The Syndrome Trap

When a label is mistaken for a disease

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The fault

A disease, in the textbook sense, is one thing. There is a mechanism, and because there is a mechanism there is a reasonably predictable course and a treatment aimed at the cause. A syndrome is different. A syndrome is a name for a cluster of findings that tend to travel together. A committee assigns the name, criteria decide the membership, and the criteria are checked off a list.

None of that makes syndromes useless. Naming a cluster is how medicine begins to study it, and some syndromes later turn out to be diseases once the mechanism is found. The fault comes one step later, when the label starts being treated as if it were already a disease: a single condition that you have or don't have, with a prognosis of its own and a treatment of its own. Logicians call the general mistake reification, treating the name as if it were the thing named. I call this instance the syndrome trap, and it is the sixth of the reasoning faults this site collects.

One plain question exposes it. *If two people have the same diagnosis, what do they actually have in common?* For a disease the answer is the mechanism. For a syndrome the answer can be close to nothing, and you can establish that by counting.

The specimen: metabolic syndrome

The cluster was described in Gerald Reaven's 1988 Banting Lecture, which observed that insulin resistance tends to travel with high triglycerides, low HDL cholesterol and high blood pressure, and named the cluster Syndrome X [1]. The National Cholesterol Education Program gave it clinical criteria in 2001 [2], and the American Heart Association and the National Heart, Lung, and Blood Institute issued the definition in common American use in 2005 [3]. You have metabolic syndrome if you meet any three of these five:

Criterion	Line that puts you over
Waist circumference	40 inches or more for men, 35 or more for women
Triglycerides	150 mg/dL or more, or on treatment for it
HDL cholesterol	Under 40 mg/dL for men, under 50 for women, or on treatment
Blood pressure	130/85 mm Hg or more, or on treatment
Fasting glucose	100 mg/dL or more, or on treatment

Notice what the table is made of. Each criterion is a line drawn across a continuous measurement, so the arbitrary-categories fault, the third on this site's list, is already at work five times before the

syndrome is even assembled. Whether 130/85 or 100 mg/dL are the right places for those lines is a fair question, but it is not today's question. Today's question is what happens after the lines are drawn.

One label, many illnesses

Any three of five criteria makes a member, and a short count shows how much room that leaves. Three criteria from five can be chosen 10 ways, exactly four can be chosen 5 ways, and all five is 1 more. Sixteen distinct clinical profiles, one name. The count itself is not the problem. The problem is what the profiles need.

Take two people who each qualify on exactly three criteria. Patient A is over the line on waist, triglycerides and HDL: a weight and lipid picture with normal pressure and normal sugar, whose chart calls for lipid treatment and weight management. Patient B is over on blood pressure, glucose and waist: a pressure and sugar picture with clean lipids, whose chart calls for antihypertensives and glucose control. They share one criterion and a diagnosis, and they need different medicine. Now add severity, which the pass-fail criteria ignore, so that a person barely over three lines and a person far over all five also carry the same label. "Metabolic syndrome" names a crowd, not a condition.

Imprecise medicine

Precision medicine is the announced direction of the field: match the treatment to the mechanism, patient by patient. A syndrome label treated as a disease points the other way. It invites treating the name, and the record of doing that is the strongest evidence that the trap is real.

No treatment was ever designed for the label. Nearly four decades after Reaven's lecture, no drug carries metabolic syndrome as an approved indication. The AHA/NHLBI statement directs clinicians to treat the components: the pressure, the lipids, the glucose, the weight [3]. The ADA/EASD joint appraisal, the diabetes establishment writing about its own label, goes further: the criteria are ambiguous, the label predicts little beyond what its components already predict, and clinicians should treat the components [4]. The people who defined the syndrome do not treat the syndrome.

Treating the checklist failed when it was tried. Low HDL cholesterol is one of the five criteria, and for years the number itself became a drug target. Torcetrapib raised HDL by roughly 70 percent and increased deaths in its outcome trial, which was stopped early [7]. Niacin raised HDL on top of statin therapy and produced no clinical benefit [8]. Moving a criterion is not treating a disease. The checklist item was a marker of trouble, not the trouble, and medicine aimed at the marker.

The treatment that finally arrived came by accident. Semaglutide, sold as Ozempic and Wegovy, and the rest of the GLP-1 class improve every criterion on the checklist: the waist, the pressure, the triglycerides, the glucose. They were not designed to. They were diabetes drugs, and their wider benefits surfaced because a 2008 FDA guidance required cardiovascular safety trials of every new diabetes drug [12]. The LEADER trial was run to show that liraglutide did not cause heart attacks and found that it prevented them [13]. SELECT then showed semaglutide cutting cardiovascular events in people with obesity and no diabetes at all [14]. So thirty-five years of the syndrome construct produced no therapy, and the therapy that works came out of a safety requirement. It works across the cluster for the reason this paper gave at the start for how a syndrome graduates toward a disease: it acts on an upstream mechanism, the dysregulated energy balance behind the adiposity, which the checklist never named. The label did not find the mechanism. The drug did. One caveat, supplied by the checklist itself:

a lean patient who qualifies on pressure, glucose and triglycerides is a profile that mechanism may not fit, and the heterogeneity returns.

Averaged prognosis. Any risk figure attached to the label is an average over sixteen profiles at all severities. Your own outlook depends on which components you have and how far over each line you are, which is also why the label adds so little predictive value beyond its parts [4].

Counted headlines and moving lines. Prevalence studies count labels: by the standard criteria, roughly a third of American adults had metabolic syndrome in the 2003 to 2012 national survey data [5], a figure that invites you to picture one epidemic of one thing. And membership tracks the committee as well as the biology. In 2003 the American Diabetes Association lowered the impaired-fasting-glucose line from 110 to 100 mg/dL [6], the 2005 syndrome criteria adopted the new line [3], and people crossed into the label overnight while their blood stayed the same.

Spectra stretch the same trap further

A spectrum is a syndrome with the variation admitted. The clearest case is autism. In 2013 the fifth edition of the psychiatric diagnostic manual folded what had been several separate diagnoses, including autistic disorder and Asperger's disorder, into a single autism spectrum disorder [9]. Now set the ends of that range side by side. A non-verbal eight-year-old who needs support around the clock and Elon Musk, who told a live television audience that he has Asperger's [10], carry the same diagnosis. Whatever those two have, it is not one disease, and no sentence of the form "autism is caused by X" or "Y helps autism" can be about both of them at once.

The research community said as much before the manual changed: a 2006 review argued that the evidence supports no single explanation for autism, at the genetic level or any other [11]. The manual itself concedes the point quietly, rating severity separately on two different symptom domains rather than placing each person at one spot on one line [9]. And lately practitioners have begun to describe a multi-dimensional spectrum, a space of traits rather than a line. That is more honest, and it is also a surrender of the disease framing, because a cluster of correlated dimensions with a committee-drawn boundary is exactly what a syndrome is. The new vocabulary has walked back to the old concept.

ADHD may be the purest specimen of all. The diagnosis is a checklist of checklists: six or more of nine listed inattention symptoms, or six or more of nine hyperactivity and impulsivity symptoms, five for adults, with the presentation named by which list you cleared [9]. Run the earlier counting on it and metabolic syndrome looks tame. Six of nine admits 130 combinations for each list, and the sharper fact needs no combinatorics at all: a purely inattentive presentation and a purely hyperactive one can share not a single symptom and carry the same diagnosis. Metabolic syndrome at least guarantees its members one criterion in common. ADHD guarantees nothing. There is no biomarker and no diagnostic test, the underlying traits run continuously through the population, and treatment response settles nothing, because stimulants sharpen attention in nearly everyone. That was shown in healthy children at the National Institutes of Health in 1978 [15]. A drug that works on a trait says nothing about whether the label carves out a disease.

Prediabetes runs the pattern on a single lab value: a band on a continuous measurement, given a name that sounds like the early stage of one disease. Some people in the band progress and many do not, but the name does the arguing before any evidence arrives.

What to do with this

The label is not useless; it is a filing system for things medicine is still sorting out, and a flag that several of your numbers deserve attention at once. The trap is only sprung when the label is read as a thing in itself. So when a syndrome or spectrum turns up in your chart or in a headline, three questions do most of the work. Which components do I actually have, and how far past each line am I? What is known about people with my components, as opposed to people with my label? And is the proposed treatment aimed at a component, or at the name?

Ask what the people under a label share. Sometimes the answer is a mechanism, and you are looking at a disease. Often the answer is a checklist. Medicine says it is heading toward precision, matching treatment to mechanism. A syndrome treated as a disease is imprecise medicine, and you do not have to accept imprecise medicine about your own body.

Sources

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