

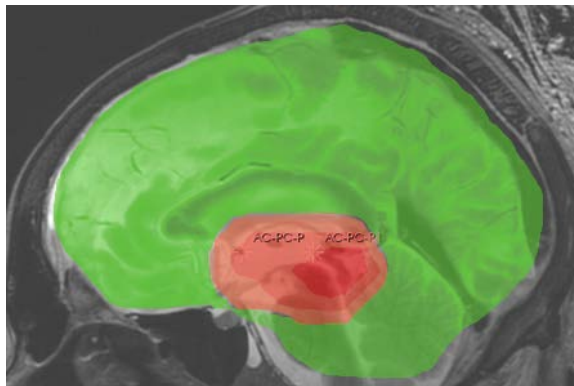
*The University of Virginia Darden School of Business - June 17-18, 2013*

## Major Workshop Findings

- 1) A validated simulation capability is needed to make effective progress toward an expanded treatment envelope for brain indications.
- 2) Simulation validation will require the support of additional detailed acoustic measurements at all clinical frequencies.
- 3) Volumetric thermometry measurements in phantoms will allow thermal safety and skull cooling times to be added to the concept of treatment envelope for brain indications.
- 4) The role of acoustic scattering versus absorption in the skull needs to be established with measurements.

## Background

In recent years, both the clinical use of focused ultrasound (FUS) and the number of indications to which it can be applied has expanded. To date, close to 100,000 patients have been treated for multiple indications.



One of the more compelling applications of this technology is for treatment of various brain indications, and 120 brain patients have already been treated. With currently available technology, a significant barrier to the adoption of FUS for brain indications is the limited treatment envelope (the area that can be safely and feasibly thermally ablated). The figure to the left is a generalized depiction of where in the brain we can effectively treat with thermal ablation today (red) and where

we would like to treat eventually (green).

The 2013 Brain Treatment Envelope workshop was organized by the Focused Ultrasound Foundation (FUSF) to discuss challenges, solutions, and the treatment envelope's limitations for specific clinical indications. The meeting aimed to focus FUSF's brain research priorities, plan research projects and collaborations, and gather clinicians, researchers, and industry scientists around a common understanding of the remaining challenges.

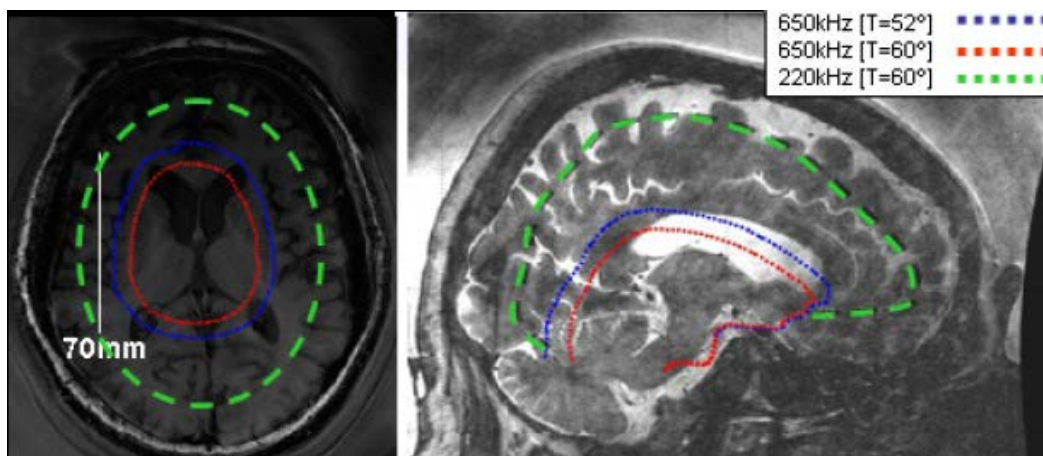
## Current Clinical Experience

The ExAblate Neuro system (Insightec, Inc, Haifa, Israel) has been used for thalamotomy in functional neurosurgery indications such as essential tremor, tremor-dominant Parkinson's disease, and neuropathic pain. It has also seen limited use for cingulotomy as a treatment for OCD patients. To date, more than 120 patients have been treated in various transcranial protocols. These anatomical targets are very central in the brain and very small in volume, but the early success of these treatments is encouraging for several other brain indications. However, the technology must evolve to safely reach much more of the intracranial space and to effectively treat larger-volume targets to achieve its maximum clinical impact and adoption as a standard of care.

## Unmet Clinical Need

The group discussed possible clinical applications of FUS in the brain, including mesial temporal lobe epilepsy (hippocampus and amygdala), trigeminal neuralgia (root entry zone of the trigeminal nerve), and tumor ablation (anywhere in the brain). Some areas (like epilepsy) likely require only modest expansion of the treatment envelope, while brain tumors may occur virtually anywhere within the brain, right up to the inner surface of the skull.

Transcranial focused ultrasound bears many similarities to radiosurgery, which currently enjoys widespread clinical adoption for the treatment of brain disorders--including tumors, vascular malformations, and movement disorders. FUS offers several key advantages over radiosurgery. It doesn't use ionizing radiation, has no cumulative dose effects, its effects are more immediate, and treatment can be monitored in real time. However, to effectively compete with radiosurgery and other technologies in the neurosurgical armamentarium, FUS must be able to reach further and treat larger volumes than what is possible today.



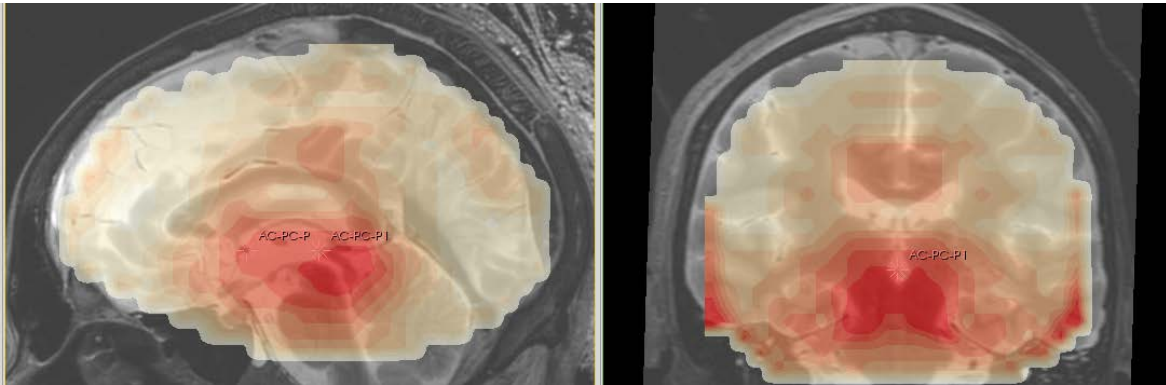
*Insightec's provided treatment envelope estimates for the two Exablate Neuro transducers.*

To expand the treatment envelope, topics discussed during the workshop included treatment envelope measurement, treatment simulation, focus correction and steering, and volumetric thermometry.

## Treatment Envelope Measurements

### Thermal Rise Survey

To describe how the current treatment envelope image was created, Matt Eames presented his treatment envelope mapping work (also presented at the 2012 International Society of Therapeutic Ultrasound meeting in Heidelberg, Germany). In addition to creating the mapping image, the study results suggested that the treatment envelope is near the center of head and that different skulls have different envelopes. Not every location in the brain could be reached using pure thermal ablation. The data suggest that the central aspect of the hippocampus could be treated (for mesial temporal epilepsy), but lateral portions may not be feasible.



Thermal rise survey results in a skull/gel phantom using the InSightec 650 kHz transducer. Dark red corresponds to ablative temperature achievable in the thalamus.

### Target-Specific Thermal Measurements

Mohamad Khaled (Neurological Surgery, University of Virginia) presented data from his treatment envelope study with the 650 kHz transducer that was designed to determine which clinically important brain targets are accessible, the maximum temperature rise that could be reached at each target, the time needed to create a lesion at the target, the reproducibility of the results with the gel phantom, and suggestions that might improve the results. Besides using the ventral intermediate nucleus (VIM) as a reference target (the VIM is the current target for essential tremor and tremor dominant Parkinson's treatments), he evaluated seven other cranial targets. He determined that, with transducer adaptations, all seven areas were accessible: internal globus pallidus (Parkinson's disease, dystonia), nucleus accumbens (addiction), anterior limb of the internal capsule (obsessive-compulsive disorder, major depressive disorder), subgenual cingulate gyrus (major depressive disorder), amygdala/hippocampus (epilepsy), the anterior 2/3 of the corpus callosum (seizures, Lennox-Gastaut syndrome), and the hypothalamus (hypothalamic hamartoma). However, volumetric targets like the hippocampus and corpus callosum required a large number of sonications to cover completely, requiring treatment times that may not be clinically feasible.

## Acoustic Treatment Envelope Measurements- 3D Mapping and Skull Database

Thilo Hoelscher and Arne Voie from UCSD presented their acoustic mapping and skull database data using the InSightec 220 kHz transducer. They collected data on peak intensity ( $\text{mW}/\text{cm}^2$ ) and peak pressure (peak negative pressure), and then performed 3D reconstruction of the intensity measurements. Their skull database currently includes 51 skulls (26 female and 14 male). The data collection process produces three distinct patterns: skull thickness, skull density, and incident angle distribution. The patterns for thickness and density are rather unique and can be used to identify a skull because every skull has a great deal of variation and every combination is very unique, like a fingerprint. The physical properties of the skull that were measured or calculated include thickness, density, and porosity for outer cortical, inner cortical, diploe skull layers.

## Phantoms

Current phantoms have their utility and limitations. Different materials are needed to work with heat applications versus mechanical/cavitation applications.

### Thermal Phantoms

The University of Virginia phantom (ex vivo skull filled with ATS tissue mimicking gel) is more convenient than the gel-embedded brain used by Jean-François Aubry in Paris. It's not good for high-power testing. It heals itself after melting but takes a long time to cool. If cavitation begins, it cannot be used again for a week. Using an ex vivo skull makes it very difficult to reproduce results across sites.

### Cavitation phantoms

Any cavitation-based study or regimen should first be done on a phantom and then in vivo to produce useful data. Future phantom material is needed to study cavitation because a good, robust model does not currently exist. UCSD is using InSightec's phantom recipe, but it's much different from real tissue. Eyal Zadicario (InSightec) suggested using a pig brain. Monkey research at BWH was unsuccessful when attempted without microbubbles, and this was possibly because the heads were too small.

## Treatment Simulations

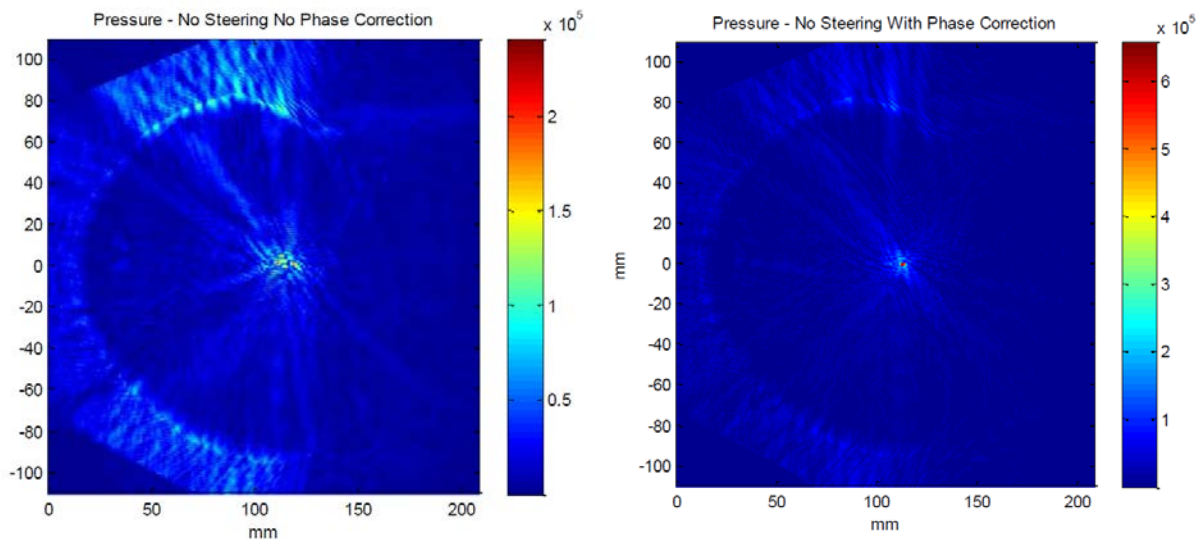
A validated method to simulate FUS application in the brain is essential for treatment planning and skull correction (every skull is different). Treatment simulation will give us the ability to answer more questions, efficiently assess the feasibility and safety of particular targets, and predict treatment times. It would also allow patient-specific simulation to account for the large variability in heating efficiency from person to person. Simulation would be a powerful tool for assisting with the design of advanced, possibly indication-specific, transducers.

We need the ability to predict results and measure focusing quality, but there is a limitation to how much can be predicted in advance because predictions do not explain everything that is seen. The positioning relationship of the transducer to the skull, the optimal way to determine the best position of the transducer, and the ability to create a system with many degrees of freedom are also important considerations that require further study.

Work in progress at three different institutions was presented and discussed:

### Hybrid Angular Spectrum Simulations

Doug Christensen presented data from his and Scott Almquist's University of Utah simulation studies where they looked at each element individually through the entire transducer. Handling the InSightec transducer with a hybrid angular spectrum (HAS) technique required the transducer to be partitioned into seven sections, simulated individually, and summed. The total computation time was approximately 10 minutes. They collected acoustic parameters for both the skull and the brain and measured the pressure and power distribution at the central focus with and without phase correction. They discussed the difficulty in mapping the speed of sound in cortical and trabecular bone.



Pressure distribution predicted by HAS simulation with and without phase correction.

### Finite Difference Time Domain (FDTD) Simulations

Jean-François Aubry presented his work on computational techniques using a three-layer FDTD model, including incidence angle, transmission coefficient, and phase shift equations (data first published in 2002). Both HAS and FDTD methods map the speed of sound with respect to Hounsfield units (HU) because they know the HU but not the density (from CT).

### Hybrid Focus Correction

Urvi Vyas presented her work at Stanford doing phase aberration correction with 2-Dimensional magnetic resonance acoustic radiation force imaging (MR-ARFI). Her hybrid simulation technique (also based on the HAS method) measures transverse aberrations. She performed simulations on one image to create an experimental picture of brain aberrations using a bone transducer. The corrected aberrations were about 85% of ideal, and she saw up to a 50% improvement in focus. The optimization can also be done iteratively. More power may be needed when using an actual skull. ARFI is critical for "practical time" rather than "real time," and work remains to be done in order to do the focusing faster, within minutes. More experimentation with the power distribution would also be valuable.

## Volumetric Thermometry

Henrik Odeen presented work from the University of Utah on volumetric thermometry. They use 3D segmented EPI acquisition, and their two approaches are 1. temporal constrained reconstruction (TCR), which enforces data fidelity and temporal smoothness, and 2. model predictive filtering (MPF), which is a thermal model that predicts temperatures using Pennes' bioheat equation. The advantage of TCR is that it requires little *a priori* information; MPF provides better real-time reconstruction and more accurately tracks rapid changes. Overall, their studies have allowed for large coverage 3D imaging that permits them to simultaneously look at the focal area and the brain-skull-interface. TCR would be suitable for preclinical safety tests, and RT-TCR and MPF for real-time reconstruction. In the future, they plan to conduct these experiments with a transcranial MRgFUS system (Supersonic Imagine, Aix-en-Provence, France) and to follow that with in vivo testing.

After the presentation, the group constructed a table showing the different thermometry methods that are being studied:

Center	Method	# of Slices	Time	Notes	Resolution
University of Utah	Seg EPI Cartesian: undersampled, constrained or predictive reconstruction	54	2-4 seconds	retrospective and/or model	2x2x3 but can make it any size it needs to be 1.25x1.25x3.0
Stanford	multi-shot EPI 3 or 5 planes 2D, 2D gradient echo	3-5	5 sec	off resonance sensitivity	~0.75x30
BWH	multi-shot EPI with 3D	24	3 sec	parallel imaging	
Vanderbilt	undersampled PR/radial	1	.32 for radial	Wondering about others temporal and spatial requirements. Spatial coverage depends.	
UVA	spiral, nascent				
MD Anderson	noise reduction				
InSightec	GRE	1	3.4 sec	0.5-0.75 mm and 3.0 around the focus (voxels)	1x2x3

The group discussed the desired imaging characteristics for brain thermometry:

- 1x1x2mm resolution would be luxury, but would like to do better than 2x2x4mm (the approximate focal spot size).
- Field of view: superior/inferior would be 100-160 mm, anterior/posterior would be 256 mm, and right/left would be 196 mm.
- Skull temperature updates every 10-15 seconds (compared to 3-5 sec for focal spot).
- The difficulty in predicting the temperature and the pressure at the focus could be studied with a simulation that could predict temperature changes in the bone, determine the absorption coefficient of the cortical bone, and predict transmission from the true scattering (scattering is important, especially in the diploë layer). The studies would produce different coefficients for the different layers of bone and the transmission through the skull.
- With regard to brain movement due to the heartbeat, the group wondered if this was an issue at the edge of the brain, how clinicians get high resolution MR images when the brain is moving, how it applies to thermometry, the relationship to Viola Riekes work with multi-baseline thermometry, and how important of an issue it really is compared to the other issues (stating that the brain does move, but it's probably a 2nd or 3rd order problem).

To wrap up the discussion on thermometry, Craig Meyer asked what it would take to get a new sequence for humans, and Eyal Zadacario suggested the possibility of using GE's fast track program, which allows research sequences to be used under a research protocol. InSightec would still have to run some safety tests with them, but it is a research path that is available for limited sites. It has to be approved by GE, and the sequence is limited to what GE will accept (it also depends on how far off it is from their approved sequences).

## Current State of the Technology

Eyal Zadacario presented a summary on the current state of FUS. Eyal said we have what we need now for the first functional targets (plain vanilla in the red dot on the first page), but the next tier of targets is on the edge of the red dot, so we really just need to expand the treatment envelope a little more to get a few more indications like epilepsy. After that, we will need to go to low frequency treatment modalities, like cavitation to further expand the treatment envelope.

The current **treatment modalities** are:

- Thermal ablation by tissue absorption
- Thermal ablation with enhanced absorption
- Non-thermal lesioning (microbubble agent)
- Blood-brain barrier opening with microbubbles
- Drug delivery with microbubbles

Straightforward thermal lesioning with absorption will always be somewhat limited. Modest improvement might expand the treatment envelope enough to epilepsy. Expanding the envelope far enough to treat brain tumor will require other modalities, and we will not reach everything with the first two modalities. Ischemic stroke may never be treatable with FUS because of severe clinical time constraints, but hemorrhagic stroke (15% of 200K cases) should be considered.

The **technical factors** that impact the treatment envelope are:

- frequency
- transducer geometry
- focusing technology (predictive algorithms, ARFI)
- power distribution between elements
- transducer positioning

The common **simulation criteria** for thermal lesioning are:

- temperature at the focus of 60 degrees for 10-20 seconds
- temperature on the skull of <43 degrees
- a dose size of 10 cc in 2 hours, dependent on cooling times
- parameters for skull/brain structures

Discussion of the **thermal parameters and cooling time** included:

- Cooling time should stay at 3 to 5 minutes until thermometry is improved. Shorter cooling periods can reduce treatment time, so it is important to study this parameter. (Heating time + cooling time = total treatment time.)
- Studying whether the cooling period actually lowers the temperature of the brain surface.
- Developing a more robust thermal measuring technique.
- The fact that the normal temperatures of the brain vary from place to place.

Possible **next steps** for research included:

- Agree on simulations with common criteria.
- Distinguish absorption from scattering.
- Validate simulations with measurements.
- Practical time ARFI.
- Measure skull heating (and cooling) with MR volumetric scans on skulls versus relying only on prediction and conservative assumptions.
- Map the acoustic intensity drop with corrected focusing in the full skull.
- Skull data analysis with respect to thermal rise in target (from treatments). What can we do to better correlate CT data with temperature or intensity data and take it a step forward to get better understanding for patient selection or skull heating?

Subsequent **discussion** included:

- Since simulation is a cross-cutting concern to many of these topics, what is the best way to achieve validated simulation?
- How to get the equipment needed to conduct the experiments.
- The possibility of adding skull data from BWH (~21 skulls) to the UCSD skull database.
- The value and time required for volumetric measurements (2 hours for 2000 data points).



- The possible formation of an Acoustic Mapping Consortium for data exchange. BWH, UCSD, and Institute Langevin could pool data and send it to Utah for corrections. They might need to resolve differences between transducers.
- Further work with ARFI, including clarification that ARFI in phantoms is easy but it is tough in the brain because the Young's modulus is so different between the gel and brain tissue. Although the DQA phantom is good mechanically, it doesn't translate clinically. ARFI might be easier in some areas of the brain than in others, and motion sensitivity is an issue.
- The possibility of measuring temperature in skull bone. Ideas discussed included using UTE, detecting T1 changes in bone and calibrating the T1 change to temperature, measuring signal intensity in bone as a function of temperature, looking at proton density (which should change as temperature changes), setting up a calibration experiment, and attempting to measure bone temperature with a water bath (initial attempts measured a the baseline T1 as much lower than is what is found in the literature). This is an interesting topic that is important, that has room for progress to be made, and that cannot be done clinically due to coil configuration.
- The possibility of measuring the tissue near the bone as a way to determine the temperature of the bone because the tissue itself may be the greater concern.
- If skull bone temperature could be measured, then the data could possibility be used to also study scattering vs. absorption.

### Mechanical (Non-thermal) Ablation with Low Frequency FUS

Nathan McDannold from Brigham and Women's Hospital described his experiments with the Insightec 220kHz system using the mechanical effects of microbubbles in monkeys. He suggested the possibility of expanding the treatment envelope through microbubble ablation using short, 10-millisecond bursts at 1% duty cycle, sonicating for several minutes, and ramping up the power until inertial cavitation is detected. This process is sensitive to different brain structures and doesn't work in white matter. A monkey skull is not as thick as a human skull. Yuval Grober's proposed UVA/Virginia Tech dog tumor study was described, and there might be opportunity for good collaboration between the UCSD and BWH groups.

## Conclusions and Collaborations

### Project 1: Acoustic Measurements to Support Simulation Validation.

Jean-François Aubry will measure a subset of the UCSD skull database to acquire the phase with the full wave form using the same setup on the Supersonic system with and without the skull. Together they will develop a protocol for the measurements, including specifying an exact location in the center of the skulls. They will outline in simple steps what needs to be recorded, the phase, waveforms, and all parameters. This collaboration would be the first set of experiments to validate simulation data vs. measured hydrophone data. They hope to measure and simulate a minimum of 3 skulls.

### **Project 2: Simulation collaboration.**

Dennis Parker and Doug Christensen at the University of Utah will lead collaboration between Utah, Stanford, UCSD, BWH, and Institut Langevin to match heating data with simulation so that acoustic measurement data can be used to validate simulations. Doug Christensen will get the exact mapping of InSightec's 220 transducer and the supersonic transducer and then compare his hybrid angular spectrum with Jean-François Aubry's simulation results. All groups who are doing simulations could also compare them to ARFI for validation. Beat Werner from Zurich University Children's Hospital will add his 650 kHz absorption and simulation data.

### **Project 3: Pre-clinical brain tumor studies.**

The UVA and UCSD groups will compare efforts on their brain tumor work in dogs and also consult with Nathan MacDannold at BWH on these projects.

### **Project 4: Volumetric temperature measurements.**

Allison Payne will lead collaboration between Institut Langevin, UVA, Stanford, Utah, BWH, and InSightec (who will provide their thermal models for the geometry/connective boundary conditions) to confirm the bone heating model with a skull/gel phantom. Wilson Miller will investigate the feasibility of using UTE for measuring skull heating.

### **Project 5: Estimation of skull absorption and scattering with micro CT.**

Jean-François Aubry suggested using micro CT to measure skull microstructure to better determine the roles of absorption and scattering at different frequencies. Steps might include hydrophone validation of simulation, acquiring data to measure heating close to the skull, comparing the bone heating measurements to the simulation results, and determining the entire volumetric heating in the skull. Wilson Miller from UVA will try to do some calibration of bone using UTE (T1 change vs. temperature).

## **Meeting Participants**

Jean-François Aubry – University of Virginia/Institut Langevin

Laurent Marsac – Supersonic Imagine/Institute Langevin

Eyal Zadicaria – InSightec

Dennis Parker – University of Utah

Doug Christensen – University of Utah

Allison Payne – University of Utah

Henrik Odeen – University of Utah

Kim Butts Pauly – Stanford University

Urvi Vyas – Stanford University

Thilo Hoelscher – University of California San Diego

Arne Voie - University of California San Diego

Beat Werner – Zurich University Children's Hospital

Nathan MacDannold – Brigham and Women's Hospital/Harvard University

Will Grissom – Vanderbilt University (via Skype)

Craig Meyer – University of Virginia  
Rich Price – University of Virginia  
Wilson Miller – University of Virginia  
Xu Zhiyuan - University of Virginia  
Mohamad Khaled – University of Virginia  
Yuval Grober – University of Virginia  
John Snell – Focused Ultrasound Foundation  
Matt Eames – Focused Ultrasound Foundation  
Arik Hananel – Focused Ultrasound Foundation  
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