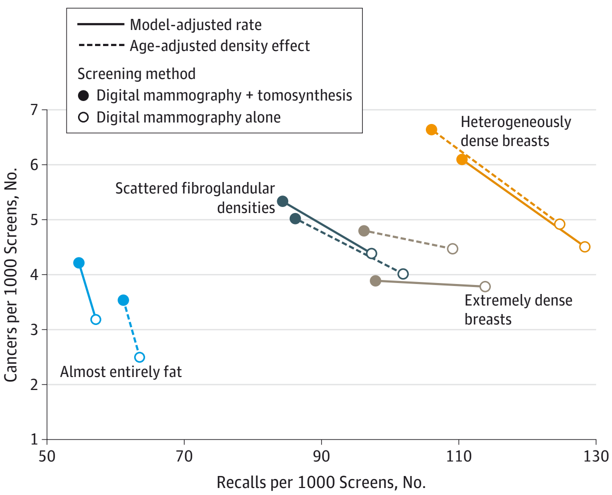
Figure. Combined Change in Recall and Cancer Detection Rates for Digital Mammography vs Digital Mammography Plus Tomosynthesis for Each Breast Density Category



The model-adjusted rate was adjusted for screening method and site. The density effect was adjusted for age to account for the potential confounding effect of age on breast density.

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Content, Readability, and Understandability of Dense Breast Notifications by State

Along with their screening mammogram results, women in nearly half of US states also receive notifications of breast density, a result of legislation intended to assist in making personalized decisions about further action. Dense breasts can mask cancer on mammography (masking bias), and are an independent cancer risk factor, but evidence does not yet indicate whether or what supplemental screening is appropriate. Rather, risk stratification is proposed to determine who may benefit from supplemental screening (eg, magnetic resonance imaging for women at high risk).[1,2]

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The text of dense breast notifications (DBNs) may affect women's ability to understand their message. We examined DBN characteristics across states to inform future policy.

Methods | We reviewed the laws requiring DBNs for states with legislation effective as of January 1, 2016 (except Delaware, whose legislation language was not sufficiently detailed to analyze DBN content). In most states, the legislation specified the exact language for DBNs. We compared the content, readability, and understandability of DBNs across states. We noted the mandates and required recipients stated in the laws and whether the DBNs addressed masking bias, density as a cancer risk factor, and supplemental screening. We measured readability using the Flesch-Kincaid reading grade level in MS Word (range: theoretical lower bound, −3.4; no upper bound) and the Dale-Chall readability grade score (range, ≤4 to ≥16).[3] Understandability was assessed using the Patient Education Materials Assessment Tool (PEMAT; range, 1% to 100%).[4] We obtained the proportion of adults in each state lacking basic prose literacy skills from available statistics,[5] comparing DBN Flesch-Kincaid readability with state population literacy level.

Results | Twenty-four states require DBNs as of January 1, 2016; we analyzed all but Delaware. Most states (n = 21, 91%) mandate specific language (**Table**); 4 states (17%) only mandate required components. Seven states (30%) require a generic DBN for every woman receiving a screening mammogram, whereas all others only require notification to those with dense findings. All DBNs mention masking bias, 18 (86%) mention the association with increased cancer risk, and 14 (67%) mention supplemental screening as an option, advising women to consult their physician. Of 14 DBNs requiring mention of supplemental screening, 6 (43%) inform women that they might benefit from such screening; 4 mention specific modalities.

Flesch-Kincaid readability levels ranged from grades 7 to 19.4 (mean, 10.5), most exceeding the recommended readability level (grades 7-8); about 20% of the population reads below a grade 5 level.[5] Dale-Chall readability grade scoring[3] produced slightly higher scores overall (grade range: 9-10 to 13-15). All DBNs scored poorly on understandability (PEMAT; range, 11%-33%). There was widespread discordance between states' DBN readability and corresponding basic literacy levels (**Figure**). Only 3 states' DBN readability level was at the grade 8 level or below; some of the highest readability levels occurred in states with the lowest literacy levels.

Discussion | We found wide variation in 23 states' DBN content, with most having readability at the high school level or above, poor understandability, and discontinuity with states' average literacy. Such problems may create uncer-

Table. Characteristics of Dense Breast Notifications (DBNs) for 23 US States That Passed Legislation[a]

		DBN Content Assessment					DBN Reading Grade Level		
	Date Legislation Became Effective	Mandate Language[b]	Masking Bias[c]	Increased Risk of Cancer[d]	Generic Language for Everyone[e]	Supplemental Screening[f]	Flesch-Kinkaid Scale[g]	Dale-Chall Scale[h]	DBN PEMAT Assessment, %[i]
Connecticut[j]	10/1/2009	✓	✓		✓	✓[k]	19.4	9.4/13-15	11
Texas	9/1/2011	✓	✓		✓	✓	13.1	8.7/11-12	11
Virginia	6/1/2012	✓	✓	✓		✓	8.5	8/11-12	33
New York	1/19/2013	✓	✓	✓		✓	7.2	7.7/9-10	33
California[l]	4/1/2013	✓	✓	✓			8.2	8.2/11-12	22
Alabama	8/1/2013	✓	✓	✓		✓	7.2	7.7/9-10	33
Maryland	10/1/2013	✓	✓	✓	✓		11.7	9.5/13-15	33
Tennessee	1/1/2014	✓	✓	✓			8.2	8.2/11-12	22
Hawaii	1/1/2014	✓	✓	✓		✓	7.9	8.2/11-12	22
Nevada	1/1/2014	✓	✓	✓		✓			
Oregon	1/1/2014	✓[m]	✓	✓		✓			
North Carolina	1/1/2014	✓	✓	✓			9.3	7.5/9-10	20
Pennsylvania	1/30/2014	✓	✓	✓	✓		10.3	9.4/13-15	20
New Jersey[j]	5/1/2014	✓	✓	✓	✓		11.1	7.4/9-10	33
Minnesota	8/1/2014	✓	✓	✓			12.6	9.1/13-15	20
Rhode Island	10/1/2014	✓	✓	✓		✓[k]	10.7	7.9/9-10	30
Arizona	10/1/2014	✓	✓	✓		✓	9.4	7.9/9-10	10
Missouri	1/1/2015	✓	✓		✓	✓	13.1	8.7/11-12	11
Massachusetts	1/1/2015		✓	✓		✓			
Ohio	3/19/2015	✓	✓				10.4	8.7/11-12	22
North Dakota[n]	4/9/2015		✓	✓					
Michigan	6/1/2015	✓	✓	✓		✓	8.4	8.4/11-12	22
Louisiana	1/1/2016	✓	✓		✓	✓	14.2	8.8/11-12	11

Abbreviations: MRI, magnetic resonance imaging; PEMAT, Patient Education Materials Assessment Tool.

[a] Excluding Delaware, whose legislation was implemented on December 15, 2015, but whose dense breast notification content requirements were not sufficiently detailed to analyze here.

[b] Mandate language indicates that the state mandates the specific language to be used in the notification.

[c] Masking bias indicates that the state requires that the notifications mention that breast density may mask cancer on a mammogram.

[d] Increased risk of cancer refers to states that require that the notifications indicate this specific risk.

[e] Generic dense breast notification sent to all mammogram recipients, regardless of breast density.

[f] Supplemental screening indicates that the state mandates that the language at least mention the possibility of supplemental screening.

[g] Flesch-Kinkaid reading level was assessed in Microsoft Word (scale range: theoretical lower bound, −3.4; no upper bound).

[h] Dale-Chall readability scale score range: grade levels, 4 or lower to 16 or higher.

[i] The PEMAT assessment evaluated understandability of the DBN (scale range, 1% to 100%).

[j] Denotes states that also mandated insurance coverage for supplemental screening.

[k] Specifically mentions the types of supplemental screening available (ultrasound and MRI).

[l] Legislation expires on January 1, 2019.

[m] Only for women with extremely dense breasts.

[n] Legislation expires on July 31, 2017.

tainty for women attempting to make personalized decisions about supplemental screening and may exacerbate disparities in breast cancer screening related to low health literacy.[6] Many DBNs appropriately encourage discussions and shared decision making between patients and physicians. The lack of evidence regarding supplemental screening may contribute to variation in DBN content and to physician difficulty explaining results and conducting personalized risk assessments. These findings add to other expressed concerns regarding DBN reporting laws.[2]

This analysis was limited by its focus on DBN text, with no data on relevant outcomes (anxiety, supplemental screening usage, or additional cancers detected). State-level literacy data were not available by sex; however, sex differences in literacy have not been detected.[5]

Efforts should focus on enhancing the understandability of DBNs so that all women are clearly and accurately informed about their density status, its effect on their breast cancer risk, and the harms and benefits of supplemental screening.

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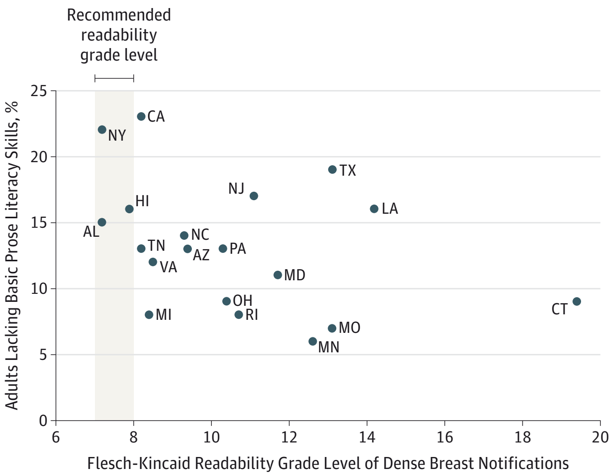
Figure. Adult Dense Breast Notification (DBN) Literacy Among 19 States



The Flesch-Kinkaid reading level scale has a theoretical lower bound of −3.4 and no upper bound.

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Correction: This article was corrected for errors in the Table, Figure, and text on May 12, 2016.

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Author Contributions: Drs Kressin and Gunn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Kressin, Gunn.
Drafting of the manuscript: Kressin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gunn.
Administrative, technical, or material support: Gunn, Battaglia.
Study supervision: Gunn, Battaglia.

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COMMENT & RESPONSE

TP53 Gene and Cancer Resistance in Elephants

To the Editor Dr Abegglen and colleagues proposed that the occurrence of multiple copies of the *TP53* gene in elephants may be an evolutionary innovation associated with cancer resistance in pachyderms.[1] These extra *TP53* copies have been described as alleles of the "ancestral" *TP53* gene. However, according to the Genetics Home Reference curated by the US National Library of Medicine, the word *allele* refers to "one of the alternative versions of a gene at a given location (locus) along a chromosome."[2] Copies of a given gene, such as the multiple *TP53* copies found in elephants, should be referred to as paralogous genes, or paralogs.[3] Alleles represent the range of biological variation of a gene in a species, including deleterious alleles responsible for mendelian disorders, whereas most paralogs perform separate biological functions, are expressed in different tissues or at different developmental stages (for example, the genes encoding globin proteins[4]), or both. Therefore, suggesting that African elephants possess "40 *TP53* alleles"[1] is not only semantically incorrect but also biologically inaccurate.

To add confusion, these extra *TP53* copies are often referred to as "retrogenes" in the article. Retrogenes are protein-coding copies of other genes that originate through a process known as gene retroposition.[5] However, new copies of the African elephant *TP53* appear to have lost the ability to encode a complete p53 protein and thus represent pseudogenes or, more appropriately, retropseudogenes.[5]

In the article, Dr Abegglen and colleagues proposed 2 mechanisms for a potential role of *TP53* copies in the p53-dependent apoptosis response to DNA damage despite their limited coding capacity. First, retropseudogenes could encode p53 fragments that act as decoys for protein repressors of the full-length p53 protein. The finding that one of these fragments binds to mouse double minute 2 homolog (Mdm2) seems to support this mechanism. However, this has been shown only for the retropseudogene 9 construct expressed in transfected human HEK293 cells. The binding of peptides encoded by *TP53* retropseudogenes to Mdm2 has yet to be demonstrated in vivo in elephant cells, and the expression of any *TP53* retropseudogene peptide in vivo remains unproven. The second mechanism points to the possible action of *TP53* retropseudogene mRNAs as decoys for micro-RNAs targeting transcripts of the ancestral *TP53* gene and is entirely speculative. Although the discovery of multiple *TP53* retropseudogenes in animals with apparent cancer resistance is intriguing, evidence of a causal link between extra *TP53* copies and cancer suppression is yet to be offered.

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