



Beyond Weight Loss: A Clinical Framework for Preserving Physiological Reserve During GLP-1 Receptor Agonist Therapy in Breast Cancer Survivorship

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Abstract

Breast cancer survivors frequently experience obesity, adverse alterations in body composition, skeletal muscle loss, bone deterioration, metabolic dysfunction, and progressive declines in physical function that collectively compromise long-term health, independence, and quality of life. The expanding use of glucagon-like peptide-1 (GLP-1) receptor agonists has generated growing interest in their role within survivorship care. Although these therapies provide well-established benefits for obesity, type 2 diabetes, and cardiometabolic disease, their incorporation into breast cancer survivorship requires a broader perspective that extends beyond weight reduction alone.

This review proposes a clinically applicable framework centered on the preservation of physiological reserve. Rather than focusing exclusively on weight loss, the framework integrates metabolic therapy with comprehensive assessment of body composition, musculoskeletal health, nutrition, exercise, functional performance, and principles of healthy aging to support long-term survivorship.

Evidence from oncology, endocrinology, metabolism, musculoskeletal biology, nutrition, exercise science, rehabilitation, immunometabolism, and mitochondrial biology was critically synthesized to examine the complex relationships between GLP-1 receptor agonist therapy, body composition, skeletal muscle, bone health, and long-term survivorship outcomes. Current evidence suggests that successful integration of GLP-1 receptor agonists should extend beyond traditional metabolic endpoints to include preservation of skeletal muscle, protection of bone health, optimization of nutritional status, resistance exercise, body composition monitoring, and comprehensive functional assessment. Emerging mechanistic evidence further highlights the interconnected roles of metabolism, musculoskeletal biology, mitochondrial function, inflammation, and immunometabolism in supporting recovery, resilience, and healthy aging.

GLP-1 receptor agonists represent an important component of contemporary metabolic management for appropriately selected breast cancer survivors but should be incorporated within a comprehensive survivorship strategy aimed at preserving physiological reserve. An integrated approach combining individualized nutrition, structured exercise, body composition assessment, bone health surveillance, and longitudinal functional evaluation has the potential to optimize long-term health beyond what weight reduction alone can achieve. Future prospective studies should evaluate multidimensional survivorship outcomes to determine how best to integrate metabolic therapies into personalized survivorship care models that prioritize functional independence, healthy aging, and quality of life.

Keywords: Breast cancer survivorship; GLP-1 receptor agonists; Physiological reserve; Body composition; Musculoskeletal health; Healthy aging

Introduction

The rapid adoption of glucagon-like peptide-1 (GLP-1) receptor agonists has transformed the management of obesity, type 2 diabetes, and cardiometabolic disease, with growing evidence demonstrating substantial improvements in weight reduction, glycemic control, and cardiovascular outcomes [1-4]. As their clinical use continues to expand, these agents are increasingly prescribed for

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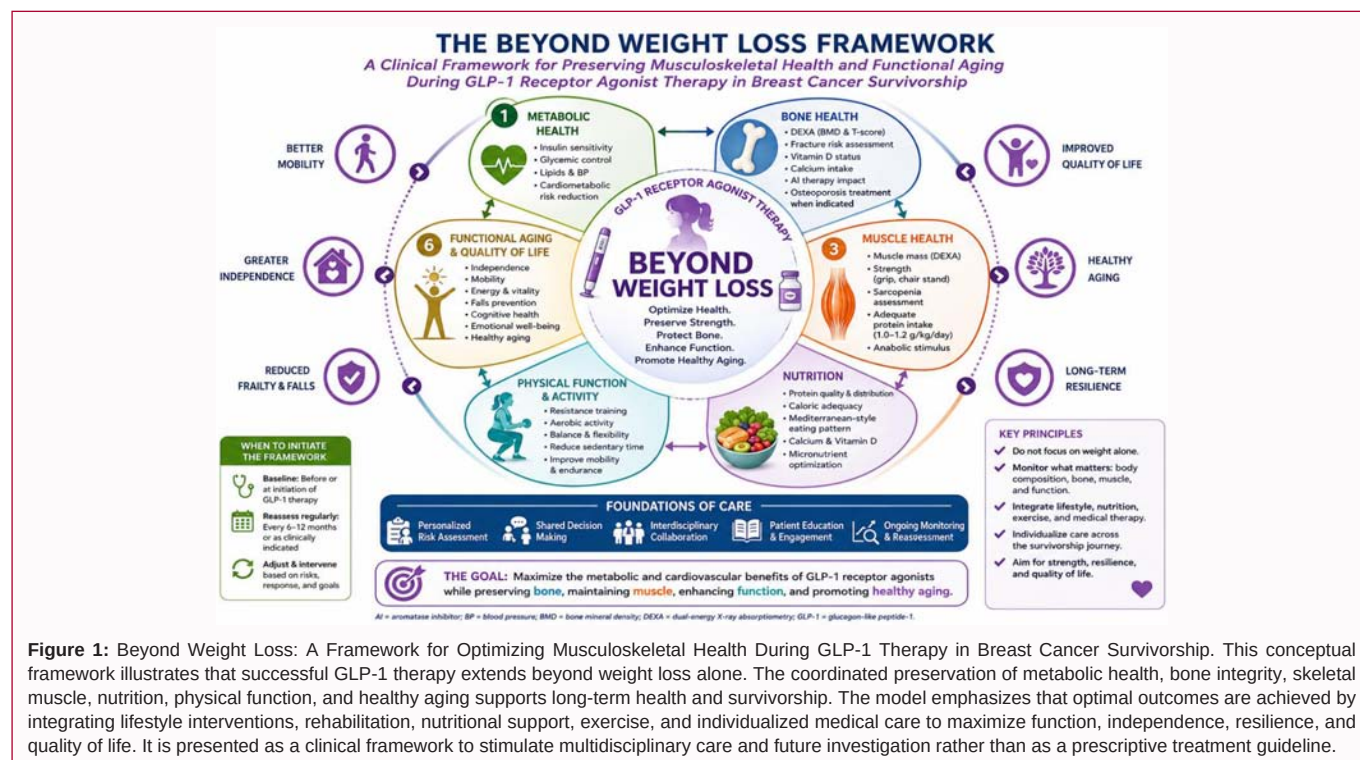


Figure 1: Beyond Weight Loss: A Framework for Optimizing Musculoskeletal Health During GLP-1 Therapy in Breast Cancer Survivorship. This conceptual framework illustrates that successful GLP-1 therapy extends beyond weight loss alone. The coordinated preservation of metabolic health, bone integrity, skeletal muscle, nutrition, physical function, and healthy aging supports long-term health and survivorship. The model emphasizes that optimal outcomes are achieved by integrating lifestyle interventions, rehabilitation, nutritional support, exercise, and individualized medical care to maximize function, independence, resilience, and quality of life. It is presented as a clinical framework to stimulate multidisciplinary care and future investigation rather than as a prescriptive treatment guideline.

breast cancer survivors who meet established treatment indications. This evolving landscape presents an important opportunity to improve metabolic health while raising critical questions regarding preservation of skeletal muscle, bone health, physical function, and healthy aging within survivorship care.

Although body weight has traditionally served as the primary measure of success in obesity management, it provides only a limited assessment of long-term health. Weight loss alone cannot distinguish reductions in adipose tissue from losses of lean body mass, nor does it adequately reflect preservation of skeletal muscle, bone integrity, functional capacity, or resilience to physiological stress [5-8]. Consequently, the clinical consequences of intentional weight reduction depend not only on the amount of weight lost but also on the composition of that loss. Weight reduction accompanied by preservation of skeletal muscle, maintenance of bone health, and retention of physical function differs fundamentally from weight loss associated with progressive sarcopenia, osteoporosis, or declining functional capacity. These distinctions are particularly important in breast cancer survivors, whose recovery is frequently influenced by chemotherapy, endocrine therapy, menopause, reduced physical activity, altered body composition, and accelerated biological aging [9-13].

The goals of breast cancer survivorship have likewise evolved. Advances in screening, systemic therapy, and supportive care have shifted clinical priorities beyond recurrence surveillance toward preservation of long-term health, functional independence, and healthy aging [14-17]. Contemporary survivorship recognizes that metabolic health, musculoskeletal integrity, nutrition, physical activity, cardiovascular health, rehabilitation, and patient-reported quality of life interact continuously to shape recovery and long-term outcomes. Consequently, clinicians are increasingly challenged to evaluate not only whether survivors remain disease free, but also whether they retain the biological capacity to remain active, resilient,

and independent throughout aging.

In this review, physiological reserve refers to the integrated biological capacity of musculoskeletal, metabolic, cardiovascular, immune, and functional systems to maintain homeostasis, adapt to physiological stress, and preserve independence throughout survivorship and aging. This concept aligns closely with the emerging principles of intrinsic capacity and healthy aging, both of which emphasize preservation of function rather than treatment of isolated impairments [18-21]. Viewed through this broader perspective, physiological reserve provides a more comprehensive measure of successful survivorship than body weight or metabolic control alone.

Although the literature on GLP-1 receptor agonists has expanded rapidly, most published reviews have focused primarily on obesity management, diabetes, cardiovascular outcomes, medication safety, or the biological mechanisms underlying these therapies [1,2,22,23]. Similarly, body composition, sarcopenia, osteoporosis, nutrition, exercise, rehabilitation, and survivorship have generally been examined as separate clinical domains. Comparatively little attention has been given to integrating these interrelated components into a clinically relevant framework for breast cancer survivors receiving GLP-1 receptor agonist therapy.

Accordingly, this review proposes an integrated clinical framework that extends beyond metabolic outcomes to emphasize preservation of physiological reserve across the breast cancer survivorship continuum. Rather than evaluating GLP-1 receptor agonist therapy solely by changes in body weight, we examine how preservation of skeletal muscle, bone health, metabolic function, nutritional status, physical performance, and patient-reported outcomes collectively shape long-term survivorship. By synthesizing evidence from oncology, endocrinology, metabolism, nutrition, exercise science, rehabilitation, musculoskeletal medicine, and healthy aging research, we present a practical multidisciplinary framework designed to

support functional independence, biological resilience, and quality of life while providing clinicians with an evidence-informed approach to comprehensive survivorship care (Figure 1).

The Breast Cancer Survivorship Journey: Windows of Opportunity to Preserve Physiological Reserve

Breast cancer survivorship does not begin when treatment ends; it begins at diagnosis and continues through surgery, systemic therapy, radiation, endocrine treatment, recovery, and long-term follow-up. Across this continuum, dynamic changes in body composition, skeletal muscle, bone remodeling, metabolic regulation, nutritional status, physical activity, and endocrine function collectively influence long-term health. Many of these adaptations develop gradually and remain clinically silent long before functional decline becomes apparent. Viewing survivorship as a continuous biological process rather than a discrete post-treatment phase creates opportunities for earlier intervention to preserve physiological reserve, maintain function, and promote healthy aging [14-17].

Historically, survivorship care has emphasized recurrence surveillance, management of treatment-related toxicities, and recognition of late complications. Although these priorities remain fundamental, contemporary survivorship increasingly recognizes that long-term outcomes are equally influenced by musculoskeletal health, metabolic resilience, nutritional status, and physical function. Alterations in body composition, skeletal muscle, bone health, and physical activity rarely occur in isolation. Instead, they evolve throughout treatment and recovery, interacting to shape resilience, independence, and quality of life [9-11,20,24,25].

This evolving perspective shifts survivorship from a predominantly reactive model toward one focused on prevention and preservation. Every stage of the breast cancer journey represents a clinical opportunity to implement nutritional optimization, resistance exercise, body composition assessment, bone health surveillance, rehabilitation, and, when clinically appropriate, metabolic therapy before irreversible physiological decline develops. In many cases, the timing of intervention may be as important as the intervention itself, as strategies introduced early are more likely to preserve function than attempts to reverse established frailty or musculoskeletal deterioration years later.

Figure 2 illustrates the breast cancer survivorship continuum and the evolving biological, metabolic, musculoskeletal, and functional challenges encountered from diagnosis through long-term recovery. Rather than depicting survivorship as a series of isolated treatment phases, the framework highlights a continuous process in which coordinated multidisciplinary care supports preservation of physiological reserve across the entire cancer journey.

Among the earliest and most clinically relevant changes during survivorship are alterations in body composition. Although body weight is routinely monitored throughout cancer treatment, it often obscures important physiological changes occurring beneath the surface. Many breast cancer survivors experience progressive reductions in skeletal muscle accompanied by increasing adiposity despite relatively stable body weight. These changes may begin during chemotherapy, continue throughout endocrine therapy, and persist long after treatment completion, contributing to impaired metabolic health, reduced physical performance, and progressive erosion of physiological reserve [26-30]. Consequently, survivorship

care is increasingly shifting beyond body weight alone toward comprehensive assessment of body composition and musculoskeletal health.

This broader perspective has also expanded the concept of muscle health beyond muscle mass alone. Muscle quantity, strength, quality, and physical performance each contribute to functional capacity and may decline at different rates during survivorship. Impaired muscle function can reduce exercise tolerance, compromise mobility, increase fatigue, diminish treatment tolerance, and threaten independence even before substantial losses of lean tissue become apparent. Moreover, baseline body composition has been associated with chemotherapy-related toxicity, treatment response, functional outcomes, and survival, supporting early assessment of musculoskeletal health rather than waiting until clinically significant sarcopenia develops [9-11, 31-33].

Bone health follows a similarly progressive trajectory. Chemotherapy-induced ovarian failure, aromatase inhibitor therapy, treatment-associated menopause, nutritional deficiencies, reduced mechanical loading, and aging collectively accelerate bone remodeling and loss of bone mineral density. Because these changes often remain asymptomatic until osteopenia, osteoporosis, or fragility fractures become clinically evident, opportunities for prevention are frequently missed. This underscores the importance of proactive surveillance and timely assessment of skeletal health as integral components of comprehensive survivorship care [24,25,34-37].

Importantly, skeletal muscle and bone function as an integrated biological unit rather than independent organ systems. Skeletal muscle provides the mechanical loading necessary to maintain bone integrity, while bone supplies structural support and endocrine signals that influence muscle metabolism and adaptation. Progressive deterioration of either tissue may therefore accelerate decline in the other, increasing vulnerability to osteosarcopenia, frailty, falls, fractures, and loss of functional independence. This biological interdependence provides a compelling rationale for integrating nutritional optimization, resistance exercise, body composition assessment, and bone health surveillance throughout survivorship rather than managing each complication separately [38-42].

Within this broader framework, GLP-1 receptor agonists should be viewed as one component of comprehensive survivorship care rather than as isolated weight-loss therapies. Their potential benefits are likely to be greatest when metabolic treatment is combined with interventions that preserve skeletal muscle, protect bone health, optimize nutritional status, encourage regular physical activity, and maintain functional performance. In this context, pharmacologic therapy complements—not replaces—a multidisciplinary strategy designed to preserve physiological reserve.

Ultimately, breast cancer survivorship is best understood as a continuum of opportunities rather than a sequence of isolated treatments. Every stage—from diagnosis through long-term follow-up—offers an opportunity to evaluate body composition, preserve skeletal muscle, protect bone health, optimize nutrition, promote physical activity, monitor functional performance, and individualize metabolic therapy. The overarching goal extends beyond preventing late complications to preserving the biological capacity that enables breast cancer survivors to maintain independence, healthy aging, and quality of life for years after completion of cancer treatment [12,18,20,21].

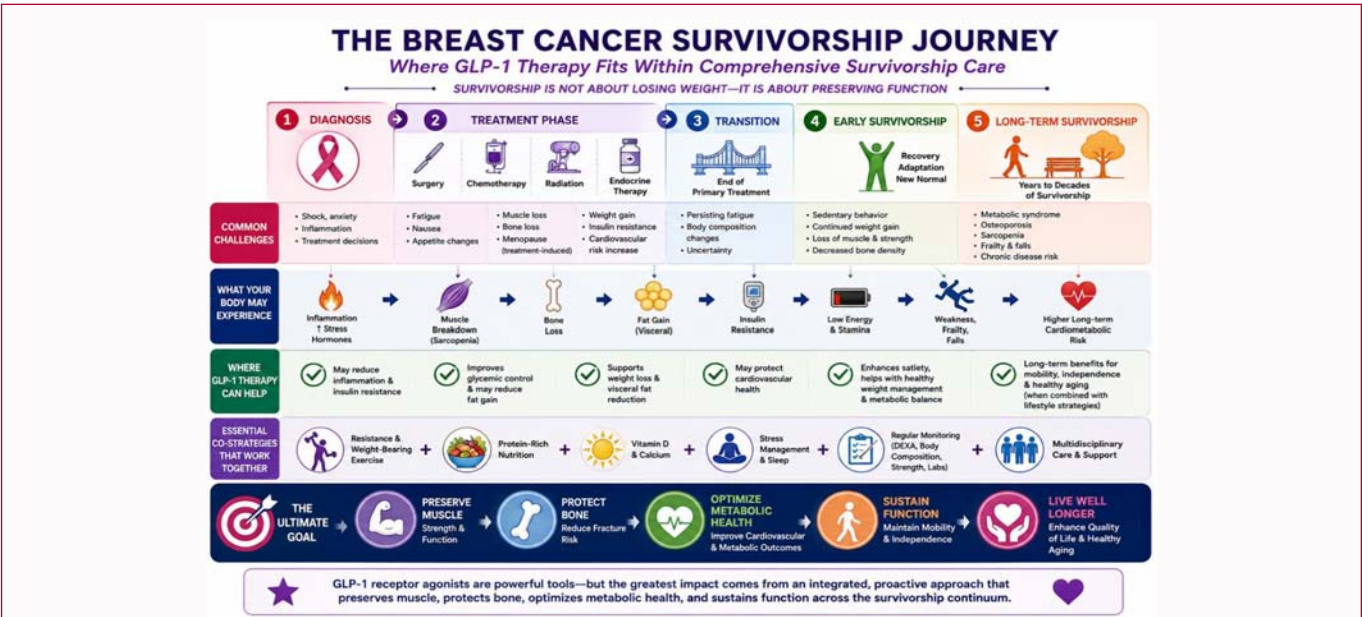


Figure 2: The Breast Cancer Survivorship Journey: Windows of Opportunity to Preserve Physiological Reserve. Conceptual framework illustrating the continuum of breast cancer survivorship from diagnosis through long-term follow-up and the evolving biological, metabolic, musculoskeletal, and functional challenges encountered across this trajectory. The figure highlights opportunities for coordinated multidisciplinary intervention—including GLP-1 receptor agonist therapy when clinically indicated, nutritional optimization, resistance exercise, rehabilitation, body composition assessment, bone health surveillance, and longitudinal follow-up—to preserve physiological reserve, maintain functional independence, and promote healthy aging. The framework is intended to illustrate an integrated survivorship model and stimulate future research rather than represent a treatment algorithm or clinical practice guideline.

Table 1: Clinical Windows of Opportunity for Preserving Musculoskeletal Health Throughout Breast Cancer Survivorship.

Stage	Major Risk	Window of Opportunity	Goal
Diagnosis	Sarcopenia, obesity, and frailty	Baseline assessment, nutrition, exercise, ± DXA	Build physiological reserve
Surgery	Deconditioning	Early mobilization, rehabilitation	Preserve mobility
Chemotherapy	Muscle loss, fatigue	Exercise, protein optimization	Preserve muscle and function
Radiation	Reduced activity	Continue rehabilitation and activity	Prevent deconditioning
Endocrine Therapy	Bone loss, fractures	DXA, calcium, vitamin D, resistance exercise	Preserve bone health
Long-Term Survivorship	Frailty, falls, aging	Longitudinal monitoring, lifestyle optimization, multidisciplinary care	Healthy aging and independence

Representative references: [9,11,17,24,26,27,31,34,35,37,43-48]

The Muscle–Bone–Metabolism Axis: An Integrated Biological Framework for Musculoskeletal Survivorship

Maintenance of musculoskeletal health depends on dynamic communication among skeletal muscle, bone, adipose tissue, metabolic pathways, and the immune system rather than the isolated function of individual organs. Together, these interconnected tissues exchange mechanical, endocrine, metabolic, and immunologic signals that regulate tissue remodeling, energy homeostasis, physical performance, and adaptation to physiological stress throughout life. Recognition of this biological crosstalk has transformed our understanding of musculoskeletal biology from an organ-based model into one that views muscle, bone, metabolism, and immunity as components of a coordinated physiological network that supports resilience during aging, illness, and recovery [38-41].

This systems-based perspective is particularly relevant to breast cancer survivorship because treatment-related physiological stress rarely affects a single tissue alone. Chemotherapy, endocrine therapy, treatment-induced menopause, reduced physical activity, nutritional compromise, chronic inflammation, and aging simultaneously

influence skeletal muscle, bone remodeling, mitochondrial function, immune regulation, and whole-body metabolism. Rather than evolving independently, these alterations interact over time, progressively diminishing physiological reserve and increasing vulnerability to frailty, falls, fractures, impaired physical performance, and loss of functional independence [9-11,24,25,36]. Appreciating this interconnected biology provides the foundation for survivorship strategies aimed at preserving function before irreversible decline becomes established.

Among these interconnected systems, skeletal muscle is now recognized as far more than a mechanical organ responsible for movement. Through secretion of myokines and other signaling molecules, skeletal muscle actively regulates bone remodeling, energy metabolism, vascular function, immune activity, and tissue repair. Bone, in turn, functions as a dynamic endocrine organ that responds to mechanical loading while releasing osteokines that influence muscle metabolism and adaptation. Together, muscle and bone operate as a coordinated biological unit whose reciprocal communication supports physical performance, metabolic homeostasis, and preservation of physiological reserve [38-40].

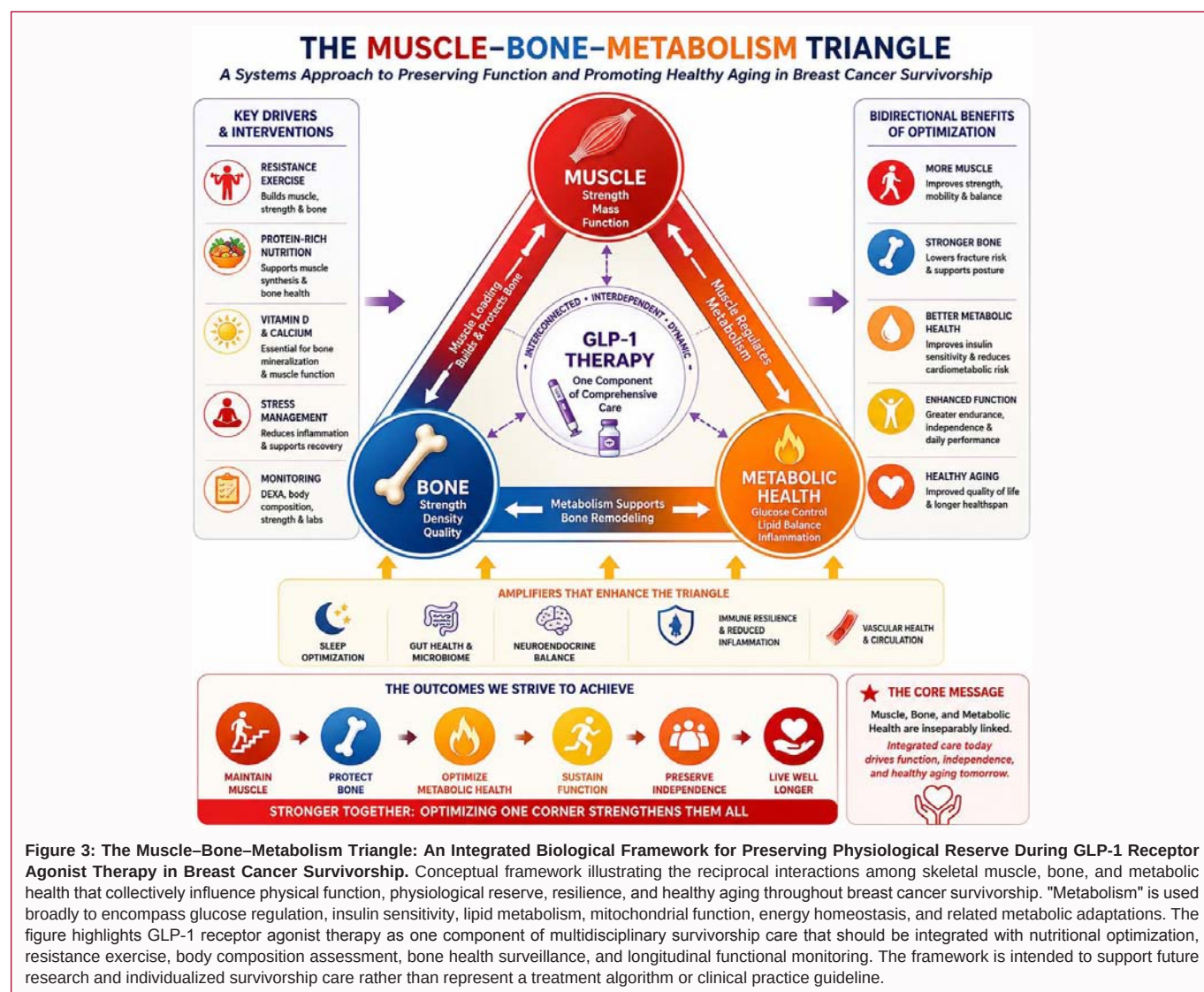


Figure 3: The Muscle–Bone–Metabolism Triangle: An Integrated Biological Framework for Preserving Physiological Reserve During GLP-1 Receptor Agonist Therapy in Breast Cancer Survivorship. Conceptual framework illustrating the reciprocal interactions among skeletal muscle, bone, and metabolic health that collectively influence physical function, physiological reserve, resilience, and healthy aging throughout breast cancer survivorship. "Metabolism" is used broadly to encompass glucose regulation, insulin sensitivity, lipid metabolism, mitochondrial function, energy homeostasis, and related metabolic adaptations. The figure highlights GLP-1 receptor agonist therapy as one component of multidisciplinary survivorship care that should be integrated with nutritional optimization, resistance exercise, body composition assessment, bone health surveillance, and longitudinal functional monitoring. The framework is intended to support future research and individualized survivorship care rather than represent a treatment algorithm or clinical practice guideline.

This biological network extends further through close interaction with metabolic and immune pathways. Immune cells respond to endocrine, metabolic, and mitochondrial signals while simultaneously regulating inflammation, tissue repair, muscle adaptation, and bone remodeling. These reciprocal relationships underpin the emerging concept of immunometabolism, in which metabolism and immune function are viewed as components of a unified adaptive system. Consequently, disruption of one component may propagate throughout the network, helping explain why treatment-related alterations in muscle, bone, metabolism, or immune regulation seldom occur in isolation and why preservation of musculoskeletal health requires coordinated support of multiple physiological pathways rather than correction of individual abnormalities alone [49-53].

Within this biological framework, GLP-1 receptor agonist therapy should be considered one component of a broader survivorship strategy rather than an isolated metabolic intervention. Although these agents improve obesity and cardiometabolic health in appropriately selected patients, their greatest contribution to breast cancer survivorship is likely to be achieved when metabolic therapy is combined with nutritional optimization, resistance exercise,

preservation of skeletal muscle, protection of bone health, and ongoing functional assessment. This perspective recognizes that reductions in body weight alone cannot fully capture the complex biological adaptations that determine resilience throughout survivorship.

Figure 3 illustrates the reciprocal interactions among muscle, bone, metabolism, and related physiological systems, emphasizing that long-term musculoskeletal health emerges from coordinated biological communication rather than isolated organ function. This framework provides the biological rationale for integrating GLP-1 receptor agonist therapy into comprehensive survivorship care instead of evaluating its success solely by reductions in body weight. Collectively, preservation of skeletal muscle, bone integrity, metabolic health, and physical function forms the biological foundation for maintaining physiological reserve, promoting healthy aging, and supporting long-term independence among breast cancer survivors.

GLP-1 Receptor Agonists Within the Integrated Biological Network

Recognition of the muscle–bone–metabolism axis provides an important biological context for understanding the role of glucagon-like peptide-1 (GLP-1) receptor agonists in breast cancer survivorship.

Beyond their established roles in obesity and glycemic management, these agents appear to influence a broad range of biological processes extending beyond body weight regulation. Experimental and clinical evidence increasingly suggests that GLP-1 signaling participates in pathways governing energy homeostasis, inflammatory regulation, vascular function, mitochondrial bioenergetics, autonomic activity, and cellular adaptation to metabolic stress [1-3,22,23]. Viewed from this broader perspective, GLP-1 receptor agonists become part of an interconnected physiological network that contributes to musculoskeletal health, resilience, and long-term survivorship.

At the same time, the current evidence should be interpreted with appropriate scientific caution. Much of our understanding derives from studies in obesity, type 2 diabetes, cardiovascular medicine, experimental models, and mechanistic investigations rather than prospective studies conducted specifically in breast cancer survivors. Accordingly, direct translation of these findings to oncology populations requires careful interpretation. Nevertheless, the remarkable consistency of observations across multiple disciplines provides a compelling biological rationale for exploring how GLP-1 receptor agonists may influence the reciprocal interactions among skeletal muscle, bone, metabolism, and immune regulation throughout survivorship [7,8,54,55].

This evolving perspective also changes how metabolic therapy is viewed. Instead of acting through a single physiological pathway, GLP-1 receptor agonists appear to influence adaptive processes that coordinate energy utilization, substrate metabolism, inflammatory signaling, and tissue homeostasis. These same pathways are simultaneously challenged by chemotherapy, endocrine therapy, treatment-induced menopause, reduced physical activity, nutritional compromise, chronic inflammation, and aging. Appreciating this shared biology helps explain why metabolic therapy should be integrated into comprehensive survivorship care instead of being evaluated solely by changes in body weight.

Breast cancer treatment rarely disrupts only one biological system. Instead, cumulative alterations in endocrine signaling, nutrition, physical activity, mitochondrial function, immune regulation, and metabolism interact over time, progressively diminishing the body's capacity to adapt to physiological stress. This concept of adaptive network resilience helps explain why restoration of long-term health cannot be achieved through isolated management of individual complications. Rather, preservation of physiological reserve requires coordinated strategies that simultaneously support multiple interacting biological pathways.

Within this integrated perspective, preservation of musculoskeletal health extends beyond maintaining skeletal muscle mass or bone mineral density alone. Long-term function depends on coordinated preservation of muscle quality, bone strength, metabolic regulation, nutritional adequacy, physical activity, mitochondrial integrity, and adaptive physiological responses. Consequently, the success of GLP-1 receptor agonist therapy should be judged not only by the magnitude of weight reduction achieved, but also by its contribution to a comprehensive survivorship strategy that preserves physiological reserve, maintains functional independence, and promotes healthy aging.

Among the systems coordinating these adaptive responses, mitochondria occupy a central position. As key regulators of cellular energetics, oxidative stress, metabolic signaling, and tissue

adaptation, mitochondria provide a mechanistic bridge linking skeletal muscle, bone remodeling, immune function, and whole-body metabolism. Appreciating this integrative role provides a logical transition to the following discussion of mitochondrial biology and its contribution to preserving physiological reserve throughout breast cancer survivorship.

Mitochondria: Integrating the Muscle–Bone–Metabolism Axis

If skeletal muscle, bone, metabolism, and immune regulation function as an integrated biological network, mitochondria represent one of its principal coordinating hubs. Once regarded primarily as the cell's energy-producing organelles, they are now recognized as dynamic regulators of oxidative stress, inflammatory signaling, apoptosis, metabolic adaptation, and tissue repair. Through these diverse functions, mitochondria influence skeletal muscle performance, bone remodeling, immune activity, and whole-body metabolism while coordinating the adaptive responses required to preserve physiological reserve throughout life [56-59].

This expanded understanding is particularly relevant to breast cancer survivorship because many consequences of cancer treatment converge on mitochondrial biology. Chemotherapy, endocrine therapy, treatment-induced menopause, aging, reduced physical activity, nutritional compromise, and chronic inflammation may each influence mitochondrial bioenergetics, oxidative balance, and cellular resilience. Although the magnitude and clinical significance of these effects vary among individuals, collectively they reinforce the concept that mitochondrial health reflects the combined influences of metabolism, nutrition, exercise, and musculoskeletal physiology rather than any single therapeutic intervention [55-57,60].

Beyond serving as cellular energy regulators, mitochondria provide an important mechanistic bridge linking skeletal muscle, bone, metabolism, and immune function. Efficient mitochondrial activity supports skeletal muscle contractility, protein turnover, and adaptation to exercise, while bone remodeling depends on adequate cellular energy availability and tightly regulated oxidative signaling. Mitochondrial function also influences immune responses and inflammatory regulation, extending its effects well beyond individual tissues. These reciprocal interactions illustrate how disruption within one component of the network may propagate across others, providing a biological explanation for why preservation of musculoskeletal health depends on coordinated support of multiple physiological systems rather than isolated protection of muscle or bone alone [38-40,50].

Importantly, strategies that preserve mitochondrial function rarely operate through a single mechanism. Regular physical activity, resistance exercise, adequate nutritional intake, maintenance of skeletal muscle, and optimization of metabolic health each promote mitochondrial adaptation while simultaneously strengthening broader physiological resilience. Viewed in this context, lifestyle interventions and pharmacologic therapies should be regarded as complementary components of comprehensive survivorship care rather than competing treatment strategies [61-65].

Although mitochondrial biology represents one of the most promising areas of contemporary survivorship research, important knowledge gaps remain. Future prospective studies integrating mitochondrial biomarkers with longitudinal assessment of body composition, skeletal muscle, bone health, physical performance,

patient-reported outcomes, and physiological reserve may provide a more comprehensive understanding of how cellular energetics influence long-term survivorship. Such multidimensional approaches may ultimately identify opportunities to personalize survivorship care while strengthening the biological foundation for multidisciplinary intervention [55,59,66,67].

Collectively, the evidence reviewed thus far suggests that preservation of physiological reserve depends not on maintaining individual organs in isolation, but on sustaining the biological communication linking skeletal muscle, bone, metabolism, immune regulation, and mitochondrial function. This systems-based perspective provides the scientific foundation for translating integrated biology into practical survivorship care, where comprehensive assessment, individualized intervention, and coordinated multidisciplinary management become the clinical expression of the interconnected mechanisms described throughout this review.

From Prescription to Preservation: Translating Systems Biology into Clinical Survivorship Care

The expanding use of glucagon-like peptide-1 (GLP-1) receptor agonists provides an opportunity to rethink how metabolic therapy is incorporated into breast cancer survivorship. Although these agents have demonstrated substantial benefits for appropriately selected patients with obesity, type 2 diabetes, and cardiometabolic disease, their successful integration into survivorship requires a broader clinical perspective than weight reduction alone. The biological framework developed throughout the preceding sections suggests that long-term outcomes depend on coordinated preservation of skeletal muscle, bone health, metabolic function, nutrition, physical activity, immune regulation, and physiological reserve. Within this context, GLP-1 receptor agonists should be viewed as one component of comprehensive survivorship care rather than a stand-alone pharmacologic intervention.

This broader perspective also reshapes the goals of clinical evaluation. Instead of documenting treatment-related changes only after they become clinically apparent, survivorship care should emphasize early recognition of physiological vulnerability and timely intervention before functional decline develops. Although body weight and body mass index remain useful clinical measures, they provide only a partial representation of long-term health. A thorough baseline assessment establishes an individualized reference point from which subsequent changes in body composition, musculoskeletal health, metabolic status, physical performance, and patient-reported outcomes can be interpreted while guiding personalized survivorship planning [14-17].

Initial evaluation should include assessment of body composition, nutritional status, habitual physical activity, skeletal muscle strength, fracture risk, bone mineral density, cardiometabolic health, comorbid conditions, functional performance, and individual survivorship goals. When clinically appropriate, dual-energy X-ray absorptiometry (DXA) provides valuable information regarding lean body mass, adiposity, and bone mineral density, complementing conventional anthropometric measurements that cannot distinguish favorable from unfavorable changes in body composition [68-72].

Functional evaluation is equally important because preservation of physiological reserve extends beyond structural measurements

alone. Measures such as gait speed, the Timed Up and Go test, frailty assessment, and patient-reported outcomes provide valuable insight into an individual's capacity to maintain independence and recover from physiological stress. Together, these complementary assessments help identify survivors who may benefit from earlier nutritional intervention, structured resistance exercise, rehabilitation, optimization of bone health, or individualized metabolic therapy before clinically meaningful functional decline develops [20,73-76].

Taken together, these assessments shift the clinical emphasis from treating isolated abnormalities to preserving the biological systems that sustain long-term health. Beyond asking whether body weight has declined, clinicians should consider whether skeletal muscle has been maintained, bone health protected, physical function preserved, metabolic health optimized, and quality of life supported throughout treatment and recovery. In this setting, GLP-1 receptor agonist therapy becomes part of a coordinated multidisciplinary strategy aimed at preserving physiological reserve while optimizing overall survivorship.

Figure 4 illustrates this patient-centered approach to clinical decision-making. Rather than depicting a rigid treatment algorithm, the framework emphasizes comprehensive baseline assessment, individualized goal setting, integration of lifestyle and rehabilitation strategies, longitudinal monitoring, and multidisciplinary collaboration throughout survivorship. By aligning metabolic therapy with nutrition, exercise, body composition assessment, bone health surveillance, and functional evaluation, this model translates systems biology into practical survivorship care while recognizing that long-term outcomes depend on coordinated preservation of multiple interacting physiological systems rather than any single therapeutic intervention.

Longitudinal Monitoring and Multidisciplinary Survivorship Care

Initiation of glucagon-like peptide-1 (GLP-1) receptor agonist therapy should be viewed not as the end of therapeutic planning but as the beginning of an ongoing process of survivorship care. Body composition, skeletal muscle, bone health, nutritional status, physical performance, and metabolic function continue to evolve throughout treatment, requiring regular follow-up as survivors adapt to both therapy and recovery. Longitudinal monitoring therefore provides an opportunity to identify emerging physiological vulnerability before clinically significant functional decline develops. Rather than relying on isolated clinical encounters, this proactive approach emphasizes continuous evaluation, timely intervention, and individualized adaptation of survivorship care over time [15-17].

This evolving process extends well beyond routine measurement of body weight. Periodic evaluation of body composition, skeletal muscle preservation, bone health, nutritional adequacy, physical function, and patient-reported outcomes provides a more complete understanding of an individual's response to treatment. Repeated assessment enables clinicians to distinguish favorable metabolic adaptation from progressive loss of lean tissue, declining musculoskeletal health, or functional deterioration that might otherwise remain unrecognized. Within this framework, the quality of weight loss becomes just as clinically important as its magnitude [26,28,68-70,77].

Among these domains, body composition offers particularly valuable insight into the physiological changes occurring during

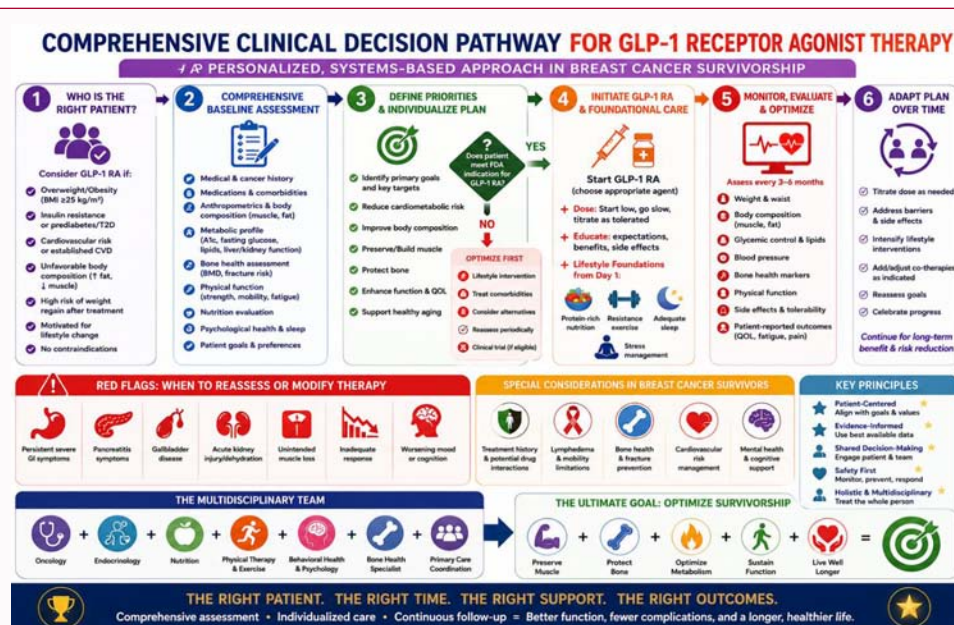


Figure 4: The Comprehensive Survivorship Decision Pathway for GLP-1 Receptor Agonist Therapy.

Figure 4 illustrates how comprehensive assessment provides the foundation for individualized clinical decision-making throughout breast cancer survivorship. Rather than representing a rigid treatment algorithm, the framework emphasizes continuous reassessment, multidisciplinary collaboration, and coordinated preservation of physiological reserve as patients progress through metabolic therapy and long-term follow-up.

treatment because body weight alone cannot distinguish beneficial adaptation from loss of metabolically important tissues. Whenever clinically appropriate, dual-energy X-ray absorptiometry (DXA) provides objective evaluation of lean body mass, adiposity, and bone mineral density, complementing conventional anthropometric measurements. Equally important, interpretation should emphasize patterns of change over time rather than isolated measurements, allowing clinicians to recognize early deterioration and individualize nutritional, rehabilitation, and metabolic interventions before irreversible functional decline develops [68-72].

Objective measurements, however, represent only one dimension of survivorship care. Imaging and laboratory studies cannot fully capture how survivors function in everyday life or how well they tolerate the physiological demands of recovery. Functional evaluation therefore provides essential complementary information. Measures such as gait speed, the Timed Up and Go test, frailty assessment, muscle strength, and validated patient-reported outcomes offer practical insight into mobility, endurance, independence, and overall physiological reserve. Improvements in body composition have limited clinical value if they are not accompanied by preservation of physical function and quality of life. Conversely, meaningful gains in mobility, confidence, daily activity, and patient-reported well-being may reflect successful preservation of physiological reserve even when reductions in body weight are relatively modest [18,20,73-79].

Nutrition and physical activity remain indispensable partners throughout metabolic treatment. Adequate protein intake, individualized nutritional counseling, resistance exercise, and regular physical activity provide the biological stimulus necessary to preserve skeletal muscle, support bone remodeling, promote mitochondrial adaptation, and maintain functional performance during intentional weight reduction. Rather than serving merely as supportive measures, these interventions should be regarded as integral therapeutic components that complement pharmacologic

management while preserving physiological reserve and optimizing long-term survivorship outcomes [61-65,80-84].

Bone health deserves equal attention throughout survivorship. Women receiving endocrine therapy or experiencing treatment-induced menopause remain at increased risk for accelerated bone loss and fracture, making ongoing surveillance an essential component of comprehensive care. Periodic evaluation of bone mineral density, fracture risk, and, when clinically indicated, calcium and vitamin D status should be accompanied by implementation of evidence-based bone-protective strategies, particularly among survivors with additional musculoskeletal risk factors. Preserving skeletal integrity supports mobility, facilitates participation in resistance exercise, and helps maintain long-term independence, reinforcing the close biological relationship between bone health and physiological reserve [24,34-37,44,48,85-87].

Ultimately, successful survivorship care depends on coordinated multidisciplinary collaboration rather than isolated clinical decision-making. Medical oncologists, endocrinologists, primary care physicians, rehabilitation specialists, physical therapists, registered dietitians, exercise professionals, nursing teams, and survivorship clinicians each contribute complementary expertise that supports long-term recovery. Effective communication among these disciplines allows body composition, nutrition, skeletal muscle, bone health, metabolic regulation, and functional performance to be managed as interconnected components of a unified survivorship strategy rather than separate clinical concerns. Within this collaborative model, GLP-1 receptor agonist therapy becomes one element of a comprehensive program designed to preserve health, function, and independence throughout the survivorship continuum [15-17,64,88].

Collectively, longitudinal monitoring and multidisciplinary management provide the clinical foundation for preserving physiological reserve. Equally important, they create the framework through which systems biology can be translated into everyday

clinical practice. Understanding why these coordinated strategies improve long-term outcomes requires consideration of the dynamic interactions among metabolism, immune regulation, and tissue adaptation. The following section therefore explores the emerging field of immunometabolism and its potential role in advancing practical breast cancer survivorship care.

Translating Systems Biology into Clinical Survivorship Care

Understanding the biological interactions described throughout this review has little practical value unless that knowledge ultimately improves patient care. The purpose of adopting a systems biology perspective in breast cancer survivorship is therefore not simply to describe complex physiological networks, but to enable earlier recognition of biological vulnerability, more comprehensive clinical assessment, and timely intervention before potentially reversible functional decline becomes established. Appreciating the dynamic interactions among skeletal muscle, bone, metabolism, mitochondrial function, immune regulation, nutrition, and physical activity provides a broader framework for survivorship care that emphasizes preservation of physiological reserve rather than isolated management of treatment-related complications.

This perspective also changes how the clinical effects of GLP-1 receptor agonists should be interpreted. Weight reduction, glycemic control, and improvements in cardiometabolic health remain important therapeutic outcomes, but they represent only part of the overall clinical picture. Long-term benefit depends equally on preservation of skeletal muscle, maintenance of bone health, nutritional adequacy, physical performance, and patient-reported function. Considered together, these factors determine whether intentional weight loss translates into meaningful improvements in health, independence, and quality of life. Within this context, GLP-1 receptor agonists are best viewed as one component of an integrated survivorship strategy rather than stand-alone therapeutic interventions [3,7,22,23].

Additional support for this framework comes from the emerging field of immunometabolism, which underscores the close relationship between metabolic regulation and immune function. Cellular metabolism influences immune-cell activation, inflammatory signaling, tissue repair, and adaptation to physiological stress, while immune responses simultaneously reshape systemic metabolism and energy utilization. These reciprocal interactions reinforce the concept that successful physiological adaptation depends on coordinated communication across multiple interconnected systems. Although many of these mechanistic observations remain to be confirmed specifically in breast cancer survivorship, accumulating evidence suggests that metabolic therapies may influence this broader physiological environment through integrated rather than isolated pathways [49,50,52,53,59,89].

At the same time, these observations should be interpreted with appropriate scientific restraint. Much of the available mechanistic evidence originates from experimental models or non-oncology populations, and prospective studies involving breast cancer survivors remain limited. Consequently, the objective of this framework is not to expand the clinical indications for GLP-1 receptor agonists beyond established evidence, but to provide a biological rationale for integrating metabolic therapy into comprehensive survivorship care for appropriately selected patients. Future translational investigations

combining molecular biomarkers with longitudinal assessment of body composition, musculoskeletal health, physical performance, physiological reserve, and patient-reported outcomes will be essential for determining how these interconnected pathways influence long-term recovery [55-57,66,67].

Collectively, the evidence reviewed throughout this manuscript suggests that successful breast cancer survivorship depends on preserving coordinated physiological function rather than optimizing any single biological system. Nutritional support, resistance exercise, rehabilitation, body composition assessment, bone health surveillance, cardiovascular risk reduction, metabolic management, and individualized pharmacologic therapy should therefore be viewed as complementary components of a unified survivorship strategy. Their greatest clinical value lies not in their individual effects, but in their combined ability to preserve resilience, sustain functional independence, and promote healthy aging.

If preservation of physiological reserve is to become a meaningful therapeutic objective, clinicians must also have reliable methods to measure it. Conventional anthropometric measurements alone cannot adequately capture the complex physiological adaptations that occur throughout survivorship. The following section therefore examines contemporary approaches to assessing body composition, skeletal muscle, bone health, and functional performance, illustrating how these complementary measures can guide individualized survivorship care while providing a more comprehensive definition of successful therapeutic outcomes.

Beyond Body Weight: Redefining Success in Breast Cancer Survivorship

For decades, success in obesity treatment has been judged primarily by reductions in body weight. Although weight loss remains an important therapeutic objective for appropriately selected patients, body weight alone provides only a limited reflection of overall physiological health. It cannot distinguish reductions in adipose tissue from loss of skeletal muscle, nor can it adequately capture changes in bone health, muscle quality, physical performance, metabolic resilience, or functional independence. As metabolic therapies become increasingly incorporated into breast cancer survivorship, these limitations underscore the need to redefine therapeutic success using measures that extend beyond the number displayed on the scale [3-7].

This shift reflects a broader evolution in survivorship care. The objective is no longer simply to achieve weight reduction but to preserve the biological systems that sustain long-term recovery, independence, and healthy aging. Among breast cancer survivors, treatment-related alterations in skeletal muscle, adipose tissue, bone remodeling, endocrine function, and physical activity frequently develop simultaneously and may persist long after completion of therapy. Consequently, individuals with similar body weights may exhibit markedly different levels of physiological reserve, functional capacity, and quality of life, illustrating that body weight alone provides an incomplete measure of survivorship [9,10,26,28,77].

Body composition provides a more meaningful window into these physiological adaptations because skeletal muscle, adipose tissue, and bone each make distinct contributions to metabolic regulation, physical performance, immune function, and resilience to physiological stress. Importantly, substantial changes within these tissues may occur despite relatively stable body weight,

meaning that conventional anthropometric measurements can substantially underestimate treatment-related physiological change. Comprehensive evaluation of body composition therefore enables clinicians to identify biological adaptations that might otherwise remain unrecognized while providing a stronger foundation for individualized survivorship care [68-72].

Body composition, however, should not be regarded as the ultimate therapeutic endpoint. Its greatest value lies in the insight it provides into recovery rather than in the measurements themselves. Favorable body composition supports skeletal muscle function, bone integrity, metabolic health, and physical performance, but improvements in these measures have limited clinical significance if accompanied by declining strength, impaired mobility, increasing frailty, or reduced participation in daily activities. Conversely, relatively modest improvements in body composition may still represent meaningful therapeutic success when survivors maintain independence, preserve mobility, and continue to enjoy a high quality of life [73-78].

These observations support a broader definition of therapeutic success. Body composition represents one important component of survivorship assessment, but it should always be interpreted alongside muscle strength, physical performance, nutritional status, bone health, functional capacity, and patient-reported outcomes. Together, these complementary measures provide a more complete understanding of physiological reserve while more accurately reflecting the biological resilience that enables survivors to remain active, independent, and engaged throughout aging. This multidimensional perspective also aligns closely with emerging concepts of healthy aging and intrinsic capacity, emphasizing that successful survivorship is defined not simply by the amount of weight lost, but by preservation of long-term function and quality of life [16,18-21].

Equally important, preservation of physiological reserve extends beyond maintenance of skeletal muscle alone. Although skeletal muscle remains a central determinant of physical function, long-term resilience also depends on preservation of bone integrity, metabolic health, cardiovascular fitness, nutritional adequacy, cognitive function, psychological well-being, and the coordinated interaction of these physiological systems. Physiological reserve therefore cannot be reduced to a single biological measurement or imaging finding. Instead, it reflects the integrated capacity of the body to adapt to physiological stress while maintaining function, independence, and quality of life throughout survivorship and aging.

Recognizing these broader dimensions of recovery naturally reshapes how musculoskeletal health is evaluated. Preservation of lean body mass alone cannot fully define successful adaptation to therapy, just as body weight alone cannot adequately define therapeutic success. Contemporary survivorship care has therefore evolved beyond simply quantifying skeletal muscle toward the broader concept of muscle health, encompassing muscle quantity, muscle quality, strength, physical performance, and functional capacity across the survivorship continuum.

From Sarcopenia to Lifelong Muscle Health

Our understanding of musculoskeletal health has evolved considerably over the past decade. Historically, clinical attention focused primarily on identifying sarcopenia after clinically significant skeletal muscle loss had already occurred. Although recognition and diagnosis of sarcopenia remain important, growing evidence

supports a broader approach that emphasizes preservation of muscle health throughout the lifespan rather than treatment of advanced muscle loss alone. This evolution reflects an important shift in clinical thinking: the objective is no longer simply to detect deterioration but to preserve the structural, metabolic, and functional characteristics of skeletal muscle that support healthy aging and long-term survivorship. Muscle quantity, strength, quality, neuromuscular function, and physical performance are now recognized as complementary dimensions of lifelong muscle health rather than isolated clinical measurements [32,33,90-92].

This contemporary perspective has particular relevance for breast cancer survivors because treatment-related changes in skeletal muscle often begin long before clinically apparent sarcopenia develops. Chemotherapy, endocrine therapy, treatment-induced menopause, nutritional compromise, and reductions in physical activity may each contribute to progressive physiological changes throughout survivorship. Consequently, preservation of muscle health should begin early, with interventions designed to prevent cumulative decline rather than respond only after substantial loss of muscle mass or function has occurred [9-11,31,43].

This shift also changes how skeletal muscle is evaluated in clinical practice. Individuals with similar amounts of lean body mass may differ substantially in muscle strength, contractile quality, mobility, exercise tolerance, and functional independence. These observations demonstrate that muscle health cannot be adequately described by muscle quantity alone but instead reflects the integrated performance of structural, metabolic, neurological, and physiological systems. Comprehensive clinical evaluation should therefore combine body composition assessment with objective measures of muscle strength, physical performance, nutritional status, and patient-reported functional outcomes to provide a more meaningful understanding of musculoskeletal health [91-93].

Body composition assessment provides an important foundation for this multidimensional approach. Dual-energy X-ray absorptiometry (DXA) remains one of the most practical and widely accepted methods for assessing lean body mass, adiposity, and bone mineral density in both clinical practice and research. However, DXA should be viewed as one component of a comprehensive musculoskeletal evaluation rather than a stand-alone measure of muscle health. Its greatest value emerges when findings are interpreted alongside assessments of muscle strength, gait speed, balance, physical performance, nutritional status, and overall clinical function, providing a more complete picture of physiological adaptation throughout survivorship [68-72,94].

This multidimensional perspective also influences interpretation of changes in lean body mass during metabolic therapy. Modest reductions in lean tissue do not necessarily indicate unfavorable clinical outcomes when accompanied by preservation of muscle strength, physical performance, nutritional adequacy, and continued independence. Conversely, maintenance of lean body mass alone should not be interpreted as therapeutic success if survivors experience progressive weakness, declining mobility, or worsening functional capacity. Meaningful evaluation of muscle health therefore requires integration of structural, functional, and patient-centered measures rather than reliance on any single biological marker [3-8].

Ultimately, preservation of muscle health serves a purpose that extends well beyond maintaining skeletal muscle itself. Healthy skeletal muscle supports mobility, metabolic regulation, bone

integrity, resilience to physiological stress, and participation in daily activities. The greatest value of these biological functions, however, lies in helping survivors remain active, independent, and engaged throughout aging. In this context, muscle health becomes an essential contributor to preserving physiological reserve rather than an isolated therapeutic endpoint.

Recognizing muscle health as a multidimensional construct naturally shifts attention toward the outcomes that matter most to patients. Preservation of skeletal muscle, bone health, and favorable body composition provides the biological foundation for successful survivorship, but the ultimate measure of success is the ability to maintain functional health, independence, and quality of life over time. These patient-centered outcomes therefore represent the most meaningful indicators of long-term therapeutic success [13,18,20,21].

Functional Health as the Ultimate Clinical Outcome

Preservation of skeletal muscle, bone health, and favorable body composition represents an important biological objective during breast cancer survivorship, but these structural measures derive their greatest value from what they enable. The ultimate goal of survivorship care is preservation of functional health—the capacity to remain physically active, recover from physiological stress, maintain independence, and participate fully in everyday life. From this perspective, body composition should be viewed not as the final measure of therapeutic success, but as an important biological marker that supports the broader objective of functional recovery.

Functional health arises from the coordinated performance of multiple physiological systems rather than the condition of any single organ or tissue. Skeletal muscle, bone, metabolic regulation, cardiovascular fitness, nutritional status, mitochondrial function, neurological integrity, and psychological well-being interact continuously to determine mobility, balance, endurance, resilience, and overall quality of life. Preservation of physiological reserve therefore depends on maintaining the coordinated function of these interconnected systems throughout the survivorship continuum rather than optimizing isolated biological variables independently [13,18,20,21].

This broader perspective also reshapes how therapeutic success should be evaluated. Improvements in body weight and body composition provide valuable information, but they should always be interpreted alongside measures of muscle strength, gait speed, balance, physical performance, falls, nutritional status, and patient-reported outcomes. Together, these complementary assessments provide a more complete understanding of how survivors function in daily life and whether therapeutic interventions translate into meaningful improvements in health, independence, and resilience rather than isolated changes in anthropometric measurements [73-79].

Within this multidimensional model, patient-reported outcomes occupy a particularly important role because they capture aspects of recovery that cannot be fully appreciated through imaging, laboratory testing, or body composition analysis alone. Fatigue, pain, mobility, confidence, participation in everyday activities, and overall quality of life frequently determine how survivors experience recovery long after treatment has ended. Incorporating validated patient-reported outcome measures into routine survivorship care therefore

complements objective physiological measurements while ensuring that clinical success reflects the outcomes that matter most to patients themselves [17,75-79].

This patient-centered perspective also aligns closely with contemporary concepts of healthy aging and intrinsic capacity, both of which emphasize preservation of physical and cognitive function rather than management of individual diseases in isolation. Within these models, successful aging is defined by the ability to maintain the biological and functional capacities needed to adapt to physiological stress, preserve independence, and remain engaged in meaningful life activities. Breast cancer survivorship shares these same objectives, reinforcing the concept that preservation of physiological reserve provides a more comprehensive measure of long-term health than body weight, lean body mass, or bone mineral density considered individually [18-21].

This broader definition of success also has important implications for future research. Studies evaluating metabolic therapies in breast cancer survivors should move beyond conventional anthropometric endpoints by incorporating multidimensional outcome measures that better reflect overall recovery. Longitudinal evaluation of body composition, muscle strength, physical performance, bone health, nutritional status, cardiometabolic health, patient-reported outcomes, and physiological reserve will provide a more comprehensive understanding of therapeutic response while helping determine whether intentional weight loss is accompanied by preservation of functional health rather than improvement in isolated metabolic parameters alone [16,61,64-69].

Ultimately, successful breast cancer survivorship cannot be defined solely by reductions in body weight, preservation of lean body mass, or improvements in metabolic biomarkers. These outcomes remain important because they contribute to a much larger objective: enabling survivors to remain strong, mobile, resilient, and independent throughout aging. Preservation of physiological reserve therefore represents the most comprehensive measure of therapeutic success because it integrates the biological, functional, and patient-centered outcomes that collectively determine long-term health and quality of life.

Recognizing physiological reserve as the ultimate clinical endpoint naturally leads to the next challenge: identifying the interventions most capable of preserving it. The following section therefore explores how nutrition, physical activity, resistance exercise, and other lifestyle interventions work together to maintain musculoskeletal health, support physiological reserve, and optimize long-term recovery throughout breast cancer survivorship.

Nutrition and Exercise: Building Physiological Reserve Through Integrated Lifestyle Therapy

No pharmacologic therapy can preserve long-term health in isolation. Although glucagon-like peptide-1 (GLP-1) receptor agonists provide substantial metabolic benefits for appropriately selected patients, preservation of physiological reserve ultimately depends on maintaining the biological systems that support skeletal muscle, bone integrity, metabolic flexibility, cardiovascular fitness, immune function, and physical performance. Nutrition and exercise should therefore be viewed not as supportive measures accompanying pharmacologic treatment, but as essential therapeutic interventions

that work alongside metabolic therapy to promote long-term recovery throughout breast cancer survivorship [2,16,61,95].

Exercise is one of the most effective interventions for preserving musculoskeletal health during intentional weight reduction. Resistance exercise provides the mechanical stimulus necessary to maintain skeletal muscle by promoting muscle protein synthesis, neuromuscular adaptation, bone remodeling, insulin sensitivity, and physical performance. Aerobic exercise provides complementary benefits through improvements in cardiovascular fitness, endothelial function, mitochondrial adaptation, metabolic flexibility, and regulation of systemic inflammation. Together, these exercise modalities produce synergistic adaptations that extend well beyond changes in body weight, reinforcing the physiological systems that sustain long-term function and recovery [64,65,83,84,96-98].

Nutrition provides the foundation that enables these adaptive responses to occur. Adequate energy intake, sufficient dietary protein, appropriate calcium and vitamin D status when clinically indicated, and adherence to high-quality dietary patterns support skeletal muscle maintenance, bone remodeling, immune competence, tissue repair, and recovery from exercise. Because nutritional requirements evolve with treatment exposures, aging, physical activity, body composition, and individual clinical circumstances, nutritional assessment should begin before initiation of metabolic therapy and continue throughout the survivorship continuum [61,62,80-82].

Importantly, nutrition and exercise should not be prescribed as separate interventions because their physiological effects are fundamentally interdependent. Dietary protein supplies the amino acids required for muscle protein synthesis, while resistance exercise provides the stimulus necessary for muscular adaptation. Likewise, adequate nutritional intake supports recovery from exercise, whereas regular physical activity enhances nutrient utilization, metabolic regulation, mitochondrial function, and preservation of lean tissue. Their reciprocal relationship illustrates why meaningful improvements in survivorship are achieved through coordinated implementation of both strategies rather than either intervention alone [63,99-101].

Within this broader framework, dietary quality is equally important. Nutritional care extends beyond achievement of individual macronutrient targets because overall dietary patterns influence cardiometabolic health, systemic inflammation, body composition, cardiovascular risk, and long-term adherence to healthy lifestyle behaviors. Mediterranean-style dietary patterns have received particular attention because of their associations with improved dietary quality, metabolic health, and sustainable lifestyle modification. Although evidence regarding direct effects on breast cancer outcomes continues to evolve, these dietary approaches complement physical activity, support musculoskeletal health, and contribute to many of the broader objectives of survivorship care [102-107].

Equally important, nutritional recommendations should remain individualized. No single dietary pattern is appropriate for every breast cancer survivor, and nutritional care should reflect age, treatment history, endocrine therapy exposure, metabolic status, comorbidities, cultural preferences, nutritional risk, and patient priorities. Individualized nutritional counseling enables clinicians to optimize protein intake, preserve nutrient density, address treatment-related symptoms, and improve long-term adherence while

supporting skeletal muscle, bone health, and overall physiological resilience [17,60,82].

Taken together, nutrition and exercise should be regarded as complementary therapeutic strategies rather than independent lifestyle recommendations. Nutrition provides the substrate for physiological adaptation, while exercise supplies the stimulus that drives musculoskeletal remodeling, metabolic regulation, mitochondrial adaptation, immune homeostasis, and functional recovery. Their combined effects extend across the interconnected systems that determine long-term health, reinforcing why both interventions should be planned, individualized, and monitored with the same level of clinical attention as pharmacologic therapy. Within this multidisciplinary model, GLP-1 receptor agonists become one component of comprehensive survivorship care rather than the central focus of treatment. The ultimate objective is not simply weight reduction, but preservation of the physiological capacity that allows breast cancer survivors to remain strong, resilient, independent, and fully engaged throughout aging.

Exercise as Medicine Across the Survivorship Continuum

Exercise has emerged as one of the most effective non-pharmacologic interventions for preserving long-term health throughout breast cancer survivorship. Although it was historically recommended to improve physical fitness and quality of life, growing evidence demonstrates that structured exercise exerts therapeutic effects across multiple physiological systems simultaneously, influencing skeletal muscle, bone remodeling, cardiovascular function, mitochondrial adaptation, immune regulation, metabolic health, and psychological well-being. Viewed in this light, exercise should not be considered merely a supportive adjunct to medical treatment but a therapeutic strategy that complements pharmacologic management while directly contributing to long-term survivorship [64,65,83,84,96,98].

This perspective is particularly relevant for breast cancer survivors because treatment-related physiological decline rarely affects a single organ system. Chemotherapy, endocrine therapy, treatment-induced menopause, reduced physical activity, nutritional compromise, and aging frequently occur together, contributing to concurrent deterioration in muscle health, bone integrity, metabolic regulation, cardiovascular fitness, and physical performance. Structured exercise addresses many of these interconnected consequences by preserving musculoskeletal function while improving endurance, balance, mobility, cardiometabolic health, and overall resilience. Unlike interventions directed toward isolated biological targets, exercise simultaneously influences multiple determinants of recovery that ultimately shape long-term functional health [9,31,38,43].

These broad clinical benefits arise through diverse physiological adaptations. Resistance training provides the mechanical stimulus required to preserve skeletal muscle by stimulating muscle protein synthesis, enhancing neuromuscular function, promoting bone remodeling, and improving insulin sensitivity. Aerobic exercise complements these effects by improving cardiovascular fitness, endothelial function, mitochondrial biogenesis, and metabolic flexibility. Regular physical activity also contributes to inflammatory regulation, immune surveillance, and systemic metabolic homeostasis. Collectively, these adaptations illustrate how a single therapeutic strategy can strengthen multiple interconnected physiological

systems that support long-term function, recovery, and resilience [39-41,96,97].

Recognizing exercise as a therapeutic strategy also changes how it should be prescribed. Exercise programs should be individualized according to each survivor's age, baseline functional capacity, treatment history, comorbid conditions, nutritional status, body composition, fracture risk, treatment-related symptoms, and personal goals. Resistance training, aerobic exercise, flexibility, balance training, and functional rehabilitation should be integrated according to individual clinical circumstances and modified as physiological needs evolve throughout survivorship. This personalized approach acknowledges that successful exercise therapy depends not simply on participation but on selecting the right intervention for the right patient at the right stage of recovery [64,65,83,84].

Prescribing exercise, however, represents only the first step. Its long-term benefits depend on sustained participation rather than short-term intervention, making adherence a fundamental determinant of clinical success. Exercise counseling should therefore begin early in treatment and remain an integral component of survivorship care throughout long-term follow-up. Integration of supervised rehabilitation programs, individualized exercise prescriptions, behavioral support, and multidisciplinary follow-up can improve adherence while maximizing preservation of physical function, independence, and quality of life [64,108-110].

Exercise should also be considered within the context of comprehensive survivorship care rather than as an isolated intervention. Resistance exercise provides the physiological stimulus that drives musculoskeletal adaptation, whereas nutritional optimization supplies the substrates required for recovery and tissue remodeling. Pharmacologic therapy, when appropriately indicated, addresses metabolic dysfunction that might otherwise limit overall health. Together, these complementary strategies create a coordinated therapeutic approach that supports skeletal muscle, bone health, metabolic resilience, and healthy aging throughout the survivorship continuum. Within this multidisciplinary model, exercise serves as the active driver of physiological adaptation, translating the biological potential created by appropriate nutrition and carefully selected metabolic therapy into meaningful improvements in functional health. This integrated approach reflects the central message of this review: long-term survivorship is best supported through coordinated multidisciplinary care rather than reliance on any single intervention.

Ultimately, the success of this therapeutic framework depends not only on the interventions themselves but also on the ability of survivors to participate actively in their own care. The final component of comprehensive survivorship management therefore extends beyond biology to emphasize patient engagement, individualized care planning, and shared decision-making as essential foundations for preserving long-term health and functional independence.

Patient Engagement, Personalization, and Shared Decision-Making

Preserving physiological reserve requires more than selecting appropriate therapeutic interventions; it depends on sustaining those interventions over the long term. Nutritional optimization, structured exercise, metabolic therapy, rehabilitation, and longitudinal monitoring all require active participation throughout the survivorship continuum. Patient engagement should therefore be viewed as a fundamental component of comprehensive survivorship

care rather than a supportive adjunct to clinical management. Helping survivors understand the purpose of these interventions encourages meaningful participation, improves adherence, and supports the long-term behavioral changes needed to maintain health, function, and independence [15-17].

Successful implementation also depends on recognizing that breast cancer survivorship is inherently individualized. Age, menopausal status, treatment history, endocrine therapy exposure, body composition, nutritional risk, baseline functional capacity, cardiometabolic health, comorbidities, psychosocial circumstances, and personal priorities all influence clinical decision-making. Personalized survivorship care therefore extends well beyond selecting pharmacologic therapy to include tailored nutritional counseling, exercise prescription, rehabilitation planning, body composition assessment, bone health surveillance, and longitudinal follow-up. This patient-centered approach acknowledges the biological and clinical heterogeneity of breast cancer survivors while establishing realistic therapeutic goals that reflect each individual's needs and priorities [61,64,65,82].

Shared decision-making provides the clinical structure through which personalized care can be translated into everyday practice. Decisions regarding metabolic therapy, nutritional interventions, physical activity, body composition assessment, and long-term monitoring should be developed collaboratively by clinicians and survivors, integrating the best available evidence with individual preferences, functional goals, treatment experiences, and quality-of-life priorities. This partnership recognizes that successful survivorship is measured not only by disease control but also by preservation of independence, participation in meaningful daily activities, and healthy aging [15,16,88].

Implementing this approach also requires effective multidisciplinary collaboration. Medical oncologists, primary care physicians, endocrinologists, rehabilitation specialists, physical therapists, registered dietitians, exercise physiologists, nursing professionals, and survivorship clinicians each contribute distinct expertise, yet their greatest value lies in coordinated rather than independent practice. An integrated survivorship model allows nutritional status, musculoskeletal health, metabolic regulation, physical performance, and patient-reported outcomes to be considered together throughout long-term follow-up. Ongoing communication among team members facilitates early recognition of emerging problems, timely adjustment of therapeutic strategies, and continuity of care as survivors' clinical needs evolve [14,15,17,111].

Digital health technologies and structured survivorship care plans may further strengthen long-term implementation of this multidisciplinary approach. Remote monitoring, patient education platforms, electronic symptom reporting, physical activity tracking, and digital self-management programs offer practical opportunities to reinforce healthy behaviors, improve communication between visits, and support sustained adherence. Although additional research is needed to define their optimal role in breast cancer survivorship, these tools have the potential to enhance continuity of care while expanding access to individualized survivorship support [110,112].

Ultimately, preservation of physiological reserve is not achieved through a single medication, dietary strategy, exercise program, or clinical encounter. Instead, it emerges through sustained collaboration among survivors, clinicians, and multidisciplinary care

teams working toward a shared objective: preserving musculoskeletal health, supporting metabolic function, maintaining physical performance, promoting healthy aging, and enabling survivors to remain active, resilient, and independent throughout life. Within this model, pharmacologic therapy complements—but never replaces—the comprehensive lifestyle, rehabilitation, and supportive care strategies that collectively determine long-term survivorship.

Taken together, the multidisciplinary approach proposed throughout this review provides a practical foundation for contemporary breast cancer survivorship care while identifying important priorities for future research. Continued advances in body composition assessment, digital health technologies, biomarkers, implementation science, and precision survivorship will further refine personalized care and strengthen our ability to preserve physiological reserve across the survivorship continuum. More importantly, these advances provide an opportunity to shift the focus of survivorship beyond treatment of disease alone toward preservation of the biological and functional capacity that enables survivors to live healthier, more independent lives long after completion of cancer therapy.

Longitudinal Surveillance: Following Physiological Reserve Across the Survivorship Continuum

Preserving physiological reserve requires more than a comprehensive baseline assessment; it requires continued surveillance throughout the survivorship continuum. Body composition, skeletal muscle, bone health, nutritional status, physical performance, cardiometabolic health, and functional capacity evolve over months and years in response to cancer treatment, aging, lifestyle, comorbidities, and metabolic therapy. Effective survivorship care therefore depends not on isolated measurements obtained at a single point in time, but on understanding the trajectory of change as survivors progress through recovery and aging.

This longitudinal approach shifts clinical attention from documenting abnormalities after they have developed to identifying physiological vulnerability while meaningful intervention remains possible. Serial evaluation enables clinicians to distinguish healthy adaptation from progressive decline, creating opportunities to refine nutritional strategies, modify exercise prescriptions, optimize rehabilitation, address bone health, and adjust pharmacologic management before irreversible impairment occurs. Instead of reacting to established disability, ongoing surveillance supports timely intervention that helps preserve long-term health, function, and independence throughout survivorship [15-17].

An equally important principle is that body weight should never be interpreted in isolation during follow-up. Similar changes in body weight may represent markedly different physiological adaptations depending on the relative preservation of skeletal muscle, adipose tissue, and bone. Consequently, follow-up should integrate body composition with assessments of muscle strength, mobility, balance, nutritional status, metabolic health, and patient-reported function to provide a more complete understanding of therapeutic response. In this context, evaluating the quality of physiological adaptation is considerably more informative than simply measuring the magnitude of weight loss [26,28,68-71].

Ongoing surveillance also allows survivorship care to adapt as

clinical needs change over time. Physiological capacity is dynamic rather than static, and aging, endocrine therapy, treatment exposure, physical activity, nutritional status, and comorbid conditions may substantially alter an individual's priorities throughout survivorship. Repeated evaluation enables clinicians to refine nutritional counseling, exercise programming, rehabilitation strategies, bone health surveillance, and metabolic therapy according to changing physiological circumstances instead of relying indefinitely on recommendations established at the beginning of treatment [61,64,65,82].

Continuous follow-up also strengthens shared decision-making by fostering an ongoing dialogue between clinicians and survivors. Serial evaluation of body composition, physical performance, nutritional status, and patient-reported outcomes allows individualized goals to be established, progress to be reviewed, and treatment plans to be adjusted collaboratively as functional needs evolve. These discussions extend beyond body weight and laboratory values to focus on outcomes that matter most to survivors, including preservation of strength, mobility, independence, participation in daily life, and healthy aging [75,76,78,79].

Viewed collectively, longitudinal surveillance transforms clinical assessment from a periodic diagnostic event into an active therapeutic strategy. Measurement alone does not preserve health; its value lies in guiding timely intervention before functional decline becomes established. Within this framework, surveillance becomes an integral component of survivorship care by informing nutritional optimization, exercise modification, rehabilitation, metabolic management, and supportive care as physiological needs evolve. The objective is not merely to observe change, but to use that information to preserve resilience, maintain functional independence, and promote healthy aging throughout survivorship.

Implementing this approach depends on reliable, reproducible methods capable of capturing the biological and functional domains that contribute to long-term health. The following section therefore examines contemporary approaches to comprehensive musculoskeletal assessment, integrating body composition analysis, bone quality, functional performance, and objective clinical measures into a multidimensional framework for evaluating physiological reserve across the breast cancer survivorship continuum.

Comprehensive Musculoskeletal Assessment: Integrating Body Composition, Bone Quality, and Functional Performance

A meaningful evaluation of physiological reserve requires consideration of multiple interconnected biological and functional domains rather than reliance on any single measurement. Although body weight remains an accessible clinical parameter, it provides only limited insight into the complex physiological adaptations that occur throughout breast cancer survivorship. A more informative approach integrates body composition, skeletal muscle, bone health, physical performance, nutritional status, and patient-reported outcomes to generate a multidimensional understanding of recovery, resilience, and long-term functional health.

Among currently available assessment tools, dual-energy X-ray absorptiometry (DXA) occupies a central role because it simultaneously evaluates lean body mass, adiposity, and bone mineral density using a standardized and widely available methodology. This combination

enables clinicians to move beyond conventional anthropometric measurements and examine the structural components that underpin musculoskeletal health. Importantly, the greatest value of DXA lies not simply in quantifying body composition, but in providing objective information that can be interpreted alongside functional, nutritional, and clinical findings to guide individualized decision-making throughout survivorship [68-72,94].

Bone health represents another essential dimension of comprehensive musculoskeletal evaluation. Breast cancer survivors frequently experience accelerated bone loss resulting from chemotherapy, endocrine therapy, treatment-induced menopause, aging, nutritional compromise, and reduced mechanical loading. Accordingly, skeletal evaluation should extend beyond bone mineral density whenever clinically appropriate. Emerging approaches such as trabecular bone score (TBS), together with established fracture-risk assessment tools and longitudinal monitoring of skeletal health, provide complementary information regarding bone quality and structural integrity that may improve identification of survivors at increased risk for osteoporosis, osteosarcopenia, falls, and fractures. Although further validation in breast cancer survivorship remains necessary, these advances support a more individualized and clinically informative approach to skeletal health than reliance on bone mineral density alone [24,35,44,85,113-115].

Structural measurements, however, cannot determine how effectively musculoskeletal tissues support everyday function. Objective measures of physical performance—including grip strength, gait speed, chair-rise performance, the Timed Up and Go test, balance assessment, and validated frailty measures—provide practical insight into strength, mobility, coordination, and functional capacity that cannot be captured through imaging alone. When interpreted alongside structural findings, these complementary measures help determine whether preservation of muscle and bone translates into meaningful physical function while identifying survivors who may benefit from earlier nutritional intervention, rehabilitation, or modification of exercise therapy [73,74,90-93].

These complementary tools are most informative when interpreted together rather than as competing assessment strategies. DXA characterizes body composition and skeletal integrity, functional testing evaluates physical performance, nutritional evaluation identifies biological capacity for adaptation, and patient-reported outcomes capture the lived experience of survivorship. Together, these domains provide a far more meaningful understanding of physiological reserve than any single measurement considered in isolation. More importantly, their combined interpretation enables clinicians to recognize emerging physiological vulnerability and translate assessment findings into timely, individualized interventions as survivors' needs evolve.

This integrated approach reflects an important evolution in survivorship care. Historically, skeletal muscle, bone health, nutritional status, and physical performance were often evaluated as separate clinical entities, with each domain considered largely in isolation. Increasingly, however, these factors are recognized as interconnected components of a dynamic biological system that collectively determines resilience, independence, and healthy aging. Comprehensive musculoskeletal evaluation therefore serves a purpose beyond diagnosis. It provides the biological and functional foundation for adaptive clinical decision-making, allowing nutritional strategies, rehabilitation, exercise prescription, metabolic therapy,

and supportive care to be refined as physiological needs change throughout survivorship.

Objective measurements remain indispensable, but they represent only one dimension of survivorship evaluation. A comprehensive understanding of physiological reserve also requires consideration of patient-reported outcomes, intrinsic capacity, and other multidimensional measures that reflect how survivors function, adapt, and participate in everyday life. Together, these complementary perspectives complete the assessment model and provide the foundation for the following discussion of patient-centered evaluation in breast cancer survivorship.

Measuring What Matters: Integrating Patient-Reported Outcomes and Intrinsic Capacity

A comprehensive evaluation of long-term survivorship extends beyond objective measurements of body composition, skeletal muscle, bone health, and physical performance. Although these assessments provide essential information regarding structural and physiological adaptation, they cannot fully capture how survivors experience recovery in everyday life. Fatigue, mobility, pain, confidence, emotional well-being, participation in daily activities, and overall quality of life represent equally important dimensions of health that are best understood through the survivor's perspective. Incorporating patient-reported outcomes into routine survivorship care therefore provides a more complete picture of treatment success by integrating objective physiological findings with the lived experience of recovery.

Patient-reported outcomes should not be viewed merely as research instruments or quality-of-life questionnaires. Instead, they are clinically meaningful measures that help determine whether biological improvements translate into tangible benefits for survivors. Improvements in body composition or metabolic health have limited clinical value if they are not accompanied by meaningful gains in mobility, independence, symptom burden, or quality of life. Conversely, improvements reported in physical function, confidence, participation, and daily activities may reflect successful adaptation even when changes in body weight or body composition are relatively modest. Integrating validated patient-reported outcome measures with objective physiological assessment therefore aligns clinical evaluation with the outcomes that matter most to breast cancer survivors while supporting a more patient-centered approach to long-term survivorship care [75,76,78,79].

An additional dimension is provided by the concept of intrinsic capacity, introduced within the World Health Organization's Healthy Aging Framework. Intrinsic capacity describes the composite physical and mental abilities that individuals rely upon to maintain function throughout life. Although originally developed within geriatric medicine, this concept has particular relevance for breast cancer survivorship because treatment-related changes frequently affect mobility, skeletal muscle, nutritional status, cognition, psychological well-being, and overall functional ability simultaneously. Assessment of intrinsic capacity therefore complements traditional oncology follow-up by shifting attention from documenting treatment-related complications toward preserving the functional abilities that support healthy aging and long-term independence [18,19,21].

Intrinsic capacity and physiological reserve represent distinct yet closely related concepts. Physiological reserve reflects the biological resilience that enables individuals to respond to physiological stress,

whereas intrinsic capacity describes how that resilience is expressed through physical, cognitive, and psychological function in everyday life. Together, these complementary perspectives provide a broader understanding of survivorship by linking biological adaptation with the functional outcomes that ultimately matter most to patients. Instead of focusing exclusively on disease-specific endpoints, this approach emphasizes preservation of strength, mobility, cognition, independence, participation, and healthy aging throughout the survivorship continuum.

No single assessment can adequately characterize these complex biological and functional interactions. Meaningful survivorship evaluation instead emerges from integrating objective measures of body composition, skeletal muscle health, bone integrity, physical performance, nutritional status, and metabolic health with patient-reported outcomes and intrinsic capacity. Considered together, these complementary domains provide a richer understanding of survivorship than any individual measurement alone. More importantly, they enable clinicians to recognize emerging vulnerability, determine whether interventions are improving daily life, and adapt long-term care according to each survivor's changing needs.

Emerging digital health technologies and survivorship care platforms may further strengthen this patient-centered approach. Electronic patient-reported outcome systems, wearable activity monitors, remote functional assessment, and digital survivorship programs offer practical opportunities to monitor physiological and functional change between clinic visits while reinforcing engagement and continuity of care. Although additional prospective investigation is needed, integrating these complementary technologies into routine survivorship practice may facilitate more individualized surveillance, earlier intervention, and improved long-term outcomes for breast cancer survivors [16,110,112].

Ultimately, comprehensive assessment provides the foundation for truly personalized survivorship care. By integrating biological measures with functional performance, patient-reported outcomes, and intrinsic capacity, clinicians gain a more complete understanding of how survivors recover, adapt, and maintain health over time. Continued advances in biological mechanisms, multidimensional clinical assessment, digital health, and precision survivorship will further refine this approach and help translate physiological insights into interventions that preserve independence, resilience, and quality of life for breast cancer survivors receiving metabolic therapies. The following section explores these emerging research priorities and their potential to further advance preservation of physiological reserve across the survivorship continuum.

Survivorship as a Dynamic Lifelong Process

Breast cancer survivorship has undergone a profound transformation over the past several decades. Advances in early detection, systemic therapies, supportive care, and long-term disease control have resulted in a rapidly growing population of survivors who frequently live for many years after completing treatment. As survivorship increasingly extends across decades rather than months, the goals of clinical care must evolve accordingly. Contemporary survivorship can no longer focus solely on surveillance for recurrence but must also prioritize preservation of physiological reserve, maintenance of functional independence, prevention of frailty, and promotion of healthy aging. Survivorship should therefore be

viewed not as a discrete phase following treatment, but as a lifelong process that requires continuous adaptation to changing biological, functional, and clinical needs [15-17].

This perspective recognizes that the challenges encountered throughout survivorship continually evolve. Priorities that dominate care during chemotherapy or endocrine therapy often differ substantially from those that emerge years later as aging, menopause, cardiovascular risk, musculoskeletal decline, metabolic dysfunction, comorbid conditions, and functional limitations increasingly shape long-term health. Survivorship is therefore best understood as a longitudinal continuum in which clinical priorities, therapeutic strategies, and monitoring approaches evolve alongside the individual rather than remaining static throughout follow-up. Such an approach shifts the emphasis from reacting to late complications toward proactively preserving health across the lifespan [2,27,116].

Within this evolving model, physiological reserve serves as a practical organizing principle for survivorship care. Rather than focusing exclusively on isolated disease-specific outcomes or treatment-related complications, this perspective encourages clinicians to consider how every therapeutic decision influences the biological resilience that enables survivors to remain active, adaptable, and independent throughout life. Equally important, physiological reserve should be recognized as a dynamic biological property rather than a fixed characteristic. It is continuously influenced by cancer therapy, endocrine treatment, aging, physical activity, nutritional status, metabolic health, comorbid conditions, and intentional weight reduction. At the same time, evidence-based interventions—including resistance exercise, nutritional optimization, rehabilitation, and appropriate metabolic management—may help preserve or partially restore physiological reserve despite ongoing treatment-related challenges. Recognizing this dynamic interplay reinforces the importance of longitudinal assessment and individualized intervention while emphasizing that preservation of function depends on continuous adaptation rather than isolated therapeutic decisions [20,21,116].

Viewing survivorship through the lens of physiological reserve also broadens the objectives of long-term care. Contemporary survivorship extends beyond preventing recurrence to preserving the biological systems that collectively support resilience, independence, and healthy aging. Rather than managing individual physiological domains in isolation, this integrated perspective recognizes the continuous interaction among musculoskeletal health, nutrition, metabolism, physical activity, cardiovascular health, and emotional well-being. Together, these interconnected systems determine how successfully survivors adapt to the combined influences of cancer treatment and aging, reinforcing the need for coordinated strategies that sustain overall physiological function throughout survivorship [17,61,64,65].

Importantly, this broader perspective does not diminish the central role of traditional oncologic follow-up. Surveillance for recurrence, management of treatment-related toxicities, and evidence-based cancer care remain fundamental components of survivorship. Instead, it expands the scope of follow-up by integrating these established priorities with proactive strategies designed to preserve musculoskeletal health, functional capacity, metabolic health, and long-term physiological resilience. In this way, survivorship care focuses not only on extending life but also on preserving the capacity to live well throughout the decades that follow treatment.

Viewed through this broader lens, survivorship is no longer defined by completion of cancer therapy. It represents an ongoing partnership between survivors and clinicians that continually adapts to changing biological, functional, and psychosocial needs over time. Long-term success is measured not only by freedom from disease but also by preservation of resilience, independence, participation in daily life, and healthy aging. This evolving perspective provides the conceptual foundation for individualized, adaptive survivorship care that responds to the changing needs of each survivor throughout life.

Because survivorship priorities continually evolve, effective care cannot be delivered by any single clinician or specialty in isolation. Preserving physiological reserve requires coordinated multidisciplinary collaboration among oncologists, primary care physicians, rehabilitation specialists, exercise professionals, registered dietitians, endocrinologists, cardiologists, mental health professionals, nurses, and survivors themselves. As biological and functional needs change over time, the contributions of each discipline evolve as well, creating a flexible, patient-centered model of care that supports long-term health, functional independence, resilience, and healthy aging across the lifespan.

Coordinated Multidisciplinary Care Across the Lifespan

Preserving physiological reserve throughout breast cancer survivorship cannot be accomplished by a single clinician or specialty alone. Survivors experience a broad spectrum of biological, functional, metabolic, nutritional, musculoskeletal, and psychosocial challenges that evolve continuously over time. Effective survivorship therefore depends on coordinated collaboration among healthcare professionals whose complementary expertise can be integrated to address each survivor's changing needs across the lifespan rather than through isolated episodes of care [2,15,117].

The value of multidisciplinary collaboration lies not simply in the number of disciplines involved, but in their ability to function as a unified clinical team. Medical oncologists, primary care physicians, endocrinologists, rehabilitation specialists, registered dietitians, physical therapists, exercise physiologists, nursing professionals, behavioral health providers, and survivorship clinicians each contribute distinct expertise that supports long-term health. When these perspectives are integrated, body composition, musculoskeletal health, nutrition, metabolic management, physical performance, cardiovascular health, and patient-reported outcomes can be considered collectively rather than as separate clinical priorities, allowing management to be guided by the overarching goal of preserving physiological reserve [17,61,64,65].

Equally important, this collaborative approach must remain adaptive rather than static. During active cancer treatment, priorities often center on treatment tolerance, symptom management, nutritional support, and maintenance of physical function. As survivors move beyond treatment, attention increasingly shifts toward cardiometabolic health, osteoporosis prevention, preservation of skeletal muscle, rehabilitation, healthy aging, and management of chronic comorbidities. This evolving model recognizes that survivorship is not defined by a single transition from oncology to primary care but by continuous collaboration among healthcare professionals whose roles evolve alongside survivors' biological and functional needs throughout life [2,15,88].

Effective communication is fundamental to the success of this

model. Fragmentation of care may delay recognition of important physiological changes, including unfavorable alterations in body composition, declining physical performance, nutritional compromise, or progressive bone loss. Regular communication among healthcare professionals enables clinical information to be synthesized, therapeutic priorities to be aligned, and interventions to be implemented before physiological decline becomes clinically significant. In this way, preservation of physiological reserve becomes a shared objective that guides decision-making across every aspect of survivorship rather than the responsibility of any single discipline.

This collaborative structure also provides the foundation for truly personalized survivorship care. Management strategies should reflect each survivor's age, treatment history, endocrine therapy exposure, metabolic health, nutritional status, body composition, fracture risk, physical function, comorbid conditions, and personal priorities. By considering these factors together, multidisciplinary assessment supports development of individualized care plans that evolve as survivors progress through different stages of recovery and aging [61, 82,110].

Emerging digital health technologies and structured survivorship care plans may further strengthen coordination by improving communication among healthcare professionals while supporting patient engagement between clinic visits. Electronic survivorship plans, remote symptom monitoring, digital self-management platforms, wearable technologies, and electronic patient-reported outcome systems provide opportunities to enhance continuity of care, facilitate earlier recognition of physiological change, and reinforce healthy lifestyle behaviors throughout long-term follow-up. Although additional investigation is warranted, these approaches may become increasingly valuable as survivorship expands across diverse healthcare settings [88,110,112].

Ultimately, multidisciplinary survivorship extends far beyond coordination of clinical services. It provides the organizational structure through which preservation of physiological reserve can be translated into routine clinical practice. By integrating expertise across disciplines while adapting management to survivors' changing biological, functional, and psychosocial needs, multidisciplinary programs offer the greatest opportunity to preserve resilience, independence, and healthy aging throughout the decades following breast cancer treatment [117].

Every survivorship encounter represents an opportunity to preserve physiological reserve. Routine follow-up visits need not focus exclusively on surveillance for cancer recurrence but can simultaneously incorporate assessment of physical activity, dietary protein intake, falls, muscle strength, mobility, body composition, nutritional status, and other indicators of musculoskeletal and functional health. Integrating these conversations into standard survivorship care may facilitate earlier recognition of physiological decline, reinforce healthy lifestyle behaviors, strengthen patient engagement, and promote timely multidisciplinary intervention before clinically significant impairment develops. Viewed in this way, preservation of physiological reserve becomes an ongoing objective embedded within every clinical encounter rather than a separate component of survivorship care.

As multidisciplinary survivorship continues to evolve, the next challenge extends beyond coordinating existing services toward developing healthcare models that proactively preserve physiological

reserve throughout life. Achieving this goal will require continued integration of biological understanding, individualized assessment, multidisciplinary collaboration, and patient-centered care into a seamless lifelong survivorship strategy. The final section therefore explores how future advances may continue to transform survivorship from episodic follow-up into a comprehensive model of lifelong health preservation.

Building a Lifelong Model of Physiological Reserve

The continued evolution of breast cancer survivorship provides an opportunity to move beyond episodic follow-up toward a proactive, lifelong approach to health preservation. Historically, survivorship care has focused primarily on surveillance for recurrence and management of treatment-related complications. Although these priorities remain fundamental, growing recognition of the long-term biological consequences of cancer treatment supports a broader vision that emphasizes preservation of physiological reserve throughout the aging process. Instead of responding only after functional decline has occurred, this approach seeks to maintain the biological resilience that enables survivors to remain active, independent, and healthy across the lifespan [2,15,17].

Achieving this goal requires translating the principles discussed throughout this review into routine clinical practice. Body composition assessment, preservation of musculoskeletal health, nutritional optimization, structured exercise, metabolic management, rehabilitation, and longitudinal surveillance should not be viewed as independent clinical initiatives. Together, these complementary strategies preserve the interconnected physiological systems that support functional capacity, adaptation to physiological stress, and healthy aging. This integrated perspective reinforces that preservation of physiological reserve cannot be achieved through any single intervention but depends on coordinated management across multiple biological and clinical domains.

Equally important, lifelong survivorship care must remain adaptive. Physiological reserve is not a fixed characteristic but a dynamic biological property that is continually influenced by aging, endocrine therapy, metabolic health, comorbid conditions, lifestyle behaviors, and changing functional demands. Survivorship care should therefore evolve alongside the individual, with periodic reassessment guiding refinement of nutritional strategies, exercise prescriptions, rehabilitation programs, metabolic therapies, and supportive interventions according to changing biological and clinical circumstances. This capacity for continuous adaptation is one of the defining characteristics of personalized survivorship care and recognizes that successful long-term management depends on ongoing refinement rather than fixed treatment algorithms [61,64,65,70].

This evolving approach also creates opportunities to incorporate emerging technologies into routine survivorship practice. Advances in digital health, remote patient monitoring, wearable technologies, electronic patient-reported outcome platforms, and increasingly sophisticated methods of body composition assessment may enable earlier recognition of physiological change while strengthening communication between survivors and multidisciplinary care teams. Although additional prospective investigation remains necessary, these innovations have the potential to support more responsive, individualized, and longitudinal care while complementing—rather

than replacing—established clinical assessment [10,112].

Ultimately, preservation of physiological reserve represents far more than a clinical objective. It provides a unifying principle that brings together oncology, endocrinology, rehabilitation, nutrition, exercise science, geriatric medicine, and survivorship care around a shared therapeutic goal: maintaining the biological resilience that supports long-term function, independence, and healthy aging. Within this perspective, the success of metabolic therapies, including GLP-1 receptor agonists, should be evaluated not solely by improvements in body weight or metabolic biomarkers, but by their contribution to preserving skeletal muscle, mobility, bone integrity, physical function, independence, and quality of life throughout survivorship.

Viewed collectively, this lifelong approach represents an evolution in the philosophy of breast cancer survivorship. Success is no longer defined solely by survival or disease control but also by preservation of the biological capacity that enables survivors to adapt, recover, and thrive throughout aging. Integrating individualized interventions, multidisciplinary collaboration, longitudinal surveillance, evidence-based lifestyle strategies, and patient-centered assessment provides a practical pathway for translating this philosophy into everyday clinical practice.

The concepts presented throughout this review support a broader vision of survivorship in which preservation of physiological reserve becomes the central organizing principle of long-term care. Rather than functioning as isolated clinical initiatives, advances in nutrition, exercise, rehabilitation, metabolic therapy, body composition assessment, digital health, patient-reported outcomes, and multidisciplinary care become complementary components of a unified strategy designed to sustain resilience across the survivorship continuum. As evidence continues to evolve, this perspective offers an opportunity to reshape survivorship from reactive management of late complications toward proactive preservation of lifelong health.

The concluding section summarizes this integrated vision while highlighting the opportunities and remaining challenges as metabolic therapies continue to reshape the future of breast cancer survivorship.

Discussion

A New Framework for Breast Cancer Survivorship

The expanding clinical use of glucagon-like peptide-1 (GLP-1) receptor agonists provides an important opportunity to reconsider how metabolic health is approached during breast cancer survivorship [118]. Although these therapies have demonstrated well-established benefits for obesity, type 2 diabetes, and cardiovascular disease in appropriately selected patients, their growing use also highlights the need to evaluate treatment success within the broader context of long-term survivorship. Rather than viewing GLP-1 receptor agonists as stand-alone metabolic therapies, this review proposes a complementary clinical perspective that integrates evidence from oncology, endocrinology, musculoskeletal biology, nutrition, exercise science, rehabilitation, and healthy aging into a unified model centered on preservation of physiological reserve.

The principal contribution of this perspective is not the proposal of a new pharmacologic intervention or an expansion of the approved indications for GLP-1 receptor agonists. Instead, it offers a broader way of evaluating therapeutic success. Beyond reductions in body weight alone, this approach emphasizes preservation of the interconnected

biological systems that collectively support long-term function, resilience, and independence. Skeletal muscle, bone health, metabolic regulation, nutritional status, physical activity, and functional performance are therefore viewed as complementary determinants of physiological reserve rather than isolated clinical outcomes. In doing so, this perspective complements existing oncology and obesity guidelines while encouraging a more comprehensive approach to survivorship care [2,15,17,61].

Moving Beyond Weight-Centered Survivorship

Historically, successful obesity management has often been defined by the magnitude of weight reduction achieved during treatment. Although weight loss remains an important therapeutic objective for appropriately selected patients, breast cancer survivorship requires a broader definition of clinical success. Body weight alone provides limited insight into preservation of skeletal muscle, bone integrity, metabolic health, physical performance, or long-term functional independence. Consequently, interpretation of intentional weight loss should extend beyond changes in body mass to include careful evaluation of its biological and functional consequences.

From this perspective, the quality of weight loss may ultimately be more clinically meaningful than its magnitude. Weight reduction that preserves skeletal muscle, protects bone health, enhances metabolic function, and maintains physical performance differs fundamentally from weight loss accompanied by progressive sarcopenia, declining bone quality, or functional impairment. Accordingly, body composition, musculoskeletal health, physical function, nutritional status, and physiological reserve should be evaluated alongside conventional anthropometric measures when determining therapeutic success.

The approach presented throughout this review therefore shifts attention from the quantity of weight lost to the quality of long-term health that weight reduction supports. Preservation of muscle health, maintenance of skeletal integrity, nutritional optimization, lifelong physical activity, and protection of functional capacity collectively determine whether metabolic improvements translate into meaningful clinical benefit. This multidimensional perspective recognizes that the ultimate objective of survivorship is not simply reduction of adiposity but preservation of the physiological reserve that enables survivors to remain active, resilient, and independent throughout aging [9,10,24,31,35,61].

From Reactive Management to Proactive Preservation

An important implication of this review is the opportunity to shift survivorship care from reactive management of established complications toward proactive preservation of physiological reserve. Traditionally, osteoporosis, sarcopenia, frailty, and functional decline have often been recognized only after clinically significant impairment has developed. Advances in body composition assessment, comprehensive musculoskeletal evaluation, functional performance testing, nutritional assessment, and patient-reported outcomes now provide opportunities to identify physiological vulnerability much earlier in the survivorship continuum.

Earlier recognition creates opportunities to implement nutritional counseling, resistance exercise, rehabilitation, metabolic optimization, bone-directed therapies, and multidisciplinary interventions before irreversible declines in physiological reserve occur. This preventive philosophy aligns closely with the evolving goals of survivorship care, which increasingly emphasize long-term

health, healthy aging, and maintenance of independence rather than management of treatment-related complications alone. Within this broader perspective, preservation of physiological reserve becomes both the primary objective and an important measure of successful survivorship [18,20,21,68,69,73].

Healthy Aging as the Ultimate Goal of Survivorship

As advances in breast cancer treatment continue to improve long-term survival, survivorship increasingly becomes a question of healthy aging rather than cancer treatment alone. Preserving mobility, maintaining independence, preventing frailty, supporting cognitive and physical function, and optimizing quality of life become progressively more important as survivors age. This evolution encourages clinicians to view survivorship not simply as follow-up after successful cancer therapy but as an opportunity to preserve physiological reserve through coordinated management of musculoskeletal health, metabolic function, nutrition, physical activity, and patient-centered outcomes.

Successful survivorship depends on far more than any single medication, laboratory value, imaging study, or lifestyle intervention. It reflects the cumulative effects of coordinated multidisciplinary care, individualized treatment planning, longitudinal surveillance, evidence-based lifestyle interventions, and sustained patient engagement over time. Within this context, GLP-1 receptor agonists represent one valuable therapeutic component of a broader survivorship strategy whose ultimate objective is preservation of physiological reserve throughout the aging process.

Preservation of physiological reserve ultimately reflects preservation of biological resilience—the capacity to withstand physiological stress, recover from illness, adapt to changing physiological demands, and maintain functional independence throughout life. For breast cancer survivors, resilience encompasses far more than successful completion of cancer treatment. It includes preserving mobility, maintaining musculoskeletal health, adapting to metabolic challenges, sustaining independence, and continuing to participate fully in everyday life despite the cumulative effects of cancer therapy and aging. Framing survivorship in terms of biological resilience therefore broadens the focus from recovery after treatment to lifelong preservation of health and function.

Viewed collectively, the concepts presented throughout this review support a broader vision of breast cancer survivorship in which preservation of physiological reserve becomes the central organizing principle of multidisciplinary care. Rather than redefining existing standards of practice, this perspective integrates metabolic therapy, nutrition, exercise, rehabilitation, body composition assessment, longitudinal surveillance, patient-reported outcomes, and coordinated multidisciplinary care into a unified strategy for promoting long-term resilience, healthy aging, and quality of life. As evidence continues to evolve, this model offers a practical and patient-centered approach for guiding the next generation of breast cancer survivorship while maintaining focus on the outcomes that matter most to survivors: strength, independence, resilience, and lifelong health.

Future Directions

The future of breast cancer survivorship lies not only in evaluating the efficacy of individual therapeutic agents but also in developing comprehensive strategies that preserve long-term health, functional

capacity, and biological resilience. As glucagon-like peptide-1 (GLP-1) receptor agonists become increasingly integrated into the management of obesity and metabolic disease among appropriately selected breast cancer survivors, they also provide an opportunity to reconsider the broader goals of survivorship care. Future investigations should therefore extend beyond conventional measures of body weight and glycemic control to determine whether these therapies can favorably influence the multidimensional determinants of healthy aging, including skeletal muscle preservation, bone health, body composition, physical performance, frailty, quality of life, and patient-reported outcomes. This shift reflects an important evolution in survivorship research—from evaluating isolated metabolic endpoints to understanding how metabolic interventions may contribute to preserving physiological reserve and lifelong functional health [9,42,73,75,76,79].

Achieving this objective will require a broader framework for evaluating treatment outcomes. Although intentional weight reduction remains an important therapeutic goal for many breast cancer survivors, future clinical trials should determine whether improvements in metabolic health are accompanied by preservation of lean body mass, maintenance of skeletal integrity, sustained physical function, and greater functional independence. Integrating body composition analysis with objective assessments of muscle strength, physical performance, frailty, and validated patient-reported outcomes will provide a more meaningful evaluation of the long-term benefits and potential limitations of GLP-1 receptor agonist therapy than reliance on body weight alone. As survivorship care increasingly emphasizes function rather than weight as the principal marker of successful aging, multidimensional outcome measures are likely to assume a more prominent role in both clinical research and routine practice.

Equally important is the continued need to clarify the biological mechanisms linking metabolic health with long-term survivorship. A growing body of evidence suggests that interactions among chronic inflammation, mitochondrial function, endocrine regulation, immunometabolism, skeletal muscle, and bone biology collectively influence recovery, functional resilience, and adaptation following cancer therapy. Future translational investigations integrating molecular biomarkers with detailed clinical phenotyping may provide important insight into the biological pathways that determine why some survivors maintain physiological resilience while others experience progressive functional decline. Longitudinal studies capable of linking mechanistic biomarkers with changes in body composition, physical performance, and patient-reported outcomes will be particularly valuable for identifying individuals at greatest risk for accelerated physiological aging and for guiding more individualized survivorship strategies [38,40,49,52,56,57,59].

Progress toward more personalized survivorship care will likewise require moving beyond the assumption that breast cancer survivors follow similar recovery trajectories. Instead, future research should seek to define distinct survivorship phenotypes by integrating clinical characteristics such as age, menopausal status, endocrine therapy exposure, obesity, diabetes, cardiovascular disease, treatment intensity, baseline body composition, physical function, and coexisting medical conditions. This approach reflects the emerging concept of precision survivorship, in which prevention, surveillance, and intervention strategies are tailored according to each survivor's biological profile, functional status, and long-term

health risks. Improved risk stratification may ultimately facilitate earlier intervention, optimize allocation of supportive care resources, and enhance long-term patient outcomes.

Continued advancement of the field will also depend on greater standardization of survivorship assessment. Harmonized approaches to body composition analysis, dual-energy X-ray absorptiometry (DXA)-derived measurements of muscle and bone, functional performance testing, nutritional evaluation, patient-reported outcomes, and assessment of physiological reserve will improve comparability across clinical studies while accelerating translation of research findings into everyday clinical practice. The development of consensus assessment frameworks may ultimately establish preservation of physiological reserve as a measurable and clinically meaningful endpoint rather than a purely conceptual objective. Such standardization will strengthen future clinical trials, facilitate comparisons across studies, and provide clinicians with more robust tools for monitoring long-term survivorship outcomes [68-72].

The continued evolution of digital health, artificial intelligence, wearable technologies, remote patient monitoring, and predictive analytics offers an unprecedented opportunity to transform the delivery of breast cancer survivorship care. Rather than relying solely on episodic clinic visits, future survivorship models may integrate longitudinal clinical data, body composition measurements, laboratory biomarkers, functional assessments, physical activity metrics, and patient-reported outcomes into coordinated platforms capable of continuously monitoring health trajectories over time. Such approaches have the potential to identify early physiological decline before clinically significant impairment develops, enabling more proactive and individualized interventions that preserve long-term health and function. Although these technologies remain at relatively early stages of clinical implementation, they may substantially enhance risk prediction, strengthen patient engagement, facilitate shared decision-making, and improve coordination among multidisciplinary healthcare teams throughout survivorship [110,112].

Scientific advances alone, however, will not improve survivorship unless they can be successfully translated into routine clinical practice. Consequently, implementation science represents one of the most important frontiers in breast cancer survivorship research. Future investigations should identify practical and scalable models that integrate oncologists, primary care physicians, endocrinologists, rehabilitation specialists, registered dietitians, physical therapists, exercise physiologists, and survivorship clinicians into coordinated systems of long-term care. Equally important will be determining how these multidisciplinary models can be implemented successfully across diverse healthcare settings, including academic medical centers, community oncology practices, and resource-limited environments. Developing sustainable and equitable models of survivorship care will ultimately be as important as continued refinement of pharmacologic therapies in ensuring that scientific advances translate into meaningful improvements in patient outcomes [61,64,65,88].

Another important priority is the integration of physiological reserve into routine clinical decision-making throughout the survivorship continuum. Rather than remaining primarily a conceptual framework, preservation of physiological reserve should evolve into a practical clinical objective that informs individualized risk assessment, therapeutic planning, longitudinal surveillance, and multidisciplinary intervention. Prospective validation of clinically



feasible assessment strategies incorporating body composition, musculoskeletal health, metabolic status, nutritional evaluation, functional performance, and patient-reported outcomes will be essential for determining whether this framework can be implemented reliably in everyday practice. Successfully translating these multidimensional assessments into standardized clinical workflows has the potential to support earlier intervention, improve personalization of survivorship care, and ultimately preserve long-term function and independence.

Perhaps the greatest contribution of GLP-1 receptor agonists to breast cancer survivorship will extend well beyond their direct metabolic effects. Their expanding role in clinical practice provides

an opportunity to reconsider how successful survivorship is defined. Rather than focusing primarily on reductions in body weight or improvements in isolated metabolic biomarkers, future models of care should increasingly emphasize preservation of functional capacity, biological resilience, musculoskeletal health, metabolic well-being, nutritional status, and patient-centered outcomes. Within this broader perspective, metabolic therapies represent one component of a comprehensive survivorship strategy designed to support healthy aging, maintain independence, and optimize quality of life across the lifespan.

Ultimately, the next era of breast cancer survivorship will be shaped by the successful integration of translational science, clinical

investigation, precision survivorship, implementation science, multidisciplinary collaboration, and patient-centered care. Progress across these complementary domains has the potential to transform survivorship from a model focused primarily on identifying and managing late treatment effects into one dedicated to preserving lifelong health, resilience, and functional independence. Perhaps the greatest achievement of future survivorship research will not simply be the development of new therapeutic interventions, but the establishment of evidence-based models of care that enable breast cancer survivors to age with greater strength, mobility, autonomy, and quality of life. By placing preservation of physiological reserve at the center of survivorship care, this evolving perspective offers a compelling vision for improving the long-term health and well-being of the growing population of breast cancer survivors.

Conclusion

The expanding clinical use of glucagon-like peptide-1 (GLP-1) receptor agonists presents an important opportunity to reconsider the role of metabolic health within breast cancer survivorship [118]. Although these therapies have demonstrated substantial clinical benefit for appropriately selected patients, their potential contribution extends beyond weight reduction alone. More importantly, they provide an opportunity to integrate metabolic management into a broader survivorship strategy that prioritizes long-term health, functional capacity, and biological resilience.

This review proposes a complementary clinical perspective that shifts the focus of survivorship beyond body weight toward preservation of physiological reserve as a central determinant of healthy aging. By integrating current evidence from oncology, endocrinology, musculoskeletal biology, nutrition, exercise science, rehabilitation, metabolism, and geroscience, this framework emphasizes coordinated assessment of body composition, skeletal muscle, bone health, physical performance, nutritional status, metabolic function, and patient-centered outcomes. Rather than functioning as isolated therapeutic targets, these interconnected domains should be considered complementary components of a dynamic biological system that collectively influences an individual's capacity to recover, adapt, and maintain independence throughout survivorship [2,17,61,68].

Importantly, the perspective presented in this review is intended to complement—not replace—established oncology, obesity, and metabolic guidelines. It does not advocate expansion of the approved indications for GLP-1 receptor agonists. Instead, it provides a practical clinical framework through which these therapies may be thoughtfully incorporated into individualized, multidisciplinary survivorship care. Within this approach, pharmacologic therapy is integrated with evidence-based nutrition, resistance exercise, rehabilitation, bone health surveillance, and longitudinal functional assessment to support preservation of physiological reserve across the survivorship continuum.

As breast cancer survivorship continues to evolve, the definition of successful treatment must evolve with it. Future progress will depend not only on optimizing metabolic outcomes but also on preserving skeletal muscle, protecting bone health, maintaining physical function, promoting healthy aging, and enhancing quality of life through coordinated multidisciplinary care. Continued prospective investigation will be essential to refine this framework, identify survivors most likely to benefit from targeted interventions,

and determine how metabolic therapies can be most effectively integrated into personalized survivorship strategies that address the complex and changing needs of this growing population.

Ultimately, the goal of breast cancer survivorship extends beyond helping patients live longer—it is to help them live well. The greatest measure of success should therefore not be defined solely by the amount of weight patients lose, but by the extent to which survivorship care preserves the physiological reserve that enables them to remain strong, independent, resilient, and fully engaged throughout life. Viewed through this broader perspective, GLP-1 receptor agonists are not simply another therapeutic option. They represent one component of a comprehensive, patient-centered survivorship strategy in which preservation of physiological reserve becomes the defining objective of long-term care.

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