



# Imaging Biomarkers and Imaging Biobanks

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## 10.1 Introduction

The main barriers limiting the widespread use of quantitative imaging biomarkers in clinical practice lie in the lack of standardization regarding their implementation on those aspects related to technical acquisition, analysis processing, and clinical validation. These developments have multiple consecutive steps, ranging from the proof of concept and mechanism, the hallmark definition, the optimization of image acquisition protocols, the source images, the analytical methodology, the type of measurements to the structured report. The overall pipeline has to provide additional value and support to radiologists in the process of diagnosis and assessment

[1]. To enable the use of quantitative imaging biomarkers in both clinical and research settings, a whole process has to be established, including display methods, image analysis guidelines, and acquisition of quantitative data and parametric images. A consensus-based multidisciplinary approach seems the best practice to achieve success.

Based on the recommendations of the Quantitative Imaging Biomarkers Alliance (QIBA), supported by the Radiological Society of North America (RSNA), and the European Imaging Biomarkers Alliance (EIBALL), which is sustained by the European Society of Radiology (ESR), a standard methodology for the development, validation, and integration of image analysis methods for the extraction of biomarkers and radiomic data, as well as for their potential implementation in clinical practice, is being applied to an increasing extent with the aim of reducing variability across centers. All analytical methods developed must comply with critical requirements such as conceptual consistency, technical performance validation (precision and accuracy assessment), clinical endpoint validation, and meaningful appropriateness. Additionally, the continuous technological advances and improvements in medical imaging hardware and software require regular reassessment of the accuracy of quantitative evaluation of medical images, radiomic features, and regular updates of the standardization requirements.

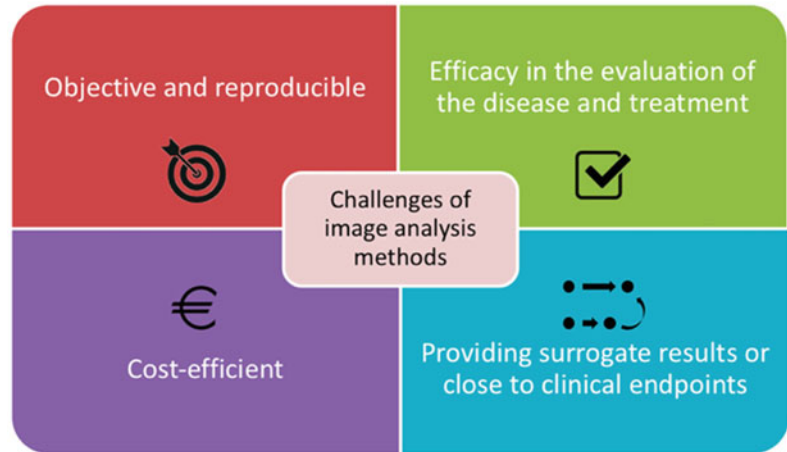
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**Fig. 10.1** Challenges for the adoption of quantitative image analysis methods within clinical routine



Besides this, there is still a risk of persistent heterogeneity of image quality through time, due to differences in technologies implemented by vendors and protocols used across centers. Therefore, standardization of image quality to be used for the analysis of different imaging biomarkers will not be feasible. Although the need for further standardization of all processes in the imaging biomarkers pipeline already started more than 10 years ago, with the intention of increasing their usage in large clinical trials and facilitating their integration in clinical practice, the solution has not arrived yet. The use of artificial intelligence (AI)-based approaches, like the one presented in Chap. 5, could be a disruptive way of changing this trend, by making it possible for complex and deep neural networks to learn from the lack of homogeneity in the collected data.

There are several challenges to be met in the adoption of advanced image analysis methods in clinical routine (Fig. 10.1). Imaging biomarkers not only have to be objective and reproducible, as mentioned earlier, but they also have to show a clear efficacy in the detection and diagnosis of the disease or in the evaluation of treatment response. This diagnostic efficacy must be confirmed by a clear relationship between the biomarkers and the expected clinical endpoints, allowing them to act as surrogate indicators of relevant clinical outcomes such as the prediction of treatment response, progression-free survival, overall survival, and other. Finally, the methodology must

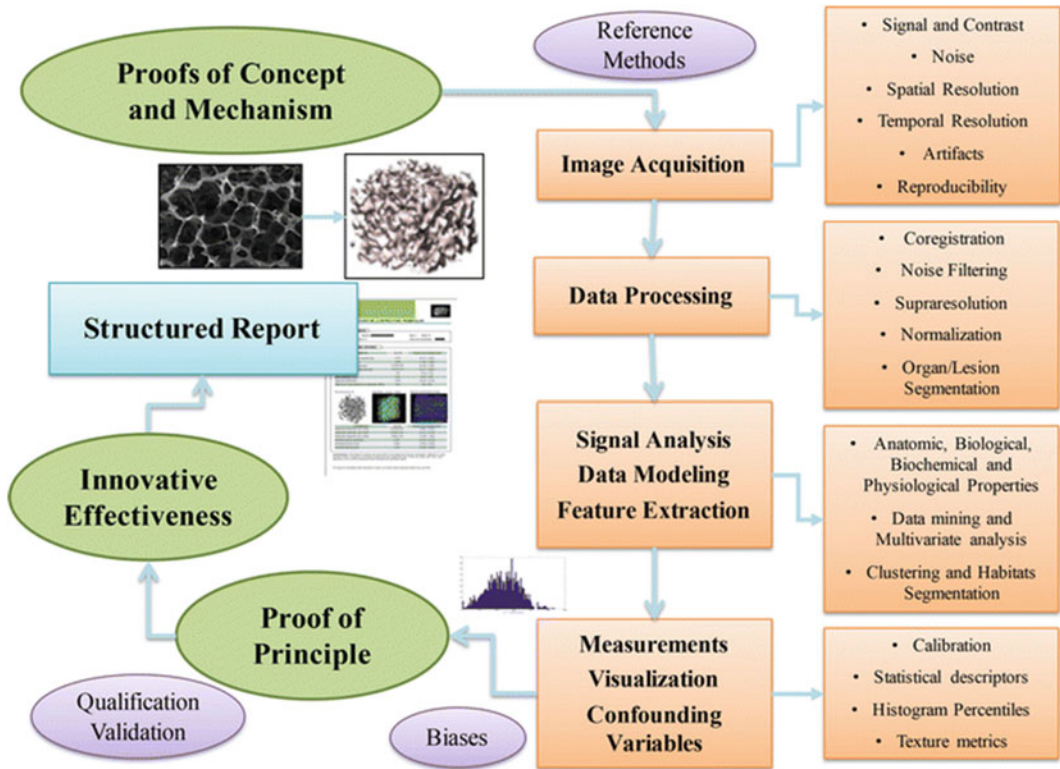
be cost-efficient in order to achieve clinical integration and further expansion of its utility.

In this chapter, the general methodology for the development, validation, and implementation of imaging biomarkers is presented. The approach consists of a systematic methodology that allows to obtain features of high precision and accuracy in the imaging biomarker results, making their integration in automated pipelines feasible, for the generation of massive amounts of radiomic data to be stored in imaging biobanks.

## 10.2 Stepwise Development

In order to brush up an established methodology for the extraction of imaging biomarkers, a summary of the stepwise methodology for radiomic development will be introduced to the reader [2].

The path to the development and implementation of imaging biomarkers involves a number of consecutive phases (Fig. 10.2), starting from the definition of the proof of concept and finalizing with the creation of a structured report including quantitative data. The final step in the development of an imaging biomarker also involves the validation of its relationship with the objective reality to which it's surrogated, either structural, physiological or clinical, and the monitoring of its overall feasibility in multicenter clinical studies. Biomarkers need to follow all phases



**Fig. 10.2** Stepwise development of imaging biomarkers [3]. The stepwise workflow starts from the definition of proof of concept and mechanism, where the clinical need is defined and the relevant information to be measured by the imaging biomarker is determined. The workflow continues with the technical development of an image analysis pipeline, from the image acquisition protocol

definition till the generation of quantitative measures. Finally, the extracted measurements are evaluated in a proof of principle within a control population and finally in patients to check for the innovation effectiveness. Finally, a quantitative structured report is generated for the integration of the new imaging biomarker in clinical routine

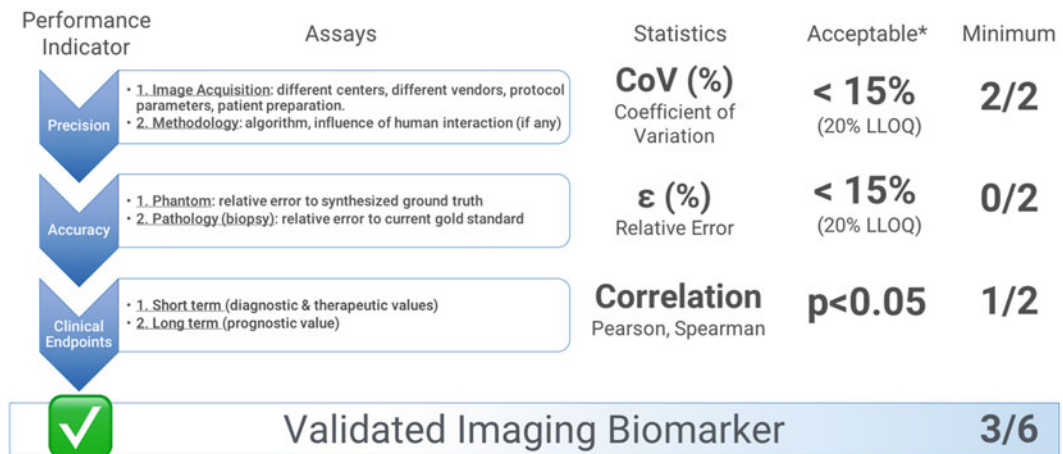
of development, validation, and implementation before they can be clinically approved [3].

Radiomics solutions should be structured in this stepwise approach, in order to foster standardization of methodologies. Integration of an imaging biomarker into clinical practice needs conceptual consistency, technical reproducibility, adequate accuracy, and meaningful appropriateness. This strategy should permeate all quantitative radiology solutions, from the user interfaces to the source codes of the algorithms. By implementing this methodology, images analysis researchers should be able to reckon the limitations and uncertainties due to limitations in any of the steps involved, such as improper quality of source images (acquisition), uncorrected bias of intensity distribution (processing), oversimplification

of mathematical models (analysis), or not statistics not representative for the whole distribution of values (measurements). For example, the reproducibility and feasibility of the implementation of a methodology for radiomic analysis will change dramatically if the segmentation process (tissue or organ) is performed in a manual, semi-automated way or in a completely automated manner supported by artificial intelligence (AI) and convolutional neural networks (CNN).

### 10.3 Validation

There is no current international consensus on how to validate imaging biomarkers. Our process proposal for validation of imaging biomarkers



\*European Medicines Agency. *Guideline on bioanalytical method validation*. 21 July 2011

**Fig. 10.3** Imaging biomarkers validation pipeline

(Fig. 10.3) considers three steps, taking into account the possible different influences that might introduce uncertainty in the measurements. This pipeline is inspired by the guidelines for the evaluation of bioanalytical methods from the European Medicines Agency (EMA) [4]. The biomarkers are validated in terms of their precision, accuracy, and clinical relationship.

The technical validation of the imaging biomarkers will determine both the precision and accuracy of the measurements, as well as their margin of confidence.

Unlike accuracy, precision can be evaluated for all imaging biomarkers. Obtaining a high precision rate is considered mandatory for the imaging biomarker validation. For precision evaluation, the coefficients of variation (CoV) of the biomarker, obtained repeatedly with the variation of different factors, are calculated. The variable factors can be related either to the image acquisition or to the methodology. In order to evaluate the influence of the image acquisition in the variability of measurements, the imaging biomarkers ideally should be calculated by testing the following variable conditions with the same subjects:

- Imaging center
- Equipment
- Vendors

- Acquisition parameters
- Patient preparation

For the evaluation of the influence of the methodology in the obtained measurements, it is recognized that imaging biomarkers should be calculated with the same subjects and acquisition protocols while changing the following conditions:

- Operator (intra-operator variability, inter-operator variability)
- Processing algorithm

The higher CoV for all the experiments (with varying acquisition characteristics, with varying the operator) should be below 15%. However, in cases with reduced image quality, which can be considered as the *lowest limit of quantification (LLOQ)*, the 15% CoV threshold can be extended to 20% (Fig. 10.3).

The accuracy of the method can be evaluated by comparing the obtained results with a reference pattern in which the real biomarker value is known. The reference pattern can be based on information extracted from a pathological sample after biopsy or from synthetic phantoms (physical or digital reference objects) with different compounds and known properties that emulate

the characteristics of the biological tissue. For accuracy evaluation, the relative error of the imaging biomarker compared to the real value from the gold standard must be calculated. The relative error should be below 15% and in *lowest limit of quantification* conditions below 20%.

In some cases, there is no reference pattern available, either because the synthesis of a stable phantom is a complex process or because the considered reference pattern also has a high variability and a coarser category-based analysis than the continuous numerical domain of imaging biomarkers (e.g., steatosis grades in pathology vs. proton density fat fraction quantification from MR). The lack of knowledge in accuracy can be compensated by surpassing the clinical sensitivity and specificity of the calculated imaging biomarker (i.e., we do not know how accurate we are, but we know that the specific imaging biomarker is related to some disease hallmarks).

The main purpose of the clinical validation is to show the relationship between the extracted imaging biomarker and the disease clinical endpoints. The imaging biomarker can be evaluated either as a short-term (assessing detection, diagnosis, and evaluation of treatment response) or long-term (prognostic patient status) measurement. The type and degree of relationship between the imaging biomarkers and clinical variables have to be analyzed based upon sensitivity, specificity, statistical differences between clinical groups, and correlation studies.

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## 10.4 Imaging Biobanks

A biobank is a collection, a repository of all types of human biological samples, such as blood, tissues, cells, or DNA, and/or related data such as associated clinical and research data, as well as biomolecular resources, including model- and microorganisms that might contribute to the understanding of the physiology and diseases of humans. In Europe, the widest network of biobanks is represented by the BBMRI-ERIC (Biobanking and BioMolecular resources Research Infrastructure) (<http://bbmri-eric.eu>).

In 2014, the European Society of Radiology established an Imaging Biobanks Working Group of the Research Committee, with the intention of defining the concept and scope of imaging biobanks, exploring their existence, and providing guidelines for the implementation of imaging biobanks into the already existing biobanks. The WG defined imaging biobanks as “*organised databases of medical images, and associated imaging biomarkers (radiology and beyond), shared among multiple researchers, linked to other biorepositories*” and suggested that biobanks (which only focus on the collection of genotype-based data) should simultaneously create a system to collect clinically related or phenotype-based data. The basis of this assumption was that modern radiology and nuclear medicine can also provide multiple imaging biomarkers of the same patient, using quantitative data derived from all sources of digital imaging, such as CT, MRI, PET, SPECT, US, X-ray, etc. [5]. These imaging biomarkers can also be classified in different types, depending on their function. Such imaging biomarkers, which express the phenotype, should therefore be part of the multiple biomarkers included in biobanks.

As an example, we have the following biomarkers for the clinical scenario of oncology [5]:

- *Predictive biomarker*: used as a tool to predict the progression and recurrence of disease.
- *Diagnostic biomarker*: used as a diagnostic tool for the identification of patients with disease.
- *Morphologic biomarker*: A biomarker measuring the size or shape of a macroscopic structure in the body
- *Staging biomarker*: used as a tool for classification of the extent of disease.
- *Monitoring biomarker*: used as a tool for monitoring the disease progression and its response to treatment.

Even more, the core content of imaging biobanks should not only exist out of images, but should also include any other data (biomarkers)

that may be extracted from images, through computational analysis. All these data should then be linked to other omics, such as genomic profiling, metabolomics, proteomics, lab values, and clinical information [6].

Two types of imaging biobanks can be defined:

1. *Population-based biobanks*: developed to collect data from the general population, in such case the aim of the data collection is to identify risk factors in the development of disease, to develop prediction models for the stratification of individual risk, or to identify markers for early detection of disease.
2. *Disease-oriented biobanks*: developed to collect multi-omics data from oncologic patients or patients affected by neurodegenerative disease, in order to generate digital models of patients. Such models will be used to predict the risk or prognosis of cancer or degenerative diseases and to tailor treatments on the basis of the individual responsiveness to therapies. On the basis of the imaging biomarkers that are currently available, cancer of the breast, lung, colorectum, and prostate seem the most suitable entities for developing disease-oriented imaging biobanks, but further applications are expected (neurological tumor such as neuroblastoma, glioblastoma, rare tumors, etc.)

### **Imaging Biomarkers and Biobanks in Artificial Intelligence**

The paradigm shift of working in local environments with limited databases to big infrastructures like imaging biobanks (millions of studies) or federations of imaging biobanks (reaching hundreds of millions of studies) requires the integration of automated image processing techniques for fast analysis of pooled data to extract clinically relevant biomarkers and to combine them with other information such as genetic profiling.

Imaging biomarkers alone will not suffice, and they must be considered in conjunction with

other biologic data for a personalized assessment of the disease [7].

As a practical example, it would be of interest to automatically detect whether a certain alteration in the radiomics signature through imaging biomarkers is present in subjects with a given mutation like BRCA. The same can be applied to the relationships between radiomics characteristics and other disease hallmarks in neurodegeneration, diffuse liver diseases, respiratory diseases, osteoarthritis, among many others. Dataset management in imaging biobanks should be able to work longitudinally with different time points along the disease course [8].

However, for these applications, standard statistics analysis methods and tools cannot be applied due to the difficulty in handling large volumes of data. For these applications, the use of advanced visual analytics solutions that help to rapidly extract patterns and relationships between variables is a must (see Fig. 10.4).

Software for imaging biobanks should allow the management of source medical images; the results of associated and labelled clinical, genetic, and laboratory tests (either in the same database or linked); the extracted imaging biomarkers as radiomic features; and data mining environments with visual analytics solutions that simplify the extraction of variable patterns in a huge number of registries.

In this setting it is predictable that the application of machine learning tools will be beneficial. The analysis, stratification among patients, and cross-correlation among patients and diseases, of a huge number of omics data contained in biobanks, are an exercise that cannot be performed by the human brain alone; therefore, a computer-assisted process is needed.

Machine learning could be fundamental for completing human-supervised tasks in a fast way, such as *image acquisition*, *segmentation*, extraction of imaging biomarkers, collection of data in biobanks, data processing, and extraction of meaningful information for the purpose of the biobank.



**Fig. 10.4** Clustering of patients by the longitudinal evolution in different radiomics features at diagnosis and after treatment in rectal cancer. The vertical axis shows patients and the clusters extracted in a non-supervised manner. The horizontal axis includes both radiomic features

and the clinical variable of relapse, which is binary (0, no relapse; 1, relapse). The slope in each box represents an increase (blue) or decrease (red) in the imaging biomarker through the different time points

### 10.5 Conclusion

Imaging biomarkers are an essential component of imaging biobanks. The interpretation of biomarkers stored in the biobanks requires the analysis of big data, which is only possible with the aid of advanced bioinformatic tools. As a matter of fact, medical informatics is already playing a key role in this new era of personalized medicine, by offering IT tools for computer-aided diagnosis and detection, image and signal analysis, extraction of biomarkers, and more recently machine learning, which means that these tools have to adopt a cognitive process mimicking some aspects of human thinking and learning through the progressive acquisition of knowledge.

- The technical validation of AI algorithms that generate imaging biomarkers will determine both the precision and accuracy of the measurements, as well as their margin of confidence.
- The imaging biomarkers generated by AI can be evaluated either as a short-term (assessing detection, diagnosis, and evaluation of treatment response) or long-term (prognostic patient status) measurement tool.
- Imaging biobanks do not only consist of images but any other data (biomarkers) that can be extracted from them through computational analysis; all these data should then be linked to other omics, such as genomic profiling, metabolomics, proteomics, lab values, and clinical information.

### 10.6 Take-Home Points

- Before clinical approval, AI algorithms and biomarkers have to follow all phases of development, validation, and implementation.

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