

State of the Field Team

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Dear Friends,

As we look back at advancements in the field of focused ultrasound in 2021, we see the beginning of a return to normalcy after the disruption of the COVID-19 pandemic. Last year, the trends and steady drumbeat of growth across the depth and breadth of scientific discovery and translation to human treatments accelerated in earnest after slower progress in 2020.

New this year, we report on the first use of focused ultrasound for noninvasive biopsies in the brain, the current status of reimbursement for focused ultrasound treatments in Italy, and a global landscape analysis of breast cancer treatment, among other topics.

The state of research and regulatory approvals is by far the most requested graphic for use in both scientific and commercial realms. We affectionately refer to it as the "rainbow chart." This year, the data underwent a major upgrade for the 2022 report, and we have added a new graphic detailing both stage of research along with the various mechanisms of action associated with each of the indications. (See page II.64.) This was a major undertaking that required several years of data gathering and database modification to produce. We are so proud to premiere this new graphic because we believe that in the coming years we will see regulatory approvals for ultrasound applications other than thermal ablation.

I encourage everyone to read this report and learn about what's new in focused ultrasound!

Until next year,

Emily White, MD *Editor in Chief*

2022 State of the Field

Thank you

A special thank you to the leadership of the Board of Directors, Council members, and generous donors who support the Foundation. We also want to thank the hundreds of scientists, clinicians, and company representatives around the globe who contribute data to this report. The vast majority of this document is based on self-reported data, and this report would not be possible without their input.

Lastly, while the scope and topics covered in this State of Field Report grow every year, our core team does not. There are four of us at the Foundation who produce the document along with the support of two consultants. Sara, Mary Rose, Mike—thank you for your incredible hard work and always showing up to our weekly meetings with a can-do attitude, ready and willing to take on the next crazy idea. You are the heart of this report and your passion and dedication to it shows.

Focused Ultrasound in Brief

Focused ultrasound is an early-stage, noninvasive therapeutic technology with the potential to improve the lives of millions of patients with a variety of serious medical disorders. It offers a disruptive, game-changing alternative or complement to surgery, radiation therapy, drug delivery, and cancer immunotherapy.

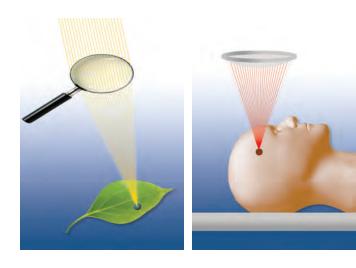
This revolutionary technology has the potential to increase the quality and longevity of life and decrease the cost of care by transforming the treatment of a range of indications.

Focused ultrasound treats tissue with multiple intersecting beams of high-frequency sound, which can be focused accurately on targets deep in the body without damaging surrounding structures, much as beams of light can be focused on a point with a magnifying glass. At the focal point where the beams converge, the ultrasound energy can act in multiple ways to induce a variety of biological effects, enabling the treatment of a wide variety of medical disorders.

Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver—thermal or mechanical—and whether the effects of treatment are permanent or transient. When focused ultrasound produces a high-power, continuous pressure wave, thermal energy accumulates rapidly at the focal point. This technique, termed thermal ablation, is currently used most frequently in the clinic, and produces permanent effects. However, additional ultrasound treatment regimens are currently under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications currently in clinical trials is a low-power, pulsed treatment that produces mild mechanical forces capable of enhancing drug delivery to the brain, by temporarily opening the blood-brain barrier. This effect is transient, and treated tissue reverts to normal function within a few hours.

The effects induced by focused ultrasound can vary greatly depending on the ultrasound application and the type of tissue being targeted. These biological effects are sometimes uniquely paired to a set of ultrasound parameters, as is the case with blood-brain barrier disruption, but others may be induced by multiple ultrasound applications. One active area of research is immunomodulation—altering the immune response in treated tissue. The altered immune response is dependent on the nature of the focused ultrasound treatment parameters, although most treatments do induce a response.

There are currently 159 clinical indications or disorders in various stages of development, and the number is increasing rapidly. Most are early stage. Worldwide, 32 indications have regulatory approval; in the US, 8 have been approved by the FDA. Focused ultrasound is not for every patient or every disorder. Much work remains to be done to determine where this technology provides significant therapeutic and cost-effective value.

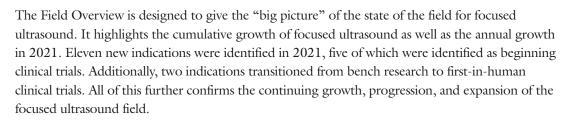


Field Overview





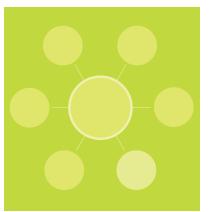
Field Overview



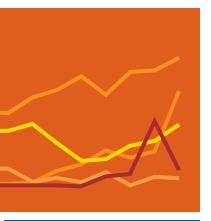
New this year are one-page summaries of the developmental stages of all the neurological and oncological indications—two of the biggest growth areas in the past few years.

As was discussed at the beginning of this report (p iii), part of the appeal of focused ultrasound as a technology platform is the depth and breadth of the way a sound wave can affect the body. We are continuing to report on the cumulative number of mechanisms of action by indication and stage of research. Soon this information will be available on our website with the added functionality of allowing you to drill down to site-specific information.

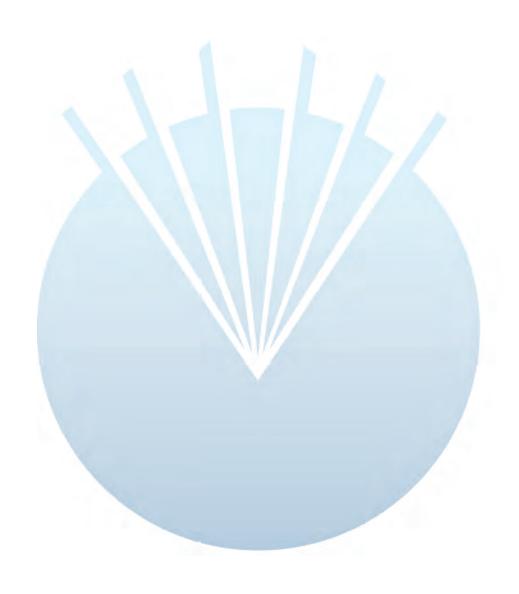
We hope the additions and changes to this year's report serve as enhancements that will further your understanding of the field as a whole.











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Development Stage Advancements and New Indications

2021

2021



New indications

	New marcations
Gastrointestinal	Nonalcoholic steatohepatitis (NASH)
Miscellaneous	Niemann-Pick diseaseSinonasal disease
Musculoskeletal	Osteopenia
Neurological	ADHDAnxietySchizophreniaBrain metastases, melanomaNeurofibromatosis
Ophthalmological	Dry eye disease
Women's health	Urinary incontinence, stress
	Development stage
	Preclinical Clinical trials

8

Indications advanced to first-in-human clinical trials

ADHD†
Anxiety† Neurofibromatosis† Schizophrenia† Stroke, intracerebral hemorrhage Stroke, thromboembolic
Urinary incontinence, stress†

† New Indication for 2021

Development stage advancements

2021 saw an addition of 11 new indications to the focused ultrasound landscape. Five of these new indications were identified for the first time at the clinical trial stage.

Eight indications advanced to first-in-human clinical trials. Details on where this research is taking place can be found in Section II of this report.

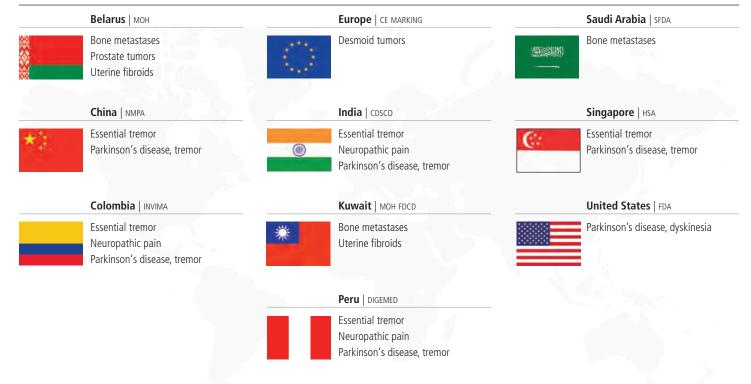
Two indications—Desmoid tumors and Parkinson's disease, dyskinesia—were added to the global approval landscape in 2021, following page. Nineteen additional indications were granted regulatory approval in new geographic regions, further expanding the global nature of focused ultrasound technology.

Development Stage Advancements and New Indications continued

2021

21

New global regulatory approvals



Industry Highlights

2021

2021

\$393m

Invested in

13

FUS industry companies

Acoustiic INC
Alpheus Medical INC
Cordance Medical INC
EDAP TMS SA
EXACT Therapeutics AS
EXO Imaging INC
IMGT CO LTD
Microvascular Therapeutics LLC
OrthoSon LTD
Shende Medical Equipment Technology CO LTD
Sonablate CORP
SonoVol INC
Vensica Therapeutics

11

New FUS industry companies

Clinical device manufacturers

4 OEM

Industry growth

2021 saw a slight increase over 2020 investment dollars in the field. Details on how and where this money was invested can be found in Section III of this report. Eleven new focused ultrasound industry companies were created in 2021—seven new clinical device manufacturers and four OEM. The names and details of the new companies started in 2021 can be found in Section III of this report.

The addition of 96 commercial treatment sites in the past year, following page, is further proof of the transition of the field from "if" the technology will be adopted to "when" it will occur. In 2021 there were 59 focused ultrasound manufacturers in full-scale commercialization efforts through their partnerships with 56 distributors.



Industry Highlights continued

New focused ultrasound commercial treatment sites worldwide

An increase over 2020 of

12%

Bringing the total number of focused ultrasound commercial treatment sites to

North America

Europe

Asia

South America

Oceania

Africa

192 289 394

State of Research and Regulatory Approvals by Body System



[†] New in 2021

State of Research and Regulatory Approvals by Body System continued



Miscellaneous

Actinic keratosis Basal cell carcinoma Dercum's disease Head & neck tumors Hypersplenism Kaposi's sarcoma Lipoma Melanoma Multiple tumors1 Obesity Heterotopic ossification Infection Niemann-Pick disease† Sinonasal disease† Wound healing

Musculoskeletal



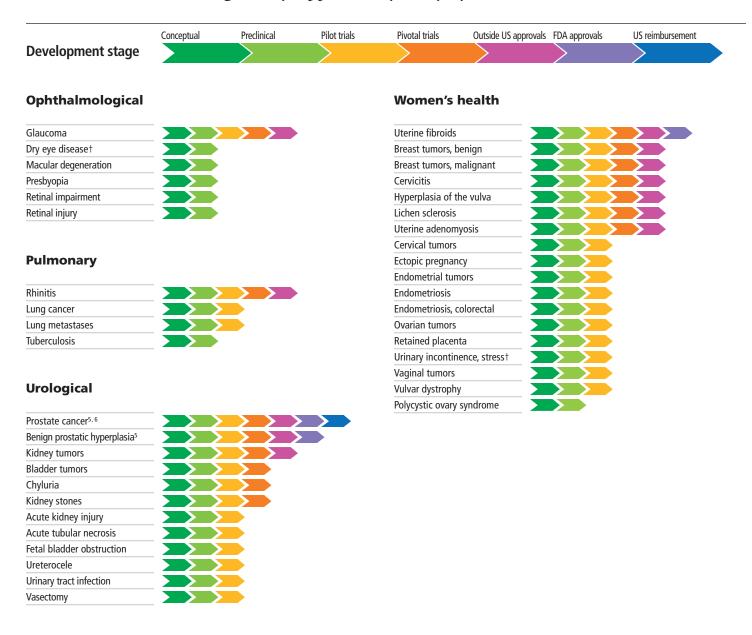
- 1 Protocols inclusive of more than one indication
- 2 Multiple myeloma approval is based on bone metastases.
- † New in 2021

State of Research and Regulatory Approvals by Body System continued



- 3 Treatment of the underlying cause of the disease
- 4 Indication was listed as migraine in the 2021 State of the Field Report.
- † New in 2021

State of Research and Regulatory Approvals by Body System continued

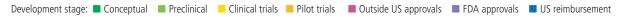


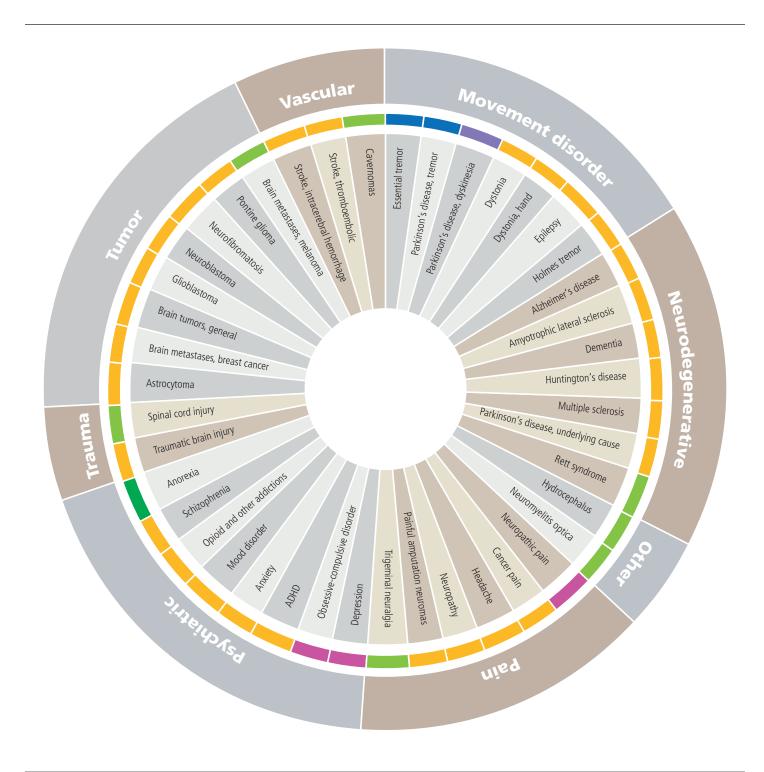
- 5 FDA approval is for prostate tissue ablation.
- 6 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
- † New in 2021



43 Neurological Indications

Out of the more than 40 neurological indications, only 6 have regulatory approval.





Indications with Anecdotal Case Reports

Indications	Date	Mechanism of action	Reference
Cardiovascular			
Arteriovenous malformations	2015	Thermal ablation, Tissue destruction	https://doi.org/10.1186/s40349-015-0042-7
Fetal heart anomalies	2012	Thermal ablation, Tissue destruction	https://doi.org/10.1002/uog.20101
Endocrine disorders			
Insulinoma	2010	Thermal ablation, Tissue destruction	https://doi.org/10.1007/s00270-010-9884-0
Gastrointestinal			
Liver alveococcosis	2015	Thermal ablation, Tissue destruction	https://doi.org/10.1007/s10396-018-0914-x
Miscellaneous			
Warts	2021	Thermal ablation, Tissue destruction	https://doi.org/10.1159/000515075





Focused Ultrasound for Diagnostics—Liquid Biopsy

Identifying the problem

There is widespread use of blood-based liquid biopsies for the diagnosis and monitoring of numerous tumors, such as pancreatic and colon cancer. However, the literature reports that the use of liquid biopsies for brain tumors is limited, likely due to the naturally occurring blood-brain barrier that prevents much-needed therapeutics within the peripheral blood from entering the brain. This barrier not only prevents drugs from entering the brain but also likely prevents brain tumor biomarkers (DNA mutations, epigenetic changes, micro-RNA, proteins) from traveling in the opposite direction out of the brain back into the bloodstream entering the circulation.

State of current treatment

Current strategies for diagnosing and monitoring brain tumor patients mainly involve clinical and radiographic follow-up, after which the patient will typically undergo invasive biopsies when possible.

Potential of focused ultrasound

By noninvasively and temporarily opening the blood-brain barrier, focused ultrasound can enable the performance of liquid biopsies, which could significantly impact care. This strategy could help clinicians noninvasively diagnose the type of brain tumor when resection or biopsy is not feasible. Additionally, by repeatedly performing FUS-induced blood-brain barrier opening (BBBO) during the course of treatment, clinicians will be able to analyze the evolution of a tumor in order to direct medicine more precisely and detect residual disease before it manifests clinically or on radiographic studies.

Evidence that FUS works for liquid biopsy

Ample preclinical evidence in various animal models has demonstrated increased yield of brain and tumor markers following focused ultrasound induced BBBO, sonobiopsy, and has paved the way for clinical studies. In 2021, a topic review article¹ detailed the preclinical evidence, clinical trials, and potential future directions to perform sonobiopsy, use focused ultrasound induced BBBO in a spatially targeted location, and enhance the release of tumor markers into the blood circulation. Numerous sites are now collecting liquid biopsy samples pre and post FUS-induced BBBO during clinical trials for enhanced drug delivery to glioblastomas (GBM).

In 2021, Meng, et al published the results of the first-inhuman clinical trial with MRgFUS enhanced liquid biopsies in patients with pathologically confirmed GBM.² In this study, 9 patients underwent low frequency MRgFUS along with adjuvant Temozolomide. The results of the prospective single arm study revealed a 2.6-, 3.2-, and 1.4-fold increase in cfDNA, neuron-derived extracellular vesicles, and brain specific protein S100b, respectively, after focused ultrasound enhanced BBBO, with no major complications reported.

Hope for the future

There are numerous ongoing clinical trials to further this revolutionary research. Please see www.fusfoundation.org/the-technology/research-sites to identify specific studies and locations.

We believe that focused ultrasound for brain liquid biopsy has significant promise to improve the care of patients with neurologic diseases including brain tumors.

In a first-ever study, Sunnybrook researchers have demonstrated that MRI-quided focused ultrasound technology can improve the detection of brain cancer biomarkers with the temporary opening of the blood-brain barrier to aid liquid biopsy."

> — Sunnybrook Health Sciences Centre March 18, 2021

- 1 Rincon-Torroella J, Khela H, Bettegowda A, Bettegowda C. Biomarkers and focused ultrasound: the future of liquid biopsy for brain tumor patients. J Neurooncol. 2022 Jan; 156(1):33-48. https://doi.org/10.1007/s11060-021-03837-0
- 2 Meng Y, Pople CB, Suppiah S, et al. MR-guided focused ultrasound liquid biopsy enriches circulating biomarkers in patients with brain tumors. Neuro Oncol. 2021 Oct 1;23(10):1789-1797. https://doi.org/10.1093/neuonc/noab057

A team of researchers led by Hong **Chen at Washington University in** St. Louis has developed a noninvasive diagnostic method for detecting glioblastomas that may one day replace the tissue biopsy with a simple blood test."

> - News Wise November 12, 2021

Areas of Interest

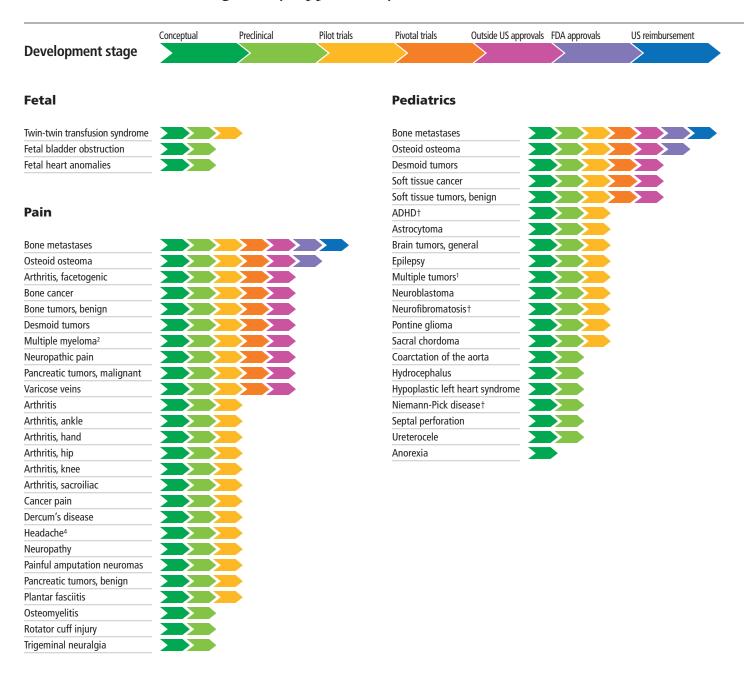
A note on multiple listings

The preceding chart's categories are body systems, comprising a group of tissues structured to perform specific functions. All indications in development for focused ultrasound treatment appear on this chart, in the body system category to which they belong. Thus, bone metastases is in the Musculoskeletal category, but nowhere else.

In an effort to see the data through a different lens, four "Areas of Interest"—Fetal, Oncology, Pain, and Pediatrics—have been identified and comprise the categories in the chart

that follows. Indications that do not match with any of the Areas of Interest will not appear in this chart, but those that do may appear in multiple categories; bone metastases, for example, appears in Oncology, Pain, and Pediatrics. Looking at the indications by "Area of Interest" reveals patterns and trends over time that might otherwise be difficult to discern.

State of Research and Regulatory Approvals by Area of Interest



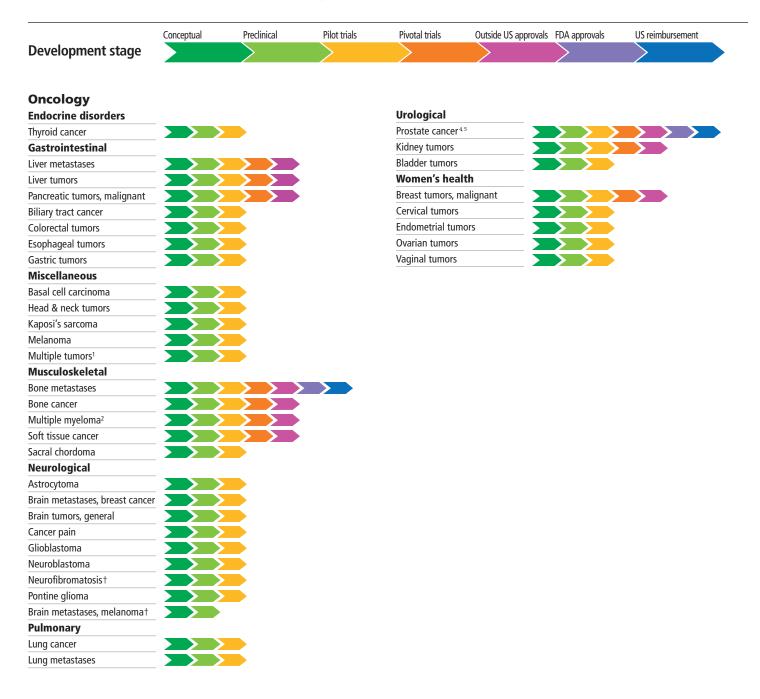
¹ Protocols inclusive of more than one indication

² Multiple myeloma approval is based on bone metastases.

 $^{4\,}$ Indication was listed as migraine in the 2021 State of the Field Report.

[†] New in 2021

State of Research and Regulatory Approvals by Area of Interest continued



¹ Protocols inclusive of more than one indication

² Multiple myeloma approval is based on bone metastases.

⁴ FDA approval is for prostate tissue ablation.

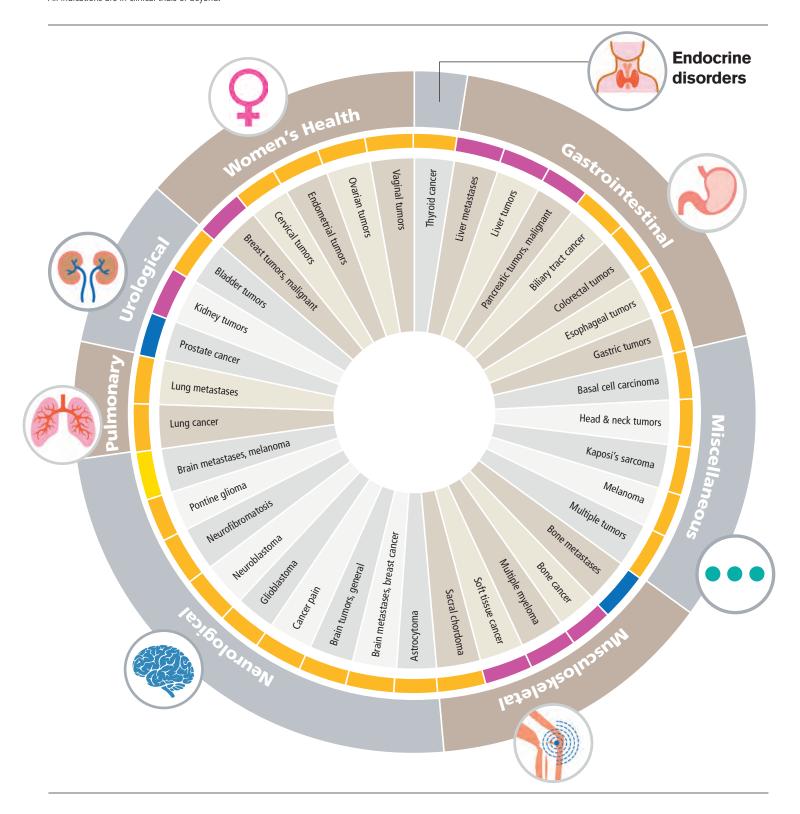
⁵ Reimbursement is for salvage therapy in radiorecurrent prostate cancer.

[†] New in 2021



37 Oncology Indications

Development stage: Conceptual Preclinical Clinical trials Outside US approvals FDA approvals US reimbursement All indications are in clinical trials or beyond.



Global Development Landscape by Body System

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
		>	>			
Cardiovascular						
Lai uiovascuiai				1		
	Arteriovenous malformations Atherosclerosis Cardiac hypertrophy Cardiac pacing Coarctation of the aorta Congestive heart failure Deep vein thrombosis Fetal heart anomalies Hematoma Hemophilia Hypoplastic left heart syndrome Mitral regurgitation Septal perforation Ventricular tachycardia	Atrial fibrillation Heart valve calcifications Peripheral artery disease Twin-twin transfusion syndrome		Varicose veins		
Endocrine diso	rder s					
	Diabetes	Grave's disease Hyperparathyroidism Thyroid cancer		Thyroid nodules		
Gastrointestina	al		•	:	•	
	Inflammatory bowel disease Irritable bowel syndrome Liver fibrosis	Biliary tract cancer Colorectal tumors Esophageal tumors Gastric tumors Malignant obstructive jaundice Nonalcoholic steato- hepatitis (NASH)† Pancreatic tumors, benign Root canal endodontia		Liver metastases Liver tumors Pancreatic tumors, malignant		

[†] New in 2021

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
			>			>
Miscellaneou	S					
	Heterotopic ossification Infection Niemann-Pick disease† Sinonasal disease† Wound healing	Actinic keratosis Basal cell carcinoma Dercum's disease Head & neck tumors Hypersplenism Kaposi's sarcoma Lipoma Melanoma Multiple tumors¹ Obesity				
Musculoskele	etal					
	Muscle atrophy Osteomyelitis Osteopenia Rotator cuff injury Tendon contracture	Arthritis Arthritis, ankle Arthritis, hand Arthritis, hip Arthritis, knee Arthritis, sacroiliac Disc degeneration Plantar fasciitis Sacral chordoma	Plantar fasciitis	Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Desmoid tumors Multiple myeloma ² Osteoid osteoma Soft tissue cancer Soft tissue tumors, benign	Bone metastases Osteoid osteoma	Bone metastases

¹ Protocols inclusive of more than one indication

² Multiple myeloma approval is based on bone metastases.

[†] New in 2021

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
			>			

Neurological					
Anorexia	Brain metastases, melanoma† Cavernomas Hydrocephalus Neuromyelitis optica Rett syndrome Spinal cord injury Trigeminal neuralgia	ADHD† Alzheimer's disease Amyotrophic lateral sclerosis Anxiety† Astrocytoma Brain metastases, breast cancer Brain tumors, general Cancer pain Dementia Dystonia Dystonia, hand Epilepsy Glioblastoma Headache4 Holmes tremor Huntington's disease Mood disorder Multiple sclerosis Neuroblastoma Neurofibromatosis† Neuropathy Opioid and other addictions Painful amputation neuromas Parkinson's disease, other³ Pontine glioma Schizophrenia† Stroke, intracerebral hemorrhage Stroke, thromboembolic Traumatic brain injury	Depression Essential tremor Neuropathic pain Obsessive-compulsive disorder Parkinson's disease, dyskinesia Parkinson's disease, tremor	Essential tremor Parkinson's disease, dyskinesia Parkinson's disease, tremor	Essential tremor Parkinson's disease tremor

³ Treatment of the underlying cause of the disease

⁴ Indication was listed as migraine in the 2021 State of the Field Report.

[†] New in 2021

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Ophthalmolo	gical					
	Dry eye disease† Macular degeneration Presbyopia Retinal impairment Retinal injury			Glaucoma		
Pulmonary						
	Tuberculosis	Lung cancer Lung metastases		Rhinitis		
Jrological						
	Acute kidney injury Acute tubular necrosis Fetal bladder obstruction Ureterocele Urinary tract infection Vasectomy	Bladder tumors Chyluria Kidney stones		Benign prostatic hyperplasia ⁵ Kidney tumors Prostate cancer ^{5,6}	Benign prostatic hyperplasia ⁵ Prostate cancer ^{5, 6}	Prostate cancer ^{5, 6}

⁵ FDA approval is for prostate tissue ablation.

⁶ Reimbursement is for salvage therapy in radiorecurrent prostate cancer.

[†] New in 2020

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
			>		>	
Vomen's heal	Polycystic ovary syndrome	Cervical tumors Ectopic pregnancy Endometrial tumors Endometriosis Endometriosis, colorectal Ovarian tumors Retained placenta Urinary incontinence, stress†		Breast tumors, benign Breast tumors, malignant Cervicitis Hyperplasia of the vulva Lichen sclerosis Uterine adenomyosis Uterine fibroids	Uterine fibroids	Uterine fibroids
		Vaginal tumors Vulvar dystrophy				

[†] New in 2021

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Development Stages of Focused Ultrasound Research

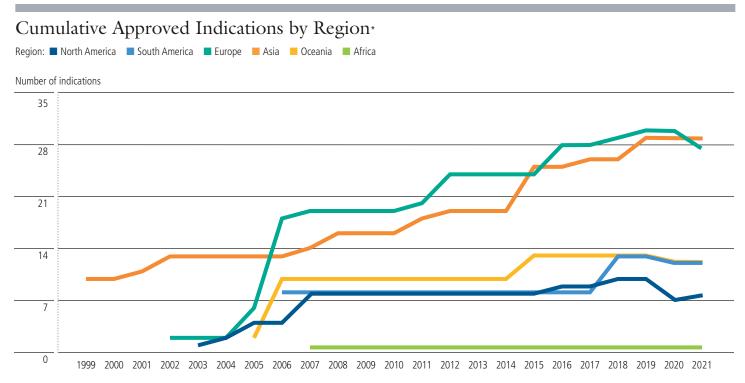




^{*}Indications with multiple mechanisms of action are counted Individually.

Development stages of focused ultrasound research

The intersection of the preclinical and clinical research lines in 2017 is an inflection point in the field of focused ultrasound. It marks the transition of the field away from an early-stage, bench research-and-development proof of concept to first-in-human clinical trials.



^{*}Device manufacturers can choose to discontinue their maintenance of a country's regulatory approval. If that country is the only one with approval for a specific indication within a geographic region, the total number of approvals will decrease.

Cumulative approved indications by region

European and Asian regulatory approvals have increased at a steady rate since the early 2000s, leading the rest of the world. This is likely attributable to the age and geographic locations of many companies in the focused ultrasound space and to an overall maturation of the industry in these regions; see Timeline of Clinical Device Manufacturers by Region on pages III.63-III.65. Regulatory agencies in these areas historically have not had efficacy standards that are equivalent to others in the regulatory landscape, though this is changing. Their concern in the past was primarily a proof-of-safety standard, thus leaving the market to sort out efficacy. 2020 marks the first year that regulatory approvals were dropped by manufacturers—likely due to lack of uptake in a particular geographic market. For more details on specific indications and countries, please see pages III.33-III.40.

Summary of Types of Research and Treatment Sites by Region

Number of sites

	Total	North America	Europe	Asia	South America	Oceania	Africa
Commercial treatments	895	192	289	394	9	4	7
Clinical research	242	60	93	84	1	4	_
Preclinical research	147	68	37	39	_	3	-
Mechanisms of action research	177	78	42	55	_	2	_
Technical research	150	61	49	39	-	1	-



Number of Research Sites and Mechanisms of Action under Investigation

Mechanisms of action research

The table that follows highlights the depth and breadth of how many different mechanisms of action are currently being investigated for each indication. The table shows that the highest numbers of mechanisms under investigation closely align with those indications where the current standard of therapy is far from ideal, that are lethal very soon after diagnosis, and/or that have a very poor quality of life.

Our website will soon allow you to drill down to specific institutions conducting the research, as is currently the case with other research types.

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Cardiovascular				·	
Cardiac					
Atrial fibrillation	1	3	1	_	4
Cardiac hypertrophy	1	1	_	_	1
Cardiac pacing	1	1	_	_	1
Congestive heart failure	*	1	_	_	1
Fetal heart anomalies	1	1	-	-	1
Heart valve calcifications	1	1	4	-	5
Mitral regurgitation	1	1	_	_	1
Ventricular tachycardia	1	2	_	-	2
Peripheral					
Arteriovenous malformations	3	1	1	2	4
Atherosclerosis	4	7	_	-	6
Deep vein thrombosis	5	8	_	-	6
Hematoma	1	1	_	_	1
Hemophilia	1	1	_	-	1
Hypertension	1	1	1	_	2
Peripheral artery disease	2	2	_	1	3
Twin-twin transfusion syndrome	3	6	1	_	5
Varicose veins	2	1	5	9	14

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

^{*} No mechanism of action was provided.

Number of Research Sites and Mechanisms of Action under Investigation continued

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Endocrine disorders				:	
Diabetes	1	2	_	_	2
Graves' disease	1	1	1	-	2
Thyroid cancer	1	2	_	-	2
Thyroid nodules	1	1	1	16	18

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

	MOAs ¹		Sites		Total ²
Indications		Preclinical	Clinical	Commercial	
Gastrointestinal					
Biliary tract cancer	1	_	1	_	1
Colorectal tumors	2	1	6	-	7
Esophageal tumors	1	-	1	_	1
Gastric tumors	2	1	1	-	2
Inflammatory bowel disease	1	1	_	_	1
Liver metastases	5	5	3	3	10
Liver tumors	9	29	37	139	182
Pancreatic tumors	2	4	6	44	54
Pancreatic tumors, malignant	14	31	20	5	34
Root canal endodontia	1	-	1	-	1

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

	MOAs ¹		Sites		Total ²
dications		■ Preclinical	Clinical	Commercial	
Miscellaneous				·	
Actinic keratosis	1	_	1	_	1
Basal cell carcinoma	1	-	2	-	2
Dercum's disease	1	_	1	-	1
Head & neck tumors	6	4	3	_	6
Heterotopic ossification	1	1	_	-	1
Hypersplenism	1	-	1	-	1
Infection	3	3	_	-	3
Kaposi's sarcoma	1	-	1	-	1
Lipoma	1	_	1	-	1
Melanoma	2	5	1	-	5
Multiple tumors	7	7	4	-	11
Niemann-Pick disease	1	1	-	_	1
Obesity	*	1	_	-	1
Sinonasal disease	1	1	-	_	1
Wound healing	3	4	_	_	3

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

^{*} No mechanism of action was provided.

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Musculoskeletal				;	
Arthritis, facetogenic	2	5	12	4	16
Arthritis, knee	1	1	1	_	2
Arthritis, sacroiliac	1	_	2	-	2
Bone cancer	1	1	6	6	13
Bone metastases	4	9	21	37	55
Bone tumors, benign	1	2	3	2	7
Desmoid tumors	2	_	6	10	15
Muscle atrophy	2	2	-	_	2
Osteoid osteoma	1	4	24	104	109
Osteomyelitis	1	1	_	_	1
Osteopenia	1	1	_	-	1
Plantar fasciitis	1	_	1	_	1
Rotator cuff injury	1	1	_	-	1
Sacral chordoma	1	-	1	-	1
Soft tissue cancer	9	8	9	2	13
Soft tissue tumors, benign	2	5	23	95	104
Tendon contracture	2	2	_	_	1

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

(Fig.	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Neurological					
Movement disorder					
Dystonia	1	-	2	1	3
Dystonia, hand	1	_	1	1	1
Epilepsy	9	20	10	2	24
Essential tremor	2	3	17	80	86
Parkinson's disease, dyskinesia	2	1	11	4	14
Parkinson's disease, tremor	3	2	11	28	39
Tremor, orthostatic	1	-	1	_	1
Neurodegenerative					
Alzheimer's disease	9	22	13	1	24
Amyotrophic lateral sclerosis	2	2	1	_	2
Dementia	2	1	1	_	2
Huntington's disease	1	1	_	_	1
Multiple sclerosis	1	-	1	_	1
Parkinson's disease, underlying cause	7	15	1	_	13
Rett syndrome	1	1	-	_	1
Other					
Hydrocephalus	1	1	_	_	1
Neuromyelitis optica	1	1	_	_	1
Pain					
Cancer pain	2	3	1	_	4
Headache ³	1	1	_	_	1
Neuropathic pain	5	6	6	3	15
Neuropathy	3	1	2	1	4
Painful amputation neuromas	1	_	1	_	1
Trigeminal neuralgia	1	_	1	1	2

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

³ Indication was listed as migraine in the 2021 State of the Field Report.

^{*} No mechanism of action was provided.

The state of the s	MOAs ¹		Sites	:	Total ²
Indications		■ Preclinical	Clinical	Commercial	
Neurological continued					
Psychiatric					
ADHD	1	_	1	_	1
Anxiety	1	1	2	_	3
Depression	2	6	7	1	10
Mood disorder	1	_	2	_	2
Obsessive-compulsive disorder	2	-	3	2	4
Opioid and other addictions	1	3	1	_	4
Schizophrenia	1	-	1	-	1
Trauma					
Spinal cord injury	1	4	-	_	4
Traumatic brain injury	2	1	3	_	4
Tumor					
Astrocytoma	2	9	2	_	11
Brain metastases, breast cancer	4	5	1	-	4
Brain metastases, melanoma	2	1	1	_	2
Brain tumors, general	18	26	4	_	16
Glioblastoma	17	48	26	_	49
Neuroblastoma	1	_	1	_	1
Neurofibromatosis	1	_	1	_	1
Pontine glioma	3	3	-	-	3
Vascular					
Cavernomas	1	1	-	_	1
Stroke, intracerebral hemorrhage	5	10	_	_	10
Stroke, thromboembolic	6	7	1	_	8

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Ophthalmological				·	
Glaucoma	2	4	7	14	23
Macular degeneration	2	2	-	_	2
Presbyopia	1	1	_	-	1
Retinal injury	1	1	_	_	1

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Pulmonary				i de la companya de	
Lung cancer	3	5	1	-	5
Lung metastases	1	1	-	-	1
Rhinitis	1	_	1	-	1
Tuberculosis	1	1	-	-	1

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

	MOAs ¹		Sites		Total ²
Indications		■ Preclinical	Clinical	Commercial	
Urological				:	
Acute kidney injury	1	1	1	_	2
Acute tubular necrosis	1	1	-	_	1
Benign prostatic hyperplasia	4	2	4	37	42
Bladder tumors	1	2	-	_	2
Chyluria	1	_	1	_	1
Fetal bladder obstruction	1	1	-	-	1
Kidney stones	2	3	1	-	2
Kidney tumors	3	7	17	94	100
Prostate cancer	6	21	56	412	446
Urinary tract infection	1	1	-	-	1

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

\	MOAs ¹		Sites		Total ²
ndications		Preclinical	Clinical	Commercial	
Women's health				į	
Breast tumors, benign	2	2	8	13	21
Breast tumors, malignant	14	29	27	96	122
Cervical tumors	3	1	5	-	6
Cervicitis	1	-	_	1	1
Ectopic pregnancy	1	_	1	-	1
Endometrial tumors	1	2	1	1	4
Endometriosis	2	1	2	2	4
Endometriosis, colorectal	1	-	4	-	4
Lichen sclerosis	1	_	1	1	2
Ovarian tumors	2	3	2	-	5
Retained placenta	1	_	1	-	1
Urinary incontinence, stress	1	-	1	-	1
Uterine adenomyosis	2	3	23	98	115
Uterine fibroids	3	16	59	325	352
Vaginal tumors	1	_	2	_	2

¹ Mechanisms of action

² For each indication, a site may examine more than one mechanism of action or may perform more than one stage of research or treatment. The total reflects unique sites, and therefore may not necessarily be the sum of the values in the preceding three columns.

Patient Treatments

Trends

A few items of note on the following pages, historically, the annual patient treatment numbers by indication tracked alongside the cumulative treatment numbers. 2019 marked the first divergence from this historical trend, with an annual uptick in oncology and brain treatments in both 2020 and 2021.

Additionally, in the last five years, there has been nearly a seven-fold increase in annual numbers of patient treatments in the brain. In 2020, multiple companies reported brainrelated patient treatments. For 2019 and prior, there was only one focused ultrasound manufacturer in this space.

- **Scots man signs own name for first** time in 20 years after groundbreaking treatment to banish violent shaking."
 - Scottish Daily Record October 11, 2021
- **WVU** addresses addiction crisis with novel ultrasound treatment."
 - WVU Medicine March 13, 2021

Manufacturer supplied data

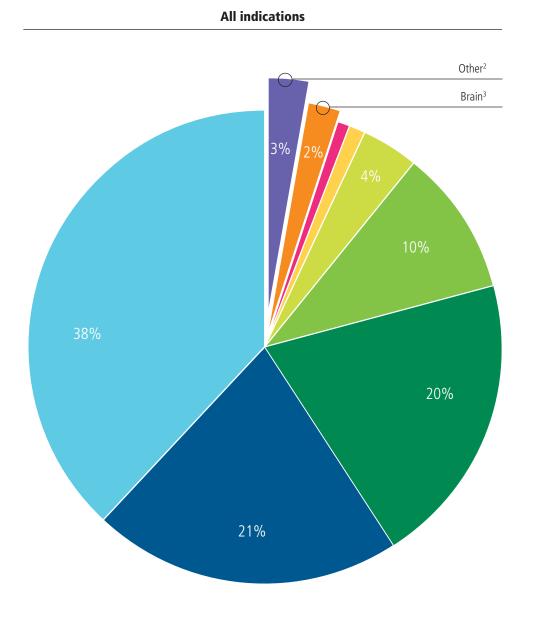
As we have mentioned previously, this report contains mostly self-reported data. The information that follows is an accumulation of data provided by the manufacturers in the industry. If we have companies with large numbers of treatment sites that do not submit data for a particular year, it can significantly influence the tables and charts. It should also be noted that this reflects patient treatments, not specifically the number of patients, as a patient can be treated more than once. Lastly, when the manufacturers report this data, they do not differentiate between treatment of a subject in a clinical trial versus a patient who was treated in a clinical setting as part of the current standard of care.

- **A** new non-invasive treatment for prostate cancer is the single biggest change in 20 years."
 - Daily Mail January 28, 2021
- **Ultrasound trial offers hope for brain** cancer patients.... A technique has been developed that could revolutionize the treatment of brain cancers and neurodegenerative diseases."
 - The Guardian October 13, 2021

Patient Treatments by Indication—Cumulative

467,162 total treatments

Uterine fibroids	179,250	38%
Liver tumors	98,014	21%
Prostate diseases	92,625	20%
Pancreatic tumors	46,246	10%
Uterine adenomyosis	17,717	4%
Other ²	13,154	3%
■ Brain³	8,417	2%
■ Glaucoma	6,179	1%
Cancer, unspecified	5,560	1%

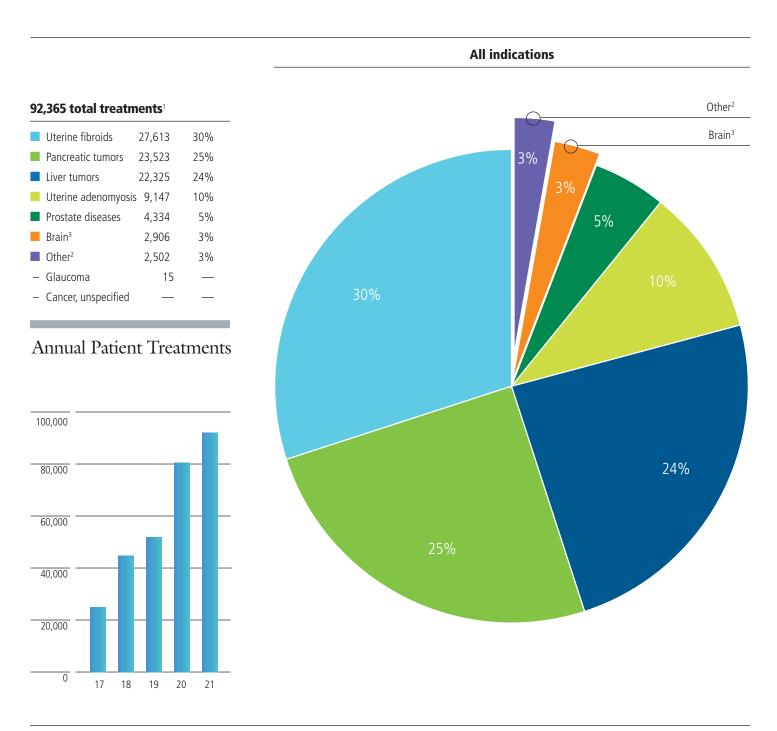


¹ The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites. Companies reporting patient treatment values this year were: Cardiawave, EDAP TMS, EyeSonix, FUSMobile, HistoSonics, Image Guided Therapy, Insightec, International Cardio, NaviFUS, OxSonics, Profound Medical, Shanghai A&S, Shenzhen PRO-HITU Medical, Sonablate, Theraclion, TheraWave, and TOOsonix.

² For an expanded list of these indications, please refer to Cumulative Other Treatments by Indication, on p. I.50.

³ For an expanded list of these indications, please refer to Brain Treatments by Indication, on p. I.48.

Patient Treatments by Indication—2021



¹ The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites.

² For an expanded list of these indications, please refer to Cumulative Other Treatments by Indication, on p. I.51.

³ For an expanded list of these indications, please refer to Brain Treatments by Indication, on p. I.49.

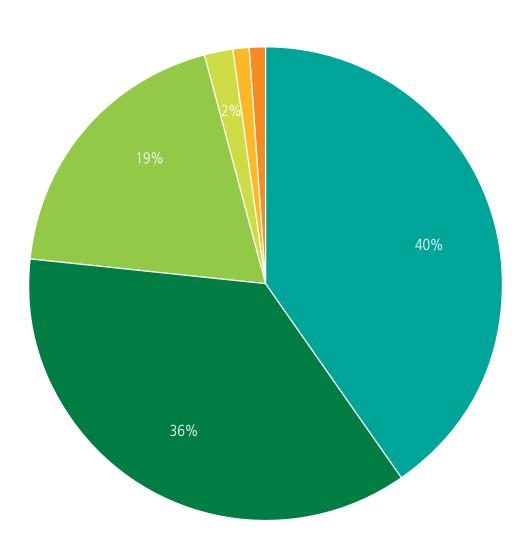
Oncology Treatments by Indication—Cumulative

Oncology indications

246,142 total treatments

Liver	tumors	98,016	40%
Pros	tate cancer	87,387	36%
Panc	reatic tumors	46,246	19%
Cano	er, unspecified	5,560	2%
Soft	tissue cancer	3,807	1%
B one	e metastases	3,587	1%
	st tumors, gnant	896	_
– Othe	er ¹	643	_

In 2021 96% of all oncology treatments were dominated by pancreatic tumors, liver tumors and prostate cancer. See pie on next page, I.47.



¹ Includes, in descending order of patient treatments: glioblastoma; endometrial tumors; brain tumors, general; glioblastoma multiforme; kidney tumors; osteosarcoma; abdominal paraganglioma; hemangioma; abdominal tumor; astrocytoma; basal cell carcinoma; diffuse intrinsic pontine glioma (DIPG); granular cell tumor of the gluteals; cervical tumors; Kaposi's sarcoma; sacral chordoma; schwannoma; spleen tumor; bone cancer; ganglioglioma; and neurofibroma

Oncology Treatments by Indication—2021

Oncology indications 52,034 total treatments Pancreatic tumors 23,523 45% 22,327 43% Liver tumors Prostate cancer 4,304 8% 8% Soft tissue cancer 2% 1,200 Bone metastases 433 1% - Other1 241 - Breast tumors, 6 malignant **Annual Oncology Treatments** 60,000 43% 48,000 36,000 24,000 12,000 18 19 20 21

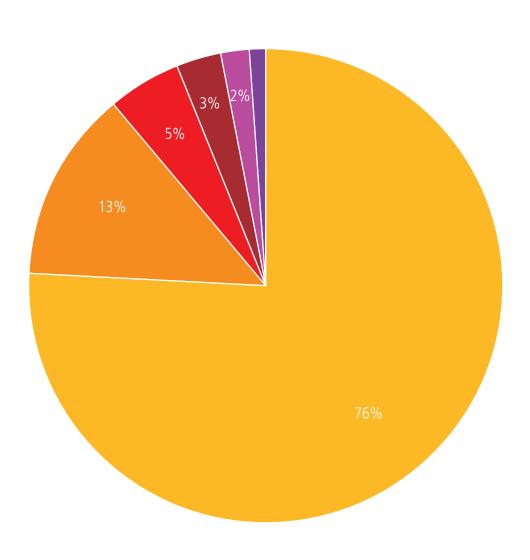
¹ Includes, in descending order of patient treatments: endometrial tumors; glioblastoma; brain tumors, general; glioblastoma multiforme; diffuse intrinsic pontine glioma (DIPG); basal cell carcinoma; and bone cancer

Brain Treatments by Indication—Cumulative

Brain indications

8,417 total brain treatments

Essential tremor	6,426	76%
Parkinson's disease	1,098	13%
■ Brain tumors¹	377	5%
■ Neuropathic pain	207	3%
Alzheimer's disease	133	2%
Mental health ²	79	1%
 Other movement disorders³ 	68	_
— Other brain ⁴	29	_



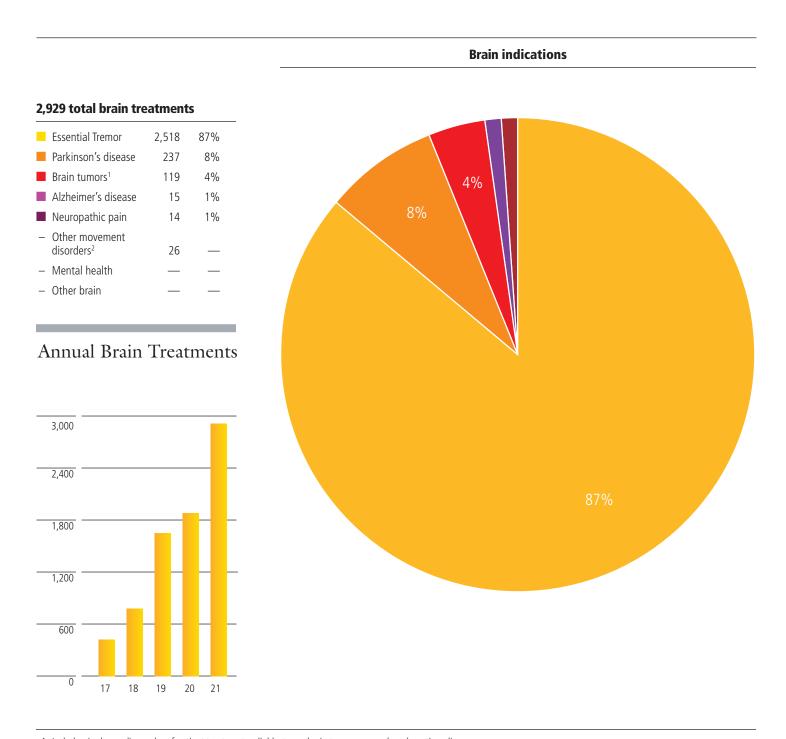
¹ Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; astrocytoma; pontine glioma; and ganglioglioma

² Includes, in descending order of patient treatments: depression, obsessive-compulsive disorder (OCD), and anxiety

³ Includes, in descending order of patient treatments: epilepsy; dystonia; and dystonia, hand

⁴ Includes, in descending order of patient treatments: traumatic brain injury and blood-brain barrier opening

Brain Treatments by Indication—2021



¹ Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; and pontine glioma

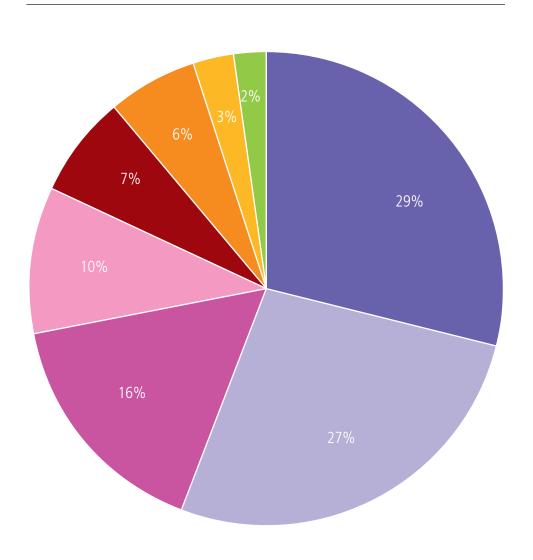
² Includes epilepsy

Other Treatments by Indication—Cumulative

Other indications

13,162 total treatments

Soft tissue cancer	3,807	29%
Bone metastases	3,587	27%
Thyroid nodules	2,057	16%
Other ¹	1,316	10%
Breast tumors, malignant	896	7%
■ Breast tumors, benign	819	6%
Arthritis, facetogenic	386	3%
Osteoid osteoma	294	2%



¹ Includes, in descending order of patient treatments: varicose veins; endometrial tumors; desmoid tumors; hypertension; endometriosis; hyperparathyroidism; actinic keratosis; arthritis; heart valve calcifications; dermatology research; tattoo removal; bone tumors, benign; kidney tumors; bone cancer; seborrheic keratosis; vascular malformations and angiomas; painful amputation neuromas; abdominal para-glioma; hemangioma; peripheral artery disease; verucca vulgaris; abdominal tumor; amyotrophic lateral sclerosis; basal cell carcinoma; arteriovenous malformations; granular cell tumor of the gluteals; cervical tumors; Kaposi's sarcoma; liver metastases; sacral chordoma; schwannoma; soft tissue tumor, benign; spleen tumor; and neurofibroma

Other Treatments by Indication—2021

Other indications 2,469 total treatments 49% Soft tissue cancer 1,200 Other¹ 487 20% ■ Thyroid nodules 433 18% Osteoid osteoma 34 1% - Arthritis, facetogenic 18% 11 - Breast tumors, malignant 6 - Breast fibroadenoma 49%

¹ Includes, in descending order of patient treatments: varicose veins, endometrial tumors, endometriosis, actinic keratosis, desmoid tumors, heart valve calcifications, seborrheic keratosis, vascular malformations and angiomas, peripheral artery disease, verucca vulgaris, liver metastases, bone cancer, and basal cell carcinoma

FUS Regulatory Approvals by Indication and Region *Graphic*



Global Landscape of Approved Indications and Manufacturers

Indication regional approvals	Indications	Manufacturers
	Cardiovascular	
• •	Varicose veins	Theraclion
	Endocrine disorders	
• •	Thyroid nodules	Theraclion
	Gastrointestinal	
	Liver metastases	Chongqing Haifu Medical Technology
	Liver tumors	Chongqing Haifu Medical Technology
		Shanghai A&S
	Pancreatic tumors	Chongqing Haifu Medical Technology
	Musculoskeletal	
	Arthritis, facetogenic	Insightec
	Bone cancer	Insightec
	Bone metastases	Insightec
		Profound Medical
		Shanghai A&S
	Bone tumors, benign	Insightec
	Desmoid tumors	Profound Medical
	Multiple myeloma	Insightec
	Osteoid osteoma	Chongqing Haifu Medical Technology
		Profound Medical
	Soft tissue cancer	Chongqing Haifu Medical Technology
•		EpiSonica
		Shanghai A&S
• •	Soft tissue tumors, benign	Chongqing Haifu Medical Technology



Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Neurological	
	Depression	Insightec
	Essential tremor	Insightec
	Neuropathic pain	Insightec
	Obsessive-compulsive disorder	Insightec
	Parkinson's disease, dyskinesia	Insightec
	Parkinson's disease, tremor	Insightec
	Ophthalmological	
• •	Glaucoma	EyeTechCare
	Pulmonary	
• •	Rhinitis	Chongqing Haifu Medical Technology
	Urological	
	Benign prostatic hyperplasia	EDAP TMS
		Insightec
		Profound Medical
		Sonablate
• •	Kidney tumors	Chongqing Haifu Medical Technology
	Prostate cancer	EDAP TMS
		Insightec
		Profound Medical
		Sonablate
	Women's health	
• •	Breast tumors, benign	Theraclion
	Breast tumors, malignant	Chongqing Haifu Medical Technology
		Shanghai A&S
•	Cervicitis	Chongqing Haifu Medical Technology

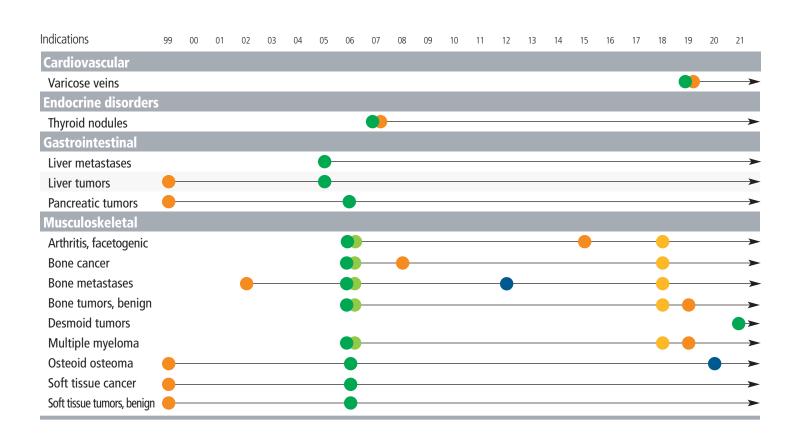


Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Women's health continued	
	Hyperplasia of the vulva	Shenzhen PRO-HITU Medical
	Lichen sclerosis	Shenzhen PRO-HITU Medical
	Uterine adenomyosis	Alpinion Medical Systems
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shenzhen PRO-HITU Medical
• •	Uterine fibroids	Alpinion Medical Systems
• •		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
• •		Shanghai A&S
• •		Shenzhen PRO-HITU Medical
•		Wuxi Haiying Electronic Medical

Approval regions North America South America Oceania Europe Africa Asia

FUS Regulatory Approvals by Indication and Region



North America

Europe

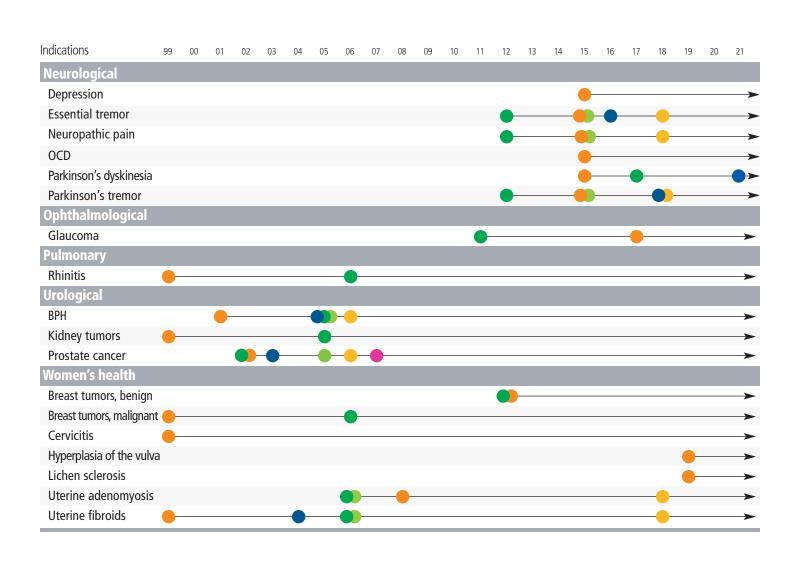
Asia

South America

Oceania

Africa

FUS Regulatory Approvals by Indication and Region continued





Abstracts Presented at FUS Symposia

Symposium	2016	2017	2018	2019	2020	2021
Focused Ultrasound Foundation Symposium, FUSF ¹	200	_	250	_	257	_
International Symposium on Therapeutic Ultrasound, ISTU	152	207	257	197 ²	*	241
Totals	352	261	507	197	257	241

FUS Abstracts Presented at Other Symposia

Symposium	2016	2017	2018	2019	2020	2021
Acoustical Society of America	64	48	39	22	13	30
American Association for Cancer Research, AACR	_	_	_	_	7	5
American Association of Physicists in Medicine, AAPM	8	16	5	7	6	4
American Institute of Ultrasound in Medicine, AIUM	2	_	9	6	*	5
American Society of Clinical Oncology, ASCO	_	_	_	_	4	1
American Society for Radiation Oncology	2	5	3	_	2	2
American Society for Stereotactic and Functional Neurosurgery	3	_	6	_	*	_
American Urological Association, AUA	11	7	4	16	*	5
Biomedical Engineering Society	12	16	14	26	9	_3
Cardiovascular and Interventional Radiology Society of Europe, CIRSE	_	_	_	_	10	8
European Association of Urology, EAU	_	_	_	_	5	6
European Conference on Interventional Oncology, ECIO	_	_	_	_	_	7
European Congress of Radiology	7	13	22	10	15	2
IEEE International Engineering in Medicine and Biology	9	5	11	11	2	2
IEEE International Ultrasonics Symposium	26	71	19	49	57	72
International Society for Magnetic Resonance in Medicine, ISMRM	_	_	_	_	33	12
Japanese Society for Therapeutic Ultrasound	39	35	48	52	*	_
Korean Society for Therapeutic Ultrasound	14	15	17	22	6	_
Radiological Society of North America, RSNA	21	17	14	26	7	4
Society for Thermal Medicine, STM	22	10	10	9	*	5
Society of Interventional Radiology	3	2	1	5	*	3
Taiwan Associated of Interventional Therapeutic Ultrasound	_	_	_	12	5	0
Totals	243	260	222	273	181	182

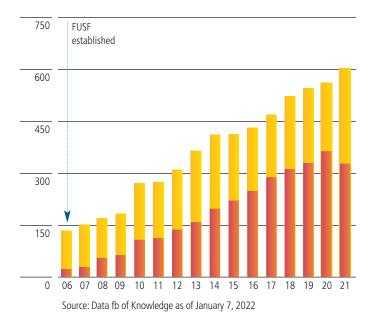
¹ Held biennially

² In 2019 the European Symposium on Focused Ultrasound, EUFUS, combined with the International Symposium on Therapeutic Ultrasound, ISTU and is now held under the title of ISTU.

^{*} Cancelled due to COVID-19 pandemic.

FUS Publications

■ Traditional journals ■ Open access



FUS Publications and Citations

Cumulative FUS publications Citations of FUS publications 2021 **FUS publications**

Source: Data fb of Knowledge as of January 7, 2022

In 2021 we continue to see a decrease in focused ultrasound abstracts presented at scientific meetings as compared to pre-pandemic levels. This is not surprising given the continued travel restrictions, researchers' concern for their own health, and research delays related to government and academic shutdowns of various lengths.

Publications in 2021 continued to stay the course, and focused ultrasound publication citations were over 24,000 for 2021 alone.

Publications—Cumulative Top Twenty-five Source Titles

Records	Scientific publication titles
452	Ultrasound in Medicine and Biology
267	International Journal of Hyperthermia
203	Physics in Medicine and Biology
193	IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control
120	Journal of the Acoustical Society of America
116	Medical Physics
112	Ultrasonics
106	Journal of Therapeutic Ultrasound
103	Scientific Reports
99	Magnetic Resonance in Medicine
95	Journal of Controlled Release
88	Ultrasonics Sonochemistry
76	IEEE Transactions on Biomedical Engineering
71	European Urology Radiology
71	Plos One
71	Radiology
68	Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Proceedings
67	Journal of Urology
65	Journal of Neurosurgery
61	BJU International
58	Journal of Ultrasound in Medicine
57	European Radiology
57	Theranostics
53	Journal of Magnetic Resonance Imaging JMRI
43	Journal of Endourology

Of particular interest, the Transparency and Openness Promotion, TOP, scores for the journals on our list of 2021 top source titles, page I.61, have increased, significantly in the case of several journals. We are hopeful this trend will continue as we strongly believe open science practices are good for the focused ultrasound research community.

Publications—2021 Top Source Titles



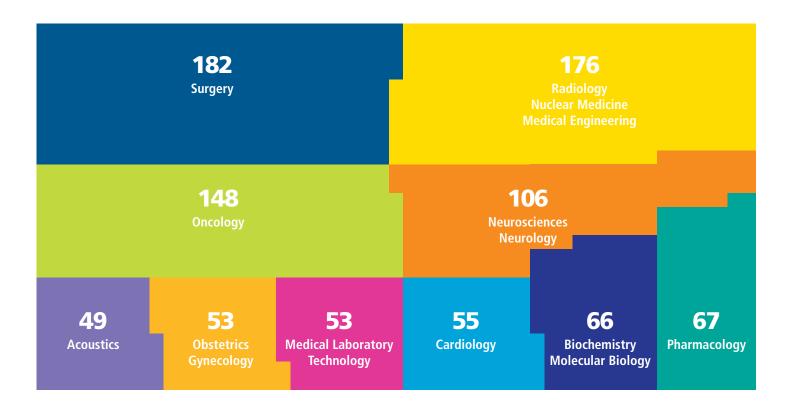
Publications—2021 Top Source Titles

Records	Impact factor	TOP score	Scientific publication titles
44	3.9	1	International Journal of Hyperthermia
38	2.7	1	IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control
23	3.0	2	Ultrasound in Medicine and Biology
15	4.5	0	IEEE Transactions on Biomedical Engineering
15	4.4	13	Scientific Reports
10	2.9	1	Ultrasonics
9	9.8	1	Journal of Controlled Release
9	5.9	9	Pharmaceutics
8	4.5	3	International Journal of Nanomedicine
8	5.1	5	Journal of Neurosurgery
8	4.1	1	Medical Physics
8	4.6	3	Neurosurgery

Publications—Cumulative Top Twenty-five Research Areas

Records	Scientific research areas
3019	Radiology, Nuclear Medicine, Medical Engineering
2848	Surgery
2266	Oncology
1597	Pathology
1302	Neurosciences, Neurology
1141	Pharmacology
1018	Cardiology
1010	Medical Laboratory Technology
915	Acoustics
915	Biochemistry, Molecular Biology
899	Urology, Nephrology
719	Gastroenterology, Hepatology
690	Anatomy, Morphology
674	Mathematics
657	Geriatrics
589	Cell Biology
562	Physics
549	Obstetrics, Gynecology
542	Computer Science
386	General Internal Medicine
371	Immunology
342	Medical Informatics
335	Hematology
319	Reproductive Biology
314	Imaging Science, Photographic Technology

Publications—2021 Top Ten Research Areas

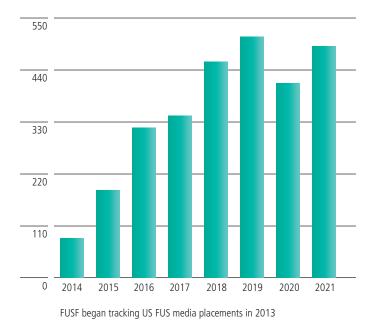


Publications—2021 Top Ten Research Areas

Records	Scientific research areas
182	Surgery
176	Radiology, Nuclear Medicine, Medical Imaging
148	Oncology
106	Neurosciences, Neurology
67	Pharmacology
66	Biochemistry, Molecular Biology
55	Cardiology
53	Medical Laboratory Technology
53	Obstetrics, Gynecology
49	Acoustics

United States FUS Media Placements

Per year



2,810

Media placements, 2014-2021

498

Media placements, 2021

Study

Targeted ultrasound destroys cancer cells.

Scientists say they've developed a low-intensity ultrasound technique that kills cancer cells without damaging healthy cells."

> — WebMD January 10, 2020

Patient treatment

Focused ultrasound is making a difference in the lives of patients across the globe.

His hands shook uncontrollably for a decade. MRI-guided ultrasound surgery finally relieved the tremors."

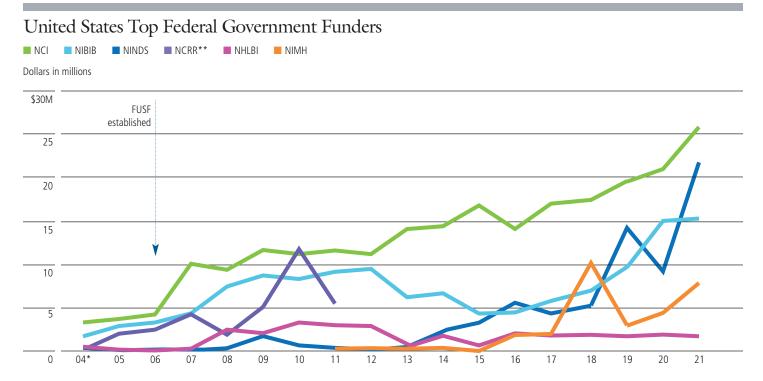
> — Washington Post March 1, 2020

New platform

An unusual approach to fighting cancer is ultrasound and microbubbles.

The new treatment platform is designed to deliver a one-two punch. First, the microbubbles attack cancer cells, then a gene beckons immune cells to further pummel the tumor."

> — Forbes June 17, 2020



^{*}The first record of funded focused ultrasound research by the United States Federal Government was in 2004.

Additional government funders are: CDMRP, CLC, CNRM, FIC, NCMHD, NEI, NHGRI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIGMS, NSF, OD, VA

Sources

Site: https://projectreporter.nih.gov/reporter.cfm

Site: https://www.usaspending.gov/search

Terms searched: "focused ultrasound", MRgFUS, HIFU, LIFU, "ultrasound ablation", LIPU

United States federal government focused ultrasound grants

Encouragingly, there continues to be an increase in federal funding for focused ultrasound–related projects in the United States. Even though the National Institutes of Health, NIH, budget has been somewhat stagnant over the last 15 years, the portion of funding allocated to focused ultrasound research is growing. Funding increases of this nature are typical for medical innovations that have shown the most potential for improving patient health. 2021 funding totals are \$23M higher than 2020 levels, with a \$13M increase in focused ultrasound spending by National Institute of Neurological Disorders and Stroke, NINDS.

^{**}Agency dissolved in 2012.

Total FUS Funding by United States Government Agencies

2021 FUS funding ¹	Total FUS funding ² 2004–2021	Granting agency
\$25,931,473	\$241,046,853	■ NCI National Cancer Institute
\$15,699,088	\$128,996,838	■ NIBIB National Institute of Biomedical Imaging and Bioengineering
\$21,845,267	\$72,174,370	■ NINDS National Institute of Neurological Disorders and Stroke
<u>—</u>	\$32,924,533	■ NCRR ³ National Center for Research Resources
\$7,613,539	\$30,519,707	■ NIMH National Institute of Mental Health
\$1,254,026	\$24,880,522	■ NHLBI National Heart, Lung, and Blood Institute
\$2,919,048	\$14,551,992	NIDDK National Institute of Diabetes and Digestive and Kidney Diseases
\$2,342,440	\$12,700,842	OD Office of the Director, NIH
\$815,265	\$11,904,326	NIA National Institute on Aging
\$4,549,414	\$9,899,209	NIDA National Institute on Drug Abuse
\$382,179	\$7,297,360	NSF National Science Foundation
_	\$7,264,005	NIGMS National Institute of General Medical Sciences
\$170,605	\$7,237,301	NICHD National Institute of Child Health and Human Development
_	\$6,988,469	CDMRP Congressionally Directed Medical Research Programs
\$391,637	\$5,528,883	NEI National Eye Institute
\$968,750	\$2,285,247	NIAAA National Institute on Alcohol Abuse and Alcoholism
_	\$1,858,361	CNRM Center For Neuroscience and Regenerative Medicine
\$361,447	\$1,789,980	NIDCR National Institute of Dental and Craniofacial Research
<u>—</u>	\$909,727	NIDCD National Institute on Deafness and Other Communication Disorders
_	\$749,990	NIMHD National Institute on Minority Health and Health Disparities
	\$576,760	NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases
_	\$223,196	NHGRI National Human Genome Research Institute
<u> </u>	\$158,851	CLC Clinical Center
_	\$67,858	FIC I John E. Fogarty International Center
\$85,244,178	\$622,535,180	TOTAL

^{1 2020} total funding for focused ultrasound was \$62,190,681.

Sources

Site: https://projectreporter.nih.gov/reporter.cfm Site: https://www.usaspending.gov/search

Terms searched: "focused ultrasound", MRgFUS, HIFU, LIFU, "ultrasound ablation", LIPU

² The first record of funding for focused ultrasound research by the US Federal Government was in 2004.

³ Agency dissolved in 2012.

State of Research and Treatment





State of Research and Treatment

Similar to previous reports, the State of Research and Treatment includes data and information on clinical, preclinical, and technical research, commercial treatment, and mechanisms of action.

2021 was another big year for commercialization in focused ultrasound. The field saw gains of nearly 100 new treatment sites worldwide. The greatest growth is in Asia with no fewer than 76 new sites. China leads the way in Asia with 56 new sites, followed by South Korea with 17.

New this year, we have detailed both the mechanisms of action and the development stage for every indication by both body system and area of interest. We hope this will illuminate the true depth and breadth of the flurry of research in focused ultrasound around the world. To date all the indications with regulatory approval, utilize thermal ablation as their mechanism of action, but as the reader will be able to see, many other mechanisms are being utilized in human clinical trials.





COMMERCIAL TREATMENT

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COMMERCIAL TREATMENT

Commercial Treatment Sites by Region

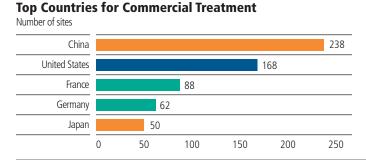
895 Commercial treatment sites worldwide

North America Europe Asia South America Oceania Africa

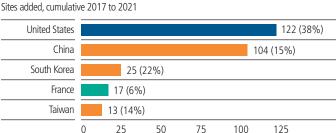
192 289 394 9 4 7

Annual growth by region from 2013–2021

26% 4% 13% 8% 22% 17%



Top Countries with Commercial Treatment Growth



2021 saw an increase of 96 new commercial treatment sites worldwide. The greatest growth is in Asia with no fewer than 76 new sites. China leads the way in Asia with 56 new sites, followed by South Korea with 17.

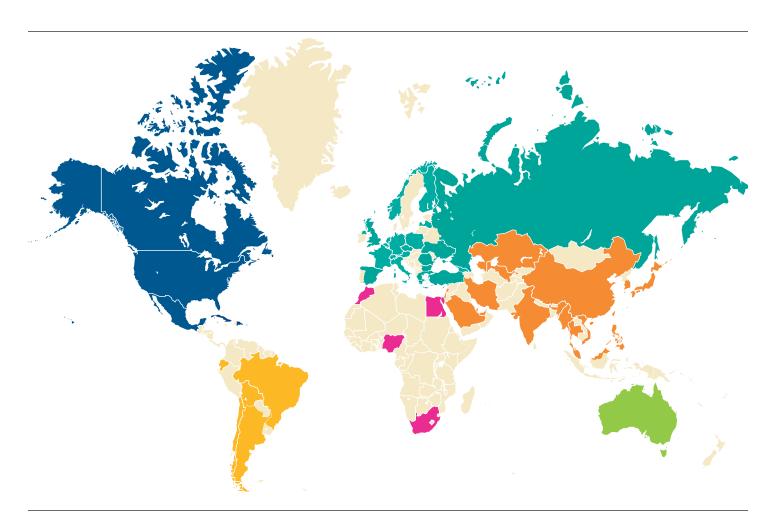
Commercial treatment additional content

For more information about specific commercial treatment sites and indications, please visit:

www.fusfoundation.org/the-technology/treatment-sites

Use the "search by disease" dropdown menu and/or location.

Commercial Treatment Sites by Country



■ North America

- 12 Canada
- 1 Cayman Islands
- 1 Cuba
- 1 Dominican Republic
- 9 Mexico
- 168 United States

South America

- 2 Argentina
- Bolivia 1
- 2 Brazil
- 2 Chile 2 Ecuador

Europe

- 3 Austria
- 1 Belgium
- Bulgaria
- 1 Czech Republic
- 1 Finland
- 88 France
- 1 Georgia
- 62 Germany
- Greece
- 37 Italy
- 1 Latvia
- Monaco
- 5 The Netherlands
- 3 Norway

- 4 Poland
- Romania
- 30 Russian Federation
- 14 Spain
- 13 Switzerland
- 3 Turkey
- 1 Ukraine
- 16 United Kingdom

Asia

- 238 China
 - 6 India
 - 1 Iran
 - 3 Israel
- 50 Japan 2 Kazakhstan
- 2 Lebanon
- 2 Malaysia Myanmar
- Philippines
- Qatar
- Saudi Arabia
- 2 Singapore

- 46 South Korea
- 32 Taiwan
- 2 Thailand
- 1 Uzbekistan
- 2 Vietnam

Oceania

4 Australia

Africa

- 3 Egypt
- 1 Morocco
- 2 Nigeria
- 1 South Africa

COMMERCIAL TREATMENT

Commercial Treatment Sites by Indication and Region*

12

Cardiovascular sites
3 indications

82

Neurological sites 13 indications **16**

Endocrine disorders sites1 indication

14

Ophthalmological sites
1 indication

148

Gastrointestinal sites 4 indications

528

Urological sites 3 indications

140

Musculoskeletal sites

8 indications

339

Women's health sites 8 indications

	Regions					Totals	
Indications	■ N. America	■ Europe	Asia	S. America	Africa	Oceania	
Cardiovascular							
Peripheral							
Arteriovenous malformations	1	1	-	-	-	-	2
Peripheral artery disease	_	1	_	_	_	_	1
Varicose veins	_	9	_	_	_	_	9
Endocrine disorders							
Thyroid nodules	_	13	3	_	_	_	16
Gastrointestinal							
Liver metastases	_	_	2	_	1	_	3
Liver tumors	2	8	128	_	1	_	139
Pancreatic tumors	_	_	43	_	1	_	44
Pancreatic tumors, malignant	1	3	1	_	_	_	5
Musculoskeletal							
Arthritis, facetogenic	1	1	1	_	_	1	4
Bone cancer	3	2	1	-	-	-	6
Bone metastases	6	22	6	_	2	1	37
Bone tumors, benign	1	1	_	_	_	_	2
Desmoid tumors	3	6	-	_	-	1	10

^{*}Indications being performed off label in a region are shown in bold italic. A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific commercial treatment sites and indications, please visit: www.fusfoundation.org/the-technology/treatment-sites.

Use the "search by disease" dropdown menu and/or location.

Commercial Treatment Sites by Indication and Region* continued

	Regions					1	otals
Indications	■ N. America	■ Europe	Asia	S. America	Africa	Oceania	
Musculoskeletal continued							
Osteoid osteoma	4	11	88	_	_	1	104
Soft tissue cancer	1	1	_	_	_	_	2
Soft tissue tumors, benign	1	6	87	_	_	1	95
Neurological							
Movement disorder							
Dystonia	_	1	_	_	_	_	1
Dystonia, hand	_	_	1	_	_	_	1
Epilepsy	_	1	1	_	_	_	2
Essential tremor	42	16	19	1	_	2	80
Parkinson's disease, dyskinesia	_	3	1	_	_	_	4
Parkinson's disease, tremor	15	6	5	1	_	1	28
Neurodegenerative							
Alzheimer's disease	_	_	1	_	_	_	1
Pain							
Neuropathic pain	_	2	_	_	_	1	3
Neuropathy	_	1	_	_	_	_	1
Trigeminal neuralgia	_	1	_	_	_	_	1
Psychiatric							
Depression	_	_	1	_	_	_	1
Obsessive-compulsive disorder	1	_	1	_	_	_	2
Tumor							
Astrocytoma	1	_	_	_	_	_	1
Ophthalmological							
Glaucoma	-	14	_	_	-	_	14
Urological							
Benign prostatic hyperplasia	5	7	25	_	_	_	37
Kidney tumors	1	5	87	_	1	_	94
Prostate cancer	149	212	41	6	3	1	412

^{*}Indications being performed off label in a region are shown in bold italic. A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific commercial treatment sites and indications, please visit: www.fusfoundation.org/the-technology/treatment-sites. Use the "search by disease" dropdown menu and/or location.

COMMERCIAL TREATMENT

Commercial Treatment Sites by Indication and Region* continued

	Regions						Totals
Indications	■ N. America	■ Europe	Asia	S. America	■ Africa	Oceania	
Women's health							
Breast tumors, benign	_	11	1	_	1	_	13
Breast tumors, malignant	1	7	88	_	-	-	96
Cervicitis	_	1	_	_	_	_	1
Endometrial tumors	_	_	1	_	_	_	1
Endometriosis	_	2	_	_	_	_	2
Lichen sclerosis	_	_	1	_	_	_	1
Uterine adenomyosis	3	7	85	_	1	2	98
Uterine fibroids	9	39	269	2	4	2	325

^{*}Indications being performed off label in a region are shown in bold italic. A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific commercial treatment sites and indications, please visit: www.fusfoundation.org/the-technology/treatment-sites. Use the "search by disease" dropdown menu and/or location.

COMMERCIAL TREATMENT

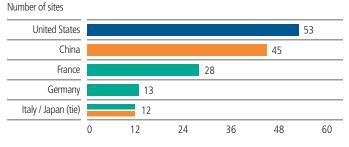
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Clinical Research Sites by Region

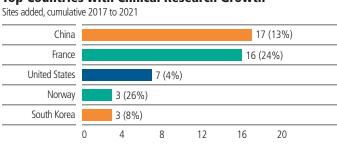
242 Clinical research sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
60	93	84	1	4	_
2 %	8%	Annual growth by reg	gion from 2013–2021 —	10%	_

Top Countries for Clinical Research



Top Countries with Clinical Research Growth



Clinical research additional content

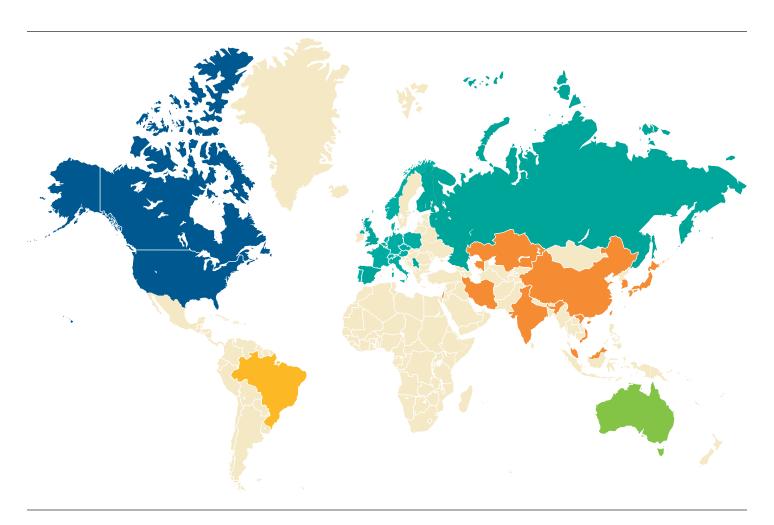
For more information about specific clinical research sites and indications, please visit:

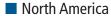
www.fusfoundation.org/the-technology/research-sites

Use the "search by disease research" and/or "search by research stage" dropdown menu.

^{*}Clinical research sites treat patients as part of a clinical study.

Clinical Research Sites by Country





- 7 Canada
- 53 United States

South America

1 Brazil

Europe

- 1 Austria
- 1 Belgium
- 1 Czech Republic
- 2 Denmark
- 1 Finland
- 28 France
- 13 Germany
- 12 Italy
- 4 The Netherlands
- 5 Norway
- 2 Poland
- 1 Portugal

5 Russian Federation

- Serbia
- 5 Spain
- 2 Switzerland
- 9 United Kingdom

Asia

- 45 China
- 2 India
- 1 Iran
- 3 Israel
- 12 Japan
- 1 Kazakhstan
- 1 Malaysia
- 1 Singapore
- 11 South Korea
- 6 Taiwan
- 1 Vietnam

Oceania

4 Australia

96 indications are being researched at clinical sites worldwide.

Cardiovascular sites
6 indications

102

Musculoskeletal sites 12 indications

76
Urological sites
6 indications

1

Endocrine disorders site 2 indications

75

Neurological sites
35 indications

83

Women's health sites 14 indications **58**

Gastrointestinal sites 9 indications

7

Ophthalmological sites1 indication

9

Miscellaneous sites 9 indications

2

Pulmonary sites 2 indications

	Regions				Totals	
Indications	■ N. America	Europe	Asia	S. America	Oceania	
Cardiovascular						
Cardiac						
Atrial fibrillation	-	1	_	-	-	1
Heart valve calcifications	_	4	_	-	-	4
Peripheral						
Arteriovenous malformations	_	1	_	-	_	1
Hypertension	_	_	1	-	_	1
Twin-twin transfusion syndrome	_	1	_	-	-	1
Varicose veins	_	3	2	-	-	5
Endocrine disorders						
Graves' disease	_	_	1	-	-	1
Thyroid nodules	_	_	1	_	_	1

^{*} A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions					Totals	
Indications	■ N. America	Europe	Asia	S. America	Oceania		
Gastrointestinal							
Biliary tract cancer	_	_	1	_	_	1	
Colorectal tumors	_	4	2	-	_	6	
Esophageal tumors	1	_	_	_	_	1	
Gastric tumors	1	_	_	-	-	1	
Liver metastases	_	3	_	_	_	3	
Liver tumors	9	14	13	-	-	36	
Pancreatic tumors	_	_	6	_	_	6	
Pancreatic tumors, malignant	2	11	2	-	-	15	
Root canal endodontia	1	_	_	-	_	1	
Miscellaneous							
Actinic keratosis	_	1	_	_	_	1	
Basal cell carcinoma	-	2	-	-	-	2	
Dercum's disease	_	_	1	-	_	1	
Head & neck tumors	2	-	-	-	-	2	
Hypersplenism	_	_	1	-	_	1	
Kaposi's sarcoma	-	1	-	-	-	1	
Lipoma	_	_	1	-	_	1	
Melanoma	1	_	_	-	-	1	
Multiple tumors ¹	2	_	2	-	-	4	
Musculoskeletal							
Arthritis, facetogenic	2	5	4	1	_	12	
Arthritis, knee	_	-	1	-	-	1	
Arthritis, sacroiliac	1	1	_	_	-	2	
Bone cancer	3	2	1	_	-	6	
Bone metastases	5	9	6	1	_	21	
Bone tumors, benign	_	3	_	_	-	3	
Desmoid tumors	3	2	1	-	-	6	

^{*} A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

¹ Protocols inclusive of more than one indication.

	Regions					Totals
Indications	■ N. America	Europe	Asia	S. America	Oceania	
Musculoskeletal continued						
Osteoid osteoma	3	7	13	1	_	24
Plantar fasciitis	_	1	_	-	_	1
Sacral chordoma	_	1	_	_	_	1
Soft tissue cancer	4	3	_	-	_	7
Soft tissue tumors, benign	2	6	14	_	1	23
Neurological						
Movement disorder						
Dystonia	_	_	2	-	_	2
Dystonia, hand	_	_	1	_	_	1
Epilepsy	8	_	2	-	_	10
Essential tremor	7	5	6	_	_	18
Parkinson's disease, dyskinesia	6	1	4	_	_	11
Parkinson's disease, tremor	4	5	2	_	_	11
Tremor, orthostatic	1	_	_	_	_	1
Neurodegenerative						
Alzheimer's disease	6	2	1	-	2	11
Amyotrophic lateral sclerosis	1	_	_	_	_	1
Dementia	_	1	-	-	-	1
Multiple sclerosis	1	_	_	_	_	1
Parkinson's disease, underlying cause	1	_	-	-	-	1
Pain						
Cancer pain	1	_	-	_	-	1
Neuropathic pain	3	2	1	_	_	6
Neuropathy	2	_	-	-	-	2
Painful amputation neuromas	_	_	1	_	_	1
Trigeminal neuralgia	1	-	_	-	-	1

^{*} A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites.

	Regions					Totals
Indications	■ N. America	Europe	Asia	S. America	Oceania	
Neurological continued						
Psychiatric						
ADHD	1	_	-	-	-	1
Anxiety	2	_	_	_	_	2
Depression	2	_	4	-	-	6
Mood disorder	2	_	_	_	_	2
Obsessive-compulsive disorder	3	_	-	-	-	3
Opioid and other addictions	_	1	_	_	_	1
Schizophrenia	-	_	1	-	_	1
Trauma						
Traumatic brain injury	2	_	1	-	-	3
Tumor						
Astrocytoma	2	-	-	-	_	2
Brain metastases, breast cancer	1	_	_	_	_	1
Brain metastases, melanoma	-	1	_	-	_	1
Brain tumors, general	1	1	1	_	_	3
Glioblastoma	11	9	3	_	-	23
Neuroblastoma	1	_	_	-	_	1
Neurofibromatosis	1	_	_	-	-	1
Vascular						
Stroke, thromboembolic	1	_	_	_	_	1
Ophthalmological						
Glaucoma	1	5	1	_	_	7
Pulmonary						
Lung cancer	1	-	_	-	_	1
Rhinitis	_	_	1	_	-	1

^{*} A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions				Totals	
Indications	■ N. America	Europe	Asia	S. America	Oceania	
Urological						
Acute kidney injury	_	_	1	_	_	1
Benign prostatic hyperplasia	-	4	_	-	_	4
Chyluria	_	_	1	_	_	1
Kidney stones	1	_	_	-	_	1
Kidney tumors	_	4	13	_	_	17
Prostate cancer	17	30	8	-	_	55
Women's health						
Breast tumors, benign	4	1	3	-	_	8
Breast tumors, malignant	3	9	13	-	-	25
Cervical tumors	2	2	1	-	_	5
Ectopic pregnancy	-	-	1	-	-	1
Endometrial tumors	_	1	_	-	_	1
Endometriosis	-	1	1	-	-	2
Endometriosis, colorectal	_	4	_	-	_	4
Lichen sclerosis	-	_	1	-	-	1
Ovarian tumors	1	1	_	-	_	2
Retained placenta	-	_	1	-	-	1
Urinary incontinence, stress	_	1	_	-	_	1
Uterine adenomyosis	-	6	15	-	2	23
Uterine fibroids	1	20	35	1	2	59
Vaginal tumors	_	2	_	-	-	2

^{*} A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

CLINICAL

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Preclinical Research Sites by Region*

147

Preclinical research sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
68	37	39	_	3	_
5 %	5 %	Annual growth by reg	gion from 2013–2021 —	6%	_

Top Countries for Preclinical Research

 Number of sites

 United States

 China

 France

 13

 Taiwan

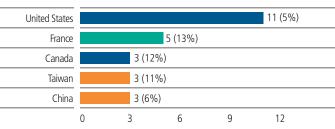
 Canada

 8

 0
 12
 24
 36
 48
 60

Top Countries with Technical Research Growth

Sites added, cumulative 2017 to 2021



^{*}Preclinical research sites conduct nonhuman FUS research to collect data in support of the safety or feasibility of clinical applications.

The United States leads the world in preclinical focused ultrasound research with over four-fold more research sites than the next closest country. This is likely a reflection of the US leading the world in medical research and the robust research infrastructure that exists in institutions of higher learning throughout the country.

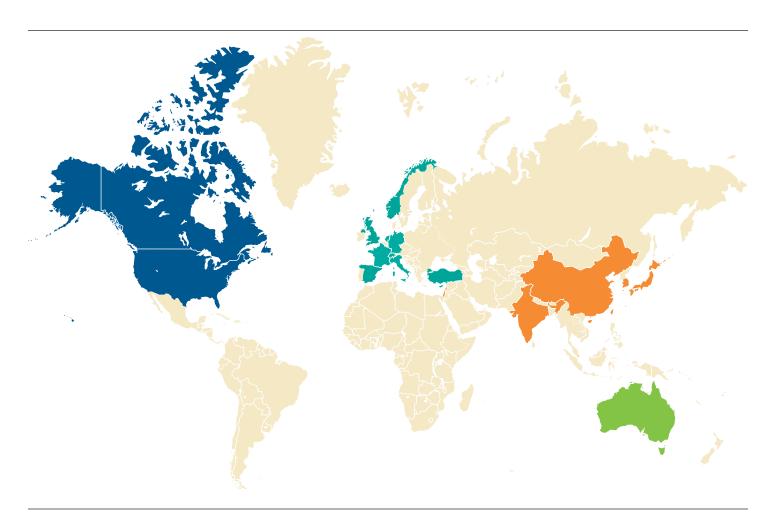
Preclinical research additional content

For more information about specific preclinical research sites and indications, please visit:

www.fusfoundation.org/the-technology/research-sites

Use the "search by disease research" and/or "search by research stage" dropdown menu.

Preclinical Research Sites by Country



■ North America

- 8 Canada
- 60 United States

Europe

- 1 Cyprus
- 13 France
- 6 Germany
- 2 Italy
- 1 The Netherlands
- 1 Norway
- 4 Spain
- 3 Switzerland
- 1 Turkey
- 5 United Kingdom

Asia

- 14 China
- 1 India
- 2 Israel
- 5 Japan
- 1 Singapore
- 7 South Korea
- 9 Taiwan

Oceania

3 Australia

108 indications are being researched at preclinical sites worldwide.

26

Cardiovascular sites
17 indications

29

Musculoskeletal sites
13 indications

29

Urological sites 9 indications

4

Endocrine disorders sites

4 indications

79

Neurological sites

30 indications

36

Women's health sites 8 indications 40

Gastrointestinal sites 7 indications

8

Ophthalmological sites 4 indications

25

Miscellaneous sites

9 indications

6

Pulmonary sites

3 indications

		Regions			
Indications	■ N. America	■ Europe	Asia	Oceania	
Cardiovascular					
Cardiac					
Atrial fibrillation	1	1	1	-	3
Cardiac hypertrophy	_	-	1	_	1
Cardiac pacing	_	1	-	-	1
Congestive heart failure	1	_	-	_	1
Fetal heart anomalies	1	-	-	-	1
Heart valve calcifications	_	1	-	_	1
Mitral regurgitation	_	1	-	-	1
Ventricular tachycardia	1	1	-	_	2
Peripheral					
Arteriovenous malformations	1	_	_	_	1
Atherosclerosis	4	1	1	-	6
Deep vein thrombosis	6	_	_	_	6
Hematoma	1	-	-	-	1

A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions				Totals	
Indications	■ N. America	■ Europe	Asia	Oceania		
Cardiovascular continued						
Hemophilia	1	_	_	_	1	
Hypertension	1	_	_	_	1	
Peripheral artery disease	2	_	_	_	2	
Twin-twin transfusion syndrome	1	3	1	_	5	
Varicose veins	_	1	_	-	1	
Endocrine disorders						
Diabetes	2	_	_	_	2	
Graves' disease	1	_	-	-	1	
Thyroid cancer	2	_	_	_	2	
Thyroid nodules	1	-	-	-	1	
Gastrointestinal						
Colorectal tumors	1	-	-	_	1	
Gastric tumors	-	1	-	-	1	
Inflammatory bowel disease	_	1	_	_	1	
Liver metastases	2	3	-	-	5	
Liver tumors	9	10	5	_	24	
Pancreatic tumors	-	-	4	-	4	
Pancreatic tumors, malignant	8	10	_	_	18	
Miscellaneous						
Head & neck tumors	2	1	1	_	4	
Heterotopic ossification	1	-	-	-	1	
Infection	2	_	1	_	3	
Melanoma	5	-	-	-	5	
Multiple tumors ¹	5	2	_	_	7	
Niemann-Pick disease	1	-	-	-	1	
Obesity	1	_	_	_	1	
Sinonasal disease	-	_	1	-	1	
Wound healing	2	_	_	1	3	

A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions					Totals
Indications	■ N. A	America	■ Europe	Asia	Oceania	
Musculoskeletal						
Arthritis, facetogenic		2	1	1	_	4
Arthritis, knee		_	_	1	-	1
Bone cancer		1	_	_	_	1
Bone metastases		4	1	3	1	9
Bone tumors, benign		1	1	_	-	2
Muscle atrophy		2	_	_	_	2
Osteoid osteoma		1	1	2	-	4
Osteomyelitis		1	_	_	-	1
Osteopenia		1	_	_	-	1
Rotator cuff injury		1	_	_	_	1
Soft tissue cancer		7	1	_	_	8
Soft tissue tumors, benign		3	_	2	_	5
Tendon contracture		1	_	_	_	1
Neurological						
Movement disorder						
Epilepsy		11	3	3	-	17
Essential tremor		_	1	2	_	3
Parkinson's disease, dyskinesia		_	_	1	-	1
Parkinson's disease, tremor		2	_	_	_	2
Neurodegenerative						
Alzheimer's disease		9	5	3	1	18
Amyotrophic lateral sclerosis		1	1	-	-	2
Dementia		_	_	1	_	1
Huntington's disease		1	_	_	-	1
Parkinson's disease, underlying cause		6	3	4	_	13
Rett syndrome		-	1	_	-	1
Other						
Hydrocephalus		1	_	_	-	1
Neuromyelitis optica		1	_	_	-	1

A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions				Totals	
Indications	■ N. America	■ Europe	Asia	Oceania		
Neurological continued						
Pain						
Cancer pain	1	2	-	-	3	
Headache	_	-	1	_	1	
Neuropathic pain	5	-	1	-	6	
Neuropathy	-	-	1	_	1	
Psychiatric						
Anxiety	1	-	_	_	1	
Depression	4	2	_	_	6	
Opioid and other addictions	1	1	1	_	3	
Trauma						
Spinal cord injury	3	-	1	_	4	
Traumatic brain injury	1	-	_	_	1	
Tumor						
Astrocytoma	4	2	3	_	9	
Brain metastases, breast cancer	3	1	_	_	4	
Brain metastases, melanoma	1	-	_	_	1	
Brain tumors, general	9	2	2	_	13	
Glioblastoma	18	9	9	_	36	
Pontine glioma	1	2	_	_	3	
Vascular						
Cavernomas	1	-	_	_	1	
Stroke, intracerebral hemorrhage	7	2	1	_	10	
Stroke, thromboembolic	4	3	_	_	7	
Ophthalmological						
Glaucoma	_	4	-	_	4	
Macular degeneration	1	1	-	_	2	
Presbyopia	_	-	1	_	1	
Retinal injury	1	-	-	-	1	

A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

	Regions				Totals
Indications	■ N. America	■ Europe	Asia	Oceania	
Pulmonary					
Lung cancer	3	1	1	_	5
Lung metastases	_	1	_	_	1
Tuberculosis	_	_	1	_	1
Urological					
Acute kidney injury	1	_	_	_	1
Acute tubular necrosis	1	_	-	-	1
Benign prostatic hyperplasia	1	_	1	_	2
Bladder tumors	2	_	_	_	2
Fetal bladder obstruction	_	_	1	_	1
Kidney stones	2	-	-	-	2
Kidney tumors	4	1	2	_	7
Prostate cancer	12	6	3	_	21
Urinary tract infection	_	1	_	_	1
Women's health					
Breast tumors, benign	1	_	1	_	2
Breast tumors, malignant	14	2	6	_	22
Cervical tumors	_	_	1	_	1
Endometrial tumors	1	_	1	_	2
Endometriosis	_	1	_	_	1
Ovarian tumors	1	_	1	1	3
Uterine adenomyosis	_	_	2	1	3
Uterine fibroids	4	2	8	1	15

A site may perform treatments on more than one indication within the same body system. Because of this, the total number of sites within a body system in the table may not equal the values provided in the summary at the top.

For more information about specific clinical research sites and indications, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by disease research" and/or "search by research stage" dropdown menu.

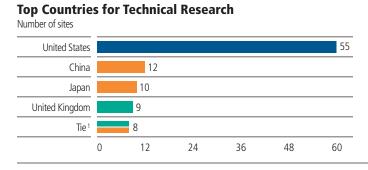
PRECLINICAL

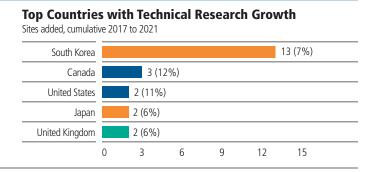
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Technical Research Sites by Region









Technical research additional content

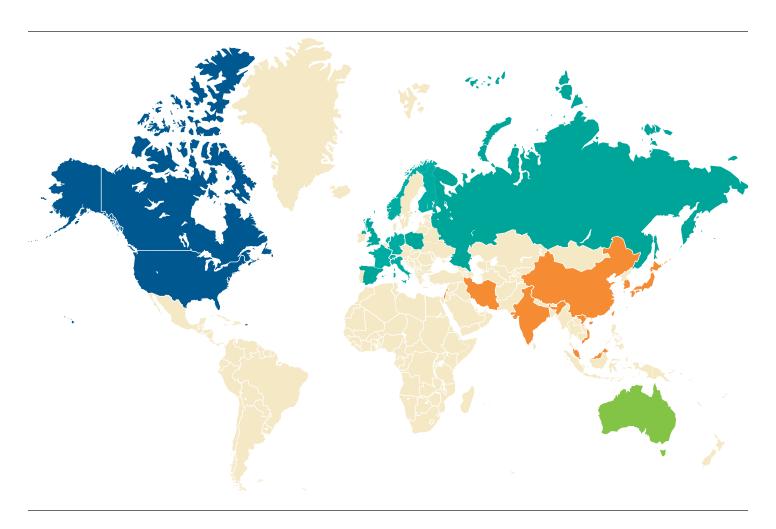
For more information about specific technical research sites, please visit:

www.fusfoundation.org/the-technology/research-sites

Use the "search by technical research" dropdown menu.

¹ Three way tie: France, Germany, and South Korea

Technical Research Sites by Country





- 6 Canada
- 55 United States

Europe

- 1 Cyprus
- 2 Finland
- 8 France
- 8 Germany
- 7 Italy
- 3 The Netherlands
- 1 Norway
- 2 Poland
- 1 Russian Federation
- 2 Spain
- 5 Switzerland
- 9 United Kingdom

Asia

- 12 China
- 1 India
- 1 Iran
- 1 Israel
- 10 Japan
- 1 Singapore
- 8 South Korea
- 4 Taiwan
- 1 Vietnam

Oceania

1 Australia

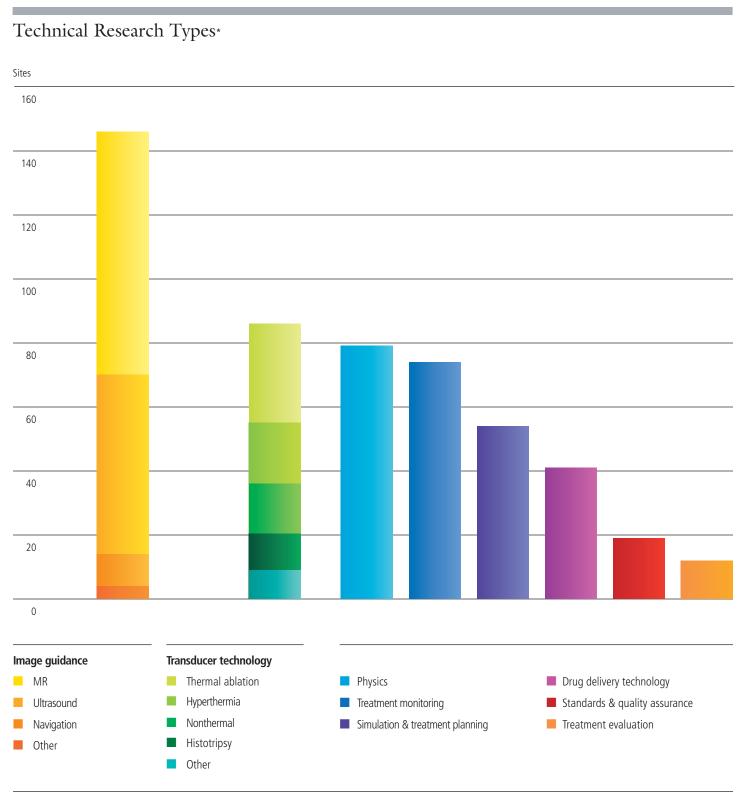
TECHNICAL RESEARCH

Technical Research Sites*

		Sites				
	<u>e</u> 3	Totals				
Image guidance	North America	Europe	Asia	Oceania	146	
MR	29	28	19	/ -		
Ultrasound	31	16	9	1-		
Navigation	1	7	2	_		
Other	1	1	2	- 75		
Transducer technology					86	
Thermal ablation	11	13	7	-		
Hyperthermia	8	8	3	Marko -		
Nonthermal	9	3	4	-		
Histotripsy	7	2	2	-		
Other	5	4	_			
Physics	40	24	15		79	
Treatment monitoring	31	28	15	_	74	
Simulation & treatment planning	25	21	8	-	54	
Drug delivery technology	25	11	4	1	41	
Standards & quality assurance	9	7	3	_	19	
Treatment evaluation	5	6	1	-	12	

Technical research programs address high-priority scientific and engineering problems that can stand in the way of the adoption of focused ultrasound as a mainstream standard of care. Solutions developed by technical sites help make clinical treatments safer, faster, less expensive, and available to a wider patient population.

^{*} Technical research sites may be working in more than one technical research area.



^{*} Technical research sites may be working in more than one technical research area.

Mechanisms of Action Research Sites by Region*

MOA research sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
78	42	55	_	2	_
8%	10%	Annual growth by reg	gion from 2013–2021 <u>–</u>	15 %	_

Top Countries for MOA Research

 Number of sites

 United States
 69

 China
 20

 France
 10

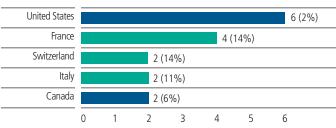
 Japan
 10

 South Korea
 10

 0
 16
 32
 48
 64
 80

Top Countries with MOA Research Growth

Sites added, cumulative 2017 to 2021



^{*}Mechanisms of action research sites conduct basic science research to understand how focused ultrasound affects the body.

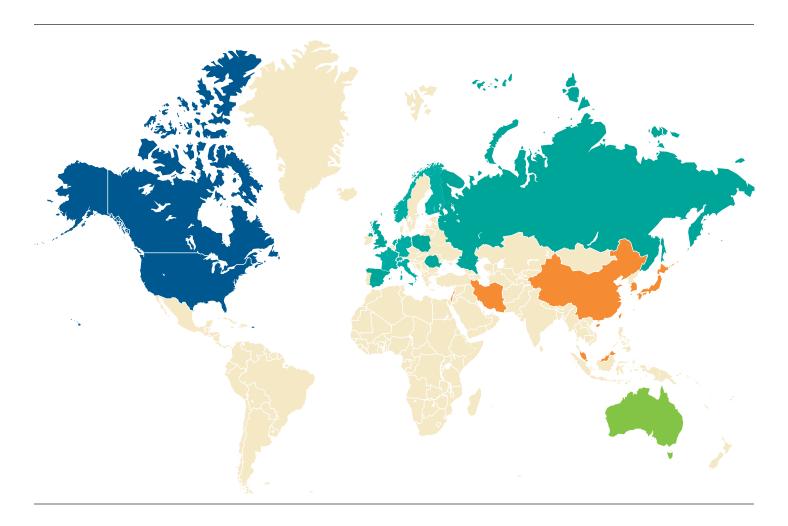
Mechanisms of action (MOA)

For more information about specific mechanisms of action research sites, please visit:

www.fusfoundation.org/the-technology/research-sites

Use the "search by biological effects research" dropdown menu.

Mechanisms of Action Research Sites by Country





- 9 Canada
- 69 United States

Europe

- 1 Bulgaria
- 1 Cyprus
- 10 France
- 5 Germany
- 6 Italy
- 2 The Netherlands
- 2 Norway 1 Russian Federation
- 2 Spain
- 5 Switzerland
- 7 United Kingdom

Asia

- 20 China
- 2 Iran
- 4 Israel
- 10 Japan
- 1 Malaysia
- 1 Singapore
- 10 South Korea
- 7 Taiwan

Oceania

2 Australia

MECHANISMS OF ACTION

Mechanisms of Action Ultrasound Applications and Biological Effects

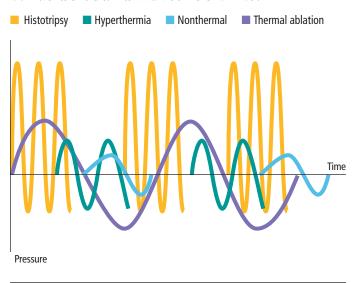
A mechanism of action occurs when an ultrasound application produces a biological effect.

Focused ultrasound is a medical technology that provides a uniquely flexible treatment platform applicable to a wide range of diseases and conditions. It can produce treatments across the spectrum of thermal to mechanical effects, and these various treatments elicit a multitude of responses in biological tissues.

Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver, thermal or mechanical, and whether the effects of treatment are permanent or transient. When focused ultrasound produces a high-power, continuous pressure wave, thermal energy accumulates rapidly at the focal point. This technique, termed thermal ablation, is currently used most frequently in the clinic, and produces permanent effects, but additional ultrasound treatment regimens are under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications being tested in clinical trials is a low-power, pulsed treatment that produces mild mechanical forces capable of enhancing drug delivery to the brain. This effect is transient, and treated tissue reverts to normal function within a few hours.

The effects induced by focused ultrasound can vary greatly depending on the ultrasound application and the type of tissue targeted. These biological effects are sometimes uniquely paired to a set of ultrasound parameters, as is the case with

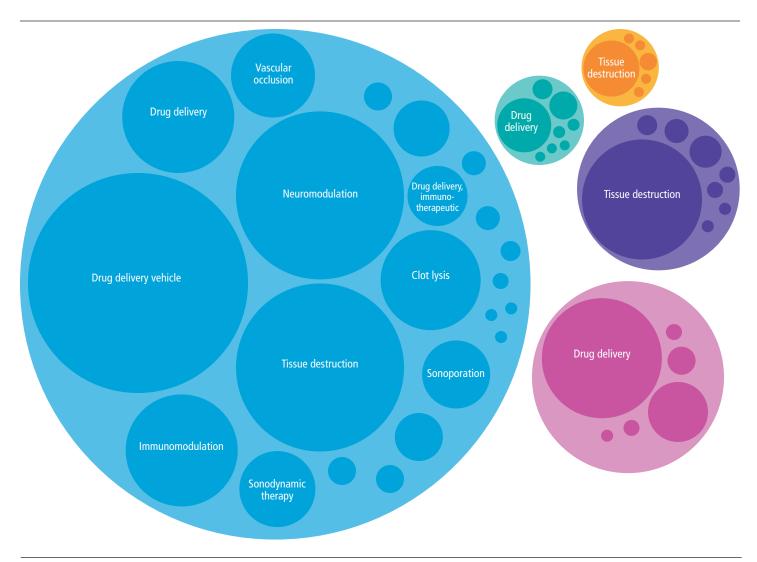
What do sound waves look like?



blood-brain barrier disruption, but others may be induced by multiple ultrasound applications. One active area of research is immunomodulation—altering the immune response to treated tissue. The immune response to focused ultrasound is dependent on the nature of the treatment parameters, although most treatments do induce a response.

In this section, we describe several ultrasound applications and the various biological effects they are known to produce. Researchers are working actively on many of these combinations of ultrasound application and biological effects, and more are discovered each year.

Mechanisms of Action Ultrasound Applications and Biological Effects



Ultrasound applications and biological effects

■ **Histotripsy** | 43 sites Amplification of cancer biomarkers Immune cell trafficking Immunomodulation Liquid biopsy Radiosensitization Tissue destruction

■ Hyperthermia | 48 sites Chemosensitization Drug delivery

> Drug delivery, immunotherapeutic Drug delivery, vehicle Immune cell trafficking Immunomodulation Radiosensitization Tissue destruction

■ Nonthermal | 320 sites

Amplification of cancer biomarkers Angiogenesis Cardiac pacing Chemosensitization Clot lysis Drug delivery Drug delivery, immunotherapeutic Drug delivery, vehicle Gene delivery Immune cell trafficking Immunomodulation Kidney stone fragmentation Liquid biopsy

Neuromodulation Radiosensitization Sonodynamic therapy Sonoporation Stem cell delivery Stem cell trafficking Tissue destruction Vascular occlusion

■ Nonthermal, BBB opening | 103 sites

Blood-brain barrier opening Drug delivery Drug delivery, immunotherapeutic

Gene delivery Immune cell delivery Stem cell delivery

Thermal ablation | 92 sites

> Amplification of cancer biomarkers Chemosensitization Hemostasis Immune cell trafficking Immunomodulation Neuromodulation Radiosensitization Tissue destruction

Ultrasound Applications and Biological Effects* *Table*

HISTOTRIPSY



biological effects

Alteration of tissue mechanics
Amplification of cancer
biomarkers
Chemosensitization
Clot lysis
Immune cell trafficking
Immunomodulation
Liquid biopsy
Radiosensitization
Tissue destruction

HYPERTHERMIA

12

biological effects

Amplification of cancer biomarkers
Chemosensitization
Drug delivery
Drug delivery,
immunotherapeutic
Drug delivery, vehicle
Immune cell delivery
Immune cell trafficking
Immunomodulation
Increased vascular
permeability
Radiosensitization
Tissue destruction
Vasodilation

NONTHERMAL

27

biological effects

Alteration of tissue mechanics
Amplification of cancer
biomarkers
Angiogenesis
Cardiac pacing
Chemosensitization
Clot lysis
Drug delivery
Drug delivery

immunotherapeutic Drug delivery, vehicle Gene delivery Immune cell delivery

Immune cell trafficking Immunomodulation Increased vascular permeability

Kidney stone fragmentation Kidney stone propulsion

Liquid biopsy Neuromodulation

Radiosensitization

Sonodynamic therapy Sonoporation

Stem cell delivery

Stem cell trafficking

Tissue destruction

Vascular occlusion Vasoconstriction

Vasodilation

NONTHERMAL, BBB OPENING

7

biological effects

BBB opening
Drug delivery
Drug delivery,
immunotherapeutic
Drug delivery, vehicle
Gene delivery
Immune cell delivery
Stem cell delivery

THERMAL ABLATION

10

biological effects

Alteration of tissue mechanics Amplification of cancer biomarkers Chemosensitization Hemostasis Immune cell trafficking

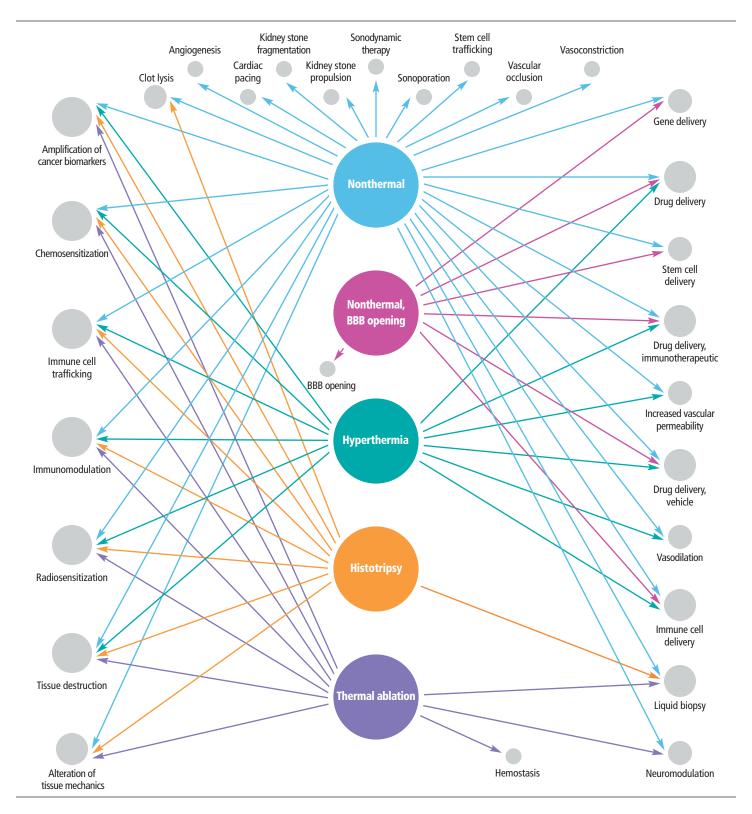
Immunomodulation Liquid biopsy Neuromodulation

Radiosensitization

Tissue destruction

^{*}This table lists all mechanisms of action utilized across all treatments and research types. Not all of these are being investigated specifically in mechanism of action research projects and may not appear in other tables in this section. All other tables reflect self-reported data by research and treatment sites.

Ultrasound Applications and Biological Effects Graphic



Mechanisms of Action Research Sites by Region

	Regions			Total	
	■ N. America	Europe	Asia	Oceania	
Histotripsy 43 sites					
Amplification of cancer biomarkers	1	_	_	_	1
Immune cell trafficking	1	_	_	_	1
Immunomodulation	6	3	_	_	9
Liquid biopsy	1	_	_	_	1
Radiosensitization	_	1	_	_	1
Tissue destruction	21	6	3	_	30
Hyperthermia 48 sites					
Chemosensitization	1	_	_	_	1
Drug delivery	14	7	3	-	24
Drug delivery, immunotherapeutic	_	1	_	_	1
Drug delivery, vehicle	1	1	-	_	2
Immune cell trafficking	1	_	_	_	1
Immunomodulation	1	1	-	_	2
Radiosensitization	3	3	1	_	7
Tissue destruction	5	2	3	_	10
Nonthermal 320 sites					
Amplification of cancer biomarkers	6	_	1	_	7
Angiogenesis	3	1	2	-	6
Cardiac pacing	_	_	1	_	1
Chemosensitization	5	2	_	_	7
Clot lysis	13	3	3	_	19
Drug delivery	13	6	2	_	21
Drug delivery, immunotherapeutic	7	2	_	1	10
Drug delivery, vehicle	29	9	20	_	58
Gene delivery	1	_	_	_	1
Immune cell trafficking	2	_	_	_	2
Immunomodulation	14	4	4	_	22
Kidney stone fragmentation	1	-	_	-	1
Liquid biopsy	4	1	_	_	5
Neuromodulation	29	10	16	1	56
Radiosensitization	5	_	_	_	5

For more information about specific mechanisms of action research sites, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by biological effects research" dropdown menu.

Mechanisms of Action Research Sites by Region continued

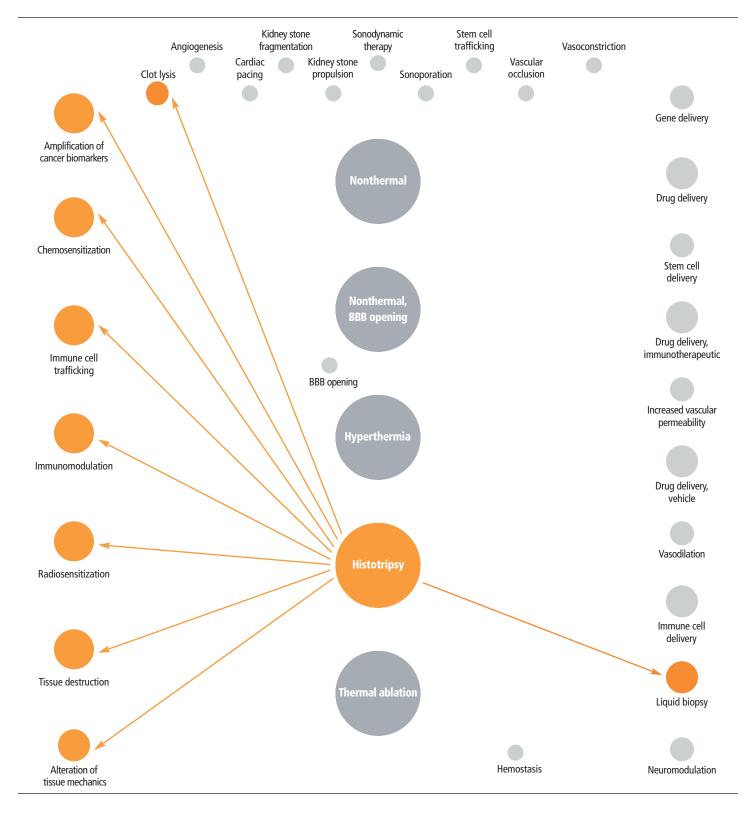
	Regions				Total
	■ N. America	■ Europe	Asia	Oceania	
Nonthermal continued					
Sonodynamic therapy	4	4	6	_	14
Sonoporation	8	2	2	_	12
Stem cell delivery	6	_	1	_	7
Stem cell trafficking	3	-	-	-	3
Tissue destruction	21	13	12	_	46
Vascular occlusion	10	3	4	-	17
Nonthermal, BBB opening 103 sites					
Blood-brain barrier opening	20	10	4	_	34
Drug delivery	24	16	20	1	61
Drug delivery, immunotherapeutic	2	1	_	_	3
Gene delivery	1	1	_	_	2
Immune cell delivery	1	_	_	_	1
Stem cell delivery	1	_	1	_	2
Thermal ablation 92 sites					
Amplification of cancer biomarkers	3	1	_	_	4
Chemosensitization	1	1	_	_	2
Hemostasis	2	_	_	_	2
Immune cell trafficking	2	1	_	_	3
Immunomodulation	6	4	2	_	12
Neuromodulation	1	_	_	_	1
Radiosensitization	1	_	_	_	1
Tissue destruction	32	19	15	1	67

Drug delivery spans three different ultrasound applications hyperthermia, nonthermal, and nonthermal BBB openingfor a total of 180 sites worldwide working on focused ultrasound-related drug delivery.

For more information about specific mechanisms of action research sites, please visit: www.fusfoundation.org/the-technology/research-sites. Use the "search by biological effects research" dropdown menu.

NEW

Ultrasound Applications and Biological Effects Graphic—Histotripsy



Histotripsy—Number of Sites for Biological Effects by Indications

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Histotripsy Alteration of tissue mechanics				
Heart valve calcifications	1	4	_	5
Liver tumors	1	_	_	1
Wound healing	1	_	_	1
Histotripsy Immunomodulation				
Brain tumors, general	1	_	_	1
Glioblastoma	1	_	_	1
Liver tumors	2	_	_	2
Melanoma	3	_	-	3
Pancreatic tumors, malignant	4	_	_	4
Soft tissue cancer	1	-	-	1
Histotripsy Liquid biopsy				
Pontine glioma	1	_	_	1
Histotripsy Tissue destruction				
Benign prostatic hyperplasia	1	_	_	1
Bone metastases	_	1	_	1
Brain metastases, breast cancer	1	_	_	1
Deep vein thrombosis	4	_	_	4
Epilepsy	1	_	_	1
Fetal heart anomalies	1	_	_	1
Glioblastoma	3	_	_	3
Hematoma	1	_	_	1
Heterotopic ossification	1	_	_	1
Infection	1	_	_	1
Kidney tumors	2	_	_	2
Liver metastases	1	_	_	1
Liver tumors	3	14	_	16
Mitral regurgitation	1	_	_	1
Multiple tumors ²	1	_	_	1
Pancreatic tumors, malignant	3	1	_	4

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

² Protocols inclusive of more than one indication

Histotripsy—Number of Sites for Biological Effects by Indications continued

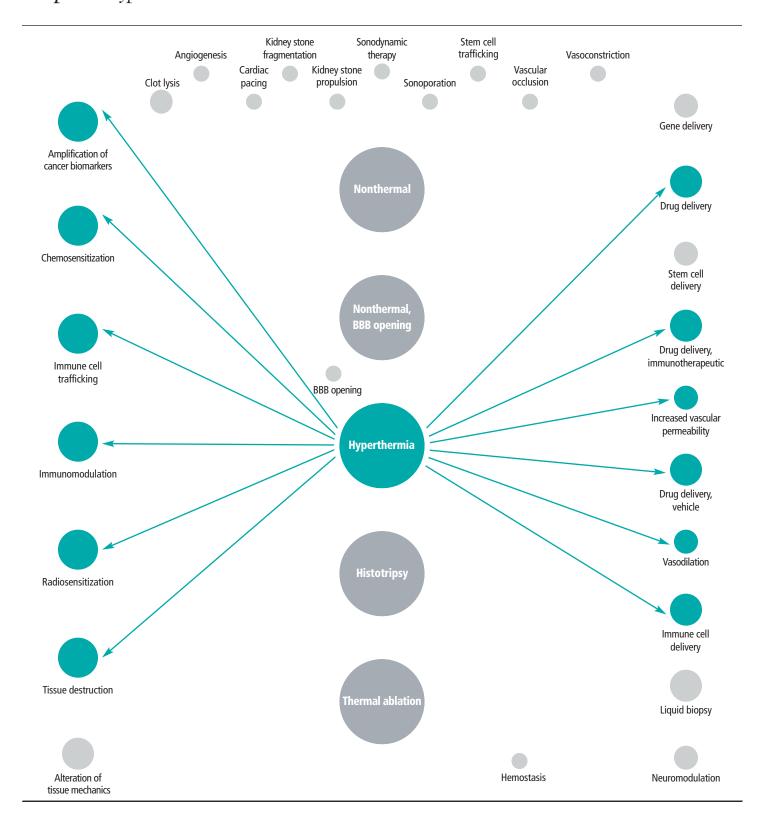
		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Histotripsy Tissue destruction continued				
Prostate cancer	1	_	_	1
Root canal endodontia	_	1	_	1
Rotator cuff injury	1	_	_	1
Soft tissue cancer	1	_	_	1
Stroke, intracerebral hemorrhage	1	_	_	1
Tendon contracture	1	-	_	1
Thyroid cancer	1	_	_	1
Uterine fibroids	1	_	_	1

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

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NEW

Ultrasound Applications and Biological Effects *Graphic—Hyperthermia*



Hyperthermia—Number of Sites for Biological Effects by Indications

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Hyperthermia Chemosensitization				
Multiple tumors ²	_	1	_	1
Pancreatic tumors, malignant	_	1	_	1
Soft tissue cancer	_	1	_	1
Hyperthermia Drug delivery				
Breast tumors, malignant	_	1	_	1
Glioblastoma	1	_	_	1
Head & neck tumors	1	_	_	1
Multiple tumors ²	2	-	-	2
Osteopenia	1	_	_	1
Pancreatic tumors, malignant	1	3	-	4
Soft tissue cancer	1	1	1	2
Wound healing	2	_	-	2
Hyperthermia Drug delivery, immunotherapeutic				
Breast tumors, malignant	1	_	_	1
Glioblastoma	1	_	_	1
Pancreatic tumors, malignant	1	_	_	1
Soft tissue cancer	1	_	_	1
Hyperthermia Drug delivery, vehicle				
Bone metastases	1	_	_	1
Soft tissue tumors, benign	1	_	_	1
Hyperthermia Immunomodulation				
Multiple tumors ²	2	_	_	2
Hyperthermia Radiosensitization				
Breast tumors, malignant	_	1	_	1
Cervical tumors	-	1	-	1
Head & neck tumors	1	1	_	2
Liver tumors	1	-	-	1

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

² Protocols inclusive of more than one indication

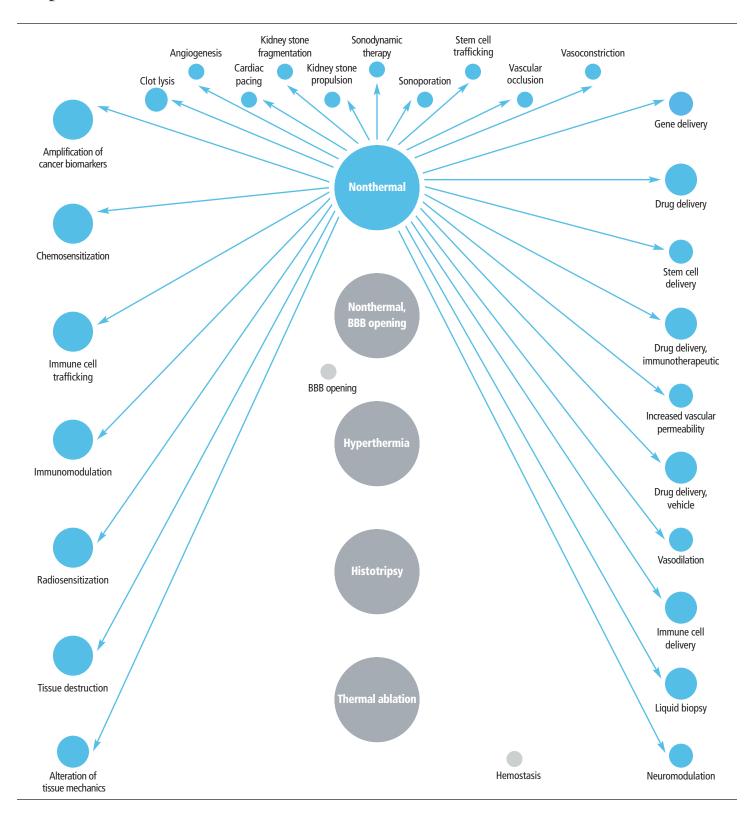
	Stages			Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Hyperthermia Tissue destruction				
Benign prostatic hyperplasia	_	1	_	1
Brain tumors, general	1	_	-	1
Breast tumors, benign	_	1	_	1
Desmoid tumors	_	_	1	1
Endometriosis	_	1	_	1
Essential tremor	_	1	_	1
Liver tumors	1	_	_	1
Lung cancer	1	_	_	1
Prostate cancer	1	1	1	3
Soft tissue cancer	_	1	-	1
Uterine adenomyosis	_	1	_	1
Hyperthermia Vasodilation				
Breast tumors, malignant	1	_	_	1

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Ultrasound Applications and Biological Effects Graphic—Nonthermal



		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal Alteration of tissue mechanics				
Alzheimer's disease	1	_	_	1
Neuropathic pain	1	_	_	1
Nonthermal Amplification of cancer biomarkers				
Brain tumors, general	1	_	_	1
Glioblastoma	-	1	_	1
Nonthermal Angiogenesis				
Muscle atrophy	1	_	_	1
Nonthermal Cardiac pacing				
Cardiac pacing	1	_	_	1
Nonthermal Clot lysis				
Deep vein thrombosis	1	_	_	1
Hydrocephalus	1	_	_	1
Nonthermal Drug delivery				
Alzheimer's disease	1	_	_	1
Atherosclerosis	3	_	-	3
Bladder tumors	1	_	_	1
Brain tumors, general	1	_	_	1
Breast tumors, malignant	-	1	_	1
Colorectal tumors	-	2	_	2
Hemophilia	1	_	_	1
Inflammatory bowel disease	1	-	_	1
Liver metastases	_	1	_	1
Macular degeneration	1	_	_	1
Pancreatic tumors, malignant	-	4	_	4
Pontine glioma	1	-	-	1
Stroke, intracerebral hemorrhage	1	_	_	1
Stroke, thromboembolic	2	-	_	2
Wound healing	1	_	_	1

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

² Protocols inclusive of more than one indication

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal Drug delivery, immunotherapeutic				
Multiple tumors ²	1	_	_	1
Pancreatic tumors, malignant	1	-	_	1
Nonthermal Drug delivery, vehicle				
Breast tumors, malignant	2	_	_	2
Cardiac hypertrophy	1	_	_	1
Deep vein thrombosis	1	_	_	1
Glioblastoma	2	-	_	2
Kidney tumors	1	_	_	1
Liver tumors	-	1	_	1
Neuropathic pain	1	_	_	1
Pancreatic tumors	1	_	_	1
Pancreatic tumors, malignant	3	-	_	3
Parkinson's disease, underlying cause	1	_	_	1
Peripheral artery disease	1	_	_	1
Prostate cancer	1	_	_	1
Stroke, intracerebral hemorrhage	2	_	_	2
Stroke, thromboembolic	1	_	_	1
Urinary tract infection	1	_	_	1
Nonthermal Gene delivery				
Brain tumors, general	1	_	_	1
Breast tumors, malignant	1	_	_	1
Epilepsy	1	_	_	1
Parkinson's disease, underlying cause	1	-	_	1
Retinal injury	1	_	_	1
Nonthermal Immune cell trafficking				
Glioblastoma	1	_	_	1

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² Protocols inclusive of more than one indication

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal Immunomodulation				
Brain tumors, general	1	_	_	1
Breast tumors, malignant	2	_	_	2
Epilepsy	1	-	-	1
Glaucoma	_	1	-	1
Glioblastoma	3	-	_	3
Pancreatic tumors, malignant	1	1	-	2
Prostate cancer	2	1	_	2
Nonthermal Increased vascular permeability				
Alzheimer's disease	_	1	_	1
Breast tumors, malignant	1	_	-	1
Deep vein thrombosis	1	_	_	1
Nonthermal Kidney stone fragmentation				
Kidney stones	2	_	_	2
Nonthermal Kidney stone propulsion				
Kidney stones	1	1	_	1
Nonthermal Liquid biopsy				
Brain tumors, general	1	-	-	1
Parkinson's disease, underlying cause	1	_	_	1
Nonthermal Neuromodulation				
ADHD	_	1	_	1
Alzheimer's disease	1	1	1	3
Anxiety	1	2	_	3
Cancer pain	1	-	-	1
Depression	5	5	_	9
Diabetes	1	_	_	1
Epilepsy	8	3	_	10
Headache	1	-	-	1
Mood disorder	_	2	_	2
Neuropathic pain	3	3	-	6

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		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal Neuromodulation continued				
Neuropathy	_	2	_	2
Obsessive-compulsive disorder	_	1	-	1
Opioid and other addictions	3	1	-	4
Parkinson's disease, tremor	1	-	-	1
Parkinson's disease, underlying cause	2	_	_	2
Schizophrenia	-	1	-	1
Stroke, intracerebral hemorrhage	1	_	_	1
Stroke, thromboembolic	-	1	-	1
Traumatic brain injury	_	3	-	3
Nonthermal Radiosensitization				
Brain tumors, general	1	_	_	1
Breast tumors, malignant	-	1	-	1
Glioblastoma	2	1	-	3
Head & neck tumors	-	1	-	1
Nonthermal Sonodynamic therapy				
Atherosclerosis	1	_	_	1
Biliary tract cancer	-	1	-	1
Brain tumors, general	2	_	_	2
Cavernomas	1	_	-	1
Deep vein thrombosis	1	_	_	1
Glioblastoma	2	1	_	3
Pancreatic tumors, malignant	2	_	_	2
Nonthermal Sonoporation				
Atherosclerosis	1	_	_	1
Head & neck tumors	1	_	-	1
Liver metastases	_	1	_	1
Liver tumors	-	1	-	1
Pancreatic tumors, malignant	1	1	_	2
Stroke, thromboembolic	1	-	-	1

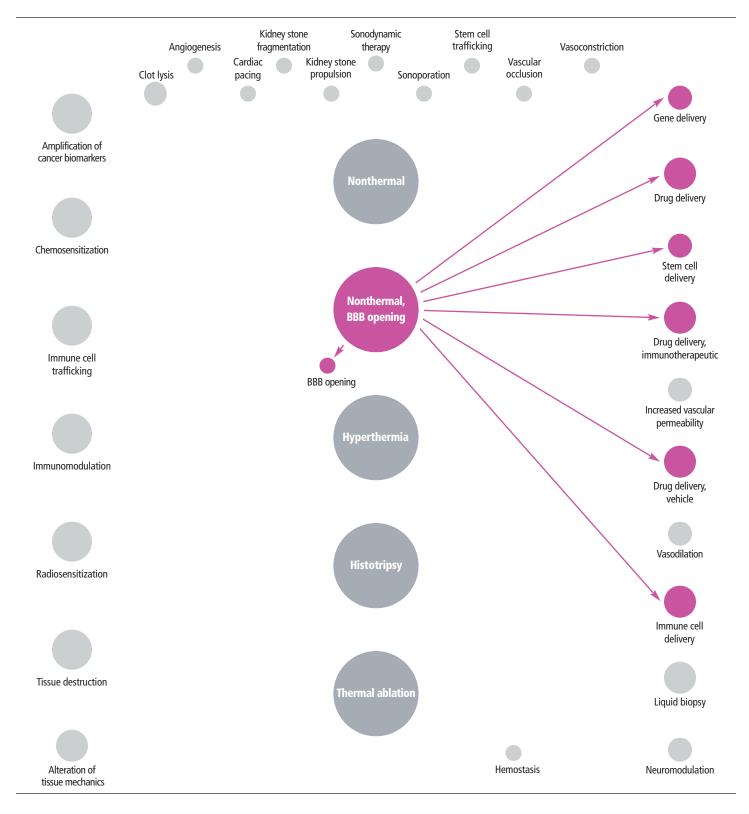
¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal Stem cell delivery				
Acute kidney injury	1	_	_	1
Acute tubular necrosis	1	_	_	1
Atherosclerosis	1	_	_	1
Muscle atrophy	1	_	-	1
Nonthermal Tissue destruction				
Arteriovenous malformations	1	_	_	1
Arthritis, facetogenic	1	_	_	1
Benign prostatic hyperplasia	1	_	_	1
Brain tumors, general	1	_	_	1
Breast tumors, malignant	2	_	_	2
Glioblastoma	1	_	_	1
Head & neck tumors	1	_	_	1
Liver metastases	1	_	_	1
Liver tumors	2	_	_	2
Pancreatic tumors, malignant	3	_	_	3
Prostate cancer	2	_	_	2
Soft tissue cancer	1	-	-	1
Uterine fibroids	1	_	_	1
Nonthermal Vascular occlusion				
Arteriovenous malformations	_	1	_	1
Brain tumors, general	1	_	-	1
Glioblastoma	1	_	_	1
Macular degeneration	1	_	_	1
Twin-twin transfusion syndrome	5	_	_	5
Nonthermal Vasodilation				
Neuropathy	1	_	-	1
Stroke, thromboembolic	1	_	_	1

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Ultrasound Applications and Biological Effects Graphic—Nonthermal, BBB opening



Nonthermal, BBB opening—Number of Sites for Biological Effects by Indications

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal, BBB opening BBB opening				
Alzheimer's disease	7	9	_	12
Amyotrophic lateral sclerosis	1	1	_	2
Brain metastases, breast cancer	1	_	_	1
Brain tumors, general	4	1	-	5
Breast tumors, malignant	1	_	_	1
Dementia	1	_	_	1
Epilepsy	1	_	_	1
Glioblastoma	1	7	_	8
Nonthermal, BBB opening Drug delivery				
Alzheimer's disease	8	2	_	9
Amyotrophic lateral sclerosis	1	_	_	1
Astrocytoma	1	_	_	1
Brain metastases, breast cancer	2	1	-	2
Brain metastases, melanoma	_	1	_	1
Brain tumors, general	4	1	_	5
Dementia	_	1	_	1
Epilepsy	2	-	_	2
Glioblastoma	16	12	_	22
Infection	1	-	_	1
Neuromyelitis optica	1	_	_	1
Parkinson's disease, tremor	1	-	_	1
Parkinson's disease, underlying cause	3	1	_	4
Pontine glioma	1	-	_	1
Spinal cord injury	2	_	_	2
Stroke, intracerebral hemorrhage	1	_	_	1
Stroke, thromboembolic	2	_	_	2
Traumatic brain injury	1	-	-	1

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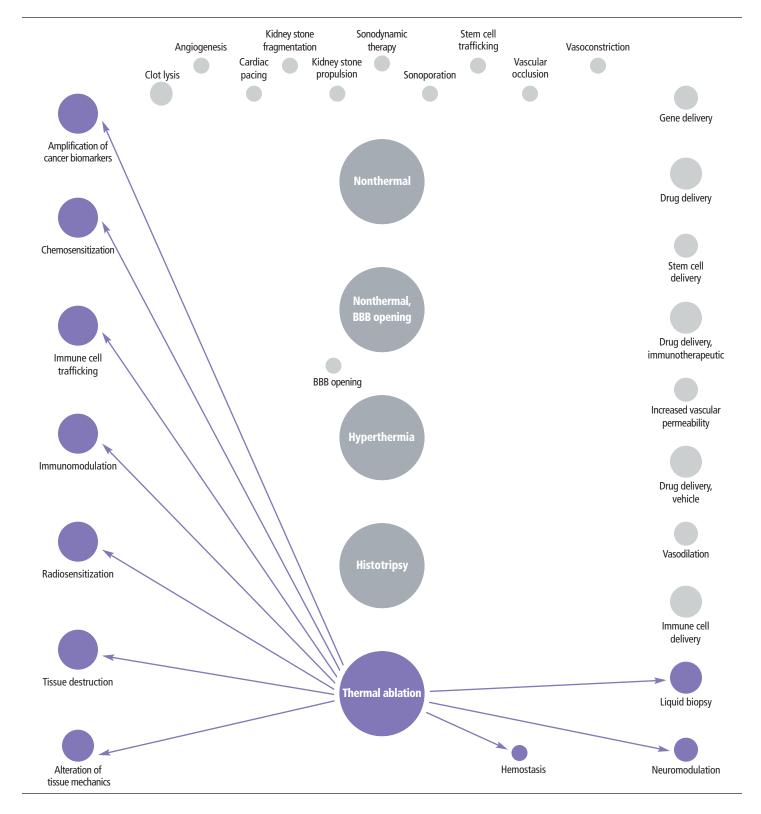
		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Nonthermal, BBB opening Drug delivery, immunotherapeutic				
Alzheimer's disease	2	_	_	2
Brain metastases, breast cancer	1	-	_	1
Brain metastases, melanoma	1	_	_	1
Brain tumors, general	2	_	_	2
Glioblastoma	1	_	_	1
Nonthermal, BBB opening Drug delivery, vehicle				
Brain tumors, general	_	1	_	1
Glioblastoma	1	_	_	1
Nonthermal, BBB opening Gene delivery				
Alzheimer's disease	1	_	_	1
Brain tumors, general	3	_	_	3
Epilepsy	1	_	_	1
Huntington's disease	1	_	_	1
Niemann-Pick disease	1	_	_	1
Parkinson's disease, dyskinesia	1	_	_	1
Parkinson's disease, underlying cause	6	_	_	6
Rett syndrome	1	-	_	1
Nonthermal, BBB opening Stem cell delivery				
Alzheimer's disease	1	_	_	1

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

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NEW

Ultrasound Applications and Biological Effects Graphic—Thermal ablation



Thermal ablation—Number of Sites for Biological Effects by Indications

	Stages			Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Thermal ablation Alteration of tissue mechanics				
Urinary incontinence, stress	_	1	_	1
Thermal ablation Chemosensitization				
Bone metastases	_	1	_	1
Thermal ablation Hemostasis				
Twin-twin transfusion syndrome	_	1	_	1
Varicose veins	1	_	_	1
Thermal ablation Immunomodulation				
Breast tumors, malignant	5	_	_	5
Cervical tumors	_	1	_	1
Esophageal tumors	_	1	_	1
Gastric tumors	-	1	_	1
Lung cancer	_	1	_	1
Melanoma	2	1	_	2
Multiple tumors ²	1	1	_	2
Ovarian tumors	1	1	_	2
Pancreatic tumors, malignant	4	1	_	4
Soft tissue cancer	1	1	_	2
Thermal ablation Liquid biopsy				
Brain tumors, general	-	1	_	1
Thermal ablation Neuromodulation				
Epilepsy	1	_	_	1
Neuropathic pain	_	1	_	1

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

² Protocols inclusive of more than one indication

Thermal ablation—Number of Sites for Biological Effects by Indications continued

Thermal ablation is the most mature of the focused ultrasound effects. This is evidenced by how few bench research sites there are working in this area, or conversely how many sites are clinical and commercial stage.

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Thermal ablation Tissue destruction				
Cardiovascular				
Arteriovenous malformations	_	_	2	2
Atrial fibrillation	2	1	_	3
Hypertension	-	1	_	1
Peripheral artery disease	_	_	1	1
Twin-twin transfusion syndrome	1	-	_	1
Varicose veins	_	5	9	14
Ventricular tachycardia	2	-	_	2
Endocrine disorders				
Graves' disease	_	1	_	1
Thyroid nodules	_	1	16	17
Gastrointestinal				
Colorectal tumors	1	4	_	5
Gastric tumors	1	-	_	1
Liver metastases	3	1	3	6
Liver tumors	13	21	139	157
Pancreatic tumors	2	5	44	51
Pancreatic tumors, malignant	6	8	5	17

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		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Thermal ablation Tissue destruction				
Miscellaneous				
Actinic keratosis	_	1	_	1
Basal cell carcinoma	_	2	_	2
Dercum's disease	_	1	_	1
Head & neck tumors	_	1	_	1
Hypersplenism	_	1	_	1
Infection	1	_	_	1
Kaposi's sarcoma	_	1	_	1
Lipoma	_	1	_	1
Multiple tumors ²	1	1	_	2
Sinonasal disease	1	_	_	1
Musculoskeletal				
Arthritis, facetogenic	2	12	4	15
Arthritis, knee	-	1	-	1
Arthritis, sacroiliac	_	2	_	2
Bone cancer	_	5	6	11
Bone metastases	5	19	37	51
Bone tumors, benign	1	3	2	6
Desmoid tumors	_	6	9	14
Osteoid osteoma	4	24	104	109
Osteomyelitis	1	_	_	1
Plantar fasciitis	_	1	_	1
Sacral chordoma	_	1	_	1
Soft tissue cancer	_	5	1	6
Soft tissue tumors, benign	2	23	95	101
Tendon contracture	1	-	-	1

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² Protocols inclusive of more than one indication

		Stages		Total ¹
Ultrasound application Biological effects	Preclinical	Clinical	Commercial	
Thermal ablation Tissue destruction continued				
Neurological				
Astrocytoma	_	2	_	2
Brain tumors, general	1	_	_	1
Cancer pain	1	1	_	2
Depression	1	2	1	2
Dystonia	-	2	1	3
Dystonia, hand	_	1	1	1
Epilepsy	3	7	2	10
Essential tremor	3	16	80	85
Glioblastoma	2	4	_	6
Multiple sclerosis	_	1	_	1
Neuroblastoma	_	1	-	1
Neurofibromatosis	_	1	_	1
Neuropathic pain	1	2	3	6
Neuropathy	_	_	1	1
Obsessive-compulsive disorder	-	2	2	3
Painful amputation neuromas	_	1	-	1
Parkinson's disease, dyskinesia	-	11	4	13
Parkinson's disease, tremor	_	11	28	37
Parkinson's disease, underlying cause	1	_	-	1
Tremor, orthostatic	-	1	-	1
Trigeminal neuralgia	-	1	1	2
Ophthalmological				
Glaucoma	4	6	14	22
Presbyopia	1	_	_	1

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	Stages			Total ¹	
Ultrasound application Biological effects	Preclinical	Clinical	Commercial		
Thermal ablation Tissue destruction continued					
Pulmonary					
Lung cancer	3	_	_	3	
Lung metastases	1	_	_	1	
Rhinitis	_	1	_	1	
Tuberculosis	1	_	_	1	
Urological					
Benign prostatic hyperplasia	_	3	37	40	
Chyluria	-	1	-	1	
Fetal bladder obstruction	1	_	_	1	
Kidney tumors	2	17	94	96	
Prostate cancer	7	54	411	436	
Women's health					
Breast tumors, benign	2	7	13	20	
Breast tumors, malignant	8	23	96	109	
Cervical tumors	1	3	_	4	
Cervicitis	-	-	1	1	
Ectopic pregnancy	_	1	_	1	
Endometrial tumors	2	1	1	4	
Endometriosis	1	1	2	3	
Endometriosis, colorectal	_	4	-	4	
Lichen sclerosis	_	1	1	2	
Ovarian tumors	2	1	-	3	
Retained placenta	_	1	_	1	
Uterine adenomyosis	2	22	98	113	
Uterine fibroids	10	59	325	348	
Vaginal tumors	-	2	-	2	

¹ A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Cardiovascular					
Cardiac					
Atrial fibrillation					
Cardiac hypertrophy					
Cardiac pacing	_				
Fetal heart anomalies					
Heart valve calcifications					
Mitral regurgitation					
Ventricular tachycardia	\odot				
Peripheral					
Arteriovenous malformations			₽ 1		
Atherosclerosis					
Deep vein thrombosis					
Hematoma					
Hemophilia					
Hypertension		②			
Peripheral artery disease			₽ 1		
Twin-twin transfusion syndrome	▲ ۞	②			
Varicose veins	©		•	•	

1 Off-label treatment

Histotripsy

- Alteration of tissue mechanics
- Immunomodulation
- Liquid biopsy
- Radiosensitization
- Tissue destruction

Hyperthermia

- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal

- ▲ Alteration of tissue mechanics
- Amplification of cancer biomarkers
- Angiogenesis
- ▲ Cardiac pacing
- ▲ Clot lysis
- ▲ Drug delivery
- ▲ Drug delivery, immunotherapeutic
- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation

- Increased vascular permeability
- ▲ Kidney stone fragmentation
- ▲ Kidney stone propulsion
- ▲ Liquid biopsy
- ▲ Neuromodulation
- ▲ Radiosensitization
- ▲ Sonodynamic therapy
- ▲ Sonoporation
- ▲ Stem cell delivery
- ▲ Tissue destruction
- ▲ Vascular occlusion
- Vasodilation

Nonthermal - BBB opening

- BBB opening
- ◆ Drug delivery
- Drug delivery, immunotherapeutic
- ◆ Drug delivery, vehicle
- ◆ Gene delivery
- ◆ Stem cell delivery

- Alteration of tissue mechanics
- Chemosensitization
- Clot lysis
- Hemostasis
- Immunomodulation
- Liquid biopsy
- Neuromodulation
- Tissue destruction



			2 10.9 22		
Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Endocrine disorders					
Diabetes					
Graves' disease		©			
Thyroid cancer					
Thyroid nodules			②	\odot	
Gastrointestinal					
Biliary tract cancer					
Colorectal tumors		▲ ۞			
Esophageal tumors					
Gastric tumors	©				
Inflammatory bowel disease					
Liver metastases			②	©	
Liver tumors			②	©	
Pancreatic tumors			②	\odot	

Histotripsy

Alteration of tissue mechanics

Pancreatic tumors, malignant

Root canal endodontia

- Immunomodulation
- Liquid biopsy
- Radiosensitization
- Tissue destruction

Hyperthermia

- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal

- ▲ Alteration of tissue mechanics
- ▲ Amplification of cancer biomarkers
- Angiogenesis
- Cardiac pacing
- ▲ Clot lysis
- ▲ Drug delivery
- Drug delivery, immunotherapeutic
- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation

- ▲ Increased vascular permeability
- ▲ Kidney stone fragmentation
- ▲ Kidney stone propulsion
- ▲ Liquid biopsy
- ▲ Neuromodulation
- ▲ Radiosensitization
- Sonodynamic therapy
- Sonoporation
- ▲ Stem cell delivery
- ▲ Tissue destruction Vascular occlusion
- Vasodilation

Nonthermal -**BBB** opening

Stages

- BBB opening
- Drug delivery
- Drug delivery, immunotherapeutic
- ◆ Drug delivery, vehicle
- ◆ Gene delivery
- ◆ Stem cell delivery

- Alteration of tissue mechanics
- Chemosensitization
- Clot lysis
- Hemostasis
- Immunomodulation
- Liquid biopsy
- Neuromodulation
- Tissue destruction



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Miscellaneous					
Actinic keratosis		•			
Basal cell carcinoma		②			
Dercum's disease		۞			
Head & neck tumors		● ▲ ۞			
Heterotopic ossification					
Hypersplenism		O			
Infection	■ ♦ ♦				
Kaposi's sarcoma		⇔			
Lipoma		۞			
Melanoma		②			
Multiple tumors ²		○ ۞ ۞			
Niemann-Pick disease	+				
Sinonasal disease	©				
Wound healing					

² Protocols inclusive of more than one indication

Histotripsy

- Alteration of tissue mechanics
- Immunomodulation
- Liquid biopsy
- Radiosensitization
- Tissue destruction

Hyperthermia

- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal

- ▲ Alteration of tissue mechanics
- Amplification of cancer biomarkers
- Angiogenesis
- △ Cardiac pacing
- ▲ Clot lysis
- ▲ Drug delivery
- ▲ Drug delivery, immunotherapeutic
- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation

- Increased vascular permeability
- ▲ Kidney stone fragmentation
- ▲ Kidney stone propulsion
- ▲ Liquid biopsy
- ▲ Neuromodulation
- ▲ Radiosensitization
- ▲ Sonodynamic therapy
- Sonoporation
- ▲ Stem cell delivery
- ▲ Tissue destruction
- ▲ Vascular occlusion
- Vasodilation

Nonthermal - BBB opening

- BBB opening
- Drug delivery
- Drug delivery, immunotherapeutic
- ◆ Drug delivery, vehicle
- ◆ Gene delivery
- ◆ Stem cell delivery

- Alteration of tissue mechanics
- Chemosensitization
- Clot lysis
- Hemostasis
- Immunomodulation
- C Liquid biopsy
- Neuromodulation
- Tissue destruction



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Musculoskeletal					
Arthritis, facetogenic	A		\odot	•	
Arthritis, knee		•			
Arthritis, sacroiliac		•			
Bone cancer			•	②	
Bone metastases	•			②	•
Bone tumors, benign			\odot	②	
Desmoid tumors			● ¹ ②	۞	
Muscle atrophy	A A				
Osteoid osteoma				۞	•
Osteomyelitis	۞				
Osteopenia					
Plantar fasciitis					
Rotator cuff injury					
Sacral chordoma					
Soft tissue cancer		• • •	● 1 ☆	•	
Soft tissue tumors, benign			©	②	
Tendon contracture					

1 Off-label treatment

Histotripsy

- Alteration of tissue mechanics
- Immunomodulation
- Liquid biopsy
- Radiosensitization
- Tissue destruction

Hyperthermia

- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal

- ▲ Alteration of tissue mechanics
- ▲ Amplification of cancer biomarkers
- Angiogenesis
- Cardiac pacing
- Clot lysis
- Drug delivery
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- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation

- Increased vascular permeability
- ▲ Kidney stone fragmentation
- ▲ Kidney stone propulsion
- ▲ Liquid biopsy
- ▲ Neuromodulation
- ▲ Radiosensitization
- Sonodynamic therapy
- Sonoporation
- ▲ Stem cell delivery
- ▲ Tissue destruction
- Vascular occlusion
- Vasodilation

Nonthermal -**BBB** opening

- BBB opening
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- Tissue destruction



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological					
Movement disorder					
Dystonia			₽ 1		
Dystonia, hand			₽ 1		
Epilepsy	■ ▲ ▲ → → →		☆ 1		
Essential tremor		•		②	②
Parkinson's disease, dyskinesia	+			②	©
Parkinson's disease, tremor	*		•	②	©
Tremor, orthostatic		⇔			
Neurodegenerative					
Alzheimer's disease	A A + + +	A + +	1		
Amyotrophic lateral sclerosis	+	*			
Dementia	*	*			
Huntington's disease	+				
Multiple sclerosis		②			
Parkinson's disease, underlying cause	▲ ▲ ▲ ▲ +	+			
Rett syndrome	+				

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Stages

Indications by body systems	Preclinical		Clinical		Commercial treatment	Outside appro	FDA approvals
Neurological continued							
Other							
Hydrocephalus	A						
Neuromyelitis optica	*						
Pain							
Cancer pain							
Headache							
Neuropathic pain		▲ ۞					
Neuropathy	A			1			
Painful amputation neuromas							
Trigeminal neuralgia				1			
Psychiatric							
ADHD							
Anxiety							
Depression							
Mood disorder							
Obsessive-compulsive disorder							
Opioid and other addictions							
Schizophrenia							

1 Off-label treatment

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Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Trauma					
Spinal cord injury	*				
Traumatic brain injury	*				
Tumor					
Astrocytoma	*	②			
Brain metastases, breast cancer	+ +	*			
Brain metastases, melanoma	*	+			
Brain tumors, general		+++•			
Glioblastoma		▲ ▲ ▲ + +			
Neuroblastoma		②			
Neurofibromatosis		②			
Pontine glioma	■ ♦ ▲				

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Mechanisms of Action by Indication and Stage—Body Systems continued

S	ta	ıg	e	S

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Vascular					
Cavernomas	A				
Stroke, intracerebral hemorrhage					
Stroke, thromboembolic	A A A +				
Ophthalmological					
Glaucoma				©	
Macular degeneration					
Presbyopia	•				
Retinal injury	A				
Pulmonary					
Lung cancer	• •	•			
Lung metastases	•				
Rhinitis					
Tuberculosis	©				

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Mechanisms of Action by Indication and Stage—Body Systems continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Urological					
Acute kidney injury					
Acute tubular necrosis					
Benign prostatic hyperplasia			©	•	•
Bladder tumors					
Chyluria					
Fetal bladder obstruction					
Kidney stones					
Kidney tumors			•	©	
Prostate cancer			● ¹ ②	©	•
Urinary tract infection	A				

¹ Off-label treatment

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Mechanisms of Action by Indication and Stage—Body Systems continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Women's health					
Breast tumors, benign		•	•	•	
Breast tumors, malignant			&	0	
Cervical tumors		• 😯 🗘			
Cervicitis			*	©	
Ectopic pregnancy					
Endometrial tumors			₽ 1		
Endometriosis			₽ 1		
Endometriosis, colorectal					
Lichen sclerosis				©	
Ovarian tumors		♦			
Retained placenta					
Urinary incontinence, stress					
Uterine adenomyosis				©	
Uterine fibroids			*	②	•
Vaginal tumors		©			

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Mechanisms of Action by Indication and Stage—Fetal

Stages					
Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Cardiovascular					
Cardiac					
Fetal heart anomalies					
Peripheral					
Twin-twin transfusion syndrome	▲ ❖				
Urological					
Fetal bladder obstruction	•				

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- ▲ Tissue destruction
- ▲ Vascular occlusion
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Mechanisms of Action by Indication and Stage—Pain

		Stages						
Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals			
Cardiovascular								
Peripheral								
Varicose veins	©		\odot	©				
Gastrointestinal								
Pancreatic tumors			\odot	⇔				
Pancreatic tumors, malignant	₩ • ▲ ▲ ▲		⇔	0				
Miscellaneous								
Dercum's disease		۞						
Musculoskeletal								
Arthritis, facetogenic			\odot	②				
Arthritis, knee		☆						
Arthritis, sacroiliac		☆						
Bone cancer				②				
Bone metastases			\odot	\odot	⇔			
Bone tumors, benign				②				
Desmoid tumors			● ¹ ②	⇔				
Osteoid osteoma			\odot	②	⇔			

1 Off-label treatment

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Hyperthermia

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Mechanisms of Action by Indication and Stage—Pain continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Musculoskeletal continued					
Osteomyelitis	•				
Plantar fasciitis		•			
Rotator cuff injury					
Neurological					
Pain					
Cancer pain					
Headache					
Neuropathic pain		▲ 😌	\odot		
Neuropathy			⊘ 1		
Painful amputation neuromas		⇔			
Trigeminal neuralgia			© 1		

¹ Off-label treatment

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Mechanisms of Action by Indication and Stage—Pediatrics

Stages

Preclinical		Commercial	Outside US	ED A
Preciiiicai	Clinical	treatment	approvals	FDA approvals
• • •				
		©	•	•
		● ¹ ②	•	
		©	•	•
	②			
		● 1 ☆	②	
		©	•	
▲ ▲ + +		⊕ 1		
	A			

¹ Off-label treatment

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² Protocols inclusive of more than one indication



Mechanisms of Action by Indication and Stage—Pediatrics continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Tumor					
Astrocytoma	*	\odot			
Brain tumors, general	■ •	+++0			
Neuroblastoma		©			
Neurofibromatosis		©			
Pontine glioma	■ ▲ ♦				

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Mechanisms of Action by Indication and Stage—Oncology

	Stages				
Indications by body systems	Preclinical	Clinical	Commercial treatment		FDA approvals
Endocrine disorders					
Thyroid cancer					
Gastrointestinal					
Biliary tract cancer					
Colorectal tumors		▲ ۞			
Esophageal tumors		©			
Gastric tumors	•	©			
Liver metastases			②	©	
Liver tumors			②	©	
Pancreatic tumors			②	©	
Pancreatic tumors, malignant			②	©	
		▲ ☆			
Miscellaneous					
Basal cell carcinoma		©			
Head & neck tumors		● ▲ ۞			
Kaposi's sarcoma		©			
Melanoma					

² Protocols inclusive of more than one indication

Histotripsy

Alteration of tissue mechanics

Multiple tumors²

- Immunomodulation
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Mechanisms of Action by Indication and Stage—Oncology continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Musculoskeletal					
Bone cancer			©	②	
Bone metastases	•		•	©	•
Sacral chordoma		③			
Soft tissue cancer		● ● ☆	1 😂	©	
Neurological					
Pain					
Cancer pain		②			
Tumor					
Brain metastases, breast cancer	+ +	+			
Brain metastases, melanoma	*	*			
Brain tumors, general		+++			
	$\triangle + + \diamondsuit$				
Glioblastoma		A A A + +			
	A A A +	②			
	*				
Neuroblastoma		②			
Neurofibromatosis		•			
Pontine glioma	A +				

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Mechanisms of Action by Indication and Stage—Oncology continued

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Pulmonary					
Lung cancer	• •	•			
Lung metastases					
Urological					
Bladder tumors					
Kidney tumors			⇔	②	
Prostate cancer			● 1 ②	⇔	⇔
Women's health					
Breast tumors, malignant			⇔	0	
Cervical tumors					
Endometrial tumors			1		
Ovarian tumors		☆ ☆			
Vaginal tumors		②			

1 Off-label treatment

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Hyperthermia

- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal

- ▲ Alteration of tissue mechanics
- ▲ Amplification of cancer biomarkers
- Angiogenesis
- Cardiac pacing
- ▲ Clot lysis
- ▲ Drug delivery
- Drug delivery, immunotherapeutic
- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation

- ▲ Increased vascular permeability
- ▲ Kidney stone fragmentation
- ▲ Kidney stone propulsion
- ▲ Liquid biopsy
- ▲ Neuromodulation
- ▲ Radiosensitization
- Sonodynamic therapy
- Sonoporation
- ▲ Stem cell delivery
- ▲ Tissue destruction
- Vascular occlusion
- Vasodilation

Nonthermal -**BBB** opening

- BBB opening
- Drug delivery
- Drug delivery, immunotherapeutic
- ◆ Drug delivery, vehicle
- ◆ Gene delivery
- ◆ Stem cell delivery

- Alteration of tissue mechanics
- Chemosensitization
- Clot lysis
- Hemostasis
- Immunomodulation
- Liquid biopsy
- Neuromodulation
- Tissue destruction

Case Study Breast Cancer

This year, we're taking a closer look at several aspects of focused ultrasound as a treatment for breast cancer.

Medical needs

Breast cancer is the most common cancer in women. It results from an uncontrollable growth of lining epithelium cells that multiply and most often form a mass in glandular tissue, ducts, or lobules. In 2020, 2.3 million women worldwide were diagnosed with breast cancer according to the World Health Organization. It is generally a disease with a good prognosis, with 90 percent survival for at least 5 years after diagnosis in high-income countries, where standard treatments include surgery, radiotherapy, hormone therapy, chemotherapy, and targeted therapies, delivered alone or in combination.

Disease control for most nonmetastatic cancers is good, but the quality of life for many breast cancer survivors can be greatly affected by the treatments' side effects, which can include pain, insomnia, breast symptoms, deteriorated physical and cognitive function, dyspnea, body image.

For metastatic cancers, the issue is different, as effective treatments are rarer and novel treatment modalities are needed.

FUS treatments are a promising alternative and/or complement to existing treatment modalities, with the potential to reduce side effects and induce a systemic response for the treatment of disseminated metastases.

Technology today

High Intensity Focused Ultrasound (HIFU) ablation is an image-guided procedure, where imaging can be used for treatment planning, targeting, monitoring, and evaluating. The HIFU devices to treat breast masses are guided by either ultrasound or MR imaging. There are two available ultrasound-guided systems for breast treatment, both consisting of a 3.0 or 3.5 MHz therapeutic transducer with an embedded imaging probe for treatment guidance. The Echopulse (Theraclion, France) has a therapeutic head mounted on an arm for positioning, with the patient treated in a supine position. The Model-JC (Chongqing Haifu, China) is a more general purpose HIFU device with the transducer inside the tabletop, and the patient in a prone position for treatment. The skin is cooled during the course of the treatment to prevent heat-associated side effects. Ultrasound guidance offers real-time visualization of the treated volume, which can therefore detect any movements during the treatment, and can also provide feedback for treatment monitoring through the presence of hyper-echoic marks, used as a surrogate of the induction of coagulative necrosis.

With the MRI-guided systems, the patient is positioned prone, with the breast placed in a chilled water tub. There are two approaches. One uses a spherical transducer integrated into the MR tabletop, with a vertical ultrasound beam, Exablate 2000 (Insightec, Israel). A second, most recently dedicated breast system, Sonalleve (Profound Medical, Canada), uses 8 multi-elements modules surrounding the breast cup, with a lateral treatment orientation so that most of the far field will remain inside the breast tissue. This system also uses a volumetric approach for heating, rather than a point-to-point positioning of individual lesions. The advantages of MRI guidance are excellent anatomical resolution, high sensitivity for the detection of breast lesions, and, of course, temperature mapping, to allow direct and accurate treatment monitoring.

Novel systems are also being assessed in clinical trials, such as the Muse MRgFUS System developed by the University of Utah.

Case Study continued Breast Cancer

Table

Title and NCT number	Location	MOA & system
Focused Ultrasound and Pembrolizumab in Metastatic Breast Cancer NCT03237572	University of Virginia USA	USg Thermal ablation, combined with IO Echopulse
High Intensity Focused Ultrasound Treatment of Breast Tumors. BRIFU Study NCT03342625	Institut Bergonie France	MRg Thermal ablation Muse system
Efficacy of MR-HIFU Ablation of Breast Cancer BRIFU Study NCT02407613	UMC Utrecht The Netherlands	MRg Thermal ablation Sonalleve
Ultrasound-enhanced Delivery of Chemotherapy to Patients with Liver Metastases from Breast and Colorectal Cancer NCT03237572	St. Olavs Hospital Norway	Drug delivery (chemotherapy) by US+Microbubbles Clinical ultrasound scanner
Focused Ultrasound Ablation and PD-1 Antibody Blockage in Advanced Solid Tumors NCT04116320	University of Virginia USA	USg Thermal ablation, combined with IO Echopulse
Image-guided Targeted Doxorubicin Delivery with Hyperthermia to Optimize Loco-regional Control in Breast Cancer (i-GO) NCT04116320	UMC Utrecht The Netherlands	MRgFUS hyperthermia for drug delivery (chemotherapy)
Focused Ultrasound and Gemcitabine in Breast Cancer (Breast 54) NCT04796220	University of Virginia USA	USg Thermal ablation, combined with chemotherapy Echopulse
Novel MRI-Guided Ultrasound Stimulated Microbubble Radiation Treatment for Patients With Chest-wall and Locally Advanced Breast Cancer (USmBRT-B) NCT04431674	Sunnybrook Health Sciences Centre Canada	MRg-FUS + Microbubbles, combined with radiotherapy
Blood-Brain Barrier Disruption (BBBD) Using MRgFUS in the Treatment of Her2-positive Breast Cancer Brain Metastases) NCT03714243	Nir Lipsman, MD, Sunnybrook Health Sciences Centre Canada	Blood-brain barrier disruption by MRg-FUS + Microbubbles for drug delivery (targeted therapy) Exablate Neuro

Case Study continued Breast Cancer

Clinical data

The feasibility of thermal ablation for breast masses has now been reported in several studies.^{3,4,5} While the early treatand-resect studies did not systematically report 100 percent ablation over the treated area, an issue that may be related to treatment parameters as well as timing and methods used to assess coagulative necrosis, more recent studies using either ultrasound-guided⁶ or MRI-guided FUS systems⁷ reported complete ablation of the treated area. FUS thermal ablation is already used for the treatment of symptomatic breast fibroadenoma in clinical routine, and results in a significant shrinkage of fibroadenoma and good symptom control.8,9 Thermal ablation of breast cancer with HIFU is considered to be safe, with low complication rates. 10 Several studies have reported successful treatments of breast cancer cases with ultrasound-guided high-intensity ultrasound, resulting in complete destruction of the tumors and a favorable local control.11 Two studies reported results of treatment follow-up without systematic tumor excision. In the first one, USgHIFU was used as the primary treatment of breast cancer, with a mean follow-up of 56 months. Among the 22 patients treated in this series, only 2 developed local recurrence in the treated area12. In a second study, 21 patients were treated with MRgFUS, and recurrence or abnormal area of residual cancer was retreated with MRgFUS or ablated by usual surgery, leading to only one case of recurrence.13

Approved indications

In some countries in Europe and Asia, HIFU has been approved for breast cancer treatment. Several regulatory agencies authorized this treatment for benign breast tumors, including Taiwan FDA, South Korea MFDS, Singapore HSA, and Hong Kong MDD. Europe CE Marking has been obtained for both benign and malignant breast tumors.

Going beyond thermal ablation

Preclinical studies on breast cancer models in recent years have indicated that FUS can result in local control and in systemic effects when utilizing mechanisms of action other than thermal ablation. Using FUS for immunosensitization or immunomodulation, especially when combined with chemotherapy and/or immunotherapy, or radiosensitization, have all demonstrated increased drug delivery to tumors.

Current clinical trials

Following recent technological developments and preclinical validation of novel modes of action, several clinical trials are currently ongoing (Table, page II.83) to assess the effectiveness of FUS for breast cancer management, either alone or in combination.

Hope for the future

Studies on focused ultrasound treatment of breast cancer started more than two decades ago, but clinical studies remain at the investigative stage and are only available in a few centers. Technical success with thermally ablating cancerous and non-cancerous breast tissues has now been demonstrated. Besides thermal ablation, preclinical discoveries have paved the way for novel modes of action, especially in the field of immunosensitization and radiosensitization, that are also undergoing clinical trials.

Focused ultrasound for breast cancer presents several potential advantages over conventional treatments. Focused ultrasound is noninvasive and nonionizing. This allows for repeat treatment when needed, without the associated increased risk of long-term side effects, such as those that can occur with radiation therapy, or the risk of infection or other complications associated with traditional breast surgery. Focused ultrasound also holds enormous potential for the treatment of metastatic breast cancer, with its unique capabilities of inducing or enhancing an anti-cancer immune response, through various other mechanisms of action—many of which will hopefully be demonstrated by clinical trials currently underway.

We are hopeful that focused ultrasound can become an alternative or complement to existing treatments for breast cancer patients in the near future.

Case Study continued Breast Cancer

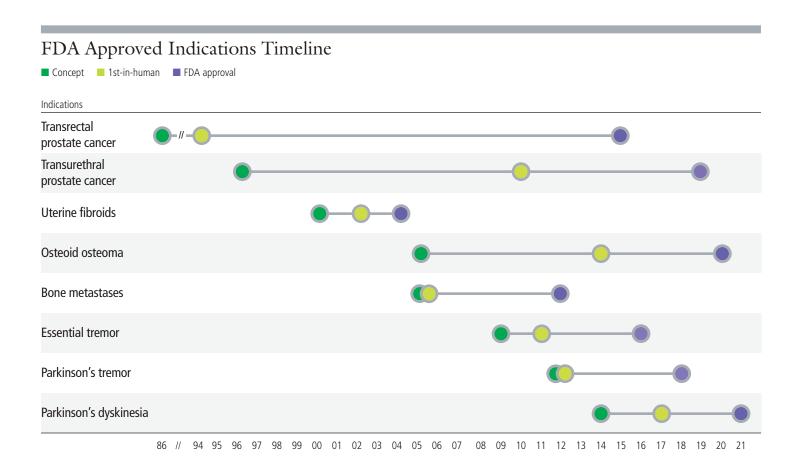
- 1 World Health Organization. Breast Cancer [Internet]. World Health Organization. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer
- 2 National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management [Internet]. NICE Guideline No.101. 2018. Available from: https://www.nice.org.uk/guidance/ng101
- 3 Peek MCL, Wu F. High-intensity focused ultrasound in the treatment of breast tumours. Ecancermedical science. 2018; 12:1–10.
- 4 Brenin DR. Ablative Treatment of Breast Cancer; Are We There Yet? Curr Breast Cancer Rep. 2019;11(2):43-50.
- 5 Feril LB, Fernan RL, Tachibana K. High-Intensity Focused Ultrasound in the Treatment of Breast Cancer. Curr Med Chem. 2021;28(25):5179-88.
- 6 Hahn M, Fugunt R, Schoenfisch B, Oberlechner E, Gruber I V., Hoopmann U, et al. High intensity focused ultrasound (HIFU) for the treatment of symptomatic breast fibroadenoma. Int J Hyperth [Internet]. 2018;35(1):463–70. Available from: https://doi.org/10.1080/02656736.2018.1508757
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- 8 Peek MCL, Ahmed M, Scudder J, Baker R, Charalampoudis P, Pinder SE, et al. High-intensity focused ultrasound in the treatment of breast fibroadenomata (HIFU-F trial). Int J Hyperth [Internet]. 2018;34(7):1002-9.
- 9 Hahn M, Fugunt R, Schoenfisch B, Oberlechner E, Gruber I V., Hoopmann U, et al. High intensity focused ultrasound (HIFU) for the treatment of symptomatic breast fibroadenoma. Int J Hyperth [Internet]. 2018;35(1):463-70.
- 10 Feril LB, Fernan RL, Tachibana K. High-Intensity Focused Ultrasound in the Treatment of Breast Cancer. Curr Med Chem. 2021;28(25):5179-88.
- 11 Peek MCL, Ahmed M, Napoli A, Ten Haken B, McWilliams S, Usiskin SI, et al. Systematic review of high-intensity focused ultrasound ablation in the treatment of breast cancer. Br J Surg. 2015;102(8):873-82.
- 12 Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, et al. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. Breast Cancer Res Treat.
- 13 Furusawa H, Namba K, Nakahara H, Tanaka C, Yasuda Y, Hirabara E, et al. The evolving non-surgical ablation of breast cancer: MR guided focused ultrasound (MRgFUS). Breast Cancer. 2007;14(1):55-8.

CASE STUDY

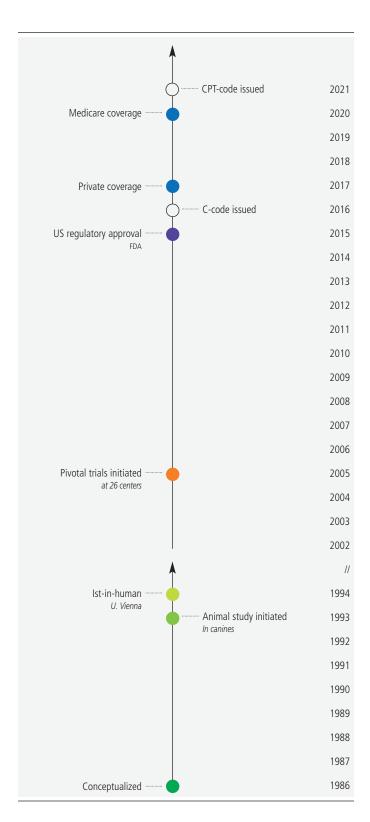
FDA Approved Indications Timeline

This year we worked with manufacturers to create a timeline from conceptual idea for an indication to FDA approval. When the technology was developed for treating the prostate, the use of focused ultrasound was truly innovative, and it took nearly three decades to go from idea to FDA-approved treatment. The indications to follow took considerably less time, with the more recent indications taking less than a decade. Essential tremor; Parkinson's disease, tremor; and Parkinson's disease, dyskinesia were approved in 7 or 8 years. The summary graph above provides a simplified overview of the timeline. A detailed timeline follows, as provided by the manufacturers for each of the FDA-approved indications.



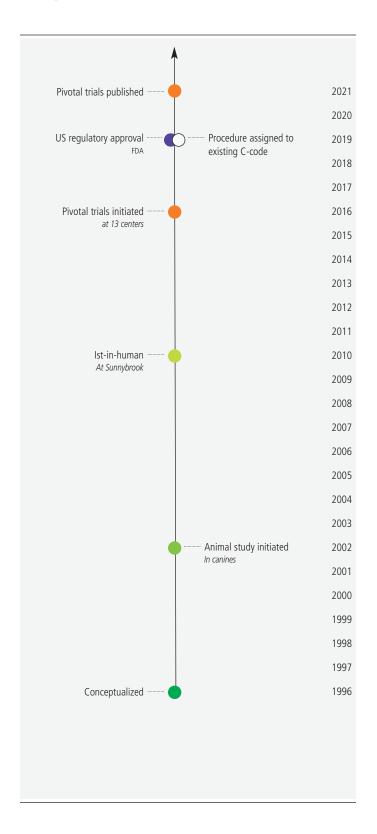
Indication Timeline—Transrectal Prostate Cancer





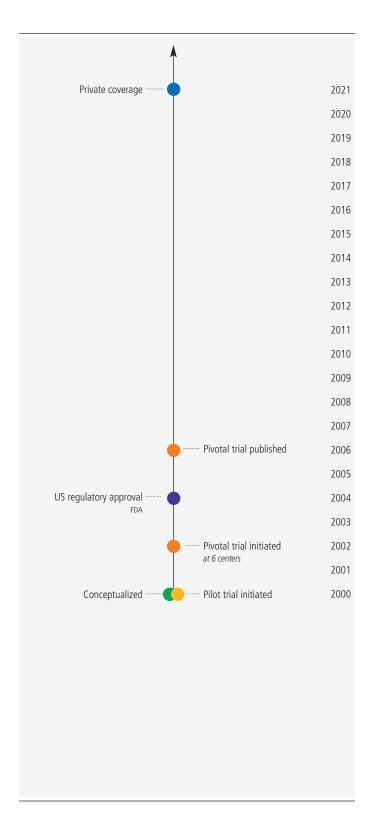
Indication Timeline—Transurethral Prostate Cancer





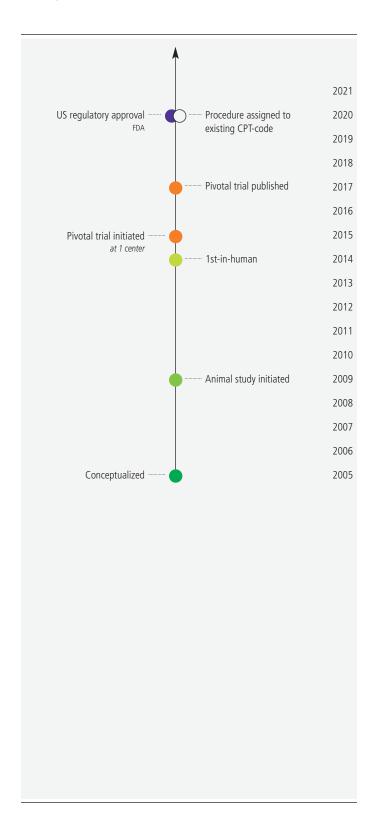
Indication Timeline—Uterine Fibroids





Indication Timeline—Osteoid Osteoma



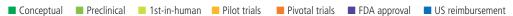


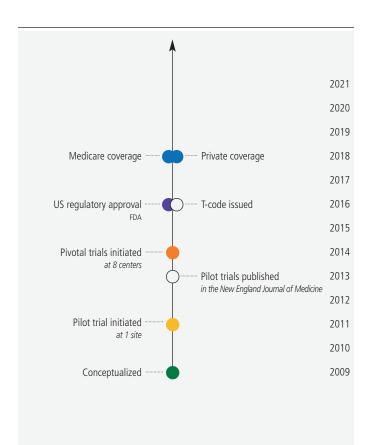
Indication Timeline—Bone Metastases





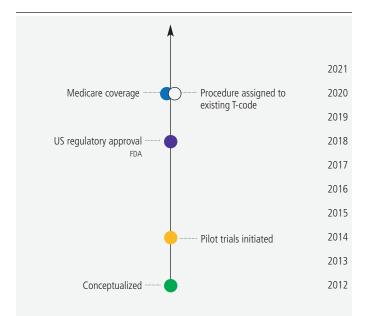
Indication Timeline—Essential Tremor





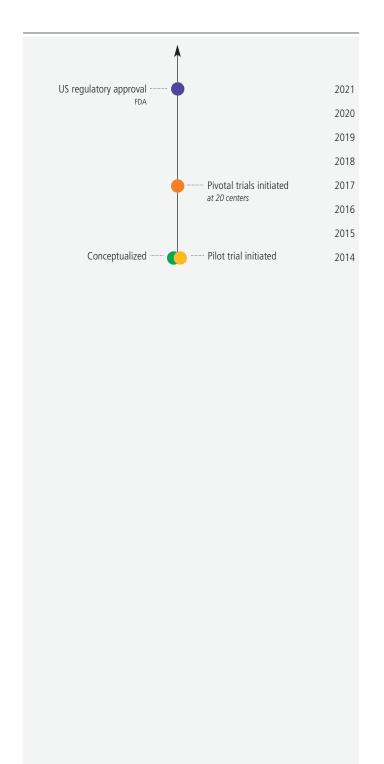
Indication Timeline—Parkinson's Tremor





Indication Timeline—Parkinson's Dyskinesia





CENTERS OF EXCELLENCE

Overview

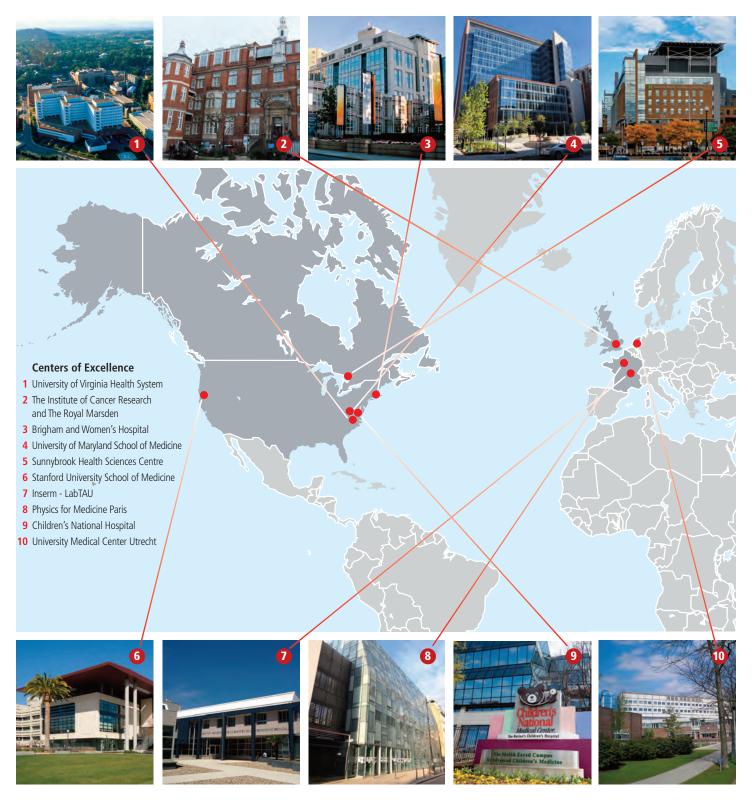
The ten research/treatment sites highlighted in this report are the Focused Ultrasound Foundation-designated Centers of Excellence, COEs. They are also listed on our website.

Established in 2009, the COE program brings together the best people and technical resources at luminary sites across the globe. The Centers are created through partnerships of academia, industry, and the Foundation to showcase focused ultrasound technology and serve as hubs for collaboration. They are the powerhouses of focused ultrasound research; in 2021, they collectively published 212 scientific journal articles on their accomplishments. These sites, which include some of the most influential leaders in the field, are cultivators of the next generation of researchers and physicians for focused ultrasound and are creating the intellectual property that will likely spur the next iteration of commercialization efforts. We encourage you to review these pages in detail, look up the publications that might interest you, and reach out to the contacts we list for each site, if you are interested in a potential collaboration.

This portion of the 2022 State of the Field Report contains a summary of self-reported data from the COEs.

Centers of Excellence		
Name	Location	Established
University Medical Center Utrecht	Utrecht, The Netherlands	2020
Children's National Hospital	Washington, DC	2020
Physics for Medicine Paris	Paris, France	2019
Inserm - LabTAU	Lyon, France	2017
Stanford University School of Medicine	Stanford, CA	2016
Sunnybrook Health Sciences Centre	Toronto, Canada	2016
University of Maryland School of Medicine	Baltimore, MD	2016
Brigham and Women's Hospital	Boston, MA	2015
The Institute of Cancer Research and The Royal Marsden	London, England	2013
University of Virginia Health System	Charlottesville, VA	2009

Overview continued



University Medical Center Utrecht

Commercial Treatments

Clinical Research

3

Preclinical Research

12

Mechanisms of Action Research 6

Technical Research

12

Publications

University Medical Center Utrecht | The Netherlands

The University Medical Center Utrecht, UMC Utrecht, is the fourth Center of Excellence in Europe. UMC Utrecht is striving to improve current cancer therapy with MRI-guided focused ultrasound, often in combination with other modalities, such as radiotherapy, chemotherapy, and surgery, leading to higher efficacy, fewer side effects, and lower costs. The emphasis of the clinical translation, in close collaboration with other nearby medical centers and international consortia, is on breast cancer, bone cancer, immune stimulation, and drug delivery for brain tumor treatment.

Contact

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Commercial treatments		
Cardiovascular	Peripheral artery disease	
Musculoskeletal	Bone metastases, Desmoid tumors	
Women's health	Endometriosis, Uterine fibroids	

Clinical research	
Musculoskeletal	Bone metastases
Women's health	Breast tumors, malignant; Uterine fibroids

Preclinical research		
Miscellaneous Head & neck tumors		
Neurological	Pontine glioma	
Ophthalmological	Macular degeneration	

Mechanisms of action research		
Histotripsy Immunomodulation, Tissue destruction		
Hyperthermia Drug delivery, Radiosensitization		
Nonthermal	BBB opening; BBB opening, drug delivery; Drug delivery; Drug delivery, vehicle; Immunomodulation; Sonoporation; Tissue destruction	
Thermal ablation	Tissue destruction	

Technical research	
Drug delivery technology	
FUS Image guidance, MR	
FUS Physics	
FUS Transducer technology, Histotripsy	
FUS Transducer technology, Thermal ablation	
FUS Treatment monitoring	

University Medical Center Utrecht continued

Research not involving thermal ablation, tissue destruction

Clinical Research - Women's health

Breast tumors, malignant Hyperthermia - Drug delivery

Preclinical Research - Miscellaneous

Head & neck tumors Nonthermal - Sonoporation

Preclinical Research - Neurological

Pontine glioma Nonthermal - Drug delivery

Preclinical Research - Ophthalmological

Macular degeneration Nonthermal - Drug delivery

Publications—2021

- Deep Correction of Breathing-related Artifacts in Real-time MR-thermometry. de Senneville BD, Coupé P, Ries M, Facq L, Moonen CTW. Comput Med Imaging Graph. 2021 Jan;87:101834. doi: 10.1016/j.compmedimag. 2020.101834. Epub 2020 Dec 8. PMID: 33352524.
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- Combining Radiotherapy and Focused Ultrasound for Pain Palliation of Cancer Induced Bone Pain; A Stage I/IIa Study According to the IDEAL Framework. Bartels MMTJ, Verpalen IM, Ferrer CJ, Slotman DJ, Phernambucq ECJ, Verhoeff JJC, Eppinga WSC, Braat MNGJA, van den Hoed RD, van 't Veer-Ten Kate M, de Boer E, Naber HR, Nijholt IM, Bartels LW, Bos C, Moonen CTW, Boomsma MF, Verkooijen HM. Clin Transl Radiat Oncol. 2021 Jan 15;27:57-63. doi: 10.1016/j.ctro.2021.01.005. PMID: 33532631; PMCID: PMC7822778.
- Long-term Outcomes of Two Ablation Techniques for Treatment of Radiorecurrent Prostate Cancer. Nair SM, Peters M, Kurver P, Lavi A, Verhoeff JJC, van der Voort van Zyp JRN, van Son MJ, Chin JL. Prostate Cancer Prostatic Dis. 2021 Mar;24(1):186-192. doi: 10.1038/s41391-020-00265-5. Epub 2020 Aug 19. PMID: 32814843
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Publications—2021 continued

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- AAPM Task Group 241: A Medical Physicist's Guide to MRI-guided Focused Ultrasound Body Systems. Payne A, Chopra R, Ellens N, Chen L, Ghanouni P, Sammet S, Diederich C, ter Haar G, Parker D, Moonen C, Stafford J, Moros E, Schlesinger D. Benedict S. Wear K. Partanen A. Farahani K. Med Phys. 2021 Sep;48(9):e772-e806. doi: 10.1002/mp.15076. Epub 2021 Jul 29. PMID: 34224149.
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CENTERS OF EXCELLENCE

University Medical Center Utrecht continued

Publications—2021 continued

Can Quantitative Analysis of Multi-parametric MRI Independently Predict Failure of Focal Salvage HIFU Therapy in Men with Radio-recurrent Prostate Cancer? Rakauskas A, Shah TT, Peters M, Randeva JS, Hosking-Jervis F, Schmainda MJ, Orczyck C, Emberton M, Arya M, Moore C, Ahmed HU. Urol Oncol. 2021 Dec;39(12):830.e1-830.e8. doi: 10.1016/j.urolonc.2021.04.017. Epub 2021 May 26. PMID: 34049783; PMCID: PMC8639607.

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Children's National Hospital

10

Clinical Research

4

Preclinical Research

7

Mechanisms of Action Research 8

Technical Research

1

Publications

Children's National Hospital | Washington, DC

In September 2020, Children's National Hospital, CNH, in Washington, DC, became the first Center of Excellence focused exclusively on pediatrics. The COE includes a multidisciplinary team of clinicians and investigators from radiology, oncology, surgery, orthopedics, neurosurgery, and urology. In recent years, the CNH team has become a leader in the translation of focused ultrasound for treating pediatric solid tumors. They are currently investigating the treatment of malignant solid tumors with focused ultrasound alone and combined with chemotherapy. Moving forward, the team plans to further explore oncological applications of focused ultrasound, particularly to augment chemotherapy and immunotherapy for hard-to-treat pediatric cancers.

Contacts

Karun V. Sharma, MD, PhD | Program Co-Director | kvsharma@cnmc.org

AeRang Kim, MD, PhD | Program Co-Director | aekim@childrensnational.org

Clinical research	
Gastrointestinal	Liver tumors
Miscellaneous	Multiple tumors ¹
Musculoskeletal	Bone cancer, Bone metastases, Desmoid tumors Osteoid osteoma, Soft tissue cancer
Neurological	Neuroblastoma, Neurofibromatosis

Preclinical research

Musculoskeletal Bone metastases; Osteoid osteoma; Soft tissue cancer; Soft tissue tumors, benign

Mechanisms of action research

Histotripsy	Immunomodulation, Tissue destruction	
Hyperthermia	Tissue destruction	
Nonthermal	Drug delivery, vehicle; Neuromodulation	
Thermal ablation	Immunomodulation, Tissue destruction	

Technical research

Drug delivery technology

FUS Image guidance, MR

FUS Image guidance, Ultrasound

FUS Simulation & treatment planning

FUS Transducer technology, Histotripsy

FUS Treatment evaluation

FUS Treatment monitoring

Standards & quality assurance

¹ Protocols inclusive of more than one indication

CENTERS OF EXCELLENCE

Children's National Hospital continued



Research not involving thermal ablation, tissue destruction			
Clinical research - Miscellaneous			
Multiple tumors ¹	Hyperthermia - Chemosensitization		
Clinical research - Muscu	loskeletal		
Bone metastases Thermal ablation - Chemosensitization			
Preclinical research - Mus	sculoskeletal		
Bone metastases	Hyperthermia - Drug delivery, vehicle		
Soft tissue cancer	Histotripsy - Immunomodulation		
Soft tissue tumors, benign	Hyperthermia - Drug delivery, vehicle		

Feasibility of Magnetic Resonance-guided High-intensity Focused Ultrasound Treatment Targeting Distinct Nodular Lesions in Neurofibromatosis Type 1. Tydings C, Yarmolenko P, Bornhorst M, Dombi E, Myseros J, Keating R, Bost J, Sharma K, Kim A. Neurooncol Adv. 2021 Aug 18;3(1):vdab116. doi: 10.1093/noajnl/vdab116. PMID: 34604751; PMCID: PMC8482787.32227606.

Physics for Medicine Paris

Clinical Research

4

5

Preclinical Research

Mechanisms of Action Research 9

Technical Research

28

Publications

Physics for Medicine Paris | France

In December 2019, Physics for Medicine Paris became the third Center of Excellence in Europe. The site focuses on accelerating the development of ultrasound-based technologies and translating these innovative technologies to the clinic, with an emphasis on cardiovascular and neurological disorders. Physics for Medicine Paris is a technological hub for new modalities of ultrasound guidance, monitoring, and treatment. The team also plays a pivotal role in educating young researchers with the training of many PhD students.

Contacts

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Jean-François Aubry, PhD | Scientific Director | jean-francois.aubry@espci.fr

Clinical research

Neurological Essential tremor

Preclinical research

Cardiovascular	Heart valve calcifications	
Neurological	Depression; Essential tremor;	
	Parkinson's disease, underlying cause	

Mechanisms of action research

Histotripsy Tissue destruction

Nonthermal BBB opening, drug delivery; Neuromodulation; Tissue destruction

Thermal ablation Tissue destruction

Technical research

Drug delivery technology

FUS Image guidance, MR

FUS Image guidance, Navigation

FUS Image guidance, Ultrasound

FUS Physics

FUS Simulation & treatment planning

FUS Transducer technology, Histotripsy

FUS Transducer technology, Thermal ablation

FUS Treatment monitoring

Research not involving thermal ablation, tissue destruction

Preclinical research - Cardiovascular

Heart valve calcifications Histotripsy - Alteration of tissue mechanics

Preclinical research - Neurological

Depression Nonthermal - Neuromodulation

Parkinson's disease, Nonthermal - Neuromodulation underlying cause

Physics for Medicine Paris continued



Publications—2021

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Focused Ultrasound Foundation | 2022 State of the Field | | 1.105

Inserm - LabTAU

Preclinical Research

Mechanisms of Action Research

Commercial Treatment

Technical Research

Clinical Research

Publications

INSERM - LabTAU | Lyon, France

In February 2017, INSERM Unit 1032, the Laboratory of Therapeutic Applications of Ultrasound, LabTAU, at the French National Institute for Health and Medical Research, INSERM, was named a Focused Ultrasound Center of Excellence. LabTAU conducts significant translational and clinical research with a multidisciplinary, highly qualified, and complementary team of physicians and scientists. The COE has special expertise in commercializing technology and creating strategic interfaces between engineering and medicine.

Contact

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Commercial treatment

Urological Prostate cancer, Hôpital Edouard Herriot

		research
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Cardiovascular	Varicose veins	
Gastrointestinal	Liver metastases, Centre Léon Bérard	
Neurological	Glioblastoma, Hôpitaux Universitaires Pitié-Salpêtrière & Hôpital Pierre Wertheimer	
Urological	Prostate cancer, Hôpital Edouard Herriot	
Women's health	Endometriosis, Hôpital Croix-Rousse	

Preclinical research

Cardiovascular	Twin-twin transfusion syndrome, Varicose veins, Ventricular tachycardia	
Gastrointestinal	Liver metastases; Liver tumors; Pancreatic tumors, malignant	
Musculoskeletal	Osteoradionecrosis	
Neurological	Cancer pain; Glioblastoma; Stroke, thromboembolic	
Ophthalmological	Glaucoma	
Urological	Prostate cancer	
Women's health	Breast tumors, malignant; Endometriosis	

Mechanisms of action research

Histotripsy	Tissue destruction	
Nonthermal	BBB opening; BBB opening, drug delivery; Chemosensitization; Clot lysis; Drug delivery; Immunomodulation; Neuromodulation; Sonodynamic therapy; Sonoporation; Tissue destruction; Vascular occlusion	
Thermal ablation	Tissue destruction	

Technical research

Drug delivery technology
FUS Image guidance, MR
FUS Image guidance, Ultrasound
FUS Physics
FUS Simulation & treatment planning
FUS Transducer technology, Other
FUS Treatment monitoring

Inserm – LabTAU continued

Research not involving thermal ablation, tissue destruction

Clinical research - Neurological Glioblastoma Nonthermal, BBB opening Preclinical research - Cardiovascular Twin-twin transfusion syndrome Nonthermal - Vascular occlusion Varicose veins Thermal ablation - Hemostasis Preclinical research - Gastrointestinal Nonthermal - Sonodynamic therapy Pancreatic tumors, malignant Nonthermal - Tissue destruction Thermal ablation - Immunomodulation Preclinical research - Neurological Nonthermal - Neuromodulation Cancer pain

Glioblastoma Nonthermal, BBB opening - drug delivery Stroke, thromboembolic Nonthermal, BBB opening - drug delivery

Preclinical research - Women's health

Nonthermal - Immunomodulation Breast tumors, malignant Nonthermal - Tissue destruction



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CENTERS OF EXCELLENCE

Inserm – LabTAU continued

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Publications—2021 continued

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Stanford University School of Medicine

9

Preclinical Research

17

Mechanisms of Action Research **12**

Commercial Treatments

nical Re

Clinical Research

8

Technical Research

37

Publications

Stanford University School of Medicine | California

Stanford's COE was established in 2016 and focuses on several clinical and preclinical projects. These include industry-sponsored trials using focused ultrasound to treat bone metastases, uterine fibroids, essential tremor, and prostate cancer, as well as investigator-initiated trials to treat soft tissue tumors. Preclinical projects have included the development of reference less methods for MR thermometry in the brain, as well as respiratory-compensated focused ultrasound in treatment of porcine liver during free-breathing. These clinical and preclinical projects involve close collaboration with clinical colleagues in radiology, obstetrics and gynecology, medical oncology, radiation oncology, neurosurgery, neurology, orthopedic surgery, urology, pathology, immunology, and electrical and mechanical engineering.

Stanford University | California University of California Davis | California

A collaboration between Stanford and UC Davis investigating the use of focused ultrasound for the treatment of liver cancer in canines is underway. The research team is using focused ultrasound to deliver microRNA to the tumors, demonstrating efficient drug delivery and a significant change in the immunogenicity of the tumor.

4

Veterinary Research

Contacts

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Commercial treatments		
Cardiovascular	Arteriovenous malformations	
Musculoskeletal	Bone cancer, Bone metastases, Desmoid tumors, Osteoid osteoma	
Neurological	Essential tremor; Parkinson's disease, tremor	
Urological	Prostate cancer	
Women's health	Uterine adenomyosis, Uterine fibroids	

Clinical research		
Gastrointestinal Pancreatic tumors, malignant		
Musculoskeletal	Bone metastases, Desmoid tumors, Osteoid osteoma	
Neurological	Epilepsy; Glioblastoma; Parkinson's disease, dyskinesia	

Preclinical research		
Gastrointestinal	Pancreatic tumors, malignant	
Miscellaneous	Melanoma	
Neurological	Epilepsy, Glioblastoma, Neuropathic pain	
Urological	Acute kidney injury	
Women's health	Breast tumors, malignant; Ovarian tumors	

Mechanisms of action research		
Hyperthermia	Drug delivery	
Nonthermal	BBB opening; BBB opening, drug delivery; Drug delivery; Drug delivery, immunotherapeutic; Drug delivery, vehicle; Gene delivery; Neuromodulation; Sonoporation; Stem cell delivery; Stem cell trafficking; Tissue destruction	
Thermal ablation	Amplification of cancer biomarkers, Chemosensitization, Immune cell trafficking, Immunomodulation, Tissue destruction	

Technical re	ocooveh
rechnical re	esearch
Drug deliver	ry technology
FUS Image	guidance, MR
FUS Physics	
FUS Simulat	tion & treatment planning
FUS Transdu	icer technology, Nonthermal
FUS Transdu	icer technology, Thermal ablation
FUS Treatme	ent evaluation
FUS Treatme	ent monitoring

esearch not involving the	ermal ablation, tissue destruction
Clinical research - Gastroint	estinal
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Clinical research - Neurolog	ical
Glioblastoma	Nonthermal, BBB opening - drug delivery
Preclinical research - Gastro	intestinal
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Preclinical research - Miscel	laneous
Melanoma	Thermal ablation - Immunomodulation
Preclinical research - Neuro	logical
Epilepsy	Nonthermal, BBB opening - drug delivery
Glioblastoma	Nonthermal, BBB opening - drug delivery
Neuropathic pain	Nonthermal - Drug delivery, vehicle
Preclinical research - Urolog	jical
Acute kidney injury	Nonthermal - Stem cell delivery
Preclinical research - Wome	n's health
Breast tumors, malignant	Nonthermal - Gene delivery Thermal ablation - Immunomodulation
Ovarian tumors	Thermal ablation - Immunomodulation
Veterinary research - Gastro	intestinal
Liver tumors	Nonthermal - Drug delivery, vehicle Nonthermal - Gene delivery Nonthermal - Immunomodulation

Publications—2021

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Sunnybrook Health Sciences Centre

Preclinical Research

Mechanisms of Action Research

Commercial Treatment

Technical Research

Clinical Research

Publications

Sunnybrook Health Sciences Centre | Toronto, Canada

Established as a COE in 2016, the Sunnybrook Health Sciences Centre is conducting research for focused ultrasound in neurology, neurosurgery, urology, orthopedics, gynecology, radiation oncology, and biomedical engineering, and has studies underway for Alzheimer's disease, obsessive-compulsive disorder, depression, Parkinson's disease, ALS, breast cancer brain metastases, and others.

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Commercial treatment

Neurological Essential tremor

linical research		
Gastrointestinal	Pancreatic tumors, malignant	
Miscellaneous	Head & neck tumors	
Musculoskeletal	Bone cancer	
Neurological	Alzheimer's disease; Amyotrophic lateral sclerosis; Brain metastases, breast cancer; Depression; Essential tremor; Glioblastoma; Multiple sclerosis; Obsessive-compulsive disorder; Parkinson's disease, underlying cause	
Women's health	Brain metastases, breast cancer; Uterine fibroids	

Preclinical research		
Cardiovascular	Atrial fibrillation, Deep vein thrombosis	
Gastrointestinal	Colorectal tumors	
Musculoskeletal	Bone metastases	
Neurological	Alzheimer's disease; Amyotrophic lateral sclerosis; Brain metastases, breast cancer; Depression; Epilepsy; Glioblastoma; Parkinson's disease, underlying cause; Spinal cord injury; Stroke, intracerebral hemorrhage; Stroke, thromboembolic	
Ophthalmological	Retinal injury	
Women's health	Brain metastases, breast cancer	

Mechanisms of action research		
Hyperthermia	Drug delivery, Radiosensitzation	
Nonthermal	BBB opening; BBB opening, drug delivery; Chemosensitization; Clot lysis; Drug delivery; Drug delivery, immunotherapeutic; Neuromodulation; Sonoporation; Stem cell delivery; Vascular occlusion	
Thermal ablation	Immune cell trafficking, Tissue destruction	

Technical research
Drug delivery technology
FUS Image guidance, MR
FUS Image guidance, Ultrasound
FUS Physics
FUS Simulation & treatment planning
FUS Transducer technology, Histotripsy
FUS Transducer technology, Hyperthermia
FUS Transducer technology, Nonthermal
FUS Transducer technology, Other
FUS Transducer technology, Thermal ablation
FUS Treatment monitoring
Standards & quality assurance

Clinical research - Gastrointes	tinal
Pancreatic tumors, malignant	Nonthermal - Drug delivery Nonthermal - Immunomodulation
Clinical research - Miscellaned	ous
Head & neck tumors	Hyperthermia - Radiosensitization Nonthermal - Radiosensitization
Clinical research - Neurologica	al
Alzheimer's disease	Nonthermal, BBB opening - Drug delivery
Amyotrophic lateral sclerosis	Nonthermal, BBB opening
Brain metastases, breast cancer	Nonthermal, BBB opening - Drug delivery
Glioblastoma	Nonthermal, BBB opening - Drug delivery
Parkinson's disease, underlying cause	Nonthermal, BBB opening - Drug delivery
Clinical research - Women's he	ealth
Breast tumors, malignant	Hyperthermia - Radiosensitization Nonthermal - Radiosensitization
Preclinical research - Cardiova	escular
Deep vein thrombosis	Histotripsy - Tissue destruction
Preclinical research - Neurolog	gical
Alzheimer's disease	Nonthermal, BBB opening - Drug delivery Nonthermal, BBB opening - Gene delivery
Amyotrophic lateral sclerosis	Nonthermal, BBB opening - Drug delivery
Brain metastases, breast cancer	Nonthermal, BBB opening - Drug delivery
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - Drug delivery
Parkinson's disease, underlying cause	Nonthermal, BBB opening - Drug delivery
Spinal cord injury	Nonthermal, BBB opening - Drug delivery
Stroke, intracerebral hemorrhage	Nonthermal, BBB opening - Drug delivery
Stroke, thromboembolic	Nonthermal, BBB opening - Drug delivery
Preclinical research - Ophthali	mological



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University of Maryland School of Medicine

14

Preclinical Research

11

Mechanisms of Action Research 1

Commercial Treatment

Clinical Research

7

Technical Research

3

Publications

University of Maryland School of Medicine | Baltimore, MD

The COE at the University of Maryland, UMD, was established in 2016. At present, the UMD departments of neurosurgery, radiology, and neurology are collaborating to study treatment of movement disorders, chronic neuropathic pain, brain tumors, and the use of enhanced drug delivery. In addition, their immunomodulation studies range from investigating cell systems to animal models and human clinical trials.

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Commercial treatment

Neurological Essential tremor

Clinical research

Neurological Glioblastoma; Neuropathic pain;

Parkinson's disease, dyskinesia; Trigeminal neuralgia

Preclinical research

 Miscellaneous
 Infection

 Neurological
 Brain tumors, general; Epilepsy; Glioblastoma; Opioid and other addictions

Mechanisms of action research

Histotripsy Immune cell trafficking

Nonthermal BBB opening; BBB opening, drug delivery,

immunotherapeutic; Chemosensitization; Immunomodulation; Liquid biopsy; Neuromodulation;

Radiosensitization; Sonodynamic therapy; Tissue destruction

Thermal ablation Tissue destruction

Technical research

Drug delivery technology

FUS Image guidance, MR

FUS Image guidance, Ultrasound

FUS Physics

FUS Simulation & treatment planning

FUS Treatment monitoring

Standards & quality assurance

University of Maryland School of Medicine continued



Clinical research - Neuro	logical
Glioblastoma	Nonthermal, BBB opening - Drug delive
Neuropathic pain	Thermal ablation - Neuromodulation
Preclinical research - Mis	cellaneous
Infection	Nonthermal, BBB opening - Drug delive
Preclinical research - Neu	ırological
Brain tumors, general	Nonthermal - Amplification of cancer biomarkers Nonthermal, BBB opening Nonthermal, BBB
ening - Drug delivery	Working Mary 200
	Nonthermal, BBB opening - Drug delive Immunotherapeutic Nonthermal - Gene delivery Nonthermal - Immunomodulation Nonthermal - Liquid biopsy Nonthermal - Sonodynamic therapy
Epilepsy	Nonthermal - Gene delivery Nonthermal - Neuromodulation
Glioblastoma	Nonthermal - Immune cell trafficking Nonthermal - Immunomodulation
Opioid and other addictions	Nonthermal - Neuromodulation

MRI Guided Focused Ultrasound- Mediated Delivery of Therapeutic Cells to the Brain: A Review of the State-of- the-Art Methodology and Future Applications. Ahmed N, Gandhi D, Melhem ER, Frenkel V. Front Neurol. 2021 Jun 17;12:669449. doi: 10.3389/fneur.2021.669449. PMID: 34220679; PMCID: PMC8248790.

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Brigham and Women's Hospital

7

Preclinical Research

12

Mechanisms of Action Research 3

Commercial Treatments

5

Clinical Research

6

Technical Research

9

Publications

Brigham and Women's Hospital | Boston, MA

Brigham and Women's Hospital was named a COE in 2015. More than 50 focused ultrasound researchers in three different laboratories span the Boston campus of Brigham and Women's Hospital where, in conjunction with Harvard Medical School, they are pioneering innovative uses of focused ultrasound and advancing these new approaches from bench to bedside.

Contacts

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Musculoskeletal Bone metastases Neurological Essential tremor Urological Prostate cancer Women's health Uterine fibroids

Clinical research	
Neurological	Epilepsy, Glioblastoma
Urological	Prostate cancer

Preclinical research		
Miscellaneous	Niemann-Pick disease	
Neurological	Alzheimer's disease; Epilepsy; Glioblastoma; Huntington's disease; Parkinson's disease, tremor	

Mechanisms of ac	tion research
Hyperthermia	Tissue destruction
Nonthermal	Amplification of cancer biomarkers; BBB opening, drug delivery; BBB opening, gene delivery; Drug delivery, vehicle; Immunomodulation; Liquid biopsy; Neuromodulation; Radiosensitization; Stem cell delivery; Tissue destruction
Thermal ablation	Tissue destruction

echnical research	
FUS Image guidance, MR	
FUS Image guidance, Ultrasound	
FUS Physics	
FUS Simulation & treatment planning	
FUS Treatment evaluation	
FUS Treatment monitoring	

Research not involving thermal ablation, tissue destruction			
Preclinical research - Neurological			
Alzheimer's disease	Nonthermal, BBB opening - drug delivery		
Epilepsy	Nonthermal - Neuromodulation		
Glioblastoma	Nonthermal - BBB opening, drug delivery Nonthermal - Tissue destruction		
Huntington's disease	Nonthermal - BBB opening, gene delivery		
Parkinson's disease, tremor	Nonthermal - Neuromodulation		

Focused Ultrasound Foundation | 2022 State of the Field | | 1.121

Brigham and Women's Hospital continued



Research not involving thermal ablation, tissue destruction

esearch not involving ti	iermai abiation, tissue destruction
Clinical research - Neurolo	ogical
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - Drug delivery
Preclinical research - Misc	ellaneous
Niemann-Pick disease	Nonthermal, BBB opening - Gene delivery
Preclinical research - Neur	ological
Alzheimer's disease	Nonthermal, BBB opening - Drug delivery
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - Drug delivery Nonthermal - Tissue destruction
Huntington's disease	Nonthermal, BBB opening - Drug delivery
Parkinson's disease, tremor	Nonthermal - Neuromodulation

Publications—2020

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ICR and The Royal Marsden

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Preclinical Research

11

Mechanisms of Action Research oveial Troptmon

Commercial Treatment

8

Technical Research

3

Clinical Research

10

Publications

The Institute of Cancer Research and The Royal Marsden | London, England

In 2013, the Focused Ultrasound Foundation and Philips entered an innovative public-private collaboration with the Institute of Cancer Research, ICR, and The Royal Marsden National Health Service Foundation Trust to create a COE in London. The Center created a state-of-the-art resource for clinicians and scientists working on focused ultrasound therapy, developing clinical evidence in oncology, and establishing best practices, treatment standards, and protocols.

Veterinary Research

Contact

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Urological Prostate cancer

Clinical research	
Gastrointestinal	Colorectal tumors; Pancreatic tumors, malignant
Urological	Prostate cancer

Preclinical research		
Cardiovascular	Twin-twin transfusion syndrome	
Gastrointestinal	Liver metastases; Liver tumors; Pancreatic tumors, malignant	
Neurological	Cancer pain, Glioblastoma	

Mechanisms of action research		
Histotripsy	Tissue destruction	
Hyperthermia	Drug delivery, Radiosensitization	
Nonthermal	Chemosensitization; Drug delivery; Drug delivery, immunotherapeutic; Tissue destruction; Vascular occlusion	
Thermal ablation	Immune cell trafficking, Immunomodulation, Tissue destruction	

Technical research
Drug delivery technology
FUS Image guidance, MR
FUS Image guidance, Ultrasound
FUS Physics
FUS Simulation & treatment planning
FUS Transducer technology, Thermal ablation
FUS Treatment monitoring
Standards & quality assurance

ICR and The Royal Marsden continued





Research not involving thermal ablation, tissue destruction

Preclinical research - Cardiov	<i>r</i> ascular
Twin-twin transfusion syndrome	Nonthermal - Vascular occlusion
Preclinical research - Gastroi	ntestinal
Pancreatic tumors	Nonthermal - Immunomodulation
Preclinical research - Neurolo	ogical
Glioblastoma	Nonthermal - Drug delivery, vehicle
Veterinary research - Urologi	cal
Bladder tumors	Thermal ablation - Immunomodulation

Publications—2021

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University of Virginia Health System

20

Preclinical Research

19

Mechanisms of Action Research 2

Commercial Treatments

13

Clinical Research

4

Technical Research

42

Publications

University of Virginia Health System | Charlottesville, VA

The Foundation's first COE was inaugurated at the University of Virginia in September 2009 through a public-private partnership between the Foundation, the Commonwealth of Virginia, the University of Virginia, Insightec, and GE. The COE has a strong history in brain research, having pioneered clinical trials for essential tremor and Parkinsonian tremor, as well as technical and preclinical studies for neurological disorders. The center also treats uterine fibroids and bone metastases, conducts cancer research, and is currently spearheading the world's first clinical trial combining focused ultrasound and immunotherapy.

Contacts

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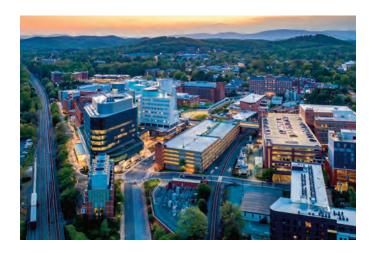
Commercial trea	ments	
Neurological	Essential tremor	
Women's health	Uterine fibroids	

Esophageal tumors, Gastric tumors		
Melanoma, Multiple tumors ¹		
Cancer pain, Epilepsy, Glioblastoma		
Lung cancer		
Breast tumors, benign; Breast tumors, malignant; Cervical tumors, Ovarian tumors		

Cardiovascular Arteriovenous malformations, Peripheral artery dise		
Gastrointestinal	Pancreatic tumors, malignant	
Miscellaneous	Melanoma	
Neurological	Brain metastases, melanoma; Brain tumors, general; Cavernomas; Epilepsy; Glioblastoma; Parkinson's disease, underlying cause; Stroke, thromboembolic	
Pulmonary	Lung cancer	
Women's health	Breast tumors, malignant	

¹ Protocols inclusive of more than one indication.

University of Virginia Health System continued



Mechanisms of ac	tion research	
Histotripsy	Tissue destruction	
Hyperthermia	Drug delivery	
Nonthermal	Angiogenesis; BBB opening; BBB opening, drug delivery; Clot lysis; Drug delivery; Drug delivery, immunotherapeutic; Drug delivery, vehicle; Immune cell trafficking; Immunomodulation; Neuromodulation; Sonodynamic therapy; Sonoporation; Stem cell delivery; Stem cell trafficking; Tissue destruction; Vascular occlusion	
Thermal ablation	Tissue destruction	

Technical research	
Drug delivery technology	
FUS Image guidance, MR	
FUS Image guidance, Ultrasound	
FUS Treatment monitoring	

	mal ablation, tissue destruction
Clinical research - Gastrointes	stinal
Esophageal tumors	Thermal ablation - Immunomodulation
Gastric tumors	Thermal ablation - Immunomodulation
Clinical research - Miscellane	ous
Melanoma	Thermal ablation - Immunomodulation
Multiple tumors ¹	Thermal ablation - Immunomodulation
Clinical research - Neurologic	al
Glioblastoma	Nonthermal, BBB opening - drug delivery
Clinical research - Pulmonary	
Lung cancer	Thermal ablation - Immunomodulation
Clinical research - Women's h	ealth
Cervical tumors	Thermal ablation - Immunomodulation
Ovarian tumors	Thermal ablation - Immunomodulation
Preclinical research - Cardiova	ascular
Arteriovenous malformations	Nonthermal - Tissue destruction
Peripheral artery disease	Nonthermal - Drug delivery, vehicle
Preclinical research - Gastroin	testinal
Pancreatic tumors	Thermal ablation - Immunomodulation
Preclinical research - Miscella	neous
Melanoma	Thermal ablation - Immunomodulation
Preclinical research - Neurolo	gical
Brain metastases, melanoma	Nonthermal, BBB opening - Drug delivery, immunotherapeutic
Brain tumors, general	Nonthermal, BBB opening - Gene delivery
Cavernomas	Nonthermal - Sonodynamic therapy
Epilepsy	Nonthermal, BBB opening - Drug delivery Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - Drug delivery Nonthermal - Drug delivery, vehicle Nonthermal - Immunomodulation Nonthermal - Radiosensitization Nonthermal - Sonodynamic therapy Nonthermal - Vascular occlusion
Parkinson's disease, underlying cause	Nonthermal - BBB opening, drug delivery
Stroke, thromboembolic	Nonthermal - Sonoporation
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Preclinical research - Women's	i iicaitii

¹ Protocols inclusive of more than one indication.

University of Virginia Health System continued

Publications—2021

- Ultrasound Contrast: Gas Microbubbles in the Vasculature. Klibanov AL. Invest Radiol. 2021 Jan;56(1):50-61. doi: 10.1097/RLI.0000000000000733. PMID: 33181574.
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CENTERS OF EXCELLENCE

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FUS Veterinary Applications

Introduction

Veterinary medicine offers a unique opportunity to expand research and commercial focused ultrasound applications into a market with reduced regulatory burdens, while also collecting data in naturally occurring disease models to support human clinical trials.

Focused ultrasound's ability to noninvasively treat tissue and enhance the efficacy of some therapies, thus reducing the length of hospital stays and total cost, is a crucial benefit for pet owners who pay out of pocket.

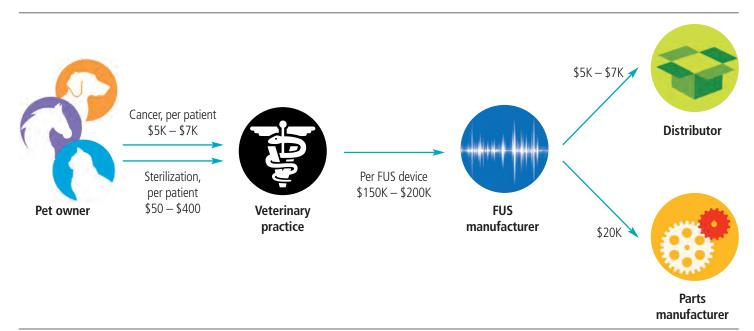
Currently, the most promising focused ultrasound applications in veterinary medicine are in oncology, particularly in indications where surgical approaches may significantly affect quality of life. Veterinary clinical trials have demonstrated that focused ultrasound is easily tolerated and effective in the treatment of soft tissue sarcomas. Ongoing clinical work will investigate focused ultrasound's utility against other

aggressive cancers, including osteosarcoma, bladder cancer, and brain cancer.

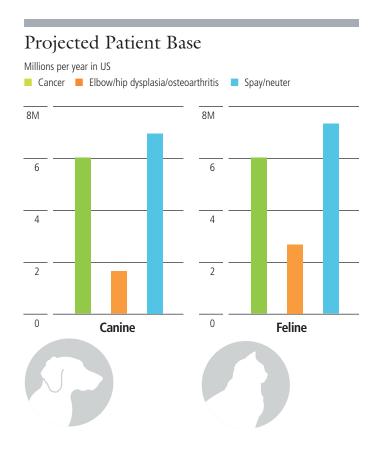
In recent years, the use of focused ultrasound in veterinary medicine has expanded beyond traditional thermally ablative procedures. Histotripsy, sonodynamic therapy, and drug delivery are all currently being explored as alternative treatment approaches. These modalities may offer advantages due to their lower risk of damaging nearby structures such as skin, bone, and nerves. This is especially important in veterinary patients due to their smaller size and the prevalence of lesions on the limbs and bodywall.

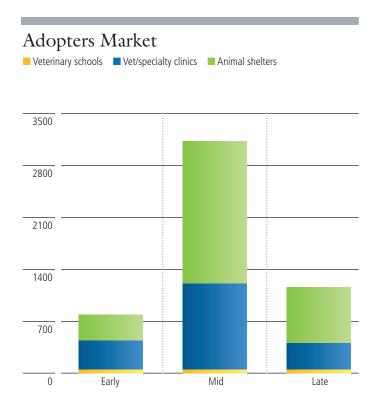
For more information visit: www.fusfoundation.org/for-researchers/high-priorityresearch-areas/veterinary-program.

Value Chain



Proposed Market





Source: Potential patient populations were calculated from multiple websites: acfoundation.org/faqs/

fda.gov/animalveterinary/resourcesforyou/animalhealthliteracy/ucm382772.htm#endnote8 animalsheltering.org/page/pets-by-the-numbers

We project that the market is capable of absorbing just under 5,000 focused ultrasound device units at a retail value of between \$150,000 and \$250,000 per device. Early adopters are likely to consist of veterinary schools, large specialty clinics (e.g. oncology and rehabilitation centers), and high-volume animal shelters. This constitutes an additional potential revenue stream for focused ultrasound manufacturers, and may represent a cost savings for veterinary clinics, particularly when compared to competing technology such as radiation therapy.

State of Research by Indication

Development stag	Proposed Clinical trial Clinical practice	Species Feline Equine	MOAs Histotripsy Nonthermal, BBB opening Hyperthermia Thermal ablation Nonthermal
Oncology			
Soft tissue tumors*	2018	99	■ Thermal ablation - immunomodulation
	2018	99	■ Nonthermal - drug delivery
	2020	\bigcirc	Histotripsy - immunomodulation
	2021	?	■ Nonthermal - sonodynamic therapy
Bladder cancer	2020	•	■ Thermal - ablation, tissue destruction
Brain tumors	2021	•	Histotripsy - tissue destruction
Chronic wound	2018	•	■ Nonthermal - drug delivery
Hepatocellular carcinoma	2016	•	Nonthermal - gene delivery
	2021	?	Histotripsy - tissue destruction
Oral tumors**	2019	•	■ Thermal ablation -immunomodulation
Osteosarcoma	2020	•	Histotripsy - immunomodulation
Sarcomas	2021	9	Histotripsy - immunomodulation
Lung cancer	2018	•	■ Thermal ablation - tissue destruction
Sarcoids	2018	0	■ Thermal ablation - tissue destruction

^{*}Soft tissue tumors includes soft tissue sarcoma and mast cell tumors.

^{**}Oral tumors includes oral melanoma, plasmacytoma (of the gums/lips), ameloblastomas, salivary gland tumors, and squamous cell carcinoma (of the gums/lips).

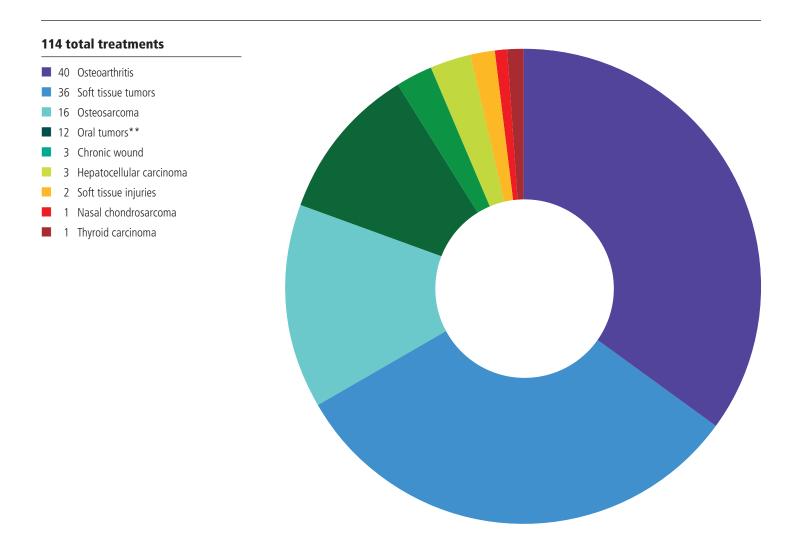
State of Research by Indication continued

Development s	Proposed Clinical trial Clinical stage	Species Canine Feline Equ	uine MOAs Histotripsy Histotripsy Thermal ablation Nonthermal
Pain			
Elbow/hip dysplasia	2018	₽	Nonthermal
Osteoarthritis	2018	990	Nonthermal
Soft tissue injuries	2018	₽	■ Nonthermal
Miscellaneous			
Miscenaneous			
Diabetes	2021	9	Nonthermal - neuromodulation
Epilepsy	2020	^	■ Thermal ablation - tissue destruction
Kidney stones	2020	9	Nonthermal - kidney stone fragmentation
Spay/neuter	2018	90	■ Thermal ablation - tissue destruction

Veterinary advances in 2021

Last year saw several major advances in the use of focused ultrasound in veterinary medicine. A new trial dedicated solely to feline patients opened, targeting vaccine-induced sarcomas. Focused ultrasound was also offered for the treatment of canine brain tumors for the first time. Most significantly, additional modes of focused ultrasound, including histotripsy, sonodynamic therapy, and drug delivery, are now in use in the veterinary space and may offer advantages over more traditional thermally ablative procedures.

Treated Patients by Indication—Cumulative



^{*}Soft tissue tumors includes soft tissue sarcoma and mast cell tumors.

^{**}Oral tumors includes oral melanoma, plasmacytoma (of the gums/lips), ameloblastomas, salivary gland tumors, squamous cell carcinoma (of the gums/lips).



Common Diseases in Popular Breeds

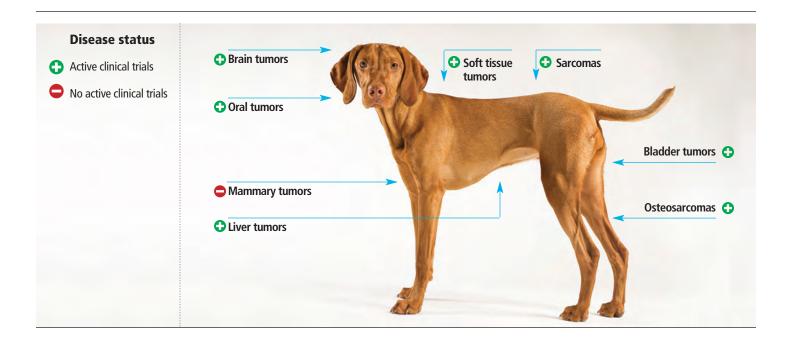
Most popular breeds	Common ailments	Common cancers	Cancer caused mortality
Labrador Retriever	Elbow and hip dysplasia, Obesity, Heart disorders, Hereditary myopathy, Eye conditions, Bloat	Lymphoma, Mast cell tumor, Melanoma, Osteosarcoma, Hemangiosarcoma	31%
German Shepherd	Degenerative myelopathy, Hip dysplasia, Bloat, Eye conditions	Hemangiosarcoma, Mast cell tumor, Melanoma, Lymphoma	20%
French Bulldog	Breathing problems, Eye conditions, Skin problems	Mast cell tumor, Brain tumor, Liver tumor	38%
Golden Retriever	Elbow and hip dysplasia, Eye conditions, Heart conditions	Mast cell tumor, Lymphoma, Oral melanoma, Brain tumor, Fibrosarcoma, Histiocytic tumors	39%
Poodle	Hip dysplasia, Eye conditions, Epilepsy	Squamous cell carcinoma, Mast cell tumor, Lymphoma	30%

Mammary and testicular cancer are common in unaltered dogs of all breeds.

Several dog breeds routinely top popularity charts worldwide, notably Labrador and golden retrievers, German shepherd dogs, and poodles. These breeds are genetically predisposed to certain diseases and cancers and can heavily skew the prevalence of these conditions, even if they are rare in other breeds. When assessing clinical unmet needs, it is important to consider the effects of breed popularity and distribution.

Diseases Where Focused Ultrasound Could Have Biggest Impact

Veterinary Indications with Active Clinical Trials



Current treatment options for these indications are limited or undesirable, requiring long hospital stays and life-altering surgical procedures such as amputation. Nearly all of these unmet needs are currently being addressed in active clinical trials.

Diseases Where Focused Ultrasound Could Have Biggest Impact continued

Incidence of Diseases in Species

Disease	Species	and incidence	Current treatment options
Brain tumors	•	Dogs— 10,000+ cases per year	Surgery, chemotherapy, radiation
Bladder tumors	99	Dogs and cats— 6,000+ cases per year	Systemic chemotherapy
Hyperthyroid	9	Cats over age 10— 12.5%	Radioiodine therapy
Oral tumors	9	Dogs— 15,000+ cases per year	Aggressive resection
Osteosarcomas	4	Dogs— 10,000+ cases per year	Amputation, chemotherapy, radiation
Sarcomas	90	Dogs and cats— 80,000+ cases per years	Surgery and radiation, amputation often required

In the News

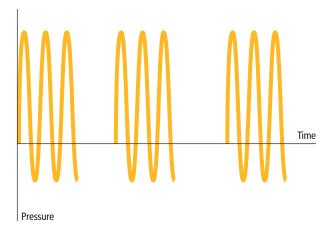
New Center

Virginia Tech opens new Animal Cancer Center, putting focused ultrasound in the spotlight.

▲ ■ Vlaisavljevich and his team have partnered with oncology clinicians at the Roanoke center for several pilot studies that use a novel technique called histotripsy, which focuses ultrasound beams to create bubbles inside a defined area. Since the technique doesn't involve heat, damage to surrounding tissues is effectively avoided."

— Virginia Tech News

Histotripsy Sound Waves



Choosing a Treatment

Professor and Head of the Department of Physiological Sciences at Oklahoma State University choses HIFU for his cat's treatment.

I would absolutely recommend HIFU. The response has really been quite remarkable, particularly with the type of tumor my cat has. It's not a tumor that responds well to just straight chemo, which is part of his treatment protocol with the HIFU. It really seems to have improved the effectiveness with very little to almost no side effects. Based upon the results of other cases so far, it seems to be really encouraging."

> — Dr. Martin Furr DVM. PhD. cat owner

Paving the Way

A clinical trial at Virginia Tech looks to help others in the future.

I know [participation in the clinical trial] may not help Hunter, but if we can help another dog or child down the road, it's worth it."

— Tasha Hoover



Case Study Osteosarcoma

As with any medical device, regulatory agencies around the world require data from laboratory animal testing before approving focused ultrasound technology for use in humans. Oncology applications require the use of expensive mouse or rat models of cancer, which typically do not accurately replicate human disease. Clinical focused ultrasound devices are seldom capable of treating small animals, which further complicates clinical translation. Large animal disease models, while more compatible with clinical focused ultrasound devices, are more expensive and less advanced.

Companion animals can offer the perfect solution to this conundrum. Client-owned animals are exposed to the same environments as their human owners and develop many of the same diseases. Unlike laboratory-induced diseases, these naturally occurring diseases in companion animals are remarkably similar to their human counterparts and respond similarly to therapy. Veterinary trials offer the ability to treat beloved pets while also collecting large animal data that is more translatable than anything from a laboratory and can dramatically accelerate clinical development.

Osteosarcoma presents the perfect example of the potential for synergy between veterinary and human medicine. In humans, osteosarcoma is a rare disease typically found in the pediatric population. While the 5-year survival rate is 60%, curative treatment requires removal of the affected bone. This often affects growth plates or necessitates amputation, leaving survivors with lifelong disabilities. Due to the rarity of the disease, less than 1000 cases diagnosed each year, clinical trial recruitment is a slow process and generating enough data for regulatory approval can take many years.

On the other hand, osteosarcoma is very common in dogs, with between 10,000 and 50,0000 cases diagnosed every year, in part owing to its prevalence in popular dog breeds like Labrador and golden retrievers. Due to a combination of a larger patient population and decreased regulatory burdens, veterinary clinical trials can rapidly screen and optimize new therapies for osteosarcoma. A single veterinary osteosarcoma trial can be completed in a matter of months. Multiple canine trials running in parallel and feeding information back to a slower-moving human clinical trial creates an iterative approach that ensures that pediatric patients always have access to the most promising new treatments.

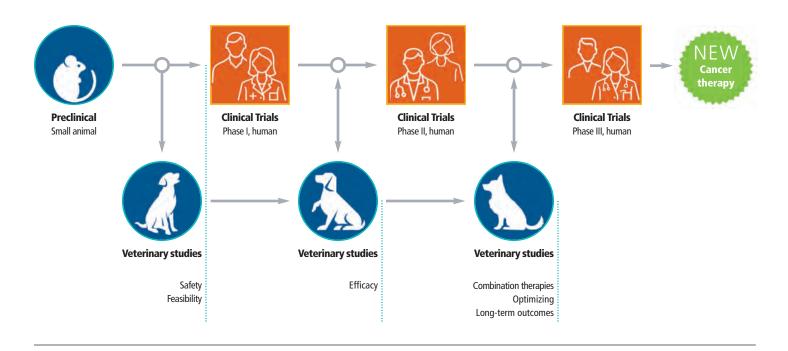
A veterinary clinical trial, led by Dr. Joanne Tuohy of the Virginia-Maryland Regional College of Veterinary Medicine, is using histotripsy to treat dogs with osteosarcoma with an expected completion date in mid-2022. Focused ultrasound's non-ionizing therapy offers significant benefits in the pediatric population and this landmark trial may open the door for focused ultrasound's use in this devastating disease.

Case Study continued

Osteosarcoma

Comparative oncology

Integrated and comparative drug development plan



Case Study continued Osteosarcoma

Canine and human population comparison

Majority of patients	> 8 years old	10-30 years old
Survival	50 % 1 year	60 % 5 years
Rates of occurrence	5% of tumors	2% of pediatric tumors
	85 % of bone tumors	56% of pediatric bone tumors

Case Study continued Osteosarcoma

Accelerating research

In humans, osteosarcoma is a rare disease typically found in the pediatric population. Due to the rarity of the disease, less than 1000 cases diagnosed each year, clinical trial recruitment is a slow process. On the other hand, osteosarcoma is very common in dogs, with between 10,000 and 50,0000 cases diagnosed every year, in part owing to its prevalence in popular dog breeds like Labrador and golden retrievers. Multiple canine trials running in parallel and feeding information back to a slower-moving human clinical trial creates an iterative approach that ensures that pediatric patients always have access to the most promising new treatments.

Comparative Populations

	Humans	Canines
Characteristics	Rare pediatric bone tumor Typically very painful and highly aggressive 5 year survival rate, 60% Survival often requires amputation Surgery affects growth plates Lifelong disability	Common tumor Typically very painful and highly aggressive 1 year survival rate, 50% Survival often requires amputation
Cases per year	<1000	10,000 – 50,000
Clinical trial recruitment	300–1,000 patients required 4% recruitment per year 7.5 years to complete	300 patients 4% average accrual rate 9 months to complete
	X	10x faster

Publications

Publications—2021

Hendricks-Wenger A, Arnold L, Gannon J, et al. Histotripsy Ablation in Preclinical Animal Models of Cancer and Spontaneous Tumors in Veterinary Patients: A Review. IEEE Trans Ultrason Ferroelectr Freq Control. 2022;69(1):5-26. doi:10.1109/TUFFC.2021.3110083

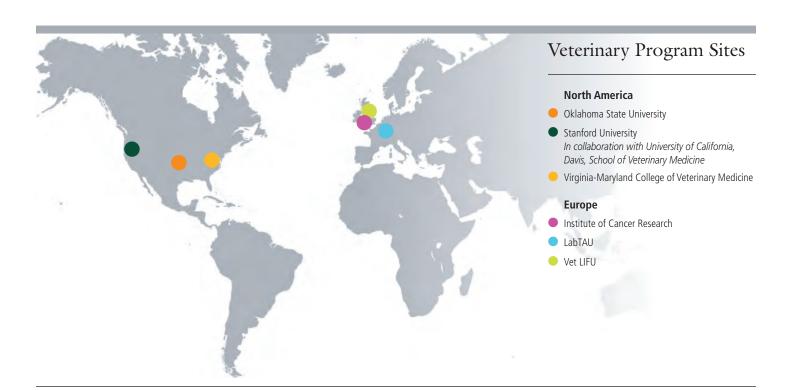
Latifi M, Hay A, Carroll J, et al. Focused ultrasound tumour ablation in small animal oncology. Vet Comp Oncol. 2021;19(3):411-419. doi:10.1111/vco.12742

Spanoudes K, Evripidou N, Giannakou M, Drakos T, Menikou G, Damianou C. A High Intensity Focused Ultrasound System for Veterinary Oncology Applications. J Med Ultrasound. 2021;29(3):195-202. doi:10.4103/JMU.JMU_130_20

Ranjan A, Kishore D, Ashar H, Neel T, Singh A, More S. Focused ultrasound ablation of a large canine oral tumor achieves efficient tumor remission: a case report. Int J Hyperthermia. 2021;38(1):552-560. doi:10.1080/02656736.2021.190358

Seward MC, Daniel GB, Ruth JD, Dervisis N, Partanen A, Yarmolenko PS. Feasibility of targeting canine soft tissue sarcoma with MR-guided high-intensity focused ultrasound. International journal of hyperthermia: the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2019;35(1):205-215. doi:10.1080/02656736.2018.1489072.

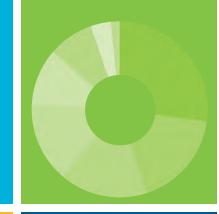
Ryu MO, Lee SH, Ahn JO, Song WJ, Li Q, Youn HY. Treatment of solid tumors in dogs using veterinary high-intensity focused ultrasound: A retrospective clinical study. Veterinary journal (London, England: 1997). 2018;234:126-129. doi:10.1016/j.tvjl.2018.02.019

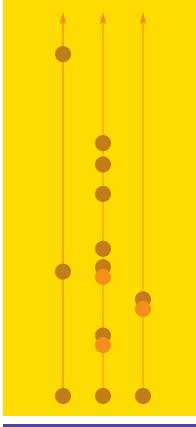


State of Commercialization



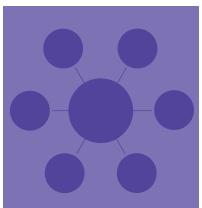
new FUS industry companies



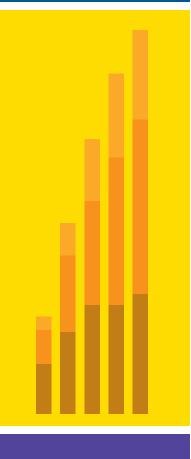


indications with regulatory approvals

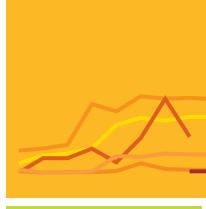
indications with
US reimbursement



1,654
employees
in the FUS industry



FUS device manufacturers



\$393 Minvested in FUS companies in 2021

State of Commercialization

In the wake of exponential advancement, the industry is at an inflection point, reflecting a shift in mindset from "if" focused ultrasound will have a critical place in the therapeutic armamentarium to "when" it will be widely available as a mainstream standard of care.

Additionally, we are seeing increasing evidence that the field is now transitioning from primarily a science-based research environment to a commercialized approach with patient treatment spaces focused on marketing and sales. As this transition gains momentum, we want to keep pace with the data points and metrics needed to understand and evaluate this global commercialization, so that we may accurately analyze the information and disseminate our findings to all stakeholders.

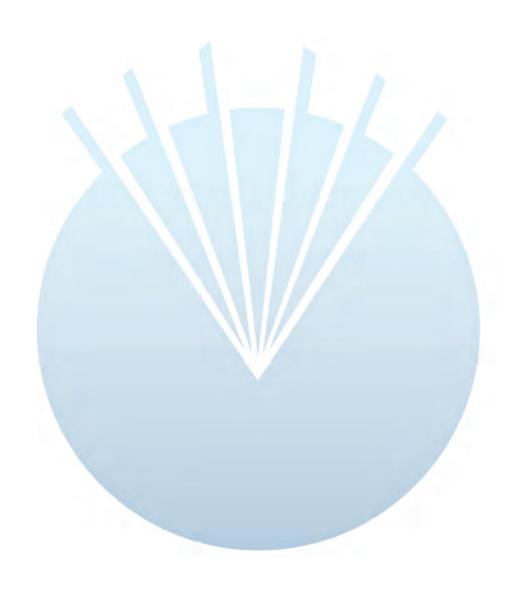
New this year, we are breaking down where the investment dollars are originating and where they are being invested. We're also looking at the geographic landscape of where devices are being used and where focused ultrasound employees are located around the globe.

A very special thank you to the industry partners in this space who, year after year, provide information on their companies so that we can collate the data in aggregate to understand the field as a whole.









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FUS Partners Role in the Industry

To help accelerate the transition of the field from a primarily science-based research environment to a state of commercialization with patient treatment spaces focused on marketing and sales, the Foundation created FUS Partners in April of 2018. The FUS Partners program serves as a galvanizing force in facilitating rapid success of the commercial stakeholder segment of the focused ultrasound ecosystem, and thus helps speed the time from laboratory research to widespread adoption and utilization of the technology.

By virtue of its reputation as a trusted, independent, unbiased third party with an extensive network, FUS Partners is uniquely positioned to advance the field significantly and effectively by identifying commercial opportunities, making connections between stakeholders, and enhancing the flow of information between strategic and financial investors and focused ultrasound companies. The program has grown from two employees in 2016 to five core team members.

Goals

- Produce a quantum change in the adoption rate of focused ultrasound as a mainstream standard of care
- Grow and rationalize the device manufacturers' segment of the focused ultrasound community, by taking a holistic approach to the support of key stakeholders within the ecosystem

Activities

Regulatory & Reimbursement

- Engage with FDA, CMS, and commercial payers to inform them of the state of the field and obtain guidance for regulatory approvals and reimbursement
- Connect manufacturers with regulatory and reimbursement consultants
- Educate manufacturers on best practices and strategy for coverage, reimbursement, and coding and billing

Financial & Human Capital

- Connect institutional, strategic, and individual investors with manufacturers in need of financing and facilitate in due diligence and preparation of investor relations materials
- Support focused ultrasound companies in attracting and hiring talent

Strategic Partnerships & Technology Transfer

 Connect manufacturers with academic research laboratories, strategic sponsors, and other manufacturers of focused ultrasound and related equipment and components

Advocacy

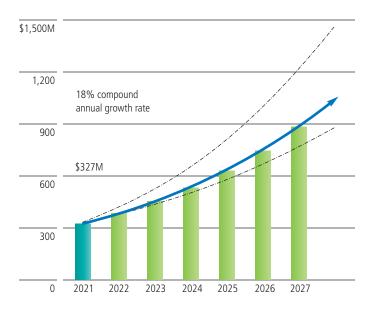
- Inform regulatory agencies, payers, and MedTech advocacy organizations about focused ultrasound
- Monitor clinical trials and potentially decrease cost of care while improving quality
- Connect and engage focused ultrasound manufacturers with advocacy organizations

Intellectual Property

- Educate academic researchers and focused ultrasound companies about why, what, and how to patent
- Connect researchers and focused ultrasound companies with intellectual property consultants

FUS Market Projection

Revenue in millions of dollars



Market value and growth rate estimates were compiled from the following websites:

https://marketprimes.com/high-intensity-focused-ultrasound-hifu-market

https://www.apexmarketsresearch.com/report/high-intensity-focused-ultrasound-system-market-962529/

https://www.marketreportsworld.com/global-high-intensity-focused-ultrasound-system-market-17233322

https://www.themarketreports.com/report/global-high-intensity-focused-ultrasound-hifu-market-research-report

https://www.qyresearch.com/index/detail/2634979/global-high-intensity-focused-ultrasound-system-market

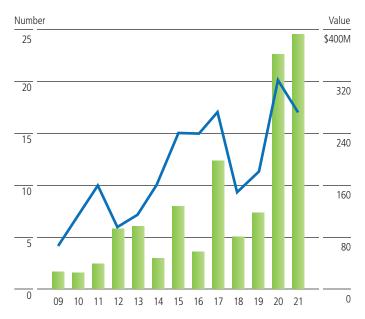
https://www.marketandresearch.biz/report/199771/global-high-intensity-focused-ultrasound-hifu-market-growth-2021-2026

https://www.marketstudyreport.com/reports/global-high-intensity-focused-ultrasound-system-market-2021-by-manufacturers-regions-type-and-application-forecast-to-2026

https://www.qyresearch.com/index/detail/4108833/global-high-intensity-focused-ultrasound-hifu-market

FUS Industry Investments Over Time

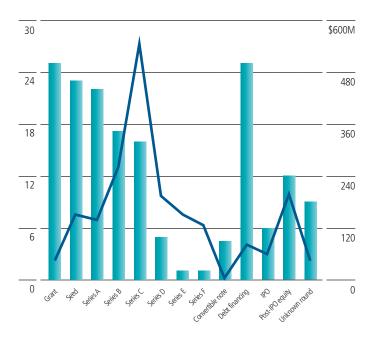
■ Number of investments ■ Value of investments in millions of dollars



Source: www.crunchbase.com and industry press releases

FUS Industry Investments by Stage

■ Number of investments ■ Value of investments in millions of dollars



www.crunchbase.com and industry press releases

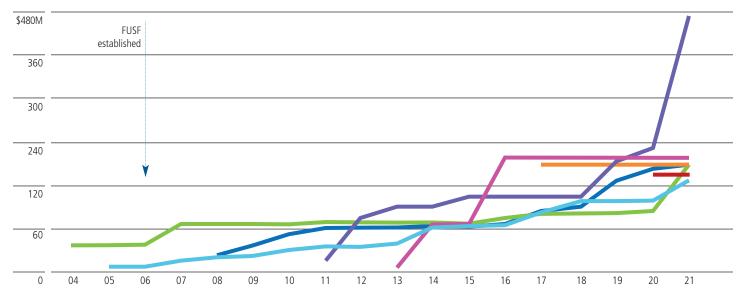
Focused ultrasound Industry Investments

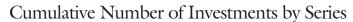
As is demonstrated by the graphs on the previous and following pages, most of the investments in this field are still early stage. 2021 included Series C financing for three different companies and comprised the bulk of the total money invested last year. New in this year's report on page III.9 is focused ultrasound Industry investments tracked over time. This time scale demonstrates that most of the money invested in the field has occurred in the last 10 years with larger amounts invested the past several years.

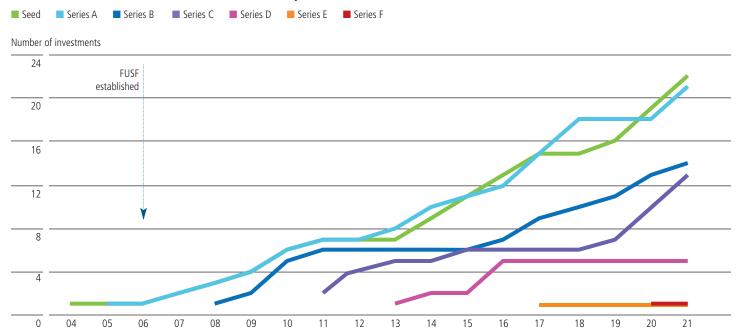


Cumulative Value of Investments by Series









FINANCIAL LANDSCAPE

2021 FUS Industry Investments*

Manufacturer	Funding type	Investors	Funding date	Money raised, millions \$US
Exo Imaging INC				
	Series C	Avidity Partners BlackRock INC Longevity Vision Fund Pura Vida Investments RA Capital Management Sands Capital Management	7.29.2021	\$220.0M
Sonablate CORP				
	Seed	SCI	7.1.2021	\$70.0M
EDAP TMS SA				
	Post-IPO Equity	_	4.1.2021	\$28.0M
Alpheus Medical INC				
	Series A	Action Potential Venture Capital LTD OrbiMed Advisors LLC American Cancer Society National Brain Tumor Society SV Health Investors	11.17.2021	\$16.0M
Vensica Therapeutics				
	Series B	Agriline Israel Biotech Fund Laborie Medical Technologies CORP Lewis Pell Trendlines Group	11.1.2021	\$16.0M
Shende Medical Equipment	Technology co	LTD		
	Series C	Chuanghehui Capital CITIC Securities Shanghai Creation Investment	12.14.2021	\$15.7M
IMGT CO LTD				
	Series C	CK Goldilocks Asset Management CO LTD DB Financial Investment CO K2 Investment Partners LLC KDB Capital Korea Investment Partners Rico Asset Management	12.17.2021	\$12.9M
OrthoSon LTD				
	Series A	Mercia Asset Management Estate of Max Mosley	8.4.2021	\$ 6.8M

^{*}Source: www.crunchbase as reported by Crunchbase press releases

2021 FUS Industry Investments* continued

Manufacturer	Funding type	Investors	Funding date	Money raised, millions \$US
Acoustiic INC				
	Grant	Air Force Research Laboratory	7.1.2021	\$ 0.2M
	Seed	Family office	7.1.2021	\$ 1.3M
		Family office	8.19.2021	\$ 3.7M
Cordance Medical INC				
	Grant	National Science Foundation	7.15.2021	\$ 1.0M
EXACT Therapeutics AS				
	Grant	Research Council of Norway	12.21.2021	\$ 0.8M
Microvascular Therapeutics	LLC			
	Grant	National Institutes of Health	7.9.2021	\$ 0.6M
Microvascular Therapeutics	LLC			
	Grant	National Institutes of Health	2.2.2021	\$ 0.1M

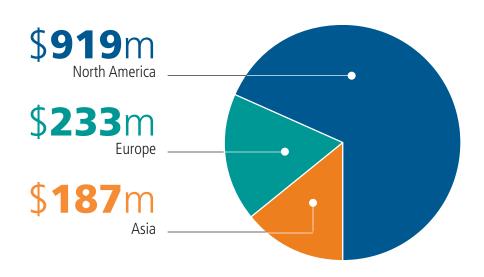
\$393.1M USD Total

New for the 2022 report on the following page, we examined both geographic origin of the money invested, and which geographic regions were the recipients of said monies. The majority of the money is invested in North American companies, with a 3x increase over other regions. Money originating in North America was generally invested in North America, and a similar trend holds for Europe. Asia is a different story: Most of the Asian money is being invested in North America.

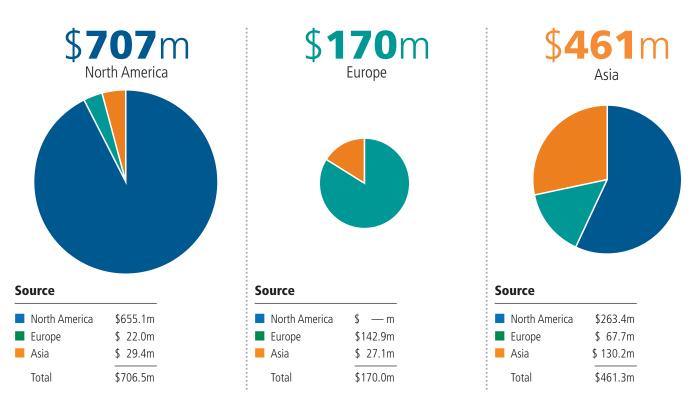
^{*}Source: www.crunchbase as reported by Crunchbase press releases

Flow of Investments

Investments by region



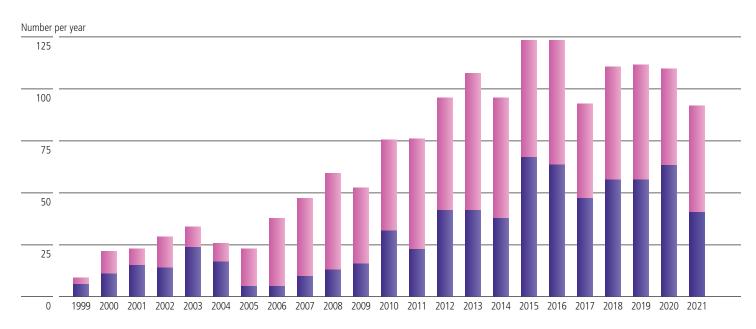
Disbursement to FUS Companies





Focused Ultrasound Industry Patents

■ US ■ Outside US



New this year, we have included a timeline of patents both in the US and throughout the rest of the world. Patents issued through the World Intellectual Property Organization, WIPO, were mostly nationalized to all countries that recognize WIPO. Notably absent from WIPO countries is China, which is home to 10 of 63 focused ultrasound device manufacturers.

Specifically reviewing the data, not depicted graphically, for the last three years, we see two-thirds of patents issued by the US Patent and Trademark Office, USPTO, were from US-based inventors or assignees, while 58 percent of WIPO patents had applicants based in the US. This is likely due to academic patent foundations in the US that are far more prolific than those of other countries. The closest runners-up

were the Netherlands, Israel, France, and South Korea, with 27, 19, 14, and 13 total patents respectively. Interestingly, there are seven FUS device companies based in France, four based in South Korea, three based in Israel, but none based in the Netherlands. All but one of the patents from the Netherlands were assigned to Philips.

Seventy percent of USPTO patents were awarded to corporate assignees, compared to 57 percent of those from WIPO. The high ratio of corporate applicants is from companies who are likely protecting their internally derived technology improvements. This indicates that proportionally more WIPO IP was derived from individuals/researchers or academic centers, compared to that of the USPTO.

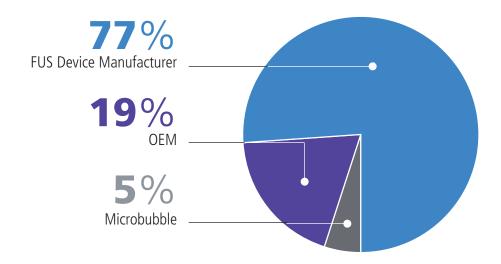
INDUSTRY DISTRIBUTION

Employment

The majority of the focused ultrasound Industry employment is by focused ultrasound device manufacturers. Despite these companies being early stage and having small workforces, they are more numerous than OEM and microbubble companies. The largest geographic location of focused ultrasound employment is the United States, followed by Israel and France. These three countries comprise 50% percent of the labor pool with the remainder of the employees broadly distributed around the globe.

NEW

Employee distribution



Employee Distribution*

13

employees

is the median company size

68%

of companies have

25 or fewer employees

10%

of the total workforce is employed by the

41 smallest companies

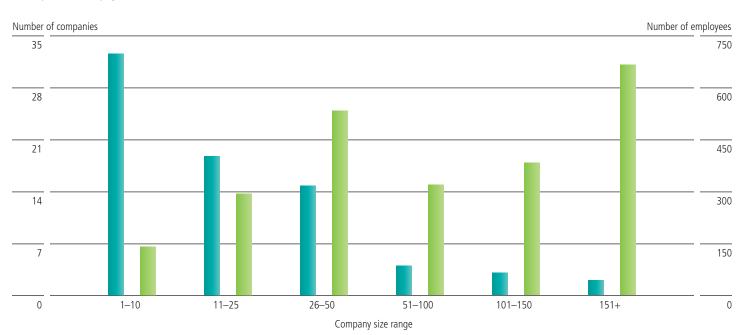
51%

of the total workforce is employed by the

7 largest companies

Numbers Employed by FUS Companies*

■ Companies ■ Employees



^{*} This analysis includes device manufacturers, OEM, and microbubble companies.

INDUSTRY DISTRIBUTION



FUS Employee Locations

1,654 employees* United States 411 Israel 254 France 210 Japan 130 China 122 Canada 107 91 Germany Taiwan 77 ■ South Korea 58 ■ United Kingdom 53 Switzerland 50 Denmark 32 Belgium 30 Finland 20 Malaysia 7 — Russia — United Arab Emirates

^{*}Number of employees as reported by device manufacturers, OEM, and microbubble companies

INDUSTRY DISTRIBUTION

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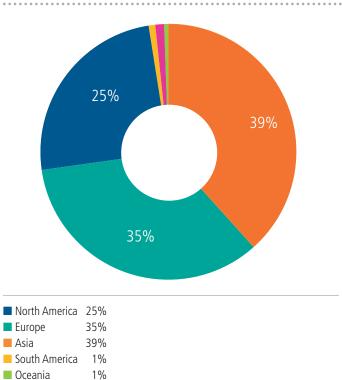


FUS Devices in Use

Number and Growth

11% Growth 2021 over 2020

Worldwide Distribution



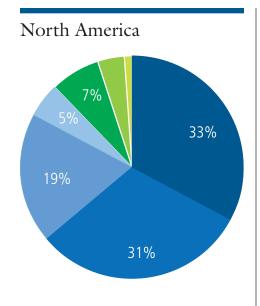
2021 saw an 11 percent growth in focused ultrasound devices used worldwide. New this year we have identified geographic distribution of the devices, and further break down specific countries per geographic region to provide even greater detail.

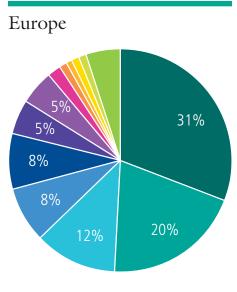
Africa

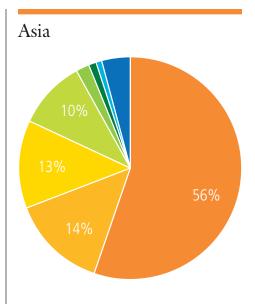
>1%

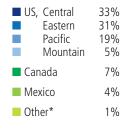


FUS Device Use by Region

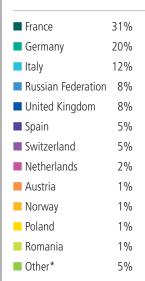








 $^{^{\}star}$ Cayman Islands, Cuba, and Dominican Republic



^{*}Belgium, Bulgaria, Czech Republic, Denmark, Finland, Georgia, Greece, Latvia, Monaco, Portugal, Serbia, Turkey, and Ukraine



^{*}Iran, Kazakhstan, Lebanon, Malaysia, Myanmar, Philippines, Saudi Arabia, Thailand, Uzbekistan, and Vietnam

Insurance Coverage by Region*

		_		
Indications	North America	Europe	Asia	Oceania
Benign prostatic hyperplasia		France	Saudi Arabia	Australia
		Germany	Singapore	
Bone metastases	United States ¹	Germany	israel	Australia
		Italy ³	Malaysia	
			Saudi Arabia	
			South Korea	
Breast tumors, benign		Germany ⁴		
Breast tumors, malignant		Germany ⁴		
Desmoid tumors		Germany ⁴		
Essential tremor	* Canada ²	Germany	Israel	
	United States ¹	Italy ³	Japan	
		Switzerland		
		United Kingdom		
Neuropathic pain		Germany	srael	
		Italy ³		
		Switzerland		
Osteoid osteoma		Germany		
		Italy ³		
Pancreatic tumors		Germany ⁴		
Parkinson's disease, tremor	United States ¹	Germany	Israel	
		Italy ³	Japan	
	Name	Switzerland		SIZ
Prostate cancer	United States ¹	France	Japan	Australia
		Germany	Saudi Arabia	
		United Kingdom	Singapore	
			South Korea	

^{*} All coverage decisions are conditional. The most current policy documents from the individual insurers should be referenced for a complete description.

¹ A detailed analysis of government and private coverage status in individual US states is available in the next section.

² In Canada, essential tremor and uterine fibroids are covered only in the province of Ontario.

³ In Italy, essential tremor and Parkinson's disease, tremor dominant are only covered in Abruzzo, Lombardia, and Sicilia. Neuropathic pain is only covered in Milano. Bone metastases and osteoid osteoma are only covered in Abruzzo, Lombardia, Emilia Romagna, and Lazio. Uterine Fibroids are covered in Abruzzo, Basilicata, Emilia Romagna, Lazio, Le Marche, Lombardia, Tuscano, and Umbria.

⁴ Codes that are not specific to FUS procedures, but can be used to bill for them

Insurance Coverage by Region* continued

Indications	North America	Europe	Asia	Oceania
Thyroid nodules		Germany ⁴		
Uterine fibroids	* Canada ²	Germany	*: China	Australia
	United States ¹	Italy ³	Israel	
			Malaysia	
			Saudi Arabia	
			South Korea	
			★ Vietnam	
Varicose veins		Germany ⁴		

Reimbursement



In medical care, reimbursement is the process of paying for healthcare services including office visits, labs/tests, imaging, and procedures, after an encounter has taken place. This is a significant difference between healthcare and other industries because the provider is not paid until after rendering a service.

After a physician or healthcare provider performs a procedure in a hospital or clinic as a treatment for a medical condition, they then send the bill to a payer. In a setting of many rules, the payer reimburses the physician, hospital/clinic, or patient for all or part of the fee for providing the treatment. Payers include private insurance companies, self-funded health plans, and government entities.

The process is not as simple as sending a bill and receiving payment. Payers collect and analyze data on patient outcomes and healthcare provider costs. They do not reimburse all procedures. Many procedures must have prior authorization to be considered for payment. Before payers will cover a new procedure or treatment, they generally require proof that, compared to the current standard of care, the new treatment is safe, is superior or equal in efficacy, and costs less in the short term or over a long period of time.

What follows on the next few pages is our detailed report on the current state of reimbursement for focused ultrasound in Italy.

^{*} All coverage decisions are conditional. The most current policy documents from the individual insurers should be referenced for a complete description.

¹ A detailed analysis of government and private coverage status in individual US states is available in the next section.

² In Canada, essential tremor and uterine fibroids are covered only in the province of Ontario.

³ In Italy, essential tremor and Parkinson's disease, tremor dominant are only covered in Abruzzo, Lombardia, and Sicilia. Neuropathic pain is only covered in Milano. Bone metastases and osteoid osteoma are only covered in Abruzzo, Lombardia, Emilia Romagna, Lazio, and Lombardia. Uterine Fibroids are covered in Abruzzo, Basilicata, Emilia Romagna, Lazio, Le Marche, Lombardia, Tuscano, and Umbria.

⁴ Codes that are not specific to FUS procedures, but can be used to bill for them

REIMBURSEMENT



Case Study FUS and Reimbursement in Italy

The Italian National Health Service (NHS)

The Italian constitution defines healthcare as a fundamental right and guarantees free medical care to the population. The National Health Service (NHS) is currently organized on three institutional levels: central, regional, and local. The Ministry of Health of the central government coordinates the NHS and ensures equal access to healthcare. The operational responsibility of healthcare lies with each of the 20 autonomous Regions. The State-Regions agreement defines the economic resources to be provided to the Regions by the central government and the Essential Levels of Assistance (LEAs) that the NHS is required to provide to all citizens. The NHS is funded through general taxation.

The Regions have great autonomy in designing their regional healthcare system and have the ability to provide additional services and treatments financed with their own

resources. They define their local operational units—the Aziende Sanitarie Locali (ASLs)—as well as which hospitals are part of an ASL, and which are autonomous organizations (Aziende Ospedaliere—AOs), independent from the ASLs.

Highly specialized services such as focused ultrasound are provided by University Hospitals and Istituti di Ricovero e Cura a Carattere Scientifico (Scientific Institutes for Hospitalization and Treatment, IRCCSs). The University Hospitals are part of the university structures and are independent of the local ASL. The IRCCSs are hospitals of excellence with strong research focus, predominantly clinical and translational research. IRCCSs have one or more areas of specialization, making them distinct from general hospitals and attractive to patients.

Reimbursement of FUS Procedures



With healthcare in Italy governed by the **20 autonomous regions**, reimbursement is largely specific to the regions where respective technology is available.

Case Study continued FUS and Reimbursement in Italy

The Italian reimbursement system

The Italian NHS guarantees the Essential Levels of Assistance (LEAs) that every citizen can access across the country. They are defined and covered by the central government. Regions also can add further levels of assistance in response to internal demand. Accordingly, there are national tariffs established by the Ministry of Health and regional tariffs established by the Regional Healthcare Departments. The latter may implement an additional reimbursement for higher costs associated with the use of specific medical devices that are more expensive than the basic tariff.

The codification system for hospital care is the International Classification of Diseases ICD-9-CM for the main diagnosis and a catalog of codes for procedures. Assigned codes are collated and linked to a Diagnostic-Related Group (DRG), in addition to the related reimbursement tariff for the procedure or treatment.

Currently, there is no LEA for any focused ultrasound procedure on the national level, so reimbursement for FUS procedures is determined and implemented on the respective regional levels of FUS sites.

Introduction of technological innovation in the Italian NHS

Health Technology Assessments (HTAs) have become a crucial step in obtaining reimbursement from the Regions. There is a formal National HTA Program that identifies and assesses medical technology; it is managed and organized by Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS), a National Agency representing the Regional Healthcare Systems. However, new emerging technologies like FUS are rarely recognized as a necessary service on the national level; usually, their value needs to be demonstrated in more than one institution at the regional level first.



Neurological

Neurological disorders

Reimbursement for essential tremor and Parkinson's disease, tremor-dominant is established in the regions where the technology is available: Abruzzo, Lombardia, and Sicilia. Reimbursement for neuropathic pain has been established in the region of Besta through individual agreements between sites and region administration.

In most regions, surgery for a neurological disorder is equated to a craniotomy, and the application of the stereotactic helmet also triggers the DRG for a craniotomy, with reimbursement of around €10,000—€12,000 per procedure.



centers

Urological

Prostate cancer

With 22 centers treating prostate cancer in Italy, there are some coverage and reimbursement agreements in place.

On average, hospitals receive €4,150 for the treatment, including 2 nights and value added tax (VAT).



- Essential tremor
 Parkinson's disease.
- tremor dominant
 Neuropathic pain



Case Study FUS and Reimbursement in Italy

The autonomous Regions have each implemented their own HTA programs, with various degrees of sophistication and respective agencies and authorities.

The regions of Abruzzo, Lombardia, Sicilia, and Veneto largely follow the structure of the National HTA Program in the assessment of new technologies, with regional agencies and their responsibilities in the process clearly identified. In Emilia-Romagna, the requirements for a new treatment to be recognized are strong scientific evidence and long-term economic viability. In this case, the presence of an HTA is critical, even though there are currently no regional guidelines on how to produce a structured, specific HTA. Other regions have different types of technology evaluation and decision-making paths, which can vary for different types of technology and are not necessarily well documented.

The case of Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan

The Besta Institute's purchase of the MR-guided FUS (MRgFUS) ExAblate 4000 system was linked to the construction of a new operating theater and the purchase of a new MRI. In 2015, the Institute received an earmarked donation to purchase the FUS device. The Region was in favor of the introduction because local patients were currently traveling to Palermo, Sicilia for essential tremor treatments. The donation received, and the competing presence of the MRgFUS in Sicilia, prompted the Region to update the LEAs and permit the treatment at IRCCS C. Besta.

To include the procedure in the LEAs and to establish reimbursement, the Region requested a study demonstrating the safety and effectiveness of the treatment. This information was included in the HTA together with an economic impact analysis.



Musculoskeleta

Bone metastases, osteoid osteoma Reimbursement for bone metastases and osteoid osteoma is established in the regions of Abruzzo, Emilia Romagna, Lazio, and Lombardia by individual agreements between sites and region administration.



Women's health

Uterine fibroids, body applications Reimbursement for uterine fibroids and other body applications is available in Abruzzo, Basilicata, Emilia Romagna, Lazio, Le Marche, Lombardia, Tuscano, and Umbria, triggered by the availability of the technology and an HTA. The procedure is reimbursed at €3,000 -€6,000.



Bone metastases

Osteoid osteoma



Uterine fibroids

Case Study continued FUS and Reimbursement in Italy

The Region recognized the tariff differentiation in the DRG 008, "Surgeries on peripheral and cranial nerves and other nervous system surgeries without CC," with a reimbursement rate of €11,799. The DRG has been attributed to Besta because of the competencies of its staff and the HTA report.

IRCCS Besta created an Alert HTA on MRgFUS, consisting primarily of an analysis of the scientific literature with the conclusions that the MRgFUS treatment can be considered an effective and safe treatment for unilateral essential tremor unresponsive to drug therapy. Therefore, MRgFUS can be considered a new option for patients for whom there are contraindications to treatment with deep brain stimulation (DBS) or radiosurgery, and a valid alternative for patients who are candidates for these treatments. The estimated cost of a procedure performed at IRCCS C. Besta is €14,583.

To date, DBS is no longer performed at IRCCS C. Besta and has been replaced by FUS treatments.

Insurance Coverage by Country*

	ВРН	Bone metastases	Breast tumors, benign	Breast tumors, malignant	Desmoid tumors	Essential tremor	Neuropathic pain	Osteoid osteoma	Pancreatic tumors	Parkinson's tremor	Prostate cancer
North Ameri	ca										
Canada ²						•					
United States ¹		•				•				•	•
Europe											
France	•										•
Germany		•	4	4	4	•	•	•	4	•	
Italy ³		•				•	•	•			
Switzerland						•	•				
United Kingdom											
Asia											
China											
China Israel		•				•	•			•	
China Israel Japan						•	•			•	•
China Israel Japan Malaysia		•				_	•				
China Israel Japan Malaysia Saudi Arabia	•					_	•				•
China Israel Japan Malaysia Saudi Arabia Singapore	•	•				_	•				
Asia China Israel Japan Malaysia Saudi Arabia Singapore South Korea Vietnam		•				_	•				•
China Israel Japan Malaysia Saudi Arabia Singapore South Korea Vietnam		•				_	•				•
China Israel Japan Malaysia Saudi Arabia Singapore South Korea		•				_	•				•

^{*} All coverage decisions are conditional. The most current policy documents from the individual insurers should be referenced for a complete description.

¹ A detailed analysis of government and private coverage status in individual US states is available in the next section.

² In Canada, essential tremor and uterine fibroids are covered only in the province of Ontario.
3 In Italy: Essential tremor and Parkinson's disease, tremor dominant are only covered in Sicily, Abruzzo, and Lombardia. Neuropathic pain is only covered in Milan. Bone metastases and osteoíd osteoma are only covered in Lombardia, Emilia Romagna, Lazio, and Abruzzo. Uteríne Fibroids are covered in Basilicata, Emilia Romagna, Lazio & Abruzzo, Lombardy, Marche, Tuscany, and Umbria.

4 Codes that are not specific to FUS procedures, but can be used to bill for them

Insurance Coverage by Country* continued

	Thyroid nodules	Uterine fibroids	Varicose veins				
North Ameri	ica						
Canada ²		•					
United States ¹		•					
Europe							
France							
Germany	4		4				
Italy³							
Switzerland							
United Kingdom							
United Kingdom Asia China		•					
Asia		•					
Asia China Israel Japan							
Asia China Israel Japan Malaysia							
Asia China Israel		•					
Asia China Israel Japan Malaysia		•					
Asia China Israel Japan Malaysia Saudi Arabia		•					

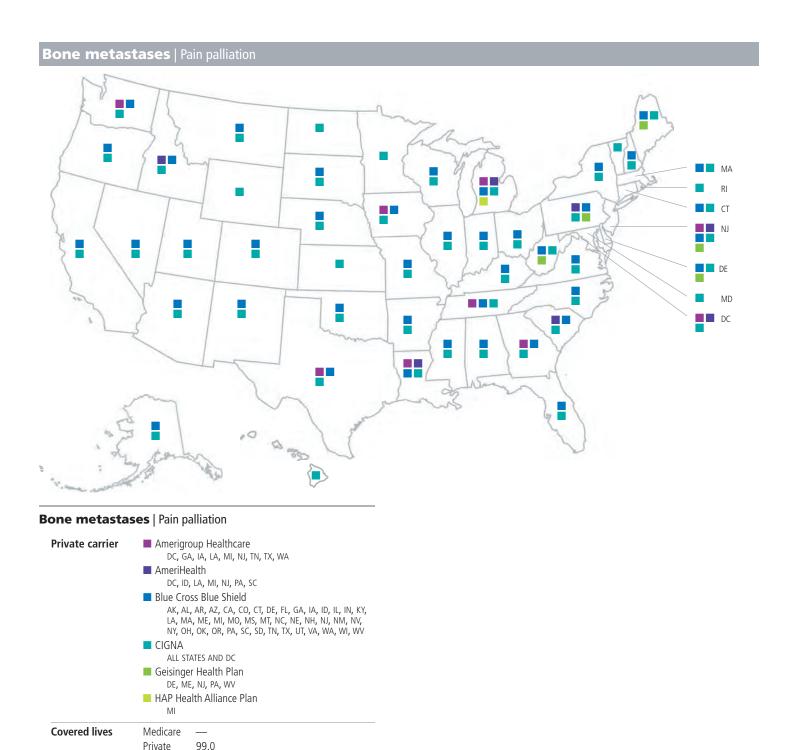
^{*} All coverage decisions are conditional. The most current policy documents from the individual insurers should be referenced for a complete description.

¹ A detailed analysis of government and private coverage status in individual US states is available in the next section.

² In Canada, essential tremor and uterine fibroids are covered only in the province of Ontario.
3 In Italy: Essential tremor and Parkinson's disease, tremor dominant are only covered in Sicily, Abruzzo, and Lombardia. Neuropathic pain is only covered in Milan. Bone metastases and osteoid osteoma are only covered in Lombardia, Emilia Romagna, Lazio, and Abruzzo. Uterine Fibroids are covered in Basilicata, Emilia Romagna, Lazio & Abruzzo, Lombardy, Marche, Tuscany, and Umbria.

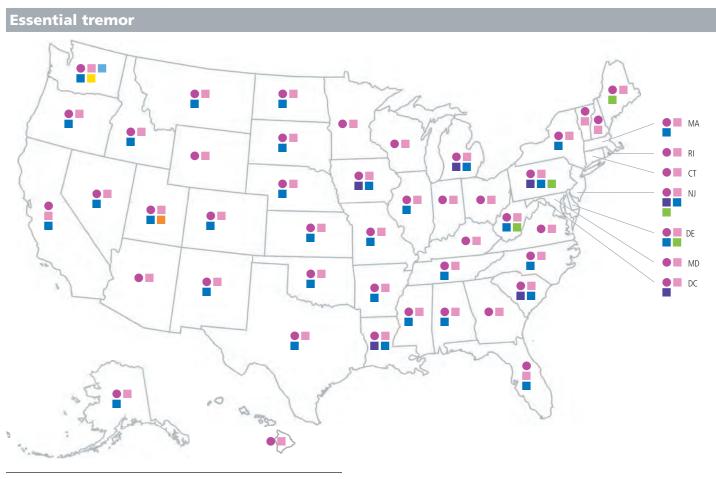
4 Codes that are not specific to FUS procedures, but can be used to bill for them

Insurance Coverage in the United States*

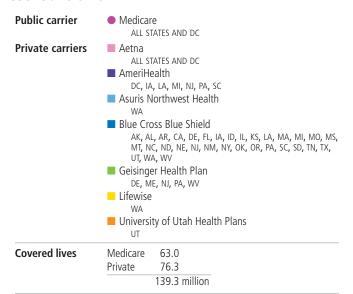


^{*} All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

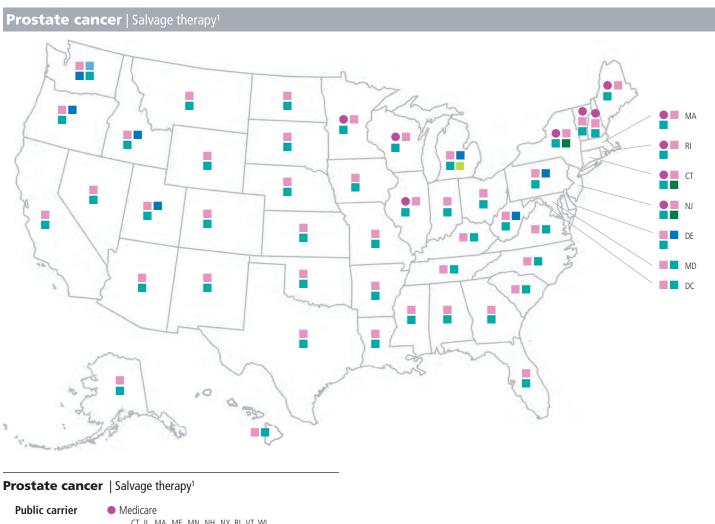
99.0 million



Essential tremor



^{*} All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.





^{*} All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

¹ Local treatment for recurrent prostate cancer following radiation therapy

Parkinson's disease, tremor



Parkinson's disease, tremor

Public carrier	,	e T, GA, IL, KY, MA, ME, MN, NC, NH, NY, OH, RI, SC, A, VT, WI, WV
Covered lives	Medicare	24.4
	Private	_
		24.4 million

^{*} All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

Uterine fibroids Uterine fibroids Private carrier Preferred One IA, MI, MN, NE, ND, SD, WI **Covered lives** Medicare Private 0.25 0.25 million

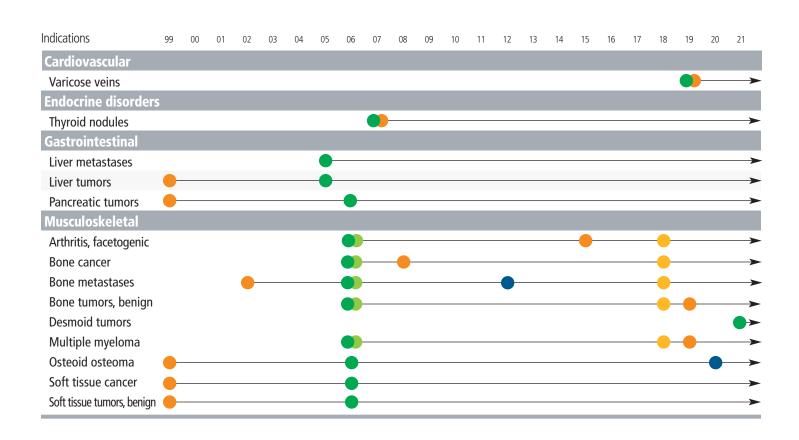
^{*} All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

REIMBURSEMENT

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REGULATORY APPROVALS

FUS Regulatory Approvals by Indication and Region



North America

Europe

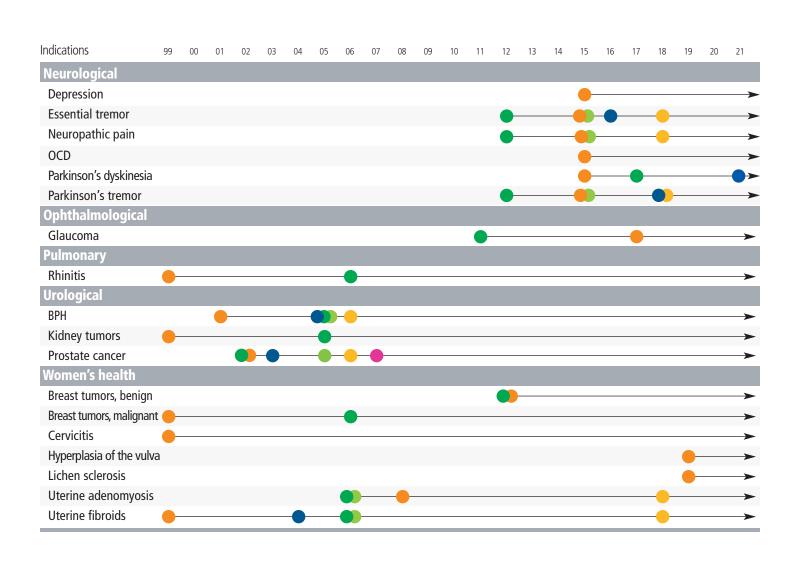
Asia

South America

Oceania

Africa

FUS Regulatory Approvals by Indication and Region continued

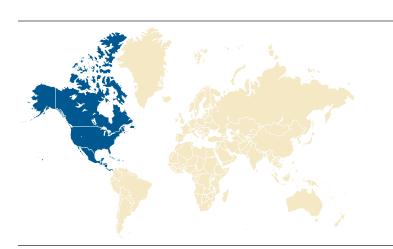




FUS Regulatory Approvals by Indication and Region Graphic



North America FUS Regulatory Approvals by Indication



North America

Bahamas, Ministry of Health

Dominican Republic, MISPAS

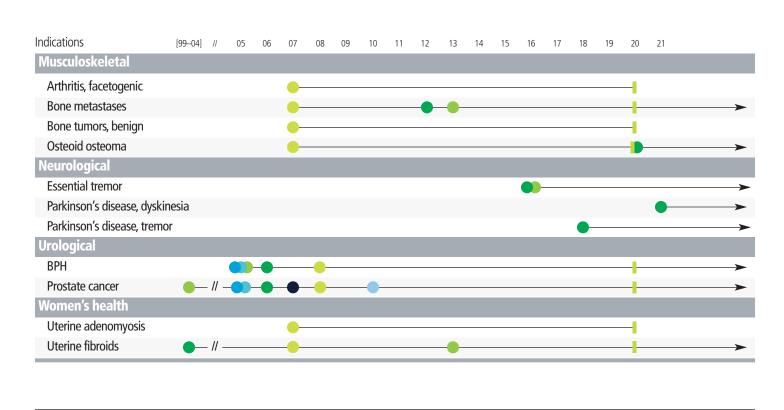
Barbados, *Ministry of Health and Wellness* Costa Rica, *Ministerio de Salud*

Approval

Approval begin date

Approval end date

8 Approvals



United States, FDA,

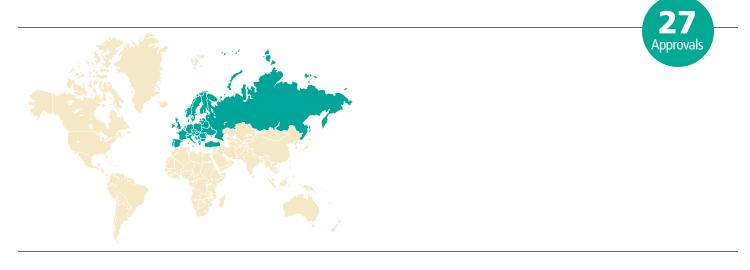
Canada, Health Canada,

Medical Devices Bureau

Center for Devices & Radiological Health

Mexico, COFEPRIS

Europe FUS Regulatory Approvals by Indication

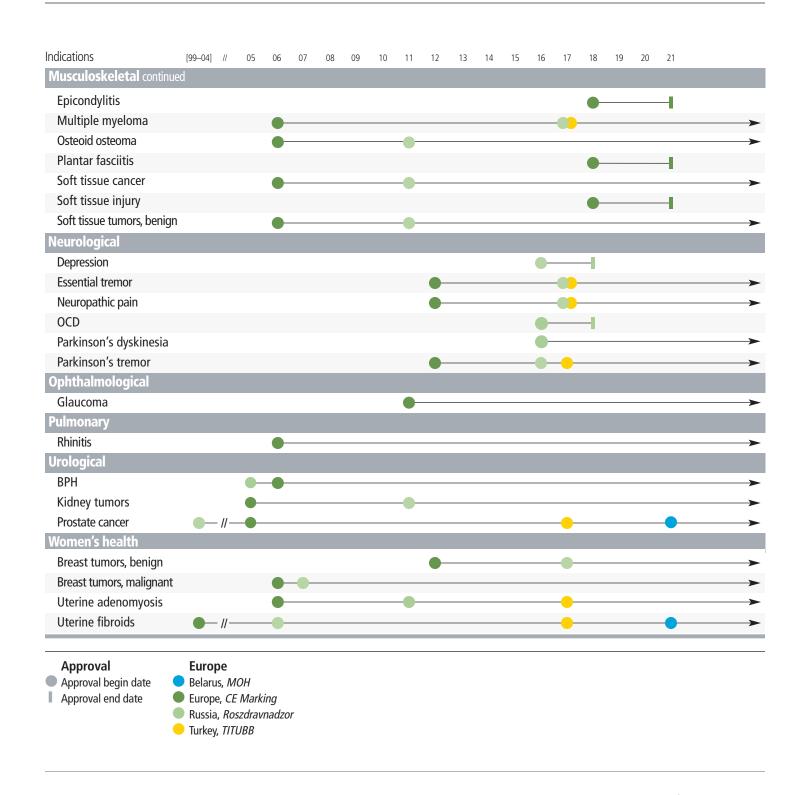




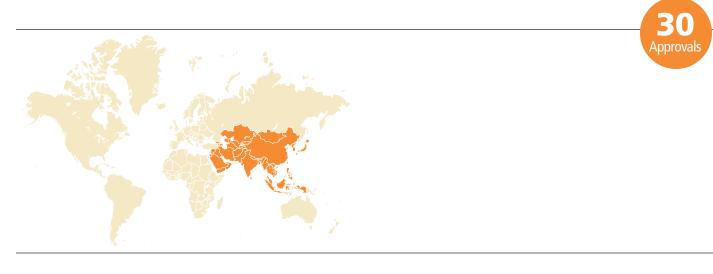


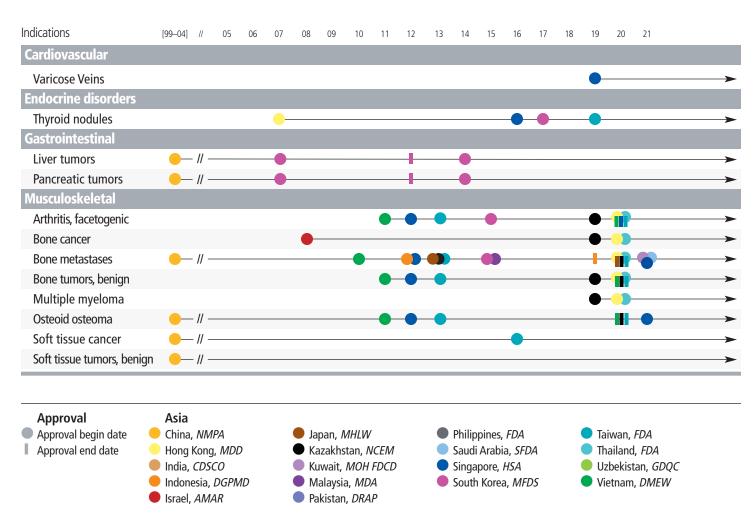
Europe

FUS Regulatory Approvals by Indication continued



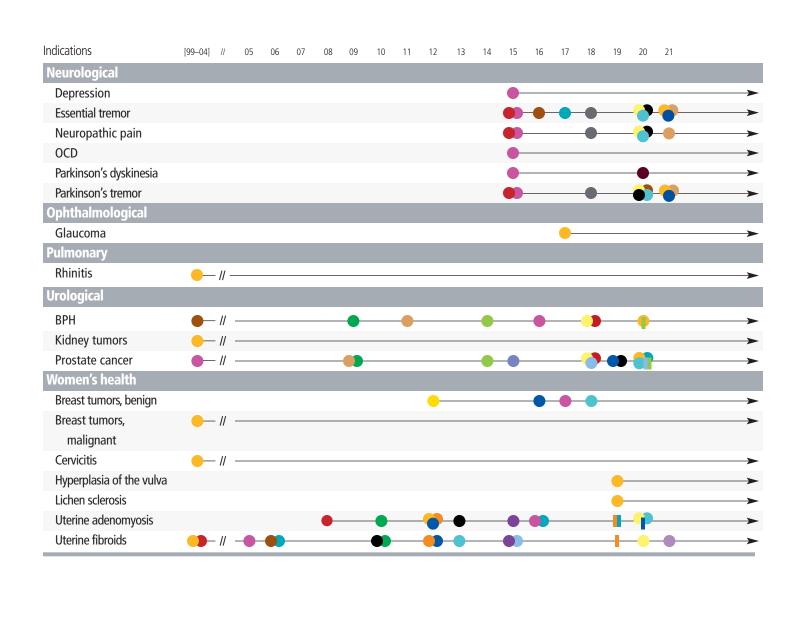
Asia
FUS Regulatory Approvals by Indication

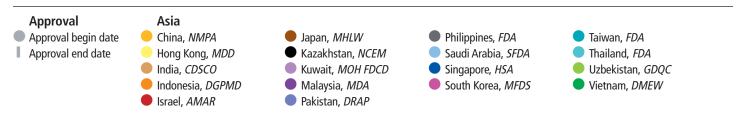




Asia

FUS Regulatory Approvals by Indication continued

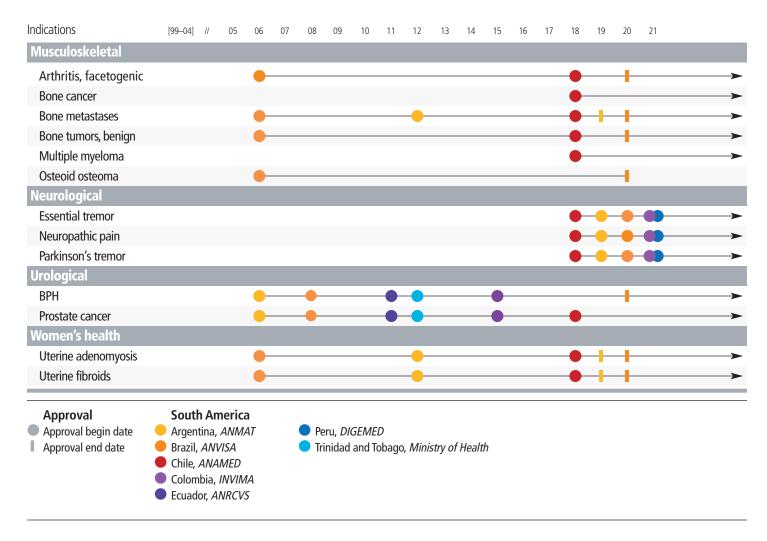




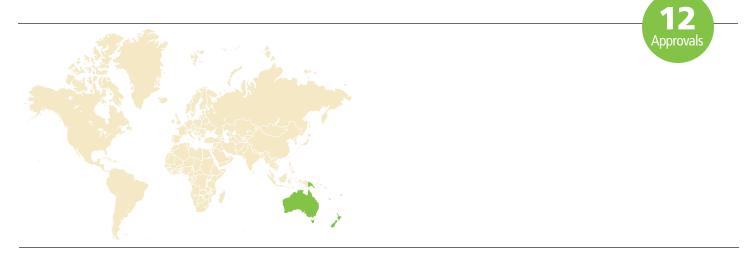
South America FUS Regulatory Approvals by Indication

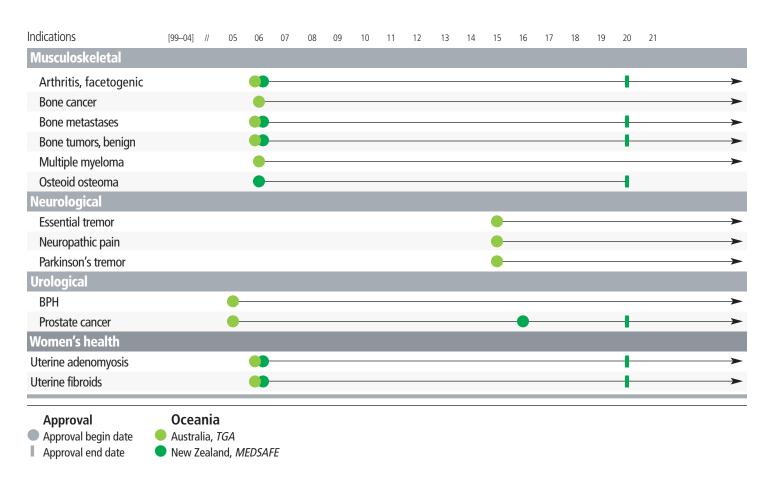


12 Approvals

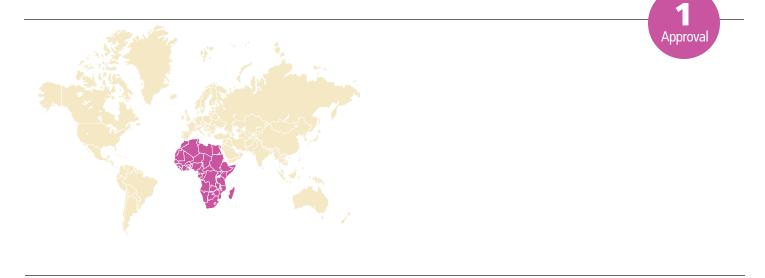


Oceania FUS Regulatory Approvals by Indication





Africa FUS Regulatory Approvals by Indication



Indications [99–04] // 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21

Urological

Prostate cancer

Approval
Approval begin date
Approval end date

Africa

South Africa, MCC



Focused Ultrasound Industry Geographic Overview

2021

	North America	Europe	Asia
88	41	22	25
FUS companies			
59 FUS device manufacturers	27	13	19
12	2	3	7
Companies with approvals			

Indication Approvals by Manufacturer

	North America	Europe	Asia	South America	Oceania	Africa
Manufacturer						
Alpinion Medical Systems	_	1	2	_	_	_
Chongqing Haifu Medical Technology	-	11	10	_	-	_
EDAP TMS	2	1	1	1	_	_
EpiSonica	-	_	3	_	-	_
EyeTechCare	_	1	1	_	_	_
Insightec	11	16	15	12	12	_
Profound Medical	4	6	5	3	4	_
Shanghai A&S Science Technology Development	-	1	5	_	-	_
Shenzhen PRO-HITU Medical Technology	_	1	4	_	_	_
Sonablate	2	2	2	2	2	1
Theraclion	_	3	3	_	_	_
Wuxi Haiying Electronic Medical Systems	-	-	1	-	-	-

Summary of Global Approvals



Companies with approved indications **Approved indications**

Regulatory Approvals for Companies by Region and Indication

■ North America

EDAP TMS

Benign prostatic hyperplasia Prostate cancer

Insightec

Benign prostatic hyperplasia Bone metastases Essential tremor Parkinson's disease, dyskinesia Parkinson's disease, tremor Prostate cancer Uterine fibroids

Profound Medical

Benign prostatic hyperplasia Osteoid osteoma Prostate cancer Uterine fibroids

Sonablate

Benign prostatic hyperplasia Prostate cancer

Europe

Alpinion Medical Systems

Uterine fibroids

Chongqing Haifu Medical Technology Breast tumors, malignant

Kidney tumors
Liver metastases
Liver tumors
Osteoid osteoma
Pancreatic tumors
Rhinitis
Soft tissue cancer
Soft tissue tumors, benign
Uterine adenomyosis
Uterine fibroids

EDAP TMS

Prostate cancer

EyeTechCare

Glaucoma

Insightec

Arthritis, facetogenic
Bone cancer
Bone metastases
Bone tumors, benign
Essential tremor
Multiple myeloma
Neuropathic pain
Parkinson's disease,
dyskinesia
Parkinson's disease,
tremor
Prostate cancer
Uterine adenomyosis
Uterine fibroids

Profound Medical

Bone metastases Desmoid tumors Osteoid osteoma Prostate cancer Uterine adenomyosis Uterine fibroids

Shanghai A&S

Uterine fibroids

Shenzhen PRO-HITU Medical

Uterine fibroids

Sonablate

Benign prostatic hyperplasia Prostate cancer

Theraclion

Breast tumors, benign Thyroid nodules Varicose veins

Asia

Alpinion Medical Systems

Uterine adenomyosis Uterine fibroids

Chongqing Haifu Medical Technology Breast tumors, malignant

Cervicitis

Kidney tumors

Liver tumors
Osteoid osteoma
Pancreatic tumors
Rhinitis
Soft tissue cancer
Soft tissue tumors, benign

Uterine fibroids **EDAP TMS**

Prostate cancer

EpiSonica

Soft tissue cancer

EyeTechCare

Arthritis, facetogenic

Glaucoma

Insightec

Bone cancer
Bone metastases
Bone tumors, benign
Depression
Essential tremor
Multiple myeloma
Neuropathic pain
Obsessive-compulsive
disorder
Parkinson's disease,
dyskinesia
Parkinson's disease.

Parkinson's disease, tremor Prostate cancer

Uterine adenomyosis Uterine fibroids

Profound Medical

Bone metastases Osteoid osteoma Prostate cancer Uterine adenomyosis Uterine fibroids

Shanghai A&S

Bone metastases Breast tumors, malignant Liver tumors Soft tissue cancer Uterine fibroids

Shenzhen PRO-HITU Medical

Hyperplasia of the vulva Lichen sclerosis Uterine adenomyosis Uterine fibroids

Sonablate

Benign prostatic hyperplasia Prostate cancer

Theraclion

Breast tumors, benign Thyroid nodules Varicose veins

Wuxi Haiying Electronic Medical

Uterine fibroids

South America

EDAP TMS

Prostate cancer

Insightec

Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Essential tremor Multiple myeloma Neuropathic pain Parkinson's disease, tremor Prostate cancer Uterine adenomyosis Uterine fibroids

Sonablate

Benign prostatic hyperplasia Prostate cancer

Oceania

Insightec

Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Essential tremor Multiple myeloma Neuropathic pain Parkinson's disease, tremor Prostate cancer Uterine adenomyosis Uterine fibroids

Sonablate

Benign prostatic hyperplasia Prostate cancer

Africa

Sonablate

Prostate cancer

FUS Regulatory Approvals by Region and Manufacturer

ı	North America	Europe	Asia	South America	Oceania	Africa
Indications	TVOTUTY WHETEG	Larope	7 Sid	30dtill therea	Оссини	7 (11100
Cardiovascular						
Varicose veins		A	A			
Endocrine						
Thyroid nodules		A	A			
Gastrointestinal						
Liver metastases		•				
Liver tumors		•	• •			
Pancreatic tumors		•	•			
Musculoskeletal						
Arthritis, facetogenic		•	•	•	•	
Bone cancer		•	•	•	•	
Bone metastases				•	•	
Bone tumors, benign			•	•	•	
Desmoid tumors						
Multiple myeloma			•	•		
Osteoid osteoma						
Soft tissue cancer		•	• • •			
Soft tissue tumors, benign		•	•			



FUS Regulatory Approvals by Region and Manufacturer continued

	North America	Europe	Asia	South America	Oceania	Africa
Indications						
Neurological						
Depression			•			
Essential tremor		•	•	•	•	
Neuropathic pain		•	•	•	•	
OCD			•			
Parkinson's dyskinesia	•	•	•			
Parkinson's tremor	•	•	•	•	•	
Ophthalmological						
Glaucoma		_	_			
Pulmonary						
Rhinitis		•	•			
Urological						
BPH				•		
Kidney tumors		•	•			
Prostate cancer						
Women's health						
Breast tumors, benign		A	A			
Breast tumors, malignant		•	• •			
Cervicitis			•			
Hyperplasia of the vulva			•			
Lichen sclerosis			•			
Uterine adenomyosis				•	•	
Uterine fibroids				•	•	



North America

Profound Medical, Canada

Sonablate, US

Europe

▲ EDAP TMS, France

LyeTechCare, France

▲ Theraclion, *France*

Asia

- Alpinion Medical Systems, South Korea
- Chongqing Haifu Medical Technology, China
- EpiSonica, *Taiwan*
- Insightec, Israel
- Shanghai A&S, China
- Shenzhen PRO-HITU Medical, China
- Wuxi Haiying Electronic Medical, *China*

North America

FUS Regulatory Approvals by Country and Manufacturer

	Bahamas	Barbados	Canada	Costa Rica	Dominican Republic	US	
Indications	Ministry of Health	Ministry of Health and Wellness	Health Canada, Medical Devices Bureau	Ministerio de Salud	MISPAS	FDA, Center for Devices & Radiological Health	
Musculoskeletal							
Bone metastases			•			•	
Osteoid osteoma							
Neurological							
Essential tremor			•			•	
Parkinson's dyskinesia						•	
Parkinson's tremor						•	
Urological							
ВРН							
Prostate cancer							
Women's health							
Uterine fibroids						•	

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea ▲ EyeTechCare, France Sonablate, US Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, Taiwan Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, *China*

Europe

FUS Regulatory Approvals by Country and Manufacturer

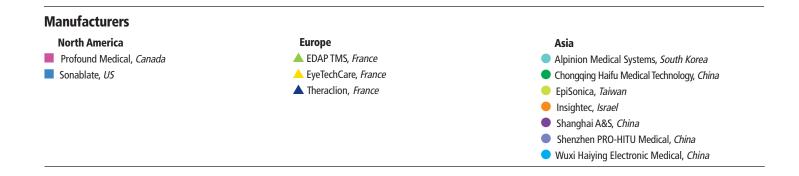
	Belarus	Europe	Russia	Turkey
Indications	МОН	CE Marking	Roszdravnadzor	TITUBB
Cardiovascular				
Varicose veins		A		
Endocrine				
Thyroid nodules		A	A	
Gastrointestinal				
Liver metastases		•		
Liver tumors		•	•	
Pancreatic tumors		•	•	
Musculoskeletal				
Arthritis, facetogenic		•	•	•
Bone cancer		•	•	•
Bone metastases	•		•	•
Bone tumors, benign		•	•	•
Desmoid tumors				
Multiple myeloma		•	•	•
Osteoid osteoma			•	
Soft tissue cancer		•	•	
Soft tissue tumors, benign		•	•	



Europe

FUS Regulatory Approvals by Country and Manufacturer continued

	Belarus	Europe	Russia	Turkey
Indications	МОН	CE Marking	Roszdravnadzor	TITUBB
Neurological				
Essential tremor		•	•	•
Neuropathic pain		•	•	•
Parkinson's dyskinesia			•	
Parkinson's tremor		•	•	•
Ophthalmological				
Glaucoma		_		
Pulmonary				
Rhinitis		•		
Urological				
BPH				
Kidney tumors		•	•	
Prostate cancer	•			•
Women's health				
Breast tumors, benign		A	A	
Breast tumors, malignant		•	•	
Uterine adenomyosis			•	•
Uterine fibroids	•		• •	•
		•		



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Asia
FUS Regulatory Approvals by Country and Manufacturer

	China	Hong Kong	India	Israel	Japan	Kazakhstan	Kuwait	Malaysia
Indications	NMPA	MDD	CDSCO	AMAR	MHLW	NCEM	MOH FDCD	MDA
Cardiovascular								
Varicose veins								
Endocrine								
Thyroid nodules		A						
Gastrointestinal								
Liver tumors	• •							
Pancreatic tumors								
Musculoskeletal								
Arthritis, facetogenic		•				•		
Bone cancer		•				•		
Bone metastases		•				•		
Bone tumors, benign		•				•		
Multiple myeloma		•				•		
Osteoid osteoma								
Soft tissue cancer	• •							
Soft tissue tumors, benign								
Neurological								
Depression								
Essential tremor		•		•	•	•		
Neuropathic pain		•		•		•		
OCD								
Parkinson's dyskinesia					•			
Parkinson's tremor		•			•	•		

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea ▲ EyeTechCare, France Sonablate, US Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, Taiwan Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, *China*

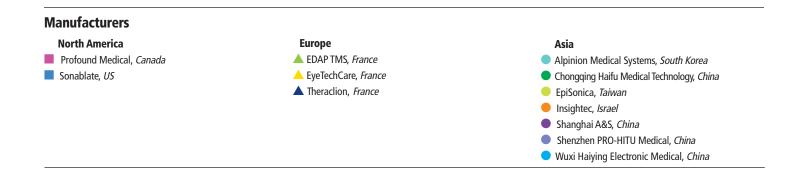
Asia
FUS Regulatory Approvals by Country and Manufacturer continued

	Pakistan	Philippines	Saudi Arabia	Singapore	South Korea	Taiwan	Thailand	Vietnam
Indications	DRAP	FDA	SFDA	HSA	MFDS	FDA	FDA	DMEW
Cardiovascular								
Varicose veins				A				
Endocrine								
Thyroid nodules				A	A	A		
Gastrointestinal								
Liver tumors					•			
Pancreatic tumors					•			
Musculoskeletal								
Arthritis, facetogenic					•		•	
Bone cancer							•	
Bone metastases			•		•		•	
Bone tumors, benign							•	
Multiple myeloma							•	
Osteoid osteoma								
Soft tissue cancer								
Soft tissue tumors, benign								
Neurological								
Depression					•			
Essential tremor		•			•		•	
Neuropathic pain		•			•		•	
OCD					•			
Parkinson's dyskinesia					•			
Parkinson's tremor		•			•			



Asia
FUS Regulatory Approvals by Country and Manufacturer continued

	China	Hong Kong	India	Israel	Japan	Kazakhstan	Kuwait	Malaysia
Indications	NMPA	MDD	CDSCO	AMAR	MHLW	NCEM	MOH FDCD	MDA
Ophthalmological								
Glaucoma	_							
Pulmonary								
Rhinitis	•							
Urological								
BPH								
Kidney tumors	•							
Prostate cancer						•		
Women's health								
Breast tumors, benign		A						
Breast tumors, malignant	• •							
Cervicitis	•							
Hyperplasia of the vulva								
Lichen sclerosis								
Uterine adenomyosis		•		•		•		
Uterine fibroids		•		•	•	•	•	
	• •							



Asia
FUS Regulatory Approvals by Country and Manufacturer continued

	Pakistan	Philippines	Saudi Arabia	Singapore	South Korea	Taiwan	Thailand	Vietnam
Indications	DRAP	FDA	SFDA	HSA	MFDS	FDA	FDA	DMEW
Ophthalmological								
Glaucoma								
Pulmonary								
Rhinitis								
Urological								
ВРН					_			
Kidney tumors								
Prostate cancer							•	
Women's health								
Breast tumors, benign				A	A	A		
Breast tumors, malignant								
Cervicitis								
Hyperplasia of the vulva								
Lichen sclerosis								
Uterine adenomyosis					• •		•	
Uterine fibroids						• •	• •	



South America

FUS Regulatory Approvals by Country and Manufacturer

	Argentina	Brazil	Chile	Colombia	Ecuador	Peru
Indications	ANMAT	ANVISA	ANAMED	INVIMA	ANRCVS	DIGEMED
Musculoskeletal						
Arthritis, facetogenic			•			
Bone cancer			•			
Bone metastases			•			
Bone tumors, benign			•			
Multiple myeloma			•			
Neurological						
Essential tremor	•	•	•	•		•
Neuropathic pain	•	•	•	•		
Parkinson's tremor	•	•	•	•		•
Urological						
ВРН						
Prostate cancer		A	•			
Women's health						
Uterine adenomyosis			•			
Uterine fibroids			•			

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea Sonablate, US LyeTechCare, France Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, Taiwan Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, China

South America

FUS Regulatory Approvals by Country and Manufacturer continued

	Trinidad and Tobago
Indications	Ministry of Health
Musculoskeletal	
Arthritis, facetogenic	
Bone cancer	
Bone metastases	
Bone tumors, benign	
Multiple myeloma	
Neurological	
Essential tremor	
Neuropathic pain	
Parkinson's tremor	
Urological	
ВРН	•
Prostate cancer	
Women's health	
Uterine adenomyosis	
Uterine fibroids	

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea Sonablate, US LyeTechCare, France Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, *Taiwan* Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, *China*

Oceania

FUS Regulatory Approvals by Country and Manufacturer

	Australia
Indications	TGA
Musculoskeletal	
Arthritis, facetogenic	•
Bone cancer	•
Bone metastases	•
Bone tumors, benign	•
Multiple myeloma	•
Neurological	
Essential tremor	•
Neuropathic pain	•
Parkinson's tremor	•
Urological	
BPH	•
Prostate cancer	
Women's health	
Uterine adenomyosis	•
Uterine fibroids	•

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea LyeTechCare, France Sonablate, US Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, Taiwan Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, *China*

Africa

FUS Regulatory Approvals by Country and Manufacturer

	South Africa		
Indications	MCC	 	
Urological			
Prostate cancer			

Manufacturers North America Europe Asia Profound Medical, Canada ▲ EDAP TMS, France Alpinion Medical Systems, South Korea Sonablate, US LyeTechCare, France Chongqing Haifu Medical Technology, China ▲ Theraclion, France EpiSonica, *Taiwan* Insightec, Israel Shanghai A&S, China Shenzhen PRO-HITU Medical, China Wuxi Haiying Electronic Medical, *China*

Global Landscape of Approved Indications and Manufacturers

Indication regional approvals	Indications	Manufacturers
	Cardiovascular	
• •	Varicose veins	Theraclion
	Endocrine disorders	
• •	Thyroid nodules	Theraclion
	Gastrointestinal	
	Liver metastases	Chongqing Haifu Medical Technology
	Liver tumors	Chongqing Haifu Medical Technology
•		Shanghai A&S
	Pancreatic tumors	Chongqing Haifu Medical Technology
	Musculoskeletal	
	Arthritis, facetogenic	Insightec
	Bone cancer	Insightec
	Bone metastases	Insightec
		Profound Medical
		Shanghai A&S
	Bone tumors, benign	Insightec
	Desmoid tumors	Profound Medical
	Multiple myeloma	Insightec
	Osteoid osteoma	Chongqing Haifu Medical Technology
		Profound Medical
• •	Soft tissue cancer	Chongqing Haifu Medical Technology
		EpiSonica
		Shanghai A&S
• •	Soft tissue tumors, benign	Chongqing Haifu Medical Technology



Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Neurological	
	Depression	Insightec
	Essential tremor	Insightec
	Neuropathic pain	Insightec
	Obsessive-compulsive disorder	Insightec
	Parkinson's disease, dyskinesia	Insightec
• • • •	Parkinson's disease, tremor	Insightec
	Ophthalmological	
• •	Glaucoma	EyeTechCare
	Pulmonary	
• •	Rhinitis	Chongqing Haifu Medical Technology
	Urological	
	Benign prostatic hyperplasia	EDAP TMS
		Insightec
		Profound Medical
		Sonablate
	Kidney tumors	Chongqing Haifu Medical Technology
	Prostate cancer	EDAP TMS
		Insightec
		Profound Medical
		Sonablate
	Women's health	
• •	Breast tumors, benign	Theraclion
• •	Breast tumors, malignant	Chongqing Haifu Medical Technology
		Shanghai A&S
	Cervicitis	Chongqing Haifu Medical Technology



Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Women's health continued	
	Hyperplasia of the vulva	Shenzhen PRO-HITU Medical
	Lichen sclerosis	Shenzhen PRO-HITU Medical
	Uterine adenomyosis	Alpinion Medical Systems
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shenzhen PRO-HITU Medical
• •	Uterine fibroids	Alpinion Medical Systems
• •		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
• •		Shanghai A&S
• •		Shenzhen PRO-HITU Medical
•		Wuxi Haiying Electronic Medical

Approval regions

North America

Europe

Asia

South America

Oceania

Africa

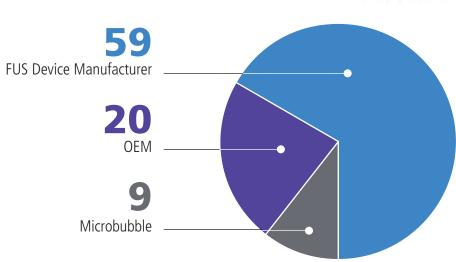
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FUS Industry Timelines

Just as a reminder, the company timelines include the year the company became involved in the focused ultrasound industry instead of the date of incorporation. For many early-stage focused ultrasound manufacturing companies, this date is one and the same; however, for the OEM manufacturers and/or microbubble companies, it is often different.

FUS companies*

Company distribution by type



^{*}Includes device manufacturers, OEM, and microbubble companies

North America—Timelines of Companies, p.III.67

¹ Harmonic Medical INC changed their name to ArrayUS Technologies INC in 2021.

² SonaCare Medical LLC changed their name to Sonablate CORP in 2021.

North America—Timelines of Companies

Clinical Device Manufacturers

North America Alpheus Medical 2021 **INIA Biosciences** 2020 AthenaCare NovusTX Devices Exo Imaging 2019 Sonosa Medical Acoustiic 2018 SonoVol Cordance Medical Sonus Microsystems 2017 MR Instruments TheraWave NeuroSonics Medical 2016 Acoustic MedSystems 2015 Aucta Technologies VeinSound 2014 Cerevast Medical FUSMobile 2013 2012 2011 Discogen ArrayUS² 2010 **FUS Instruments** 2009 HistoSonics Profound Medical 2008 International Cardio 2007 EyeSonix 2006 2005 Sonablate² 2004 BrainSonix 2003 2002 2001 2000 1999 1998 1997 1996 1995 1994 // 1990

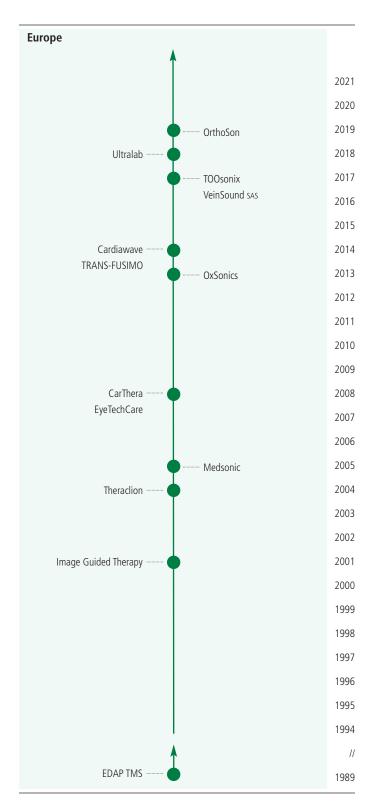
Other FUS Companies



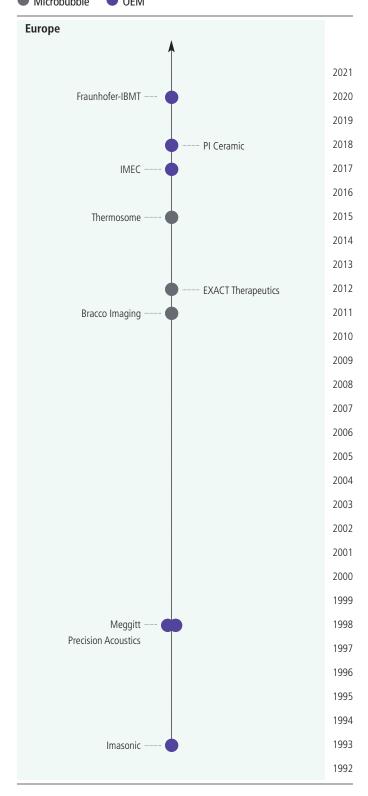
MANUFACTURERS

Europe—Timelines of Companies

Clinical Device Manufacturers



Other FUS Companies Microbubble OEM

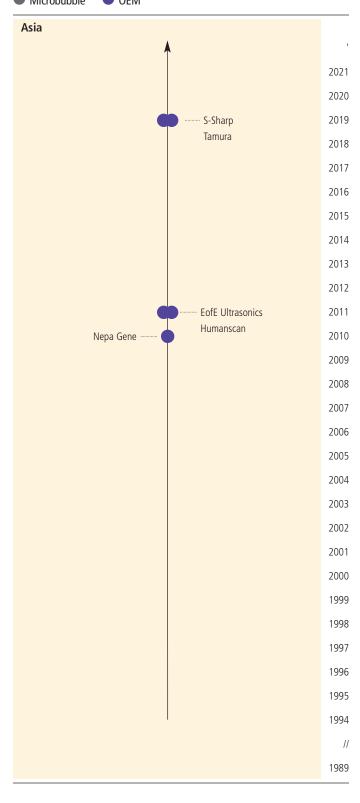


Asia—Timelines of Companies

Clinical Device Manufacturers



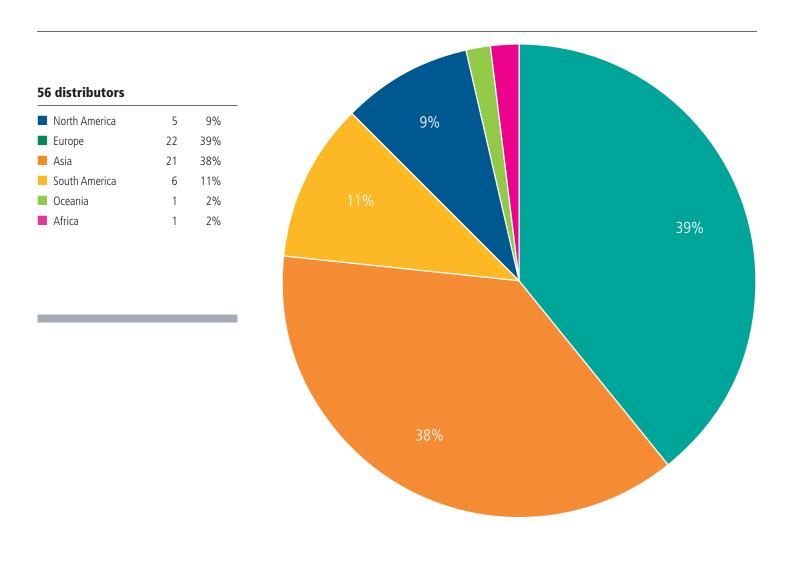
Other FUS Companies Microbubble OEM



MANUFACTURERS



FUS Device Distributors by Region





FUS Device Distributors by Region continued

Europe

ab medica SPA

Andromed Tıbbi Cihazlar ve Sağlık Hizmetleri

Angiomedic DOO

Brainbox LTD

Consultronix sa

Elanus Medical AG

Intermedica LTD

Kungshusen Medicinska AB Levi Danismanlik ve Ticaret AS

Medicina Analítica Consumibles SA

Medistim Danmark APS

Medkonsult sno

Palex Medical sa

Promedica Bioelectronics SRL

ProMedical oy

Sigmacon UK LTD

SofMedica

Synektik Group

Tema Sinergie SPA

Timko sp zoo

Vingmed As

VIVAX Pharmaceuticals sRo

Asia

Allmed Solutions

AMI Technologies LTD

Amos Gazit LTD

Beijing Beike Digital Medical Technology co LTD

CanAm Scientific

Century Scientific and Equipment co WLL

Demakai со цтр

Double Success co LTD

DSS Imagetech PVT LTD

ECHO Healthcare INC

Ekpac China LTD

Huons Medical

imedtac co LTD

Medfocus co LTD

Nanomedix PVT LTD

Pro Chime Enterprise CORP

Sumo Corporations LTD

Takai Hospital Supply co LTD

Transmedic PTE LTD

Varitron

Yangde Instrument co LTD

South America

Cencomex sa

Imemed Bolivia

MedicinelasersA

Protrauma sa

Strattner & Cia LTDA

Oceania

C+---++--- --- 0 C:

Strattner & Cia LTDA

North America

American HIFU LLC

Cyber Robotic Solutions SA de CV

HIFU Prostate Services LLC

Soluciones Medicas Avanzadas sas

Vituro Health LLC

Africa

SARL Medimatec

FUS Industry by Region

North America

41

CLINICAL DEVICE MANUFACTURERS

Acoustic MedSystems INC | Savoy, Illinois, United States, acousticmed.com

Acoustiic INC | Seattle, Washington, United States, www.acoustiic.com

Alpheus Medical INC | North Oakdale, Minnesota, United States, www.alpheusmedical.com

ArrayUS Technologies INC | Burlington, Ontario, Canada, arrayus.ca

AthenaCare LLC | Salt Lake City, Utah, United States

Aucta Technologies INC | Minneapolis, Minnesota, United States, www.linkedin.com/company/aucta-technologies

BrainSonix CORP | Sherman Oaks, California, United States, www.brainsonix.com

Cerevast Medical INC | Bothell, Washington, United States, cerevast.com

Cordance Medical INC | Mountain View, California, United States, cordancemedical.com

Discogen | Weston, Florida, United States, discogen.com

Exo Imaging INC | Redwood City, California, United States, www.exo-imaging.com

EyeSonix | Long Beach, California, United Sates, eyesonix.com

FUS Instruments INC | Toronto, Ontario, Canada, www.fusinstruments.com

FUSMobile INC | Alpharetta, Georgia, United Sates, www.fusmobile.com

HistoSonics INC | Ann Arbor, Michigan, United States, www.histosonics.com

INIA Biosciences INC | Boston, Massachusetts, United States, www.iniabiosciences.com

International Cardio CORP, LLC | Edina, Minnesota, United States, www.hifu-rx.com

MR Instruments INC | Hopkins, Minnesota, United States, mrinstruments.com

NeuroSonics Medical INC | Baltimore, Maryland, United States, neurosonicsmedical.com

NovusTX Devices INC | Calgary, Alberta, Canada, novustx-devices.com

- Profound Medical CORP | Mississauga, Ontario, Canada, profoundmedical.com
- Sonablate CORP | Charlotte, North Carolina, United States, www.sonablate.com

Sonosa Medical INC | Baltimore, Maryland, United States, www.sonosamedical.com

SonoVol INC | Durham, North Carolina, United States, sonovol.com

Sonus Microsystems | Vancouver, British Columbia, Canada, sonusmicrosystems.com

TheraWave Bio INC | New York, New York, United States

VeinSound INC | Sunnyvale, California, United Sates

[🛨] Manufacturers with regulatory approvals. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.50.

North America continued

MICROBUBBLE

Advanced Microbubbles INC | Newark, California, United States, www.advancedmicrobubbles.com
Artenga INC | Ottawa, Ontario, Canada, www.artenga.com
Dynaflow INC | Jessup, Maryland, United States, www.dynaflow-inc.com
Lantheus Medical Imaging INC | North Billerica, Massachusetts, United States, www.lantheus.com
Microvascular Therapeutics LLC | Tucson, Arizona, United States, www.mvtpharma.com
SonoGene LLC | Glen Ellyn, Illinois, United States, www.sonogene.com

OEM

Daxsonics Ultrasound INC | Halifax, Nova Scotia, Canada, www.daxsonics.com
Electronics and Innovation LTD | Rochester, New York, United States, www.eandiltd.com
JJ & A Instruments LLC | Rathdrum, Idaho, United States, jja-instruments.com
Onda CORP | Sunnyvale, California, United States, www.ondacorp.com
Piezo Technologies | Indianapolis, Indiana, United States, www.piezotechnologies.com
Sonic Concepts INC | Bothell, Washington, United States, www.sonicconcepts.com
Ultrasonic S-Lab LLC | Concord, California, United States, www.ultrasonic-s-lab.com
Verasonics INC | Kirkland, Washington, United States, verasonics.com

Europe

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CLINICAL DEVICE MANUFACTURERS
 Cardiawave sa | Paris, France, cardiawave.com

 CarThera sa | Paris, France, www.carthera.eu

- ➡ EDAP TMS sa | Vaulx-en-Velin, France, www.edap-tms.com
- EyeTechCare SA | Lyon, France, eyetechcare.com

 Image Guided Therapy SA | Pessac, France, www.imageguidedtherapy.com

 Medsonic LTD | Limassol, Cyprus, www.medsonic.com.cy

 OrthoSon LTD | Oxford, England, United Kingdom, www.orthoson.com

 OxSonics LTD | Oxford, England, United Kingdom, www.oxsonics.com
- + Theraclion sa | Malakoff, France, www.theraclion.fr
- TOOsonix A/s | Hørsholm, Denmark, www.toosonix.com
 TRANS-FUSIMO | Bremen, Germany, www.trans-fusimo.eu
 Ultralab LTD | Çankaya/Ankara, Turkey, www.ultralabltd.com
 VeinSound sas | Lyon, France, www.veinsound.com

⁺ Manufacturers with regulatory approvals. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

Europe continued

MICROBUBBLE

Bracco Imaging SPA | Milano, Italy, www.braccoimaging.com

EXACT Therapeutics SA | Oslo, Norway, www.exact-tx.com

Thermosome GMBH | Planegg/Martinsried, Germany, www.thermosome.com

OEM

Fraunhofer-Institut für Biomedizinische Technik | Sulzbach, Germany, www.ibmt.fraunhofer.de Imasonic sa | Voray-sur-l'Ognon, France, www.imasonic.com imec | Leuven, Belgium, www.imec-int.com

Meggitt A/s | Kvistgård, Denmark, www.meggittferroperm.com

PI Ceramic GmbH | Lederhose, Germany, www.piceramic.com

Precision Acoustics LTD | Dorchester, England, United Kingdom, acoustics.co.uk

Asia

25

- CLINICAL DEVICE MANUFACTURERS
- + Alpinion Medical Systems CO LTD | Seoul, South Korea, www.alpinion.com
- + Changjiangyuan Technology Development co LTD | Beijing, China, www.cjykj.com
- + Chongqing Haifu Medical Technology co LTD | Chongqing, China, www.haifumedical.com
- **★** EpiSonica CORP | Hsinchu, Taiwan, www.episonica.com

 IMGT CO LTD | Seongnam, South Korea, www.nanoimgt.com
- ♣ Insightec LTD | Tirat Carmel, Israel, www.insightec.com
 - MBInsight Systems INC | Taiwan
 - Mianyang Sonic Electronic LTD | Mianyang City, China, www.ultrasound.cn
 - NaviFUS corp | New Taipei City, Taiwan, www.navi-fus.com
 - Neurosona co LTD | Seoul, South Korea, www.neurosona.com
 - NINA Medical LTD | Nazareth, Israel, ninamed.com
- 🛨 Shanghai A&S Science Technology Development со LTD | Shanghai, China, www.aishen.com.cn
- → Shende Medical Equipment Technology CO LTD | Shanghai, China, shendehc.com Shenzhen Huikang Medical Apparatus CO LTD | Shenzhen, China, www.eswl.cn
- Shenzhen PRO-HITU Medical Technology CO LTD | Shenzhen, China, pro-hifu.com SONIRE Therapeutics INC | Tokyo, Japan, www.sonire-therapeutics.com Suntec Industries CO LTD | Shanghai, China Vensica Therapeutics | Misgav, Israel, vensica.com
- ➡ Wuxi Haiying Electronic Medical Systems co LTD | Wuxi, China, www.haiyingmedical.com.cn

⁺ Manufacturers with regulatory approvals. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

Asia continued

OEM

EofE Ultrasonics co LTD | Seoul, South Korea, ultrasonics.co.kr
Humanscan co LTD | Ansan, South Korea, www.humanscan.co.kr
Nepa Gene co | Chiba, Japan, www.nepagene.jp
S-Sharp CORP | New Taipei City, Taiwan, www.s-sharp.com
Tamura CORP | Tokyo, Japan, www.tamuracorp.com
YoungTek Electronics | Hsinchu City, Taiwan, www.ytec.com.tw

FUS Devices with Treatment and Planning Guidance

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
North America				
Acoustic MedSystems	ACOUSTx TheraVision	Ultrasound, CT-fluoroscopy, MRI, and 3D targeting	_	
Acoustiic	AcuFUSS	MR guidance	MR guidance	
ArrayUS	Symphony	US & MR guidance	–	
Aucta Technologies	DECIMA	Unguided	_	
BrainSonix	BXPulsar 1001 LIFUP BXPulsar 1002 LIFUP	MR guidance MR guidance	MR guidance MR guidance	
Cerevast Medical	Aureva Pulse Reflow RVO	US guidance US guidance	-	
Exo Imaging	Performance Ultrasound Platform	_	_	
EyeSonix	TUG - Therapeutic Ultrasound for Glaucoma	Unguided	Visual guidance	
FUS Instruments	DS-50 LP-100 RK-100 RK-20 RK-300 RK-50	MR guidanceOther guidanceMR guidanceOther guidance	- - - -	
FUSMobile	Neurolyser	Other guidance	Not used	
HistoSonics	Edison	US guidance	US guidance	
International Cardio	HIFU Synthesizer	US guidance	US guidance	
MR Instruments	DuoFLEX ACCESS Coil MR-guided TRUST (Transcranial Ultrasound Stimulation)	MR guidance MR guidance	MR guidance MR guidance	
NeuroSonics Medical	NeuroSonics (prototype)	US guidance	MR guidance	
Profound Medical	Sonalleve TULSA-PRO	MR guidance MR guidance	MR guidance MR guidance	+
Sonablate Corp.	Sonablate Sonatherm	US guidance US guidance	MR/US fusion US quidance	+
Sonosa Medical	Sonosa Therapeutic	US guidance	Not used	

FUS Devices with Treatment and Planning Guidance continued

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
North America continued				
TheraWave	Ultranav (prototype)	Image fusion	Neuronavigation	
VeinSound, Inc.	VeinSound (prototype)	US guidance	US guidance	

Europe				
Cardiawave	Valvosoft	US guidance	US guidance	
CarThera	SonoCloud 1	Unguided	Not used	
	SonoCloud 9	Unguided	Not used	
	SonoProbe	MR guidance	MR guidance	
EDAP TMS	Ablatherm	Image fusion	US guidance	+
	EDAP (prototype)	US guidance	US guidance	
	Focal One	Image fusion	MR & US guidance, Biopsies	+
EyeTechCare	EyeOP1	Unguided	_	+
Image Guided Therapy	3Bop	Stereotactic frame	_	
	LabFUS	MR guidance	MR guidance	
	Rodent FUS System	MR guidance	MR guidance	
	TargetedFUS	MR guidance	MR guidance	
	UFOGUIDE	MR guidance	MR guidance	
Medsonic	Bone phantoms - Medsonic	MR guidance	_	
	MR-Compatible Transducers	MR guidance	_	
	Robotic Systems	MR guidance	_	
	Shinsei motor electronic system	MR guidance	_	
	Skull phantoms - Medsonic	MR guidance	_	
OxSonics	SonoTran System	US guidance	US guidance	
Theraclion	Echopulse	US guidance	US guidance	+
	SONOVEIN	US guidance	Not used	+
TOOsonix	System ONE-M	Image fusion	Visual guidance	+
	System ONE-R	Image fusion	Visual guidance	
TRANS-FUSIMO	TransFUSIMO Treatment System	MR guidance	MR guidance	

MANUFACTURERS

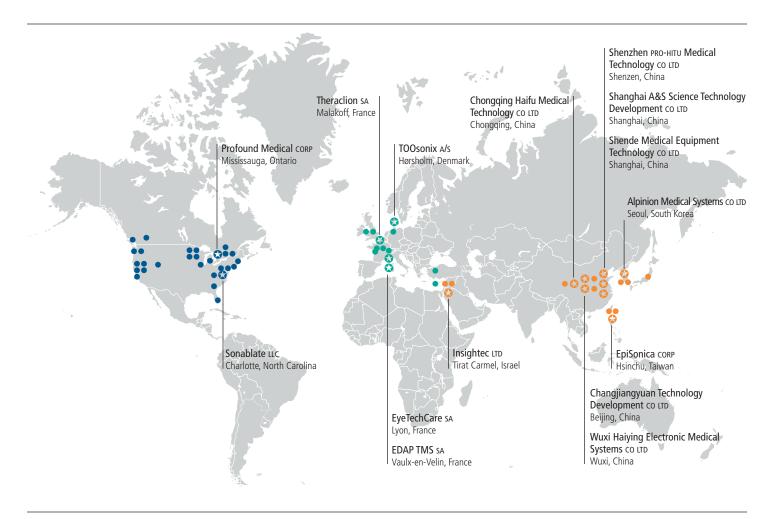
FUS Devices with Treatment and Planning Guidance continued

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
Asia				
Alpinion Medical Systems	Alpius 900	US guidance	_	+
	VIFU2000	US guidance	_	
Changjiangyuan Technology Development	NUTAS — Non-invasive Ultrasound Tumor			
	Ablation System	US guidance	US guidance	+
	SUPER Knife-Focused Beam Therapy System	MR & US guidance	_	+
Chongqing Haifu Medical Technology	CZB	US guidance	_	+
	CZF	US guidance	_	+
	CZG300	US guidance	_	
	JC	US guidance	_	+
	JC200	US guidance	_	+
	JC200D	US guidance	_	
	JC300	US guidance	_	
EpiSonica	ArcBLATE (ARC-100M)	MR guidance	MR guidance	+
IMGT	IMD10	US guidance	US guidance	
Insightec	Exablate MRgFUS	MR guidance	MR guidance	+
	Exablate Neuro	MR guidance	MR/CT fusion	+
	Exablate Prostate	MR guidance	MR guidance	+
Mianyang Sonic Electronic	CZ901	US guidance	_	
NaviFUS	NaviFUS System (Model 001)	Neuronavigation	MR/CT fusion	
	NaviFUS System (Model 101)	Other guidance	MR/CT fusion	
	NaviFUS System (Model 101-K)	Other guidance	MR/CT fusion	
Neurosona	Neurosona NS-US100	Other guidance	_	
NINA Medical	LOTUS-1	US guidance	US guidance	
Shanghai A&S	HIFUNIT9000	US guidance	MR guidance	+
Shende Medical Equipment Technology	Aceso	MR guidance	_	+
Shenzhen Huikang Medical Apparatus	HIFU 2001	US guidance	_	
Shenzhen PRO-HITU Medical	PRO2008	US guidance	US guidance	+
	PRO300	US guidance	US guidance	+
	PRO3008	US guidance	US guidance	
	PRO5G	Other guidance	Visual guidance	+
	UT1000	Unguided	Not used	

FUS Devices with Treatment and Planning Guidance continued

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
Asia				
Suntec Industries	Suntec System	US guidance	_	
Vensica Therapeutics	The Vibe	-	_	
	Vensica (prototype)	US guidance	_	
Wuxi Haiying Electronic Medical	HY2900	US guidance	_	+





- Clinical device manufacturers that have a device or devices with regulatory approvals by regional location.

 Company listings of devices, approved indications, and regulatory agencies granting approvals are found on the subsequent pages.
- Location of clinical device manufacturers without approved devices by region.

As the map of manufacturers on the previous page indicates, the field is large, but still quite young. Only a handful of companies have earned regulatory approvals and reached the stage of 'commercialization.'

New to the report this year is a more comprehensive overview of each of the focused ultrasound manufacturers who have regulatory approvals. We have formatted the data for each company in a way so readers can easily compare and understand the differences. Our goal is to continue to build out this section with a more comprehensive snapshot of each company in future years.

To do so will require working closely in conjunction with each of the manufacturers. Luckily, the Foundation is fortunate to have partners in the commercialization sector who are collaborative and understand that their participation with our efforts helps the field of focused ultrasound move forward more quickly and strategically.

Summary of Global Approvals



289
Approvals

worldwide

35
Regulatory agencies



Alpinion Medical Systems co LTD

Devices					
2 Total devices	Approved device				
Name	Status	Treatment guidance	Planning guidance		
Alpius 900	+	Ultrasound			
VIFU2000	_	Ultrasound	_		

Approvals					
2 Approved indications	2 Regions	2 Countries	Total approvals		
Indication	Region	Country	Agency and date		
Women's health					
Uterine adenomyosis	Asia	South Korea	MFDS, 2018		
Uterine fibroids	■ Europe ■ Asia	Europe South Korea	CE Marking, 2016 MFDs, 2014		

[♣] Devices with regulatory approvals.

Alpinion Medical Systems co LTD continued

Clinical research					
2 Indications	T Region	Country	2 Sites		
Indication	Region	Country	Site		
Gastrointestinal					
Pancreatic tumors, malignant	1	1	1		
Women's health					
Uterine fibroids	1	1	1		



Chongqing Haifu Medical Technology co LTD

Devices				
7 Total devices	4. Approved devices			
Name	Status	Treatment guidance	Planning guidance	
CZB	+	Ultrasound	_	
CZF	+	Ultrasound	_	
CZG300	_	Ultrasound	_	
JC	+	Ultrasound	_	
JC200	+	Ultrasound	_	
JC200D	_	Ultrasound	_	
JC300	_	Ultrasound	_	

Approvals					
12 Approved indications	2 Regions	4 Countries	33 Total approvals		
Indication Gastrointestinal	Region	Country	Agency and date		
Liver metastases	■ Europe	Europe	CE Marking, 2005		
Liver tumors	EuropeAsiaAsia	Europe Russia China South Korea	CE Marking, 2005 Roszdravnadzor, 2011 NMPA, 1999 MFDS, 2014		

[♣] Devices with regulatory approvals.

Chongqing Haifu Medical Technology co LTD continued

Approvals continued			
Indication	Region	Country	Agency and date
Gaatrointestinal continue	ed		
Pancreatic tumors	EuropeEuropeAsiaAsia	Europe Russia China South Korea	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999 MFDS, 2014
Musculoskeletal			
Osteoid osteoma	EuropeAsia	Europe Russia China	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999
Soft tissue cancer	■ Europe ■ Europe ■ Asia	Europe Russia China	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999
Soft tissue tumors, benign	EuropeAsia	Europe Russia China	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999
Pulmonary			
Rhinitis	EuropeAsia	Europe China	CE Marking, 2006 NMPA, 1999
Urological			
Kidney tumors	EuropeAsia	Europe Russia China	CE Marking, 2005 Roszdravnadzor, 2011 NMPA, 1999
Women's health			
Breast tumors, malignant	■ Europe ■ Europe ■ Asia	Europe Russia China	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999
Cervicitis	Asia	China	NMPA, 1999
Uterine adenomyosis	■ Europe ■ Europe	Europe Russia	CE Marking, 2006 Roszdravnadzor, 2011

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Chongqing Haifu Medical Technology co LTD continued

Approvals continued					
Indication	Region	Country	Agency and date		
Women's health continued					
Uterine fibroids	■ Europe	Europe	CE Marking, 2006		
	■ Europe	Russia	Roszdravnadzor, 2011		
	■ Asia	China	NMPA, 1999		
	■ Asia	South Korea	MFDS, 2014		

Clinical research			
15 Indications	2 Regions	4. Countries	12 Sites
Indication	Region	Country	Site
Gastrointestinal			
Liver tumors	1	3	3
Pancreatic tumors	1	1	1
Pancreatic tumors, malignant	1	3	4
Musculoskeletal			
Desmoid tumors	1	1	1
Osteoid osteoma	1	1	1
Sacral chordoma	1	1	1
Soft tissue cancer	1	1	2
Soft tissue tumors, benign	1	3	3
Pulmonary			
Rhinitis	1	1	1

Devices with regulatory approvals.

Chongqing Haifu Medical Technology co LTD continued

Clinical research continued			
Indication	Region	Country	Site
Urological			
Kidney tumors	1	2	2
Women's health			
Breast tumors, malignant	1	2	3
Cervical tumors	1	1	1
Retained placenta	1	1	1
Uterine adenomyosis	1	2	3
Uterine fibroids	2	4	6



EDAP TMS SA

Devices			
3 Total devices	2 Approved devices		
Name	Status	Treatment guidance	Planning guidance
Ablatherm	+	Image fusion	Ultrasound
EDAP (Prototype)	_	Ultrasound	Ultrasound
Focal One	+	Image fusion	MR, Ultrasound, Biopsies

Approvals			
2 Approved indications	4. Regions	6 Countries	14. Total approvals
Indication	Region	Country	Agency and date
Urological			
Benign prostatic hyperplasia	■ North America	United States	FDA, 2015
Prostate cancer	■ North America	Canada	Health Canada, 2003
	■ North America	United States	FDA, 2015
	■ Europe	Europe	CE Marking, 2005
	■ Europe	Russia	Roszdravnadzor, 2002
	Asia	South Korea	MFDS, 2002
	South America	Brazil	ANVISA, 2009

[♣] Devices with regulatory approvals.

EDAP TMS sa continued

Clinical research			
5 Indications	2 Regions	6 Countries	28 Sites
Indication	Region	Country	Site
Gastrointestinal			
Liver metastases	1	1	1
Urological			
Benign prostatic hyperplasia	1	1	1
Prostate cancer	2	6	25
Women's health			
Endometriosis	1	1	1
Endometriosis, colorectal	1	1	4

EDAP TMS designs, produces, and markets medical equipment dedicated to minimally invasive therapies based on robotic therapeutic ultrasound. Our lead product, Focal One®, combines the latest technologies in imaging and treatment modalities."

— EDAP TMS sa



EpiSonica corp

Devices			
Total device	Approved device		
Name	Status	Treatment guidance	Planning guidance
ArcBLATE (ARC-100M)	+	MR	MR

Approvals				
Region	1 Country	Total approvals		
Region	Country	Agency and date		
■ Acia	Tajwan	FDA, 2016		
	_	Region Country		

Devices with regulatory approvals.



EyeTechCare SA

Devices			
Total device	Approved device		
Name	Status	Treatment guidance	Planning guidance
EyeOP1	+	Unguided	_

Approvals				
1 Approved indication	2 Regions	2 Countries	Total approvals	
Indication	Region	Country	Agency and date	
Ophthalmological				
Glaucoma	■ Europe	Europe	CE Marking, 2011	
	■ Asia	China	NMPA, 2017	

Clinical research				
1 Indication	2 Regions	4. Countries	6 Sites	
Indication	Region	Country	Site	
Ophthalmological				
Glaucoma	2	4	6	

[♣] Devices with regulatory approvals.



Insightec INC

Devices			
3 Total devices	Approved devices		
Name	Status	Treatment guidance	Planning guidance
Exablate MRgFUS	+	MR	MR
Exablate Neuro	+	MR	MR/CT
Exablate Prostate	+	MR	MR

Approvals			
15 Approved indications	5 Regions	25 Countries	150 Total approvals
Indication	Region	Country	Agency and date
Musculoskeletal			
Arthritis, facetogenic	■ Europe	Europe	CE Marking, 2006
	■ Europe	Russia	Roszdravnadzor, 2017
	■ Europe	Turkey	TITUBB, 2017
	■ Asia	Hong Kong	MDD, 2020
	■ Asia	Kazakhstan	NCEM, 2019
	■ Asia	South Korea	MFDS, 2015
	■ Asia	Thailand	FDA, 2020
	■ South America	Chile	ANAMED, 2018
	■ Oceania	Australia	TGA, 2006

[♣] Devices with regulatory approvals.

Approvals continued			
Indication	Region	Country	Agency and date
Musculoskeletal continued			
Bone cancer	 Europe Europe Asia Asia Asia South America Oceania 	Europe Russia Turkey Hong Kong Israel Kazakhstan Thailand Chile Australia	CE Marking, 2006 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 AMAR, 2008 NCEM, 2019 FDA, 2020 ANAMED, 2018 TGA, 2006
Bone metastases	North America North America Europe Europe Europe Asia Asia Asia Asia Asia South America Oceania	Canada United States Belarus Europe Russia Turkey Hong Kong Kazakhstan Kuwait Saudi Arabia South Korea Thailand Chile Australia	Health Canada, 2013 FDA, 2012 MOH, 2021 CE Marking, 2006 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 NCEM, 2019 MOH FDCD, 2021 SFDA, 2021 MFDS, 2015 FDA, 2020 ANAMED, 2018 TGA, 2006
Bone tumors, benign	 Europe Europe Asia Asia Asia South America Oceania 	Europe Russia Turkey Hong Kong Kazakhstan Thailand Chile Australia	CE Marking, 2006 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 NCEM, 2019 FDA, 2020 ANAMED, 2018 TGA, 2006

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Approvals continued			
Indication	Region	Country	Agency and date
Musculoskeletal continued			
Multiple myeloma	EuropeEuropeAsiaAsiaAsiaSouth AmericaOceania	Europe Russia Turkey Hong Kong Kazakhstan Thailand Chile Australia	CE Marking, 2006 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 NCEM, 2019 FDA, 2020 ANAMED, 2018 TGA, 2006
Neurological			
Depression	■ Asia	South Korea	MFDS, 2015
Essential tremor	North America North America Europe Europe Asia Asia Asia Asia Asia Asia Asia Asia	Canada United States Europe Russia Turkey China Hong Kong India Israel Japan Kazakhstan Philippines Singapore South Korea Taiwan Thailand Argentina Brazil Chile Colombia Peru	Health Canada, 2016 FDA, 2016 CE Marking, 2012 Roszdravnadzor, 2017 TITUBB, 2017 NMPA, 2021 MDD, 2020 CDSCO, 2021 AMAR, 2015 MHLW, 2016 NCEM, 2020 FDA, 2018 HSA, 2021 MFDS, 2015 FDA, 2017 FDA, 2020 ANMAT, 2019 ANVISA, 2020 ANAMED, 2018 INVIMA, 2021 DIGEMED, 2021

Approvals continued			
Indication	Region	Country	Agency and date
Neurological continued			
Essential tremor	Oceania	Australia	TGA, 2015
Neuropathic pain	Europe Europe Leurope Asia Asia Asia Asia Asia Asia Asia South America South America South America South America South America South America Coceania	Europe Russia Turkey Hong Kong India Israel Kazakhstan Philippines South Korea Thailand Argentina Brazil Chile Colombia Peru Australia	CE Marking, 2012 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 CDSCO, 2021 AMAR, 2015 NCEM, 2020 FDA, 2018 MFDS, 2015 FDA, 202 ANMAT, 2019 ANVISA, 2020 ANAMED, 2018 INVIMA, 2021 DIGEMED, 2021 TGA, 2015
Obsessive-compulsive disorder	Asia	South Korea	MFDS, 2015
Parkinson's disease, dyskinesia	North AmericaEuropeAsiaAsia	United States Russia Japan South Korea	FDA, 2021 Roszdravnadzor, 2017 MHLW, 2020 MFDS, 2015
Parkinson's disease, tremor	 North America Europe Europe Asia Asia Asia Asia Asia Asia Asia Asia 	United States Europe Russia Turkey China Hong Kong India Israel Japan	FDA, 2018 CE Marking, 2012 Roszdravnadzor, 2017 TITUBB, 2017 NMPA, 2021 MDD, 2020 CDSCO, 2021 AMAR, 2015 MHLW, 2020

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Approvals continued			
Indication	Region	Country	Agency and date
Neurological continued			
Parkinson's disease, tremor	Asia Asia Asia Asia Asia South America South America South America South America South America South America Oceania	Kazakhstan Philippines Singapore South Korea Thailand Argentina Brazil Chile Colombia Peru Australia	NCEM, 2020 FDA, 2018 HSA, 2021 MFDS, 2015 FDA, 2020 ANMAT, 2019 ANVISA, 2020 ANAMED, 2018 INVIMA, 2021 DIGEMED, 2021 TGA, 2015
Urological			
Benign prostatic hyperplasia	■ North America	United States	FDA, 2021
Prostate cancer	 North America Europe Europe Europe Asia Asia Asia South America Oceania 	United States Belarus Europe Russia Turkey Hong Kong Kazakhstan Thailand Chile Australia	FDA, 2021 MOH, 2021 CE Marking, 2016 Roszdravnadzor, 2017 TITUBB, 2017 MDD, 2020 NCEM, 2019 FDA, 2020 ANAMED, 2018 TGA, 2016
Women's health			
Uterine adenomyosis	EuropeEuropeAsiaAsiaAsiaAsiaAsia	Europe Turkey Hong Kong Israel Kazakhstan Thailand	CE Marking, 2006 TITUBB, 2017 MDD, 2020 AMAR, 2008 NCEM, 2019 FDA, 2020

Insightec INC continued

Approvals continued			
Indication	Region	Country	Agency and date
Women's health continued			
Uterine adenomyosis	South America Oceania	Chile Australia	ANAMED, 2018 TGA, 2006
Uterine fibroids	North America North America Europe Europe Europe Asia Asia Asia Asia Asia Asia Asia Asia	Canada United States Belarus Europe Russia Turkey China Hong Kong Israel Japan Kazakhstan Kuwait Saudi Arabia Singapore South Korea Taiwan Thailand Chile	Health Canada, 2013 FDA, 2004 MOH, 2021 CE Marking, 2006 Roszdravnadzor, 2006 TITUBB, 2017 NMPA, 2013 MDD, 2020 AMAR, 2003 MHLW, 2006 NCEM, 2019 MOH FDCD, 2021 SFDA, 2021 HSA, 2012 MFDS, 2011 FDA, 2006 FDA, 2020 ANAMED, 2018
	Asia Asia Asia Asia Asia Asia Asia Asia	Kazakhstan Kuwait Saudi Arabia Singapore South Korea Taiwan Thailand	NCEM, 2019 MOH FDCD, 2021 SFDA, 2021 HSA, 2012 MFDS, 2011 FDA, 2006 FDA, 2020

Insightec is a global healthcare company creating the next generation of patient care by realizing the therapeutic power of acoustic energy. Insightec is dedicated to the research and commercial application of focused ultrasound in multiple indications."

— Insightec іNС

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Clinical research			
40 Indications	5 Regions	16 Countries	67 Sites
Indication	Region	Country	Site
Gastrointestinal			
Liver tumors	1	1	2
Pancreatic tumors, malignant	2	2	2
Miscellaneous			
Head & neck tumors	1	2	2
Musculoskeletal			
Arthritis, facetogenic	2	5	6
Arthritis, knee	1	1	1
Bone cancer	1	1	2
Bone metastases	3	7	8
Bone tumors, benign	1	1	1
Desmoid tumors	1	1	1
Osteoid osteoma	2	3	5
Soft tissue cancer	2	2	2
Soft tissue tumors, benign	2	2	2
Neurological			
Alzheimer's disease	2	3	5
Amyotrophic lateral sclerosis	1	1	1
Astrocytoma	1	1	2
Brain metastases, breast cancer	1	1	1
Brain metastases, melanoma	1	1	1
Brain tumors, general	1	1	1

Insightec INC continued

Clinical research continued

Indication	Region	Country	Site
Neurological continued			
Cancer pain	1	1	1
Dementia	1	1	1
Depression	2	2	2
Dystonia	1	2	2
Dystonia, hand	1	1	1
Epilepsy	2	2	8
Essential tremor	3	10	17
Glioblastoma	3	7	14
Multiple sclerosis	1	1	1
Neurofibromatosis	1	1	1
Neuropathic pain	2	2	2
Obsessive-compulsive disorder	1	1	2
Painful amputation neuromas	1	1	1
Parkinson's disease, dyskinesia	3	4	11
Parkinson's disease, tremor	3	7	11
Parkinson's disease, underlying cause	1	1	1
Tremor, orthostatic	1	1	1
Trigeminal neuralgia	1	1	1
Urological			
Prostate cancer	2	2	7
Women's health			
Endometriosis	1	1	1
Uterine adenomyosis	3	4	5
Uterine fibroids	3	8	11



Profound Medical CORP

Devices				
2 Total devices	2 Approved devices			
Name	Status	Treatment guidance	Planning guidance	
Sonalleve	+	MR	MR	
TULSA-PRO	+	MR	MR	

Approvals			
7 Approved indications	3 Regions	9 Countries	24 Total approvals
Indication	Region	Country	Agency and date
Musculoskeletal			
Bone metastases	EuropeAsiaAsiaAsia	Europe Malaysia Singapore Vietnam	CE Marking, 2011 MDA, 2015 HSA, 2021 DMEW, 2010
Desmoid tumors	■ Europe	Europe	CE Marking, 2021
Osteoid osteoma	North AmericaEuropeAsia	United States Europe Singapore	FDA, 2020 CE Marking, 2020 HSA, 2021

Devices with regulatory approvals.

Profound Medical corp continued

Approvals continued			
Indication	Region	Country	Agency and date
Urological			
Benign prostatic hyperplasia	■ North America	United States	FDA, 2019
Prostate cancer	North AmericaNorth AmericaEuropeAsia	Canada United States Europe Singapore	Health Canada, 2019 FDA, 2019 CE Marking, 2016 HSA, 2019
Women's health			
Uterine adenomyosis	EuropeAsiaAsia	Europe Malaysia Vietnam	CE Marking, 2010 MDA, 2015 DMEW, 2010
Uterine fibroids	North America Europe	Canada Europe	Health Canada, 2013 CE Marking, 2009
	Asia	China	NMPA, 2018
	Asia	Malaysia	MDA, 2015
	■ Asia	Saudi Arabia	SFDA, 2015
	Asia	Singapore	HSA, 2021
	Asia Asia	South Korea Vietnam	MFDS, 2012 DMEW, 2010

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Profound Medical corp continued

Clinical research			
22 Indications	3 Regions	10 Countries	22 Sites
Indication	Region	Country	Site
Gastrointestinal			
Liver tumors	1	1	1
Pancreatic tumors, malignant	1	1	2
Miscellaneous			
Head & neck tumors	1	1	1
Multiple tumors ¹	1	1	1
Musculoskeletal			
Arthritis, facetogenic	1	1	1
Arthritis, sacroiliac	1	1	1
Bone cancer	1	2	3
Bone metastases	2	4	6
Bone tumors, benign	1	2	2
Desmoid tumors	2	2	3
Osteoid osteoma	1	1	1
Plantar fasciitis	1	1	1
Soft tissue cancer	1	2	3
Soft tissue tumors, benign	2	2	2
Neurological			
Neuroblastoma	1	1	1
Urological			
Benign prostatic hyperplasia	1	3	3
Prostate cancer	2	5	8

¹ Protocols inclusive of more than one indication

Profound Medical corp continued

2

1

Uterine fibroids

Vaginal tumors

Clinical research continued Indication Region Country Site Women's health Breast tumors, malignant 2 2 2 1 Cervical tumors Uterine adenomyosis 2 2 2

6

1

Profound is commercializing TULSA-PRO®, for customizable and predictable ablation of prostate volume, and Sonalleve®, an innovative therapeutic platform to treat uterine fibroids, desmoid tumors, osteoid osteoma, and pain from bone metastases."

1

— Profound Medical CORP



Shanghai A&S Science Technology Development co, LTD

Devices			
Total device	Approved devices		
Name	Status	Treatment guidance	Planning guidance
HIFUNIT9000	+	Ultrasound	MR
Approvals			
5	2	4	8
Approved indications	Regions	Countries	Total approvals
Indication	Region	Country	Agency and date
Gastrointestinal			
Liver tumors	■ Asia	China	NMPA, 2002
Musculoskeletal			
Bone metastases	■ Asia	China	NMPA, 2002
Soft tissue cancer	Asia	China	NMPA, 2002
Women's health			
Breast tumors, malignant	■ Asia	China	NMPA, 2002
Uterine fibroids	EuropeAsiaAsiaAsia	Europe China South Korea Thailand	CE Marking, 2008 NMPA, 2002 MFDS, 2007 FDA, 2013

⁺ Devices with regulatory approvals.

Shanghai A&S Science Technology Development co, LTD continued

Clinical research				
1 Indication	T Region	Country	1 Site	
Indication	Region	Country	Site	
Gastrointestinal				
Liver tumors	1	1	1	

L Shanghai A&S Science Technology

Development is a leading company focused on high intensity focused ultrasound for tumor ablation with ultrasound guidance. Based in Shanghai, A&S has expanded business in Asia with over 200 installations."

— Shanghai A&S Science Technology Development со LTD



Shenzhen PRO-HITU Medical Technology co, LTD

Devices				
5	3			
Total devices	Approved devices			
Name	Status	Treatment guidance	Planning guidance	
PRO2008	+	Ultrasound	Ultrasound	
PRO300	+	Ultrasound	Ultrasound	
PRO3008	_	Ultrasound	Ultrasound	
PRO5G	+	Other guidance	Visual guidance	
UT1000	_	Unguided	Not used	

Approvals			
4. Approved indications	2 Regions	4 Countries	7 Total approvals
Indication	Region	Country	Agency and date
Women's health			
Hyperplasia of the vulva	Asia	China	NMPA, 2019
Lichen sclerosis	■ Asia	China	NMPA, 2019
Uterine adenomyosis	Asia Asia	China South Korea	NMPA, 2012 MFDS, 2016
Uterine fibroids	EuropeAsiaAsia	Europe China Taiwan	CE Marking, 2012 MDA, 2012 FDA, 2018

Devices with regulatory approvals.

Shenzhen PRO-HITU Medical Technology co, LTD continued

Clinical research				
2 Indications	1 Region	1 Country	4. Sites	
Indication	Region	Country	Site	
Women's health				
Uterine adenomyosis	1	1	3	
Uterine fibroids	1	1	3	

Shenzen PRO-HITU Medical Technology

was established in 2003, focusing on R&D of large ultrasonic treatment equipment. Vision: The pioneering of Non-Invasive Therapy. Mission: Respect Life in Therapy."

— Shenzen PRO-HITU Medical со, LTD



Sonablate corp

Devices				
2 Total devices	2 Approved devices			
Name	Status	Treatment guidance	Planning guidance	
Sonablate	+	Ultrasound	MR/US fusion	
Sonatherm	+	Ultrasound	Ultrasound	

Approvals			
2 Approved indications	6 Regions	23 Countries	39 Total approvals
Indication	Region	Country	Agency and date
Urological			
Benign prostatic hyperplasia	North America North America North America North America Europe Asia Asia Asia Asia Asia Asia Asia Asia	Canada Costa Rica Dominican Republic United States Russia China Hong Kong India Israel Japan South Korea	Health Canada, 2005 Ministerio de Salud, 2005 MISPAS, 2005 FDA, 2006 Roszdravnadzor, 2005 NMPA, 2020" MDD, 2018 CDSCO, 2011 AMAR, 2018 MHLW, 2001 MFDS, 2016 DMEW, 2009

Devices with regulatory approvals.

Sonablate corp continued

Approvals continued			
Indication	Region	Country	Agency and date
Urological continued			
Benign prostatic hyperplasia	South AmericaSouth AmericaSouth AmericaSouth AmericaOceania	Argentina Colombia Ecuador Trinidad and Tobago Australia	ANMAT, 2006 INVIMA, 2015 ANRCVS, 2011 Ministry of Health, 2012 TGA, 2005
Prostate cancer	North America Europe Europe Asia Asia Asia Asia Asia South America South America South America South America	Bahamas Barbados Canada Costa Rica Dominican Republic United States Europe Russia China Hong Kong India Israel South Korea Pakistan Taiwan Vietnam Argentina Colombia Ecuador Trinidad and Tobago Australia	Ministry of Health, 2007 Ministry of Health and Wellness, 2010 Health Canada, 2005 Ministerio de Salud, 2005 MISPAS, 2005 FDA, 2006 CE Marking, 2006 Roszdravnadzor, 2005 NMPA, 2020 MDD, 2018 CDSCO, 2011 AMAR, 2018 MFDS, 2016 DRAP, 2015 FDA, 2020 DMEW, 2009 ANMAT, 2006 INVIMA, 2015 ANRCVS, 2011 Ministry of Health, 2012 TGA, 2005
	AsiaSouth AmericaSouth AmericaSouth AmericaSouth America	Vietnam Argentina Colombia Ecuador Trinidad and Tobago	DMEW, 2009 ANMAT, 2006 INVIMA, 2015 ANRCVS, 2011 Ministry of Health, 2012

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Sonablate corp continued

Clinical research			
6 Indications	3 Regions	5 Countries	15 Sites
Indication	Region	Country	Site
Gastrointestinal			
Colorectal tumors	1	1	2
Urological			
Prostate cancer	3	5	15
Women's health			
Cervical tumors	1	1	2
Endometrial tumors	1	1	1
Ovarian tumors	1	1	1
Vaginal tumors	1	1	1

Sonablate is the leading innovator in minimally invasive ablation technology using high intensity focused ultrasound (HIFU). The Sonablate® prostate ablation system incorporates MRI/US image fusion for whole-gland, hemi, or focal procedures."

— Sonablate CORP



Theraclion SA

Devices				
2 Total devices	Approved devices			
Name	Status	Treatment guidance	Planning guidance	
Echopulse	+	Ultrasound	Ultrasound	
SONOVEIN	+	Ultrasound	Not used	

Approvals			
3 Approved indications	2 Regions	6 Countries	14 Total approvals
Indication	Region	Country	Agency and date
Cardiovascular			
Varicose veins	■ Europe ■ Asia	Europe Singapore	CE Marking, 2019 HSA, 2019
Endocrine disorders			
Thyroid nodules	EuropeAsiaAsiaAsiaAsiaAsiaAsia	Europe Russia Hong Kong South Korea Singapore Taiwan	CE Marking, 2007 Roszdravnadzor, 2017 MDD, 2007 MFDS, 2017 HSA, 2016 FDA, 2019

Devices with regulatory approvals.

MANUFACTURERS

Clinical Device Manufacturers with Regulatory Approvals continued

Theraclion sa continued

Approvals continued			
Indication Women's health	Region	Country	Agency and date
Breast tumors, benign	EuropeEuropeAsiaAsiaAsiaAsiaAsia	Europe Russia Hong Kong South Korea Singapore Taiwan	CE Marking, 2012 Roszdravnadzor, 2017 MDD, 2012 MFDS, 2017 HSA, 2016 FDA, 2018

Clinical research			
13 Indications	3 Regions	6 Countries	10 Sites
Indication	Region	Country	Site
Cardiovascular			
Varicose veins	2	3	3
Endocrine disorders			
Graves' disease	1	1	1
Thyroid nodules	1	1	1
Gastrointestinal			
Esophageal tumors	1	1	1
Gastric tumors	1	1	1
Pancreatic tumors, malignant	1	1	1
Miscellaneous			
Melanoma	1	1	1
Multiple tumors ¹	1	1	1

¹ Protocols inclusive of more than one indication

Theraclion sa continued

Clinical research continued			
Indication	Region	Country	Site
Pulmonary			
Lung cancer	1	1	1
Women's health			
Breast tumors, benign	3	3	6
Breast tumors, malignant	2	2	2
Cervical tumors	1	1	1
Ovarian tumors	1	1	1

Theraclion believes that surgery, as we know it, is outdated. We replace it with a robotic treatment from outside the body using HIFU. Our leading-edge platforms are CE marked for varicose veins, breast fibroadenomas and thyroid nodules."

— Theraclion sa



TOOsonix A/s

Devices			
2 Total devices	Approved device		
Name	Status	Treatment guidance	Planning guidance
System ONE-M	+	Image fusion	Visual guidance
System ONE-R	_	Image fusion	Visual guidance

Approvals				
O Approved indications ¹	Region	Country	Total approvals ¹	
Indication	Region	Country	Agency and date	
_	■ Europe	Europe	CE Marking, 2020	

Devices with regulatory approvals.

¹ This device is currently approved for aesthetic indications, which are not tracked by the Foundation.

TOOsonix s/A continued

Clinical research			
3 Indications	T Region	1 Country	2 Sites
Indication	Region	Country	Site
Miscellaneous			
Actinic keratosis	1	1	1
Basal cell carcinoma	1	1	2
Kaposi's sarcoma	1	1	1

TOOsonix is a Danish medical device company committed to the field of dermatology. Our CE marked 20 MHz HIFU systems deliver noninvasive ultrasound to target areas in the human skin, destroying target tissue, while surrounding tissue remains unharmed."

— TOOsonix A/s



Wuxi Haiying Electronic Medical Systems со, цтр

1	1		
Total device	Approved device		
Name	Status	Treatment guidance	Planning guidance
HY2900	+	Ultrasound	

Approvals			
Approved indication	Region	Country	Total approval
Indication	Region	Country	Agency and date
Women's health Uterine fibroids	■ Asia	China	NMPA, 2016

Devices with regulatory approvals.

MANUFACTURERS

Focused Ultrasound Foundation Overview

The Foundation is a unique medical research, education, and advocacy organization created as the catalyst to accelerate the development and adoption of focused ultrasound and thereby reduce death, disability, and suffering for countless patients. To achieve its goals, the Foundation utilizes an approach that is entrepreneurial, high impact, high performance, market driven, and results oriented.

By identifying opportunities and overcoming barriers, the Foundation is shortening the time from laboratory research to widespread treatment.

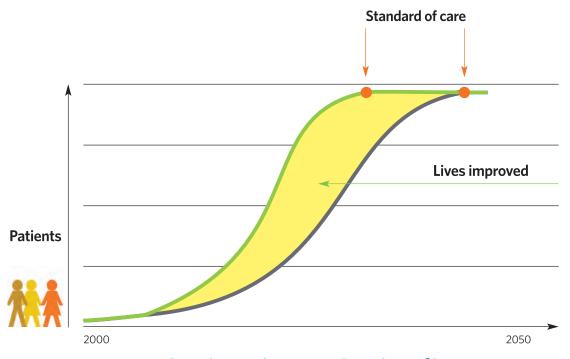
Major initiatives include

- Influencing the direction of the field, setting research priorities, and creating an urgent, patient-centric culture
- Providing resources, both human and financial capital
- Fostering collaboration and stimulating innovation
- Creating, aggregating, and sharing knowledge
- Cultivating the next generation of clinicians and scholars
- Increasing awareness

The Foundation has a robust research program and organizes, conducts, and supports clinical trials and preclinical laboratory studies with an emphasis on brain disorders, oncology, and immunotherapy. It is the largest nongovernmental source of focused ultrasound research funding in the world.

Our mission is to accelerate the development and adoption of focused ultrasound as a mainstream standard of care. Through hard work, calculated risk-taking, and innovation, we are committed to ensuring that focused ultrasound is widely available in the shortest time possible.

fusfoundation.org



Saving time = Saving lives

The Focused Ultrasound Foundation wishes to thank its exceptional Board of Directors and Council for their steadfast dedication to helping make focused ultrasound a clinical reality and improving the lives of millions of patients.

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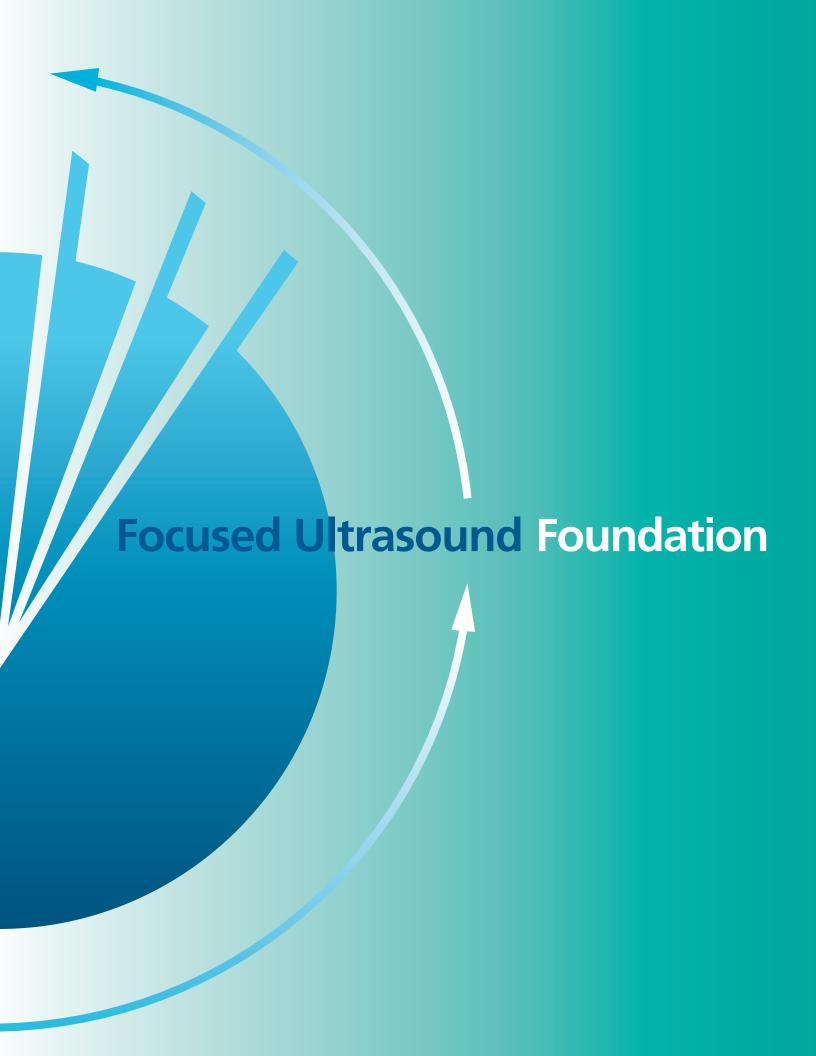
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Date 7.29.2022

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The Focused Ultrasound Foundation strives to provide the most accurate information possible and therefore works proactively with the manufacturers and research sites to collect the most current data available in advance of the release of this publication. This report is based on data through December 31, 2021. The Focused Ultrasound Foundation assumes no responsibility for any errors or omissions as every precaution has been taken to verify the accuracy of the information contained herein. No liability is assumed for damages that may result from the use of information contained within. If you note something out of date or inaccurate, please submit the new information/updates to: info@fusfoundation.org.







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