A new challenge in Radiology: Radiomics in breast cancer diagnostics

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Abstract

Breast cancer is one of the most common and widespread cancers that women can have. In order to prevent the occurrence of cancer, it is important to perform a preventive examination, which includes ultrasound and mammography. Radiology as a branch of medicine has seen rapid development in recent decades thanks to the development of technology, and artificial intelligence is increasingly used in radiology. Radiomics is a new method of radiological image processing that uses software programs to analyse tissue during diagnostic imaging. It is a combination of multiple imaging modalities with the aim of highlighting pathological formations that are not visible to the naked eye or are less significant. The aim of the paper is to introduce to the readers with radiomics and to explain in more detail how it works, and how it was integrated into certain radiological diagnostics and greatly facilitated the image processing process and the diagnosis of breast cancer. Many studies have confirmed that radiomics is a method with numerous advantages, but like any new field, it has its drawbacks. The main limitation is the computer system, which must be standardised so that radiomic data processing can be used in all institutions and so that these institutions can exchange information with each other without difficulty. The problem is also false positive findings, which greatly increase the costs of institutions and the time it takes for patients to reach a diagnosis. The solution to these allegations is the development of new computer algorithms and an increase in the sensitivity of computer detection of lesions. Radiomics will certainly play an important role in diagnostics and image analysis over a period of time. Given that artificial intelligence is still in the process of development, radiomics may not have an independent application, but it will certainly make the work of doctors easier in the analysis of radiological images.

Keywords: artificial intelligence; breast cancer; mammography; radiomics

Abbreviations and acronyms: AAA (Advanced Accelerator Applications), ADC (Apparent Diffusion Coefficient), AI (Artificial Intelligence), ANN (Artificial Neural Network), BI-RADS (Breast Imaging Reporting and Data System), CAD (Computer-Aided Diagnosis), CEM (Contrast-Enhanced Mammography), CT (Computed Tomography), DBT (Digital Breast Tomosynthesis), DCE-MRI (Dynamic Contrast Enhanced Magnetic Resonance Imaging), DICOM (Digital Imaging and Communications in Medicine), DL (Deep Learning), DWI (Diffusion Weighted Imaging), LVI (Lymph vascular Invasion), PET (Positron Emission Tomography), PACS (Picture Archiving and Communication System), RFM (Radiomics Feature Maps), ROI (Region of Interest), ROC (Receiver Operating Characteristic Curve)

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Introduction

Breast cancer is one of the most common causes of death in women and represents 25% of all malignant diseases, and it occurs most often in the period after menopause at the age of over 50. Men can also get breast cancer, but only in 1% of all cases [1]. Breast cancer arises from abnormal cells of the breast tissue that reproduce through the process of division and create nodules in the breast tissue, i.e. cancer. The earliest stage of breast cancer is non-invasive, stage 0; confined within the ducts of the breast and does not spread to healthy tissue. The non-invasive stage of breast cancer is also known as carcinoma in situ. The second type of breast cancer is the invasive type, characterised by extension beyond the ducts of the breast into healthy tissue, most often into the surrounding lymph nodes, but also by transplants into other organs, stage I-IV [2]. According to the latest data in Croatia,
mortality from breast cancer has decreased by 25 percent [3].

Although breast cancer is a serious and proliferative disease, with early detection and prevention it is possible to control and cure it. Accordingly, since 2006, the National Breast Cancer Early Detection Program - “MAMMA” has been implemented in Croatia, which includes mammography, breast x-ray in two projections and breast self-examination [4]. The gold standard for detecting breast cancer is mammography, and depending on the results, for a more precise diagnosis, the examination can be completed with ultrasound and magnetic resonance imaging.

With the development of technology and radiology as a science, the shortcomings of the aforementioned methods of choice for diagnosing breast cancer have been observed. Due to these observations, several computer programs were developed to increase the sensitivity with the same specificity, diagnosis and screening. Radiomics is a combination of multiple medical imaging modalities with the aim of highlighting pathological formations that are not visible to the naked eye or are less significant with the methods used so far [5]. Radiomics is increasingly used in oncology to improve the diagnosis, prognosis and treatment of cancer. This method requires a multidisciplinary approach, the cooperation of radiologists, oncologists, radiologic technologists and individual scientists for data and image processing. The workflow includes tumour segmentation, image pre-processing, feature extraction, model development, and validation. Certain features describe the distribution of signal intensity and the spatial relationship of pixels within the region of interest [6].

Radiomics

Radiomics is a new imaging method that uses software algorithms based on quantitative analysis [7]. In 2012, Dutch scientist Philippe Lambin first proposed the concept of radiomics and defined it as extracting a large amount of information from images [8]. Radiomics is divided into two parts, conventional and deep radiomics (Figure 1). In conventional radiomics, it is important to delineate regions of interest, ROI (Region of Interest), which includes morphology, texture and shape. Deep radiomics links biological features such as genomics and dissects each step in radiomics analysis in detail [9]. Radiomics image analysis involves five stages. The first phase includes the selection of the participant, that is, the patient on whom the analysis is performed. The second stage requires imaging performed by a radiologic technologist. The third stage is the extraction of radiomics features, the fourth stage is research analysis and the last stage is modelling [10].

The aim of the article

The aim of the article is to describe radiomics as a new method of image analysis, to explain the procedures during analysis, and to highlight important factors that influence the quality of the analysis. This is a review paper, supported by scientific research of the last ten years. It provides the necessary information and points out the advantages and disadvantages of this new field compared to other modalities in the detection of breast cancer.

Application of radiomics in the radiological system

The radiological system requires a precise data organisation of individual radiological diagnostics, therefore a large space for storing data and radiological images is necessary for the work and the quality of the results. Radiomics in the radiology system brings great challenges for the entire radiology team. Radiomics performs an analysis based on the difference in the density of the examined tissues, shows certain suspicious lesions based on basic data as biological markers that indicate pathological formation [11]. The disadvantage is the non-standard equipment of the system in hospital institutions. Scientist Zhovannik I. and colleagues investigated the Conquest system, an open image archiving system, PACS (Picture Archiving and Communication System) that stores DICOM (Digital Imaging and Communications in Medicine) metadata. The software in use today does not support the direct integration of PACS systems and radiomics images, but the Conquest system allows easier connection between institutions and the exchange of radiomics images [11].

Integration of radiomics in oncology

In addition to radiology, radiomics also plays an important role in oncology. The research of Shen C. and colleagues showed that the clinical research in the third phase of

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**Figure 1.** Evolution of radiomics

Source: https://towardsdatascience.com/what-is-radiomics-d9fb790a58c7
application and testing of the therapy is not effective, and that the results are unsatisfactory. The main factor in the treatment of cancer patients is time. Radiomics provides a detailed analysis of the radiological image and, based on the density, shape and volume of the tissue, can determine whether it is a malignant or benign tumour [12]. Oncology specialists benefit greatly from radiomics because it provides them with reliable diagnosis, prognosis and support in patient decisions and treatment. Radiomics uses an algorithm to classify samples and segment them into specific categories. This method of image analysis is multidisciplinary and requires the cooperation of specialist radiologists, radiological technologists, specialist oncologists and a data storage team [13].

**Application of radiomics in mammography**

The gold standard for diagnosing breast cancer is mammography, but with the advancement of technology, certain diagnostic methods have also improved. Scientist Chuqian L. and colleagues described a radiomics model that would analyse the image immediately after the obtained mammogram and as a result would show whether the lesion is malignant or benign. The model revealed calcifications that were negative on ultrasound, based on the results they concluded that radiomics is a potential method for image analysis [14]. Ning M. et al examined the effectiveness of radiomics in mammography compared to digital mammography. The research was based on radiomic characteristics obtained from mammograms, and the data were classified according to similarity [15]. In the study by Wang S. and colleagues, the efficiency of mammography with contrast was examined. CEM (Contrast-Enhanced Mammography) is introduced after the perceived lack of digital mammography, which has 30-50% sensitivity in women with more homogeneous breasts. The method shows morphological and angiogenic characteristics of lesions after the initiation of iodine-based contrast (Figure 2)[16].

**Application of radiomics in digital breast tomosynthesis**

Radiomics features obtained from DBT (Digital Breast Tomosynthesis) do not distinguish between benign and malignant microcalcifications. DBT provides a series of images in which the structures within the breast overlap compared to 2D, ROI could be a safer choice for determining the lesion in DBT compared to classical mammography [17]. DBT in digital mammography increases the detection rate of breast cancer compared to digital mammography alone without DBT. The risk is an increased dose of radiation, therefore a method was developed for the reconstruction of images from the information obtained during DBT imaging [18]. The DBT method is currently not in use for cancer screening, which slows down further data processing. This is why artificial intelligence and radiomics play a very important role (Figure 3). Artificial intelligence in the DBT method indicates the focal field of increased density and microcalcification, and it also contains a system for recognizing when the probability of the presence of cancer is very low [19].

DBT plays an important role in the diagnosis of breast cancer, but also in the detection of lymph vascular invasion. The combination of radiomics and DBT achieved a specificity of 95% in predicting lymph vascular invasion, which is higher than other methods [20]. In a research study of exploratory radiomics analysis of DBT in women with more homogeneous breasts and mammographically negative results, radiomics analysis showed a difference between cancerous and normal breast tissue with evidence of correlation with tumour size and estrogenic receptors [21].

**The application of radiomics in ultrasound**

Ultrasound is a non-invasive imaging method that does not use ionising radiation; therefore, it plays an important role in the diagnosis of breast cancer. One of the key aspects of breast cancer progression is vascularization. Peripheral vascularization includes metastatic lymph nodes, while central vascularization is more active in the absence of malignancy [22]. If the axillary lymph nodes are affected in patients with an early stage, accurate identification of the nodes is important in order to provide appropriate treatment and avoid unnecessary lymph node removal. Zheng X. et al investigated the integration of radiomics into the procedure with the fine needle biopsy. In conclusion, radiomics facilitated the examination process and improved diagnosis (figure 4) [23].

![Figure 2. The process of radiomics analysis of mammograms](https://www.frontiersin.org/files/Articles/600546/fonc-11-600546-HTML-r1/image_m/fonc-11-600546-g004.jpg)
Lua WQ and colleagues research compared biological markers and radiomics features, thus biological markers showed the heterogeneity of cancer, while radiomics features showed the shape and volume of cancer. The results showed that radiomics in ultrasound could show the difference between benign and malignant formations with its further development and progress [24]. In the work of de Faria and Marcomini, histological analysis of pathological tissue was used. Using radiomics, a threshold value of malignancy of ±10% of the margin of error was determined according to the Youden index [25]. The Youden index represents the maximum efficiency of the biomarker, which is shown using the ROC curve (Receiver Operating Characteristic Curve) (Figure 5).

Biomarker level assessment has become an important method in disease research and diagnosis. The diagnosis of diseases according to biomarkers depends on the correlation between the level of biomarkers and the state of the disease, whereby the levels of biomarkers for a certain diseased population are different. The cut point that achieves the maximum is called the optimal cut point because it is the point that optimises the ability to discriminate biomarkers when sensitivity and specificity are given equal weight [26].

Figure 3. Radiomics in DBT
Source: https://ars.els-cdn.com/content/image/1-s2.0-S107663322200188X-gr2.jpg

Figure 4. Ultrasound of an axillary lymph node with metastases with the help of radiomics

Figure 5. Representation of the Youden index using sensitivity and specificity
Source: https://media.springernature.com/full/springer-static/image/art%3A10.1186%2F1471-2407-14-730/MediaObjects/12885_2014_Article_4918_Fig2_HTML.jpg
Radiomics based on MR diagnostics is still in the early stages of development. It has shown promising results in studies focusing on breast cancer patients (Figure 6) in improving diagnosis and response to therapy. Radiomics non-invasively quantifies the phenotype of the entire cancer for multiple lesions simultaneously, in contrast to a biopsy that samples only a small portion of the tissue [27]. Quantitative analysis in magnetic resonance imaging is challenging due to variability in signal intensity distribution, acquisition and type of MR device and field inhomogeneity presents problems. Due to the aforementioned characteristics, radiomics as a method in MR diagnostics occasionally encounters image interpretation problems because it has limited technological possibilities depending on the device on which the examination is performed [28].

Several studies performed to distinguish between benign and malignant breast cancers in a small number of patients with a limited number of radiomics features have given excellent results (Table 1). Research objective of Lee SH. and associates was to determine the potential ability of diffusion MR radiomics analysis to determine the malignancy of breast lesions detected on screening mammography. The sequences they used in their research are diffusion weighted imaging, DWI (Diffusion Weighted Imaging) and T2 weighted sequences. Two radiomics classifications made it possible to differentiate between benign and malignant lesions more accurately than the average diffusion coefficient parameter itself, ADC (Apparent Diffusion Coefficient) [29]. In addition to quantitative analysis of the image, morphological analysis of the image and texture of the lesions is also used. Scientist Nie K. and colleagues processed the data obtained with the DCE sequence Dynamic Contrast-Enhanced) and an approach to automated segmentation of lesions, quantitative feature extraction and selection of diagnostic features using artificial neural network ANN (Artificial Neural Network) and lesion classification was carried out. Eight morphological parameters and 10 image texture features were obtained from each lesion [30]. Radiomics based on customized diffusion imaging helps distinguish mammographic findings suspicious for cancer.

In the research of Bickelhaupt S. et al., in addition to diffusion-weighted imaging, DWI was used as a non-contrast imaging method that could be useful for differentiating lesions that are suspicious for cancer without the need for contrast agent administration and within a relatively short examination time. The lesions that were observed on the obtained recordings were classified according to the BI-RADS provisions, and the lesions classified as BI-RADS 4 and BI-RADS 5 were described [31].

A 3D dynamic contrast-enhanced magnetic resonance imaging, DCE-MRI consists of a large number of images in various stages of enhancement that are used to identify and characterise breast lesions. Scientists Wang TC. et al presented as a result a computer-aided algorithm for tumour segmentation and characterization.
Table 1. Summary of the results of radiomics analyses in breast MR imaging

<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>INDICATION</th>
<th>MODALITY</th>
<th>NUMBER OF PATIENTS</th>
<th>RADIOMIC CHARACTERISTICS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nie i sur. [30]</td>
<td>Prediction of malignancy</td>
<td>MRI: DCE</td>
<td>71</td>
<td>18</td>
<td>Quantitative analysis of morphological and textural features showed relatively high accuracy</td>
</tr>
<tr>
<td>Bickelhaupt i sur. [31]</td>
<td>Prediction of malignancy</td>
<td>MRI: DWI, T2WI</td>
<td>222</td>
<td>359</td>
<td>Radiomic features are better than just using ADC (Apparent Diffusion Coefficient).</td>
</tr>
<tr>
<td>Wang i sur. [32]</td>
<td>Prediction of malignancy</td>
<td>MRI: DCE</td>
<td>99</td>
<td>30</td>
<td>Radiomic features and pharmacokinetic factors distinguished benign and malignant masses</td>
</tr>
<tr>
<td>Cai i sur. [33]</td>
<td>Prediction of malignancy</td>
<td>MRI: DCE, DWI</td>
<td>234</td>
<td>28</td>
<td>Developed features based on GLCM (Grey-Level Co-occurrence Matrix) from DCE-MRI with ADC, as well as kinetic and morphological features</td>
</tr>
<tr>
<td>Li i sur. [34]</td>
<td>Correlation with pathology</td>
<td>MRI: DCE</td>
<td>91</td>
<td>38</td>
<td>MRI-based phenotypes were significantly associated with receptor status, and heterogeneity was an important feature to distinguish between different subtypes</td>
</tr>
<tr>
<td>Parekh i sur. [35]</td>
<td>Prediction of malignancy</td>
<td>MRI: DCE, T2WI, DWI</td>
<td>124</td>
<td>30</td>
<td>Entropy RFM was found to be the most reliable</td>
</tr>
</tbody>
</table>

Figure 7. Concept of the framework for mapping radiomics features
Source: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5686135/bin/41523_2017_45_Fig3_HTML.jpg](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5686135/bin/41523_2017_45_Fig3_HTML.jpg)
using kinetic information and morphological features of a three-dimensional DCE-MRI image [32].

Scientists Cai H., colleagues, and they estimated that four different groups of features, compared to pathological tests, comprehensively characterise the imaging properties of each lesion obtained by the segmentation method performed the radiomics analysis of dynamic magnetic resonance. The result of the research is that seven features are statistically different between malignant and benign groups, and their combination achieved the highest classification accuracy [33].

In the research of Lia H. and colleagues, an immunohistochemical molecular classification was performed, which included the segmentation of lesions and the extraction of the cancer phenotype. Quantitative radiomics can extract the tumour phenotype based on magnetic resonance imaging, and molecular classification of invasive breast cancers is also possible. The results of this research provide insight into cancer biology, including its heterogeneity. The use of imaging phenotypes to identify molecular subtypes can aid in clinical diagnosis and treatment planning. Imaging data and radiomics can serve as a virtual biopsy that is non-invasive and includes the entire tumour analysis [34].

The study by Parekh et al. proved the correlation between radiomics features and the breast tissue of interest, and based on this data, they created a map of radiomics features, RFM (Radiomics Feature Maps) for the evaluation and analysis of radiological images (Figure 7).

Malignant lesions showed higher entropy values, entropy RFM was the most reliable in differentiating between malignant and benign lesions, thus reflecting tumour heterogeneity and its vascular status (Figure 8) [35].

Radiomics bases on the hypothesis that extracted imaging features correlate with genotypic and phenotypic characteristics of breast cancer tissue. F-18-FDG PET/MR enables high-quality radiomics analysis for breast cancer phenotyping (Figure 9) and cancer characterization using information on functional, metabolic and morphological data [36].

Radiomics in PET/CT

The use of PET/CT in the diagnosis of breast cancer is becoming more and more common, and the main reason is the progress of technology, the accuracy of diagnostic information and the simplicity of performance (Figure 10). The success of the diagnosis often depends on the properties of the tissue, and the absorption of FDG (Fludeoxyglucose) is affected by the density and homogeneity of the breast tissue [37].

Radiomics in PET/CT has a similar workflow as in other diagnostics. The collected data and images are reconstructed, followed by segmentation and extraction, as well as data processing [38]. Technical factors, recording parameters and image reconstruction play an important role. Different features show different variables when changing the acquisition, i.e. 2D vs. 3D, matrix size, reconstruction algorithms, and individual filters. The biggest problem with analysis is image noise. Studies that measure tumour heterogeneity using PET use an ROI that contains a threshold defined for cancer segmentation. In
order for cancer homogeneity measurements to be accurate, the matrix must contain a certain number of voxels [38].

In breast cancer detection, F-18-FDG PET/CT shows low sensitivity, but high specificity and accuracy [39]. In addition to the well-known F-18-FDG, F-18-FLT (fluorothymidine) is often used in PET/CT diagnostics. F-18-FLT was produced by an advanced accelerator application, AAA (Advanced Accelerator Applications) with radiochemical purity and specific activity >95%, i.e. >1 Ci/μmol. Research examining F-18-FLT confirmed its consistency in image analysis [40].

Scientist Pio BS. et al. concluded that the average change in F-18-FLT uptake in primary and metastatic tumours after the first cycle of chemotherapy showed a significant correlation with late changes in tumour markers. By comparing the uptake of F-18-FLT after one cycle of chemotherapy compared to the late changes of the cancer imaged by CT, F-18-FLT was a good predictor of cancer response [41].

![Figure 9. Presentation of breast cancer using F-18-FDG PET/ MR](https://www.researchgate.net/publication/336091760/figure/fig2/AS:807729014796288@1569589012002/18-F-FDG-PET-MRI-scan-Images-of-a-57-year-old-patient-with-a-breast-heteroplasia-with.png)

![Figure 10. Radiomics in the diagnosis of breast cancer in PET/CT](https://ars.els-cdn.com/content/image/1-s2.0-S1044579X20300833-gr1.jpg)
Application of radiomics in computer-assisted diagnosis

In order to reduce these errors in the interpretation of findings to a minimum level, computer programs for computer-aided detection, CADe (Computer-Aided Detection) and computer-aided diagnosis CADx (Computer-Aided Diagnosis) were developed. The CADe system enables double-checking and with the help of this system, the radiologist can check the accuracy of his image interpretation [42]. The CADx system assesses whether the detected lesion is benign or malignant. CADe and CADx systems use special algorithms that are specified to detect suspicious lesions based on certain features selected by physicians as main guidelines during the protocol [43].

CAD and radiomics require special computer programs and algorithms, and the main goal is to reduce errors in image detection and analysis and to establish an accurate diagnosis [44]. In radiomics analysis, the cancer is segmented from its surroundings and different characteristics of the cancer are distinguished (eg intensity, shape, size or volume and density of the samples). Once high quality and well-chosen datasets are available, they can be used for processing, which refers to the process of discovering patterns in large datasets (Figure 11) [45].

Gopichand D. et al investigated the pros and cons of the CAD system. Two CAD processes for the classification of lesions were tested (Figure 12). The first process had four steps, i.e. an adaptive algorithm for the growth of the topographic region for the segmentation of lesions, and the calculation of radiomics characteristics. The second CAD process bases on the previous classification using the convolutional neural network ResNet50. Both CAD processes were tested using the cross-validation method. The results showed that the lesion segmentation was satisfactory, a small percentage of data (<5%) required manual correction [46].

Application of radiomics in artificial intelligence

Artificial intelligence, AI plays an important role in post-processing, segmentation and computer-aided diagnosis of lesions. In the last decade, AI has been used in image processing for disease detection, classification, organ
segmentation, lesion segmentation and treatment response assessment, especially in oncology. One of the most interesting advantages of using AI is the possibility of creating a drug specific to the patient [47].

There are several clinical applications of AI and radiomics in radiology. One can apply AI in cancer imaging in two ways. The first way is to extract radiomics features from ROIs that can be fed into machine learning methods for subsequent processes, the second way is to use the whole image or a series of images used with a deep learning model, DL (Deep Learning) for cancer detection, characterization and monitoring (Figure 13). Radiomics features have the potential to obtain biological and pathophysiological information from ROIs, and appropriate quantitative features can provide rapid and accurate non-invasive biomarkers for cancer diagnosis, prognosis, and monitoring treatment response [48].

The scientific work of Koçak B. and associates highlights radiomics and its ability to manipulate a large amount of data compared to the traditional way of data processing. AI algorithms can analyse numerical data providing predefined or handcrafted radiomics features. They can directly analyse the images to design automatically their own radiomics features [49].

Radiomics models have shown just as good results as classical biopsy in diagnosing and determining the stage of cancer. The models predicted metastases, overall survival and regression in different types of cancer. Radiomics features have greatly contributed to the planning and evaluation of treatment (Figure 14) [50].

Radiomics and radiogenomics

Radiogenomics refers to the relationship between imaging characteristics of a certain pathology and various genetic and molecular characteristics (Figure 15). Radiogenomics uses radiomics as a source of quantitative data; therefore, the two methods are closely related [51].

Radiogenomics was first defined and described by Andreassen et al in 2002 as an analogy to pharmacogenomics that studies genetic variation associated with drug responses [52]. Radiomic models can help doctors make more accurate diagnoses in less time. By dividing patients into certain groups, radiogenomics would have a great impact on the selection of candidates for targeted therapies where therapy can be determined...
non-invasively for the entire cancer, without using a biopsy that analyzes all the tissues affected by the cancer (Figure 16) [53].

Cellular and molecular heterogeneity is common in solid tumours. Human cancers contain divergent genomic clones in varying proportions, each with distinct gene expression and biological functions. Genomic diversity may sometimes have adverse clinical outcomes due to resistance to therapy and reduced overall survival [54]. Doctors often treat cancer patients with radiotherapy, but not all patients have a verified genetic profile of the disease. Genomic profiling of the disease is performed at a specific location in the cancer and is exposed to sampling errors, in order to reduce these errors to a minimum, further tests and expansion of current knowledge are needed [55].
Conclusion

Breast cancer is the third most common cancer that affects women, but sometimes also men. Scientists and doctors are working intensively to reduce the rate of breast cancer patients. National breast cancer screening programs have made it easier to detect and control the disease, but the percentage of people cured of breast cancer is still not satisfactory. Radiomics is a new method in analyzing radiological images, but it is still in development. So far, it has shown good and satisfactory results with some deviations. The radiomics analysis procedure bases on computer algorithms and data classification, ensures a positive outcome of the entire process, fast and accurate diagnosis, along with non-invasive treatment of the patient. Scientists are developing a model that will determine the malignancy or benignity of a lesion, speed up the process of diagnosis and treatment while bypassing methods that require more time and additional material for processing.

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