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Abstract

Multimodality medical imaging offers a key role in disease diagnosis, while providing accurate staging and defining disease extent in many instances. Recent developments are increasingly leading to quantitative assessment of medical images, allowing both definition of disease extent, giving insight into the phenotypes of diseases and offering capabilities of monitoring response to therapy. Combined with other tools, such as genetic profiling, this is a powerful way of improving diagnosis and treatment of patients, enabling a personalised approach to delivering healthcare. It is highly likely that software tools will become integrated into the routine workflow of radiology reports. This special report describes some of the crucial areas where applications are being introduced and speculate on the potential impact on radiologists and clinicians.

Keywords: Radiology, Imaging, Biomarkers, Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography, Therapy Assessment, Quantification, Emphysema, Aortic Valve Stenosis

Background of imaging biomarkers

Radiologic imaging has made a huge impact in the overall management of patients, allowing rapid and accurate diagnosis for many diseases in one way or another. The range of imaging includes anything from ultrasound to plain film radiography and more complex procedures with or without the need for ionising radiation. However, in spite of using imaging as a diagnostic test, it takes more work to develop an imaging-based biomarker.

An imaging biomarker is a biologic feature or characteristic, that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or biological responses to a therapeutic intervention, detectable in an image.[1,2] In medicine, an imaging biomarker is a feature of an image relevant to a patient's diagnosis. As such, it has been postulated that imaging biomarkers can be used as a surrogate to predict outcome and to monitor disease response, thus replacing traditional methods such as clinical outcomes (e.g. recurrent disease or death). Surrogate biomarkers are thought to assess treatment effects more quickly, thus enabling more rapid determination and potential to change patient management.

Although this all sounds relatively new, imaging has been used for many decades as an aid to diagnosis, to evaluate extent of disease and to help demonstrate efficacy of treatment. Initially this was done using plain radiography methods, and even today plain radiographs are commonly used for assessment and classification of spinal and other fractures and for follow-up of known lung nodules for instance. With the advent of advanced imaging methods, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), there is now increasing clarity in images that enable quantification in real terms, which in turn allows for more precise diagnosis and assessment. This is a key component to the planning of "Precision Medicine", as improving the phenotype description in the context of genetic testing is a very powerful method to indicate likely success of newly developed molecular targeted treatments. Thus, it becomes possible to relate images to anything from normal biological patterns up to pathophysiological findings and measurements of treatment effectiveness. Good examples of this type of imaging biomarker are the assessment of chemotherapy effects in cancer treatment (RECIST criteria) [3] and also the PET response in patients following treatment of head-neck cancer [4] and staging and therapy assessment of lymphoma [5].

Summary of the main advanced imaging methods

Computed tomography (CT) is a method of ionising radiation transmission and measures density differences of the tissues. The method allows for a three-dimensional assessment of the targeted volume of the body, and displays are now used which depict isovolumetric volumes of tissue (voxel), which can be probed in all three dimensions. Software tools allow for precise display of density maps across these volumes, direct measurements of size of abnormalities and analysis of contrast enhancement patterns in the presence of iodinated contrast agents. This imaging technique is both versatile, easily available and is therefore applied frequently in clinical settings. The caveat is that density measurements may be affected by different CT reconstruction methods, the protocol applied and the use of intravenous contrast agents. Standardisation can be achieved, but requires highly dedicated quality assurance.

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Positron emission tomography (PET) relies on the injection of radioactive tracers, which mimic a normal metabolic pathway in the body. The most commonly used compound, 18F fluoro-deoxy-glucose (18F-FDG) is a glucose analog that is taken up by cells and starts the Krebs cycle. However, once converted to 18F-FDG-phosphate, the next step of the cycle is unable to take place and the substrate is trapped in the cell. Cells with increased glucose uptake, such as cancer cells or at sites of inflammation, will demonstrate higher radioactivity, which can be measured by gamma cameras capable of picking up high energy (511 keV) photons, which are the result of the annihilation reaction between protons and electrons. PET is now almost always combined with a cross-sectional imaging technique, such as CT or MRI, for direct correlation with anatomical structures, as this allows more precise localisation of the increased uptake of radiotracer. The technique was traditionally reserved for oncology, but, in combination with development of more targeted radiotracers, it is increasingly applied in areas such as cardiovascular diseases, cerebral diseases and for evaluation of cellular activity in transplantation for instance. With appropriate quality assurance, it is possible to measure absolute radiation values in relation to body mass and injected radiotracer, which allows for standardisation of the technique.

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Imaging has captured the attention of regulatory authorities, such as the FDA [8] with other initiatives such as the NIH Roadmap [9], the Clinical Trials Transformation Initiative[10], the RSNA's Quantitative Imaging Biomarkers Alliance [11] and the European Radiology Society's Imaging Biomarkers Alliance [12]. They all have in common the wish and commitment to develop, qualify and validate imaging biomarkers to allow for better utility of imaging in clinical trials.

How do we qualify and validate imaging biomarkers?

Imaging biomarker qualification and validation is a multi-step process, requiring a number of important milestones.[13] Every step is a process which takes up several years, and the method may fail anywhere along the line of development.
Before an imaging method can be considered as a biomarker, it is vital that the method is standardised such that it can be applied routinely at any site which wishes to introduce it. There is a need for greater standardisation, as both scanner manufacturers, individual preferences and patient handling can all affect the imaging parameters being studied. This is particularly true for the more advanced imaging studies, and it is a major focus of a number of collaborations, largely under guidance from the main professional organisations mentioned above. Once a standardised protocol has been achieved, the actual qualification of a biomarker can commence.

First, the imaging biomarker must be demonstrated as closely linked to the presence (or absence) of the target disease. This usually requires observational studies, whereby the imaging biomarkers is correlated to disease presence, extent of disease and prognostic value compared to existing methodologies, including clinical assessment using standard diagnostic techniques as well as longer-term outcome. This process will generate sensitivity and specificity of the diagnostic test.
Second, as with any diagnostic test, the biomarker requires to be accurate and reproducible in both short term and long term measurements. This process should start as soon as there is a suggestion that there is a correlation (step 1), and requires the application of repeated measurements during a short period of time in patients with and without the disease process (immediate and longer reproducibility), multiple assessments by several observers (intra- and interobserver varability) and the correlation with the actual disease process severity.
Lastly, any changes measured over time need to be directly related to the changes of the target condition. This will require longer-term repeated testing in correlation with standard measurements of disease status (e.g. clinical status) with follow-up over several years.
As shown, the qualification is quite a long and arduous process, hence the working together of many scientists and organisations is required to pool resources appropriately. It is not surprising, therefore, that this process takes many years and only now are we starting to see results, having started this work over a decade ago.

The validation of a qualified imaging biomarker is the final step in this process. Initially, the evidence built up during the course of the qualification process will allow a consensus to be formed among the scientific community that the test is likely to be fit for purpose as a biomarker. Subsequently, the efficacy of the biomarker to

demonstrate treatment effects that are not seen in non-treated controls, while a comparison with routine standards, such as clinical outcome is sought. Regulatory authorities, including the FDA and MHRA, are able to collate the evidence of a proposed (imaging) biomarker and determine whether the test is acceptable as a surrogate endpoint for a clinical trial. These bodies have clearly indicated their ascent to the incorporation of surrogate end points for clinical trials, provided these end points have been adequately developed and validated. [13] Thus, if there is a positive outcome on a surrogate endpoint, this would be regarded as a positive result towards market approval for the new treatment.

Examples of clinical approaches to the use of imaging biomarkers

There are many clinical areas where imaging biomarkers are effectively in use, particularly in oncologic staging and treatment response assessment. These methods are reasonably well established, and offer direct management direction for clinicians based on imaging findings (staging) or based on pre and post therapy changes in terms of tumour size or change in metabolic activity using PET imaging. In other areas, imaging biomarkers are being used as inclusion/exclusion criteria for clinical trials where new therapies are being tested that have a known metabolic point of interaction (e.g. amyloid plaque PET imaging in qualification of patients for new Alzheimer's disease drugs or bone mineral density assessment for exclusion of patients with osteoporosis in drugs that can negatively influence bone mass). It is not possible to give an overview of every imaging-based biomarker being tested or available at present. Therefore, two areas of interest will be highlighted, where imaging-based biomarkers are at the cusp of routine clinical application (emphysema) or are in an advanced state of development (aortic valve stenosis).

The use of imaging biomarkers for lung diseases has been piloted for some time. The problems encountered largely evolved around standardisation of CT scanner systems, but with appropriate quality control and setting the protocols, it is feasible to determine some significant phenotypes, which can be used longitudinally to study the potential effects of new treatments. Thus, CT-based quantification of emphysema both correlates with pulmonary function and mechanics, but additionally offers further insights into the phenotypical distribution and extent of disease. [14]
One of the first attempts demonstrating the feasibility of an imaging-based biomarker was made for a large trial evaluating the utility of lung volume reduction surgery in patients with severe emphysema, where CT based density distribution was capable of predicting outcomes directly. [15] Subsequent imaging analysis further highlighted the extent of the correlation between CT quantified findings and the outcomes in the surgical and control arms of this large study. [16] This work is now continuing with the advent of interventional bronchoscopic methods for lung volume reduction surgery, where CT is both used as a tool to determine patient eligibility for the procedure and for the planning and assessment of treatment response. [17]
A longitudinal observational cohort study used CT as a way to determine the extent of emphysema, as well as the change over time. [18] Lung density at baseline was influenced by a number of variables, including age, sex, body-mass index, current smoking status and smoking history, and severity of airflow limitation. Importantly, the study could measure annual lung function decline as quantified by CT lung density at rates of -1.13 g/L, but with variability due to sex and smoking status. [18]

Thus, the CT measurements gave a clearer indication of changes over a one-year period compared to pulmonary function tests.
The COPDGene study enrolled a large cohort of patients (10,000) in multiple centres in the USA, who were screened for obstructive outflow disease including genetic assessment and the application of CT. [19] The CT protocol was centrally set-up with quality assurance rigorously applied. An analysis of 9,313 subject CT scans demonstrated a clear quantifiable pattern of low-attenuation findings on CT. [20] Additionally, measures of mild emphysema in smokers with preserved lung function could be demonstrated as quantifiable low-attenuation changes on CT, allowing for earlier diagnosis. [20]
Subsequent analysis of 10,192 smokers in the COPDGene study demonstrated the ability of CT to identify patients with varying degrees of emphysema, as well as the presence or absence of airways disease. [21] This enabled identification of four subgroups of smokers that were closely associated with clinical characteristics of COPD and known COPD-associated genetic variants. [21]
A third large cohort study, SPIROMICS, deserves mention, as it is closely monitoring various serum and plasma biomarkers in combination with CT in 3,200 participants. [22] A sub-study evaluated airway measurements in a total of 1,559 subjects, and demonstrated that airway walls are thinner and lumen size is smaller in patients with COPD compared to controls, and this closely correlated with pulmonary function tests. [22] Thus, the study confirmed the findings in the COPDGene study, which gave similar findings. [23]
Overall, where lung imaging is concerned, it is clear that CT-based measures are essentially ready to be used as biomarkers. Several measurements are available, depending on the specific study questions, and it is vital to ensure protocols are appropriately chosen and quality assurance is maintained. The software tools are now available for incorporation into routine workstations. This last piece of the puzzle will allow more seamless performance of pulmonary CT investigations, which will include reporting of quantitative measures of emphysema and airways as part of the standard clinical report. Only with this type of workflow can imaging-based biomarkers make a difference in clinical practice.

Another area where imaging biomarkers are actively being developed is in cardiac applications. Traditionally, invasive cardiac catherization in combination with echocardiography and nuclear medicine studies have evaluated the presence of coronary artery stenosis, perfusion changes and heart valves. More recently, work has been ongoing to delve deeper in the mechanism of aortic valve stenosis and coronary atherosclerosis using 18F-sodiumfluoride PET imaging.
Initial work focused on demonstrating the direct link between the 18F NaF uptake in the areas of aortic valve and the histological correlation with the calcific process. [24] Subsequently, during a follow-up study of these subjects, it was demonstrated that the extent of radiotracer uptake directly correlated with the increase in calcific aortic valve disease and functional decline. [25, 26] This work suggests that the detection of this process can be achieved much earlier using 18F-NaF PET imaging compared to either CT or echocardiographic measurements, and the application of this imaging biomarker will likely affect management as the uptake is directly correlated with progression of disease.
In parallel with this work, it was noticed that some patients with aortic valve pathology had uptake in coronary arteries. A subsequent study demonstrated that 18F-NaF PET imaging is correlated with acute myocardial events, and it was postulated

that uptake is a reflection of vulnerable plaque, which would be a more accurate and important parameter to predict acute coronary artery events than simple angiographic methods (which are focussed on level of stenosis). [27] Another study in 40 patients with myocardial infarction and 40 patients with stable angina evaluated the role of 18F-fluorodeoxyglucose uptake in the aorta. [28] This study demonstrated a direct correlation between the extent of radiotracer uptake in the aorta and early recurrent myocardial infarction, likely due to systemic atherosclerotic inflammatory exacerbation and plaque destabilisation. [29] These studies similarly could alter future disease management, potentially leading to better identification of active disease and the area of plaque most at risk for developing acute myocardial events. In particular, more targeted approaches to plaque stabilisation as well as the ability to monitor changes over time, will allow development of dedicated new therapies. Further studies in this field are ongoing, focused on short and long-term reproducibility and long-term follow-up of patients to assess disease progression or modification and clinical outcomes in relation to the imaging test.

Future perspective

It is highly likely that imaging biomarkers will continue to develop into clinical tools, enabling precision and personalised medicine to thrive. Some novel imaging biomarkers are now making their inroads into routine clinical practice, others are under development, while yet others have hurdles to take (although these are not unsurmountable). It will be vital to continue the rigorous process outlined, as this will be the only way that regulatory authorities will be able to safely accept these imaging biomarkers to be used in routine clinical practice.

Ultimately, the aim of imaging biomarkers will be a challenge to the training of radiologists, who will need to address workflow and reporting changes that are required for imaging biomarkers to gain full impact for clinical management of patients. It will no longer be sufficient to just describe the findings. They will require more precise description in quantitative terms, actual changes over time and combination of quantitative imaging findings in relation to prognosis. Imaging biomarkers will be used in a variety of ways, some for patient selection, others for patient exclusion. This will need to be anticipated by the radiologists as clinicians increasingly rely on imaging to provide answers to clinical management questions. Training the radiologists of the future to deal with the increased demand and changing reporting requirements is a challenge that will need to be addressed in this context.

Conclusions

Imaging biomarkers are already reality, but will continue to be developed to allow for more precise assessment of disease, indication for different therapeutic options and measure therapy response. This is what will drive individualised patient care pathways, where imaging biomarkers will be a core tool, which will have a major impact on health economics as a result. The end result will be more appropriate treatment of patients at reduced overall costs in terms of both (avoidable) complications and overall healthcare costs.

The challenges of developing imaging biomarkers and to train the radiologists of the future go hand-in-hand, but the rewards are improved patient care while maintaining affordability. That is a result worth investing in.

Executive summary

- Imaging biomarkers are of interest in order to serve as surrogate endpoints in clinical trials, as they can lead to a reduction of sample size due to earlier measurement of treatment effects, thus reducing the overall time from start of the clinical trial to end point.
- Imaging biomarkers need to be developed using quite strict qualification and validation methodologies, as only this approach will allow useful and trustworthy imaging biomarkers to be acceptable for clinical practice.
- Imaging biomarkers are increasingly making their way into clinical routine applications on the back of their efficacy in clinical trials, allowing for assessment of disease extent, phenotyping of diseases with multiple genetic underlying pathophysiology and response to therapy.
- Imaging biomarkers have a broad potential, and will likely deliver on the approaches to more individualised treatments due to greater targeted assessments of suitability.
- It is important to train radiologists into the utility of imaging biomarkers and to develop integrated workflow systems to allow for reporting of quantifiable data as part of the routine clinical report.

Financial disclosure

Prof van Beek is founder/owner of Quantitative Clinical Trials Imaging Services, Ltd.

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How do we qualify and validate imaging biomarkers?

Imaging biomarker qualification and validation is a multi-step process, requiring a number of important milestones.[13] Every step is a process which takes up several years, and the method may fail anywhere along the line of development.
Before an imaging method can be considered as a biomarker, it is vital that the method is standardised such that it can be applied routinely at any site which wishes to introduce it. There is a need for greater standardisation, as both scanner manufacturers, individual preferences and patient handling can all affect the imaging parameters being studied. This is particularly true for the more advanced imaging studies, and it is a major focus of a number of collaborations, largely under guidance from the main professional organisations mentioned above. Once a standardised protocol has been achieved, the actual qualification of a biomarker can commence.

First, the imaging biomarker must be demonstrated as closely linked to the presence (or absence) of the target disease. This usually requires observational studies, whereby the imaging biomarkers is correlated to disease presence, extent of disease and prognostic value compared to existing methodologies, including clinical assessment using standard diagnostic techniques as well as longer-term outcome. This process will generate sensitivity and specificity of the diagnostic test.
Second, as with any diagnostic test, the biomarker requires to be accurate and reproducible in both short term and long term measurements. This process should start as soon as there is a suggestion that there is a correlation (step 1), and requires the application of repeated measurements during a short period of time in patients with and without the disease process (immediate and longer reproducibility), multiple assessments by several observers (intra- and interobserver varability) and the correlation with the actual disease process severity.
Lastly, any changes measured over time need to be directly related to the changes of the target condition. This will require longer-term repeated testing in correlation with standard measurements of disease status (e.g. clinical status) with follow-up over several years.
As shown, th~~Th~~e qualification is quite a long and arduous process, hence the working together of many scientists and organisations is required to pool resources appropriately~~as mentioned above~~. ~~There are multiple steps required to demonstrate the necessary robustness of the imaging test, followed by testing in clinical studies to evaluate the true value in comparison with routine outcome measures.~~ It is not surprising, ~~T~~therefore, that this process takes many years and only now are we starting to see results, having started this work over a decade ago.

The validation of a qualified imaging biomarker is the final step in this process. Initially, the evidence built up during the course of the qualification process will allow

a consensus to be formed among the scientific community that the test is likely to be fit for purpose as a biomarker. Subsequently, the efficacy of the biomarker to demonstrate treatment effects that are not seen in non-treated controls, while a comparison with routine standards, such as clinical outcome is sought. Regulatory authorities, including the FDA and MHRA, are able to collate the evidence of a proposed (imaging) biomarker and determine whether the test is acceptable as a surrogate endpoint for a clinical trial. These bodies have clearly indicated their ascent to the incorporation of surrogate end points for clinical trials, provided these end points have been adequately developed and validated. [13] Thus, if there is a positive outcome on a surrogate endpoint, this would be regarded as a positive result towards market approval for the new treatment.

Examples of clinical approaches to the use of imaging biomarkers

There are many clinical areas where imaging biomarkers are effectively in use, particularly in oncologic staging and treatment response assessment. These methods are reasonably well established, and offer direct management direction for clinicians based on imaging findings (staging) or based on pre and post therapy changes in terms of tumour size or change in metabolic activity using PET imaging. In other areas, imaging biomarkers are being used as inclusion/exclusion criteria for clinical trials where new therapies are being tested that have a known metabolic point of interaction (e.g. amyloid plaque PET imaging in qualification of patients for new Alzheimer's disease drugs or bone mineral density assessment for exclusion of patients with osteoporosis in drugs that can negatively influence bone mass). It is not possible to give an overview of every imaging-based biomarker being tested or available at present. Therefore, two areas of interest will be highlighted, where imaging-based biomarkers are at the cusp of routine clinical application (emphysema) or are in an advanced state of development (aortic valve stenosis).

The use of imaging biomarkers for lung diseases has been piloted for some time. The problems encountered largely evolved around standardisation of CT scanner systems, but with appropriate quality control and setting the protocols, it is feasible to determine some significant phenotypes, which can be used longitudinally to study the potential effects of new treatments. Thus, CT-based quantification of emphysema both correlates with pulmonary function and mechanics, but additionally offers further insights into the phenotypical distribution and extent of disease. [14]
One of the first attempts demonstrating the feasibility of an imaging-based biomarker was made for a large trial evaluating the utility of lung volume reduction surgery in patients with severe emphysema, where CT based density distribution was capable of predicting outcomes directly. [15] Subsequent imaging analysis further highlighted the extent of the correlation between CT quantified findings and the outcomes in the surgical and control arms of this large study. [16] This work is now continuing with the advent of interventional bronchoscopic methods for lung volume reduction surgery, where CT is both used as a tool to determine patient eligibility for the procedure and for the planning and assessment of treatment response. [17]
A longitudinal observational cohort study used CT as a way to determine the extent of emphysema, as well as the change over time. [18] Lung density at baseline was influenced by a number of variables, including age, sex, body-mass index, current smoking status and smoking history, and severity of airflow limitation. Importantly, the study could measure annual lung function decline as quantified by CT lung

density at rates of -1.13 g/L, but with variability due to sex and smoking status. [18] Thus, the CT measurements gave a clearer indication of changes over a one-year period compared to pulmonary function tests.

The COPDGene study enrolled a large cohort of patients (10,000) in multiple centres in the USA, who were screened for obstructive outflow disease including genetic assessment and the application of CT. [19] The CT protocol was centrally set-up with quality assurance rigorously applied. An analysis of 9,313 subject CT scans demonstrated a clear quantifiable pattern of low-attenuation findings on CT. [20] Additionally, measures of mild emphysema in smokers with preserved lung function could be demonstrated as quantifiable low-attenuation changes on CT, allowing for earlier diagnosis. [20]

Subsequent analysis of 10,192 smokers in the COPDGene study demonstrated the ability of CT to identify patients with varying degrees of emphysema, as well as the presence or absence of airways disease. [21] This enabled identification of four subgroups of smokers that were closely associated with clinical characteristics of COPD and known COPD-associated genetic variants. [21]

A third large cohort study, SPIROMICS, deserves mention, as it is closely monitoring various serum and plasma biomarkers in combination with CT in 3,200 participants. [22] A sub-study evaluated airway measurements in a total of 1,559 subjects, and demonstrated that airway walls are thinner and lumen size is smaller in patients with COPD compared to controls, and this closely correlated with pulmonary function tests. [22] Thus, the study confirmed the findings in the COPDGene study, which gave similar findings. [23]

Overall, where lung imaging is concerned, it is clear that CT-based measures are essentially ready to be used as biomarkers. Several measurements are available, depending on the specific study questions, and it is vital to ensure protocols are appropriately chosen and quality assurance is maintained. The software tools are now available for incorporation into routine workstations. This last piece of the puzzle will allow more seamless performance of pulmonary CT investigations, which will include reporting of quantitative measures of emphysema and airways as part of the standard clinical report. Only with this type of workflow can imaging-based biomarkers make a difference in clinical practice.

Another area where imaging biomarkers are actively being developed is in cardiac applications. Traditionally, invasive cardiac catherization in combination with echocardiography and nuclear medicine studies have evaluated the presence of coronary artery stenosis, perfusion changes and heart valves. More recently, work has been ongoing to delve deeper in the mechanism of aortic valve stenosis ~~coronary atherosclerosis~~ and coronary atherosclerosis ~~aortic valve stenosis~~ using 18F-sodiumfluoride PET imaging.

Initial work focused on demonstrating the direct link between the 18F NaF uptake in the areas of aortic valve and the histological correlation with the calcific process. [24] Subsequently, during a follow-up study of these subjects, it was demonstrated that the extent of radiotracer uptake directly correlated with the increase in calcific aortic valve disease and functional decline. [25, 26] This work suggests that the detection of this process can be achieved much earlier using 18F-NaF PET imaging compared to either CT or echocardiographic measurements, and the application of this imaging biomarker will likely affect management as the uptake is directly correlated with progression of disease.

In parallel with this work, it was noticed that some patients with aortic valve pathology had uptake in coronary arteries. A subsequent study demonstrated that 18F-NaF PET imaging is correlated with acute myocardial events, and it was postulated that uptake is a reflection of ~~likely detects~~ vulnerable plaque, which would be a more accurate~~ly~~ and important parameter to predict acute coronary artery events- than simple angiographic methods (which are focussed on level of stenosis). [27] Another study in 40 patients with myocardial infarction and 40 patients with stable angina evaluated the role of 18F-fluorodeoxyglucose uptake in the aorta. [28] This study demonstrated a direct correlation between the extent of radiotracer uptake in the aorta and early recurrent myocardial infarction, likely due to systemic atherosclerotic inflammatory exacerbation and plaque destabilisation. [29] These studies similarly could alter future disease management, potentially leading to better identification of active disease and the area of plaque most at risk for developing acute myocardial events. In particular, more targeted approaches to plaque stabilisation as well as the ability to monitor changes over time, will allow development of dedicated new therapies. Further studies in this field are ongoing, focused on short and long-term reproducibility and long-term follow-up of patients to assess disease progression or modification and clinical outcomes in relation to the imaging test.

Future perspective

It is highly likely that imaging biomarkers will continue to develop into clinical tools, enabling precision and personalised medicine to thrive. Some novel imaging biomarkers are now making their inroads into routine clinical practice, others are under development, while yet others have hurdles to take (although these are not unsurmountable). It will be vital to continue the rigorous process outlined, as this will be the only way that regulatory authorities will be able to safely accept these imaging biomarkers to be used in routine clinical practice.

Ultimately, the aim of imaging biomarkers will be a challenge to the training of radiologists, who will need to address workflow and reporting changes that are required for imaging biomarkers to gain full impact for clinical management of patients. It will no longer be sufficient to just describe the findings. They will require more precise description in quantitative terms, actual changes over time and combination of quantitative imaging findings in relation to prognosis. Imaging biomarkers will be used in a variety of ways, some for patient selection, others for patient exclusion. This will need to be anticipated by the radiologists as clinicians increasingly rely on imaging to provide answers to clinical management questions. ~~have studies that demonstrate the robustness of quantitative imaging techniques and measurements, but as this field progresses, with the incorporation of imaging based treatment response assessment into clinical trials, the natural progression is one where radiologists will be offering both a morphological/visual assessment together with image analytical tools to provide greater insight into the extent of disease, the potential selection of patients for (often expensive) specific treatments and the ultimate therapeutic effectiveness. Only with this approach, will the additional value of diagnostic imaging become apparent.~~ Training the radiologists of the future to deal with the increased demand and changing reporting requirements is a challenge that will need to be addressed in this context.

Conclusions

Imaging biomarkers are already reality, but will continue to be developed to allow for more precise assessment of disease, indication for different therapeutic options and measure therapy response. This is what will drive individualised patient care pathways, where imaging biomarkers will be a core tool, which will have a major impact on health economics as a result. The end result will be more appropriate treatment of patients at reduced overall costs in terms of both (avoidable) complications and overall healthcare costs.

The challenges of developing imaging biomarkers and to train the radiologists of the future go hand-in-hand, but the rewards are improved patient care while maintaining affordability. That is a result worth investing in.

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Executive summary

- Imaging biomarkers are of interest in order to serve as surrogate endpoints in clinical trials, as they can lead to a reduction of sample size due to earlier measurement of treatment effects, thus reducing the overall time from start of the clinical trial to end point.
- Imaging biomarkers need to be developed using quite strict qualification and validation methodologies, as only this approach will allow useful and trustworthy imaging biomarkers to be acceptable for clinical practice.
- Imaging biomarkers are increasingly making their way into clinical routine applications on the back of their efficacy in clinical trials, allowing for assessment of disease extent, phenotyping of diseases with multiple genetic underlying pathophysiology and response to therapy.
- Imaging biomarkers have a broad potential, and will likely deliver on the approaches to more individualised treatments due to greater targeted assessments of suitability.
- It is important to train radiologists into the utility of imaging biomarkers and to develop integrated workflow systems to allow for reporting of quantifiable data as part of the routine clinical report.

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Prof van Beek is founder/owner of Quantitative Clinical Trials Imaging Services, Ltd.

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