Changing the Rules

By H. Gilbert Welch, M.D., M.P.H.

STOCKSNAPPER

The incidence of conditions like hypertension and diabetes has skyrocketed in recent years. Some of that increase is real. But some of it is due to changes in the way diseases are defined. In this excerpt from a soon-to-be-published book, a member of the DMS faculty explains the downsides of that trend.

For a WEB EXTRA with links to a podcast interview with Welch, as well as to the video of a Grand Rounds presentation he made at DHMC on this subject, see dartmed.dartmouth.edu/w10/we01.

Many modern diseases are defined by a numerical rule. If your blood pressure is above a certain number, for example, you have hypertension. If it isn't above that number, you don't. And hypertension isn't the only condition defined by a numerical rule. There are many diseases that you can be labeled with simply because you are on the wrong side of a number, not because you have any symptoms. Diabetes is defined by a number for blood sugar, hyperlipidemia by a number for cholesterol, and osteoporosis by a number for bone density (called a T score). By establishing these numerical targets, of course, we doctors are trying to get ahead of patients' symptoms—to make diagnoses early in order to prevent bad events such as leg amputation and blindness from diabetes, heart attacks and strokes from high cholesterol, and wrist and hip fractures from osteoporosis.

The conventional wisdom tells us this is good: finding problems early saves lives because we have the opportunity to fix small problems before they become big ones. What's more, we believe there are no downsides to looking for things to be wrong.

But the truth is that early diagnosis is a double-edged sword. While it has the potential to help some people, it also has a hidden danger: overdiagnosis—the detection of abnormalities that are not destined to ever bother us. Some people diagnosed with diabetes, high cholesterol, and osteoporosis, in other words, will never develop symptoms or die from those conditions. This is most likely the case for those in whom the condition is mild.

The numerical rules used to define conditions are really important. They typically involve a single number: if you fall on one side of the number you are defined as being well; if you're on the other, you are defined as being ill. These numbers—called cutoffs or thresholds—determine who has a condition and who doesn't. They determine who gets treatment and who doesn't. And they determine how much overdiagnosis occurs.

Cutoffs are set by expert panels of physicians. I wish I could say that their determinations result from purely scientific processes. But they are more haphazard than that: they involve value judgments and even financial interests. The experts who select the cutoffs have particular sets of beliefs about what is important. Because these doctors care greatly about the conditions they specialize in, I believe they sometimes lose a broader perspective. Their focus is to do everything they can to avoid the bad events associated with that condition; their main concern is not missing anyone who could possibly benefit from diagnosis and treatment. So they tend to set cutoffs that are expansive, leading many people to be labeled ill or abnormal. They tend to either ignore or downplay the major pitfall of this strategy: treating those who will not benefit. This is a problem because almost all treatments have the potential to do some harm.

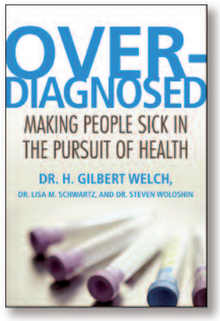
Over the past few decades, many cutoffs have been changed in a way that dramatically increases the number of individuals who are labeled with these conditions and others. It means that the threshold to make a diagnosis has fallen. Even if this is done with the best of intentions—to avoid more bad events—it can lead to an undesirable consequence: more overdiagnosis and thus more treatment of people who won't benefit but can potentially be harmed.

I want to emphasize, however, that the concepts I explain here do not apply to people who are really sick, for whom medical care offers much. Nor are they an apology for sloppy diagnosis of a serious illness. And they are not a condemnation of all of American medicine, nor a call for alternative medicine. I'm conventionally trained in Western medicine, and I believe doctors can do a lot of good. If you are sick, you should see one.

Unintended consequences

This is not a happy story. Mr. Roberts was a 74-year-old man whose major medical problem was ulcerative colitis—an inflammatory condition of his colon (the large intestine). It's a disease that causes symptoms such as severe abdominal pain and diarrhea, and it also increases the risk of colon cancer. Because his disease was so severe, he had part of his colon surgically removed. Although this led him to have frequent bowel movements, he learned to deal with his situation quite well.

One day, as a result of a routine lab test, Mr. Roberts was found to have elevated blood sugar. It wasn't that high, but the finding prompted some more testing. And that confirmed a diagnosis of diabetes. He had type 2 diabetes, the form of the disease that typically occurs in older adults (as opposed to type 1, which usually starts in childhood). Although he had no symptoms of diabetes, over the past few decades doctors had gotten much more aggressive about treating it early, so his primary-care physician started him on glyburide—a drug that lowers blood sugar. The medication worked well.



This feature is excerpted—with the kind permission of Beacon Press—from a forthcoming book titled Over-Diagnosed: Making People Sick in the Pursuit of Health *(copyright 2010, Beacon Press). The book was written by Dr. H. Gilbert Welch, together with his colleagues Drs. Lisa M. Schwartz and Steven Woloshin. All three are professors of medicine and of community and family medicine at Dartmouth Medical School, as well as members of the VA Outcomes Group at the Dartmouth-affiliated Veterans Affairs Medical Center in White River Junction, Vt. The book's scheduled on-sale date is January 18, 2011.*

Six months later, he blacked out while driving on the local interstate. His car went off the road and rolled over. He fractured his sixth and seventh cervical vertebrae—in other words, broke his neck. The paramedics on the scene measured his blood sugar. It was *very* low. The medication had worked *too* well. I'd hate to have been the doctor who prescribed him glyburide.

But I was that doctor. I'm not sure what happened. I had used the standard starting dose of the medication. He had tolerated it well for six months. Maybe he hadn't eaten normally that day or maybe he had the flu or a stomach virus—any of which could affect the medication's action. I don't know.

Mr. Roberts was in the hospital for over a month. When I next saw him in clinic, he was wearing a halo brace. The halo is a metal ring that encircles the head, much like the brim of a hat, except the halo doesn't sit on the head—it is secured to the skull with pins. Attached to it are two metal rods that extend to the shoulders and are connected to a tightly fitted plastic jacket. With this apparatus, the neck is both immobilized and stretched so that the fracture can heal. I felt terrible. And—maybe it goes without saying—I didn't restart Mr. Roberts on the glyburide.

Mr. Roberts is now 90 and still a patient of mine. He has not been treated for diabetes since the accident, nor has he had any complications from diabetes. I think he was overdiagnosed. He was lucky. He suffered no permanent injury. He has recovered fully from the problem caused by his unneeded treatment. But I'm not sure I have.

Diagnostic adjustment

Diabetes can be a very serious disease. Some patients with the disease—usually children—first come to medical attention because they lose consciousness. They are in a diabetic coma: their blood sugar is elevated (as much as 10 times normal), their potassium stores are extremely low, and their body fluids are dangerously acidic (a state called metabolic acidosis). Without treatment, they will die.

Treating someone in a diabetic coma is one of the most rewarding experiences in medicine. The patient comes in near death and generally about two days later feels fine. All the patient needs is lots of intravenous fluids, some potassium, and the hormone that was lacking—insulin. Insulin is the hormone that allows sugar to move from the blood into the cells. Giving it, along with the fluid and potassium, normalizes the blood sugar and the acid-base balance. Most important, the patient wakes up. It's really something to see.

But what I have just described is actually the less common form of diabetes—type 1. Patients with type 2, the much more common form, are usually adults and have plenty of insulin. Their problem is that the insulin doesn't work because the body has become resistant to it. These patients are frequently overweight (the best treatment is losing weight). While it does not tend to lead to a diabetic coma, type 2 diabetes can still be a very bad disease. Either type can lead to severe complications, including blindness, kidney failure, heart disease, impaired healing of wounds, and leg infections that sometimes require amputation. But type 2 diabetes can also be a totally asymptomatic condition. There is a spectrum of abnormality in diabetes. Some people with the diagnosis will develop the aforementioned complications; others will not. Although we are never sure exactly who these "others" are, they have been overdiagnosed.

So how do we decide who has diabetes? When I was in medical school, the numerical rule was this: if you had a fasting blood sugar over 140 (milligrams of glucose per deciliter of blood, that is), then you had diabetes. But in 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus redefined the disorder. Now if you have a fasting blood sugar over 126, you have diabetes. So everyone who has a blood sugar between 126 and 140 used to be normal but now has diabetes. That little change turned more than 1.6 million people into patients.

Is that a problem? Maybe, maybe not. Because we changed the rules, we now treat more patients for diabetes. That may mean that we have lowered the chance of diabetic complications for some of these new patients. But since these patients have milder diabetes (because their blood sugars are only moderately high rather than very high), they are at relatively low risk for these complications to begin with. So people with mildly abnormal blood sugar levels have less to gain from treatment. (The same is true for people with mild hypertension and mild osteoporosis. The numerical cutoffs for these conditions have also been lowered in recent years.)

The graph on the facing page illustrates the effect of lowering the number that defines diabetes—moving to the left on the spectrum of abnormality—on the benefit of treatment. The same relationship applies to many other disorders: just replace the "mild diabetes" and "severe diabetes" poles of the spectrum with "nearly normal cholesterol" and "very high cholesterol" or "mild osteoporosis" and "severe osteoporosis," and you'll get the picture.

In fact, this relationship applies to any kind of medical care. As we expand treatment to people who have progressively milder abnormalities, their potential to benefit from treatment becomes progressively smaller.

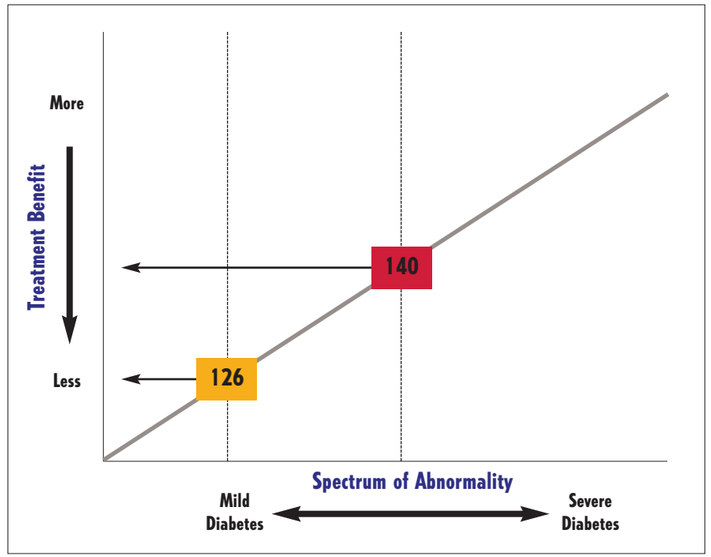
Severe abnormalities are different. It's clearly bad to have really high blood pressure or really high blood sugar. You want to take action to lower both. But remember: it's also bad to have blood pressure that is too low. Or blood sugar that is too low—just ask Mr. Roberts.

The problem of overdiagnosis was dramatically demonstrated in a recent randomized trial funded by the National Institutes of Health. The trial was designed to determine whether intensively lowering blood sugar reduced the risk of having or dying from a heart attack or stroke. The trial enrolled over 10,000 patients with diabetes who were at high risk for these events. About 5,000 were randomized to receive standard diabetes therapy—treatment to lower their average blood sugar to a more acceptable, though not normal, range. The other 5,000 were randomized to receive intensive drug therapy—treatment to bring their blood sugar down to a normal level. Half of the patients in the latter group achieved the goal: the average blood sugar level of those who got intensive therapy was below 140. Because the average included blood sugars measured right after eating (which tend to be high), it is safe to assume that their fasting blood sugars were considerably lower.

The trial started in 2003 and was supposed to continue to 2009. But on February 6, 2008, the National Heart, Blood, and Lung Institute issued a press release saying they were "changing" the intensive therapy regimen "due to safety concerns." *Changing* wasn't the most accurate word to describe what they were doing; *stopping* would have been a better choice. And the safety concern was that patients receiving the intensive therapy were dying more often than patients receiving the standard therapy. After three years, 5% of the patients receiving intensive therapy had died, compared with 4% of those receiving standard therapy. That is a 25% increase in the risk of death, and the researchers were confident that it was not a statistical fluke. There was little doubt: intensive treatment was worse than standard treatment.

You might wonder how making people's blood sugar normal could end up killing them. It's probably because we can't simply dial a patient's blood sugar to a specific number; our therapies aren't that precise. Instead, blood sugar bounces around, and if we try to have blood sugar bounce around normal, sometimes it will bounce too low. And having your blood sugar too low increases your risk of death. The investigators might argue that hypoglycemia (low blood sugar) was not the cause of the increased risk of death. But by their own admission, they were not sure what explained the increased mortality. In the official report, lead author Hertzel Gerstein wrote: "Despite detailed analyses, we have been unable to identify the precise cause of the increased risk of death in the intensive blood sugar strategy group. . . . Our analyses to date suggest that no specific medication or combination of medications is responsible. We believe that some unidentified combination of factors tied to the overall medical strategy is likely at play."

My view is that if the trial had shown a mortality benefit, the authors would have been quick to ascribe that benefit to intensive control of blood sugar (as I think would have been correct in that case). But since the trial showed a mortality harm, that must also be ascribed to intensive control of blood sugar. That's the point of a randomized trial.



This graph shows that changing the cutoff for diabetes from the previous fasting blood sugar level of 140 to the current level of 126 means that those with a milder form of the disease benefit less from treatment.

What does this study tell us about where to set the threshold to diagnose diabetes? My take is this: if it's not good to make diabetics have nearly normal blood sugars, then it's not good to label those with nearly normal blood sugars as diabetics. Why? Because doctors will treat them. People with mild blood sugar elevations are the least likely to gain from treatment—and arguably the most likely to be harmed, as Mr. Roberts was.

Beyond diabetes

This problem goes well beyond diabetes. The tendency to lower the threshold of diagnosis has been repeated in a number of other common conditions, including hypertension. The unit of measurement for blood pressure is mmHg, or millimeters of mercury, and a blood pressure reading is expressed as two numbers: 120/80, for example, is considered normal. The number on the top is systolic pressure—the highest pressure in your arteries, just after your heart contracts. The number on the bottom is diastolic pressure—the lowest pressure in your arteries, just before your heart contracts.

Prior to 1997, many physicians did not treat patients with mild hypertension. Although the Joint

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National Committee on High Blood Pressure recommended treating such individuals, the group acknowledged that reasonable doctors might disagree with this recommendation, observing that "in the absence of target organ damage (e.g., no eye, kidney, or heart problems) and other major risk factors, some physicians may elect to withhold antihypertensive drug therapy." But in 1997, the committee took a hard line and strongly advocated drug therapy for all patients with mild hypertension, regardless of their risk of cardiovascular disease.

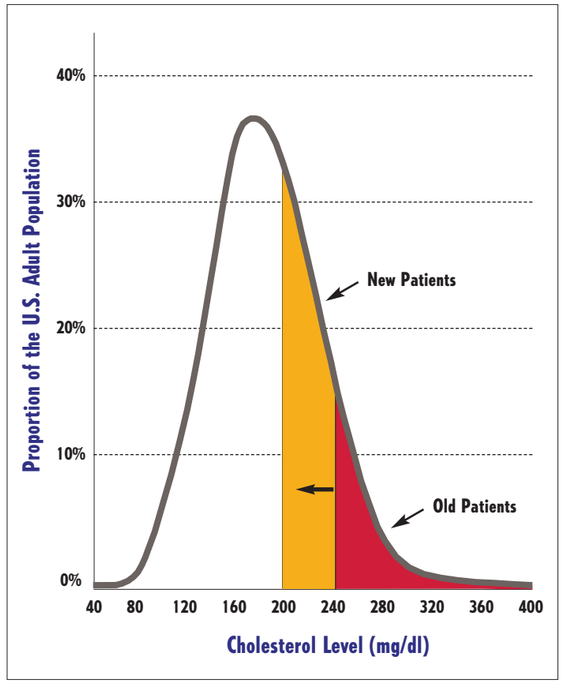
This stance effectively redefined the level of hypertension that requires pharmacologic treatment. Diastolic pressures above 90 mmHg (instead of 100) now required treatment. And systolic blood pressures above 140 mmHg (instead of 160) now required treatment. This apparently small change had a big effect. It meant an additional 13 million Americans met the criteria for antihypertensive therapy.

The same pattern played out with cholesterol. The definition of abnormal cholesterol has changed so often since I finished medical school that it is hard for me to keep track. The only thing that has been consistent is the direction of the change—always lower and lower thresholds to define cholesterol as abnormally high. Our bible in medical school was a book called *Harrison's Principles of Internal Medicine* (mine was the 8th edition; it is now in its 17th edition). My edition recommended that therapy be reserved for patients whose total cholesterol was over 300.

Soon the measurement of cholesterol got much more complex. We could measure various types of cholesterol: low-density cholesterol (known as LDL, the so-called "bad cholesterol") and high-density cholesterol (known as HDL, the so-called "good cholesterol"). Having subtyped cholesterol, we could develop ratios—LDL to HDL, LDL to total, and so forth. Recommendations were then tailored based on each patient's other risk factors for heart disease, such as smoking, high blood pressure, or a prior heart attack. While some of this made good sense—particularly being more aggressive in those who had already had a heart attack, for whom the benefit of lowering cholesterol is greatest—it resulted in a very complex set of recommendations.

Despite this complexity, by the mid-1990s large health-care organizations (such as the Department of Veterans Affairs, for which I work) had settled on defining a total cholesterol above 240 as being abnormal and warranting therapy.

Then in 1998, a major randomized trial changed things yet again. The Air Force/Texas Coronary Atherosclerosis Prevention Study demonstrated a reduction in what was called "first acute major coronary events" (a combination of fatal and nonfatal heart attacks, unstable angina, and sudden cardiac death) when what was then considered normal cholesterol was lowered from an average of 228 to 184. Over five years, about 5% of patients with untreated normal cholesterol had one of these events, while only 3% of patients with treated



This graph shows the distribution of cholesterol levels in adult Americans, and the effect of changing the numerical cutoff for high cholesterol from 240 to 200 mg/dl.

normal cholesterol did. Thus the chance of benefit was 2% (5% minus 3%). So for every 100 patients treated over five years, 2 were helped and 98 were not.

All of a sudden the threshold for abnormal total cholesterol fell from greater than 240 to greater than 200. This change affected a lot of people—an additional 42 million "new cases" of high cholesterol were created overnight. That's a big number—42 million people. You might wonder why so many people were affected. The graph above shows the pattern of cholesterol levels in American adults (statisticians call this the distribution of cholesterol in the population). A cholesterol of 200 is almost in the middle, just about average for the U.S. adult population. Moving the cutoff so close to the average had a huge effect on the number of people diagnosed.

You may notice something else in this graph: there are a lot more people with cholesterol in the 200-to-240 range than there are in the 240-to-280 range. And there are more people with cholesterol levels in the 240-to-280 range than there are in the 280-to-320 range. In other words, mildly abnormal cholesterol levels are much more common than markedly abnormal cholesterol levels. This is true for diabetes and osteoporosis and many other conditions as well. So an apparently small change in the cutoff can dramatically affect the number of people who are turned into patients. And as with diabetes and hypertension, people with mildly elevated cholesterol stand to benefit less from treatment than do those with severely elevated cholesterol. Lowering the cutoff for what is considered abnormal not only turns a large number of people into patients but also produces patients with the mildest form of the condition.

Osteoporosis, too

Then there's osteoporosis. My medical school classmates and I didn't think much about the early diagnosis of osteoporosis. It was a clinical diagnosis reserved for patients experiencing symptoms—usually painful, spontaneous fractures of the back (known as vertebral compression fractures). Osteoporosis is often referred to colloquially as "thinning of the bones." In fact, the word osteoporosis means that the bones (that's the *osteo-* prefix) become more porous. It's a process that invariably occurs as we age, although it is more rapid in some people than in others. In the past, frankly, doctors didn't have a reliable way to measure this process, so we focused instead on its clinical consequences.

Then bone mineral density testing came along. It is an x-ray of a specific bone (usually the spine, hip, or wrist). But it's not used to see if the bone is broken; it is used to measure how dense the bone is—that is, how much bone is there. The advent of this test allowed doctors to determine how dense people's bones are by using a T score. A T score quantifies the bone density of a patient compared to "normal"—which is defined as the average bone density of white women aged 20 to 29. (For this condition, women have historically been the focus.) If your bone density is the same as that of the typical 20- to 29-year-old white woman—regardless of your own age and ethnicity—then your T score would be 0. If your bones are a whole lot *denser* than average, your T score could be as high as 3. If your bones are a whole lot *thinner* than average, your T score could be as low as –3.

Negative numbers have a way of making things more difficult, so it is unfortunate that most women will have negative T scores. The reason is that most women who are tested for osteoporosis are considerably older than the group to which they are being compared. Because bones thin with age, older women generally have thinner bones than younger women. Thus, their T scores are typically less than 0. The World Health Organization originally defined osteoporosis as a T score of less than –2.5. It was an arbitrary number to pick. But they were correct in saying that women with T scores of less than –2.5 (farther from zero, that is—for example, –2.8) are at higher risk for fracture than women with T scores greater than –2.5 (closer to zero—for example, –2.2). Of course, this could be said about any cutoff: women with T scores less than 0 are at higher risk than women with T scores above 0, women with T scores less than –1 are at higher risk than women with T scores above –1, and so on.

Perhaps recognizing this, the National Osteoporosis Foundation in 2003 advocated treating all women with T scores of less than –2.0 for osteoporosis. The argument for expanding the definition was based on the observation that most hip fractures occurred in women whose bone densities were above a T score of –2.5. Now, you wouldn't think the difference between –2.5 and –2.0—a measly 0.5—would matter that much. But just as with cholesterol, mildly abnormal T scores are more common than markedly abnormal T scores. So perhaps you won't be surprised to learn that literally overnight, 6.7 million American women "developed" osteoporosis.

The table above summarizes what transpired after the thresholds were changed for four common

Americans Considered Diseased

Condition	Old Definition	New Definition	New Cases	Increase
Diabetes				
Fasting sugar 140 → 126	11,697,000	13,378,000	1,681,000	14%
Hypertension				
Systolic BP 160 → 140 Diastolic BP 100 → 90	38,690,000	52,180,000	13,490,000	35%
Hyperlipidemia				
Total cholesterol 240 → 200	49,480,000	92,127,000	42,647,000	86%
Osteoporosis in women				
T score –2.5 → –2.0	8,010,000	14,791,000	6,781,000	85%

This table shows how many people were turned into patients after the thresholds used to diagnose these four diseases were lowered in recent decades—millions and millions of "new cases" were created overnight.

In other words, mildly abnormal cholesterol levels are much more common than markedly abnormal cholesterol levels. This is true for diabetes and osteoporosis and many other conditions as well. So an apparently small change in the cutoff can dramatically affect the number of people who are turned into patients.

conditions. You can see how changing the cutoffs dramatically increased the number of people labeled with the conditions (and thus then said to require treatment). Whether or not that was a good thing for the affected individuals is a tough question. But there's no question about whether or not it was a good thing for business. These changes substantially increased the market for treatments—and the money to be made from them.

There are widespread concerns about the independence of the experts who set the cutoffs for these conditions and others. The head of the diabetes cutoff panel was a paid consultant to Aventis Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Merck, and Pfizer—all of which make diabetes drugs. Nine of the 11 authors of recent high blood pressure guidelines had some kind of financial ties—as paid consultants, paid speakers, or grant recipients—to drug companies making high blood pressure drugs. Similarly, eight of the nine experts who lowered the cholesterol cutoff were paid consultants to drug companies making cholesterol drugs. And the first cutoff for osteoporosis was established by a World Health Organization panel in partnership with the International Osteoporosis Foundation—an organization with a corporate advisory board consisting of 31 drug and medical equipment companies.

To be fair, many of these experts may be true believers, people who want to do everything they can not to miss anyone who could possibly benefit from diagnosis. But the fact that there is so much money on the table may lead them to overestimate the benefits and ignore the harms of overdiagnosis. These decisions affect too many people to let them be tainted by the businesses that stand to gain from them.

Problems with treatment

But let's say you don't care that cutoffs may have been lowered merely to make money. So what if doctors have expanded the definitions of these conditions and turned millions of Americans into patients? Some of these patients were destined to develop a disease—and suffer symptoms, complications, and even death. And some fraction of these people (but not all of them) could be helped by treatment initiated because of early diagnosis. No question about it—that's good, you might think.

But as a group, the additional patients who are diagnosed because of the lowered thresholds have the mildest abnormalities of any patients with the condition. That means they are at the lowest risk of developing the bad events associated with their conditions. So while some are destined to develop problems, most are not; those who would never have developed symptoms have been overdiagnosed and can only be harmed by diagnosis and treatment.

This is the tension inherent in the concept of overdiagnosis. A few people may be helped, a lot will be overdiagnosed, and some of them will be harmed. And no one knows who is in which group.

The conventional ethos of medicine has been to focus on the potential benefit for the few and to downplay the rest. So medical experts search for those who are plausibly at higher risk and then suggest that doctors should identify and treat them. But consider the best data to use when thinking about the trade-off: the data from randomized trials.

For cholesterol, the previously mentioned Air Force/Texas Coronary Atherosclerosis Prevention Study is a good example. It studied the effects of lowering near-normal cholesterol levels (levels between 200 and 240) in people without heart disease. Let's first focus on the people whose cholesterol was not treated (people randomized to the placebo group). Over five years, 5% of untreated patients had their first major heart events.

To get a sense of how much overdiagnosis happens, we need an estimate of the chance of an event occurring over a lifetime. That reflects the ultimate criterion for overdiagnosis: at the end of life, if the person never developed a problem from her condition, she has been overdiagnosed. To calculate the chance over a lifetime, I extrapolated the five-year experience to 24 years (the life expectancy of a 58-year-old, the average age of the people in the trial). This approach produces the following estimate: 22% of untreated patients in the trial would be expected to experience a first major heart event in their lifetimes. That means the other 78% were overdiagnosed.

You may be wondering how well treatment works over a lifetime (because cholesterol medicines are prescribed for a lifetime). After 24 years (if the benefit in the study persists), 14% of treated patients will have had a first major heart event (as compared with 22% of the untreated patients). That means that only 8% (22% minus 14%) would have been helped by treatment.

So, given these estimates, the table on the facing page explains the deal for patients with near-normal cholesterol: Diagnose and treat 100 patients, and 8 of them are winners—they are helped by treatment because they avoid a first major heart event. For 14 of them, the effort was all for naught—they have their first major heart events despite treatment (they are not overdiagnosed, but they are also not helped, and they may have experienced side effects from treatment). The remaining 78 are losers—they've been overdiagnosed. Even without treatment, none of them was going to have a heart attack.

Here are the same calculations for osteoporosis, using the data from another randomized trial: the Fracture Intervention Trial. It studied the effect of increasing near-normal bone density in women who had not had fractures previously. Over four years, 14% of untreated patients had symptomatic fractures—mostly compression fractures of the spine. Extrapolating to an 18-year period (the life expectancy of the typical woman in the trial, a 68-year-old), 49% of untreated women would have gotten fractures. That means 51% were overdiagnosed.

How does this work over a lifetime? After 18 years (if the benefit found in the study persists), 44% of treated women will have had fractures (compared to 49% of untreated women). So only 5% (49% minus 44%) are helped by treatment.

So, as shown by the table on page 35, if you diagnose and treat 100 patients, five of them are winners—they are helped because they avoid fractures. For 44 of them, the effort was all for naught—they have bad events despite treatment (they are not overdiagnosed, but they are also not helped, and they may have experienced side effects from treatment). The remaining 51 are losers—they have been overdiagnosed.

Would you take the offer of treatment or would you pass? There's no right answer. It's a tough call.

You might say, *Why* not *take it?* Well, there are really good reasons to avoid being overdiagnosed with diabetes and hypertension: you don't want either your blood sugar or your blood pressure to go too low. Is it bad to have a cholesterol level that's too low? We don't think so now, but we don't have any long-term data on this question. Some scientists are concerned because the human body needs some cholesterol to build and repair cells. The medications commonly used to lower cholesterol—a class of drugs called statins—are generally very safe. Sometimes a new one is withdrawn for health concerns (so try to stick with the old ones), and they all have a tiny risk of a big problem: the rapid breakdown of muscles. But by and large they are as good as medicines get—particularly for preventing a second heart attack.

Is it bad to have too high a bone density? I'd say probably not. But I'm even less sure of this, since we have less experience with the commonly used medications to increase bone density, a class of drugs called bisphosphonates. There is some concern about the long-term effects of these drugs; they may actually make bones more brittle by changing the bone architecture. They can also disturb calcium metabolism, lead to ulcers in the esophagus, and, very rarely, cause bone to die. Hopefully we'll know more with longer-term studies.

But the real downside of accepting all these changes in the rules of diagnosis is that it is a slippery slope that is turning more and more of us into patients. Too many of us are already on too many medications. To be sure, some people may feel safer having their potential problems diagnosed and treated. For some, that may make the treatment side effects and hassle factors seem worth it. But this sense of being safer is partly the product of powerful messages that have systematically overstated the benefits of the diagnosis and treatment of mild abnormalities and largely said nothing about the potential harms. Thus the sense of being safer is likely an exaggerated view of reality.

If 100 patients are diagnosed with just-above-normal cholesterol and are treated for their lifetimes, here's how many will be . . .

Winners	
(Treatment saved them from their first major heart events)	8
Treated for naught	
(They had first major heart events despite treatment)	14
Losers	
(They were overdiagnosed—treatment couldn't help them because they were never going to have heart events)	78

This table shows the effects of treating people diagnosed with a very mild form of a condition—in this case, high cholesterol: only a few are helped and the vast majority are overdiagnosed and may even be harmed.

And there's more to come

In 1997, the Joint National Committee on High Blood Pressure considered the creation of a new disease category: high-normal blood pressure, which would include people whose diastolic blood pressures ranged between 85 and 89 or whose systolic blood pressures ranged between 130 and 139. Then about 10 years later, high-normal blood pressure got a new name: prehypertension. A large randomized trial demonstrated that giving people with prehypertension medicines to lower their blood pressure reduced their chances of going on to develop hypertension. (Why am I not surprised? Of course taking blood pressure medication lowers blood pressure!)

The first two years of the randomized trial compared a treatment group (using a drug called candesartan) to a no-treatment group (using placebos). At the end of the two-year period, 14% of the treatment group had developed hypertension, while 40% of the no-treatment group had developed hypertension. That's a big difference—particularly when expressed as a "66% reduction" in the chance of developing hypertension. But of course this is going to happen—giving a drug that lowers blood pressure will indeed lower people's blood pressure

The real downside of accepting all these changes in the rules of diagnosis is that it is a slippery slope that is turning more and more of us into patients. Too many of us are already on too many medications. The sense that this is safer is likely an exaggerated view of reality.

and prevent many from developing hypertension. It tells you nothing about whether they benefit from the drug.

To be fair, the study did ask a second question. For the second two years, the randomized trial continued by giving both groups placebos. At the end of the four-year period, 53% of people in the group that had received treatment for two years had developed hypertension, versus 63% of the people in the group that had never received treatment. I'll admit—that's more interesting. It looks like treating for two years and then stopping leads to less hypertension than not treating at all. But the effect is small. And the bigger question remains: is it useful to prevent hypertension by treating the condition before it occurs? Why not wait and treat only those who develop hypertension? The important issue is whether treating prehypertension helps people avoid heart attacks, strokes, and death. We don't know whether treating prehypertension changes anybody's risk of heart attack, stroke, or death. But we do know that it's an enormous market—about 18 million new patients.

In 2002, the American Diabetes Association coined a new term—"prediabetes," meaning blood sugar levels that are higher than normal but not yet high enough to be diagnosed as diabetes. They said (and I have no reason to question this) that there were 57 million people in the United States with prediabetes. That's an even bigger market, with huge ramifications for overdiagnosis and overtreatment.

Low-cholesterol advocates are also looking to expand their condition: they now argue we should test children. The American Academy of Pediatrics says doctors should be performing cholesterol screening in kids who are overweight or who have parents with heart disease or high cholesterol. Because so many parents are diagnosed with high cholesterol, this will affect a lot of kids. Screening is supposed to start before age 10 but after age 2. Drug treatment is supposed to wait until age 8.

To their credit, experts at the National Osteoporosis Foundation have refined their guidelines for treating that disease. They have expanded the T score cutoff for treatment to –1.0, but they are clear that this by itself is not enough to warrant treatment. They say a patient should also have a greater than 3% chance of fracturing a hip in the next 10 years. This probability is calculated using a World Health Organization algorithm that has been adapted for the United States. That algorithm requires doctors to go to a website and enter the patient's age, weight, height, and T score. It also requires data about whether the patient smokes; uses steroid medications; has a prior history of fractures, rheumatoid arthritis, or any disorder strongly associated with osteoporosis; or has three or more alcoholic drinks per day. If the doctor scrolls down, he or she will find detailed definitions of each of these risk factors, which the doctor needs to understand before interviewing the patient. The doctor then interviews the patient and enters the data into the algorithm, and the computer does a series of calculations to determine the patient's chance of having a hip fracture in the next 10 years. If the number is higher than 3%, treatment is suggested.

This is a step forward in terms of better defining who is at high risk of fractures. But we really don't know whether this refinement helps because treatment hasn't been evaluated in women who have other risk factors in conjunction with a nearly normal bone density (such as a T score of –1.0). Furthermore, the recommendation is sufficiently complex and time-consuming that I wonder how many physicians will simply default to treating every woman with a T score less than –1.0. That would mean virtually all older women. And now there is a movement for treating osteoporosis in men . . .

Cascade of events

Lara lives on the outskirts of New York but regularly comes north to Vermont to escape the city; I've gotten to know her over the years during her northern visits. Lara is a healthy 65-year-old who nonetheless has managed to get entangled in quite a cascade of diagnosis and intervention.

(In case you are struck by the discrepancy in the way I've referred to "Lara" and "Mr. Roberts," the difference is that Lara is a friend, Mr. Roberts a patient. I've always addressed my patients using Mr., Mrs., or Ms., as I think it's an important way to show respect. My mother was pretty clear that she expected me to toe this line, since few things bothered her more than having some new doctor, a third her age, waltz in and say, "I'm Dr. X. How are you today, Katharine?")

Lara's cascade started when she was screened for osteoporosis almost a decade ago. Her bone mineral density test showed that her T score was –1.8. Although no one calls that osteoporosis (yet), her primary-care doctor told her she was at risk for fracture even though she had none of the aforementioned risk factors. (In a way, we are all at risk.) She was also told that treatment was both easy and effective.

She told me that her reaction at the time was *Why not?* So she was started on hormone replacement therapy, which has been shown to increase bone density and reduce the chance of fracture. She tolerated the medicine well. Then along came the major randomized trials of hormone replacement therapy that confirmed its beneficial effects on bone strength but also demonstrated some harmful effects—an increased risk of heart attack and stroke, and an increased risk of breast cancer. Her doctor suggested she stop that medication and instead try a different one for osteoporosis.

Lara was started on a bisphosphonate and did all right—for a while. Then she developed terrible pain when swallowing. She was referred to a gastroenterologist, who performed an endoscopy (a procedure in which a fiber-optic scope is passed through the mouth and into the stomach) and found that she had severe inflammation and ulcers in her esophagus—a known side effect of bisphosphonates. She was switched to another medicine. The esophagitis healed, but a painful rash appeared all over her body. So she was referred to a dermatologist, who suspected that the rash was due to the medication. The medication was stopped, and the rash went away.

Doctors couldn't figure out how to treat Lara; she had become a medical challenge. She was referred to an endocrinologist. Because osteoporosis is considered an endocrine disorder, endocrinologists are thought to be the experts in its treatment—just the people to care for an osteoporosis patient who is a medical challenge.

Lest you forget, Lara didn't even have osteoporosis. At worst, she had osteopenia (you can think of that as preosteoporosis). And she didn't have any of the risk factors that would make a fracture more likely. Ideally, the specialist would rethink the most fundamental question: is this a condition that warrants treatment? Based on Lara's T score and the absence of other fracture risk factors, her chances of having a fracture were low; consequently, the benefit of treatment would be small at best.

But the endocrinologist didn't raise this point; he was dealing with a medical challenge. So he conducted a thorough evaluation of all her glands and hormones. The evaluation included a careful physical exam of Lara's thyroid gland, and the endocrinologist thought he felt a lump. So Lara was referred to a radiologist, who did an ultrasound exam of her thyroid and found three lumps—the largest of which was about an inch in diameter. She had needles stuck in all of them and some fluid removed from each. Some of the cells in the fluid looked concerning under the microscope. The pathologist was worried that they might be cancer, but the only way to know for sure was to remove her thyroid. So she was referred to a surgeon.

Imagine that. You feel fine, but someone suggests a test to see how strong your bones are. The test shows your density is just a little below average for your age. But you are considered at risk for fracture and encouraged to take action. Three medications and three specialists later, you are told you might have thyroid cancer. Quite a cascade. At least there's a happy ending in this case. The surgeon Lara saw—I would say a prudent one—put a stop to this cascade of events. He knew that virtually all adults have some evidence of thyroid cancer. Most important, Lara is fine—I just saw her kayaking on the Connecticut River—but now she's a little more hesitant to look for things to be wrong.

I can't tell you how often these diagnosis-and-treatment cascades occur—no one keeps tabs on this sort of thing. But I can tell you that, while they won't happen to most people, they are not that uncommon. It's another downside to becoming a patient prematurely.

If 100 patients are diagnosed with just-below-normal bone density and are treated for their lifetimes, here's how many will be . . .

Winners	
(Treatment saved them from a fracture)	5
Treated for naught	
(They had a fracture despite treatment)	44
Losers	
(They were overdiagnosed—treatment couldn't help them because they were never going to have a fracture)	51

This table shows the effects of treating people diagnosed with a very mild form of another condition—in this case, osteoporosis: only a few are helped and the majority are overdiagnosed and may even be harmed.

Concluding thoughts

It is easy to argue that rules should be changed and numbers altered to redefine what is considered abnormal. A case can always be made that doing so could conceivably help a few more people. The discussion typically ends there. But even small changes can turn millions of people into patients. This can lead to an explosion of overdiagnosis and, in turn, an explosion of treatment. Even if a few people end up being helped, labeling large numbers of people as abnormal and thus as needing treatment is not something to be taken lightly. Small harms from therapy become magnified simply because so many people are exposed to them. Some, like Lara, get entangled in a cascade of diagnosis and treatment. We all have to wonder about the paradox of promoting health by encouraging policies that lead more people to view themselves as sick.

Unfortunately there is no scientific method or mathematical equation that will result in a single answer to the question of what should be defined as normal. But the practical reality is that the medical community is engaged in a relentless drive to change the rules in a way that is continuing to narrow that definition. ■

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