QIBA key criteria for Plaque Imaging by CT Angiography

Proposed Biomarkers and Context: CT angiography (CTA) for risk prediction, early diagnosis and monitoring of treatment of atherosclerotic disease. We propose a Atherosclerosis Biomarkers Committee (ABC), starting with CTA across two different arterial beds (coronary and carotid), with potential expansion in the future based on progress to incorporate additional arterial beds such as peripheral arteries and intracranial arteries, and different modalities, such as MR, US or NM.

Currently, clinical application of CTA and atherosclerosis imaging is widely available as a technique used as a first line investigation of coronary vascular disease and in carotid as a second line for assessment of the plaque structure in order to choose the therapeutic approach (best medical treatment or revascularization). Evaluation of atherosclerotic arterial plaque characteristics is currently based-on ***qualitative*** markers. However, the reproducibility of such findings is poor even among experts (JCCT. 2017 Dec 5. pii: S1934-5925(17)30255-1. [Epub ahead of print]). While certain imaging biomarkers such as carotid stenosis and coronary calcium scores are well accepted in clinical practice, there are opportunities to add further biomarkers currently only applied in the research arena.

Quantitative imaging markers have been shown to have additive value above traditional qualitative imaging metrics and clinical risk scores regarding patient outcomes (JCCT. 2016 Mar-Apr;10(2):97-104.). However, many definitions and cut-offs are present in the current literature, therefore standardization of quantitative evaluation of CTA datasets is needed before becoming a valuable tool in daily clinical practice. In order to establish these biomarkers in clinical practice, techniques to standardize quantitative imaging across different manufacturers with cross-calibration is required. Moreover, post processing of atherosclerotic disease segmentation needs to be optimized and standardized.

- ***Transformational*** *- addresses a critical gap in the imaging biomarker qualification/validation process and/or may otherwise transform the process of how imaging biomarkers are developed, approved, and applied in the future.*

Currently, research and clinical application of plaque imaging biomarkers is only available in a small number of centers, using a wide variety of scan protocols, analysis software from different manufacturers, different parameters and thresholds. In order to establish these biomarkers in clinical practice technique, standardization of quantitative imaging across different protocols, anatomical locations and different manufacturers with cross-calibration is required. In particular, in CTA use, the precise standardization of the parameters is important because several of these could affect the HU attenuation (especially the energy used: kVs and mAs). A recent paper of carotid artery vessel wall imaging summarizes the recent state-of-the-art (Saba et al, AJNR 2018;39(2):E9-E31). In order to establish CT and MR arterial plaque compositional biomarkers in clinical practice, standardized quantitative imaging across different CT manufacturers is needed. Reliable quantitation using more sophisticated techniques than simple HU thresholding without specific mitigation of known limitations where ground truth of tissue is objectively determined, using routine clinical CTA, is new but energizing, given the widespread use of the modality such that new scans are not needed, applicability to multiple arterial beds, and utilizing existing hardware. But this nascent field would greatly benefit from the multi-stakeholder approach to rapidly implement clinical arterial plaque compositional analysis.

For the wide spread use in clinical practice and in clinical trials testing outcomes and therapies – standardized approach will be needed. There is an opportunity to create standard for future application of plaque imaging in terms of quantitative analysis. Increased reproducibility of measurements is important – standardization will open way

for the use as a surrogate marker in trials. Incorporation in clinical reporting will require defining most reproducible, most valuable, and easy to measure and report measurements – we can define those.

Cross-calibration phantoms need to be available that guarantee comparability of data across different clinical sites and obtained with different sequences and from different manufacturers. Moreover, technical performance standards and guidelines are urgently needed to drive the implementation of compositional atherosclerosis imaging for clinical trials and clinical practice.

Comparisons with histology need to be available to determine optimal techniques (with lesser dependence on simple thresholds) and guarantee comparability of data across different clinical sites, anatomical locations and obtained with different protocols and from different manufacturers.

- ***Translational*** *— addresses a significant medical biomarker need (either in clinical care or research).*

Atherosclerosis is a major health concern for our aging population. The most significant underlying disease cause of mortality and morbidity in individuals older than 55 years and becoming the leading cause of death worldwide. Given the devastating impact of this widespread disease on individuals and population reflected in spiraling healthcare costs, biomarkers for better risk assessment and diagnosis at early stages, and monitoring of atherosclerosis will have a significant impact on public health. Noninvasive imaging biomarkers that would provide this information will have an impact to transform health care delivery and management. There is a critical gap in the biomarker qualification process, which needs to be addressed in order to move these quantitative imaging biomarkers forward.

The presence of atherosclerosis and the amount and type of arterial plaque have strong predictive value for acute events and for future cardiovascular events. Moreover, plaque composition may change dramatically over a few years and cardiovascular risk factors play a major role in these changes – changes that can be tracked with imaging. Further, recent evidences show that atherosclerosis is not only a progressive disease but it is possible to obtain also the plaque reversion. Intensive medical (lipid-lowering and anti-inflammatory) therapies may drive plaque reversion and conversion to a stable phenotype by strengthening the need to objectively quantify the amount and composition of the atherosclerotic plaque in order to monitor the plaque's response to the therapies. Multiple platforms and approaches exist in plaque assessment. They included both qualitative and quantitative methods. Many of these methods have been associated with outcomes.

CT angiography (CTA) offers the potential to non-invasively detect, quantify and characterize atherosclerotic plaque. Accurate identification and quantification of plaque components using CTA is challenging because of the technical limitations of CTA and requires optimization of image quality, however, CTA may provide valuable information for characterization of plaques. Plaque composition is associated with the likelihood for rupture and downstream ischemic events, but is known to be highly variable presently. Standardized protocols and analysis of plaque characteristics can increase early identification of patients at increased risk for adverse events.

Plaque imaging has been widely used to show association with ACS in acute chest pain setting. Data on prognostic value for 2-4 year follow up are also available (e.g., PROMISE, CONFIRM). Atherosclerosis compositional imaging biomarkers allow earlier diagnosis, better prediction and more sensitive monitoring of vessel wall disease. In particular, compositional atherosclerotic biomarkers (lipid core, calcification, plaque hemorrhage, vessel wall volume) represent quantitative measures that could reduce the size and duration as well as increase the objectivity of clinical, multi-center trials. The

key advantage of these measures is earlier detection before atherosclerotic plaque progression and end organ symptom presentation. Compositional atherosclerotic biomarkers have already been moved into clinical care to better assess vascular disease for planning surgery in carotid stenotic disease. They have also provided risk scores for the coronary artery disease (CAC). More specific compositional biomarkers (lipid core, calcification, plaque hemorrhage, vessel wall volume) are currently being investigated in the research domain but, because they are acquired during the same CTA scanning technique, their eventual translational into the clinical domain, if clinically useful, is assured.

While certain ranges of Hounsfield Units have been shown to correlate with LRNC and IPH in arterial plaques with no/minimal calcifications, reliable depiction of LRNC in the presence of calcifications has only been reported with recent advances in software analysis to reduce blurring and partial volume effects. LRNC was shown to be measured with a high correlation and low bias between in vivo software analysis of CTA from multiple vendors and *ex vivo* histopathological analysis (Sheahan et al, Radiology 2018;286(2):622-631). More challenging is currently the IPH detection with CTA because there are contradicting results that could be due to the different techniques used.

Through quantification, objectification of plaque analysis could be achieved. As qualitative assessment relies on experience, it is hard to create reproducible imaging biomarkers. Quantitative biomarkers on the other hand, have the potential to become standardized metrics, which could decrease patient sample sizes needed for scientific studies. Several studies have shown the potential of quantitative plaque volumes in predicting patient outcomes (JCCT. 2018 Jan 6. pii: S1934-5925(18)30011-X. [Epub ahead of print]). Furthermore, only quantitative metrics allow precise plaque burden follow-up (JACC-CVI. 2017 Apr;10(4):437-446.), which seems to be a promising factor for the identification of high-risk patients and a cost effective surrogate end-pont in clinical trials. In addition to risk assessment, monitoring the effect of preventative therapies may pave the road towards precision medicine.

Several factors necessitate the need for standardization of quantitative plaque metrics. For example, variability of scanners and also readers segmentations significantly affect lesion volumes (Radiology. 2016 Dec;281(3):737-748.). Reconstruction algorithms may also significantly change plaque volumes (Eur J Radiol. 2017 Feb;87:83-89.) as well as the compositional classification. In this scenario it is also necessary to consider that in CTA the plaque analysis if performed after contrast material shows tissue attenuation values different if compared with the basal scan because of the effect of the carotid artery plaque neovascularization.

- ***Feasible*** *— an idea or program whose end goals (e.g., use as an endpoint in drug development or integration into clinical practice) can likely be achieved in a specific timeframe (e.g., 3 - 5 years) and that has a reasonable prospect of producing the expected outcomes.*

Multiple publications showing feasibility of plaque quantification by CTA in both clinical and research setting.

Feasibility of plaque characterization with CTA in the management and risk prediction in coronary and carotid has been demonstrated in several trials. However, lack of standardization and a multitude of different software approaches and differences in the use of parameters is significantly decreasing the clinical implementation because of the methodological heterogeneity. First steps would be to standardize imaging protocols for each arterial bed, select the most optimal parameters and pool results from different software approaches, clinical centers and vendors, which would allow optimization of protocols to provide homogeneous data throughout the community. In parallel, provide objective performance assessment techniques with standardized

metrology metrics and nomenclature for software analysis of CTA data sets, for example by developing calibration phantoms and specific technical guidelines for structural measures, and use of histological ground truth, which would allow diverse analytical techniques to be assessed from different vendor platforms. Recently published histological validation techniques provides specific quantitative standards to detect/measure LRNC across four scanner models from two manufacturers. This needs to be expanded to include other CTA vendors and models.

As statin eligibility can potentially be determined based-on CTA findings and not based on risk factors, such as blood cholesterol levels, therefore quantification of plaque volume (and sub-components volume) needs to move from 'Centers of Excellence' to everyday clinical practice. As scanners, acquisition settings, segmentations, reconstruction filters and cut-off values all affect plaque volumes standardization is as must to receive reproducible results. Power calculations similar to Symons et al. (Radiology. 2016 Dec;281(3):737-748.) are needed to define sample sizes to identify different degree of plaque change. For example, using a different scanner to assess follow-up scans, more than 500 patients are needed to identify 5% non-calcified plaque change with a power of 90%. However, after consensus is reached regarding settings used for quantification, current software applications used for CTA analysis all have the capability to report quantitative results.

Cross-sectional observational studies are needed using CTA detected LRNC to predict future ipsilateral carotid TIA/stroke, to evaluate the effect of modified medical therapy on the size of LRNC, or to test the hypothesis that individualizing medical therapy of atherosclerosis would result in improved clinical outcomes. For the last several decades and up to now, percent reduction in luminal diameter of the carotid and coronary arteries remains considered as the key parameter for the choice of the therapeutic approach (revascularization – best medical treatment) This resulted from the study design of clinical trials conducted during the 1970s to 1990s. At that time, diameter luminal narrowing (angiography) was the only parameter that could be non-invasively detected with imaging techniques. Now, we need to test the information we can obtain from the plaque imaging (volume – LRNC – IPH – Ratio of the subcomponents) in order to redefine the treatment strategies. Given the high utilization of CTA and the recent availability of computer aided phenotyping to quantify LRNC, future observational studies are feasible to evaluate the correlation of new ipsilateral carotid events with presence/size of CTA quantified LRNC in routine clinical practice. It would also be feasible to design studies to evaluate CTA quantified LRNC as an effective biomarker in the management of carotid atherosclerotic disease.

- ***Practical*** *— leverages preexisting resources (e.g., intellectual capital, personnel, facilities, specimens, reagents, data) wherever possible; warrants access to RSNA resources and support.*

Although there have been general recommendations on how to perform and standardize atherosclerosis compositional measurements, there are no technical performance standards to ensure consistent and reliable results between different clinical sites, vendors, scanner type, settings, and times. As outlined above there is a significant body of literature regarding atherosclerosis imaging repeatability and reproducibility, which will serve as the basis for the proposed work and to identify any remaining groundwork that must be accomplished.

The proposed biomarker committee will utilize prior published data, follow the recommendations in the Metrology Working Group's *Statistical Methods for Medical Research* publications, and utilize the current claims guidance and profile template recommendations from the Process Committee.

For comprehensive evaluation of the needed tasks to achieve standardization, joint efforts are needed from QIBA and RSNA as well as EIBALL (European Imaging

Biomarkers Alliance) committee of the European Society of Radiology (ESR). We propose a position white paper discussing the elements and the need of standardization. With joint forces of the representative scientific communities and key opinion leaders of the scientific community a significant leap could be made by introducing standards of quantitative coronary and carotid CTA. With the support of such documents, the value and the quality of research could be greatly increased further increasing our knowledge of quantitative imaging.

The proposed biomarker committee will utilize and combine prior published data from different centers and different fields to uniform the used parameters and thresholds over different software vendors and image protocols. By including experts from different fields, clinical, technical and include different companies the outcomes will have a broad support throughout the imaging community increasing timely adoption.

- ***Collaborative*** *— would uniquely benefit from the multi-stakeholder composition and approach of QIBA and could be feasibly executed under its policies, e.g., resulting in extension or adoption in product development among hardware, software, or imaging agents. The biomarker has enough support in the stakeholder community to sustain continued efforts.*

Only a collaboration can meet the needs for standard in nomenclature of arterial plaque characteristics, standard classification of plaque, and definition of quantitative plaque measures, e.g. plaque volumes, plaque type volumes, remodeling index, plaque burden. The collaboration between imaging specialists – radiologist, cardiologist, vascular medicine, hardware vendors and plaque quantification software developers, as well as imaging physics and statistical specialties are involved.

The proposed QIBA Atherosclerosis Biomarkers Committee (ABC) will be composed of members from multiple centers of excellence within North America and Europe utilizing different CTA vendors, acquisitions and scanner types, and analysis software vendors. Furthermore, stakeholders from different manufacturers will be included in the committee, who are interested in working closely with the committee in optimizing imaging biomarkers for scientific trials and clinical routine use. The Biomarker Committee will develop technical performance standards to serve as atherosclerosis compositional biomarkers. Moreover, we will involve stakeholders from different societies, in addition to the RSNA, for example ASNR, SCCT, ACR, etc.

Development and dissemination of technical performance standards for compositional atherosclerosis imaging biomarkers will greatly facilitate application in clinical trials and clinical practice. Furthermore, vendors and users alike would benefit from conformance specifications and guidance based on such technical performance standards. With the support of QIBA, new standards of CTA evaluation could be promoted. As currently the scientific society lacks standardization of CTA evaluation, much effort is needed to enforce these views. With a white paper the scientific community as well as the manufacturers would be obligated to reinforce these standards into their clinical practice and their evaluation software. With strong commitment, we can expect manufacturers to implement these standards into their software platforms in the upcoming years which would greatly help the implementation of such standards. With strict standards, multi-center trails could help to broaden our understanding of atherosclerosis, as standardization of such techniques would allow robust evaluation of quantitative metrics from multiple sites.

Development and dissemination of technical performance standards for plaque characteristics will greatly facilitate application in clinical trials and clinical practice. Furthermore, vendors and users alike would benefit from uniform specifications, protocols, tissue specific thresholds and parameter descriptions based on technical performance standards.