

A health-system-scale, episode-resolved multimodal atlas of cancer cachexia

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Cancer cachexia is a wasting syndrome with outsized impact on morbidity and mortality, yet its drivers and systemic consequences remain poorly defined. In this study, we repurposed longitudinal clinicogenomic data from 52,236 patients with cancer profiled by MSK-IMPACT (2010–2024) at Memorial Sloan Kettering Cancer Center to define episode-resolved trajectories of consensus-defined cachectic weight loss and linked these events to outcomes, serology and tumor genotypes. Cachectic episodes clustered near periods of disease progression and were associated with inferior outcomes in nearly all cancer types. Across diverse malignancies, cachectic weight loss episodes exhibited a consistent serologic signature characterized by lower albumin and hemoglobin and higher levels of liver enzymes. Numerous somatic tumor genotypes, including *TP53* mutation across several diseases, were also associated with more frequent onset of cachectic episodes. Motivated by these observations, we developed a multivariate model to predict impending risk of cachectic weight loss in patients with lung, colorectal and prostate cancer, validated in an independent, external cohort from Dana-Farber Cancer Institute ($n = 5,785$). Routine clinicogenomic data are, therefore, a scalable resource for discovery in cancer cachexia.

The uncontrolled cellular growth and local tissue disruption produced by tumorigenesis elicit a complex host response, including chronic inflammation, metabolic reprogramming and endocrine dysfunction^{1,2}. These systemic changes can emerge early and persist throughout the disease course, contributing to profound alterations in appetite, energy balance, tissue composition and immune function^{3,4}. Together, they underlie debilitating syndromes such as fatigue, anorexia and cachexia. Understanding these pathophysiologies in human patients with cancer requires integrated, longitudinal measurements of host physiology and tumor biology.

Cancer cachexia (herein, ‘cachexia’) is a paraneoplastic metabolic syndrome characterized by progressive, unintentional weight loss^{3,5,6}

accompanied by muscle wasting⁷ that affects approximately half of all patients with cancer^{3,8}. Cachexia is associated with reduced quality of life^{9,10}, premature termination of therapy, increased treatment complications and elevated risk of death^{11–13}. Despite its prevalence and well-acknowledged consequences for morbidity and mortality, the underlying causes of cachexia are poorly understood. Recently, murine and fly models of cachexia have identified tumor-intrinsic molecular events, circulating factors and behavioral factors that mediate cachexia and its severity^{3,14–16}. However, despite these advances, there remains a major gap in understanding the manifestation of cachexia, and its molecular underpinnings, in human patients with cancer^{17,18}. This gap exists because of the heterogeneous application of clinical definitions¹⁹,

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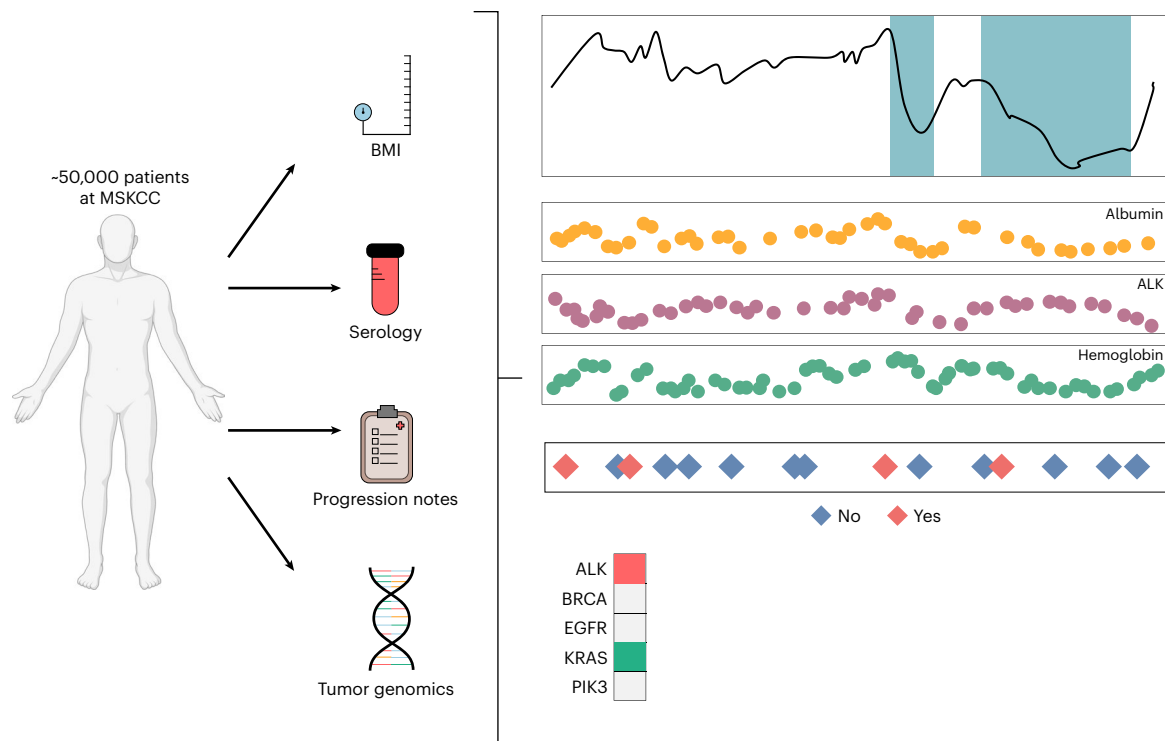


Fig. 1 | Multimodal data coverage. Overview of available modalities in the MSK-IMPACT cohort ($n = 52,236$ patients), including longitudinal BMI trajectories, serologic laboratory tests, radiology-derived progression annotations and tumor genomic profiling. Human silhouette created in BioRender; Castillon, V.J. <https://biorender.com/vsueti8> (2026).

and because molecular studies of cancer largely focus (with important exceptions^{20–22}) on measurements of malignant tissue and fail to capture measurements of wasting in non-malignant muscle and adipose compartments affected by cachexia.

By repurposing clinicogenomic measurements collected in the routine care of 52,236 adult patients with cancer, we interrogated the clinical evolution and molecular basis of cachexia through the analysis of weight loss episodes. Using this rich, longitudinally collected, multimodal dataset, we characterized how weight loss episodes present and evolve across cancers. These episodes cluster around disease progression and are coupled to inferior outcomes. Integrating serologic measurements, we discovered characteristic and cancer-type-agnostic changes in blood biomarkers that accompany these episodes. Finally, through genomic analysis, we discovered that certain tumor genotypes, and especially the presence of *TP53* mutations, are associated with an increased risk of cachectic episodes. On the basis of these discoveries, we produced novel, prospective models of the impending risk of meaningful weight loss in patients with lung, colorectal and prostate cancer.

Results

Population-scale identification of cachexia consensus-defined weight loss in cancer

To quantitatively study cancer cachexia, we obtained multimodal clinical and molecular data on 52,236 adult patients (Fig. 1 and Extended Data Fig. 1a) enrolled in the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) prospective clinical sequencing protocol, covering 589 distinct cancer histologies (Extended Data Fig. 1b). The cohort comprised a pan-cancer population with broad variation in age, sex, stage and baseline body mass index (BMI), with linked longitudinal body weight measurements, routine and specialized serology, disease progression annotations and tumor genomic profiling (Table 1). Across the cohort, we observed a mean of 33.3 BMI measurements (interquartile

range (IQR): 13–44) over an average of 52.4 months of follow-up, 41.4 serologic measurements among those with laboratory data (IQR: 19–65, $n = 40,165$ patients) and 5.8 radiology-derived progression events (IQR: 2–8, $n = 36,944$ patients).

Leveraging 1,741,505 longitudinal BMI measurements, we developed an episode-resolved algorithm to identify discrete time intervals during which a patient satisfied the consensus weight loss criteria for cachexia¹¹—that is, $\geq 5\%$ weight loss over a 6-month window or $\geq 2\%$ weight loss for patients with baseline BMI $< 20 \text{ kg m}^{-2}$ (Fig. 2a and Extended Data Fig. 1c). Using this framework, we identified 30,938 discrete episodes, affecting 46.63% of all patients (Fig. 2b), with 22.56% of those experiencing more than one episode (Fig. 2c). Normalizing to longitudinal follow-up, patients spent a mean of 13.7% of observed time in a cachectic episode-defined state (Fig. 2d), with a mean weight loss magnitude of 10.45% (Extended Data Fig. 2a). An analogous approach captured more severe episodes at $\geq 10\%$ weight loss (affecting 19.4% of all patients) and $\geq 15\%$ weight loss (6.9%) over a 6-month period (Extended Data Fig. 2b).

Consistent with previous literature, the prevalence of weight loss episodes varied significantly across cancer types^{8,23}. Gastrointestinal cancers were most frequently affected, with particularly high prevalence in pancreatic adenocarcinoma (PAAD; 72.7%), stomach adenocarcinoma (STAD; 71.7%) and colorectal adenocarcinoma (COADREAD; 49.6%). By contrast, prevalence was lower in prostate adenocarcinoma (PRAD; 26.1%) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 19.9%) (Fig. 2e). A similar pattern persisted under more stringent $\geq 10\%$ and $\geq 15\%$ thresholds, with gastrointestinal cancers remaining the most affected (Extended Data Fig. 2c).

Applying the same framework to an independent validation cohort from Dana-Farber Cancer Institute (DFCI; $n = 5,785$ patients), 55.2% of patients met the weight loss criterion at least once, and 22.4% and 7.0% met $\geq 10\%$ and $\geq 15\%$ thresholds, respectively (Extended Data Fig. 2d). Among these, 32% experienced two or more episodes (Extended Data Fig. 2e), and gastrointestinal

Table 1 | Baseline characteristics of the MSK pan-cancer cohort

Characteristic	Level	n (%)
Total patients		52,236
Age (in years)	Mean (IQR)	60.1 (IQR: 52.0–70.0)
Sex	Female	27,720 (53.1%)
Sex	Male	24,516 (46.9%)
Stage	Stage I–III	27,885 (53.4%)
Stage	Stage IV	22,021 (42.2%)
Stage	Missing	2,330 (4.5%)
Baseline BMI category	Overweight (25–29.9)	18,636 (35.7%)
Baseline BMI category	Normal (18.5–24.9)	17,132 (32.8%)
Baseline BMI category	Obese (≥ 30)	15,490 (29.7%)
Baseline BMI category	Underweight (< 18.5)	978 (1.9%)
Survival status	Alive	31,348 (60.0%)
Survival status	Dead	20,888 (40.0%)

Baseline demographics and clinical features for 52,236 adult patients included in the primary analysis. Age is summarized as mean (IQR) at diagnosis. Stage reflects clinical stage at diagnosis (stage I–III, stage IV or missing). Baseline BMI category was defined using the first recorded BMI within the baseline window and categorized as underweight, normal, overweight or obese, measured in kg m^{-2} . ‘Survival status’ indicates whether a death date was recorded during follow-up.

malignancies similarly ranked among the highest-prevalence cancers (Extended Data Fig. 2f).

Rates of cachectic weight loss also varied across histologically distinct tumor types arising from the same tissue (Supplementary Table 1), including non-small cell lung cancer (NSCLC), where adenocarcinoma showed lower odds of meeting the weight loss criterion than squamous cell (odds ratio (OR) = 0.76, $P = 0.001$; Fig. 2f); uterine cancer, where endometrioid tumors had substantially lower odds than the clinically more aggressive serous subtype²⁴ (OR = 0.33, $P = 1.8 \times 10^{-23}$; Fig. 2g); and hematologic malignancies, where diffuse large B cell lymphoma was associated with higher odds than follicular lymphoma (OR = 2.36, $P = 4.61 \times 10^{-11}$; Fig. 2h). Demographic correlates were also assessed using regression models with baseline age, sex and BMI category. In pan-cancer analyses, males were less likely to meet the criterion ($\log_2\text{OR} = -0.23$), whereas patients who were underweight at baseline were more likely to meet the criterion ($\log_2\text{OR} = 1.19$) (Supplementary Table 2).

To account for differences in baseline BMI, detected episodes were annotated using the weight loss grading system (WLGS)²⁵. Each of the episodes was mapped to the WLGS grid using baseline BMI at episode start and weight loss magnitude over its duration (Extended Data Fig. 3a). Across these episodes, grades were predominantly moderate to severe (WLG3: 49.1%; WLG2: 28.6%; WLG4: 12.5%), with fewer episodes classified as low grade (Extended Data Fig. 3b,c and Supplementary Table 3). Episodes spanned distinct severity strata across baseline BMI, with lower-BMI patients enriched for higher-grade events and higher-BMI patients distributed across a broader range of grades. Among episodes with higher baseline BMI (BMI > 25), grades remained frequently moderate to severe, with 51.6% in WLGS grades 3–4 and 33.5% in grade 2, and 44.0% of these episodes in patients with obesity met a $\geq 10\%$ weight loss threshold and 16.5% met $\geq 15\%$, consistent when stratified by cancer type.

Although cachexia is widely linked to inferior patient outcomes^{26,27}, quantitative estimates of its association with survival remain limited. We carried out survival analysis using time-independent and

time-dependent Cox proportional hazards across 18 cancer types ($n \geq 500$ patients). In time-independent, fixed models, ever meeting the episode-defined weight loss criterion was associated with significantly increased mortality risk in 17 of 18 cancer types, with glioblastoma (GBM) as an exception. In lung adenocarcinoma (LUAD), for example, patients who met the criterion for weight loss had significantly reduced survival compared to those who did not (hazard ratio (HR) = 2.68, $P < 1 \times 10^{-6}$; Fig. 2i), a pattern also observed pan-cancer (HR = 3.02, $P < 1 \times 10^{-6}$; Fig. 2j).

These cachexia-defined weight loss episodes, however, may occur at any point along a patient’s trajectory; we, therefore, extended our analysis to time-dependent Cox models. Episode onset was associated with inferior overall survival across all 18 cancers (Fig. 2k and Extended Data Table 1), with the strongest associations observed in prostate cancer (HR = 11.10, 95% confidence interval (CI): 9.64–12.79), uterine endometrioid carcinoma (HR = 9.27, 95% CI: 6.71–12.83) and clear cell renal cell carcinoma (HR = 9.19, 95% CI: 6.40–13.18). Associations remained significant after multivariate adjustment for age and sex (Supplementary Table 4) and were consistent at higher thresholds (Extended Data Fig. 3d and Supplementary Table 5), with progressively worse survival at higher weight loss grade (Extended Data Fig. 3d and Supplementary Table 6).

Finally, cachectic weight loss is often accompanied by compartment-specific changes in body composition that reflect underlying tissue dynamics^{13,28}. To characterize this, we quantified L3-level subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in a subset of patients with LUAD with abdominal computed tomography imaging at episode start, end and post-episode follow-up. Paired start–end scans (272 episodes, 237 patients) showed that mean SAT and VAT decreased by 23.5% and 27.2%, respectively, consistent with substantial adipose depletion during episodes. We additionally quantified post-episode regain, finding that 26.7% of episodes were followed by significant weight regain ($\geq 5\%$ BMI gain from episode end) and 12.5% within 6 months. This observation was corroborated at the tissue level, where paired-end–follow-up scans (117 episodes, 101 patients) showed that mean SAT and VAT increase by 32.0% and 24.9%, respectively; however, post-episode trajectories were heterogeneous, with SAT increasing in 64.1% of episodes and VAT increasing in 58.1% of episodes (Extended Data Fig. 3e,f). These compartment-resolved measurements provide tissue-level context for the BMI-defined episodes, supporting marked adipose loss during weight loss intervals.

Moments of disease progression are enriched during episodes

Previous studies have reported that cachexia prevalence in most cancer types is typically higher in advanced disease, suggesting that the most extreme forms of wasting arise late in the disease^{23,29}. However, the timing of weight loss can vary across patients, and, in our cohort, the majority of patients’ first episodes occurred within 5 years of diagnosis (92.7%), with prevalence and survival associations preserved when restricting to this window. To characterize when weight loss emerges during the clinical course and their subsequent evolution, we systematically mapped the temporal incidence across each patient’s clinical trajectory (Fig. 3a).

Within 180 days of diagnosis, 23.23% of early-stage patients untreated at diagnosis (stage I–III; $n = 20,554$) developed a weight loss episode. Early-onset burden varied substantially by cancer type (Fig. 3b), with the highest rates and enrichment in PAAD (59.6%, OR = 5.64, false discovery rate (FDR) $< 1 \times 10^{-6}$) and STAD (57.6%, OR = 4.57, FDR $< 1 \times 10^{-6}$) (Supplementary Table 8). By contrast, COADREAD and LUAD, commonly associated with cachexia in previous studies^{30,31}, showed relatively reduced early-onset odds (20.5% and 19.7%, respectively; OR = 0.84 and OR = 0.80; Fig. 3b and Supplementary Table 8). These findings suggest that significant weight loss can begin early after diagnosis in a substantial fraction of patients, and the same trend persisted when episodes were defined

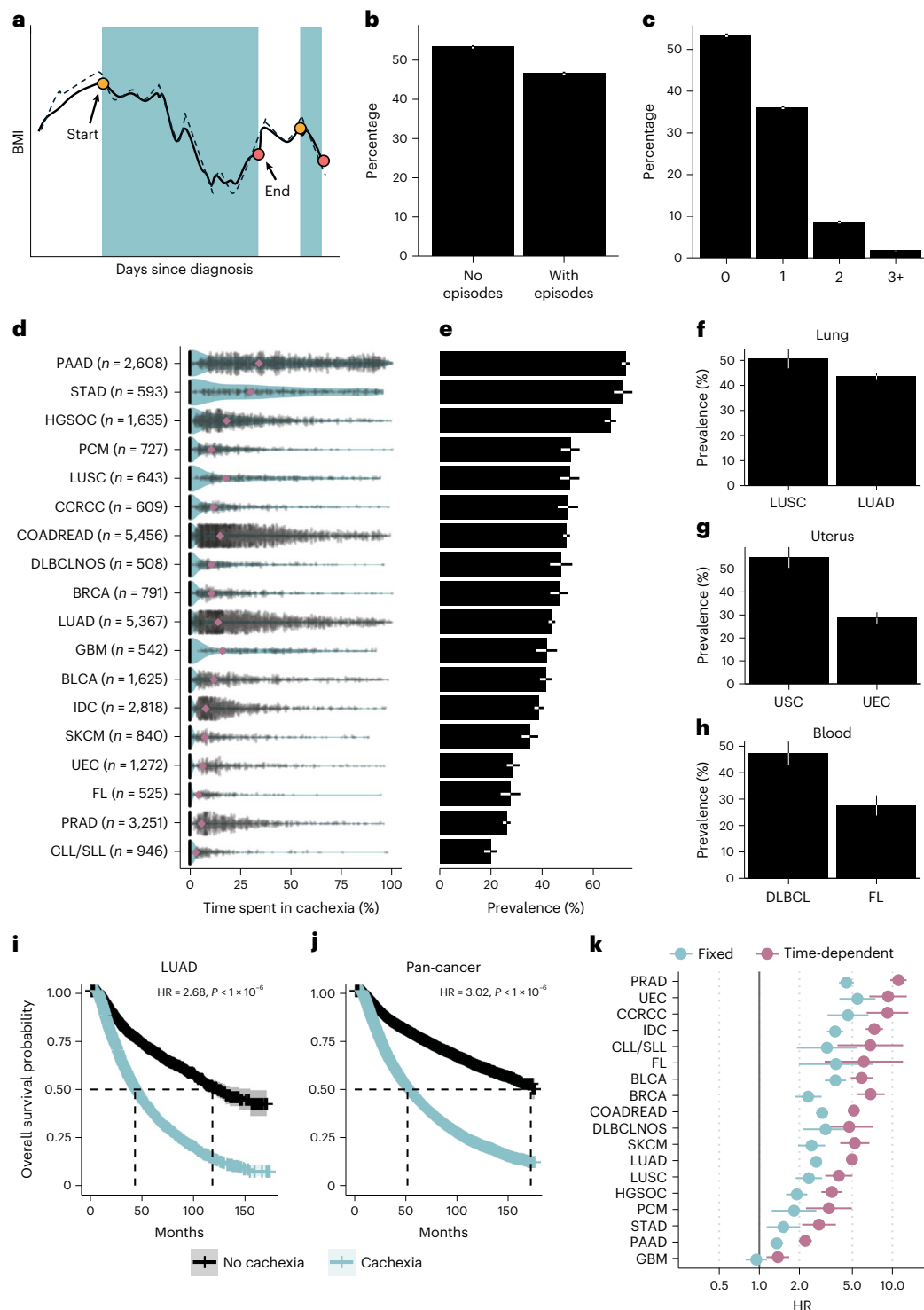


Fig. 2 | Prevalence and demographic associations of cachexia consensus-defined weight loss. **a**, Example BMI trajectory illustrating algorithmically defined episodes. **b**, Fraction of patients meeting the criterion at least once ($n = 52,236$). **c**, Distribution of episode counts per patient. **d**, Burden of cachectic weight loss across the 18 cancer types with at least 500 patients each, shown as the percent of observed follow-up time spent in an episode; sample sizes are given along the axis. Each dot is a patient, with the violin showing the distribution and the diamond marking the mean. **e**, Prevalence of meeting the consensus weight loss criterion across the same cancer types and sample sizes as in **d**, with error bars showing 95% CIs. **f-h**, Heterogeneity across histologic subtypes within shared tissue origins, with lower odds of meeting the criterion in LUAD versus lung squamous cell carcinoma (LUAD, $n = 5,367$ versus LUSC, $n = 643$; **f**) and in uterine endometrioid carcinoma versus uterine serous carcinoma/uterine papillary serous carcinoma (UEC, $n = 1,272$ versus USC, $n = 469$; **g**) and higher

odds in diffuse large B cell lymphoma versus follicular lymphoma (DLBCL, $n = 508$ versus FL, $n = 525$; **h**), compared using two-sided Fisher's exact tests ($P = 0.00105$, 1.82×10^{-23} and 4.61×10^{-11} , respectively); error bars are as in **e**. **i, j**, Kaplan-Meier overall survival curves stratified by ever meeting the episode-defined criterion (fixed exposure) in LUAD (**i**; HR = 2.68, $P < 1 \times 10^{-6}$) and pan-cancer (**j**; HR = 3.02, $P < 1 \times 10^{-6}$), from univariate Cox models with two-sided Wald tests. **k**, Association between cachectic weight loss and overall survival across the same 18 cancer types, using univariate Cox models with weight loss episodes treated either as a fixed exposure ('ever-episode', blue) or a time-varying status (plum); points show HRs with 95% CIs, and exact P values (two-sided Wald tests) are reported in Extended Data Table 1. BLCA, bladder urothelial carcinoma; BRCA, invasive breast carcinoma; CCRCC, clear cell renal cell carcinoma; DLBCLNOS, diffuse large B cell lymphoma, not otherwise specified; HGSO, high-grade serous ovarian cancer; PCM, plasma cell myeloma; SKCM, cutaneous melanoma.

using $\geq 10\%$ and $\geq 15\%$ thresholds (Extended Data Fig. 4a,b and Supplementary Table 8).

Conversely, cachexia is frequently observed near the end of life, consistent with systemic decline^{3,32–34}. To test this, we examined patients with BMI follow-up within 30 days of death ($n = 9,088$ patients). In this near-death cohort, 53.85% experienced death during or within 30 days after an episode (Fig. 3b). STAD and PAAD, also among the highest-burden early-onset cancers, had among the highest near-death prevalence (STAD: 65.5%, PAAD: 60.7%; Fig. 3b and Supplementary Table 9). These malignancies showed a trend toward enrichment for near-death episodes (OR = 1.64 and OR = 1.36, respectively), although only PAAD remained significant after FDR correction (FDR = 0.003 versus FDR = 0.13 for STAD; Supplementary Table 9). By contrast, GBM showed markedly reduced odds of episodes occurring near death (OR = 0.28, FDR = 1.4×10^{-7} ; Supplementary Table 9). Under stricter thresholds, 24.9% and 9.9% of this cohort met the $\geq 10\%$ and $\geq 15\%$ thresholds, respectively (Extended Data Fig. 4a,b and Supplementary Table 9). These findings point to a trajectory in which weight loss builds across the disease course, with greatest burden near death, consistent with refractory cachexia driven by heightened catabolic processes^{34–36}.

We then reasoned that the elevated rate of weight loss episodes near end of life may reflect increased risk of weight loss during progression on therapy. To test this, we asked whether radiographically confirmed progression events fall within episodes more often than expected by chance (Fig. 3c). Using 212,618 progression events, we repeatedly randomized episode timing within each patient timeline (1,000 permutations) to construct a null distribution. In COADREAD (0.318 versus 0.233 null), LUAD (0.267 versus 0.204) and PAAD (0.446 versus 0.382), progression events fell within episode windows significantly more often than expected by chance (all $P < 0.001$; Fig. 3d–f). By contrast, GBM showed no significant deviation from expectation (0.193 versus 0.183 null, $P = 0.42$; Fig. 3g). With this exception, 17 of 18 cancer types showed significant enrichment of progression events during episodes (Fig. 3h and Extended Data Table 2), a pattern that persisted under $\geq 10\%$ and $\geq 15\%$ thresholds, with attenuation in follicular lymphoma and CLL/SLL (Extended Data Fig. 4c and Supplementary Table 10). This suggests that episode-resolved weight loss concentrates around progression, a marker of worsening disease.

Disease-agnostic serologic signatures reveal systemic perturbations during weight loss episodes

Beyond weight loss, cachexia disrupts systemic physiology, leading to widespread metabolic and inflammatory perturbations^{37–39}, particularly in cancer and other chronic conditions, where persistent inflammation and tumor-derived factors further exacerbate catabolic processes^{2,40,41}. Interrogating such systemic phenotypes is challenging with tumor-tissue-focused molecular data such as DNA/RNA sequencing but highly amenable to routinely collected blood laboratory measurements from complete blood counts (CBCs) and comprehensive metabolic panels (CMPs).

To assess the physiologic changes associated with the episodes, we examined 30 routinely collected blood serologic biomarkers using mixed-effects models comparing episode versus non-episode

intervals (Fig. 4a). The association between episodes and each serologic marker was highly consistent across cancer types, suggesting a disease-agnostic signature of cachectic weight loss (Fig. 4b and Supplementary Table 11). Markers of circulating protein and nutritional status were among the most strongly decreased, including albumin (mean $\log_2(\text{OR}) = -0.89$; 95% CI: -1.01 to -0.76) and total protein (mean $\log_2(\text{OR}) = -0.48$; 95% CI: -0.61 to -0.34), reflecting nutritional depletion and inflammation-associated suppression of plasma proteins^{42,43}. Moreover, hemoglobin (-1.14 ; -1.30 to -0.98), hematocrit (-1.08 ; -1.23 to -0.93) and red blood cell count (-0.92 ; -1.11 to -0.74) were consistently depleted during episodes, suggesting an episode-associated anemia that may be driven by catabolic stress and reduced red blood cell production⁴⁴. Episodes were also associated with changes in homeostatic markers, including significantly higher glucose (0.15; 0.08–0.22; 16 of 18 cancer types) together with lower CO_2 (-0.20 ; -0.29 to -0.10) and consistent decreases in key electrolytes such as sodium, potassium and calcium. Inflammatory and tissue stress signals were also elevated during episodes, including higher neutrophils (0.33; 0.18–0.47) and monocytes (0.12; 0.02–0.22), alongside higher alkaline phosphatase (ALK, 0.49; 0.38–0.6) and aspartate aminotransferase (AST, 0.10; 0.01–0.18), pointing to increased tissue stress^{45,46}. When aggregated across diseases (Fig. 4c), these shifts converged on a disease-agnostic signature preserved under more stringent thresholds (Extended Data Fig. 5a), highlighting a phenotype of weight loss marked by nutritional depletion, anemia, hepatic stress and inflammation, although it is important to note that several of these markers are also plausible correlates of concurrent cytotoxic chemotherapy rather than cachexia biology alone.

Although episodes revealed broad disease-agnostic serologic shifts, these were reflected in modest distributional changes, with measures largely remaining within clinical reference ranges. Despite having the strongest decreases, 28.4% of albumin measurements during episodes fell below the normal range (3.4 – 5.4 g dl^{-1})⁴⁷ compared to 12.0% outside episodes (Fig. 4d). In COADREAD, subnormal albumin occurred in 32.4% of measurements during episodes, relative to 13.6% outside, corresponding to threefold higher odds ($P < 1 \times 10^{-6}$; Fig. 4d). Albumin levels were also lower during episodes even after accounting for standardized time ($\Delta = -0.189 \text{ g dl}^{-1}$, $P < 2 \times 10^{-16}$), whereas both trajectories largely remained within the normal clinical range (Fig. 4e). We also observed a temporal rise in ALK, a marker of hepatic and skeletal stress⁴⁶, after time adjustment ($\Delta = +22.4 \text{ U l}^{-1}$, $P < 2 \times 10^{-16}$; Fig. 4e), with measurements generally remaining within the reference interval (44 – 147 IU l^{-1} (ref. 48); Extended Data Fig. 5b), although the upward trajectory still implied an organ stress signature.

To capture broader systemic changes beyond routine laboratory values, we derived five composite indices from routine clinical labs focusing on inflammation and nutritional status. The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation^{49,50}, was significantly elevated during episodes in 16 of 18 cancer types (mean $\log_2(\text{OR}) = 0.37$, 95% CI: 0.25–0.50), with out-of-range NLR values more common during episodes than outside them (6.63% versus 5.00%, respectively; Extended Data Fig. 5c). The prognostic nutritional index (PNI) decreased in 16 of 18 cancer types as well (-0.56 ; -0.72 to -0.39), consistent with nutritional depletion

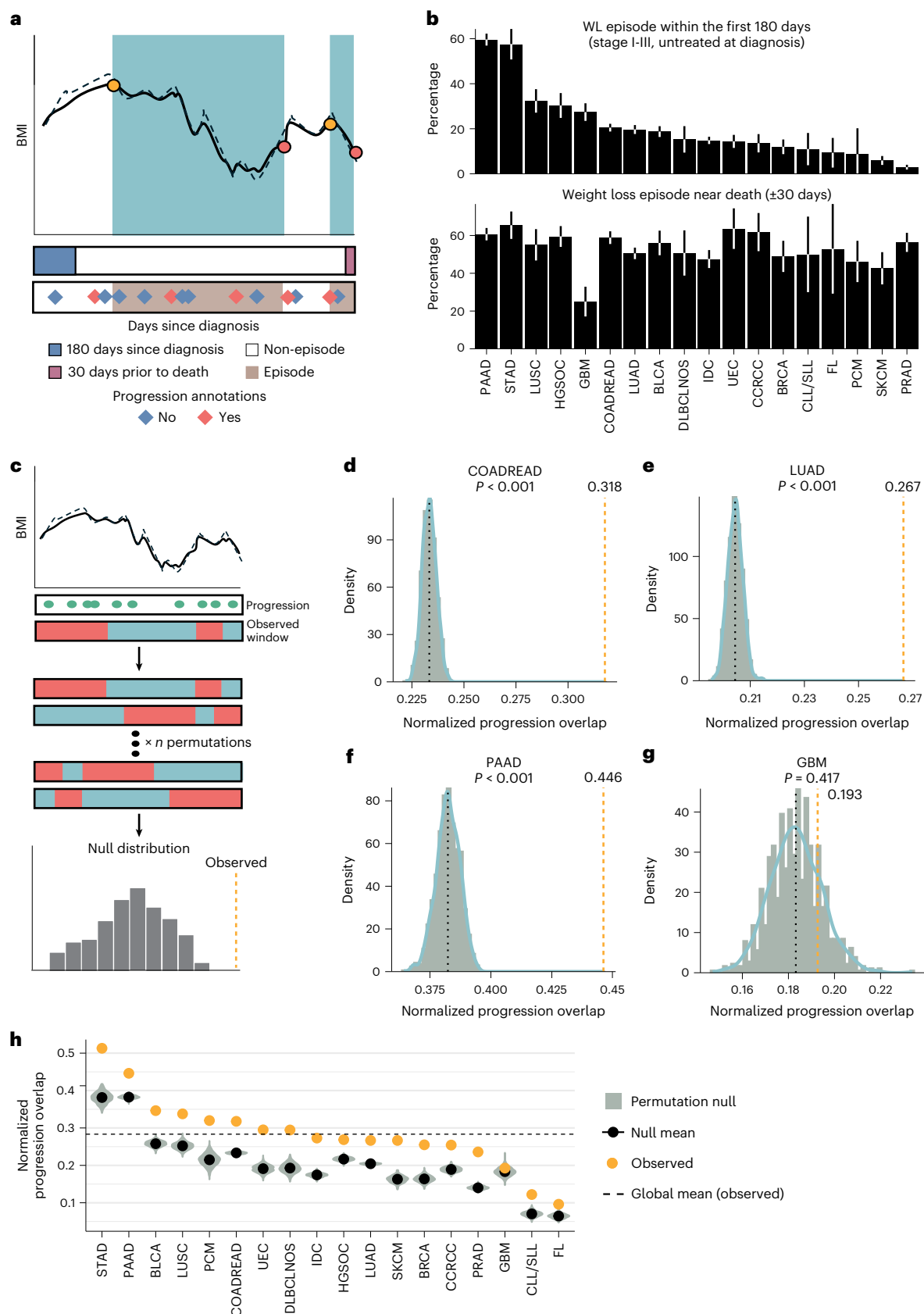
Fig. 3 | Cachexia consensus-defined weight loss is associated with progression on cancer therapy. **a**, Schematic illustrating the anchored clinical timeline used to map consensus-defined weight loss episodes relative to diagnosis and end of life, alongside longitudinal radiographic progression annotations. **b**, Cancer-type-stratified prevalence of consensus-defined weight loss episodes occurring early after diagnosis (≤ 180 days; stage I–III patients untreated at diagnosis; top, exact n per cancer type in Supplementary Table 8) and near end of life (patients with BMI follow-up within 30 days of death; bottom, n per cancer type in Supplementary Table 9), with burden varying substantially by cancer type at both timepoints. Error bars show 95% CIs. **c**, Permutation framework for

estimating the null distribution of episode–progression overlap by randomly reassigning patient spans within each timeline while preserving span duration and cachexia status. **d–g**, Progression events fell within episode windows more often than expected by chance in most cancer types, shown as observed overlap (dashed line) against the permutation-derived null distribution (histogram) from 1,000 random reassignments of patient spans per cancer type; significance was assessed with a two-sided permutation test. Examples are shown for COADREAD (**d**, $P < 0.001$), LUAD (**e**, $P < 0.001$), PAAD (**f**, $P < 0.001$) and GBM (**g**, $P = 0.42$). **h**, Summary of cachexia–progression overlap across cancer types ($n \geq 500$ patients).

and immune suppression. Additional indices showed consistent shifts, including higher AST/alanine aminotransferase (ALT) ratio (0.24; 0.15–0.34), higher corrected calcium (0.24; 0.15–0.33) and lower blood urea nitrogen (BUN)/creatinine ratio (–0.41; –0.51 to –0.32) (Fig. 4f),

preserved under more stringent episode definitions and after stratifying by stage (Extended Data Fig. 5a).

Finally, we examined additional markers that were available in a subset of patients. Among these, C-reactive protein (CRP), a direct



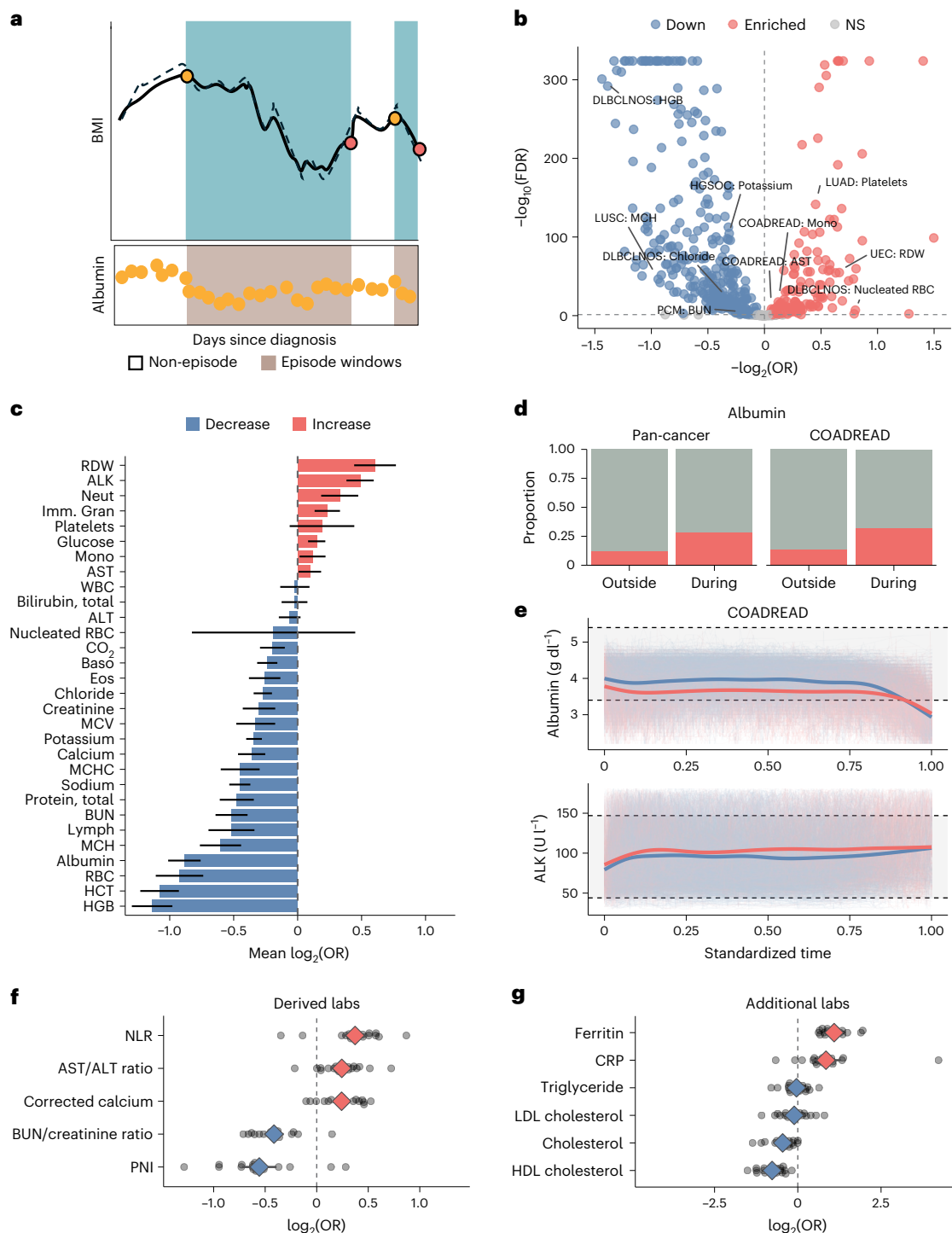


Fig. 4 | A serologic signature of cancer cachexia episodes. a, Schematic depicting measurements of albumin overlaid with a BMI trajectory. To identify signatures of cachexia, laboratory values in the shaded region are compared to those in the non-shaded region. **b**, Results of univariate analysis identifying differences in laboratory values during consensus-defined episodes relative to laboratory values outside of episodes. **c**, Tissue-agnostic summary of laboratory value associations with cachexia, derived from mixed-effects models; bars show the mean $\log_2(\text{OR})$ across the 18 cancer types in **b**, with error bars showing 95% CIs (per-cancer-type values in Supplementary Table 11). **d**, Frequency of subnormal albumin values within and outside episodes pan-cancer (left) and in COADREAD (right), using clinically defined reference ranges. **e**, Top, albumin trajectories in COADREAD, plotted over standardized time, are shifted downward during episodes relative to non-episode intervals. **e**, Bottom, ALK trajectories

in COADREAD are shifted upward during episodes, with the greatest elevations observed toward episode end. **f**, Composite indices derived from routine clinical labs show consistent episode-associated shifts relative to non-episode intervals; each dot is 1 of 18 cancer types, with the diamond marking the mean and 95% CI. **g**, Additional serologic markers available in subsets of patients beyond CBC/CMP exhibit concordant episode-associated alterations in inflammatory and nutritional status, shown as in **f**. Baso, basophils; Eos, eosinophils; HGB, hemoglobin; HCT, hematocrit; Imm. Gran, immature granulocytes; Lymph, lymphocytes; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Mono, monocytes; Neut, neutrophils; NS, not significant; RBC, red blood cells; RDW, red blood cell distribution width; WBC, white blood cells.

readout of interleukin 6 (IL-6)-mediated inflammation^{51,52}, exhibited a pronounced increase in 10 of 18 cancer types (mean $\log_2(\text{OR}) = 0.85$, 95% CI: 0.39–1.30). The proportion of abnormal CRP values (clinical reference, 0–10 mg l⁻¹) rose from 8.6% outside episodes to 15.3% during episodes, corresponding to higher odds of elevated CRP during episodes ($\text{OR} = 1.92$, $P < 1 \times 10^{-16}$) (Extended Data Fig. 5d). Ferritin also increased (1.09; 0.91–1.27), consistent with an acute-phase response and altered iron handling that may accompany the episode-associated anemia. Across lipid markers, episodes were associated with lower high-density lipoprotein (HDL) and total cholesterol (–0.77 and –0.45, respectively), whereas low-density lipoprotein (LDL) (–0.11) and triglycerides (–0.04) showed smaller and more variable shifts (Fig. 4g), an observation that is conserved at higher thresholds (Extended Data Fig. 5a). These patterns underscore systemic physiologic reprogramming during weight loss, likely reflecting a combination of cachexia-intrinsic biology and cytotoxic therapy exposure.

Somatic mutations to *TP53* and other genes are associated with an elevated risk of consensus-defined weight loss

Somatic driver mutations are determinants of therapeutic vulnerability, metastatic competency and clinical outcome. Recent evidence suggests that certain somatic mutations, such as *STK11* loss-of-function mutations in LUAD^{53–55} and *KRAS* mutations in PAAD^{56,57}, may directly promote cancer cachexia. Testing this at population scale, however, requires episode-resolved timing of weight loss events as well as rich clinicogenomic data.

We used competing risk models to calculate the cumulative incidence of weight loss episodes over time since tumor diagnosis, accounting for death as a competing event, testing all cancer type–gene combinations with at least 5% mutant cases in a given disease. We identified 34 significant associations ($\text{FDR} < 0.1$) linking 23 somatic mutations to differential risk of weight loss episodes across 14 distinct cancer types (Extended Data Table 3). In COADREAD, mutations of three genes, *TP53* ($\text{HR} = 1.16$, $\text{FDR} = 0.02$), *SMAD4* ($\text{HR} = 1.30$, $\text{FDR} = 3.03 \times 10^{-4}$) and *KRAS* ($\text{HR} = 1.17$, $\text{FDR} = 2.21 \times 10^{-3}$), were significantly associated with higher cumulative incidence, whereas mutations of eight genes (*AMER1*, *ARID1A*, *KMT2B*, *PIK3CA*, *PTEN*, *SOX9*, *TCF7L2* and *FBXW7*) were associated with lower incidence (Fig. 5b and Extended Data Table 3). Notably, *TP53* mutations were significantly associated with increased episode risk in nine cancers, including breast invasive ductal carcinoma (IDC), PRAD and LUAD (Fig. 5d), whereas *KMT2B* (Fig. 5e) was associated with significantly lower risk in multiple cancers, including COADREAD, suggesting a potential protective effect.

To corroborate these findings, we performed the same genotype association analysis in the DFCI cohort. Across 11 cancer types ($n \geq 200$ patients), we identified 20 significant associations ($\text{FDR} < 0.1$) (Fig. 5c and Supplementary Table 12). *TP53* again emerged as a recurrent risk genotype, significantly associated in six cancers, including NSCLC (Fig. 5f), pancreatic cancer and prostate cancer. We also found reduced risk associated with *FGFR3* in bladder cancer ($\text{HR} = 0.36$) and *PTEN* in endometrial cancer ($\text{HR} = 0.58$) (Extended Data Fig. 6c) and, specific to this cohort, a strong protective association for *IDH1* in glioma ($\text{HR} = 0.41$) and *PIK3CA* in colorectal cancer ($\text{HR} = 0.71$).

We next assessed whether genotype associations persisted across a spectrum of weight loss severity using stricter thresholds. At $\geq 10\%$ weight loss, 25 of the 34 primary associations remained significant (Extended Data Fig. 6a and Supplementary Table 13). Increasing the threshold to $\geq 15\%$, 13 associations retained significance ($P < 0.05$) (Extended Data Fig. 6b and Supplementary Table 14). The association of *TP53* mutations with increased risk remained significant in LUAD, PRAD and IDC across all levels, and protective associations involving *KMT2B* and *ARID1A* mutations in COADREAD were also preserved. The conservation of these associations at higher severity highlights mutations that are consistently correlated with weight loss burden. As an additional sensitivity analysis, restricted to clonal mutations, which

are likely early and ubiquitous events in tumor evolution, 30 of the 34 associations remained significant, confirming the robustness of our findings (Supplementary Table 15).

Associations identified in univariate analysis can be confounded by demographic and clinical covariates. We therefore performed a post hoc multivariable analysis, adjusting for age at diagnosis, sex, sample type, tumor mutational burden (TMB), microsatellite instability (MSI), Eastern Cooperative Oncology Group–Karnofsky Performance Status (ECOG–KPS) score, cancer stage and baseline BMI. This confirmed 15 of the 34 tumor genotype–weight loss risk associations independent of other clinical factors. *TP53* ($\text{HR} = 1.28$, $\text{FDR} = 3.57 \times 10^{-6}$) and *STK11* ($\text{HR} = 1.44$, $\text{FDR} = 2.34 \times 10^{-6}$) were independently associated with increased episode risk in LUAD (Fig. 5g and Supplementary Table 16), consistent with *TP53* association in the DFCI NSCLC cohort ($\text{HR} = 1.30$, $\text{FDR} = 0.02$; Fig. 5i). In COADREAD, *SMAD4* ($\text{HR} = 1.22$, $\text{FDR} = 6.99 \times 10^{-3}$) and *KRAS* ($\text{HR} = 1.14$, $\text{FDR} = 1.35 \times 10^{-2}$) were significant predictors of higher episode risk (Fig. 5h and Supplementary Table 17). These analyses confirm that the increased risk is not explained by more advanced disease, indicating that certain tumor-intrinsic genotypes carry a differential risk of cachexia independent of disease severity.

Motivated by the broad application of existing risk models in oncology, we developed multivariable predictive models to estimate impending episode risk in three diseases—LUAD, PRAD and COADREAD—using covariates significantly associated with episode risk from previous multivariable analysis. This included stage, ECOG–KPS, *TP53*, *STK11* and baseline BMI for LUAD; stage, ECOG–KPS, baseline BMI, *TP53* and *SPOP* for PRAD; and stage, ECOG–KPS, *SMAD4*, *KRAS*, MSI status, tumor sidedness and baseline BMI for COADREAD. These variables were used to compute individualized risk scores over time, evaluated using bootstrapped sampling across 200 iterations. The average concordance index (C-index) was 0.648 (95% CI: 0.635–0.661) for lung, 0.670 (95% CI: 0.653–0.691) for prostate and 0.639 (95% CI: 0.628–0.650) for colorectal. Models trained on randomly selected subsets of 50% of the cohort and tested on the remaining 50% of patients also demonstrated good calibration between predicted and observed 1-year, 2-year and 3-year episode incidence across all three diseases (Extended Data Fig. 7a–c). Time-dependent receiver operating characteristic (ROC) analysis showed area under the curve (AUC) values of 0.679, 0.710 and 0.733 in LUAD (Extended Data Fig. 7d), 0.631, 0.667 and 0.676 in PRAD (Extended Data Fig. 7f) and 0.638, 0.683 and 0.712 in COADREAD (Extended Data Fig. 7e).

Lastly, we assessed out-of-sample performance in the DFCI lung cancer cohort. Because ECOG–KPS was unavailable externally, we applied a reduced trained model restricted to shared covariates (clinical stage, baseline BMI and *TP53* and *STK11* status). The model showed modest but reproducible discrimination, with a C-index of 0.625 ($n = 1,159$, 516 events) and AUCs of 0.623, 0.644 and 0.658 at 1 year, 2 years and 3 years, respectively (Extended Data Fig. 7h), with reasonably well-aligned external calibration (Extended Data Fig. 7g). These results support the potential clinical utility of our models for early identification of high-risk patients and the development of proactive interventions.

Discussion

Previous human studies of cancer cachexia provided prevalence estimates for select cancers and some candidate biomarkers but lacked power to resolve temporal dynamics or genomic determinants^{22,23}. More recently, longitudinal analyses have quantified weight dynamics over time, and electronic health record (EHR)-based machine learning approaches have been proposed for earlier identification of cachexia^{58,59}. Building upon these approaches, this analysis of 52,236 patients and approximately 1.7 million body weight measurements demonstrates that consensus-defined weight loss episodes arise in discrete intervals, are enriched around progression and are associated with robust serologic phenotypes and somatic tumor genotypes.

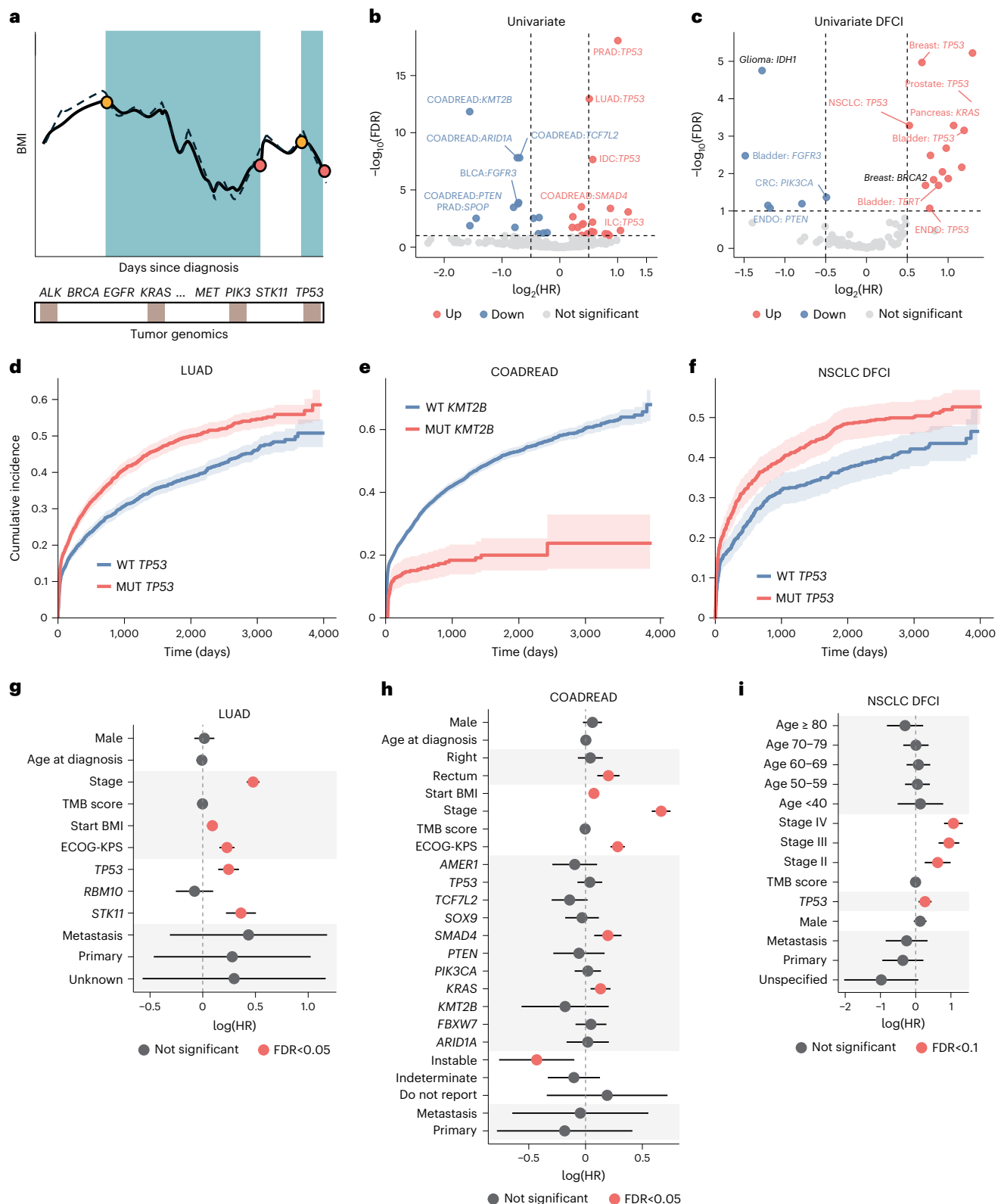


Fig. 5 | Driver mutations are associated with risk of consensus-defined weight loss episodes. a, Tumor genotypes from prospective clinical sequencing were linked to longitudinal BMI-derived consensus-defined weight loss episodes and clinical follow-up. **b**, Univariate association between the presence of driver mutations and episodes from a competing Cox regression, identifying 34 significant associations across 14 cancer types. **c**, Independent cohort validation of genotype–episode risk associations in DFCI, using the same modeling framework (Methods). **d**, TP53 mutations are associated with increased risk of consensus-defined weight loss episodes in LUAD ($n = 4,978$; wild-type $n = 2,666$, mutant

$n = 2,312$); shaded bands show 95% CIs. **e**, KMT2B mutations are associated with decreased, potentially protective, risk of consensus-defined weight loss episodes in COADREAD ($n = 5,380$; wild-type $n = 5,105$, mutant $n = 275$); shaded bands show 95% CIs. **f**, TP53-associated elevated episode risk replicates in an independent DFCI NSCLC cohort ($n = 1,213$; wild-type $n = 585$, mutant $n = 628$); shaded bands show 95% CIs. **g–i**, Multivariable Cox models confirming that these associations are independent of demographic and clinical covariates, for episode onset in LUAD (**g**), COADREAD (**h**) and DFCI NSCLC (**i**); points show HRs with 95% CIs. CRC, colorectal cancer; ENDO, endometrial cancer; MUT, mutant; WT, wild type.

Cachectic weight loss episodes affected nearly half of all patients in our cohort, with diverse timing patterns. Whereas pancreatic and gastric malignancies showed early onset, others exhibited episodes later in the disease course or near treatment resistance. Episodes frequently recurred and often clustered around periods of disease progression, highlighting a dynamic phenotype rather than a static event, with a notable fraction followed by subsequent weight regain. This reflects the time-bounded nature of weight loss and contributes to broader conversations around cachexia definitions and reversibility. Physiologically, this was accompanied by conserved serologic signatures, including reductions in albumin and hemoglobin, consistent with nutritional depletion and anemia, and elevations in inflammatory and tissue stress markers such as neutrophils and liver enzymes. These changes support a view of cachectic weight loss as a systemic metabolic and inflammatory state, where tumor burden and host response converge to drive catabolism and tissue loss.

Consistent with longstanding clinical observations⁵, gastrointestinal malignancies emerged as the cancers most strongly associated with weight loss episodes in our cohort, a finding that is not unexpected given the central role of the gastrointestinal tract in nutrient assimilation and energy balance. Multiple mechanisms likely converge in these diseases to amplify risk: tumor-induced obstruction and altered motility impair oral intake, and mucosal disruption and surgical resections compromise nutrient absorption⁶⁰. The dense inflammatory microenvironments of gastric tumors also likely promote systemic cytokine release that suppresses appetite and drives catabolism⁶¹. These mechanisms are compounded by chemotherapy^{62,63}, which involves intensive cytotoxic regimens that directly damage the intestinal epithelium, accelerating the onset of malnutrition. Together, these pathways explain why gastrointestinal tumors consistently dominate the cachexia landscape and reinforce the urgent need for interventions that preserve appetite, nutrient absorption and host metabolism.

Tumor-intrinsic molecular features were also associated with episode risk. *TP53* mutations were consistently linked to increased risk across multiple cancers, whereas *ARID1A* and *KMT2B* were associated with lower risk in specific diseases, suggesting that distinct oncogenic programs modulate host systemic physiology. These associations point toward the interplay in which tumor genotype may influence inflammatory signaling, metabolic reprogramming or tissue cross-talk driving weight loss. Building upon these findings, we integrated molecular and clinical variables into a predictive risk model capable of stratifying patients by their likelihood of developing episodes of weight loss. This model, although moderate in predictive power, highlights that risk can be quantified early and suggests a path toward incorporating cachexia surveillance into oncology practice.

A major open question in the field, which this study does not address, is the etiologic cause of weight loss. Although our analyses revealed consistent physiologic and serologic signatures of cachexia across diverse cancers, it is unlikely that this syndrome arises from a single causative factor. Weight loss in cancer can reflect a spectrum of mechanisms, including altered appetite and behavior^{63,64}, inflammation^{41,51,53} and cytokine signaling¹⁴ and metabolic effects of tumors or therapy^{35,62}. The challenge for the field is to disentangle these overlapping drivers, as no single pathway likely explains the breadth of cachexia observed in patients. Our framework of defining cachectic time intervals provides a path toward subtyping by aligning molecular, physiologic and radiographic features with discrete episodes of wasting, enabling precision approaches to cachexia management.

Cachexia, like many paraneoplastic syndromes, is a physiologic phenomenon captured by simple measurements taken during routine clinical care. Many of the key discoveries reported here are the direct consequence of careful analysis of otherwise routine data. Although contemporary cancer biology focuses on the molecular and cellular factors driving tumorigenesis, disease progression and response, our approach here motivates the alternative idea that clinical data

itself can address major questions in cancer biology, at a scale that dwarfs molecular data and at no additional cost. The space of clinically significant questions that could be addressed with a similar approach is likely very large.

Our study has several key limitations. The most significant of these limitations is that weight loss is a complex convolution of loss of different tissue compartments, including, but not limited to, the density and area of muscle and fat. The consensus definition of cachexia specifies that patients with skeletal muscle index consistent with sarcopenia and any weight loss greater than 2% over 6 months should be considered cachectic, but we were not able to implement this criterion given inadequate radiographic imaging data across our full cohort. Furthermore, in patients with obesity, sarcopenic obesity may obscure the extent of underlying muscle wasting, as clinically meaningful tissue depletion can occur despite preserved or excess body weight, a distinction that cannot be reliably ascertained from BMI alone. Linking these weight loss episodes to complementary body composition and functional assessments would provide a clearer understanding of the underlying phenotype and subsequent staging. The key challenge of future work, therefore, will be refining the observations made here with detailed measurements of body composition.

We also acknowledge that therapeutic exposure, as well as surgery and tumor resection, likely modifies the risk of developing cachexia and its subsequent consequences. Sophisticated statistical models will be necessary to adequately capture the convolved effects of different combinations of therapy on cachexia and of cachexia on therapeutic receipt and efficacy. In addition, the consensus weight loss definition further specifies weight loss that is unresponsive to conventional nutritional support, yet supportive-care interventions such as nutrition counseling, supplementation and structured exercise programs are not uniformly captured in the available structured data, precluding direct assessment or modeling of these exposures and their potential influence on episode detection. Our single-center design within a tertiary cancer hospital may further limit generalizability to community or non-tertiary settings. Finally, as with all observational analyses, our findings establish associations rather than causation, underscoring the need for prospective interventional studies to validate the mechanisms and biomarkers identified here.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04689-9>.

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Methods

Ethical approval and consent

This study was approved by the institutional review board (IRB) of Memorial Sloan Kettering Cancer Center under protocol 12-245. Patients enrolled in the MSK-IMPACT (NCT01775072) prospective sequencing protocol provided written informed consent for research use of their clinical and genomic data as part of routine clinical care. The DFCI validation cohort under DFCI IRB protocol 19-033 was analyzed under institutional approvals and data-use agreements between DFCI and MSK. No compensation was provided to participants.

Study design and cohorts

The cohort was derived from MSK-IMPACT, a prospective observational study of tumor evolution. We obtained multimodal clinical, genomic and serologic data on 79,240 patients. These data were linked to EHR-derived longitudinal BMI measurements, treatment records and serologic tests (including CBCs and CMPs). We restricted analyses to an adult cohort and applied exclusions consistent with the cohort flow diagram (Extended Data Fig. 1a). Patients with multiple primary cancers were excluded to avoid ambiguity in attributing longitudinal weight change to a single disease course. Patients with diagnosis dates occurring after the first available BMI measurement were also excluded to preserve consistent temporal anchoring of trajectories to diagnosis. For patients with multiple recorded tumor diagnosis dates of the same cancer, we retained the diagnosis date closest to the sequencing date and tumor resection to standardize anchoring to the genomic profiling timepoint. Pediatric patients (age <18 years) were excluded due to distinct growth and weight dynamics and differences in clinical management. Patients without BMI data were then excluded because longitudinal weight trajectories were required for episode identification. Finally, patients with fewer than two BMI measurements or fewer than 180 days of BMI follow-up were excluded to ensure sufficient measures to detect 6-month weight loss episodes with minimal sensitivity to single-point noise. The final cohort comprised 52,236 adult patients.

Patients in the DFCI cohort underwent tumor genomic profiling with OncoPanel, a targeted sequencing platform analogous to MSK-IMPACT. These data were also linked to EHR-derived longitudinal BMI measurements and clinical follow-up. We applied inclusion and exclusion criteria analogous to the cohort derived from MSK-IMPACT and performed the same episode detection and quality control framework to identify weight loss episodes. The resulting dataset included 5,785 patients covering 12 cancer types used for cancer-type-stratified replication analyses.

Data preprocessing

Clinical data. Clinical variables were obtained from EHR-linked clinical records and standardized across patients. Tumor diagnosis date was used as the time origin for longitudinal analyses, and follow-up was defined from diagnosis to death or last clinical encounter date in the EHR. Patient age at diagnosis and sex were obtained from clinical records, with sex recorded as female or male. We excluded BMI values <10 or >100 kg m⁻² as biologically implausible and most consistent with measurement, unit or data entry errors. These BMI data span multiple decades, and historical metadata on scale model, calibration and institution-wide standard weighing procedures are not uniformly available in the structured record; hence, we cannot provide a single validated, time-invariant estimate of instrument calibration error for the full time range and treat individual EHR weights as potentially noisy. Baseline BMI for covariate adjustment was defined as the measurement closest to diagnosis within a 90-day window, and episode-level baseline BMI was defined at episode start for WLGs annotation. Clinical stage and performance status (ECOG–KPS), when available, were used for covariate adjustment in multivariable models together with baseline demographics; analyses requiring these covariates were restricted to patients with non-missing values.

Serological laboratory values. We collected 30 routinely collected serologic markers from CBC and CMP tests. All measurements were converted to standard clinical units to ensure consistency across patients and timepoints. Clinical reference ranges used to define in-range versus out-of-range values were taken from institutional laboratory standards and were applied using sex-specific cutoffs provided by the laboratory. To minimize noise, we excluded biologically implausible values and restricted analysis to measurements collected during active clinical follow-up.

In addition to individual serologic measurements, we computed five derived indices from routinely collected laboratory tests to better capture systemic inflammation and nutritional NLR, PNI, AST/ALT ratio, BUN/creatinine ratio and corrected calcium. The NLR was calculated as the ratio of absolute neutrophil-to-lymphocyte counts. The PNI was defined as albumin (g dl⁻¹) + 5 × lymphocyte count (10⁹ per liter), consistent with previous literature⁶⁵. The AST/ALT and BUN/creatinine ratios were calculated directly from raw laboratory values, with thresholds for abnormality based on clinical references (for example, AST/ALT > 2.0 and BUN/creatinine > 20). Corrected calcium was computed using the following formula: calcium + 0.8 × (4 – albumin)⁶⁶.

Six additional biomarkers that are not routinely measured but were available in subsets of patients, including CRP, ferritin and lipid markers (HDL cholesterol, LDL cholesterol, total cholesterol and triglycerides), were collected. These measurements underwent the same unit standardization and quality control filtering as routine labs and were analyzed using the same episode-aligned framework.

Progression annotations from natural language processing. Radiographic progression was defined from radiology report impressions using the MSK-CHORD natural language processing (NLP) pipeline⁶⁷. Reports were segmented to the ‘Impression’ section and classified using a transformer model fine-tuned against human-curated progression labels. ‘Progressing/Worsening/Enlarging’ and ‘Mixed’ classifications were treated as progression positive, and all other categories were treated as negative. Report-level progression calls may generate multiple progression events per patient. To avoid double-counting duplicate calls, progression-positive reports with identical timestamps for the same patient were collapsed to a single event. The progression timestamp used in our analyses was the radiology report date for each progression-positive Impression.

Targeted DNA sequencing with MSK-IMPACT. Targeted DNA sequencing was performed using MSK-IMPACT, a hybridization-capture-based next-generation sequencing assay conducted in a Clinical Laboratory Improvement Amendments (CLIA)-certified molecular laboratory. Genomic DNA from formalin-fixed paraffin-embedded (FFPE) primary or metastatic tumors and matched normal samples was sequenced to high depth (median coverage >500×) using panel versions targeting 341, 410, 468 or 505 genes. Somatic alterations, including single-nucleotide variants, indels, copy number alterations and structural variants, were called against matched normal using established clinical pipelines. Variants were annotated with OncoKB, and analyses were restricted to alterations labeled oncogenic. For gene-level alteration frequencies, denominators were adjusted for panel version by restricting to samples in which the gene was assayed.

Consensus-defined weight loss episode identification

Episodes were identified using weight loss criteria consistent with established clinical definitions, primarily a ≥5% body weight loss or a ≥2% weight loss for patients with baseline BMI < 20 within a 6-month window⁴¹. To robustly capture these episodes from longitudinal BMI measurements, patient BMI trajectories were first smoothed using an exponentially weighted moving average (EWMA; α = 0.2), reducing short-term fluctuations while preserving longer-term trends. All episode criteria were then applied to the smoothed BMI trajectory.

After this, a 180-day sliding-window approach was used to scan each patient trajectory for intervals meeting the episode criteria. Specifically, a candidate episode is triggered at the first timepoint where EWMA BMI decline met the corresponding weight loss threshold (5% weight loss or 2% if BMI < 20). Overlapping candidate windows were merged into contiguous episodes, and episodes were retained only if they spanned at least 15 days and met the cumulative weight loss threshold. Episode start was recorded as the first qualifying timepoint. Subsequently, episode end was defined as the last day supported by observed BMI measurements for which the trajectory continued to meet the weight loss criterion; if subsequent measurements showed stabilization or regain such that the criterion was no longer satisfied in any 180-day window, the episode was terminated at the last qualifying measurement. If follow-up BMI measurements were unavailable, episode end was right-censored at the last recorded BMI measurement, and episodes were not extended across gaps or assumed to persist until death. Additional episode labels were generated for sensitivity analyses using more stringent thresholds of $\geq 10\%$ and $\geq 15\%$ weight loss over 180 days, applying the same detection, merging, duration and quality control criteria. An episode-level summary table containing deidentified identifiers, episode timing and key clinical covariates is provided at <https://doi.org/10.5281/zenodo.22045313> (ref. 68).

Edema-based quality control. To reduce misclassification driven by fluid shifts, we implemented an edema-based quality control step that detects transient, reversible weight gain patterns that can create spurious weight loss windows. Using the log-smoothed BMI trajectory, we defined edema-like windows as intervals in which BMI increased by at least 5% relative to a local baseline and subsequently returned to within 2% of that baseline within 30 days. Cachexia episodes were then excluded if they overlapped any edema-like window.

WLGS. To quantify cachexia severity, we applied the WLGS as described by Martin et al.²⁵. For each episode, we extracted baseline BMI at episode start and computed episode-specific percent weight loss over the evaluation window. Episodes were then mapped to WLGS grades (0–4) using the published WLGS grid, which assigns severity based on the combination of baseline BMI and percent weight loss, enabling stratification of episodes into clinically interpretable severity categories.

Post-episode weight regain. For each detected episode, BMI measurements recorded after episode end were identified and used to assess subsequent weight trajectory. Significant weight regain was defined as a $\geq 5\%$ BMI gain relative to the episode end value, evaluated within two windows: within 6 months of episode end and at any point during follow-up but before the start of a subsequent episode or death.

Survival analysis

We evaluated the association between consensus-defined weight loss episodes and overall survival using Cox proportional hazards models. Overall survival was defined from tumor diagnosis to death, with censoring at last contact. We fit both time-independent (fixed) and time-dependent models. In time-independent models, patients were classified as episode positive if they experienced one or more episodes during follow-up ('ever-episode'). In time-dependent models, episode status was defined as a step function that switched from 0 to 1 at the onset of the first episode and remained 1 thereafter, capturing mortality risk after episode onset. Models were fit using the 'coxph' function in the R 'survival' package with robust variance estimation clustered by patient (cluster (patient ID)) and multivariable models additionally adjusted for age at diagnosis, sex and cancer type as specified below.

The following equations were used, where - in equations denotes 'is modeled as a function of':

- (1) Survival - episode + age + sex + cancer type + cluster (patient ID)
- (2) Survival - episode (time varying) + cluster (patient ID)
- (3) Survival - episode (time varying) + age + sex + cancer type + cluster (patient ID)
- (4) Survival - WLGS (0–2) (time varying) + cluster (patient ID)
- (5) Survival - WLGS (3–4) (time varying) + cluster (patient ID)

To assess robustness, proportional hazards assumptions were assessed using Schoenfeld residual tests. Cancer types exhibiting evidence of non-proportionality were refit allowing time-varying effects using `tt()`, and HRs were summarized at 6, 12, 24 and 60 months; these estimates showed consistent direction and similar magnitude to the primary models (Supplementary Table 7).

Mixed-effects regression model

To quantify serologic differences during consensus-defined weight loss episodes, we fit mixed-effects regression models stratified by cancer type (restricted to cancer types with ≥ 500 patients). Laboratory measurements were aligned to episode status by timestamp overlap with episode intervals and labeled as occurring during an episode versus outside episodes. We performed this analysis for the 30 routinely measured CBC/CMP biomarkers, the five derived indices (NLR, PNI, AST/ALT ratio, BUN/creatinine ratio and corrected calcium) and additional non-routinely ordered biomarkers available in subsets of patients (CRP, ferritin, HDL, LDL, total cholesterol and triglycerides).

Models were fitted using mixed-effects logistic regression ('glmer', R package 'lme4') with a random intercept for patient (patient ID) to account for repeated measurements. Fixed effects included the laboratory value as continuous predictor, age at diagnosis and sex:

- (1) Episode - lab + age at diagnosis + sex + (1 | patient ID)

P values were adjusted across tests using the Benjamini–Hochberg procedure. Sensitivity analyses repeated the serologic modeling (1) after stratifying patients by clinical stage (stage I–III versus stage IV) and (2) using more stringent episode definitions based on $\geq 10\%$ and $\geq 15\%$ weight loss over 6 months, applying the same alignment and modeling framework.

Permutation analysis

To test whether radiographically confirmed progression events occurred during weight loss episodes more often than expected by chance, we performed a cancer-type-stratified permutation test. For each patient, we quantified the observed overlap as the fraction of progression events whose report date fell within any episode interval. We then generated a patient-specific null distribution by randomly reassigning episode timing within the patient's observed follow-up window while preserving the number of episodes and their durations. This randomization was repeated 1,000 times per cancer type to estimate the expected overlap under the null hypothesis of no temporal coupling between progression and episodes. Empirical *P* values were computed as the two-sided proportion of permutations whose absolute deviation from the null mean was at least as large as the absolute deviation of the observed overlap from the null mean. An enrichment was considered significant at $P < 0.05$. Sensitivity analyses were also performed for more stringent weight loss thresholds ($\geq 10\%$ weight loss and $\geq 15\%$ weight loss).

Time-to-event analysis

To investigate the influence of somatic alterations on episode risk, we integrated mutation calls from the MSK-IMPACT panel with curated clinical covariates. For each cancer type with sufficient sample size ($n > 200$), we first identified candidate genes through univariate analyses (Benjamini–Hochberg-adjusted $P < 0.1$). Only oncogenic mutations with a mutation frequency greater than 5% were tested. Cumulative incidence of cachexia in wild-type and mutant genes was calculated

separately using the `AalenJohansenFitter` function in the ‘lifelines’ Python package (version 0.27.8). We repeated the univariate screening using more stringent episode definitions ($\geq 10\%$ and $\geq 15\%$ weight loss over 6 months) and assessed whether the significant gene–cancer associations remained nominally significant ($P < 0.05$) under these thresholds. This method accounts for death as a competing event that might prevent the event of interest (consensus-defined weight loss episode) from ever occurring. Significant genes were then evaluated using multivariate cause-specific Cox proportional hazards models for time from tumor diagnosis to episode onset, with patients censored at death. Models were stratified by cancer type and adjusted for demographic and clinical features, including age at diagnosis, sex, sample type, TMB, disease stage, ECOG performance status and baseline BMI (categorized and scaled as described). For colorectal, gastric and endometrial cancers, MSI status was additionally included, and, for colorectal cancer, we also adjusted for tumor sidedness. Models were fit using the `CoxPHFitter` function in the ‘lifelines’ Python package (version 0.27.8), with the following equations:

- (1) Univariate: `time_to_episode ~ gene`
- (2) Multivariate: `time_to_episode ~ sig_gene + age + sex + starting BMI + stage + TMB + ECOG + sample type`
- (3) Multivariate (gastric, endometrial): `time_to_episode ~ sig_gene + age + sex + starting BMI + stage + TMB + ECOG + sample type + MSI`
- (4) Multivariate (colorectal): `time_to_episode ~ sig_gene + age + sex + starting BMI + stage + TMB + ECOG + sample type + MSI + sidedness`

Clonal validation. As an additional sensitivity analysis, we assessed whether significant gene–cancer type associations were driven by clonal, rather than subclonal, mutations. Mutation clonality was determined using FACETS-based tumor purity and copy number estimation, with each oncogenic mutation classified as clonal, subclonal or indeterminate based on cancer cell fraction. For each of the significant gene–cancer type pairs identified in the primary univariate analysis, we repeated the univariate cause-specific Cox model restricted to patients harboring a clonal mutation in the gene of interest, with all other patients coded as wild type. Associations were considered validated if they remained nominally significant ($P < 0.05$) using clonal-only mutation calls.

Nomogram construction and calibration

To provide individualized prediction of cachexia risk, we constructed nomograms based on multivariable Cox regression models using the covariate framework that were tested significantly associated with cumulative incidence of consensus-defined weight loss. Models were trained on cancer-specific cohorts, and the regression coefficients were scaled to assign point values to each predictor. The cumulative point total was mapped to the predicted probability of an episode at fixed time horizons (1, 2 and 3 years after diagnosis).

The predictive performance of the models was assessed for discrimination and calibration using an internal validation approach. For calibration and time-dependent AUC analyses, the cohort was split once at the patient level into 50% training and 50% test sets. Discrimination—the model’s ability to distinguish between patients who develop an episode earlier versus later—was evaluated using two metrics: (1) the C-index with 95% CIs estimated from 200 bootstrap resamples of the full cancer-specific cohort and (2) time-dependent AUCs at 1, 2 and 3 years computed using `cumulative_dynamic_auc` from the Python ‘`sksurv`’ package.

We measured calibration—the agreement between the model’s predicted probabilities and the actual observed outcomes—by generating calibration plots for the test cohort. Patients in the test set were stratified into quartiles based on their nomogram-predicted risk of an episode. Within each quartile, the mean predicted risk was plotted

against the observed episode incidence. A perfect calibration would present a 45° diagonal line.

DFCI reduced model validation. To evaluate generalizability beyond the discovery cohort, the LUAD nomogram was additionally assessed in the independent DFCI cohort. Because ECOG–KPS was not available in the DFCI dataset, a reduced Cox model restricted to shared covariates such as clinical stage, baseline BMI and *TP53* and *STK11* mutation status was trained on the MSK-IMPACT LUAD cohort and applied without refitting to DFCI patients. External discrimination was assessed using the C-index and fixed horizon AUCs at 1, 2 and 3 years.

Manual segmentation

Adipose tissue composition was quantified from abdominal computed tomography imaging using Aquarius iNtuition (TeraRecon Inc.). For each patient, an abdominal computed tomography series was identified, and a single axial slice at the L3 vertebral level was selected, with slice level confirmed by a radiologist. SAT and VAT areas were quantified using the built-in fat analysis tool, which performs automated compartment segmentation and reporting. Segmentations were manually reviewed and corrected when needed to address misclassified regions or boundary discontinuities. The same workflow was applied across scans, and a subset of segmentations underwent secondary review to confirm consistency of slice selection and compartment segmentation.

Statistics and reproducibility

This is a retrospective, observational study using clinicogenomic and EHR-derived data from patients enrolled in the MSK-IMPACT prospective sequencing protocol, with external validation in an independent cohort from DFCI. Sample size was determined by the number of patients meeting inclusion criteria within the study period; no statistical method was used to predetermine sample size. Data were excluded for patients with multiple primary cancers, pediatric patients (age < 18 years), implausible BMI values (< 10 or > 100 kg m $^{-2}$) and patients with insufficient longitudinal BMI follow-up (fewer than two BMI measurements or fewer than 180 days of follow-up). Survival, serologic and progression enrichment analyses were restricted to cancer types with at least 500 patients; genotype association analyses used a lower threshold of at least 200 patients per cancer type (or at least 5% mutant carriers for a given gene–cancer combination), reflecting the smaller subgroup sizes required to test individual mutation associations. Statistical analyses included time-independent and time-dependent Cox proportional hazards models, mixed-effects logistic regression, competing risk regression and permutation-based enrichment testing and were performed in R (version 4.1.1) and Python (version 3.13.12) using standard statistical libraries, including ‘`survival`’ and ‘`lme4`’ (R) and ‘`lifelines`’ and ‘`scikit-survival`’ (Python). Unless otherwise specified, statistical tests were two-sided, and multiple testing correction was performed using the Benjamini–Hochberg procedure. The experiments were not randomized. The investigators were not blinded to allocation during experiments and outcome assessment, as no subjective judgments were involved in data collection or analysis.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data are accessible through cBioPortal for Cancer Genomics at <https://www.cbioportal.org>, with additional study data available via Zenodo at <https://doi.org/10.5281/zenodo.22045313> (ref. 68). Please note that patients with ages at diagnosis greater than 89 years are coded as ‘ > 89 ’. Deidentified data can also be requested for research use from the corresponding author. For questions regarding access to the DFCI cohort data, please contact A.G. Source data are provided with this paper.

Code availability

Code for reproducing the results, figures and associated tables is available via GitHub at <https://github.com/reznik-lab/cachexia>.

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Author contributions

E.R. conceived of and supervised the study and acquired funding. E.R., V.J.C. and A.X.X. led data acquisition, designed formal analysis and performed experiments. S.B., E.T., N.R., J.W. and Z.B. assisted with methods and contributed to the study through discussion and scientific input. M.W., C. Fu, C. Fong and J.J. carried out the data acquisition and collection. M.S., T.B. and A.G. performed initial experiments for the DFCI cohort. W.P., U.A.S., A.A.H., P.I., J.J., E.W., T.J. and M.D.G. provided clinical input and scientific interpretation. All authors reviewed and approved the final paper.

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were not involved in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests

Z.B. reports honoraria from UpToDate and serves as an associate editor at the *Journal of Clinical Oncology Clinical Cancer Informatics (JCO CCI)*, unrelated to the present study. W.P. reports relationships with American Physician Institute for Advanced Professional Studies LLC, Astellas, EXACT Therapeutics AS, Integrity Continuing Education Inc. and Revolution Medicines and an uncompensated relationship with Break Through Cancer. U.A.S. reports institutional research funding from Celgene/Bristol Myers Squibb and Janssen, institutional support from Sabinsa Pharmaceuticals and M&M Labs and personal fees from Janssen Biotech, Sanofi and i3Health, outside the submitted work. P.I. reports relationships with AstraZeneca and GE Healthcare and uncompensated relationships with AstraZeneca UK Limited and Incyte. M.D.G. holds equity in Faeth Therapeutics and Skye Biosciences; has consulting/advisory roles with Almac Discovery, Faeth Therapeutics, Genentech, Scorpion Therapeutics, Skye Biosciences and Third Arc Bio; has received honoraria from Novartis, Pfizer and Genentech; and reports patents/royalties/intellectual property with Weill Cornell Medicine and Faeth Therapeutics. The remaining authors declare no competing interests.

Additional information

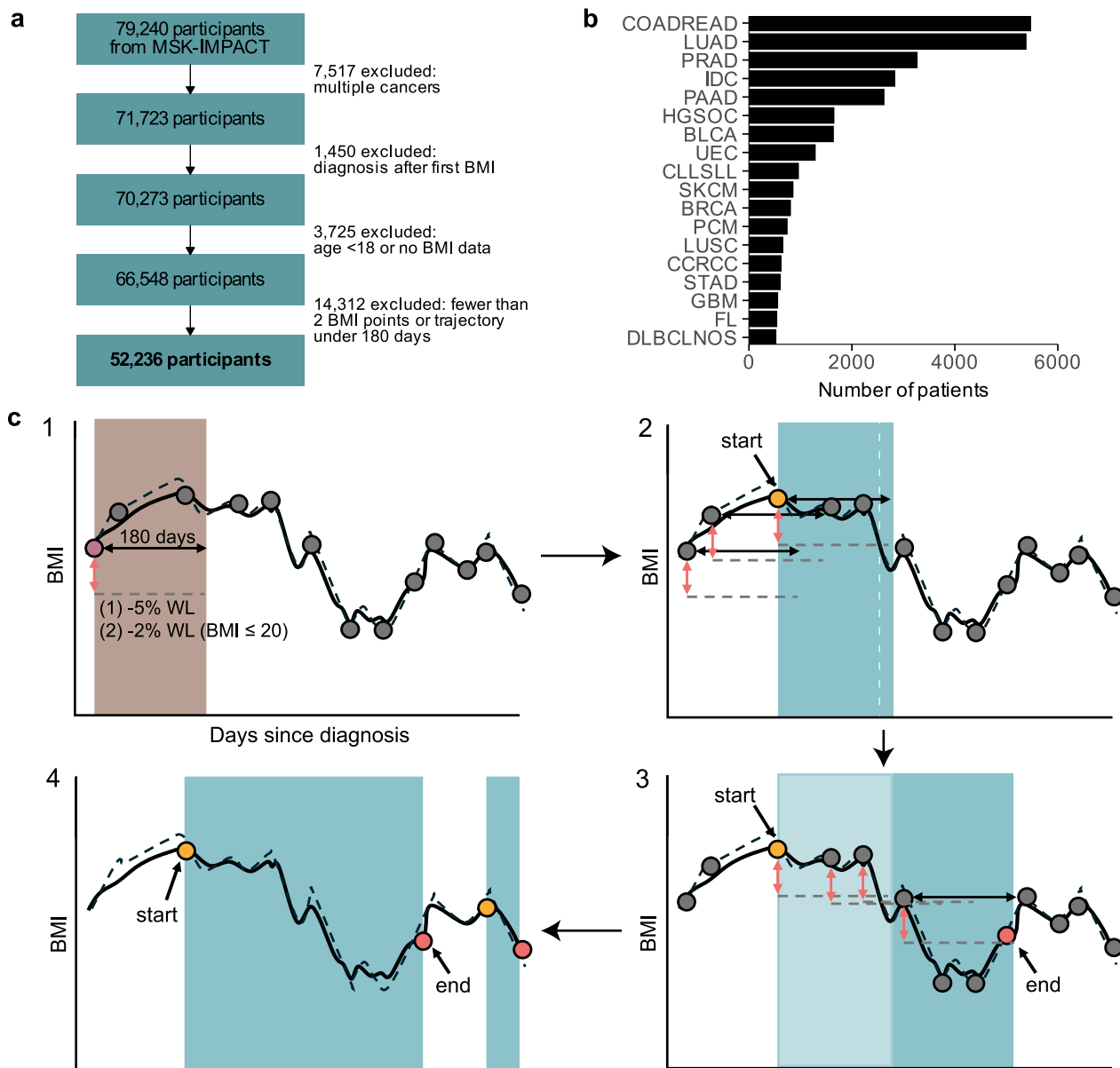
Extended data is available for this paper at <https://doi.org/10.1038/s41591-026-04689-9>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-026-04689-9>.

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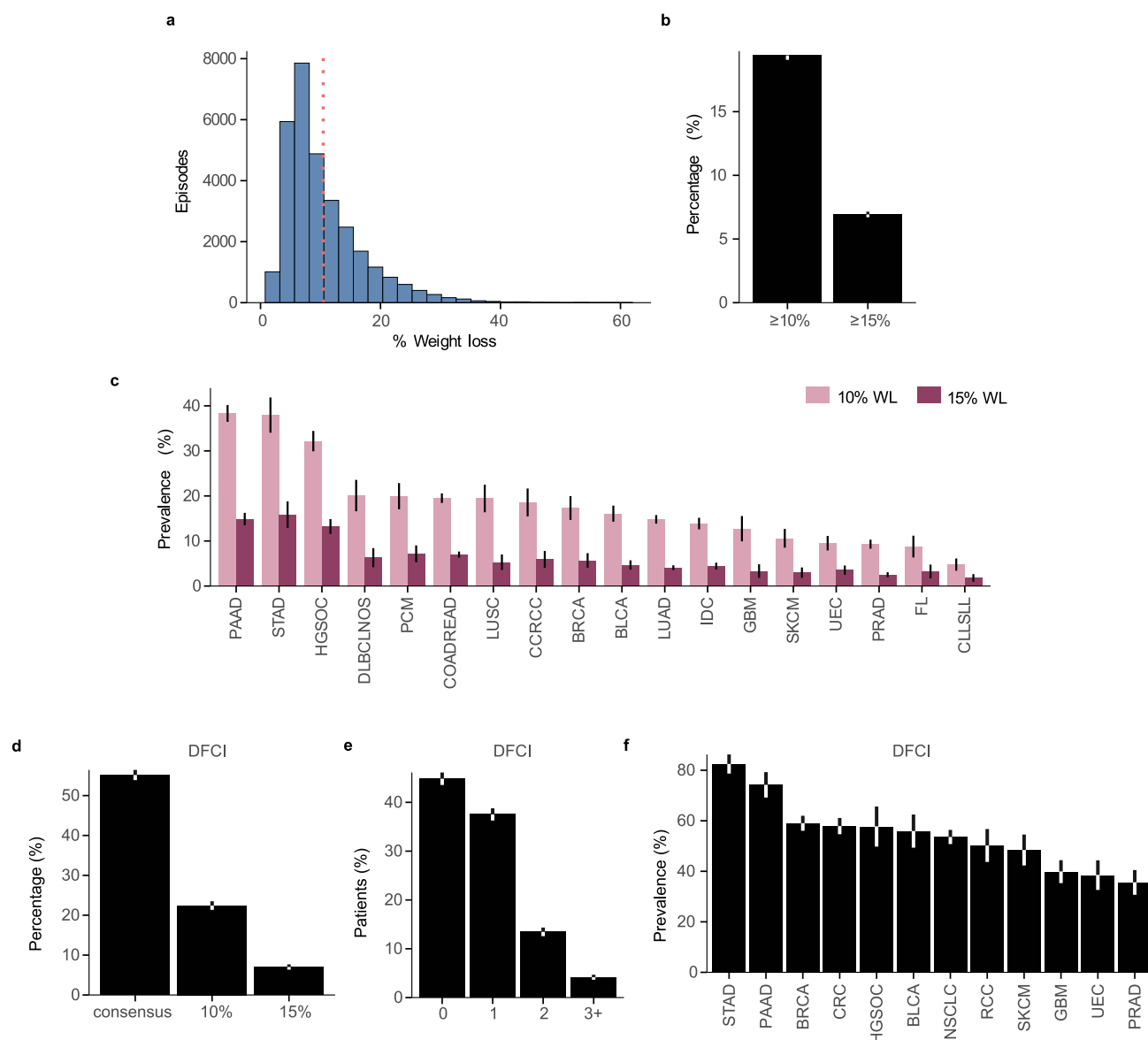
Peer review information *Nature Medicine* thanks Ghulam Rasool, who co-reviewed with Sabeen Ahmed; Jennifer Ose; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available. Primary Handling Editor: Ulrike Harjes, in collaboration with the *Nature Medicine* team.

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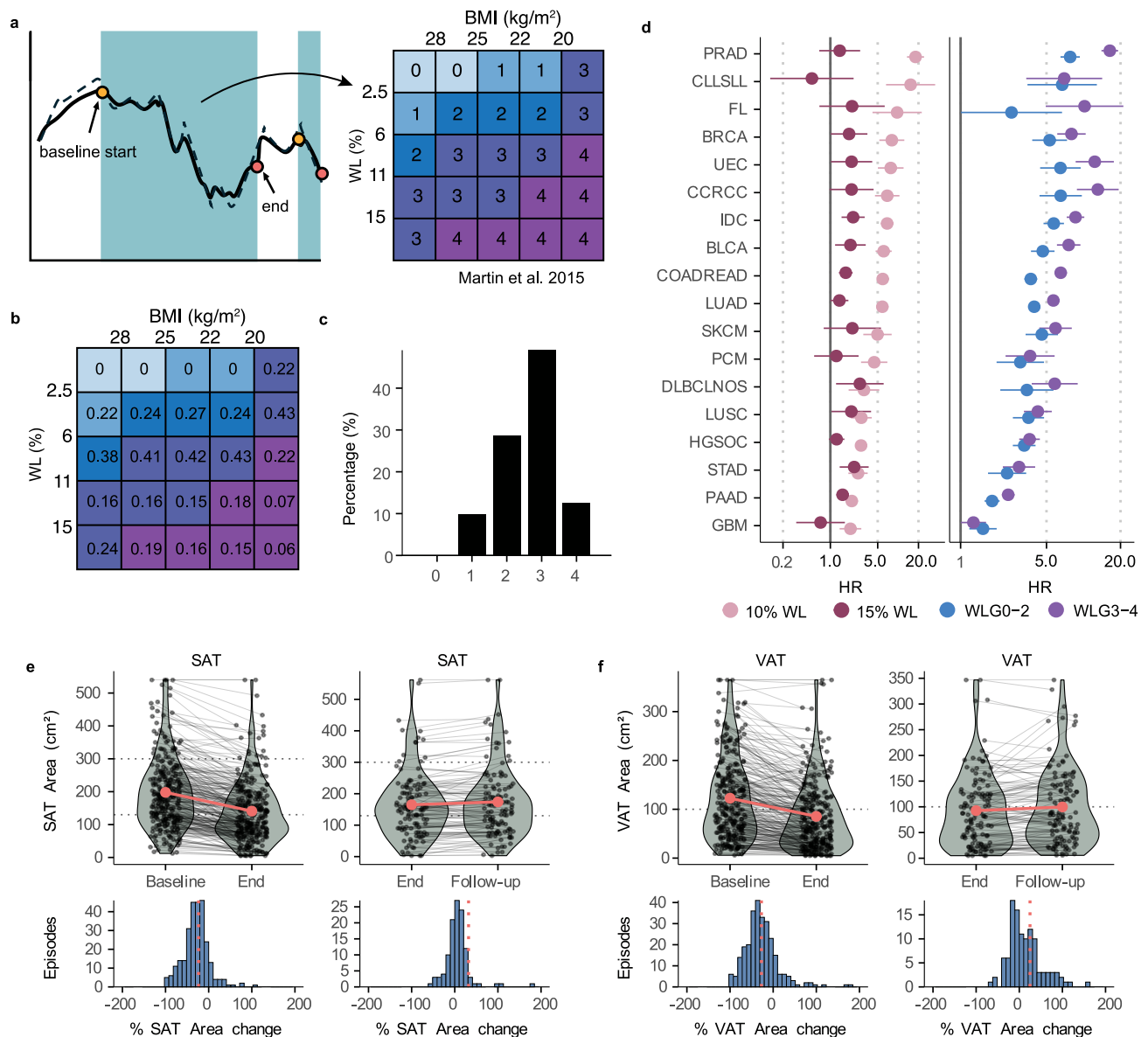
Extended Data Fig. 1 | Cohort assembly, cancer type distribution, and episode-detection algorithm. (a) Flow diagram of cohort assembly from the MSK-IMPACT cohort (79,240 participants) to the final analytic cohort (52,236 participants), showing the number of participants excluded at each sequential exclusion step. (b) Number of patients per cancer type among the 18 cancer types with at least 500 patients in the final cohort. (c) Step-by-step illustration of the episode-detection algorithm applied to a single patient's BMI trajectory:

candidate episode onset is identified within a 180-day window using the consensus weight-loss criteria ($\geq 5\%$ weight loss, or $\geq 2\%$ for patients with baseline BMI ≤ 20) (1); episode start is set at the first qualifying timepoint (2); overlapping candidate windows are merged and episode end is set at the last timepoint still meeting criteria (3); the same logic applied across a full trajectory can yield multiple discrete episodes per patient (4).



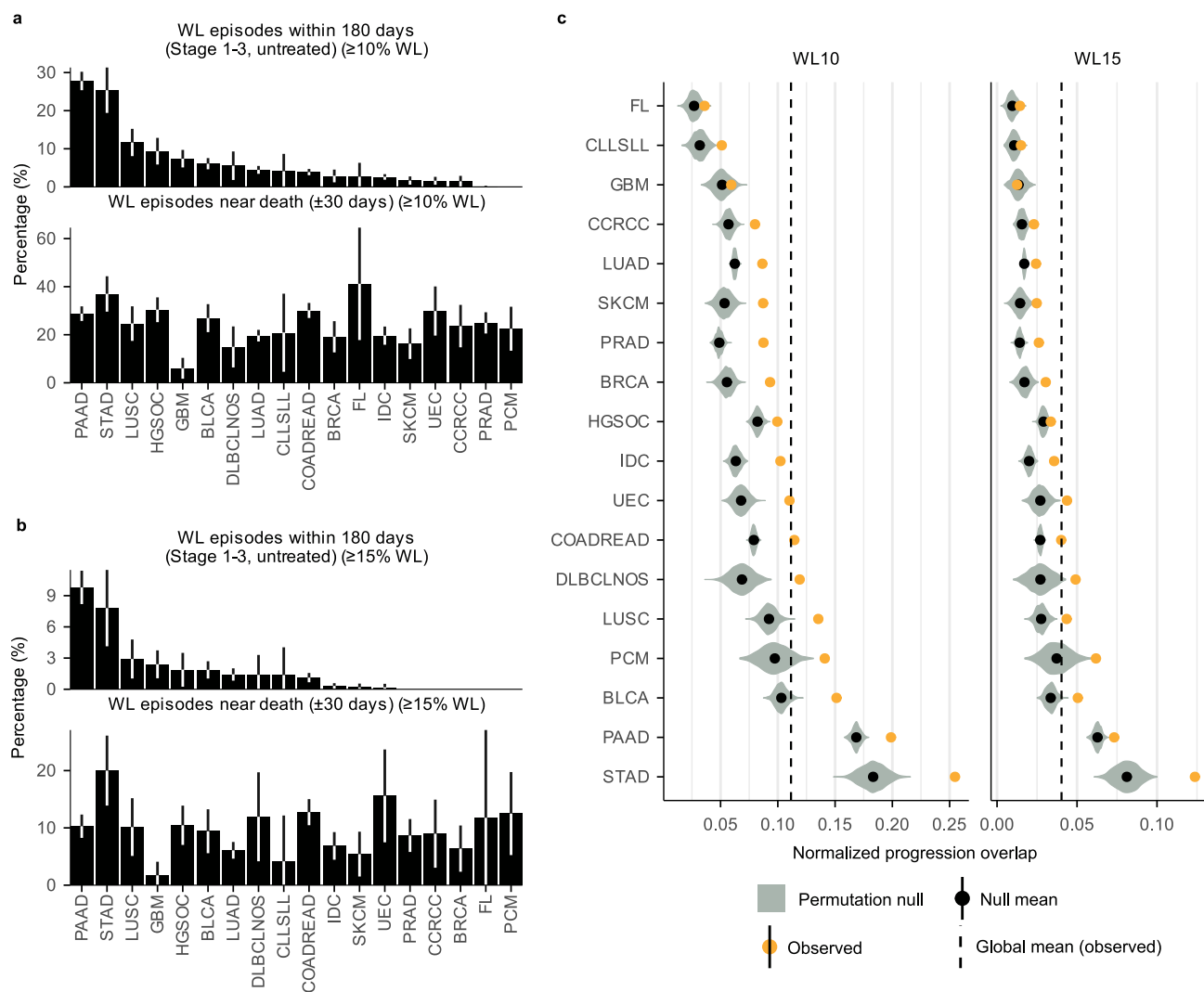
Extended Data Fig. 2 | Episode-defined weight loss severity and independent validation. (a) Histogram of percentage weight loss across all detected episodes ($n = 30,938$ episodes; mean=10.45%, dotted line). (b) Prevalence of episodes detected at stricter weight-loss thresholds ($\geq 10\%$ and $\geq 15\%$) in the full cohort ($n = 52,236$), using the same episode-detection framework as the consensus definition. Error bars show 95% confidence intervals. (c) Cancer-type prevalence at the same two thresholds, across the same 18 cancer types shown in Fig. 2d,e;

relative differences across cancer types are preserved at stricter thresholds. Error bars are as in b. (d-f) Independent validation in the Dana-Farber Cancer Institute (DFCI) cohort ($n = 5,785$ patients across 12 cancer types): prevalence of meeting the consensus, $\geq 10\%$, and $\geq 15\%$ weight-loss criteria at least once (d); distribution of episode counts per patient (e); and prevalence by cancer type (f). Error bars are as in b.



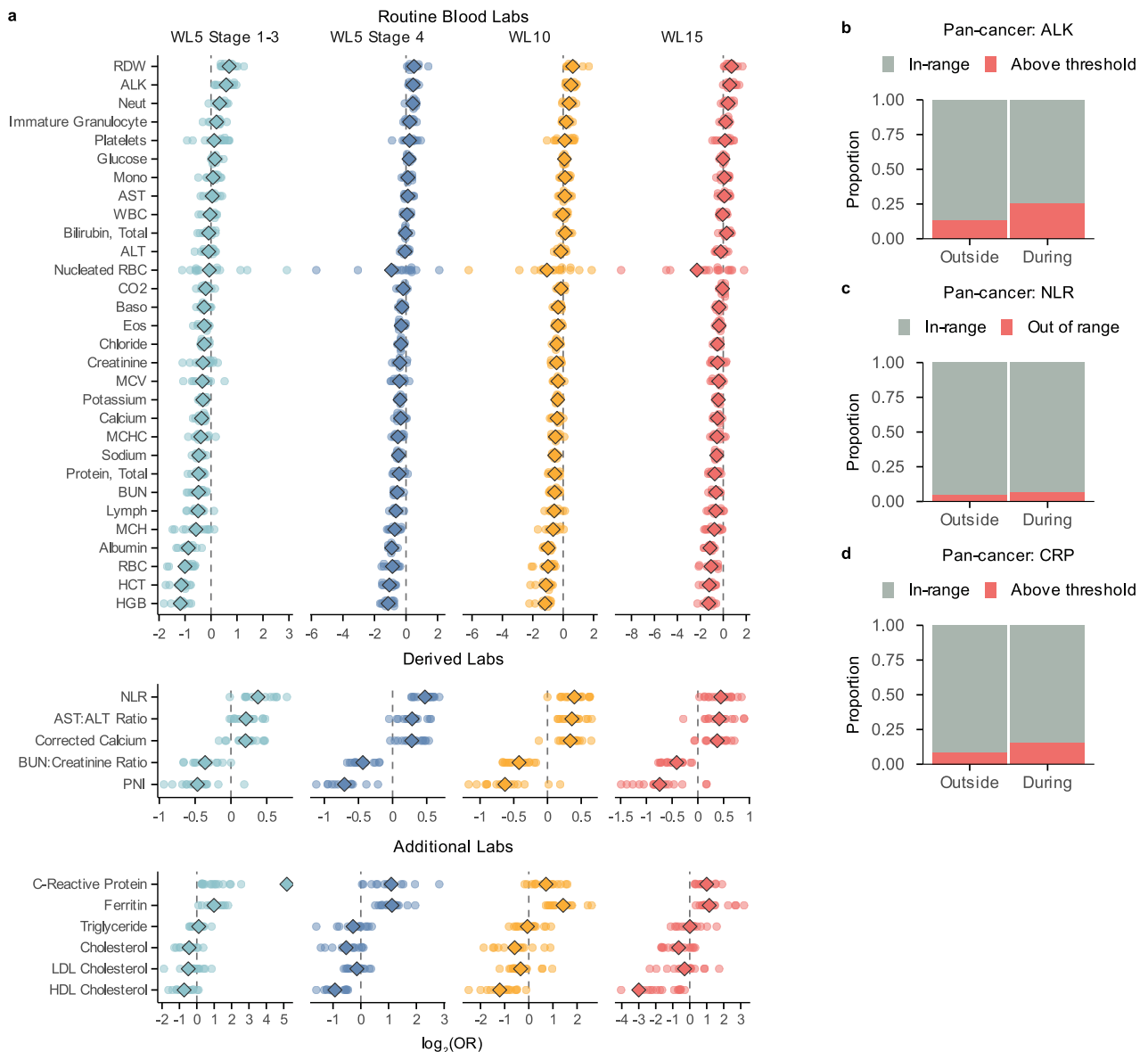
Extended Data Fig. 3 | Weight-loss grade stratification, survival sensitivity, and body composition dynamics. (a) Weight-loss grade system (WLGS) mapping each episode according to baseline BMI at episode onset and weight-loss magnitude over the evaluation period. (b) WLGS grid matrix showing the proportion of detected episodes by baseline BMI category. (c) Overall distribution of WLGS grades across all detected episodes. (d) Survival sensitivity analyses: time-dependent Cox associations with 10% and 15% WL episode definitions (left) and stratification by WLGS grade (right; WLGO-2 vs WLGS-4),

across the same 18 cancer types. Points show hazard ratios with 95% confidence intervals. (e) LUAD CT-derived subcutaneous adipose tissue (SAT) area at episode baseline and end (left; $n = 272$ episodes, 237 patients) and at episode end and post-episode follow-up (right; $n = 117$ episodes, 101 patients); histograms (bottom) show the corresponding distributions of percent SAT change, with the mean (dotted line). (f) LUAD CT-derived visceral adipose tissue (VAT) dynamics, shown as in e.



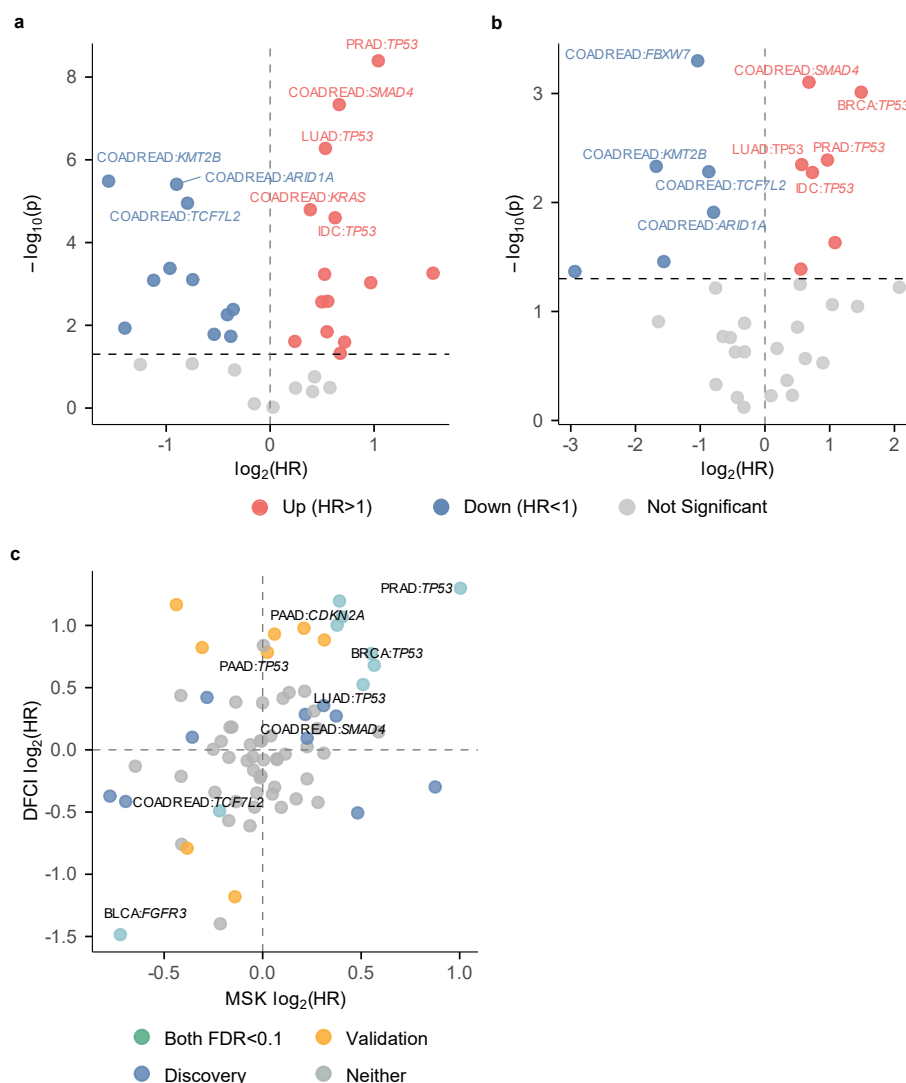
Extended Data Fig. 4 | Robustness of episode timing and progression overlap under stringent weight-loss thresholds. (a-b) Cancer-type-stratified prevalence of weight-loss episodes at $\geq 10\%$ (**a**) and $\geq 15\%$ (**b**) thresholds, for early onset after diagnosis (≤ 180 days; stage I-III, untreated; top; n per cancer type in Supplementary Table 8) and near end of life (bottom; n per cancer type in

Supplementary Table 9). Error bars show 95% confidence intervals. **(c)** Episode-progression overlap across the same 18 cancer type ($n \geq 500$ each) at $\geq 10\%$ (left) and $\geq 15\%$ (right) thresholds: violins show the permutation null distribution, black points show the null mean, orange points show the observed overlap, dashed line shows the global mean.



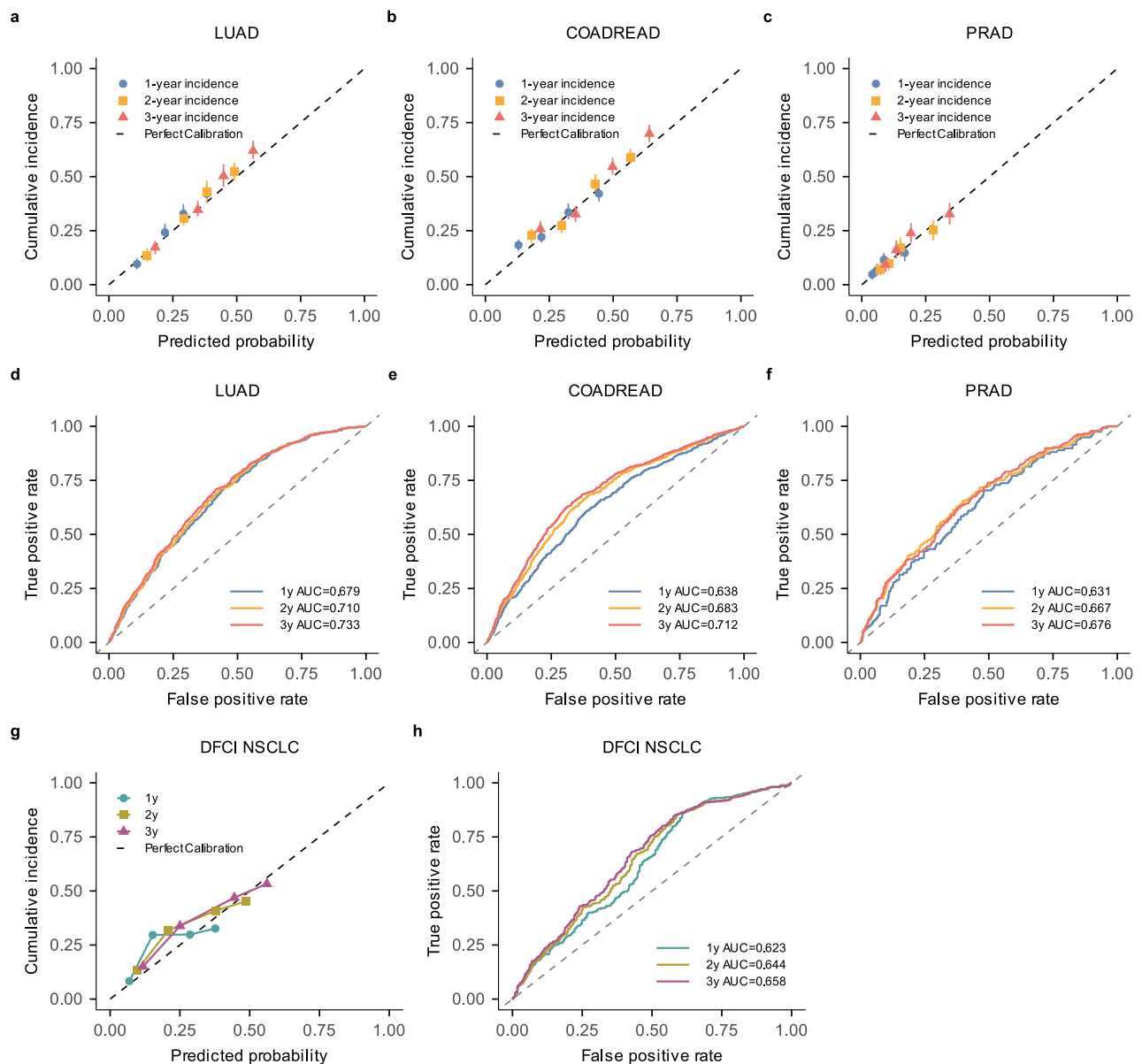
Extended Data Fig. 5 | Prevalence of abnormal serologic values during cachexia episodes and robustness of the serologic signature across episode-definition thresholds. (a) Sensitivity analyses showing that the direction and relative magnitude of the serologic signature are preserved across routine blood labs, derived composite indices, and additional serology markers under more stringent episode definitions ($\geq 10\%$ and $\geq 15\%$ weight loss) and after stratification by stage. Each point is the $\log_2(\text{odds ratio})$ of an abnormal value during versus outside episodes from a univariate mixed-effects logistic regression fit separately per cancer type ($n = 15\text{--}18$ cancer types per lab and threshold, restricted to cancer types with ≥ 500 patients each; see Methods); diamonds show the mean $\log_2(\text{OR})$ across cancer types. A small number of

extreme outlier points beyond the 2nd/98th percentile per lab and threshold are omitted from the plotted distributions. (b) Pan-cancer proportion of ALK measurements above the clinical reference threshold (>147 U/L), outside episodes ($n = 856,450$ measurements) versus during episodes ($n = 408,002$ measurements). (c) Pan-cancer proportion of NLR measurements outside the non-episode 95% reference interval, outside episodes ($n = 1,038,990$ measurements) versus during episodes ($n = 554,730$ measurements). (d) Pan-cancer proportion of CRP measurements above the clinical reference threshold (>10 mg/L), outside episodes ($n = 22,207$ measurements) versus during episodes ($n = 15,257$ measurements).



Extended Data Fig. 6 | Robustness of genotype-episode-risk associations to weight-loss threshold and cross-cohort replication. (a) Univariate competing-risk regression (death as a competing event) re-evaluating the 34 cancer-gene pairs significant at the primary discovery threshold ($\geq 5\%$ weight loss, FDR < 0.1), with episodes redefined at a stricter $\geq 10\%$ weight-loss threshold. Red points indicate hazard ratio (HR) > 1 and blue points indicate HR < 1 at $p < 0.05$; gray points were not significant. 25 of 34 associations remained significant. (b) Univariate competing-risk regression re-evaluating the same

34 cancer-gene pairs with episodes redefined at a stricter $\geq 15\%$ weight-loss threshold. 13 of 34 associations remained significant ($p < 0.05$). (c) Cross-cohort concordance of genotype-episode-risk effect sizes for matched gene-cancer-type tests in the MSK discovery cohort (x-axis) and the independent DFCI validation cohort (y-axis), $n = 73$ matched cancer-gene pairs, Pearson $r = 0.43$. Teal points were significant (FDR < 0.1) in both cohorts ($n = 9$), blue points were significant in MSK only, orange points were significant in DFCI only, and gray points were not significant in either cohort.



Extended Data Fig. 7 | Performance of cachexia risk-prediction models in the discovery cohort and external validation. (a–c) Calibration of predicted versus observed 1-, 2-, and 3-year cumulative incidence of weight-loss episodes for the multivariable Cox models in lung adenocarcinoma (**a**; $n = 4,176, 1,844$ events), colorectal adenocarcinoma (**b**; $n = 4,760, 2,317$ events), and prostate adenocarcinoma (**c**; $n = 2,508, 699$ events), assessed on a 50% held-out test set. Points show observed incidence within predicted-risk quartiles; error bars show 95% bootstrap confidence intervals (200 resamples). **(d–f)** Time-dependent receiver operating characteristic (ROC) curves for the same models and

test set, with area under the curve (AUC) at 1, 2, and 3 years shown for lung adenocarcinoma (**d**), colorectal adenocarcinoma (**e**), and prostate adenocarcinoma (**f**). **(g–h)** External validation of the lung adenocarcinoma model, restricted to covariates available in both cohorts (stage, baseline BMI, *TP53* and *STK11* status) and trained on the full MSK lung adenocarcinoma cohort ($n = 4,813, 2,056$ events) without refitting, then applied to an independent Dana-Farber Cancer Institute (DFCI) non-small cell lung cancer cohort ($n = 1,159, 516$ events). Calibration (**g**) and time-dependent ROC curves (**h**) in the external cohort.

Extended Data Table 1 | Association between weight-loss episode onset and overall survival across 18 cancer types

Cancer Code	N patients	N deaths	Hazard ratio (95% CI)	P value	FDR
BLCA	1625	534	5.88 (4.86-7.10)	4.22e-75	1.52e-74
IDC	2818	901	7.32 (6.30-8.49)	1.60e-150	7.19e-150
CLLSSL	946	61	6.82 (3.87-12.04)	3.29e-11	3.94e-11
COADREAD	5456	2067	5.12 (4.63-5.67)	1.99e-215	1.19e-214
SKCM	840	284	5.22 (4.05-6.72)	1.77e-37	3.19e-37
DLBCLNOS	508	129	4.74 (3.16-7.09)	4.29e-14	5.94e-14
FL	525	40	6.10 (3.09-12.01)	1.75e-07	1.85e-07
GBM	542	454	1.38 (1.13-1.68)	1.32e-03	1.32e-03
HGSOC	1635	767	3.51 (2.92-4.21)	3.30e-41	6.60e-41
BRCA	791	316	6.85 (5.37-8.75)	6.06e-54	1.82e-53
LUAD	5367	2479	4.97 (4.56-5.42)	1.24e-290	2.23e-289
LUSC	643	348	3.96 (3.13-5.01)	2.88e-30	4.32e-30
PAAD	2608	1794	2.22 (1.98-2.48)	8.62e-43	2.22e-42
PCM	727	129	3.33 (2.24-4.96)	2.74e-09	3.08e-09
PRAD	3251	969	11.10 (9.64-12.79)	6.68e-245	6.01e-244
CCRCC	609	211	9.19 (6.40-13.18)	2.14e-33	3.51e-33
STAD	593	319	2.81 (2.10-3.76)	4.19e-12	5.39e-12
UEC	1272	203	9.27 (6.71-12.83)	2.48e-41	5.58e-41

Time-dependent, univariate Cox proportional hazards models (cachexia episode onset as a time-varying covariate) for overall survival, restricted to cancer types with at least 500 patients. P values were adjusted for multiple testing using the Benjamini-Hochberg procedure (FDR).

Extended Data Table 2 | Enrichment of weight-loss episodes near disease progression, permutation test

Cancer code	N (Patients with progression event)	Observed overlap proportion	Permutation null mean	P value
BLCA	956	0.346	0.258	<0.001
IDC	1501	0.273	0.174	<0.001
CLLSLL	484	0.122	0.07	<0.001
COADREAD	3832	0.318	0.233	<0.001
SKCM	652	0.267	0.163	<0.001
DLBCLNOS	357	0.295	0.193	<0.001
FL	388	0.096	0.065	<0.001
GBM	385	0.193	0.183	0.417
HGSOC	1377	0.269	0.217	<0.001
BRCA	586	0.255	0.164	<0.001
LUAD	4465	0.267	0.204	<0.001
LUSC	521	0.338	0.252	<0.001
PAAD	2266	0.446	0.382	<0.001
PCM	352	0.32	0.215	<0.001
PRAD	2077	0.236	0.14	<0.001
CCRCC	497	0.254	0.189	<0.001
STAD	438	0.513	0.381	<0.001
UEC	545	0.295	0.191	<0.001

For each cancer type, the observed proportion of radiographically confirmed progression events falling within a weight-loss episode window ($\geq 5\%$ weight loss) was compared to a null distribution generated by permuting episode timing within each patient (1,000 permutations). P values are two-sided empirical permutation p-values; <0.001 indicates no permuted statistic was as extreme as the observed one across all 1,000 permutations. N reflects patients with a documented radiographic disease-progression event.

Extended Data Table 3 | Univariate associations between somatic driver mutations and weight-loss episode risk

Cancer code	Gene	N patients	N mutant	Mutant %	HR (95% CI)	P	FDR
BLCA	<i>FGFR3</i>	1578	320	20.3	0.61 (0.49-0.75)	3.81e-06	1.63e-04
BLCA	<i>RB1</i>	1578	267	16.9	1.30 (1.07-1.58)	9.20e-03	9.46e-02
BLCA	<i>TP53</i>	1578	765	48.5	1.31 (1.12-1.53)	5.79e-04	1.04e-02
IDC	<i>TP53</i>	2689	1234	45.9	1.48 (1.31-1.68)	3.87e-10	2.20e-08
ILC	<i>TP53</i>	438	57	13	2.27 (1.55-3.33)	2.93e-05	8.36e-04
COADREAD	<i>AMER1</i>	5380	310	5.8	0.77 (0.65-0.93)	6.04e-03	6.77e-02
COADREAD	<i>ARID1A</i>	5380	530	9.9	0.60 (0.51-0.70)	1.93e-10	1.54e-08
COADREAD	<i>FBXW7</i>	5380	708	13.2	0.78 (0.69-0.88)	1.07e-04	2.61e-03
COADREAD	<i>KMT2B</i>	5380	275	5.1	0.34 (0.26-0.45)	1.26e-14	1.44e-12
COADREAD	<i>KRAS</i>	5380	2300	42.8	1.17 (1.08-1.26)	8.42e-05	2.21e-03
COADREAD	<i>PIK3CA</i>	5380	1004	18.7	0.86 (0.77-0.95)	4.29e-03	5.44e-02
COADREAD	<i>PTEN</i>	5380	288	5.4	0.61 (0.50-0.75)	2.63e-06	1.29e-04
COADREAD	<i>SMAD4</i>	5380	633	11.8	1.30 (1.16-1.45)	7.98e-06	3.03e-04
COADREAD	<i>SOX9</i>	5380	553	10.3	0.82 (0.72-0.94)	4.92e-03	6.01e-02
COADREAD	<i>TCF7L2</i>	5380	546	10.1	0.62 (0.53-0.72)	2.26e-10	1.54e-08
COADREAD	<i>TP53</i>	5380	3978	73.9	1.16 (1.06-1.27)	1.28e-03	1.90e-02
SKCM	<i>BRAF</i>	805	317	39.4	1.40 (1.10-1.77)	5.66e-03	6.68e-02
SKCM	<i>TP53</i>	805	184	22.9	0.58 (0.42-0.81)	1.20e-03	1.89e-02
UCEC	<i>PPP2R1A</i>	239	38	15.9	2.07 (1.29-3.31)	2.46e-03	3.51e-02
UCEC	<i>TP53</i>	239	129	54	1.78 (1.17-2.70)	6.87e-03	7.34e-02
BRCA	<i>TP53</i>	725	307	42.3	1.48 (1.20-1.83)	3.29e-04	6.62e-03
LUAD	<i>RBM10</i>	4978	466	9.4	0.73 (0.62-0.86)	1.43e-04	3.06e-03
LUAD	<i>STK11</i>	4978	543	10.9	1.24 (1.09-1.41)	1.22e-03	1.89e-02
LUAD	<i>TP53</i>	4978	2312	46.4	1.42 (1.31-1.55)	6.35e-16	1.09e-13
PAAD	<i>KRAS</i>	2446	2170	88.7	1.32 (1.13-1.55)	4.83e-04	9.17e-03
THPA	<i>TERT</i>	282	163	57.8	1.81 (1.16-2.82)	9.41e-03	9.46e-02
PRAD	<i>APC</i>	2946	155	5.3	1.50 (1.14-1.97)	3.72e-03	4.89e-02
PRAD	<i>SPOP</i>	2946	382	13	0.57 (0.45-0.73)	9.74e-06	3.33e-04
PRAD	<i>TP53</i>	2946	774	26.3	2.01 (1.74-2.32)	2.58e-21	8.82e-19
CCRCC	<i>MTOR</i>	577	40	6.9	1.73 (1.17-2.55)	6.14e-03	6.77e-02
STAD	<i>KMT2B</i>	578	42	7.3	0.37 (0.22-0.61)	1.41e-04	3.06e-03
UEC	<i>FGFR2</i>	1247	146	11.7	1.83 (1.40-2.41)	1.34e-05	4.16e-04
UEC	<i>POLE</i>	1247	87	7	0.34 (0.18-0.64)	7.86e-04	1.34e-02
UEC	<i>TP53</i>	1247	209	16.8	1.46 (1.14-1.89)	3.16e-03	4.32e-02

Competing-risk regression (death as a competing event) testing cancer-type-gene combinations, restricted to cancer types with at least 200 patients and genes with at least 5% mutant carriers in that cancer type; 34 associations were significant at FDR < 0.1. Mutant % is the proportion of patients in that cancer type carrying the listed mutation.

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☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
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Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	Clinical, molecular and laboratory data were extracted from institutional databases using standard query pipelines; no custom software was developed specifically for data collection for this study.
Data analysis	All analyses were performed in R (v4.1.1) and Python(v3.13.12), using publicly available packages (Methods). Code is available at https://github.com/reznik-lab/cachexia . Requirements.txt for both R and Python were added on the github page.

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Clinical and genomic sequencing data analyzed in this study have been deposited in the cBioPortal for Cancer Genomics and are available for online browsing and download. Additional study data is also available at <https://zenodo.org/records/22045313?preview=1> (2026). Raw sequencing data are restricted to protect patient

privacy in accordance with applicable federal and state laws and institutional policies. Additional de-identified individual-level clinical data may be made available from the corresponding authors upon reasonable request and subject to institutional review and execution of an appropriate data use agreement. Code used for analysis is available at <https://github.com/reznik-lab/cachexia>

Research involving human participants, their data, or biological material

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Reporting on sex and gender	Sex was recorded in the electronic health record as assigned at birth and extracted from institutional clinical databases; it was not self-reported for the purposes of this study. Sex was included as a covariate in all multivariate analyses, including logistic regression models, mixed-effects models, time-dependent and fixed Cox proportional hazards models, and the time-to-cachexia predictive model. In pan-cancer demographic analyses, male sex was associated with lower odds of meeting the weight-loss episode criterion ($\log_2\text{OR} = -0.23$; Supplementary Table 2). Serologic measurements with established sex-specific reference ranges were adjusted using sex-specific thresholds accordingly (Methods). In our cohort, 27,720 patients (53.1%) were female and 24,516 (46.9%) were male; this breakdown is provided in Supplementary Table 18. Gender identity was not separately assessed, as it was not available in the source clinical data.
Reporting on race, ethnicity, or other socially relevant groupings	NA. Race and ethnicity (including ancestry) were not analyzed in this study and were not included as covariates.
Population characteristics	The study cohort comprised 52,236 adult cancer patients. Median age at diagnosis was 60.6 years (IQR 52.3–70.4). Sex distribution was 27,720 female (53.1%) and 24,516 male (46.9%). Clinical stage was I–III in 27,885 (53.4%), stage IV in 22,021 (42.2%), and missing in 2,330 (4.5%). Baseline BMI categories were underweight (<18.5) 978 (1.9%), normal (18.5–24.9) 17,132 (32.8%), overweight (25–29.9) 18,636 (35.7%), and obese (≥ 30) 15,490 (29.7%). At last follow-up, 31,348 (60.0%) were alive and 20,888 (40.0%) were deceased.
Recruitment	NA
Ethics oversight	The study is independently approved by the IRB of MSK under 12-245 Appendix C.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

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Sample size	Sample size was determined by the availability of eligible patients in the institutional dataset meeting prespecified inclusion criteria. After applying exclusions, the final cohort comprised 52,236 adult patients (age ≥ 18 years) with a single primary cancer type classification and sufficient longitudinal BMI follow-up to enable episode detection. No a priori power calculation was performed for this retrospective observational study.
Data exclusions	For stratified and within cancer analyses, we restricted to cancer types with >500 patients. For gene-level analyses, within each cancer type, we tested genes observed in $>5\%$ of sequenced tumors.
Replication	Genomic findings were corroborated in an external cohort of 5785 patients at Dana Farber Cancer Institute.
Randomization	There was no experimental allocation. Patient groups came from existing clinical and genomic records, not from investigator assignment. Covariates such as age, sex, and cancer stage were adjusted for using multivariable regression.
Blinding	Investigators were not blinded during data collection and analysis. Blinding does not apply here because group membership (for example, meeting the weight-loss criterion or tumor genotype status) comes directly from each patient's existing clinical and genomic records. Investigators did not assign patients to groups

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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

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Clinical trial registration	NCT01775072
Study protocol	https://clinicaltrials.gov/study/NCT01775072
Data collection	Tumors were sequenced using the MSK-IMPACT assay through 9/19/2024, at study locations listed in the clinical trial protocol. This is a retrospective study using data from patients enrolled in the MSK-IMPACT prospective clinical sequencing protocol at Memorial Sloan Kettering Cancer Center, a single tertiary cancer center, between 2010 and 2024. An independent external validation cohort of 5,785 patients was obtained from Dana-Farber Cancer Institute.
Outcomes	The primary outcome was occurrence of a consensus-defined cachectic weight-loss episode. Episodes were detected from longitudinal BMI measurements using a 5% weight loss threshold over a 6-month window, or 2% for patients with baseline BMI under 20. Secondary outcomes included overall survival, changes in serologic markers during episodes, and associations between tumor genotype and episode risk. These were assessed using Cox models, mixed-effects models, and competing risk regression, as described in the Methods.

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA