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What do biomarkers add: Mapping quantitative imaging biomarkers research

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ABSTRACT

Purpose: To understand the contribution of the concept of "biomarker" to quantitative imaging research.
Method: The study consists of a bibliometric and a network analysis of quantitative imaging biomarkers research based on publication data retrieved from the Web of Science (WoS) for the period 1976–2017. Co-authorship is used as a proxy for scientific collaboration among research groups. Research groups are disambiguated and assigned to an institutional sector and to a medical specialty or academic discipline. Co-occurrence maps of specialties are built to delineate the collaborative network structure of this emerging field.
Results: Two very distinct growth patterns emerged from the 5432 publications retrieved from WoS. Scientific production on «quantitative imaging biomarkers» (QIB) began 20 years after the first publications on «quantitative imaging» (QI). The field of QIB has exhibited rapid growth becoming the most used term since 2011. Among the 12,882 institutions identified, 56% include the term QIB and 44% include the term QI; among the 14,734 different research groups identified, 60% include the term QIB and 40% the term QI. QIB is characterized by a well-established community of researchers whose largest contributors are in medical specialties (radiology 17%, neurology 16%, mental 10%, oncology 10%), while QI shows a more fragmented and diverse community (radiology 13%, engineering 13%, physics 10%, oncology 9%, neurology 6%, biology 4%, nuclear 3%, computing 3%). This suggests a qualitative difference between QIB and QI networks.
Conclusions: Adding biomarkers to quantitative imaging suggests that medical imaging is rapidly evolving, driven by the efforts to translate quantitative imaging research into clinical practice.

1. Introduction

Extraction of quantifiable parameters from digital imaging has demonstrated its potential to enhance the value of radiology for multiple diseases. This data are used increasingly in preclinical studies, clinical research and advanced medical practice [1]. One of the most promising advancements in this field is the idea that characteristics extracted from images can act as biomarkers, i.e., as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [2]. Possible applications of medical imaging data as biomarkers range from prediction of possible future pathologies, early detection, severity classification and spread, assessment of treatment responses, and projection of final event prognoses [3].

Abramson et al. [4] proposed the relation between quantitative imaging (QI) and quantitative imaging biomarker (QIB). They state that "QI refers to the extraction and use of numerical/statistical features from medical images", and that as a research field "QI includes the development, standardization, optimization, and application of anatomical, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures, as well as the validation of QI results against relevant biological and clinical data" while QIB is "an objectively measured characteristic, derived from a medical image, that can be correlated with anatomically and physiologically relevant

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Abbreviations: IB, Imaging Biomarkers; QI, Quantitative Imaging; QIB, Quantitative Imaging Biomarkers; STEM, Science Technology Engineering Mathematics; WoS, Web of Science.

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parameters". These relevant parameters should be surrogated to a clinically significant endpoint: "a characteristic or variable that reflects how a patient feels, functions, or survives" [2,3].

Our view of the differences between QI and QIB, in which the latter is a more clinically focused stage, supports our analysis of the contribution of the concept of biomarker to research in QI. While QIB research deals specifically with the correlation of medical imaging data with disease endpoints, QI research includes activities such as image acquisition and the processing methods required prior to any evaluation of clinical impact. Bibliometrics, built upon publication data, allow for a systematic examination of scientific research in specific disciplines, fields, or specialties, their evolution through time as well as visualizing their cognitive structure. In the case of radiology, a number of studies have analyzed issues such as radiological research in Europe [5], the Spanish magnetic radiological scientific production [6], the evolution of gender differences in French academic radiology [7] or the research trends in high-impact radiology journals [8]. However, our review of the literature highlight the near absence (Gong et al. [9] is an exception) of work that provide a detailed overview of QIB research. Based on a selection of key terms that identify this emerging field, we analyzed QI and QIB in the scientific literature worldwide from 1976 to 2017 to: 1) examine the patterns of growth in this literature; 2) identify the types of institutions, research groups and specialties that have contributed; and 3) understand the patterns of collaboration and the cognitive diversity of the research groups involved.

2. Materials and methods

Our research uses bibliometrics and network analysis to examine the cognitive structure and knowledge generation processes involved in QIB research [10,11]. No institutional review board approval was needed to conduct this research. We identified publications on QI and QIB using the search terms "quantitative imaging", "imaging biomark*" and "quantitative imag* biomark*" in titles, abstract, and keywords in documents indexed in the Web of Science (WoS) between 1976 and 2017 (the first document was published in 1976 and 2017 was the last complete year prior to the searches). The search terms selected were based on the definition of biomarkers established by the Biomarkers Definitions Working Group [2] and the European Society of Radiology [3] and were thoroughly discussed and validated by an expert radiologist.

We considered all document types (hereafter referred to as papers) indexed in the WoS Core Collection. The resulting papers were categorized as QI or QIB. Papers identified using the search term "imaging biomark*" (IB) are included in the QIB group. Papers whose titles included both terms were assigned to QI or QIB based on the term that was most often used in the publication.

We used co-authorship as a proxy to outline the collaborative dynamics in the field (i.e. the multiple affiliation addresses given in journal articles – "Address" field in WoS). Thus, we define collaboration as a publication co-authored by researchers affiliated to two or more organizational units (i.e., publications with more than one address) [12]. To examine institutional diversity, we categorized the publications according to type(s) of institutional sector(s) of authors: academic institution, hospital, research institute, industry, other (e.g. medical-scientific society, non-governmental organization, medicine evaluation agency, consultant services). To identify the medical specialty and discipline contributing to QIB or QI research, we considered a more disaggregated level of analysis: the research group (e.g. department, laboratory, care service). This corresponds to the author's organizational unit (e.g. "Dana Farber Canc. Inst; Dept. Radiol") [13]. The research groups then were classified according to the corresponding medical specialty or discipline.

The most popular classification system is the schema included in the WoS database, which consists of about 250 research areas, referred to as subject categories. Two reasons prevented us from using it to classify the research groups. First, publications are not directly assigned to research areas. Instead, the journal determines the research area(s) to which the publications belong. Second, WoS subject categories are rather general (e.g. "Radiology, Nuclear Medicine & Medical Imaging" are one category). Thus, we built an *ad hoc* classification, based on identification of the relevant terms in the affiliation data. In the main, the labels used to identify medical specialties and disciplines correspond to the institutional affiliation of the authors [12]. The exception is the specialty "mental", which groups related specialties such as psychiatry, psychology, aging, and associated mental/cognitive disorders. Imaging includes research groups working on biomedical imaging (molecular, anatomic or functional) and interdisciplinary medical imaging centers with computational services for processing and analysis. The university organizational units include departments and laboratories; and hospital units include care services and units. Note that the *ad hoc* schema was tested in an initial set of publications. When differences to identify the specialty or discipline of a research group arose, the criteria of the radiology expert prevailed.

The use of science maps to extract the intellectual, social and conceptual structure of a research field is common practice in bibliometric and science policy contexts [14,15]. Science maps have the potential to show the relations among disciplines, fields, specialties, papers or authors based on spatial layouts [15]. Science maps have been used to provide an overview of the collaborative network structure in the fields of cardiology and oncology [16,17]; reproductive biology [18]; neglected tropical diseases [19,20]; tuberculosis [21]; vaccine development [22]; health management [23]; and big data in medicine [24]. In our case, they take the form of term maps of medical specialties and disciplines which allowed identification of clusters and their associations. We built symmetrical co-occurrence matrices of specialties/disciplines for QI and QIB which represent the collaborative links among research groups (i.e. publications co-authored by research groups belonging to different specialties). We took the temporal dimension into account and built three cumulative sub-networks corresponding to three different periods (1976–2007; 1976–2011; 1976–2017 for QI and the same periods for QIB starting in 1998, when the first QIB papers were published). Each period was defined based on the publication trends and some key milestones for the development of quantitative imaging biomarkers: the foundation of Quantitative Imaging Biomarkers Alliance –QIBA– in 2007 and the year when QIB surpass QI as the most frequent term (2011). This cumulative approach allows examination of the structure and evolution of the co-authorship networks over time.

To visualize the structure of the interrelationships among specialties, we applied network analysis and clustering methods using VOSviewer software (version 1.6.14). We used Association Strength to normalize the strength of the association between specialties [25,26]. If research groups from two different specialties/disciplines are named on the same publication this indicates a link between their particular topics. The more co-occurrences between two specialties/disciplines, the stronger their association. That is, specialties/disciplines located close to each other in the map tend to be strongly related. Note that the density of the links is the sum of the co-occurrences between two specialties, and the size of the nodes is indicative of the number of co-occurrences of each specialty in the selected period. To reduce the effect of medical specialties and disciplines with a marginal presence we excluded the 2% at the bottom of the co-occurrence distribution.

3. Results

3.1. Publication patterns in QI and QIB research: outputs, institutions, and research groups

Papers published between 1976 and 2017 total 5432 ("quantitative imaging" QI = 2824; "imaging biomark*" "quantitative imag* biomark*" QIB = 2608 papers), of which 4187 (77%) have been produced in collaboration between two or more different organizational units.

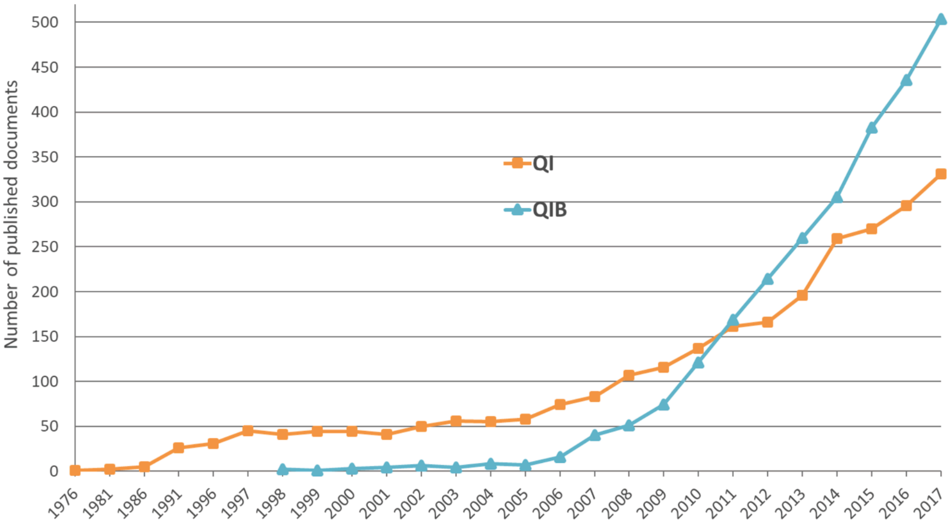

Fig. 1. Evolution of the volume of papers published according to search terms (QI-QIB).

Fig. 1 depicts their distribution over time, and shows two distinct patterns. QI shows a gradual increase between 1990 and 2007, and a significant increase after 2008 (more than 100 publications per year) to a peak in 2013 of approximately 200 publications per year. QIB shows a different growth pattern. The first two papers did not appear until 1998 and between 1998 and 2005 only 35 papers on QIB were published. From 2006 there was a sustained increase to more than 500 publications in 2017. Note that up to 2010, QI was the most frequent term but since 2011 the most frequent term has been QIB. This difference between the growth patterns in the use of both terms is confirmed by the mean year-on-year growth during 1999–2017, larger for QIB (45%) compared to QI (12%). Only 56 publications contained both terms in their titles, abstract and keywords (1% overlap).

During the period 1976–2017, we identified 12,882 institutions, 7206 (56%) used the term QIB in their publications, and 5676 (44%) used the term QI. As already mentioned, institutions were classified as: academic institutions, hospitals, research institutes, industry, and others. Fig. 2 depicts the share of publications related to each type of institution. Research groups at academic institutions are the most frequent (more than 50% in both QIB and QI), followed by hospitals and research institutes. Industry participation is comparatively small (5% in both QIB and QI). However, note the larger contribution of hospitals to publications on QIB (32%) compared to QI (20%).

We identified 14,734 different research groups which were classified as above: 8772 groups use the term QIB (60%) in titles, summaries or keywords, while 5962 groups use the term QI (40%). In the case of groups publishing in QIB, 10 medical specialties and disciplines account for 80% of the total papers: they include radiology (17%), neurology (16%), mental (10%), oncology (10%), imaging (9%), nuclear (4%), and engineering (4%). In the case of QI, the largest contributors are: radiology (13%), engineering (13%), physics (10%), oncology (9%), imaging (8%), neurology (6%), biology (4%), nuclear (3%), computing (3%) and chemistry (2%). QIB research involves a larger number of medical specialties. A more diverse contribution was noticeable among the medical specialties and STEM disciplines in QI publications (see Fig. 3).

3.2. *The collaborative network structure of QI and QIB: Medical specialty and discipline maps*

The medical specialty and discipline maps describe the general structure of QI and QIB and their temporal evolution, based on the collaborative links among research groups. The early stage of QI (1976–2007) runs in parallel with the development and diffusion of two ground-breaking medical imaging technologies: computed tomography scanner and nuclear magnetic resonance (Fig. 4). This period is characterized by the mutual dependency between, on the one hand,

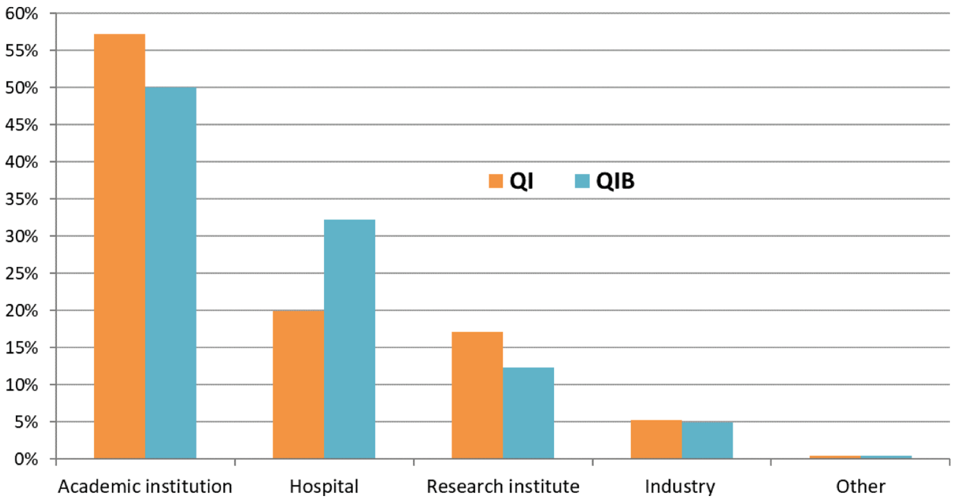

Fig. 2. Percentage of collaborative papers by institutional sector on QI and QIB.

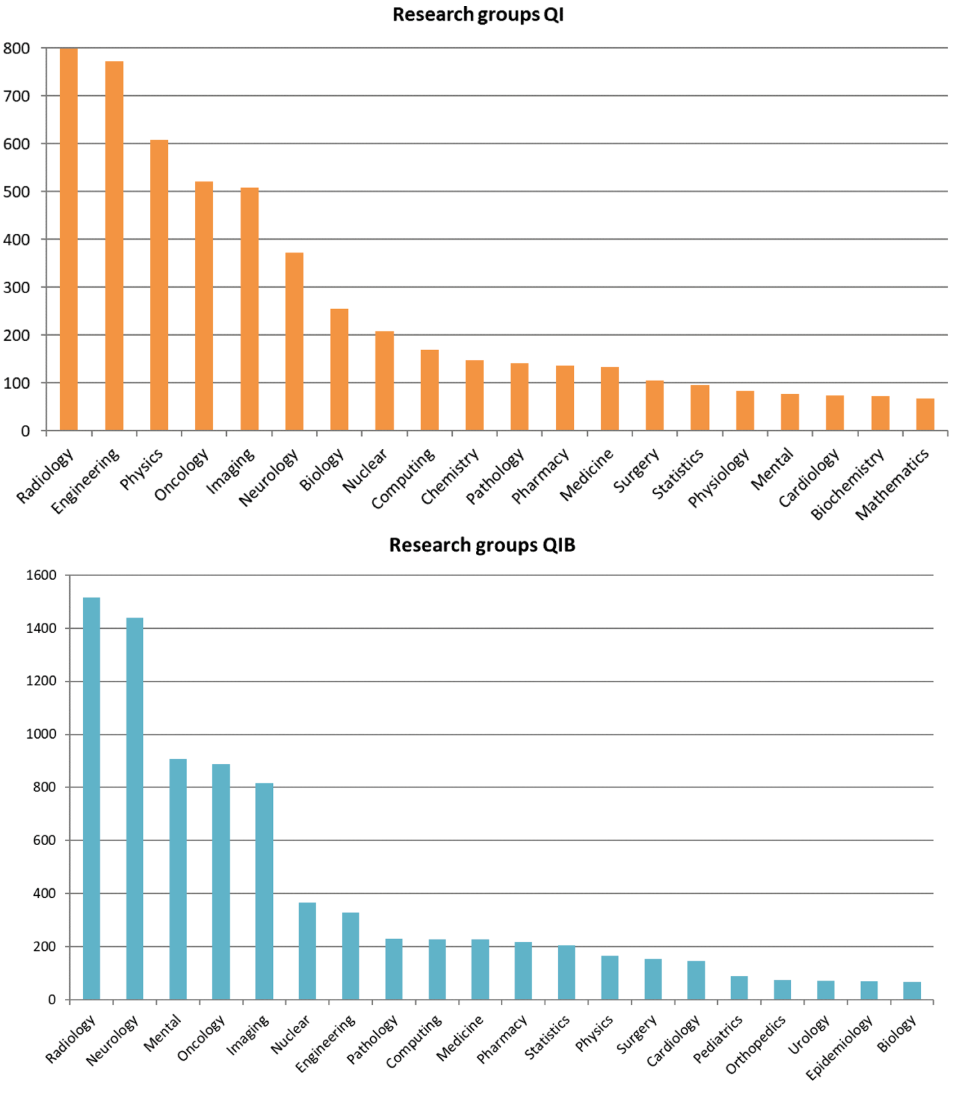

Fig. 3. Numbers of research groups by specialty/discipline (QI-QIB). Figures account for 90% of all research groups in QI and 94% in QIB.

radiologists and neurologists (*purple cluster*) and, on the other hand, physicists and engineers (*red cluster*) to solve accuracy and image processing related problems and to move these new technologies into clinical practice. Such mutual dependency and strong collaborative ties are reinforced throughout the second period (1976–2011). Radiology continues to be the central specialty in the field but gets closer to physics, engineering and nuclear (*green cluster*), while neurology and imaging begin to form their own clusters. This growing diversity is confirmed when the most recent period is examined (1976–2017). We identified four large QI clusters: *red cluster* with 16 specialties whose primary node is medicine; *green cluster* with 8 specialties, whose primary node is radiology; *blue cluster* with 6 specialties whose primary node is neurology; and *yellow cluster* with 5 specialties whose primary node is engineering. On the one hand, radiology occupies a central position in the network; on the other hand, collaboration is more intense between radiology, oncology, engineering, imaging, and physics specialties.

The time evolution of the QIB network displayed in Fig. 5 is different from QI. The papers published during the early stage of QIB (1998–2007) reveal an incipient and disperse community of researchers: an isolated clique (chemistry, mathematics, computing and nuclear) and two other small clusters with radiology acting as a bridge. The intermediate stage (1998–2011) shows apparent signs of growing collaborative links among research groups from distinct medical specialties and disciplines, with radiology and neurology as the central nodes. The last period (1998–2017) reflects the outburst of scientific publications on QIB and the establishment of a multidisciplinary community of researchers. We identified three large clusters in the QIB network: *red cluster* with 14 specialties whose primary node is radiology; *green cluster* with 12 specialties whose primary node is medicine; and *blue cluster* with 5 specialties whose primary node is neurology. The largest clusters are the *red* and the *blue clusters*. In the *red cluster*, radiology dominates with strong links to imaging and oncology. The *blue cluster* centers around neurology with strong links to mental, nuclear, and computing.

Comparison of the most recent maps (QI: 1976–2017 vs QIB: 1998–2017) shows the higher concentration of medical specialties in the QIB network (Fig. 5) compared to the QI network (Fig. 4), with a smaller number of clusters and greater proximity between medical specialties and STEM disciplines within a single cluster. A Chi-square test ($\chi 2 = 2344.93$, $p < 0.000$) confirms that the frequency distribution of medical specialties and disciplines is significantly different between QI and QIB. For example, the *blue cluster* in the QIB network plays a central role and is comprised of strongly interrelated medical specialties (neurology and mental). In turn, both of these collaborate closely with STEM disciplines (computing and statistics). The central nodes in the *red cluster* are medical specialties (radiology, oncology), and imaging which consists of research groups working on medical imaging and interdisciplinary centers with computational services for processing and analysis. These three nodes are closely linked (they appear to form a clique) but also

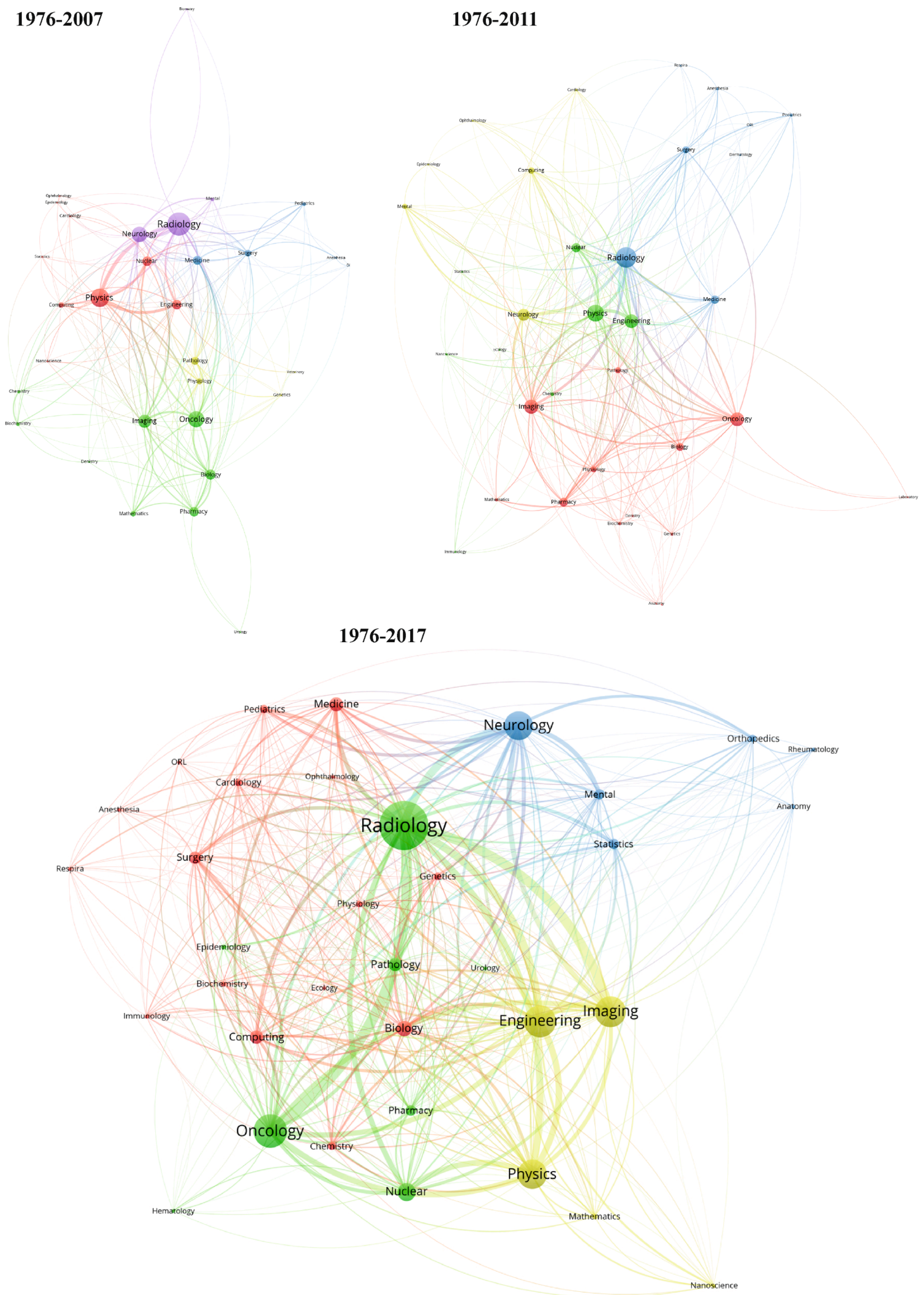

Fig. 4. QI co-authorship cumulative networks: maps of medical specialties and disciplines based on the collaborative links between research groups.

collaborate with STEM research groups (engineering and physics). The QI map is more weakly connected with a larger number of disparate clusters and many specialties occupying peripheral positions. The collaboration between research groups belonging to medical specialties and STEM disciplines is less well-established: the two most important STEM nodes (engineering and physics), are in a different cluster from the most relevant medical specialties such as radiology and oncology.

4. Discussion

Our study applies a search approach to map the global landscape of QIB research based on the consideration of QIB as a more clinically focused stage within QI, which is the broader field. We examined the papers published over time, institutions, and research groups. Besides, we disclose the cognitive structure of the field by analyzing the collaborative links among research groups. Our study shows that “adding” the term «biomarker» to quantitative imaging reflects the development and

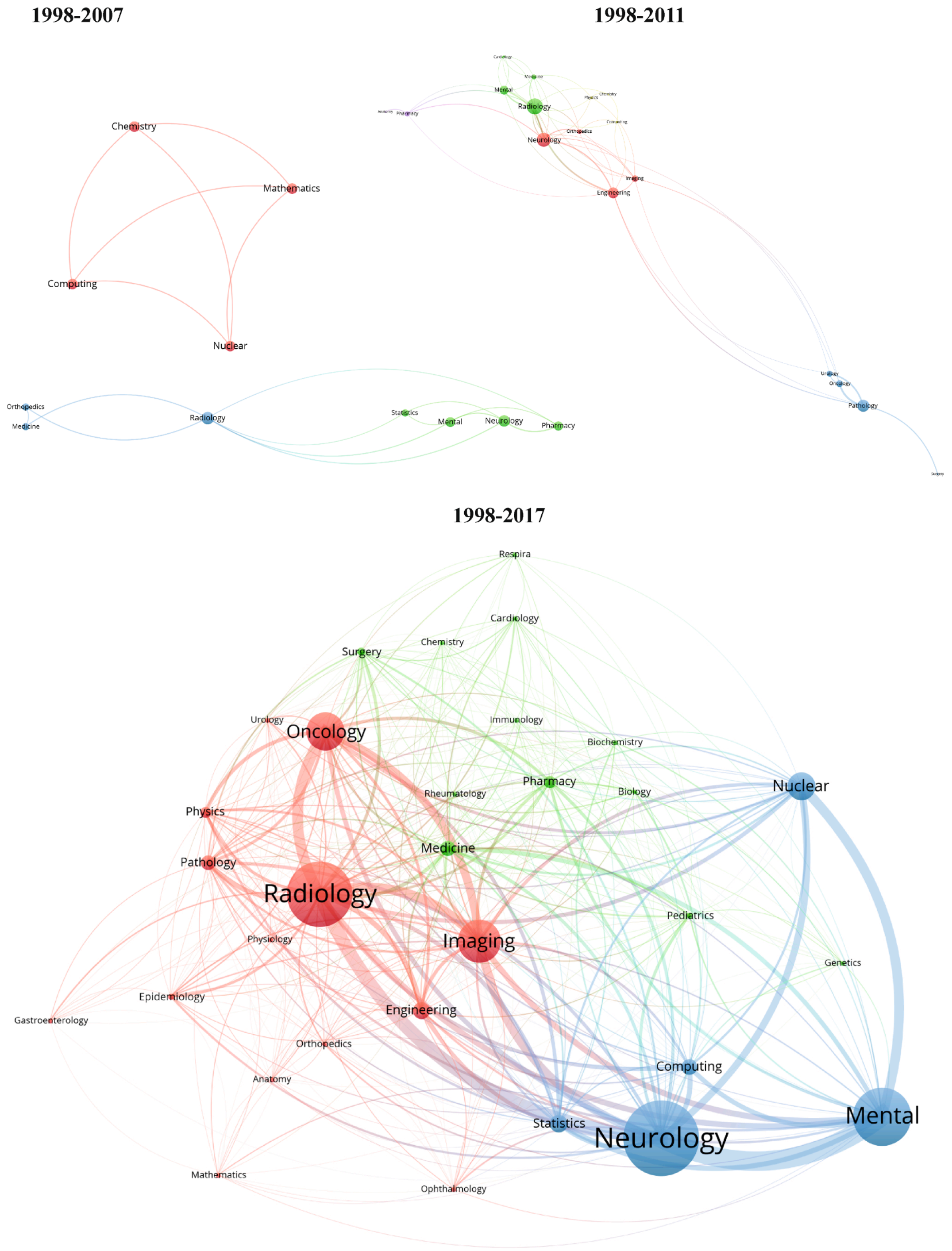

Fig. 5. QIB co-authorship cumulative networks: maps of medical specialties and disciplines based on the collaborative links between research groups.

implementation of computational medical imaging, which is characterized by the efforts jointly undertaken by a diverse and multidisciplinary community of researchers.

Previous studies have pointed to the increasingly variety of medical specialties and disciplines contributing to radiology research. Lim et al. [27] found an increased number of articles between 2001 and 2010 in the top two radiology journals whose first author affiliation corresponded to a non-radiology medical specialty. Similarly, Ray et al. [28] noted a trend towards a decrease in the number of radiology experts as primary authors in three major American journals during two distinct 24-month time periods (1992–1993 and 2002–2003), while Song et al. [29] found that first author's affiliations in radiomics research published between 2013 and 2018 mostly correspond to non-clinical researchers. Our findings confirm this pattern of multidisciplinary collaboration in the QIB research field by examining all authors' affiliation regardless of their position in the byline. Although first author usually contributes most, middle and last author positions are relevant [30]. For instance, last author often gets as much credit as first author and is assumed to be the driving force behind the research [31]. Therefore, to gain a better understanding of the knowledge generation processes is important to consider all actors at play.

The maps show the existence of strong collaborative links between medical specialties and STEM. However, there are also clear differences between these categories. QIB is distinguished by a larger concentration of medical specialties and greater proximity between medical specialties and STEM which suggests a well-established community of research groups that work together and rely on different bodies of knowledge. QI shows a more fragmented and dispersed community of researchers. Although radiology remains the medical specialty with the largest number of contributions, there is an important presence of research groups from other medical specialties (such as neurology, mental, oncology and nuclear) and from STEM disciplines (such as imaging, engineering and computing related to QIB; and engineering, physics, imaging, biology, and computing related to QI). Thus, development and innovation in medical technologies seems increasingly to depend on interdisciplinary research and the breaking down of institutional boundaries [32].

The significant increase in the number of publications from 2006 parallels the increase in the number of collaborative projects integrating advances in QI and QIB in clinical practice, clinical trials, and biomedical imaging research. We refer to initiatives spearheaded by scientific institutions such as QIBA – 2007 within RSNA, QIN – 2008 under the *National Cancer Institute*, and EIBALL – 2015 by ESR. These projects arose from the need to overcome certain obstacles to the development and application of QIB. These obstacles include the large cost and large amount of time required for regulatory agency approval for marketing and clinical use, and the difficulties involved in bridging translational gaps and clinical decision-making processes [33,34]. All of these alliances are based on close collaboration and coordination among very diverse organizations such as manufacturers, regulatory agencies, health service providers, academic institutions, groups leading imaging in clinical trials, biopharmaceutical companies, contract research organizations, professional associations, and medical practitioners [1].

Of note is that the very small overlap of 1% between the two groups of papers suggests that the QIB research field, in addition to having a distinct qualitative difference in the structure of its collaborative network, is evolving independently towards QI which is the broader field. Various technical papers stress the importance of multidisciplinary interaction between medical specialties and STEM disciplines when designing new biomarkers, for example as in the "stepwise development of imaging biomarkers approach" [35,36]. The process for the development and validation of imaging biomarkers needs to comply with conceptual coherence, technical reproducibility, sensitivity, and specificity. To achieve this requires: proof of concept, proof of mechanism, acquisition, image processing and analysis, proof of principle, and performance and effectiveness tests. At each step, different knowledge and methods from different specialties are incorporated. For example, the development of an imaging biomarker for the study of articular cartilage requires the integration of knowledge on the pathogenesis of the disease being studied (practiced in medical specialties and biology) with knowledge of dynamic imaging analysis with contrast (practiced in the collaborations between STEM disciplines and clinical specialties) [37]. Our results point also to need for collaboration among researchers with diverse expertise, knowledge, and technical skills to develop increasingly complex technologies. We found that research groups contributing to QIB form research networks that are cognitively diverse and are mutually dependent on one another's knowledge and expertise [38].

Our research has some limitations. The first is that we classified the research groups into medical specialties and disciplines based on a specially created *ad hoc* list of categories since the WoS subject categories were not suitable. WoS subject categories are at journal level, lack the specificity, and are largely the result of groupings based on citation patterns between journals [39]. The second limitation is that we chose to include publications on imaging biomarkers and quantitative imaging biomarkers in a single research field, choosing QIB as the category identifying both document sets. Our choice is supported by the fact that these terms are used interchangeably by scientific societies that pursue the same objectives and collaborate closely. For instance, QIBA and EIBALL, which suggest two significant concepts with the same significance in the scientific literature. Third, we have taken researchers' affiliations as representative of their area of expertise. We assume that engineers or physicists working in radiology departments are likely to be closer to radiological knowledge than their peers working in, for example, physics departments. The last but not least limitation is to make explicit that the search approach of this study represents a proxy for examining quantitative imaging biomarkers research. Emerging fields are constantly evolving in the use of its terms as well as in the shared understanding of the concepts. Certainly, radiology is changing rapidly, and these conceptual novelties have not yet reached the necessary stability throughout the scientific community.

4.1. Policy implications

Our study is also relevant from a policy perspective. The emergence of a new scientific concept, such as adding the term "biomarker" to the field of quantitative imaging, must go in hand with research policy initiatives that support the idea that the evolution from quantitative imaging to imaging biomarkers represents a paradigm shift that requires clinical impact evaluation, substantial investments in financial resources and interdisciplinary collaborations. This need has been documented by Hilgartner [40] for the case of the genomics revolution. QIBA mission stresses the importance of collaboration to identify needs, barriers and solutions to create consistent, reliable, valid and achievable quantitative imaging results. Our results support this view and point to the need to develop formal research structures encompassing diverse and multidisciplinary research teams and stakeholders. Such research structures would accelerate the translation of research on quantitative imaging subrogate biomarkers into clinical trials, innovative developments and improved patient care.

5. Concluding remarks

In conclusion, quantitative imaging biomarkers is an emerging research field aiming to translate quantitative imaging research into clinical practice. Our findings on the very small overlap between quantitative imaging and quantitative imaging biomarkers papers suggests that both fields are evolving independently.

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CRediT authorship contribution statement

Enrique Meseguer: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **David Barberá-Tomás:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Carlos Benito-Amat:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Adrián A. Díaz-Faes:** Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Luis Martí-Bonmatí:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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