In this era of precision medicine, the traditional role of the radiologist providing high quality (albeit qualitative) images needs to evolve further in order to help clinicians in their decision-making and contribute to the radiology value chain. Integrating quantitative imaging biomarkers into clinical practice allows us to measure the underlying pathophysiological mechanisms non-invasively, revealing properties relevant to detection, diagnosis, prognosis or response to therapy. The data sets produced by the imaging modalities can be extracted and analyzed and thus act as valid and reproducible surrogates of the intrinsic biological processes.1

It is therefore important for radiologists to become acquainted with the process of implementation, validation, and standardization of imaging biomarkers that are considered in viva (or, more accurately in silico) virtual biopsies2

In this review, diffusion-weighted imaging (DWI) of the breast will be analyzed from the perspective of the development of an imaging biomarker and its potential future role in the field of breast imaging.

THE DEVELOPMENT AND VALIDATION OF DIFFUSION-MRI AS AN IMAGING BIOMARKER
The stepwise development of imaging biomarkers, provides an orderly framework within which to discuss the technique of DWI, as well as its clinical applications and its validation as an imaging biomarker (Figure 1).

The proof of concept in DWI
The first phase is the proof of concept, whereby the underlying pathophysiological mechanism to be evaluated by DWI is demonstrated. Diffusion is the process of random motion of water molecules in a free medium. In vivo, water mobility or diffusivity is limited by intracellular and extracellular compartments, as well as tissue cellularity. Although the motion of water molecules is said to be “restricted” in tissues with a high cellular density (e.g. tumor tissue), in fact, there are three principal physical modes of diffusion: free, hindered and restricted diffusion.3–5 Free diffusion describes the random or Brownian motion of water molecules due to thermal agitation in the absence of any obstacles that follows a Gaussian distribution. Hindered diffusion refers to the delay of passage as they navigate around cellular obstacles, as in the extracellular space. Restricted diffusion is a term classically used to describe the trapping of water molecules within an enclosed compartment (i.e., the cell plasma membrane). The degree of water diffusion in tissue is inversely correlated with tissue cellularity and the integrity of cell membranes.

The proof of mechanism in DWI
The proof of mechanism refers to the relationship between the extracted imaging biomarker and the relevant disease. In order for the biomarker to become a surrogate of the underlying biological process, it has to undergo a process of technical and biological validation.
DWI is used to visualize the degree of water molecule diffusion at in vivo MR imaging. DWI was initially applied in the clinical setting in the mid 1990s for the diagnosis of acute stroke⁵ and in 1997, Englander et al⁶ investigated the possibility of applying DWI to the human breast.

**Image acquisition**
The first step in the proof of mechanism of an imaging biomarker is the image acquisition, whereby data quality has to be checked regarding signal and contrast-to-noise ratios, spatial and temporal resolution, artifacts and reproducibility.

**Description of the EPI sequence**
In clinical imaging, the sequence used is a $T_2$ weighted spin-echo sequence with two motion-probing gradients next to the 180° refocusing pulse.⁷ where segmented or single shot echoplanar readout techniques (EPI) are used to accelerate data acquisition. The faster a molecule diffuses, the greater the attenuation after applying the diffusion gradients and the weaker the corresponding pixel signal intensity at DWI. Thus, regions with restricted diffusion (i.e. higher density of cells) will show a higher signal than regions with fast water mobility. Typical DWI acquisitions have a diffusion time in the range of 30–50 ms, corresponding to an approximate displacement of 14–17 µm for unrestricted free water at body temperature. The degree of diffusion weighting, described by the $b$-value and determined by the strength and timing of the applied diffusion gradients (in s/mm²), is the primary factor that affects the sensitivity of the diffusion sequence to water motion. In human tissues, the diffusion process is not free and is influenced by a combination of mechanisms (diffusion, microstructural restrictions, microcirculation) that contribute to the final signal attenuation. In vivo signal decay is considered mono-exponential within intermediate $b$-value ranges, but due to the fact that the diffusion environment is highly complex, the concept of a single diffusion coefficient is arguable and as such is reported as an “apparent” diffusion coefficient or ADC.

At higher $b$-values, the signal decay fits the multiexponential model in vivo. At lower $b$-values ($b < 150$ s/mm²), the ADC is influenced by tissue microperfusion and can lead to overestimations of the ADC. Thus, the choice of the optimal $b$-values will influence the conspicuity of the lesions in the DWI images but will also modify the ADC value. Pereira et al⁸ analyzed the ADC values of breast cancers at $b$-values ranging from 0 to 1000 s/mm² and found that the ADC value calculated for a combination of $b$-values of 0 and 750 s/mm² showed a slightly better sensitivity and specificity than did the ADC value calculated for other $b$-value combinations. Current recommendations propose two $b$-values of 50 and 800 s/mm².⁹ Pereira et al⁸ also analyzed the ADC values of benign and malignant breast tumors with various combinations of $b$-values (0, 250, 500, 750, and 1000 s/mm²) and found that it is not necessary to use multiple $b$-values because the sensitivity of ADC with two $b$-values is equivalent to that with multiple $b$-values and the specificity of $b$-values 0 and 750 is higher than that of multiple $b$-values.
The ADC describes the average area occupied by a water molecule per unit time (mm²/s) and as a reference point, the ADC value of free water molecules at 37°C is $3.0 \times 10^{-3}$ mm²/s. In general, determination of ADC is performed by acquiring images at two $b$-values and fitting the corresponding signal intensities into a monoexponential model. ADC values can be influenced by which $b$-values are applied, a fact that highlights the need for consistent and standardized protocols. At higher $b$-values, ADC decreases in normal breast tissue, fibrocystic changes and breast cancer.⁷,⁹

The observed ADC value depends on many factors: fluid viscosity, membrane permeability, water transport mechanisms and the microstructure of the compartment containing diffusing water. Thus, ADC value can provide a specific information on the proof of concept (tissue microstructure, cellularity). For DWI acquired with two or more different $b$-values, ADC can be calculated for each voxel in the image and presented as a parametric map. Malignant lesions will appear brighter on DWIs and darker on ADC maps compared with normal fibroglandular tissue (Figures 2 and 3). ADC is indeed the surrogate biomarker

Figure 2. Breast images obtained with DWI in a patient with a Triple Negative subtype breast cancer in the left breast. Corresponding slices from DCE postcontrast image (a), DWI at $b = 0$ s/mm² (b), DWI at $b = 700$ s/mm² (c), ADC map (d). Invasive tumors show reduced diffusivity on DW imaging, appearing hyperintense on $b = 700$ s/mm² image (c) and hypointense on the ADC map (arrows) (d). ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted imaging.

Figure 3. Breast images obtained with DWI in a patient with a HER-2 subtype breast cancer in the left breast. Corresponding slices from DCE postcontrast image (a), DWI at $b = 0$ s/mm² (b), DWI at $b = 700$ s/mm² (c), ADC map (d). Invasive tumors (arrows) show reduced diffusivity on DW imaging, appearing hyperintense on $b = 700$ s/mm² image (c) and hypointense on the ADC map (arrow) (d). ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted imaging.
of diffusion that has to undergo all the necessary technical and biological validation steps in order to become a clinically useful imaging biomarker.

EPI-related technical issues

Conventional EPI-based DWI sequences provide fast motion-freezing imaging but DWI acquisition protocols must be optimized to reduce artifacts and achieve adequate signal-to-noise ratio (SNR).

Common EPI-related artifacts must be avoided during image acquisition in order to evade ADC quantification imprecisions.

- **The magnetic susceptibility artifact**, due to magnetic field inhomogeneities, can cause severe image distortions at the interface of materials with different magnetic susceptibilities such as the air/tissue or adipose/glandular tissue interfaces. Good patient positioning (avoiding skin folds) and improved shimming to reduce magnetic field inhomogeneities can avoid this artifact.

- **Motion artifacts** can cause misregistration, leading to false ADC values. Parallel imaging shortens acquisition times and minimizes these artifacts, ultimately leading to decreased image distortion (but also reduces SNR).

- **Chemical shift artifacts** can be overcome by adequate fat suppression and good-quality shimming.

- **Ghosting artifacts** are caused by phase mismatch during the EPI readout introduced by eddy currents or inadequate shimming, causing a mirror image that is shifted in the phase direction by half the field of view. Eddy currents are caused by strong gradients (especially evident in diffusion tensor imaging or DTI) and also originate image distortions, causing inaccuracies in ADC calculation.

- **Low spatial resolution** is a limitation of DWI that can be overcome by a higher SNR, afforded by higher magnetic field strength MR units.

**Image analysis**

The second phase in the proof of mechanism of DWI as an imaging biomarker is **image analysis**.

Once the source image quality is improved by implementation of noise reduction techniques, avoidance of artifacts and improvement of spatial resolution, signal analysis and feature extraction will yield the calculated tissue properties obtained from each voxel. In DWI, the final image with different ADC values calculated for each voxel is the parametric ADC map. ADC maps have poor anatomic detail and should be analyzed in conjunction with other MR images such as DWI, T2 weighted or 2 weighted images obtained without diffusion gradients and a DWI that reflects the water mobility but is also a T2 weighted image. In tissues with long relaxation times, the strong T2 signal might be an even more accurate way of assessing intra tumoral heterogeneity.

2. **ADC measurements** of lesions differ depending the ROI techniques, especially in large or non-mass lesions. Small ROI placed over the most hypointense area of the $b = 700$ s/mm² or $b = 800$ s/mm² image may provide more accurate measures in heterogeneous lesions while placing the ROI over the whole lesion may provide more reproducible results. Semiautomated ROI selection methods may allow for more consistent results and lately some authors claim histogram analysis might be an even more accurate way of assessing intra tumoral heterogeneity.

3. The T2 shine-through effect is a confounding variable that has to be taken into account when interpreting DW images. The standard diffusion image generates a T2 weighted reference image obtained without diffusion gradients and a DWI that reflects the water mobility but is also a T2 weighted image. In tissues with long relaxation times, the strong T2 signal might be an even more accurate way of assessing intra tumoral heterogeneity.

**Biomarker validations. The proof of principle in DWI**

To be clinically useful, a biomarker needs to undergo validation (performance of the test) and qualification (clinical approval) in order to ensure that the obtained measurements have a precise relationship with the underlying biological reality. Several validations including technical, biological and clinical have to be conducted before a biomarker is introduced in clinical research. These initial pilot tests performed on a small group of subjects are known as the proof of principle, to verify that the concept and related methods have the potential of being used before embarking on large-scale multicenter projects and clinical trials. Accuracy, repeatability and reproducibility studies of ADC and related methods have the potential of being used before embarking on large-scale multicenter projects and clinical trials. Accuracy, repeatability and reproducibility studies of ADC and related methods have the potential of being used before embarking on large-scale multicenter projects and clinical trials. Accuracy, repeatability and reproducibility studies of ADC and related methods have the potential of being used before embarking on large-scale multicenter projects and clinical trials.

Technical evaluations of DWI are performed using different measurements related to image acquisition, processing, analysis and ADC measurements. These measurements are done with phantoms and in healthy volunteers or in patients evaluating the different factors that may affect ADC's precision. Precise measurement of ADC is important since the dynamic range of the biomarker is quite small, from approximately $0.5 \times 10^{-3}$ mm²/s in densely packed cells to $3.0 \times 10^{-3}$ mm²/s in fluid-filled cysts.

**Biological validation** shows the link to tumor biology and is the correlation between preclinical disease models or human studies and reference methods such as histopathology, immunohistochemistry or genomics. In these studies, the influence of epidemiological data (sex, age, physiological status) and genuine biological variations has to be studied.

1. **Correlation with histopathology**. It has been proven that ADC values correlates well with the degree of cellular density in breast cancers as well as with the extravascular extracellular fraction in preclinical models.

2. **Influence of hormonal status**.
1. Menstrual cycle. Although initial studies posited increased ADC values during the second half of the menstrual cycle, these variations were non-statistically significant and subsequent studies confirmed no influence of the menstrual cycle or background parenchymal enhancement on ADC values.

2. Lactation. Breast tissue ADC values in lactating females are significantly reduced probably due to high lipid content and viscosity of the milk, but do not influence breast cancer ADC measurements.

3. Menopausal status. ADC is significantly lower in postmenopausal compared with premenopausal patients, probably related to changes in water content, microcirculation and adipose content with age. A recent paper by Horvat et al does not find any difference in ADC values between benign and malignant lesions in patients stratified by BPE level, amount of fibro-glandular tissue or menopausal status.

3. Intravenous contrast. The influence of contrast administration on DW is controversial, most likely due to the different acquisition parameters in the published papers. A meta-analysis by Dorrius et al confirmed that contrast administration does not significantly affect breast lesion ADC values. The EUSOBI consensus statement recommends performing DWI before DCE-MRI and consistency in timing across examinations is also advocated.

Clinical validations to see how well the biomarker works are initially performed as single-center observational studies in small groups of patients or meta-analyses of these studies.

In the realm of DWI, these studies focus mainly on three distinct clinical applications: lesion characterization, the prognostic value of ADC and response evaluation to neoadjuvant treatments with DWI. Screening with DWI has also been explored and will be included in the section on future perspectives of DWI (see below).

1. Lesion characterization with DWI. The most investigated clinical application of DWI is as an adjunct sequence to reduce the false positives encountered in contrast-enhanced MRI and avoid unnecessary biopsies. Since the first publication by Guo et al, many studies have shown breast malignancies have significantly lower ADC values than benign lesions. Two meta-analyses evaluating the diagnostic performance of quantitative breast DW imaging demonstrated overall better specificity than DCE MR imaging. More recently, another meta-analysis of 14 studies confirmed that DWI can increase the accuracy of DCE-MRI with a resulting area under the ROC curve of 0.94. Variations in DWI acquisition protocols as well as types of lesions (mass vs non-mass) and patient cohorts across studies prevent the issuance of an optimal ADC threshold value to distinguish benign from malignant lesions due to dependence of lesion ADC measures on choice and combination of b-values. Dorrius et al showed that despite the influence of choice of b values on ADC measurements, sensitivity and specificity are not significantly affected by choice of b-value. Moreover, a meta-analysis of 61 studies by Shi et al found that there was no significant difference in diagnostic accuracy for breast cancer between 1.5 and 3.0 T scanners. The EUSOBI consensus statement offers a proposal for an analysis and interpretation scheme based on both qualitative and quantitative ADC value ranges on which future research protocols could be based in order to standardize DWI.

2. The prognostic value of ADC. An area of active research is the correlation of ADC with molecular or traditional pathologic prognostic factors, as well as surrogate tumor phenotypes or recurrence scores. Although most of the associations have been non-significant to date, with as many studies finding significant or no significant correlation, there is a trend of concordance between ADC and more aggressive cancer features. This characterization of biological aggressiveness can be of help for selecting adequate treatments. In the most recent published literature, some authors find an inverse significant relationship between ADC and tumor grade, while others do not extending the debate that has been taking place since the earliest publications in 2009. On the other hand, most authors agree on the inverse correlation between ADC and the ki67 proliferation index, a fact that could be of weight in considering neoadjuvant treatment, although a recent multicenter analysis in 845 patients did not find any relationship. Although the earliest papers found a significant inverse correlation between ER-positive tumors and ADC, the latest publications either find a significant relationship or not, which is also in line with the fact that ER positive tumors are...
slow-growing and lower-grade cancers and suggests that studies with larger number of patients and in multiple centers are needed. Most studies dealing with HER-2-positive tumors and ADC have found a positive correlation, possibly due to a higher degree of angiogenesis overcoming cellularity in this type of breast cancers. As would be expected by the underlying biological cellular density, most recent studies dealing with the difference in ADC values between invasive and in situ tumors have found lower ADC values in invasive cancers. Moreover, some authors can predict invasiveness in pure-DCIS lesions by detecting the areas with the lowest ADC values or indexes and even use ADC to up-grade to malignancy in high-risk or B3 lesions. Attempts to differentiate between low grade and high-grade ductal carcinoma in situ (DCIS) are in the center of the debate over the necessity of surgically treating all DCIS and previous as well as current literature does not find ADC a significant biomarker to stratify patients. Associations between DWI characteristics (ADC and contrast-to-noise ratio) and recurrence scores in ER-positive, HER-2-negative breast cancers have yielded promising results and can potentially help stratifying patients into avoiding chemotherapy as well as being more cost-effective than the current recurrence scores schemes.

3. Response evaluation to neoadjuvant chemotherapy with DWI. One of the advantages of imaging biomarkers is to be able to non-invasively monitor response to drug treatments in a spatially- and time-resolved manner. The main utility of imaging techniques in this clinical setting is dual: to predict response early in the treatment course in order to spare the patients side-effects of unnecessary chemotherapeutic treatments and to accurately assess the extent of residual disease before surgery in order to plan the most adequate surgical approach. Lately, it has become even more important to predict pathological complete response (pCR) in order to omit surgery in patients with the highest pCR rates (tumoral subtypes HER2 and triple negative).

1. Early response prediction. Cytotoxic effects of chemotherapeutic agents (apoptosis, cell lysis) increase the mobility of water in the tissues, reflected in the increase of ADC value. Early studies with mice showed that increased diffusivity could be shown within days of therapy onset in implanted breast cancers. DWI may be able to offer earlier and more precise information on treatment response than DCE-MRI, as macroscopic volume changes are only the downstream manifestations of underlying patho-physiological phenomena (cell swelling and cell death) which occur early after treatment, and DCE can also show enhancement due to inflammatory changes. Several studies in breast cancer patients have proven that ADC can be an early predictor of response, as early as after the first cycle and earlier than DCE-MRI (Figure 6). The introduction of histogram analysis or voxel-by-voxel functional maps to parametrize response can be of help especially in very heterogeneous tumors and might be helpful in overcoming bias related to tumor segmentation techniques. Baseline ADC does not seem to predict response in all tumor subtypes and the usefulness of this parameter pre-treatment is not clear.

2. Residual disease evaluation. Residual disease has traditionally been evaluated with DCE-MRI and meta-analyses comparing both techniques have shown that DWI adds sensitivity for predicting pCR to the high specificity of DCE-MRI for residual disease. Both techniques combined achieve the best diagnostic accuracy. A recent meta-analysis focusing solely on DWI revealed a pooled sensitivity of 0.89 and a specificity of 0.72 for detecting pCR. The data definitely support the use of DWI in response evaluation, although future trials must incorporate rigorous quality assurance and control and reproducibility measures as well as multicenter designs in order to ensure the standardization of ADC as a response biomarker.

The proof of effectiveness and clinical qualification in DWI

Through qualification of a biomarker, the link between surrogate and clinical endpoints is established and it becomes a clinical...
Figure 6. Breast images obtained in a patient with a Triple Negative subtype breast cancer in the left breast (same patient from Figure 1): baseline pre-neoadjuvant chemotherapy, early after two cycles and pre-surgery after eight cycles. Slices from baseline, early (after two cycles) and pre-surgical (after eight cycles) DTI in the top row. Corresponding slices (bottom row) from baseline post-contrast image, T2 weighted image after two cycles and post-contrast image after eight cycles, pre-surgery. Note that in the DTI images after two cycles, there is a functional qualitative partial major almost complete response whilst in the corresponding T2 weighted image, the morphologic response is minor or minimal. When comparing the DTI images after eight cycles with the corresponding DCE image, there is a complete response in the DTI images (arrow, top row) and a residual enhancement in the DCE images (arrow, bottom row) interpreted as partial major response. The final pathology confirmed a complete response that was already predicted by the early DTI exam after two cycles. DCE, dynamic contrast-enhanced; DTI, diffusion tensor imaging.

Radiomics

The main objective of radiomics is the discovery of signatures (imaging biomarkers) which have strong associations with patient’s prognoses or tumor subtype classification. Imaging biomarkers have the potential to capture the entire tumoral area, including its heterogeneity in a non-invasive and quick way. In radiomics, a great number of image features (shape, histogram, texture features) are extracted from medical images. Through specific selection methods of stability analysis (repeatability and reproducibility tests) significant features are chosen and their prognostic powers are tested in order to choose a subset of significant features or signatures that will have prognostic information. When these phenotypic signatures are correlated with genotypes, it is called radio-genomics or even panomics (genomics, proteomics, metabolomics) to better stratify patients with genotypes, it is called radio-genomics or even panomics (genomics, proteomics, metabolomics) to better stratify patients.

CONCLUSIONS

DCE-MRI is a technique that provides complementary information to DCE-MRI exams. It has proven its value in single-center studies on lesion characterization and response evaluation, with a less clear role in tumor profiling through prognostic associations. Technical issues due to standard echoplanar imaging being solved but the technique must be completely standardized and clear interpretation guidelines must be issued in order for DCE-MRI to become more widely incorporated in breast cancer diagnosis and response evaluation. Potential areas of growth include contrast enhancement with DCE-MRI without contrast agents, investigation of additional biological properties through DCE-MRI and analysis of tissue microenvironment and its physical barriers to diffusion using higher b-value ranges than DWI (b > 1000 s/m²). Recent studies have explored this technique in lesion characterization. Radiomics is the discovery of signatures (imaging biomarkers) which have strong associations with patient’s prognoses or tumor subtype classification. Imaging biomarkers have the potential to capture the entire tumoral area, including its heterogeneity in a non-invasive and quick way. In radiomics, a great number of image features (shape, histogram, texture features) are extracted from medical images. Through specific selection methods of stability analysis (repeatability and reproducibility tests) significant features are chosen and their prognostic powers are tested in order to choose a subset of significant features or signatures that will have prognostic information. When these phenotypic signatures are correlated with genotypes, it is called radio-genomics or even panomics (genomics, proteomics, metabolomics) to better stratify patients with genotypes, it is called radio-genomics or even panomics.

1. DTI characterizes the diffusivity (rate of water diffusion) and the directionality (anisotropy) of water molecules, providing data on the microarchitecture through anisotropy measures. It has proven its role in both lesion characterization and response evaluation.

2. Intravoxel Incoherent Motion (IVIM) explores the microvascularity of the tissues through a bi-exponential signal decay model. It has likewise proven useful in lesion characterization and response evaluation.

3. Non-Gaussian diffusivity (diffusion kurtosis, stretched exponential diffusion) explores the complexity of the tissue microenvironment and its physical barriers to diffusion using higher b-value ranges than DWI (b > 1000 s/m²). Recent studies have explored this technique in lesion characterization.

DCE-MRI exams. It has proven its value in single-center studies on lesion characterization and response evaluation, with a less clear role in tumor profiling through prognostic associations. Technical issues due to standard echoplanar imaging being solved but the technique must be completely standardized and clear interpretation guidelines must be issued in order for DCE-MRI to become more widely incorporated in breast cancer diagnosis and response evaluation. Potential areas of growth include contrast enhancement with DCE-MRI without contrast agents, investigation of additional biological properties through DCE-MRI and analysis of tissue microenvironment and its physical barriers to diffusion using higher b-value ranges than DWI (b > 1000 s/m²). Recent studies have explored this technique in lesion characterization.
radiomics classifiers in order to better stratify patients and enable a real precision medicine.

Multicenter trials are clearly needed to validate single-center studies and establish DWI as a useful clinical decision-making tool.

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