3D Ultrasound Volume Flow Measurement as a New QIBA Biomarker in Association with AIUM

(Note that a biomarker does not necessarily have to meet all criteria exceptionally well in order to be considered appropriate for a QIBA committee.)

- **Transformational** *(Addresses a significant medical biomarker need with a likely considerable impact on public health, and addresses a critical gap in the biomarkers qualification/validation process)*

This Biomarker will be transformational, in that 3D volume blood flow measurements are not now commercially available. Currently a one dimensional measurement is made from a 2D image and a volume flow estimate is made by estimating the Doppler angle and assuming laminar flow and circular vessel cross section. In many clinical practices, almost every scan performed has some component of blood flow imaging using color or power Doppler. These are just done to show the presence or absence of flow. Very conservatively 20% of scans actually are performed where blood flow is quantified to some degree. These measures are all heuristic and are either qualitative or semi-quantitative representations of true flow, at best. There are about 200,000 ultrasound machines in the United States based on the 2014 Klein Report, which based on the 2013 Klein Report produce about 136 million exams. Multiplying by 20% for the percentage of scans where flow measurements are made, there are about ***27 million*** ultrasound scans performed per year in the USA where a true flow measurement might be of interest.

- **Translational** *(Will likely result in significant improvement in the development, approval, or delivery of care to patients)*

These 3D volume flow measurements are not now available on commercial ultrasound systems. This QIBA Biomarker effort will accelerate such commercial implementation among leading systems manufacturers. The QIBA process will help assure that the measurements are performed with the low, cross-platform, variance and bias that is possible with the multistakeholder effort facilitated by the QIBA process and planned here.

- **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)***

Any company with a 2D array or mechanically swept array would only have to define optimal parameters and design a user interface. We guess that this would only take a few months. Company interest is illustrated by the statements listed below* from representatives of three companies involved in 3D/4D imaging that expressly supported a systematic investigation and validation of umbilical cord volume flow by QIBA. This can already be done in a research mode with four commercial systems from two leading companies. We transitioned the proposal to renal artery blood flow, a clinical application of high importance, but much lower case volume than umbilical cord measures because of the availability of direct validation during transplant surgery. Once commercially available, it will be used in many applications.

Once a user interface is defined and implemented by a company, we suspect that at least one year would be required in order for at least two groups to run phantom tests to confirm consistency and estimate biases. The time would require standardization of phantom experiments and running these experiments. It would be important that the phantoms be standardized before obtaining measurements. Making and standardizing a phantom would probably require a year as well. So, the total time to first grounded profile would be about 2 years. In another year the U of Michigan could complete studies during renal transplantation with direct validation of the blood flow measurements for a total of 3 years to initial clinical validation. FDA qualification of this biomarker will be another year unless the process will be a simple matter, given the existing, very crude volume flow measures on most ultrasound systems.
After further discussion, this time schedule might be accelerated. Such a schedule will follow these steps:

Rely on existing data for initial profile draft (Year 1).
Obtain a phantom for shipment to manufacturers and the second clinical/academic site.
Perform small human study with local support, 2 sites, Years 2 & 3.
Initial clinically validated profile, end of Year 3.

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

Pre-existing research at the U of Michigan in association with GE health systems has provided evidence that these volume flow measurements are clinically feasible, with acceptable variability and bias in several applications. Results have been obtained or are on-going on the following systems:

GE Logiq 9 (4D3CL, 4DE8C, 4D10L, 4D16L, all mechanically swept arrays)
GE Logiq E9 (RAB 6-D, mechanically swept array)
GE Vivid 7 (V3, 2D array, time-resolved volume flow)
GE Voluson 730 (RAB 2-5L, mechanically swept array)
Philips Epic 7 (X6-1, 2D array)

2 manufacturers, 5 systems, 8 scan heads

Good data acquisition for the measurements is as easy or easier to perform as the existing crude measurements with Duplex Doppler. There are two CPT codes that we charge for Doppler studies: full Doppler code: #93975 - $900, limited Doppler code: #93976 - $600. They could be applied to this biomarker or the quantitative measure added as part of the procedure already being performed. Machines that can perform color Doppler, power Doppler, and 3D should already have the capability to estimate volume flow. The cost to implement this much more accurate method should be small. Once implemented, the time required to perform a volume flow measurement should be a matter of a few minutes. The method is angle, flow profile, and vessel geometry independent. All one needs to do is image the vessel in an orientation that would permit a constant depth C-surface to intersect it. There is no pain and no risk to the patient.

- **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)*

We expect at least two major companies to participate with research software. The primary requirement for commercial implementation and extensive clinical utility is enough clinical demand and simple enough FDA approval to raise this meaningful realization of the volume flow biomarker to the level of clinical application. In this case other companies will follow rapidly. Most of the work has been accomplished by radiologists and imaging research scientists and engineers, with support from companies and NIH.

The American Institute of Ultrasound in Medicine, AIUM, agreed in principle to cosponsor this effort and they are considering a specific proposal. See the attached budget spreadsheet.

Planned initial committee members and leadership are:

Chair: J. Brian Fowlkes, PhD, Professor of Radiology, University of Michigan
Cochair: Oliver D. Kripfgans, PhD, Research Asso. Prof. Radiology, University of Michigan
Members: Jonathan M. Rubin, MD, PhD, Professor of Radiology, University of Michigan
Mark E. Lockhart, MD, MPH, Prof. of Radiology, Univ. of Alabama at Birmingham
Jing Gao, MD, Assistant Professor of Radiology, Weill Cornell Medical College
Randall S. Sung, MD, Associate Professor of Surgery, University of Michigan
James Jago, PhD, and Ron Leichner, PhD, Philips Healthcare
Dave Dubberstein, PhD, Rimon Tadross, MS, GE Healthcare

Communication:
For the initial planning and conduct of this work we will have 1 teleconference meeting per month (1-1½ h, with staff support by AIUM). In addition, Drs. Fowlkes, Kripfgans and Rubin have a weekly meeting to cover volume flow research and will coordinate regular communications related to this activity through email and served files access. We will also coordinate participation as needed at the following meetings:

QIBA meeting at RSNA (plan and conduct breakout meeting, total 3 hours)
Steering Committee meeting (January 27th, 2016, O'Hare 1-8 p.m.)
Steering Committee and annual meeting April 12th-14th, 2016, Alexandria

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***Company statements**

Daniel Buckton, GE/Kretz: "GE Healthcare Austria GmbH & Co OG (Voluson) is interested in the technology of quantitative volumetric blood flow measurements and its applications. An imaging biomarker profile for umbilical blood flow based on volume flow would significantly add to patient care where vascular status is critical. GE Austria has supported the University of Michigan team previously with hardware and other support and we are looking forward to future efforts in which we can be partners."

Jim Walchenbach, Sr. Director, General Imaging, Philips: "…., we are interested in volume flow and its applications. Should QIBA choose to develop a quantitative imaging biomarker profile on volume flow imaging of the umbilical vein, that should simplify FDA approval of providing a new quantitative measure. We would be pleased to participate in that effort."

Won-Chul Bang, Ph.D., Samsung: "I am a principal researcher and the R&D head of the advanced ultrasound imaging division in Health and Medical Equipment Business of Samsung Electronics, currently leading four research projects to differentiate the radiology-designated ultrasound systems of Samsung. ….. In medical imaging, quantitative volumetric blood flow assessment will be a useful clinical feature if it can be shown that measurements can be user independent, fast, robust and accurate.

Example references

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