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Accuracy of clinical breast examination's abnormalities for breast cancer screening: cross-sectional study

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ABSTRACT

Objectives: The guidelines for breast cancer screening with clinical breast examination (CBE) are diverging CBE is recommended in France, whereas it is not recommended in the United States and Canada, given the lack of clear benefit and the risk of overmedication. To assess the accuracy of abnormalities found during CBE for in breast cancer screening.

Study design: A cross-sectional study included women over 18 years with no history of breast cancer coming for a mammography at 3 ambulatory radiology practices in Paris. A questionnaire collected the risk of breast cancer on mammography according to the Breast Imaging-Reporting And Data System (Bi-RADS) (high risk: Bi-RADS 4 or 5 *versus* lower risk: other Bi-RADS categories), the risk factors for breast cancer and the breast clinical abnormalities (none, mass, skin abnormality, oedema, pain, nipple discharge, lymph nodes . . .) For each abnormality, sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated.

Result: Among the 3218 included patients (mean age 55.1 +/-10 years), 713 (22.2%) had an abnormal CBE and 133 (4.1%) had high-risk mammography. The sensitivity of CBE was 36%[28%;45%] and the specificity was 78%[77%;80%]. The PPV and NPV for each clinical abnormality were low, except for nipple discharge, retraction and lymph nodes, for which the PPV were 10.5[3.7;29.9], 6.6[1.4;31.6], and 5.0[1.5;17.1], respectively, but these abnormalities were rare (0.5%, 0.2% and 0.5% respectively). These values were similar across all age groups.

Conclusion: The accuracy of CBE for breast cancer screening appeared to be low which did not support recommending regular CBE in France.

Introduction

Breast cancer was the most common cancer among women and the leading cause of cancer mortality among women in France in 2012 [1]. The management of risk factors and the implementation of prevention and screening actions are essential to prevent the progression of this pathology and reduce breath cancer mortality [2,3]. Thus, the French Health Authority (Haute Autorité de Santé, HAS) recommended an annual clinical breast examination (CBE) performed by a general practitioner or a gynecologist for women from 25 years, possibly combined with mammography follow-up according to breast cancer risk factors as part of individual screening. For the individual screening, patients were referred by a physician, mostly general practitioner or gynaecologist, for a mammography because of an abnormal CBE or because of an estimated higher risk of breast cancer regardless the result of the CBE. In addition, from the age of 50, patients were invited every 2 years to undergo a mammography screening by an organized screening. They automatically receive a mammography prescription from the French healthcare system. With this national program, 7,5% cancer were diagnosed in 1000 screened women in 2011–2012 [4] These recommendations for screening and follow-up with annual CBE have been in place for many years now based on the fact that breast cancer may be asymptomatic or manifested by the presence of one or more clinical abnormalities [5]. Thus, French women 50 and 74 years can undergo mammography with the organized screening or with the individual screening instead, if they request it to their doctor even with a normal CBE.

However, Canadian and American guidelines no longer recommend systematic CBE, although any symptomatic patient should be assessed promptly by a mammography [6,7]. In fact, some studies found that there was no clear benefit of regular CBE and that it could lead to over-diagnosis, over-treatment and iatrogenic complications [8,9].

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Thus, the clinical relevance of systematic CBE is little studied and its efficacy has not been demonstrated. We hypothesis that CBE might not be reliable enough to be recommended for breast cancer screening in France. The objective of our study was to assess the diagnostic accuracy of the clinical abnormalities found during CBE, performed by a physician, as part of the breast cancer screening.

Materials and methods

A multicenter, cross-sectional study included consecutively women over 18 years who came to perform mammography in 3 radiology practices in Paris between July 2017 and January 2018. The mammography could be indicated because the patients were involved in the organized screening, or in an individual screening (replacing the organized screening or because of a higher individual risk of breast cancer) or because of an abnormal CBE. Patients were informed of the study using an information sheet and consent was obtained prior to mammography. Patients with a personal history of breast cancer were excluded from our study. If necessary, the radiologists could, according to their current practice, complete the mammography with an ultrasonography.

A medical questionnaire completed by the radiologist collected the age of the patient, the screening method (individual or organized screening), the abnormalities found with the CBE just before the mammography (none, breast mass, skin retraction, oedema, erythema, orange peel, ulceration, pain, nipple discharge, lymph nodes, other), personal and family history of breast cancer, number of pregnancies, and the risk of breast cancer assessed according to American College of Radiology criteria (Bi-RADS) after the mammography [10,11]. In this study, 15 radiologists included patients and conducted clinical examination just before the mammography. They were specialised in senology and qualified to perform CBE.

The primary outcome was the Bi-RADS score for each mammography. This risk of breast cancer was reclassified as high risk of malignancy for Bi-RADS 4 and 5, and lower risk for other Bi-RADS categories (Bi-RADS 0, 1, 2 and 3).

As the prevalence of abnormal mammography was 12% [12] and the CBE sensitivity was estimated to be near 60% [13,14], we needed to include 3100 patients to reach an absolute precision of 0.05 with α equal to 5% according to Buderer's formula [15].

Univariate analyses between breast cancer risk and explanatory variables were performed with Chi-2 tests or Fisher's test for categorical variables, and Student tests for continuous variables.

The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), as well as the positive (LR+) and negative (LR-) likelihood ratios for each of the clinical abnormalities as a function of malignancy risk were calculated for all patients and according to patient age. We considered that LR + and LR- significantly contribute to the diagnosis when they were over 5 and below 0.1, respectively. Statistical analyses were performed using the R software (http://cran.r-project.org/).

Patients could refuse to participate or withdraw their consent at any time. The study protocol was approved by the Institutional Review Board of CPP SUD EST 1 (IRB No 2018-24 Paris Descartes RIPH 3). The study did not receive any funding.

Result

During the inclusion period, 3218 women were included (Fig. 1). Their median age was 55 years (Interval Interquartile (IQR)= [48–63]), 957 patients (29.7%) were under 50 years of age, 2190 (68.1%) were between 50 and 74 years, and 71 (2.2%) were over 74 years of age (Table 1).

In our patients, 713 (22.2%) had an abnormal clinical examination. The main abnormalities found in women with abnormal CBE were breast masses in 469 patients (14.6%), breast pain in 126 patients (3.9%), nipple discharge in 16 women (0.5%), axillary nodes in 17 patients (0.5%) (Fig. 1).

According to table 1, 133 women (4.1%) had a high-risk mammography for breast malignancy. Among these women with

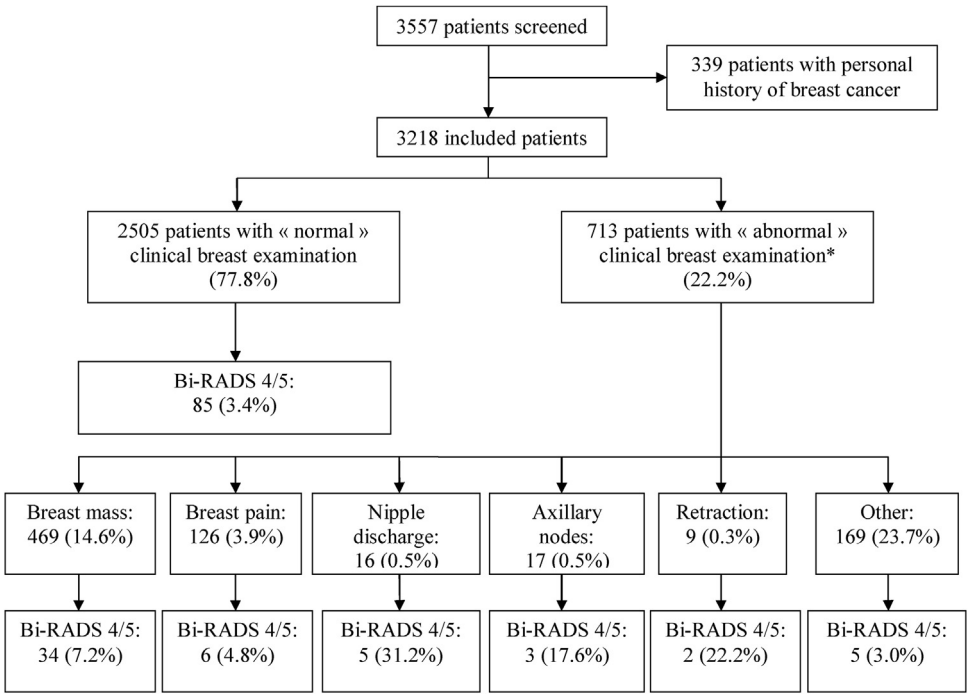

Fig. 1. Flow chart describing the patients and their clinical abnormalities.
*Patients could have more than one abnormality.

Table 1
Characteristics of patients depending on the mammography result.

	Overall population N = 3218 n(%)	High risk N = 133 n(%)	Lower risk N = 3085 n(%)	p
Patients characteristics				
Age mean (standard deviation)	55.1 (10.4)	53.8(12.4)	55.2 (10.3)	0.15
Organised screening	512 (15.9%)	18 (13.5%)	494(16.0%)	0.52
Familial history of breast cancer	1285 (39.9%)	48 (36.1%)	1237 (40.1%)	0.40
History of benign breast neoplasm	420 (13.1%)	26 (19.5%)	394 (12.8%)	**0.03**
Nulliparous	885 (27.5%)	46 (34.8%)	839 (27.3%)	0.07
Clinical breast examination				
Any clinical abnormality[a]	713 (22.2%)	48 (36.1%)	665 (21.6%)	**<0.01**
≥ 2 clinical abnormalities[a,b]	88 (2.7%)	8 (6.0%)	78 (2.5%)	**0.02**
Breast mass	469 (14.6%)	34(25.6%)	435 (14.1%)	**<0.01**
Pain	126 (3.9%)	6 (4.5%)	102 (3.9%)	0.64
Nipple discharge	16 (0.5%)	5 (3.8%)	11 (0.4%)	**<0.01**
Axillary nodes	17 (0.5%)	3 (2.3%)	14 (0.5%)	**0.03**
Retraction	9 (0.3%)	2 (1.5%)	7 (0.2%)	0.05
Erythema	5 (0.2%)	0	5 (0.2%)	1
Œdema	2 (0.1%)	2 (1.5%)	0	**<0.01**
Other	116 (3.6%)	3 (2.3%)	113 (3.7%)	0.63

[a] Clinical abnormalities could be: mass, retraction, oedema, erythema, orange skin, ulceration, pain, nipple discharge, axillary node, other (including breast erythema, breast oedema, hematoma, varicose veins).
[b] Among these 88 women, 2 patients had 3 abnormalities and had a high risk mammography.

high-risk mammography, 48 (36.1%) had abnormal CBE, compared to 665 (21.6%) among those with low to moderate risk mammography ($p < 0.01$). Associated factors with a high-risk mammography in multivariate analysis were the presence a mass (OR = 1.8; 95% Confidence Interval (95%CI)=[1.1;2.7]; $p = 0.01$), a nipple discharge (OR = 11.3; 95%CI=[3.5;32.0]; $p < 0.01$), a lymph node (OR = 6.3; 95%CI=[1.7;20.2]; $p < 0.01$), and nulliparous status (OR = 1.5; 95%CI=[1.0;2.1] ; $p = 0.04$).

Patients performing mammography with the individual screening had more abnormal CBE compared to patients in organized screening (24.3% *versus* 10.7% ; $p < 0.01$) but they did not have a more high-risk mammography (4.2% *versus* 3.5% ; $p = 0.52$).

In the overall population, CBE sensitivity was 36% (95%CI=[28%; 45%]) and its specificity was 78% (95%CI=[77%; 80%]). LR + and LR- were low 1.7 (95%CI= [1.3; 2.1]) and 0.8 (95%CI=[0.7; 0.9]), respectively. Concerning the presence of breast mass, the results were similar: the sensitivity was 26% (95%CI=[18%; 34%]), the specificity 86% (95%CI= [85%; 87%]). Sensitivity and specificity for nipple discharge were 4% (95%CI=[1%; 9%]) and 100% (95%CI=[99%; 100%]), for retraction 2% (95%CI=[0%; 5%]) and 100%(95%CI=[100%; 100%]), and for axillary nodes 2% (95%CI=[0%; 6%]) and 100% (95% CI=[99%; 100%]), respectively. Their LR + were 10.5 (95%CI=[3.7; 29.9]), 6.6 (95%CI=[1.4; 31.6]) and 4.97 (95%CI=[1.5; 17.1)], respectively but these clinical abnormalities were very rare (Table 2).

Among women under 50 years, CBE sensitivities were low, ranging from 2 to 38%, while specificities were good, between 73% and 99%. However, likelihood ratios were, between 0.4 and 8.1 for LR + and between 0.9 and 1.0 for LR- (Table 3).

In patients aged from 50 to 74 years, the overall results were similar. Sensitivities ranged from 1% to 36%, and specificities were between 80% and 100%. LR + were high for nipple discharge and retraction (LR+ = 17.4 ; 95%CI=[2.9; 102.5] for both) (Table 4).

For patients the 71 patients aged over 74 years, the results were similar for any CBE abnormalities combined: the sensitivity was 29% [4%; 19%], the specificity 88% [77%; 94%], the PPV 20% [3%; 56%] and the NPV 92% [82%; 97%], the LR + 2.3 (95%CI=[0.6; 8.7]) and the LR- 0.8 (95%CI = 0.5; 1.3]). The small numbers of patients over 75 years did not allow analysing each clinical abnormality individually.

Discussion

Summary

In this study, 22% of all patients had an abnormal clinical examination and 11% among patients involved in the organized screening. CBE abnormalities had a good specificity (between 78% and 100%) and a poor sensitivity (36% to 0%) in the included population to detect high risk mammography, which was an original and relevant outcome for clinicians. Indeed, for any anomaly combined, the sensitivity of the CBE was 36% and the specificity 78%. For women from 50 to 74 years, and those under 50 years, the sensitivity and the specificity of the CBE were similar to that found for the overall population.

Table 2
Accuracy of clinical breast examination for the overall population.

	N = 3218 n (%)	Se [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]
Any clinical abnormality*	713 (22%)	36% [28%; 45%]	78% [77%; 80%]	7% [5%; 9%]	97% [96%; 97%]
≥ 2 clinical abnormalities*	86 (3%)	6% [3%; 12%]	97% [97%; 98%]	9% [4%; 18%]	96% [95%; 97%]
Breast mass	469 (15%)	26% [18%; 34%]	86% [85%; 87%]	7% [5%; 10%]	96% [96%; 97%]
Retraction	9 (0.2%)	2% [0%; 5%]	100% [100%; 100%]	22% [3%; 60%]	96% [95%; 97%]
Oedema	2 (0.1%)	2% [0%; 5%]	100% [100%; 100%]	100% [9%; 100%]	96% [95%; 97%]
Erythema	5 (0.1%)	0% [0%; 4%]	100% [100%; 100%]	0% [0%; 64%]	96% [95%; 97%]
Pain	126 (4%)	5% [2%; 10%]	96% [95%; 97%]	5% [2%; 10%]	96% [95%; 97%]
Nipple discharge	16 (0.5%)	4% [1%; 9%]	100% [99%; 100%]	31% [11%; 59%]	96% [95%; 97%]
Axillary node	17 (0.5%)	2% [0%; 6%]	100% [99%; 100%]	18% [4%; 43%]	96% [95%; 97%]
Other	116 (4%)	2% [0%; 6%]	96% [96%; 97%]	3% [1%; 7%]	96% [96%; 96%]

(Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval).
* Clinical abnormalities could be: mass, retraction, oedema, erythema, orange skin, ulceration, pain, nipple discharge, axillary node, other.

Table 3
Accuracy of clinical breast examination for patients under 50 years.

	N = 957 n(%)	Se [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]
Any clinical abnormality*	262 (27%)	38% [24%; 53%]	73% [70%; 76%]	6% [4%; 10%]	96% [94%; 97%]
≥ 2 clinical abnormalities*	41 (4%)	4% [1%; 15%]	96% [94%; 97%]	5% [1%; 17%]	95% [94%; 97%]
Breast mass	170 (18%)	27% [15%; 42%]	83% [80%; 85%]	7% [4%; 12%]	96% [94%; 97%]
Pain	53 (6%)	2% [0%; 12%]	94% [93%; 96%]	2% [0%; 10%]	95% [94%; 96%]
Nipple discharge	11(1%)	7% [1%; 18%]	99% [98%; 100%]	27% [6%; 61%]	96% [94%; 97%]
Axillary node	7 (1%)	4% [1%; 15%]	99% [99%; 100%]	29% [4%; 71%]	95% [94%; 97%]

(Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval).
* Clinical abnormalities could be: mass, retraction, oedema, erythema, orange skin, ulceration, pain, nipple discharge, axillary node, other.

Table 4
Accuracy of clinical breast examination for patients between 50 and 74 years.

	N = 2190 n(%)	Se [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]
Any clinical abnormality*	441 (20%)	36% [25%; 47%]	80% [79%; 82%]	7% [4%; 9%]	97% [96%; 98%]
≥ 2 clinical abnormalities*	44 (2%)	7% [3%; 15%]	98% [98%; 99%]	14% [5%; 27%]	97% [96%; 97%]
Breast mass	290 (13 %)	25% [16%; 36%]	87% [86%; 89%]	7% [4%; 10%]	97% [96%; 98%]
Retraction	5(0.2%)	2% [0%; 9%]	100% [100%; 100%]	40% [5%; 85%]	96% [96%; 97%]
Pain	73 (3%)	6% [2%; 14%]	97% [96%; 97%]	7% [2%; 15%]	96% [96%; 97%]
Nipple discharge	5(0.2%)	2% [0%; 9%]	100% [100%; 100%]	40% [5%; 85%]	96% [96%; 97%]
Axillary node	10 (0.5%)	1% [0%; 7%]	100% [99%; 100%]	10% [0%; 45%]	96% [95%; 97%]

(Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval).
* Clinical abnormalities could be: mass, retraction, oedema, erythema, orange skin, ulceration, pain, nipple discharge, axillary node, other.

A breast mass found during the CBE did not present good accuracy. Whatever the age of the women, its sensitivity was about 26%, its specificity 86% and the likelihood ratios were low (LR+ = 1.8 and LR- = 0.8). In the overall study population, the LR + and LR- of the CBE and of each abnormality contributed little to the diagnosis, with the exception of nipple discharge, retraction and axillary nodes, for which the LR + were greater than 5. However, the frequency of these 3 abnormalities seemed too low for breast cancer screening to rely on their presence.

Strengths and limitations

Our study was one of the rare recent studies evaluating the accuracy of the CBE by a healthcare professional, and the only one conducted in French population although some powerful studies already found low performance of CBE in other settings. One of the main strengths of our study was the consecutive recruitment of patients limiting selection bias. CBE is a difficult and clinically dependent examination. In order to overcome this disadvantage, we deliberately limited the number of inclusion centers in order to obtain more reproducible results. Thus, the CBE was performed by experts in senology from radiology practices, but it is likely that CBE would be less effective if performed by a general practitioner.

However, our study has some weaknesses. First, we used the high-risk of malignancy depending on the Bi-RADS classification on mammography as the primary endpoint, rather than cancer diagnosis, because it was impossible to follow the patients to know the results of any biopsies performed if they were indicated. Thus we could have overestimated high-risk patients compared to the actual number of patients with breast cancer, increase the sensitivity of CBE and lower its specificity. However, our criterion of judgment is clinically relevant because the results of the mammography lead to a modification of the management by the physician: in case of mammography with Bi-RADS 4 or 5, the physician will prescribe a biopsy. Second, mammography may not be the reference for young women because of the high breast density at these ages. Thus, according to their current practices, radiologists could complete the mammography with a breast ultrasound before assessing the risk of malignancy. Third, the radiology practices in our study were specialized senology centers. There may therefore have been a selection bias within our study, with a female population that might be more symptomatic than the general population. Similarly, the prevalence of high-risk mammography was probably different from that general population. Given that many patients were participating in individualized screening, the number of symptomatic patients with high-risk mammography may also be partly due to missed screening opportunities with organized screening in previous years. Thus, PPV and NPV values may be difficult to generalize. However, the inclusion of patients in several centers may have reduced this bias. Fourth, the low number of patients with skin abnormalities, erythema, ulceration, oedema, nipple discharge, or skin retraction did not allow calculating every parameter in all age's categories. Finally, in women participating to an individual screening, it was not possible to differentiate between women who were referred following the discovery of a clinical abnormality by a professional and those referred for routine mammography as part of an individual screening, but this data was not necessary to assess the diagnostic accuracy of CBE.

Comparison with existing literature

Despite only few studies have been conducted to evaluate the effectiveness of CBE alone, our results are in line with the North-American guidelines and with the other studies. A British study carried out in 1992, found a CBE sensitivity of 64% [13]. In the same year, a Canadian study found a sensitivity of 69% in women aged 40–49 and 63% in women aged 50–59 [14].These higher sensitivities compared to the results of our study can be explained by the time at which they were conducted. Radiological tools were less effective than today [16,17], more cancers might be diagnosed following clinical examination, thus increasing the sensitivity of the CBE. A study conducted in 2002 estimated a sensitivity of 35% [18] which is consistent with our study and reinforces its validity. In primary care setting, our results are consistent other studies finding that breast cancer was associated with breast lump and nipple discharge [19,20]. Nevertheless, we did not find any increase of PPV of breast mass between younger patients and patients over 70 years, probably because breast cancer effecting elderly women in 2000–2009 were not discovered with breast screening programs at a younger age.

Until then, CBE was also offered to women aged 50–74 at the annual screening visit, to minimize the risk of not detecting radio-occult cancers and because it could help to diagnose more aggressive breast cancer than mammography alone [21]. But when the mammography's result was initially considered normal, an abnormality was detected at CBE in only 0.2% of cases in 2010 [22]. However, CBE could remain relevant and should be performed in low and middle income countries (LMICs) where the access to mammography may be more difficult. In these countries, CBE can reduce delay to diagnose breast cancer and it is associated with earlier stage cancer [23]. The average size of breast tumours at the time of their discovery in France was 1.9 cm, whereas it was 5 cm in Tunisia for example [24]. Nevertheless, mammography should be encouraged as biennial mammography reduced in breast cancer deaths compared to annual CBE alone [25]. In the same way, self breast examination was not recommended by North-American guidelines because it did not reduce breast cancer mortality in clinical trials [6,7,26], but it could help to detect breast cancers at early stages in LMICs [27].

Implications for research and practice

In the current state of knowledge, it is not possible to distinguish cancers that will evolve from those that will not or only slightly evolve: all the lesions detected are therefore treated, implying over-diagnosis and over-treatment. Various studies and meta-analyses estimate that 30% to 50% of diagnosed breast cancers are over-diagnosed [8,28]. In the United Kingdom, the concept of "breast awareness", teaching patients "red flags" that the physicians can also check, seems to have relevant results in terms of breast cancer screening [29]. Thus, it seems essential to develop primary prevention measures for this cancer. In fact, the breast cancer prevention strategy implemented in 2017 by the French National Institute for Cancer (INCa) suggested two information and prevention medical consultations at 25 and 50 years [30]. They aimed at raising awareness of the risk factors for breast cancer, and means of prevention such as food hygiene and regular physical activity [2,31]. These measures could help to prevent 20,000 breast and colon cancers each year [32]. In patients between 50 and 74 years, health educational programmes could also increase women's breast cancer awareness and influence their participation in screening [33,34].

Conclusion

CBE does not seem to provide reliable and reproducible additional information compared to mammography. Our results were consistent with the other studies and were not in favour of its application in France for the regular gynaecological follow-up of women between 50 and 74 years. CBE could have a better place in the follow-up of breast lesions but not for screening or diagnosis. Nevertheless, the implementation of prevention measures and the development individualized screening on each patients risk with screening tools [35] or genomics [36] could reduce the incidence of this cancer and optimize screening by limiting over-diagnosis.

Conflict of interest

The authors declared they have no conflict of interests.

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