Proposal for Pulse-Echo Quantitative Ultrasound measurements as a new QIBA biomarker, in collaboration with AIUM

I. Transformational: [the biomarker] addresses a significant medical biomarker need with a likely considerable impact on public health, and addresses a critical gap in the biomarker's qualification/ validation process.

Tissue acoustic attenuation and scattering properties are affected by the development of different diseases such as neoplasms, inflammation, and edema. Ultrasound imaging has the potential to inform concerning these changes. However, the operator- and system-dependence of ultrasound limits its efficacy as an objective clinical decision support tool. Since the seminal work of Chivers and Hills [1] in 1975, the possibility to provide objective measures of ultrasound imaging features has motivated multiple efforts to quantify backscatter properties of tissue. For example, the hepatorenal index tissue 'echogenicity' (the relative B-mode image brightness of liver compared to that of the renal cortex) or the 'echogenicity' of a breast tumor compared to nearby breast fat can be measured on an absolute scale using the acoustic backscatter coefficient. Similarly, high concentration of fat in hepatocytes causes aberration resulting in decreases in spatial resolution, depth of penetration, and increases in liver 'echogenicity'. The first of these effects is related to a decrease in the sound speed with increasing fat content. The decrease in depth of penetration is caused by an increase in acoustic attenuation including aberration. Thus, the acoustic backscatter coefficient, sound speed and attenuation have potential to serve as pulse-echo quantitative ultrasound (PEQUS) imaging biomarkers.

Many studies have shown the transformational potential of PEQUS features to improve the specificity of image-based diagnosis[2] and disease staging[3], and the accuracy of prediction of treatment response.[4] However, early commercial implementations in the mid-1980s failed, in part, because of a lack of clear understanding of sources of biological variability. Appropriate protocols were not considered, and the technology was pulled from the market before sources of variance could be understood. Recently, new commercial implementations of PEQUS features have been introduced.[5]–[7] Thus, there is a pressing need to standardize PEQUS techniques, to understand sources of bias and variance, and to reach consensus on how PEQUS features should be reported.

This proposal seeks to form a PEQUS QIBA committee to respond to this need. Several PEQUS features are included in this committee effort because many of them are based on the same data acquisition criteria and initial processing steps. This offers the potential of extracting independent descriptors of tissue acoustic properties from a single data acquisition. Further, many are applied to the same clinical tasks. This QIBA effort will attempt to reach consensus on how to report PEQUS features among manufacturers (type of metric to be reported, e.g., attenuation coefficient, specific attenuation, etc.) and under equivalent conditions (e.g., frequency range for a specific application). Also, special

emphasis will be put to provide quantitative assessment on the quality of the reported values.

II. Translational: Will likely result in significant improvement in the development, approval, or delivery of care to patients.

There is substantial evidence about how to estimate PEQUS features using clinical imaging systems.[8]–[11] Also, since the late 1990s various studies in tissue mimicking phantoms and animal models have been conducted to evaluate the levels of accuracy, precision and inter-system reproducibility of various PEQUS techniques.[12], [13], [22], [14]–[21] This substantial body of evidence can help define a fast track (20 months) to achieve the goals of the proposed PEQUS committee. QIBA offers a framework to coordinate a synergistic, multi-stakeholder effort that brings together clinicians, scientists, and industry to develop consensus in exactly what to report to the clinical community from these parameter estimates. This responds to the competing interest in other quantitative imaging technologies (MR Proton density fat fraction quantification and the Controlled Attenuation Parameter in the Echosens Fibroscan), as well as to the recent implementation of PEQUS features in clinical systems, such as the Attenuation Imaging tool on the Canon Aplio i900 and i800 systems.

III. Feasible: An idea or program whose end goals can likely be achieved in a specific timeframe and that has a reasonable prospect of producing the expected outcomes; ideal programs are those which could result in regulatory qualification of a biomarker in three years.

The large body of existing work, the interest among all stakeholders, and the recognition of the potential for commercial failure has motivated this proposal. The initial goal of this committee is to reach Stage 1 (public comment) of QIBA's profile creation process within 20 months. To this end, we will focus on producing version 1 of the biomarker profile (profile version 1, or PV1) based on a systematic, phantom-based standardization and validation of PEQUS features that result on initial accuracy and precision claims. To reach Stage 1, the following specific aims are proposed:

- **Specific Aim 1 (6 months) – Produce the first draft of PV1:** We will start by drafting the biomarker proposal and seeking approval by QIBA Steering Committee. Once the proposal is approved, we will compile evidence from literature on sources of bias and variability, as well as covariates and confounders (physical, technical, and biological) of current PEQUS methods. An initial consensus will be reached on how to report biomarkers (i.e., attenuation vs. frequency slope or attenuation at a given frequency). Examples of useful references are [12], [13], [22], [14]–[21] This information will serve to prepare the first draft of PV1 as well as protocols for image acquisition, quality control, and biomarker reporting.

- **Specific Aim 2 (6 months in parallel with activities of Specific Aim 1) – Design and manufacture phantoms for standardization and validation:** We will define criteria for the structure and composition of tissue-mimicking phantoms to be used in Specific Aim 3, and whether currently available phantoms fulfill these criteria or new phantoms need to be fabricated. In the latter case, a phantom subcommittee will be defined to coordinate design and fabrication of the required phantoms. Support from commercial phantom manufacturers (e.g. CIRS and Sun Nuclear) will be key to reach specific aim 2.

- **Specific aim 3 (12 months) – Perform phantom-based groundwork.** A multi-site prospective study will be carried out with participating academic and health institutions and industry will evaluate intrinsic scanner variability as well as intra- and inter-operator bias and variance. Only PEQUS techniques supported by evidence of continuous development in the literature (simulations, phantom-based studies, pre-clinical and clinical implementations) will be included based on the assessment of Specific Aim 1. The end product of this stage will be claims of accuracy and precision and the conditions under which they were achieved. This information will be used to refine the draft of PV1.

- **Specific aim 4 (2 months) – Review, approve and publish public comment draft**. Claims produced by specific aim 3 will be incorporated in PV1. Two months will be given to review, discuss and refine PV1 within committee members. By the end of this period, PV1 will be published for public comment.

Publication of PV1 will be followed by the next stages of QIBA's profile creation process including public comment, as well as technical, claim, and clinical confirmation. These last two stages will be focused on testing the performance of the proposed biomarkers for liver fat fraction quantification and their correlation with MRI proton density evaluation, given the increased incidence of fatty liver disease worldwide, the increasing awareness of this disease's impact on health and cardiovascular disease, and the increasing attention placed on this disease by clinicians, pharmaceutical companies, and the lay public. Clinical confirmation will be organized by the Liver Fat Quantification task force of the American Institute of Ultrasound in Medicine (AIUM LFQ), at multiple sites with large patient population. Several sites have already expressed interest in participating including UT Southwestern Medical Center, UC San Diego Medical Center, Mayo clinic, Massachusetts General Hospital, Memorial Sloan Kettering Cancer Center. As part of this task force, multiparametric strategies will be tested to improve the diagnostic performance for this specific task. In parallel, the QIBA committee will continue conducting tests to improve the profile. To this end, synthetic digital phantoms will be created to compare performance of new quantification algorithms (regularization methods for attenuation compensation, use of single-channel data for sound speed estimation, data compounding strategies).

IV. Practical: Leverages preexisting resources (e.g., intellectual capital, personnel, facilities, specimens, reagents, data) wherever possible; warrants access to RSNSA resources and support.

Pre-existing research from various academic institutions around the world has provided initial and independent evaluation of the technical feasibility of the clinical implementation of PEQUS. These studies have made use of clinical systems including Siemens Antares and Acuson S2000 and S3000, GE logic E, Philips, Mindray Zonare, Ultrasonix, Verasonics Vantage, and Visualsonics Vevo. Novel PEQUS methods have been proposed to improve the accuracy and precision of different PEQUS features.[10], [11], [23]

The use of conventional radiofrequency echo signals provided by clinical scanners makes QBUS a practical and low-cost technology. In addition, systems with GPUs have the potential to provide parametric images of PEQUS features in real time.

V. 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 the support of the stakeholder community with the organizational impetus to sustain continued efforts.

At least five major ultrasound companies and two phantom manufacturers have expressed interest in participating in this effort (Philips, GE, Siemens, Canon, and Supersonic Imagine; and CIRS and Sun Nuclear). We expect more involvement after the initial stages of the profile process. We expect that the 40+ year evidence behind PEQUS and the systematic approach described in section IV will facilitate FDA approval of PEQUS.

Planned initial committee members and leadership are:

Chair (clinician): Anthony Samir, MD,MPH (Harvard Medical School and Massachusetts General Hospital)
Co-chair (academia): Ivan Miguel Rosado Mendez, PhD (Universidad Nacional Autónoma de México)
Co-chair (industry): Michael Wang, PhD – GE Healthcare

Communication: During the 20 months of the proposed strategy, participants will hold monthly teleconferences to discuss progress. In addition, the co-chairs will meet weekly to review current PEQUS literature, organize communication and file transfer among members of the committee, and coordinate participation in relevant meetings.

VI. Example References

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