

Against Diagnosis

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The act of diagnosis requires that patients be placed in a binary category of either having or not having a certain disease. Accordingly, the diseases of particular concern for industrialized countries—such as type 2 diabetes, obesity, or depression—require that a somewhat arbitrary cut-point be chosen on a continuous scale of measurement (for example, a fasting glucose level >6.9 mmol/L [>125 mg/dL] for type 2 diabetes). These cut-points do not adequately reflect disease biology, may inappropriately treat patients on either side of the cut-point as 2 homogenous risk groups, fail to incorporate other risk factors, and are invariable to patient prefer-

ence. This article discusses risk prediction as an alternative to diagnosis: Patient risk factors (blood pressure, age) are combined into a single statistical model (risk for a cardiovascular event within 10 years) and the results are used in shared decision making about possible treatments. The authors compare and contrast the diagnostic and risk prediction approaches and attempt to identify the types of medical problem to which each is best suited.

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The concept of diagnosis is essentially binary: You either have a certain disease or you do not. Differential diagnosis, often considered to be the highest expression of a physician's art, is a matter of considering a list of possible diseases and then deciding that the patient has disease *a*, but not disease *b*, *c*, *d*, or *e*. Now consider the following set of diseases of particular concern for industrialized countries: cardiovascular disease; type 2 diabetes; obesity; depression; developmental disorders, such as autism and hyperactivity; back pain; arthritis; cancer; and HIV. We contend that, with the exception of HIV, all of these diseases are continuous, reflecting a range of severity, and that categorizing patients as either having or not having the disease depends on choosing a somewhat arbitrary cut-point of severity.

For example, the current definition of hypertension includes a systolic blood pressure of 140 mm Hg or higher. But of course, there is no particular biological relevance of 140 mm Hg, such that individuals with a blood pressure of 141 mm Hg qualitatively differ from those with blood pressure of 139 mm Hg. Similarly, there is no particular cut-point for blood lipid levels (such as 6.21 mmol/L [240 mg/dL] for cholesterol) or obesity (such as a body mass index of 30 kg/m²), such that everyone above the cut-point is in one homogenous risk category and everyone below it in another. Even arteriosclerosis is a matter of degree, because most adults have at least some level of endothelial dysfunction.

Type 2 diabetes is another good example of how a continuous end point is turned into a binary disease state. Fasting blood glucose level varies from individual to individual; patients with a fasting glucose level above 6.9 mmol/L (>125 mg/dL) are said to have diabetes. The corollary—6.8 mmol/L (124 mg/dL) is not a serious problem,

whereas 7.0 mmol/L (126 mg/dL) is the same as 10.3 mmol/L (185 mg/dL)—similarly has no biological basis.

The psychological and developmental disorders on our list of diseases are also a matter of degree. Such disorders are typically diagnosed by comparing a patient's symptoms or behaviors against a checklist. To receive a diagnosis of depression, for example, patients must have at least 5 symptoms for at least 2 weeks and a level of severity great enough to upset usual routines, seriously impair work, or interfere with relationships. But the choice of these 3 cut-points might reasonably be changed (what about 4 symptoms for 3 weeks?) and, accordingly, does not define a natural binary state of depression versus no depression.

What about cancer, one of the most feared diagnoses? Under the "multiple hit" theory, cancer is a continuous process: A cell undergoes a series of mutations as it moves through early stages of dedifferentiation (the preneoplastic lesion) to a local tumor and then on to metastatic disease. What we choose to define as "cancer" is thus a judgment call as to the stage of the carcinogenic process that we think is severe enough. This can vary from pathologist to pathologist (1) and also depends on the organ: A lesion that does not invade through the basement membrane is described as carcinoma if it occurs in the breast but not if it occurs in the prostate.

Moreover, many types of cancer are diagnosed long before they cause symptoms. Prostate cancer is a well-known example. A large proportion of men who die of causes other than cancer have detectable cancer on pathologic analysis of the prostate on autopsy—an estimate is 40% of men at age 70 years (2)—and yet only about 2% to 3% of deaths in men are caused by this disease (3). The best way to think about a diagnosis of localized prostate cancer, therefore, is as a risk factor for advanced prostate cancer and prostate cancer-specific death. Yet many men who are told that a low-risk prostate cancer is unlikely to harm them say: "I have cancer, I want it out." Indeed, one might speculate that if such tumors were called something other than "cancer," rates of unnecessary surgery and radiation therapy would decrease drastically. There is a name

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for this problem: overdiagnosis. In our view, one solution might be to avoid the concept of diagnosis altogether.

RISK PREDICTION AS AN ALTERNATIVE

Physicians often recommend mastectomy, a major surgical procedure, to some women without breast cancer, such as a young woman positive for *BRCA2*, but they advise a very minor procedure, excisional biopsy, for some women with active cancer, such as an older woman with comorbid conditions and carcinoma in situ. The reason is prediction: We predict that the *BRCA2*-positive woman is at high risk for dying of breast cancer, even though cancer has not been diagnosed; conversely, the older woman is at low risk for breast cancer morbidity or mortality.

We propose that thinking about disease in terms of risk prediction is often superior to thinking about disease in terms of diagnosis. The diagnostic approach to blood pressure is to divide the population into 2 groups, those with hypertension and those without hypertension, and then to treat one group but not the other. The prediction alternative is to use a statistical model to estimate the probability that a patient will have a clinically important event, such as a myocardial infarction, within a certain period, such as 10 years. Blood pressure would be one of the predictors in this particular model; others might include cholesterol, diabetes, age, sex, and smoking history. One could then compare the risk predictions at the patients' current blood pressure and then assume some reduction in blood pressure associated with treatment. Typically, one might find that a younger man with few risk factors other than a systolic blood pressure of 145 mm Hg is at very low risk for a serious cardiac event, and his level of risk is barely affected by a change in blood pressure. Conversely, an older male smoker with high cholesterol and a similar blood pressure is at high risk, and he would have substantially decreased risk if blood pressure could be reduced.

What we are describing is the statistical model developed on the basis of the Framingham Heart Study (sometimes known as the Framingham Risk Calculator). This shows that prediction modeling can be implemented readily by using available data and technology. Indeed, many guidelines for the treatment of hyperlipidemia incorporate risk prediction, mandating more aggressive control of lipid levels in patients at predicted higher risk (4).

Prediction models have 2 particular advantages over our standard way of thinking about diagnosis. First, traditional cut-points are invariable to patient preference. For example, we might think of using a higher-than-usual cut-off for a patient who had troublesome side effects from treatment. But how does one choose an appropriate value of, for example, blood pressure in light of the side effects? A prediction model provides probabilities of events, and a patient can weigh these according to his or her preferences: It makes sense to ask patients whether they would accept treatment for a 2% vs. a 4% absolute reduction in the risk

for a cardiovascular event, but not whether 150 or 160 mm Hg is a more appropriate treatment threshold given poor drug tolerance.

Second, prediction models can incorporate multiple patient characteristics. A patient with high blood pressure benefits more from control of cholesterol than does a patient with normal blood pressure. For prostate cancer, the situation is reversed, with the patient at high risk for cardiovascular death less likely to benefit from prostatectomy, because he is more likely to die before his cancer progresses sufficiently to affect his survival or quality of life.

This point is likely to become more important with the development of molecular and genomic markers in the next few years. Physicians should presumably be more aggressive in treating blood pressure in a patient at high genomic risk for myocardial infarction and less aggressive if some other marker, such as one for inflammation, was favorable. It is difficult to know how to incorporate such markers into a diagnosis without making diagnostic subcategories exponentially more complex as each new marker becomes available. Conversely, adding a new marker to a multivariable model makes little difference to the clinical consultation.

The risk prediction approach is not new to the practice of clinical medicine. Physicians have traditionally called on multiple variables to risk-stratify patients in the clinic, usually weighting each variable on the basis of their clinical experience and judgment. For example, a patient with a mildly elevated cholesterol level might be recommended dietary discretion and exercise, whereas the same patient might be prescribed a statin if there was a family history of heart disease. Moreover, many of the diseases discussed now include some measure of risk stratification, such as "prediabetes," different "stages" of hypertension, and overweight/obese/morbidly obese categories. The use of prediction models, however, adds a quantitative estimate to general risk groupings and to physicians' informal processes of risk adjustment. The models guide the physician to the variables that should have the greatest influence on management choices. Furthermore, prediction models give physicians explicit information to use in shared decision making with patients, such as the risk for heart attack with or without treatment.

WHY DIAGNOSE?

The clinical literature is replete with case histories demonstrating diagnostic conundrums solved by a senior physician with unusual acumen or by application of a sound medical principle. Here is a recent example from the *New England Journal of Medicine*: A woman presents with malaise and yellowing of the eyes. The physicians make a preliminary diagnosis of an intrahepatic cholestatic disorder. Shortly afterward, the woman experiences a rash, which, in combination with a point from her history (unprotected sex with an unfaithful partner 5 months previ-

ously), suggests syphilitic hepatitis. This is confirmed by a blood test and treated with antibiotics, leading to resolution of all symptoms and abnormalities (5). Or take a missed diagnosis much in the news at the time of writing: Groopman (6) explains a case where he treats chest pain with antacids, leading a patient to die of a torn aorta.

Such cases share several characteristics. First, unlike many of the disorders discussed above, there is an unambiguous finding that can place the patient in a binary category of either having the disorder or not having it: A physician can see syphilis under the microscope, but we have yet to identify a lesion underlying, for example, depression. Accordingly, there is no need for a quantitative prediction: The physician does not give a percentage probability of syphilis—a number that could conceivably be shifted up or down were new markers or genomic information to become available—he or she gives a binary diagnosis. Second, once the diagnosis is made, the course of treatment is unambiguous: Syphilis is easily cured by antibiotics, and a torn aorta can be treated surgically. As a corollary, patient preference plays no important role. Two men may make different decisions about prostate cancer treatment because they weigh the benefits of extended life relative to the risks for sexual and urinary dysfunction differently. But the harms of untreated syphilis or a torn aorta cannot seriously be compared with those of antibiotics or surgery.

CHALLENGES FOR THE RISK PREDICTION APPROACH

Despite its benefits, prediction modeling is arguably more difficult to implement in clinical practice than the diagnostic approach. For example, if a physician is given a blood pressure measurement, it is easier to classify patients as having hypertension or not and prescribe treatment ac-

cordingly than to enter blood pressure into a computer, calculate a predicted risk, explain what this risk means to the patient, and then make a shared decision on treatment. Moreover, the risk prediction approach depends on the availability of a good prediction model—ideally, one that has been evaluated using decision analysis methods to determine its effects in clinical terms. Although some cases have shown that use of a prediction model to determine treatment would lead to better patient outcomes (7–9), most prediction models have been evaluated only with respect to their accuracy (9, 10). Whether use of a prediction model, even a relatively accurate one, would improve an outcome is not entirely clear. More widespread use of prediction modeling in medical decision making would therefore require fuller integration of prediction models with clinical information systems; a better understanding of how quantitative information on risk should be used in the consultation; more prediction models based on large data sets; and decision analysis studies demonstrating whether use of a prediction model would improve clinical outcome.

CONCLUSION

Despite our provocative title, we are not against diagnosis. Diagnosis does and always will play a central role in clinical medicine. Nonetheless, we argue that an approach based on risk prediction can be of greater value for many diseases of greatest concern to industrialized countries. The Table shows typical characteristics of disorders best dealt with diagnosis or risk prediction. Syphilitic hepatitis or a torn aorta does indeed need to be diagnosed. But these disorders are a good deal less common than those best suited to a risk prediction approach—such as cancer, cardiovascular disease, and diabetes. Classification of these more complex disorders exists on a continuum, which can

Table. Comparison of Typical Features of Diagnostic and Risk Prediction Approaches

Variable	Diagnosis	Risk Prediction
Approach	Patients are given a diagnosis: Either they have the disease or they do not	Patients are given a probability of a future event
Example	Syphilitic hepatitis	Cardiovascular event within 10 years
Lesion	Unambiguous	Nonexistent or equivocal
Example	Torn aorta	Depression
Treatment effectiveness	Often highly effective	Helpful, but patients may have event with treatment or avoid the event even if untreated
Example	Antibiotics for syphilis	Statins for high cholesterol level
Course of treatment	Dictated by diagnosis	Open to discussion
Example	Surgical treatment of a torn aorta	Treatment of early-stage prostate cancer
Patient preference	Generally of minor importance	Often of major importance
Example	Antibiotics for syphilis	Treatment of early-stage prostate cancer
Symptoms	Patient has distressing symptoms	Patient is often asymptomatic: Disorder is a risk factor for a future event
Example	Syphilitic hepatitis	Hyperlipidemia

perhaps be best understood in terms of risks for associated outcomes, based on multiple variables. If we are to deal most effectively with the diseases currently of greatest importance to industrialized countries, it is surely time for us to move beyond the binary, diagnostic thinking that has dominated medicine for so long and embrace a quantitative approach to patient management.

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