

NANCY HO, MD

Division of Gastroenterology,
Department of Medicine,
University of Maryland, Baltimore

JULIE KIM, MD

Department of Medicine,
Northwestern University,
Chicago, IL

VINAY PRASAD, MD

Medical Oncology Branch, National
Cancer Institute, National Institutes
of Health, Bethesda, MD

Dense breasts and legislating medicine

RECENTLY, NEVADA,¹ NORTH CAROLINA, and Oregon joined a number of other US states (as of this writing, nine other states) in enacting laws that require informing women if they have dense breast tissue detected on mammography.² Laws are pending in other states. Federal legislation has also been introduced in the US House of Representatives.

See related commentary, page 761

■ THE POWER OF ADVOCACY TO CHANGE MEDICAL PRACTICE

One such bill³ was introduced as a result of the advocacy of a single patient, Nancy Cappello, a Connecticut woman who was not informed that she had dense breasts and was later found to have node-positive breast cancer.⁴

While new medical practices are rarely credited to the efforts of single physician or researcher, these “dense-breast laws” show the power a single patient may play in health care. The evidence behind these laws and their implications bring to the forefront the role of advocacy and legislation in the practice of medicine.

Dense-breast laws are the latest chapter in how legislative action can change the practice of medicine. Proof that advocacy could use law to change medical practice emerged in the early 1990s in the wake of AIDS activism. Patient-advocacy activists lobbied for early access to investigational agents, arguing that traditional pathways of clinical testing would deprive terminally ill patients of potentially lifesaving treatments. These efforts led the US Food and Drug Administration (FDA) to create the Accelerated Approval Program,

which allows new drugs to garner approval based on surrogate end-point data for terminal or neglected diseases. Accelerated approval was codified into law in 1997 in the FDA’s Modernization Act.⁵ In 2012, legislative action further broadened the ability of the FDA to approve new products based on surrogate data,⁶ with the FDA’s Safety and Innovation Act, which provides for first-time approval of a drug based on “pharmacologic” end points that are even more limited.⁶

Although proponents have declared success when legislative action lowers the bar for drug and device approval, independent analyses have been more critical. In 2009, accelerated approval underwent significant scrutiny when the Government Accountability Office issued a report summarizing 16 years of the program.⁷ Over the program’s life span, the FDA called for 144 postmarketing studies, but more than one-third of these remained incomplete. Moreover, in 13 years, the FDA never exercised its power to expedite the withdrawal of a drug from the market.

Many accelerated approvals have created considerable controversy. Bevacizumab for metastatic breast cancer was ultimately found to confer no survival benefit, and its approval was revoked.⁸ Gemtuzumab ozogamicin for acute myeloid leukemia may be effective, but not at the dose that was approved.⁹ And midodrine hydrochloride and many other drugs remain untested.¹⁰

■ DOES THIS INFORMATION HELP PATIENTS? WHAT WOULD THEY DO WITH IT?

The question with dense-breast laws is similar to that facing other legal efforts to change medicine: Does it actually help patients? Will the information doctors disclose lead to appropriate interventions that improve health

Like accelerated drug approval, mandating disclosure of breast density is an intervention with uncertain efficacy

The views and opinions of Dr. Prasad do not necessarily reflect those of the National Cancer Institute or the National Institutes of Health.

doi:10.3949/ccjm.80a.13048

outcomes, or, instead, lead to cascades of testing and biopsies that worsen overdiagnosis?

Like accelerated approval, mandating disclosure of breast density is an intervention with uncertain efficacy. While increased breast density has been shown to increase a woman's risk of developing breast cancer, it is also neutral regarding a woman's chances of dying of breast cancer.¹¹ In other words, it does not identify patients who experience aggressive disease.

Next comes the larger question of what women would do with this information. Will they simply be more compliant with existing screening recommendations, or will they seek additional testing? This is where the greatest uncertainty lies. The utility of additional testing with ultrasonography or magnetic resonance imaging (MRI) remains uncertain in this population. We will certainly find more cancers if we use MRI to screen women, but it remains unclear if this translates to improved outcomes.

A recent study shows just this.¹² In Connecticut, breast density notification is mandatory, as is insurance coverage for screening (or whole-breast) ultrasonography. Since the passage of these laws, the Yale Medical Center has screened 935 women with dense breasts using ultrasonography. Over this time, they performed roughly 16,000 mammograms; thus, the breast density law applied roughly to 1 out of 16 (6.25%) studies. Of the 935 women, biopsies were performed in 54 (5.8%). These were mostly needle biopsies (46), but 3 patients underwent surgical excision, and five cysts were aspirated. From these efforts, two sub-centimeter cancers were found and one case of ductal carcinoma in situ was found. Thus, only 3.7% of women undergoing biopsy and fewer than 1% of women undergoing ultrasonography were found to have cancer.

Of course, given the nature of this study, we cannot know what would have happened without referral and testing. However, empirical research suggests that detecting a breast cancer with screening does not mean a life was saved.¹³ In fact, only a minority of such women (13%) can credit screening with a survival gain.¹³

In a study¹⁴ that compared women with dense breasts who underwent annual vs biannual screening, no difference in the rate of

advanced or metastatic disease was seen with more frequent screening, but the rates of false-positive results and biopsies were higher.¹⁴

Notably, dense-breast legislation comes at a time when fundamental questions have been raised about the impact of screening on breast cancer. A prominent study of trends in US breast cancer incidence and death rates over the last 30 years shows that even under the most favorable assumptions, mammography has led to a huge surplus in the diagnosis of breast cancer but little change in the breast cancer mortality rate.¹⁵ It is entirely possible that more-aggressive screening in women with dense breasts will only exacerbate this problem. Advocacy may harm rather than help these patients.

We are often told that laws such as the dense-breast bills are motivated by the public's desire and patient advocacy. However, we are unsure if the vocal proponents of dense-breast laws represent the average women's desires. These efforts may simply be another case of how a vocal and passionate minority can overcome a large and indifferent majority.¹⁶

■ LEGISLATING MEDICAL PRACTICE IS A BOLD STEP

Dense-breast laws present an additional challenge: they cannot be changed as quickly as scientific understanding. In other words, if the medical field comes to believe that notification is generally harmful because it leads to increased biopsies but not better health, can the law be changed rapidly enough to reflect this? There is a large precedent for the reversal of medical practices,^{17,18} particularly those based on scant evidence, including cases of recommended screening tests (most notably, recent changes to prostate-specific antigen guidelines). But in all these other cases, law did not mandate the practice or recommendation. Laws are often slow to adapt to changes in understanding.

Legislating medical practice is a bold step, and even those who feel it is occasionally warranted must hold themselves to a rational guiding principle. We have incontrovertible evidence that flexible sigmoidoscopy can reduce the number of deaths from colorectal cancer, but no state mandates that doctors

Dense-breast laws remind us that good intentions may be necessary for sound policy, but are not sufficient

inform their patients of this fact. A patient's ejection fraction serves as a marker of benefit for several lifesaving drugs and devices, yet no state mandates that physicians disclose this information to patients after echocardiography.

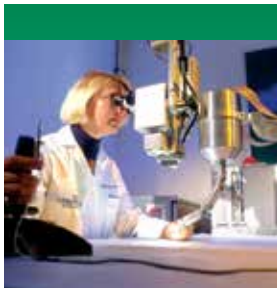
All of us in health care—physicians, research-

ers, nurses, practitioners, and patients—are patient advocates, and we all want policies that promote human health. However, doing so means adhering to practices grounded in evidence. Dense-breast laws serve as a reminder that good intentions and good people may be necessary—but are not sufficient—for sound policy. ■

REFERENCES

1. **Nevada Legislature.** Requires the notification of patients regarding breast density. (BDR 40-172). <http://www.leg.state.nv.us/Session/77th2013/Reports/history.cfm?ID=371>. Accessed November 7, 2013.
2. **ImagingBIZ Newswire.** Nevada Governor Signs Breast Density Law. June 10, 2013. <http://www.imagingbiz.com/articles/news/nevada-governor-signs-breast-density-law>. Accessed August 1, 2013.
3. **Are You Dense Advocacy.** H.R.3102 Latest 112th Congress. Breast Density and Mammography Reporting Act of 2011 <http://www.congressweb.com/areyoudenseadvocacy/Bills/Detail/id/12734>. Accessed November 7, 2013.
4. **The New York Times.** New Laws Add a Divisive Component to Breast Screening. <http://www.nytimes.com/2012/10/25/health/laws-tell-mammogram-clinics-to-address-breast-density.html?pagewanted=all>. Accessed November 7, 2013.
5. **Reichert JM.** Trends in development and approval times for new therapeutics in the United States. *Nat Rev Drug Discov* 2003; 2:695–702.
6. **Kramer DB, Kesselheim AS.** User fees and beyond—the FDA Safety and Innovation Act of 2012. *N Engl J Med* 2012; 367:1277–1279.
7. **US Government Accountability Office (GAO).** New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints. GAO-09-866. <http://www.gao.gov/products/GAO-09-866>. Accessed November 7, 2013.
8. **Ocaña A, Amir E, Vera F, Eisenhauer EA, Tannock IF.** Addition of bevacizumab to chemotherapy for treatment of solid tumors: similar results but different conclusions. *J Clin Oncol* 2011; 29:254–256.
9. **Rowe JM, Löwenberg B.** Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug. *Blood* 2013; 121:4838–4841.
10. **Dhruva SS, Redberg RF.** Accelerated approval and possible withdrawal of midodrine. *JAMA* 2010; 304:2172–2173.
11. **Gierach GL, Ichikawa L, Kerlikowske K, et al.** Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. *J Natl Cancer Inst* 2012; 104:1218–1227.
12. **Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE.** Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology* 2012; 265:59–69.
13. **Welch HG, Frankel BA.** Likelihood that a woman with screen-detected breast cancer has had her “life saved” by that screening. *Arch Intern Med* 2011; 171:2043–2046.
14. **Kerlikowske K, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium.** Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. *JAMA Intern Med* 2013; 173:807–816.
15. **Bleyer A, Welch HG.** Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012; 367:1998–2005.
16. **New York Review of Books.** Facing the Real Gun Problem. <http://www.nybooks.com/articles/archives/2013/jun/20/facing-real-gun-problem>. Accessed November 7, 2013.
17. **Prasad V, Gall V, Cifu A.** The frequency of medical reversal. *Arch Intern Med* 2011; 171:1675–1676.
18. **Prasad V, Cifu A, Ioannidis JP.** Reversals of established medical practices: evidence to abandon ship. *JAMA* 2012; 307:37–38.

ADDRESS: Vinay Prasad, MD, Medical Oncology Branch, National Cancer Institute, National Institutes of Health, 10 Center Dr. 10/12N226, Bethesda, MD 20892;
e-mail: vinayak.prasad@nih.gov



LET US HEAR FROM YOU

- Let us hear your opinions about the *Cleveland Clinic Journal of Medicine*.
- Do you like current articles and sections?
- What topics would you like to see covered and how can we make the *Journal* more useful to you?

PHONE 216.444.2661
FAX 216.444.9385
E-MAIL ccjm@ccf.org
WWW <http://www.ccjm.org>

CLEVELAND CLINIC JOURNAL OF MEDICINE
Cleveland Clinic
1950 Richmond Rd., TR404
Lyndhurst, Ohio 44124

