

Contrast Enhanced Ultrasound Quantification of Flow Dynamics as a New QIBA Biomarker

- **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*)

Tissue perfusion is affected in many pathologies including neoplasms, inflammation, and ischemia. Quantitative assessment of perfusion would impact a wide range of clinical situations such as tumor response to therapy for colorectal and other liver metastases, hepatocellular carcinoma (HCC), and inflammatory bowel disease. Transformational need is further evidenced by the existence and progression of the Perfusion, Diffusion and Flow – MRI Biomarker Committee. Convenient, inexpensive access to perfusion quantification, in the form of specific contrast kinetic measures using ultrasound (CEUS), would further transform diagnosis and treatment. CEUS has several advantages over CT and MRI agents. It is the only truly intravascular agent, has increased spatial and temporal resolution, no ionizing radiation, higher safety profile than CT and MRI contrast agents, and is not hepato- or nephrotoxic.

- **Translational** (*Addresses a significant medical biomarker need [either in clinical care or research], with a likely considerable impact on public health.*)

CEUS quantification tools are already available from many equipment manufacturers as well as pharma/agent manufacturers, however the lack of standardization of method, equipment and software between vendors has restricted translation to wider use. QIBA engagement of academics, clinicians and vendors provides the best opportunity to translate these tools to daily clinical care. The reference section has several examples of biomarker performance and reproducibility in the literature of single system and agent configurations which would set the stage for clinically focused QIBA work.

- **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.*)

Recent FDA approval of Lumason (Bracco Diagnostics) for the characterization of liver lesions supports the clinical and technical feasibility of CEUS quantification. Further evidence can be found in the literature for single system configurations and agents. A successful standardization effort would result in a widely available, robust, biomarker for clinical use. Depending on the outcome of the initial phantom proposal, a 3 to 5 year timeline is reasonable.

- **Practical** (*Leverages preexisting resources wherever possible; warrants access to RSNA resources and support.*)

<<Although the words Practical and Feasible mean sort of the same thing, the point of this section is to describe existing work/resources/tools/datasets/people/projects/trials that can be borrowed/built-on/hijacked ☺ and brought to the QIBA table so RSNA and/or NIH don't have to fund a soup-to-nuts R&D initiative. It sounds like you can point to some since there is already products and FDA approvals among other things. I'd describe that and replace the next paragraph.>>

Groundwork studies at a few centers world-wide have indicated the practicality of CEUS quantification. The methods are slightly different but each technique has only been validated for one ultrasound contrast agent on one ultrasound system. The missing element has been standardization of methods between vendors to support more robust adoption and widespread clinical application. The QIBA structure and process provides the best opportunity to achieve standardization.

- **Collaborative** (*Would uniquely benefit from the multi-stakeholder composition and approach of QIBA and could be feasibly executed under its policies. The biomarker has enough support in the stakeholder community to sustain continued efforts.*)

7 Ultrasound vendors, 3 CEUS agent vendors, 2 Chemotherapy agent vendors, 10 leading global clinicians in the application of CEUS and 7 leading global scientists in CEUS development, detection and applications have expressed their intent to participate actively if the Biomarker Committee is approved.

Selected references

1. Leen E, Averkiou M, Arditi M, et al. Dynamic contrast enhanced ultrasound assessment of the vascular effects of novel therapeutics in early stage trials. *Eur Radiol* (2012) 22:1442-1450.
2. Lassau N, Bonastre J, Kind M, et al. Validation of Dynamic Contrast-enhanced Ultrasound in Predicting Outcomes of Antiangiogenic Therapy for solid Tumors. *Invest Radiol* 2014; 49:794-800
3. Dietrich CF, Averkiou MA, Correias JM, et al. An EFSUMB Introduction into Dynamic Contrast-Enhanced Ultrasound (DCE_US) for Quantification of Tumor Perfusion. *Ultraschall in Med* 2012;33:344-351.