Biomarkers for Medical Imaging

Luis Martí-Bonmatí
Luis.Marti@uv.es
Medical Imaging

Medical Imaging is a key tool in diagnosis, treatment monitoring and prediction of therapeutic response of the disease. It is also a fundamental tool for guiding many minimally invasive therapeutic procedures.

Traditional radiological diagnosis is based on the integration and qualitative assessment of imaging findings obtained from conventional radiography, ultrasound, CT and MRI.

With the advent of digital environments, images are no longer considered just a final product for the diagnosis but sometimes an intermediate product from which different information, apart from qualitative or visual, can be extracted.

Technology and engineering have changed the approach to obtain information from medical imaging. The knowledge of the biological basis of the disease has also boosted the use of these new parameters, known as biomarkers.
Joint Cartilage

Structure, Function and Composition

Chondrocytes

Free collagen fibers, proteoglycans and glycosaminoglycans

Collagen fibers around the chondrocytes
Learning Objectives

Definition

• To understand what are imaging biomarkers and how can they improve diagnosis and treatment follow-up

Types

• To describe the different types of biomarkers

Development

• To analyze the process of biomarkers development, including validation, qualification and standardization
What are biomarkers?

Any characteristic of a tissue that can be objectively measured and that represents a parameter of its biological, functional or structural organization.

An imaging biomarker is any parameter obtained with standard and advanced techniques to explore, quantify and represent a tissue specific property.

These properties are hidden parameters (structural, physiological, functional, cellular, biochemical) that can be extracted after applying to the acquired images different computational models and specific statistical processing.

The parametric maps represent the spatial distribution in the analysed tissue. In these synthetic images, the pixel signal is proportional to the magnitude of the biomarker or change.
Derived secondary images which pixels represent the distribution values of a given parameter (morphological or functional) usually obtained by the numerical adjustment of a mathematical model.
Different anatomical, functional and molecular tumour characteristics can be used as imaging biomarkers.

In cancer treatment, CT and MRI measurements of changes in tumour size are the base of the RECIST (Response Evaluation Criteria in Solid Tumours) criteria.

RECIST-based markers are unable to depict early tumor response.

RECIST-based markers are suboptimal to assess the effect of some targeted treatments that do not cause regression of tumour volume, but rather increase in the extent of tumour necrosis.
Functional biomarkers obtained with several imaging methods have the potential to complement or even replace the RECIST criteria (tumour perfusion, oxygen level, glucose metabolism).

Relative to molecular biomarkers, which are target-specific, functional biomarkers have the advantage of probing general capabilities of disease, such as cell death, proliferation, glycolysis, hypoxia, tumour invasiveness, angiogenesis, lymphangiogenesis, inflammation and fibrosis.

Important efforts of qualification and standardization remain to be done before the acceptance of some of these functional biomarkers as surrogate endpoints.
**Types of imaging biomarkers**

- **Prognostic biomarkers**: those that affect the outcome of patients in terms of a clinical endpoint.
- **Predictive biomarkers**: which affect the effect of a specific treatment on a clinical endpoint.
- **Surrogate biomarkers**: those measurements which may replace a clinical endpoint in clinical trials carried out to evaluate the effect of a specific treatment.
Define a clinical and therapeutic target for a disease: prediction, detection, staging, grading or therapeutic response

Is it possible to develop an imaging biomarker that can solve the problem?

Define a study that can be used as a proof of principle and validation of the biomarker

Are the results satisfactory in terms of sensitivity / specificity / utility?

Is it robust and reproducible?

Innovation and clinical application

Can it be improved?

Biomarkers and Medical Imaging

Biological and clinical knowledge

Technical and methodological knowledge

Statistical knowledge

Technical advances
The Ideal Biomarker

- Must be clinically useful, allowing a measurable clinical improvement.
- Must (usually indirect or substitute) measure the target process adequately.
- Must be standardized in terms of image acquisition (technical parameters), image preparation, image processing and data measurement.
- Must have a high sensitivity to correctly classify as abnormal a true altered finding.
- Must have a high specificity to correctly identify healthy people as negative or not having the condition.
The Ideal Biomarker

- Must be reproducible to replicate the obtained value, so that it remains lower than the intended differences, obtaining similar results in different equipments.
- Must be obtained at the lowest possible costs (low-priced) and in the shortest time (fast).
- Must be safe and harmless to the patient.
- Must have the potential to become a "clinical endpoint" or a "virtual biopsy".
The Ideal Biomarker

- Sensitivity
- Specificity
- Reproducibility
- Clinical validity
- Standardization
- Cost

Medical Imaging Area


Normal

Initial Chondropathy

Sensitivity

Specificity

Reproducibility

Clinical validity

Standardization

Cost
The process required to integrate an imaging biomarker into both clinical practice and clinical trials is complex and must meet the criteria of conceptual consistency, technical reproducibility, sensitivity and specificity.

The innovation path to biomarker development, expansion and subsequent implementation involves a number of consecutive steps.
**Proof of Concept**

Define the reasons why a specific aspect of the disease has to be measured.

Demonstrate that a specific biological process, seen as a cause and effect chain, may be studied using the available imaging and computational techniques.
Initial Development of Biomarkers: Cartilage

Concept

- The joint cartilage is initially resistant to vascular invasion from the subchondral bone

- As the joint cartilage degenerates, there is a change with overexpression of the vascular endothelial growth factor (VEGF). This angiogenesis signaling protein is strongly expressed

- New vessels and capillaries are formed

Mechanism

- Imaging biomarkers of neovascularization may be used to evaluate initial degeneration, progression of degeneration and vascular response to treatment
Initial Development of Biomarkers: Brain

Proof of Concept
Several morphometric and functional abnormalities have been reported in patients suffering from psychiatric and neurodegenerative disorders. Neurobiological mechanisms are difficult to understand by interpreting functional and structural data separately.

Both functional and neuronal density abnormalities may coexist in schizophrenic patients in specific regions.

Mechanism
If proven, these functional abnormalities coexisting with focal brain reductions in patients with neurodegenerative and psychiatric disorders may have both grading and therapeutic interest.
Initial Development of Biomarkers: Liver

Liver tumors → ↑Energetic demands → ↑Blood (oxygen + nutrients) → Angiogenesis and neovascularization

Diagnostic markers

Angiogenesis and neovascularization → -Flow -Volume -Disorder -VEGF

Can we use DCE-MR imaging to model angiogenesis?

Angiogenesis and neovascularization: complex and expensive

1. Microvascular density (MVD)
2. Determination of intratumoral VEGF
3. Monitoring vascular permeability

Quantitative parameters obtained from the pharmacokinetic modeling of DCE-MR images

Disease assessment → Treatment evaluation

Radiology 2009;251:317-35
J Natl Cancer Inst 2005;97:172-87

Initial Development of Biomarkers: Prostate

- There is a relationship between pathological alterations (cell density, interstitial space and angiogenesis) and water molecules diffusion.
- *In vivo* quantification of the diffusion properties of water molecules in biological tissues should provide information about cellularity and microstructural organization.
- Diffusion coefficients are elevated in structures with a reduced cell density and increased interstitial space.

- Water molecules behavior in tissues can be quantified by MR imaging from the capacity of the proton spin to rephase after the application of two symmetrical field gradients.
- The purpose of DW-MR sequence is to estimate the diffusion coefficient of water molecules in tissues.
- The sensitivity to diffusion can be controlled by means of the so called ‘b value’, which depends on the pulses characteristics:

\[
b = \gamma^2 \cdot G^2 \cdot \delta^2 \cdot \Delta - \frac{\delta}{3}\]

- Gyromagnetic constant
- Gradient strength
- Gradient duration
- Gradient separation

\[
b \text{ [s/mm}^2\text{]}\]
From a certain age and a negative skeletal balance, bone involution determines a bone mass reduction.

In osteoporosis, trabecular structure maintains its shape while beams become thinner augmenting inter-trabecular spacing, resulting in a more porous structure and a reduction of whole bone quantity.
Proof of Mechanism

Demonstrate the interrelationship between the biomarker and the concept, focusing on the effect (in magnitude and direction) that a specific disease or a treatment have on the biomarker.
**Image Acquisition**

Appropriate images are essential for the extraction of useful biomarkers. Irrespective of the technique used (radiography, ultrasound, CT, MRI, SPECT or PET), several issues must be taken into consideration.
Acquisition and analysis of Biomarkers: Brain

T1W-GRE 3D High Resolution morphometric analysis

- TE / TR: 3.9 / 8.3  FA: 8°
- Orientation: Sagittal; Matrix: 256 x 256
- Slices: 160; Voxel: 0.94x0.94x1; Gap: 0
- Acquisition time: 5:20’

EPI T2* for functional MR evaluation

- TE / TR: 19 / 2275  FA: 90°
- Orientation: Axial; Matrix: 80 x 80; Slices: 48
- Voxel: 2.88x2.88x2.60; Gap: 0
- Acquisition time: 2’; Dynamics: 80
Acquisition and analysis of Biomarkers: Prostate

➢ DWI: MR signal decays while the b-value increase.
➢ Using different b-values, an estimation of the diffusion coefficient can be obtained from the fitting and modeling of the signal decay.
➢ These models can be based on either a monoexponential or biexponential modelling of the MR signal decay.
   ➢ Monoexponential: Non standardized.
   ➢ Bi-exponential: Calculation of fast and slow components (D, D*) with the IVIM theory.

General recommended guidelines:
➢ Excellent SNR provided by SE-EPI sequences. Parallel imaging techniques to reduce EPI factor. Spectral fat suppression (SPIR, SPAIR) combined with gradient reversal to avoid fat overlapping artifacts. Respiratory synchronization. VCG synchronization in cardiac DWI.
➢ Acquisition of multiple b-values to be specified by the Cramer-Rao lower bound theory.
Acquisition and analysis of Biomarkers: Liver

- Spatial resolution with whole anatomical coverage (24 slices)
- In-plane resolution (1.5x1.5 mm)
- Slice thickness (7 mm)
- Temporal resolution: 40 dynamics, 3.7 s each
Acquisition and analysis of Biomarkers: Cartilage

- Perfusion PKM
- Spatial resolution with whole anatomical coverage (10 slices)
- In-plane resolution (0.78x0.78), slice thickness (7 mm)
- Temporal resolution and Sampling rate: 80 dynamics, 2.7 s each
- Acquisition of multiple images at different echo times to optimized contrast and signal.

Signal to Noise vs. Contrast to Noise ratio (SNR and CNR)
Acquisition and analysis of Biomarkers: Bone

- Trabecular Bone Structure: Field Strength of 3 Tesla
- High spatial resolution: 180 µm³ (isotropic)
- T1-weighted Gradient Echo, FA=25°, TE=5ms, TR=16ms
- 60 axial slices
Prior to the analysis and modeling of the signals, images must be processed making sure that the acquired data are optimal for the analysis.
Acquisition and analysis of Biomarkers: Cartilage

- Arterial input function (popliteal artery)
- Patellar cartilage segmentation
- Femoral cartilage segmentation
Acquisition and analysis of Biomarkers: Brain

Normalization and registration

Average filter

Smoothing filter

Segmentation

Bias inhomogeneity noise correction

Extract brain tissue
Acquisition and analysis of Biomarkers: Prostate

Image registration through all the b-values of the study

- SPM-based
- Reference: b=0
- Minimize apparent displacements produced by the Eddy currents effect through the b-values
- Minimize localization errors due to patient motion during acquisition
Acquisition and analysis of Biomarkers: Liver

Registration
Movement correction
Rigid + elastic deformation models

Intensity to Concentration conversion

\[ C(t) = \frac{1}{T1(t)} - \frac{1}{T1(0)} \]

\[ S(\alpha) = M \cdot \sin \alpha \frac{1 - e^{-\frac{TR}{T1}}}{1 - \cos \alpha \cdot e^{-\frac{TR}{T1}}} \]
Acquisition and analysis of Biomarkers: Bone

Proof of concept → Proof of mechanism → Image acquisition → Image preparation → Image processing → Measurement → Proof of principle → Proof of efficacy and effectiveness → Structured report

Segmentation

Equalization

Sub-voxel processing

Binarization

3D model

Medical Imaging Area
Acquisition and analysis of Biomarkers: Brain

Proof of concept → Proof of mechanism → Image acquisition → Image preparation → Image processing → Measurement → Proof of principle → Proof of efficacy and effectiveness → Structured report

Tissue specific templates

Original data → Noise filtering → Bias correction → Segmentation → Anatomical data

Original data → Realign → Slice Timming → Corregis tration → Normalization

Morphometric Maps → Functional Maps

Gray matter → White matter → CSF
Calculation of diffusion properties by the application of the IVIM model

- Voxel-by-voxel analysis
- Curve fitting
- Calculation of $D$, $D^*$ and $f$

$$S_I = S_0 \cdot f \cdot e^{-b \cdot (D + D^*)} + S_0 \cdot (1 - f) \cdot e^{-b \cdot D}$$
Acquisition and analysis of Biomarkers: Cartilage

Pharmacokinetic modeling (PKM)

- Arterial capillary permeability: \( K_{\text{trans}} \) (ml/min/100ml)
- Washout rate: \( k_{ep} \) (ml/min/100ml)
- 1st compartment: vascular space fraction: \( v_p \) (%)
- 2nd compartment: interstitial space fraction: \( v_e \) (%)

\[
C_t(t) = v_p C_a(t) + \int_0^t (K_{\text{trans}} C_a(\tau) e^{k_{ep}(t-\tau)}) d\tau
\]

\[
v_e = \frac{K_{\text{trans}}}{k_{ep}}
\]
Acquisition and analysis of Biomarkers: Liver

- Proof of concept
- Proof of mechanism
- Image acquisition
- Image preparation
- Image processing
- Measurement
- Proof of principle
- Proof of efficacy and effectiveness
- Structured report

Voxel-based analysis

Pharmacokinetic modeling

- Arterial / Venous permeability: \( K_{\text{trans1}} / K_{\text{trans2}} \) (ml/min/100ml)
- \( k_{\text{ep}} \) (ml/min/100ml)
- \( v_p \) (%)
- \( v_e \) (%)
Acquisition and analysis of Biomarkers: Bone

Morphometry
1. Morphology
2. Fractal complexity
3. Topology
4. Anisotropy

Mechanical
1. Meshing
2. Model generation
3. Model simulation
4. Young’s modulus estimation

Medical Imaging Area
**Image processing**

Extract information about the biomarkers from the digital images using the appropriate computational processes.

Parametric images depict the spatial distribution of the biomarker.

In multivariate images, the colour of each voxel is determined by a multivariate statistical function, which is in turn a combination of several parameters or biomarkers.
Biomarker measurement: Brain

Medical Imaging Area

Proof of concept → Proof of mechanism → Image acquisition → Image preparation → Image processing → Measurement → Proof of principle → Proof of efficacy and effectiveness → Structured report

- Original structural data
  - Morphometry with selected ROIs
  - Functional Contrast Maps
    - Functional with ROI selection
  - Coincidence Maps

Multivariate approach
Biomarker Multivariate Approach

Source images → Computational models → Parametric images → Statistical models → Nosologic image → Relevance

Redundancy

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Parametric images, both conventional and multivariate, provide measurements from either the whole tissue or organ being studied or only from those areas considered more representative or abnormal (histograms analysis).
**Biomarker measurement: Cartilage**

What should we measure?

Parametric map of the cartilage surface representing the value of T2* (proportional to the amount of water [edema] and loss of collagen)

Parametric maps of capillary permeability (Ktrans) of the patellar joint cartilage

- Normal
- Chondromalacia
- Arthrosis
**Biomarker measurement: Liver**

- **Proof of concept**
- **Proof of mechanism**
- **Image acquisition**
- **Image preparation**
- **Image processing**
- **Measurement**
- **Proof of principle**
- **Proof of efficacy and effectiveness**
- **Structured report**

**Biomarker measurement:**

- **Liver**
- **Mean** – **Standard deviation** – **Median**
- **Asymmetry** – **Kurtosis** – **Relevant Percentiles (10%, 25%)**
- **Heterogeneity:** Histogram signature

*Medical Imaging Area*
Biomarker measurement: Prostate

Parametric mapping and ROI evaluation in DWI-IVIM:

- Histogram-based analysis of the diffusion parameters
- Parametric information overlay on anatomic images
- Threshold results for the depiction of regions with a higher water restriction.

Medical Imaging Area

D

f

D*
Biomarker measurement: Bone

Healthy values

<table>
<thead>
<tr>
<th>Morphologic Parameter</th>
<th>Men (n = 19)</th>
<th>Women (n = 21)</th>
<th>Total (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone volume-to-total volume ratio</td>
<td>0.24 ± 0.01</td>
<td>0.21 ± 0.01</td>
<td>0.22 ± 0.01</td>
</tr>
<tr>
<td>Trabecular thickness (µm)</td>
<td>198.49 ± 3.19</td>
<td>190.35 ± 0.95</td>
<td>194.22 ± 1.70</td>
</tr>
<tr>
<td>Trabecular separation (µm)</td>
<td>816.52 ± 26.46</td>
<td>886.90 ± 24.61</td>
<td>853.47 ± 18.66</td>
</tr>
<tr>
<td>Trabecular number (10⁻³ · µm⁻¹)</td>
<td>1.22 ± 0.04</td>
<td>1.10 ± 0.04</td>
<td>1.16 ± 0.03</td>
</tr>
</tbody>
</table>

Bias: variations due to ROI dimensions
Different tissue components coexist in the liver parenchyma.
Fat-Water-Iron Liver Quantification

Proof of concept → Proof of mechanism → Image acquisition → Image preparation → Image processing → Measurement → Proof of principle → Proof of efficacy and effectiveness → Structured report

\[ M_{xy} \] vs \( T2^* \)

- \( H_2O \)
- \( Fat \)
- \( Fe \)

Medical Imaging Area
**Biomarker validation**

**Proof of Principle**

Validate the proof of concept and the proof of mechanism, which are both theoretical, in a small sample (case-control), before embarking on large-scale clinical trials.
Medical Imaging Area

Permeability (Ktrans) parametric maps


Glucosamine Treatment Effectiveness
**Biomarker validation**

Proof of Efficacy and Effectiveness

Analyze the ability of the biomarker in large sample sizes, studying the power of health technology both under perfect control (efficacy) and under usual (effectiveness) conditions.
Biomarker validation: Liver

- Measurements are potentially useful for intra-center studies:
  - Longitudinal studies with/without treatment
  - Intra-center normality values

- Reproducibility analysis are generally included:
  - Image acquisition and analysis methods
  - Inter- and intra-observer variability

But...
- Relatively few patients
- Lack of strong validation (clinical endpoints, anatomical-pathological proof, etc.)
- Difficulties for meta-analysis
- No true standards yet

So there is still a lot to do for the...
Structured Report

To innovate in clinical practice, the results provided by the biomarkers need to be conveyed in an intuitive way. The Structured Report (SR) must comprise complete and accurate information including the assessment of potential bias and a generalization of the results.

Medical Imaging Area
The Radiological Report with Biomarkers: Cartilage

Structured report

Medical Imaging Area
The Radiological Report with Biomarkers: Bone

Structured report
Joint Cartilage Example

- MR images in high resolution digital format, suitable for morphological, structural and functional analysis of the cartilage
- Segmentation of the cartilage for its regional analysis (pixel by pixel)
- Quantitative parameterization of thickness, T1 and T2 relaxation times, pharmacokinetic parameters, delayed enhancement
- Validation of the reproducibility, bias and normality ranges
- Validation of the clinical efficacy in the diagnosis, grading and monitoring of the disease
Biomarkers and Medical Imaging
Biomarkers and Medical Imaging
Radiologic Workflows

Consultancy

Study

Demand

Citation

Report

Performance

Specific meetings
Multidisciplinary committees
Treatment planning and monitoring
Clinical research

Appropriateness
Decision Support Systems
Adequate protocol and algorithm
Clinical situation

Standardized Structured reporting
Diagnosis assistance
Effective communication
Second opinion

Technical Quality
Innovation Criteria
Standardization
Use of Biomarkers
Workload
RIS - PACS

Medical Imaging Area
Conclusion

- Digital medical imaging and computer processing allow to extract parametrizable information that can be considered functional or structural imaging biomarkers.
- In clinical practice, these biomarkers can be of great interest because of the benefits they provide to the diagnostic, treatment and follow-up processes in numerous diseases.
- The integrity of imaging biomarkers cycle should be controlled from conception to implementation.
- The combination of digital imaging, contrast media and computer processing is some kind of magic, where the occult and mysterious becomes visible. Its ultimate goal is to achieve professional success, understood as excellence in personalized-care medicine.

- All these advantages are the result of multidisciplinary work of different professionals who come together to provide a better patient care and a greater biological understanding of the diseases.