Overdiagnosis of Disease

A Modern Epidemic

MOST OF US LEARNED THAT BRAIN HERniation is about as close to death as a living patient can get. But a clinically important proportion of patients with head computed tomography (CT)-defined herniation are awake and alert (personal communication, Kelli O'Laughlin, MD, MPH, December 1, 2011).[1,2] Is herniation far less grave than we have always thought? Does this mean that we need to order even more CT scans so as not to miss "occult" herniation in normal-appearing patients?

Tsai et al[3] provide evidence that the case fatality rate in pulmonary embolism (PE) has diminished markedly over time. Given the absence of any new therapy to explain improved outcomes, and the fact that the absolute number of deaths from PE is essentially unchanged, it seems clear that the use of highly sensitive newer technologies has resulted in increased diagnosis of "cases" in which the risk is much less than it was when PE was diagnosed primarily in patients with severe cardiopulmonary symptoms.[4] Pulmonary embolism is a model for the modern phenomenon of overdiagnosis—the "true-positive" identification of a condition that now takes on a meaning very different than what we have traditionally understood that condition to imply.

This phenomenon is certainly not unique to PE—there are multiple examples of overdiagnosis that arise when technology, rather than clinical findings, are the catalyst for finding disease. Sophisticated technology has identified many other cancers that similarly exist in these two very different forms—one of which is truly "malignant," while the other does not act at all like "cancer" as humankind has always known it.[5] Prostate cancer can be highly lethal, but widespread screening has identified a huge reservoir of cases that are technically "prostate cancer" but have an entirely different clinical trajectory; few such cases would have any clinical consequence if the "cancer" had never been identified. Ultrasensitive troponins will now identify many patients with "myocardial infarction" (MI)—patients for whom MI would previously have been ruled out—with unclear consequences.[6] Every time a new and more sensitive test becomes the standard for diagnosing a disease (or even a "predisease"), it changes both the definition of that disease and, most importantly, the balance between harm and benefit derived from treatment.

Advocates of ever more sophisticated technology suggest that this is all for the good. After all, as Prasad et al[4] point out, physicians have always believed it critical not to miss *any* cases of PE, and that goal is much more likely to be achieved when such sensitive testing is done.[4] We believe, however, that identifying clinically occult cases that can be found only by sophisticated technologies is unlikely to confer much benefit, and is certain to lead to substantial harm.[7]

Increased reliance on CT scanning owing to concerns about missing a potentially fatal disease has led to a massive increase in the number of PE cases diagnosed. This has both medical and economic costs, including not only diagnostic irradiation and adverse effects of treatment, but also the transformation of *people* into *patients*, a proliferation of false-positive test results (that increase in proportion to the increase in testing), and the identification and subsequent workup of incidentalomas. Many of these harms also accrue to individuals who are tested and found not to have PE; this already extremely large group, which cannot benefit from testing, grows exponentially as we keep lowering the threshold for testing because each generation of scanners finds even smaller PEs "missed" by clinical judgment.

These concerns are relevant to reliance on technology in general, but are massively exacerbated by *overdiagnosis*.[5] For most conditions, the benefit of a given treatment is *relative*, reducing bad outcomes in a percentage of patients who have the condition. Treatments also produce harm, usually in a *fixed* percentage of those treated, independent of whether they have the disease for which the treatment was intended. For example, consider a new antibiotic, "gorillacillin." Although gorillacillin is so toxic that it kills 10% of those who receive it, it is tremendously beneficial among patients with the dreaded "infectiosis," decreasing mortality from 50% to 25%. Gorillacillin is less attractive, however, when only 20% of treated patients actually have infectiosis; the 10 lives saved among the 20 patients who would have died are completely offset by the 10 drug-related deaths among 100 patients treated.

As problematic as this is when diagnosis is difficult—such that many treated patients do not actually have the target disease—it is a *massive* problem following overdiagnosis. Imagine that all 100 patients actually have infectiosis, but 90% were diagnosed by sophisticated tests performed despite the absence of the classic fearsome symptoms of infectiosis, "just to be sure"—such that precious few have the deadly form of the disease. Since virtually none of these 90 were at risk of dying,

gorillacillin would save 5 of the 10 truly at risk, but by killing 10, it would cause net harm! Overdiagnosis inevitably means that many individuals are subjected to the potential harms of treatment while being afforded almost none of its benefits.

While we chose these numbers for the sake of simplicity, the actual numbers for the modern approach to PE yield precisely the same conclusion—we are harming more than we are helping.[7]

Finally, the more we overdiagnose "diseases" that do not have the same consequences of their older, clinically identified relatives, the more uncertain we will be about what to do when we find them. This is already familiar, for example with regard to *watchful waiting* for screen-identified prostate cancer. Now imagine the ultimate iteration of our modern romance with technology—suppose that someone invents a CT scanner with electron-microscopic resolution that is able to find microscopic clots. Almost everyone tested with this marvelously "advanced" machine would test "true positive," since intravascular clotting is a routine phenomenon in normal life.[8-10] Would such information be beneficial, by identifying "disease" early? Or would such knowledge actually be catastrophic, raising questions we simply cannot answer?

So what is to be done? First, we strongly support the recommendation of Prasad et al[4] to change the funding of clinical trials. As long as someone is selling a test or a treatment the use of which increases in proportion to the number of disease cases diagnosed, we will be prodded to overdiagnose and then to overtreat.[4] Second, we must recognize the enormous difference between a disease that presents clinically and "the same" disease that is found only because we have decided to search for it, in the absence of compelling clinical concern. Finally, we must question the notion that as technology advances, it always provides improved solutions to clinical problems. On the contrary, we believe that medicine's growing faith in technology and "objective" tests to supplant clinical judgment—coupled with the inevitable technologic advances that are more and more able to diagnose conditions of less and less clinical meaning—is already one of the most critical problems that we face and will only become increasingly hazardous in the future.

Jerome R. Hoffman, MA, MD
Richelle J. Cooper, MD, MSHS

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Author Affiliations: Department of Emergency Medicine, Keck School of Medicine, University of Southern California, Los Angeles (Dr Hoffman); and Department of Medicine/Emergency Medicine, University of California, Los Angeles (UCLA), School of Medicine (Drs Hoffman and Cooper).
Correspondence: Dr Cooper, UCLA Emergency Medicine Center, 924 Westwood Blvd, Ste 300, Los Angeles, CA 90024 (Richelle@ucla.edu).
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