted, LBW has been used as a scalar for drug dosing in patients with obesity. This dosing scalar has been shown to be optimal for drugs like fentanyl, sufentanil, remifentanil, and induction agents such as propofol and thiopental.²⁰³ However, in contrast imaging agents such as iopamidol, LBW may not offer a clear advantage over TBW. This was demonstrated in the trial by Zanardo et al., where dosing iopamidol for abdominal CT based on LBW did not yield more consistent liver contrast enhancement compared to TBW-based dosing.²⁰⁴ However, as

highlighted in a systematic review and meta-analysis by Gulizia et al., LBW-based dosing of contrast agents can lead to a significantly lower contrast volume while maintaining equivalent image quality.²⁰⁵ These findings suggest that while LBW-based dosing may not always demonstrate superiority over TBW-based dosing, it could offer advantages in optimizing dosing strategies for critical drugs, reducing contrast agent usage, and mitigating associated economic burdens. This warrants further investigation in specific clinical contexts to refine its clinical applicability.

Among several equations developed for estimating LBW, the LBW₂₀₀₅ equation is widely recognized for its stability across different body sizes, including standard, and individuals with mild to severe obesity. McLeay et al. applied the LBW₂₀₀₅ equation in a pharmacokinetic model for propofol and adjusted doses to achieve the recommended amount for a male patient with a body mass index (BMI) of 21.6 Kg/m², successfully predicting plasma propofol levels.²⁰⁶ In another study by Friesen, lean-scaled weight (LSW) is introduced as an effective weight scalar for dosing in patients with obesity.²⁰⁷ This approach involves multiplying the LBW₂₀₀₅ equation by a scale factor so that the LSW for a patient with a BMI of 22 equals that patient's total body weight. LSW remains proportional to LBW and is adjusted to scale accurately across various weights and heights. The scale factors applied to the male and female LBW equations are 1.2332 and 1.5262, respectively.

Given that LSW is a mathematically modified version of LBW₂₀₀₅, we also correlated DEXA-derived LBW with LSW to determine whether this could further improve LBW estimation. Although LSW was identified as a significant variable, the univariate regression analysis showed a lower correlation between DEXA-derived LBW and LSW (R-squared = 0.60) than LBW₂₀₀₅ (R-squared = 0.78). After incorporating SMA into the model, the correlation improved dramatically, achieving values comparable to those obtained with the LBW₂₀₀₅ equation (R-squared = 0.83 at L3 and 0.85 at T12). These findings once again underscore the robustness of the LBW₂₀₀₅ equation in estimating LBW and highlight the additional benefit of integrating CT morphometrics for improved precision in LBW estimation.

Furthermore, assessing and monitoring LBW holds significant value, as it can offer pivotal opportunities to identify critically ill patients at high nutritional risk early on and guide metabolic support following ICU admission.²⁰⁸ Current equations often overestimate LBW in critically ill patients.²⁰⁹ Recently, the use of advanced imaging technologies such as CT scans to

achieve a more precise LBW has gained traction and wider acceptance in the ICU setting. For instance, in a prospective observational study at Massachusetts General Hospital involving 231 surgical ICU patients who underwent a CT scan within five days post-extubation, LBW was linked to pneumonia, unfavorable discharge disposition, and 30-day mortality.²¹⁰ Notably, CT scans taken during the ICU stay clearly highlighted the negative consequence of the ICU stay on LBW, which must be considered alongside the patient's pre-ICU condition. Additionally, in a multicenter study conducted at 12 ICUs in North America, Moisey et al. revealed a significant discrepancy between the calculation of LBW using CT imaging and four conventional predictive equations, such as the LBW₂₀₀₅ equation.²⁰⁹ Therefore, using these equations is discouraged in ICU patients due to overestimating LBW and underestimating nutrition risk. An ICU-specific LBW equation could offer a valuable tool for more accurate identification of patients in need of targeted interventions and enable more precise dosing tailored to their unique needs. The growing interest in utilizing CT scans for estimating LBW in the ICU is reflected in our model, which integrates the CT modality with the established LBW₂₀₀₅ equation. This combination indicates that our model may warrant further evaluation for potential application in critical care settings as well.

To summarize, traditional dosing approaches may often fail to capture the variability in muscle and fat distribution, especially in older or clinically diverse populations. The opportunistic utilization of routinely acquired CT scans for body composition analysis shows promise for improving personalized dosing strategies in clinical practice, particularly for patients with obesity, where accurate LBW estimation is crucial. By leveraging DEXA-derived LBW, which directly reflects the metabolically active portion of body weight, through the LBW₂₀₀₅ equation and CT morphomics we offer a more precise and personalized measure that could improve the precision of body composition estimations and optimize drug dosing. Future research aimed at validating our findings in larger populations, particularly those that benefit more from weight-based dosing, such as elderly patients with obesity, critically ill patients, and others are acknowledged.

This study has several limitations. First, the sample size is small (n=63), and these findings require validation in larger target cohorts. This is partly due to the limited availability of patients with both DEXA and CT images and introduces selection biases based on those who have both scans. Second, the cross-sectional design precludes any inference of causality. Third,

the study is single-institutional, introducing hospital-based selection bias (Berkson's bias), which may limit the generalizability of the results to other populations. Next, measurements were available for only four vertebral levels in our dataset, potentially overlooking the significance of measurements at other levels, which may vary by patient characteristics. Additionally, the cohort primarily consisted of female participants with severe obesity, which may affect the generalizability of the results to broader populations, including males or individuals with different body composition and lower BMI. Furthermore, due to the relatively small sample size, we were unable to perform subgroup analyses stratified by sex, BMI category, or age. Consequently, we could not determine which specific subpopulations may derive the greatest benefit from the improved LBW estimation method.

Despite these limitations, this study provides evidence supporting the incremental value of CT imaging in improving LBW estimation, with potential applications in weight-based medication dosing. Future research should explore the integration of CT-derived morphomic measurements into clinical workflows, particularly for improving body composition assessments in more diverse cohorts with obesity.

2.5 Conclusion

In conclusion, CT variable SMA was significantly correlated with DEXA-derived LBW. Our study showed that morphomic variable implementation (such as SMA), may improve the precision of existing equations for estimating LBW. Future studies are encouraged to validate these findings in a larger and more diverse population of patients who benefit more from weight-based dosing, especially older adults with obesity, to enhance their translational pharmacotherapeutic impact.

Chapter 3 Correlating Radiomics-Derived Morphomic Age Against the Models of Kidney Function

3.1 Introduction

Chronological age (CA) serves as the standard factor used to characterize the interindividual variability of aging in population pharmacokinetic analyses²¹¹. Recent research suggests biological age better reflects the physiological consequence of aging, and that can be a superior predictor of health outcomes than CA²¹². While CA advances uniformly across all individuals, biological age exhibits variation influenced by numerous insults including physiological and environmental factors.²¹³ Given this heterogeneity, some people may need to manage multimorbidity and polypharmacy in their 80s, while other peers may not encounter significant health issues, leading an active life without needing regular medical intervention^{214,215}. A notable example of this inter-individual variability in organ systems is observed in the kidneys, which progressively deteriorate in conjunction with aging.²¹⁶ Kidney function declines after the CA of 40 years.²¹⁷ Moving forward, an 80-year-old can have a glomerular filtration rate (GFR) ≥ 90 mL/min or a significantly reduced GFR ≤ 30 mL/min if comorbidities exist.

Recent advancements in omics technologies have driven the development of new tools that can quantitatively characterize biological age^{2,218}. One such tool is radiomics, which offers a non-invasive means of measuring biological age²⁹. Radiomic-based biomarkers have been used to successfully develop models of brain age and heart age to predict functional outcomes after stroke and cardiovascular events, respectively^{219,220}. Radiomics is also capable of providing valuable information about age-related body composition changes²²¹. However, clinical pharmacology applications of radiomic-based models of biological age are presently understudied and are sparsely reported in the literature.

Personalized radiomic-based body composition biomarkers offer the potential for a better understanding of human body aging by replacing standard measures of age and body composition in dosing medications^{23,222}. To this end, assessing kidney function in older adults is

especially important for accurate dosing. Numerous equations for estimating kidney function exist with differing accuracy and precision²¹⁷. As models of kidney function are typically developed as a function of age and body composition, we hypothesized that radiomic-based biomarkers of aging are significant factors in predicting kidney function. To test our hypothesis, we developed biological age indices from Computed Tomography (CT) images and compared them to CA, an essential covariate of aminoglycoside clearance (Cl) through population pharmacokinetic (Pop-PK) analysis. Aminoglycosides undergo routine therapeutic drug monitoring and serve as model compounds for estimating kidney function because their clearance reflects the glomerular filtration rate (GFR). Consequently, this study aims to better understand how radiomic biological age affects kidney function, to improve drug dosing precision.

3.2 Materials and Methods

Data from 363 adult participants with available CT scan images were retrieved retrospectively from the medical record and the Picture Archive and Communication System (PACS) at the University of Michigan Health System. Approval from the internal review board (IRB) was secured before starting the study (HUM00041441). Informed consent was waived by the IRB and all methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki. Inclusion was restricted to patients with at least three doses and concentrations of aminoglycoside whose IDs matched the aminoglycoside PK data. Patients who underwent treatment with Amikacin were excluded. The final cohort consisted of 156 subjects, having several CT-based biomarkers (n=28) measured at different vertebra numbers. A complete list of these biomarkers along with their definition and vertebra number is provided in Appendix Tables A.1 and A.2.

Analyses were primarily restricted to measurements at L3 due to its prevalent use in clinical research. CT scans measuring the cross-sectional skeletal muscle area at L3 are commonly used to evaluate sarcopenic low muscle mass^{223,224}. Since other vertebral levels can correlate with L3, measurements from neighbor lumbar vertebrae (L2 or L4) were used as a proxy in cases of unavailable L3 measures for biomarkers (Appendix Table A.1). Some of these biomarkers contained missing values in a few patients, which were handled using the mice

package v3.16.0 with the random forest method for data imputation in R Statistical Software (v4.4.1; R Core Team 2024; <http://www.R-project.org>).²²⁵

Aminoglycoside plasma concentrations were analyzed using nonlinear mixed-effects modeling with the stochastic approximation expectation minimization (SAEM) algorithm in Monolix®. Model development employed a multistage approach based on a 1-compartment PK model. Initially, a linear model for infusion administration with no delay parameterized with V and Cl was tested. The log-normal distribution was adopted for all individual parameters. Various error models (constant, proportional, or combined) were evaluated to assess residual variability.

To achieve this project's goal, various combinations of CT-based biomarkers were developed as a BAmor index and tested against the aminoglycoside Cl in Pop-PK models to improve kidney function. The biomarkers were either identified as significant in Monolix® or established as a marker of body composition in previous studies. After evaluating different combinations, we selected three BAmor indices (BAmor_1, BAmor_2, BAmor_3), as shown in Table 3.2. Along with these indices, the effects of covariates such as age, sex, drug type, serum creatinine (Scr), and CT-based biomarkers on aminoglycoside Cl were investigated. Considering kidney function is inversely correlated with age, both CA and inverted CA (1/CA) were tested on aminoglycoside Cl.²²⁶ Each covariate's effect was tested and determined whether they should be added to the model by Pearson's correlation to the between-subject variability of pharmacokinetic parameters. Model discrimination was based on an at least two-point reduction in the Akaike information criterion (AIC) between models. Model performance was assessed by evaluating the goodness of fit between observed and predicted concentrations, ensuring that the pharmacokinetic parameters exhibited a low relative standard error, and examining the distribution of individual weighted residuals (IWRES) and normalized prediction distribution errors (NPDE). These metrics were collectively used to gauge the model's accuracy, precision, and predictive reliability.

3.3 Results

Table 3.1 summarizes the descriptive statistics for patient demographics and the radiomic biomarkers for this study. A total of 156 patients were included in this study, and the percentage of females was slightly higher than that of males (~52%). The subjects had a median age [min,

max] of 58 [21, 93] years and weight [min, max] of 81 [43.8, 139.3] Kg. Tobramycin was administered to treat 89 patients (57%), and the remainder received gentamicin. Among the significant CT-acquired abdominal biomarkers, psoas expanded muscle area and psoas expanded muscle density measured at the fourth lumbar vertebra (L4) and dorsal muscle group expanded muscle area (dmgexpmarea) measured at L2 were selected due to having the least missing values. The remaining biomarkers were analyzed at their L3 measures.

Table 3.1 Descriptive statistics of the dataset's patient demographics and morphomic variables.

Characteristic	Data	Range (min, max)
Number of subjects	156	
Age, Median (IQR) (Year)	58 (22)	21 – 93
Gender		
Female (%)	81 (51.92)	
Drug		
Tobramycin (%)	89 (57.05)	
Weight, mean (SD) (Kg)	81.0 (21.06)	43.8 – 139.3
Height, mean (SD) (cm)	170.5 (10.79)	147.3 – 203.2
Scr, Median (IQR) (mg/dL)	0.75 (0.57)	0.17 – 5.5
Psoas Muscle Area at L4, mean (SD) (mm²)	1953.7 (748.63)	455.5 – 4353.5
Psoas Muscle Density at L4, mean (SD) (HU)	46.28 (11.73)	0.24 – 72.64
Dorsal Muscle Group Area at L2, mean (SD) (mm²)	4030 (1123.49)	1024 – 7950
Fascial Area at L3, mean (SD) (mm²)	50625 (14102.61)	26787 – 112550
Visceral Fat Area at L3, mean (SD) (mm²)	12790 (10708.68)	40 – 49471
Subcutaneous Fat Density at L3, mean (SD) (mm²)	-89.03 (12.76)	-112.08 – -59.83
Bone Mineral Density at L3, mean (SD) (HU)	182.23 (63.03)	46.35 – 588.30
Vertebral Slab Height at L3, mean (SD) (mm)	32.78 (3.83)	20.46 – 42.13

Abbreviations: Scr: serum creatinine; IQR: interquartile range; SD: standard deviation; HU: Hounsfield Unit

Numerous structural models were investigated to fit the Pop-PK model of aminoglycosides. The model selection process is detailed in the Appendix Table A.3. A model featuring a 1-compartment structure, including an infusion administration with no delay, linear Cl model, and combined error model (lognormal distribution) showed superior fitting and was

set as the base model (AIC= 2617.07). The initial population estimates for the plasma model were 5.6 L/h for Cl and 56.81 L for volume of distribution (V). The best model was determined using AIC, goodness-of-fit, and the residual standard estimates (RSE%) of population parameters.

Three Morphomic Biological Age indices (BA_{Mor_1}, BA_{Mor_2}, BA_{Mor_3}), and Scr were found to exert the most significant influence on Cl and the drug type on the distribution of aminoglycosides. The expansion of the developed BA_{Mor} indices is provided in Table 3.2. Scr was incorporated into the models as a denominator of BA_{Mor}, which more closely mimicked the Cockcroft-Gault equation and resulted in a lower AIC than adding indices and Scr separately to the model. Table 3.3 summarizes the final Pop-PK models stratified by age index. Our results demonstrated that BA_{Mor}-based Pop-PK models had significantly lower AIC (2607.38, 2611.90, 2609.25) than the CA-based model (2618.49). Also, among the BA_{Mor}-based models, the model developed by BA_{Mor_3} exhibited the best fit to the aminoglycoside Cl. Using this index, we could also fit another CT-based biomarker, subcutaneous fat density (subcutfathu_mean), into the aminoglycoside Cl model. The final model developed by BA_{Mor_3} exhibited the lowest AIC, a reduction of approximately 19 points compared to the base model (from 2617.07 to 2598.33).

Table 3.2 Expansion of the models of biological morphomic age.

BA _{Mor_1}	$(Psoas\ muscle\ area * BMD) / Fascia\ area$
BA _{Mor_2}	$Psoas\ muscle\ area * Psoas\ muscle\ density * Vb\ slab\ height$
BA _{Mor_3}	$(Dorsal\ muscle\ group\ area * BMD) / Visceral\ fat\ area$

Note: Psoas muscle area: Psoas Expanded Muscle Area; BMD: Bone Mineral Density; Fascia area: Area of Fascia; Psoas muscle density: Psoas Expanded Muscle Density; Vb slab height: Vertebra Slab Height; Dorsal muscle group area: Dorsal Muscle Group Expanded Muscle Area; Visceral fat area: Visceral Adipose Tissue Area.

Table 3.3 Complete Pop-PK models of aminoglycoside clearance stratified by the type of age in Monolix.

	Model	AIC
	Base (1-compartment Combined-2)	2617.07
CA	Base + CA/creat_Cl	2618.49
	Base + 1/(CA*creat)_Cl	2609.99
	Base + 1/CA_Cl	2608.62
	Base + 1/(CA*creat)_Cl + drug_V	2602.12
BA _{Mor 1}	Base + BA _{Mor 1} _Cl	2612.44
	Base + BA _{Mor 1} /creat_Cl	2607.38
	Base + BA _{Mor 1} /creat_Cl + drug_V	2601.57
BA _{Mor 2}	Base + BA _{Mor 2} _Cl	2615.93
	Base + BA _{Mor 2} /creat_Cl	2611.90
	Base + BA _{Mor 2} /creat_Cl + drug_V	2601.71
BA _{Mor 3}	Base + BA _{Mor 3} _Cl	2613.97
	Base + BA _{Mor 3} _Cl + subcutfathu_Cl	2609.01
	Base + BA _{Mor 3} /creat_Cl + subcutfathu_Cl	2609.25
	Base + BA _{Mor 3} /creat_Cl + subcutfathu_Cl + drug_V	2598.33

¹ BA_{Mor 1}: $\frac{Psoasexpmuscareaa * BMD}{Fasciaarea}$; ² BA_{Mor 2}: $Psoasexpmuscareaa * PsoasexpmusHU * Vbslabheight$;

³ BA_{Mor 3}: $\frac{DMGexpmareaa * BMD}{VATarea}$; ⁴ subcutfathu: subcutaneous fat density

A summary of the population parameter estimates for the final model of each age type is provided in Supplementary Table 4. The population estimates for Cl and V in the best model were 2.62 L/h and 45.89 L, respectively. The predicted aminoglycoside Cl value in the best model was comparably lower than that with BA_{Mor 1}, BA_{Mor 2}, and CA (2.62 L/h vs. 5.80, 5.72, and 5.82 L/h). The power of BA_{Mor} indices for Cl ($\beta_{Cl_BA_{Mor}}$) was slightly lower than the power of CA for Cl ($\beta_{Cl_CA} = 0.19$) in their second decimal; however, the power of subcutaneous fat density in the final model was significantly greater than the CA ($\beta_{Cl_subcutfathu} = -0.93$). The fixed effects for the volume of distribution stratified by drug type in BA_{Mor}-based models were generally lower than the CA-based model, with BA_{Mor 3} having the lowest value for both drugs (45.89 L for gentamicin and 60.75 L for tobramycin) and

BA_{Mor_1} having the lowest RSE% (6.66 for gentamicin and 5.17 for tobramycin) among other types of age. The standard deviation (SD) of the random effects associated with V and Cl (Ω_V and Ω_{Cl}) were relatively similar across the four age types, with BA_{Mor_3} having a slightly lower Ω_V which indicates less variability among individuals. Regarding the error model parameters α and β , BA_{Mor_1} exhibited a lower α than CA, while BA_{Mor_2} and BA_{Mor_3} demonstrated a lower β than CA. Figure 3.1 represents the Visual predictive check (VPC) plot for the best aminoglycoside Cl model. The final Pop-PK model equation is as follows:

$$\log(Cl) (L/h) = 0.42 + 0.12 \times \log\left(\frac{BA_{Mor_3}}{Scr*300}\right) - 0.92 \times \frac{SubcutfatHU}{90} + \exp(\eta_{Cl}) \quad (1)$$

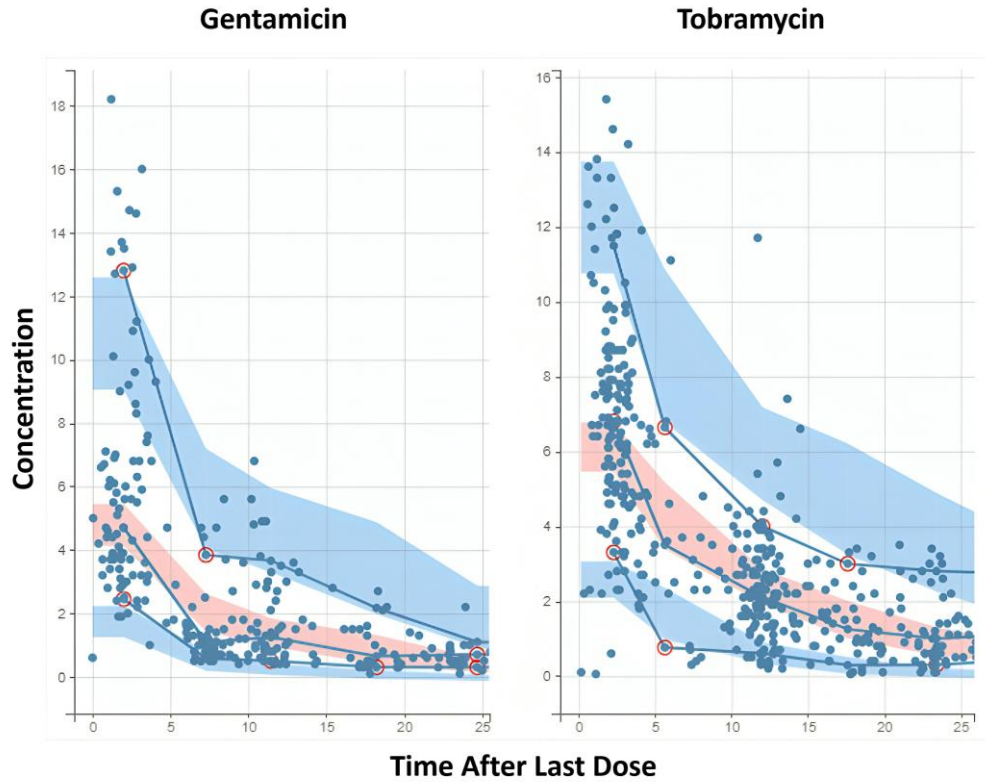


Figure 3.1 Visual predictive check (VPC) plot for the final aminoglycoside clearance model stratified by drug type. The observed data are depicted as dots, with prediction intervals shown as shaded areas. Red circles highlight observed data points that deviate from the predicted range, suggesting potential outliers.

In the next step, we removed Scr and drug type from the models to compare the effect of only CA and BA_{Mor} alone on aminoglycoside Cl. As expected, CA was significant in predicting aminoglycoside Cl. The results for BA_{Mor} indices revealed that BA_{Mor_1} and BA_{Mor_3} remained

significant in predicting aminoglycoside clearance even after withholding other covariates. However, BA_{Mor_2} lost its significance in the absence of other covariates. The CA-only Pop-PK model showed a comparably lower AIC than each BA_{Mor} index alone (2608.62 vs. 2612.44, 2615.93, and 2613.97). The model fit with CA was better than BA_{Mor_2} , equal to BA_{Mor_1} , and weaker than BA_{Mor_3} . Although the age indices were found significant in the BA_{Mor_1} - or CA-only Pop-PK models, each model was considered incomplete in Monolix® (version 2024R1; Lixoft, Antony, France), and required additional covariates such as drug type under volume of distribution, to be complete. Yet, we could successfully model a Pop-PK model for aminoglycoside Cl using *only* BA_{Mor_3} and subcutaneous fat density biomarkers. Table 13 provides the AIC of the three Pop-PK models for each age index: 1) Pop-PK model with an age index only; 2) Pop-PK model with CA or BA_{Mor} to creatinine ratio; 3) Pop-PK model with the ratio in model 2 and drug type under volume of distribution.

The summarized population parameter estimates for the age-only models after stratifying by age are provided in Appendix Table A.5. It reveals that the population estimates for volume were similar across the ages, whereas the model with BA_{Mor_3} remained the model with the lowest predicted Cl (2.62 L/h). After removing the effect of other covariates, the power of BA_{Mor} and CA indices for Cl ($\beta_{Cl_BA_{Mor}}$ and β_{Cl_CA}) persisted almost unchanged, except for BA_{Mor_2} , which was notably dropped (0.12 vs. 0.089). Similar to the final models for each age index, the SD of the random effects associated with V and Cl (Ω_V and Ω_{Cl}) were pretty similar across the four age types, and no meaningful association was found. Furthermore, although the error model parameter α for BA_{Mor_2} and BA_{Mor_3} were reduced, the RSE% of this parameter was increased in both indices.

3.4 Discussion

This study's objective was to identify improved predictors of kidney function to replace age and body composition. We examined how our new BA_{Mor} indices compare with CA in improving the precision of estimating kidney function in Pop-PK models. Our findings indicate that a leveraged BA can be used as a reliable alternative to CA to construct models that can improve the precision of estimating kidney function (Figure 3.2). The BA_{Mor} indices in this study were developed based on two rationales:

1. An index that contains age-related biomarkers for major body composition components including muscle, bone, and fat (BA_{Mor_1} and BA_{Mor_3}).
2. An index for muscle mass to reflect creatinine production by human muscles (BA_{Mor_2}).

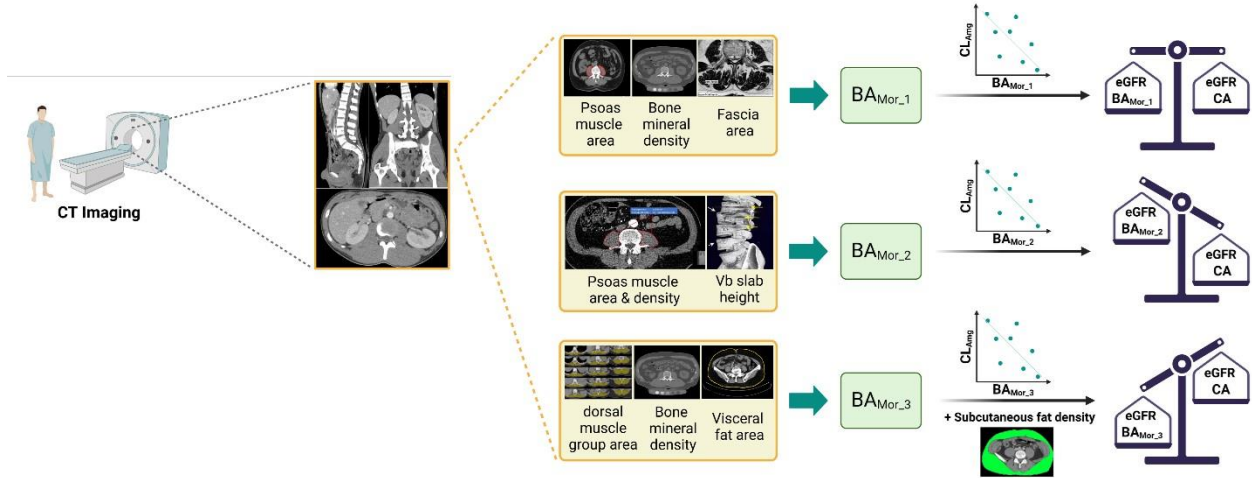


Figure 3.2 Schematic of comparing the effectiveness of three proposed BA_{Mor} with chronological age in predicting kidney function. (Made with BioRender.com)

Herein, we have provided a concise overview of the individual elements that make up each of the BA_{Mor} indices:

The kidney's long axis runs parallel to the lateral edge of the psoas muscle and is positioned in front of the quadratus lumborum muscle, a type of dorsal muscle situated deep in the lower back, adjacent to the intrinsic muscles of the spine^{227,228}. Due to this parallel alignment with the psoas muscle, the kidneys are oriented at an oblique angle, with the superior pole being more medial and posterior compared to the inferior pole²²⁸. This distinctive position supports the correlation between kidney function and BA_{Mor_1} and BA_{Mor_2} , which incorporated psoas muscle area and/or psoas muscle density in themselves, and BA_{Mor_3} , which involved dorsal muscle area.

BA_{Mor_1} integrates the psoas muscle area, bone mineral density (BMD), and fascia area. The psoas muscle is previously validated as a key indicator of overall muscle health and aminoglycoside Cl ^{121,229}. The BMD component reflects bone strength, which typically decreases with age²³⁰. It can also be associated with the vitamin D_3 activating function of kidneys indirectly, resulting in a faster loss of bone mass²³⁰. The fascia area acts as a structural component, influencing the functionality of muscles, tissues, and organs (i.e. kidneys)²³¹. This

index, therefore, provides a composite measure that combines aspects of body composition changes with increasing age, related to kidney function. The resulting measure seems to match CA in kidney function estimation.

BA_{Mor_2} is a composite index of muscle mass, muscle tissue quality, and skeletal health. Other than the psoas muscle area discussed earlier, this index involves psoas muscle density, which reflects the quality of muscle tissue, potentially indicating fat infiltration and overall muscle conditioning, as well as vertebral slab height, an indicator of cumulative life course biomechanical strain, that could be linked to kidneys as the kidney length should be between three and four vertebral body lengths^{232,233}. As this index was primarily intended to represent muscle mass and creatinine production, the poor performance was surprising when other covariates were withheld and suggests that although the index may seem fundamentally intuitive, combining these biomarkers might introduce variability that doesn't improve the prediction of kidney function as effectively.

BA_{Mor_3} combines the area of the dorsal muscle group with BMD, normalized by the visceral fat area. Combining the dorsal muscle area with BMD provides a robust indicator of musculoskeletal integrity, as dorsal muscles are crucial for posture and overall musculoskeletal health when it comes to complications such as muscle fatigue, back pain, and spinal dysfunction^{234,235}. Normalizing by visceral fat area adjusts for metabolic health, as high visceral fat can be associated with obesity and metabolic syndrome²³⁶. Most importantly, increased visceral fat accumulation leads to the accumulation of fat around the kidneys and within the renal sinus, which can ultimately result in increased intrarenal pressure, reduced renal blood flow, greater sodium reabsorption, glomerular hyperfiltration, and kidney dysfunction²³⁷. Thus, a high amount of visceral fat is a crucial indicator of kidney prognosis in patients with CKD^{238,239}. BA_{Mor_3}'s outperformance in our models suggests that this index captures a more holistic view of biological aging in body composition that better correlates with kidney function than CA or other BA_{Mor} indices.

While these findings are promising, the BA-structured models were not significantly different from the CA-structured model. While this study only focused on the radiomic biological age, alternate composite measures of BA should be tested for their significance with aging in the future. A more precise measurement of aging could improve kidney function estimation on the individual level, which is required for precision dosing and staging chronic

kidney disease. Our findings underscore composite age-informed radiomic biomarkers encompassing body composition from various dimensions to improve kidney function estimates better than CA. These findings are particularly important for populations requiring more precise dosing, such as older adults, patients with obesity, and patients with impaired kidney function, as radiomic biomarkers provide a nuanced and personalized assessment of changes in body composition with aging. Our results provide initial evidence, yet further positive evidence is needed to support the clinical implementation of radiomics in biologically informed drug dosing, particularly given existing barriers such as cost and the complexity of data analysis. Future research is encouraged to validate our findings in the target population and incorporate other biomarkers such as kidney-specific imaging metrics or epigenetic factors to refine the BA indices. Also, longitudinal studies assessing changes in BA indices over time and their correlation with kidney function decline could provide deeper insights into the kidney function changes with biological aging.

This study is, to our knowledge, the first to apply radiomic-based BA for a clinical pharmacology application. However, it has some limitations. First, this work is cross-sectional, and results cannot indicate a causal relationship. Second, the study has hospital-based selection bias (Berkson's bias) and may not be generalizable to other populations. Third, the sample size is small, consisting of only 156 patients. Future studies with larger sample sizes are needed to validate the robustness of these proposed indices. Next, the biological indices were primarily developed using measurements at the L3 vertebra level to simplify the analysis and overlooked potentially significant measurements at other vertebral levels. Next, we did not have access to any kidney-specific CT biomarkers, such as kidney parenchyma volume. We relied heavily on biomarkers representing major body composition components instead of kidney-specific imaging biomarkers. Finally, we used only Scr as the endogenous kidney biomarker and could not incorporate serum cystatin C into our models because it was unavailable for our patients. Regardless, this work provides evidence to support the use of radiomics in pharmacological investigations for stronger estimation of interindividual variability as well as control of related statistical confounding.

3.5 Conclusion

In conclusion, CT-derived morphomic age indices provided a slight improvement over chronological age in predicting aminoglycoside clearance as a surrogate of kidney function. Among the three indices developed, BA_{Mor_3} , incorporating dorsal muscle group area, BMD, and visceral fat area, demonstrated the best model fit, achieving a greater reduction in AIC than the CA model. These findings suggest that composite radiomic biomarkers capturing multiple dimensions of body composition aging can better reflect physiological variability relevant to renal drug elimination than CA alone, though larger prospective studies are needed to validate these indices and establish their clinical utility for precision dosing.

3.6 Appendix A: Supplemental Materials

Table 3.4 List of the morphomic variables and their pragmatic means in the final cohort (n=156)

Morphomic variable	Selected vertebra no.	Mean
Mean_ptsonborder_skin	L3	0.11761
Vbslabheight	L3	32.78
Bmdhuvbaligned	L3	182.23
Fascia2frontskin	L3	19.809
Vb2fascia	L3	114.87
Sp2backskin	L3	31.958
Bodydepth	L3	260.2
Fasciadepth	L3	213.6
Fasciaarea	L3	50625
Visceralfatarea	L3	12790
Visceralfathu_mean	L3	-86.70
Subcutfatarea	L3	18731.42
Subcutfathu_mean	L3	-89.03
Dmgexpmarea	L2	4030
Dmgndmarea	L2	2470.6
Dmgldmarea	L2	979.4
Dmgexpmmeanhu	L2	38.651
Expmuscarearea	L3	13185
Hdmarea	L3	242.31
Ndmarea	L3	7517.9
Ldmarea	L3	3638.0
Vldmarea	L3	1791.2
Expmuscmmeanhu	L3	34.6695
Total_psoas_expmaarea	L4	1953.7
Total_psoas_ndmarea	L4	1453.17
Total_psoas_ldmarea	L4	367.665

Avg_psoas_expmmmeanhu	L4	46.2854
Wallpcent_calc	L3	14.661

Table 3.5 List of Potential Morphomic Parameters Extracted by Vertebral Level

Body Measures	
bodydepth	Front-to-back body distance (aligned to body habitus) (mm)
bodywidth	Left-to-right body distance (aligned to body habitus) (mm)
vbslabheight	Height of body slab at the vertebra (mm)
mean_ptsonborder_skin	Average number of points on the skin border detected during image segmentation.
sp2backskin	Distance - posterior tip of spinous process to back skin (central back fat depth) (mm)
vb2fascia	Distance - anterior vertebral body to prevertebral fascia (mm)
fascia2frontskin	Linear distance from anterior fascia to anterior skin (central sub-cutaneous depth) (mm)
fasciadepth	thickness or depth of the fascial layer from the superficial to deep fascia (mm)
Muscle (skeletal) Measures	
expmuscarearea	Cross sectional area of the muscle pixels (-29 to 150 HU) between the muscle wall and fascia boundaries (excluding filled bone, spinal canal, and disk) (mm ²)
expmuscmehnu	Mean pixel intensity of the skeletal muscle pixels (-29 to 150 HU)
vldmarea	Cross sectional area of the skeletal muscle falling in a very low density muscle HU range (-29 to -1) (mm ²)
ldmarea	Cross sectional area of the skeletal muscle falling in a low density muscle HU range (0 to 30) (mm ²)
ndmarea	Cross sectional area of the skeletal muscle falling in a normal density muscle HU range (30 to 100) (mm ²)
hdmarea	Cross sectional area of the skeletal muscle falling in a high-density muscle HU range (100 to 150) (mm ²)

Muscle (Psoas) Measures	
Total_psoas_expmarea	(PMA) Cross sectional area of the muscle pixels (-29 to 150 HU, expanded range) within the perimeter of the left and right psoas. (mm ²)
Total_psoas_ndmarea	Cross sectional area of the psoas falling in a normal density muscle HU range (31 to 100) (mm ²)
Total_psoas_ldmarea	Cross sectional area of the psoas falling in a low-density muscle HU range (0 to 30) (mm ²)
Avg_psoas_expmmeanhu	Mean pixel intensity of all pixels inside the total psoas area. (HU)
Muscle (Dorsal muscle group) Measures	
Dmgexpmarea	Cross sectional area of the muscle pixels (-29 to 150 HU, expanded range) within the DMG perimeter. (mm ²)
Dmgndmarea	Cross sectional area of the DMG falling in a normal density muscle HU range (31 to 100) (mm ²)
Dmgldmarea	Cross sectional area of the DMG falling in a low density muscle HU range (0 to 30) (mm ²)
Dmgexpmmeanhu	Mean pixel intensity of muscle pixels (-29 to 150 HU) within the DMG boundary. (HU)
Fat Measures	
subcutfatarea	Area between skin and fascia meeting fat density thresholds (-205 to -51 HU) (mm ²)
visceralfatarea	Area inside fascia meeting fat density thresholds (-205 to -51 HU) (mm ²)
subcutfathu	Median pixel intensity of fat-intensity pixels (-205 to -51 HU) in the subcutaneous region.
visceralfathu	Median pixel intensity of fat-intensity pixels (-205 to -51HU) inside the visceral cavity.
Spine (trabecular bone) Measures	

bmdhuvbaligned	Average pixel intensity (in CT Hounsfield Units) inside central bone core sample (HU)
Miscellaneous	
wallpct_calc	Calculated percentage of the abdominal aortic wall that is occupied by calcification (%)

Table 3.6 Summary of key models leading to selection of the final model, reported based on AIC and software proposal.

No.	Model expansion	AIC	Findings	Note
1	Base(constant)	3117		
2	Base(proportional)	2622.66		
3	Base(combined1)	2622.74		
4	Base(combined2)	2617.07	Best model	Set as base model
5	Base + log(Age/50)_CL	2608.62	- Significant reduction in AIC - Beta_CL_logAge: -0.39 Proposal: add drug V	
6	Base + log(1/(Age*creat)/0.03)_CL	2609.99	- Beta_CL_Index: 0.19 - Proposal: keep it and add psoas_expmuscarea to CL	Can we find any morphomic covariate with comparable AIC?
6.1	Base + log(1/(Age*creat)/0.03)_CL + drug_V	2602.12	- Proposal: keep it and add psoas_expmuscarea to CL	Current model is NOT complete
7	Base + log((psoasexparea2fasciaarea)/0.04)_CL	2614.52	- AIC worsened - Beta_CL_Index: 0.21 - Proposal: Model6+psoas	
8	Base + log(psoasexpmuscarea/2000)_CL	2616.54	- Beta_CL_Index: 0.18 - Proposal: Model6+psoas	

9	Base + log(psoasexpmuscareat/2700)_CL	2609.48	- Beta_Cl_Index: 0.23 - RSE for “a” NOT intuitive - Proposal: keep the model and add Drug_V	Higher strength beta_Cl_Index: 0.23
10	Base + log(dmgeexpmuscareat/5500)_CL	2611.64	- Beta_Cl_Index: 0.21 - Parameter estimates good Proposal: remove index, add bmd_CL and drug_V_CL	
10.1	Base + log(dmgeexpmuscareat/3800)_CL	2624.06	Proposal: remove dmg, add psoasexpmuscareat	Not a good index alone
11	Base + log(bmd2creat/250)_CL	2610.2	- Beta_Cl_Index: 0.18 - Proposal: keep it and add drug_V	
11.1	Base + log(bmd/180)_CL	2612.12	- Beta_Cl_Index: 0.29 Proposal: remove the index, add bmd_CL and drug_V_CL	Weight of bmd is pretty high
11.2	Base + log(bmd/180)_CL + log(Age/50)_CL	2609.23	Proposal: remove bmd and keep age, add drug_V_CL	Weight of bmd decreases in the presence of age
12	Base + log(expmuscareat/18300)_CL	2613.05	- AIC worsened - Proposal: remove index and add logAge_CL	Higher strength beta_Cl_Index: 0.22
13	Base + (wallpcent_calc2creat)/20_CL	2618.12	- AIC worsened, beta reduced dramatically - Proposal: remove index, add logAge_CL and drug_V	Could not do log-transform for wallpcent_calc

14	Base + log(psoasexpmuscare / psoasexphu2creat/85)_CL	2615.88	- AIC worsened - Proposal: remove index, add logAge_CL and drug_V	Muscle area to density not working
15	Base + log(psoasexparea*bmd)2creat/555200)_CL	2607.08	- Lowest AIC so far - Beta_CL_Index: 0.18 - parameter a RSE: 74% - Proposal: keep it w/o adding anything else	Good index.
16	Base + log(psoasexparea*bmd)/VATarea 2creat/320)_CL	2612.62	- AIC increased - Beta_CL_Index: 0.074 - Proposal: keep the index and add SubQhu_CL	Adding SubQ is interesting and a good sign, hopefully be able to add a better fat index to the model * also try VAT/SAT
17	Base + log(psoasexparea*bmd)/VATarea 2creat/320)_CL + subQhu/90_CL	2607.04	Proposal: keep the model	Actually, very similar to model 15
18	Base + (psoasexparea*bmd)/ (VATarea*subQhu)2creat/5)_CL	2618.2	Proposal: remove the index, add bmd_CL and logAge_V	Could not log- transform subQhu, so removed log for the entire index but it didn't work.
19	Base + log(psoasexparea*bmd)/Fasciaarea 2creat/10)_CL	2607.38	- AIC good - Beta_CL_Index: 0.16 - Proposal: keep the index and add drug_V	

19.1	Base + log(psoasexparea*bmd)/Fasciaarea 2creat/10)_CL + drug_V	2601.57	Model fit is pretty good! Proposal: Keep the model	One potential final model
20	Base + log(psoasexparea)/Fasciaarea 2creat/0.05)_CL	2610.85	- Parameter estimates pretty good - Beta_Cl_Index: 0.19 - Proposal: keep the model	Bmd improves AIC, but reduces beta
21	Base + log(expmuscare*a*bmd)/Fasciaarea 2creat/80)_CL	2609.35	- parameter a RSE: 109% - Beta_Cl_Index: 0.16 - Proposal: keep the index and add logAge_CL	Psoasexpmusc is better than expmsuc
22	Base + log(expmuscare*a*bmd2creat/3580000)_CL	2608.11	- Beta_Cl_Index: 0.19 - Proposal: keep the index and add drug_V	
23	Base + log(expmuscare/fasciaarea2creat/0.4)_CL	2612.35	Proposal: remove the index and add logAge_CL	This index is not working
24	Base + log(VAT/SAT2creat)_CL	2618.17	Proposal: remove the index, add bmd_CL and drug_V_CL	VAT/SAT is an important morphomic index but it is not working here.
25	Base + log(psoasexpmuscare*a*psoasexp *vbslabheight2creat/4200000)	2611.9	Proposal: Keep the index and add drug_V Beta_Cl index: 0.13	
25.1	Base + log(psoasexpmuscare*a*psoasexp *vbslabheight2creat/4200000) + drug_V	2601.71	Model fit is pretty good!	Another potential final model

			Proposal: Keep the model	
26	Base + log(weight2creat/120)	2616.54	Proposal: remove the index and add bmd_CL, drug_CL and logAge_V	At least, morphomics works better than weight.
Additional morphomics ratio from articles				
27	Base + log(psoasexparea*bmd)/Fasciaarea*fasciadept(2creat/10)_CL	2609.02	Proposal: keep the model as it is. - RSE for “a”: 82	
28	Base + log(dmgl/dmgnd/creat)	2618.25	- Not a good model - Proposal: remove index, add logAge_V_CL	Found this ratio at UM morphomics website
29	Base + log(dmexp*bmd/VATarea/creat)/580)	2612.38	- Parameter estimates good - Proposal: keep index, add subQhu/90_CL and drug_V	
29.1	Base + log(dmexp*bmd/VATarea/creat)/580) + subQhu/90	2609.25	- Proposal: keep the model - Drug_V significant	
29.2	Base + log(dmexp*bmd/VATarea/creat)/580) + subQhu/90 + drug_V	2598.33	- Lowest AIC - Proposal: keep the model - No other significant covariates	Another potential final model
Modeling morphomic indexes ONLY				
30	Base+log(morphomic_index1)_CL	2612.44	Higher AIC than Age Proposal: keep it and add age_V	Parameter estimate pretty good

31	Base+log(morphomic_index2/3000000)_CL	2615.93	Proposal: remove it, add 1/(age*creat)_CL, drug_V and psoasexparea CL	
32	Base+log(morphomic_index3)_CL	2613.97	Proposal: keep it and add subQhu CL	
32.1	Base+log(morphomic_index3)_CL+ subQhu_CL	2609.01	Proposal: keep the model as it is Beta_CL_index: 0.12 Beta_CL_subQhu: - 0.92	
33	Base+log(psoasarea.bmd/300000)_CL	2612.69	Beta_CL_index: 0.17 Proposal: keep it and add 1/(age*creat) CL	
34	Base+log(age/creat/80)_CL	2618.49	- Beta_CL_index: - 0.016 - RSE for index is insane! - Proposal: remove index, add bmd_CL, drug CL, age V	
34.1	Base+log(age/creat/80)_CL + drug_V	2608.97	Proposal: remove index and add bmd CL	

Table 3.7 Final population PK model parameters for the aminoglycosides stratified by age index.

[illegible]

a	0.049 (0.023)	46.7	0.12 (0.043)	34.9	0.13 (0.038)	30.5	0.069 (0.037)	53.5
b	0.4 (0.013)	3.38	0.38 (0.014)	3.59	0.39 (0.014)	3.67	0.4 (0.014)	3.51

Table 3.8 Final population PK model parameters for the aminoglycosides built upon age type ONLY.

Model number	30 (BA _{Mor 1})		31 (BA _{Mor 2})		32.1 (BA _{Mor 3})		5 (CA)	
	Value (SE)	RSE%	Value (SE)	RSE%	Value (SE)	RSE%	Value (SE)	RSE%
Fixed effects								
V _{pop}	56.75 (2.52)	4.45	56.75 (2.7)	4.75	56.11 (2.56)	4.57	56.28 (2.44)	4.33
Cl _{pop}	4.18 (0.48)	11.5	5.69 (0.27)	4.66	2.62 (1.04)	39.8	5.69 (0.25)	4.38
Beta _{cl} (BA _{Mor} /creat)	0.16 (0.059)	36.6	0.089 (0.051)	57.6	0.12 (0.038)	31		
Beta _{Cl} (subcutfathu)					-0.92 (0.38)	41.6		
Beta _{Cl} (CA/creat)							-0.39 (0.12)	31.6
Standard deviation of the random effects								
Omega _V	0.4 (0.039)	9.89	0.39 (0.04)	10.1	0.39 (40.15)	9.93	0.38 (0.036)	9.57
Omega _{Cl}	0.5 (0.032)	6.41	0.51 (0.034)	6.57	0.49 (0.032)	6.42	0.49 (0.031)	6.38
Error model parameters								
a	0.049 (0.022)	45	0.065 (0.065)	101	0.085 (0.085)	55.1	0.07 (0.038)	54.6
b	0.39 (0.013)	3.37	0.4 (0.015)	3.75	0.4 (0.015)	3.77	0.4 (0.014)	3.53

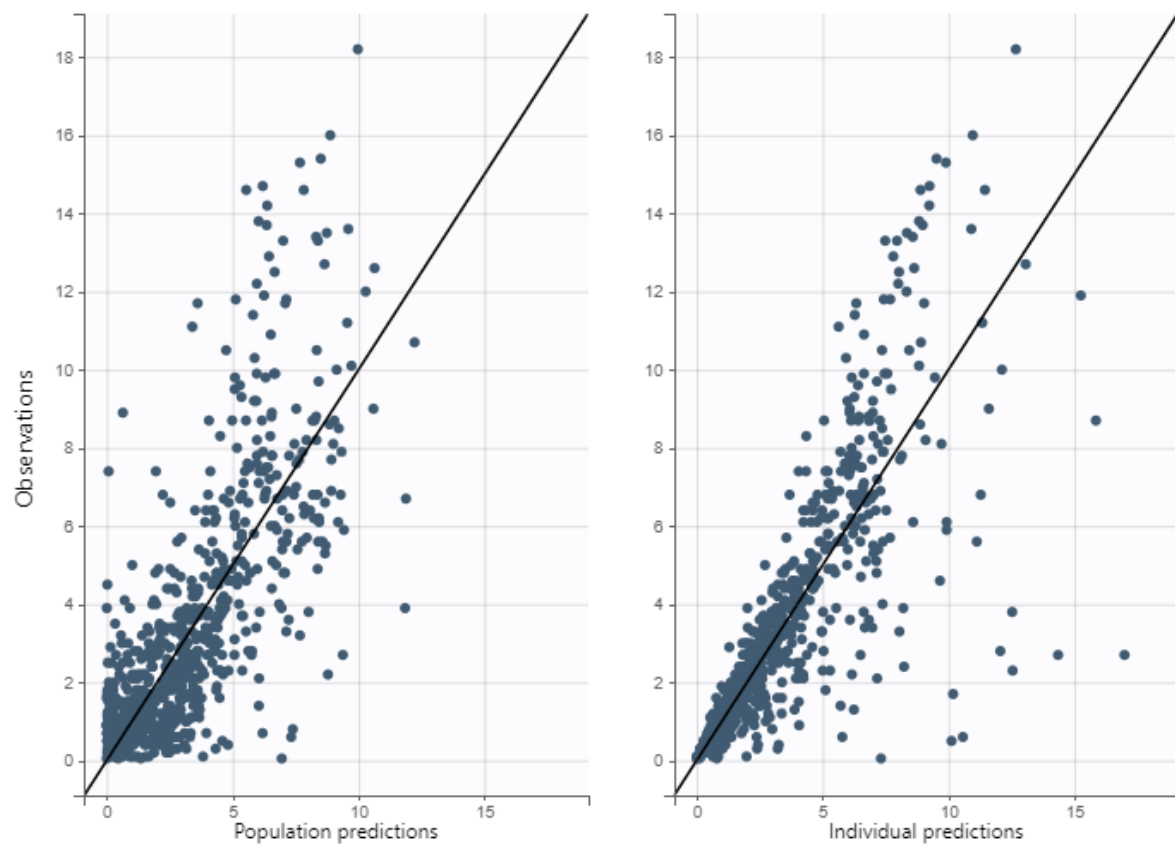


Figure 3.3 Observed versus population and individual predicted concentrations for the final model.

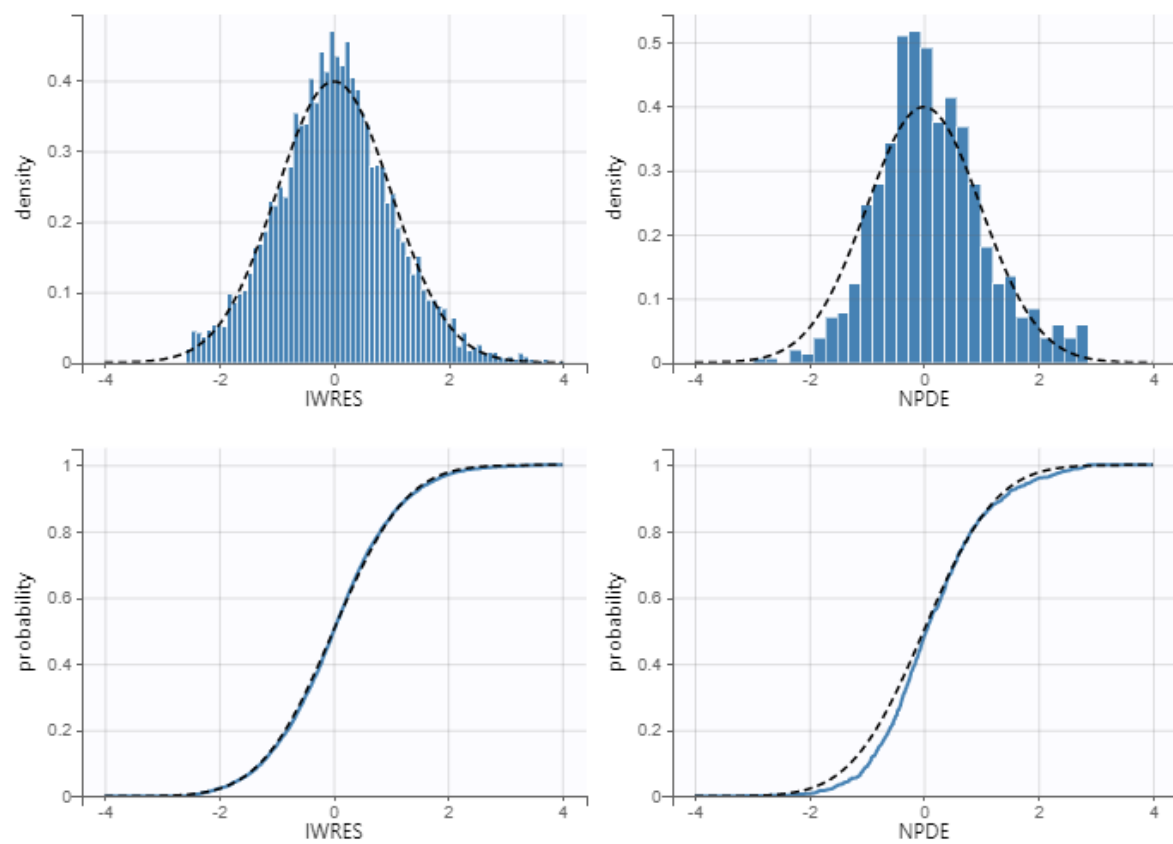


Figure 3.4 Distribution of the individual weighted residuals and nonparametric distributional errors for the final model.

Chapter 4 Investigating Epigenetic Age and Metabolic Age as Potential Biomarkers of Kidney Function

4.1 Introduction

In pharmacokinetic modeling, age is frequently treated as a key covariate intended to capture age-dependent changes in drug clearance given its correlation with organ function. For years, it has been widely assumed that human metabolic rate and organ function decline at a consistent pace after the age of 40 years. However, recent studies suggest that this relationship is not as straightforward^{240–242}. Metabolic rate is not solely determined by chronological age; rather, it is influenced by multiple factors including body weight, size, composition, tissue development, overall health, lifestyle, cultural and ethnic background, and geographic location^{243,244}. Additionally, biological sex, exposure to stressors, and other individual variables contribute to metabolic variations²⁴⁵. This complexity underscores why clinicians rely on metabolic biomarkers such as Basal Metabolic Rate (BMR) to assess metabolic age, as it often diverges significantly from chronological age²⁴³.

BMR and resting metabolic rate (RMR) are often used interchangeably, though they represent distinct physiological measures²⁴⁶. BMR refers to the minimum caloric requirement necessary to sustain basic physiological functions at rest, whereas RMR, also known as resting energy expenditure (REE) reflects the actual number of calories expended while at rest^{6,247}. Despite their slight differences, RMR is generally considered a reliable approximation of BMR, with variations between the two typically within 10%²⁴⁸. BMR and RMR can be transformed into measures of metabolic age using simple mathematical equations²⁴⁹. Metabolic age can be assessed through various methods such as: bioimpedance analysis, which estimates body composition and BMR by transmitting a low-intensity electrical current through the body to measure tissue resistance²⁵⁰; indirect calorimetry, which calculates RMR by analyzing oxygen consumption and carbon dioxide production²⁵¹; and incorporating body fat percentage measured via Dual-Energy X-ray Absorptiometry (DEXA) into standardized equations validated against the general population²⁵².

The growing emphasis on biological age as a more precise indicator of aging is driving efforts to replace chronological age with this novel biomarker^{253,254}. In this context, metabolic age serves as an attempt to represent an individual's biological age via health and fitness markers^{249,255}. Currently, peer-reviewed studies on metabolic age remain limited, and the concept is not widely recognized within the medical community. A general guideline suggests that if an individual's metabolic age is lower than their chronological age, it indicates a more efficient metabolic rate, often associated with higher muscle mass and greater caloric expenditure at rest²⁵⁶. Conversely, if metabolic age is higher than chronological age, it may suggest a need for lifestyle modifications, such as improved nutrition and increased physical activity, to enhance metabolic function. Accordingly, it is presumed that aging adults with age-related conditions such as type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) may have a higher metabolic age than their healthy peers^{257,258}. Yet, further research is necessary to determine whether metabolic age can enhance personalized dosing strategies in well-designed clinical studies.

CKD is influenced by several well-established risk factors, including obesity, hypertension, diabetes, and metabolic abnormalities, all of which are associated with alterations in basal metabolic rate (BMR)^{259,260}. Additionally, advanced CKD is often characterized by low muscle mass and malnutrition, frequently accompanied by systemic inflammation²⁵⁹. However, it remains unclear whether metabolic rate is affected by CKD itself or by the changes in body composition driven by aging and associated comorbidities. Renal oxygen consumption increases proportionally with glomerular filtration rate (GFR), and in healthy individuals, the kidneys contribute approximately 7% of REE²⁶¹. Evidence now indicates that REE is significantly lower in non-dialyzed patients with reduced estimated GFR (eGFR)^{262,263}. While this decline in REE is generally assumed to persist in patients with end-stage renal disease (ESRD), recent studies demonstrated that REE per unit of body weight is elevated in ESRD²⁶⁴. Despite these findings, research exploring the relationship between metabolic rate and kidney function remains limited and inconsistent, with some studies reporting no direct association between reduced kidney function and metabolic rate²⁵⁹.

Iohexol clearance is a recognized standard method for measuring GFR and kidney function²⁶⁵. Following intravenous administration, it is excreted unchanged by glomerular filtration without undergoing metabolism, deiodination, or biotransformation, with

approximately 90% of the administered dose eliminated within 24 hours ²⁶⁶. This pharmacokinetic profile makes iohexol an ideal marker for assessing true kidney function. Therefore, the objective of this study was to investigate the correlation between biological metabolic age using RMR and kidney function (iohexol clearance), in adult patients with and without T2DM. Figure 4.1 illustrates the study objective schematically, showing the hypothesized relationship between metabolic age progression, body composition changes assessed by medical imaging, and corresponding kidney function across different GFR categories.

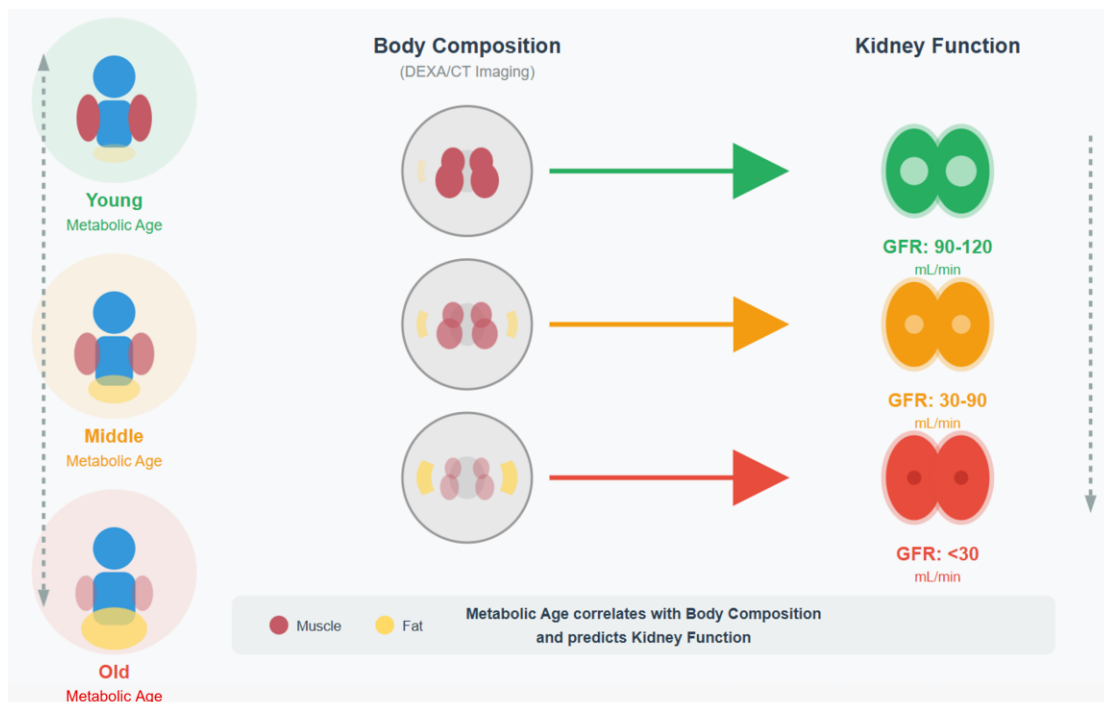


Figure 4.1 Conceptual framework linking metabolic age, body composition, and kidney function. Created using Claude AI (Anthropic).

4.2 Methods

4.2.1 Study Design and Patient Population

This open-label, single-dose pharmacokinetic study entitled, “Projecting Age-related Changes in Kidney Elimination (Kidney-PACE) study” consisted of a 6-hour study visit to investigate the relationship between metabolic age and iohexol clearance, the gold standard

method for measuring kidney function. Adult participants with a history of receiving care at Michigan Medicine or the University of Michigan's Elizabeth Weiser Caswell Diabetes Institute with a range of eGFRs, calculated by the 2021 CKD-EPI serum creatinine (SCr) equation, were contacted for screening and enrollment. Participants were equally divided into two groups: 12 individuals diagnosed with Type 2 diabetes and 12 controls without Type 2 diabetes.

To be eligible, participants had to meet the following criteria: be between 40 and 70 years old, have an eGFR between 30 and 120 mL/min, and have a body mass index (BMI) between 27 and 35 kg/m². Exclusion criteria included a history of allergic reactions to iodinated contrast agents, iodine, or shellfish; thyroid conditions such as multinodular goiter, Graves' disease, autoimmune thyroiditis, thyroid storm, or autonomously functioning thyroid nodules; and myasthenia gravis. Participants were also excluded if they were taking diuretics, beta-blockers, chemotherapy, or nephrotoxic medications. Additional exclusions applied to pregnant or breastfeeding women, individuals who had experienced acute kidney injury within the past six months, those with sickle cell disease, and individuals with indwelling nephrostomy tubes. A complete list of eligibility criteria can be found in Appendix Table B.1.

The study received approval from the Institutional Review Board of the University of Michigan Medical School (IRBMED) (Study ID: HUM00251313). All participants provided electronically signed informed consent before undergoing any study-related procedures. Study visits were conducted at the Michigan Diabetes Research Center–Clinical Research Unit (MDRC–CRU) located in Ann Arbor, Michigan.

4.2.2 Drug Administration and Pharmacokinetic Sampling

A schematic overview of the Kidney-PACE study visit is shown in Figure 4.2 After fasting overnight for at least 10 hours, participants received a single intravenous bolus injection of 2.5 mL iohexol solution (647 mg/mL; Omnipaque-300). Blood samples (10 mL each) were collected at the following time points: before dosing (0 min), and at 30, 60-, 180-, 240-, and 300-minutes post-injection. Samples were collected in red-cap serum separator tubes (BD, Franklin Lakes, NJ, USA).

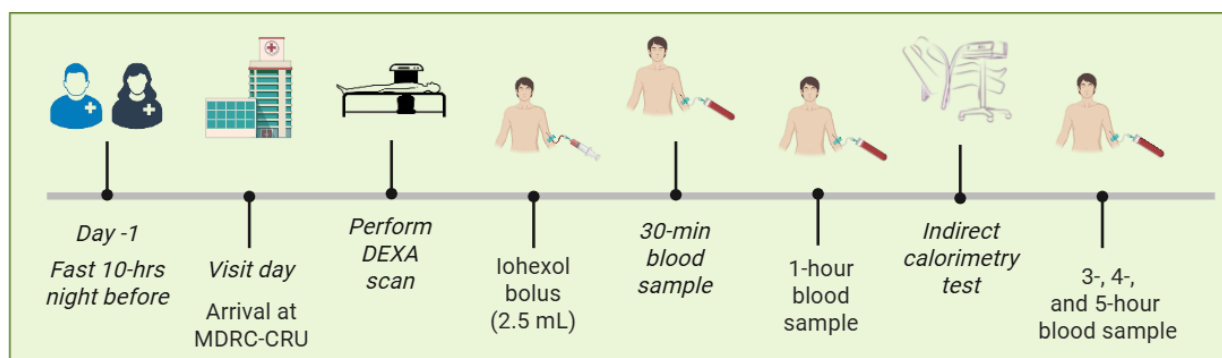


Figure 4.2 Kidney-PACE study visit timeline showing sequence of procedures and blood sampling schedule following iohexol administration. Created in <https://BioRender.com>.

Following a 30-minute clotting period at room temperature, samples were centrifuged at $2,000 \times g$ for 10 minutes at 4°C to separate the serum. Each sample was then divided into three aliquots and stored at -80°C . A separate 5 mL portion of the pre-dose sample was saved for measuring SCr and cystatin C (CysC). These measurements were performed at Michigan Medicine Laboratories (MLabs) using a colorimetric rate assay for SCr and a particle-enhanced immunoturbidimetric assay for CysC.

4.2.3 Body Composition Assessment Testing and Calculating Metabolic Age

After collecting the vital signs, body composition was measured using a LUNAR iDXA device equipped with enCORE v18 software (GE Medical Systems Ultrasound & Primary Care Diagnostics, LLC). During the procedure, a wide scanning arm emitted a narrow beam of low-dose X-rays that moved across the participant's body to capture full-body images. This allowed for a detailed evaluation of muscle, fat, and bone components. Each scan lasted between 10 and 20 minutes.

The RMR test was performed following the 60-min blood draw. RMR was assessed using indirect calorimetry (TrueOne 2400; Parvo Medics, Sandy, UT), a standard technique that estimates energy expenditure by measuring oxygen consumption and carbon dioxide production. During the test, participants lay supine with a ventilated canopy hood positioned over their head and upper torso. A blower drew ambient air through the hood at a constant flow rate, and the air was continuously analyzed by the connected metabolic cart to measure oxygen consumption and

carbon dioxide production. The breath measurement procedure took 30 minutes, with the latter 20 minutes of steady-state data used for analysis to ensure accurate metabolic measurements. Participants were required to avoid exercise for 24 hours before the appointment and to remain relaxed both in the morning and while traveling to the clinic to help ensure accurate and reliable RMR measurements.

Metabolic age was calculated using four methods. Three of these were based on established equations: the original Harris-Benedict equation (1918), the revised Harris-Benedict equation by Roza and Shizgal (1984), and the Mifflin-St Jeor equation (1990) (Table 4.1). The last method estimated metabolic age based on each individual's total body fat percentage (measured by DEXA), weight, and height, by comparing these values to standardized reference data for average men and women from the general population ²⁴⁹.

Table 4.1 Expansion of the utilized equations for calculating metabolic age

BA _{Met} type	Equation	Sex	Expansion
BA _{Met_1}	Original Harris–Benedict	M	$[(13.7516 * \text{weight_kg}) + (5.0033 * \text{height_cm}) - \text{RMR} + 66.473] / 6.755$
		F	$[(9.5634 * \text{weight_kg}) + (1.8496 * \text{height_cm}) - \text{RMR} + 655.0955] / 4.6756$
BA _{Met_2}	Revised Roza–Shizgal	M	$[(13.397 * \text{weight_kg}) + (4.799 * \text{height_cm}) - \text{RMR} + 88.362] / 5.677$
		F	$[(9.247 * \text{weight_kg}) + (3.098 * \text{height_cm}) - \text{RMR} + 447.593] / 4.330$
BA _{Met_3}	Revised Mifflin–St Jeor	M	$[(10 * \text{weight_kg}) + (6.25 * \text{height_cm}) - \text{RMR} + 5] / 5$
		F	$[(10 * \text{weight_kg}) + (6.25 * \text{height_cm}) - \text{RMR} - 161] / 5$

* **Abbreviations** RMR: resting metabolic rate; M: male; F: female; kg: kilograms, cm: centimeters.

4.2.4 Epigenetic Age Sample Collection

At baseline, whole blood samples (10 mL) were collected from participants in green-top Zymo DNA/RNA Shield Blood Collection Tubes. Samples were aliquoted (2 mL) and shipped to Zymo Research Corporation, (Irvine, CA) for preliminary BA_{Epi} analysis. DNA extraction and methylation profiling were performed using the Illumina Infinium MethylationEPIC BeadChip array. BA_{Epi} was calculated using the Horvath Clock algorithm, which quantifies the pace of biological aging from DNA methylation patterns.

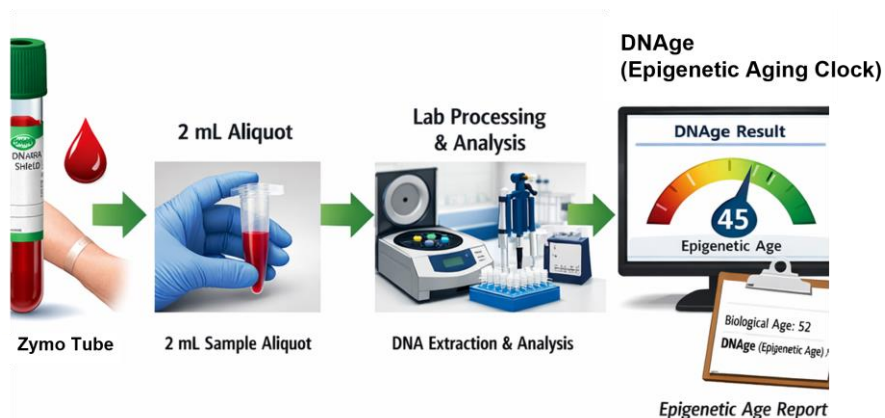


Figure 4.3 Schematic overview of epigenetic age (DNAge) assessment methodology from sample collection through laboratory analysis.

4.2.5 Quantification of Iohexol in Plasma

Serum concentrations of iohexol were measured using liquid chromatography–mass spectrometry (LC-MS). High-purity solvents (acetonitrile, methanol, and formic acid) were purchased from Fisher Chemical (MI), while the analyte iohexol was obtained from Sigma-Aldrich (MO). The internal standard, iohexol-d5 (purity >99%), was sourced from Cayman Chemical (MI), and all water used in the analysis was purified using a Millipore system (MA).

For sample preparation, 20 μL of plasma was mixed with 480 μL of methanol containing 0.72 μg of iohexol-d5 (1.5 $\mu\text{g}/\text{mL}$). The mixture was vortexed for 10 minutes and then centrifuged at 10,000 rpm for another 10 minutes. From the resulting supernatant, 50 μL was diluted with 100 μL of water, vortexed again for 10 minutes, and centrifuged at 4,000 rpm for 10

minutes. The final supernatant was transferred to a 96-well autosampler plate for LC-MS analysis.

Calibration standards were prepared by spiking pooled blank human plasma (Valley Biomedical, Winchester, VA) with known amounts of iohexol, covering a concentration range of 0.1 to 500 µg/mL. Quality control (QC) samples at low, mid, and high concentrations were prepared separately and included at multiple points in the run to monitor precision and accuracy.

Chromatographic separation was carried out using a Shimadzu LC-20AD HPLC system (Kyoto, Japan) equipped with a Phenomenex Kinetex® Polar C18 column (2.6 µm, 50 × 4.6 mm I.D.) maintained at 25°C. Detection was performed on an AB Sciex QTrap 4500 mass spectrometer (ABI-Sciex, Canada) using positive-ion electrospray ionization in multiple reaction monitoring (MRM) mode. Data was processed with Analyst software (version 1.6).

4.2.6 Population Pharmacokinetic Modeling

Population pharmacokinetic (Pop-PK) modeling was carried out using MonolixSuite 2024R1 (Lixoft SAS, France), a nonlinear mixed-effects modeling software. Selection of the base structural model was based on the fit of iohexol concentration-time data, evaluated using the Akaike Information Criterion (AIC), residual diagnostics, and trends in observed versus predicted values. Covariate selection followed a stepwise approach, guided by improvements in AIC. A range of demographic, clinical, and laboratory variables was explored as potential covariates. The full list of variables is available in Appendix Table B.6.

The final model's performance and robustness were assessed through both graphical and statistical methods, including goodness-of-fit plots, bootstrap resampling, and visual predictive checks. Statistical significance was defined a priori as a p-value less than 0.05. All summary statistics and visualizations were generated using R (v4.4.1; R Core Team 2024; <http://www.R-project.org>)

4.3 Results

A total of 24 adult volunteers were evenly divided into two groups: individuals diagnosed with T2DM and those without T2DM. Descriptive statistics for the study population are summarized in Table 4.2. The cohort predominantly consisted of Caucasian males, with 15

participants (62.5%) identifying as male and 19 (79.2%) identifying as Caucasian. The median age was 61.5 years (interquartile range [IQR]: 11.75), and the BMI was 30.57 kg/m² (standard deviation [SD]: 2.42). The mean RMR measured via indirect calorimetry was 1539 kcal/day (SD: 222.29), closely aligning with the DEXA-derived estimate of 1535 kcal/day (SD: 227.72). Notably, all four metabolic age indices exceeded the median chronological age, suggesting that the study participants were metabolically older than their age-matched peers. The median (IQR) values for each metabolic age measure were as follows: BA_{Met_IC1}, 90.25 (19.08); BA_{Met_IC2}, 96.82 (25.74); BA_{Met_IC3}, 80.89 (28.25); and BA_{Met_DEXA}, 89.00 (14.00).

Table 4.2 Descriptive statistics of patient demographics for the Kidney-PACE study.

	Total (N=24)		T2DM Arm (N=12)		Non-T2DM Arm (N=12)	
Characteristic	Data	Range	Data	Range	Data	Range
Age, median (IQR) (Years)	61.5 (11.75)	44 – 70	62.5 (8)	51 – 68	59 (15.75)	44 – 70
Sex						
Male (%)	15 (62.5)		8 (66.67)		7 (58.34)	
Race						
Caucasian (%)	19 (79.2)		8 (66.67)		11 (91.67)	
BMI, mean (SD) (Kg/m ²)	30.57 (2.42)	24 – 33.9	31.60 (1.78)	28.80 – 33.90	29.53 (2.59)	24 – 33.4
Total body fat, mean (SD) (%)	38.33 (7.20)	21.8 – 54.1	37.38 (7.83)	21.80 – 48.60	39.28 (6.72)	31.80 – 54.10
RMR _{IC} , mean (SD) (Kcal/day)	1539 (222.29)	1102 – 1855	1538 (207.39)	1102 – 1845	1541 (245.56)	1115 – 1855
RMR _{DEXA} , mean (SD) (Kcal/day)	1535 (227.72)	1106 – 1965	1596 (215.83)	1196 – 1965	1474 (231.76)	1106 – 1805
BA _{Met_IC1} , median (IQR) (Years)	90.25 (19.08)	40.81 – 122.5	93.34 (31.95)	59.84 – 122.5	87.67 (22.22)	40.81 – 103.47
BA _{Met_IC2} , median (IQR) (Years)	96.82 (25.74)	36.40 – 133.49	98.55 (34.27)	62.81 – 133.49	92.64 (26.59)	36.40 – 109.42
BA _{Met_IC3} , median (IQR) (Years)	80.89 (28.25)	19.70 – 124.28	82.08 (34.74)	41.22 – 124.28	73.49 (31.47)	19.70 – 99.52
BA _{Met_DEXA} , median (IQR) (Years)	89 (14)	47 – 110	90 (14.75)	47 – 110	87 (14.5)	73 – 110

* **Abbreviations** T2DM: type 2 diabetes mellitus; IQR: inert-quartile range; SD: standard deviation.

In the T2DM group, two-thirds of participants were Caucasian males, with a median (IQR) age of 62.5 (8.0) years, a mean (SD) BMI of 31.60 (1.78) kg/m², and a mean (SD) total body fat percentage of 38.33 (7.20)%. All four metabolic age (in years) measures in the T2DM arm were slightly higher than the overall cohort averages: B_{AMet_IC1}, 93.34 vs. 90.25; B_{AMet_IC2}, 98.55 vs. 96.82; B_{AMet_IC3}, 82.08 vs. 80.89; and B_{AMet_DEXA}, 90 vs. 89.

The non-T2DM arm consisted of 7 (58.34%) male participants, of whom 11 (91.67%) were Caucasian, with a median age (IQR) of 59 (15.75) years and a mean BMI (SD) of 29.53 (2.59) Kg/m². The non-T2DM arm's mean measured RMR was 1541 Kcal/day, whereas their mean DEXA-estimated RMR was 1474 Kcal/day. On average, the non-T2DM arm had a lower metabolic age (in years) than both the total average cohort [B_{AMet_IC1}, 87.67 vs. 90.25; B_{AMet_IC2}, 92.64 vs. 96.82; B_{AMet_IC3}, 73.49 vs. 80.89; and B_{AMet_DEXA}, 87 vs. 89] and the T2DM arm [B_{AMet_IC1}, 87.67 vs. 93.34; B_{AMet_IC2}, 92.64 vs. 98.55; B_{AMet_IC3}, 73.49 vs. 82.08; and B_{AMet_DEXA}, 87 vs. 90], respectively.

Additionally, sex-stratified analysis revealed expected differences in body composition and metabolic parameters (Table 4.3). Men demonstrated higher lean body mass (58.56 vs. 42.91 kg), lower body fat percentage (34.80% vs. 45.60%), and correspondingly higher RMR (1681 vs. 1379 kcal/day by indirect calorimetry). Most metabolic age indices were higher in males, except B_{AMet_DEXA}, which was similar between sexes. Creatinine-based eGFR was higher in men (103.10 vs. 81.70 mL/min), while cystatin C-based eGFR showed minimal sex difference (88.60 vs. 90.20 mL/min), consistent with the muscle mass dependence of creatinine and relative independence of cystatin C from body composition.

Table 4.3 Summarized statistical comparison of the relevant physiologic and metabolic parameters of the study cohort stratified by sex

Parameter	Sex Median (IQR)	
	M	F
Age, Years	62 (13.5)	61 (8)
BA _{Met} IC ₁ , Years	92.24 (19.65)	86.12 (20.58)
BA _{Met} IC ₂ , Years	100.91 (22.65)	85.89 (22.64)
BA _{Met} IC ₃ , Years	85.65 (27.14)	66.40 (31.87)
BA _{Met} DEXA, Years	89 (12.5)	89 (13)
Weight, Kg	97.5 (11.35)	78.5 (12.3)
Lean Body Mass, Kg	58.56 (11.5)	42.91 (9.07)
Body Mass Index, Kg/m ²	30.0 (3.55)	31.9 (1.5)
Total Body Fat, Percent	34.80 (2.35)	45.60 (5.3)
RMR _{IC} , Kcal/day	1681 (226)	1379 (262)
RMR _{DEXA} , Kcal/day	1631 (235)	1303 (187)
eGFR CKD-EPI 2021 _{Scr} , mL/min	103.10 (20.2)	81.70 (23.9)
eGFR CKD-EPI 2021 _{Scr-Scys} , mL/min	96.6 (26.9)	86.5 (14.7)
eGFR CKD-EPI 2021 _{Scys} , mL/min	88.60 (35.7)	90.20 (21.5)

* **Abbreviations** IQR: inter-quartile range; M: male; F: female; Kcal: kilocalories; Scr: serum creatinine, Scys: serum cystatin C

4.3.1 Distribution of Measured Glomerular Filtration Rate

The distribution of participants across measured GFR (mGFR) groups demonstrated adequate representation across different stages of kidney function (Appendix Table B.3). Seven participants (29.2%) had an mGFR ≥ 90 mL/min with a mean (SD) of 109.45 mL/min (14.52), representing normal kidney function. Most participants (n=11, 45.8%) had mGFR between 60-89 mL/min (mean: 75.84 mL/min, SD: 7.22), reflecting mildly decreased kidney function. Four participants (16.7%) demonstrated moderately decreased kidney function with mGFR of 45-59 mL/min (mean: 53.01 mL/min, SD: 4.95), while two participants (8.3%) had mGFR of 30-44 mL/min (mean: 36.11 mL/min, SD: 5.57), indicating moderately to severely decreased kidney function. The coefficient of variation ranged from 9.34% to 15.43% across groups, demonstrating relatively consistent variability within each category.

4.3.2 Univariate and Multivariate Covariate Analysis

Univariate analyses identified several significant covariates associated with iohexol clearance (CL_{IOH}) (Appendix Table B.4). Among kidney function estimators, the CKD-EPI 2021

equations incorporating cystatin C demonstrated the strongest associations. Specifically, eGFR calculated using CKD-EPI 2021 having both creatinine and cystatin C adjusted to individual body surface area (BSA) showed the highest statistical significance (eGFR_CKD_EPI_cr_cys_bsa_m, BSA adjusted by Mosteller formula: $p = 2.19 \times 10^{-3}$; eGFR_CKD_EPI_cr_cys_bsa_dd, BSA adjusted by Du Bois method: $p = 2.36 \times 10^{-3}$). The cystatin C-only CKD-EPI 2021 equations also showed strong associations when adjusted to BSA (eGFR_CKD_bsa_m and eGFR_CKD_EPI_cysc_bsa_dd: $p = 4.32 \times 10^{-3}$ and 4.38×10^{-3}). CysC showed a significant association ($p = 3.5 \times 10^{-2}$) as well. Among metabolic parameters, RMR measured by DEXA ($p = 2.72 \times 10^{-2}$), fat-free mass ($p = 2.71 \times 10^{-2}$), lean mass ($p = 2.65 \times 10^{-2}$), and total body weight ($p = 2.73 \times 10^{-2}$) all demonstrated significant associations with CL_{IOH} . Notably, none of the four metabolic age indices (BAMet_IC1, BAMet_IC2, BAMet_IC3, or BAMet_DEXA) were significant against CL_{IOH} in univariate analysis. Traditional body size descriptors, including adjusted body weight, dosing weight, and Cockcroft-Gault creatinine clearance using actual body weight, all showed significant associations ($p < 0.05$). Interestingly, chronological age showed no significant relationship with CL_{IOH} ($p = 9.85 \times 10^{-1}$).

In addition, a multivariate linear regression model incorporating age, metabolic, and kidney parameters on measured iohexol clearance revealed complex relationships (Appendix Table B.5). Multiple parameters, including age, metabolic age indices, total body fat percentage, lean body mass, CysC, and RMR measurements, showed significant associations with iohexol clearance when adjusted for confounding factors.

4.3.3 Population Pharmacokinetic Model Development

The base population pharmacokinetic model was a two-compartment model with proportional error, yielding initial parameter estimates of: $CL = 72.01$ mL/min, central volume of distribution ($V1$) = 5874.99 mL, intercompartmental clearance (Q) = 193.19 mL/min, and peripheral volume of distribution ($V2$) = 7664.97 mL. The final base model demonstrated good parameter precision with relative standard errors ranging from 7.58% to 19.61% for fixed effects and 11.99% to 35.71% for random effects (Appendix Table B.7).

Step-by-step model building and covariate evaluation tested conventional kidney function equations, age, metabolic age indices, and metabolic rate parameters (Table 4.4). Among conventional equations, eGFR calculated by CKD-EPI 2021 having both creatinine and cystatin

C adjusted to BSA by the Mosteller formula on clearance, provided the greatest improvement ($\Delta\text{AIC} = -8.88$ compared to base).

Table 4.4 Comparison of model performance based upon the metabolic and renal biomarkers

Model	AIC	ΔAIC (relative to Base)
Base*	-627.25	0
Base + CL(eGFR_CKD-EPI_cr_cys_bsa_m)	-636.13	-8.88
Base + CL(eGFR_EKFC_cys)	-631.73	-4.4
Base + CL(CrCl.CG_weight)	-630.82	-3.57
Base + CL(Age_years)	-625.15	+2.1
Base + CL(BA_{Met_IC1})	-624.92	+2.33
Base + CL(BA_{Met_IC2})	-625.31	+1.94
Base + CL(BA_{Met_IC3})	-625.51	+1.74
Base + CL(BA_{Met_DEXA})	-625.32	+1.93
Base + CL(RMR_IC)	-627.9	-0.65
Base + CL(RMR_IC/(Scr*Scys-C))	-634.1	-6.85
Base + CL(RMR_IC/Scys-C)	-636.23	-8.98
Base + CL(RMR_IC/Scys-C) + Correlation (CL-V1)	-645.92	-18.67
Base + CL(RMR_DEXA)	-630.84	-3.59
Base + CL(RMR_DEXA/(Scys-C))	-638.45	-11.2
Base + CL(RMR_IC/Scys-C) + Correlation (CL-V1)	-645.52	-18.27

* Base model: 2-compartment with proportional error model

Abbreviations AIC: Akaike Information Criterion

Surprisingly, neither chronological age nor any of the four metabolic age indices significantly improved the base model for predicting iohexol clearance. Models incorporating chronological age alone ($\Delta\text{AIC} = +2.1$) or chronological age combined with both kidney parameters SCr and CysC ($\Delta\text{AIC} = -1.27$) showed minimal or no improvement. Similarly, models incorporating the four different metabolic age indices (BA_{Met_IC1}, BA_{Met_IC2}, BA_{Met_IC3}, and BA_{Met_DEXA}) performed poorly, with ΔAIC values ranging from +1.74 to +2.33, indicating no improvement over the base model (Table 4). These findings were unexpected, given the hypothesis that metabolic age would better capture biological aging than chronological age. The lack of improvement from both chronological and metabolic age indices suggested that these summary measures, derived from population-based equations, may not adequately capture the physiological heterogeneity relevant to kidney function. This prompted exploration of direct metabolic rate measurements rather than age-derived indices.

4.3.4 Development of the Metabo-Renal Ratio

A novel approach incorporating the ratio of RMR to CysC emerged as the optimal predictor of CL_{IOH} . The model including RMR from indirect calorimetry divided by CysC as a covariate of CL_{IOH} , achieved a $\Delta AIC = -8.98$, demonstrated a performance comparable to the optimal conventional kidney function equation (CKD-EPI 2021 SCr and CysC adjusted to BSA by Mosteller formula) while incorporating metabolic information. The final model incorporated the RMR to CysC ratio on clearance, along with CL-V1 correlation, which further improved the model performance and achieved $\Delta AIC = -18.67$.

To validate these findings, RMR measured by indirect calorimetry was replaced by the RMR measured by DEXA in the ratio. The modified ratio achieved similar improvements (ΔAIC ranging from -3.59 to -18.27), confirming the performance demonstrated by indirect calorimetry-based RMR models. The superior performance of direct metabolic rate measurements over both chronological and metabolic age indices underscores the importance of individualized functional assessment rather than population-derived age estimates for predicting kidney function.

The final Pop-PK model for iohexol clearance is described by the following equation:

$$\log(CL_i) (mL/min) = \log(CL_{pop}) + \beta_{CL} \times \log\left(\frac{RMR_{IC,i}}{cysCi \times 1500}\right) + \eta_{CL,i} \quad \text{Equation (1)}$$

$$\log(CL_i) (mL/min) = \log(72.03) + 0.6 \times \log\left(\frac{RMR_{IC,i}}{cysCi \times 1500}\right) + \eta_{CL,i} \quad \text{Equation (2)}$$

where CL_{pop} represents the typical population clearance (72.03 mL/min), β_{CL} is the coefficient for the normalized RMR/CysC ratio (0.6), and $\eta_{CL,i}$ represents the individual random effect on clearance with between-subject variability of 27.83% (CV). The random effects for CL and V1 were correlated ($\rho = 0.68$), indicating that individuals with higher clearance tended to have proportionally higher central volumes. The final model parameter estimates are presented in Table 4.5, demonstrating good precision with relative standard errors below 30% for all fixed effects. Furthermore, the visual predictive check (VPC) plot demonstrated generally adequate model performance, with most observed iohexol concentrations falling within the prediction intervals, supporting the model's ability to describe iohexol PK in this population. (Figure 4.3)

Table 4.5 Final population PK model parameters for iohexol using the metabo-renal ratio.

Parameter	Value	Stoch. Approx.				
		S.E.	R.S.E.(%)	P2.5	P97.5	
Fixed Effects						
Cl_pop	71.65	4.2	5.86	63.89	80.35	
beta_Cl_RMR_IC_cysC_ratio	0.58	0.17	28.94	0.25	0.91	
V1_pop	5849.02	756.25	12.93	4553.71	7512.79	
Q_pop	177.86	28.67	16.12	130.45	242.5	
V2_pop	7176.03	741.53	10.33	5869.71	8773.06	
Standard Deviation of the Random Effects						
	Value	C.V.(%)				
omega_Cl	0.26	26.78	0.044	16.86	0.19	0.36
omega_V1	0.62	67.97	0.092	14.98	0.46	0.82
omega_Q	0.46	48.23	0.17	37.54	0.23	0.9
omega_V2	0.38	39.3	0.092	24.32	0.24	0.6
Correlations						
corr_V1_Cl	0.67		0.13	19.69	0.33	0.86
Error Model Parameters						
b	0.11		0.014	12.73	0.084	0.14

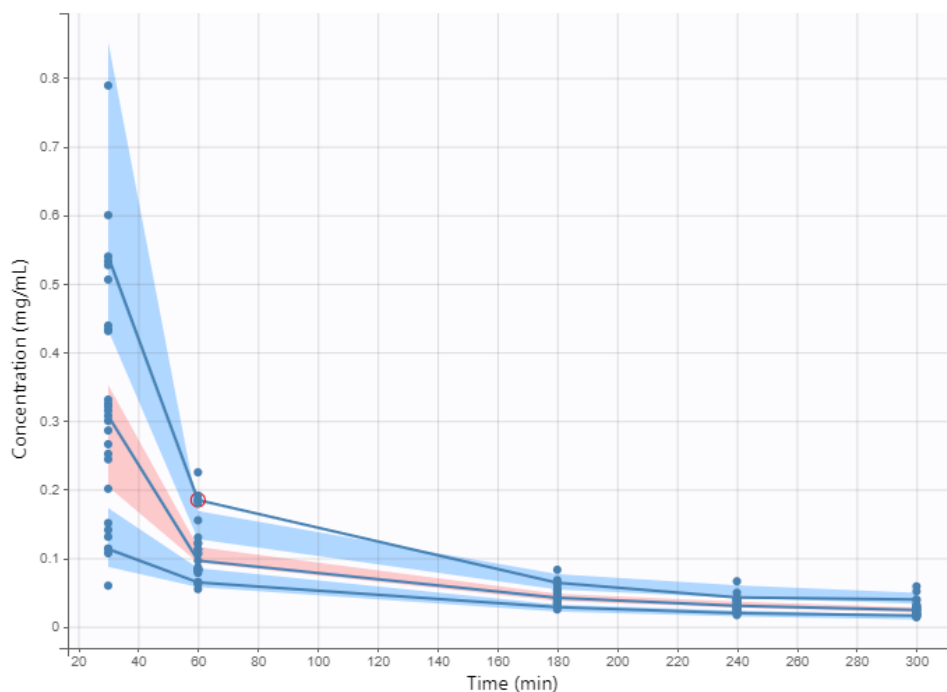


Figure 4.4 Visual predictive check (VPC) plot for the final iohexol clearance model by incorporating the ratio of RMR measured by indirect calorimetry to Serum cystatin C (RMR_IC/CysC). The observed data are depicted as dots, with prediction intervals shown as shaded areas. The red circle highlights an observed data point that deviated from the predicted range, suggesting a potential outlier.

4.3.5 Preliminary Assessment of BA_{Epi} in the Kidney-PACE Cohort

In addition to metabolic age assessment, BA_{Epi} was evaluated in a subset of participants to explore its potential as a biomarker of kidney function. Nine whole blood samples were shipped for BA_{Epi} analysis. However, the laboratory successfully extracted sufficient DNA for methylation profiling from only seven samples. The BA_{Epi} (DNAge) and corresponding differences from chronological age ($\Delta DNAge$) are presented in Table 4.6. Contrary to expectations, the differences between BA_{Epi} and chronological age were not sufficiently large or consistent to warrant inclusion of epigenetic age as a covariate in the population pharmacokinetic models or the linear regression analyses of iohexol clearance. The absolute $\Delta DNAge$ values ranged from 0.08 to 5.31 years, with a mean absolute difference of 2.80 years. The greatest divergence was observed in participant #9, who exhibited a BA_{Epi} of 63.31 years compared to a chronological age of 58 years ($\Delta DNAge = 5.31$ years).

Table 4.6 Summary results of DNAge in a subset of Kidney-PACE participants.

Patient No.	DNAge	Age	Δ DNAge
2	65.08	65	0.08
3	67.03	63	4.03
4	61.24	62	-0.76
6	47.01	51	-3.99
7	59.44	61	-1.56
8	63.16	67	-3.84
9	63.31	58	5.31

To validate these preliminary findings and address concerns about potential assay variability, an independent confirmation was performed for participant #9 using the NOVOS Age test kit (NOVOS Labs, New York, NY). Following the manufacturer's protocol, a blood sample was collected and shipped to the NOVOS laboratory for processing. The reported BA_{Epi} from this confirmatory analysis was 62 years, corresponding to a Δ DNAge of 4 years relative to the chronological age of 58 years. While this represented a modest reduction in the estimated age acceleration compared to the DNAge result (4 years versus 5.31 years), both assessments confirmed that the BA_{Epi} discrepancy for this individual remained relatively small.

It is worth noting that the decision not to pursue BA_{Epi} in PK modeling was based on a comprehensive evaluation of 30 total samples, including the 7 samples from the current study and 23 additional samples from a parallel study conducted by our group. Across all processed samples, Δ DNAge values predominantly ranged from -0.5 to 4 years, with the greatest absolute divergence being 8.23 years (Appendix Table B.9).

These findings indicated that, within the Kidney-PACE cohort, BA_{Epi} did not demonstrate the substantial deviations from chronological age that would be necessary to improve the prediction of measured kidney function (CL_{IOH}) beyond traditional age-based models or metabolic biomarkers. The limited variability observed in Δ DNAge across participants suggests that epigenetic aging clocks, as currently implemented, may not capture the specific physiological changes most relevant to renal clearance capacity in this population. This contrasts with the metabolic biomarkers evaluated in this study, particularly the RMR to cystatin C ratio, which demonstrated significant associations with directly measured kidney function.

4.4 Discussion

This study investigated the relationship between metabolic age and directly measured kidney function using iohexol clearance. Our findings revealed that metabolic biomarkers, particularly when expressed as a ratio of resting metabolic rate to CysC, provided predictive value comparable to established kidney function estimation equations. This "metabo-renal ratio" achieved comparable performance to the CKD-EPI 2021 creatinine-cystatin C equation, one of the current standards for estimating GFR.

A striking finding was that chronological age demonstrated no significant association with measured iohexol clearance in our cohort, despite the well-established decline in kidney function with aging in population studies. This apparent paradox may reflect several important considerations. First, our study population demonstrated metabolic ages substantially elevated above their chronological ages across all measurement methods, with median metabolic ages ranging from 80.89 to 96.82 years compared to a median chronological age of 61.5 years. This divergence suggests that traditional aging-related decline in kidney function may be more closely tied to metabolic and body composition changes than to years lived.

The most significant contribution of this study was the development and validation of a metabo-renal ratio incorporating RMR and cystatin C. The optimal formulation (RMR/cystatin C), achieved a model improvement comparable to the conventional eGFR equation, CKD-EPI 2021 creatinine–cystatin C. This finding suggests that metabolic rate, when appropriately normalized to a kidney function biomarker, captures clinically relevant variation in true GFR.

The physiologic rationale for this ratio is compelling and centers on the complementary nature of its components in capturing body composition-dependent and body composition-independent aspects of kidney function. RMR serves as an indirect but robust indicator of muscle mass and body composition. Individuals with greater lean body mass, particularly those who are more athletic or have higher muscle content, exhibit higher caloric expenditure at rest, resulting in elevated RMR. This relationship exists because skeletal muscle is a metabolically active tissue that contributes substantially to resting energy expenditure, accounting for approximately 20–30% of RMR in healthy adults²⁶⁷. Consequently, RMR provides a functional assessment of body composition that reflects the metabolic activity of lean tissue mass. On the other hand, CysC represents a body composition-independent marker of kidney function. Unlike SCr, which is derived from muscle creatine metabolism and thus varies substantially with muscle mass, CysC

is produced at a constant rate by all nucleated cells regardless of muscle content ²⁶⁸. CysC is freely filtered by the glomerulus and is an endogenous marker of GFR that is not confounded by muscle mass, age, or body composition ^{136,268}. Meanwhile, some studies have reported associations with body fat and BMI ^{136,269}. Nevertheless, cystatin C remains substantially less dependent on muscle mass than creatinine and provides more accurate GFR estimation in populations with altered body composition. This independence from muscle mass may be particularly relevant in our study population, where all participants had a BMI between 27-35 Kg/m², as creatinine-based equations are known to perform suboptimally in overweight and obese individuals due to altered muscle mass and body composition ²⁷⁰. This characteristic of CysC forms the basis for its inclusion in contemporary GFR estimation equations and its utility in the metabo-renal ratio.

By creating a ratio of RMR to CysC, we developed a composite biomarker that simultaneously incorporates body composition information (through RMR) while normalizing for kidney filtration capacity in a body composition-independent manner (through CysC). The ratio may be conceptualized as representing the efficiency of renal filtration relative to the body's metabolically active tissue mass. In individuals with higher lean mass and correspondingly higher RMR, we would expect proportionally higher kidney function to maintain metabolic homeostasis, while elevated CysC (indicating reduced filtration) would decrease the ratio, reflecting diminished kidney function relative to metabolic demand.

As discussed earlier, our findings demonstrated that metabolic markers could achieve predictive performance approaching that of established kidney function equations. The CKD-EPI 2021 creatinine-cystatin C equation normalized to BSA achieved $\Delta AIC = -8.88$, while our final metabo-renal model achieved $\Delta AIC = -18.67$. Interestingly, cystatin C-based equations consistently outperformed creatinine-based equations in our cohort, likely reflecting the influence of muscle mass variation in our overweight to obese population. The Cockcroft-Gault equations achieved modest improvements in the Pop-PK models ($\Delta AIC = -2.34$ to -3.57), likely reflecting limitations in capturing the complex interplay between body composition, age, and kidney function in this population. The cystatin C-based EKFC equation achieved $\Delta AIC = -4.4$, intermediate between the Cockcroft-Gault and CKD-EPI equations. This pattern reinforces the importance of cystatin C as a filtration marker less influenced by muscle mass than creatinine, particularly relevant in populations with altered body composition.

Our study population demonstrated substantial metabolic heterogeneity as well. Total body fat percentage ranged from 21.8% to 54.1%, BMI ranging from 24y.0 to 33.9 Kg/m², with lean body mass showing similarly wide variation. This heterogeneity in body composition likely contributed to the superior performance of metabolic rate measurements over simple anthropometric predictors.

The metabo-renal ratio's incorporation of both RMR and CysC may also inherently account for sex-related differences in body composition and metabolic rate, potentially obviating the need for sex-specific equations. This represents an important advantage, as efforts to eliminate race coefficients from kidney function equations have highlighted the need for biomarkers less influenced by demographic proxies for unmeasured physiologic variables ²⁷¹.

Participants with T2DM demonstrated consistently higher metabolic ages across all measurement methods compared to controls, despite similar chronological ages. This elevation in metabolic age occurred alongside differences in body composition, with T2DM participants showing higher BMI (31.60 vs. 29.53 kg/m²) and slightly higher body fat distribution. The higher metabolic ages in the T2DM group, combined with potential alterations in renal metabolic efficiency, may contribute to the complex relationship between metabolic rate, kidney function, and disease progression observed in diabetic kidney disease.

The relationship between T2DM and kidney function in our cohort was complex. While T2DM is a well-established risk factor for CKD progression, our study design captured participants across a range of kidney function stages in both groups. The metabo-renal ratio's strong performance across both participants with and without T2DM suggests that this biomarker may capture metabolic-renal activity regardless of underlying disease state, though longitudinal studies would be needed to assess its use in predicting CKD progression.

BA_{Epi} was not a strong predictor of kidney function or drug clearance in this study, likely due to a fundamental mismatch between what blood-based epigenetic clocks measure and the biological processes governing renal elimination. Epigenetic clocks derived from peripheral blood primarily reflect cumulative, systemic aging and immune-related processes rather than contemporaneous, organ-specific functional capacity of the kidney. Drug clearance, in contrast, depends on real-time physiological processes such as glomerular filtration, renal blood flow, and tubular handling, which may not be directly captured by blood DNA methylation patterns. In addition, epigenetic aging is highly tissue-specific, and methylation signatures in blood may not

reflect aging processes within renal parenchymal compartments, including glomeruli, tubules, and the renal vasculature. The limited variability in BA_{Epi} relative to chronological age within this relatively healthy cohort further constrained its explanatory

Several important limitations warrant our discussion. First, the relatively small sample size ($n=24$) limits generalizability and the ability to perform robust subgroup analyses. The single-center design also limits geographic generalizability and may introduce selection bias. Second, the cohort was predominantly Caucasian (79.2%), limiting assessment of performance across diverse racial and ethnic groups. Next, the BMI range (27-35 kg/m^2) limits extrapolation to normal-weight or severely obese individuals. The relationship between metabolic rate, body composition, and kidney function may differ substantially at BMI extremes. Furthermore, this study precludes assessment of causality or predictive value for kidney function decline. Whether the metabo-renal ratio can predict future GFR trajectory or identify individuals at risk for progressive kidney disease remains unknown and represents an important area for future investigation. Finally, the inclusion of both individuals with and without T2DM in the study population introduces disease-related heterogeneity that may have influenced the observed relationships. While this heterogeneity more closely reflects clinical populations and supports the metabo-renal ratio's applicability across disease states, disease-specific validation studies would strengthen confidence in the findings.

Despite these limitations, our findings have several important implications. First, they provided proof-of-concept that metabolic biomarkers can achieve predictive performance comparable to established kidney function equations. This suggests that metabolic assessment may represent an underutilized dimension in kidney function evaluation, particularly in populations with altered body composition where traditional equations may perform suboptimally. Also, the findings support the emerging paradigm that biological age, assessed through functional biomarkers, may better capture aging-related physiologic decline than chronological age. The lack of association between chronological age and iohexol clearance in our cohort, combined with the strong performance of metabolic biomarkers, reinforces this concept. This has implications beyond kidney function assessment, potentially informing drug dosing and other clinical decisions guided by chronological age. Furthermore, the study demonstrated the feasibility of integrating advanced metabolic assessment into PK studies. While indirect calorimetry and DEXA scanning remain specialized techniques, their incorporation

provided novel insights into the physiological determinants of drug clearance. As body composition assessment becomes more accessible through advances in imaging and bioimpedance technology, integration of metabolic markers into PK modeling may become increasingly practical.

Several important research directions emerge from this work. First, external validation of the metabo-renal ratio in independent cohorts is essential. Particular attention should be paid to performance in populations historically underrepresented in kidney function equation development. Second, longitudinal studies assessing whether the metabo-renal ratio predicts kidney function decline, cardiovascular events, or mortality would establish its prognostic value beyond cross-sectional GFR estimation. Next, investigation of the metabo-renal ratio's response to interventions (dietary, exercise, pharmacologic) could provide insights into mechanisms of kidney function preservation or decline. Next, the development of more accessible metabolic assessment methods would facilitate clinical implementation. While indirect calorimetry provides an accurate and robust RMR measurement, technologies like portable metabolic analyzers, advanced bioimpedance devices, or machine learning-based estimation from routinely available clinical data might also provide promising estimations with greater accessibility. Furthermore, application of the metabo-renal concept to drug dosing for renally eliminated medications beyond iohexol would test its clinical utility. If metabolic markers improve the prediction of clearance for medications with narrow therapeutic indices, it could enhance precision medicine approaches to dosing, particularly in populations with altered body composition. Finally, exploration of other biological age biomarkers, such as composite organ-specific aging indices, in relation to kidney function and drug clearance would advance our understanding of how different dimensions of biological aging interact. Integration of multiple biological age domains might provide an even more precise assessment of kidney function and PK parameters.

4.5 Conclusion

This study demonstrated that metabolic biomarkers, particularly a novel RMR to CysC ratio, can achieve predictive performance for measured kidney function comparable to established eGFR equations. The metabo-renal ratio outperformed chronological age and metabolic age indices, achieving model improvements similar to or exceeding the CKD-EPI

2021 creatinine-cystatin C equation. These findings support the concept that biological aging, assessed through functional metabolic markers, may better capture kidney function variability than chronological age in adults with metabolic heterogeneity.

4.6 Appendix B: Supplemental Materials

Table 4.7 Complete list of eligibility criteria for the Kidney-PACE study participants.

Inclusion Criteria	Exclusion Criteria
• Age 40-70 years • Diagnosis of T2DM • BMI of 27 to 35 kg/m² • eGFR between 30-120 mL/min based on CKD-EPI 2021 eGFR_{cr} equation at screening visit • Willingness to remain on site for an approximately 6-hour visit and tolerate venipunctures for blood sample collection. • Ability to provide independent informed consent.	• Change in body weight of ≥ 5 kg in the last 30 days • Patients with a prior bariatric surgical procedure • Change in diabetes regimen in the past 90 days • Patients initiated on GLP1 agonists • History of a hypersensitivity reaction to CT contrast, iodine, or shellfish • Recent (≤ 30 days) iodinated contrast administration • History of bronchial asthma, multiple and or severe allergies to drugs, or history of severe anaphylactic reactions • History of any of the following conditions: multinodular goiter, Graves' disease, autoimmune thyroiditis, thyroid storm, autonomously functioning thyroid nodule, or myasthenia gravis. • History of multiple myeloma and or para-proteinaceous diseases • Currently taking diuretics, chemotherapy, beta blockers, or other drugs known to cause acute kidney injury. • Recent (≤ 6 months) episode of acute kidney injury, have sickle cell disease, or have current indwelling nephrostomy tubes • Participants with a history of liver disease or cardiovascular disease such as severe congestive heart failure, pacemaker implant, and/or aortic stenosis • Females who are currently pregnant or breastfeeding • Whole-or partial-limb amputation. • Inadequate venous access for blood sampling. • Participants with pheochromocytoma

Table 4.8 Body size descriptors and kidney function estimation equations used in this study

Descriptor	Full Name	Unit
wt	Weight	Weight in kg
ht	Height	Height in cm
bmi	Body mass index	Computed in kg/m ²
ibw	Ideal body weight	Estimated in kg
adxbw	Adjusted body weight	Estimated in kg
dw	Dosing weight	Estimated in kg
lbw	Lean body weight	Estimated in kg
bsa_m	Body surface area using Mosteller's adaptation	Estimated in m ²
bsa_dd	Body surface area using Dubois-DuBois equation	Estimated in m ²
clcr_wt	Creatinine clearance using the Cockcroft-Gault equation and weight	Estimated in mL/min
clcr_ibw	Creatinine clearance using the Cockcroft-Gault equation and ideal body weight	Estimated in mL/min
clcr_adxbw	Creatinine clearance using the Cockcroft-Gault equation and adjusted body weight	Estimated in mL/min
clcr_dw	Creatinine clearance using the Cockcroft-Gault equation and dosing weight	Estimated in mL/min
egfr_ckdepi_cr	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatinine Equation without race published in 2021	Estimated in mL/min/1.73 m ²
egfr_ckdepi_cr_bsa_m	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatinine Equation without race published in	Estimated in mL/min

	2021 normalized to individual body surface area- Mosteller equation	
egfr_ckdepi_cr_bsa_dd	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatinine Equation without race published in 2021 normalized to individual body surface area-Dubois Dubois equation	Estimated in mL/min
egfr_ckdepi_cr_cys	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatine-cystatin C Equation without race published in 2021	Estimated in mL/min/1.73 m ²
egfr_ckdepi_cr_cys_bsa_m	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatinine-cystatin C Equation without race published in 2021 normalized to individual body surface area- Mosteller equation	Estimated in mL/min
egfr_ckdepi_cr_cys_bsa_dd	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – Creatinine-cystatin C Equation without race published in 2021 normalized to individual body surface area-Dubois Dubois equation	Estimated in mL/min
egfr_ckdepi_cys	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – cystatin C Equation	Estimated in mL/min/1.73 m ²
egfr_ckdepi_cys_bsa_m	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – cystatin C Equation without race published in 2021 normalized to individual body surface area- Mosteller equation	Estimated in mL/min
egfr_ckdepi_cys_bsa_dd	Glomerular filtration rate using the Chronic Kidney Disease Epidemiology – cystatin C Equation without race published in 2021 normalized to individual body surface area-Dubois Dubois equation	Estimated in mL/min

scr_q	Serum creatinine normalized values for EKFC equation	unitless
egfr_ekfc_cr	European Kidney Function Consortium (EKFC) equation based on Creatinine	Estimated in mL/min/1.73 m ²
egfr_ekfc_cr_bsa_m	Glomerular filtration rate using the EKFC equation based on Creatinine without race published in 2020 normalized to individual body surface area- Mosteller equation	Estimated in mL/min
egfr_ekfc_cr_bsa_dd	Glomerular filtration rate using the EKFC equation based on Creatinine without race published in 2020 normalized to individual body surface area- Dubois-DuBois equation	Estimated in mL/min
scr_q	Serum cystatin C normalized values for EKFC equation	unitless
egfr_ekfc_cys	European Kidney Function Consortium (EKFC) equation based on cystatin C	Estimated in mL/min/1.73 m ²
egfr_ekfc_cys_bsa_m	Glomerular filtration rate using the EKFC equation without race published in 2023 normalized to individual body surface area- Mosteller equation	Estimated in mL/min
egfr_ekfc_cys_bsa_dd	Glomerular filtration rate using the EKFC equation without race published in 2023 normalized to individual body surface area- Dubois-DuBois equation	Estimated in mL/min

Table 4.9 Distribution of participants across measured glomerular filtration rate groups, including central tendency and variance of the population to support simulations

mGFR Group	N	Population%	Mean (mL/min)	Standard Deviation	Coefficient of Variation
≥ 90 mL/min	7	29.2	109.45	14.52	13.27%
60–89 mL/min	11	45.8	75.84	7.22	9.52%
45–59 mL/min	4	16.7	53.01	4.95	9.34%
30–44 mL/min	2	8.3	36.11	5.57	15.43%

Table 4.10 Univariate analyses to identify significant covariates on CL_{IOH}

CL _{IOH}	COEFF	STATISTICS	P-VALUE
race		1.1	3.07e-1
sex		0.87	3.6e-1
studyarm_0H_1D		0.81	3.79e-1
ABW_Kg	0.4	2.02	5.61e-2
BAmet_dexa	-0.011	-0.052	9.59e-1
BAmet_original_HB	0.072	0.34	7.39e-1
BAmet_revised_HB_Mifflin_Jeor	0.17	0.8	4.3e-1
BAmet_revised_HB_Roza_Shizgal	0.12	0.56	5.78e-1
CG_CLcr_AdjBW	0.4	2.03	5.46e-2
CG_CLcr_DW	0.41	2.11	4.63e-2
CG_CLcr_IBW	0.34	1.72	9.91e-2
CG_CLcr_wt	0.44	2.31	3.05e-2
IBW_Kg	0.33	1.63	1.17e-1
LBM2005_Kg	0.34	1.68	1.07e-1
RMR_dexa	0.45	2.37	2.72e-2
RMR_indirect_calorimetry	0.33	1.63	1.17e-1
Scr_mg_dL	-0.18	-0.85	4.05e-1
ScysC_mg_L	-0.43	-2.25	3.5e-2
age_yrs	0.004	0.019	9.85e-1
bmd	0.28	1.35	1.89e-1
bmi	0.21	1.02	3.2e-1

dosing_weight_Kg	0.42	2.17	4.09e-2
eGFR_CKD_EPI_cr	0.36	1.79	8.79e-2
eGFR_CKD_EPI_cr_bsa_dd	0.44	2.32	2.97e-2
eGFR_CKD_EPI_cr_bsa_m	0.45	2.38	2.65e-2
eGFR_CKD_EPI_cr_cys	0.5	2.74	1.2e-2
eGFR_CKD_EPI_cr_cys_bsa_dd	0.59	3.44	2.36e-3
eGFR_CKD_EPI_cr_cys_bsa_m	0.59	3.47	2.19e-3
eGFR_CKD_EPI_cysc	0.46	2.43	2.4e-2
eGFR_CKD_EPI_cysc_bsa_dd	0.56	3.18	4.38e-3
eGFR_CKD_EPI_cysc_bsa_m	0.56	3.18	4.32e-3
eGFR_ekfc_cr	0.31	1.5	1.47e-1
eGFR_ekfc_cr_bsa_dd	0.08	0.38	7.09e-1
eGFR_ekfc_cr_bsa_m	0.082	0.39	7.02e-1
eGFR_ekfc_cys	0.48	2.58	1.73e-2
eGFR_ekfc_cys_bsa_dd	0.33	1.66	1.12e-1
eGFR_ekfc_cys_bsa_m	0.33	1.66	1.12e-1
fat_free_mass_Kg	0.45	2.37	2.71e-2
fat_mass_Kg	0.18	0.86	3.99e-1
height_cm	0.35	1.76	9.31e-2
lean_mass_Kg	0.45	2.38	2.65e-2
total_fat_percent	-0.2	-0.97	3.42e-1
weight_Kg	0.45	2.36	2.73e-2

Table 4.11 Multivariate analyses of age, metabolic, and kidney parameters on CL_{IOH} (mGFR)

```
Call:
lm(formula = mGFR_ioh_CL ~ age_yrs + BAmet_original_HB + BAmet_revised_HB_Roz
a_Shizgal +
  BAmet_revised_HB_Mifflin_Jeor + BAmet_dexa + Scr_mg.dL +
  ScysC_mg.L + total_fat_percent + RMR_indirect_calorimetry +
  RMR_dexa, data = kidneyPACE_complete)
```

Residuals:

Min	1Q	Median	3Q	Max
-38.284	-3.402	1.746	4.257	29.729

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	-169.81790	36.94848	-4.596	9.89e-06	***
age_yrs	1.04725	0.21269	4.924	2.47e-06	***
BAmet_original_HB	-5.80199	1.20239	-4.825	3.77e-06	***
BAmet_revised_HB_Roza_Shizgal	5.80316	1.34051	4.329	2.92e-05	***
BAmet_revised_HB_Mifflin_Jeor	-1.59120	0.43563	-3.653	0.000372	***
BAmet_dexa	-0.35315	0.14890	-2.372	0.019137	*
Scr_mg.dL	-32.52203	22.51248	-1.445	0.150916	
ScysC_mg.L	-36.12223	8.95665	-4.033	9.23e-05	***
total_fat_percent	5.12492	0.71937	7.124	5.95e-11	***
RMR_indirect_calorimetry	-0.14781	0.02723	-5.429	2.61e-07	***
RMR_dexa	0.26618	0.02975	8.947	2.74e-15	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 15.05 on 133 degrees of freedom

Multiple R-squared: 0.6625, Adjusted R-squared: 0.6371

F-statistic: 26.1 on 10 and 133 DF, p-value: < 2.2e-16

Table 4.12 Initial Parameter Estimates for the base pharmacokinetic model

Mean Parameter Estimates	Pop PK
CL (mL/min)	72.01
V1 (mL)	5874.99
Q (mL/min)	193.19
V2 (mL)	7664.97

Table 4.13 Parameter estimates of the base pharmacokinetic model

Parameter	Value		Stoch. Approx.			
			S.E.	R.S.E.(%)	P2.5	P97.5
Fixed Effects						
Cl_pop	72.54		5.5	7.58	62.56	84.1
V1_pop	5905.54		759.25	12.86	4604.05	7574.93
Q_pop	179.27		35.15	19.61	123.33	260.56
V2_pop	7497.62		769.01	10.26	6141.77	9152.78
Standard Deviation of the Random Effects						
	Value	C.V.(%)				
omega Cl	0.35	35.89	0.055	15.84	0.26	0.47
omega V1	0.61	67.66	0.091	14.86	0.46	0.82
omega Q	0.55	59.6	0.2	35.71	0.29	1.05
omega V2	0.36	37.01	0.1	28.95	0.21	0.61
Error Model Parameters						
b	0.1		0.013	11.99	0.083	0.13

Table 4.14 Stepwise population pharmacokinetic model development in Monolix, showing tested covariates on iohexol clearance, corresponding AIC values, change from base model (Δ AIC), and selection rationale.

Model no.	Model expansion	AIC	Findings	Note	Δ AIC (relative to Base)
1	1cmpt_base(constant)	-383.69			
2	1cmpt_base(prop)	-443.09			
3	1cmpt_base(comb1)	-381.37			
4	1cmpt_base(comb2)	-441.81			
5	2cmpt_base(constant)	-605.03			
6	2cmpt_base(prop)	-627.25	Proposal: add CL-ckd_epi_cr_cys_bsa_m; V2-CG_clcr_ibw and RMR_IC and; CL-V1-Q correlated	Base model	0
7	2cmpt_base(comb1)	-624.95			
8	2cmpt_base(comb2)	-625.04			
a. Checking with significant conventional equations					
9	Base + CL(ckd_epi_cr_cys_bsa_m)	-636.13	Proposal: keep CL-parameter; add V2-studyarm; CL-V1-Q corr	Most improve among the equations	-8.88
10	Base + CL(ckd_epi_cys_bsa_m)	-634.7	Proposal: keep CL-parameter; add V2_lean_mass; CL-V1-Q corr	2 nd best	-7.45
11	Base + CL(ekfc_cys)	-631.73	Proposal: replace CL-ckd_epi_cr_cys_bsa_m; add V2-studyarm and V2-IC; CL-V1 corr		-4.4
12	Base + CL(CG_clcr_dw)	-629.59	Proposal: replace CL-ckd_epi_cr_cys_bsa_m; add V2-lean_mass; CL-V1-Q corr		-2.34

13	Base + CL(CG_clcr_weight)	-630.82	Proposal: replace CL-ckd_epi_cr_cys_bsa_m; add V2-lean_mass; CL-V1-Q corr		-3.57
b. Testing age and kidney parameters					
14	Base + CL_log(50/age)	-625.15	Proposal: add CL-ckd_epi_cr_cys_bsa_m; add V2-studyarm and V2-IC; CL-V1-Q corr		+2.1
15	Base + CL_log(50/(age*cysC))	-628.92	Proposal: add CL-ckd_epi_cr_cys_bsa_m; add V2-CG_clcr_ibw and V2-IC; CL-V1-Q corr	Parameter estimates pretty good!	-1.67
16	Base + CL_log(50/(age*Scr*cysC))	-628.52	Proposal: keep the ratio; Add lean_mass under both CL and V2 CL-Q corr	Best ratio for chronological age	-1.27
17	Base + CL_log(50/(age*Scr))	-625.77	Proposal: add CL-ckd_epi_cr_cys_bsa_m; add V2-lean_mass; CL-V1-Q corr		+1.48
c. Testing BA_{Met} and kidney parameters					
18	Base + Cl(log-BA _{Met} _original HB/100)	-624.92	- RMR_dexa, Scys, FFM, LBM, eGFR_CKD_EPI_cysc_bsa_dd, eGFR_CKD_EPI_cysc_bsa_m, eGFR_CKD_EPI_scr_cysc_bsa_dd, eGFR_CKD_EPI_scr_cysc_bsa_m, significant on Cl Proposal: remove BA _{Met} , add bmd_V2; add correlation Cl-v1-Q		+2.33

19	Base + Cl(log-BAmet_HB Roza Shizgal/100)	-625.31	- RMR_dexa, Scys, FFM, LBM significant on Cl - proposal: remove Cl_BAmet; add Cl_Scys, V2_RMR_IC; add V2_studyarm; add Cl-V1-Q corr		+1.94
20	Base + Cl(log-BAmet_DEXA/100)	-625.32	Proposal: remove BAmet_DEXA Add BAmet_original_HB, LBW and studyarm under V2; Add eGFR_CKD_EPI_scr_cysc_bsa_m under CL; Add Cl-V1-Q corr		+1.93
21	Base + CL_log(BAmet_Mifflin Jeor/70)	-625.51	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Add V1-BAmet_dexa,CG_clcr_DW, ScysC, age_yrs, ckd_epi_cys_bsa_m; Add V2-studyarm, RMR_IC; CL-V1-Q corr		+1.74
22	Base + CL_log(70/BAmet_Mifflin Jeor)	-625.51	Proposal: same as above	Not really a difference whether as nominator or denominator	+1.74
23	Base + CL_log(70/BAmet_Mifflin Jeor*Scr))	-625.27	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Add V2_BMD; CL-V1-Q corr		+1.98
24	Base + CL_log(70/(BAmet_Mifflin Jeor*cysC))	-625.43	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Add V2_studyarm, CG_clcr_adjbw, RMR_IC; CL-V1-Q corr		+1.82

25	Base + CL_log(BAmet_Mifflin Jeor/(70*cysC))	-628.02	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Move ratio under V1(!); Add V2_studyarm, RMR_IC; CL-V1 corr	BAmet as nominator works better in the ratio when incorporated with a kidney biomarker And cysC is better than Scr	-0.77
26	Base + CL_log(BAmet_Mifflin Jeor/(70*Scr*cysC))	-628.64	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Move ratio under V1(!); Add V2_lean_mass; CL-V1 corr		-1.39
d. Testing RMR alone and kidney biomarkers					
27	Base + CL(RMR_IC)	-627.9	Proposal: add CL-ckd_epi_cr_cys_bsa_m; Move RMR_IC under V2; Add V2_studyarm; CL-V1-Q corr		-0.65
28	Base + CL(RMR_IC/cysC)	-636.25	Proposal: Keep the ratio; Add V2_Scr; CL-V1 corr	ΔAIC similar to model #9!	-9.0
29	Base + CL(RMR_IC/(Scr*cysC))	-636.1	Proposal: Keep the ratio; Add CL_weight; Add V2_RMR_IC and V2_studyarm; CL-V1 corr		-8.85
30	Base + CL(log(RMR_IC/(cysC*1500)))	-636.23	Proposal: Keep the ratio; Add V2_bmd; CL-V1-Q corr		-8.98
31	Base + CL(log(RMR_IC/(cysC*1500))); Fixed V2, CL-V1 corr	-642.02	Proposal: keep the ratio;		-14.77

			Add CL_lean_mass and V1-age, race; CL-V1-Q corr		
32	Base + CL(log(RMR_IC/(cysC*1500)) + log(lean_mass/))	-636.41	Proposal: keep the ratio, remove lean_mass; Add V2-RMR_IC and V2-studyarm; CL-V1-Q corr	No need to add more parameters under CL	-9.16
33	Base + CL(log(RMR_IC/(cysC*1500))), CL-V1 Corr	-645.92	Proposal: keep the ratio and the correlation; Add CG_crcl_IBW and RMR_IC under V2	We are done! (final model)	-18.67
e. Replacing RMR_IC with RMR_DEXA to validate					
34	Base + CL(RMR_dexa)	-630.84	Proposal: keep RMR_dexa but also add RMR_IC/cysC ratio under CL; Also add V2-RMR_IC and studyarm; CL-Q corr	Much better than RMR_IC	-3.59
35	Base + CL(log(RMR_dexa/(cysC*1500)))	-638.45	Proposal: keep the ratio; Add the ratio under V1; Also add egfr_ekfc_cys under V1; Add lean_mass under V2; Add CL-V1-Q Corr	Confirming findings w/ RMR_IC	-11.2
36	Base + CL(log(RMR_dexa/(cysC*1500))) + CL-V1 Corr	-645.52		Confirming findings w/ RMR_IC (final model for RMR_dexa)	-18.27

Table 4.15 Complete list of estimated DNAge in all processed samples (n=30) across two parallel clinical studies conducted by our group.

Sample ID	Sample Name	DNAge® (years)	Age (years)	ΔDNAge® (years)
ZR18128_1	G1_S1	31.7	30	1.7
ZR18128_2	G1_S2	26.41	27	-0.59
ZR18128_3	G1_S3	38.72	33	5.72
ZR18128_4	G1_S4	40.6	36	4.6
ZR18128_5	G1_S5	30.66	31	-0.34
ZR18128_6	G1_S6	22.63	22	0.63
ZR18128_7	G1_S7	25.01	24	1.01
ZR18128_8	G1_S8	18.12	22	-3.88
ZR18128_9	G2_S1	46.17	46	0.17
ZR18128_10	G2_S2	70.9	69	1.9
ZR18128_11	G2_S3	57.23	61	-3.77
ZR18128_12	G2_S4	59.52	59	0.52
ZR18128_13	G2_S5	57.77	66	-8.23
ZR18128_14	G2_S6	53.06	52	1.05
ZR18128_15	G2_S7	65.42	66	-0.58
ZR18128_16	G2_S8	66.64	69	-2.36
ZR18128_17	G3_S1	60.97	67	-6.03
ZR18128_18	G3_S2	61.9	66	-4.1
ZR18128_19	G3_S4	60.88	68	-7.12
ZR18128_20	G3_S5	52.76	53	-0.24
ZR18128_21	G3_S6	45.21	41	4.21
ZR18128_22	G3_S7	62.85	58	4.85
ZR18128_23	G3_S8	74.63	71	3.63
ZR18128_25	S02	65.08	65	0.08
ZR18128_26	S03	67.03	63	4.03
ZR18128_27	S04	61.24	62	-0.76
ZR18128_29	S08	47.01	51	-3.99
ZR18128_30	S09	59.44	61	-1.56
ZR18128_31	S11	63.16	67	-3.84
ZR18128_32	S12	63.31	58	5.31

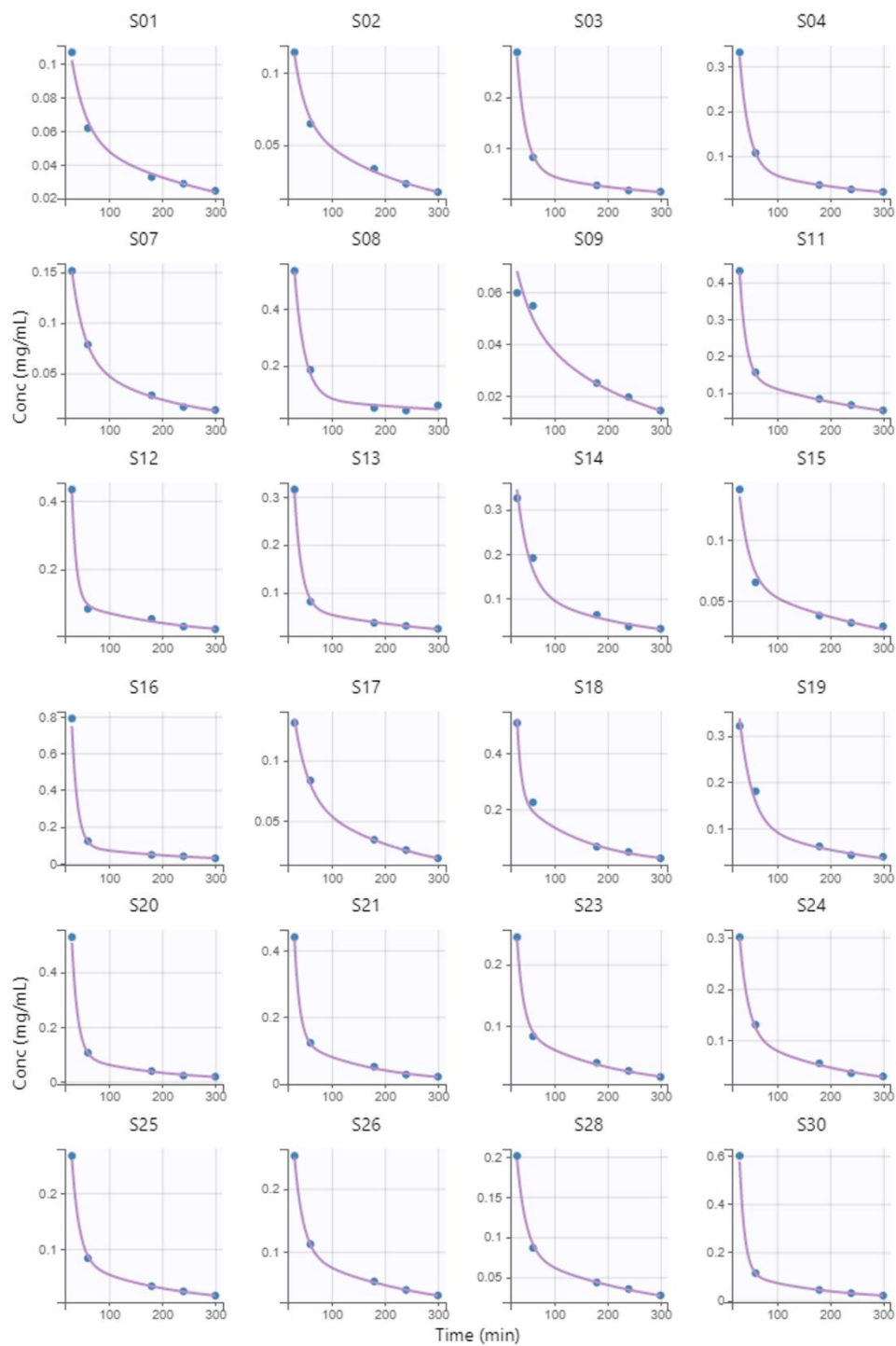


Figure 4.5 Observed iohexol concentration–time profile for each study participant.

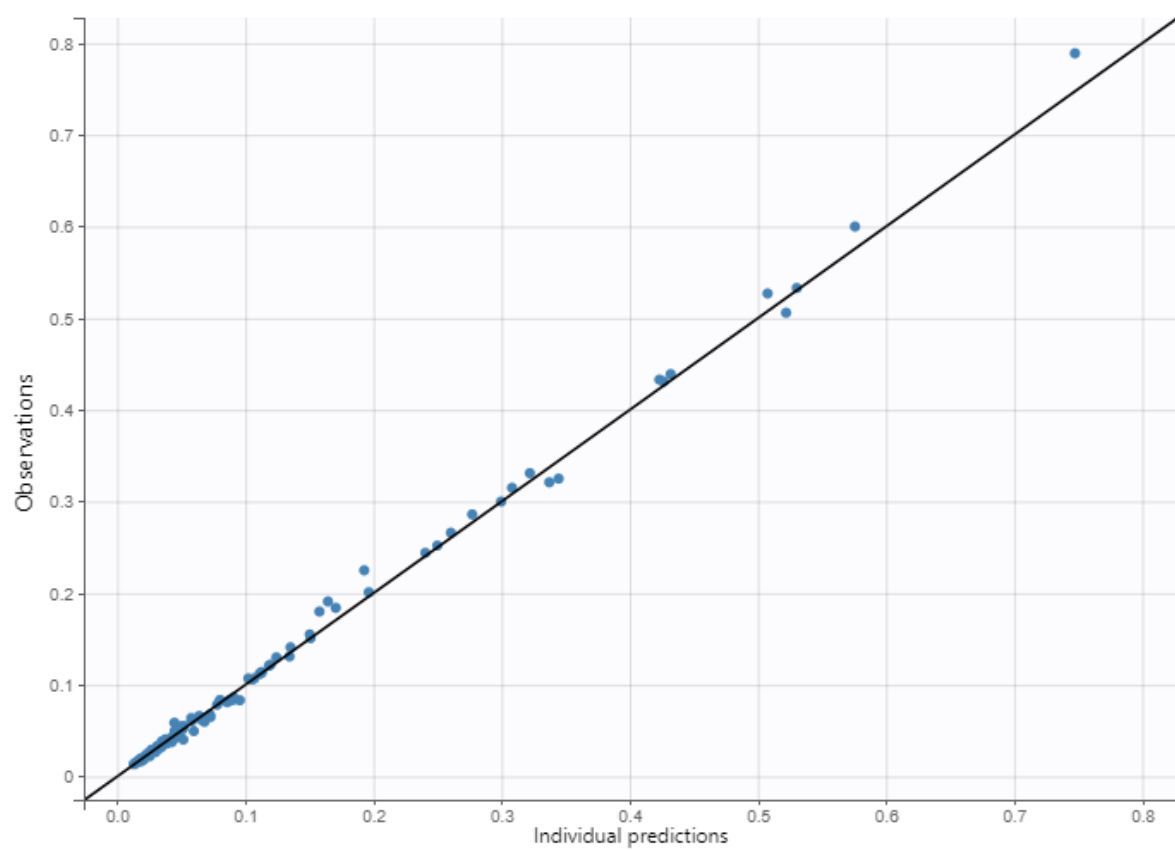


Figure 4.6 Individual observed and model-predicted iothexol concentration-time profiles (outliers proportion: 1.67%).

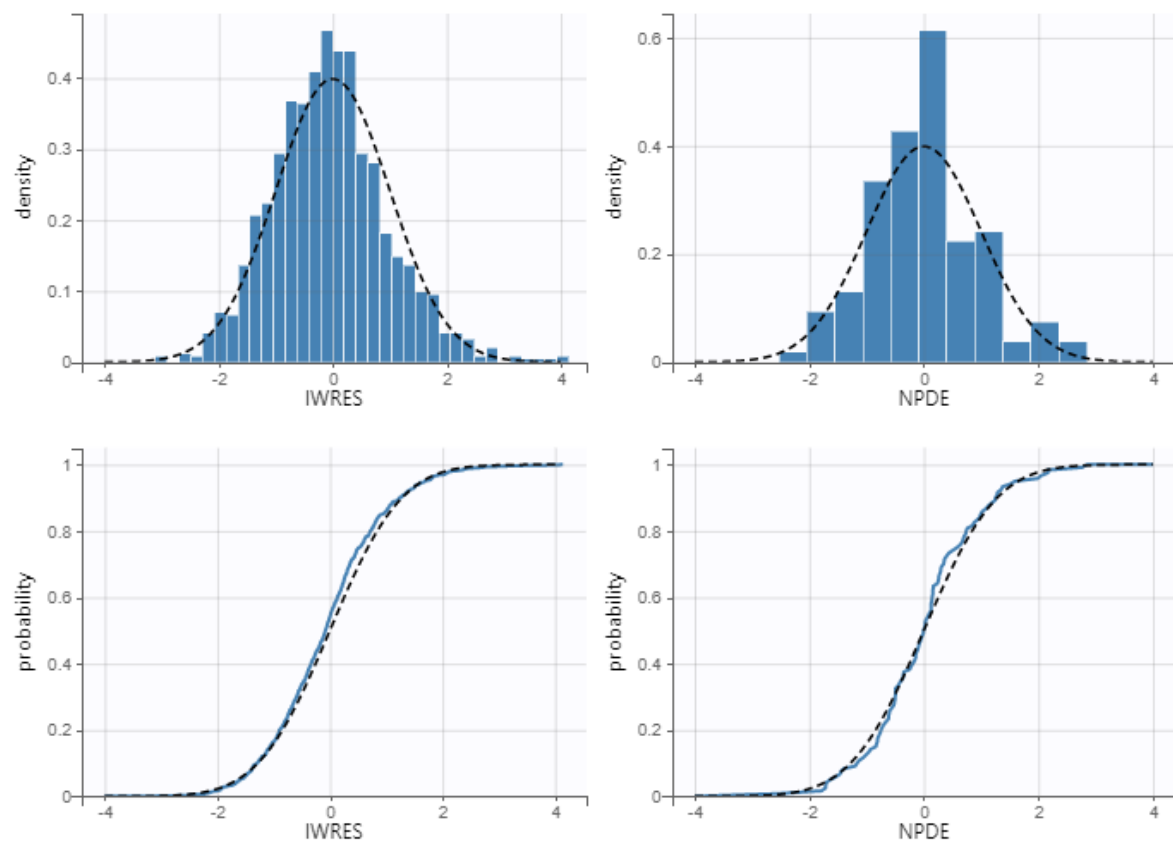


Figure 4.7 Distribution of the individual weighted residuals and nonparametric distributional errors for the final model.

Chapter 5 Conclusion and Future Directions

This dissertation investigated the use of biological age biomarkers derived from radiomics, epigenetics, and metabolic measurements as predictors of kidney function and drug clearance in older adults. The overarching hypothesis was that biological age assessments would capture interindividual variability in physiological aging more accurately than chronological age alone, thereby improving precision dosing strategies. Through three complementary aims, this work evaluated radiomic body composition biomarkers, morphomic age indices, and metabolic age parameters in relation to kidney function, while also exploring epigenetic age as a potential biomarker.

5.1 Summary of Key Findings

Aim 1: Improving Lean Body Weight Estimation Using CT-Derived Skeletal Muscle

Biomarkers. In a cohort of 63 patients with obesity participating in the Michigan Weight Management Program, CT-derived skeletal muscle area (SMA) demonstrated strong correlations with DEXA-measured lean body weight (LBW), with R^2 values of 0.80, 0.77, and 0.76 at the L3, L4, and T12 vertebral levels, respectively. Integration of SMA into the established Janmahasatian LBW equation substantially improved predictive accuracy, increasing R^2 from 0.76 to 0.86 at T12 and from 0.78 to 0.84 at L3. The enhanced equations demonstrated excellent performance, with mean absolute percentage errors of 6.53% (T12) and 6.13% (L3), and 83-88% of predictions falling within $\pm 10\%$ of DEXA-measured values. These findings establish that opportunistic use of existing CT scans can significantly improve LBW estimation precision, with important implications for weight-based drug dosing in patients with obesity.

Limitations: The findings from Aim 1 should be interpreted in light of several limitations. First, the analysis relied on opportunistic CT imaging obtained for clinical indications, which may

limit generalizability to populations without available imaging or with differing imaging protocols. Second, the cohort was derived from a single center and enriched for individuals with obesity, which may constrain extrapolation to lean or highly sarcopenic populations. Third, DEXA was used as the reference standard for LBW; while DEXA is widely accepted, it does not directly assess muscle quality or function, which may be relevant for certain PK applications. Finally, the analyses were cross-sectional and focused on predictive accuracy rather than prospective dosing outcomes. These limitations underscore the need for prospective validation of radiomic-enhanced LBW estimates in drug dosing studies across diverse populations and clinical settings.

Aim 2: Correlating Radiomics-Derived Morphomic Age (BA_{Mor}) Against Models of Aminoglycoside Clearance as Kidney Function Surrogates. Building upon these body composition measurements, the second aim tested whether composite morphomic age indices could improve the prediction of renal drug clearance. Using population PK modeling in 156 patients receiving aminoglycosides, three composite morphomic age indices (BA_{Mor}) were developed from CT-based body composition biomarkers and tested against chronological age. All three BA_{Mor} indices demonstrated superior model fit compared to chronological age, with the best-performing index (BA_{Mor_3}) achieving an AIC reduction of approximately 19 points relative to the base model. BA_{Mor_3} , which incorporated skeletal muscle metrics, bone density, visceral fat area, and subcutaneous fat density, provided more accurate predictions of aminoglycoside clearance than traditional age-based models. These results support the hypothesis that radiomic assessments of biological age better capture physiological variability relevant to renal drug clearance than chronological age alone.

Limitations: Limitations should be considered when interpreting the results of Aim 2. The morphomic age indices were developed using radiomic features that are inherently correlational and may reflect broader physiologic reserve rather than direct measures of renal function. As such, causal inference regarding kidney-specific aging cannot be established from these models. In addition, the population PK analyses were conducted in patients receiving aminoglycosides, a drug class with well-characterized renal elimination, which may limit extension of these findings to drugs with mixed or nonrenal clearance pathways. Potential confounding by disease severity

and comorbid conditions, which may independently influence both body composition and drug clearance, also warrants consideration despite model adjustment. Furthermore, radiomic feature extraction depends on image quality and segmentation consistency, which may vary across institutions. These limitations highlight the importance of external validation and evaluation of morphomic age indices across drug classes and clinical contexts.

Aim 3: Investigating Epigenetic Age (BA_{Epi}) and Metabolic Age (BA_{Met}) as Biomarkers of Kidney Function. The third aim extended this investigation by evaluating metabolic and epigenetic biomarkers using the gold standard measure of iohexol clearance. In the Kidney-PACE study of 24 adults (12 with type 2 diabetes, 12 controls), directly measured kidney function was evaluated in relation to both metabolic and epigenetic biomarkers. A novel ratio of resting metabolic rate to cystatin C (RMR/CysC) emerged as a significant predictor of measured kidney function, achieving predictive performance comparable to established estimated GFR equations. Notably, neither chronological age nor any of the four metabolic ages significantly improved kidney function prediction, and epigenetic age assessments (DunedinPACE) showed minimal deviation from chronological age (mean absolute difference 2.80 years) and did not contribute to improved predictions. These findings demonstrated that functional metabolic biomarkers may offer advantages over composite age indices for precision dosing applications.

Limitations: The conclusions from Aim 3 should be interpreted within the context of several important limitations. The Kidney-PACE study was designed as a mechanistic, proof-of-concept investigation with a modest sample size, which limits power to detect small or secondary effects and precludes definitive population-level inference. Epigenetic age was assessed using blood-based DNA methylation measures, which may not reflect tissue-specific aging processes within the kidney and may therefore be misaligned with determinants of renal drug clearance. In addition, the study cohort consisted of relatively healthy adults with and without type 2 diabetes, potentially restricting the range of biological aging and kidney dysfunction observed. The cross-sectional design further limits the assessment of longitudinal relationships between biological aging biomarkers and changes in kidney function over time. Nevertheless, the use of gold-standard iohexol clearance provides a robust physiologic reference, and these limitations inform

the design of larger, longitudinal studies needed to evaluate the clinical utility of metabolic and epigenetic biomarkers for precision dosing.

Collectively, these three aims provide convergent evidence that biological assessments of aging and physiological function can enhance precision pharmacotherapy, though with important nuances. CT-derived morphomic biomarkers consistently demonstrated value across multiple applications, from improving body composition estimates (Aim 1) to predicting drug clearance (Aims 2 and 3). The success of these radiomic approaches stems from their ability to quantify tissue-specific physiological changes that directly impact pharmacokinetics: muscle mass influences volume of distribution and creatinine production, adipose tissue distribution affects drug partitioning, and these composite measures correlate with overall metabolic health. The differential performance of various biological age metrics, however, highlights that not all aging biomarkers are equally relevant for pharmacological applications. BA_{Epi} , while powerful for predicting long-term health outcomes and mortality risk, showed limited utility for estimating current kidney functional capacity. In contrast, metabolic rate measurements, which reflect real-time physiological function, provided clinically meaningful associations with kidney clearance. This pattern suggests that for drug dosing applications, functional biomarkers that capture current physiological status may be more relevant than molecular markers that reflect cumulative aging processes.

The practical implications of these findings center on the opportunistic use of existing clinical data. CT scans are routinely performed for various clinical indications (cancer staging, surgical planning, trauma evaluation), generating body composition data that are typically overlooked. This dissertation demonstrates that extracting morphomic measurements from these existing scans, without additional patient burden, radiation exposure, or cost, can meaningfully improve dosing precision. As artificial intelligence and automated image analysis tools become more sophisticated and integrated into clinical workflows, such approaches could be implemented at scale to personalize drug therapy, particularly for renally eliminated medications in vulnerable populations such as older adults with obesity or chronic kidney disease.

5.2 Future Directions

The most immediate priority involves validating these morphomic approaches in prospective clinical studies. Pragmatic randomized trials could compare standard dosing algorithms to morphomic-informed dosing for high-risk medications, with the expected utility varying by drug class. Morphomic muscle biomarkers are likely most relevant for hydrophilic, renally eliminated drugs with low volumes of distribution (e.g., vancomycin, aminoglycosides), whereas adipose-derived CT biomarkers may better inform dosing of lipophilic agents with high volumes of distribution where drug partitioning into fat tissue is clinically significant. Such studies should assess both PK endpoints (target attainment, steady-state concentrations) and clinical outcomes (efficacy, toxicity, length of stay). Integration with electronic health records and automated image analysis pipelines would facilitate real-world implementation at scale.

Beyond clinical validation, the development of simplified morphomic indices optimized for specific drug classes represents another translational priority. Rather than comprehensive body composition profiling, streamlined indices using 2-3 key biomarkers might provide 80-90% of the predictive value with substantially reduced computational burden. Machine learning approaches could identify optimal biomarker combinations for different therapeutic scenarios, making implementation more feasible across diverse clinical settings.

Special populations warrant particular attention, given their unique pharmacokinetic challenges. Critically ill patients experience rapid body composition changes that standard dosing equations cannot capture; serial morphomic assessments from routine ICU imaging could improve dosing adjustments. Similarly, pediatric applications, where body size scaling is already emphasized, might benefit from maturation-adjusted morphomic indices. Additionally, pregnant women, who undergo dramatic physiological changes affecting pharmacokinetics, represent another understudied population where functional biomarkers could enhance dosing precision.

This dissertation relied primarily on cross-sectional analyses, which limit causal inference. Longitudinal studies tracking morphomic changes over months to years would provide crucial insights into temporal relationships. How do morphomic age trajectories relate to pharmacokinetic changes over time? Can interventions (exercise, nutrition, metabolic treatments) that favorably alter body composition translate to improved drug handling? Cohorts with serial imaging (e.g., cancer surveillance, chronic disease management) offer natural opportunities to address these questions.

Such longitudinal designs would also clarify whether biological age acceleration predicts future kidney function decline. If morphomic age at baseline predicts rates of GFR loss over 5-10 years, these indices could identify patients who need enhanced monitoring or early intervention. Such prognostic applications would complement the diagnostic and dosing applications demonstrated in this dissertation, expanding the clinical utility of morphomic assessments.

While BA_{Epi} showed limited utility for kidney function prediction in this work, future research should explore how combining multiple biological age modalities might provide complementary information. BA_{Epi} may capture long-term disease risk and frailty, BA_{Mor} reflects current body composition and metabolic health, and functional assessments (grip strength, gait speed, cognitive testing) quantify physiological reserve. Integrating these orthogonal measures through machine learning or composite scoring systems could yield comprehensive aging assessments that predict both immediate PK behavior and long-term outcomes.

Emerging technologies such as proteomics and metabolomics offer additional aging biomarkers that warrant investigation in pharmacology contexts. Multi-omic approaches that combine radiomics with molecular signatures might identify patient subgroups with distinct drug handling characteristics, enabling more granular precision dosing strategies. As these technologies mature and become more accessible, integrating them with morphomic assessments could further refine biological age estimation and its application to precision pharmacotherapy.

This dissertation demonstrated that biological age assessments, particularly CT-derived morphomic biomarkers and functional metabolic measures, can improve the estimation of kidney function and drug clearance beyond traditional chronological age-based approaches. The work provides foundational evidence for opportunistic use of existing clinical imaging to extract pharmacologically relevant body composition data, with particular promise for renally eliminated medications in older adults with obesity or chronic kidney disease. The medications highlighted in Table 1.3 of the introductory chapter represent the potential primary clinical targets for biological age-informed dosing strategies developed in this dissertation. As healthcare increasingly embraces precision medicine, the path forward requires collaborative efforts across clinical pharmacology, radiology, informatics, and implementation science to translate these findings from academic proof-of-concept to routine clinical practice, ultimately improving medication safety and efficacy for aging populations.

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