The Syndrome Trap

When a label is mistaken for a disease

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The fault

A disease is one thing. It has a mechanism, and because it has a mechanism it has a predictable course and a treatment aimed at the cause. A syndrome is a name for findings that tend to appear together. A committee picks the name and writes the criteria, and a patient qualifies by checking enough boxes. Naming a cluster is useful, and some syndromes become diseases once a mechanism is found. The fault is the syndrome trap: treating the label as if that had already happened, as if everyone with the name had the same thing and needed the same treatment. The example the course uses is metabolic syndrome, and the question that exposes the fault: if two people have the same diagnosis, what do they actually have in common?

The example: metabolic syndrome

You have metabolic syndrome if you meet any three of five criteria: waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose, each a line drawn across a continuous measurement, so fault 3 is at work five times before the syndrome is assembled. Choosing three from five can be done exactly ten ways. Each is a different patient type with a different chart, and two people who each qualify on three criteria need share only one. A weight-and-lipid patient and a pressure-and-sugar patient hold the same diagnosis with a single overlapping measurement. Map each combination to treatment, waist to weight management, the lipid criteria to lipid therapy, pressure to antihypertensives, glucose to glucose control, and the mix changes from type to type.

Filled dot = over the line for that criterion.

	Waist	Trig	HDL	BP	Glucose	What the chart calls for
1	●	●	●	○	○	Weight · Lipids
2	●	●	○	●	○	Weight · Lipids · Pressure
3	●	●	○	○	●	Weight · Lipids · Glucose
4	●	○	●	●	○	Weight · Lipids · Pressure
5	●	○	●	○	●	Weight · Lipids · Glucose
6	●	○	○	●	●	Weight · Pressure · Glucose
7	○	●	●	●	○	Lipids · Pressure
8	○	●	●	○	●	Lipids · Glucose
9	○	●	○	●	●	Lipids · Pressure · Glucose
10	○	○	●	●	●	Lipids · Pressure · Glucose

Left: the ten ways to qualify. Filled dot: over the line for that criterion. Right: the same ten rows with what the chart calls for.

The syndrome identifies ten different patient types and gives them all one name.

Grundy SM et al. Diagnosis and management of the metabolic syndrome: AHA/NHLBI scientific statement. Circulation 2005;112:2735–2752.

No pill for the label

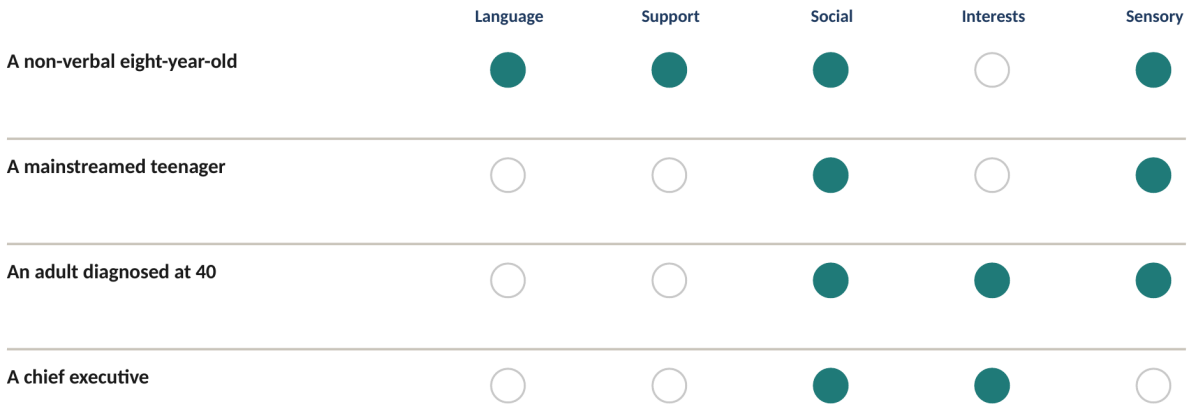
Nearly four decades after the syndrome was named, no drug carries metabolic syndrome as an approved indication. The statement that defines it directs clinicians to treat the components, and in 2005 the American Diabetes Association and its European counterpart published a joint appraisal of the label they had helped build: ambiguous criteria, little predictive value beyond its parts, treat the parts. Treating the checklist failed when tried. Low HDL is a criterion, and the number became a drug target: torcetrapib raised HDL by roughly 70% and raised deaths; niacin added to statins raised HDL and produced no clinical benefit. Moving a criterion is not treating a disease.

The treatment that finally arrived came by accident. Semaglutide and the GLP-1 class improve every criterion on the checklist, and they were diabetes drugs whose wider benefits surfaced because a 2008 FDA rule required cardiovascular safety trials of every new diabetes drug: LEADER, run to show liraglutide did not cause heart attacks, found it prevented them, and SELECT showed semaglutide cutting cardiovascular events in people with obesity and no diabetes. The drug works because it acts upstream, on a mechanism the checklist never named.

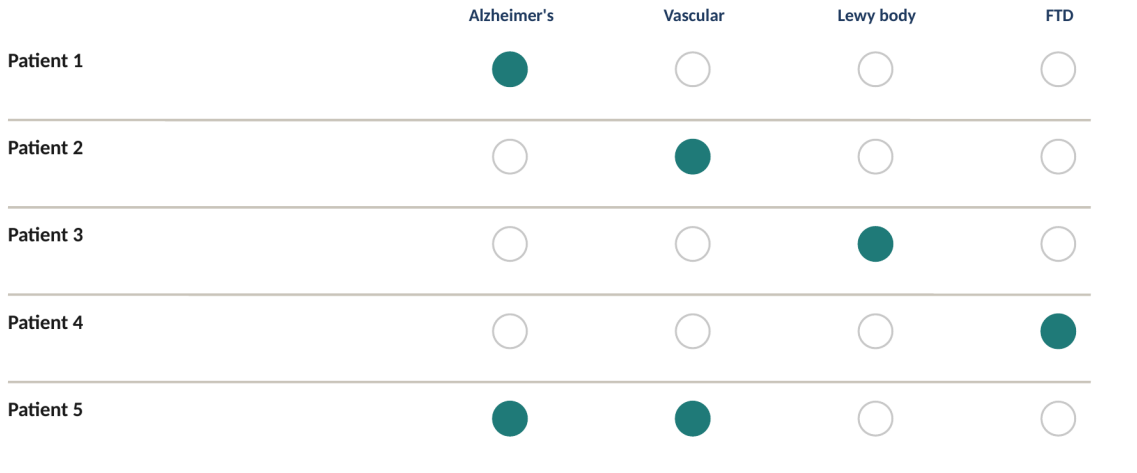
Kahn R et al. Diabetes Care 2005;28:2289–2304. Barter PJ et al. (ILLUMINATE). N Engl J Med 2007;357:2109–2122. AIM-HIGH Investigators. N Engl J Med 2011;365:2255–2267. Marso SP et al. (LEADER). N Engl J Med 2016;375:311–322. Lincoff AM et al. (SELECT). N Engl J Med 2023;389:2221–2232.

Spectra and umbrellas: autism and dementia

A spectrum is a syndrome with the variation admitted. In 2013 the DSM-5 folded several diagnoses into a single autism spectrum disorder, and one label now spans a non-verbal eight-year-old who needs support around the clock and a chief executive who announced his Asperger's on live television. No sentence of the form "autism is caused by X" can be about both of them at once, and the field's own research finds no single explanation at any level. Dementia is not a disease but an umbrella over distinct ones, Alzheimer's, vascular, Lewy body, frontotemporal, and most often mixed, and here treating at the label level can harm: antipsychotics prescribed for "dementia" are hazardous in Lewy body disease, and the new anti-amyloid drugs work only in early Alzheimer's with confirmed amyloid. "A cure for dementia" is a category error.



Four people, one label. Filled dot: prominently affected. Rows are illustrative.



Five patients, one word. Filled dot: the disease process actually present.

American Psychiatric Association, DSM-5, 2013. Happé F, Ronald A, Plomin R. Nat Neurosci 2006;9:1218–1220. Schneider JA et al. Neurology 2007;69:2197–2204. McKeith IG et al. Neurology 2017;89:88–100. van Dyck CH et al. (CLARITY AD). N Engl J Med 2023;388:9–21.

Why it happens

Labels are what medicine can bill, code, study, and headline. A checklist diagnosis can be made in a visit; a mechanism can take a generation to find. The incentive at every level, from the clinic to the journal to the newsroom, favors the name over the thing, and once a name exists it acquires the grammar of a disease, causes, cures, and prevalence, whether or not anything under it shares a mechanism. Progress arrives when medicine targets a mechanism inside the label and never the label itself.

What to ask

- 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?
- Is the proposed treatment aimed at a component, a mechanism, or just the name?
- What do the people under this label actually share? Sometimes a mechanism. Often a checklist.