BMJ Best Practice

Assessment of unintentional weight loss

The right clinical information, right where it's needed

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Summary

- Unintentional weight loss is often defined as weight loss of at least 5% of the patient's usual body weight that occurs within the preceding 6 to 12 months, and that is not the expected consequence of treatment of a known illness.[1] It is a diagnostic challenge because, while an underlying illness may be found after a thorough history and physical exam, the aetiology may also remain elusive and only be discovered through additional testing, the passage of time, or not at all. The most pressing concern is the assessment for the presence of cancer or other conditions for which early diagnosis may lead to better outcomes. There is a broad range of causes of unintentional weight loss including medical diseases, psychiatric illnesses, and social factors. These conditions may occur in isolation or in combination.

- **Classification :**
  There is no formal consensus definition of unintentional weight loss; however, the weight loss must be considered unintentional by the patient and treating practitioner. The degree of weight loss has been defined in case series as being between 5% and 10% weight loss compared with usual body weight.[2] [3] [4] [5] [6] [7] [8] [9] Similarly, there is no strict definition of the time period in which the unintentional weight loss should occur; however, most case series used the criteria of weight loss developing within the preceding 3 to 12 months.
  Related syndromes include cachexia and sarcopenia. Cachexia is a syndrome of weight loss characterised by decreased muscle mass in the presence of the metabolic effects of an underlying illness such as some types of cancer or advanced heart failure.[10] While all patients with cachexia have unintentional weight loss, not all patients with unintentional weight loss have cachexia. Sarcopenia is a geriatric syndrome of diminished muscle mass and function, which may or may not be accompanied by unintentional weight loss.
  A consensus definition of malnutrition includes unintentional weight loss (>5% in 3 months, or >10% of indefinite time) as a component of one set of diagnostic criteria.[11]

- **Epidemiology :**
  In population-based cohort studies, the prevalence of unintentional weight loss varies between 7% and 13%, with differences attributable to both demographics and duration of follow-up.[12] [13] [14] For patients with the most clinically applicable presentation (i.e., weight loss occurring within the preceding 6 months), the prevalence is approximately 7%.[14] An association with mortality and unintentional weight loss has been demonstrated in epidemiological studies of overweight and obese subjects,[12] and in older patients with unintentional (but not intentional) weight loss.[15] In patients with recent (i.e., within 6 months) unintentional weight loss, weight loss of 5% or greater was associated with an increase in subsequent mortality.[14] Unintentional weight loss has been associated with increased perioperative complications in patients undergoing colorectal surgery and surgery for disseminated cancer.[16] [17]
  Unintentional weight loss mounts a striking contrast to the epidemics of obesity in many countries and the commonplace experience of unsuccessful attempts at intentional weight reduction. Furthermore, unintentional weight loss may be under recognised in the primary care setting.[18]

- **Pathophysiology :**

The pathophysiology varies depending on the aetiology. Weight homeostasis is a complex process that includes the availability of food, physical activity, possible environmental exposures, and hormonal control with peptides such as leptin, cholecystokinin, and ghrelin.[19] Unintentional weight loss owing to cachexia is associated with cytokines (e.g., tumour necrosis factor-alpha) that suppress appetite, promote muscle and fat breakdown, and increase energy expenditure.[20] [21] Normal homeostasis signaling is disrupted in cachexia syndromes, while these mechanisms are preserved in the setting of weight loss due purely to inadequate caloric intake.

◊ **Differential diagnosis :**

The differential diagnosis is extremely broad. In case series, the most common aetiologies are:

- Malignancy
- Gastrointestinal conditions
- Psychiatric causes.

Other aetiologies that should be considered include:

- Cachexia syndromes associated with organ failure (e.g., heart failure, chronic obstructive pulmonary disease, renal failure)
- Endocrinopathies (e.g., hyperthyroidism, diabetes mellitus, adrenal insufficiency)
- Serious infections (e.g., tuberculosis and HIV)
- Medication side effects
- Substance abuse
- Social factors that prevent adequate access to food.

Aetiology

The aetiology of unintentional weight loss comprises a broad range of clinical conditions. Nearly every organ system or disease classification has a syndrome that may result in unintentional weight loss. As a diagnostic challenge, it resembles fever of unknown origin in its breadth. The most important considerations for initial work-up are to detect an underlying malignancy that could have improved outcomes if identified early, and other conditions of high morbidity and mortality. In most case series, the aetiology remains unidentified in a small percentage of cases despite exhaustive work-up. For these patients, ongoing follow-up is required.

Malignant

Cancer is a common cause of unintentional weight loss in published case series (i.e., 6% to 36% of patients).[1] [9] While many cancers can cause unintentional weight loss, solid tumours are more likely to present with weight loss. In particular, gastrointestinal cancers and lung cancers are associated with significant weight loss.[22]

Weight loss can also occur in haematological malignancies (e.g., leukaemia, lymphoma, multiple myeloma). Chronic leukaemia is more likely to present with weight loss compared with acute leukaemia, and chronic lymphocytic leukaemia and lymphoma more commonly present with weight loss compared with chronic myelogenous leukaemia. In acute leukaemia, the weight loss may occur over a shorter time period. Multiple myeloma is more common in older patients.

Certain cancers do not typically present with weight loss unless they are either metastatic or at an advanced stage. These cancers include breast, ovarian, cervical, endometrial, and prostate cancer. Endometrial and cervical cancer more commonly present with local symptoms.

Other cancers that are associated with unintentional weight loss include head and neck cancers (e.g., laryngeal, oropharyngeal), bladder cancer, and brain tumours. Weight loss at presentation is not common with primary brain tumours such as glioblastoma.

Neuroendocrine tumours (e.g., carcinoid tumours, gastrinoma from Zollinger-Ellison syndrome, VIPoma) are rare entities and may cause weight loss due to their hormonal effects (or the presence of diarrhoea). However, only 3% of neuroendocrine tumours present with weight loss.[23] [24] Zollinger-Ellison syndrome arises from a gastrinoma and over-secretion of gastrin, and is associated with multiple endocrine neoplasia type 1. In one case series, 17% of patients with Zollinger-Ellison syndrome presented with unintentional weight loss.[25]

Risk factors for malignancy include age, exposure to radiation, previous chemotherapy, immunosuppression, smoking, and organ-specific risk factors such as a history of colon polyps or hepatitis B infection. In the most difficult cases there may be no risk factors or examination findings other than unintentional weight loss.

Gastrointestinal (non-malignant)

Non-malignant gastrointestinal conditions are a common cause of unintentional weight loss in published case series (i.e., 6% to 22% of patients).[1] [9] A variety of conditions can lead to chronic diarrhoea and weight loss, including:

- Coeliac disease: a common cause; however, it is important to establish the diagnosis and rule out other causes of weight loss

- Exocrine pancreatic insufficiency: may be due to prior episodes of pancreatitis or cystic fibrosis. Extensive disease may result in endocrine pancreatic insufficiency and type 1 diabetes. Unintentional weight loss usually only occurs in severe cases
- Inflammatory bowel disease: typically presents in younger patients, but there is a second peak in the sixth decade. Crohn's disease may present in a myriad of ways and does not always have all of the typical findings
- Ischaemic bowel disease: cardiovascular disease may present as mesenteric ischaemia, typically in older patients. Weight loss may be severe.[26] Superior mesenteric artery and coeliac artery stenoses may be more likely to develop weight loss[27]
- Peptic ulcer disease: may cause weight loss due to pain and nausea which can result in decreased oral intake. Must also consider inflammatory bowel disease and gastric cancer if patient has symptoms of peptic ulcer disease and severe weight loss.

Other gastrointestinal conditions that can cause unintentional weight loss, albeit it more rarely, include oesophageal webs/rings/diverticula, chronic hepatitis, gastroparesis, small intestinal bacterial overgrowth, and post-surgical complications.

Other diarrhoeal syndromes do not typically cause unintentional weight loss. For example, irritable bowel syndrome (IBS) is common but does not usually cause significant weight loss. Patients with coeliac disease or inflammatory bowel disease may have comorbid IBS, and a diagnosis of IBS should not preclude suspicion for these conditions should weight loss be present. Microscopic colitis does not typically result in severe weight loss.

Severe oropharyngeal disorders such as stomatitis, and dental problems (particularly in older people),[9] can also result in decreased oral intake and subsequent weight loss.

Psychiatric

Psychiatric illnesses commonly present with weight change. Weight changes can be variable, and significant unintentional weight loss can occur. In published series of patients presenting with unintentional weight loss, psychiatric or psychosocial causes (variously defined) were found in 9% to 33% of cases.[1] [9]

Major depressive disorder can be associated with unintentional weight loss or gain. Bipolar disorder, in either the manic or depressive phase, may also result in significant weight loss. Weight change is considered common in anxiety disorders, although its prevalence is not well studied, and it is not currently part of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria for generalised anxiety disorder.

In patients with medical comorbidities, some of the somatic symptoms of depression (e.g., fatigue, psychomotor slowing, weight loss) may overlap with medical illnesses. Further complicating this symptom overlap is the comorbid pathology of depression and serious medical conditions. Patients are at increased risk for depression following stroke and myocardial infarction,[28] [29] and both depression and anxiety disorders are prevalent in patients with cancer.[30]

Eating disorders such as anorexia nervosa and bulimia nervosa present with weight loss, and often the history is not forthcoming as to the patient's distorted body perception and fear of weight gain. Depression, anxiety, and obsessive compulsive disorder are common comorbidities.

Substance use disorders, when severe, may result in weight loss due to inadequate attention paid to nourishment in the setting of time and resources spent toward the addiction. Progressive loss of functioning

and societal networks may further lead to undernourishment. Comorbid depression and anxiety are common and may contribute to barriers to treatment.

Neurological

Neurological conditions frequently present with unintentional weight loss.

Advanced dementia may present with weight loss owing to decreased executive function, apathy, decreased taste, and decreased swallowing and chewing function.

Neuromuscular disorders may impair the patient's ability to eat. In multiple sclerosis (MS), weight loss may occur due to global weakness, diminished ability to self-feed, and decreased control of swallowing function with progressive disease. Fatigue and depression are common in MS and may also contribute to weight loss. In amyotrophic lateral sclerosis, weight loss may occur from muscle atrophy and an impaired ability to eat. In Parkinson's disease, weight loss may occur as a consequence of impaired oropharyngeal function, decreased ability to self-feed, or cognitive impairment. Prion disease should also be considered in the differential, although weight loss is not common.

Cardiovascular

Unintentional weight loss can occur in patients with cardiovascular disease. While patients with heart failure frequently present with weight gain due to volume overload, in cases of advanced heart failure a syndrome of cardiac cachexia may develop. In most cases, patients already have a preceding diagnosis of severe heart failure and cardiac cachexia is an advanced-stage manifestation. Both unintentional weight loss and cardiac cachexia are predictors of mortality.[31] [32] Pericardial disease may rarely lead to a cachexia syndrome.

Patients who have suffered a stroke may lose weight from the direct effects of the stroke on oropharyngeal muscles or from a diminished ability to self-feed due to arm or hand weakness. Additionally, post-stroke depression is common and associated with weight loss.[33]

Valvular heart disease may lead to weight loss through heart failure and cardiac cachexia.

Pulmonary (non-malignant)

End-stage chronic obstructive pulmonary disease (COPD) may result in cachexia due to increased work of breathing and neurohormonal changes, and is associated with increased mortality.[34] While COPD is the best-studied model of cachexia in pulmonary disease, other severe chronic lung disease (e.g., interstitial lung disease) may also result in weight loss due to increased work of breathing and a similar cachectic process. Patients with chronic respiratory disease who present with unintentional weight loss should not be assumed to have a pulmonary cachexia syndrome, as COPD and lung cancer have smoking as a common aetiological agent. Therefore, patients with COPD and unintentional weight loss should still be evaluated for lung cancer. Only 25% of patients with COPD will develop cachexia, and those with less severe COPD who present with unintentional weight loss should still be assessed for other potential aetiologies.[34]

Cystic fibrosis generally presents in childhood and a multitude of factors lead to unintentional weight loss, including gastrointestinal malabsorption, malnutrition, increased metabolic rate due to respiratory disease, and cystic fibrosis-related diabetes.[35] [36]

Renal

Although renal failure typically leads to weight gain due to diminished renal excretion and consequent volume retention, end-stage renal disease can result in a syndrome of renal cachexia.[37] Vasculitides may also

present with unintentional weight loss. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides such as microscopic polyangiitis frequently have renal involvement.

Patients with renal disease are often on loop diuretics to maintain volume status. Unintentional weight loss should be distinguished from this intended weight loss. If a patient has greater weight loss than expected, or suffers weight loss despite a stable dose of diuretic, then evaluation for unintentional weight loss should be performed.

Endocrinological

In patients with new-onset type 1 diabetes, weight loss is due to polyuria and insulin deficiency. Ketosis, if present, compounds the weight loss because of decreased appetite. Type 2 diabetes less frequently presents with weight loss due to polyuria.

Hyperthyroidism may present with a myriad of symptoms, including weight loss. However, older patients may not present with typical symptoms, and the presentation may be dominated by unintentional weight loss without other manifestations.[38]

Adrenal insufficiency presented with weight loss in 25% of patients in one case series.[39] Aetiologies of primary adrenal failure include metastatic tumours, tuberculosis, and autoimmune endocrinopathies. With the commonplace use of corticosteroids, tertiary adrenal insufficiency should be considered in patients with a history of glucocorticoid exposure, although it less commonly causes significant weight loss.

Hypopituitarism may manifest in multiple endocrine axes. However, hypothyroidism, hypogonadism, and growth hormone deficiency, while they may cause transformation of body mass with reduction in muscle, do not typically cause severe weight loss. Secondary adrenal insufficiency may cause weight loss but usually not as severe as in primary adrenal insufficiency.

Phaeochromocytoma is a rare entity that may cause weight loss due to hormonal effects. It may be part of multiple endocrine neoplasia type 2.

Rheumatological/inflammatory

Rheumatological conditions frequently present with unintentional weight loss as a component of systemic inflammation. Rheumatoid arthritis, systemic lupus erythematosus, and mixed connected tissue disorders can all cause unintentional weight loss. Sarcoidosis is an inflammatory disorder characterised by non-caseating granulomas. While it frequently involves the lungs, eyes, and skin, nearly any organ system can be involved and systemic symptoms include weight loss.[40]

Vasculitides may also present with unintentional weight loss. Polyarteritis nodosa is a small-to-medium vessel vasculitis that frequently has renal involvement. It can also cause vasculitis of the mesenteric arteries, and is often associated with hepatitis B and C. Autoimmune conditions that involve the respiratory tract, such as granulomatosis with polyangiitis (Wegener's granulomatosis), often present with anorexia and weight loss.[41]

While many rheumatological disorders can have systemic features, including weight loss, several can cause weight loss as a consequence of direct gastrointestinal tract involvement (e.g., systemic sclerosis/scleroderma).

Infectious diseases

Any severe infection can result in temporary weight loss. This topic considers only infections that may result in a more chronic or subacute weight loss where the weight loss itself may be a prominent feature of the presentation.

HIV infection may cause severe cachexia as one of its manifestations due to either the virus itself or the presence of opportunistic infections. Patients with low CD4+ cell counts are at particular risk for disseminated mycobacterium avium-intracellulare which can result in profound weight loss.[42] [43] Tuberculosis in HIV-positive patients may also present with particularly severe weight loss.[44]

Tuberculosis frequently presents with weight loss.[45] [46] Weight loss prior to treatment and a <5% weight gain during treatment are associated with a risk of relapse.[47] In contrast, non-tuberculous mycobacterial infections such as Mycobacterium avium-intracellulare less frequently present with weight loss compared with tuberculosis.[48]

Many infectious conditions can cause a chronic or subacute diarrhoea and weight loss, including parasitic infections (e.g., amoebiasis, giardiasis, cryptosporidiosis, cystoisosporiasis, cyclosporiasis, strongyloidiasis). In immunosuppressed patients, including those with HIV and solid organ transplant recipients, opportunistic infections (e.g., amoebiasis, cytomegalovirus, cryptosporidiosis) can cause profound weight loss.[49]

Disseminated histoplasmosis presents with constitutional symptoms, including weight loss, in more than 85% of cases in both HIV-positive and HIV-negative patients.[50] Dissemination is more common in the immunosuppressed patient.

Infective endocarditis has a variable presentation depending on the infecting organism, host factors, and the presence of prosthetic cardiac valves and implanted cardiac devices. While it can present suddenly with acute heart failure, it may also present subacutely with weight loss. While many patients have risk factors such as prosthetic valves and devices or injection drug use, some have no obvious risk factors at all, highlighting the need to consider this condition. Other valvular heart disease may lead to weight loss through heart failure and cardiac cachexia.

Infections that rarely cause unintentional weight loss include Whipple's disease and cat-scratch disease (*Bartonella henselae* infection).

Medication-related

Multiple classes of medications have been implicated in causing weight loss as an adverse effect. Any new medication associated temporally with the occurrence of unintentional weight loss should be scrutinised carefully. Medications include:

- Anticonvulsants (e.g., topiramate, zonisamide)[51] [52]
- Antidepressants (e.g., selective serotonin-reuptake inhibitors, bupropion)
- Stimulants (e.g., dexamfetamine)
- Diabetes medications (e.g., metformin; exenatide, liraglutide, and other glucagon-like peptide-1 receptor agonists), although sometimes the weight loss with these drugs is considered a benefit[53]
- Antibiotics and other medications that cause diarrhoea
- Cholinesterase inhibitors (e.g., donepezil).[54]

Some medications may be misused to cause weight loss, including laxatives, diuretics, and thyroid hormone. In these cases, the patient's weight loss may be noticed by the clinician or the patient's close contacts, and the history may not be forthcoming.

Withdrawal of medications that may have been supporting or maintaining weight may produce weight loss, for example discontinuation of pancreatic enzymes or mirtazapine.

Social factors

Inadequate food and caloric intake is an important consideration. This can be due to poverty or inadequate resources. In older people, fewer social interactions during meals can all contribute to decreased oral intake. Patients may not readily report inadequate access to food to their physician, and access to food and types of food should be investigated as part of the history. Unintentional weight loss from inadequate access is readily reversed with restoring appropriate caloric intake and does not have the neurohormonal changes associated with cachexia syndromes.

Exposure to violence, traumatic stress, and other forms of abuse has been associated with both weight gain and weight loss and may not be initially disclosed to the treating physician.[55]

Urgent considerations

(See **Differential diagnosis** for more details)
In most cases, unintentional weight loss is a subacute clinical problem. Patients who lose around 5% of their usual body weight over several months can usually receive an expeditious outpatient work-up. However, several conditions are potentially life-threatening and may present with unintentional weight loss as a significant part of the clinical syndrome. Many of these conditions typically present with other characteristic signs and symptoms when fulminant; however, unintentional weight loss may be a prominent feature at an earlier stage in time.

Adrenal crisis

While adrenal insufficiency presents subacutely with fatigue, anorexia, weakness, orthostasis, and weight loss, adrenal crisis presents suddenly with hypotension and reduced organ perfusion and can be precipitated by a stress such as an infection. Acute abdominal pain has been reported. Primary adrenal insufficiency is more likely than secondary or tertiary adrenal insufficiency to present with adrenal crisis due to mineralocorticoid deficiency. Treatment requires immediate volume resuscitation and intravenous administration of either hydrocortisone or dexamethasone. Ideally, laboratory studies should be drawn prior to glucocorticoid administration.

Thyroid storm

While hyperthyroidism is common and may present with unintentional weight loss, thyroid storm, the life-threatening manifestation of thyrotoxicosis, is rare. Patients may present with fever, altered mental status, tachyarrhythmia, and/or cardiac dysfunction causing hypotension and shock. It may also cause gastrointestinal symptoms. Resuscitation is targeted toward the presenting symptoms and includes management of the arrhythmia and any concomitant cardiac dysfunction, intravenous fluids and beta-blockers if not in decompensated heart failure, glucocorticoids, and treatments to block synthesis of the thyroid hormone.

Diabetic ketoacidosis/hyperosmolar hyperglycaemic state

New-onset type 1 diabetes presents with subacute weight loss, polyuria, polydipsia, and malaise, but may also present emergently with diabetic ketoacidosis. Volume repletion and correction of electrolyte and acid-base abnormalities requires hospital care.

While type 1 diabetes more commonly presents with weight loss compared with type 2 diabetes, patients with type 2 diabetes may develop a subacute syndrome of severe hyperglycaemia (i.e., hyperosmolar hyperglycaemic state). Severe hyperglycaemia leads to glycosuria, caloric wasting, polyuria, polydipsia, and weight loss, and, in its most severe form, causes altered mental status and may progress to obtundation and coma.

Eating disorders

Extreme starvation presents with a severely low BMI and can have life-threatening bradycardia, hypothermia, hypotension, cardiomyopathy, and arrhythmia. Treatment is supportive and includes correcting electrolyte imbalances and careful restoration of body weight. Nutritional support must be performed carefully to prevent re-feeding syndrome (i.e., hypokalaemia, hypophosphataemia, thiamine deficiency, and heart failure associated with nutritional replacement). If the diagnosis is suspected but not known, other causes should be ruled out while psychiatric assessment is performed. Patients must be assessed for the risk of suicide.

Suicidal ideation

Psychiatric conditions associated with unintentional weight loss may also be associated with risk of suicide, including depression, bipolar disorder, and anorexia nervosa.

Life-threatening infections

Certain infections that are associated with subacute weight loss may require urgent evaluation, including infective endocarditis, pulmonary tuberculosis, and advanced HIV infection with opportunistic infection, as a delay in treatment would cause substantial morbidity.

Severe weight loss (any aetiology)

Severe diarrhoeal syndromes and malignancy may result in significant weight loss. Any patient with profound weakness or signs of organ failure may require hospitalisation to halt the loss of weight and restore organ function. Re-feeding syndrome should be monitored for carefully in these settings and a prompt work-up for underlying aetiology should be conducted.

Red flags

- Stomach cancer
- Colorectal cancer
- Oesophageal cancer
- Pancreatic cancer
- Hepatoma
- Cholangiocarcinoma
- Small cell lung cancer
- Non-small cell lung cancer
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Acute leukaemia
- Chronic leukaemia
- Oropharyngeal cancer
- Laryngeal cancer
- Ovarian cancer
- Prostate cancer

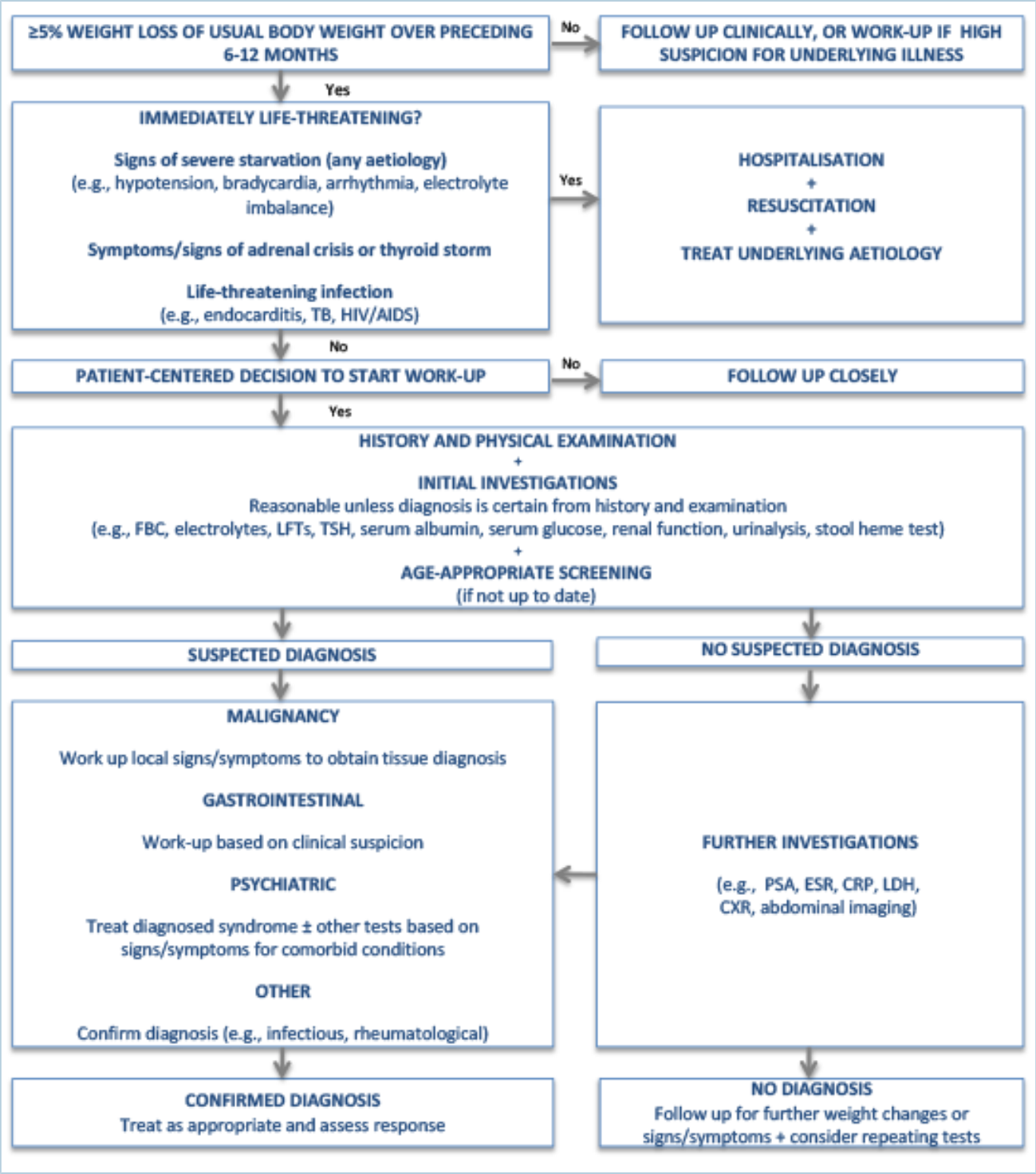
- Breast cancer
- Zollinger-Ellison syndrome
- Crohn's disease
- Ulcerative colitis
- Mesenteric ischaemia
- Depression
- Bipolar disorder
- Anorexia nervosa
- Bulimia nervosa
- Cardiac cachexia syndrome
- Post-stroke complications
- Pulmonary cachexia syndrome
- Cystic fibrosis
- Microscopic polyangiitis
- Diabetes mellitus
- Hyperthyroidism
- Adrenal insufficiency
- Hypopituitarism
- Pheaochromocytoma
- Granulomatosis with polyangiitis (Wegener's)
- Polyarteritis nodosa
- Adult-onset Still disease
- HIV infection
- Tuberculosis (pulmonary)
- Tuberculosis (extrapulmonary)
- Infective endocarditis

Step-by-step diagnostic approach

Due to the high percentage of underlying serious aetiologies, all patients who present with unintentional weight loss should receive a thorough history and physical exam. Particular attention should be paid to symptoms and signs of cancer, gastrointestinal conditions, and psychiatric conditions.

Not all patients present with unintentional weight loss as a chief complaint. Routine weight monitoring over time may detect weight loss. Physicians may not always document unintentional weight loss as a red flag symptom.[56] Epidemiological evidence has linked unintentional weight loss to increased mortality, but the overall benefit of detecting unreported weight loss is as yet unclear.

As a truly general syndrome, unintentional weight loss requires some detective work and a broad approach to the work-up.



Diagnostic algorithm for the work-up of unintentional weight loss

From Christopher J. Wong

When to initiate a work-up

A reasonable starting point to initiate a work-up is unintentional weight loss of 5% or more of the patient's usual body weight within the preceding 6 to 12 months.[1] If measured weights are not available, the physician may use indirect means of assessment (e.g., patient's self-reported estimate of weight loss, change in clothing size, a friend or relative corroborating the weight loss).[2] Clinical judgment must be

used as some patients may not have a witness to their weight loss, access to scales, or the numeracy skills required to estimate their weight loss. These patients still merit a work-up for unintentional weight loss.

The criteria above should only be considered a starting point. Patients with weight loss over a longer period of time, or those with just under a 5% loss of body weight, but in whom there is a concern for an underlying illness, should still be considered for evaluation. In addition, patients in whom intentional weight loss appears to occur too easily, especially if previous attempts at intentional weight loss were unsuccessful, should be evaluated for whether such weight loss was, in hindsight, unintentional, and therefore requires further evaluation.

In some cases, unintentional weight loss may present suddenly (e.g., onset of hypotension, rapidly progressive infection). In these cases, immediate hospital work-up may be required.

The decision to initiate a work-up should be made in concert with the patient's wishes. For example, in some cases, an older patient with other serious medical conditions may adopt a palliative approach or a limited work-up rather than be subjected to multiple diagnostic tests with consequent risks.

History

The initial history should be thorough as this step can often lead toward the correct diagnostic pathway.

Age:

- Younger age: consider psychiatric or gastrointestinal conditions, or cancers which have a younger age of onset (e.g., leukaemia, lymphoma). Other conditions that are more common in younger patients include multiple sclerosis, amyotrophic lateral sclerosis (ALS), and cystic fibrosis. Coeliac disease typically occurs in younger patients, although in mild cases the diagnosis may be delayed.
- Older age: consider cardiovascular conditions or cancer. These conditions increase in incidence with increasing age. Neurological conditions such as dementia and Parkinson's disease are also more common in older patients.

Social factors:

- The patient should be asked about abuse, neglect, and access to food. Inadequate food and caloric intake is an important consideration.

Pre-existing medical conditions:

- The physician should ascertain whether there are any pre-existing conditions that may have deteriorated, for example:
    - Advanced-stage heart failure, COPD, interstitial lung disease, or renal failure: patients may develop a cachexia syndrome with advanced disease[37]
    - Cystic fibrosis: patients may develop new-onset or worsening gastrointestinal malabsorption
    - Coeliac disease: non-adherence to a gluten-free diet can worsen symptoms
    - Bipolar disorder: episodes of mania may arise in previously well-controlled patients.
- Other conditions that can result in unintentional weight loss include:
    - Bariatric surgery: gastric bypass surgery may lead to small intestinal bacterial overgrowth
    - Pancreatitis: prior episodes of pancreatitis may lead to exocrine pancreatic insufficiency

- Hepatitis B or C infection: often associated with polyarteritis nodosa.

Cancer screening status:

- Status of age-appropriate cancer screening (e.g., cervical, breast, colorectal, lung) should be documented.

Medication history:

- Multiple classes of medications have been implicated in causing weight loss as an adverse effect and include:
  - Anticonvulsants (e.g., topiramate, zonisamide)[51] [52]
  - Antidepressants (e.g., selective serotonin-reuptake inhibitors, bupropion)
  - Stimulants (e.g., dexamfetamine)
  - Diabetes medications (e.g., metformin; exenatide, liraglutide, and other glucagon-like peptide-1 receptor agonists), although sometimes the weight loss with these drugs is considered a benefit[53]
  - Antibiotics and other medications that cause diarrhoea
  - Cholinesterase inhibitors (e.g., donepezil).[54]
- Medications that can be misused to cause weight loss include:
  - Laxatives
  - Diuretics
  - Thyroid hormone.
- Withdrawal of medications that may have been supporting or maintaining weight may produce weight loss.

  Examples include:
  - Pancreatic enzymes
  - Mirtazapine.
- Treatment of renal disease often includes loop diuretics to maintain volume status. Unintentional weight loss should be distinguished from this intended weight loss. If a patient has greater weight loss than expected, or suffers weight loss despite a stable dose of diuretic, evaluation for unintentional weight loss should be performed.

Psychiatric history and screening:

- The patient should be assessed for depression, anxiety, bipolar disorder, exposure to violence and trauma, and eating disorders. Depression and anxiety disorders are prevalent in patients with cancer.[30] Patients are also at increased risk for depression following stroke.[28] [29]
- Patients who have not been diagnosed with a psychiatric condition previously should be screened for depression and anxiety disorders.[57] [58] The Patient Health Questionnaire-9 (PHQ-9) and the Generalised Anxiety Disorder-7 (GAD-7) are useful initial screening tools which are freely available in multiple languages

- Screening for eating disorders should be performed and, if positive, the patient should be evaluated according to the current Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria
- Screening for substance use disorders, including alcohol, prescription opioids, and illicit drugs should also be performed.

Risk factors:

- Risk factors for malignancy:
    - Smoking/tobacco use: increases risk of lung, head and neck, and bladder cancers. Lung cancer classically occurs in older patients with an extensive smoking history. While cigarette cessation reduces the risk of subsequent lung cancer, the risk does not resolve completely and even past smokers should be assessed for lung cancer in the setting of unintentional weight loss.[59] Importantly, lung cancer may also occur in non-smokers (approximately 10% of cases in the US and up to 25% of cases worldwide).[60] [61]
    - Previous radiation exposure: patient may be at risk of thyroid cancer or leukaemia
    - Previous chemotherapy: patients may be at risk for secondary malignancies such as leukaemia
    - Immunosuppression (e.g., HIV infection, medications): increases the risk of squamous cell cancers and lymphoma
    - Environmental exposures: asbestos exposure increases the risk of lung cancer
    - Infections: human papilloma virus (HPV), hepatitis B (with or without cirrhosis), hepatitis C (with cirrhosis), or *Helicobacter pylori* (in stomach cancer) can increase the risk of malignancy
    - Alcohol use: a common risk factor for head and neck cancers.
- Risk factors for infections:
    - HIV: unprotected sex, injection drug use, or transfusions of blood or blood products before adequate testing was introduced or currently in areas without adequate testing
    - Opportunistic infections: often seen in HIV or with immunosuppressive medications
    - Parasitic: travel history including travel to regions with endemic gastrointestinal parasites
    - Tuberculosis: known contacts, homelessness, or incarceration.

Symptoms

Degree of weight loss:

- It is generally considered that cancers, gastrointestinal illnesses, and severe infections (e.g., HIV) can cause a higher degree of weight loss compared with other conditions. However, many conditions can cause severe weight loss when in the advanced stages. Cancer has been reported to cause particularly rapid weight loss in the elderly, but other studies have not been able to associate the degree or rapidity of weight loss with a particular aetiology.[3] [7]

Systemic:

- Weakness: a common symptom that accompanies weight loss
- Fever, chills, night sweats: may be associated with infection, haematological malignancies, vasculitides, or rheumatological conditions
- Patients with advanced cardiac, renal, or pulmonary disease can present with a cachexia syndrome (i.e., muscle wasting and weight loss).

Gastrointestinal:

- Dysphagia: should prompt evaluation for oesophageal, oropharyngeal, or laryngeal cancer, especially in older patients
- Abdominal pain: may suggest gastrointestinal cancer or peptic ulcer disease, especially if anaemia is also present. Right upper quadrant pain and jaundice may indicate hepatoma. In pancreatic cancer, abdominal pain may not occur until the cancer is at an advanced stage. May also suggest gastrointestinal conditions such as coeliac disease, inflammatory bowel disease, and exocrine pancreatic insufficiency
- Post-prandial pain: may be due to mesenteric ischaemia or peptic ulcer disease. Asymptomatic stenoses of mesenteric arteries have been found in case series.[62] For patients with unintentional weight loss, work-up for mesenteric ischaemia should be undertaken only with appropriate clinical suspicion
- Heartburn: patients with Zollinger-Ellison syndrome often present with symptoms of GERD/peptic ulcer disease and commonly have diarrhoea[25]
- Diarrhoea: may indicate gastrointestinal conditions such as coeliac disease, inflammatory bowel disease, and exocrine pancreatic insufficiency. Carcinoid tumours can cause weight loss due to diarrhoea. Other conditions that may cause diarrhoea include cystic fibrosis and gastrointestinal infections
- Bloody stools: may indicate inflammatory bowel disease or lower gastrointestinal tract malignancy
- Black/tarry stools: may indicate upper gastrointestinal bleeding
- Oily/floating stool: suggestive of malabsorption conditions such as coeliac disease or exocrine pancreatic insufficiency
- Dysentery/diarrhoea: parasitic infections (e.g., amoebiasis, giardiasis, cryptosporidiosis, cystoisosporiasis, cyclosporiasis, strongyloidiasis) can cause dysentery[49]
- Rectal bleeding: common in colorectal cancer.

While peptic ulcer disease itself may cause weight loss, other causes including gastric cancer, inflammatory bowel disease, and mesenteric ischaemia should be also considered.

Genitourinary:

- Haematuria: may be from a medium vessel vasculitis (e.g., polyarteritis nodosa) or a rheumatological/inflammatory condition if systemic symptoms are also present
- Lower urinary tract symptoms: may be suggestive for prostate cancer, especially if pelvic or bone pain is also present
- Lower pelvic pain: may indicate ovarian cancer, especially if abdominal bloating and increased abdominal girth are also present.

Neurological:

- Symptoms (e.g., headache, seizures, neuropathy) may suggest a mass lesion or vasculitis.

Endocrinological:

- Fatigue, palpitations, anxiousness, and heat intolerance: suggests hyperthyroidism. Older patients may not present with typical symptoms, and their presentation may be dominated by unintentional weight loss without other manifestations[38]
- Polyuria and polydipsia: may indicate diabetes. Type 1 diabetes more commonly presents with weight loss compared with type 2 diabetes. Chronically poor glycaemic control may lead to polyuria,

polydipsia, and weight loss in type 1 diabetes. Significant unintentional weight loss in the setting of type 2 diabetes, in the absence of causative medications, may arouse suspicion of a comorbidity such as infection or a pancreatic tumour. Patients may also present suddenly with diabetic ketoacidosis; severe cases may have a decreased level of consciousness due to a hyperosmolar state

- Fatigue, orthostasis, and weakness: may indicate adrenal insufficiency.

Pulmonary:

- Haemoptysis: may indicate tuberculosis or lung cancer
- Cough: may indicate tuberculosis or lung cancer. Mycobacterium avium-intracellulare may produce an indolent syndrome of chronic cough.

Physical exam

After the history, the physical examination is the next critical step as the history may not yield a leading diagnosis despite exhaustive effort.

Vital signs:

- Tachycardia: may be a sign of hyperthyroidism; however, it is non-specific and is common to multiple syndromes with volume depletion
- Blood pressure: many patients will have low blood pressure; however, high blood pressure or orthostasis in combination with paroxysmal headaches and sweats may suggest phaeochromocytoma
- Fever: may be a sign of multiple aetiologies including infectious, malignant, and inflammatory conditions. A daily spiking fever (with rash and joint pains) is indicative of adult-onset Still disease; however, this disease is rare, and it should be noted that multiple conditions can cause spiking fevers.

Mental status:

- Delirium and altered mental status: may be caused by electrolyte imbalances (e.g., hyponatraemia or hypercalcaemia can be a feature of multiple conditions, including syndrome of inappropriate antidiuretic hormone [SIADH] and cancer), endocrinopathies (e.g., hyperthyroidism), infections, or CNS vasculitis
- Cognitive impairment: should prompt an evaluation for dementia.

Systemic:

- Lymphadenopathy: may indicate malignancy, especially if mass lesions are present and the patient has risk factors for cancer. It may also indicate an infection. Lymphadenopathy may be mediastinal or intra-abdominal; therefore, a negative lymph node examination in a patient with prominent B symptoms (fever, weight loss, night sweats) should not dissuade further work-up for lymphoma
- Bone or joint pain: may indicate metastatic cancer or a rheumatological condition
- Paraneoplastic syndromes: small cell lung cancer may be associated with a variety of paraneoplastic syndromes including hypercalcaemia, Lambert-Eaton myasthenic syndrome, and SIADH.

Gastrointestinal:

- Mass lesions, hepatomegaly, splenomegaly, or ascites: may indicate malignancy
- Bruits: may be consistent with mesenteric ischaemia but are neither specific nor diagnostic.

Genitourinary :

- Mass lesions: rectal, prostate, or pelvic masses may indicate malignancy.

Cardiovascular:

- Cardiac murmur: new regurgitant murmurs may suggest infective endocarditis
- Signs of decompensated heart failure: lung rales, peripheral oedema, and elevated jugular venous pressure may indicate heart failure or pericarditis.

Pulmonary:

- Pleural effusion: may indicate malignancy or serositis
- Hyperinflation: may be suggestive of COPD or cystic fibrosis
- Rales and consolidation: usually a sign of chronic lung disease.

Dermatological:

- Dermatitis herpetiformis: consistent with a diagnosis of coeliac disease
- Mass lesions: may indicate skin cancer; however, it does not typically cause unintentional weight loss unless it is metastatic
- Janeway lesions or Osler nodes: diagnostic for infective endocarditis
- Rash: malar or discoid rash may indicate SLE
- Livedo reticularis: may indicate polyarteritis nodosa
- Hyperpigmentation: may be seen with primary adrenal insufficiency
- Skin tightening or thickening: common in systemic sclerosis (scleroderma).

Breast exam:

- Should be performed in the appropriate age groups, or at any age if symptoms suggest a malignancy
- Although uncommon, men may develop breast cancer, and breast examination should not be overlooked in male patients who present with unintentional weight loss, especially if other aetiologies are not apparent
- While breast cancer is more common in patients over 40 years of age, it may rarely present in young patients.[63]

Dental exam:

- Poor dentition: many older patients have decreased oral intake because of poor dentition; this may also be a risk factor for infective endocarditis.

Laboratory testing

In most cases of significant unintentional weight loss, a basic laboratory work-up should be performed. Even if there is a leading diagnosis after the initial history and physical examination such a work-up is prudent as many patients who present with unintentional weight loss are older and have risk factors for malignancy and cardiovascular disease. For example, an older patient with unintentional weight loss may be diagnosed with depression, but may also have an occult malignancy as a comorbid condition.

The basic initial laboratory work-up should include the following:

- FBC
- Serum electrolytes
- Serum glucose

- Serum calcium
- Serum creatinine/urea
- Urinalysis
- LFTs
- Serum albumin
- Thyroid stimulating hormone (TSH)
- Stool haem test.

HIV serology should be ordered if the patient has risk factors for HIV infection. It is also reasonable to complete age and risk-factor appropriate cancer screening (e.g., colorectal, breast, cervical) if not already done.

Assessment of initial history, exam, and laboratory testing

If a diagnosis is suspected at this stage, then confirmatory tests should be undertaken. For example, a suspect tumour mass should be biopsied or resected as appropriate. Haematological malignancies may require bone marrow biopsy or lymph node excision. Upper GI endoscopy (with biopsy) should be performed in patients with unintentional weight loss, anaemia, and upper abdominal pain to assess for stomach cancer and in patients with progressive dysphagia, which suggests oesophageal cancer. Colonoscopy is indicated for patients with unintentional weight loss, anaemia, haem-positive stools or gross rectal bleeding, abdominal pain, or change in stool calibre. A patient with signs of a lower gastrointestinal tract malignancy should still be re-evaluated even if the patient has received a prior negative colonoscopy, as a new cancer may arise even before the next interval screening exam.

If there is no diagnosis readily apparent at this stage, it is reasonable to obtain additional testing. While there is no consensus approach, the following tests should be considered:

- Prostate-specific antigen (PSA): in most cases, a patient with prostate cancer who presents with weight loss usually also has urinary symptoms or symptoms of metastatic disease such as bone pain. Even in the absence of these symptoms, if no other cause is found, ordering a PSA level is considered to be reasonable in men.
- ESR, CRP, LDH: while non-specific, an elevated LDH may indicate malignancy, and a markedly elevated ESR or CRP suggests an inflammatory, infectious, or malignant aetiology
- Chest x-ray: may reveal a mass on the lung or evidence of other lung lesions including granulomatosis with polyangiitis (Wegener's granulomatosis), a mediastinal mass, or lymphadenopathy
- Abdominal imaging: consider abdominal ultrasound or abdomen/pelvis CT for suspected malignancy.

The yield of endoscopy (oesophagogastroduodenoscopy or colonoscopy) is much higher (about 5-fold),[64] in patients with gastrointestinal symptoms compared to those with isolated unintentional weight loss. Therefore its use in undiagnosed cases may be considered but not necessarily recommended in all situations. There is no single test for cardiac cachexia; however, it is reasonable to recheck an echocardiogram, renal function, haematocrit, and thyroid function to assess for other potential causes of weight loss in a patient with heart failure. While inflammatory cytokines are elevated in cardiac cachexia, these are not routinely ordered.

Follow-up

Despite a thorough work-up, no diagnosis was found in 11% to 28% of patients in case series.[2] [3] [4] [5] [6] [7] [8] [18] [9]However, in one study, which included a more extensive follow-up, a diagnosis was ultimately

found in the vast majority of cases.[65]In the largest cohort study, a significant number of patients who were initially undiagnosed were later found to have malignancy either in follow up or at autopsy.[9]

Close clinical follow-up is, therefore, essential. In cases where a diagnosis is made, if the weight loss continues, the physician should consider the following:

- Treatment failure
- Incorrect diagnosis
- Presence of comorbid diseases.

For undiagnosed cases, continued follow-up may reveal a diagnosis as new symptoms or signs arise.

Indicators of likely malignancy

Based on different case series, predictive tools have been developed. One tool found that the following factors were predictive of malignancy:[66]

- Age >80 years
- WBC count >12,000 cells/microlitre
- Alkaline phosphatase >300 units/L
- LDH >500 units/L.

Another study found that the risk of cancer increased with the following factors:[67]

- Age >62 years
- Haemoglobin <100 g/L (10 g/dL)
- ESR >29 mm/hour.

However, these tools have not been replicated and their clinical utility in a real-world population is currently uncertain.

Differential diagnosis overview

Common
Stomach cancer
Colorectal cancer
Oesophageal cancer
Pancreatic cancer
Hepatoma
Small cell lung cancer
Non-small cell lung cancer
Non-Hodgkin's lymphoma
Hodgkin's lymphoma
Chronic leukaemia
Multiple myeloma
Oropharyngeal cancer
Laryngeal cancer
Ovarian cancer
Prostate cancer
Breast cancer
Coeliac disease
Exocrine pancreatic insufficiency
Crohn's disease
Ulcerative colitis
Mesenteric ischaemia

Common

- Depression
- Bipolar disorder
- Generalised anxiety disorder
- Anorexia nervosa
- Substance abuse
- Parkinson's disease
- Dementia
- Hyperthyroidism
- Tuberculosis (pulmonary)
- Adverse drug effects

Uncommon

- Cholangiocarcinoma
- Acute leukaemia
- Zollinger-Ellison syndrome
- VIPoma
- Carcinoid syndrome
- Peptic ulcer disease
- Chronic hepatitis
- Oesophageal webs, rings, and diverticula
- Small intestinal bacterial overgrowth (SIBO)
- Gastroparesis
- Post-surgical complications

Uncommon
Stomatitis
Bulimia nervosa
Multiple sclerosis
Amyotrophic lateral sclerosis
Prion disease
Cardiac cachexia syndrome
Post-stroke complications
Pulmonary cachexia syndrome
Cystic fibrosis
Microscopic polyangiitis
Renal cachexia syndrome
Diabetes mellitus
Adrenal insufficiency
Hypopituitarism
Pheaochromocytoma
Rheumatoid arthritis
Systemic lupus erythematosus
Granulomatosis with polyangiitis (Wegener's)
Polyarteritis nodosa
Systemic sclerosis (scleroderma)
Sarcoidosis
Mixed connective tissue disease (overlap syndromes)

Uncommon

Adult-onset Still disease
HIV infection
Tuberculosis (extrapulmonary)
Mycobacterium avium-intracellulare (MAI)
Histoplasmosis
Amoebiasis
Giardiasis
Cryptosporidiosis
Cystoisosporiasis
Cyclosporiasis
Strongyloidiasis
Infective endocarditis
Whipple's disease
Bartonella infection
Inadequate nutrition
Elder abuse/neglect
Child abuse/neglect

Differential diagnosis

Common

◊ Stomach cancer

History	Exam	1st Test	Other tests
Helicobacter pylori infection, prior gastric ulcer or atrophic gastritis, epigastric/ abdominal pain, nausea, haematemesis, melaena, dysphagia	epigastric tenderness or mass, lymphadenopathy, hepatomegaly, signs of anaemia, abrupt onset of multiple seborrhoeic keratoses (rare)	»**upper GI endoscopy with biopsy:** tumour visualised »**stool haeme test:** positive for occult blood	»**FBC:** anaemia »**serum iron:** decreased »**CT abdomen/pelvis:** metastatic lesions Used for broad assessment of intra-abdominal malignancy.

◊ Colorectal cancer

History	Exam	1st Test	Other tests
rectal bleeding, abdominal pain, change in stool calibre; more likely to be advanced if presenting with unintentional weight loss	abdominal distention or tenderness, abdominal or rectal mass	»**colonoscopy:** tumour visualised »**stool haem test:** positive for occult blood	»**FBC:** anaemia »**serum iron:** decreased »**CT abdomen/pelvis:** metastatic lesions Used for broad assessment of intra-abdominal malignancy.

◊ Oesophageal cancer

History	Exam	1st Test	Other tests
smoking, alcohol use (squamous cell carcinoma), Barrett's oesophagus, progressive dysphagia, painful swallowing, fatigue, pain, nausea	may be normal	»**oesophagogastroduodenoscopy (OGD) with biopsy:** mucosal lesion, histology (squamous cell carcinoma or adenocarcinoma)	»**FBC:** may show microcytic anaemia

◊ Pancreatic cancer

History	Exam	1st Test	Other tests
unintentional weight loss very common, nausea, anorexia,	abdominal tenderness/ mass, jaundice	»**abdominal ultrasound:**	»**pancreatic protocol CT:** pancreatic mass, extent of spread

DIAGNOSIS

Common

◊ Pancreatic cancer

History	Exam	1st Test	Other tests
abdominal bloating, upper abdominal pain/ discomfort		pancreatic mass, biliary dilation Typically ordered if LFTs indicate possible obstruction. »**LFTs:** abnormal	Pancreatic protocol CT is more sensitive compared with CT abdomen/pelvis. »**endoscopic ultrasound:** small tumours in pancreas May be used as an adjunct to pancreatic protocol CT to detect small tumours and vein involvement.

◊ Hepatoma

History	Exam	1st Test	Other tests
cirrhosis, hepatitis B or C infection, right upper quadrant pain	right upper quadrant mass, abdominal tenderness, jaundice, hepatomegaly, ascites	»**abdominal ultrasound:** intrahepatic mass »**CT abdomen/pelvis:** intrahepatic mass »**LFTs:** abnormal	

◊ Small cell lung cancer

History	Exam	1st Test	Other tests
cough, haemoptysis, dyspnoea, chest pain; bone pain, headache, seizures (metastases); altered mental status, abdominal pain, muscle weakness (paraneoplastic syndromes)	lung examination may be normal or show abnormalities (e.g., wheeze, rales, egophony, dullness to percussion); confusion, personality changes (metastases)	»**CT chest:** pulmonary mass, mediastinal lymphadenopathy, pleural effusion, consolidation Higher sensitivity for small tumours and better visualisation of the mediastinum compared with chest x-ray. »**chest x-ray:** pulmonary mass, mediastinal lymphadenopathy,	»**MRI/CT brain:** brain metastases »**serum electrolytes:** may show hypercalcaemia, hyponatraemia

Common

◊ Small cell lung cancer

History	Exam	1st Test	Other tests
		pleural effusion, consolidation	

◊ Non-small cell lung cancer

History	Exam	1st Test	Other tests
cough, haemoptysis, dyspnoea, chest pain; bone pain, headache, seizures (metastases)	lung examination may be normal or show abnormalities (e.g., wheeze, rales, egophony, dullness to percussion); confusion, personality changes (metastases)	»**CT chest:** pulmonary mass, mediastinal lymphadenopathy, pleural effusion, consolidation Higher sensitivity for small tumours and better visualisation of the mediastinum compared with chest x-ray. »**chest x-ray:** pulmonary mass, mediastinal lymphadenopathy, pleural effusion, consolidation	»**MRI/CT brain:** brain metastases »**serum electrolytes:** may show hypercalcaemia, hyponatraemia

◊ Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
night sweats, fatigue/ malaise, enlarged lymph nodes	fever, lymphadenopathy, splenomegaly, hepatomegaly	»**FBC:** leukocytosis, leukopaenia, anaemia, thrombocytopenia (variable) »**LDH:** elevated	»**CT chest and abdomen/pelvis:** may show enlarged lymph nodes and other sites of disease Image the symptomatic region first (if identified). Can order if lymphoma is suspected and examination does not reveal lymphadenopathy. »**bone marrow biopsy:** positive

Common

◊ Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
			Performed as part of staging. »**flow cytometry:** clonal population of lymphoma cells identified Can send from peripheral blood, or preferably from lymph node sample.

◊ Hodgkin's lymphoma

History	Exam	1st Test	Other tests
usually young adults but has second peak in sixth decade, night sweats, chest pain (if mediastinal mass present), generalised pruritus	fever, lymphadenopathy (rubbery, firm, non-tender), splenomegaly, hepatomegaly	»**FBC:** leukocytosis, anaemia, thrombocytopenia, eosinophilia (variable) »**LDH:** elevated	»**serum electrolytes:** possible hypercalcaemia »**CT chest and abdomen/pelvis:** may show enlarged lymph nodes and other sites of disease Image the symptomatic region first (if identified). Can order if lymphoma is suspected and examination does not reveal lymphadenopathy. »**excisional lymph node biopsy:** Hodgkin cells Goal of work-up is to identify a lymph node accessible to biopsy.

Common

◊ Chronic leukaemia

History	Exam	1st Test	Other tests
unintentional weight loss more common compared with acute leukaemia, night sweats	fever, lymphadenopathy	»**FBC:** anaemia, neutropaenia, thrombocytopenia Autoimmune haemolytic anaemia may be seen. »**peripheral blood smear:** increased lymphocytes »**flow cytometry:** clonal population of lymphocytes	»**bone marrow biopsy:** may show marrow infiltration by leukaemic cells (CLL); granulocytic hyperplasia (CML)

◊ Multiple myeloma

History	Exam	1st Test	Other tests
fatigue, bone pain, infections	pallor, pathological fractures	»**FBC:** anaemia »**serum electrolytes:** possible hypercalcaemia »**serum creatinine:** elevated »**serum/urine electrophoresiss:** monoclonal M protein band present Not ordered unless suspicion for multiple myeloma based on history, exam, or other lab findings.	»**bone marrow biopsy:** >10% myeloma plasma cells »**x-ray bone series:** may see lytic lesions

◊ Oropharyngeal cancer

History	Exam	1st Test	Other tests
smoking/chewing tobacco, alcohol use, oral pain, sore throat, dysphagia	neck mass, cervical swelling or lymphadenopathy, tumour may be seen with laryngoscopy	»**CT head and neck:** tumour visualised Further staging involves additional imaging.	

Common

◊ Oropharyngeal cancer

History	Exam	1st Test	Other tests
		»**biopsy of lesion:** positive Indicated if lesion is easily accessible.	

◊ Laryngeal cancer

History	Exam	1st Test	Other tests
smoking/chewing tobacco, alcohol use, dysphagia, painful swallowing, sore throat, hoarseness	neck mass, cervical swelling or lymphadenopathy, supraglottic/glottic mass may be seen with laryngoscopy	»**CT head and neck:** tumour visualised Further staging involves additional imaging.	

◊ Ovarian cancer

History	Exam	1st Test	Other tests
pelvic pain/pressure, abdominal bloating, increased abdominal girth (bulky disease or ascites), constipation, nausea, gastrointestinal or vaginal bleeding (less common); weight loss more common in advanced disease or metastases	adnexal mass, ascites	»**pelvic ultrasound:** adnexal mass Order if mass found on exam, or if history is concerning for ovarian cancer; not ordered as a general screen for unintentional weight loss of unknown aetiology. If a mass is found, it should be evaluated by a gynaecologist/ oncologist for staging and tissue diagnosis.	»**CA-125 level:** increased Consider if suspicious mass confirmed on imaging.

◊ Prostate cancer

History	Exam	1st Test	Other tests
obstructive urinary symptoms, bone pain, pelvic pain; weight loss more common in	enlarged prostate with nodule or asymmetry, bone tenderness	»**prostate specific antigen (PSA) level:** elevated	

Common

◊ Prostate cancer

History	Exam	1st Test	Other tests
advanced disease or metastases		Usually markedly elevated if presenting with unintentional weight loss. »**prostate biopsy:** abnormal cells	

◊ Breast cancer

History	Exam	1st Test	Other tests
breast lump, bone pain; weight loss more common in advanced disease or metastases	palpable breast mass, lymphadenopathy, bone tenderness	»**mammogram:** breast mass Diagnostic mammogram and/or ultrasound is recommended if clinically palpable mass. Screening mammogram if no palpable breast mass and presenting with unintended weight loss without an aetiology found. Consider age of patient. »**breast ultrasound:** breast mass	

◊ Coeliac disease

History	Exam	1st Test	Other tests
diarrhoea, bloating, abdominal pain/discomfort, fatigue	pallor, dermatitis herpetiformis	»**IgA-tissue transglutaminase (tTG) level:** elevated titre »**IgG-deamidated gliadin peptide (DGP) level:** elevated titre	»**total IgA level:** may be low Useful if positive IgG-DGP level but negative IgA-tTG; a small percentage of patients have coexisting IgA deficiency.

Common

◊ Coeliac disease

History	Exam	1st Test	Other tests
		Older generation (non-deaminated) antigliadin antibody is not sufficiently specific. Useful for people with IgA deficiency.	»**endoscopy with small bowel biopsy:** villous atrophy, increased lymphocytes Perform prior to starting gluten-free diet.

◊ Exocrine pancreatic insufficiency

History	Exam	1st Test	Other tests
previous pancreatitis, cystic fibrosis, diarrhoea, oily/floating/ foul-smelling stools; unintentional weight loss usually only occurs in severe cases	abdominal tenderness (chronic pancreatitis)	»**faecal fat:** high	»**vitamin A, D, E, K levels:** may show low levels Do not need to order to confirm diagnosis.

◊ Crohn's disease

History	Exam	1st Test	Other tests
can occur in younger patients (15-40 years) and peaks again in sixth decade, abdominal pain, diarrhoea (may be bloody), bloating, fatigue	abdominal tenderness, perianal lesions, blood in stool	»**FBC:** anaemia Non-specific, but commonly abnormal. »**stool haem test:** positive for occult blood »**endoscopy:** typical lesions seen (e.g., aphthous ulcers, oedema, cobblestoning, skip lesions) Endoscopic evaluation - either colonoscopy, sigmoidoscopy, or upper GI endoscopy - should be performed depending on the suspected portion of the gastrointestinal tract involved.	

Common

◊ Crohn's disease

History	Exam	1st Test	Other tests
		»**tissue biopsy:** mucosal bowel biopsies demonstrate transmural involvement with non-caseating granulomas	

◊ Ulcerative colitis

History	Exam	1st Test	Other tests
can occur in younger patients (20-40 years) and peaks again in sixth decade, abdominal pain, diarrhoea (usually bloody), rectal bleeding, fatigue, arthritis	abdominal tenderness, blood in stool	»**FBC:** anaemia Non-specific, but commonly abnormal. »**stool haem test:** positive for occult blood »**colonoscopy:** rectal involvement, continuous uniform involvement, loss of vascular marking, diffuse erythema, mucosal granularity, normal terminal ileum »**tissue biopsy:** continuous distal disease, mucin depletion, basal plasmacytosis, diffuse mucosal atrophy, absence of granulomata, anal sparing	

◊ Mesenteric ischaemia

History	Exam	1st Test	Other tests
cardiovascular risk factors, post-prandial pain (mild-to-severe), nausea/vomiting, diarrhoea, haematochezia/melaena; weight loss may be severe	abdominal tenderness, abdominal bruits may be present; examination may be normal	»**mesenteric angiography:** high-grade stenoses in coeliac/superior mesenteric arteries Order only if there is clinical suspicion for mesenteric ischaemia,	»**CT scan with contrast/CT angiogram:** bowel wall thickening, bowel dilation, pneumatosis intestinalis, portal venous gas, occlusion of the mesenteric vasculature, bowel wall thickening

Common

◊ Mesenteric ischaemia

History	Exam	1st Test	Other tests
		as stenoses may be asymptomatic.	with thumbprinting sign suggestive of submucosal oedema or haemorrhage Order only if there is clinical suspicion for mesenteric ischaemia, as stenoses may be asymptomatic.

◊ Depression

History	Exam	1st Test	Other tests
comorbid medical/ psychiatric conditions (may coexist with other conditions in differential for unintentional weight loss), anhedonia, depressed mood, functional impairment, appetite changes, sleep disturbance, libido changes, low energy, poor concentration, excessive guilt, suicidal ideation; weight change (loss or gain) can be variable	psychomotor slowing	»**clinical diagnosis:** diagnosis is made based on history and exam; should meet Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria Screening tools (e.g., patient health questionnaires) may be used. Positive screens should be followed by clinical assessment.	

◊ Bipolar disorder

History	Exam	1st Test	Other tests
episodes of mania (elevated mood, increased energy, perceived decreased need for sleep, impulsivity) with periods of depression; weight loss may be significant	grandiosity, pressured speech, irritability, psychosis, depression (depending on whether manic or depressive episode)	»**clinical diagnosis:** diagnosis is made based on history and exam; should meet Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria	

Common

◊ Generalised anxiety disorder

History	Exam	1st Test	Other tests
excessive worry for at least 6 months, anxiety, muscle tension, functional impairment, irritability, restlessness, poor concentration, fatigue, sleep disturbance; weight loss is not part of diagnostic criteria	usually normal	»**clinical diagnosis:** diagnosis is made based on history and exam; should meet Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria Screening tools (e.g., patient health questionnaires) may be used. Positive screens should be followed by clinical assessment.	

◊ Anorexia nervosa

History	Exam	1st Test	Other tests
comorbid psychiatric disorders, fear of gaining weight, food restriction, distorted body image, amenorrhoea, suicidal ideation, bingeing/ purging, history may be denied by patient	low BMI, bradycardia, hypothermia, hypotension, hair loss, muscle wasting, dental erosion (if co-existing bulimia), signs of cardiomyopathy; should meet Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria	»**FBC:** may have anaemia, mild leukopaenia, or thrombocytopenia »**basic metabolic panel:** may be deranged »**serum glucose level:** hypoglycaemia »**serum creatinine level:** variable Generally low due to decreased muscle mass. May be elevated if renal failure present. »**TFTs:** low T3, normal T4, normal TSH Important to exclude thyroid disorders. »**LFTs:** may be abnormal	

Common

◊ Substance abuse

History	Exam	1st Test	Other tests
substance use/abuse (e.g., opioids, cocaine, amfetamine, cannabis, inhalant, hallucinogen, benzodiazepine, alcohol), comorbid psychiatric disorders, inadequate nutrition; weight loss when abuse is severe	depends on substance	»**clinical diagnosis:** diagnosis is made based on history and examination and depends on substance	

◊ Parkinson's disease

History	Exam	1st Test	Other tests
bradykinesia, cognitive impairment, dementia	rigidity, resting tremor, shuffling gait, cogwheeling	»**clinical diagnosis:** diagnosis is made based on history and exam Primarily a clinical diagnosis. Neuroimaging may be used for difficult cases.	

◊ Dementia

History	Exam	1st Test	Other tests
progressive cognitive dysfunction, memory loss, taste changes; weight loss generally associated with advanced disease	cognitive impairment	»**cognitive testing:** cognitive impairment Screening tests. Clinical judgment must be used to assign diagnosis of dementia. Neuropsychiatric testing can be used for uncertain cases.	»**MRI brain:** Infarcts and/or white matter disease May be useful as adjunct in the assessment of vascular dementia.

Common

◊ Hyperthyroidism

History	Exam	1st Test	Other tests
palpitations, tremor, fatigue, weakness (may be subtle), heat intolerance, hair thinning/loss, anxiousness; older patients have fewer classic symptoms	tachycardia, fine tremor, hyperreflexia, bilateral lid retraction, proptosis	»**serum TSH level:** suppressed (primary) If the hypothalamic-pituitary-thyroid axis is functional, the TSH alone is an adequate initial screening test. Usually ordered for most patients with unintentional weight loss even if not all classic symptoms are present	

◊ Tuberculosis (pulmonary)

History	Exam	1st Test	Other tests
exposure to infection, endemic location, immunosuppression, cough, night sweats, malaise, haemoptysis, dyspnoea; weight loss is more common with reactivation	fever, rales, pleural effusion, lymphadenopathy	»**chest x-ray:** hilar lymphadenopathy, infiltrates or consolidation, pleural effusion »**sputum smear:** positive for acid-fast bacilli »**sputum culture:** positive (may take 4-8 weeks)	

◊ Adverse drug effects

History	Exam	1st Test	Other tests
started new medication; common drugs include anticonvulsants (e.g., topiramate, zonisamide), antidepressants (e.g., selective serotonin-reuptake inhibitors, bupropion), stimulants (e.g., dexamfetamine), diabetes medications	usually normal	»**medication withdrawal trial:** reversal of weight loss Weigh the need for the medication against the potential effects of discontinuation and the likelihood that the medication	

Common

◊ Adverse drug effects

History	Exam	1st Test	Other tests
(e.g., metformin; exenatide, liraglutide, and other glucagon-like peptide-1 receptor agonists), antibiotics and other medications that cause diarrhoea, cholinesterase inhibitors (e.g., donepezil), diuretics, laxatives, thyroid hormone (from misuse); withdrawal of drugs that support/maintain weight loss (e.g., pancreatic enzymes, mirtazapine); no other significant history		is causing the weight loss. Medication can be discontinued if there is a high level of suspicion for causing weight loss and there are acceptable risks once the medication is discontinued. Further work-up for other causes may be required.	

Uncommon

◊ Cholangiocarcinoma

History	Exam	1st Test	Other tests
primary sclerosing cholangitis, fever, right upper quadrant pain, pruritus; usually presents late	right upper quadrant mass, abdominal tenderness, jaundice, hepatomegaly	»**LFTs:** abnormal; typically greater elevation in bilirubin and alkaline phosphatase than aminotransferases »**abdominal ultrasound:** biliary duct dilation, bile duct tumour May follow with MRCP or ERCP. If high suspicion, can obtain MRCP as initial imaging test.	»**serum CA 19-9 level:** elevated Not specific for cholangiocarcinoma. »**serum CEA level:** elevated Not specific for cholangiocarcinoma.

Uncommon

◊ Acute leukaemia

History	Exam	1st Test	Other tests
unintentional weight loss less common compared with chronic leukaemia/lymphoma, fatigue, infections, bone pain, bleeding	fever, pallor, hypotension, petechiae, bone tenderness, ecchymosis	»**FBC:** anaemia, leukopaenia, thrombocytopenia »**peripheral blood smear:** presence of blasts; Auer rods (acute myelogenous leukaemia)	»**LDH:** elevated »**bone marrow biopsy:** presence of >20% blasts; Auer rods (acute myelogenous leukaemia)

◊ Zollinger-Ellison syndrome

History	Exam	1st Test	Other tests
GORD, peptic ulcer disease, diarrhoea, abdominal pain, fatigue, weight loss uncommon; may be part of multiple endocrine neoplasia syndrome (type 1) or associated with hyperparathyroidism or pituitary tumours	abdominal tenderness, pallor	»**fasting serum gastrin level:** elevated Elevated levels also seen in *H pylori* infection.	

◊ VIPoma

History	Exam	1st Test	Other tests
young-to-middle age, profuse watery diarrhoea (non-bloody), nausea, fatigue	flushing, poor skin turgor	»**VIP radioimmunoassay:** elevated Reasonable to order in the presence of flushing and a negative work-up for carcinoid tumour or multiple endocrine neoplasia. Pursue other causes of secretory diarrhoea first as this is a rare condition.	

Uncommon

◊ Carcinoid syndrome

History	Exam	1st Test	Other tests
diarrhoea, wheezing, GI bleeding, weight loss due to diarrhoea is uncommon	flushing, tumour is not usually palpable	»**24-hour urinary 5-hydroxyindoleacetic acid:** elevated	

◊ Peptic ulcer disease

History	Exam	1st Test	Other tests
non-steroidal anti-inflammatory drug (NSAID) use, *Helicobacter pylori* infection, epigastric pain (especially after meals, classically with a delay of a few hours), dark stools (if bleeding)	epigastric tenderness	»**H pylori breath test or stool antigen test:** positive if *H pylori* present »**stool haem test:** positive for occult blood »**upper GI endoscopy:** peptic ulcer visualised	

◊ Chronic hepatitis

History	Exam	1st Test	Other tests
risk of exposure (hepatitis B or C), fatigue, malaise, right upper quadrant pain, pruritus	fever; jaundice, oedema, ascites (cirrhosis); examination may be normal	»**LFTs:** abnormal »**serology:** hepatitis B antigen: positive; hepatitis C antibody: positive	»**HBV or HCV PCR:** positive »**serum bilirubin level:** may be elevated in advanced disease

◊ Oesophageal webs, rings, and diverticula

History	Exam	1st Test	Other tests
usually asymptomatic; dysphagia, decreased oral intake (severe cases)	usually normal	»**endoscopy:** oesophageal pathology visualised	»**esophagram:** oesophageal pathology visualised May be better to detect rings compared with endoscopy; however, cannot perform biopsy without endoscopy.

Uncommon

◊ Small intestinal bacterial overgrowth (SIBO)

History	Exam	1st Test	Other tests
prior gastrointestinal surgery/short bowel syndrome, systemic sclerosis (scleroderma), diarrhoea, abdominal pain, bloating; unintentional weight loss in severe cases	usually normal	»**hydrogen breath test:** increased hydrogen after administration of sugar/ carbohydrate Order only if high level of suspicion for SIBO.	»**FBC:** may have anaemia, variable

◊ Gastroparesis

History	Exam	1st Test	Other tests
diabetes mellitus, post-prandial epigastric pain or nausea/vomiting; unintentional weight loss in severe cases	usually normal	»**gastric emptying scintigraphy:** delayed transit time through stomach	

◊ Post-surgical complications

History	Exam	1st Test	Other tests
prior gastrointestinal surgery/short bowel syndrome, diarrhoea, abdominal pain, nausea	surgical scars, abdominal tenderness	»**clinical diagnosis:** diagnosis is made based on history and exam	

◊ Stomatitis

History	Exam	1st Test	Other tests
malnutrition, dentures, prior radiotherapy or chemotherapy, oral trauma, oral pain, xerostomia	erythema or ulceration of oral mucosa	»**clinical diagnosis:** diagnosis is made based on history and exam	

◊ Bulimia nervosa

History	Exam	1st Test	Other tests
recurrent episodes of binge eating and compensatory	dental erosion, Russell's sign (scarring over dorsum of hands	»**FBC:** may have anaemia	

Uncommon

◊ Bulimia nervosa

History	Exam	1st Test	Other tests
behaviour (e.g., purging, fasting, exercise), depression, low self-esteem, concern about body image/weight, menstrual irregularities	from inducing vomiting), arrhythmia, parotid hypertrophy; should meet Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria	»**basic metabolic panel:** may be deranged »**LFTs:** may be abnormal	

◊ Multiple sclerosis

History	Exam	1st Test	Other tests
focal neurological deficits lasting >24 hours in different regions, vision loss, numbness, pain, weakness, dizziness, fatigue, depression	internuclear ophthalmoplegia, limb weakness, sensory deficits	»**MRI brain:** white matter plaques Usually sufficient to make the diagnosis. »**MRI spinal cord:** demyelinating lesions Should be ordered for suspected myelopathy.	»**CSF evaluation:** increased oligoclonal bands With advances in neuroimaging, a patient with classic history, exam, and CNS imaging does not always require this.

◊ Amyotrophic lateral sclerosis

History	Exam	1st Test	Other tests
progressive upper and lower motor neuron deficits, limb weakness, dementia (uncommon), dyspnoea	muscle atrophy, fasciculations, weakness (lower motor neuron involvement); muscle atrophy, weakness, hyperreflexia (upper motor neuron involvement); facial or oropharyngeal weakness (bulbar involvement); decreased air movement, crackles from atelectasis (respiratory involvement)	»**electromyography:** evidence of diffuse, ongoing, chronic denervation	

Uncommon

◊ Prion disease

History	Exam	1st Test	Other tests
Creutzfeld-Jakob disease, prion exposure, rapidly progressive cognitive dysfunction, sleep disturbance, personality changes, dementia	myoclonus, altered mental status, ataxia	»**MRI brain:** often demonstrates hyperintensity in the cerebral cortex (cortical ribboning), basal ganglia (caudate and putamen), and thalamus on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences, and hypointensity (restricted diffusion) on attenuated diffusion coefficient map (ADC) sequences May be helpful in combination with history and exam.	»**EEG:** generalised slowing, focal or diffuse, and periodic polyspike-wave complexes and sharp waves May also be helpful, but is not by itself diagnostic. »**brain biopsy:** vacuolation (spongiform changes), neuronal loss, astrogliosis, presence of pathogenic prion (PrPSc) by immunohistochemistry or western blot, may show amyloid

◊ Cardiac cachexia syndrome

History	Exam	1st Test	Other tests
symptoms of advanced heart failure (e.g., dyspnoea on exertion, fatigue, orthopnoea and paroxysmal nocturnal dyspnoea, peripheral oedema)	muscle wasting/atrophy, signs of advanced heart failure (e.g., S3 gallop, rales, lower extremity oedema, elevated jugular venous pressure, neck vein distention); distinguish intentional weight loss (i.e., diuretic therapy) from unintentional (i.e., cardiac cachexia)	»**clinical diagnosis:** diagnosis is made based on history and exam; patient has a prior diagnosis of heart failure There is no single test for cardiac cachexia; however, it is reasonable to recheck an echocardiogram, renal function, haematocrit, and thyroid function to assess for other potential causes of weight loss in a patient with heart failure. While inflammatory cytokines are elevated in cardiac	

Uncommon

◊ Cardiac cachexia syndrome

History	Exam	1st Test	Other tests
		cachexia, these are not routinely ordered.	

◊ Post-stroke complications

History	Exam	1st Test	Other tests
prior stroke, depression, cognitive impairment, dysphagia, arm/hand weakness	decreased oropharyngeal function, speech and/or swallowing impairment	»**swallow study:** inability to swallow properly Recommended if stroke affects swallowing function, or if choking or aspiration is witnessed.	

◊ Pulmonary cachexia syndrome

History	Exam	1st Test	Other tests
symptoms of advanced COPD or interstitial lung disease (e.g., cough, dyspnoea)	muscle wasting/ atrophy, signs of advanced COPD or interstitial lung disease (e.g., decreased breath sounds and air movement, increased work of breathing, lung crackles, wheezing, hypoxia, tachypnoea)	»**clinical diagnosis:** diagnosis is made based on history and exam; patient has a prior diagnosis of COPD or lung disease A diagnosis of exclusion. PFTs are not diagnostic but are useful to restage disease. As smoking is a common risk factor for COPD and lung cancer, chest x-ray/CT should be considered.	

◊ Cystic fibrosis

History	Exam	1st Test	Other tests
cough, dyspnoea, diarrhoea, oily/floating stool, failure to gain	lung hyperinflation, rales (if infection), wheezing	»**sweat test:** positive	»**genetic testing:** positive

Uncommon

◊ Cystic fibrosis

History	Exam	1st Test	Other tests
weight (children), chronic pulmonary/ sinus infections			

◊ Microscopic polyangiitis

History	Exam	1st Test	Other tests
overlap with granulomatosis with polyangiitis (Wegener's granulomatosis) and lung disease, haematuria, arthritis	fever, joint tenderness or synovitis	»**urinalysis:** presence or red blood cells, casts »**antineutrophil cytoplasmic antibody (ANCA):** positive PR3 antibodies are negative. »**antimyeloperoxidase antibody:** positive	

◊ Renal cachexia syndrome

History	Exam	1st Test	Other tests
symptoms of advanced renal failure (e.g., fatigue, oedema)	muscle wasting/atrophy, symptoms of uraemia (e.g., confusion, bleeding, pericardial rub)	»**clinical diagnosis:** diagnosis is made based on history and exam; patient has a prior diagnosis of renal failure No specific tests; however, it is reasonable to check serum creatinine/urea, electrolytes, FBC, and serum albumin.	

◊ Diabetes mellitus

History	Exam	1st Test	Other tests
polyuria, polydipsia, infections, history of poor glycaemic control may be chronic	acetone breath, Kussmaul respiration, abdominal tenderness (diabetic ketoacidosis);	»**HbA1c:** 48 mmol/mol (6.5%) or greater	»**serum creatinine level:** elevated (diabetic ketoacidosis)

Uncommon

◊ Diabetes mellitus

History	Exam	1st Test	Other tests
symptoms of type1; nausea, vomiting, anorexia (diabetic ketoacidosis); type 1 more frequently presents with or is complicated by weight loss than type 2, and ketosis compounds weight loss	dry mucous membranes, hypotension, tachycardia, tachypnoea, decreased level of consciousness (diabetic ketoacidosis or hyperosmolar hyperglycaemic state)	»**plasma glucose:** elevated	»**serum sodium level:** hyponatraemia (diabetic ketoacidosis) »**serum potassium level:** hyperkalaemia (diabetic ketoacidosis) »**ABG:** acidosis (diabetic ketoacidosis)

◊ Adrenal insufficiency

History	Exam	1st Test	Other tests
metastases, tuberculosis, autoimmune endocrinopathies (primary adrenal insufficiency); glucocorticoid exposure (tertiary adrenal insufficiency); fatigue, decreased appetite, weakness, diarrhoea, abdominal pain	orthostasis, hyperpigmentation (primary adrenal insufficiency), shock (adrenal crisis)	»**morning serum cortisol:** <83 nmol/L (3 micrograms/dL) High values (i.e., >414 nanomol/L [15 micrograms/dL]) make adrenal insufficiency unlikely. Values of 83-414 nanomol/L (3-15 micrograms/dL) are uncertain. If there is a high level of suspicion for the diagnosis, an ACTH stimulation test should be ordered. »**high-dose ACTH stimulation test:** serum cortisol <497 nanomol/L (18 micrograms/dL) A reasonable initial screen unless the morning cortisol is performed first.	»**serum sodium level:** hyponatraemia »**serum potassium level:** possible hyperkalaemia

Uncommon

◊ Hypopituitarism

History	Exam	1st Test	Other tests
infiltrative disease (e.g., sarcoidosis, haemochromatosis), hypotension, fatigue; headache, vision loss (pituitary adenoma)	coarse voice, thickened skin, bradycardia, delayed deep tendon reflexes (hypothyroidism); decreased muscle mass, testicular atrophy (hypogonadism); increased fat mass, decreased muscle mass (growth hormone deficiency); no hyperpigmentation; loss of body hair	»**TFTs:** low TSH and T4 »**insulin-like growth factor (IGF-1) level:** low »**8 a.m. cortisol and ACTH:** low »**testosterone, FSH, LH (men):** low »**estradiol, FSH, LH (women):** low	

◊ Pheaochromocytoma

History	Exam	1st Test	Other tests
may be part of multiple endocrine neoplasia syndrome (type 2); symptoms can be episodic; headache, sweats, palpitations, tremor, weakness	tachycardia, diaphoresis, hypertension, orthostasis	»**serum catecholamines:** elevated Should be ordered only if there is clinical suspicion for phaeochromocytoma because weight loss is an uncommon presentation of this rare disease. Positive test should be followed up with imaging.	»**24-hour urine collection for catecholamines and metanephrines:** elevated Less convenient than serum test.

◊ Rheumatoid arthritis

History	Exam	1st Test	Other tests
symmetric polyarthritis, joint pain/swelling	joint subluxation/ destruction (advanced disease)	»**rheumatoid factor:** positive Approximately 20% of patients do not have a positive result and rheumatoid factor may be positive in	»**FBC:** mild anaemia »**ESR and CRP:** elevated Not diagnostic, normal values do not exclude diagnosis.

Uncommon

◊ Rheumatoid arthritis

History	Exam	1st Test	Other tests
		other conditions (e.g., hepatitis C). »**anticyclic citrullinated peptide antibody:** positive More specific for RA compared with rheumatoid factor. Multiple assays are available. »**x-ray affected joints:** erosive arthritis, osteopaenia May be normal early in disease course.	

◊ Systemic lupus erythematosus

History	Exam	1st Test	Other tests
rash, fatigue, arthralgia/ arthritis, Raynaud phenomenon, chest pain, dyspnoea	fever, malar rash, joint tenderness, haematuria, pleural effusion, pericardial rub, confusion (lupus cerebritis), thrombosis	»**antinuclear antibody (ANA), anti-dsDNA:** positive Not specific; order only if clinical suspicion of SLE. »**FBC:** anaemia, leukopaenia, thrombocytopenia »**serum creatinine level:** elevated »**urinalysis:** haematuria, proteinuria »**ESR and CRP:** may be elevated	»**antiphospholipid antibody:** may be positive

◊ Granulomatosis with polyangiitis (Wegener's)

History	Exam	1st Test	Other tests
cough, dyspnoea, haemoptysis, sinusitis,	fever, haematuria, skin lesions (e.g., purpura),	»**chest x-ray:** lung mass, infiltrates,	

Uncommon

◊ Granulomatosis with polyangiitis (Wegener's)

History	Exam	1st Test	Other tests
earache, fatigue, arthralgia/arthritis, myalgia, numbness, muscle weakness, abdominal pain, diarrhoea, nausea/ vomiting; presentation variable depending on systems affected	joint tenderness/ swelling, may have signs of consolidation (single lung nodules may have otherwise normal lung exam)	pleural effusion, lymphadenopathy »**CT chest:** lung mass, infiltrates, pleural effusion, lymphadenopathy »**antineutrophil cytoplasmic antibody (ANCA):** positive	

◊ Polyarteritis nodosa

History	Exam	1st Test	Other tests
history of hepatitis B or C, myalgia/arthralgia, paraesthesia, abdominal pain, purpura, livedo reticularis, skin ulcers, muscle tenderness	fever, high diastolic BP, mononeuritis multiplex	»**FBC:** anaemia, elevated platelets and WBC count »**ESR and CRP:** elevated »**complement:** reduced »**antineutrophil cytoplasmic antibody (ANCA):** negative »**antinuclear antibody (ANA), anti-dsDNA:** negative »**rheumatoid factor:** negative »**anticyclic citrullinated peptide antibody:** negative	

◊ Systemic sclerosis (scleroderma)

History	Exam	1st Test	Other tests
positive family history, hand swelling, Raynaud's phenomenon, skin thickening/tightness, loss of hand function, dysphagia, heartburn,	digital pits/ulcers, sclerodactyly, joint tenderness, telangiectasias, crackles	»**antinuclear antibody (ANA):** positive »**FBC:** may be normal or show anaemia	

Uncommon

◊ Systemic sclerosis (scleroderma)

History	Exam	1st Test	Other tests
abdominal bloating, melaena, myalgia/ arthralgia, fatigue		»**ESR and CRP:** may be elevated	

◊ Sarcoidosis

History	Exam	1st Test	Other tests
cough, dyspnoea, fatigue, arthralgia, photophobia, vision changes; symptoms are highly variable and depend on organ involved	wheezing, rhonchi, lymphadenopathy	»**chest x-ray:** hilar and/or paratracheal adenopathy with upper lobe predominant, bilateral infiltrates; pleural effusion (rare) »**FBC:** may show anaemia or leukopaenia »**LFTs:** abnormal »**serum creatinine:** may be elevated »**serum calcium:** hypercalcaemia »**PFTs:** restrictive or obstructive pattern (or mixed)	

◊ Mixed connective tissue disease (overlap syndromes)

History	Exam	1st Test	Other tests
digital pallor/ pain, Raynaud's phenomenon, arthralgia/arthritis, myalgia, swollen hands, dyspnoea, cough, heartburn	sclerodactyly, nail fold vascular changes, lymphadenopathy, haematuria	»**FBC:** may show anaemia or leukopaenia »**ESR and CRP:** elevated »**rheumatoid factor:** may be positive »**antinuclear antibody (ANA):** positive »**anticyclic citrullinated peptide antibody:** may be positive	

Uncommon

◊ Mixed connective tissue disease (overlap syndromes)

History	Exam	1st Test	Other tests
		»**antiribonucleoprotein antibodies:** positive	

◊ Adult-onset Still disease

History	Exam	1st Test	Other tests
daily-spiking fevers, rash, abdominal pain, nausea, arthralgia/ arthritis	salmon-colored rash (especially during febrile periods), lymphadenopathy, joint tenderness/swelling	»**serum ferritin level:** may be very high A thorough work-up for other causes should still be performed. »**FBC:** anaemia, leukocytosis »**ESR and CRP:** elevated	

◊ HIV infection

History	Exam	1st Test	Other tests
injection drug use, unprotected sex, needle stick injury, transfusions of blood or blood products before adequate testing was introduced or currently in areas without adequate testing, night sweats, diarrhoea, oral ulcers, altered mental status, opportunistic infections; weight loss more common with advanced disease	fever, skin rashes, oral thrush, muscle wasting (advanced disease), Kaposi's sarcoma	»**serum HIV ELISA:** positive Recommended screening is anti-HIV 1 and 2 antibody, and p24 antigen. Very early cases may be detected by PCR testing, although these are unlikely to present with unintentional weight loss. »**serum p24 antigen:** positive »**serum HIV DNA PCR:** positive Very early cases may be detected, although these patients are unlikely to present with	

Uncommon

◊ HIV infection

History	Exam	1st Test	Other tests
		unintentional weight loss.	

◊ Tuberculosis (extrapulmonary)

History	Exam	1st Test	Other tests
variable depending on system involved; abdominal pain/ swelling, change in bowel habits, dysuria, haematuria, frequency, skeletal pain, chest pain, headache, neck stiffness	fever, lymphadenopathy	»**chest x-ray:** abnormal typical for TB; abnormal atypical for TB; normal »**sputum smear:** positive for acid-fast bacilli »**sputum culture:** positive (may take 4-8 weeks)	»**biopsy of affected area:** positive For example: lymph node, pleural, synovial, liver, bone marrow, peritoneal biopsy.

◊ Mycobacterium avium-intracellulare (MAI)

History	Exam	1st Test	Other tests
underlying lung disease, cough, dyspnoea, fatigue	fever, lymphadenopathy, rales, or consolidation	»**blood culture:** positive for MAI »**sputum culture:** positive for MAI »**lymph node biopsy:** positive for MAI Obtain sample from symptomatic area diagnosis. Stains may be negative and culture may be slow growing.	

◊ Histoplasmosis

History	Exam	1st Test	Other tests
exposure to spores, endemic region, immunosuppression, cough, dyspnoea, headache, abdominal pain, chest pain; weight	fever, scattered crackles, bronchial breathing, distant breath sounds	»**chest x-ray/CT:** may be normal or show focal infiltrates, hilar and mediastinal lymphadenopathy, calcified granulomas,	

Uncommon

◊ Histoplasmosis

History	Exam	1st Test	Other tests
loss more common with disseminated disease		pulmonary nodules, diffuse interstitial or reticulonodular infiltrates, cavitary lesions, or pleural effusion »**sputum culture:** positive for *Histoplasma capsulatum* »**antigen testing:** positive for *H capsulatum* antigen	

◊ Amoebiasis

History	Exam	1st Test	Other tests
exposure history (e.g., visit to endemic area), immunosuppression, diarrhoea, dysentery, abdominal pain	fever, abdominal tenderness	»**stool antigen detection:** positive for parasite antigen »**PCR of stool:** amplification of amoebic DNA »**serum antibody test:** positive for anti-amoebic antibodies	

◊ Giardiasis

History	Exam	1st Test	Other tests
exposure history (contaminated water), non-bloody diarrhoea (severity varies), malaise, bloating; weight loss in severe and/or chronic disease	may have abdominal tenderness	»**stool antigen detection:** positive for cyst wall ELISA or direct fluorescence antibody.	

Uncommon

◊ Cryptosporidiosis

History	Exam	1st Test	Other tests
exposure history (contaminated water), diarrhoea, abdominal pain, loss of appetite; may be mild and self-limiting unless patient is immunosuppressed	may have abdominal tenderness	»**stool microscopy:** positive for *Cryptosporidium* cysts Usually not seen with routine test; request special evaluation.	

◊ Cystoisosporiasis

History	Exam	1st Test	Other tests
exposure history to *Cystoisospora belli* (contaminated food or water), non-bloody diarrhoea; may be mild and self-limiting unless patient is immunosuppressed	may have abdominal tenderness	»**stool microscopy:** positive for *Cystoisospora belli* oocysts Usually not seen with routine test; request special evaluation.	

◊ Cyclosporiasis

History	Exam	1st Test	Other tests
exposure history to *Cyclospora* (contaminated food or water), non-bloody diarrhoea; may be mild and self-limiting unless patient is immunosuppressed	may have abdominal tenderness	»**stool microscopy:** positive for *Cyclospora* cysts Usually not seen with routine test; request special evaluation.	

◊ Strongyloidiasis

History	Exam	1st Test	Other tests
history of exposure (e.g., contaminated soil), abdominal pain, change in bowel habit; pulmonary syndrome (e.g., cough, wheezing) may develop; weight loss can occur in	may be normal	»**stool microscopy:** positive for strongyloides larvae »**FBC:** eosinophilia »**serology:** positive Serology testing by ELISA.	

Uncommon

◊ Strongyloidiasis

History	Exam	1st Test	Other tests
immunosuppressed patients			

◊ Infective endocarditis

History	Exam	1st Test	Other tests
prior dental work, injection drug use, prosthetic heart valves, cough, haemoptysis, dyspnoea, night sweats, fatigue, myalgia/arthralgia, weakness	fever, cardiac murmur, Osler nodes, Janeway lesions	»**blood culture:** bacteraemia, fungaemia Certain organisms may be more difficult to culture. »**echocardiogram:** valvular vegetation	

◊ Whipple's disease

History	Exam	1st Test	Other tests
male gender, diarrhoea, abdominal pain, joint pain	fever, may be normal	»**endoscopy with biopsy:** villous blunting with periodic acid-Schiff (PAS) staining in macrophages Owing to its rarity, consider only if all other work-up for these symptoms is negative.	

◊ Bartonella infection

History	Exam	1st Test	Other tests
Bartonella henselae often follows bite or scratch from a cat (other types are associated with travel or indigent/homeless people), abdominal pain, nausea/vomiting	fever, papular/pustular lesion	»**serology (Bartonella henselae):** positive »**culture:** positive for *B henselae* »**lymph node biopsy:** granuloma formation, microabscesses, follicular hyperplasia	

Uncommon

◊ Inadequate nutrition

History	Exam	1st Test	Other tests
older age, poverty, inadequate resources, taste changes, dental problems, fewer social interactions, reduced or no access to food and different types of food	signs of starvation	»**clinical diagnosis:** diagnosis is made based on history and exam	

◊ Elder abuse/neglect

History	Exam	1st Test	Other tests
recurrent injuries, unstable home environment, inconsistent/changing history, unexplained/ inconsistent injuries	signs of starvation, ecchymosis, burn marks, bone fractures, head injuries	»**x-ray/CT area of injury:** may show bone fracture or intracranial bleeding	

◊ Child abuse/neglect

History	Exam	1st Test	Other tests
recurrent injuries, unstable home environment, inconsistent/changing history, unexplained/ inconsistent injuries	signs of starvation, ecchymosis, burn marks, bone fractures, head injuries	»**x-ray/CT area of injury:** may show bone fracture or intracranial bleeding	

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Images

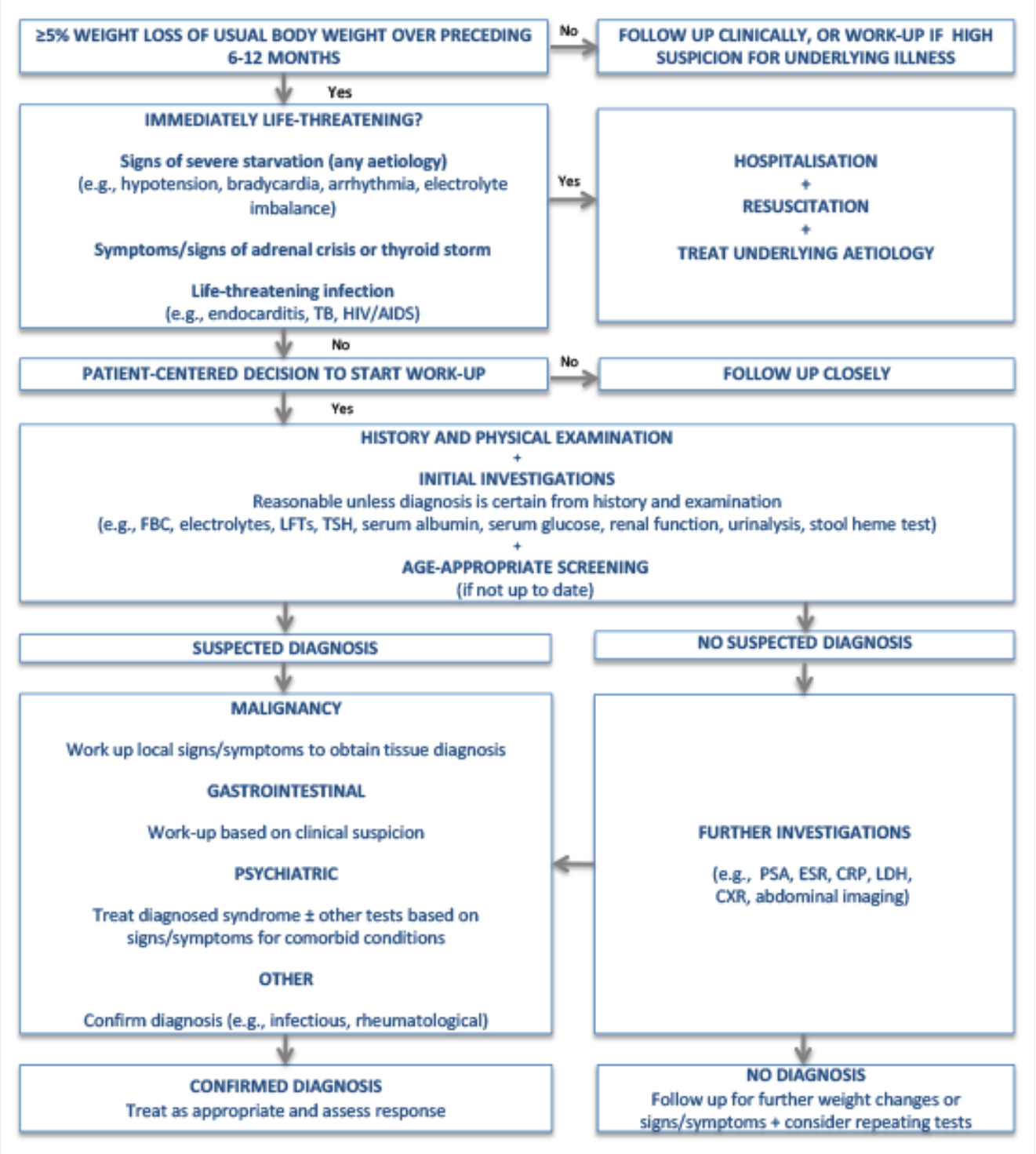

Figure 1: Diagnostic algorithm for the work-up of unintentional weight loss

From Christopher J. Wong

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