



DECODING FATIGUE

A Systematic Clinical Funnel and Differential Diagnosis

Based on 'Fatigue: Comprehensive Differential Diagnosis and Clinical Approach' (PsychoPharmRef). Data current as of May 2026.

The Diagnostic Challenge: A Universal Symptom

10–20%

of adults experience persistent (>2 weeks) fatigue.

1–3%

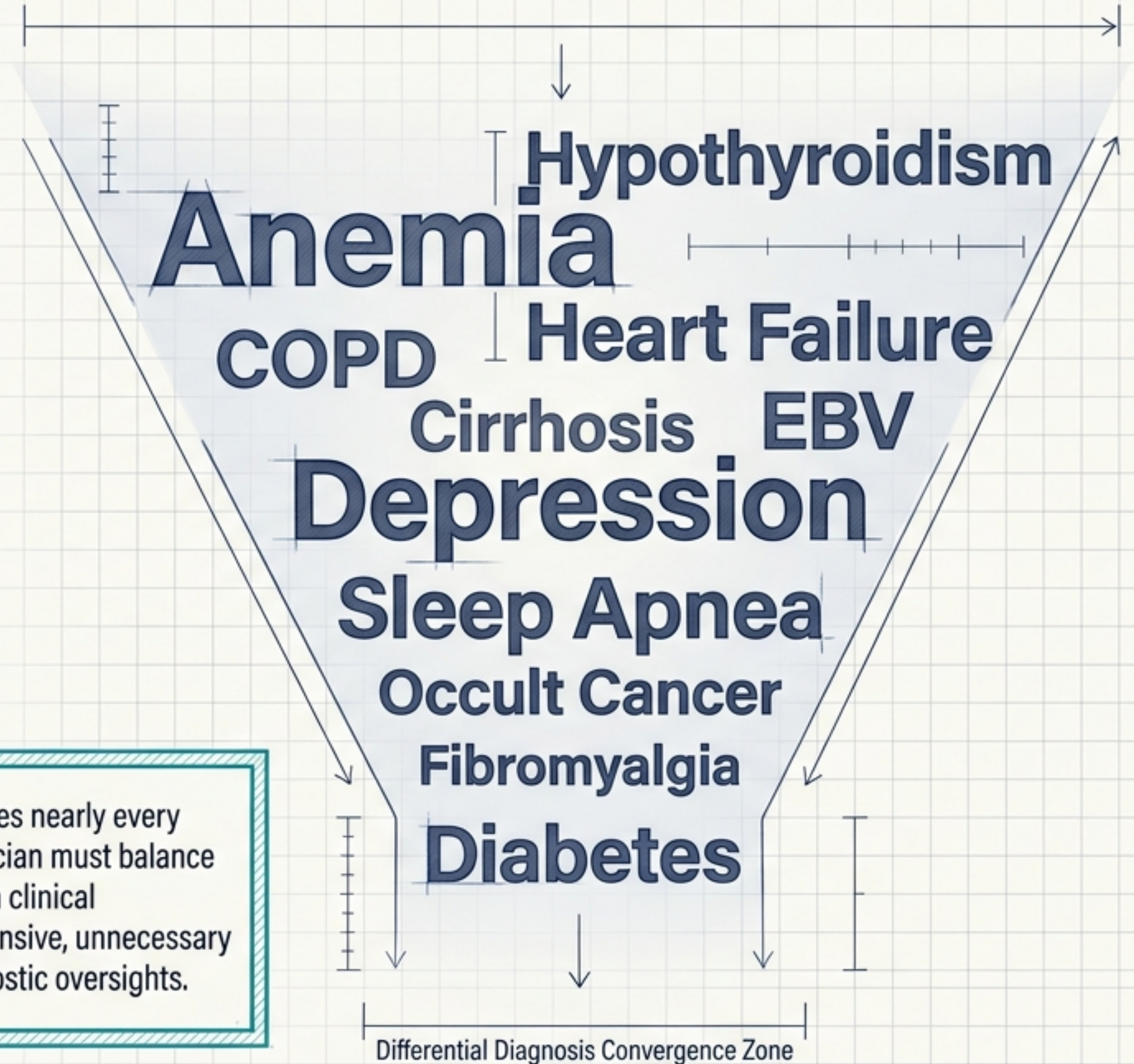
of all primary care office visits.

Up to

90%

of patients with depression cite fatigue as a primary symptom.

The Problem: Fatigue bridges nearly every physiologic domain. The clinician must balance diagnostic thoroughness with clinical efficiency, avoiding both expensive, unnecessary testing and dangerous diagnostic oversights.



The Fatigue Triad: Distinguishing the Subjective Complaint



Physical Fatigue



Mental (Cognitive) Fatigue



Sleepiness (Somnolence)

Subjective Complaint

Muscular weakness, reduced endurance, inability to perform physical tasks despite adequate sleep.

Mental sluggishness, reduced motivation, difficulty concentrating or maintaining attention.

Irresistible urge to sleep, propensity to fall asleep, difficulty maintaining wakefulness.

Clinical Implications

Points to systemic, metabolic, or end-organ supply/demand mismatch.

Primary central nervous system or mood/affective disruption.

Primary disorder of sleep architecture or circadian rhythm.

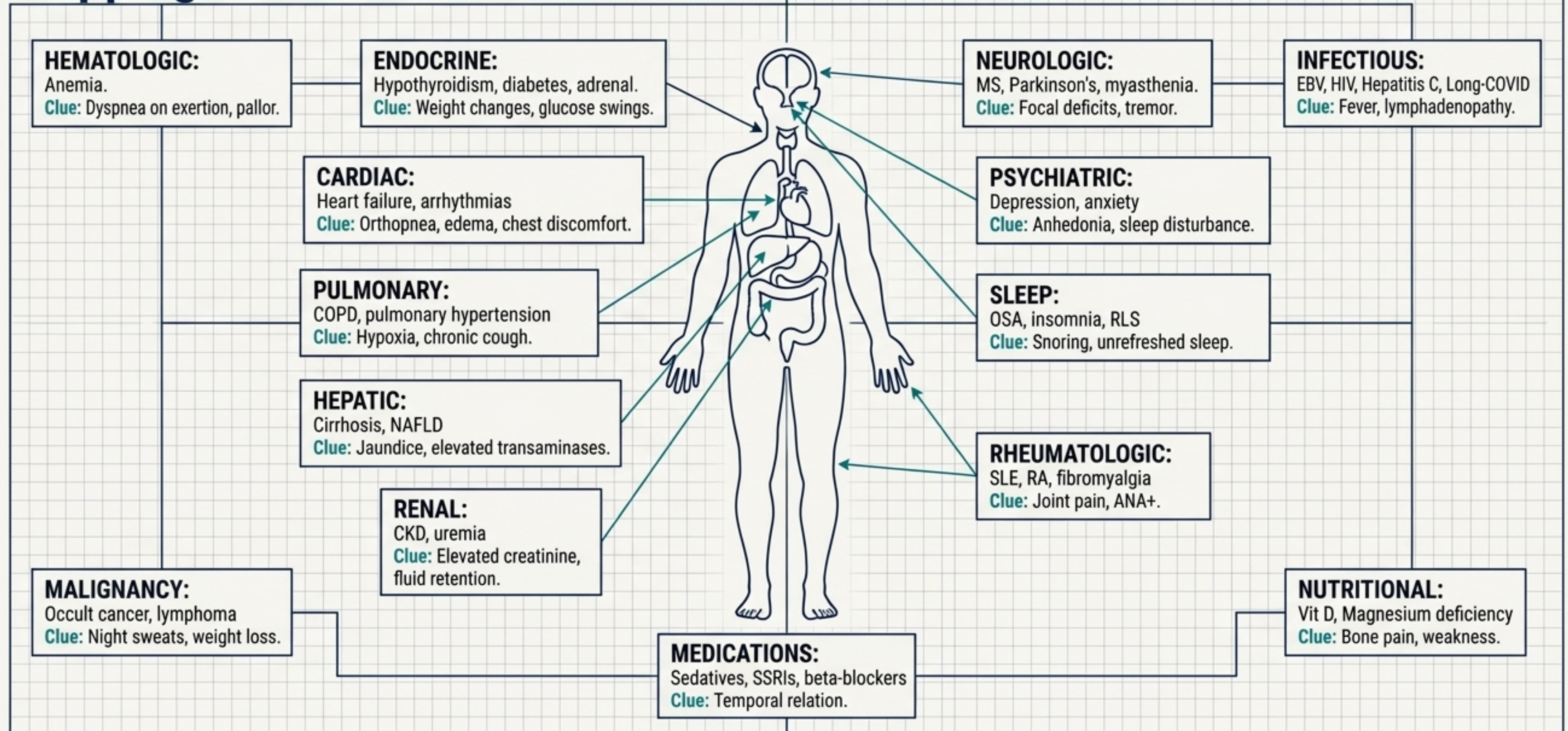
Typical Etiologies

Cardiovascular, hematologic (anemia), metabolic, neuromuscular pathology.

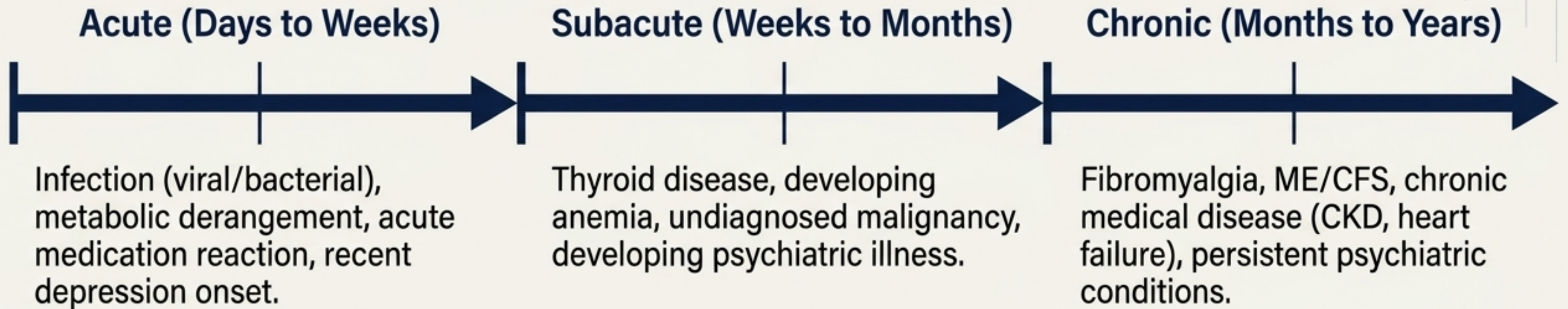
Depression, anxiety, cognitive disorders, sleep deprivation, neurologic conditions.

Obstructive sleep apnea (OSA), narcolepsy, insufficient sleep, sedating medications.

The Anatomy of Fatigue: Mapping the Differential



Temporal Filtering: The Clinical Timeline of Fatigue



Fluctuating (Variable)

Mood disorders, sleep variability, intermittent medication/substance effects.

Does fatigue improve with rest?

Improvement suggests physical deconditioning or depression. No improvement suggests systemic illness, sleep disorder, or neurologic condition.

The Diagnostic Interview & Red Flags

High-Yield History (The 15-Minute Filter)

Pattern:
Morning predominance (poor sleep quality, sleep apnea, depression) vs. **Afternoon dip** (glucose, circadian nadir) vs. **Evening** (anemia, cardiac).

Sleep Quality:
>10 hours but still tired? (Depression, hypothyroidism, OSA, narcolepsy). **Insomnia/early awakening?** (Primary insomnia, anxiety).

Medications:
SSRIs, beta-blockers, antihistamines, statins, opioids, cannabis, alcohol.

Exercise Tolerance:
"Can you climb stairs?" (Objective limitation = medical pathology; "Too tired to try" = depression).

Red Flags (Urgent Evaluation Required)



Constitutional:
Unintentional weight loss (>10% in 6 months), drenching night sweats, fever, lymphadenopathy. (Malignancy / Infection)

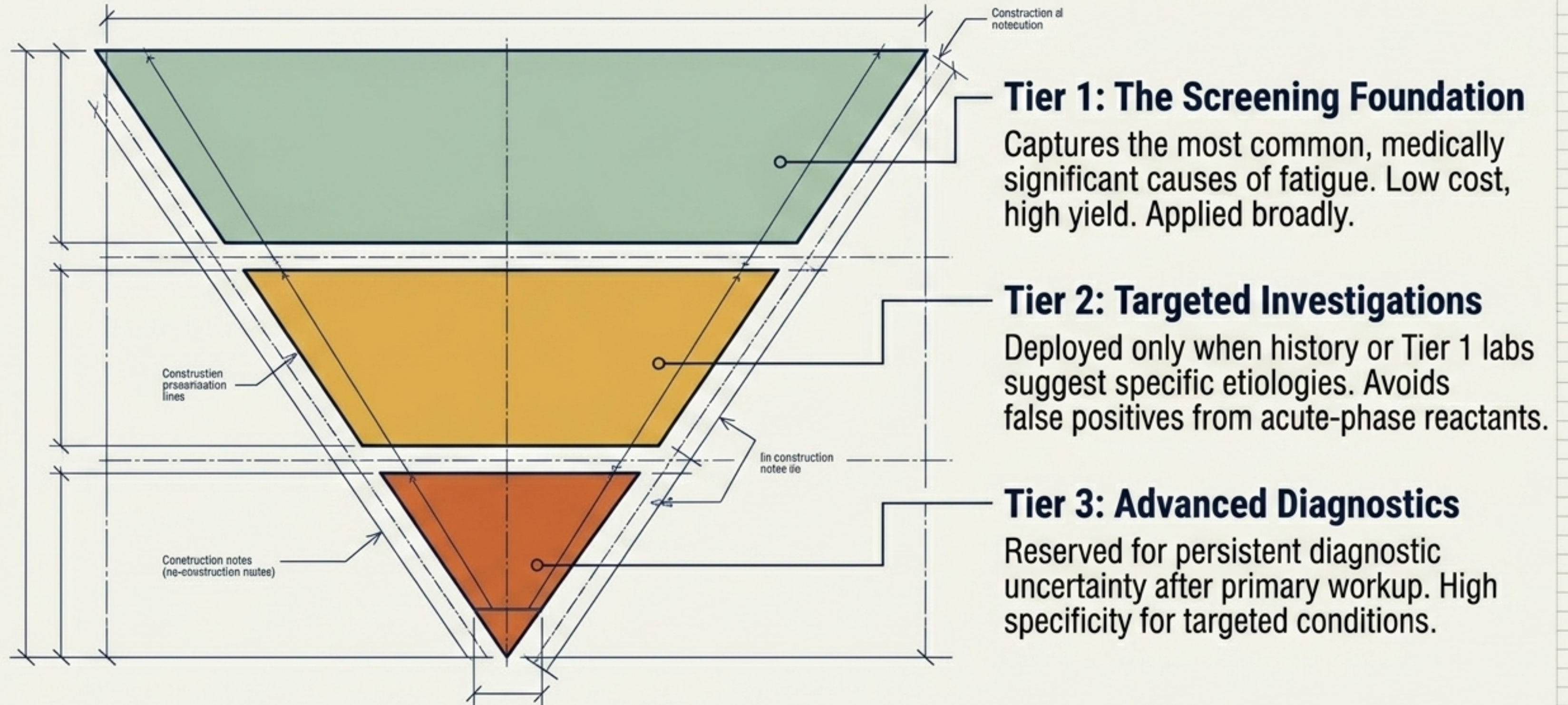


Cardiopulmonary:
Acute dyspnea, chest pain, syncope. (Cardiac / Pulmonary)



Neurologic:
New focal deficits or altered mental status.

The Testing Funnel: A Rational, Tiered Approach



Tier 1: The Screening Foundation

CBC with Differential

Detects anemia (microcytic <80 = iron/chronic; macrocytic >100 = B12/alcohol), leukopenia, left shift (infection).
Note: Even mild anemia (Hb 10-12 g/dL) causes noticeable fatigue.

Comprehensive Metabolic Panel (CMP)

Checks elevated creatinine/low eGFR (CKD), elevated AST/ALT (liver disease), electrolyte shifts, hypercalcemia, low albumin.

TSH (Thyroid)

Hypothyroidism is a top easily missed cause. TSH >4.0 mIU/L indicates primary hypothyroidism. TSH <0.1 suggests hyperthyroidism.

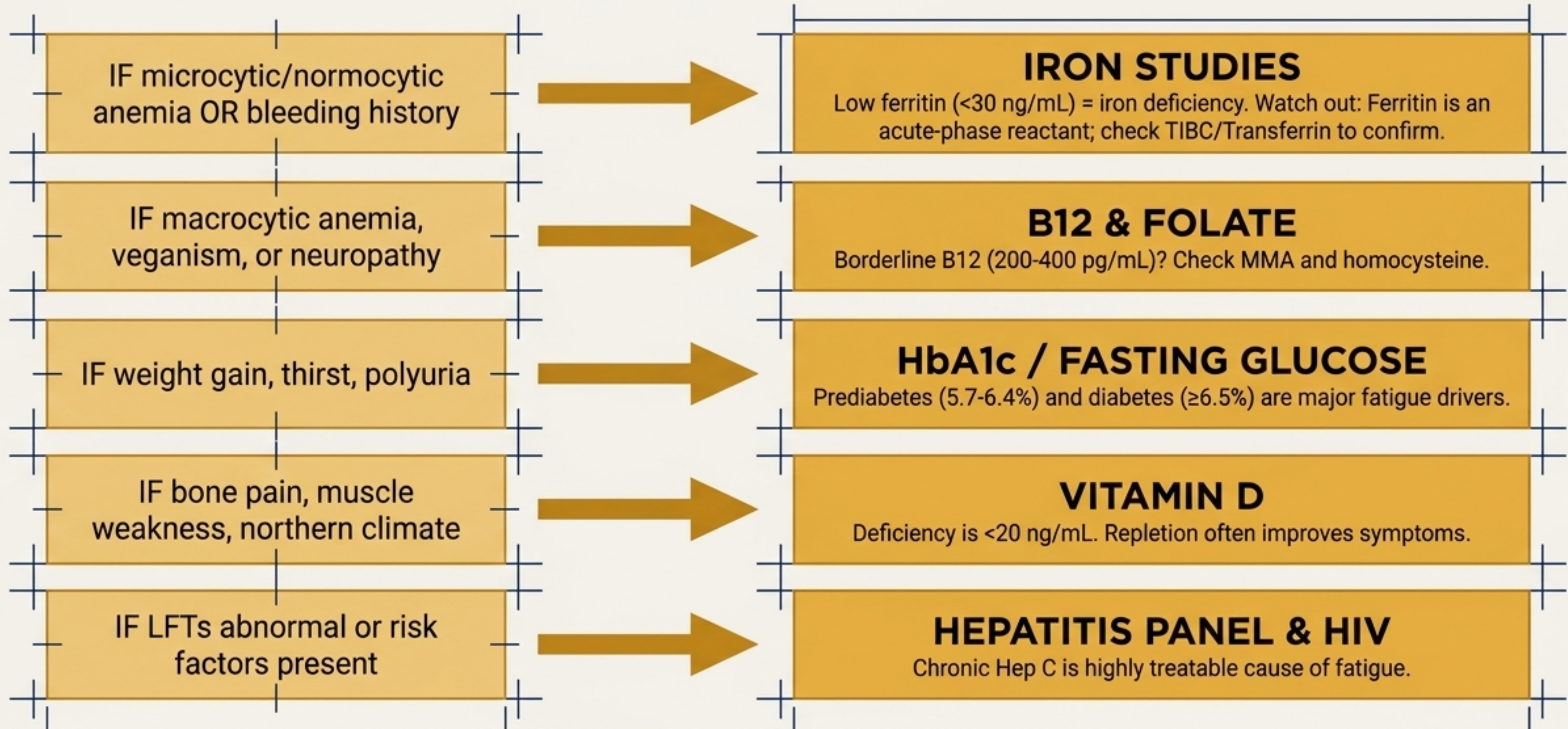
Urinalysis

Screens for UTI (especially in older adults), glycosuria (undiagnosed diabetes), proteinuria (kidney disease, lupus).

ESR & CRP

Nonspecific inflammatory markers. Elevation without clear findings warrants ANA, RF, CXR, or infectious workup.

Tier 2: Targeted Investigations



Tier 3: Advanced Diagnostics



ANA

Antinuclear Antibody (ANA)

Trigger: Joint pain, rash, dry eyes/mouth, elevated ESR/CRP. Screens for SLE, Sjögren's.



CORTISOL

Morning Cortisol (8-9 AM) & ACTH

Trigger: Hypotension, hypoglycemia, hyperpigmentation. <5 mcg/dL is abnormally low. Borderline requires ACTH stimulation test.



TESTOSTERONE

Testosterone & LH

Trigger: Men with low libido, ED. Testosterone <300 ng/dL causes significant fatigue.



POLYSOMNOGRAPHY

Polysomnography (Sleep Study)

Trigger: Snoring, witnessed apneas, obesity, unrefreshed sleep.



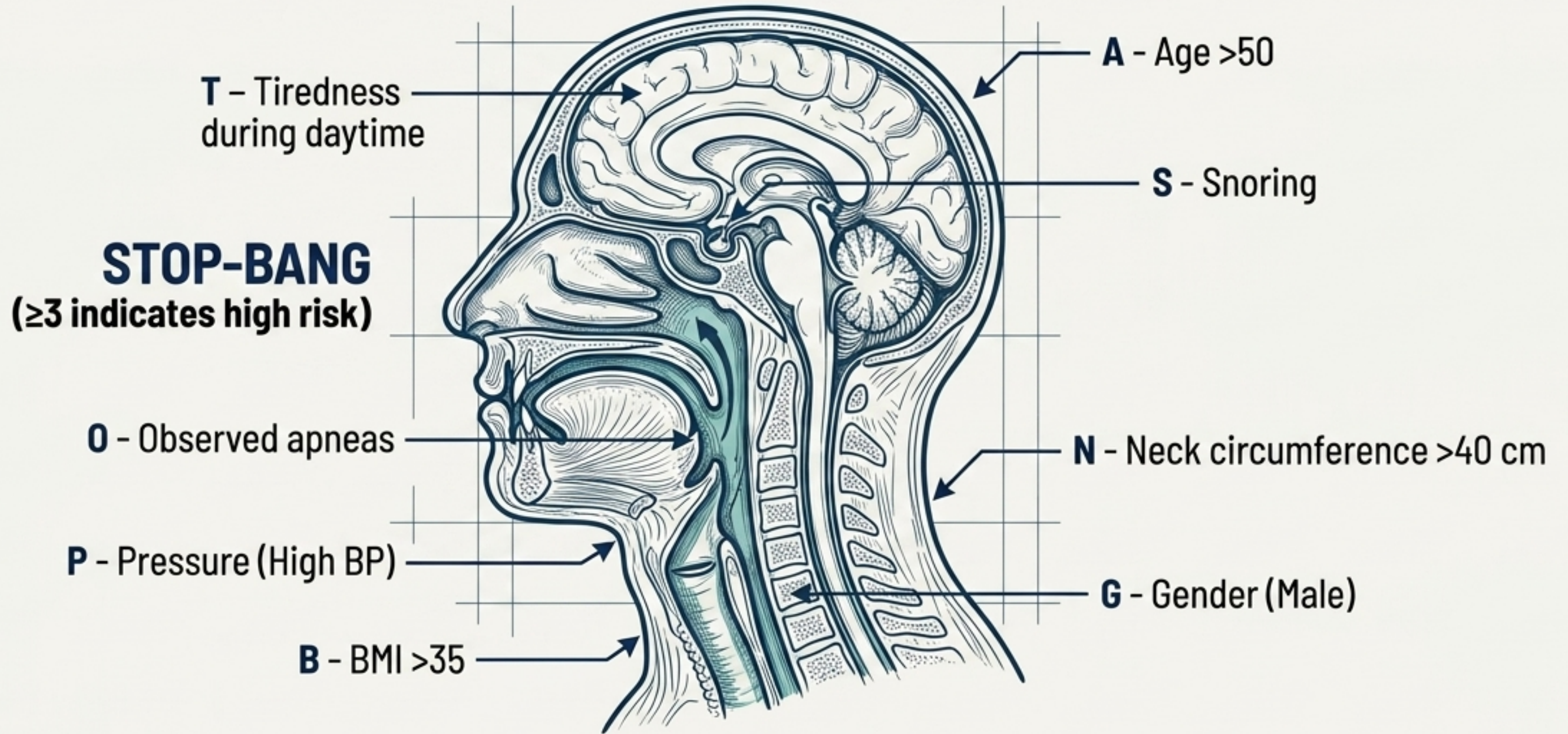
ECHO/CXR

Echocardiogram & Chest X-Ray

Trigger: Murmur, dyspnea on exertion, cough, or ruling out cor pulmonale in suspected OSA.

The Hidden Driver: Obstructive Sleep Apnea

Affects 2–7% of adults (up to 50% in obese populations). Repeated airway collapse triggers microarousals, oxygen desaturation, and profound daytime fatigue. AHI ≥ 5 indicates OSA. First-line treatment is CPAP to splint the airway patent.

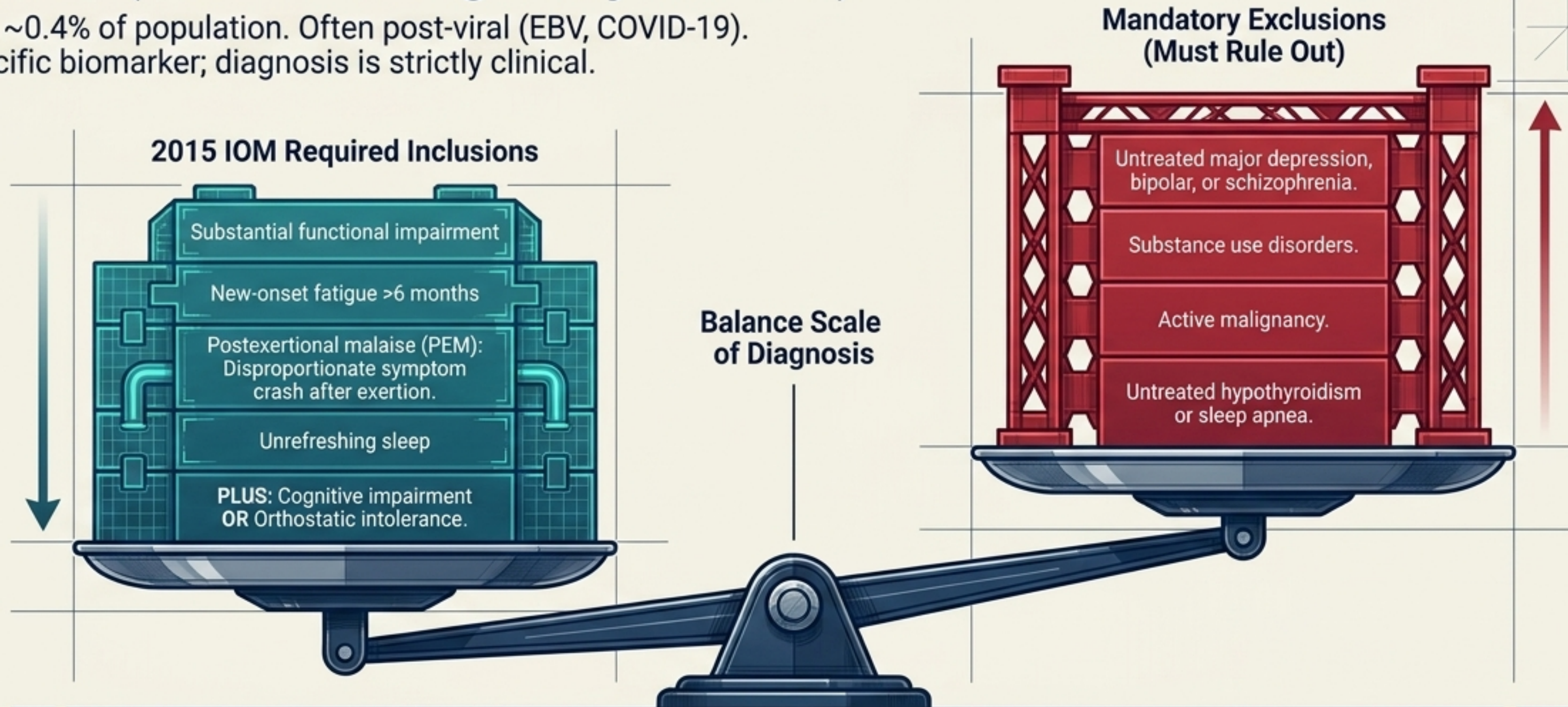


Beyond Apnea: The Sleep Disruptors Matrix

OSA (Baseline)	RLS / PLMD	Narcolepsy	Circadian Rhythm Disorders
Daytime sleepiness, witnessed apneas, snoring.	Evening urge to move legs (RLS) / periodic leg jerks during sleep causing microarousals (PLMD).	Irresistible daytime sleep urges, cataplexy (loss of muscle tone), sleep paralysis, hallucinations.	Delayed or advanced sleep phase causing circadian misalignment and poor sleep quality.
Polysomnography (AHI ≥ 5).	Clinical (RLS) / Polysomnography (PLMD). Check Ferritin!	Multiple Sleep Latency Test (MSLT) + Polysomnography (Hypocretin deficiency).	Clinical sleep log / Actigraphy.
CPAP.	Iron repletion, dopamine agonists (pramipexole), gabapentin.	Stimulants (modafinil), sodium oxybate. Often misdiagnosed as ADHD/Depression.	Light therapy, melatonin, behavioral scheduling.

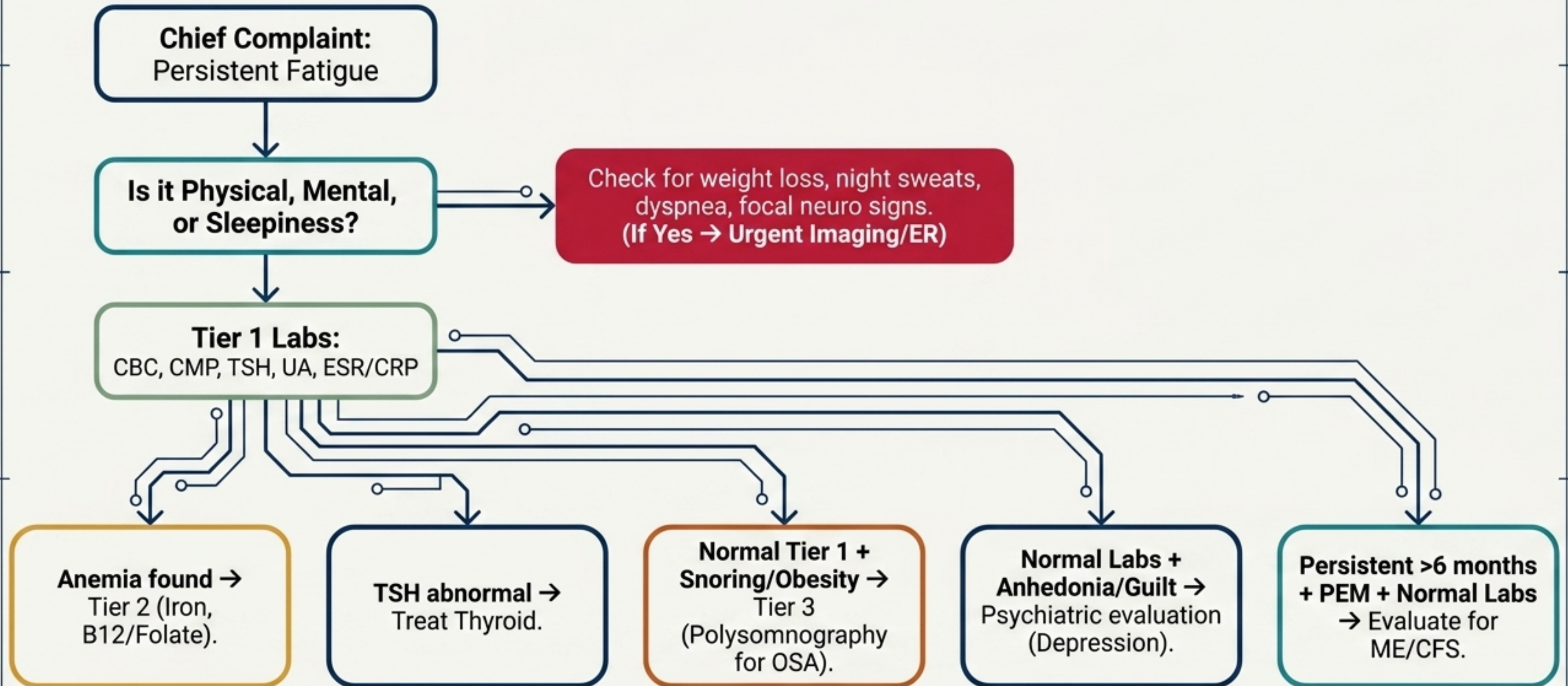
The Scale of Diagnosis: ME/CFS (Chronic Fatigue Syndrome)

Affects ~0.4% of population. Often post-viral (EBV, COVID-19).
No specific biomarker; diagnosis is strictly clinical.



Management Note: No cure. Avoid "boom-bust" cycles. Pacing strategies; graded exercise therapy (GET) is controversial as it may worsen PEM.

The Diagnostic Blueprint: Master Synthesis Algorithm



Final Routing: Urgent Escalation & Subspecialty Referral

Urgent / ER Escalation (Red Flags)



Acute dyspnea or chest pain (Rule out MI/PE).



Syncope or significant orthostatic hypotension.



Acute severe anemia or altered mental status.



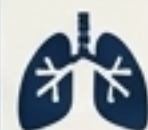
Weight loss >10% + Night Sweats + Lymphadenopathy (Oncology consult).

Subspecialty Routing



Cardiology

Suspected **heart failure** (edema), **arrhythmia**, structural disease on echo.



Pulmonology

COPD, Restrictive Lung Disease, unexplained hypoxia.



Endocrinology

Refractory **diabetes**, **adrenal insufficiency** (abnormal morning cortisol), secondary hypogonadism.



Sleep Medicine

Suspected **Narcolepsy**, CPAP-refractory OSA, complex parasomnias.



Rheumatology

Positive **ANA** with **joint pain/swelling**, elevated ESR/CRP without infection.