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ORIGINAL ARTICLE

Imaging Biomarker Ontology (IBO): A Biomedical Ontology to Annotate and Share Imaging Biomarker Data

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Abstract
Imaging biomarkers refer to radiological measurements that characterize biological processes of imaged subjects and help clinicians particularly in the assessment of therapeutic responses and the early prediction of pathologies. Several imaging features (size of a lesion, volume of a tumor, blood perfusion in a specific anatomical region, anisotropic water diffusion in a particular tissue region, etc.) are quantified and reported in the clinical practice. The growth of the number of research studies addressing imaging biomarkers and the increasing use of these measurements in the radiological routine necessitates the use of semantic research tools. The use of semantic technologies will enable to efficiently retrieve imaging-related data and to enhance the interoperability in the biomedical field. While many efforts have been conducted regarding the definition of a standardized vocabulary to support the sharing of the imaging biomarker knowledge, the definition of the term "imaging biomarker" stills inconsistent. In this paper, we introduce our motivation for semantically describing this concept and we outline shortcomings of the state-of-the-art methods. Here, we propose a semantic representation of the imaging biomarker concept that is based on the articulation of its three main semantic axes, namely the measured quality, the measurement tool and the decision tool. The developed ontology is called the Imaging Biomarker Ontology (IBO) and uses existing biomedical ontologies. A preliminary use case is studied to illustrate the utility of IBO in annotating quantitative and qualitative imaging data from the TCGA (The Cancer Genome Atlas) collection.

Keywords Knowledge representation · Imaging biomarker · Ontology development · Biomedical ontologies

1 Background

Quantitative imaging [27] refers to the extraction and use of numerical characteristics that are extracted from medical images. Its ultimate objective is to improve multi-scale understanding of pathologies at the anatomical, functional and molecular level through the use of advanced digital techniques [9,24]. The National Institute of Health has defined the concept of imaging biomarker as "characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic process or biological responses to a therapeutic intervention" [39]. For example, response evaluation criteria in solid tumors criteria (RECIST) [18] enable clinicians to assess tumor evolution via the measurement of the tumor size from computed tomography (CT) images.

1.1 The Importance of the Imaging Biomarker Concept

The importance of biomarkers in general is widely acknowledged in the scientific literature, due to their potential role in future clinical practice [8,19], but also due to the critical role biomarkers play in the development of new drugs, e.g., as surrogate endpoints in clinical trials [26]. Notably, imaging biomarkers allow testing new drugs at an early non-symptomatic stage of pathology, potentially leading to significant reduction in costs [1,30]. This perspective of wide-scale use and reuse of imaging biomarkers in medical research and clinical practice makes it very important to be able to share information about biomarkers, e.g., what they actually measure and their degree of validation for specific intended uses (e.g., link with clinical outcome).

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1.2 Challenges

It becomes important to be able to share information relative to imaging biomarkers to ensure understanding, reuse and integration of their meta-data and support clinical research studies [2,22]. However, this concept is not easy to define because it involves multiple notions such as the measured biological quality, the measurement process and the decision making tool. Till now, the way the term "imaging biomarker" is used in literature is somewhat confusing. In 2010, the Institute of Medicine stressed the need to define a consistent and precise way the vocabulary related to biomarkers [3].

Recent works from different communities (imaging research, clinical radiology, genetics, pharmaceutical industry, knowledge management, etc.) showed interest in consistently representing imaging biomarkers [31]. Actually, none of the existing works in the literature has succeeded in defining a vocabulary that covers this domain in a coherent way. In some works [12], this term refers to some substance that can be assessed, and in others [33], it refers to a measurement method which ensures a reproducible and precise measurement of imaging biomarker values. In other cases [19], it is considered as a decision making tool used to assess the progression of some pathology (e.g., cancer, Alzheimer's disease and cardiovascular diseases) or the response to some therapeutic intervention. For the reasons cited above and given the large-scale use of the imaging biomarker concept, we propose here to define in a coherent way the vocabulary associated with it.

1.3 Objective

The objective of this work is to define explicitly, by means of an ontology, the vocabulary pertaining to imaging biomarkers. Our proposed ontology is entitled Imaging Biomarker Ontology (IBO), and it is based on existing biomedical ontologies. Ontologies are widely acknowledged as a means to specify explicitly the meaning of concepts in a domain of interest, and to facilitate consistent sharing of data and knowledge pertaining to them.

In our context, ontologies can help addressing the major challenges mentioned above, by providing: (1) a standard vocabulary to describe imaging biomarker information, covering and articulating the various meanings attached to this term in the medical imaging and image processing communities, and (2) a formal language to reason about this information. The latter will be more and more needed in the future in the context of the development of decision support systems that will be involved in medical decision processes, such as choosing the diagnostic procedure that is best suited to the patient case. Such choice will involve some reasoning aiming (1) at determining which quantitative imaging biomarkers data are best appropriate to diagnose the patient, and then choosing the relevant image acquisition protocol and organizing the acquisition and processing of the images in such a way to deliver the imaging biomarkers. Once available, these biomarkers can be used, together with other medical data relevant to the patient, to make actual medical decisions about therapy and patient management.

Our work addresses the specific goal of delivering a core ontology, supposed to be valid across the whole domain of medical imaging, but still relatively abstract. Once validated this core ontology will be further extended to cover the specific needs related to the various imaging modalities, medical specialties and diseases. In this paper, we will illustrate how IBO can be used to annotate imaging biomarkers results and answer to some competency questions as:

- Q1: retrieve all imaging biomarker data about (patient, images, measurements, etc.) in studies of patients with a specific disease (GBM, Alzheimer, etc.).
- Q2: find all regions of interest (ROI) of images and retrieve their associated values.
- Q3: describe how the imaging biomarker values were obtained; what processes were executed?
- Q4: find all scalar measurements associated to a given imaging study.
- etc.

This paper is organized as follows: Sect. 2 presents a survey of existing works related to the representation of imaging biomarkers and it outlines their limitations. In Sect. 3, we define the scope and methodology of our work and the existing ontologies which have been reused. In Sect. 4 entitled development of the Imaging Biomarker Ontology, the structure and the most salient aspects of our ontology are detailed. Section 5 gives some illustrative examples to show how we can annotate imaging features with the IBO ontology. Finally, the advantages and limits of our work are discussed in Sect. 6.

2 Related Works

2.1 DICOM Structured Reports Format

The DICOM standard (Digital Imaging and Communications in Medicine) specifies a data structure for SR (Structured Reports) [15] as a set of rules constraining their organization and a vocabulary (coded concepts associated to their meanings) covering the domain of imaging observations. Such DICOM SR objects allow representing a wide range of imaging observations, including measurements and qualitative assessments, (e.g., the presence or not of a mass, its dimension and its position), their relationships with image evidence and with inferred diagnosis.

Despite the wide use of the DICOM standard in clinical practice, DICOM SR has had limited success for exchanging imaging reports in clinical settings. In this survey [4], radiologists expressed that the use of DICOM SR is a time- and an energy-consuming task. Moreover, they mentioned that the use of SR templates had restricted their freedom in terms of expression given that they do not enable them to add free texts to enrich the contents of their reports. Most participants to this survey pointed out the necessity to find a better way to enter input data so that the implementation of SR does not affect productivity.

Only a limited number of imaging biomarkers can be represented using DICOM SR, yet, together with their associated provenance data. Clunie et al. [14] have proposed extensions of (e.g., DICOM codes and SR templates) to facilitate encoding and exchange of oncology clinical trial results in this work. Moreover, DICOM has intrinsic limitations regarding querying; the absence of formal definitions makes the reasoning on DICOM data difficult. DICOM data should be complemented with data expressed in an ontological format to improve data querying capabilities. Until today, there is no DICOM ontology, although some research has focused on the question of the semantic representation of the DICOM standard, e.g., [7].

2.2 Annotation and Image Markup Model

The AIM (Annotation and Image Markup) model [13] was developed within the framework of the caBIG (Cancer Biomedical Informatics Grid). This information model was designed to support the representation of the radiological annotations that refer to measurements, texts, observations, graphic shapes delimiting regions of interest, etc. The AIM model is used to manage radiological annotations in the research context. AIM data can be stored in XML files, and open source tools AIM (i.e., API Web Page,[1] ipad tool [34]) exist to help developers in the serialization of AIM data into their application.

In summary, the AIM model has introduced the most relevant entities in image annotation, but its implementation lacks formal semantics because it is not based on ontologies. As a consequence, we can not represent complex entities or perform logic-based to infer new knowledge about the content of the image.

2.3 Quantitative Imaging Biomarker Alliance

In order to overcome the problems of standardization and to ensure the reproducibility of imaging biomarkers, the QIBA (Quantitative Imaging Biomarker Alliance) group of the RSNA (Radiological Society of North America) [14] has defined standardized profiles to formalize the definition, generation and use of quantitative imaging biomarkers in clinical trials and clinical practice:

- The QIBA profile "FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy" indicates the technical specifications that are suitable for quantifying the absorption of the Fluorodeoxyglucose (FDG) tracer by tumor tissues. The FDG is a glucose analogue that enables the detection of the increase in the consumption of glucose by the tumor tissues. (In cancerology, cancer cells capture FDG more than normal cells). Standardized approaches to the measurement of SUV (Standardized Uptake Value) and machine calibrations are described in the document.
- The QIBA profile "CT tumor change volume" provides standardized methods for measuring the volume of a lesion in a reproducible and repeatable manner to evaluate therapeutic response of patients.
- etc.

The goal of this initiative is to "establish processes and profiles that will lead to acceptance of quantitative imaging biomarkers by the imaging community, clinical trial industry and regulatory agencies as proof of biology, proof of changes in pathophysiology, and surrogate endpoints for changes in the health status of patients." The aim of QIBA profiles is to standardize the production and use of imaging biomarker data by means of imaging protocols. Until now, these profiles are presented in free text format, which is certainly relevant for assisting clinical users in the definition of image acquisition and image processing protocols, but insufficient with regard to providing information models for implementing the interoperable repositories of imaging biomarker data that are needed in both medical facilities and for biomedical research.

Nevertheless, QIBA profiles can be of great help for defining important aspects that need to be considered to correctly cover the imaging biomarkers domain, especially the different steps that compose the measurement process and the modalities of their execution (used tools, imaging parameters, etc.).

2.4 Quantitative Imaging Biomarker Ontology

Buckler et al. [10] have proposed the QIBO (Quantitative Imaging Biomarker Ontology) to improve the management of imaging biomarker data and to enable advanced research on image databases. This initiative is the first to use semantic web technologies to represent concepts related to quantitative imaging biomarkers. QIBO is a first attempt for untangling the various entities involved, especially biological subject, biological intervention, contrast agent, biological

[1] https://web.stanford.edu/group/qil/cgi-bin/mediawiki/index.php/AIM-API.

target, imaging instrument, algorithm, measurement, indicated biology and biomarker application. Nevertheless, this project stalled, and the model is far from being usable.

QIBO has three main limits. First, it does not reuse any foundational ontology, which is a major problem because the domain of imaging biomarker involves many complementary domains, for which ontologies exist but need to be consistently integrated. Second, QIBO does not reuse any existing ontology to cover the domain. Third, it lacks internal consistency, which is partly due to the lack of formal definitions of its entities and object properties.

For example, in terms of modeling, QIBO does not provide any formal axioms to relate the class `QIBO:quantitative imaging biomarker` to classes that describe provenance (biological quality, measurement method, etc.) of the measured value. Moreover, the classification of qualitative and quantitative imaging biomarkers should be revised given that it is not correct. For example, the class `QIBO:shape parameter` is defined as a `QIBO:quantitative imaging biomarker` whereas it describes a `PATO:shape`, which is defined as a qualitative quality.

2.5 Biomarker Retrieval and Knowledge Reasoning System

The BiomRKRS system (Biomarker Retrieval and Knowledge Reasoning System) [31] is a similar project but with a broader scope (i.e., not limited to imaging biomarkers), with particular emphasis on providing a model for facilitating the interoperation of biomarkers' databases. In contrast with QIBO, BiomRKRS has reused existing relevant domain ontologies (e.g., Gene Ontology [20], Experimental Factor Ontology [28], QIBO) and terminologies (Systematized Nomenclature of Medicine - clinical terms, Logical Observation Identifier Names and Codes,[2] International Classification of Diseases,[3] etc.). However, the BiomRKRS ontology has not been made broadly available for reuse, yet.

2.6 Representation Based on the Ontology for General Medical Science (OGMS)

In this paper [12], Ceusters and Smith have used the OGMS ontology (Ontology for General Medical Science) [35] to define the biomarker concept as an observable and evaluable characteristic, i.e., "a characteristic that is always identifiable in a process of observation and evaluation." Thus, they have defined the biomarker as an `OGMS:bodily feature` which subsumes three categories of biomarkers which are disjoint: The first category is the Material biomarker which refers to the anatomical structure `OGMS:bodily component`, the second category is the Quality biomarker which describes the quality associated with the observed anatomical structure (modeled as an `OGMS:bodily quality`), and the third category is the biomarker process which evaluates whether the process performed is normal or pathological (modeled as an `OGMS:bodily process`). Therefore, according to them the semiformal definition of the biomarker concept is as follows: Biomarker= def. Material Biomarker, Quality Biomarker or Process Biomarker. The first limitation of this proposal is that it has defined biomarkers as entities that are observed in the body of the human being and that it has not included the measurement process aspect. This exclusion of the measurement aspect was not justified although it is an important aspect of imaging biomarkers (as explained by the QIBA group).

2.7 Shortcomings

All these works are interesting and complementary, but do not provide a solution that is ready to use. The more mature ontology is probably BiomRKRS, but it is not publicly available, and apparently does not cover in detail the domain of imaging biomarkers, in which we are primarily interested. QIBO is also an interesting starting point, although it has many limits. Finally, QIBA protocols constitute interesting contributions, especially concerning protocols (acquisition protocols and reconstruction protocols, image processing) to guarantee the accuracy and reproducibility of the biomarkers. However, such information is not modeled as an ontology but in free text.

3 Methodology

Our scope embraces both qualitative and quantitative representations of imaging biomarkers. Indeed, quantitative biomarkers better correspond to what we traditionally consider as a measurement, but it is also important to take into account qualitative measurements which are widely acknowledged in, e.g., radiogenomic studies [17], and therefore interesting to establish correlations between imaging features and tissue pathology at a gene expression level.

3.1 Alignment to a Foundational Ontology

Our proposed ontology involves many diverse entities that are related to the imaging biomarker concept, and these entities concern many domains (medical imaging, biology, image processing, metrology, clinical research, etc.). In this context, the use of a foundational ontology is important to ensure the semantic consistency of the model.

[2] https://loinc.org/international/.

[3] http://wwww.who.int/classifications/icd/en/.

Therefore, IBO relies on BFO (Basic Formal Ontology) as well as on the principles of the OBO (Open Biomedical Ontologies) foundry. Hence, entities are divided into `BFO:continuant` and `BFO:occurrent`. The category `BFO:continuant` denotes entities that persist through time (medical images, imaging devices, imaging contrast agents, biomarker values, biomarker measurement protocols, etc.), and the category `BFO:occurrent` represents events in which continuants participate (imaging biomarker measurement process, imaging biomarker application, etc.). In this work, we have reused several ontologies (listed and briefly described hereafter) covering—at least in part—the entities needed in biomarkers modeling. Most of them are aligned with BFO and were developed according to the OBO foundry principles, thus facilitating the integration work. However in most cases, only subsets of these ontologies are needed.

3.2 Reuse of Biomedical Ontologies

In particular, we mainly used the following ontologies to standardize the representation of information that are related to imaging biomarkers:

- Ontology for Biomedical Investigations (OBI) [5] and Information Artifact Ontology (IAO) [11] to represent data related to the measurement process: protocols, used material, generated data (measure, conclusion, predicted value, etc.), study objective, etc.
- Foundational Model of Anatomy (FMA) ontology [32] to represent studied anatomical structure (brain, heart, knee, breast, etc.) of the subject;
- Chemical Entities of Biological Interest (ChEBI) Ontology [16] to specify imaging agents (contrast agents, radiopharmaceuticals, etc.) that are used to help in measuring the imaging parameter;
- Dataset processing (ONL-DP) ontology[4] to represent original imaging datasets (anatomical, functional, metabolic), image processing processes (registration, re-sampling, segmentation, quantitative parameter estimation, etc.) and processed images (registration dataset, segmentation dataset, parameter quantification dataset, etc.).
- Unit ontology (UO) [21] to specify the unit of measure of scalar imaging biomarkers.
- Phenotypic Quality Ontology (PATO) [29] to qualify physical characteristics that are measured by imaging biomarkers (e.g., size, shape, structure, radioactivity and concentration).
- Gene Ontology (GO) [20] to describe biological processes (anisotropic cell growth, cell death, cell division, etc.) that are estimated by imaging biomarkers.
- Human Disease Ontology (HDO) [36] to refer to the studied pathologies (nervous system disease, cardiovascular system disease, etc.) for which the biomarker is measured.

We adopted a modular architecture, consisting of a main ontology file importing several modules. The main motivation for such a modular architecture was the ability to easily re-extract entities from existing ontologies. However, several situations must be considered, depending on the reused ontologies. As for BFO2, the whole ontology is imported, since it is a foundational ontology, providing the basic modeling framework for the whole ontology. Concerning the others, e.g., PATO, we selected from PATO the list of classes that seemed to us interesting in the context of imaging biomarkers. We are aware that the decision about the relevant subset is quite subjective, and this is precisely why it is important to have those terms in a module that can be re-extracted if needed in some particular application domain. This strategy is certainly the best possible one with regard to the domain of anatomy, since it is certainly difficult to anticipate all the anatomical terms that may be useful in the imaging biomarkers domain, given the large spectrum of imaging modalities and medical specialties. The solution we provide allows the user to easily re-extract the ontology modules from the original ontology sources, and to tune this extract to their specific application needs.

We used the OntoFox tool[5] that implements the MIREOT (Minimum Information to Reference an External Ontology Term) methodology [40] to build the modular architecture of IBO that is mainly based on OBO modules from OBI, PATO, IAO, UO, FMA, CHEBI and OGMS. To extract an OBO module from an existing ontology using this tool, three basic parameters must be specified in the input file: source ontology, terms to be extracted (i.e., low level source term URIs, top level source term URIs and target direct superclass URIs and setting for retrieving intermediate source terms) and source annotation URIs. The OntoFox tool automatically generates the extracted OWL module in an RDF/XML format from the input file.

We made our selection of ontologies by taking into account mainly the following aspects: (1) the free availability of the ontology on the web, (2) the good definition of the classes and relationships of the ontology in order to ensure the appropriate reuse of the ontology extracts, (3) the coverage of the targeted domain to create a minimum set of terms to cover our use case and (4) the stability of the ontology, so that future changes do not affect our model. In our work,

[4] http://purl.bioontology.org/ontology/ONL-DP.

[5] http://ontofox.hegroup.org/.

we analyzed and selected manually classes and relationships to be extracted. The following paragraphs illustrate how we applied these principles in the extraction of OBI and FMA ontologies.

We chose to use OBI for three main reasons: First, OBI is one of the main ontologies of the OBO library and the most suitable terminological resource that expresses investigations in the oncology field. It has been reused in OBIB (Ontology for Biobanking) [6,22] to semantically describe meta-data of bio-banks (e.g., cancer tumor specimen, genomic data, etc.). Second, OBI meets some of main modeling needs that are expressed in QIBA profiles as the description of entities that describe different types of measurements (scalar value, nominal value, etc.), planned processes (imaging processing, statistical calculation, etc.), imaging devices, roles (patient, participant, study group, etc.), study objectives, experimental protocols and other interesting entities. Added to this, OBI includes annotations, formal descriptions and examples to illustrate the usefulness of entities. Third, in terms of implementation, OBI is easy to integrate given that it is based on the foundational ontology BFO.

Our ontology reuses the following OBI entities: `OBI:assay objective`, `OBI:data transformation objective`, `OBI:study design`, `OBI:value specification`, `OBI:genetic characteristics information`, `OBI:dose`, `OBI:study group role`, etc. We retained also some subclasses of the entity `OBI:planned process` like `OBI:assay`, `OBI:data transformation`, `OBI:investigation`, `OBI:investigation`, `OBI:material processing`, etc.

We chose to use the FMA ontology because it is one of the most "expressive" ontological resources in the biomedical field and a reference ontology for modeling the anatomical structures of the human body. FMA is intended according to its authors to be reused in part and adapted to a specific field. We used the FMA ontology to represent the anatomical sites that are described in radiological reports. We did not use the entire FMA ontology, and we only included key entities that describe anatomical sites of lesions that are cited in [14]. For example, IBO refers to `FMA:liver`, `FMA:pancreas`, `FMA:breast`, `FMA:neck`, `FMA:pelvis`, `FMA:brain`, etc.

4 Development of the Imaging Biomarker Ontology

We have designed the IBO ontology in OWL2 (Ontology Web Language)[6] format using the version 5 of Protégé [23]. It contains 4622 concepts, 135 object properties and 3 data properties. The IBO ontology articulates the three basic aspects of imaging biomarkers namely, measured biological characteristic, measurement protocol and role in decision making applications, and it is available through this link.[7]

The set of involved instances in our illustrative examples (see Section 5) has been generated using the Protégé tool. We exploited instances with the CORESE search engine[8] via the execution of SPARQL queries. Results are presented in an XML format and can be visualized in a structured table via the graphic interface of CORESE.

The following paragraphs introduce the most salient aspects of each of these semantic axes; classes are partitioned into two categories `BFO:continuant` (see Fig. 1) and `BFO:occurrent` (see Fig. 2). In this section, labels of terms and relationships are used (rather than actual IRI), for the sake of legibility. The pivotal entity of IBO is `IBO:imaging biomarker value`, representing the value of the measurement of a biological characteristic, and it results from the realization of a plan specified by a protocol (i.e., `IBO:imaging biomarker measurement protocol`). An `IBO:imaging biomarker value` can then be used in various decision processes modeled as `IBO:imaging biomarker application`.

4.1 Measurement Process of Imaging Biomarker

An `IBO:imaging biomarker measurement protocol` specifies how imaging biomarkers should be produced, as a result of some `IBO:imaging biomarker measurement process`. Such processes are usually composed of three main sub-processes: `IBO:subject preparation` (e.g., administration of an imaging agent), `OBI:image creation` (the image acquisition process involves physical participation of the subject) and `ONL-DP:dataset processing`. All these processes are modeled as an `OBI:study design execution` and associated with the related protocol by the `IBO:hasRealization Protocol` object property. The `ONL-DP:dataset processing` class subsumes these processes: `IBO:image reconstruction`, `ONL-DP:registration`, `ONL-DP:restoration`, `ONL-DP:segmentation`, `IBO:image analysis` (leading to biomarker values), etc. The image analysis has two subclasses `ONL-DP:quantitative image analysis` and `IBO:qualitative image analysis`.

This part of the ontology plays a major role for specifying how biomarkers should be obtained, and for recording provenance information. This involves many material entities such as `QIBO:imaging subject`, `OBI:device`,

[6] http://www.W3.org/TR/owl2-syntax/.

[7] https://medicis.univrennes1.fr/_media/members/bernard.gibaud/ibo-final-version.zip?id=members%3Abernard.g-ibaud%3Aindex_cache=cache.

[8] https://www.w3.org/2001/sw/wiki/Corese.

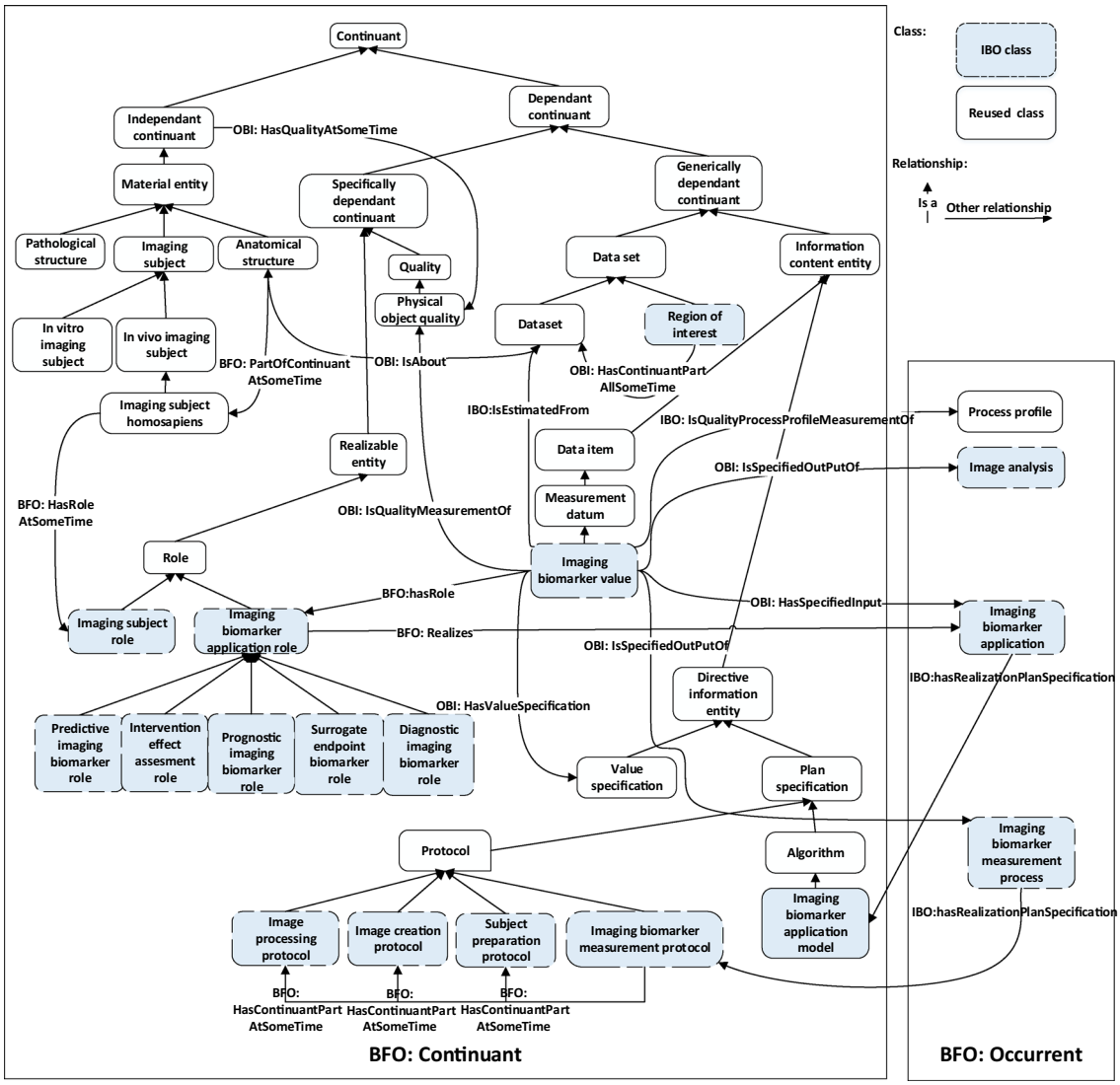

Fig. 1 An extract illustrating the core structure of the BFO: continuant part defining the IBO ontology. Boxes represent classes (blue ones refer to main concepts of semantic axes) and arcs refer to relationships between them: axioms and subsumption relationships. The subsumption "is a" relationship is denoted by unlabeled arcs (color figure online)

`QIBO:imaging agent`, `FMA:anatomical structure`, as well as roles realized in the context of the processes in which they participate, e.g., `IBO:imaging subject role`, `OBI:patient role`, `OBI:material to be added role`.

4.2 Measured Quality of Imaging Biomarker

An `IBO:imaging biomarker value` is a subclass of the `IAO:measurement datum` class that subsumes both categorical and numerical (count, percent, fraction and scalar) values that are defined by the `OBI:value specification` entity. The qualitative imaging biomarkers include nominal and dichotomous values, nominal and unordered values, and nominal and ordered values. In contrast, quantitative imaging biomarkers define continuous values (ratios, values with units of measure, etc.) and discrete values. Quantitative biomarker values are the output of some `ONL-DP:quantitative parameter estimation` process, and `IBO:qualitative biomarker values` are the output of some `IBO:qualitative parameter estimation` process. Both entities are subsumed by the `IBO:image analysis` entity.

A key feature of the `IBO:imaging biomarker value` class is its relationship with the estimated physical characteristic of the imaged object or process. In our work, we have distinguished between two kinds of quali-

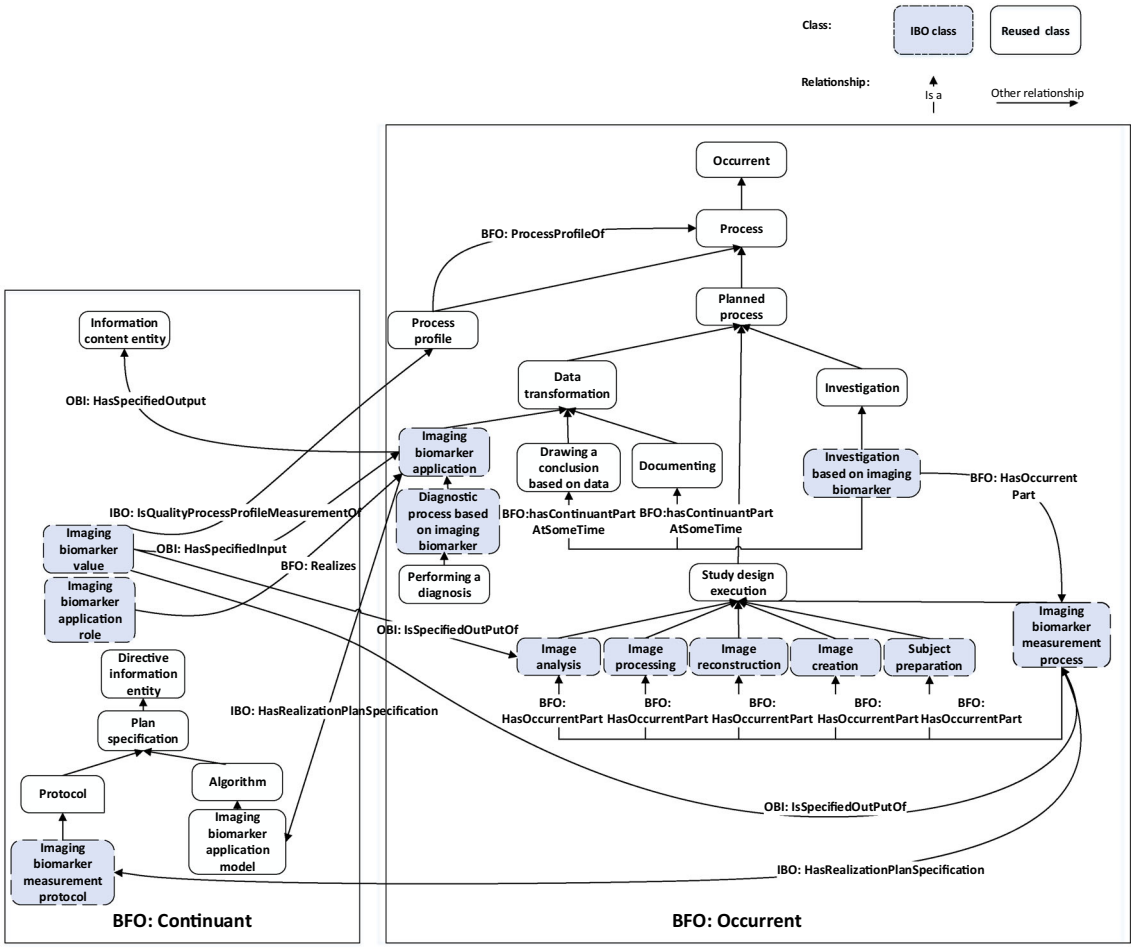

Fig. 2 An extract illustrating the core structure of the BFO: occurrent part defining the IBO ontology. Boxes represent classes (blue ones refer to main concepts of semantic axis), and arcs refer to relationships between them: axioms and subsumption relationships. The subsumption "is a" relationship is denoted by unlabeled arcs (color figure online)

ties: qualities that are related to a continuant (e.g., tumor size, tumor volume, etc.) and qualities that describe an occurrent (e.g., the variability of the tumor size value). The relationship between a biomarker value and the quality characterizing the object is modeled by means of the `OBI:isQualityMeasurementOf` object property. The relationship between a biomarker value and the process being measured is modeled by means of the `OBI:isProcess ProfileMeasurementOf` object property. Both object properties are sub-properties of the `IAO:isAbout` object property. Qualities of physical objects (e.g., anatomical structures, lesions) are modeled using the `PATO:physical object quality` entity, whereas process profiles are modeled using `BFO:process profile` that we have specialized with the basic process profile categories suggested in the BFO2 documentation, namely `IBO:quality process profile`, `IBO:rate process profile` and `IBO:beat process profile`.

4.3 Clinical Role of Imaging Biomarker

IBO recognizes the importance of imaging biomarkers for certain specific clinical purposes, e.g., establishing the presence of a disease, predicting the probable outcome of a disease, predicting responses to particular therapies or choose the appropriate drug, monitoring therapy based on the assessment of actual effects. In IBO, all such entities are subsumed by the `IBO:imaging biomarker application` class that is a subclass of the `OBI:data transformation class`. An `IBO:imaging biomarker application` class involves some `IBO: imaging biomarker value` class which bears a particular role. Each class of biomarker role determines a class of `IBO:imaging biomarker application`: e.g., `IBO:imaging biomarker-based diagnosis` is an `OBI:performing a diagnosis` which `OBI: hasSpecifiedInput` an `IBO:image biomarker`

value that bears some IBO:diagnostic imaging biomarker role. Similar roles were introduced to model prognostic, predictive, effect assessment and surrogate endpoint biomarkers' roles, as illustrated in Fig. 1.

5 Application of IBO: TCGA GBM Imaging Features Use Case

In this section, we show how the IBO model can be used to represent imaging features from the Cancer Imaging Archives TCGA (The Cancer Genome Atlas) GBM (glioblastoma multiforme) collection [38]. Thus, we consider a retrospective study, described in this paper [25] that focuses on the combination of morphologic and functional imaging biomarkers of the NER (non-enhancing region) in GBM tumors. The resulted radiology dataset is saved in a spreadsheet file that is available from this link.[9] This study hypothesizes that morphologic features of the NER are insufficient to predict patient survival and that perfusion parameters namely the relative cerebral blood volume rCBVNER value may lead to a more exact prognostic information.

We note that the Visually Accessible Rembrandt Images terminology called VASARI terminology [37] was used to describe the non-enhancing part of the tumor. VASARI is a controlled vocabulary that describes thirty observations of gliomas in conventional MRI. For this study, the following seven VASARI features that describe the NER of the tumor were included: proportion of NER, proportion of edema, definition of NER margins, T1/FLAIR ratio, deep white matter involvement, NER crossing of the midline and NER area.

The following realistic use-cases illustrate how our model can answer to some competency questions thanks to the axioms that formalize the description of imaging biomarker meta-data.

5.1 Use Case 1: Representation of the Mean rCBV MR perfusion Parameter

Here, we represent the quantification of the mean rCBV value of the non-enhancing region that is measured from the perfusion imaging. The measuring process includes three main processes namely: subject preparation, image acquisition and image processing. During the preparation of the subject, an MRI contrast agent is used to visualize the CER (contrast enhancing region) part. After that, a set of T2 star weighted perfusion images is generated from the image acquisition step. Acquired images are processed to correct contrast agent leakage from the intravascular to the extracellular space, and then, the rCBV value of the CER is estimated from the rCBV map. Figure 3 illustrates the semantic description of the measurement process using the IBO model, and Table 1 specifies some details about the used classes.

Let us consider the query Q1 (see Sect. 1.3) to ask for retrieving some meta-data of mean rCBV values (patient, disease, image, image modality, biomarker name, biomarker value) in TCGA studies. Bellow, Q1 is expressed in SPARQL language (Listing 1).

Listing 1 SPARQL query 1. obo:OBI_0000312 denotes the relation BFO:isSpecifiedOutputOf. obo:OBI_0000293 corresponds to the relation OBI:hasSpecifiedInput. obo:RO_0000053 refers to the relation RO:bearOf and obo:IAO_0000004 denotes the relation OBI:hasMeasurementValue. the class obo:OBI_0001007 corresponds to the entity OBI:image creation and obo:DOID_3068 denotes the entity doid:glioblastoma multiforme.

```
Q1: Select ?patient ?disease ?datasettype ?dataset ?
      biomarker ?biomarkervalue
Where {
?datasetclass rdfs:subClassOf* onl–ds:parameter–
      quantification–dataset
?datasetinst rdf:type ?datasetclass
?datasetclass rdfs:label ?datasettype
?datasetinst rdfs:label ?dataset
?imagecreation rdf:type obo:OBI_0001007
?datasetinst obo:OBI_0000312 ?imagecreation
?patientinst rdf:type ibo:imaging_subject_human
?patientinst rdfs:label ?patient
?imagecreation obo:OBI_0000293 ?patientinst
?diseaseinst rdf:type obo:DOID_3068
?diseaseinst rdfs:label ?disease
?patientinst obo:RO_0000053 ?diseaseinst
?imageanalysisclass rdfs:subClassOf* ibo:image_analysis
?imageanalysis rdf:type ?imageanalysisclass
?imageanalysis obo:OBI_0000293 ?datasetinst
?imageanalysis obo:OBI_0000299?biomarkerinst
?biomarkerinst rdfs:label ?biomarker
?biomarkerinst obo:IAO_0000004 ?biomarkervalue
}
```

The XML result of the execution of Q1 is generated by CORESE in a table format where the column names are the variables of the SELECT section of the query (Fig. 4).

5.2 Use Case 2: Representation of the Non-enhancing Margin Definition

Here, we represent the assessment of the non-enhancing part of the tumor using MR VASARI scores. In this process, radiologists identify the non-enhancing region of the tumor from T1 pre-contrasts and FLAIR MR images. Then, they assign scores to the corresponding VASARI features. In our example, we consider the non-enhancing margin definition criterion that assesses "if most of the outside of the non-enhancing margin of the tumor is well defined and smooth versus if the margin is irregular" [37]; the semantic description of this VASARI feature is described in Fig. 5.

[9] https://wiki.cancerimagingarchive.net/download/attach/18514300/JainPoisson2014_Radiology_Dataset.xlsx?.

Table 1 Used classes in the use cases 1 and 2

Class label	Parent class label
IBO:subject preparation	OBI:planned process
OGMS:disease	BFO:disposition
OBI:target to material addition role	BFO:role
OBI:material to be added role	BFO:role
OBI:MRI contrast agent	CHEBI:pharmaceutical
OBI:adding a material entity into a target	OBI:material combination
OBI:adding material objective	OBI:material combination objective
OBI:image creation	OBI:planned process
OBI:homosapiens	OBI:organism
IBO:imaging subject role	BFO:role
ONL-DP:T2 star weighted MR dataset	ONL-DP:functional dataset, ONL-DP:MR dataset, ONL-DP:reconstructed-dataset
OBI:image acquisition function	OBI:measure function
OBI:image creation device	OBI:device
ONL-DP:dataset processing	OBI:data transformation
ONL-DP:segmentation	ONL-DP:dataset processing
IBO:non-enhancing region of interest	ONL-DP:segmentation dataset
IBO:FLAIR dataset	ONL-DP:parameter quantification dataset
ONL-DP:regional cerebral blood volume estimation	ONL-DP:quantitative parameter estimation
ONL-DP:regional cerebral blood volume dataset	ONL-DP:parameter quantification dataset, ONL-DP:hemodynamic dataset
IBO:mean regional cerebral blood volume measurement datum	OBI:average value, IBO:imaging biomarker volume measurement datum
OBI:scalar value specification	OBI:numeric value specification
UO:volume unit	IAO:measurement unit label
IBO:qualitative parameter estimation	IBO:parameter estimation
IBO:non-enhancing margin definition	IBO:categorical VASARI criterion
IBO:non-enhancing margin definition value specification	IBO:categorical value specification
IBO:non-enhancing margin definition label option	IBO:categorical label

In this use case, we consider the competency question Q2 (see Section 1.3) to illustrate how the semantic description of VASARI features can facilitate the retrieval of image content. Listing 2 formulates in SPARQL language Q2 that finds all ROIs of datasets with their associated measures. The result of Q2 is illustrated in Fig. 6.

Listing 2 SPARQL query 2. obo:BFO_0000176 denotes the relation BFO:hasContinuantPartAtSomeTime. obo:OBI_0000312 corresponds to the relation BFO:isSpecifiedOutputOf. obo:IAO_0000004 refers to the relation OBI:hasMeasurementValue and The class obo:OBI_0000312 denotes the entity OBI:image creation.

```
Q2: ?dataset ?ROI ?biomarker ?biomarkervalue
Where{
?datasetclass rdfs:subClassOf* onl-ds:parameter-
    quantification-dataset.
?datasetinst rdf:type ?datasetclass.
?roiinst rdf:type ibo:image_region.
?roiinst rdfs:label ?ROI.
?roiinst obo:BFO_0000176 ?datasetinst.
?datasetinst rdfs:label ?dataset.
?imagecreation rdf:type obo:OBI_0001007.
?datasetinst obo:OBI_0000312 ?imagecreation.
?imageanalysis rdf:type ibo:image_analysis.
?imageanalysis obo:OBI_0000293 ?datasetinst.
?biomarkerclass rdfs:subClassOf* ibo:non-
    enhancing_margin_definition_VASARI_criteria.
?biomarkerinst rdf:type ?biomarkerclass.
?biomarkerclass rdfs:label ?biomarker.
?biomarkerinst obo:OBI_0000312 ?imageanalysis.
?biomarkerinst obo:IAO_0000004 ?biomarkervalue.
}
```

We note that the classification task using the Fact++ reasoner of Protégé is estimated to 0.25s. And we should mention that IBO ontology can be used to semantically anno-

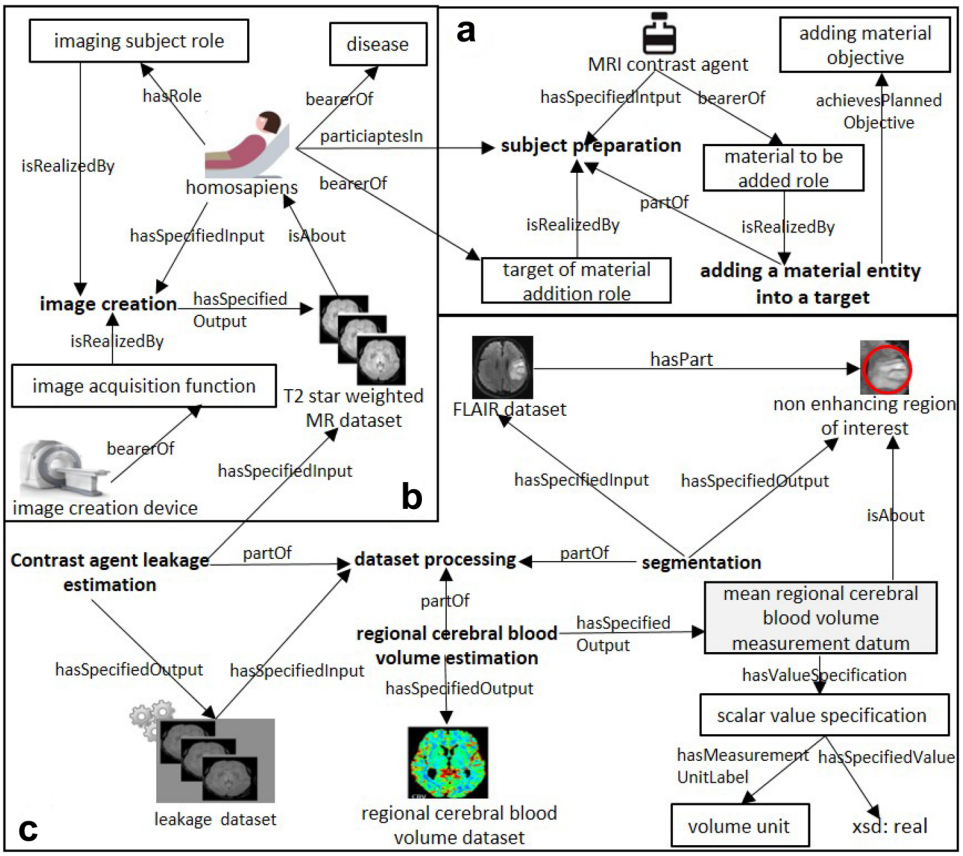

Fig. 3 Representation of the mean rCBV measurement process with the IBO ontology: box "**a**" describes the entities that are involved in the subject preparation process, box "**b**" corresponds to the image creation process, box "**c**" details the dataset processing processes. We note that processes are represented in bold, classes that are not processes are contained in boxes and relationships are denoted with arcs

Graph | XML | Table | Validate

?patientID	?diseasename	?datasettype	?datasetID	?biomarkername	?biomarkervalue
f66d92ff-85ad-4c83-b127-ce34c8488040	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0127-rcbvd	mean rcbv	4,243
31e6e6c8-9197-4927-bfe4-8f6836f963...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0128-rcbvd	mean rcbv	1,388
9ad6c241-ccc5-4532-a6ac-098271b13...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0132-rcbvd	mean rcbv	2,173
0133e584-111e-450a-b451-77a2799ef...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0133-rcbvd	mean rcbv	2,435
d0de6676-6ba1-4d79-a9b0-ec3f1e8a8...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0137-rcbvd	mean rcbv	2,53
5bbeb8a7-3ac2-4ef1-bd48-6f83bc994a...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0139-rcbvd	mean rcbv	2,112
357e2b63-6876-4c69-9728-c52fada81...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0143-rcbvd	mean rcbv	2,393
562d2831-ea9e-4ee1-bcee-77138e0a...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0147-rcbvd	mean rcbv	2,24
9ad6535c-da13-4f16-9df9-2b5df9aafe8c	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0164-rcbvd	mean rcbv	1,768
4a85a43b-4dbc-4081-b552-df06eef1a...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0166-rcbvd	mean rcbv	3,038
224235c1-5b6e-48d5-a5d1-777dfede0...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0168-rcbvd	mean rcbv	1,37
ada9c707-d49c-43d5-bee6-3e007327...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0173-rcbvd	mean rcbv	2,027
be8fa1fb-5696-4719-af16-2059f6b9d270	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0175-rcbvd	mean rcbv	2,12
bdb95e64-da10-4f2a-bac9-9a534cf564...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0177-rcbvd	mean rcbv	1,368
f3158197-173b-4917-ac3b-ed3ba04a5...	glioblastoma multiforme	regional cerebral blood volume dataset	TCGA-06-0179-rcbvd	mean rcbv	2,51

Fig. 4 Table displaying the results of Q1 query in CORESE

tate other GBM imaging biomarkers of the dataset as, for example, the major axis length, the minor axis length and the max of rCBV.

These two use cases illustrate that the use of OWL for the description of imaging results allows their formal processing. Thus for example, the annotation of imaging biomarkers with IBO should mainly allow: the consistent description of the input and output data, the aggregation of disperse imaging datasets, the performance of advanced search capabilities in clinical or research contexts, etc. Thanks to the knowledge embedded in the ontology, IBO can respond to diverse relevant queries.

The annotation of imaging result data with the same ontology can insure a sort of a collaboration between multiple investigators creating data about entities of the same types. Thus, data providers will not organize the data based on their predefined schema but, they will adopt a federated approach in data sharing.

6 Discussion

Our work shows that it is possible to cover the main three semantic axes of the imaging biomarker concept by

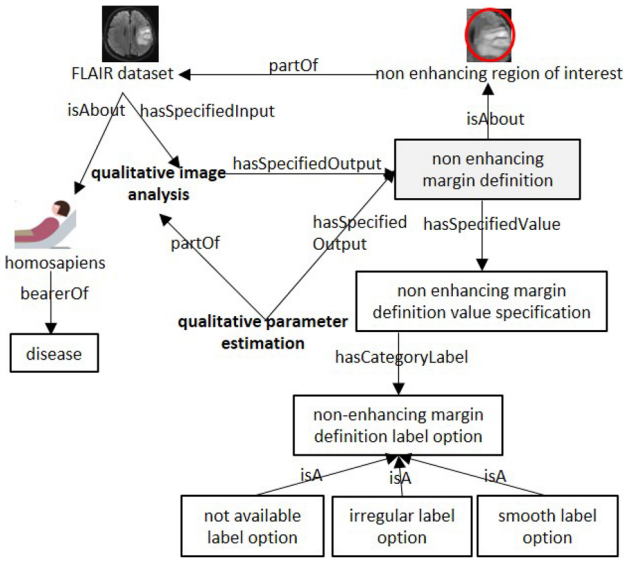

Fig. 5 Representation of the VASARI feature non-enhancing margin definition with the IBO ontology. We note that processes are represented in bold, classes that are not processes are contained in boxes and relationships are denoted with arcs

integrating and specializing classes from existing biomedical ontologies. We have created a generic ontology whose main objective is to define precisely this concept of imaging biomarker and to remove the ambiguity regarding it. Throughout our work, we have taken into consideration the limits of previous state-of-the-art works. We have followed an ontology development methodology that is different from QIBO; three major differences can be mentioned. First we created IBO using concepts coming from specialized ontologies (FMA, OBI, PATO, etc.) and that are well recognized by the OBO community, and others such as ONL-DP focusing medical imaging data. Second, IBO has been built in a modular way that facilitates its reuse and potential extension by future users. (Subsets of external ontologies are extracted with the OntoFox tool.) Finally, unlike QIBO, which was not aligned with a high-level ontology, IBO is based on BFO. (Table 2 shows how QIBO main semantic axes are represented in the IBO ontology with extended or new terms from terms other specialized ontologies.)

We have modeled the concept of imaging biomarker in a different way from that proposed in [12]. Contrary to their proposal, our proposal articulates the concept of biomarker

Graph | XML | Table | Validate

?dataset	?ROI	?biomarker	?biomarkervalue
TCGA-06-0127-T2-star	TCGA-06-0127-ner	non-enhancing margin definition VASARI criteria	Poorly-defined
TCGA-06-0128-T2-star	TCGA-06-0128-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0132-T2-star	TCGA-06-0132-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0133-T2-star	TCGA-06-0133-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0137-T2-star	TCGA-06-0137-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0139-T2-star	TCGA-06-0139-ner	non-enhancing margin definition VASARI criteria	poorly defined
TCGA-06-0143-T2-star	TCGA-06-0143-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0147-T2-star	TCGA-06-0147-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0149-T2-star	TCGA-06-0149-ner	non-enhancing margin definition VASARI criteria	poorly defined
TCGA-06-0149-T2-star	TCGA-06-0149-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0166-T2-star	TCGA-06-0166-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0168-T2-star	TCGA-06-0168-ner	non-enhancing margin definition VASARI criteria	poorly defined
TCGA-06-0173-T2-star	TCGA-06-0173-ner	non-enhancing margin definition VASARI criteria	poorly defined
TCGA-06-0177-T2-star	TCGA-06-0177-ner	non-enhancing margin definition VASARI criteria	well defined
TCGA-06-0179-T2-star	TCGA-06-0179-ner	non-enhancing margin definition VASARI criteria	well defined

Fig. 6 Table displaying the results of query Q2 in CORESE

Table 2 Top-level classes mapping to cover the upper-level classes of the QIBO ontology

Classes QIBO	Correspondence	Representation dans IBO
QIBO:biological target	⊆	OBI:target of material addition
QIBO:biological intervention	=	OBI:material processing
QIBO:biomarker use	⊆	OBI:planned process
QIBO:imaging agent	⊆	OBI:material to be added
QIBO:imaging subject	⊆	IBO:imaging subject role
QIBO:imaging technique	=	ONL-DP:dataset
QIBO:indicated biology	⊆	GO:biological process, OGMS:disease
QIBO:post-processing algorithm	⊆	OBI:data transformation
QIBO:quantitative imaging biomarker	⊆	OBI:measurement datum

We note that the symbol "=" denotes that the two referred classes are equivalent and the symbol "⊆" denotes a subsumption relation

with the aspects of protocol and measurement process. We made this choice to take into account the basic aspect of the imaging biomarker concept that a biomarker is a characteristic that is objectively evaluated and measured. According to the Institute of Medicine and to the QIBA group, the term objectively means precisely and reproducibly. However, these two aspects of accuracy and reproducibility can only be achieved by defining measurement protocols. This approach differs from that of [12], for whom objectivity is related to the intrinsic properties of observed quality and not to the measurement process.

We believe that the concept of imaging biomarker is better represented with IBO for the two following reasons. First we have added fundamental concepts that are not present in QIBO, BiomRKRS and the work of Ceusters et al., such as qualitative biomarkers, regions of interest, measurement protocols and the roles of imaging biomarkers. Whereas Ceusters and Smith [12] introduce biomarkers as a disjunction of the three categories of imaging biomarkers, we have articulated the latter explicitly. The main limitation of our contribution is that IBO must be extended by other specific classes before its application to a specific pathology. (QIBO and BiomRKRS have the same limitation.) In this paper, we have demonstrated how IBO can be used to annotate important imaging features in the glioblastoma domain and for these two use cases, we extend some part of our ontology to answer to some specific needs of the domain.

7 Conclusion

The importance of imaging biomarkers in biomedical research and drug design is well acknowledged in the literature, calling for appropriate standards and guidelines for biomarker development, validation and qualification. Beyond that, the development of precision medicine, the key role that imaging biomarkers will play in medical decision processes and the development of decision support systems make it absolutely necessary to define explicit and consensual semantics of the conceptual entities within this complex domain. The IBO core ontology of imaging biomarkers is a first step in this direction that reuses preliminary work from QIBO and BiomRKRS as well as relevant biomedical ontologies.

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