EVALUATION OF TOMOSYNTHESIS IN THE CHARACTERIZATION AND MANAGEMENT OF BREAST LESIONS

EVALUATION DE LA TOMOSYNTHESE DANS LA CARACTERISATION ET LA PRISE EN CHARGE DES LESIONS MAMMAIRES

"ETOLE"

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La recherche sera conduite conformément au protocole, aux bonnes pratiques en vigueur et aux dispositions législatives et réglementaires en vigueur.

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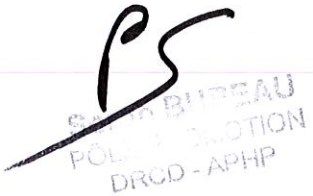

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1- ABSTRACT

1.1 RESUME

Titre complet	Evaluation de la tomosynthèse dans la caractérisation et la prise en charge des lésions mammaires
Acronyme	ETOLE
Investigateur coordonnateur	Professeur *Cédric DE BAZELAIRE* Service de Radiologie Hôpital Saint-Louis, Paris Tél : +33 1 42 49 91 33 Courriel : cedric.de-bazelaire@aphp.fr
Promoteur	Assistance Publique – Hôpitaux de Paris
Justification scientifique	La tomosynthèse est une technique innovante développée en mammographie numérique permettant d'obtenir une image en coupe du sein. La mammographie a pour principal inconvénient d'être une imagerie en projection qui crée des superpositions, ce que permet d'éliminer la tomosynthèse.
Objectif et critère d'évaluation principal	L'objectif de cette étude est d'évaluer si la classification BiRads obtenue par **tomosynthèse** avec mammographie synthétique est supérieure à celle obtenue par **mammographie conventionnelle** en termes de spécificité tout en étant non-inférieure en termes de sensibilité.
Objectifs et critères d'évaluation secondaires	Les objectifs secondaires sont: • d'évaluer si la tomosynthèse avec mammographie synthétique permet de mieux détecter les **signes de mauvais pronostic** des lésions malignes, • d'évaluer si la tomosynthèse avec mammographie synthétique modifie le **nombre d'examens complémentaires**, modifie la **dose d'irradiation** reçue par la patiente. • d'évaluer si la tomosynthèse réduit le nombre d'échographie nécessaire et comparer les différences de classification BiRads obtenue par la **tomosynthèse** avec mammographie synthétique seules puis avec échographie aux différences de classification obtenues avec la mammographie seule puis combinée avec **l'échographie**. • si la tomosynthèse avec mammographie synthétique améliore la reproductibilité de la classification BiRads. • d'évaluer si les **coûts** de l'acte et de l'impact de la stratégie tomosynthèse avec mammographie synthétique versus la mammographie.

Schéma expérimental	Il s'agit d'une étude prospective randomisée multicentrique. Pendant la durée des inclusions (18 mois), le même modèle de mammographe numérique avec tomosynthèse est installé dans chacun des quatres sites par le constructeur. Toutes les patientes adressées pour une anomalie clinique et/ou en imagerie du sein dans chacun des centres pendant la période de l'étude et acceptant de participer (consentement éclairé) seront randomisées entre un bras mammographie numérique conventionnelle et un bras tomosynthèse avec mammographie synthétique. La randomisation sera équilibrée entre les groupes et stratifiée sur le centre. Les patientes enceintes, à haut risque de cancer du sein ou suivies pour un cancer du sein en cours de traitement ne pourront pas être incluses.
Population concernée	Femme avec des lésions mammaires
Critères d'inclusion	• Patiente ayant des anomalies d'imagerie clinique ou du sein classés comme BIRADS 3, 4, 5 (tableau 1). (5) • Patiente de plus de 18 ans • Signature d'un consentement éclairé
Principaux critères de non inclusion	• Patiente à haut risque de cancer du sein, les mutations BRCA 1 ou 2 opérateurs, Li Fraumeni, ou l'histoire d'un rayonnement thoracique seront exclus en raison de leur plus grande sensibilité aux rayonnements ionisants. (11) • Patiente incapable de donner un consentement éclairé pour des raisons physiques, mentales ou morales. • Patiente non affilié à l'assurance française de sécurité sociale. • Patiente sous traitement pour un cancer du sein. • Lorsque la mammographie n'est pas recommandée conformément aux bonnes pratiques par l'Autorité de Santé française (HAS). • Patiente enceinte.
Méthode diagnostique à l'essai	Evaluation de la tomosynthèse dans la caractérisation et la prise en charge des lésions mammaires
Méthode diagnostique de référence	Mammographie conventionnelle
Autres actes ajoutés par la recherche	Tomosynthèse
Risques ajoutés par la recherche	Risque B
Déroulement pratique	Toutes les patientes adressées pour une anomalie clinique et/ou en imagerie du sein dans chacun des centres pendant la période de l'étude et acceptant de participer (consentement éclairé) seront randomisées entre un bras mammographie numérique conventionnelle et un bras tomosynthèse avec mammographie synthétique. La randomisation sera équilibrée entre les groupes et stratifiée sur le centre. Les patientes enceintes, à haut risque de cancer du sein ou en cours de traitement pour un cancer du sein ne pourront pas être incluses.

Nombre de sujets nécessaires	2000 patientes
Nombre de centres	4 centres (Hôpital Saint-louis, Hôpital Lariboisière, HEGP, Hôpital Tenon)
Durée de la recherche	• Durée d'inclusion : 18 mois • Durée de participation (suivi) : 24 mois • Durée totale : 42 mois
Nombre d'inclusions prévues par centre et par mois	Hôpital Saint-louis : 70 Hôpital Tenon : 70 Hôpital Lariboisière : 30 HEGP : 30
Analyse statistique	L'analyse du **critère de jugement principal** reposera sur la construction d'un intervalle de confiance simultané pour les rapports des taux de vrai négatifs et faux négatifs obtenus avec chacune des méthodes. Une formulation de supériorité sera adoptée pour le rapport des spécificités alors qu'une formulation de non-infériorité sera adoptée pour le rapport des faux négatifs. Le classement sera jugé par comparaison au gold-standard détaillé ci-dessous. Le nombre et le type d'examens complémentaires prescrits sera comparé entre les deux bras de randomisation. la reproductibilité de la classification BiRads sera évalué par coefficients kappas pondérés. La randomisation sur quatres sites permettra de limiter les biais liés à l'effet centre. Un comité indépendant de surveillance évaluera la dose d'irradiation reçue dans les deux bras après inclusion de 1/3, 2/3 et 100% des patientes par bras, afin de garantir la sécurité des patientes. **Gold-standard** : Les prélèvements seront analysés par un anatomopathologiste spécialisé. En cas de lésions malignes, la patiente aura une prise en charge thérapeutique. En cas de lésions bénignes, une surveillance clinique et radiologique à 24 mois sera entreprise. Les lésions classées ACR III bénéficieront d'une surveillance clinique et radiologique à 6, 12 et 24 mois. **Deux mille** patientes seront inclues dans cette étude. Avec un risque de première espèce global de 0,05 et une puissance globale de 90% et une analyse appariée, il faut 187 malades et 710 non malades par bras. L'inclusion de 2000 patientes correspond à 52% de l'activité d'interventionnelle en sénologie réalisée sur une période de 18 mois dans les 4 centres d'inclusion à l'hôpital Tenon , Lariboisière , HEGP et Saint-Louis. La période d'inclusion durera 18 mois et la surveillance sera poursuivie pendant 2 ans.
Source de financement	PHRC 12-070
Comité de Surveillance Indépendant (CSI)	Oui

1.2 SYNOPSIS

Full title	Evaluation of tomosynthesis in the characterization and management of breast
Acronym	ETOLE
coordinating investigator	Professor *Cédric de Bazelaire* Service de Radiologie Hôpital Saint-Louis, Paris Tél : +33 1 42 49 91 33 Courriel : cedric.de-bazelaire@aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Rationale	Tomosynthesis is an innovative technique developed in digital mammography for obtaining a sectional image of the breast. Mammography has the main disadvantage of being an imaging projection that creates overlays, which eliminates tomosynthesis.
Objective and primary endpoint	• Evaluate if BiRads classification obtained with tomosythesis is superior to classification obtained by conventional mammography in terms of specificity and non-inferior in terms of sensitivity. • Joint analysis of true negative and false negative rates according to BiRads scale as compared to the histological results (or follow-up outcome, see "gold standard", below)
Objectives and secondary endpoints	Evaluate • If tomosynthesis with synthetic tomography allows a better detection of certain signs of poor prognosis for malignant lesions (size and multicentricity of the tumour, lymph node extension, skin or pectoral infiltration). • If tomosynthesis with synthetic tomography modifies the number of additional views and/or number of additional examinations including ultrasound, breast MRI and biopsy. • assess whether tomosynthesis reduces the necessary number of ultrasound and compare the differences in ratings BIRADS obtained by tomosynthesis with synthetic mammography and then with ultrasound to the differences obtained with conventional mammography alone and then combined with ultrasound. • If tomosynthesis with synthetic mammography changes the radiation dose received by the patient. • If tomosynthesis with synthetic mammography improves the reproducibility of the BiRads classification for abnormalities. • The costs analysis of tomosynthesis with synthetic mammography compared to mammography and/or mammography + ultrasound.

Experimental design	A randomized multi-centric study (phase III diagnostic study according to the classification of Gluud & Gluud. (1) During the inclusion phase (18 months) a tomosynthesis system will be installed at each site by the manufacturer. All patients with a clinical or breast imaging abnormally at each of these sites during the study period and having given informed consent will be randomized to either a conventional mammography or tomosynthesis (4 incidences) with synthetic mammography.
Population concerned	Women having clinical or breast imaging abnormalities
Inclusion Criteria	• Patient having clinical or breast imaging abnormalities classified as BiRads 3, 4, 5 (Table 1). (5) • Patient over 18 years old • Signed informed consent
Non-Inclusion Criteria	• Patients at high risk of breast cancer, mutations BRCA 1 or 2 carriers, Li Fraumeni, or history of thoracic radiation will be excluded because of their greater sensitivity to ionizing radiation. §3.3.15.1.4 (11) • Patient unable to give informed consent for physical, mental, or legal reasons. • Patient not affiliated with French Social Security Insurance. • Patient under treatment for breast cancer. • When mammography is not recommended according to good practice by the French Health Authority (HAS). • Pregnant patient.
Diagnostic method	Evaluation of tomosynthesis in the characterization and management of breast.
Reference diagnostic method	Conventional digital mammography
Other acts added by research	Conventional digital mammography + tomosynthesis
Added risks through research	Risk B
Practical course	All patients referred for clinical abnormalities and / or breast imaging in each center during the study period and agreeing to participate (informed consent) will be randomized between a conventional digital mammography arm and atomosynthesis armwith synthetic mammography. Randomization will be balanced between groups stratified on the center. Pregnant patients at high risk of breast cancer or followed for breast cancer may not be included.
Number of subjects required	2000 subjects
Number of centers	4 centers (Saint-Louis Hospital, Tenon Hospital, Lariboisière Hospital and HEGP)
Research duration	• Inclusion duration : 18 month • Subject participation: 24 month • Total duration : 42 month

Number of inclusions under center per month	Saint-Louis Hospital : 70 Tenon Hospital : 70 Lariboisière Hospital : 30 HEGP : 30
Statistical Analysis	The analysis comparison of the BiRads classifications obtained by mammography and then by tomosynthesis will rely on the construction of simultaneous confidence intervals for the ratios of true negative rates (specificity) and false negative rates (1-sensitivity) obtained with each technics in the mammography + tomosynthesis arm, as described by Alonzo et al.
Source de financement	PHRC 12-070
DSMB (Data Safety Monitoring Board)	Yes

2-BACKGROUND

2.1 Description of the knowledge of the relevant pathology

Among cancers in women, breast cancer is the primary cancer in terms of incidence (53,000 new cases in 2011 in France) and remains the primary cause of death by cancer amongst women (11,400 deceased in 2011 in France). Thus, breast cancer is of great importance for the public health in France, as seen in the cancer plan 2009-2013. (4) Despite an increasing incidence of breast cancer (+2.4% per year between 1980 and 2005), mortality remains stable (-0.4% per year between 1980 and 2005). This stability is probably related to the discovery of cancers at an early stage with a better prognosis due to screening. This stability can also be explained by an optimized management of aggressive cancers with an initial radiological assessment that does not underestimate the factors of poor prognosis.

The imaging technique works as well in the screening as for diagnostic or treatment management. Screening is done with an analogic or digital mammography system. At the diagnostic work-up, the characterization of lesions is obtained with mammographic images, but also with the help of tomosynthesis, ultrasound and possibly MRI. The percutaneous biopsies guided by ultrasound, stereotactic and MRI allows therapeutic management. Imaging can help the surgeon in localizing lesions in the breast with harpoons. MRI, Ultrasound and mammography can control the effectiveness of adjuvant or neoadjuvant chemotherapy and checks for relapse after treatment. As an aid for interpretation of breast imaging, the American College of Radiology (ACR) has published the BiRads (Breast Imaging Reporting and Data System) catalog to harmonize interpretation of images obtained with the three techniques: mammography, ultrasound, and MRI.

2.1.1 BiRads classification

The American College of Radiology defines three stages of the interpretation (Table 1): (5) The first stage describes the density of the breast in four categories. (6) In mammography, the density may be Type 1 indicating fatty breasts, Type 2 with some remaining fibroglandular structures, Type 3 indicating heterogeneously dense breasts, or Type 4 corresponding to extremely dense breasts. The relative risk of breast cancer has been correlated with the density with a relative risk (RR) of 1.79% for the BiRads Type 1 breasts, RR = 2.11 for type 2, RR = 2.92 for type 3, and RR = 4.64 for type 4. (7) The second stage is to describe the lesions according to the BiRads lexicon. The radiologist must specify the type of lesion (microcalcifications, masses, architectural distortions…). For the microcalcifications, the distribution, shape, number, and density must be described. For the masses the radiologist must specify the shape, contours, and density of the mass. Masses with irregular shape or a cluster of casting-type microcalcifications are examples of suspicious lesions. (5) Finally, the lesions must be classified according to the BiRads criteria in seven categories: BiRads 1 (negative), BiRads 2 (benign lesion), BiRads 3 (probably benign lesion), BiRads 4A (low suspicion of malignancy), BiRads 4B (medium suspicion of malignancy), BiRads 4C (high suspicion of malignancy), and BiRads 5 (strongly suggesting cancer). (5)

2.1.2 Prognostic factors

The primary prognostic factor is the size of the lesion: masses of less than two centimeters and clusters of microcalcifications of less than 3 cm have a better prognosis (Standards, Options et Recommendations de Saint-Paul de Vence 2007). The detection of associated lesions is important in the initial assessment because it is better to avoid repeated surgery or miss abnormalities at the time of initial diagnosis including the contralateral lesion (3.1% of cancer not visible by mammography and found in MRI) that are not addressed by the surgical treatment or radiotherapy. (8) Lymph node metastases are also a critical prognostic factor. A patient with a fixed axillary lymph node (N2) has a worse survival rate, than a patient with no palpable lymph node (N0) during the initial staging and may benefit from adjuvant chemotherapy. Extensions to the skin or pectoral muscle increase the risk of relapse in the absence of initial radical treatment and require a mastectomy. Thus, accurate detection of these signs of poor prognosis is essential to optimize the treatment of patients.

2.1.3 Radiation

The dose delivered to patients is an important public health concern. According to the group BEIR VII (Biologic Effects of Ionizing Radiation) from the American academy of science, mammography examinations would be associated with 1.3 to 1.7 cases of breast cancer deaths among 100 000 women of 40 years of age. (9) Similarly, annual screening conducted from 40 to 80 years would be responsible for 20 to 25 cases of fatal breast cancer in 100 000 women. The risk is halved by using bi-annual screening and also diminishes with age. The radiation dose increases with the breast thickness. (10) The risk of breast cancer depends of the radiation sensitivity of breast that varies between women. The BRCA1 and BRCA2 gene products are involved in the normal repair of DNA damage of the type caused by ionizing radiation, and BRCA-deficient cells are hypersensitive to radiation. (11)

The reduction of radiation must remain a priority in the radiological assessment of patients.

2.2 Hypothesis

Our hypothesis is that tomosynthesis with synthetic image has an higher diagnostic value than digital mammography. If this use of tomosynthesis has a real diagnostic value, it could remplace mammography, reduce the number of additional examinations and the radiation dose.

2.3 Description diagnotic techniques

2.3.1 Mammography

Mammography is the first line technique for screening and for diagnostic imaging despite a number of limitations. The sensibility of mammography is estimated between 80 to 90% in less dense breasts (type 1 and 2). However, the sensibility falls between 50 to 60% for breasts density type 3 and 4. (12) According to some studies the sensibility may even be as low as 45% for the extremely dense breasts. (13) One of the explanations of the loss of sensibility in dense breasts is that the superposition of fibroglandular tissue may mask the contours of cancers. Additional images are thus often required to compensate for the lack of sensibility of mammography and especially when clinical abnormalities are presents: extra views (other projections, compression and magnification), ultrasound (recommendations for one ultrasound for type 3 and 4 breasts: Saint Paul de Vence 2009 and SOFMIS 2010), MRI, fine

needle aspiration and biopsies in certain cases (14-16). This process augments the anxiety of the patient and has a high cost for the management of lesions being often benign. MRI is a very sensitive technique (95 to 100%) for detecting cancers, but remains non-specific, expensive and relatively unavailable. These last years new techniques have been emerging to improve the sensibility of mammography, including digital mammography, (17-20) computer-aided detection (CAD), (21-23) angiography and tomosynthesis. (17, 18, 21-26) The use of digital mammography systems has slightly improved the detection of cancers in dense breasts especially, (19) but few studies show any significant differences in terms of diagnostic performance between analog and digital systems for the general population. (19, 27-29) The superimposition of breast tissue, similar to an "anatomical noise", limits the visibility of lesions more than the sensitivity of the detector itself. (24, 30) Some recent clinical studies with relatively few cases (N = 36 (24), N = 30 (23)) seem to confirm this hypothesis by showing an increased of both sensitivity and specificity with tomosynthesis that allows a visualization of the breast in three dimensions and lowers the impact of tissue overlap. (23) (25, 26, 31)

2.3.2 Tomosynthesis technique

In digital mammography, the x-rays are emitted by a fixed tube towards a digital detector that transforms the x-rays into electric charge. The tomosynthesis technique derives from tomography, which utilizes a moving x-ray tube and film-screen. A series of exposures are made on the same film while the tube and film move in opposite directions. One of the limits of tomography is that each film only clearly depicts one plan at a fixed height. If the depth of the lesion is not known in advance it is necessary to make several exposures at different heights, which leads to an increased radiation dose. In tomosynthesis, the x-ray tube is still moving in an arc but the detector is digital. (32, 33) Several exposures are obtained and data is sent to the workstation. The images are reconstructed with mathematical algorithms similar to those used in Computed Tomography (CT) that creates a stack of images that are in focus at different heights. (24, 30, 34-36) Tomosynthesis improves the visibility of structures in the plane of focus and reduces the contrast and visibility of structures outside this plan. (Figure 1) Reconstruction provides a stack of slices of 1mm thickness. The number of slices depends on the breast thickness.

Different manufacturers use different tomosynthesis techniques. The tomosynthesis angle can vary from 11° to 40° depending on the manufacturers. (21, 37) A higher tomo angle reduces the slice thickness (z direction) but deteriorates the resolution in the plan of the slice (x, y directions). The acquisition is made using different incremental angles giving 11 to 25 slices and may be done in static or continuous fashion. The duration of a scan is estimated to 4s for the system that will be used. If static acquisition is used the scan time is longer and it may be sensitive to motion blur due to vibrations. Furthermore, it is not possible to use a grid in tomosynthesis to remove scattered radiation and these results in a poor image quality for many of the systems. The pixel size in the reconstructed images varies between 50 and 120 µm. There is no consensus yet regarding the acquisition parameters such as dose, number of projections, and tomosynthesis angle. These parameters depend largely on the detector characteristics. It seems that the detection of lesions is improved with increased dose and tomosynthesis angle. At a fixed dose and scan angle, the performances diminish beyond a certain number of projections, which indicates that a higher number of projections don’t necessarily improve performance. (38)

Digital detectors today have a great dynamic range with a linear response to dose that allows for a lower x-ray dose per exposure. The total dose in tomosynthesis is similar to that of analog mammography for each manufacturer. (23, 37, 39) It varies between 0.50 mGy and 1.45 mGy.

The tomosynthesis images benefit from the advantages of digital mammography compared to analog mammography: good reproducibility, less noise and artifacts, and digital storage. (40) Furthermore, according to the study by Poplack et al, the tomosynthesis would allow to obtain image of comparable quality (subjective analysis) to that of digital mammography. (23) The tomosynthesis images seem to be reproducible. Sinha et al observed an offset of 1 to 3 mm between tomosynthesis performed at 1 minute, 6 months, and 1-year intervals. (41) Knowing that the average size of tumors found by mammography in a population of 332 926 patients was 20 mm (median = 15 mm), (42) an offset of 10% appears to be negligible. This reproducibility is particularly important for evaluating the effectiveness of neoadjuvant chemotherapy in which we compare tumor sizes measured on examinations performed every 2 or 3 months.
Several studies have shown that digital breast tomosynthesis, used in conjunction with mammography, improves cancer detection rates and decreases false positives (4–6). digital breast tomosynthesis alone seems to be less accurate for depicting microcalcifications clusters (7–9), suggesting that a combination of digital breast tomosynthesis and mammography is desirable. However, the exposure from both tests is a concern. Manufacturers have been focusing on the issue, improving reconstruction software to generate a synthetic mammography directly from the digital breast tomosynthesis dataset, effectively eliminating a standard mammography altogether. The Food and Drug Administration acknowledged the potential for such a solution in 2013.(10) Initial studies have shown that using 2D synthetic imaging could reduce the average glandular exposure by 40–50%.(11). However, little has been published on the diagnostic performance of synthetic mammography, either as a standalone tool (12) or in combination with digital breast tomosynthesis (11). Initial studies have shown that using 2D synthetic imaging could reduce the average glandular exposure by 40–50%.(11). However, little has been published on the diagnostic performance of synthetic mammography, either as a standalone tool (12) or in combination with digital breast tomosynthesis (11).

2.4 Expected benefices

Most of studies published have shown that the mammography in conjunction with tomosynthesis improves the sensitivity and specificity of detection of breast cancer in comparison with mammography (4–6,14–16). Adding tomosynthesis to mammography increases with a factor of 1.1 to 1.3 the number of cancer detected in American series (comparison into two groups of different patients) (6,14–17) and with a factor of 1.3 to 1.5 in European series (STORM trial) (5). However, few studies have evaluated tomosynthesis with synthetic mammography as a standalone tool. If performances of tomosynthesis with synthesic mammography are as high than mammography, mammography may be avoided and radiation doses dramatically reduced for patient.

2.4.1 Improving the BiRads classification by combining tomosynthesis with synthetic mammography

In the first study published in 2012, Gur and al reported a lower sensibility of Synthetic mammography + tomosynthesis in comparison with mammography + tomosynthesis (19). However, this publication was based on data acquired with the first experimental version of the software used to create synthetic mammography. In the OSLO trial, Per Skaane et al. well demonstrated the impact of the version of the software used for the creation of synthetic 2D

images from tomosynthesis images (4,11). In the first period of this trial, the first version of the software was used and a lower cancer detection rate was found for Synthetic mammography (7.4 ‰) than for mammography (8‰). In the second period of this same trial performed with the second version of the software, no difference was found between Synthetic mammography (7.7‰) and mammography (7.8‰). Two others studies (12,18,20) were also conducted with the second version of the software and reported also no significant difference in accuracy between Synthetic mammography and mammography + tomosynthesis.

2.4.2 Reduction in recall errors and in prescribed additional examinations

Poplack et *al.* were the first to publish a clinical study of tomosynthesis. (23) This study is based on 98 patients recalled after screening. They observed that tomosynthesis allowed a 40% reduction of unnecessary recall of patients, corresponding to false positives. Tomosynthesis eliminated images constructed by superimpositions of fibroglandular tissues and improved the characterization of benign lesions (e.g. cysts, fatty contents, benign calcifications). The false negatives of tomosynthesis seem to be similar to that of mammography: a carcinoma in situ without microcalcifications and a mucinous cancer that look like a cyst. Similarly, the study by Gur et al shows that the combination of tomosynthesis and mammography has the potential to reduce the false positive rate by 30% in screening, reducing also the number of additional examinations. (49) Tomosynthesis may improve the positive predictive value of additional examinations by reducing the number of unnecessary additional examinations and biopsies, which saves cost, time, and stress for the patient. (21) For symptomatic patients, current standards recommend the couple mammography + ultrasound. To our knowledge there is no study comparing mammography + ultrasound versus tomosynthesis.

2.4.3 Detection of prognostic factors

The lesions seem less often measurable in mammography (49.67%) than in tomosynthesis (63.86%) due to superimposed tissue that masks the lesion contours. In ultrasound, lesions are measurable in 60% of the cases. The measurements in tomosynthesis are better correlated with pathology (R = 0.86) than those obtained by mammography (R = 0.71) and ultrasound (R = 0.85). Nevertheless all the techniques underestimate the tumor size, especially for lesions over 20 mm, among which one finds more multifocal and spiculated cancers and more in situ breast carcinoma without microcalcification. (51)

By reducing the “anatomical noise” tomosynthesis improves visibility of the lesions, the lymph nodes and the skin. Tomosynthesis might also improve visibility of additional lesions (multifocality) and the precision of measurements. Andersson et al have compared the visibility of cancers in mammography and in tomosynthesis in 40 patients with breast cancer. They concluded that tomosynthesis might offer a better visibility of lesions compared to mammography. (26)

Furthermore, by suppressing the tissue overlap, tomosynthesis would allow a better analyze of glandular retractions and skin or pectoral muscle infiltration and a better detection of associated lesions (masses, microcalcifications, architectural distortions). (47, 52)

2.4.4 Reduction in radiation dose

In France, mammography without tomosynthesis remains the reference standard method for screening especially due to the problem of radiation exposure. The dose received by the patient during the multiple projections of a single tomosynthesis sequence is substantially equivalent to that received during 2D mammography (21–24). Thus, additional radiation

exposure is approximately by a factor of 2. Then, as a second line technique after a positive mammography, tomosynthesis can be used as a substitute of spot views thanks to an equivalence in diagnostic performance and radiation exposure (25–28). For screening issues, using tomosynthesis systematically in addition to mammography increases clearly radiation exposure but also reading and interpretation time (47% longer) (29) in relation with an increase in the number of images obtained. (29–31). Our study shows that synthetic mammography with tomosynthesis is better than mammography in terms of sensibility and specificity. This results may suggest that synthetic mammography + tomosynthesis could replace mammography without significant increase of average glandular dose (i.e. 1.9mGy for mammography and 2.1mGy for tomosynthesis), the better diagnostic performance of synthetic mammography + tomosynthesis on mammography justifying a longer interpretation time.

2.4.5 Reproducibility

To our knowledge there is no prospective analysis of the reproducibility of the interpretation of the combination of tomosynthesis and synthetic mammography. However, several authors have studied the importance of training in reading tomosynthesis images. It seems that training in reading tomosynthesis images is essential to improve the diagnostic performances of radiologists. (23, 25) This training is needed to recognize abnormal lesions and also to recognize normal tissue. This training also appears useful for radiologists familiar to digital mammography, who obtain more false positives in tomosynthesis (23, 49).

3. OBJECTIVES

Our hypothesis is that tomosynthesis with synthetic mammography improves the diagnostic performance compared to conventional mammography. If tomosynthesis with synthetic mammography has a real diagnostic value, it could reduce the number of additional examinations and the radiation dose.

3.1 Primary Objective

Evaluate if BiRads classification obtained with tomosynthesis with synthetic mammography is superior to classification obtained by conventional mammography in terms of specificity and non-inferior in terms of sensitivity.

3.2 Secondary Objectives

Evaluate:

- If tomosynthesis with synthetic mammography allows for better detection of certain signs of a poor prognosis for malignant lesions (size and multicentricity of the tumour, lymph node extension, skin or pectoral infiltration).
- If tomosynthesis with synthetic mammography modifies the number of additional views and/or number of additional examinations including ultrasound, breast MRI and biopsy.
- We would like to evaluate whether BiRads classification obtained with mammography + ultrasound is superior to BiRads classification obtained with tomosynthesis + synthetic mammography and if BiRads classification obtained with tomosynthesis + synthetic mammography + ultrasound is superior to all other combinations, in terms of specificity and non-inferior in terms of sensitivity.
- If tomosynthesis + synthetic mammography changes the radiation dose received by the patient.
- If tomosynthesis + synthetic mammography improve the reproducibility of the BiRads classification for anomalies detected clinically or mammographically.
- The costs analysis of tomosynthesis compared to mammography and mammography + ultrasound.

4. STUDY DESIGN

4.1 Primary endpoint

Joint analysis of true negative and false negative rates according to BiRads scale as compared to the histological result (or follow-up outcome, see "gold standard").

4.2 Methodology

4.2.1 Experimental design

4.2.1.1 Experimental design type

This is a diagnostic randomized study (diagnostic phase III study according to the Gluud & Gluud classification), carried out in two centers. (1) All patients fulfilling the inclusion and exclusion criteria in the 4 centers during the period of enrollment will be invited to participate in the study. The enrollment phase will last for 18 months.

4.2.1.2 Study workflow

The workflow will be the following, consisting of four phases (Figure 1)

1. Enrolment and randomization of patients
2. Mammographic examination
3. Additional examinations and biopsies
4. Follow-up

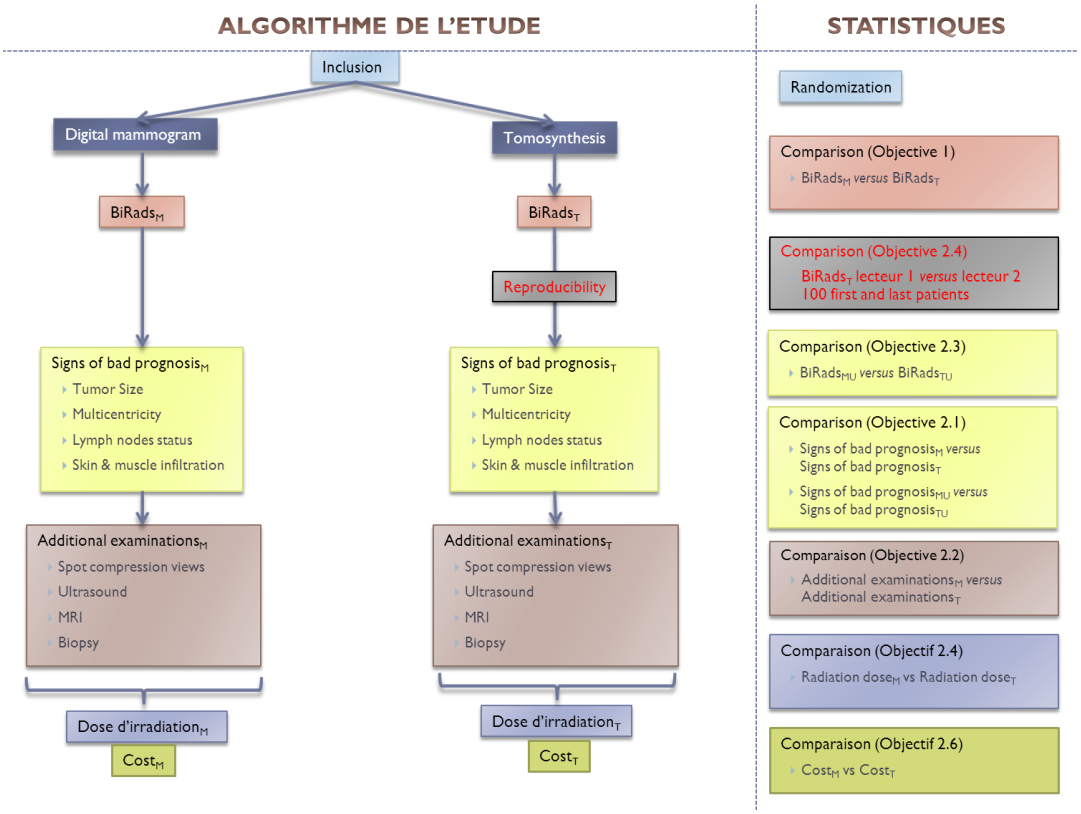

Figure 1. Study design

The following elements of the patient management include additional imaging tests, biopsies and monitoring. The decision to use these techniques will be guided by clinical practice and will be based on the recognized standards for patients more than 18 years with clinical or mammographic breast abnormalities.

The ethnicity of the patient will be collected. This information is useful for analysis of breast density. Indeed the risk of breast cancer increases with breast density (69), breast density change with ethnicity (70), and the risk of cancer would be different by ethnicity (71).

4.2.1.3 Number of centers

Four centers: Saint Louis Hospital Lariboisière Hospital , HEGP and Tenon Hospital, AP-HP, Paris

4.2.1.4 Randomisation

During the enrollment period all patients presenting in the four centers with a clinical abnormally (palpable mass, nipple discharge, asymmetry) or with a lesion discovered in mammographic screening, breast imaging, or in follow-up will meet an investigator radiologist. This person will verify the inclusion and exclusion criteria of the patient and will ask the patient to participate, explaining clearly the purpose of the study and what it entails.
The patient will receive an information leaflet and the informed consent sheet (in three copies), which the investigator radiologist will have signed with the date of the examination. If the patient agrees to participate, she will sign the consent form before doing the mammography examination. The study radiologist will keep two dated and signed copies of the consent form, and the patient will keep the third copy.
The investigator radiologists are Cédric de Bazelaire, Emmanuelle Cauderlier, Marine Bricout, Carmen Moise and Marcella Albiter at Saint-Louis hospital, Isabelle Thomassin, Jocelyne Chopier, Benjamin Fedida, and Sophie Dechoux at Tenon hospital, Vinciane Placé at Lariboisière Hôspital and Caroline Rousseau, Alexandre Bellucci, Marie Brisa, Samia Belaroussi, Lamya Meziti and Foucauld Chamming's, Bendavid Sandra, Dautry Raphaël, Oprea Raluca at George Pompidou European Hospital. All investigators radiologists have more than 5 years of breast imaging experience.
Patients accepting to participate will be randomized to either the conventional mammography arm or the tomosynthesis arm with synthetic tomography. The randomization will be centralized and performed with a web server (Cleanweb).
The randomization list will be performed by the study statistician following the operating procedures of the Department of Clinical Research and Development (DRCD) of Assistance Publique – Hôpitaux de Paris (AP-HP). Randomization will be centralized and balanced between the two arms and center-stratified.

4.2.1.5 Evaluated parameters

For the 100 first and 100 last patients, two radiologists will interpret the tomosynthesis + synthetic mammography ($BiRads_T$), independently. For the other patients, only one investigator radiologists will provide an interpretation depending to the arms. In mammography arm : $\mathbf{BiRads_M}$ based on mammography datas and in tomosynthesis arm : $BiRads_T$ based on tomosynthesis and synthetic mammography datas.
When breast ultrasound is required, the reader will provide a BiRads classification, based on combination of ultrasound + mammography ($\mathbf{BiRads_{MU}}$) in mammography arm. In

tomosynthesis arm, the radiologist will provide a BiRads classification, using results of ultrasound + tomosynthesis (**$BiRads_{UT}$**).

4.2.1.5.1 Primary evaluation parameter

The primary evaluation parameter will be the classification error of tumors according to the BiRads scale (divided into categories 4 and 5 versus 1 to 3) obtained by mammography (**$BiRads_{M}$**) and by tomosynthesis (**$BiRads_{T}$**) according to the gold standard.

Gold standard

Results of additional examinations

The evaluation of certain lesions requires additional examinations that may formally eliminate a cancer according guidelines (Table 1). (5) In some cases these images will be classified as BiRads 2 with an adapted follow-up. The final diagnosis will be made at the end of the clinical and radiological follow-up.

Histologic results

Lesions classified as BiRads 4 and 5 after radiological examinations will undergo biopsy. The samples will be analyzed by one trained pathologists specialized in breast diseases. The final diagnosis will be based on the pathology results.

Follow-up results

For lesions classified as BiRads 1-3 the final diagnosis will be made at the end of the follow-up of 24 month.

Primary criterion: BiRads classification

In the tomosynthesis arm, the investigator radiologist will performed a BiRads classification (**$BiRads_{T}$**) for each patient, based on tomosynthesis with synthetic mammography according to known guidelines (Table 1). (5)
In the mammography arm, the investigator radiologist will performed a first BiRads classification (**$BiRads_{T}$**) for each patient, based on mammography alone according to known guidelines (Table 1). (5)

4.2.1.5.2 Secondary evaluation criteria

Criteria for a poor prognosis

In both arms, we will compare the **visibility** (presence or absence) of signs of poor prognosis criteria.In addition, we will compare the visibility of poor prognosis criteria seen on mammography + ultrasound and seen on tomosynthesis with synthetic mammography + ultrasound. The criteria for a poor prognosis for malignant lesions are described in detail paragraph above.

Number of additional examinations

The **number of additional examinations** will be compared between both arms.
The additional examinations are described in paragraph above.

BiRads classification taken into account ultrasound results

In mammography arm, the reader will establish a BiRads classification based on both ultrasound and mammography (**$BiRads_{MU}$**). In tomosynthesis arm the radiologist will provide a classification taken into account ultrasound + tomosynthesis results (**$BiRads_{UT}$**).
We will evaluate ultrasound usefulness in both arms, by comparing **$BiRads_{MU}$** to **$BiRads_{M}$** and **$BiRads_{UT}$** to $BiRads_{T}$ classifications. The number of ultrasound exams will be compared in both arms.

Radiation dose

The **total radiation dose** will be compared between both arms (with mammography and with tomosynthesis).
The total radiation dose will be calculated according to paragraph above.

Agreement between readers

The reproducibility of the interpretation of tomosynthesis will be assessed with differences of classifications $\mathbf{BiRads_T}$ observed between the two radiologists with the 100 first and 100 last cases.
The **difference** of classifications $\mathbf{BiRads_T}$ between the 100 first and 100 last cases will show the learning effect.

Cost of the diagnostic strategies

The total cost of each diagnostic strategy in both arms will be estimated from the viewpoint of the payer (following the current recommendations of the National Health authority – HAS –). In the absence of a tariff for tomosynthesis, the cost of tomosynthesis will be estimated by micro costing.

1) Cost of tests
    a. Tomosynthesis
    The resources used by tomosynthesis will be recorded during the trial period, by direct observation of: time spent by professionals (time-motion study) supplies and consumables. These resources will be valued using salary + charges for personnel cost and purchase prices.
    The equipment cost will be estimated from the theoretical purchase price and 5- year deprecation. The total number of test per year will be estimated from actual utilization during the trial and extrapolation to the post trial period.
    Overheads and other logistics costs will be estimated from the hospitals' cost accounting departments, and allocated to each test using time as the allocation key.

    b. Other tests (mammography and ultrasound) already have a tariff which will be used in the economic evaluation

2) Cost of the strategy

Total test utilization by patient will be recorded in the CRF and valued. The total cost of the strategy is the sum of all diagnosis tests performed added to the costs of consultations and possible (but unlikely) hospitalizations.

4.2.1.5.3 Role in the teams

Enrollments

The patient inclusion and collection of informed consent will be done by one of the investigator radiologists:

- Tenon Hospital: Isabelle Thomassin, Jocelyne Chopier, Benjamin Fedida, and Sophie Dechoux
- Saint-Louis Hospital: Cédric de Bazelaire, Emmanuelle Cauderlier, Marine Bricout, Carmen Moise and Marcella Albiter
- Lariboisière Hospital : Vinciane Placé, Bendavid Sandra, Dautry Raphaël, Oprea Raluca
- George Pompidou European Hospital : Caroline Rousseau, Alexandre Bellucci, Marie Brisa, Samia Belaroussi, Lamya Meziti and Foucauld Chamming's

Reading mammography and tomosynthesis

In the four centers, for the 100 first and 100 last patients, two radiologists, with more than five years of experience in breast imaging, will make separate interpretations of tomosynthesis (**$BiRads_T$**).

For the other patients, mammography or tomosynthesis will be interpreted by only one investigator radiologist with more than five years of experience in breast imaging. For each patient the reader should interpret mammography or tomosynthesis following established guidelines and the report should include:

- **$BiRads_M$** and **$BiRads_T$** classifications
- Required additional examinations
- Visibility of signs of poor prognosis
- Radiation dose

Additional examinations and follow-up

All additional examinations and follow-up may be performed and interpreted in centers under the supervision of a different investigator radiologist except for the additional mammographic views, which are part of the mammography exam.

5. INVESTIGATIONAL PLAN

Before any discussion or action related to the research, the investigator collects the free and informed consent in writing of the person who lend themselves to research or his legal representative.

5.1 Visite d'inclusion

Verification of inclusion and non-inclusion criteria.

5.1.1 Mammographic examination

The mammographic or tomosynthesis examination are intended to eliminate or to find, localize, and characterize one or several abnormalities before a potential biopsy in patients presenting for a clinical or mammographic abnormally.

At enrollment, a mammographic or tomosynthesis examination following the protocol indicated below will be made, after information to the patient and informed consent has been given. These examinations will be made on a digital mammography system, Selenia Dimensions, from Hologic, capable of doing 2D, 2D+3D or 3D examination.

The mammographic or tomosynthesis examinations will be made by experienced study radiographers trained on using the Selenia Dimensions from Hologic.

5.1.2 tomosynthesis arm

The patients in the tomosynthesis arm will have a tomosynthesis with synthetic mammogram interpreted by a single radiologist following the BiRads classification (Table 1). (5) The decision to complementary examinations and biopsies will be made by the reader following the BiRads recommendations.

In all centers, for the 100 first and 100 last patients, two radiologists will make separate interpretations of tomosynthesis.

5.1.3 Mammography arm

The patients in the mammography arm will have a digital mammogram interpreted by a single radiologist following the BiRads classification (Table 1). (5) In this case indications for additional examinations are based on the mammography alone.

5.1.4 Additional examinations

Additional examinations may be carried out under the supervision of a different investigator radiologist than first reader except for the additional mammographic views, which are part of the mammography exam.
In each arm, indications for additional examinations will be evaluated in the following order:

Additional mammographic views

After mammography the first additional examination to be discussed should be additional mammographic views. The additional views used will be other projections, magnification and compression views that reduce anatomical noise by separating with direct pressure the overlapping tissues. The additional views will be made on the day of the study enrollment.

Breast ultrasound

The ultrasound examination will be made on the day of the enrollment in the study. The investigator radiologist will provide a BiRads classification combining ultrasound and mammography results ($BiRads_{MU}$) in mammography arm and a BiRads classification based on tomosynthesis with synthetic mammogram plus ultrasound in tomosynthesis arm ($BiRads_{TU}$).

Breast MRI

The decision to do an MRI will be made for the patients in both arms by the investigator radiologists according to the recommendations of the European Society of Breast Imaging published in 2010. (53) MRI should be considered for cases with clinical abnormally or abnormal imaging but inconclusive findings on conventional imaging (mammography and ultrasound) where it is not possible to perform a needle biopsy. MRI should be considered also for Patients with discrepancy in size >1 cm between Mammography and Ultrasound with expected impact on treatment decision. MRI should not be used as an alternative to needle biopsy when needle biopsy can be performed. MRIs will be performed up to 15 days after the enrollment in the study.

Biopsy

Patients classified as BiRads 4 and 5 will undergo a biopsy according to the known guidelines (Table 1). (5) Fine needle biopsies with ultrasound guidance for masses visible in ultrasound. Stereotactic large gauge biopsies for mammographic abnormalities without mass visible in ultrasound. MRI guided biopsy for lesions with suspicious contrast enhancement in MRI without correspondence in ultrasound or mammography.
All biopsies will be performed at the center of enrollment with a maximum delay of ten days between discovery and biopsy.

5.2 Follow-up

The follow-up will be carried out under the supervision of a different investigator radiologist than first reader.

In each arm, patients classified as BiRads 1 or 2 after the mammography and additional examinations if any, will undergo standard follow-up of 24 month with a mammographic examination yearly or bi-yearly according to their risk factors at the enrollment center. Patients classified as BiRads 3 will have follow-up examinations at the enrollment center following known guidelines at 6, 12, and 24 months (54).
Lesions classified as BiRads 4 and 5 after the mammography or tomosynthesis will undergo biopsy. The biopsy samples will be analyzed by one pathologist specialized in breast diseases. If the biopsy shows malignancy, the patient will undergo adequate treatment according to recognized standards. In case of benign biopsy, the patient will have a follow-up examination at 6 months and 1 year according to the recommendations of French Health Authority (HAS). They will be classified as definitely benign if the lesion remains stable or if it has diminished. If the lesion grows, another biopsy will be performed.
The study protocol doesn't require any further follow-up examinations. During the follow-up, the decision on additional examinations (mammography, ultrasound, MRI) will be based on clinical signs.

5.3 Expected duration of the research

The inclusion period will be 18 months and the follow-up time will be two years after finding a lesion classified as BiRads 3 that doesn't require biopsy, a benign BiRads 2 lesion or in patients without findings classified BiRads 1.
The total duration of the research is 42 months.

5.4 Flowchart

Actions	J0 (**Inclusion Visit)**	J7 +/- 7 j	[3]M6 +/- 15 J	[3]M12 +/- 15 J	[3]M24 **(End of study)**
Informed consent	X				
Fax inclusion[1]	X				
History	X				
Clinical Exam	X	X	X	X	X
Mammography or Tomosynthesis[1]	X		X	X	X
Additional Imaging[2]	X		X	X	X
Ultrasonography[2]	X		X	X	X
MRI[2]		X	X	X	X
Biopsy[2]		X	X	X	X
Adverse Events	X	X	X	X	X

[1] According to randomization arm.
[2] Examinations if necessary according to recommenadations of l'HAS.
[3]. In case of injury found in the inclusion visit classified BiRads 3.

6. Rules of withdrawal

6.1 Criteria and procedures for premature withdrawal or exclusion from research

Any subject can stop participating in the research and leave the test at any time and for any reason whatsoever. The investigator may suspend or discontinue the participation of a subject looking for any reason to be in the best interests of the particular subject for serious adverse events. In this case, it will notify the sponsor (s) event (s) spam (s) grave (s) and (s) through to its (their) resolution.

It is necessary to distinguish the following situations:

- Temporary cessation of treatment, the investigator must document the reason
- Early termination of treatment, but the subject remains in the research, until the end of their participation, the investigator must document the reason
- Aborting processing and testing output. The investigator should:
    - o Document the reason (s) (effectiveness or failure effect (s) spam (s) grave (s), other medical problems , personal reasons)
    - o Collect the evaluation criteria at the time of the test output if the subject agrees
    - o Provide patient follow-up , especially if serious adverse effect
    - Topic lost sight of: we do not know what happened to the subject. The investigator should:
    - o Make every effort to resume contact with the subject
    - o In order to know at least if the subject is alive or dead
    - o And if the subject is contacted ,

♣ Document the reason (s)

♣ He proposed to realize the extent of the evaluation criteria , if the subject agrees.

If test output, or lost sight of a subject, the data may be used for in the absence of opposition to it. The explicit withdrawal of consent is a particular situation is rare, where the subject clearly expressed (sometimes in writing) to withdraw the consent he signed. In case of withdrawal of consent, data on the subjects can not be used unless the subject expresses no objection to their use in writing. In practice, the subject is outside the test.

Conversely, all test outputs are not due to an explicit withdrawal of consent. Indeed , the subject may come out of the research and / or investigator may remove the person searching for one or more reasons: the subject's condition improves or worsens, the subject has a serious adverse effect , other medical problems, personal reason of the subject (family, work ...), without the patient withdraws consent.

The report form should list the various reasons for test output:

- o Efficiency
- o Ineffective
- o Serious adverse event, poor tolerance
- o Other medical problems
- o Personal Reason

The output of the search for a patient will not change his usual care with respect to its condition.

In the case of premature discontinuation of study due to toxicity, a serious adverse event notification will be sent by fax (01 44 84 17 99) to the promoter. The serious adverse events will be followed until resolution.

If an independent monitoring committee was set up, it will identify and / or validate the methods to be followed.

6.2 Stop part or all of the research

It is necessary to distinguish the following three decisions:
- Premature and temporary interruption of research suspension inclusions
- Early termination of a definitive research arm
- Final premature interruption of the entire research

For these three decisions, we must distinguish two situations for the treatment :
- Premature and immediate interruption of therapy in all patients at the decision
- The subjects are allowed to finish taking their treatment

The AP- HP or the Competent Authority (ANSM) promoter may prematurely interrupt temporarily or permanently all or part of the research, following the recommendations of an Independent Monitoring Committee (if applicable) in the following situations :
- First, in case of unexpected serious adverse reactions (SUSARs) in a treatment arm or an imbalance of serious adverse events between the two treatment arms , requiring a reassessment of the risk / benefit ratio of the research.
- If interim analysis : stop to demonstrate the effectiveness of a treatment arm or hand stop for futility.
- Similarly, unexpected events, new product information , upon which the objectives of the research or clinical program are unlikely to be met, may cause the AP- HP or the Competent Authority (ANSM) promoter interrupt early research.
- The AP- HP promoter reserves the right to suspend the inclusions permanently, at any time, if it appears that the inclusion objectives are not achieved.

In all cases stop a search, how to care for patients during participation in research must be specified. It should include clarifying whether patients included in the research should be monitored until the end of their participation , as required by the protocol.

6.3 Criteria for cancellation of the study

After the inclusion and follow-up of 1/3, 2/3 and 100% of patients, an independent safety committee will decide on the results of these intermediate analyses of the difference in total radiation dose observed between the two arms. The committee will be able to stop the study if the risk is too high compared to the benefit for patients

6.4 Patients' right to withdraw from the study

The patient retains her right to withdraw from the study at any moment.

In case of premature termination of the research, the decision and the rationale is transmitted by the AP-HP sponsor within 15 days from the Competent Authority (ANSM) and the CPP, together with the recommendations of the DSMB (Data Safety Monitoring Board)

7. Eligibility CRITERIA

7.1 Inclusion and non inclusion criteria

7.1.1 Inclusion criteria

- Signed informed consent
- Patient having clinical or breast imaging abnormalities classified as BiRads 3, 4, 5 (Table 1). (5)
- Patient over 18 years old.

7.1.2 Non-inclusion criteria

- Patients at high risk of breast cancer, mutations BRCA 1 or 2 carriers, Li Fraumeni, or history of thoracic radiation will be excluded because of their greater sensitivity to ionizing radiation. (11)
- Patient unable to give informed consent for physical, mental, or legal reasons.
- Patient not affiliated with French Social Security Insurance.
- Patient under treatment for breast cancer.
- When mammography is not recommended according to good practice by the French Health Authority (HAS).
- Pregnant patient.

7.2 Methods of recruitment

7.2.1 Justification for number of patients

The sample size in the "mammography + tomosynthesis" arm was computed according to the method proposed by Alonzo et al. (2). It was assumed that mammography had a sensitivity of 90% and a specificity of 83%. (3) We also assumed that we wanted to detect an improvement in specificity from 83 to 90% while ensuring that the false negative rate would not be increased more than from 10 to 15%. With an overall type I error rate of 0.05 and a total power of 90% (after correcting for the joint test on both criteria) and a paired design, 187 patients with disease and 710 healthy patients have to be recruited in the study. A total number of 1000 patients ensure a probability higher than 80% to obtain such numbers of patients and healthy controls, assuming that the prevalence is 20% in our population. It was also decided to include the same number of patients in the "mammography" arm.

7.2.2 Feasibility

All patients addressed at the two study centers that fulfill the selection criteria will be included.

The average number of available patients per year is 1,386 patients at Saint-Louis, 1,160 at Tenon, 300 patients at Lariboisière and 1000 patients at HEGP. These data are based on the activity reports of breast imaging in the radiology departments of Tenon, HEGP, Lariboisière and Saint Louis hospitals (Table 2) taking into account the patients referred for clinical abnormalities, abnormal mammogram or a biopsy (corresponding to the target population for this study).

Inclusion of 2,000 patients corresponds to 52% of the interventional activities in breast imaging during an 18-month period at the four centers.

The large number of radiologist investigators spreads the stain and prevent a reduction of inclusions during the holidays.

The presence of a clinical study Technician on the four sites every day during the period of inclusion will facilitate the work of investigator radiologists and warranty a maximum rate of inclusion.

8. Mammography and tomosynthesis (Technical)

8.1 Protocol and acquisition parameters

The acquisition parameters and the digital mammography systems are identical in both centers (Tenon and Saint-Louis Hospitals).

8.1.1 Acquisition protocol

Hologic will provide two tomosynthesis system for the research project and for an additional period before the study for training. Installation, training will be done by Stephanix, French exclusive distributor for Hologic.
In the mammographic arm, the patients will have a digital mammography examination.
In the tomosynthesis arm the patients will have in a single compression a tomosynthesis.
For the digital mammogram four projections are obtained: Cranio Caudal (CC) and mediolateral-oblique (MLO) views for each breast.
For the tomosynthesis, four set of projections are obtained: CC and MLO for each breast. In addition, 4 synthetic mammograms are reconstructed : CC and MLO for each breast.

8.1.2 Technical parameters

System characteristics

Digital mammography system

Hologic's mammography system uses a direct conversion amorphous selenium digital detector.
The system uses an HTC grid, an honeycomb like grid structure that reduces scatter radiation in both directions while preserving contrast.
During tomosynthesis acquisition, the grid is automatically retracted and filter changes to aluminium.

The system uses an **Automatic Exposure Control (AEC)** that controls the exposure factors (kV, mAs,) as a function of the breast thickness and of the density of the breast. The kV varies from 22 to 49 Kv with 1kV increment, and mAs from 3 to 500.
The images cover the full field of 24 x 29 cm.
The system can perform all projections: CC, MLO, and ML.
In conventional 2D digital mammography, the system is capable of doing magnification views with a mag factor of X1.8 or X1.5 as well as spot compression views
The average glandular dose delivered on the MTM-100 (45mm breast phanton) is around 1,2 mGy.

The tomosynthesis scan angle is 15 degrees (-7,5°/+7,5°),15 projections are acquired in less than 4s.
The average dose delivered in tomosynthesis for the same phanton used in 2D is 1,4 mGy.
A filtered backprojection algorith is used for image reconstruction. The spatial resolution is around 100 µm (90 to 110 µm)and slices are reconstructed with 1mm thickness.

Monitor characteristics

All examinations will be archived in the center's PACS and on an external hard drive for an additional secure storage.

The images will be read on two Barco Coronis Tomosynthesis approved 5 Mega Pixel screens with a native resolution of 2048x2560 pixels, a viewing angle of 170°, a contrast in a darkened room of 600:1, luminosity calibrated at 500 cd/m² (145.9 fl.), 700 cd/m² (204 fl.) maximum. The stabilization, calibration, and Q/A are automated by I-Guard on Dual DVI (complying to VESA DVI).

Image interpretation

Interpretation system

Before the study, the tomosynthesis and the workstations will be installed several months in advance in all centers to allow investigator radiologist to learn how to interpret tomosynthesis images. The training will be performed on exams of patients referred in both centers in the same conditions as for research. Data from this training will not be used for research.

Interpretation method

BiRads classification on mammography and tomosynthesis

Breast density on mammography and synthetic mammograms will be defined by the reader according subjective criterion defined above and objective data provided by the mammograph.

The lesions seen in mammography or tomosynthesis will be described following the BiRads guidelines (Table 1). (5) Lesions will be sorted in four categories: masses, asymmetric densities, microcalcifications, and architectural distortions. The interpretation must describe the shape, density, contours, topography, and size for masses. For microcalcification clusters, the investigator radiologist will record the size and shape of the cluster, and the type and number of microcalcifications.

During the interpretation of the tomosynthesis images, the reader will pay particular attention to the **definitive absence of suspicious criteria** such as architectural distortion associated with a mass or microcalcifications, spicules around irregular masses, microcalcifications that are numerous, pleomorphic, fine branching or casting with a linear or segmental distribution (duct-shaped patterns).

Mammography and tomosynthesis will be classified according to BiRads guidelines. The worst sign found with one of both techniques will be taken into account for classification, except if this sign is found to be clearly benign with one of both techniques:

- BiRads 1 (negative)
- BiRads 2 (benign lesion)
- BiRads 3 (probably benign lesion)
- BiRads 4A (low suspicion of malignancy)
- BiRads 4B (medium suspicion of malignancy)
- BiRads 4C (high suspicion of malignancy)
- BiRads 5 (strongly suggesting cancer)

Additional examinations

Spot compression views confirm the presence of a lesion if it persists under compression after eliminating fibro glandular tissue overlapping (BiRads 4 or 5). The presence of a lesion is dismissed if the feature disappears, interpreted as superposition of glandular tissues (BiRads 2 or 3). (60, 61)

Magnification may prove microcalcifications and masses characterization.

Additional profile views (ML) may prove microcalcifications to be benign by showing sedimentation or pyramid characteristics (BiRads 2 or 3). (62)
Ultrasound: An investigator radiologist blinded to tomosynthesis results will perform ultrasound. Ultrasound will be interpreted taking into account both the results of ultrasound and mammography according BiRads criteria (Table 1). (5) Ultrasound may eliminate suspicion of malignancy by showing a simple cyst appearance (BiRads 2). (63) However, ultrasound can also plead for cancer by showing solid hypo echogenic mass with irregular shape, speculated borders and posterior attenuation (BiRads 4 or 5). The combination of ultrasound + tomosynthesis will be classified according to BiRads guidelines. The worst sign found with one of both techniques will be taken into account for classification, except if this sign is found to be clearly benign with one of both techniques.
MRI may eliminate suspicion of malignancy for masses or architectural distortion by showing the absence of contrast enhancement (BiRads 2). (16, 64)

Signs of Poor prognosis

In the tomosynthesis arm the signs of a poor prognosis are studied for the mammographic data separately and then with the combination of tomosynthesis and combination of mammography + ultrasound if any. These factors include:

- **Multifocality-Multicentricity**: if lesions are located around the primary lesions or in the same quadrant, or if lesions are situated in different quadrants.
- **Bilaterality**: Lesions in the contralateral breast.
- **Size**: if the large axis of the lesion is > 2 cm.
- **Lymph node status**: loss of fatty hilum, round aspect, small axis > 10 mm.
- **Appearance of skin**: thickening of skin compared to contralateral side.

Patient radiation dose

The patient radiation dose is calculated by the system. The **total radiation dose** is calculated by adding dose values from digital mammography, tomosynthesis, and additional imaging if any.
An independent safety committee will analyze the total radiation doses received by the patient after inclusion of 1/3, 2/3 and 100% of the patients. This monitoring should avoid an excessive radiation for patients linked with tomosynthesis.

Safety evaluation – Undesired effects

Tomosynthesis acquisition is done as for classical mammogram with compressed breast which can be painful.
Biopsies may be requested after the analysis of tomosynthesis views. Risks for patients undergoing biopsies are benign hematoma (5%) and infection (< 0.1%).
The research protocol may require injection of contrast if breast MRI is requested after analysis of the tomosynthesis views. Risks for patients undergoing MRI examinations are related to the contrast agent (gadolinium chelate). They include allergy (0.001%) and nephrogenic systemic fibrosis in case of kidney failure (clearance < 30 ml/min) (65). In case of previous allergy to gadolinium chelate or kidney failure, no MRI will be performed.
This study modifies the management of the patient by integrating in the mammography + tomosynthesis arm four tomosynthesis views. The radiation dose related the 4 tomosynthesis views is equivalent to four digital mammograms on the Hologic-Stephanix system, and only two views for other systems on the market. The U.S. *Food and Drug Administration* has recognized in 2010 the benefit of tomosynthesis by granting approval for using four mammographic views together with four tomosynthesis views with the Hologic-Stephanix system. Additional mammographic views may be required according to the tomosynthesis results and should increase the total radiation dose. Nonetheless, the study by Gennaro (66) shows that tomosynthesis alone is not inferior in terms of diagnostic performance to

mammography. Gur et al also show that in screening the combination of tomosynthesis and mammography may reduce the false positive rate in mammography by 30%, reducing also the number of additional examinations (49).
However, an independent safety committee will monitor the total radiation dose observed between the two study arms after the inclusion of 1/3, 2/3 and 100% of patients. The committee will be authorized to stop the study if tomosynthesis is suspected to increase the total radiation dose and if the safety committee believes that the risk is too high compared to the benefit for patients.

9. ADVERSE EVENT REPORTING

9.1 Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.
All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through to the end of the designated follow-up period.

9.2 Serious Adverse Events

A serious adverse event is defined as one that suggests a significant hazard or side effect, regardless of the investigator's or sponsor's opinion on the relationship to investigational product.

This includes, but may not be limited to, any event that (at any dose):

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- is a persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless

fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.
If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.
For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.
Second malignancies must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures. All secondary cancers will be reported for each participant to a minimum of 3 years after the last dose of the experimental medicine, a steady reminder of all investigators participating in this research will be conducted every 6 months to collect any new cases of secondary cancers. All cases of secondary cancers will be declared to ANSM according to the modalities of declaration of the Suspected Unexpected Serious Adverse Reaction.

9.3 Classification of Severity

For both AE and SAE, the investigator(s) must assess the severity of the event. The severity of the adverse events (AEs) will be graded on a scale of 1 to 5 according to the last available version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE). The NCI CTCAE can be viewed on-line at the following NCI web site: *http://ctep.cancer.gov/reporting/ctc.html*. If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event.

Grade Definition

1 Mild : Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2 Moderate : Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3 Severe : Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4 Life-threatening : Immediate risk of death; requires hospitalization and clinical intervention
5 Death

9.4 Classification of relationship/causality of adverse events to study device

The investigator(s) must determine the relationship between the study device nd the occurrence of an AE/SAE as “Not suspected” or “Suspected” as defined below:

- Not suspected: the temporal relationship of the adverse event to study device administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Suspected: the temporal relationship of the adverse event to study device administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

9.5 Reporting Procedures for All Adverse Events

All adverse events occurring after the inform consent form is signed (whether or not attributed to investigational product), will be reported on the CRF. Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable. The following attributes must be assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may be asked to provide follow-up information.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the subject was permanently withdrawn from the study or investigational product due to a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report Form or the EOS Case Report Form. The severity of adverse events will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE).

9.6 Serious Adverse Event Reporting Procedures

All serious adverse events must be reported to the sponsor (AP-HP) within one working day of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report form, and faxed to the sponsor:

Sponsor: AP-HP / DRCD **Fax: 01 44 84 17 99**

The sponsor will inform relevant Regulatory Authorities and the Ethics Committee:

- of all relevant information about serious unexpected adverse events suspected to be related to the study device, study procedure and use of study device that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.
- of all other serious unexpected events suspected to be related to the study medication as soon as possible , but within a maximum of fifteen days of first knowledge by the investigator.

9.7 Pregnancies

If a woman becomes pregnant through research or in some cases if it's his mate who is involved in research (drug up to the seminal line of man), pregnancy must be notified to the sponsor on time it has defined. The investigator sends by fax 01 44 84 17 99 pole Vigilance in the standard form of «initial data collection of pregnancy." This form must contain the

expected date of delivery, contact the obstetrician and maternity scheduled for delivery if the pregnancy continues.
The investigator should follow the patient until the end of the pregnancy or its termination and notify the sponsor after the standard collection form after pregnancy.
If the outcome of pregnancy is part of the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, birth defects, ...) the investigator must follow the procedure for reporting SAEs.

9.8 Any other safety issues

"Any other safety issues" are defined by any new safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial

10. STATISTICS

10.1Justification for number of patients

The sample size in the "mammography + tomosynthesis" arm was computed according to the method proposed by Alonzo et al. (2). It was assumed that mammography had a sensitivity of 90% and a specificity of 83%. (3) We also assumed that we wanted to detect an improvement in specificity from 83 to 90% while ensuring that the false negative rate would not be increased more than from 10 to 15%. With an overall type I error rate of 0.05 and a total power of 90% (after correcting for the joint test on both criteria) and a paired design, 187 patients with disease and 710 healthy patients have to be recruited in the study. A total number of 1000 patients ensures a probability higher than 80% to obtain such numbers of patients and healthy controls, assuming that the prevalence is 20% in our population. It was also decided to include the same number of patients in the "mammography" arm.

10.2Feasibility

All patients addressed at the two study centers that fulfill the selection criteria will be included.
The average number of available patients per year is 1,386 patients at Saint-Louis, 1,160 at Tenon, 300 patients at Lariboisière and 1000 patients at HEGP. These data are based on the activity reports of breast imaging in the radiology departments of Tenon, HEGP, Lariboisière and Saint Louis hospitals (Table 2) taking into account the patients referred for clinical abnormalities, abnormal mammogram or a biopsy (corresponding to the target population for this study).
Inclusion of 2,000 patients corresponds to 55% of the interventional activities in breast imaging during an 18-month period in centers.
The large number of radiologist investigators spreads the stain and prevent a reduction of inclusions during the holidays.
The presence of a clinical study Technician on the four sites every day during the period of inclusion will facilitate the work of investigator radiologists and warranty a maximum rate of inclusion.

10.3Strategy for analysis

Dr Matthieu RESCHE RIGON (Service de Biostatistique et Information Médicale – hôpital Saint-Louis) will be responsible for the statistical analysis, performed with R version 2.10.1 or later (The R Foundation for Statistical Computing, Vienna, Austria).

The analysis strategy for the different objectives to avoid inflation of the type I error rate is as follows:

- The main objective being the comparison of BiRads classification obtained by mammography and mammography + tomosynthesis, respectively, the analyses pertaining to this objective will be carried out at a type I error rate of 0.05. Secondary analysis will only be carried out with formal statistical testing if this first analysis is significant, to limit multiplicity issues.
- In case of a significant main objective, then the BiRads classification obtained with mammography + ultrasound will be compared to that obtained with tomosynthesis, and the BiRads classification obtained with tomosynthesis + ultrasound will be compared to that obtained with other combinations. To control the overall type I error rate at 0.05, these tests will be performed with local levels adjusted according to Hochberg's method.

10.4 Descriptive analysis

Information about the patients will be available regarding age, risk of breast cancer (hormonal treatment, family history…) along with the information from mammography and tomosynthesis.
Suspicious findings in the mammography arm and tomosynthesis arm will be described separately.
A subjective analysis by the readers on the visibility of different features from the BiRads catalog will be described, and lesions will be described on a five-point scale: Much better, better, equal, worse. The subjective evaluations will be compared with a Wilcoxon paired test.
Regarding additional examinations, lesions not detected with tomosynthesis will be registered to find the factors influencing false negatives for tomosynthesis.
Quantitative variables will be presented with a mean value (interval type) or median (25^{th} to 75^{th} percentile) according to their distribution, the qualitative values of interest and percentages.

10.5 Comparison of BiRads classification for mammography and tomosynthesis

The analysis comparison of the BiRads classifications obtained by mammography and then by tomosynthesis will rely on the construction of simultaneous confidence intervals for the ratios of true negative rates (specificity) and false negative rates (1-sensitivity) obtained with each technics in the tomosynthesis arm, as described by *Alonzo et al.* and detailed hereunder. (2) A formulation of superiority will be used for the ratio of specificities, while a formulation of non-inferiority will be adopted for the ratio of false negative rates. The classification will judge as compared to the « gold standard » described above.

The method of *Alonzo et al.* relies on simultaneous confidence intervals for two ratios of rates. In the present case, the two rates are the true negative rate (specificity) and the false negative rate, respectively. The simultaneous confidence interval is equivalent to a statistical test controlling an overall type I error rate α (here fixed at 0.05). For such a goal, the confidence limits for each ratio of rates have level $1-\alpha^*$, with $\alpha^*=1-\sqrt{(1-\alpha)}$. For the true negative rate (TNR), we define the ratio rTNR as the TNR obtained with mammography + tomosynthesis

divided by the TNR obtained with mammography alone, and the ratio of false negative rates rFNR in a similar manner.
Let us additionally define the null and alternative hypotheses for the superiority and non-inferiority tests as

$$H_{0,1}: rTNR = 1$$
$$\text{vs } H_{1,1}: rTNR = \delta_1 = 0.9/0.83 = 1.08$$

and

$$H_{0,2}: rFNR = \delta_2 = 0.1/0.15 = 0.67$$
$$\text{vs } H_{1,2}: rFNR = 1$$

The method consists in computing confidence limits at a global α level (with local levels α^* for rTNR and rFNR). Then H is rejected if the lower confidence limit of rTNR is > 1 (superiority) and H is rejected if the lower confidence limit of rFNR is > 0.67 (non-inferiority). This procedure controls the global type I error rate α.

10.6 Comparison of BiRads classification for mammography + ultrasound and tomosynthesis

The method of analysis for this objective will be similar as described above, but with alpha levels corrected according to Hochberg's method.
As Hochberg's method is based on p-values ranking, obtaining corrected local levels for the simultaneous confidence intervals is not straightforward, all the more than two hypotheses are simultaneously tested (superiority for TNR and non-inferiority for FNR). The strategy is as follows: As the computation of confidence intervals in Alonzo et al. relies on a normal approximation for the distribution of the log ratio (rTNR or rFNR), a Wald test will first be performed for each null hypothesis. Then, the p-values will be ranked separately for the tests concerning the rTNRs and the tests concerning the rFNRs. According to these ranks and the numerical values of the p-values, adjusted levels are computed for each test. Let us denote "adj" such a level. The confidence interval is then computed with a modified adjusted level $\alpha^* = -\sqrt{(1-\alpha_{adj})}$ to account for simultaneously constructing a confidence interval for the rTNR and the rFNR. Note that for a given comparison such as for mammography + ultrasound and mammography + tomosynthesis for instance, the adjusted levels may be different for the rTNR and the rFNR, according to the results obtained for the other comparisons. But the whole procedure should control the global type I error rate α=0.05.

10.7 Comparison of BiRads classification for tomosynthesis + ultrasound with other combinations

The method of analysis for these objectives will be similar as described above, but with alpha levels corrected according to Hochberg's method, as described above.

10.8 Comparison of detection of signs of a poor prognosis between Modalities

Mammography versus Tomosynthesis
Mammography versus Mammography + Ultrasound
The sensitivity and specificity for both modalities for detection of criteria for a poor prognosis described above will be estimated with a 95% confidence interval and compared with McNemar tests. As two comparisons are performed, p-values will be adjusted according to Hochberg's method.

10.9 Comparison of number of additional examinations

The number and type of additional examinations will be described for both arms.
The number of additional examinations will be compared between the two arms with a Welch modified t-test (this test accounts for different variances between the groups; given the

number of patients, it should be equivalent to a z-test). The difference between the mean numbers of additional examinations will be presented with a 95% confidence interval.
The ultrasound, additional views, MRIs, and biopsies will be compared between the two groups using a chi-squared test (or if necessary by an exact Fisher test). The absolute and relative differences between the two arms will be given with their 95% confidence interval.
The total cost of performed additional examinations will be compared between the arms using a Welch modified t-test. The mean difference between the arms will be presented along with its 95% confidence interval.

10.10 Comparison of density of mammographic

The density of mammographies will be compared using a Welch modified t-test. The mean difference between arms and the 95% confidence interval will be presented. All previous analyses will be repeted in the high and low density groups defined by the median of the observed density.

10.11 Comparison of received radiation dose in the two branches

The accumulated dose to the patients from mammographic examinations will be compared using a Welch modified t-test. The mean difference between arms and the 95% confidence interval will be presented.

10.12 Evaluation of agreement between readers

The agreement between the BiRads classifications for the two readers will be evaluated with the weigthed kappa. Results will be presented with a 95% confidence interval.

10.13 Comparison of costs

Costs of diagnostic strategies will be compared using non-parametric tests. Univariate sensitivity analyses will explore the contribution of utilization time of the machine, time per examination and learning curve in addition to the purchase price of the equipment.

11. Monitoring and Quality Assurance

The Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of the study under the second paragraph of Article L1121.1 of the French Public Health Low (Code de la Santé Publique). The AP-HP is represented by the department of clinical research and development (DRCD and DIRC Ile de France). The sponsor will pay the fee to the French Agency for the Safety of Health Products (AFSSAPS) and will obtain a registration number for the research.
The sponsor will present the research protocol and the patient information form to the Person Protection committee (CPP - Ile de France IV).
The sponsor will supervise the research. The patient management in both study centers will be performed according to the Helsinki declaration and good practice recognized.

11.1Monitoring procedures

The clinical research assistants (CRA), representing the sponsor will perform investigating visits at intervals matching the monitoring of patients, the enrollments and the risk level attributed to the research by the sponsor.
- Opening visit before enrollments, to establish the protocol and familiarization with the various stakeholders in biomedical research.
- For following visits, electronic Case Report Forms (eCRF) will be reviewed by the CRA according to the state of advancement of the research. The principal investigator and the other investigators agreed to receive the CRAs at regular intervals. During the visits, according to good clinical practice, the following elements will be reviewed:

• Protocol and research procedures are respected,
• Verification of informed consent from patients,
• Review of source documents and comparison with data reported in the eCRF for accuracy, missing data, data consistency according to the DRCD rules.
- Final visit: retrieval of eCRF, biomedical research documents, archiving.
Outside these visits, the CRA will be at the disposal of the investigators to meet their needs for information or advice.

11.2Transcription of data in case report forms

A clinical study Technician (CST) will be recruited to assist the project in compliance with the Protocol and its circuits as well as filling of eCRF in the recruitment centers.
All information required by the protocol will be provided in the eCRF and the investigator in case of missing data will give an explanation.
The data must be recorded in the eCRF as soon as they are obtained both for clinical and non-clinical data.

11.3Steering group

A steering group will be formed consisting of the radiologists in charge of the project, a biostatistician, and representatives from the sponsor and from the Clinical Research Unit (URC) nominated for this research.
This group will define the general organization and the running of the research, coordinate information and decide during the research how to handle unforeseen events, survey the conduct of research in particular in terms of tolerance and adverse events.

11.4Independent committee for evaluation of critical events

Pilot and coordinating committee:
This committee will consist of two gynecologists specialized in breast imaging and two radiologist non-investigators. The committee will review all records to validate the morbid events and determine for each patient whether or not a qualifying condition (presence or absence of cancer). This validation, independent from the investigator radiologists, will be made without knowing the results of the tomosynthesis.

Independent DSMB:
This study involves additional irradiation for patients. An evaluation by the CPP will be conducted before the study. In addition, an independent safety committee (DSMB: Data Monitoring safety Board) of two biophysicists will be in charge to monitor the total radiation dose received by the patients in both arms (mammography and tomosynthesis). This committee will review the total radiation doses after inclusion of 1/3, 2/3 and 100% of the patients. The committee will compare the difference in radiation dose between both arms and morbid events related to radiation. This committee will be authorized to stop the study if tomosynthesis is suspected to increase the total radiation dose and if the reading committee estimated that the risk is too high compared to the benefit for patients.

11.5Data management and data storage

11.5.1 Data management

For each patient all items defined in chapter 0 will be filled out by the investigator radiologists, including:
- Initials (first name and last name), patient number, date and place of birth,
- Prior medical or surgical history of interest,

An eCRF will be created to collect all data.
Documents under the law on biomedical research must be archived during 15 years after the end of research (see BPC, chapter 8: essential documents).
This indexed archive includes:
· Copies of the letter of authorization from ANSM and the mandatory opinion of CPP
· Successive versions of the protocol (identified by version number and date)
· Correspondences with the sponsor
· Signed consent forms in sealed storage with a list or register of enrollments
· eCRF completed and validated for each patient
· All the appendices specified in the study
· The final study report, statistical analysis and quality control for the study (double forwarded to the sponsor)
· Audit certificates from any audits done during the research
. Reports from the independent safety committee in charge of monitoring the total radiation dose of the patient
The database for the statistical analysis should also be archived by the person responsible of the analysis (paper or computer).

11.5.2 Right of access to data and source documents

Persons with direct access of data and source documents in accordance with the laws, including articles L.1121-3 and R.5121-13 of the French Public Health Low (code de santé publique) take all necessary precautions to ensure the confidentiality of information relating to experimental drug trials, testing, and persons involved, particularly regarding their identity and the obtained results. The data collected by these persons during quality control or audits will be anonymized.

11.5.3 Quality control

The quality control of data entered in the eCRF will be done by the CRA (representative of the sponsor) according to procedures of the sponsor.

11.6 Ethical and legal considerations

The sponsor is defined by the law 2004-806 from Aug 9, 2004. During this research, AP-HP is the sponsor and the Department of Clinical Research and Development (DRCD) will ensure that the rules are followed.
Before starting the research, each investigator will provide to a representative of the sponsor a copy of their personal CV dated and signed, with their inscription number at the French College of Physicians (Ordre des Médecins).
Patients will be informed of the execution of the protocol in a detailed information leaflet.
The study radiologist will collect the signed informed consent during the radiology examination. The patient retains the right to withdraw their consent at any time, according to the law.

11.7 Request for permission by ANSM

To be able to start the research, the sponsor (AP-HP) must submit an application to request authorization of ANSM The organization, defined in the article L. 1123-12, guards the security of persons that consent to biomedical research, considering especially the safety and quality of products used in research, with regards to existing referential, their conditions of use, and the safety of persons with regards to performed actions and methods used, and methods used to track persons.

11.8Request for the opinion of the CPP

In accordance with article L.1123-6 in French Public Health Laws (code de santé publique), the research protocol must be sent by the sponsor to a CCP. The opinion of this committee is given to the competent authority by the sponsor before to start of the study.

11.9Modifications

During the whole project, DRCD must be informed of changes to the protocol by the coordinating investigator. Modifications must be qualified as substantial or not.
A substantial modification is a change that modifies the warranties given to patients consenting to biomedical research (modification of inclusion criteria, extension of length of enrollment, participation of new centers…). After the first inclusion, any substantial modification must obtain, prior to its implementation, an agreement from the committee and authorization from the competent authority. In that case, if necessary, the committee will ensure that a new consent from persons participating in the research is used.
Otherwise, all extension of research (substantial modification to therapeutic workflow or to the included population, extension of treatment and/or treatment not initially foreseen in the protocol) must be considered as a new research project.
Any substantial modification will require an application to ANSM and/or an application for review by CPP.

11.10 French Commission of Informatics and Freedom (CNIL) Declaration

The law envisions that notification of computerized files of personal data must be done before the start of the research.
A specific reference method for handling personal data made in biomedical research as defined by the law 2004-806 from Aug 9, 2004 as falling within the scope of articles L.1121-1 of the French public health Law (Code de Santé Publique) was established by CNIL in January 2006.
This methodology permits a simplified notification procedure if the nature of the data collected in research is in accordance with the list provided by CNIL in their reference document.
When the protocol gets a quality control of data by a CRA representative from the sponsor and enters into the scope of the simplified application procedure by CNIL, the DRCD as sponsor will demand of the person responsible for the data files to give a written statement on compliance with the methodology of reference MR06001 simplified.

11.11 Information letter and informed consent

During the enrollment period, all patients presenting at the two centers with a clinical abnormality (palpable mass, nipple discharge, asymmetry) or with a lesion discovered in screening or follow-up will meet an investigator radiologist. This person will verify the inclusion/exclusion criteria of the patient and propose participation in the study, explaining clearly the objective of the study and what will happen. They will give an information letter to the patient and the consent form (triple copies), signed and dated by the investigator radiologist at the examination. If the patient agrees to participate, she will sign the consent form on the day of the examination with the study radiologist, before doing the mammography examination according to protocol. The study radiologist will keep two dated and signed forms, and the patient will keep the third.
The consent forms with the name of the patient must be verified the same day. The original will be kept by the principal investigator in the study archives (archived for 15 years). The third copy will be sent to the sponsor at the end of the study in a sealed envelope.

A separate register will cross-reference the patient number in the study with their name and hospital number. This list will be kept by the principal investigator in the archive.

11.12 Final research report

The final research report will be written by the coordinator in collaboration with the biostatistician. This report will be sent to all investigator radiologists for comments. Once consensus has been reached, the final version will be endorsed by the signature of each study radiologist and submitted to the sponsor as soon as possible after the effective end of the research. A report edited according to the reference plan of the competent authority must be sent to the competent authority and to CPP within a year after the end of the study, defined as the end of the follow-up for the last patient. This delay is 90 days in case of premature termination of the research.

11.13 Finance and insurance

11.13.1 Insurance

The AP-HP (Assistance Publique- Hôpitaux de Paris) is the sponsor of this study. In accordance with the law of biomedical research, AP-HP has insurance with the company GERLING KonZern for the full duration of the research, ensuring its own liability and that of all personnel (doctor or personnel involved in research) (law number 2004-806, Art L.1121-10 by French Public Health Law).
AP-HP reserves the right to cancel the research at any moment for medical or administrative reasons; In that case, a notification will be provided to the principal investigator.

11.13.2Scientific commitment

Each investigator commits to respect the law and to handle the research while respecting the terms of the Helsinki declaration in force. In order to do so, a copy of the scientific commitment (document type DRCD) dated and signed by each study investigator at each center will be provided to a representative of the sponsor.

11.14 Rules concerning publication

AP-HP owns the data and no use or transfer to a third party may be done without prior agreement. This includes persons signing the publications, persons having participated in the drafting of the protocol and the drafting of the results. AP-HP must be mentioned as the sponsor of biomedical research and financial support as appropriate. The name “Assistance Publique- Hôpitaux de Paris » must appear in the list of authors. Scientific publications will be the responsibility of the principal investigator. The participation of centers in publications will follow two rules: number of enrollments in the study and proposal by the investigators involved in a supplementary publications.
To be published in one of the journals of the International Committee of Medical Journal Editors (ICMJE, see http://www.icmje.org/jrnlist.html). Clinical trials should be listed, prior to enrollment of the first patient, at the website http://www.clinicaltrials.gov/. Only that site by the FDA/NIH corresponds today to the requirements of the editors of ICMJE.

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13. ANNEXES

Tables

Table 1. (68)

Mammographic Evaluation	Characteristic
Calcifications	
Description	
Typically benign	Vascular
	Coarse or popcornlike
	Rodlike
	Round
	Punctate
	Lucent center
	Rim or eggshell
	Milk of calcium
	Suture
	Dystrophic
Intermediate	Amorphous or indistinct
	Coarse heterogeneous
Higher probability of malignancy	Pleomorphic
	Fine branching or casting
Distribution	Grouped or clustered
	Linear
	Segmental
	Regional
	Diffuse or scattered
Number	<5
	5–10
	>10
Masses	
Shape	Round
	Oval
	Lobular
	Irregular
Margins	Circumscribed
	Microlobulated
	Indistinct or ill defined
	Spiculated
Density	High
	Equal
	Low
	Fat containing
Architectural Distortion	
Special cases	Intramammary lymph node
	Tubular density or dilated duct
	Global asymmetry
	Focal asymmetry
Associated findings	Skin retraction
	Nipple retraction
	Skin thickening
	Trabecular thickening
	Skin lesion
	Axillary adenopathy

BI-RADS® – Mammography, Fourth Edition: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext/BIRADSMammographyFourthEdition.aspx

Table 2

Years	Saint-Louis	Tenon	Lariboisière	HEGP
2005	1024	1443	-	-
2006	1226	1294	-	-
2007	1185	1013	-	-
2008	1597	1052	-	-
2009	1899	997	-	-
Mean (5 years)	**1386**	**1160**	**300**	**1000**

Figures

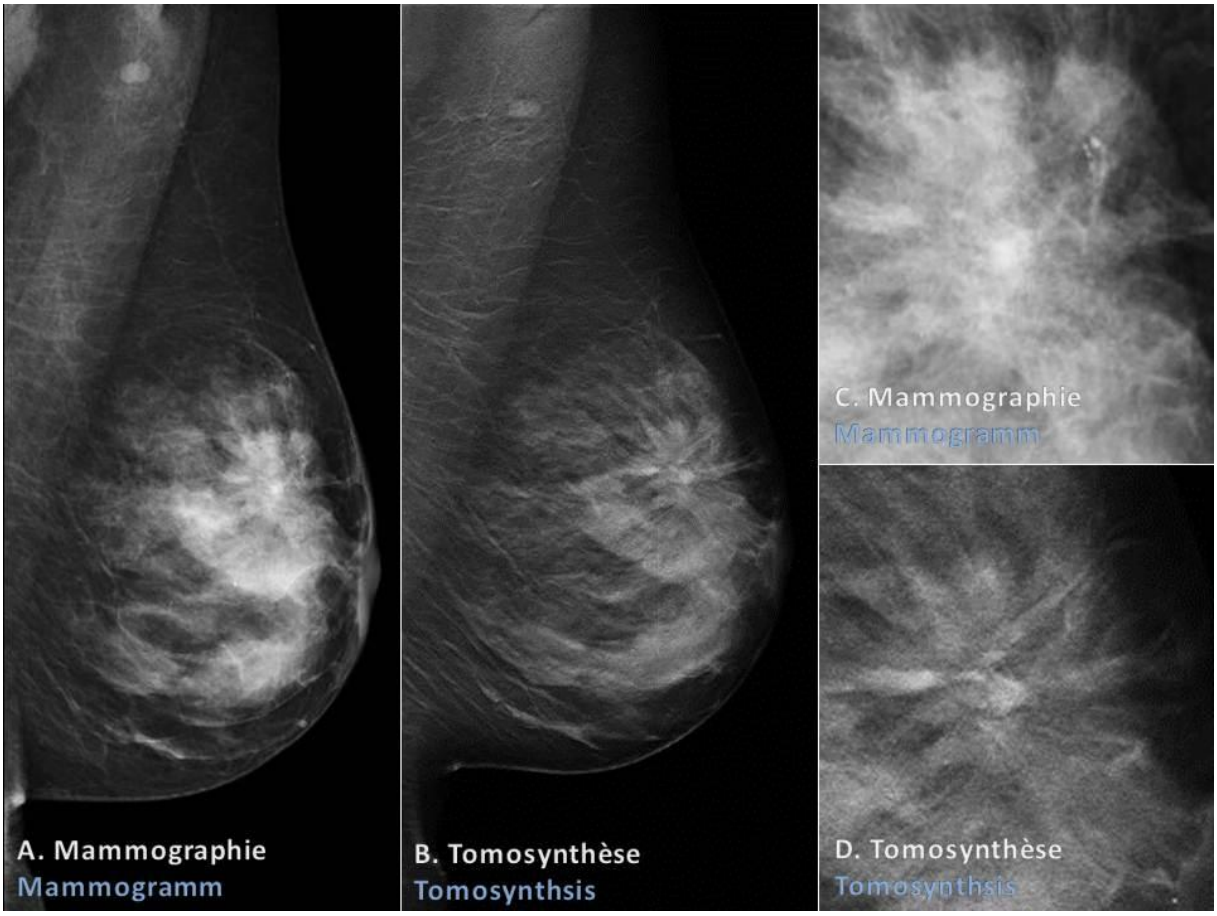

Figure 1. Example of breast cancer seen on mammography (C and D) and with tomosynthesis (A and B). Tomosynthesis improves spiculated masse visibility.

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GRILLE DE NOTIFICATION DES EVENEMENTS INDESIRABLES

Grille de Notification des Evénements Indésirables pour une Recherche Biomédicale portant sur un DM (Art. R. 1123-54 du Code de la Santé publique)			ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
ETOLE	Codes projet : **P120121 – IDRCB 2013-A00686-39**	Risque de la Recherche : **B**	CSI / DSMB : Oui ☒ **Non** ☐
«EVALUATION DE LA TOMOSYNTHESE DANS LA CARACTERISATION ET LA PRISE EN CHARGE DES LESIONS MAMMAIRES »			

A NE PAS NOTIFIER AU PROMOTEUR **Evénements recensés dans le protocole comme ne devant pas être notifiés mais qui pourront être recueillis dans le cahier d'observation (CRF)**		**A NOTIFIER SANS DELAI** AU PROMOTEUR **Envoi du formulaire de notification d'EIG par fax au 01 44 84 17 99 et à recueillir dans le CRF**	
Événements pouvant être graves **mais non liés à la tomosynthèse, ni aux actes et procédures ajoutés par la recherche.**	**Effets Indésirables Non Graves ATTENDUS** Connus pour être liés à la tomosynthèse ou aux actes et procédures de la recherche.	**Événements Indésirables Graves (EIG) ATTENDUS**	**Effets Indésirables Graves INATTENDUS (SUSARs)**

Description : ➢ Tout ce qui est en rapport avec l'évolution naturelle et habituelle de la pathologie : • hospitalisation programmée ou non pour suivi de la pathologie ; • aggravation de la maladie. ➢ Tout effet indésirable grave susceptible d'être lié aux traitements prescrits dans le cadre du soin pendant le suivi de la recherche	Description - Effets indésirables liés à la tomosynthèse : L'acquisition d'une tomosynthèse est réalisée sous compression de la même manière qu'en mammographie. Cette compression peut être douloureuse comme en mammographie. - Effets indésirables liés à un acte ou une procédure de la recherche : Il est possible que la tomosynthèse conduise à la réalisation d'examens supplémentaires comportant des risques propres: tel qu'une échographie (angoisse), une IRM (allergie au produit de contraste tel qu'un urticaire), une biopsie (douleur, hématome) ou une surveillance (angoisse).	Description - Effets indésirables liés à la tomosynthèse : Aucun Effet indésirable n'est attendu. - Effets indésirables liés à un acte ou une procédure de la recherche : Il est possible que la tomosynthèse conduise à la réalisation d'examens supplémentaires comportant des risques propres: une IRM (allergie au produit de contraste avec réaction anaphylactique)	Notifier tous les événements présentant l'un des critères de gravité noté ci-dessous, à l'exception de ceux recensés dans le protocole comme ne devant pas être notifiés : 1- Décès 2- Mise en jeu du pronostic vital 3- Nécessite ou prolonge l'hospitalisation 4- Séquelles durables 5- Anomalie ou malformation congénitale 6- Evénement jugé grave par l'investigateur (raison à préciser) ATTENTION : toute découverte d'une GROSSESSE au décours d'une recherche biomédicale doit être immédiatement déclarée au promoteur et fera l'objet d'un suivi jusqu'à l'accouchement.

FORMULAIRE DE NOTIFICATION DES EVENEMENTS INDESIRABLES GRAVES