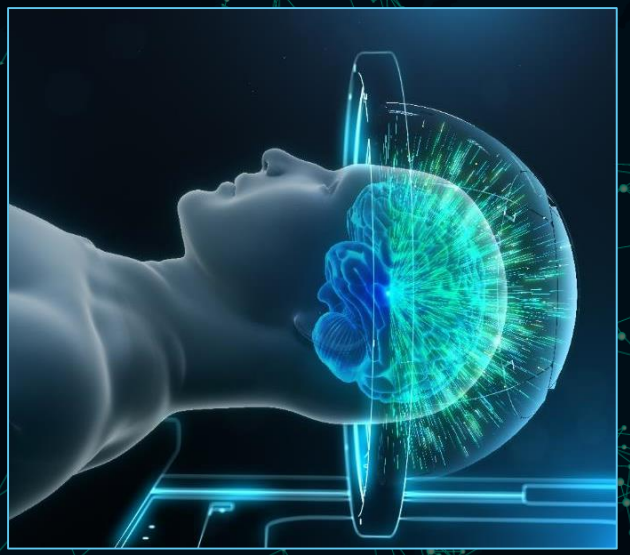
SNO 2019
Stresa, 11 May 2019

Ing. Giulia Frazzetta
Clinical R&D Engineer - Neurosurgery

INSIGHTEC

Company Profile

INSIGHTEC is a global medical technology innovator transforming patient lives through incisionless surgery:



- We are the global leader of MRgFUS
- Multiple indications
- Advanced clinical research
- Proven global regulatory strategy
- ~$300M invested in research
- Worldwide install base in 80 leading academic sites
- ~300 employees worldwide

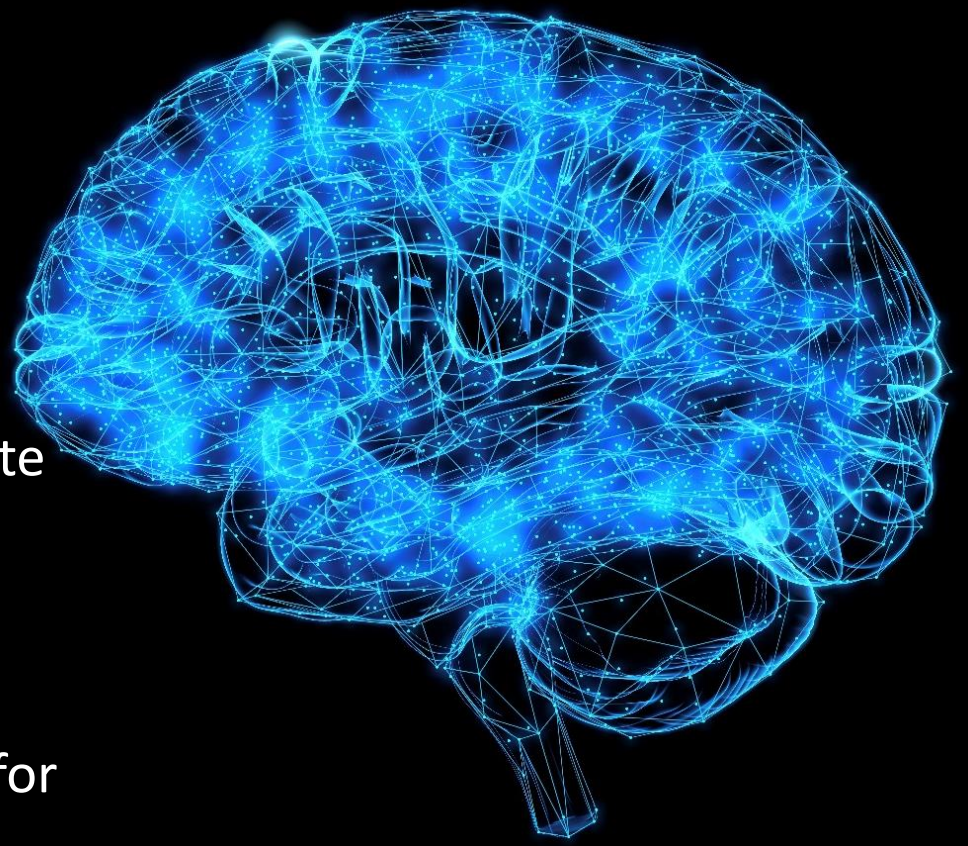
Redefining Surgery with 0 Cuts

Benefits:

- Minimal to no risk of infection
- Rapid recovery
- High safety profile with minimal complications[1]
- Single session treatment

[1]hiips://www.insightec.com/media/ 31393/exablateneuroinformationforprescribers0usa.pdf

Incisionless Brain Surgery

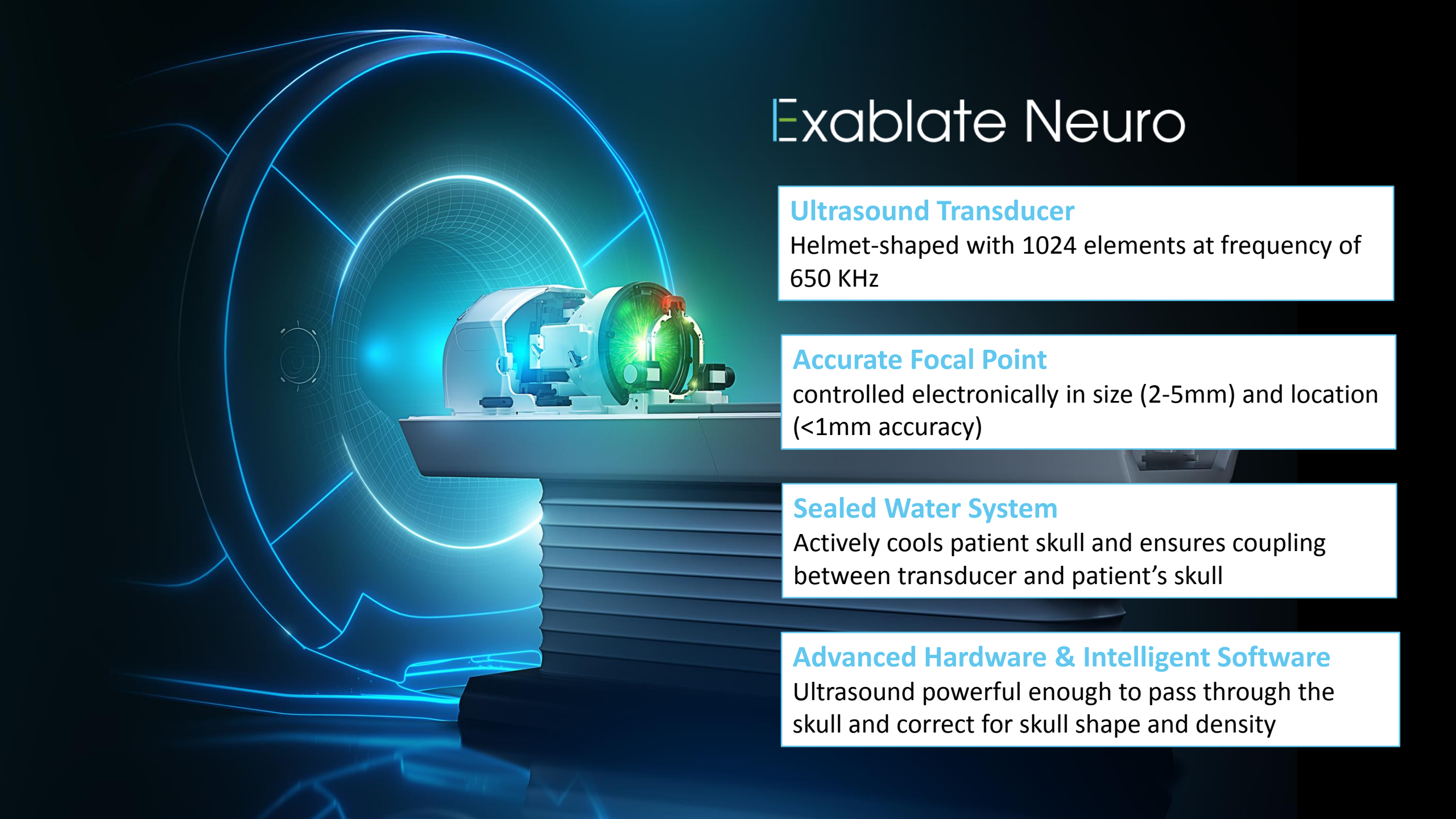


Next Generation Thalamotomy:

- The award-winning Exablate Neuro™ delivers up to 1024 ultrasound waves across the skull to heat and precisely ablate the Vim of the thalamus with no surgical incisions or burr holes.
- MR-guided focused ultrasound (MRgFUS) can be an option for medication-refractory ET and TDPD patients.

RESULT: Immediate and durable improvement of hand tremor with minimal complications.[1]

[1]hiips://www.insightec.com/media/ 31393/exablateneuroinformationforprescribers0usa.pdf



Exablate Neuro

Ultrasound Transducer

Helmet-shaped with 1024 elements at frequency of 650 KHz

Accurate Focal Point

controlled electronically in size (2-5mm) and location (<1mm accuracy)

Sealed Water System

Actively cools patient skull and ensures coupling between transducer and patient’s skull

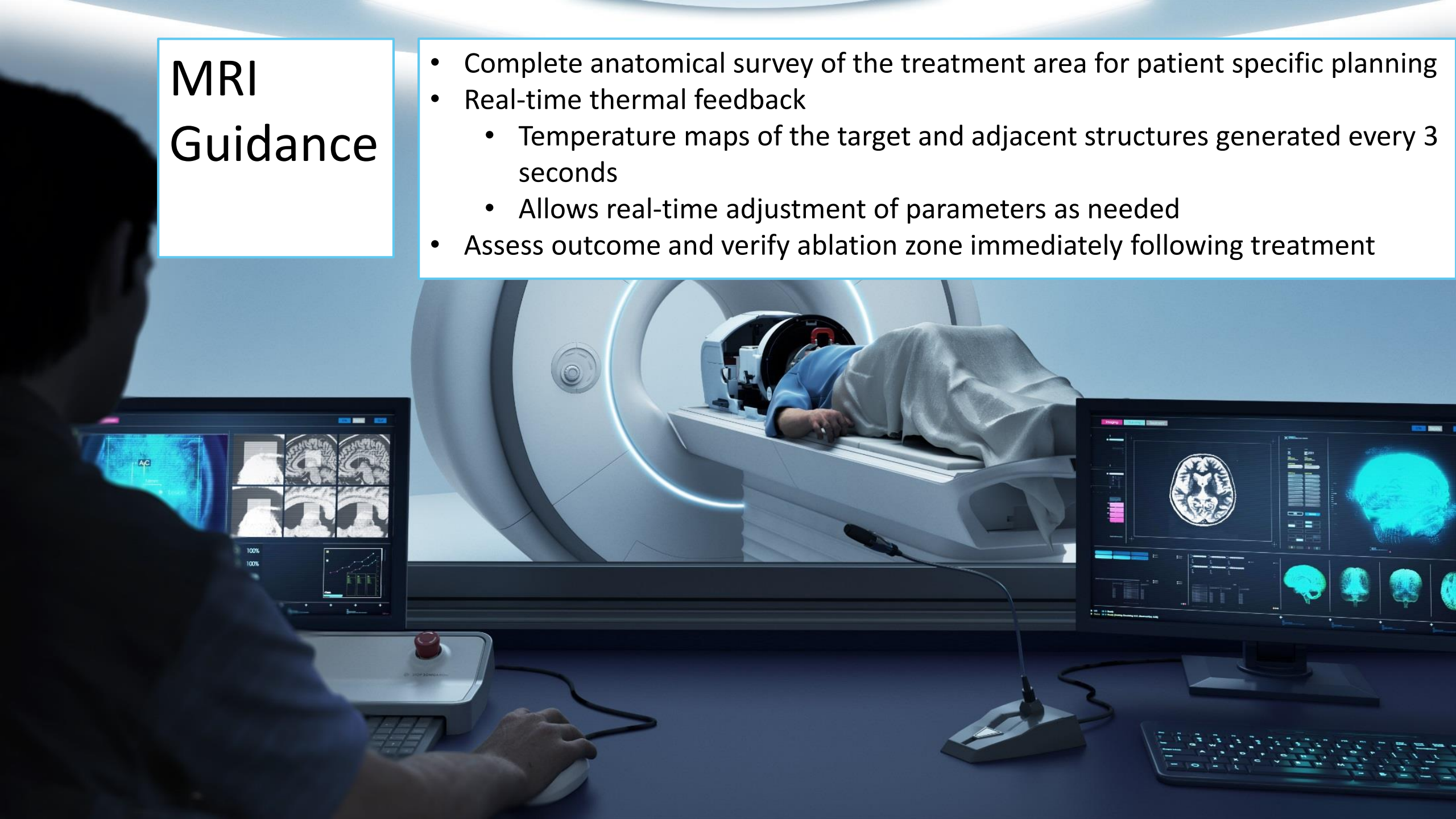
Advanced Hardware & Intelligent Software

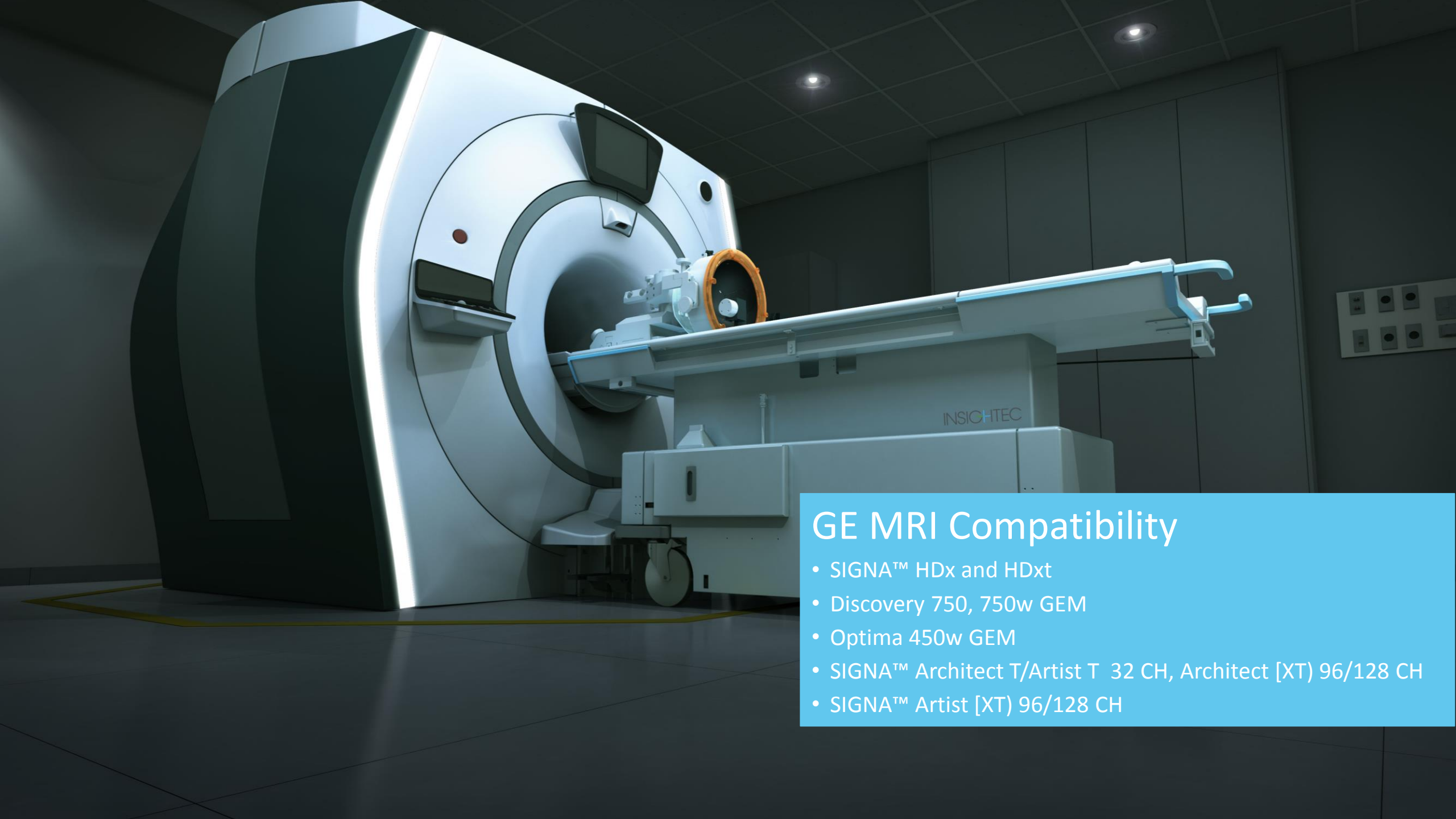
Ultrasound powerful enough to pass through the skull and correct for skull shape and density

Focused ultrasound waves safely and accurately ablate target tissue using **MR imaging** to plan and monitor the procedure in real-time.

MRI Guidance

- Complete anatomical survey of the treatment area for patient specific planning
- Real-time thermal feedback
  - Temperature maps of the target and adjacent structures generated every 3 seconds
  - Allows real-time adjustment of parameters as needed
- Assess outcome and verify ablation zone immediately following treatment

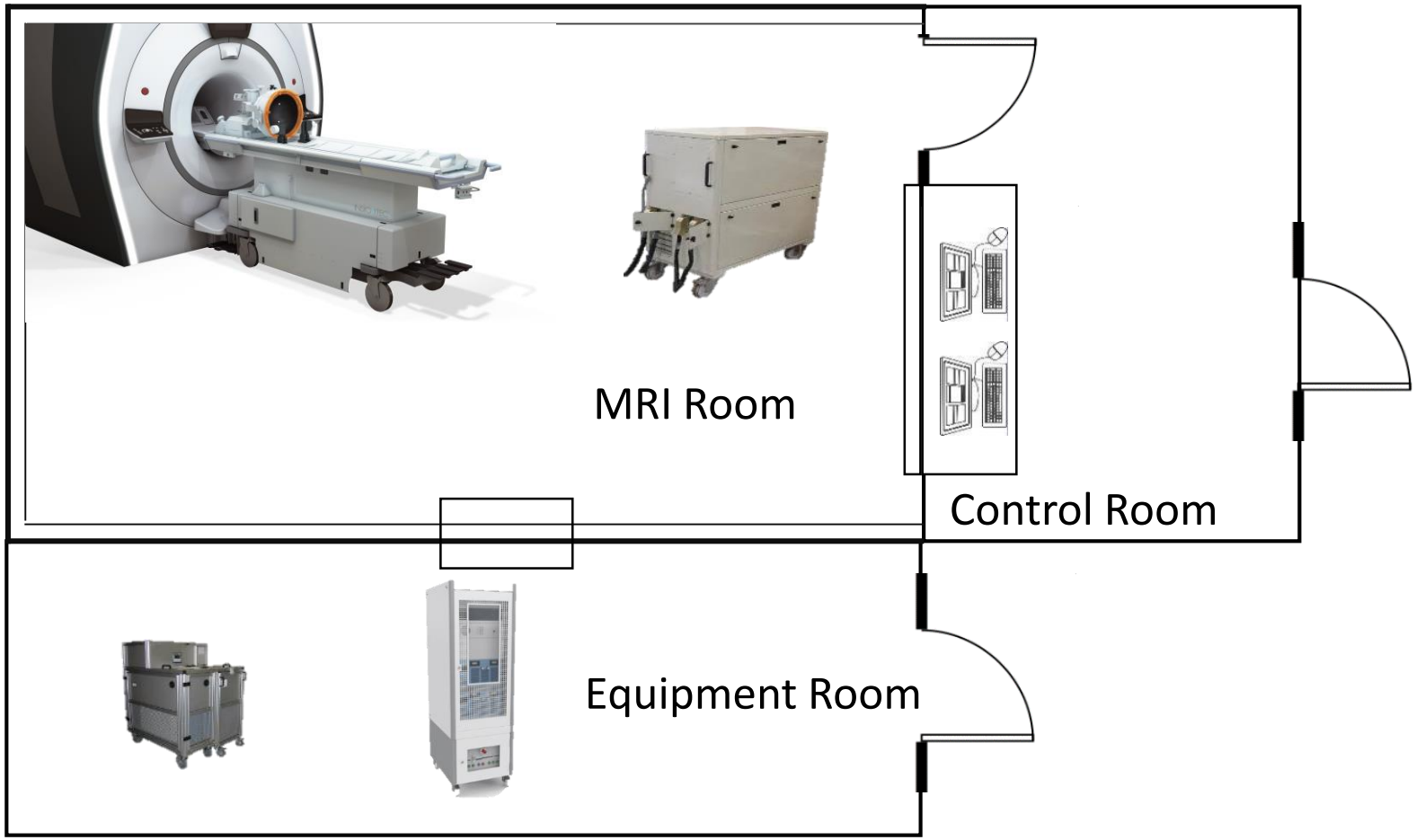




GE MRI Compatibility

- SIGNA™ HDx and HDxt
- Discovery 750, 750w GEM
- Optima 450w GEM
- SIGNA™ Architect T/Artist T 32 CH, Architect [XT) 96/128 CH
- SIGNA™ Artist [XT) 96/128 CH

Exablate Neuro for GE Set-up

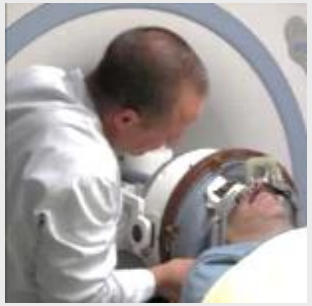


Need prep space for:

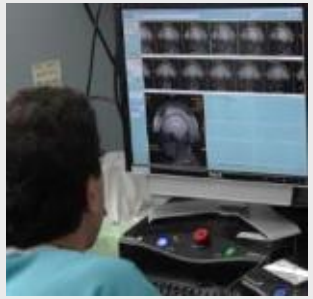
- Head shaving
- Stereotactic frame placement (with local injection)
- IV insertion
- Post-treatment recovery

Treatment Process

1 Patient Preparation

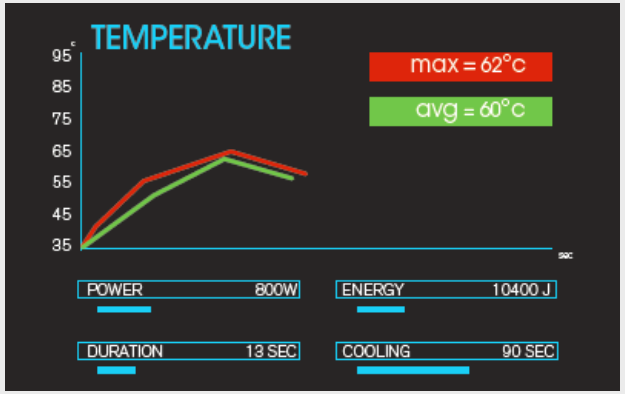


2 Planning



3 Target Verification

4 Treatment

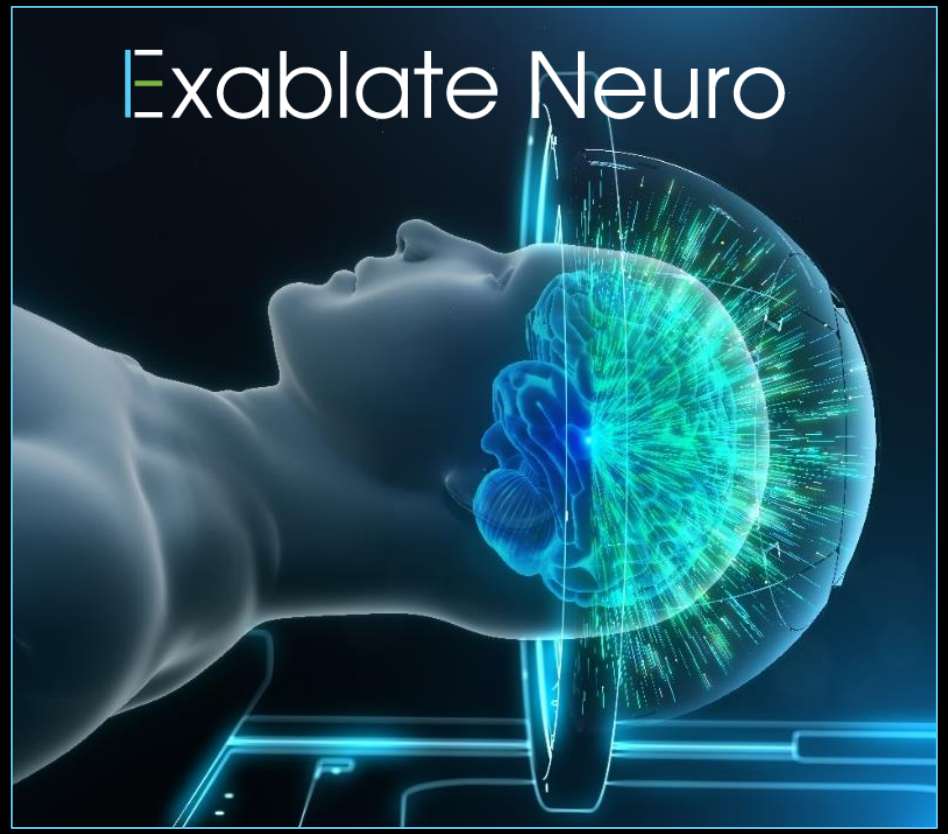


5 Assessment

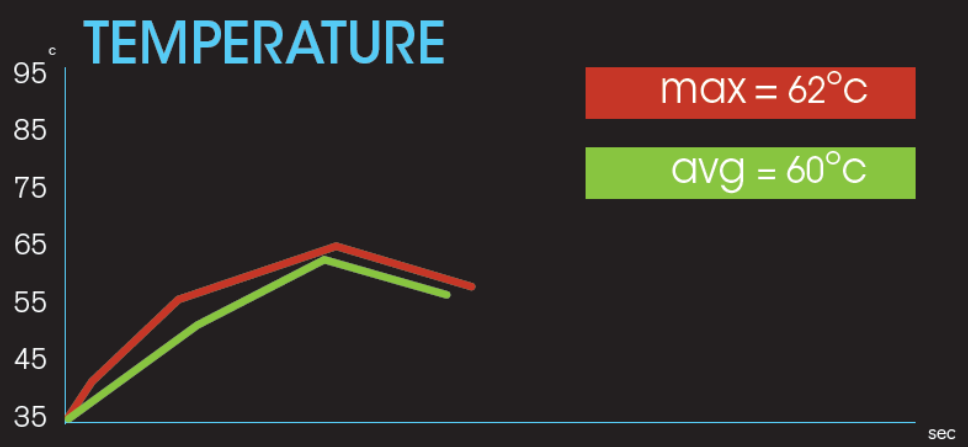
Treatment Benefits

- **Incisionless Treatment** → No general anesthesia required; No risk of infection; Performed on outpatient basis
- **Tremor improvement** → Immediate tremor improvement post-procedure; Stably maintained at 3 years; Improved quality of life
- **Personalized treatment** → Neurologic evaluation of patient response and potential side effects before final lesion
- **Safe & Effective** → Majority of adverse events were minor or, moderate, and were or transient.

*hiips://www.insightec.com/media/ 31393/exablateneuroinformationforprescribers0usa



Clinical Benefits



Testing

Testing allows verification of the target, adjustments if necessary and identification of potential side effects before performing final lesion

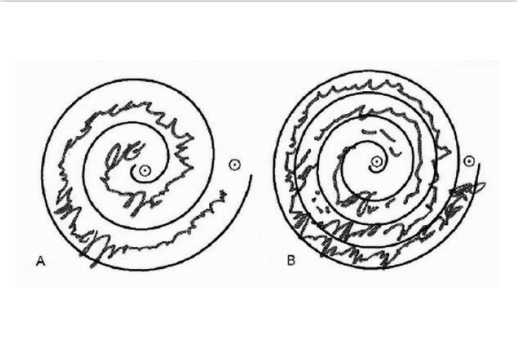
Accuracy

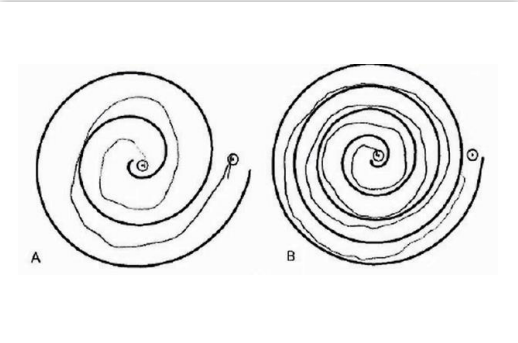
Focal point can be controlled electronically in size (2-5mm) and location (< 1mm accuracy)

Real-Time Feedback

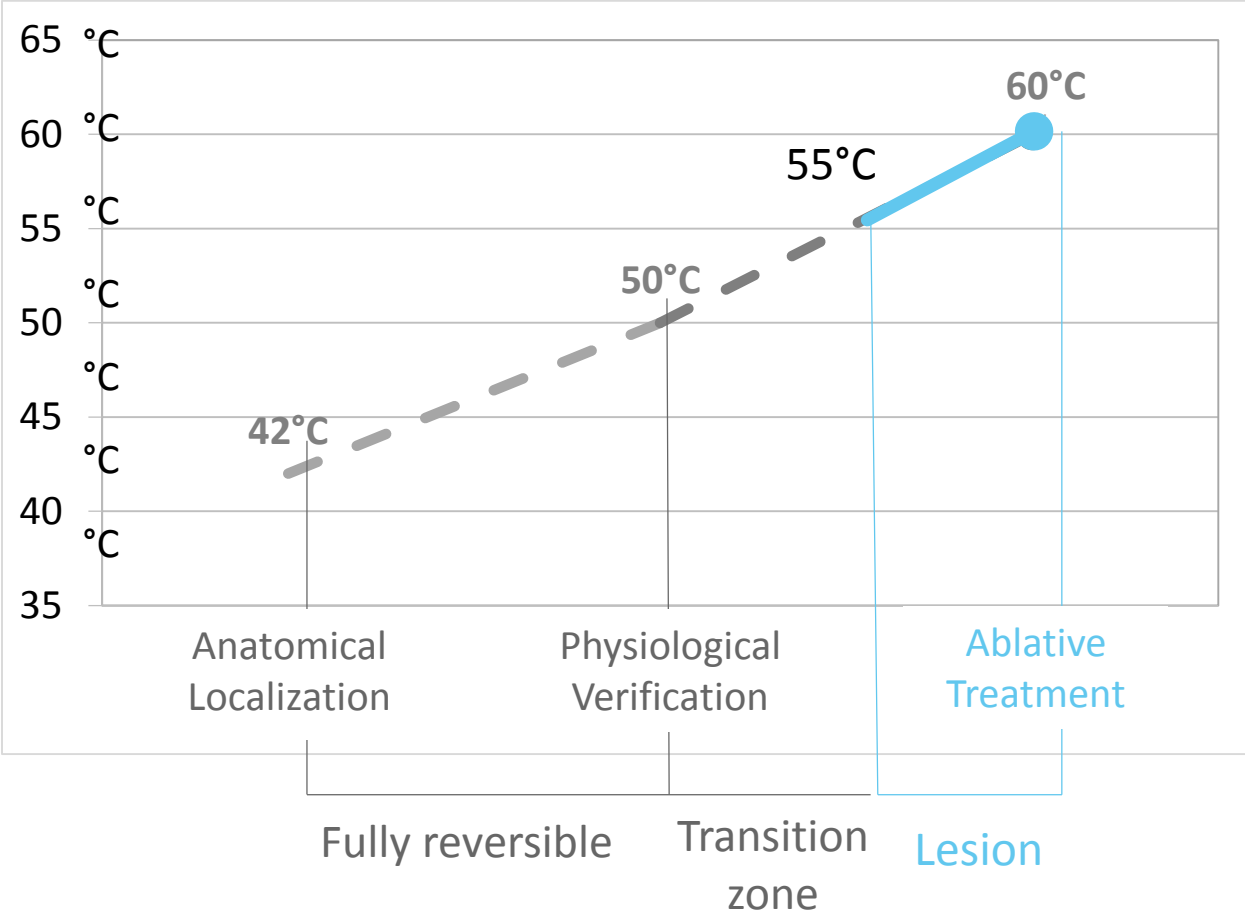
- Intra-operative physiologic tests to assess treatment outcomes
- MRI thermal maps of the target and adjacent structures for procedure control

Intraoperative Feedback

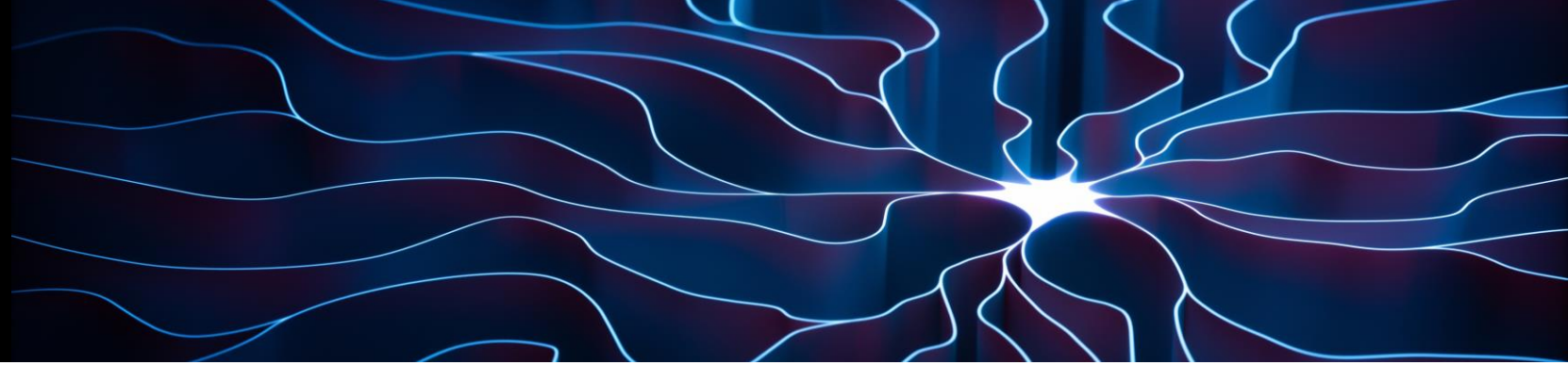




Fully reversible, sub-lethal sonications allow continuous assessment of tremor improvement and identification of any potential side effects before final lesion



Contraindications



- Standard contraindications for MRI including non-MRI compatible implanted metal devices (such as cardiac pacemakers), allergies to MRI contrast agent(s), or other reasons for MR ineligibility.
- Pregnant women.
- Patients with advanced kidney disease or on dialysis.
- Patients with unstable heart conditions or severe hypertension.
- Patients exhibiting any behavior consistent with ethanol or substance abuse.
- Patients with a history of abnormal bleeding, hemorrhage, and/or blood clotting disorders (coagulopathy) or those currently taking anticoagulant drugs or drugs known to increase the risk of hemorrhage (unless physician determines it is safe to stop medications prior to the procedure).
- Patients with a history of cerebrovascular disease (strokes) or brain tumors.
- Patients who are not able to tolerate the prolonged stationary position during treatment.
- Patients who have an overall skull density ratio of 0.45 (± 0.05) or less as calculated from a screening Computed Tomography (CT).

Labeling for Exablate Neuro

FDA

- Exablate Neuro is intended for use in the unilateral thalamotomy treatment of idiopathic Essential Tremor patients age 22 or older with medication-refractory tremor.

CE Mark

- Exablate Neuro is intended to ablate targets in the thalamus, sub thalamus and pallidum regions to treat essential tremor, tremor-dominant Parkinson's disease and neuropathic pain.

Exablate Neuro Treatment Centers

North America (24 sites)

- University of Virginia
- Stanford University
- Swedish Medical Center, Seattle
- University of Maryland
- Brigham and Women's Hospital
- Sunnybrook Health Ctr., Toronto
- Ohio State University
- Toronto Western Hospital
- Cornell Medical Center
- Miami Children's Hospital
- University of Pennsylvania
- Foothills Hospital, Calgary
- Mayo Clinic, Rochester
- Sperling Imaging, Boca Raton, FL
- Montreal Neurological Institute
- NYU, New York
- West Virginia Univ., Morgantown
- Cleveland Clinic Foundation
- University of Utah
- Virginia Tech/Carillion, Norfolk VA
- UCLA Medical Center, Los Angeles*
- Baptist Hospital, Miami*
- Catholic University, Santiago Chile*
- University of South Florida, Tampa*

Europe (16 sites)

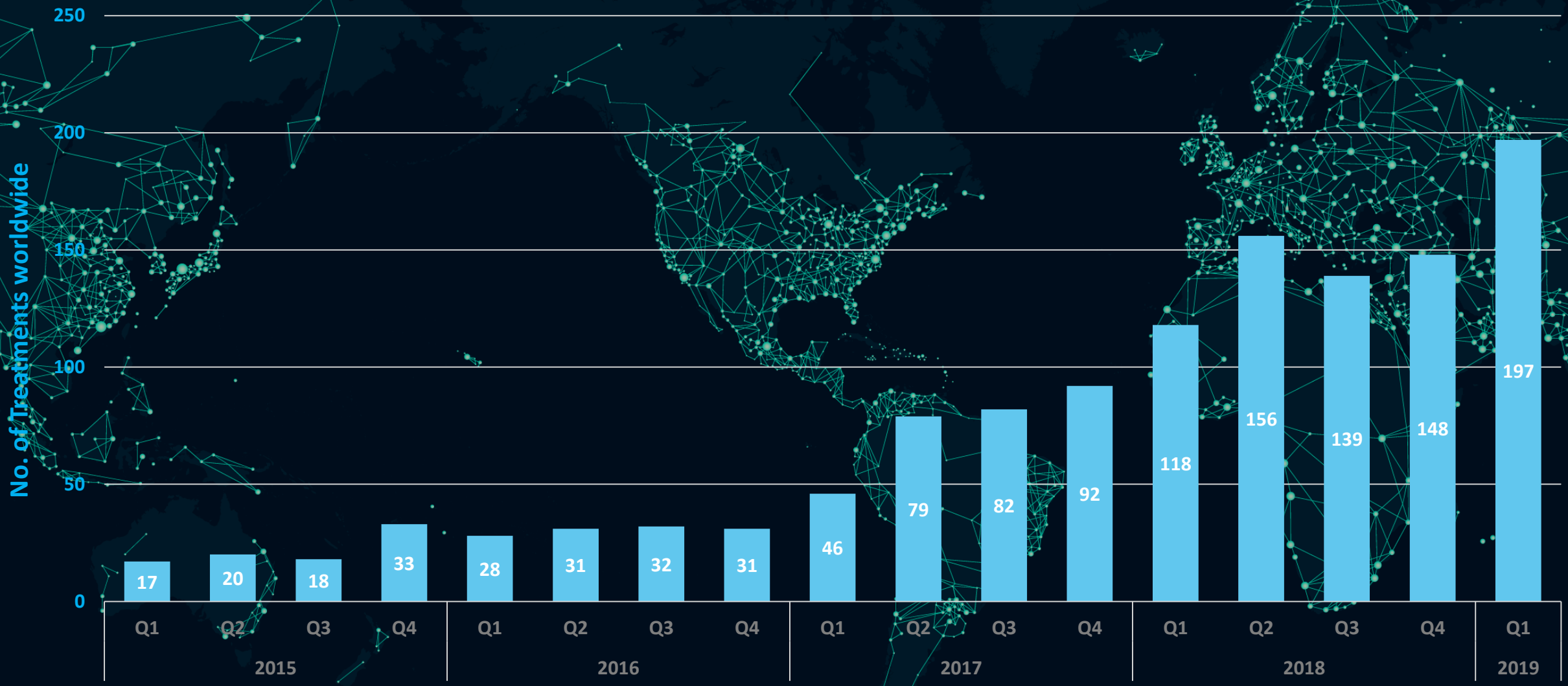
- University Hospital Zurich, Switzerland
- SoniModul Center of FUS Neurosurgery, Solothurn, Switzerland
- Rambam Hospital, Haifa, Israel
- Palermo University, Italy
- Sheba Hospital, Tel Aviv, Israel
- HM Hospitales, Madrid, Spain
- ResoFUS Alomar/Hosp. Clinic, Barcelona
- Imperial College, London, UK
- Ospedale Borgo Trento, Verona, Italy
- Ospedale San Salvatore, L'Aquila, Italy
- Uniklinikum, Bonn, Germany
- Clinical Univ. Navarra, Pamplona ,Spain
- Santa Elena, Valencia Spain
- Istituto Carlo Besta, Milan, Italy
- Institute Langevin, Paris*
- IRCCS Neurolesi, Messina, Italy

Asia (19 sites)

- Yonsei University (YUMC), Seoul, Korea
- Shin-Yurigaoka/Tokyo Women's U., Japan
- Sadamoto Hospital, Japan
- Hokuto Hosp./Kumamoto U., Japan
- Saito Yukokai / Osaka U., Japan
- Ohnishi Hosp. / Nara U., Japan
- Hokkaido Ono Hosp. / Sapporo U, Japan
- Shonan Fujisawa Tokshukai, Japan
- Kumagaya Hospital, Japan
- Show Chwan Hospital, Taiwan
- Nagoya Kyoritsu / Nagoya U., Japan
- St. Vincent's, Sydney Australia
- PLA 301 Beijing China
- Henan Provincial, China
- CMUH, Taiwan
- Inst. of Human Brain, St Petersburg, Russia
- Toyoda Eisei / Hamamatsu U., Japan*
- Siriraj Hospital, Bangkok, Thailand
- Ufa Hospital, Russia*

As of March 2019 - * Being installed

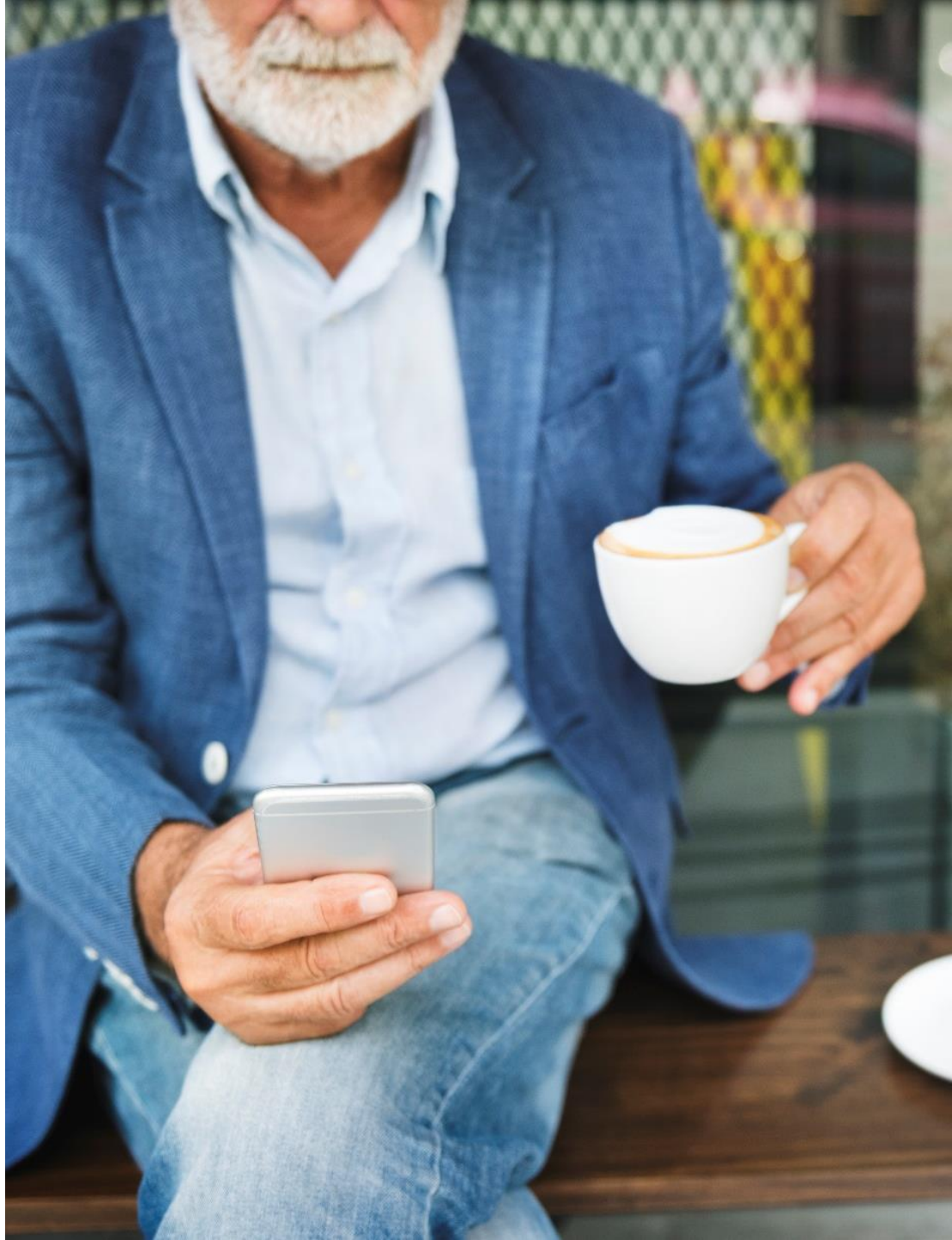
Exablate Neuro Treatment Numbers



ET Facts

- 41 million patients worldwide.[1]
- Essential tremor is a neurological condition that causes shaking of the hands, head, and voice, but it can also cause legs and trunk to shake.
- Quality of life is a key issue as daily activities such as feeding, drinking, grooming and writing become difficult if not impossible.
- Many people with ET are embarrassed to go out in public

[1] hiip://www.londonmdc.ca/research/tremor.html



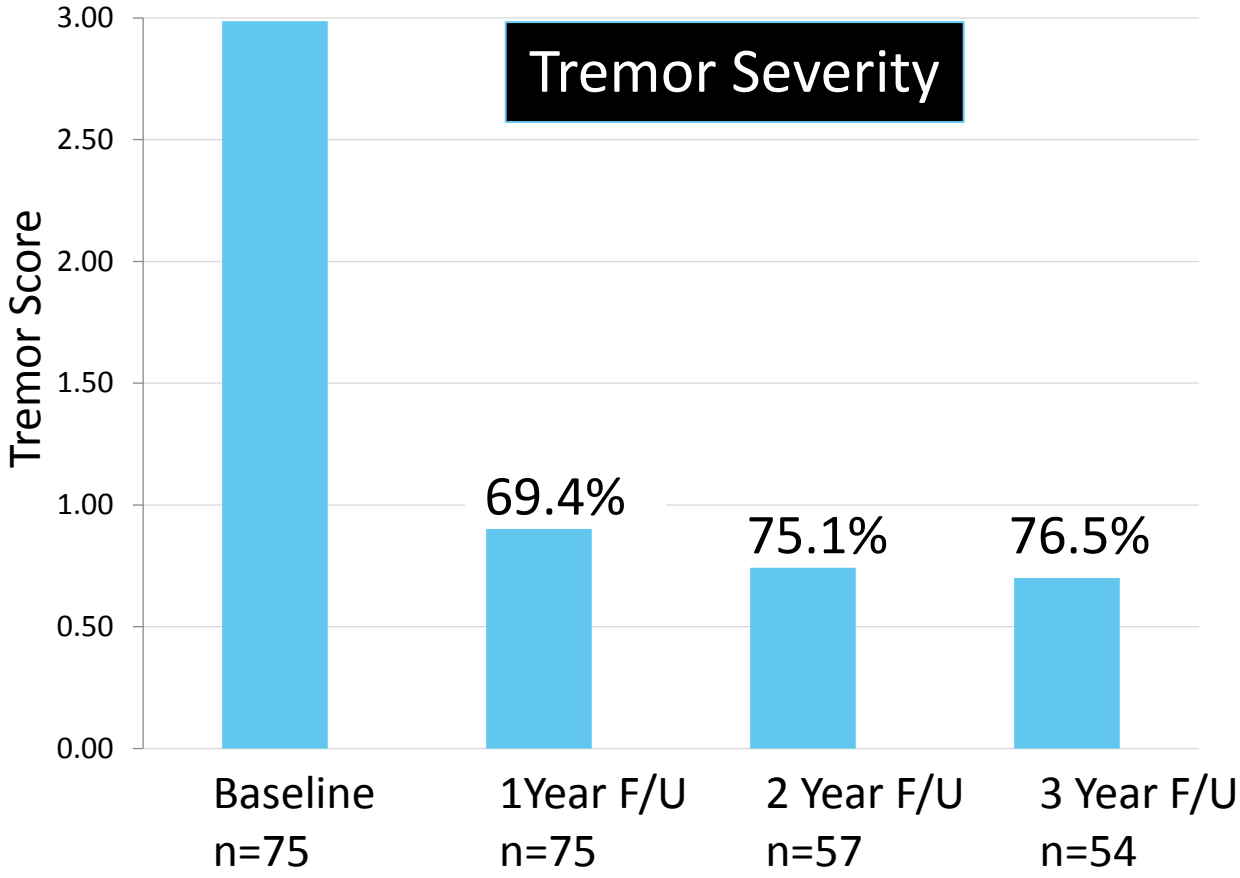
Clinical Evidence: 3 Year Follow Up Pivotal Study of Focused Ultrasound for Essential Tremor [1]

Population
Of these 75 subjects, a total of 57 subjects are included in the 2-year and 54 in the 3-year analysis of the long-term study results.

Safety
Persistent adverse events (AEs) at 3 years were mild or moderate and included gait disturbance (2%), imbalance (4%), musculoskeletal weakness (2%), unsteadiness (4%) and numbness (9%). Long-term safety profile confirms that 74% of AEs were mild and the rest were moderate. Of the total AEs, 48% resolved within 30 days of the procedure.

Efficacy
The tremor severity score (CRST Part A) improved 75.1% and 76.5% over baseline at 2- and 3-year follow-up, respectively. for combined (Exablate Neuro and crossover) subjects.

Additionally, the improvement of 53.1% in tremor/motor function (CRST Part A + B) was sustained from 1 to 3 years.
The functional disability improvement of 56.9% improvement was maintained at Year 3. While there was some dimunition in quality of life at Year 3, the improvement was remained at 38.9 at Year 3.



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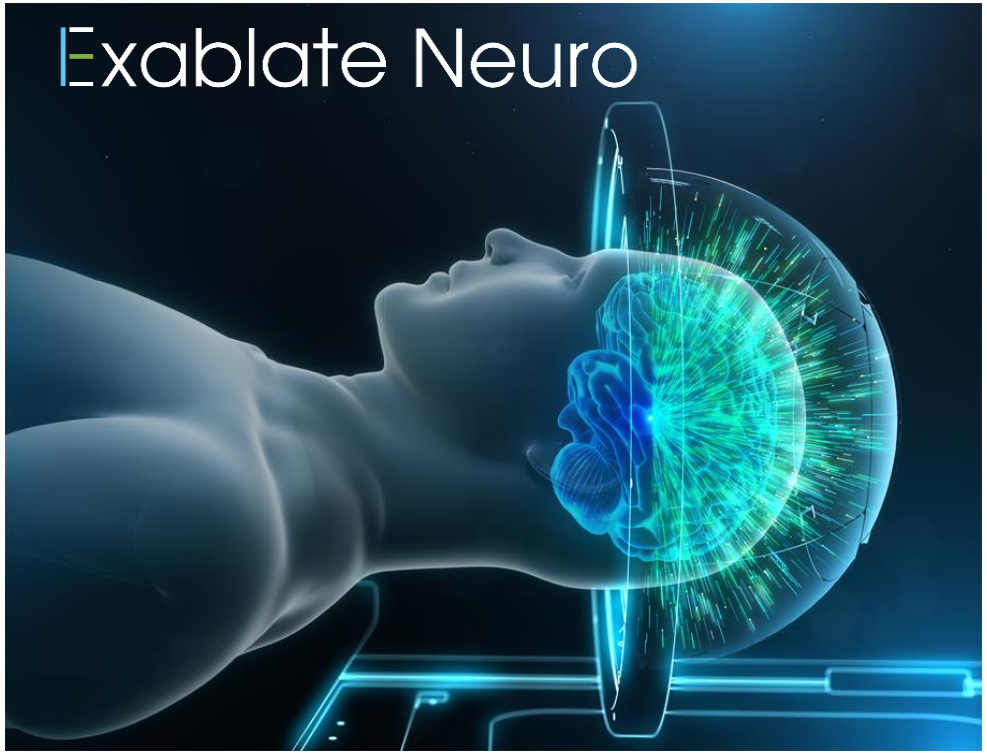
Tremor-dominant Parkinson’s disease (PD) and Focused Ultrasound

- Parkinson's disease is a chronic, degenerative disorder with key symptoms including tremor, rigidity, slow movement (bradykinesia) and postural instability.
- In an estimated 20%[1] of PD patients, the primary symptom is tremor.
- For many of these patients, tremor has a severe impact on their daily activities.
- Focused ultrasound (FUS) treatment may be an option to treat this main disabling symptom and restore quality of life.
- Thalamotomy does not close the door on future surgical options.



[1]Grosset, D. (2009). Clinical diagnosis of parkinsonism and tremor. In M. Okun, K. Grosset, H. Fernandez, D. Grosset (Eds.), *Parkinson's Disease: Clinican's Desk Reference* (pp. 33). Boca Raton, Florida: CRC Press.

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TDPD FDA Labeling & Pilot Study

FDA Labeling:

- The Exablate Neuro is intended in the unilateral thalamotomy (ventralis intermedius) treatment of Tremor-dominant Parkinson's disease with medication-refractory tremor.
- Patients must be at least 30 years of age.

Pilot Study:

- Randomized, double-blinded sham pilot study to assess the safety and efficacy of unilateral focused ultrasound thalamotomy for subjects with idiopathic tremor-dominant PD with medication-refractory tremor
- 27 subjects were randomized (2:1) to FUS (n=20) or sham (n=7) at 2 centers from October, 2012, to January, 2015

TDPD Safety & Efficacy results

Safety results:

- Very favorable safety profile
  - 95% of AEs reported were mild or moderate. Most transient.
- Most common treatment-related AEs:
  - Numbness/tingling (7%), imbalance (4%), gait disturbance (2%) and unsteady (1%).
- Two serious adverse events (SAEs) reported:
  - Ataxia/hemiparesis which resolved in 30 days and one severe hemiparesis.

NOTE: Improvements in targeting, MR thermal monitoring, and cavitation detection have been implemented since the study was conducted.

Efficacy results:

- Improvement in tremor-motor sub-scores (CRST Part A & B) over baseline was significant and maintained to 12-month follow-up
  - 51.6% for treatment group compared to 12.7% for sham
- Posture score (CRST Part A) improved markedly over baseline and compared to the sham group
- Improvements were observed in functional disabilities (CRST Part C) and Quality of Life (QUEST).

Information for Prescribers, 2018.

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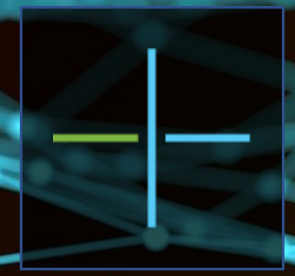
Thank you!



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Contacts:
www.insightec.com
giuliaf@insightec.com