

From Dependent to Independent

Treatment Options for Essential Tremor
and Parkinson's Disease with MR-Guided
Focused Ultrasound

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Houston Methodist Neurological Institute



Key Milestones in FUS Development



20+ Years of Milestones with MR-Guided Focused Ultrasound

Key Milestones in FUS Development

Essential tremor
UNILATERAL



2016

Parkinson's disease
UNILATERAL
Tremor



2018

Parkinson's disease
UNILATERAL
Motor complications



2021

Essential tremor
STAGED BILATERAL*



2022

Parkinson's disease
STAGED BILATERAL*
Motor complications



2025

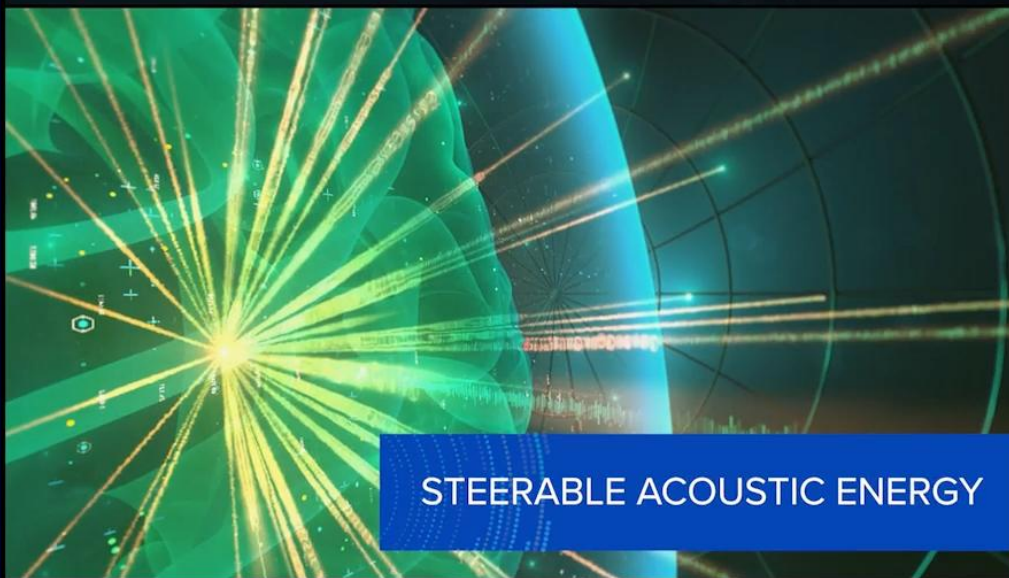
20+ Years of Milestones with MR-Guided Focused Ultrasound



20 YEARS IN THE MAKING



CLOSED LOOP SYSTEM WITH REAL TIME
IMAGING AND THERMOMETRY



STEERABLE ACOUSTIC ENERGY

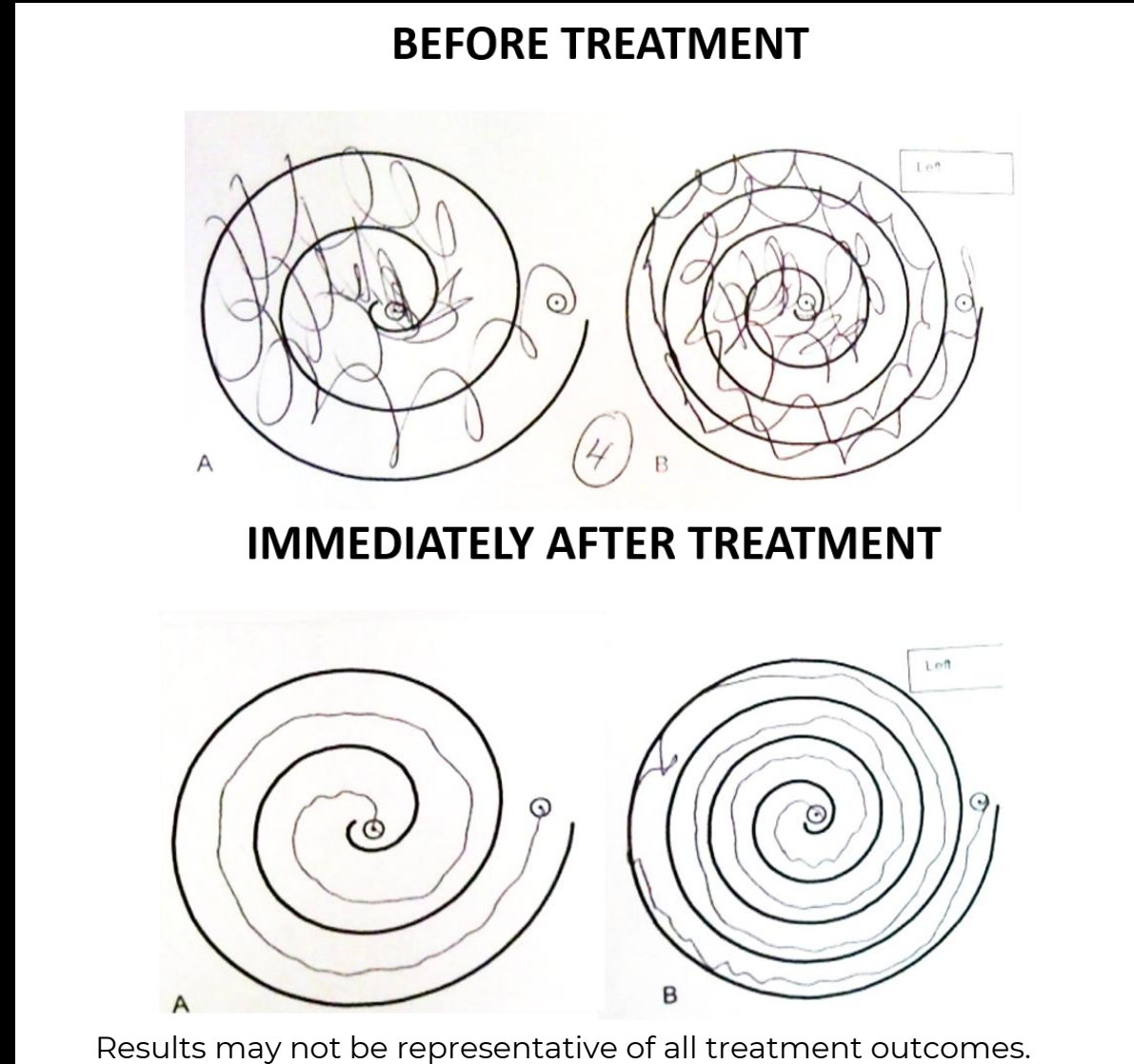


NON-IONIZING RADIATION

FUS Treatment of Essential Tremor

The therapeutic power of focused ultrasound

- Sound waves are directed from a helmet-shaped device with no incisions
- Where the sound waves meet, a lesion about the size of a pea is made to disrupt the abnormal circuits
- The target is the VIM of the thalamus, same as used for deep brain stimulation (DBS) and surgical thalamotomy
- Many patients experience immediate tremor improvement with minimal complications



Who is Suitable for FUS Treatment?

- Confirmed diagnosis of medication-refractory essential tremor or tremor-dominant PD
- 22 years or older for ET, 30 years or older for tremor-dominant PD
- Can tolerate the procedure with minimal medications and without sedation
- Able to communicate sensations during the procedure
- Can fit in the MRI scanner and activate the “Stop Sonication” button
- Contraindications:
 - Standard contraindications for MRI including non-MRI compatible implants
 - Patients with skull density ratio of 0.45 ($\pm$ 0.05) or less as calculated from a screening CT



PROCEDURES

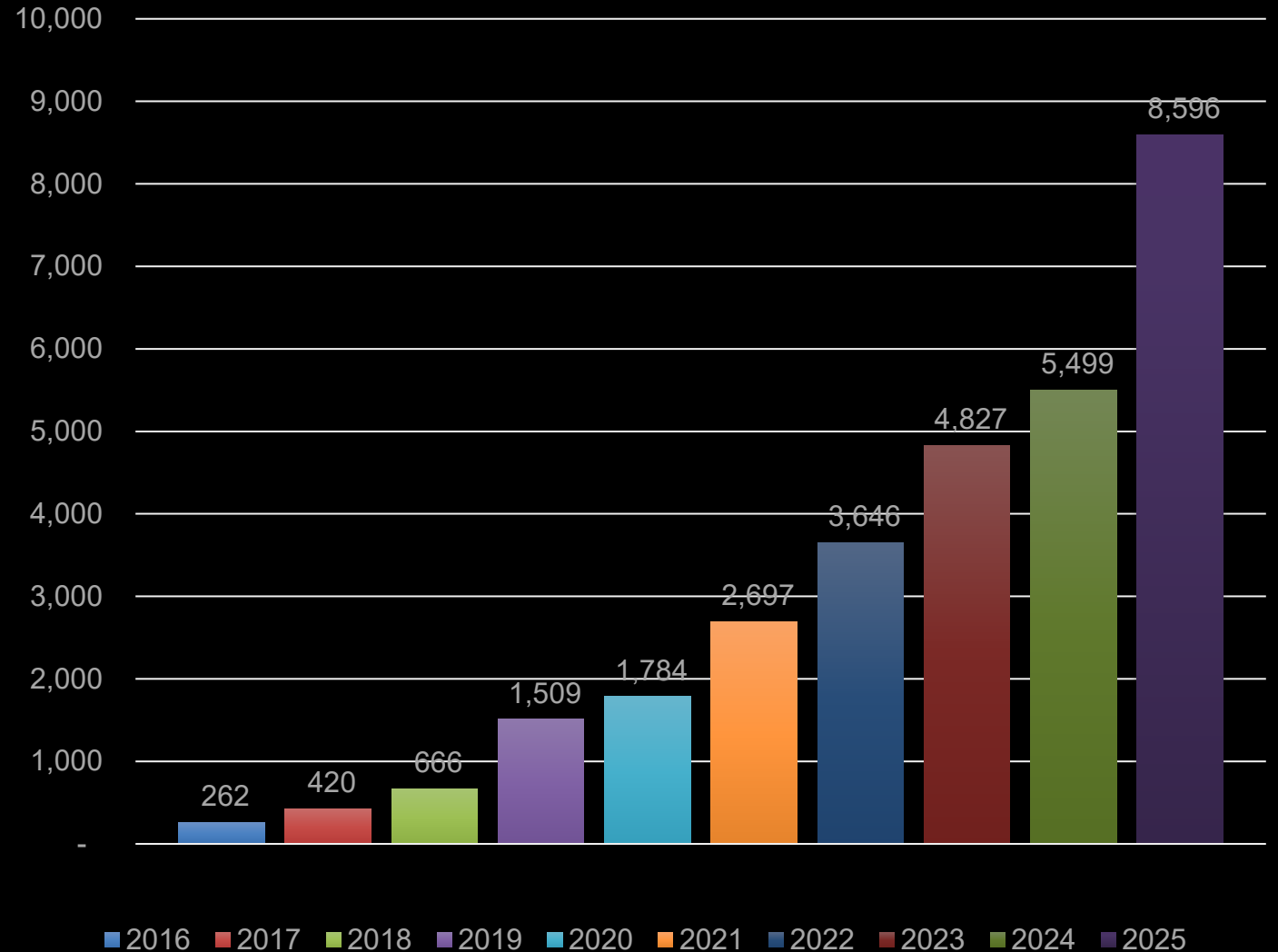
30,000+

Essential Tremor and
Tremor-dominant PD
patients treated (including
research)

- In 2021, FUS surpassed DBS as the most common interventional procedure for ET
- Patients are asking! In 2022 alone, there were >66,000 inquiries from Insightec digital campaigns.

EXABLATE NEURO

Total Number of Global FUS Thalamotomies



Multi-Year Data and Professional Society Support



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D., Ryder Gwinn, M.D., Jennifer Witt, M.D., Susie Ro, M.D., Howard M. Eisenberg, M.D., Ph.D., Paul S. Fishman, M.D., Ph.D., Dheeraj Gandhi, M.D., M.B., B.S., Casey H. Halpern, M.D., Rosalind Chuang, M.D., Kim Butts Pauly, Ph.D., Travis S. Tierney, M.D., Ph.D., Michael T. Hayes, M.D., G. Rees Cosgrove, M.D., Toshio Yamaguchi, M.D., Ph.D., Keiichi Abe, M.D., Takaomi Taira, M.D., Ph.D., and Jin W. Chang, M.D., Ph.D.

Annals of
NEUROLOGY

A Prospective Trial of Magnetic Resonance–Guided Focused Ultrasound Thalamotomy for Essential Tremor: Results at the 2-Year Follow-up

Jin Woo Chang, MD, PhD,^{1*} Chang Kyu Park, MD,^{1*} Nir Lipsman, MD, PhD,² Michael L. Schwartz, MD,² Pejman Ghanouni, MD, PhD,³ Jaimie M. Henderson, MD,⁴ Ryder Gwinn, MD,⁵ Jennifer Witt, MD,⁶ Travis S. Tierney, MD, PhD,⁷ G. Rees Cosgrove, MD,⁸ Binit B. Shah, MD,⁹ Keiichi Abe, MD,¹⁰ Takaomi Taira, MD, PhD,¹⁰ Andres M. Lozano, MD,¹¹ Howard M. Eisenberg, MD,¹² Paul S. Fishman, MD, PhD,¹³ and W. Jeffrey Elias, MD¹⁴

JNS JOURNAL OF
NEUROSURGERY
OFFICIAL JOURNALS OF THE AANS SINCE 1944

Magnetic resonance imaging–guided focused ultrasound thalamotomy for essential tremor: 5-year follow-up results

G. Rees Cosgrove, MD,¹ Nir Lipsman, MD, PhD,² Andres M. Lozano, MD, PhD,³ Jin Woo Chang, MD, PhD,⁴ Casey Halpern, MD,⁵ Pejman Ghanouni, MD, PhD,⁶ Howard Eisenberg, MD,⁷ Paul Fishman, MD, PhD,⁸ Takaomi Taira, MD, PhD,⁹ Michael L. Schwartz, MD, MSc,² Nathan McDannold, PhD,¹⁰ Michael Hayes, MD,¹¹ Susie Ro, MD,¹² Binit Shah, MD,¹³ Ryder Gwinn, MD,¹⁴ Veronica E. Santini, MD, MA,¹⁵ Kullervo Hynynen, PhD,¹⁶ and W. Jeff Elias, MD¹⁷

Neurology®

Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor

Casey H. Halpern, MD, Veronica Santini, MD, Nir Lipsman, MD, PhD, Andres M. Lozano, MD, PhD, Michael L. Schwartz, MD, Binit B. Shah, MD, W. Jeff Elias, MD, Garth R. Cosgrove, MD, Michael T. Hayes, MD, Nathan McDannold, PhD, Christina Aldrich, RN, MSN, Howard M. Eisenberg, MD, Dheeraj Gandhi, MD, Takaomi Taira, MD, PhD, Ryder Gwinn, MD, Susie Ro, MD, Jennifer Witt, MD, Na Young Jung, MD, Jin Woo Chang, MD, Jarrett Rosenberg, PhD, and Pejman Ghanouni, MD, PhD

Neurology® 2019;93:e1-e10. doi:10.1212/WNL.00000000000008561

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assfn American Society for Stereotactic and Functional Neurosurgery

ASSFN Position Statement on

MR-guided Focused Ultrasound for the Management of Essential Tremor

First Side – 5-Year Clinical Trial Results

73.8%

tremor improvement
at five-year follow-up

What else does the data tell us?

- No serious adverse events recorded
- No new or worsening adverse events
- Significant ADL and QoL improvement
 - 44.5% functional disability improvement remained at 5 years (CRST Part C: Activities of Daily Living / Quality of Life functional)

After treatment, the most common adverse events

(AEs) included:

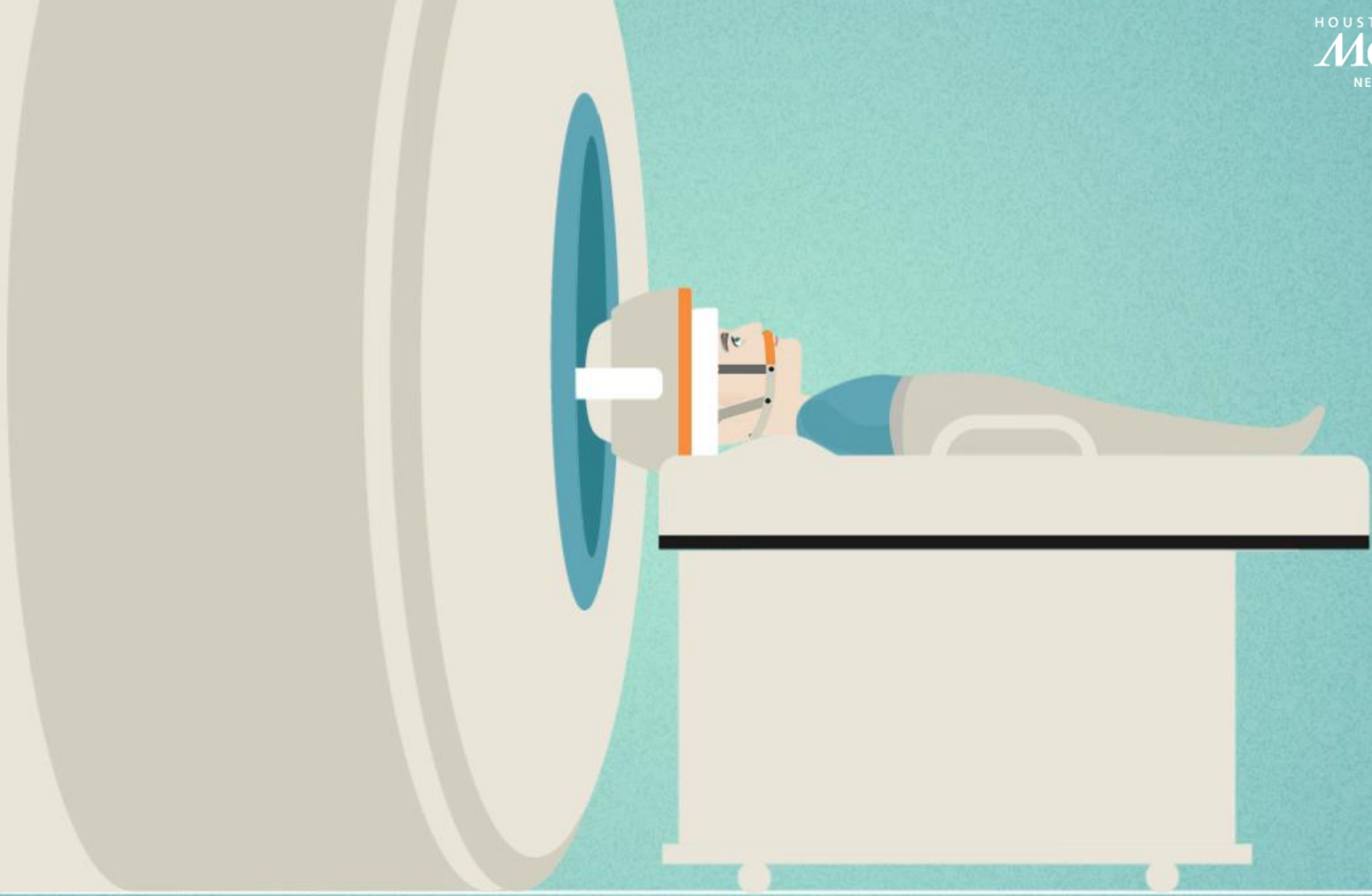
- Imbalance/gait disturbance (26% of study subjects)
- Numbness/tingling (33% of study subjects)
- Headache/head pain (51% of study subjects)

Of all AEs, 48% resolved within 30 days. Additional infrequent events include dizziness, taste disturbance, slurred speech, fatigue and vomiting

At five years, persistent AEs were reported to remain moderate or mild and NO NEW AEs were reported. The most common adverse event was:

- Paresthesias (20% of study subjects)

Additional infrequent events include unsteadiness, limb weakness, gait disturbance, dysmetria, and dysgeusia.



Day of the Procedure – What to Expect



PATIENT PREP

The patient's head is shaved so nothing interferes with the ultrasound waves. After local numbing medication is applied, a frame is secured to their head to prevent it from moving during treatment.



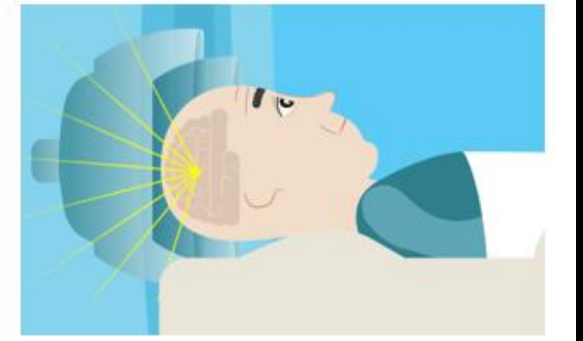
PLANNING

During the treatment, the patient is awake and lies on the MRI table which moves in and out of the MRI scanner. MRI images are taken to plan the treatment according to the patient's anatomy.



TARGET & TEST

Light doses of energy are applied to accurately pinpoint the target and assess the temporary tremor improvement and identify any potential side effects. Sub-millimeter target adjustments can be made.



TREATMENT

High energy is applied to create a small ablation and provide a therapeutic effect, improvement of the hand tremor.

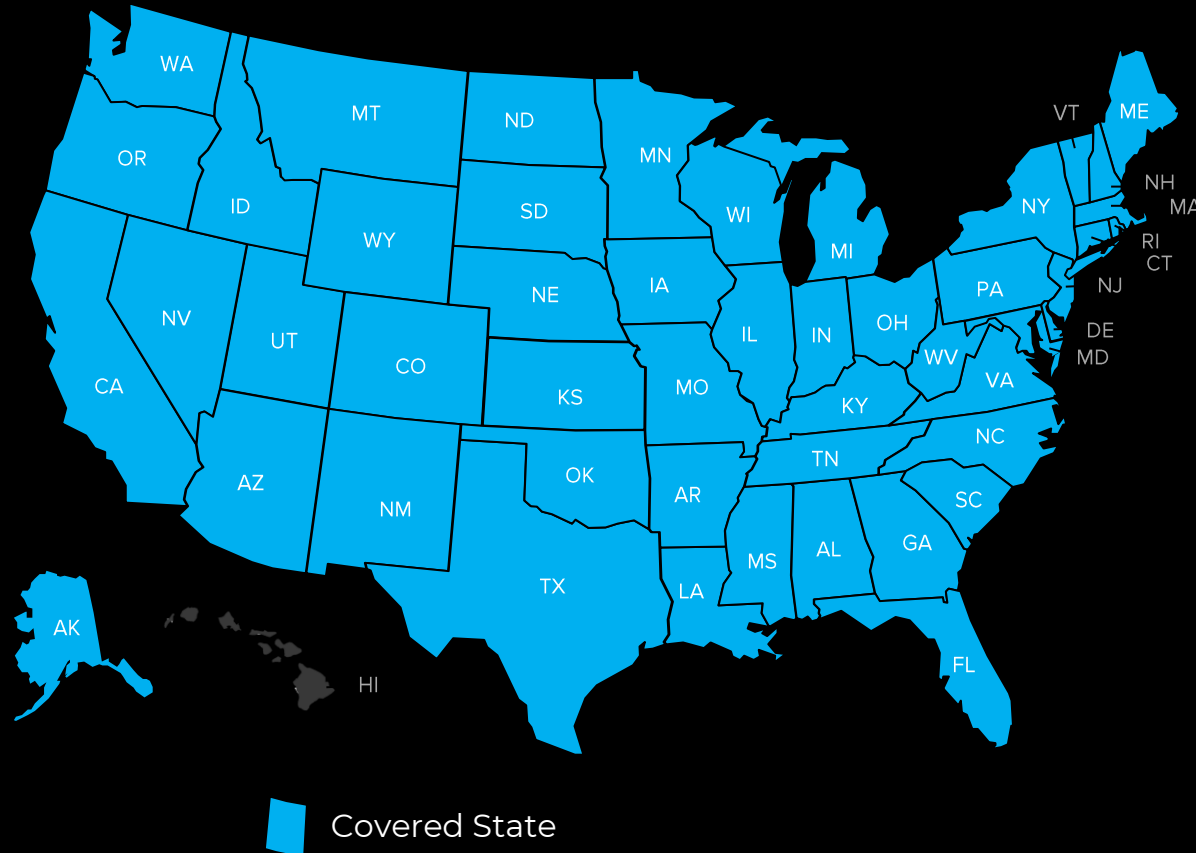
Benefits for patients.

- Immediate and durable tremor improvement
- Significant improvement in Quality of Life
- Outpatient, home the same day
- Little to no risk of infection
- No implants, probes or ionizing radiation
- No anesthesia
- Minimal complications



Before and After Focused Ultrasound Treatment





- Medicare coverage in all 50 states for essential tremor, through Local Medicare Administrative Contractor Coverage Determinations
- 43 Independent BSBS plans in 44 states cover treatment of first side essential tremor, including BCBS Federal Employee Plan (Nationally)
- Second Side coverage is determined on a case-by-case basis
- Patient should contact their health plan's Member Service department by calling the phone number listed on the back of their insurance ID card to confirm that MR-guided Focused Ultrasound for treating essential tremor (CPT code 61715, formerly 0398T) is a covered benefit in the outpatient setting based on their independent plan benefits.

Who is Suitable for Second Side Treatment?

- Essential Tremor patients with medication-refractory tremor
- Treatment of the contralateral side (that was not previously treated) must be staged by at least 9 months after the first thalamotomy
- Patients must be at least age 22
- The designated area in the brain responsible for movement disorder symptoms (Ventralis Intermedius) must be identified and accessible for targeted thermal ablation by the Exablate device

Second Side – FDA and Clinical Trial Results

80.2%

tremor improvement
at 6-month follow-up.

Tremor/ Motor Function – 64.3% improvement

- Effective improvement immediately following treatment, with results sustained through at least six months.
- Consistent with treatment of the first side.

Functional Disability – 74.3% improvement

- This significant and sustained improvement in functional disability is clinically meaningful and suggests that subjects have enhanced independence in activities of daily living.

After treatment, the most common adverse events

(AEs) included:

- Numbness / Tingling (31% of study subjects)
- Dysarthria – (29% of study subjects)
- Ataxia – (23% of subjects)

Majority of events were mild or moderate

- No device related adverse events.
- Only one related serious event occurred (urinary tract infection following use of a catheter during the procedure).
- Additional infrequent (< 2%) adverse events include weakness, decrease in synchronicity, dizziness, dry mouth, hypoesthesia, intermittent diplopia, sialorrhea, and voice change.

Prime System Overview

Experience the Future of Surgical Precision & Efficiency with Exablate Prime.

Today and for years to come.

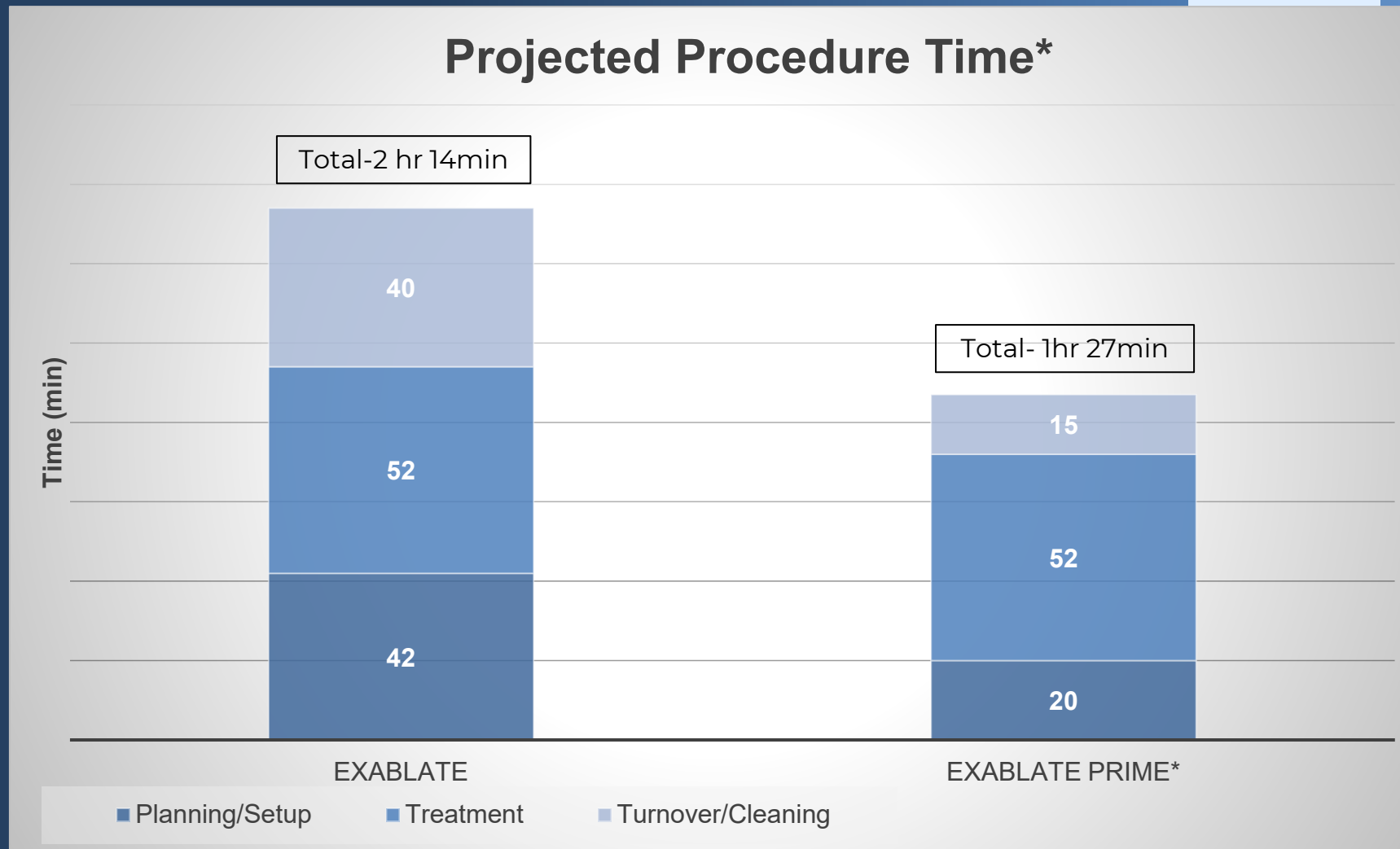


A decade of research perfected for you

- Intuitive, guided UI
- Automated software workflows
- Smart, fast algorithms
- Updated hardware
- Improved computing power and display
- Self-cleaning/time saving water system

Efficiency meets Elegance

Shorter procedure times



*projected savings times based on internal testing and data, actual case times may vary

SCREENING TO DETERMINE SKULL DENSITY RATIO (SDR)

Exablate Prime

PREPARATION SESSION LOGIN

12/18/2023 2:16 PM

SCREENING

Intended Target Location

Left VIM

Calculate

Save results

CT exam details:

Manufacturer GE MEDICAL SYSTE...

Filter BONEPLUS

Thickness 0.6mm ,Spacing 0.0mm

Size 512x512

Calculation Results:

Calculated SDR

Skull Area

Active Elements

Skull Thickness

Always use images conforming with Insightec CT acquisition guidelines. Actual parameters during treatment may vary from pre-calculated results.

QUIT

Cycle

View

Measure

Overlays

Delete

Compare

Axial

A

R

P

100mm [50mm]

Air Threshold -5500

Bone Threshold 500

Sagittal

S

A

P

100mm [50mm]

Coronal

S

R

I

100mm [50mm]

CT 142/283 536.1

CT 206/411 R0.3

CT 206/411 A4.1

5:17 PM, 1/1/1900

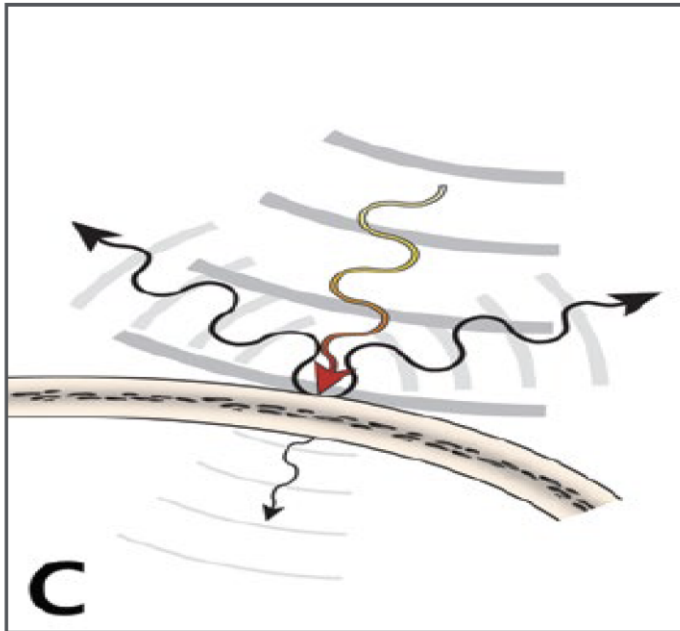
5:17 PM, 1/1/1900

5:17 PM, 1/1/1900

Lower skull density ratio:

More reflections

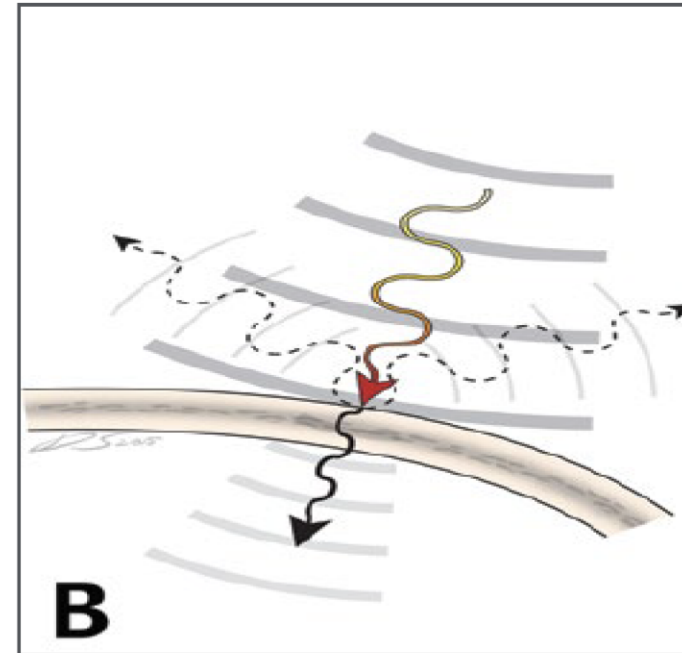
Lower energy transmission across skull



Higher skull density ratio:

Less Reflections

Higher energy transmission across skull



PLANNING WITH ACCURATE AUTOMATIC CO-REGISTRATION

INSIGHTEC

PLAN

CALIBRATION

SCAN

NPR REVIEW

REGISTRATION

AC-PC PLANE

TARGETING

Always enabled

THERAPY

END TREATMENT

Skull Overlay

Auto Register

Clear Images

Reference set: YES

Approve set

Ensure information in all orientations is sufficient and consistent prior to approval

Load Pre-Treatment Plan

Cycle

View

Measure

Overlays

Delete

Fusion

Linked

Show/Hide

Color

Clear Images

R7.2 P38.4 S54.9

Intra-Op 62/122 R7.2

Pre-Tx CT

T2 FSE 2D 2NEX

10:15 AM, 12/8/2021

100mm

INTRA-OPERATIVE

Exam 277

Tx Sag

SAG (122)

CT

Exam 22026

Pre-Tx CT Ax

AX (250)

Intra-Op 66/130 S11.9

Pre-Tx CT

T2 FSE 2D 2NEX

10:15 AM, 12/8/2021

100mm

Pre-Tx CT

T2 FSE 2D 2NEX

10:15 AM, 12/8/2021

100mm

MRI Not using

Not connected

Not connected

AUTOMATED LOCALIZATION STREAMLINES TARGETING

INSIGHTTEC

PLAN

CALIBRATION

SCAN

NPR REVIEW

REGISTRATION

AC-PC PLANE

TARGETING

Always enabled

THERAPY

END TREATMENT

AC

Mark AC

PC

Mark PC

AC-PC Overlay

Recalculate

Go to AC-PC

Clear Images

AC-PC length: 27.6mm

Approve AC-PC

Review and adjust AC PC and Midline as needed prior to approval

Cycle

View

Measure

Overlays

Delete

Compare

R5.3 A31.8 S5.0

AC-PC: -0.7 30.6 -0.0

AC

PC

30mm

+

INTRA-OPERATIVE

Exam 277

Tx Sag

SAG (122)

CT

Exam 22026

Pre-Tx CT Ax

AX (250)

30mm

Spot distance from transducer focus is above threshold.

TARGET VISUALIZATION DURING TREATMENT

PLAN

CALIBRATION

SCAN

NPR REVIEW

REGISTRATION

AC-PC PLANE

TARGETING

THERAPY

END TREATMENT

Target Coordinates: AC-PC | RAS

L13.2 A7.6 S0.0

Left Anterior Superior

Grid Overlay

Place Target

Valid Spot: NO

Stop Sonication Button: OK

Distance to Focal Point: OK

[R1.4] [A0.1] [I1.7]

Right Anterior Inferior

Update Transducer Location

Finalize Target

Refreshing

Show Patient Info

Cycle View Measure Overlays Delete Compare

Axial (AC-PC) RAS

Source: R128.8 P81.8 I18.5

AC-PC: R123.8 P84.8 I0.0

14.0mm 8.9mm

100mm [50mm]

T2 FSE 2D 2NEX LAI

10:15, 08/12/2021

Intra-Op 107/198 S1.6

Coronal (AC-PC) RPS

Intra-Op 100/199 A12.4

T2 FSE 2D 2NEX LAI

10:15, 08/12/2021

Sagittal (AC-PC) RPS

Intra-Op 64/126 R7.3

T2 FSE 2D 2NEX LAI

10:15, 08/12/2021

INTRA-OPERATIVE Exam 277

T2 FSE 2D 2NEX SAG (122)

PRE-OPERATIVE Exam 88911

FGATIR 180slice AX (180)

Exam 7650438

SAG T2 SPACE... SAG (208)

CT Exam 22026

BONE PLUS AX (250)

MRI Not using

Not connected

Not connected

Invalid spot/target side location.

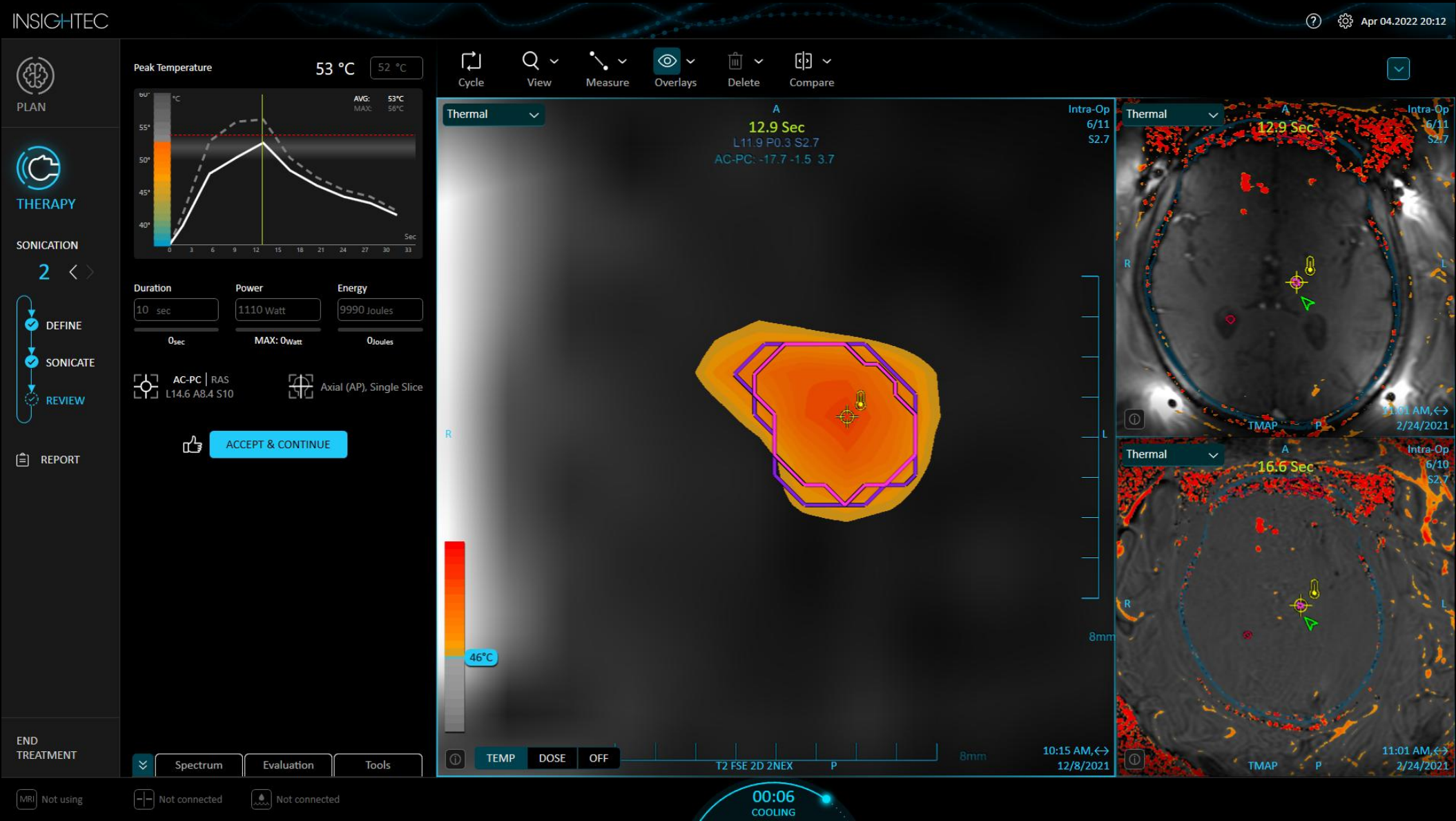
TARGET VISUALIZATION DURING TREATMENT



PRECISE TARGET HEATING DURING TREATMENT



PRECISE TARGET HEATING DURING TREATMENT



VERIFICATION OF TARGET HEATING DURING TREATMENT

Exablate Prime

07-Dec-23 00:29

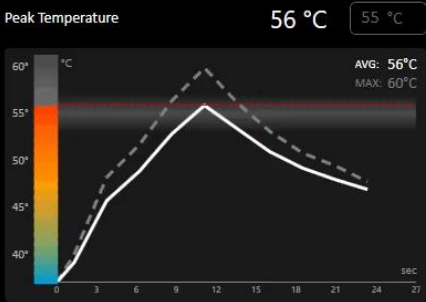


REPLAY

SONICATION

10/11< >

REPORT



Duration 11 sec 11sec
Power 850 Watt MAX:808Watt
Energy 8500 Joules 8531Joules

AC-PC | RAS
R14.0 A6.1 S1.0
Axial (RL), Single Slice

Cycle View Measure Overlays Delete Compare

Axial (AC-PC) RAS
Legend Source: R3.9 A98.2 I24.3
AC-PC: R5.4 A16.8 S1.4



REPLAY MODE



QUIT

MRI Not using Not connected Not connected

inDiscover(GE,3T), DV26.0, SW 9.0.536, CPC 8.0

Exblate Prime 3T Head Coil Kit



Example planning image courtesy of Rambam Hospital Haifa, Israel and Insightec

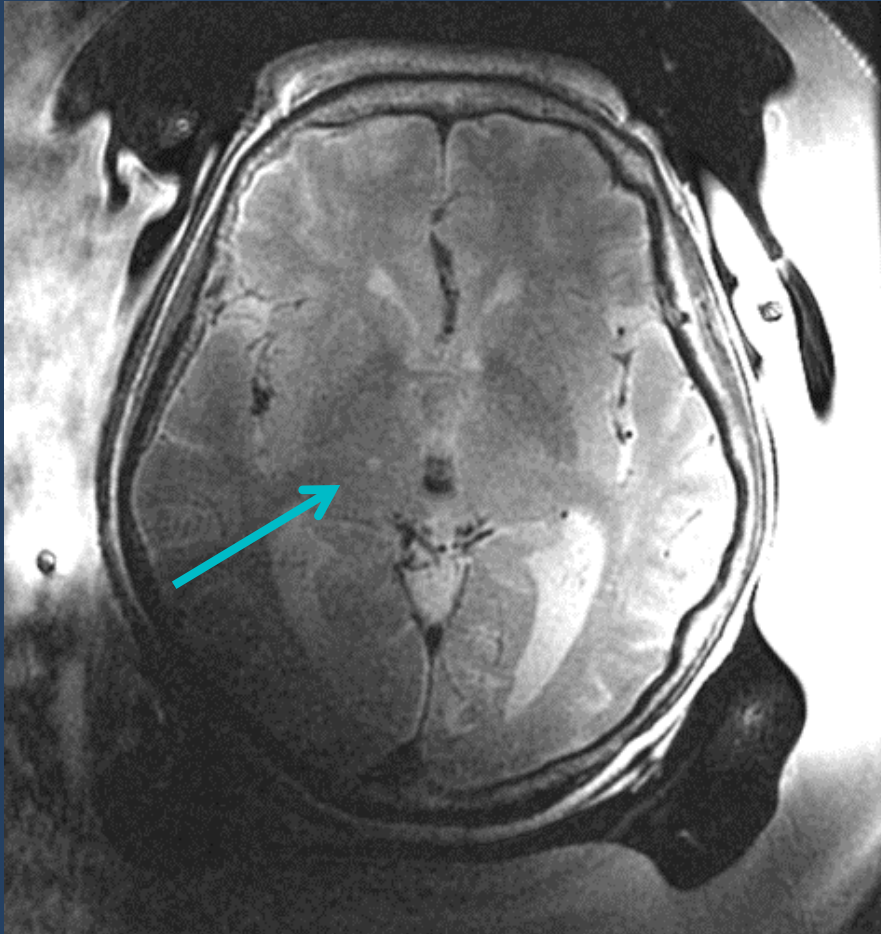
Maximize Prime with our latest imaging innovation*

See more clearly

- Integrated head coil & optimized imaging sequences
- Improved SNR
- Enables volumetric scan acquisition
- 2X faster/3X better quality
- Better anatomical visualization for planning and therapy delivery

*as compared to the 3T Membrane only, purchased separately
Claims based on Insightec data.

Exblate Prime 3T Head Coil Kit



Maximize Prime with our latest imaging innovation*

Treat more confidently

- Finer resolution of real-time data acquisition
- Multi-slice thermometry
- 3D predicted thermal volume visualization
- Refined Intra-op lesion evaluation

Example lesion image courtesy of Rambam Hospital Haifa, Israel and Insightec

*as compared to the 3T Membrane only, purchased separately
Claims based on Insightec data.