 background/main objective, methodology and expected results.

BACKGROUND:

Breast cancer screening has had a major impact on reducing breast cancer mortality. In breast screening programmes, mammography (MG) is the most commonly used modality to diagnose breast cancer, although other modalities such as magnetic resonance imaging (MRI) or ultrasound (US) provide complimentary information. In addition to genetic mutations, family history and age, among others, parenchymal breast structure is regarded as an important risk factor associated with breast cancer. It is also widely accepted that breast cancer treatment not only depends on the stage at which the cancer has been detected but also on its molecular structure, being some cancers more aggressive than others. For instance, the triple negative breast cancer (TNBC) is one of the most aggressive for which is also difficult to find an effective treatment. There is also early evidence that imaging features could provide significant information to discriminate molecular sub-types.

MAIN OBJECTIVE

The main objective of DECODER is to develop tools to extract radiomic information using x-ray and MRI modalities based on deep learning. These radiomics will: (i) provide enough discriminative power to predict breast cancer sub-types at an early stage and (ii) demonstrate a strong association between the radiomics and breast cancer. Deep learning methods, with the technological improvement of the GPUs have increased the capability to extract richer features and to learn deeper models. In breast imaging this can be crucial to extract novel and more complex radiomic features that can help in predicting molecular cancer sub-types and that can also provide a richer information compared to current breast density information. This could have an impact in breast screening: improving early diagnosis, less biopsies and lower recall rates and allowing a faster, personalised and targeted treatment.

METHODOLOGY

This is a multidisciplinar coordinated project with computer science doctors, radiologists, epidemiologists, breast cancer researchers, all with a strong background and experience within the field. The project will consist in the following essential blocks: data collection, development of the tools, and clinical validation of the tools in terms of molecular sub-type prediction and proposing new and personalised risk factor.

RESULTS

Automated and universal tools, tested using different scanners and combination of imaging modalities to be integrated into clinical practice, will able to discriminate cancer sub-types using radiomic features alone. These will potentially improve early diagnosis and will provide enough discrimination power to enhance current breast density risk factors.

**1 Presentation of the hypothesis and description of the project objectives**  
(maximum 500 words)

An important aspect of personalised medicine is being able to provide tailored, patient-specific medical treatment according to individual patients and their tumour characteristics. Cancer detection and subsequent staging, grading, and classification of breast cancer sub-types allow patients to be categorised into sub-populations that may benefit from risk stratification and targeted treatment.

In this regard, breast cancer is a particularly heterogeneous disease and evolves continuously following systemic treatment. Being able to correlate imaging radiomics to molecular subtypes could be helpful in achieving the goals of precision medicine. In particular, TNBCs tend to be more aggressive than other types of cancers. Hence, an early diagnosis (i.e. based on imaging radiomics) and a fast and specific treatment response are key aspects for the survival rates of women suffering for this sub-type of cancer. In addition, risk stratification models could benefit from incorporating imaging radiomics as an additional risk factor, which is regarded as an initial but important step towards obtaining accurate personalised risk models.

The main hypothesis of DECODER is that breast imaging features (referred in this project as radiomics) obtained using medical image computing methods, can provide enough discriminative power to detect and classify breast cancer sub-types at an earlier stage. Methods based on deep learning techniques automatically extract and learn structural information from images. This set of techniques, specially the convolutional neural networks, together with the technological improvement of the GPUs have increased the capability to extract richer features and in fact to learn deeper models. In the medical area, this can be crucial to improve the performance of current state-of-the-art methods but also to extract novel and more complex radiomic features that can help in predicting molecular cancer sub-types. This could have an impact in various aspects of breast screening: improving early diagnosis and patient stratification (detecting high risk women), lowering numbers of biopsy procedures and recall rates, and allowing a faster, personalised and targeted treatment. Figure 1 illustrates the current breast cancer diagnosis and treatment workflow (left) and how DECODER would impact (right): more sensitivity in the radiologists diagnosis (i.e. less biopsies, note sizes of arrows in figure), earlier prediction of molecular sub-type (for both pathologists and oncologists) in order to speed up the treatment in critical cases (i.e. TNBC), and improved risk models including the proposed radiomic information.

**Main Objective:** The overall aim of DECODER is to develop novel radiomic features based on the analysis of breast images taking into account lesions, local and global glandular tissue measurements, and structural distortions. Those radiological features will be used to develop methods for the early detection and classification of breast cancer molecular sub-types and to improve the discriminative power of breast density cancer risk factors. Algorithms developed will be based on deep learning techniques, specially paradigms focusing on adversarial networks and convolutional neural networks (CNNs) and evaluated with clinically relevant amounts of patient data.

**2. Background and state of the art, including relevant bibliography**  
(maximum 2000 words)

Breast cancer is the second dominant cause of cancer death among women. Breast cancer mortality reduction due to the implementation of breast screening programs is estimated around 30%, with sensitivity reaching around 90% at a higher specificity (around 95-98%), especially in Europe [Seely18]. Although overall breast cancer (BC) incidence (the fact of developing the illness) is estimated in 1 in 10 women, it is commonly accepted that the risk of developing it (also referred to BC risk) is not the same for all women. Although in current screening programs all women undergo the same procedure (mammography), there is an increasing consensus that this should change into a stratified screening, where women are classified as being at high or low BC risk. Higher BC risk responds to women under certain circumstances: carrying BRCA gene mutations, having a dense breast and/or with family history of breast cancer, among the most important factors. Obviously, these high risk groups will have an increased probability to develop BC estimated to be 5 to 7 times larger (i.e. for gene mutations or high density) compared to low risk women.

In breast screening programmes, standard mammography (MG) is the most commonly used modality to diagnose BC, although in certain population groups (i.e. high risk or young women) other modalities such as magnetic resonance imaging (MRI) or ultrasound (US) are likely to be used to provide complimentary information. In recent years, Digital Breast Tomosynthesis (DBT) is slowly being adopted as a substitute of MG. In addition to MG, which is a 2D projection image, DBT provides pseudo-3D images, which in principle could lead to better sensitivity and specificity [Hodgson16]. However, increased costs, dose and reading times still prevent this technology from being widely used in screening programs.

It is widely accepted that breast cancer treatment depends on the stage at which the cancer has been detected but also, more importantly, on its molecular structure, being some cancers more aggressive than others. For instance the triple negative breast cancer (TNBC) is one of the most aggressive for which is also difficult to find an effective treatment. There is also early evidence that imaging features could play an important role in discriminating molecular sub-types in breast cancer patients.

**Breast cancer and risk factors**

The most common models of predicting risk of breast cancer in individuals are the Gail and the Tyrer-Cuzick models. Those models take into account different factors to determine a risk for developing breast cancer. For instance, the Gail model uses woman’s age, age at menarche, age at first live birth, number of previous benign breast biopsies, and number of first-degree relatives with breast cancer. Though it gives accurate predictions of the number of women in a given population who are likely to develop the disease, the model is less successful at determining the individual risk. This is however crucial for the development of a personal stratification and screening protocol. Most of today's risk models ignore individual breast structure and density as a personal risk factor. This is partly due to the complex nature of the relation between breast density and personal breast cancer risk and the lack of objective quantitative measures to characterise breast structural complexity. Methods for obtaining this information will be investigated in DECODER, and are expected to contribute to the ability of risk models to predict individual risk.

**Molecular sub-types and Triple Negative Cancers**

Most BC cells also receptive to estrogen and progesterone hormones. However, BC cells tend to present an increased number of receptors compared to normal healthy tissue which makes them grow and divide quickly. If the BC cells respond positive to a certain type of receptor, such cells can be used to perform personalised hormonal therapies targeted to the specific BC types (also known as molecular sub-type). For instance, 20-30% of all BC have large number of HER2 (human epidermal growth factor receptor 2) receptors which make them grow and divide quickly. Hormonal therapies and HER2-targeted therapies work to interfere with the effects of hormones and HER2 on BC, which can slow or even stop the growth of BC cells.

Approximately, 2 out of 3 women have BC that test positive for hormone receptors. Still, about 10-20% of BCs show negative results for both hormone receptors and HER2, thus they are considered to be **triple-negative breast cancers** (TNBC). TNBC means that the cells result negative for estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-). TNBC tends to be more aggressive BC, often implying a more aggressive treatment: mastectomy (rather lumpectomy), or higher dose of chemotherapy. Moreover, they are likely to spread beyond the breast and more likely to recur after treatment. These risks appear to be highest in the first few years after treatment.

In addition, and although their lower incidence, TNBC are of particular importance:

* **Lower survival rate**. Survival rates (especially within the five first years after diagnosis) tend to be lower for TNBC. A 2007 study of more than 50,000 women with all stages of breast cancer found that 77% of women with TNBC survived at least 5 years, versus 93% of women with other types of breast cancer [Dent07].
* **Higher grade (more malign)**. TNBC tends to report higher grades compared to other sub-types. The higher the grade, the less the cancer cells resemble normal, healthy breast cells in their appearance and growth patterns. On a scale 1-3, TNBC often is 3.
* **Basal like cell types**: Some TNBC cells resemble a type of cells called basal cells, that look similar to outer (basal) cells surrounding the mammary ducts. Basal-like cancers are considered a new subtype of cancer with similar characteristics to the TNBC.

**Deep Learning for medical image analysis**

Deep Learning has had a huge success in many areas of computer vision and medical image analysis. For instance, there is an immense potential of performance improvement in breast cancer computer aided diagnosis and detection (CADx/CADe) systems by analysing and integrating diagnostic information used by radiologists. Deep Learning is a recent and popular machine learning technique based on using neural networks but with many layers which allow the extraction of a complex hierarchy of features from images, resulting in a low dimensional space that can be further used for classification or segmentation. The features are learned and tuned at training time through a convex optimization process better known as back propagation. The rapid increase in GPU processing power has allowed training with millions of images achieving impressive results and generalization capabilities. Deep Learning algorithms come in many forms depending on the simplifications and abstractions employed, these include deep Boltzmann machines, deep neural networks and convolutional neural networks (CNNs), the most commonly used for image segmentation and classification. CNNs were first introduced in 1989, gaining great interest after the excellent results on the ImageNet competition in 2012, using millions of images depicting objects from a thousand different classes. As 3D and 4D medical imaging are becoming routine in the clinical practice, and with physiological and functional imaging increasing, medical imaging data is increasing in size and complexity. Deep learning techniques are gaining popularity in many areas of medical image analysis, such as computer-aided detection of breast lesions, computer-aided diagnosis of breast lesions and pulmonary nodules, and in histopathological diagnosis (see [Shen17] for a complete review on deep learning for medical imaging).

**Radiomics and cancer sub-types**

Although medical image analysis and computer aided diagnosis and detection (CADx/CADe) systems have been the main research strategy for many years in mammography, radiomics is a relatively novel concept. This refers to the extraction and analysis of a large amount of quantitative imaging features from medical images, in order to demonstrate the predictive or prognostic associations between such features and the medical diagnostic outcome. Radiomic features, traditionally hand crafted features but more recently automatically learnt by deep learning architectures, have been typically used for lesion detection, tissue classification or breast density estimation, among others. The extraction of the traditional features have been mainly driven by texture descriptors such as grey-level co-occurrence matrices (GLCM), local binary patterns (LBP), contrast and shape and size information. A recent review on those radiomic features for breast cancer can be found in [Valdora18], or the work of Saha et al [Saha18] on the review and evaluation of radiomic features for breast MRI (in particular Dynamic Contrast Enhanced (DCE-MRI)). In this regard the PI and the image analysis research team in the proposal have been working on the development of imaging features and biomarkers for improving breast cancer diagnosis in different aspects (supported by list of publications found in the IP and research group profile) including lesion detection and segmentation, dense tissue characterisation in US, MRI and mammography/DBT or multi-modal correspondence.

The aim of the **DECODER** project goes beyond the goal of detection/classification of lesions or characterisation of breast density. DECODER focuses on using radiomics to determine the first imaging signs of molecular sub-type of cancer, which, as stated previously, has a clear impact on patient prognosis and survival. Equally important, these radiomic features are regarded as crucial information cues for improving current risk models into personalised risk models. To this date, researchers have not deeply investigated the radiomic and molecular sub-type relationship, although some initial publications suggest that cancer molecular sub-types show common radiomic features, that could be used to classify/discern those types of cancers from their radiomic profile. In this line, [Ma18] found that features extracted from x-ray mammography images can be used to predict the cancer subtype. However, the small number of images used (some cancers up to 10-20 images), and the proposed methods (Naïve Bayes Classifier and adhoc features related to size and morphology), may be considered as a rather simplistic approach to such a complex problem. Moreover, Ma et al [Ma18] work focuses only on mammography images, and the DECODER project aims to also explore other imaging modalities such as DBT and MRI. Nevertheless, their work suggests that a correlation may exist between molecular breast cancer subtype and radiomic features. One should also mention the earlier work of Guo et al. [Guo15] from the University of Chicago, where they analysed several radiomic and genomic features for determining different molecular features (also referred to phenotypes) in breast MRI. They concluded, not surprisingly, that genomic features were more discriminative than the radiomic ones, although radiomic showed some discriminant power. However, the main limitation is the number of cases used, 91 patients, and the class imbalance of the different molecular sub-types. Finally, [Kim15] also suggested that not only appearance of the lesions and breast tissue are important features, but also its location is characteristic of certain molecular subtypes, specially for TNBC. This finding will be further investigated in this project. Regarding risk assessment, breast density and, more recently, parenchymal structure complexity have shown to have an added value in risk assessment models [Kontos19], however, this relationship needs to be explorer even further specially using latest deep learning advancements providing more informative automatically learnt radiomic features.

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