To date, mammography remains the golden standard for early detection of breast cancer. Breast cancer is the most common cancer, accounting for about 25% of all cases, in women worldwide [1]. The ability to scan a breast for dense masses using a fast and efficient procedure has led to widespread incorporation of x-ray mammography into cancer screening programs around the world [2]. Mammograms provide the clinician with a 2D projection of tissue-induced energy attenuation. Dense, highly attenuating structures appear bright, whereas fatty tissues appear dark. Despite these appealing properties, current mammography has its drawbacks.

First of all, the procedure is commonly found unpleasant as a consequence of the strong physical compression required to squeeze the breast between the emitter and detector plates. Second, the radiation that illuminates the breast is ionizing. While it should be noted that the clinical gains of imaging as a screening tool are typically worth the risk, x-rays are notorious for their ability to induce DNA mutations. These could ultimately lead to the development of cancer [3]. Generally, a single-view standard mammogram is considered safe enough to be used in routine screening [4], where the amount of ionizing radiation is limited by restricting the imaging modality to 2D. This poses another limitation: 2D density images often fail to provide sufficient insight to reliably specify bright anomalies as malignant or benign, especially when the breast is generally denser. This condition is more likely to occur in younger women, who have a predominance of dense glandular tissue [5]. Therefore, a positive mammogram requires additional testing to confirm the presence of cancer via, for example, invasive biopsy, MRI or ultrasound imaging (US). Where biopsies are invasive and MRI is costly and time-consuming [6], US has the potential to shine as a cost-effective, noninvasive technique that can limit the diagnostic burden on the healthcare system and the patient via an effective and accurate imaging protocol.
Over the last three decades, US has been providing clinicians with an ever growing set of diagnostic tools, both on the anatomical as well as the functional side. Standard B-mode (or grayscale) imaging gives insight into anatomical structure, and can indicate anomalies, such as cysts or solid masses (fibrous nodules or malignancies). B-mode breast US was shown to provide a more accurate diagnosis for pathologies than x-ray mammography in young subjects with dense breasts [7].

Doppler sonography allows functional blood flow imaging by detecting the US Doppler shifts induced by the transport of blood cells. Using color Doppler, Yang et al. showed that malignant axillary lymph nodes display significantly higher peripheral flow in 135 woman with primary breast cancer [8].

Contrast-enhanced US (CEUS) enables visualization of microvascular perfusion by administering an intravenous injection of US contrast agents which are then transported along the blood stream. For cancer diagnostics, several quantitative CEUS strategies exist that aim at visualizing tumor-induced angiogenesis, an important marker of cancer-disease progression. Angiogenic vasculature is notably chaotic and inefficient, a typical feature that was exploited to localize prostate cancer with CEUS in [9–11].

Invasive breast cancers are notoriously stiff compared with benign tissue. Physicians assess nodular firmness by palpation, a subjective technique with a long history in medicine. Today, tissue stiffness can more reliably be evaluated using US elastography [12]. By palpating tissue using the ultrasound probe and consequently tracking the resulting echo displacements over time, tissue strain can be measured and displayed as a measure of elasticity. The applied stress can be imposed mechanically or via acoustic radiation force.

A fully quantitative measure of lesion stiffness can be obtained by shear wave elastography (SWE), a method that uses a high-intensity acoustical push pulse to produce laterally propagating shear waves that can be tracked to obtain the shear velocity, which is in turn related to the Young’s modulus. In [13], SWE and grayscale imaging are used to differentiate benign from malignant solid breast masses, yielding an accuracy of 86% for the detection of malignancy.

Finally, ultrasound computed tomography (UCT) enables quantification of pure acoustic parameters, such as sound speed and attenuation from their projections across the organ, being TOF and amplitude decay, respectively [14]. This type of acoustical characterization is valuable in the context of tumor-localization, as sound waves travel differently through dense fibrotic structures and tumors as compared with fat. While US is well known for its inability to effectively penetrate bone, making suitable projections in the human body often hard to acquire, the breast is an organ that is particularly suited for this line of technology.

Although it is reasonable to believe that all these diagnostic options allow a clinician to harvest a broad and useful spectrum of information, the possibilities may be overwhelming, and clinicians rely mostly on experience to select the tools they need. As a consequence, the full potential of US has most likely not been reached.

In another domain, an important clinical breakthrough was recently made by the introduction of multiparametric MRI [15], in which the rich but complex toolset provided by MRI is exploited by devising diagnostic protocols that combine multiple MRI parameters. With this achievement in mind, it seems logical to translate it to the field of US by incorporating the full set of US tools into a clearly defined multiparametric protocol (mpUS). The ultimate goal is to provide an operator-independent mpUS solution that suits the clinical workflow, and enables not only the detection of lesions in 3D space but also their risk-assessment with an accurate Breast Imaging Reporting and Data System score.

On the technical side, one can imagine a matrix of US elements (e.g., cylindrical or hemispherical) that encapsulates the entire breast, and is able to perform a sequence of experiments based on the US tools described above. Similar transducer systems are already being developed and tested for UCT [16], and are able to generate reproducible 3D echo (reflectivity) and sound speed images of the breast. The adaptation of the full range of US tools to such a system is another technical challenge that has to be addressed. Its ability to generate high-pressure push pulses and perform high frame-rate tracking for SWE, as well as reaching a suitable sensitivity to US contrast agents are vital in this context. With respect to the latter, a feasibility study of dynamic contrast-enhanced UCT has recently been published [17].

After the acquisition phase, all information extracted by the various investigations can be combined in a multiparametric fashion based on either: a clinician scoring and grading the
elements individually, and using a scheme that combines these scores into an overall Breast Imaging Reporting and Data System score (as for multiparametric MRI) or machine learning technology to combine the available information using advanced computer algorithms [18,19].

While the availability of such technology would most likely put ultrasound in a very competitive position with respect to other post-screening exams, a major question remains unanswered. Can ultrasound-based technology replace x-ray mammography for screening? This depends on many factors. Is mpUS more accurate than mammography? Is it time-wise feasible in clinical routine? Is it more cost effective? In this regard, one should evaluate whether all aspects of mpUS should already be incorporated at the screening level. For instance, CEUS requires an intravenous injection of relatively costly contrast agents and about 2-min acquisition time. One may therefore wonder whether a CEUS measurement is feasible for screening.

In any case, the future for US-based technologies looks bright, covering an increasingly broad spectrum of anatomical and functional imaging while retaining the high cost-effectiveness that makes it so appealing.

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Papers of special note have been highlighted as:
• of interest; ** of considerable interest
• Underlines the challenges of x-ray mammography for the dense breast.
** Describes various contrast-enhanced ultrasound imaging quantification (CEUS) strategies.
** Describes various CEUS quantification strategies.
** Describes various CEUS quantification strategies.
• Describes how shear wave elastography aids Breast Imaging Reporting and Data System classification based on grayscale ultrasound.
** The development of an ultrasound computed tomography system for breast imaging.
• Shows the feasibility of dynamic contrast-enhanced ultrasound computed tomography.
• Here, a multiparametric CEUS strategy based on machine learning is proposed.