

# In clinical practice, more information is not always good: The problem of overdiagnosis

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## ■ INTRODUCTION

The definition of disease is not as straightforward as it may seem. The combination of signs and symptoms, together with interpretation of the results of confirmatory ancillary tests, allows us to have a probabilistic estimate of disease but we can never be absolutely sure that a non-ambiguous clinical entity is in play.

This is because of the clinical uncertainty of biological phenomena, which makes the interpretation of the components of a clinical history so difficult: a present symptom can be typical of a disease that the patient in fact does not have (a false positive) or is absent in a disease that the patient indeed has (a false negative). Irrespective of the diagnostic characteristics of a test (or a symptom, or a sign) – its sensitivity and specificity, its likelihood ratios – there exists no test that can discriminate 100% of the time between disease and its absence.

Another problem is, of course, the definition of “normal”.

It would be nice if the frequency of all the data collected on a patient or a healthy person were distributed in a such a way that would allow us to differentiate between normal and abnormal every time. But of course this is not the case (except for some genetic conditions), because diseases are progressive with smooth evolution from low to high values (in nephrology, the paradigmatic case is creatinine measurement to detect chronic kidney insufficiency) and the frequencies almost always overlap between both groups<sup>1</sup>.

What criteria should then be used to divide normal from abnormal?

Classically there are three criteria that have proven useful:

1. Abnormal equals being unusual. This is a statistical definition: for example, by convention, we call abnormal all values beyond 2 standard deviations from the mean of the average values of a test, gathered in a sample of non-diseased people. One immediate consequence is that, assuming a normal (bell-shaped) distribution, 2.5% of the findings are considered abnormal, but in fact there is no disease present (the findings came from a normal individual).
2. Abnormal equals being ill. Distinguishing normal from disease means that we consider abnormal all observations that are associated with a risk of having, or developing, some disease, or increase the possibility of dying.
3. Abnormal equals being treatable. Here we say that abnormality is present when treatment leads to a better clinical outcome (note that not every condition conferring an increased risk can be successfully treated). This makes intuitive sense, especially for asymptomatic pathologies (where we should not treat a condition that is causing no problems), but even in symptomatic patients it may be worth pausing before treating when we are faced with a situation in which we do not know how to interpret the clinical findings. For example, with the new, more powerful, imaging techniques at our disposal we are detecting things which are hard to interpret as being (or not) a cause of our patient's symptoms.

Having defined some fairly good basis for abnormality – and this is just a simple approach; there is much more to it – we can now turn to the problem of overdiagnosis.

## OVERDIAGNOSIS

The definition of overdiagnosis can be found in a paper from Moynihan et al.: "...overdiagnosis happens when a diagnostic label is applied to people with mild symptoms or at very low risk of future illness, for whom the label and subsequent treatment may do more harm than good<sup>2</sup>." This means that overdiagnosis medicalizes more people and therefore induces overtreatment i.e. unnecessary interventions that do more harm than good.

There are several causes and drivers of overdiagnosis<sup>3,4</sup>: increased sensitive biomarker testing, technological changes detecting smaller and smaller abnormalities, commercial and professional interests, potential legal punishment for missing the diagnosis (but not overdiagnosis), health system model of business (more tests and treatments bring in more income), cultural beliefs in preventive measures (faith in early detection) and a tenet for good clinical practice being "more is better". However, the most important factor is changing disease and treatment thresholds by expert panels producing expanded disease definitions (the number one criteria above).

The modulating of threshold levels of laboratory or imaging tests can significantly modify the prevalence of disease. One classical example is the ever-changing reference values in clinical practice guidelines (CPG), based on more or less clear evidence of the benefit of lowering thresholds for initiating treatment. In so doing, experts from the CPG committees suddenly change the absolute number – and therefore the prevalence – of the subjects considered at risk. One consequence is that all of a sudden there is now an all-new group of patients eligible for treatment.

The tendency to reduce the diagnostic threshold has been prevalent in many diseases. Looking at some prevalent risk factors and diseases we can appreciate the problem:

1. Diabetes. For many years the diagnostic value for diabetes mellitus was a fasting blood glucose of 140 mg/dL. But in 1997 the American Expert Committee on the Diagnosis and Classification of Diabetes Mellitus decided to lower this value to 126 mg/dL. In so doing, almost two million people became diabetic literally overnight.
2. Hypertension. For a long time, there was no recommendation to treat mild hypertension without target organ damage. However, in 1997 (definitely a bad year!) the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advocated the treatment of these patients, regardless of their baseline cardiovascular risk<sup>5</sup>, labelling almost 14 million patients as new cases of hypertension.
3. Hyperlipidaemia. The classical approach was to treat total cholesterol above 300 mg/dL. This value has been steadily decreasing as the basis for drug intervention, especially after the publication of the AFCAPS/TexCAPS trial which defined a target value of 240 mg/dL, based on an absolute risk reduction of 2% (meaning that out of 100 patients subjected to therapy two would benefit but 98 would not)<sup>6</sup>. When the value was once again later reduced to 200 mg/dL, almost 43 million patients were suddenly eligible to take a statin (an increase in prevalence of 86% in a single shot!).
4. Osteoporosis. Bone mineral density testing, through comparisons with young healthy women, produces a T-score defined as abnormal by the

### Table

The effect of lowering diagnostic thresholds

CONDITION Change in the lab or imaging threshold value	Disease prevalence			
	Old definition	New definition	Number of new cases	Absolute increase
<b>DIABETES</b> <i>Fasting blood sugar: 140 to 126 mg/dL</i>	11 697 000	13 378 000	1 681 000	14%
<b>HYPERTENSION</b> <i>Systolic BP: 160 to 140 mmHg Diastolic BP: 100 to 90 mmHg</i>	38 690 000	52 180 000	13 490 000	35%
<b>HYPERLIPIDAEMIA</b> <i>Total cholesterol: 240 to 200 mg/dl</i>	49 480 000	92 127 000	42 647 000	86%
<b>OSTEOPOROSIS</b> <i>T-Score -2.5 to -2.0</i>	8 010 000	14 791 000	6 781 000	85%

Adapted from<sup>8</sup>.

WHO when its value is below 2.5. When the American National Osteoporosis Foundation suggested lowering the T-score to less than -2.0, almost 7 million American women “developed” osteoporosis<sup>7</sup>.

In the table below we can see the effect of lowering these diagnostic thresholds in terms of increased disease prevalence.

Of course this problem is not exclusive of laboratory data. For example, between 1975 and 2012 the incidence of thyroid cancer tripled, but the death rate did not change. This rise is best explained by increased imaging testing with better definition than by a real change in cancer incidence<sup>9,10</sup>.

## ■ OVERDIAGNOSING CHRONIC KIDNEY DISEASE

Is nephrology free of this problem?

Not really.

In a recent paper, Moynihan et al. commented on the 2012 definitions (updated from 2002) of chronic kidney disease. Based largely on laboratory measurements of kidney function and the belief that identifying chronic kidney disease early slows progression towards kidney failure, the new definition labelled 1 in 8 adults (around 14%) as having chronic kidney disease. Before 2002 the prevalence in the US was not well defined due to lack of a consistent definition but one study suggested a figure of 1.7% of the population. If this increase in prevalence to 12.3% is false, then we have a problem that many of those diagnosed will never progress to symptomatic forms of kidney disease, but will have the psychological effect of a disease label and the burden and costs of repeated evaluation, testing and potentially unnecessary treatment. The authors conclude by saying that “...Clinicians should be sceptical about the current definition of chronic kidney disease and cautious about labelling patients, particularly older people.”<sup>11</sup>

## ■ CONCLUSIONS

In all medical specialties, overdiagnosis is a problem worth tackling. One should be very careful to not harm people who effectively have no disease.

To do this we must be alert to the possibility of overdiagnosis, for example when incidence increases while mortality stays the same, the shifting in diagnostic definitions or thresholds with no evidence that benefits are greater than harms and labelling of a risk factor or biomarker to sound like a disease.<sup>12</sup>

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