

The Disease Before the Disease

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The proposition we defend

A threshold is not the moment an illness begins. We argue that many chronic disease processes have a measurable preclinical trajectory during which compensation conceals loss of reserve until conventional diagnostic criteria are met. The formal diagnosis is often a crossing of an administrative or clinical boundary, not the biological birth of pathology.

Clinical thresholds are useful but can hide slow trajectories toward dysfunction. The provocative hypothesis is that some disease transitions are preceded by slower recovery, changing variability and altered coordination among signals—detectable before a diagnostic threshold is crossed.

Why the mechanism deserves to be taken seriously

Complex systems nearing certain tipping points may show prolonged relaxation time after perturbation, sometimes termed critical slowing down. Longitudinal blood-marker research has examined loss of resilience with age. In physiology, the question is whether these abstract dynamic signatures generalize to clearly defined disease endpoints with acceptable false-positive rates.

The causal argument

Blood pressure, glycemic control, vascular function and kidney filtration can change gradually, while each system initially compensates. Once regulatory flexibility is reduced, a modest additional stressor can generate an abrupt observable event. The thesis becomes strongest when a longitudinal trajectory reveals an acceleration, interaction or loss of response before the label appears. It also challenges studies that compare disease and healthy controls at one time point: the real causal transition may have occurred years earlier, and the apparent new abnormality may be a late effect.

Causal architecture under closer examination

Diagnostic thresholds are valuable for decisions, but they can give the impression that pathology begins on the day a number crosses a line. Biological processes often accumulate continuously. Insulin resistance can be compensated by increased insulin secretion; vascular stiffness may rise gradually; kidney reserve may decline before an overt filtration threshold is reached. The true causal question is when compensation begins to fail and which trajectory features predict that failure. A single mildly abnormal biomarker is not necessarily preclinical disease; population variation is broad, some trajectories regress, and measurement noise can mimic progression. Longitudinal evidence allows stronger claims because rates, accelerations and correlations among physiological systems can be observed before the eventual diagnosis. The paper should therefore contrast threshold classification with dynamic causal inference rather than declare clinical cutoffs meaningless. Clinical thresholds can still be indispensable to deciding when evidence supports treatment.

A concrete physiological case

Imagine serial metabolic measurements in a person who develops type 2 diabetes. Glucose may remain within a diagnostic boundary for years while insulin response and body composition change. On the day fasting glucose

crosses the threshold, nothing magical happens to cellular metabolism; a long trajectory becomes formally classifiable. Yet not every mildly abnormal trend predicts future disease, and diagnostic thresholds can still be useful for clinical decisions.

Original conceptual illustration

A person's recovery from minor physiological perturbations may become slower over time even while average measurements remain within accepted ranges. If that slowing reliably precedes a specific clinical endpoint, it could add value. If it simply reflects age, medications, sleep loss or sensor artifacts without independent prediction, the apparent early warning is not clinically useful. The model must count false alarms as seriously as true positives.

What established physiology already supports

Preclinical disease and compensatory physiological change are familiar clinical concepts. The original proposal is to give *trajectory shape and reserve loss* greater explanatory status and to study interactions before categorical disease onset.

The strongest counterargument—and the answer

A strong counterargument is that earlier detection can lead to overdiagnosis and unnecessary treatment. Many subclinical changes regress or never progress. The model needs prospective prediction, not retrospective storytelling in people already known to become ill.

Not every disease emerges through a smooth critical transition. Trauma, embolism and infection can begin abruptly, and noisy wearable data often reflect ordinary activity or device artifacts. A system-wide “pre-disease” label could cause anxiety and overtesting if not carefully validated.

The discriminating experiment

Use repeated measurements across years to compare linear trend, acceleration, variability and response to routine stressors. Predefine which trajectory features forecast clinically important events better than standard risk factors and validate them in independent populations. A marker that adds no discrimination should not become another “early disease” label.

Prospective blinded analyses should predefine endpoints and test whether trend-based warnings outperform conventional predictors in independent populations. Poor calibration or high false alarms would undermine practical usefulness even if a statistically significant signal existed.

Decisive comparisons and limits of inference

A rigorous cohort study would measure multiple candidate variables repeatedly in people initially free of the diagnosed syndrome. Investigators could model slope, acceleration, response variability and interactions among markers, then test prediction of meaningful future events in separate populations. One of the most informative outcomes would be an early nonlinear shift in reserve despite values that remain technically normal. But retrospective examination of people already known to become ill creates a serious risk of finding apparently predictive patterns by chance. Pre-registration and external validation protect against that illusion. The theory becomes more compelling when a forecast changes under a targeted, evidence-based intervention and improves functional outcomes, not simply when it provides a dramatic narrative of hidden pathology. The provocative statement is that disease has a history before it has a name. This invites deeper measurement of trajectory and compensation while rejecting the harmful tendency to pathologize every variation in a healthy person's physiology.

A second prediction from the original model

Early warning only becomes clinically meaningful with adequate calibration and actionable lead time. A predictor that flags too many healthy people, or provides no useful intervention, may cause more harm than benefit.

Why the hypothesis matters if correct

A diagnosis often marks a threshold crossing in a long biological trajectory. The paper argues that some disease processes begin earlier as changing compensation, altered response curves or progressively restricted reserve. That makes prospective trajectories more informative than retrospective stories about when a lab first became abnormal. The challenge is to avoid turning every small trend into a preclinical diagnosis, since many fluctuations never progress. A useful model must outperform standard risk assessment in predicting meaningful events and must be validated in new populations. The thesis could shift attention from the threshold alone to the shape and interactions of changes leading toward it. Its controversial point is that biology does not wait for the medical chart to acquire a label. The chart's cutoff can remain clinically useful while the causal process under investigation began long before it.

The clinical and conceptual consequence

The thesis reframes diagnosis as one moment in a longer process. Scientific attention should move upstream to the earliest measurable breakdown in adaptation, while clinical language avoids diagnosing disease solely from speculative precursor patterns.

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Source bibliography: verification pending

- Pyrkov TV et al. Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. Nat Commun. 2021.

Editorial and clinical boundaries

This paper advances a causal thesis and identifies observations that would support or defeat it. It does not establish a new diagnosis or treatment, and it should not be used to discontinue medically indicated care. Bibliographic entries inherited from the original edition have not all been independently verified.