

U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0134 for "Mammography Quality Standards Act: Amendments to Part 900 Regulations"

To Whom It May Concern:

We appreciate the opportunity to comment on the proposed rule pertaining to the Mammography Quality Standards Act. As an evidence-based patient advocacy organization, the National Breast Cancer Coalition (NBCC) deems it imperative that health care policy be guided by high-level scientific evidence. As such, NBCC raises a number of concerns regarding the proposed rule change, specifically around the breast density notification proposal.

Problem #1: Variability/Unreliability in Breast Density Measurement. There is considerable variability and subjectivity among radiologists in classifying breast density of patients. Studies have shown that density status is reclassified on subsequent examination for 1 in 5 women (23%) by the same radiologist, and for 1 in 3 women (33%) by a different radiologist.¹

Dense breasts are defined by how they appear on a mammogram using the American College of Radiology's (ACR's) Breast Imaging Reporting and Data System (BIRADS). This system classifies breasts as "almost entirely fatty," "scattered fibroglandular densities," "heterogeneously dense," or "extremely dense." With these classifications, approximately 43 percent of all women between the ages of 40 and 74 years have dense breasts (either "heterogeneously dense" or "extremely dense"). This system leads to significant variations and does not benefit women.

Problem #2: Increase in Harm to Women and Costs to Society. The additional screening resulting from the notification contemplated will result in harm to women and significant unnecessary cost to the system. There is no concomitant benefit. Much of the push for notification is based on the assumption that a mammogram is less likely to "find" a lump in dense breasts, and therefore a woman who has dense breasts should undergo additional screening following a normal mammogram. But to what benefit? One recent analysis² examined the impact in New Jersey of density reporting requirements on the use of additional screening following normal mammograms in women with high density breasts. It demonstrated a 651 percent increase in the use of

¹ Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst.* 2014;106.

² Sanders LM, King AB, Goodman KS. Impact of the New Jersey Breast Density Law on Imaging and Intervention Volumes and Breast Cancer Diagnosis. *J Am Coll Radiol.* 2016 Oct;13(10):1189-1194.

ultrasounds for supplemental screening, and a 59 percent increase in the use of breast MRIs. This presents huge cost implications for the U.S. health care system when one considers how common dense breast are (43% of all women).³

While these additional imaging procedures may detect a small number of cancers missed by mammography, they will also dramatically increase the number of false-positive results which lead to additional procedures, including unnecessary biopsies and their associated risk. And we can't ignore the potential risks that supplemental screening modalities themselves pose to patients, such as the use of gadolinium contrast required for breast MRI. Gadolinium-based contrast agents have been associated with nephrogenic systemic fibrosis in patients with acute kidney injury or chronic kidney disease,⁴ and more recent research has shown that IV gadolinium exposure may be associated with neuronal tissue deposition, even in patients with normal renal function.⁵ Likewise, supplemental screening by digital breast tomosynthesis results in additional breast radiation exposure.⁶

Problem #3: Increased Overdiagnosis. This proposed national rule change will almost certainly expand the already too high rate of breast cancer testing and overdiagnosis⁷ (~20%)—the identification of slow-growing, harmless cancers that won't kill a person and don't need to be found and treated in the first place—with resulting overtreatment. This is simply unacceptable absent solid evidence of benefit in patient-relevant survival outcomes. It may benefit the medical imaging community and oncologists, but not women in general.

Problem #4: Increased Breast Density Does Not Increase a Woman's Risk of Dying From Breast Cancer. The FDA justifies this proposed rule change by citing its own Regulatory Impact Analysis⁸, which claims that there will be a cost savings from implementing this rule change because of improvements in morbidity and mortality that would result. There simply is no evidence to support this claim. In fact, scientific studies have shown that among women ultimately diagnosed with breast cancer, increased breast density is not related to breast cancer death.^{9 10 11 12 13}

³ Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst.* 2014;106.

⁴ Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ. Gadolinium-based contrast agents: A comprehensive risk assessment. *J Magn Reson Imaging.* 2017 Aug;46(2):338-353.

⁵ McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology.* 2015 Jun;275(3):772-82.

⁶ Miglioretti DL, Lange J, van Ravesteyn N, et al. Radiation-induced breast cancer and breast cancer death from mammography screening. AHRQ Publication no. 14-05201-EF-5. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

⁷ Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness. *N Engl J Med.* 2016 Oct 13;375(15):1438-1447.

⁸ Mammography Quality Standards Act; Amendments to Part 900 Regulations; Preliminary Regulatory Impact Analysis Initial Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis.

<https://www.regulations.gov/document?D=FDA-2013-N-0134-0081>. Accessed June 11, 2019.

⁹ Siu AL. Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2016;164(4):279-296.

¹⁰ Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. *J Clin Oncol.* 2009;27(36):6124-6128.

¹¹ Kuhl CK, Strobil K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. *Radiology.* 2017;283(2):361-370.

¹² Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA.* 2012;307(13):1394-1404.

¹³ 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(16):1218-1227.

In 2012, investigators¹⁰ actually studying this question using data from the Breast Cancer Surveillance Consortium (BCSC) concluded that high mammographic breast density is not associated with increased risk of death from breast cancer or death from any cause after accounting for other patient and tumor characteristics. Likewise, in 2018 another group of researchers using data from the Population-Based Research Optimizing Screening Through Personalized Regimens (PROSPR) consortium similarly demonstrated that breast density is not associated with breast cancer that has a poorer prognosis.¹⁴ Both of these studies are consistent with the U.S. Preventive Services Task Force (USPSTF) conclusions in the comprehensive synthesis it prepared on this topic in 2016.⁸ Thus, the requirement to provide notification about the status of breast density lacks any supporting evidence to do so, and in such a limited context is likely to be confusing, anxiety-provoking, and not at all informative for patients.

Problem #5: Why Just This Risk Factor? While evidence suggests that high breast density may slightly increase breast cancer risk (but again, not mortality), there are many known risk factors, most of which, like density, cannot be changed. Moreover, breast density ranks much lower in terms of absolute risk compared to other risk factors: age, family history, obesity, genetics. Notifying patients about their breast density elevates this one risk factor out of context. Additionally, women receiving normal or low breast density assessments may erroneously be given a false sense of security and not consider their other more important individual risks... assuming of course they can do something about them, other than worry.

If This Rule Change Is Implemented: FDA must involve educated advocates in determining how to respond to this Congressional mandate, including the drafting of ANY information that will be provided to patients. Moreover, information to be included in the lay summary that is ultimately given to patients must explain the limitations of mammography and other screening modalities, the potential for overdiagnosis and overtreatment and the fact that there is no evidence that information about breast density would lower risk of getting or dying of breast cancer... or have any benefit at all.

Respectfully,



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¹⁴ McCarthy AM, Barlow WE, Conant EF, et al; PROSPR Consortium. Breast cancer with a poor prognosis diagnosed after screening mammography with negative results. *JAMA Oncol.* 2018;4(7):998-1001.