TREATMENT OF ESSENTIAL TREMOR USING CRANIAL MR GUIDED FOCUSED ULTRASOUND

Introduction:

The purpose of this Newsletter is to educate healthcare providers and laypersons about a common disabling neurologic movement disorder called Essential Tremor (AKA: Familial Tremor). After reading the following, the reader will better understand treatment options and become familiar with a new technology called InsightTec that is now available at HCA Orange Park Hospital, Orange Park, Florida. This device, the first of its kind in the Jacksonville/Northwest Florida region, provides Neurosurgeons the ability to painlessly and non-invasively reduce the severity of Essential Tremor using MRI Guided Focused Ultrasonic Energy on an outpatient basis without the need for general anesthesia or skin incisions.

NOTE: While the InsighTec system can also be utilized to treat Parkinson's Disease tremor, this indication will be discussed in a pending Newsletter as the treatment target and neuroanatomy differ from that of Essential Tremor.

Essential Tremor (ET):

The International Parkinson and Movement Disorder Society defines Essential Tremor (ET) as an isolated 4-7 Hz tremor syndrome of bilateral arms and hands during movement (kinetic tremor; intention tremor) lasting at least 3 years. Tremor may or may not involve other areas such as the head, voice, trunk, and lower limbs. Isolated tremors of the voice or head, orthostatic tremors with a frequency > 12 Hz, and task and position specific tremors are excluded from the ET category.

ET (AKA: benign tremor; familial tremor) is the most common movement disorder with a 4% prevalence in those $\geq$ 40 years of age. This disorder usually first presents with uncontrolled shaking (4-7 Hz in the arms during voluntary movement. Shaking may occur at rest in some individuals and abnormal movement may progress and extend to the head, jaw, legs, trunk, and voice resulting in unsteadiness when ambulating, titubation (head shake) and abnormal language cadence. Gait and balance may also be disturbed. In addition to the tremor symptoms described above, individuals with ET may also over time develop gait ataxia, eye motion abnormalities (impaired smooth pursuit), difficulty with cognitive activities such as executive functions and memory, olfactory deficits, and hearing loss.

While common perception is that 50% of ET cases are inherited (autosomal dominant; gene location remains elusive), some investigators believe this number may be closer to 20%. This lower percentage may be supported by the finding that only 60-63% of monozygotic twins

concordantly experience ET. This genetic subset of patients is typically affected at younger ages than those without a genetic predisposition. Non familial cases typically present between the ages of 40-50.

Signs and symptoms of ET may be worsened by stress, fever, medications, tiredness, hypoglycemia, and elevated emotions. ET should not be confused with separate disease states such as Parkinson's Disease. The latter is due to a paucity of dopamine due to degeneration of a segment of the brain called the substantia nigra. The etiology of ET remains unknown (AKA: Idiopathic) although it most likely relates to abnormalities of the cerebellum and its related projections.

If ET is severe enough it may hamper activities of daily living such as writing, feeding oneself, drinking, speaking clearly and ambulating. In such cases treatments may include beta blockers (propranolol), anticonvulsants (primidone), and/or sedative medications. Propranolol and primidone are reported to reduce tremor by 60% in 50% of those treated. As such, they are the first treatment of choice. In some instances, however, these pharmaceutical agents can lose their effectiveness or cause intolerable side effects such as fatigue, lightheadedness, nausea, and addiction. Botox injections which induce temporary muscle weakness may reduce symptoms but can lead to unwanted side effects including swallowing difficulties (dysphagia) and intolerable finger weakness.
(https://ninds.nih/health-information/disorders/essential-tremor).

ET diagnosis is based upon patient history and examination. No single blood or imaging test or group of tests can diagnose the movement disorder. Nevertheless, before an individual can be said to suffer from ET, their health care provider will usually rule out the existence of:

Hyperthyroidism
Liver and kidney disease
Multiple sclerosis
Anxiety
Brain tumor
Parkinson's Disease
Medication side effects
Drugs, Toxins, and Medications that can worsen mild tremors.
- Antihistamines
- Amiodarone
- Amphetamines
- Atorvastatin
- Caffeine
- Tegretol
- Corticosteroids
- Cyclosporine A
- Epinephrine
- Pseudoephedrine

- Fluoxetine
- Haloperidol
- Hypoglycemic medications
- Lead
- Lithium
- Metoclopramide
- Methylphenidate
- Nifedipine
- Nicotine
- Terbutaline
- Theophylline
- Thyroid hormone replacements
- Tricyclic antidepressants
- Valproic acid
- Verapamil

Illicit drug use
B12 deficiency
Excessive alcohol use
Alcohol and other drug withdrawal

Differentiating between Essential Tremor (ET) and Parkinson's Disease (PD):

Although ET and PD both involve shaking of the upper and lower extremities, there are key differences between the two diseases (medicacodingbuff.com)

PARKINSON'S DISEASE	**ESSENTIAL TREMOR**
Tremors worse at rest	Tremors worse during movement
Tremors are higher amplitude and lower in frequency	Tremors are lower in amplitude and higher in frequency
Family history <10%	Family history ≥ 20-50%
Tremors often start unilaterally and may remain asymmetrical	Tremors are usually bilateral from the beginning
Tremors improve with levodopa therapy	Tremors do not response to levodopa
Tremors do not improve with alcohol	Tremors improve with alcohol
Other symptoms include rigidity, slowed movements, difficulty with walking and balance	Tremors are the primary symptom
Usually develops after age 60	May occur at any age but may be bimodal
Handwriting gets smaller (micrografia)	Handwriting gets larger

Neuroanatomic and Neurofunctional Mechanism of Essential Tremor:

The underlying pathology responsible for ET remains unknown. Some investigators believe the disease is neurodegenerative in nature since 75% of ET patient brains have been shown to harbor cerebellar degenerative changes that include a 40% reduction in Purkinje cells and a 6x increase in Purkinje cell axonal swelling (a sign of cell injury). Lewy body increase (a marker for brain dysfunction) in the locus ceruleus (LC) has also been identified. While the LC is primarily responsible for providing noradrenaline to the forebrain, thus influencing arousal, this small pontine reticular activating system structure also has projections to other parts of the brain that control cognition, emotion, motivation, and memory. LC projections to the cerebellum are thought to be important for development and maintenance of Purkinje cells. Hence, damage to the LC, as evidenced by the presence of Lewy bodies in the LC, may contribute to the loss of Purkinje cells in the cerebellum of those suffering from ET while also contributing to the cognitive changes seen in the patients as well (Louis ED. Essential tremors. A family of neurodegenerative disorders. Arch Neurol 2009; 66(10):1202-1208).

Relevant Anatomy:

Figure 1: Right and left thalami (orange structure) in the brain.

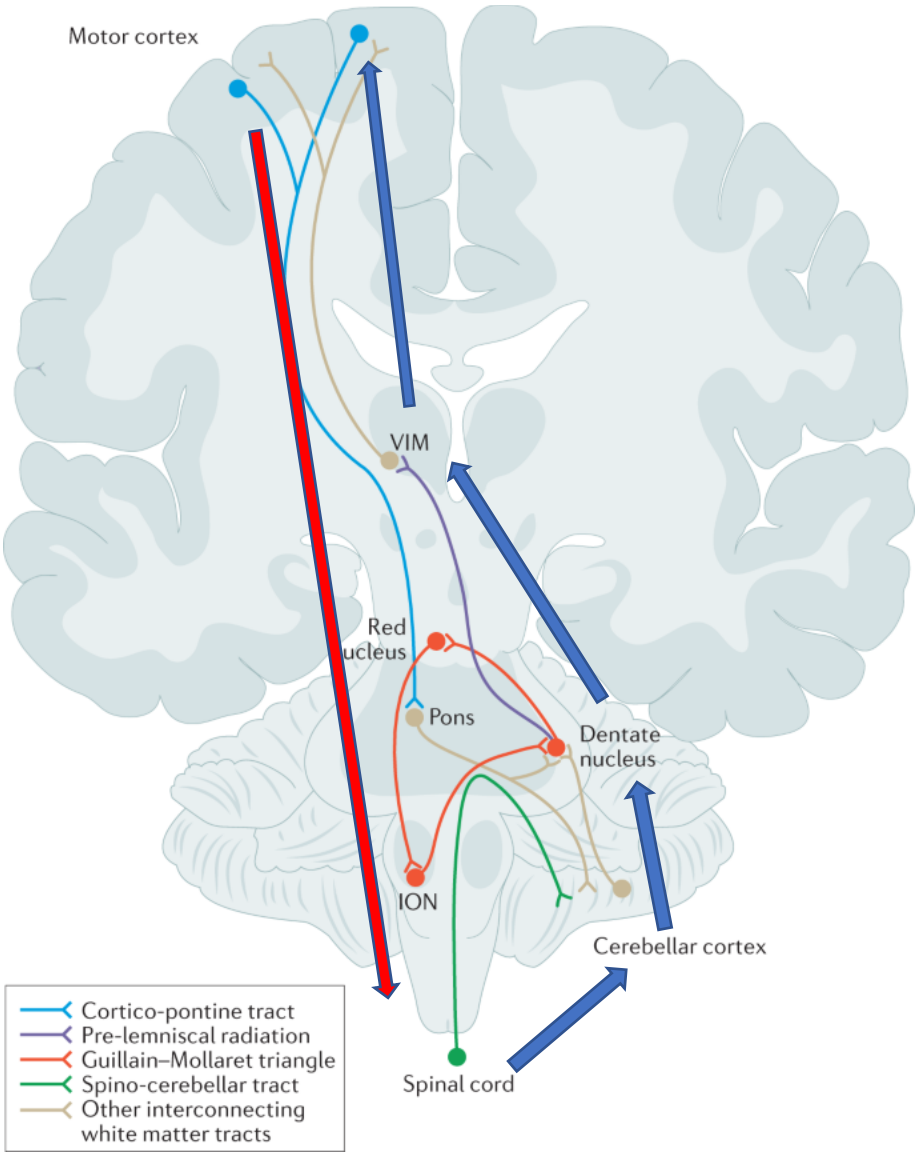

Figure 2: This simplified figure shows the key connections (blue arrows) and directional flow of information between the spinal cord, cerebellar cortex Purkinje cells, Dentate nucleus of the cerebellum, VIM of the thalamus, and motor cortex (blue arrows). The red arrow shows information being sent from the motor cortex to the muscles of the limbs and head. Treatments discussed below involve influencing the activity within the VIM of the thalamus.

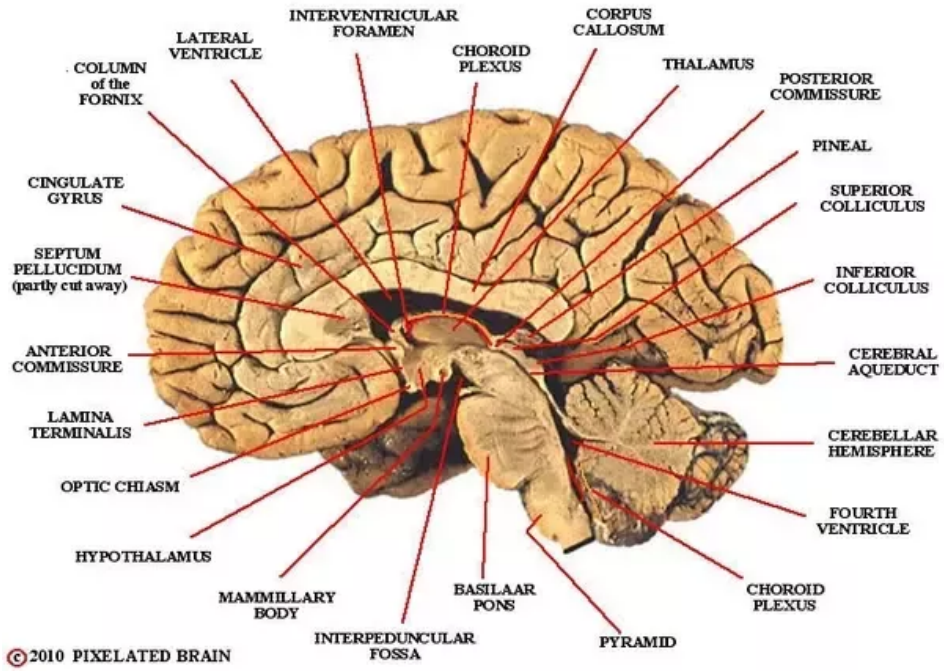

Figure 3: Location of right thalamus in right half of the brain

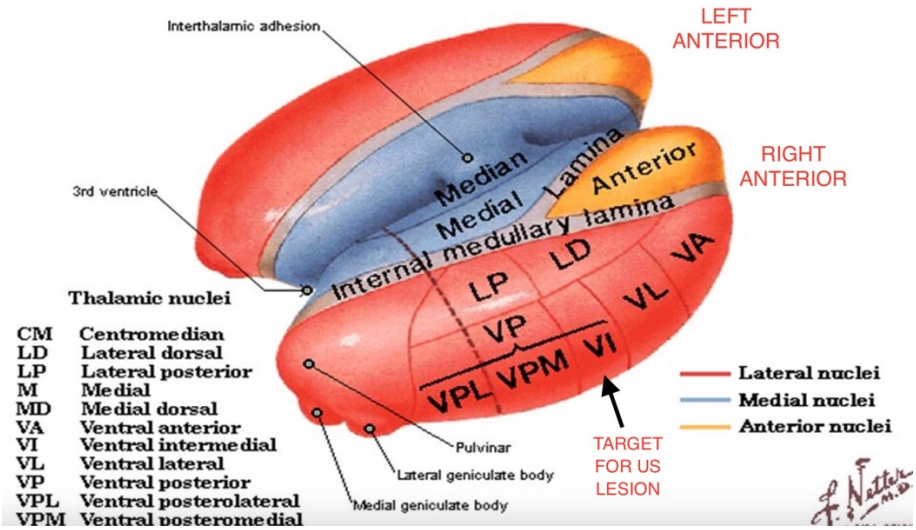

Figure 4: Segments of the left and right thalamus

Cerebellum

The cerebellum is the portion of the brain primarily responsible for coordinating, modifying and fine-tuning motor functions. This structure receives sensory information from the extremities, inner ear vestibular structures, cortex, and brainstem. The cerebellum interprets the incoming information and in turn sends signals to the brain's motor cortex. These signals allow the motor cortex to generate signals to the limbs and other motor structures that are coordinated with respect to amplitude, time, and direction. Coordinated motor movements permit the body to perform complex tasks efficiently, accurately, and quickly within the four recognizable space-time dimensions.

Thalamus

For signals from the cerebellum to reach the motor cortex, they must first travel through a relay station located in the center of the brain. The brain's right and left hemispheres each contain an egg-shaped structure called the thalamus. This structure functions as the relay station. Sensory signals (hearing, taste, sight, touch) and cerebellar instructions travel to the thalamus from sensory organs and from cerebellar neurons/nuclei. Once arriving at the thalamus transmissions are sent to appropriate cortical regions that interpret these signals. In simplified terms, the right and left thalami are similar to a central train station. Impulses (train cars) travel along neuronal axons (train tracks) to the thalamus (train station). Once the impulses (train cars) reach the thalamus (station) they are placed onto other axons (train tracks) and are sent to their destination (other regions of the brain). Once the impulses (trains) reach their destination they discharge chemical signals (train passengers) that provide information to the parts of the brain that are responsible for interpreting information and creating responses to the information.

Treatment:

Deep Brain Stimulation

Non-medical treatment for ET has included surgical deep brain stimulation (DBS) of the Ventralis Intermediate Nucleus (VIM). This collection of neurons (a subnucleus) is located within the Ventrolateral thalamus that has connections from the cerebellum and to the brain's motor cortex.

DBS is an invasive surgical procedure that involves advancing electrodes through the skull such that the electrode tip sits within the VIM. The electrode is connected to wires that in turn connect to a battery/pulse generator which sends electrical stimulation to the VIM. By adjusting the amplitude and frequency of the electrical stimulation, physicians can modify activity within the VIN which in turn helps to reduce tremor severity. The electrode, wires and battery are all located beneath the skin thus allowing patients to be freely mobile and relatively free of activity restrictions.

According to the American Association of Neurological Surgeons (www.aans.org) and a 2018 publication by Fishman, et al (Fishman PS, et al. Neurological adverse events profile of magnetic imaging guided focused ultrasound thalamotomy for essential tremor. Movement Disorders 2018; DOI: 10.10.1002/mds.27401) the risks/shortcomings of DBS include:

- 0.5 – 4% risk of brain hemorrhage including stroke
- 1-5% risk of infection
- Device malfunction
- Loss of battery power over time
- Headache
- Sensation of muscle contraction during stimulation
- Tingling in the face and limbs
- Speech or vision problems
- Loss of balance

Deep Brain Radiofrequency Induced Lesioning and Gamma Knife Radiosurgery

While these two modalities have been utilized in the past to damage thalamic nuclei and axonal pathways in the hope of reducing ET, they have fallen out of favor. Unlike DBS and Focused Ultrasound Thalamotomy, Radiofrequency and Radiosurgery create a permanent target injury that cannot be as easily controlled, reversed and/or tested prior to it being permanent. When Radiosurgery is used, the procedural effects and complications are not immediate, but rather are delayed in onset since it takes time for the radiation energy to have its final influence on the targeted tissue.

Cranial MR- guided Focused Ultrasound Thalamotomy (MRgFUT)

MRI- guided Focused Ultrasound Thalamotomy (MRgFUT) uses MRI localization of the VIM in conjunction with simultaneous computer guided delivery of ultrasonic energy to the VIM to create a thermal lesion within the VIM. Precise delivery of US thermal energy to the VIM allows the neurosurgeon and radiologist to avoid damaging adjacent structures which include the corticospinal tracts, dentato-rubro-thalamic tracts and the media lemniscus. These fiber pathways conduct motor, cerebellar, and sensory (body position, vibration, fine touch, 2-point discrimination) information to and from the spinal cord and brain cortex, respectively.

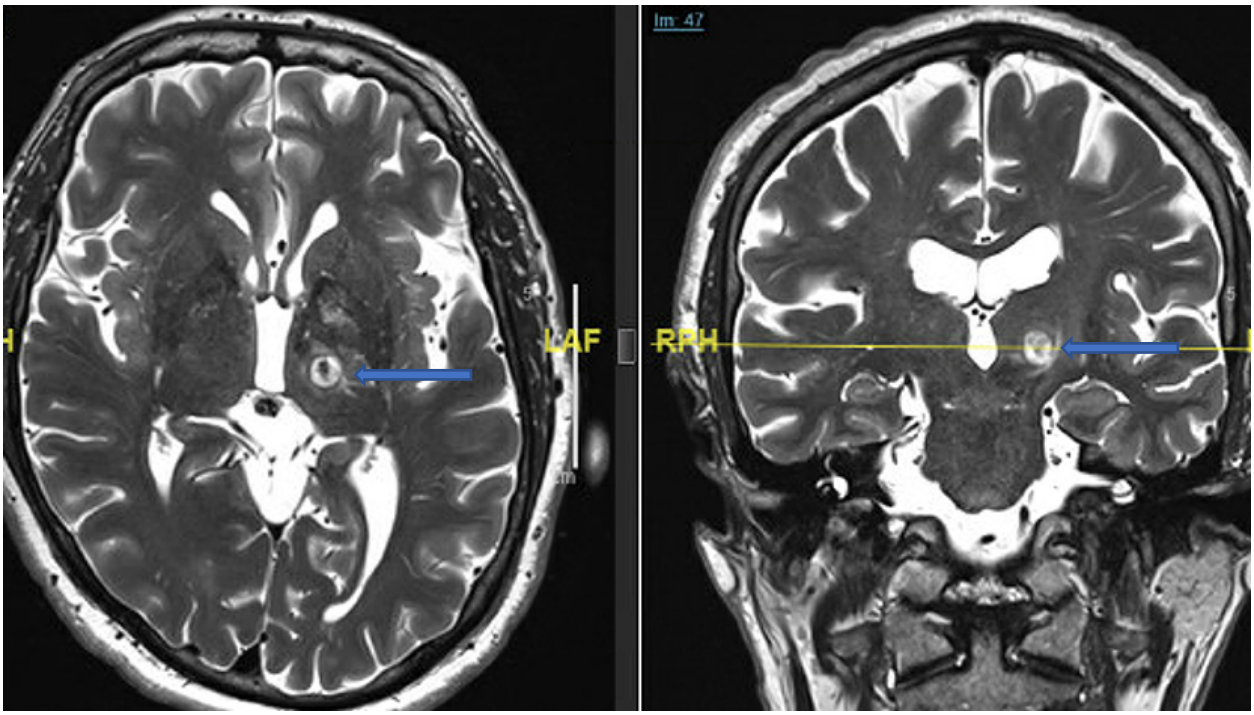

Figure 5: MRI images of the brain following Focused US Thalamotomy for treatment of ET shows the lesion (blue arrow) involving the left VIM. Left sided thalamic lesions are used to treat right sided tremor while right sided lesions are used to treat left sided tremors (Lak AM, et al. MRI Guided Focused Ultrasound Thalamotomy. A Single Center Experience with 160 Procedures. Front. Neurol. Volume 13. February 18, 2022).

MRgFUT is painless and can be performed in the MRI scanner with the patient awake. Results are immediate with respect to reducing the severity of ET and individuals avoid overnight hospital stay as it does not require a surgical incision nor the implantation of electrodes, wires, batteries, and electrical pulse wave generators.

Results from 2016 published in the New England Journal of Medicine for a prospective, randomized, blinded, placebo-controlled study demonstrated safety and effectiveness when MRgFUT was used to treat ET in patients with moderate to severe symptoms who previously failed at least two trials of medical therapy (Elias JW, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2016;375:730-9). Significant improvements in function and quality of life persisted 12 months after the procedure. Contralateral (treated side of the body) tremor scores were reduced by an average of 47% in all 56 treated patients. Complications included sensory changes or numbness in 38% and gait disturbance in 36%. By 12 months, however, sensory changes were only reported in 14% of patients, gait disturbance was only reported in 9%, weakness was reported in 4%, and 5% reported cerebellar deficits. There were no incidences of bleeding or infection. If side effects were to develop, they appeared to peak in terms of intensity by the end of the first week followed by gradual improvement.

In 2019, Park, et al. reported follow-up in a group of 12 patients treated using MRgFUT. These investigators found that four years after treatment hand tremor score remained improved by 56%, disability score was improved by 63%, postural score was improved by 70% and the action score was improved 63%. These authors also reported no permanent adverse events (Park YS, et al. Four -year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. Mov Disord 2019; 34(5):727-734).

A separate publication in 2018 by Fishman, et al also focused on post thalamic lesioning adverse events in a larger patient cohort (Fishman PS, et al. Neurological adverse event profile of magnetic imaging guided focused ultrasound thalamotomy for essential tremor. Movement Disorders. 2018. DOI: 10.1002/MDS.27401). This study reviewed 186 patients treated at 14 different centers and found that serious adverse events (SAE) occurred in 5 patients (1.7 % of cases). Two of these SAEs were transient (resolved within 24 hours). SAE as defined by the FDA met one of the following criteria:

1. Life threatening
2. Resulted in permanent impairment of a body function or damage to an unintended body structure.
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

All other identified Adverse Events were mild (79%; minor inconvenience not affecting activities of daily living) or moderate (20%; bothersome, interfering with routine daily activities).

It should be noted that unilateral thalamic lesioning only improves the opposite (contralateral) arm and leg tremor. Some axial improvement can also be seen. Minimal improvements are seen with head, neck and voice tremors. Interestingly, a study by Hess, et al. suggested that patients treated with unilateral thalamotomy (treating the dominant hand) were just as satisfied with their post treatment quality of life as were patients treated with bilateral thalamotomies (Huss DS, et al. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. Movement Disorders 2015; 30(14): 1937-1943). A later 2021 publication by Iorio-Morin, et al, however, found that three months after completing two staged bilateral treatment of both VIM (right and left) using MRgFUT, patients reported an improved quality of life as compared to their quality of life after only a single sided lesion (Iorio-Morin C, et al. Bilateral focused ultrasound thalamotomy for essential tremor (BEST-FUS Phase 2 Trial. Movement Disorders 2021; 36(11):2653-2662). While the complication rates were low in this study, additional larger studies are necessary to determine the overall safety and effectiveness of bilateral MRgFUT for bilateral, medication resistant ET.

Summary and Conclusion:

HCA Orange Park Hospital located in Orange Park, FL is the first medical center in the Jacksonville/Northeast Florida region to install and operate the InsightTec device which will allow neurosurgeons to non-surgically, non-invasively and painlessly treat Essential Tremor, the most common form of neurologic movement disorder. This outpatient procedure is completed without the need for general anesthesia and patients are discharged home on the same day with a high likelihood of significant tremor reduction and a low risk of serious complications. It is especially useful for patients who have tried medical therapy and not tolerated medication side effects, not received any relief, or become resistant to the medication's prior benefits.

If you would like to hear more about InsightTec and schedule an appointment to learn if you or someone you treat or know can be helped by this technology please contact:

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