



Pre-clinical Safety of the NeuroAccess Focused Ultrasound Platform for Blood- Brain Barrier Opening

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Clinical Challenges for Brain Tumors

The BBB Stops our most effective Cancer Tools

Liquid Biopsy



Not Used:
Too little DNA in peripheral blood

Tissue Biopsy



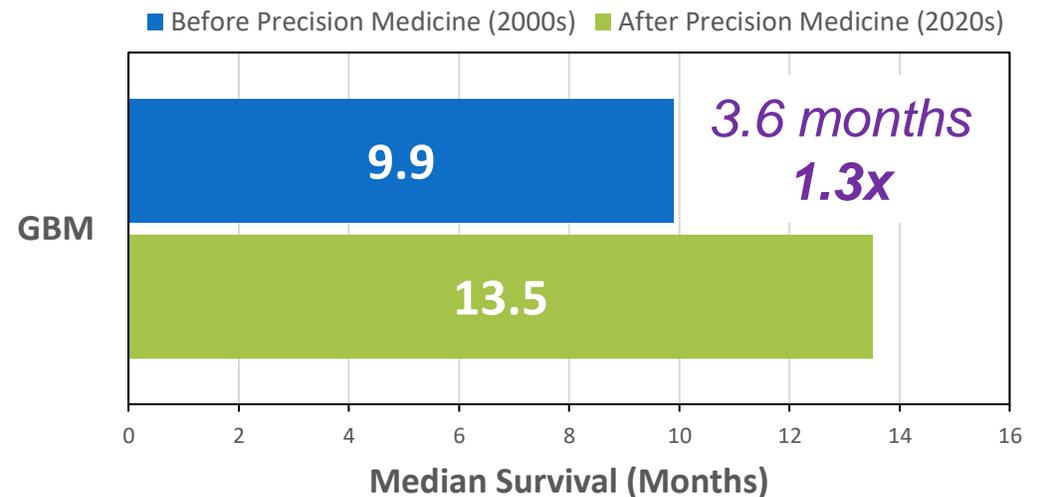
Rarely Used & Highly Variable:
High side-effect profile limits utility & access

Systemic Therapies



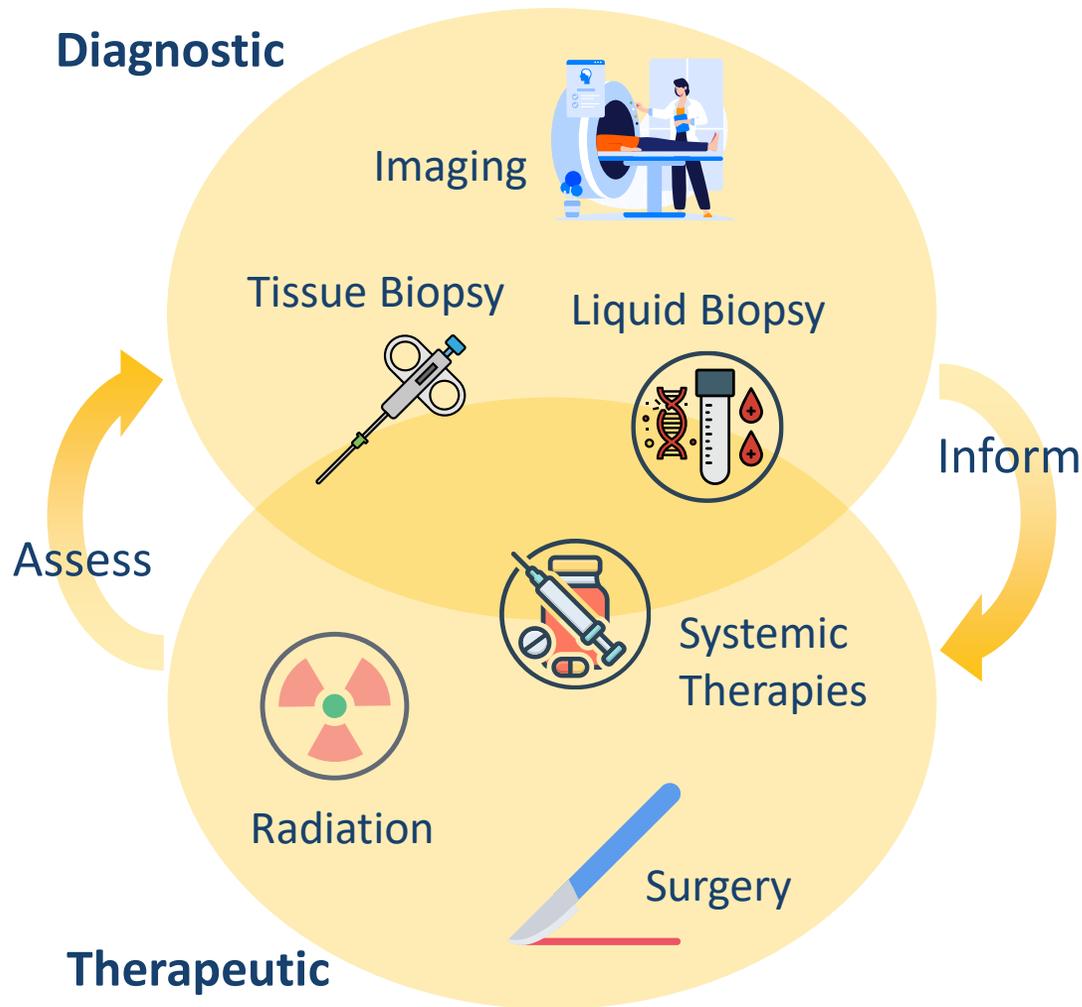
Limited Benefit:
Drugs have limited clinical benefit

Median Survival for New GBM Patients



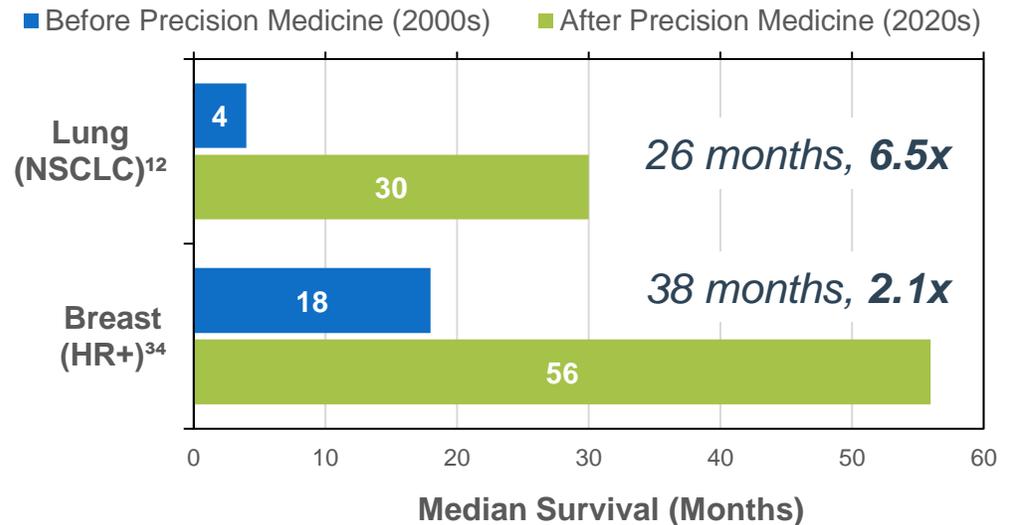
Primary Brain Tumor: GBM, Glioblastoma multiforme

Precision Medicine in Oncology



Value of Oncology Precision Medicine (PM) Paradigm*

Median Survival for New Metastatic Patients



1. Karynsa Cetin et al. *Clinical Epidemiology* (2011). 2. C.M. Cramer-van der Welle et al. *Scientific Reports* (2021). 3. Shaheena Dawood et al. *Journal of Clinical Oncology* (2008). 4. D.J. Slamon et al. *Annals of Oncology* (2021).

* Improved outcomes in metastatic diseases are driven by multiple factors for which precision medicine plays an enormous role, including aiding drug development, clinical development, patient selection, therapeutic efficacy, earlier detection of metastatic disease, and mechanism of resistance detection.

NeuroAccess™ Platform Objective

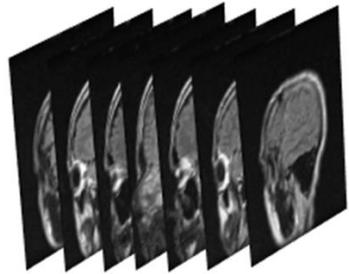
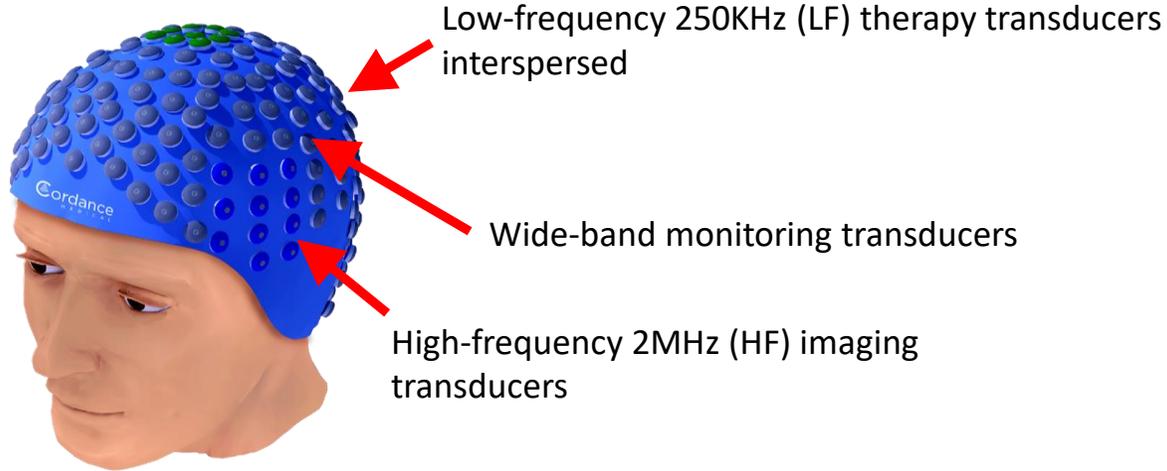
To enable **Precision Medicine** for Brain Diseases by temporarily opening the Blood-Brain Barrier enabling **Liquid Biopsy** and **Drug Delivery** in the *community-setting*.

Key Desired Features:

- **Patient Friendly:** no head shaving, quick interaction (minutes not hours)
- **Patient Comfort:** no frames, no isolation
- **Globally Accessible & Provider Friendly:** compatible with community Oncology/Neurology Clinics with a small footprint & low unit cost
- **Disease Accessibility:** ability to target >90% of brain volume



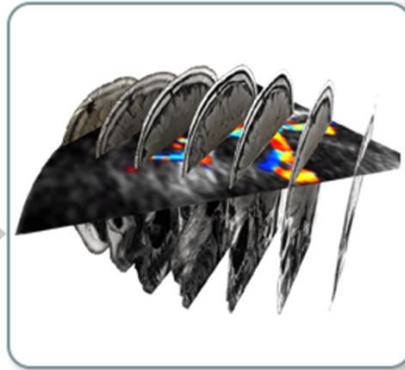
NeuroAccess™ Commercial Product



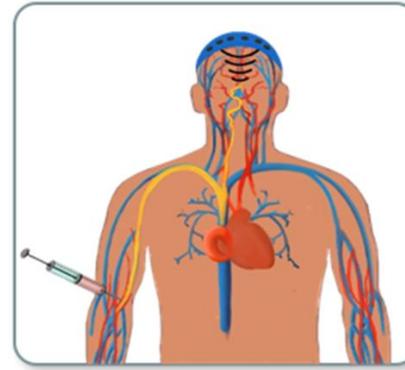
ROI on Dx MR



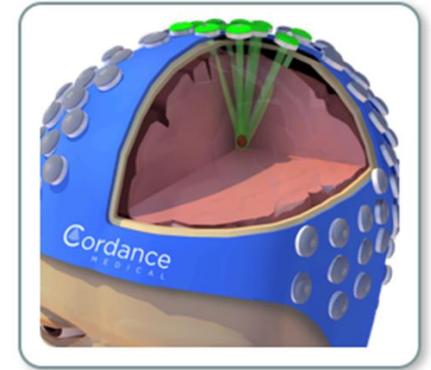
Patient puts on cap



Real-time dynamic tracking of target location(s)



Microbubbles are administered

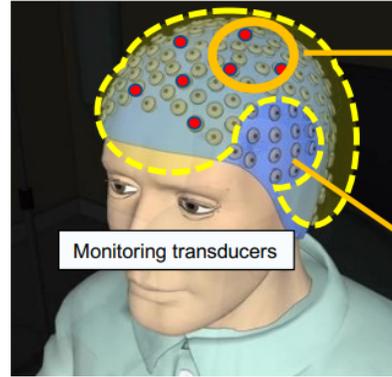


BBB opening, enabling liquid biopsy or drug delivery

NeuroAccess™ Clinical Trial Product

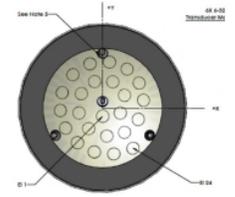
Clinical Trial Product Objectives:

- Retain all of functionality and safety of final version
- Quick to trial
- Reduced Costs
- Alignment with FDA



- Design small portions of cap (modules) with the appropriate transducers.
- Test modules on animals.
- **We have successfully designed such a module and have good results on animals**
- Use multiple modules on humans.
- FDA acknowledges this design strategy

Custom module – working design!



Use commercial ultrasound system for TCD imaging

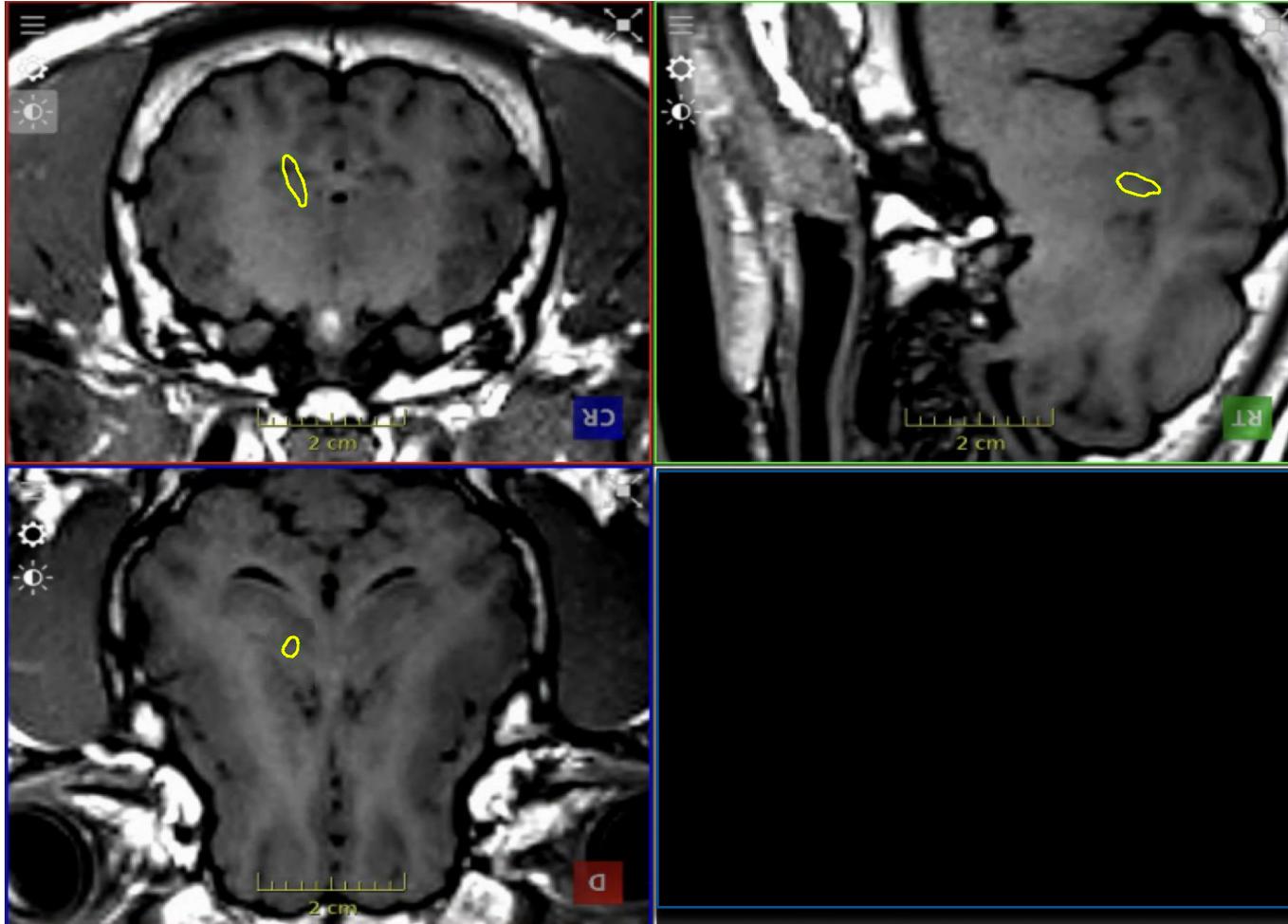


Clinical Trial Product:

Three module system that retains all the key features of commercial version.

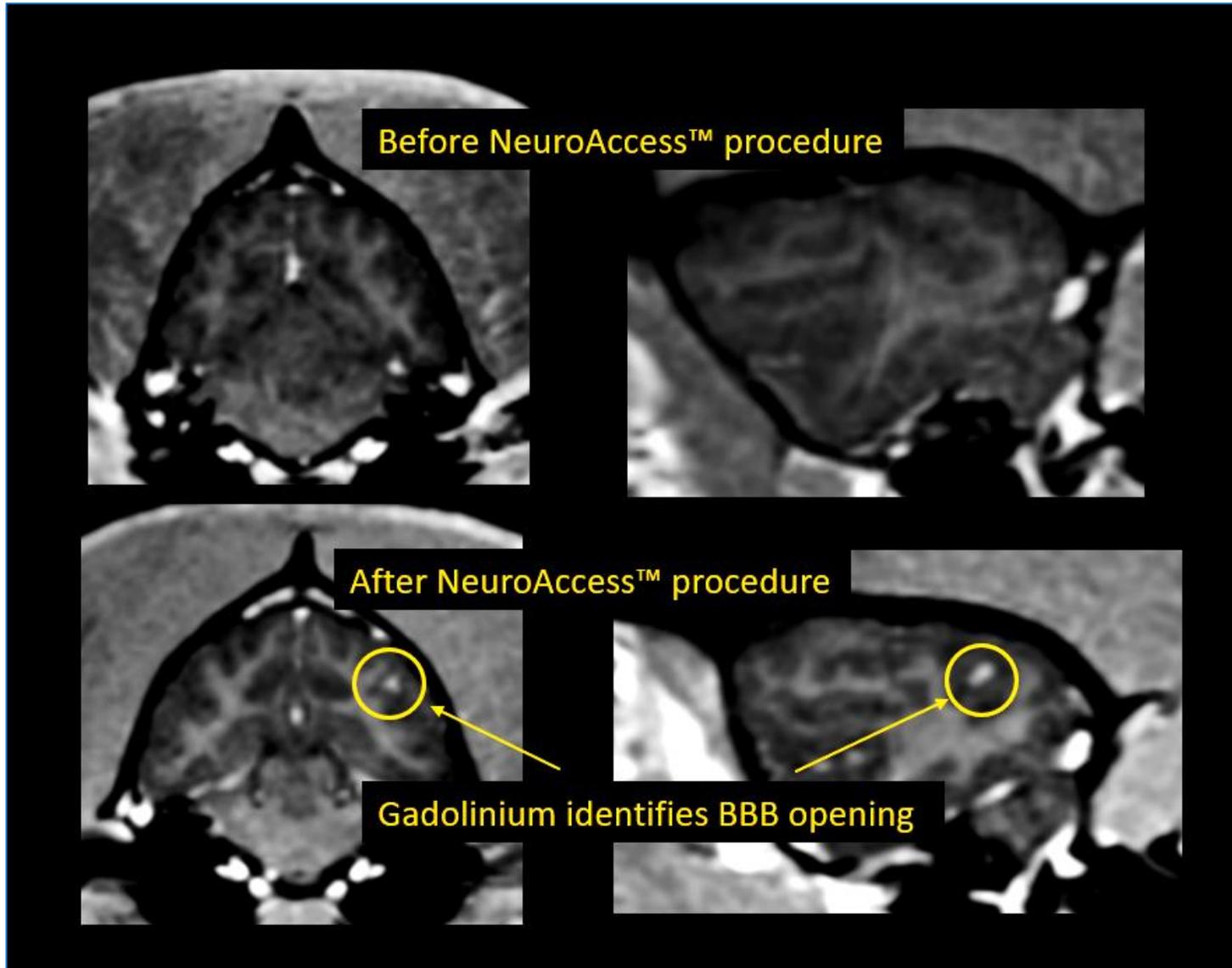
NeuroAccessTM Treatment Planning

Example of pre-sonication planning



- Obtain pre-sonication CT and MR
- Personalized planning (based upon skull size & shape)
- Pick multiple targets within the brain of a large animal using MR
- For each target, calculate beamforming for that particular subject, correcting for skull thickness and shape)
- For Human system: beamforming can change real-time based upon patient movement

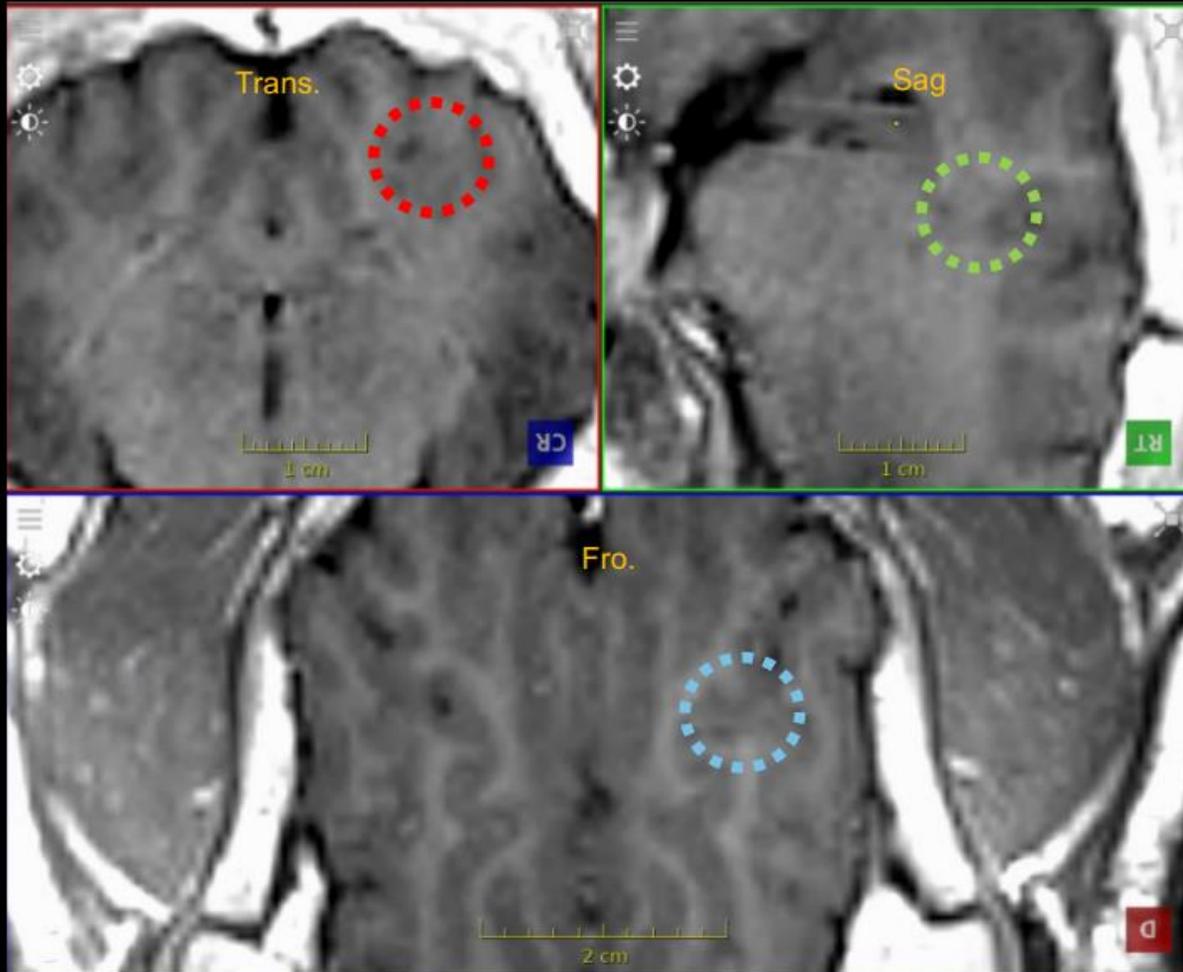
NeuroAccess™ Opening of the BBB



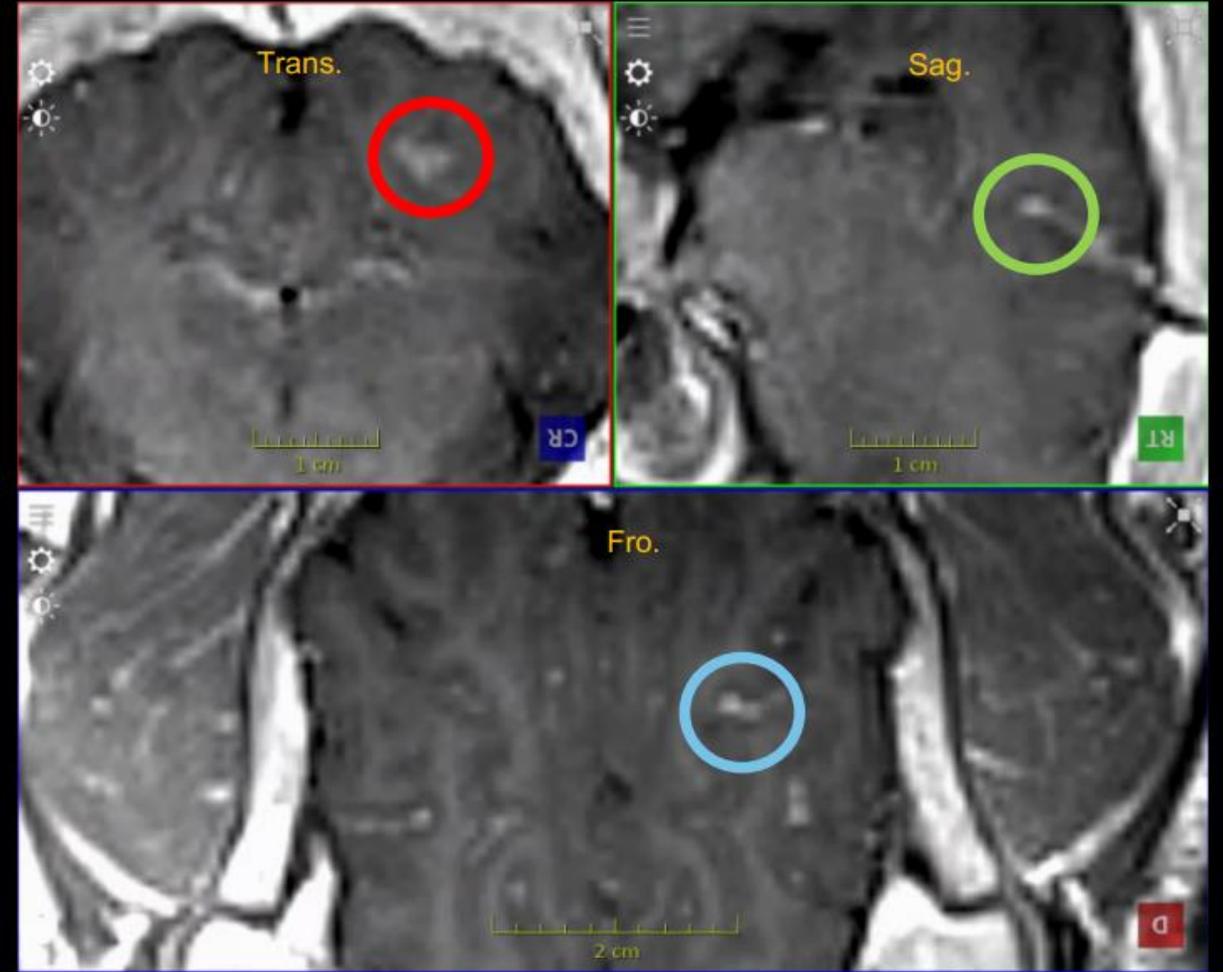
Evans Blue Histology Stain of Canine Brain

Porcine Model BBB Opening

Pre-sonication post-gadolinium



Post-sonication post-gadolinium



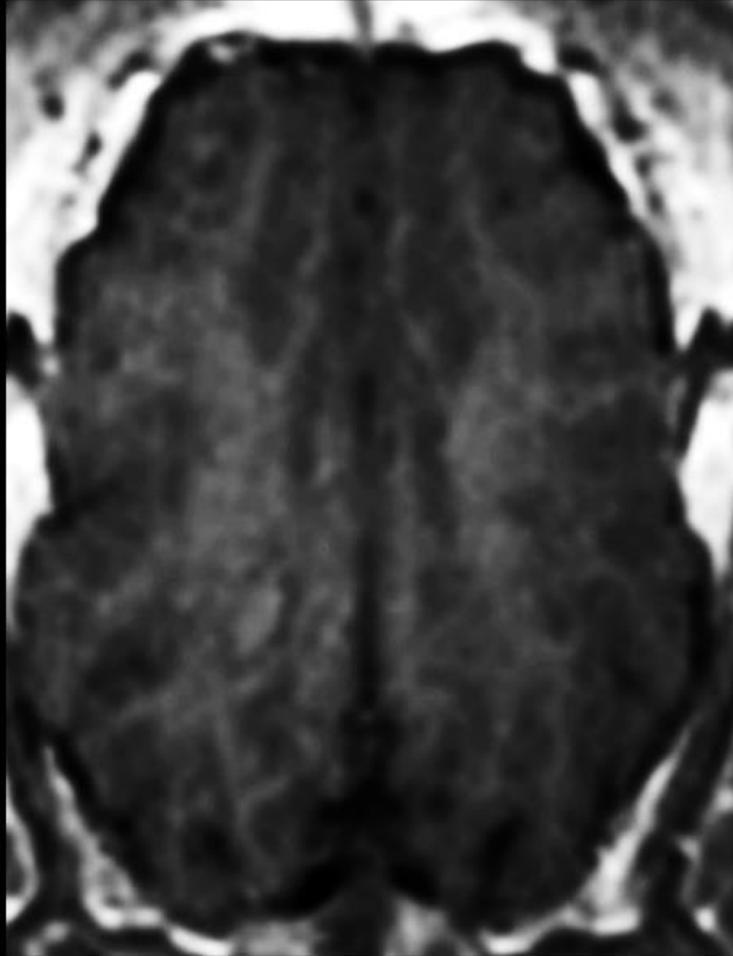
Legend:
Trans. : Transverse plane
Sag: Sagittal plane
Fro: Frontal plane

Dashed circles indicate no opening in pre-sonication image

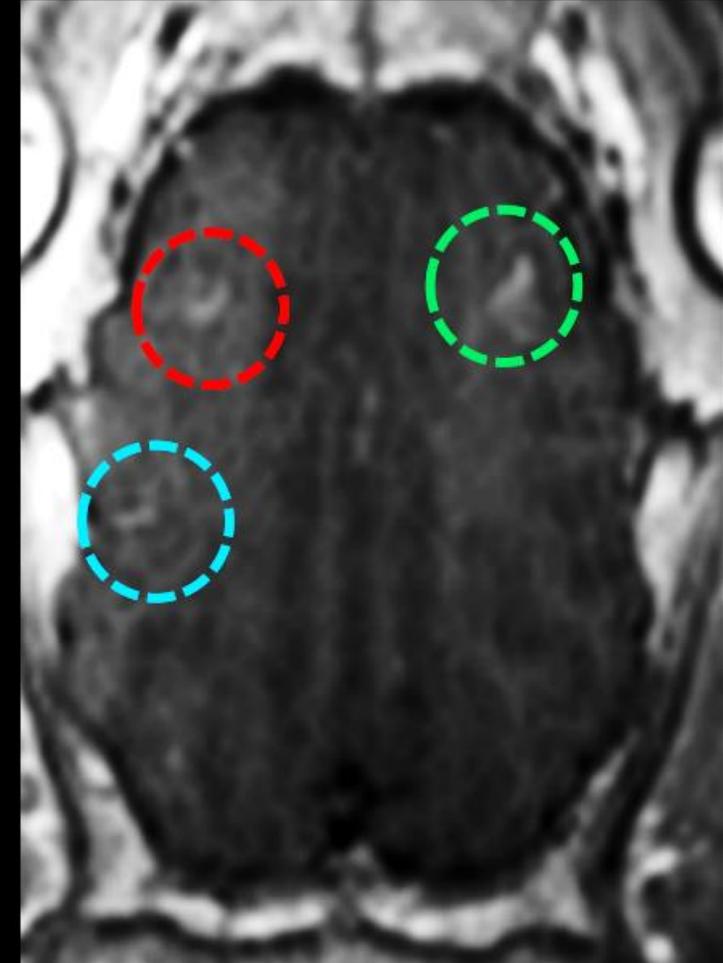
Solid circles indicate gadolinium leakage due to BBB opening post-sonication

Porcine Model Multi-Target Opening

Pre-sonication post-gadolinium



Post-sonication post-gadolinium

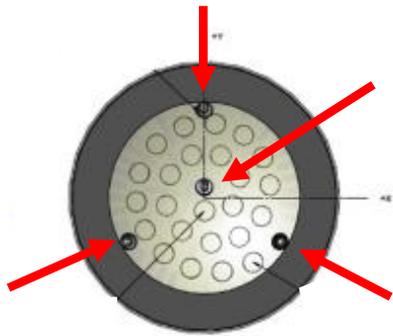


- Coronal plane showing three openings
- The module designed for use in humans was used

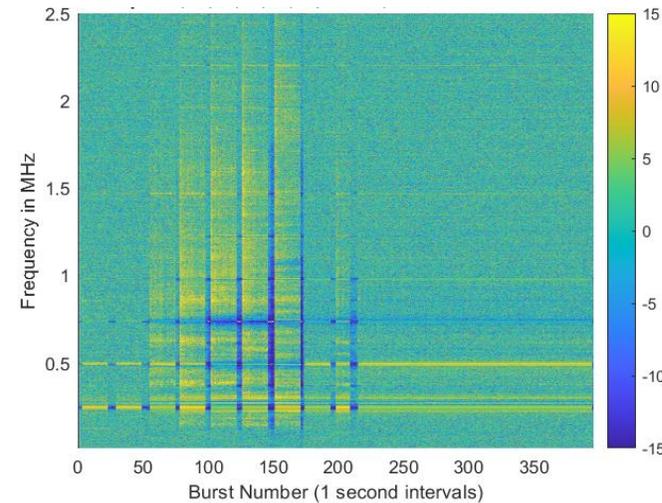
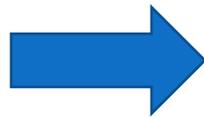
High-Sensitivity Monitoring System

Safe opening of BBB using FUS depends on monitoring signals from microbubbles. Therefore, it is critical that high-sensitivity receivers are used.

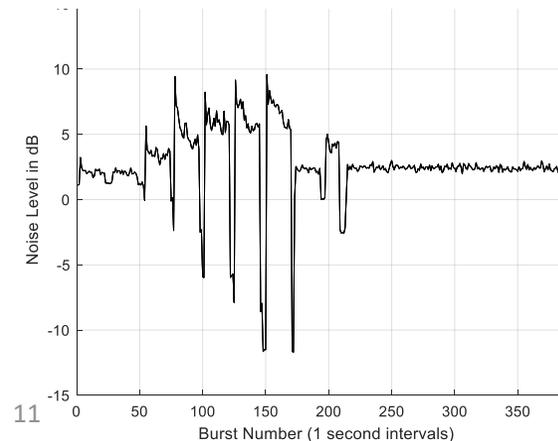
NeuroAccess device has 4 highly sensitive receivers per module.



- The red arrows indicate where the sensors are placed.
- Each receiver has a sensitivity spec of 15-20 V/MPa which is approximately 5-10x more than that of typical hydrophones over the frequency range of interest ($f_0 - 3f_0$)



Normalized spectrogram/burst in dB
Steps: 0.1, 0.1.0.2.0.3, 0.4.0.5, 0.5 MPa and sonicate at 0.2 MPa



Average Normalized noise level/burst in dB

Conclusions

- We have developed a clinical trial device which can be scaled to a commercial device which meets key clinical product requirements from patients & providers and can be globally scalable to out-patient community practices.
- Device has demonstrated safe (no micro hemorrhaging by T2 SWI) BBB opening within high accuracy (<2mm targeting accuracy) in dogs and pigs.
- Clinical trials to enable precision medicine (liquid biopsy & drug delivery) are planned.