2022

State of the Field

Focused Ultrasound Foundation

State of the Field Team

Emily White, MD, *Editor in Chief*
Michael Broad, PhD, MBA, *Data Acquisition & Validation*
Sara Myhre, *Co-Project Manager*
Mary Rose Serafini, *Co-Project Manager*
Anne Chesnut, *Graphic Design Consultant*
Margo Browning, *Editorial Consultant*
Deborah Heishman, *Salesforce Platforms Director*
Jordan Knupp, *Survey Web Developer*
Thomas Andreae, PhD, *Europe Outreach*
Jessica Che-yi Chao, *Asia Outreach*

Focused Ultrasound Foundation

The Focused Ultrasound Foundation encourages widespread distribution of the *2022 State of the Field Report* in part or its entirety. Inquiries for reproduction can be directed to Emily White at ewhite@fusfoundation.org.

Date 7.29.2022

CONTENTS

FOCUSED ULTRASOUND FOUNDATION

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.

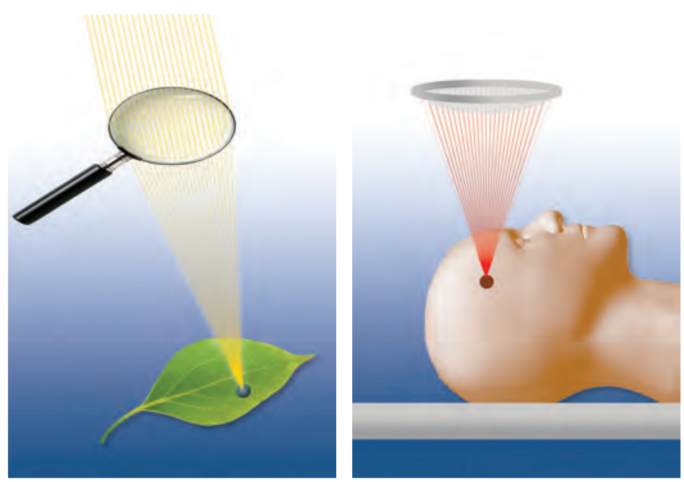
This revolutionary technology has the potential to increase the quality and longevity of life and decrease the cost of care by transforming the treatment of a range of indications.

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.

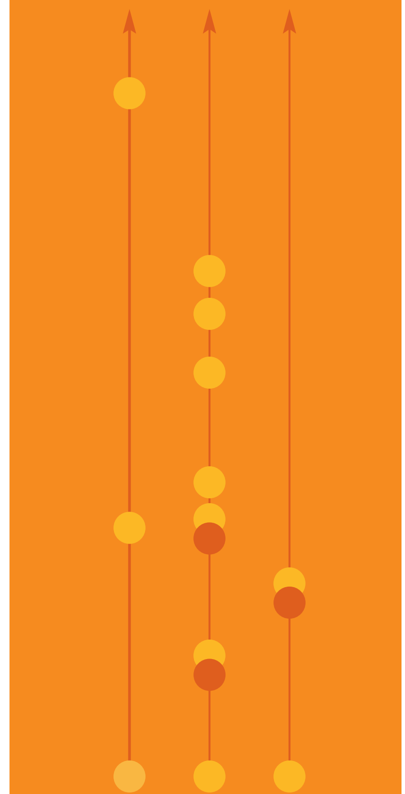
There are currently 159 clinical indications or disorders in various stages of development, and the number is increasing rapidly. Most are early stage. Worldwide, 32 indications have regulatory approval; in the US, 8 have been approved by the FDA. Focused ultrasound is not for every patient or every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



2022 Field Overview

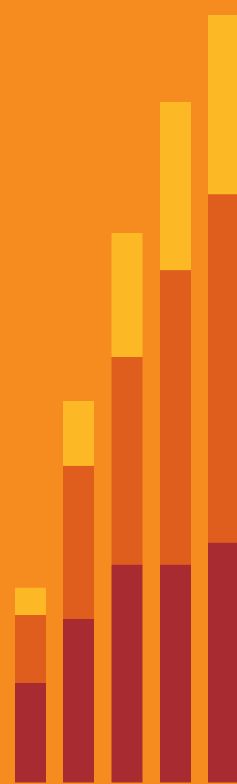
Focused Ultrasound Foundation

92,365
patient treatments
in 2021



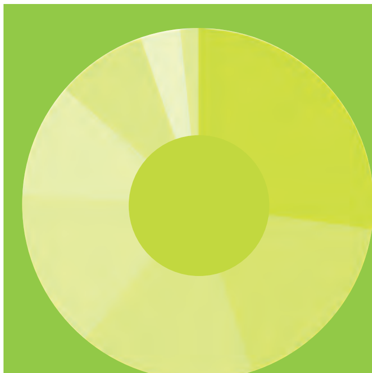
159
distinct indications
in 2021

21
new
regulatory approvals



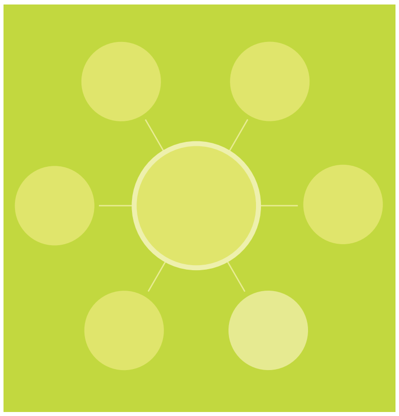
$393M
invested in
FUS companies
in 2021

11
new
FUS industry companies



52,034
oncology treatments
in 2021

Field Overview



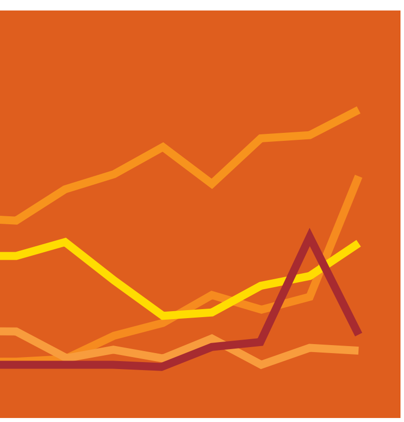
The Field Overview is designed to give the "big picture" of the state of the field for focused ultrasound. It highlights the cumulative growth of focused ultrasound as well as the annual growth in 2021. Eleven new indications were identified in 2021, five of which were identified as beginning clinical trials. Additionally, two indications transitioned from bench research to first-in-human clinical trials. All of this further confirms the continuing growth, progression, and expansion of the focused ultrasound field.

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.

11
new indications
identified



96
new
FUS treatment sites

Contents

I. Field Overview

Development Stage Advancements and New Indications

2021

11

New indications

Gastrointestinal	Clinical trials	Nonalcoholic steatohepatitis (NASH)
Miscellaneous	Preclinical	Niemann-Pick disease
	Preclinical	Sinonasal disease
Musculoskeletal	Preclinical	Osteopenia
Neurological	Clinical trials	ADHD
	Clinical trials	Anxiety
	Clinical trials	Schizophrenia
	Preclinical	Brain metastases, melanoma
	Preclinical	Neurofibromatosis
Ophthalmological	Preclinical	Dry eye disease
Women's health	Clinical trials	Urinary incontinence, stress

Development stage

Preclinical Clinical trials

2021

8

Indications advanced to first-in-human clinical trials

Gastrointestinal	Nonalcoholic steatohepatitis (NASH)†
Neurological	ADHD†
	Anxiety†
	Neurofibromatosis†
	Schizophrenia†
	Stroke, intracerebral hemorrhage
	Stroke, thromboembolic
Women's health	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

Belarus | MOH
- Bone metastases
- Prostate tumors
- Uterine fibroids

Europe | CE MARKING
- Desmoid tumors

Saudi Arabia | SFDA
- Bone metastases

China | NMPA
- Essential tremor
- Parkinson's disease, tremor

India | CDSCO
- Essential tremor
- Neuropathic pain
- Parkinson's disease, tremor

Singapore | HSA
- Essential tremor
- Parkinson's disease, tremor

Colombia | INVIMA
- Essential tremor
- Neuropathic pain
- Parkinson's disease, tremor

Kuwait | MOH FDCD
- Bone metastases
- Uterine fibroids

United States | FDA
- Parkinson's disease, dyskinesia

Peru | DIGEMED
- Essential tremor
- Neuropathic pain
- Parkinson's disease, tremor

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

7 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.

NEW

Industry Highlights continued

2021

96

New focused ultrasound commercial treatment sites worldwide

An increase over 2020 of

12%

Bringing the total number of focused ultrasound commercial treatment sites to

895

North America	Europe	Asia	South America	Oceania	Africa
192	289	394	9	4	7

State of Research and Regulatory Approvals by Body System

Development stage: Conceptual → Preclinical → Pilot trials → Pivotal trials → Outside US approvals → FDA approvals → US reimbursement

Cardiovascular

Cardiac	
Atrial fibrillation	Pilot trials
Heart valve calcifications	Pilot trials
Cardiac hypertrophy	Preclinical
Cardiac pacing	Preclinical
Coarctation of the aorta	Preclinical
Congestive heart failure	Preclinical
Fetal heart anomalies	Preclinical
Hypoplastic left heart syndrome	Preclinical
Mitral regurgitation	Preclinical
Septal perforation	Preclinical
Ventricular tachycardia	Preclinical
Peripheral	
Varicose veins	Outside US approvals
Peripheral artery disease	Pilot trials
Twin-twin transfusion syndrome	Pilot trials
Arteriovenous malformations	Preclinical
Atherosclerosis	Preclinical
Deep vein thrombosis	Preclinical
Hematoma	Preclinical
Hemophilia	Preclinical

Endocrine disorders

Thyroid nodules	Outside US approvals
Graves' disease	Pilot trials
Hyperparathyroidism	Pilot trials
Thyroid cancer	Pilot trials
Diabetes	Preclinical

Gastrointestinal

Liver metastases	Outside US approvals
Liver tumors	Outside US approvals
Pancreatic tumors, malignant	Outside US approvals
Biliary tract cancer	Pilot trials
Colorectal tumors	Pilot trials
Esophageal tumors	Pilot trials
Gastric tumors	Pilot trials
Malignant obstructive jaundice	Pilot trials
Nonalcoholic steatohepatitis (NASH)†	Pilot trials
Pancreatic tumors, benign	Pilot trials
Root canal endodontia	Pilot trials
Inflammatory bowel disease	Preclinical
Irritable bowel syndrome	Preclinical
Liver fibrosis	Preclinical

There are 159 distinct indications for 2021.

† New in 2021

State of Research and Regulatory Approvals by Body System continued

Development stage: Conceptual → Preclinical → Pilot trials → Pivotal trials → Outside US approvals → FDA approvals → US reimbursement

Miscellaneous

Actinic keratosis	Pilot trials
Basal cell carcinoma	Pilot trials
Dercum's disease	Pilot trials
Head & neck tumors	Pilot trials
Hypersplenism	Pilot trials
Kaposi's sarcoma	Pilot trials
Lipoma	Pilot trials
Melanoma	Pilot trials
Multiple tumors[1]	Pilot trials
Obesity	Pilot trials
Heterotopic ossification	Preclinical
Infection	Preclinical
Niemann-Pick disease†	Preclinical
Sinonasal disease†	Preclinical
Wound healing	Preclinical

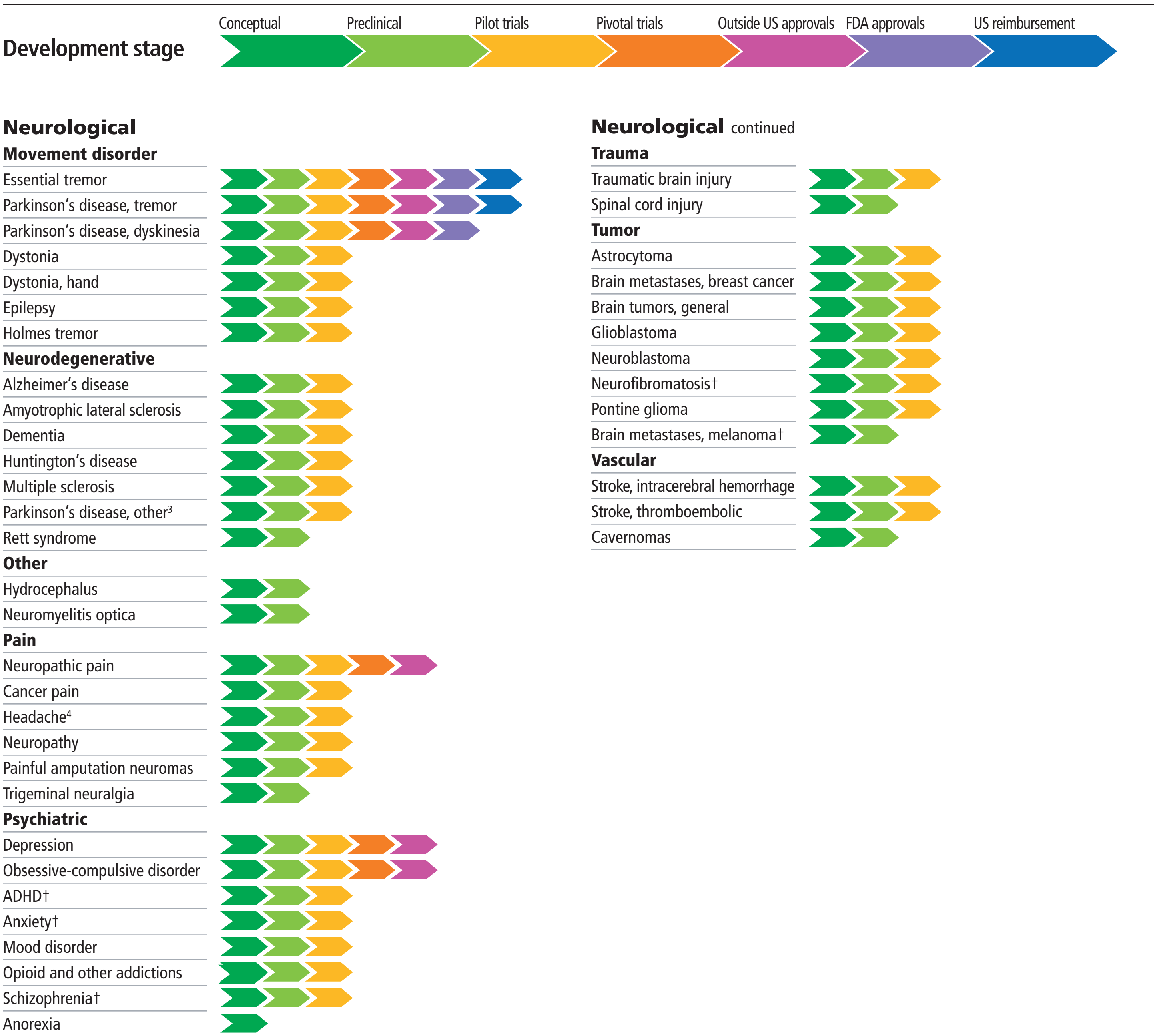
Musculoskeletal

Bone metastases	US reimbursement
Osteoid osteoma	FDA approvals
Arthritis, facetogenic	Outside US approvals
Bone cancer	Outside US approvals
Bone tumors, benign	Outside US approvals
Desmoid tumors	Outside US approvals
Multiple myeloma[2]	Outside US approvals
Soft tissue cancer	Outside US approvals
Soft tissue tumors, benign	Outside US approvals
Arthritis	Pilot trials
Arthritis, ankle	Pilot trials
Arthritis, hand	Pilot trials
Arthritis, hip	Pilot trials
Arthritis, knee	Pilot trials
Arthritis, sacroiliac	Pilot trials
Disc degeneration	Pilot trials
Plantar fasciitis	Pilot trials
Sacral chordoma	Pilot trials
Muscle atrophy	Preclinical
Osteomyelitis	Preclinical
Osteopenia	Preclinical
Rotator cuff injury	Preclinical
Tendon contracture	Preclinical

There are 159 distinct indications for 2021.

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

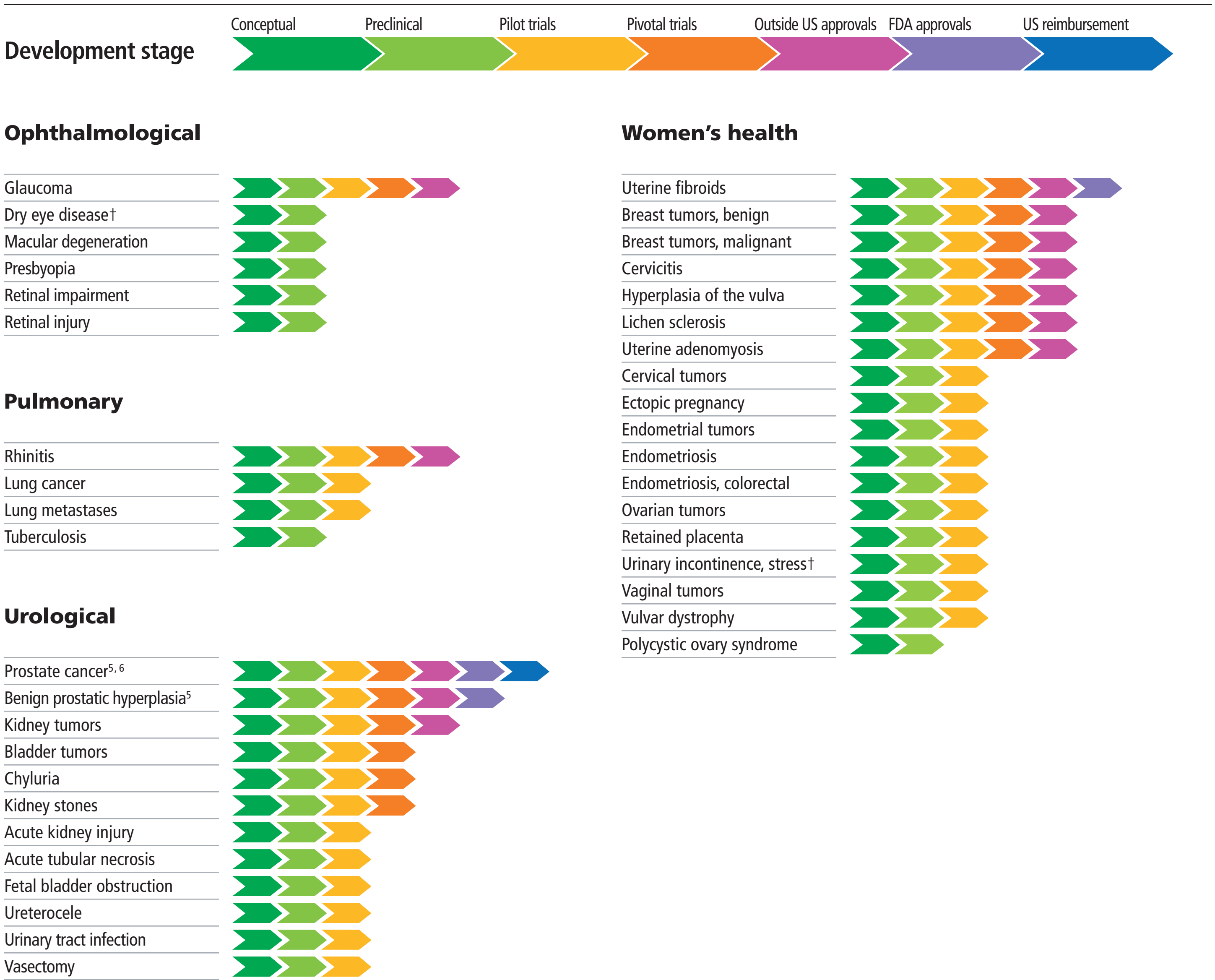
State of Research and Regulatory Approvals by Body System continued



There are 159 distinct indications for 2021.

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



There are 159 distinct indications for 2021.

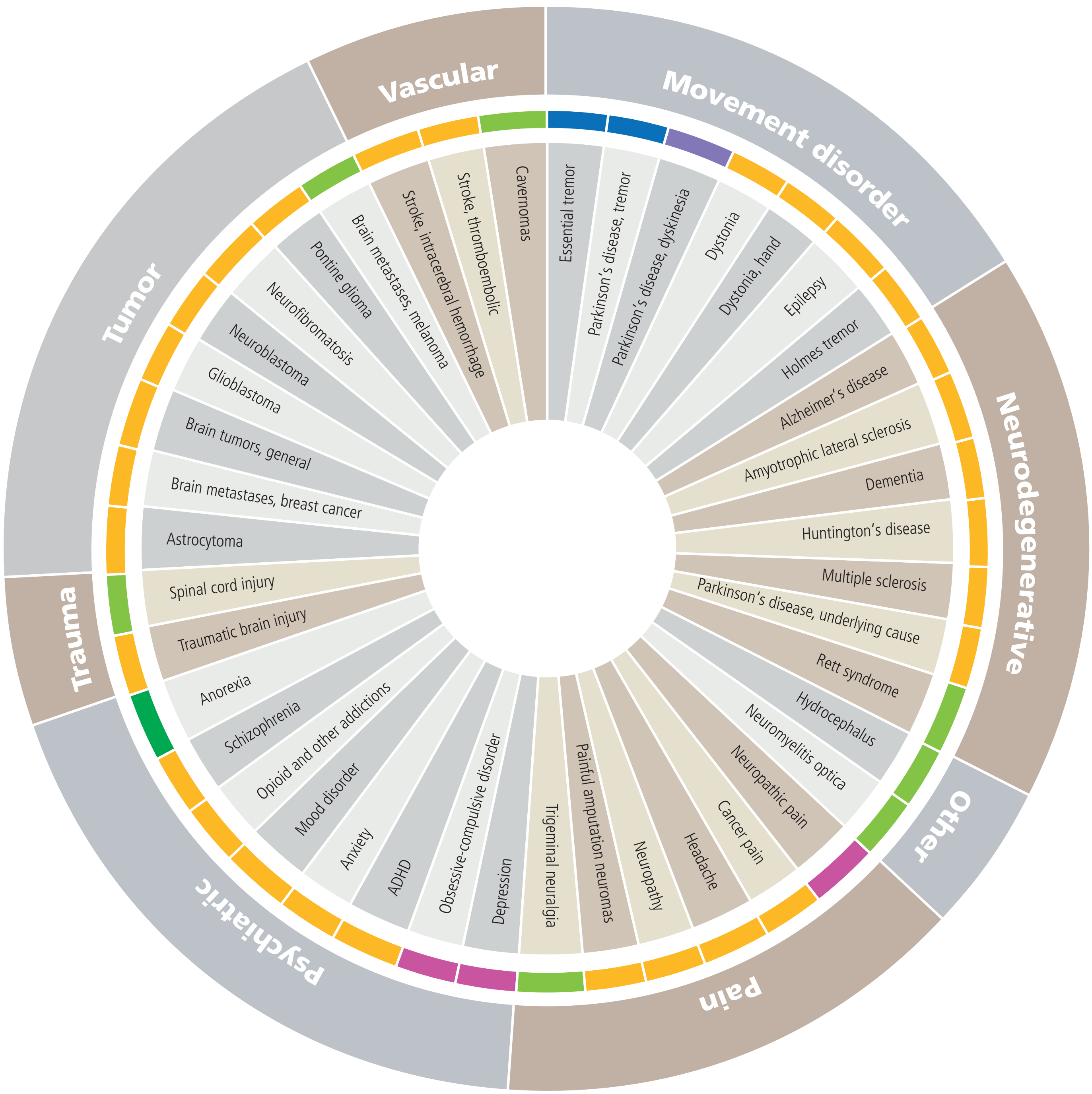
5 FDA approval is for prostate tissue ablation.
6 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
† New in 2021

NEW

43 Neurological Indications

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

Development stage: Conceptual · Preclinical · Clinical trials · Pilot trials · Outside US approvals · FDA approvals · US reimbursement



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

FIELD OVERVIEW

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 article[1] 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-in-human 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-guided 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

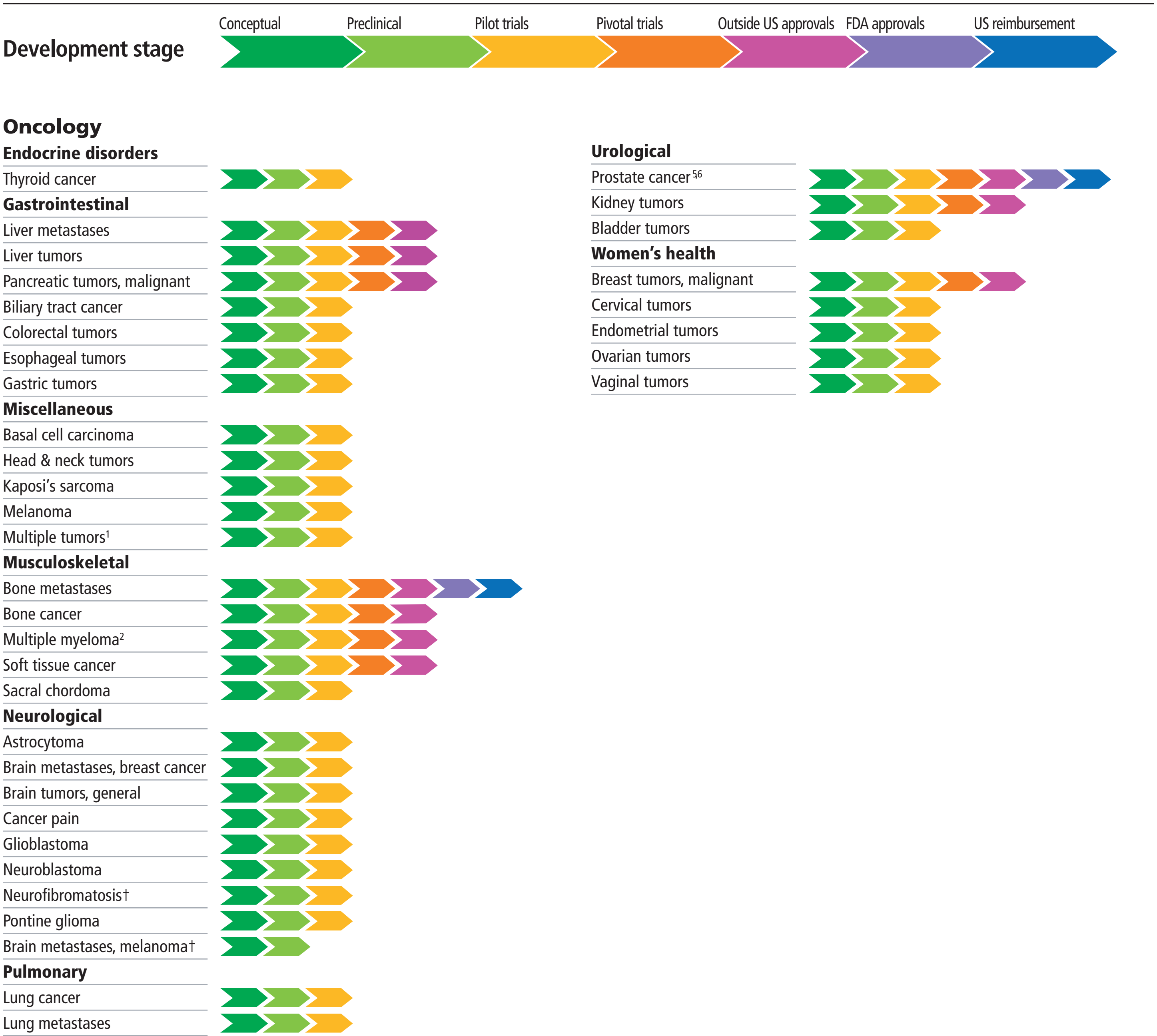
The preceding chart's categories are body systems, comprising a group of tissues structured to perform specific functions. All indications in development for focused ultrasound treatment appear on this chart, in the body system category to which they belong. Thus, bone metastases is in the Musculoskeletal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

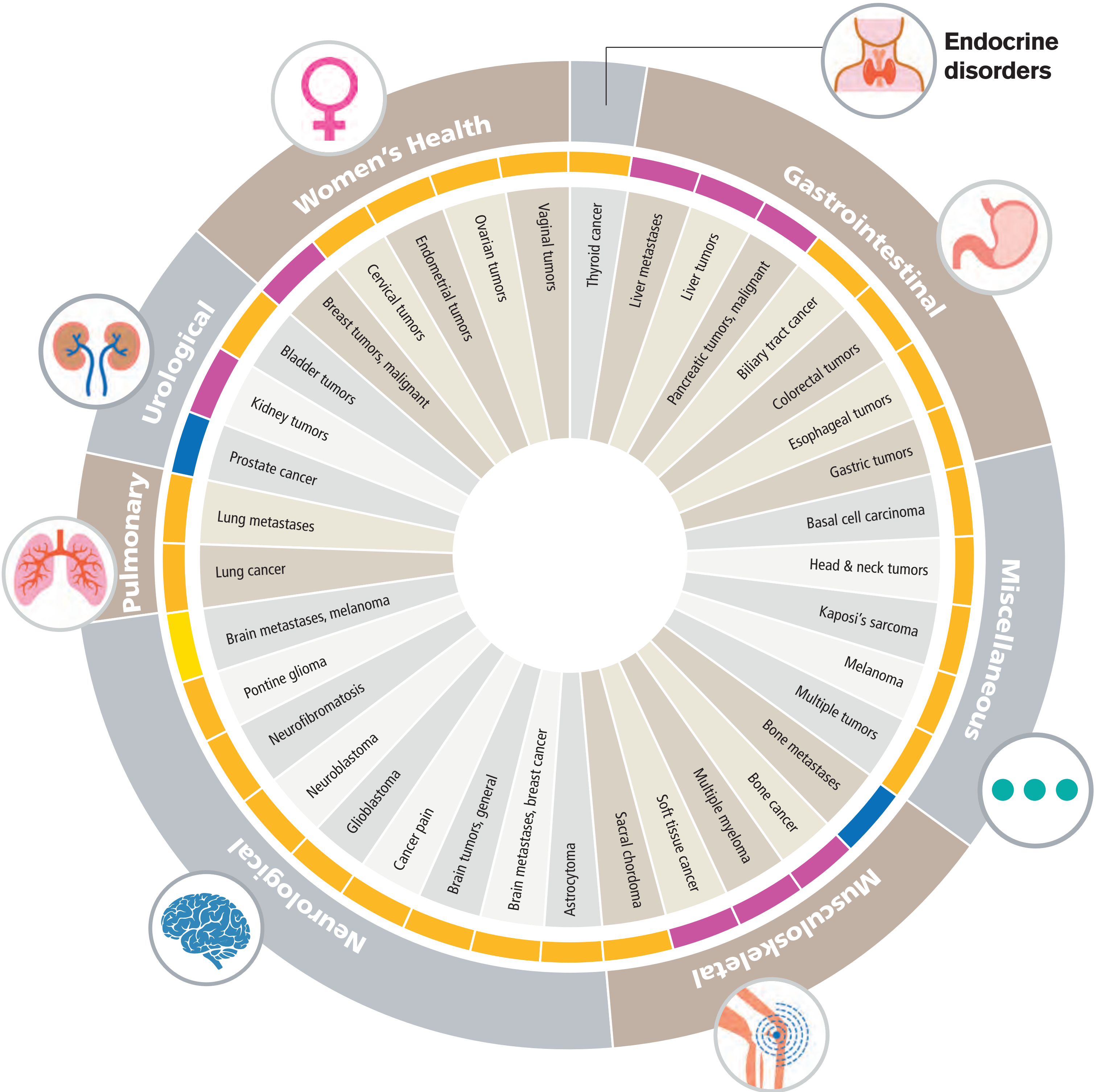


1 Protocols inclusive of more than one indication
2 Multiple myeloma approval is based on bone metastases.
5 FDA approval is for prostate tissue ablation.
6 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
† New in 2021

NEW

37 Oncology Indications

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



Global Development Landscape by Body System

Cardiovascular

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

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Diabetes	Grave's disease Hyperparathyroidism Thyroid cancer		Thyroid nodules		

Gastrointestinal

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Inflammatory bowel disease Irritable bowel syndrome Liver fibrosis	Biliary tract cancer Colorectal tumors Esophageal tumors Gastric tumors Malignant obstructive jaundice Nonalcoholic steatohepatitis (NASH)† Pancreatic tumors, benign Root canal endodontia		Liver metastases Liver tumors Pancreatic tumors, malignant		

† New in 2021

Global Development Landscape by Body System continued

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Miscellaneous						
	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 tumors[1] Obesity				
Musculoskeletal						
	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

Global Development Landscape by Body System continued

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Neurological						
Anorexia	Brain metastases, melanoma†	ADHD†		Depression	Essential tremor	Essential tremor
	Cavernomas	Alzheimer's disease		Essential tremor	Parkinson's disease, dyskinesia	Parkinson's disease, tremor
	Hydrocephalus	Amyotrophic lateral sclerosis		Neuropathic pain	Parkinson's disease, tremor	
	Neuromyelitis optica	Anxiety†		Obsessive-compulsive disorder		
	Rett syndrome	Astrocytoma		Parkinson's disease, dyskinesia		
	Spinal cord injury	Brain metastases, breast cancer		Parkinson's disease, tremor		
	Trigeminal neuralgia	Brain tumors, general				
		Cancer pain				
		Dementia				
		Dystonia				
		Dystonia, hand				
		Epilepsy				
		Glioblastoma				
		Headache[4]				
		Holmes tremor				
		Huntington's disease				
		Mood disorder				
		Multiple sclerosis				
		Neuroblastoma				
		Neurofibromatosis†				
		Neuropathy				
		Opioid and other addictions				
		Painful amputation neuromas				
		Parkinson's disease, other[3]				
		Pontine glioma				
		Schizophrenia†				
		Stroke, intracerebral hemorrhage				
		Stroke, thromboembolic				
		Traumatic brain injury				

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

Global Development Landscape by Body System continued

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Ophthalmological						
	Dry eye disease† Macular degeneration Presbyopia Retinal impairment Retinal injury			Glaucoma		
Pulmonary						
	Tuberculosis	Lung cancer Lung metastases		Rhinitis		
Urological						
	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

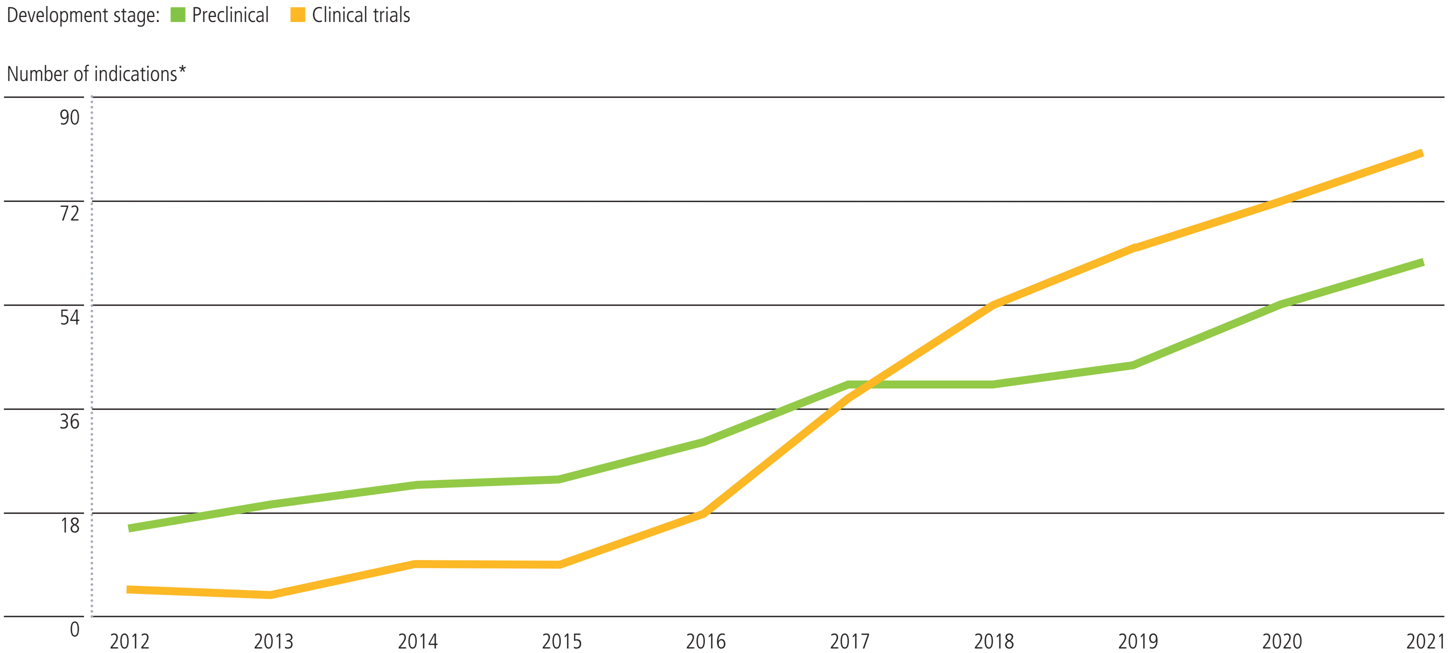
Global Development Landscape by Body System continued

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

† New in 2021

Page intentionally left blank

Development Stages of Focused Ultrasound Research

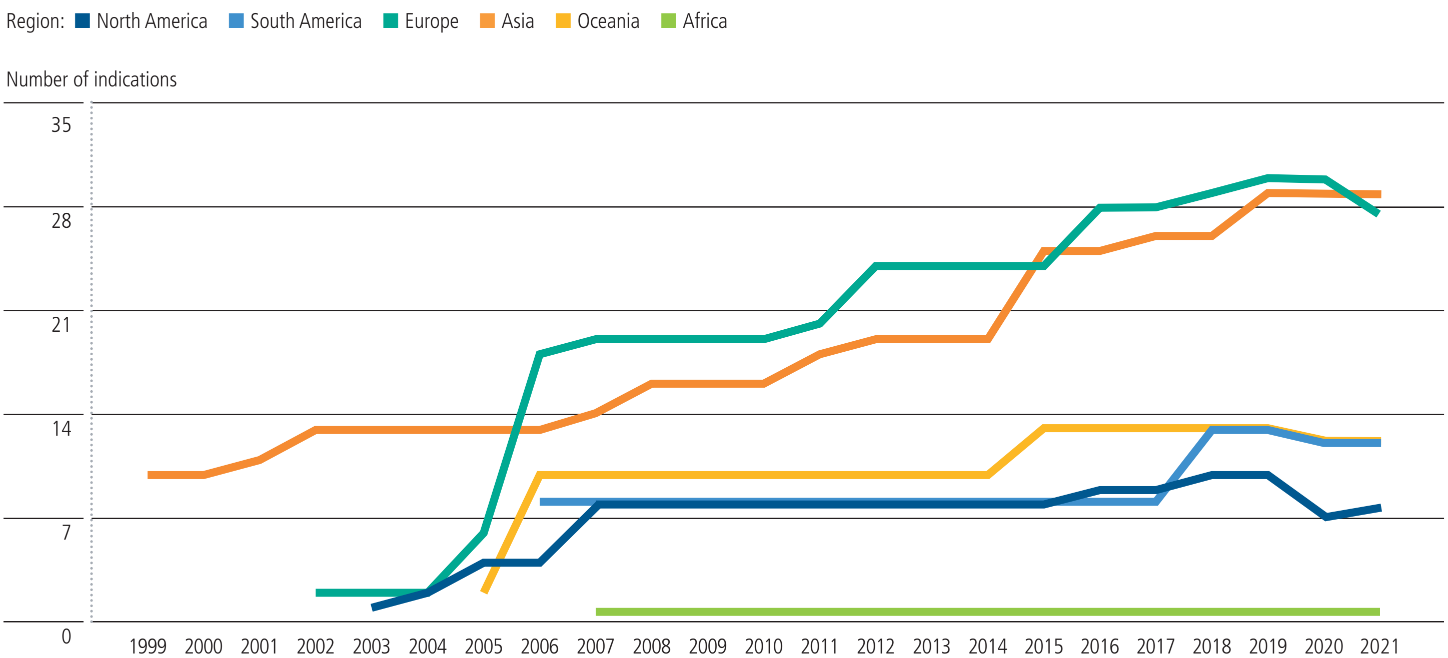


*Indications with multiple mechanisms of action are counted Individually.

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.

Cumulative Approved Indications by Region*



*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	–

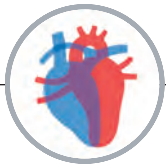
Number of Research Sites and Mechanisms of Action under Investigation

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.

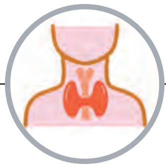
Number of Research Sites and Mechanisms of Action under Investigation



Indications	MOAs[1]	Sites: Preclinical	Sites: Clinical	Sites: Commercial	Total[2]
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



Indications	MOAs[1]	Sites			Total[2]
		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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites: Preclinical	Sites: Clinical	Sites: Commercial	Total[2]
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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites: Preclinical	Sites: Clinical	Sites: Commercial	Total[2]
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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites: Preclinical	Sites: Clinical	Sites: Commercial	Total[2]
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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		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.

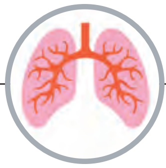
Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		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.

Number of Research Sites and Mechanisms of Action under Investigation continued

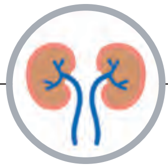


Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Pulmonary					
Lung cancer	3	5	1	–	**5**
Lung metastases	1	1	–	–	**1**
Rhinitis	1	–	1	–	**1**
Tuberculosis	1	1	–	–	**1**

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.

Number of Research Sites and Mechanisms of Action under Investigation continued



Indications	MOAs[1]	Sites			Total[2]
		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.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites: Preclinical	Sites: Clinical	Sites: Commercial	Total[2]
Women's health					
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 brain-related patient treatments. For 2019 and prior, there was only one focused ultrasound manufacturer in this space.

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

> **"Scots man signs own name for first time in 20 years after groundbreaking treatment to banish violent shaking."**
>
> — Scottish Daily Record
> October 11, 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

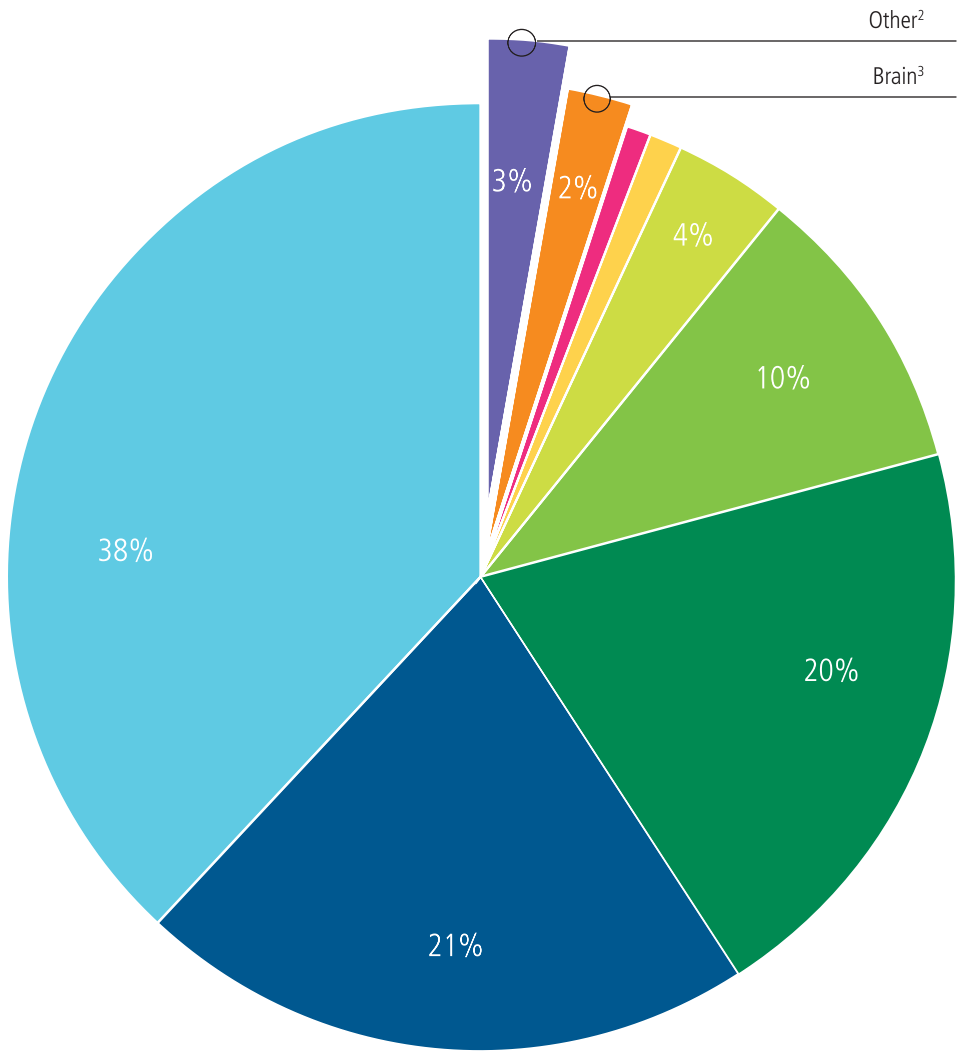
> **"WVU addresses addiction crisis with novel ultrasound treatment."**
>
> — WVU Medicine
> March 13, 2021

Patient Treatments by Indication—Cumulative

467,162 total treatments[1]

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%
Brain[3]	8,417	2%
Glaucoma	6,179	1%
Cancer, unspecified	5,560	1%

All indications



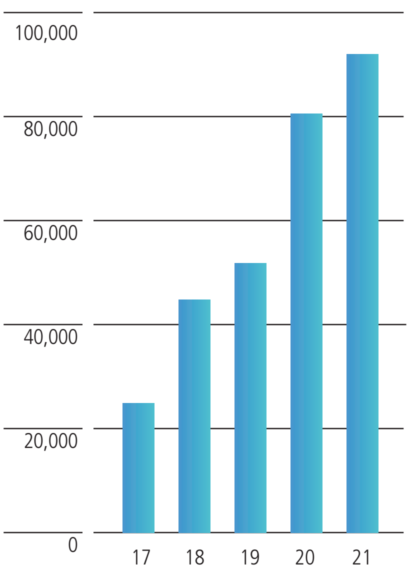
1 The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites. Companies reporting patient treatment values this year were: Cardiawave, EDAP TMS, EyeSonix, FUSMobile, HistoSonics, Image Guided Therapy, 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

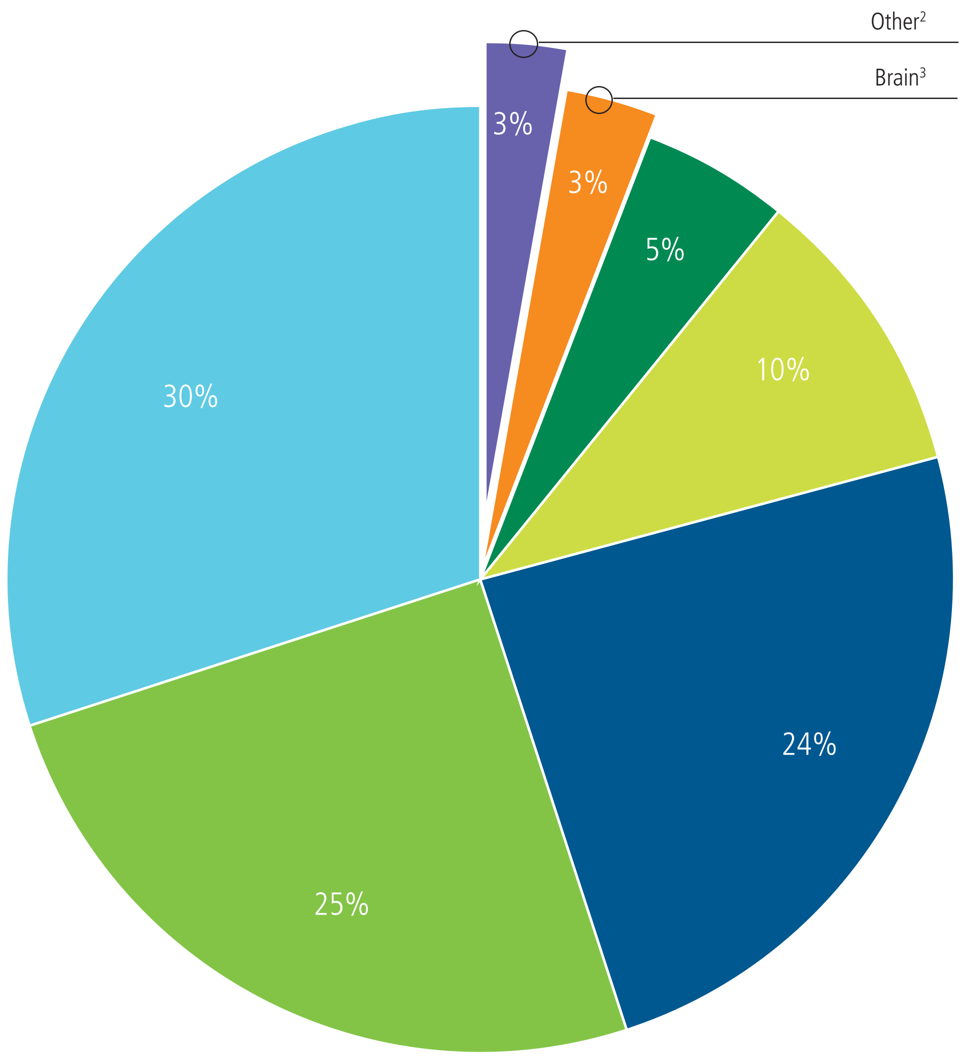
92,365 total treatments[1]

Uterine fibroids	27,613	30%
Pancreatic tumors	23,523	25%
Liver tumors	22,325	24%
Uterine adenomyosis	9,147	10%
Prostate diseases	4,334	5%
Brain[3]	2,906	3%
Other[2]	2,502	3%
– Glaucoma	15	—
– Cancer, unspecified	—	—

Annual Patient Treatments



All indications



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.

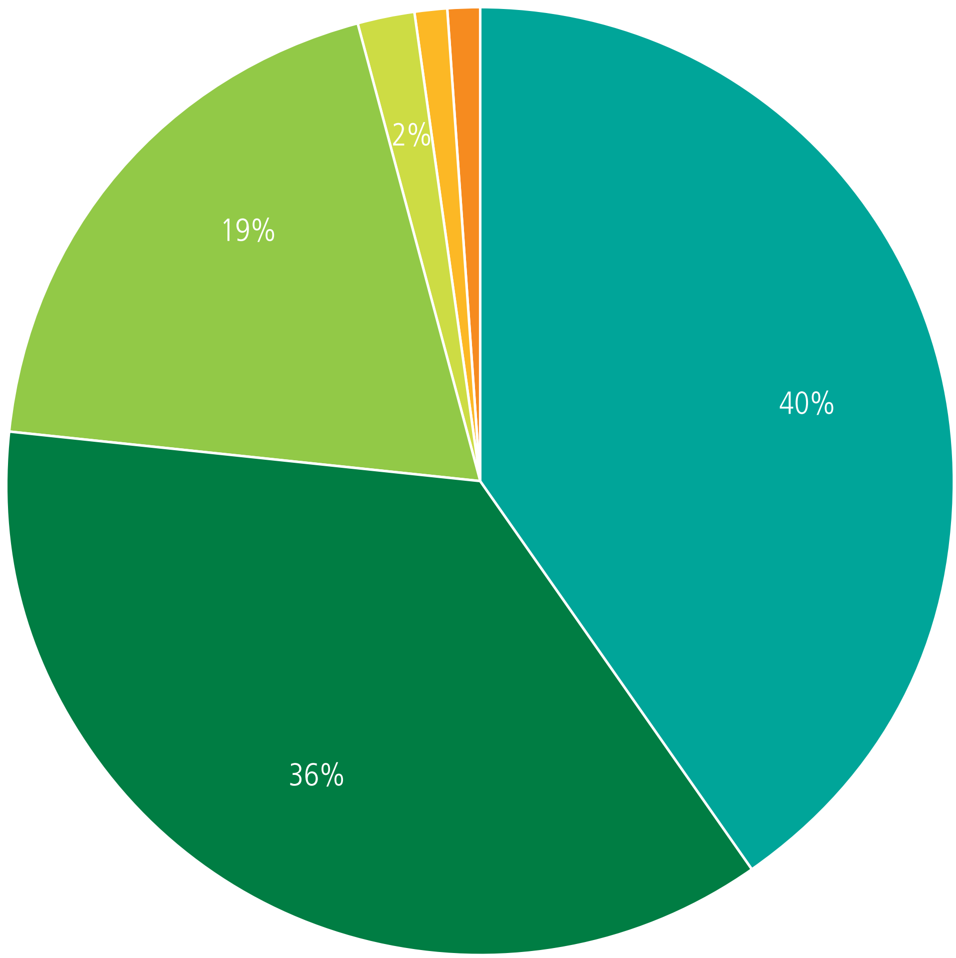
Oncology Treatments by Indication—Cumulative

246,142 total treatments

■	Liver tumors	98,016	40%
■	Prostate cancer	87,387	36%
■	Pancreatic tumors	46,246	19%
■	Cancer, unspecified	5,560	2%
■	Soft tissue cancer	3,807	1%
■	Bone metastases	3,587	1%
–	Breast tumors, malignant	896	—
–	Other[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.

Oncology indications



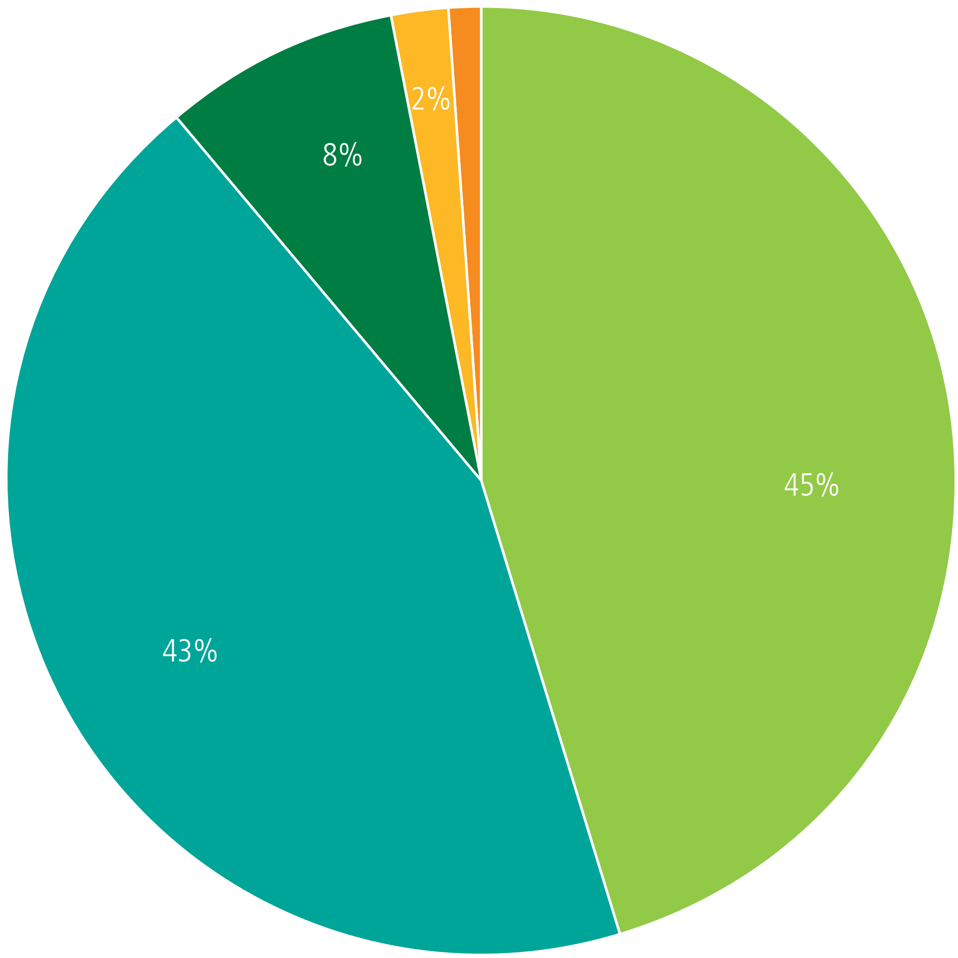
1 Includes, in descending order of patient treatments: glioblastoma; endometrial tumors; brain tumors, general; glioblastoma multiforme; kidney tumors; osteosarcoma; abdominal paraganglioma; hemangioma; abdominal tumor; astrocytoma; basal cell carcinoma; diffuse intrinsic pontine glioma (DIPG); granular 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

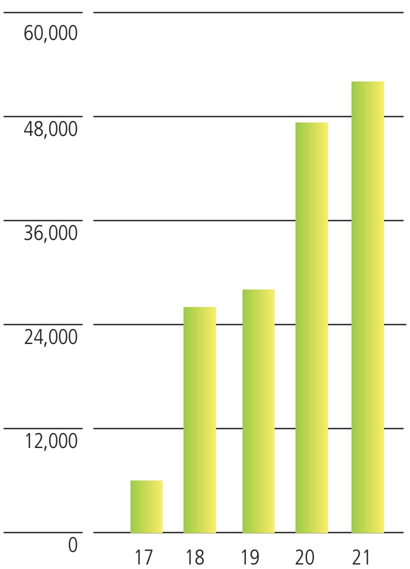
52,034 total treatments

Pancreatic tumors	23,523	45%
Liver tumors	22,327	43%
Prostate cancer	4,304	8%
Soft tissue cancer	1,200	2%
Bone metastases	433	1%
– Other[1]	241	—
– Breast tumors, malignant	6	—

Oncology indications



Annual Oncology Treatments



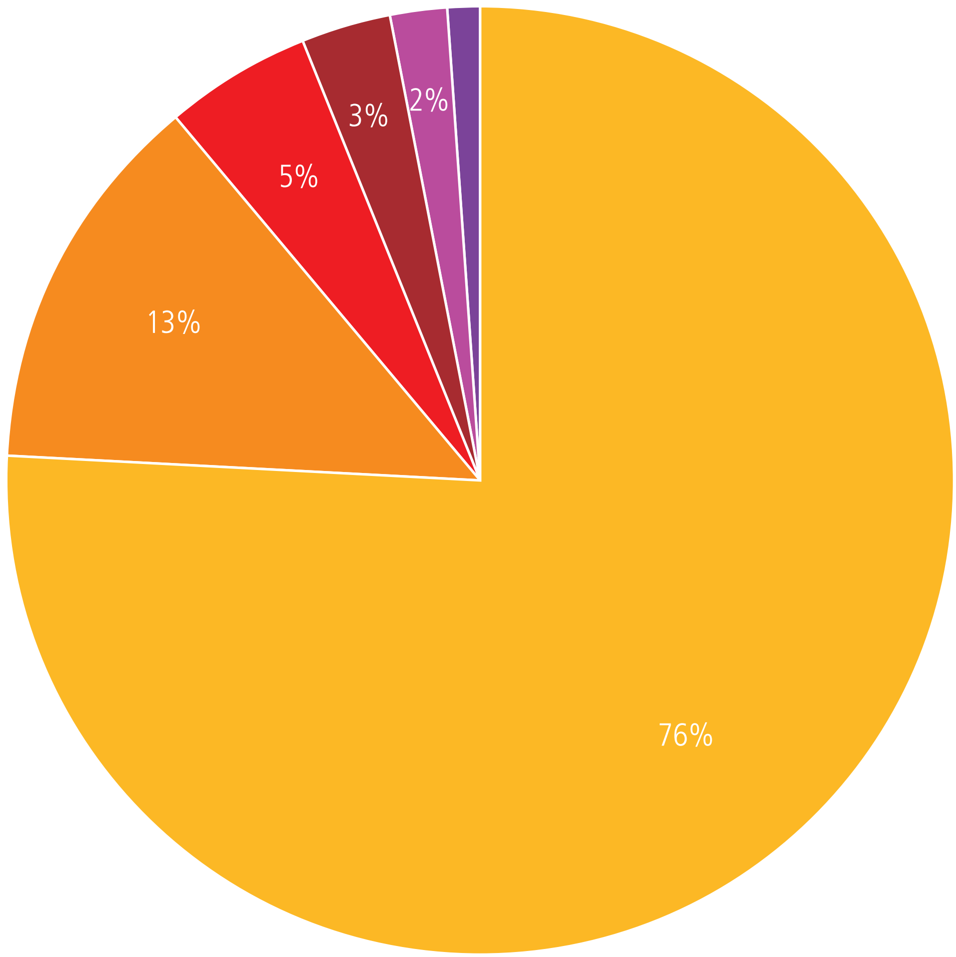
1 Includes, in descending order of patient treatments: endometrial tumors; glioblastoma; brain tumors, general; glioblastoma multiforme; diffuse intrinsic pontine glioma (DIPG); basal cell carcinoma; and bone cancer

Brain Treatments by Indication—Cumulative

8,417 total brain treatments

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

Brain indications



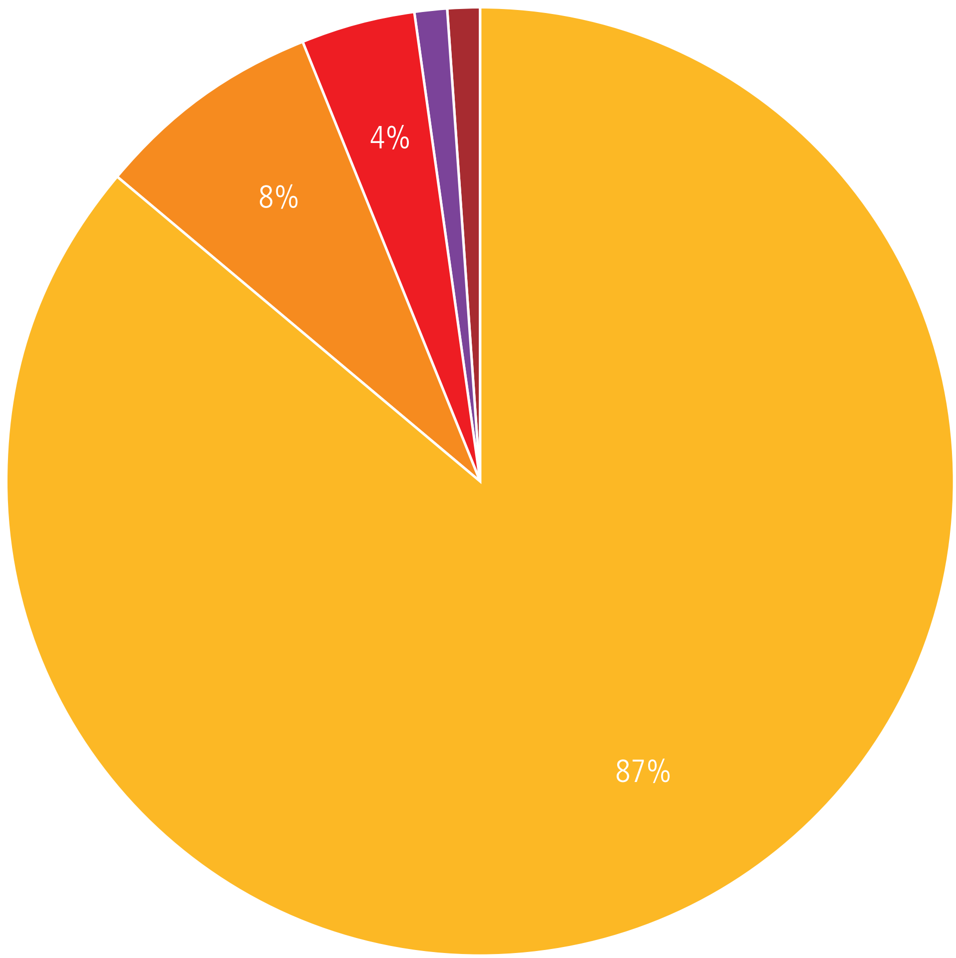
1 Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; astrocytoma; pontine glioma; and ganglioglioma
2 Includes, in descending order of patient treatments: depression, obsessive-compulsive disorder (OCD), and anxiety
3 Includes, in descending order of patient treatments: 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

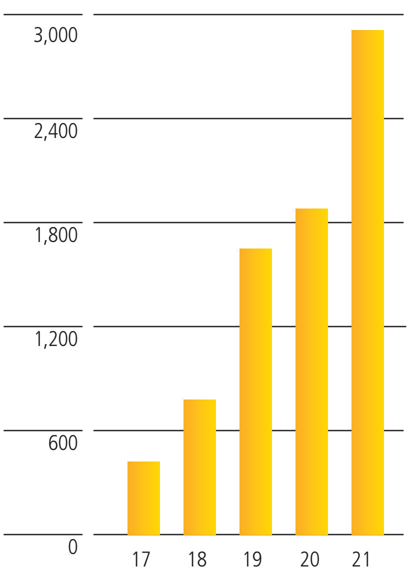
2,929 total brain treatments

Essential Tremor	2,518	87%
Parkinson's disease	237	8%
Brain tumors[1]	119	4%
Alzheimer's disease	15	1%
Neuropathic pain	14	1%
– Other movement disorders[2]	26	—
– Mental health	—	—
– Other brain	—	—

Brain indications



Annual Brain Treatments



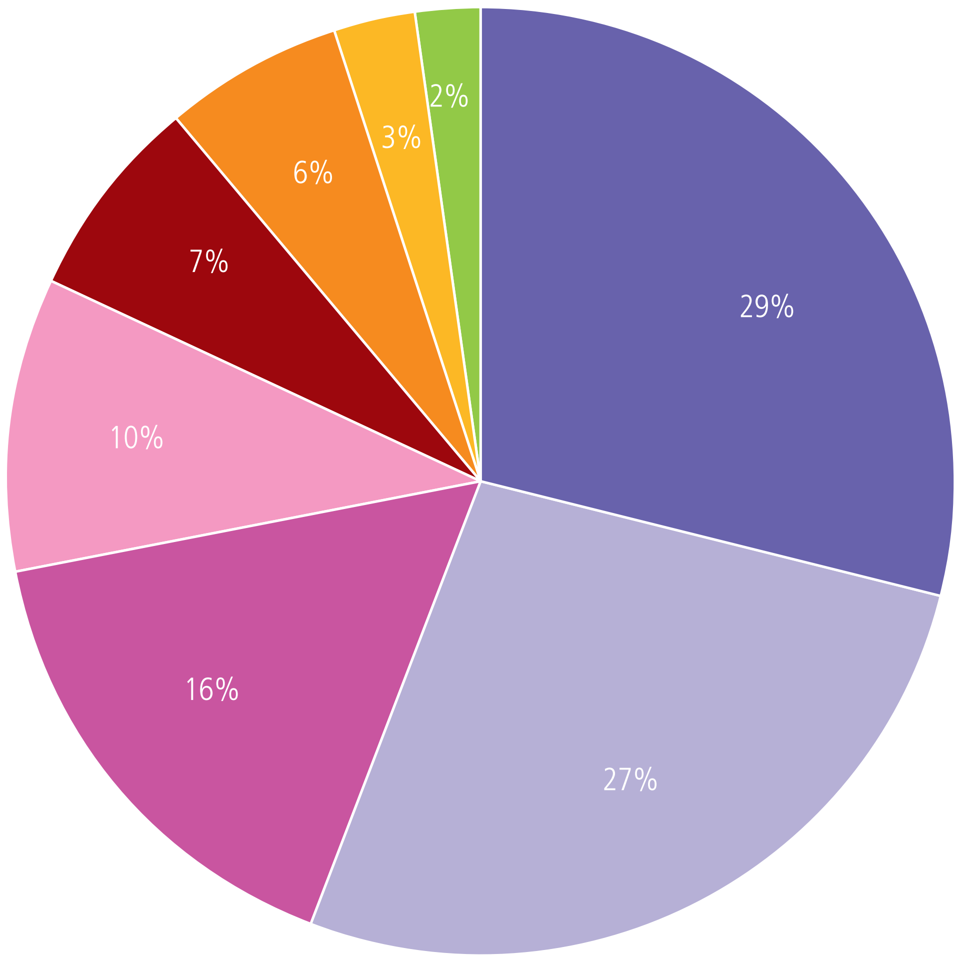
1 Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; and pontine glioma
2 Includes epilepsy

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%



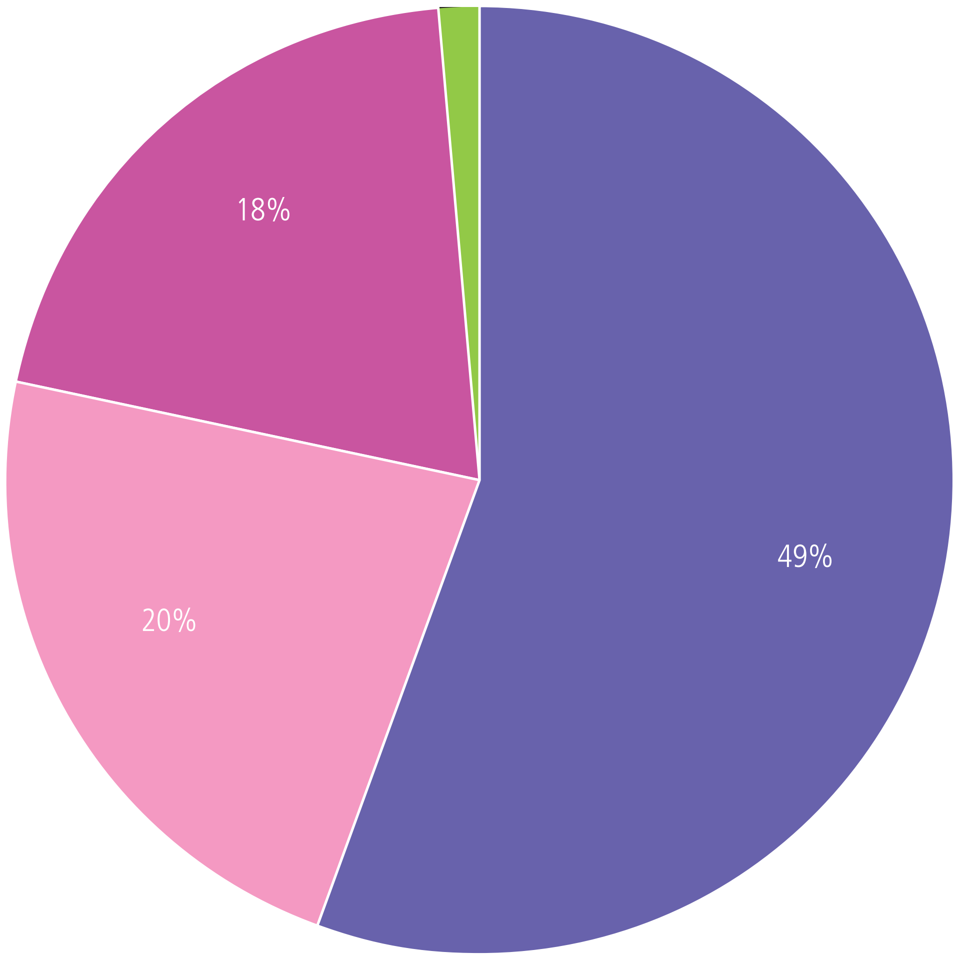
1 Includes, in descending order of patient treatments: varicose veins; endometrial tumors; desmoid tumors; hypertension; endometriosis; hyperparathyroidism; actinic keratosis; arthritis; heart valve calcifications; dermatology research; tattoo removal; bone tumors, benign; kidney tumors; bone cancer; 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

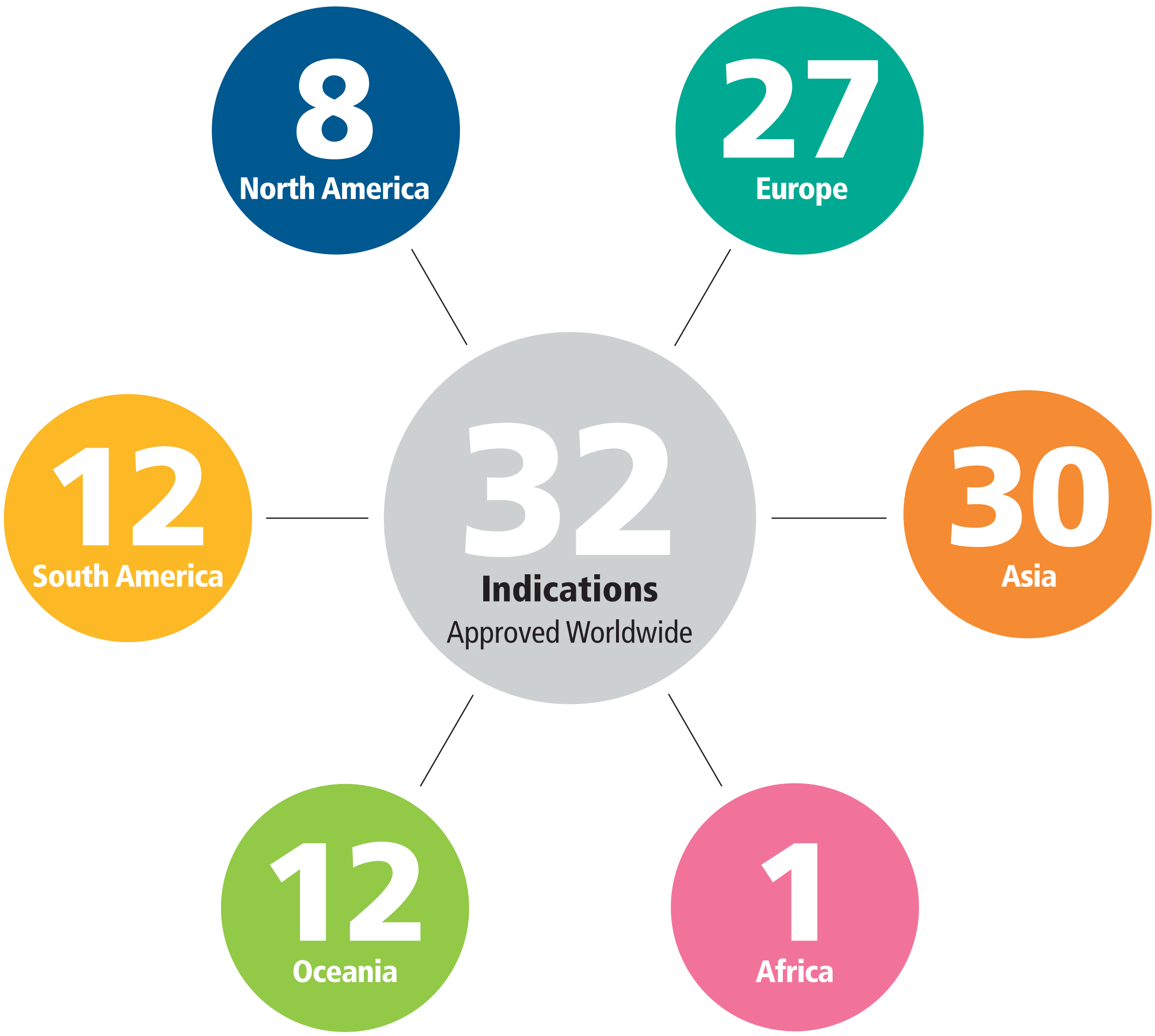
2,469 total treatments

Soft tissue cancer	1,200	49%
Other[1]	487	20%
Thyroid nodules	433	18%
Osteoid osteoma	34	1%
– Arthritis, facetogenic	11	—
– Breast tumors, malignant	6	—
– Breast fibroadenoma	—	—



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	
Europe, Asia	Varicose veins	Theraclion
	Endocrine disorders	
Europe, Asia	Thyroid nodules	Theraclion
	Gastrointestinal	
Europe	Liver metastases	Chongqing Haifu Medical Technology
Europe, Asia	Liver tumors	Chongqing Haifu Medical Technology
Asia		Shanghai A&S
Europe, Asia	Pancreatic tumors	Chongqing Haifu Medical Technology
	Musculoskeletal	
Europe, Asia, South America, Oceania	Arthritis, facetogenic	Insightec
Europe, Asia, South America, Oceania	Bone cancer	Insightec
North America, Europe, Asia, South America, Oceania	Bone metastases	Insightec
Europe, Asia		Profound Medical
Asia		Shanghai A&S
Europe, Asia, South America, Oceania	Bone tumors, benign	Insightec
Europe	Desmoid tumors	Profound Medical
Europe, Asia, South America, Oceania	Multiple myeloma	Insightec
Europe, Asia	Osteoid osteoma	Chongqing Haifu Medical Technology
North America, Europe, Asia		Profound Medical
Europe, Asia	Soft tissue cancer	Chongqing Haifu Medical Technology
Asia		EpiSonica
Asia		Shanghai A&S
Europe, Asia	Soft tissue tumors, benign	Chongqing Haifu Medical Technology

Approval regions

- North America
- Europe
- Asia
- South America
- Oceania
- Africa

Global Landscape of Approved Indications and Manufacturers continued

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

Approval regions
- North America
- Europe
- Asia
- South America
- Oceania
- Africa

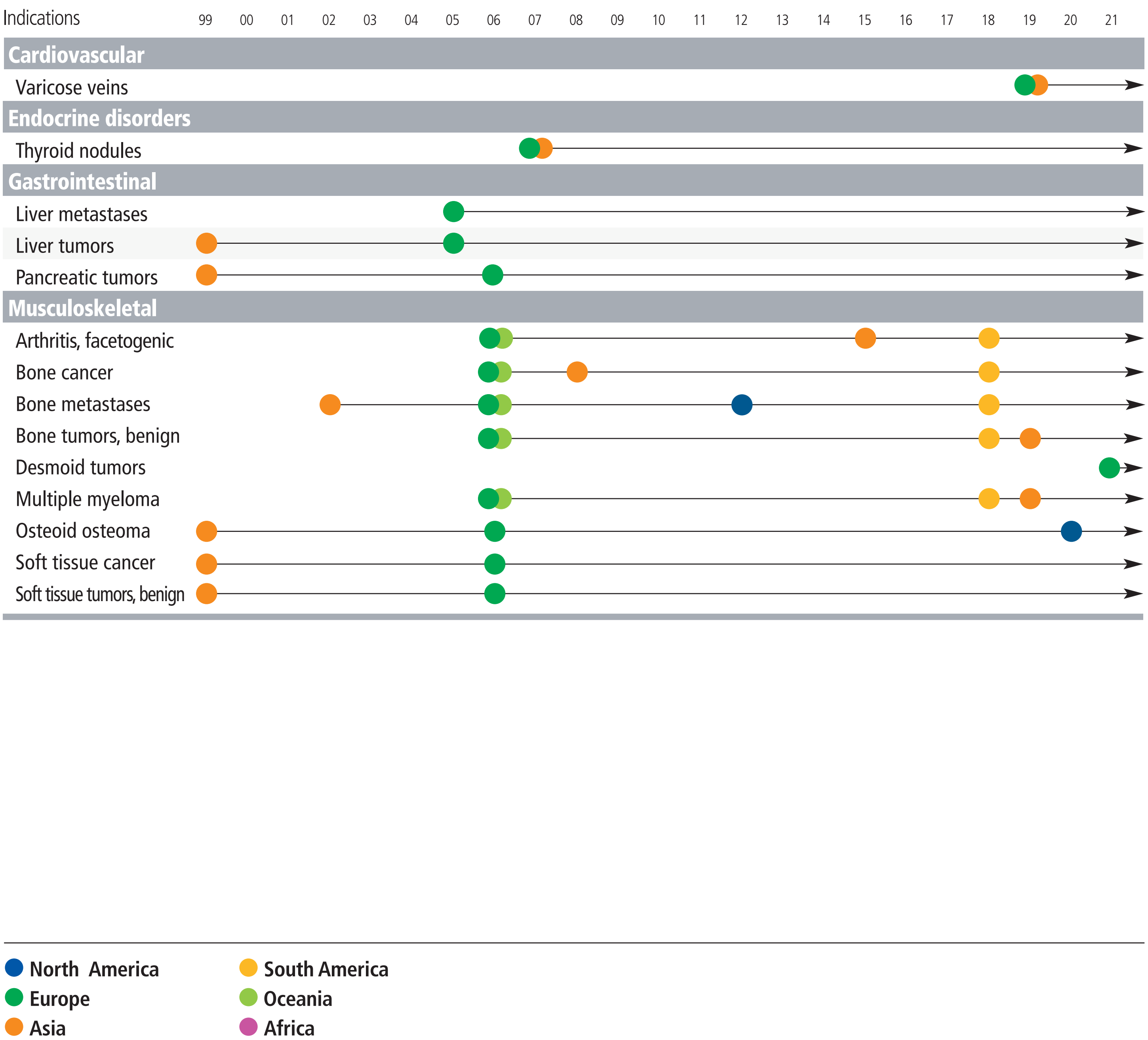
Global Landscape of Approved Indications and Manufacturers continued

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

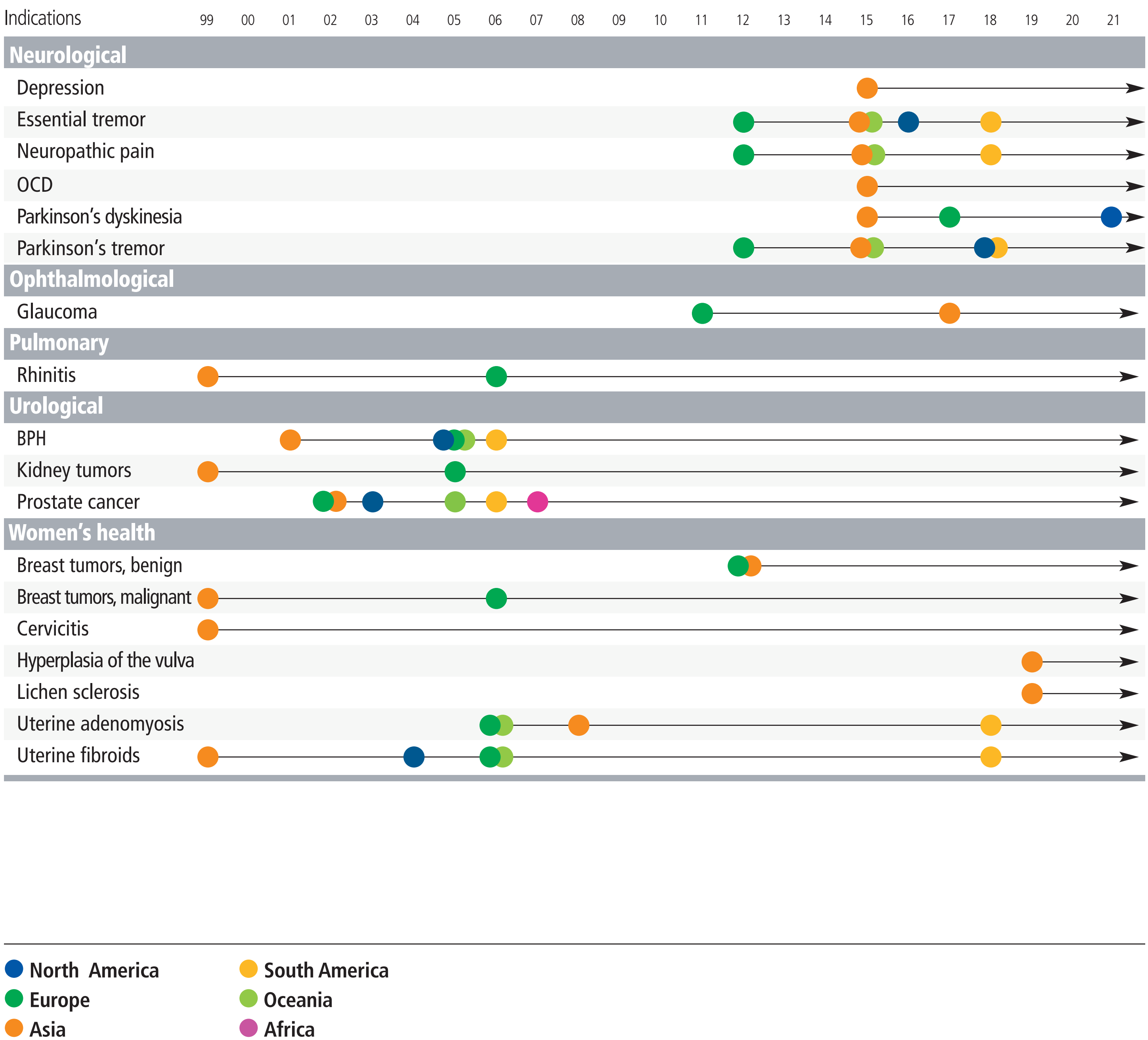
Approval regions

- North America
- Europe
- Asia
- South America
- Oceania
- Africa

FUS Regulatory Approvals by Indication and Region



FUS Regulatory Approvals by Indication and Region continued



Abstracts Presented at FUS Symposia

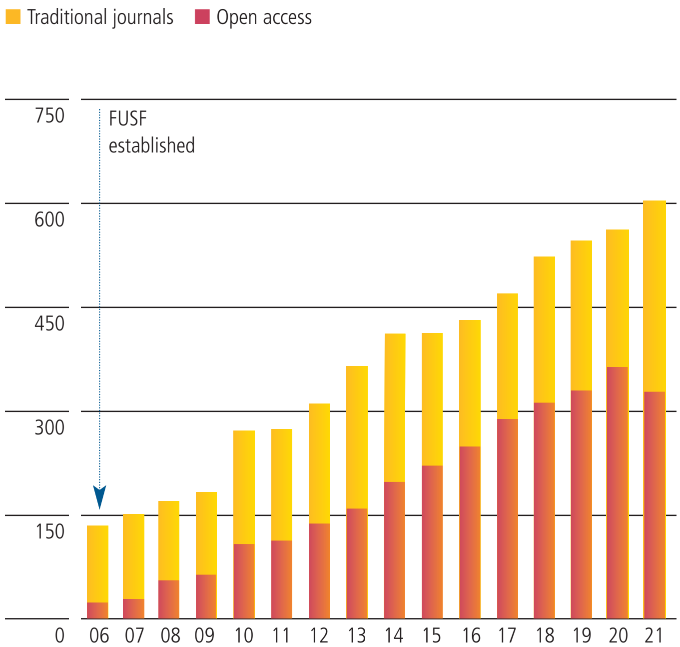
Symposium	2016	2017	2018	2019	2020	2021
Focused Ultrasound Foundation Symposium, FUSF[1]	200	–	250	–	257	–
International Symposium on Therapeutic Ultrasound, ISTU	152	207	257	197[2]	*	241
Totals	**352**	**261**	**507**	**197**	**257**	**241**

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



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

FUS Publications and Citations

Cumulative

6,558
FUS publications

184,334
Citations of FUS publications

2021

612
FUS publications

24,112
Citations of 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.

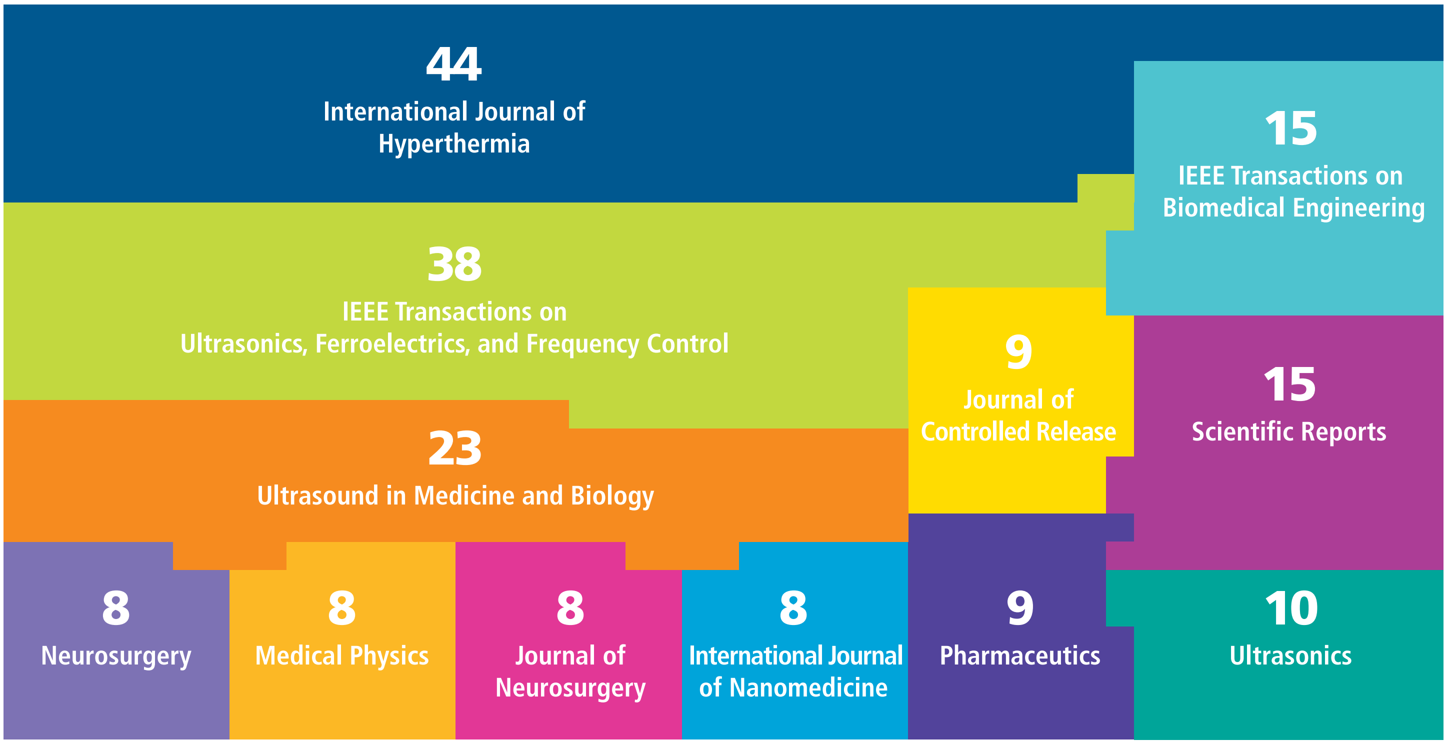
Publications in 2021 continued to stay the course, and focused ultrasound publication citations were over 24,000 for 2021 alone.

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



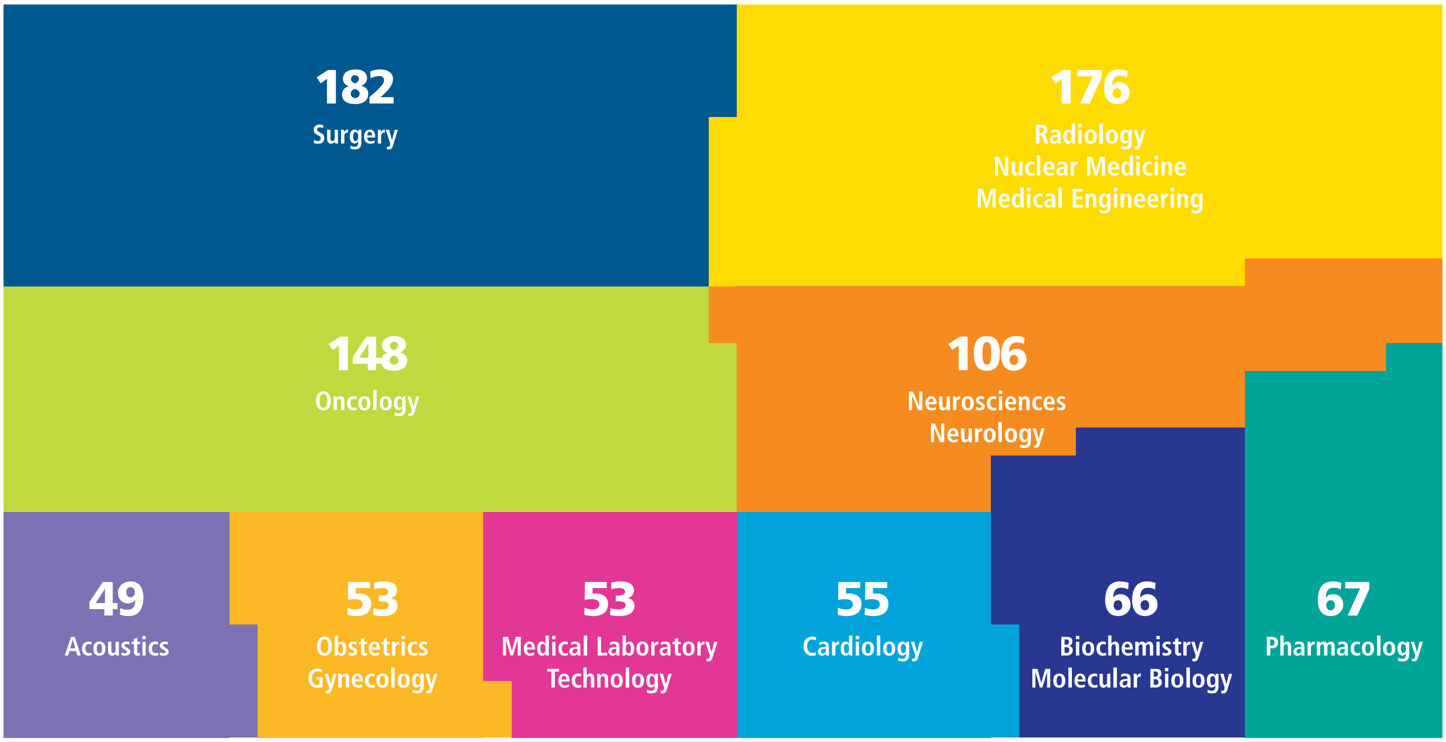
Publications—2021 Top Source Titles

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

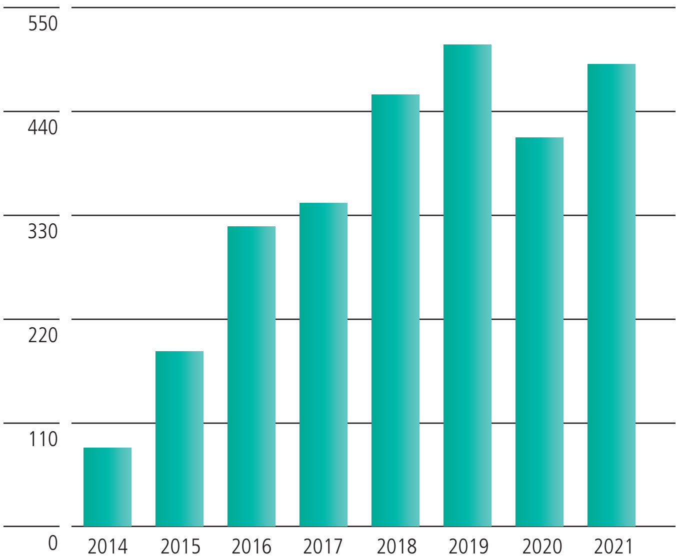


Publications—2021 Top Ten Research Areas

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



FUSF began tracking US FUS media placements in 2013

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

New platform

An unusual approach to fighting cancer is ultrasound and microbubbles.

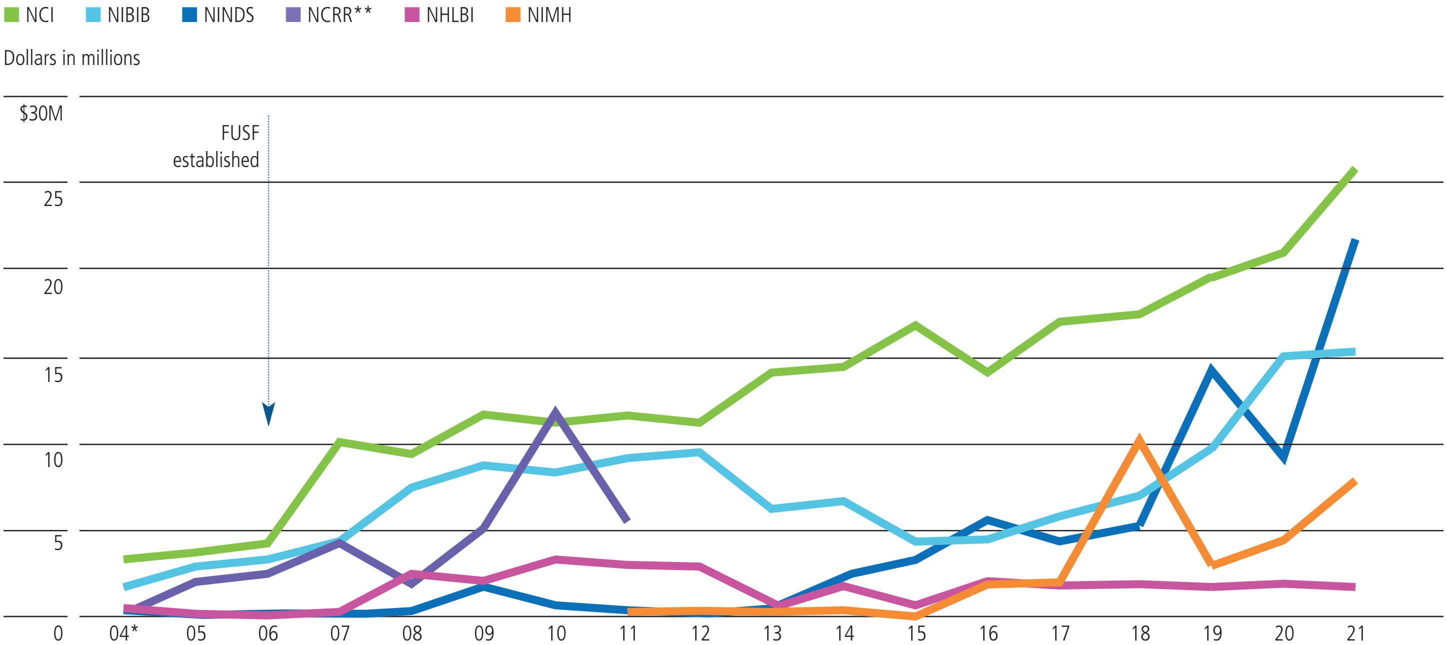
> **"The new treatment platform is designed to deliver a one-two punch. First, the microbubbles attack cancer cells, then a gene beckons immune cells to further pummel the tumor."**
>
> — Forbes
> June 17, 2020

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

United States Top Federal Government Funders



*The first record of funded focused ultrasound research by the United States Federal Government was in 2004.
**Agency dissolved in 2012.
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.

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** I National Cancer Institute
$15,699,088	$128,996,838	**NIBIB** I National Institute of Biomedical Imaging and Bioengineering
$21,845,267	$72,174,370	**NINDS** I National Institute of Neurological Disorders and Stroke
—	$32,924,533	**NCRR**[3] I National Center for Research Resources
$7,613,539	$30,519,707	**NIMH** I National Institute of Mental Health
$1,254,026	$24,880,522	**NHLBI** I National Heart, Lung, and Blood Institute
$2,919,048	$14,551,992	**NIDDK** I National Institute of Diabetes and Digestive and Kidney Diseases
$2,342,440	$12,700,842	**OD** I Office of the Director, NIH
$815,265	$11,904,326	**NIA** I National Institute on Aging
$4,549,414	$9,899,209	**NIDA** I National Institute on Drug Abuse
$382,179	$7,297,360	**NSF** I National Science Foundation
—	$7,264,005	**NIGMS** I National Institute of General Medical Sciences
$170,605	$7,237,301	**NICHD** I National Institute of Child Health and Human Development
—	$6,988,469	**CDMRP** I Congressionally Directed Medical Research Programs
$391,637	$5,528,883	**NEI** I National Eye Institute
$968,750	$2,285,247	**NIAAA** I National Institute on Alcohol Abuse and Alcoholism
—	$1,858,361	**CNRM** I Center For Neuroscience and Regenerative Medicine
$361,447	$1,789,980	**NIDCR** I National Institute of Dental and Craniofacial Research
—	$909,727	**NIDCD** I National Institute on Deafness and Other Communication Disorders
—	$749,990	**NIMHD** I National Institute on Minority Health and Health Disparities
—	$576,760	**NIAMS** I National Institute of Arthritis and Musculoskeletal and Skin Diseases
—	$223,196	**NHGRI** I National Human Genome Research Institute
—	$158,851	**CLC** I 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.
2 The first record of funding for focused ultrasound research by the US Federal Government was in 2004.
3 Agency dissolved in 2012.

Sources
Site: https://projectreporter.nih.gov/reporter.cfm
Site: https://www.usaspending.gov/search
Terms searched: "focused ultrasound", MRgFUS, HIFU, LIFU, "ultrasound ablation", LIPU

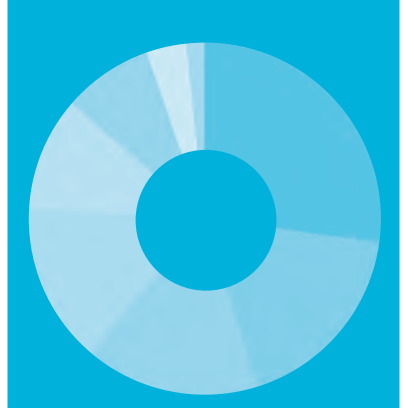
2022 State of Research and Treatment

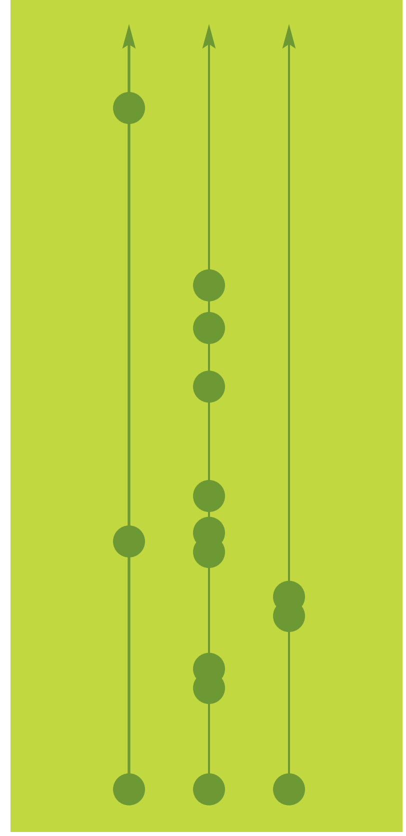
Focused Ultrasound Foundation

528

sites treating

3 urological indications





178

sites working on

drug delivery

76

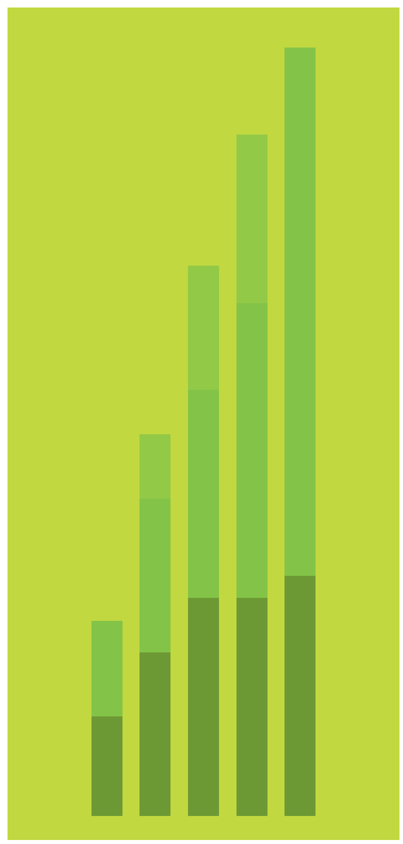
new commercial sites

in China

208

COE publications

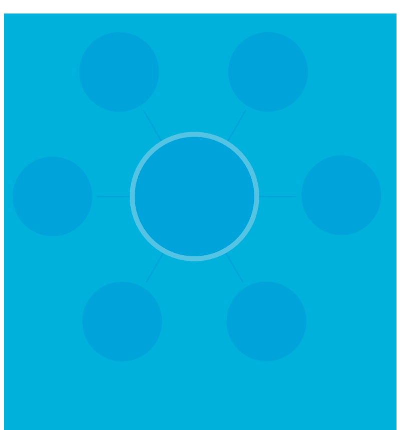
in 2021



54

sites working on

FUS simulation & treatment planning



75

sites conducting

neurological clinical trials

State of Research and Treatment

18

sites conducting preclinical **Alzheimer's research**

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.

Contents

II. State of the Research and Treatment

Contents continued

Commercial Treatment Sites by Region

895 Commercial treatment sites worldwide

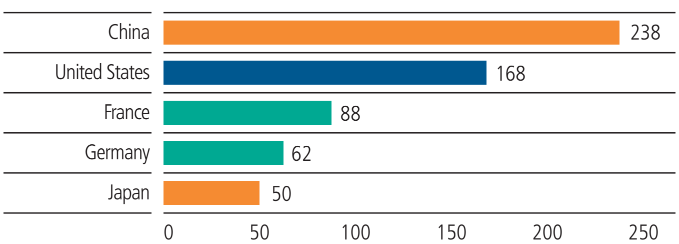
North America	Europe	Asia	South America	Oceania	Africa
192	289	394	9	4	7

Annual growth by region from 2013–2021

North America	Europe	Asia	South America	Oceania	Africa
26%	4%	13%	8%	22%	17%

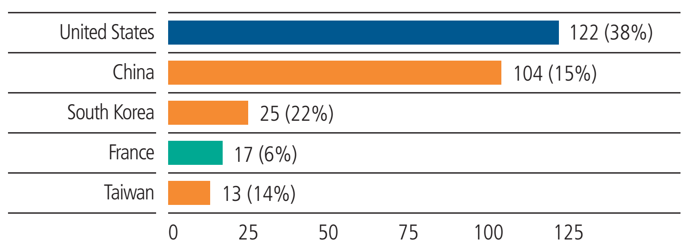
Top Countries for Commercial Treatment

Number of sites



Top Countries with Commercial Treatment Growth

Sites added, cumulative 2017 to 2021



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.

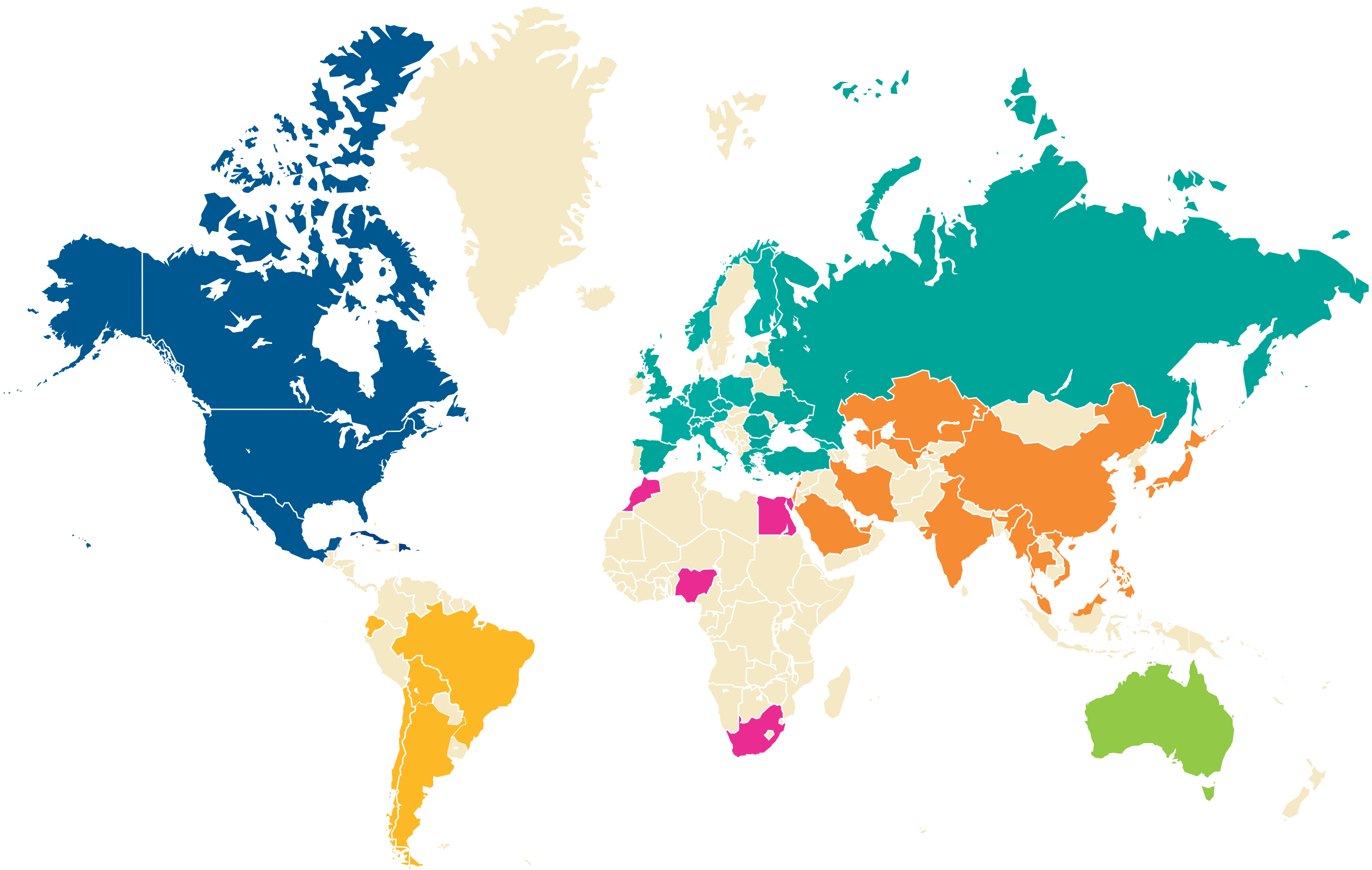
Commercial treatment additional content

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
1 Bolivia
2 Brazil
2 Chile
2 Ecuador

Europe

3 Austria
1 Belgium
1 Bulgaria
1 Czech Republic
1 Finland
88 France
1 Georgia
62 Germany
2 Greece
37 Italy
1 Latvia
1 Monaco
5 The Netherlands
3 Norway
4 Poland
1 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
1 Myanmar
1 Philippines
1 Qatar
2 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 Sites by Indication and Region*

12
Cardiovascular sites
3 indications

82
Neurological sites
13 indications

16
Endocrine disorders sites
1 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

Indications	N. America	Europe	Asia	S. America	Africa	Oceania	Totals
	Regions						
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

Indications	N. America	Europe	Asia	S. America	Africa	Oceania	Totals
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 Sites by Indication and Region* continued

Indications	Regions						Totals
	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.

Page intentionally left blank

Clinical Research Sites by Region

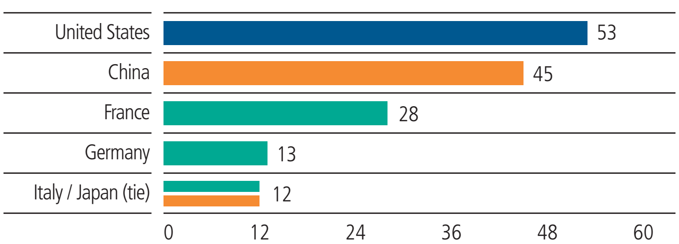
242 Clinical research sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
60	93	84	1	4	–

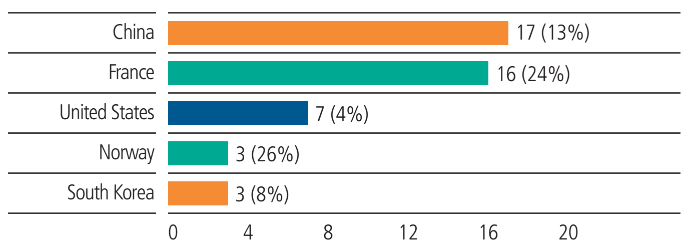
Annual growth by region from 2013–2021

North America	Europe	Asia	South America	Oceania	Africa
2%	8%	10%	–	10%	–

Top Countries for Clinical Research
Number of sites



Top Countries with Clinical Research Growth
Sites added, cumulative 2017 to 2021



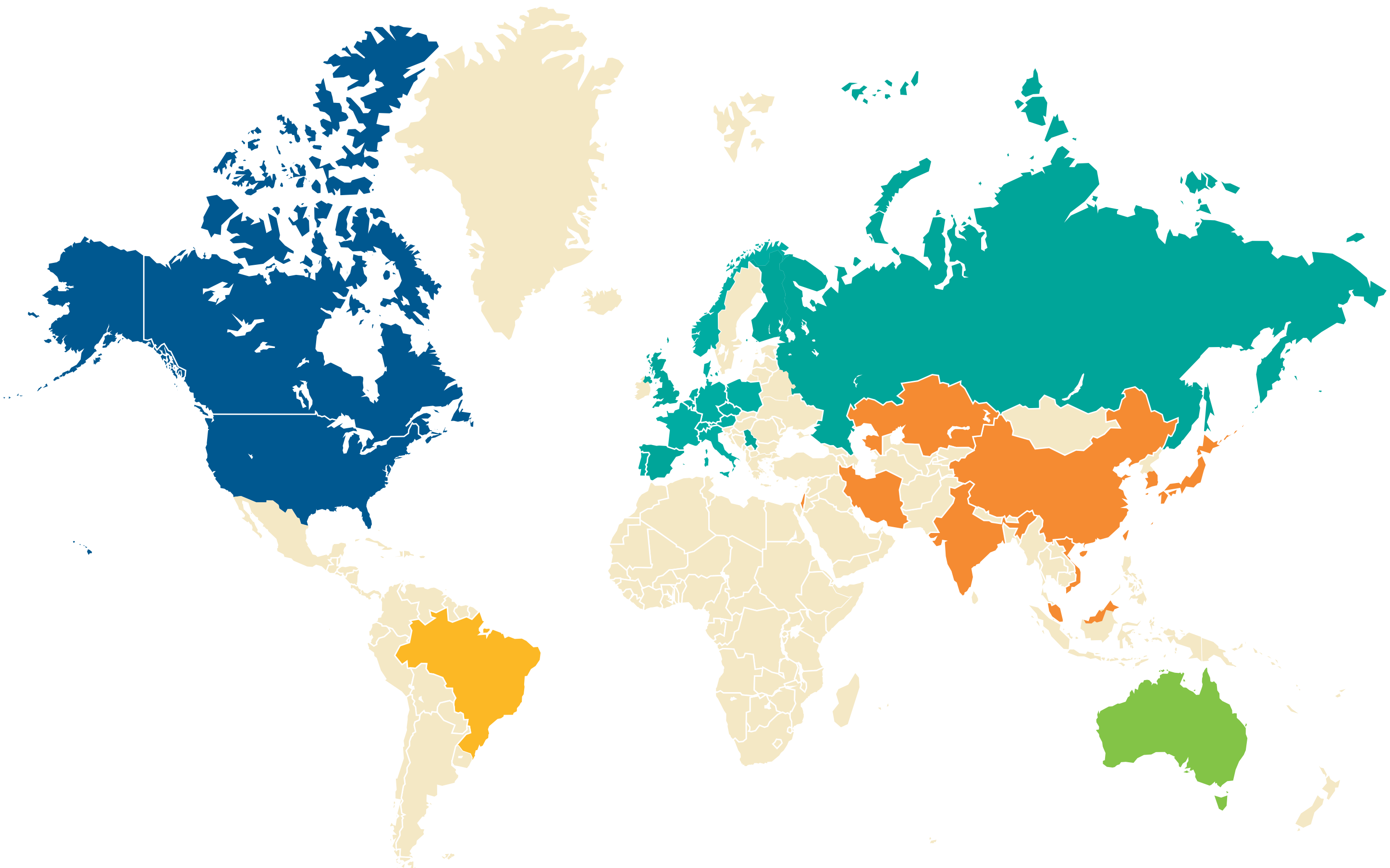
*Clinical research sites treat patients as part of a clinical study.

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 by Country



North America

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
1 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

Clinical Research Sites by Indication and Region*

96 indications are being researched at clinical sites worldwide.

13 Cardiovascular sites, 6 indications	**1** Endocrine disorders site, 2 indications	**58** Gastrointestinal sites, 9 indications	**9** Miscellaneous sites, 9 indications
102 Musculoskeletal sites, 12 indications	**75** Neurological sites, 35 indications	**7** Ophthalmological sites, 1 indication	**2** Pulmonary sites, 2 indications
76 Urological sites, 6 indications	**83** Women's health sites, 14 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.

Clinical Research Sites by Indication and Region* continued

96 indications are being researched at clinical sites worldwide.

Indications	N. America	Europe	Asia	S. America	Oceania	Totals
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.

Clinical Research Sites by Indication and Region* continued

96 indications are being researched at clinical sites worldwide.

Indications	N. America	Europe	Asia	S. America	Oceania	Totals
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.

Clinical Research Sites by Indication and Region* continued

96 indications are being researched at clinical sites worldwide.

Indications	N. America	Europe	Asia	S. America	Oceania	Totals
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.

Clinical Research Sites by Indication and Region* continued

96 indications are being researched at clinical sites worldwide.

	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.

Page intentionally left blank

Preclinical Research Sites by Region*

147 Preclinical research sites worldwide

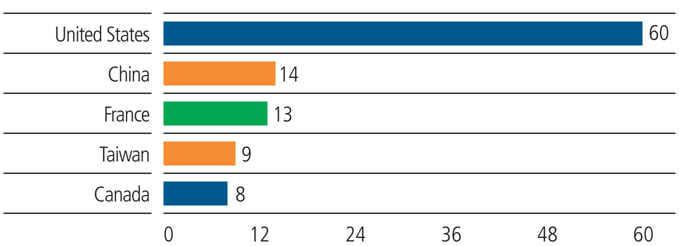
North America	Europe	Asia	South America	Oceania	Africa
68	37	39	–	3	–

Annual growth by region from 2013–2021

North America	Europe	Asia	South America	Oceania	Africa
5%	5%	13%	–	6%	–

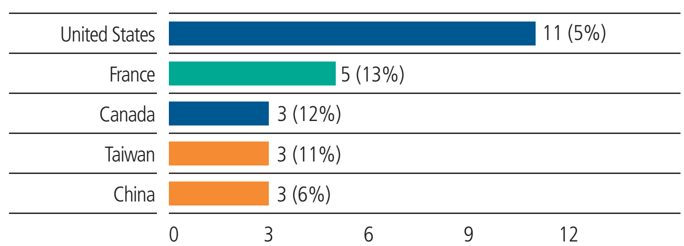
Top Countries for Preclinical Research

Number of sites



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.

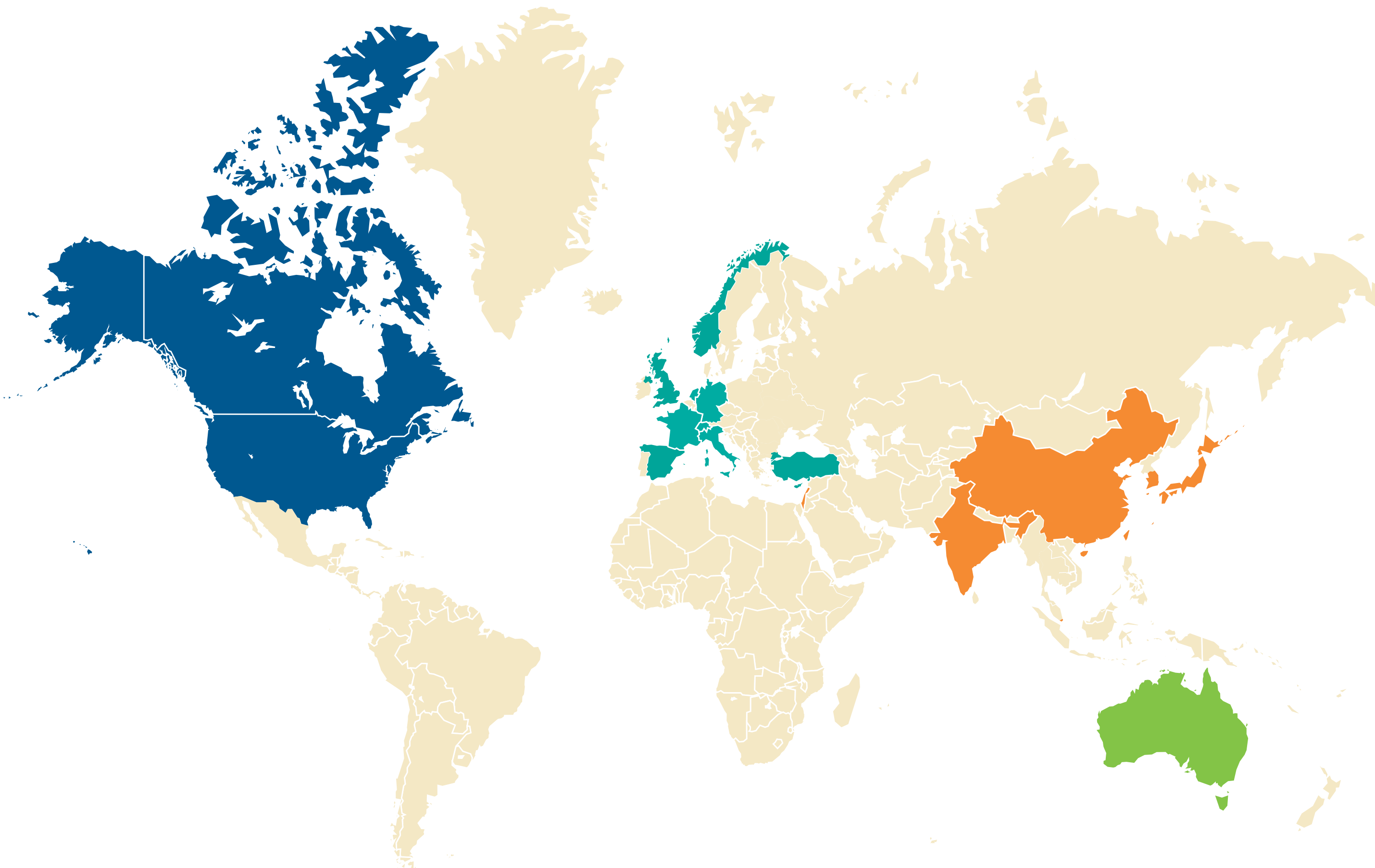
The United States leads the world in preclinical focused ultrasound research with over four-fold more research sites than the next closest country. This is likely a reflection of the US leading the world in medical research and the robust research infrastructure that exists in institutions of higher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

Preclinical Research Sites by Indication and Region*

108 indications are being researched at preclinical sites worldwide.

26 Cardiovascular sites 17 indications	**4** Endocrine disorders sites 4 indications	**40** Gastrointestinal sites 7 indications	**25** Miscellaneous sites 9 indications
29 Musculoskeletal sites 13 indications	**79** Neurological sites 30 indications	**8** Ophthalmological sites 4 indications	**6** Pulmonary sites 3 indications
29 Urological sites 9 indications	**36** Women's health sites 8 indications		

Indications	Regions: N. America	Europe	Asia	Oceania	Totals
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.

Preclinical Research Sites by Indication and Region* continued

108 indications are being researched at preclinical sites worldwide.

Indications	Regions: N. America	Europe	Asia	Oceania	Totals
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.

Preclinical Research Sites by Indication and Region* continued

108 indications are being researched at preclinical sites worldwide.

Indications	N. America	Europe	Asia	Oceania	Totals
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.

Preclinical Research Sites by Indication and Region* continued

108 indications are being researched at preclinical sites worldwide.

Indications	Regions: N. America	Europe	Asia	Oceania	Totals
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.

Preclinical Research Sites by Indication and Region* continued

108 indications are being researched at preclinical sites worldwide.

Indications	Regions: N. America	Europe	Asia	Oceania	Totals
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.

Page intentionally left blank

Technical Research Sites by Region

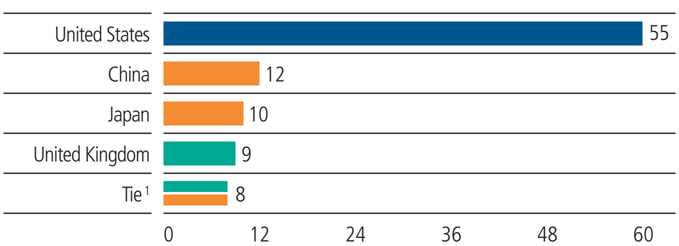
150 Technical research sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
61	49	39	–	1	–

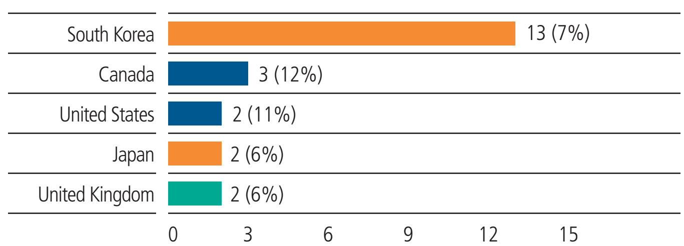
Annual growth by region from 2013–2021

North America	Europe	Asia	South America	Oceania	Africa
5%	12%	38%	–	–	–

Top Countries for Technical Research
Number of sites



Top Countries with Technical Research Growth
Sites added, cumulative 2017 to 2021



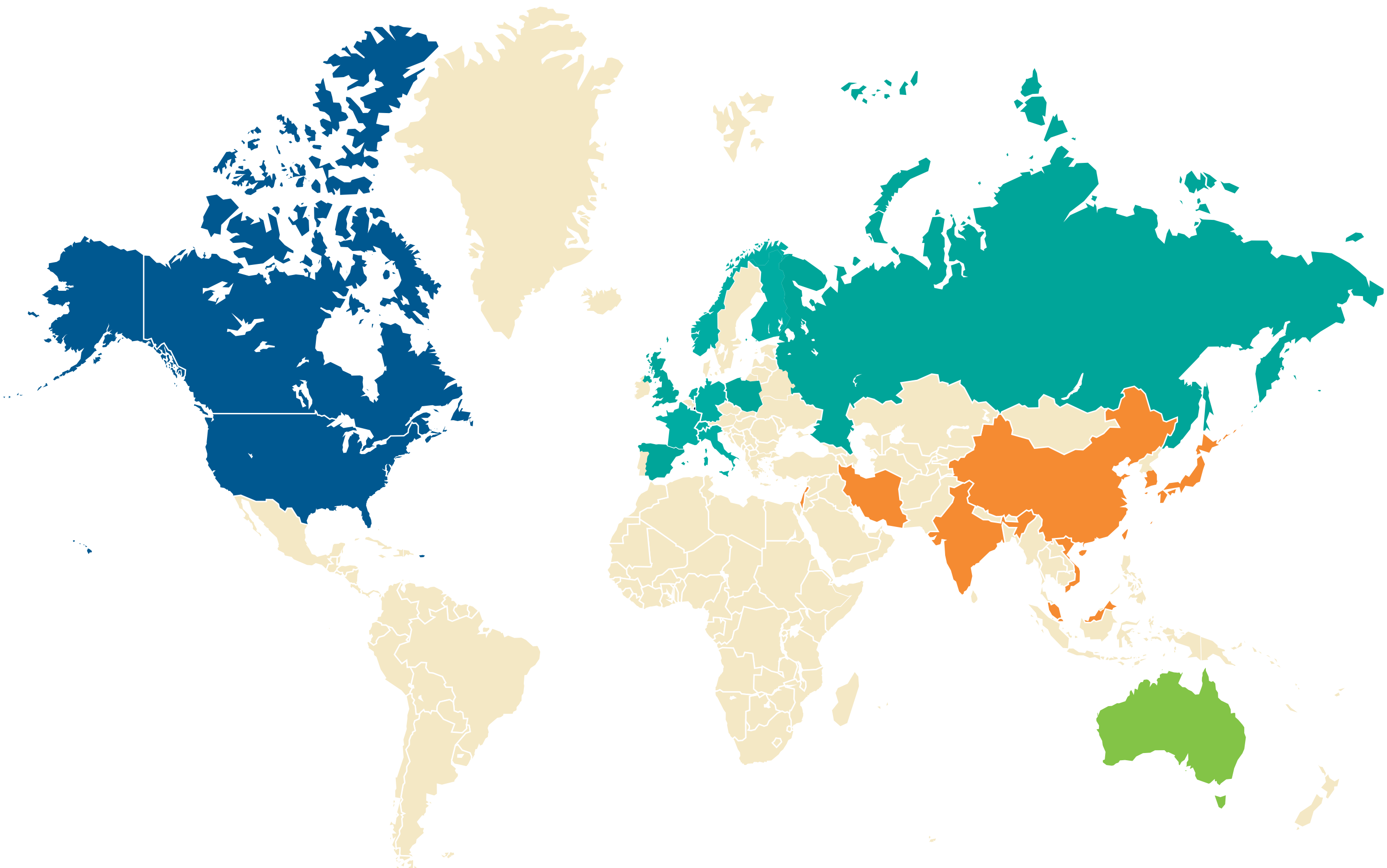
Technical research additional content

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



North America

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

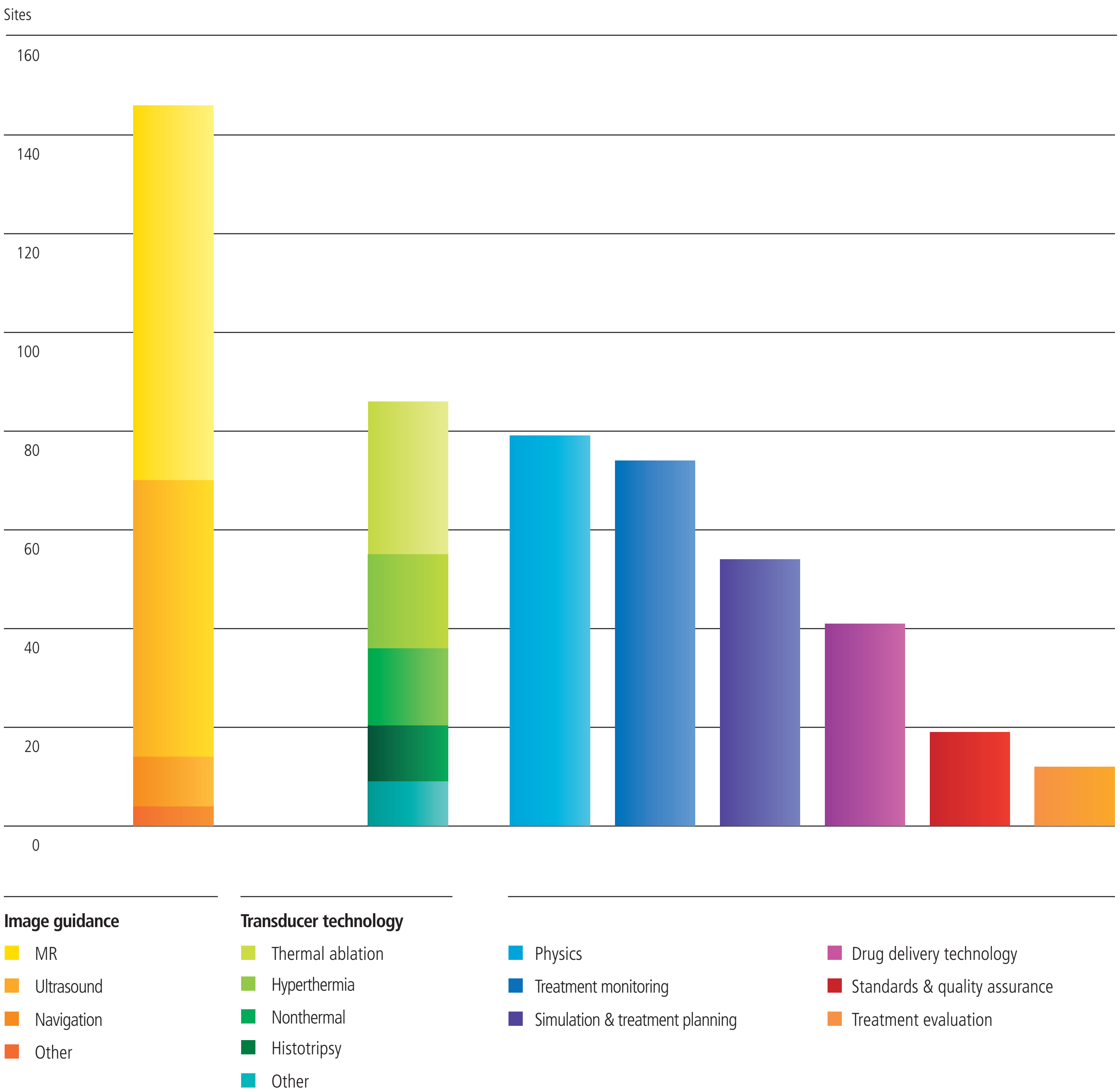
Technical Research Sites*

	Sites				Totals
	North America	Europe	Asia	Oceania	
Image guidance					**146**
MR	29	28	19	–	
Ultrasound	31	16	9	–	
Navigation	1	7	2	–	
Other	1	1	2	–	
Transducer technology					**86**
Thermal ablation	11	13	7	–	
Hyperthermia	8	8	3	–	
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 Types*



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

Mechanisms of Action Research Sites by Region*

177 MOA research sites worldwide

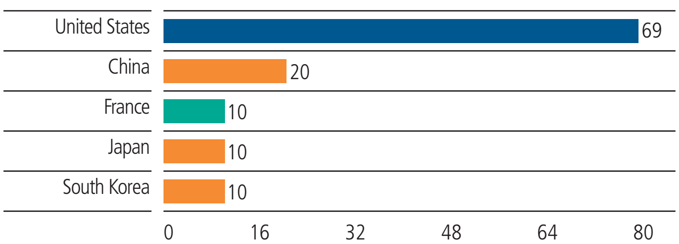
North America	Europe	Asia	South America	Oceania	Africa
78	42	55	–	2	–

Annual growth by region from 2013–2021

North America	Europe	Asia	South America	Oceania	Africa
8%	10%	32%	–	15%	–

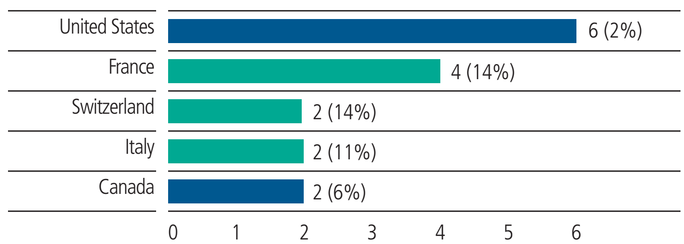
Top Countries for MOA Research

Number of sites



Top Countries with MOA Research Growth

Sites added, cumulative 2017 to 2021



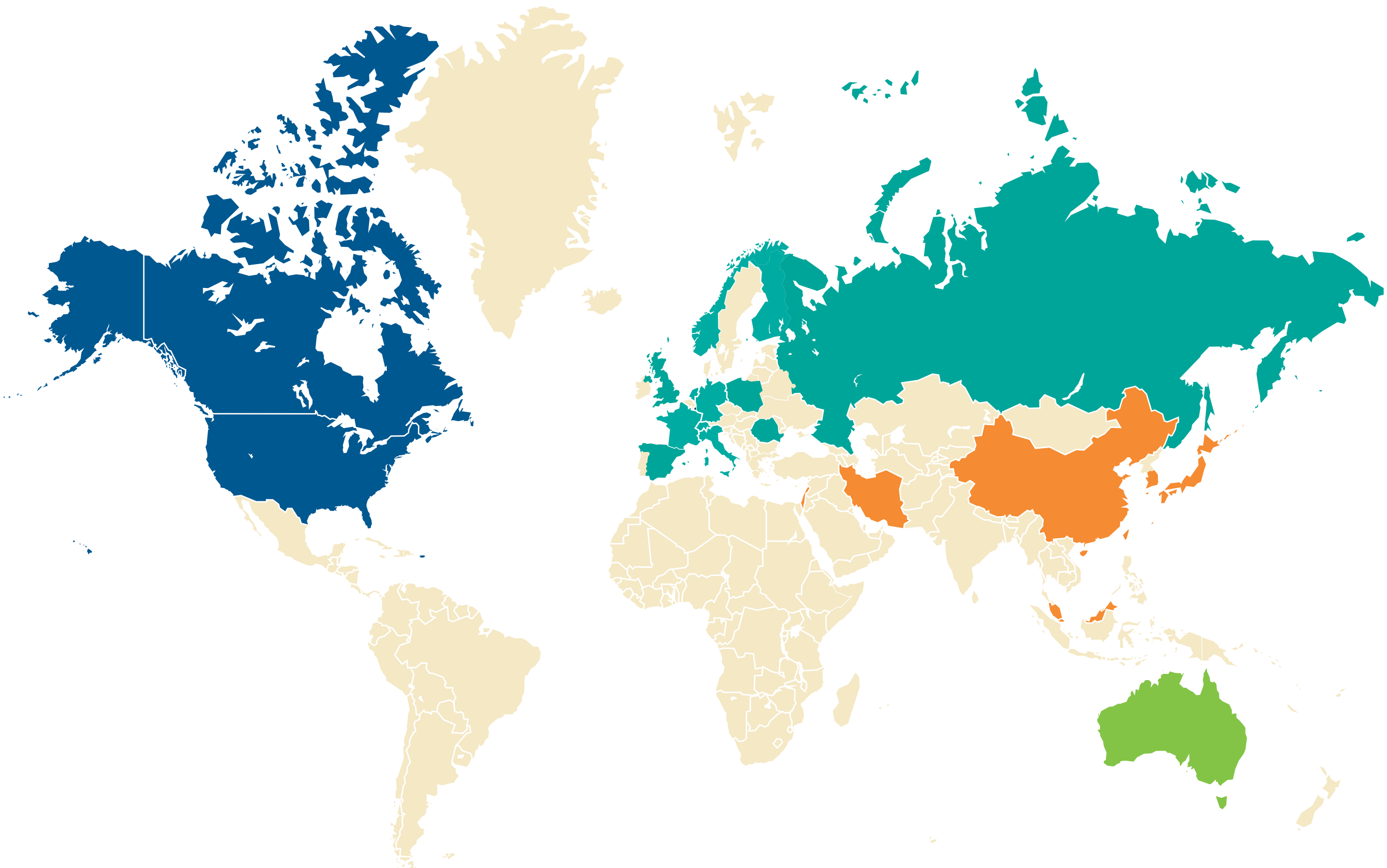
*Mechanisms of action research sites conduct basic science research to understand how focused ultrasound affects the body.

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



North America

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
Ultrasound Applications and Biological Effects

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

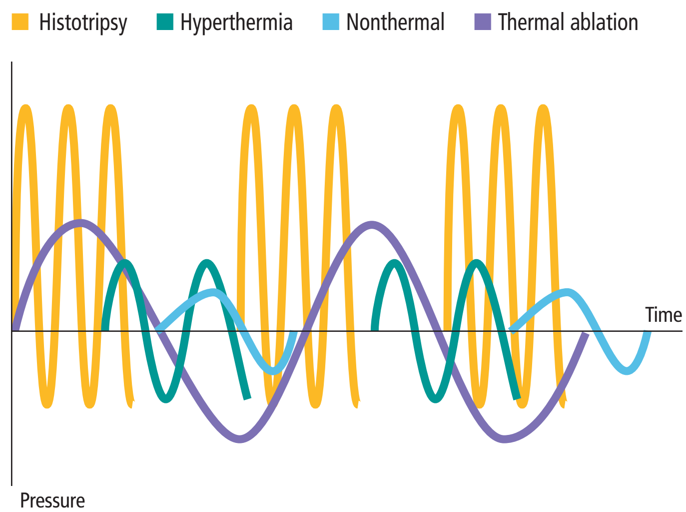
Focused ultrasound is a medical technology that provides a uniquely flexible treatment platform applicable to a wide range of diseases and conditions. It can produce treatments across the spectrum of thermal to mechanical effects, and these various treatments elicit a multitude of responses in biological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

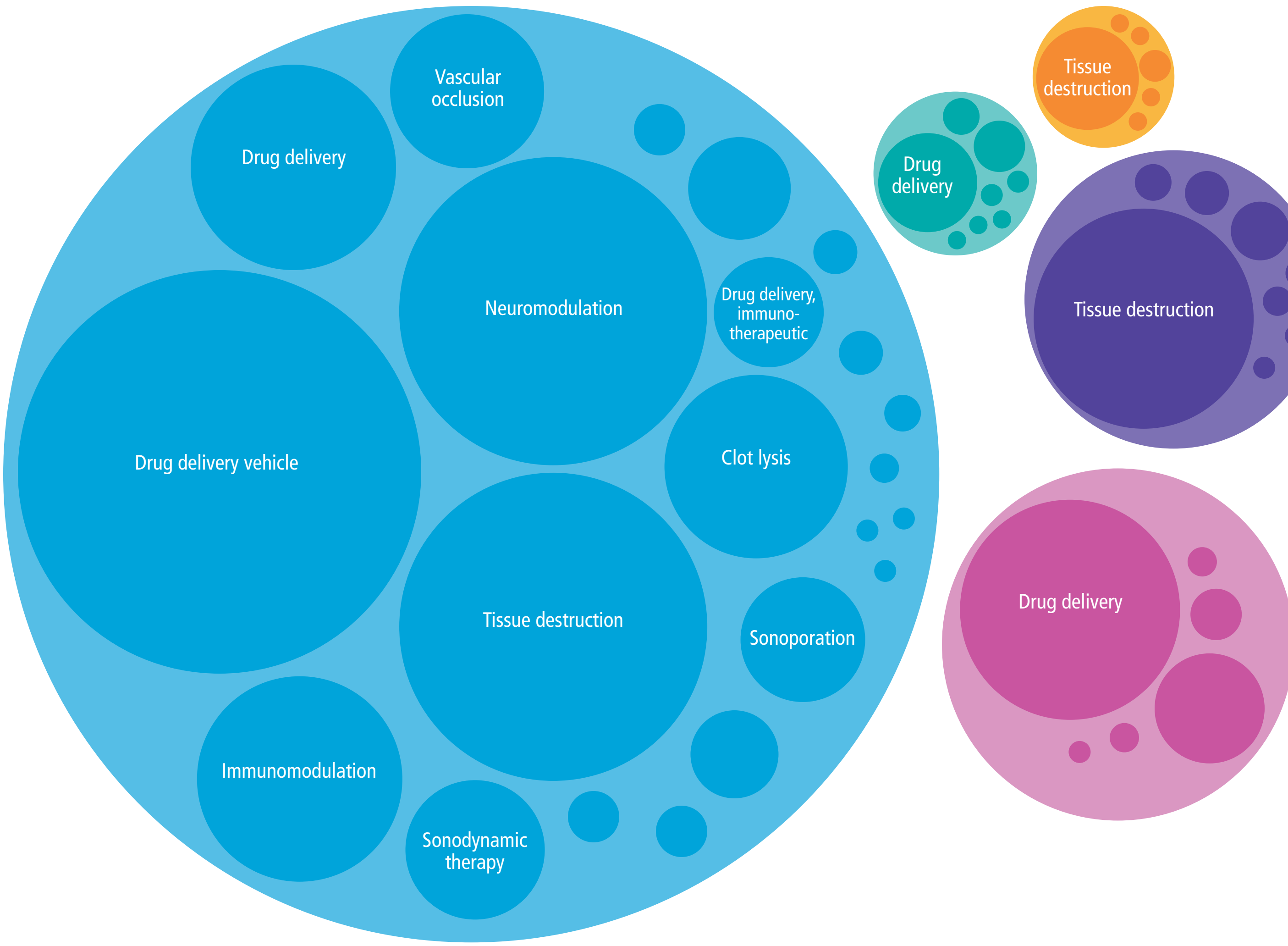
The effects induced by focused ultrasound can vary greatly depending on the ultrasound application and the type of tissue targeted. These biological effects are sometimes uniquely paired to a set of ultrasound parameters, as is the case with blood-brain barrier disruption, but others may be induced by 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.

What do sound waves look like?



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

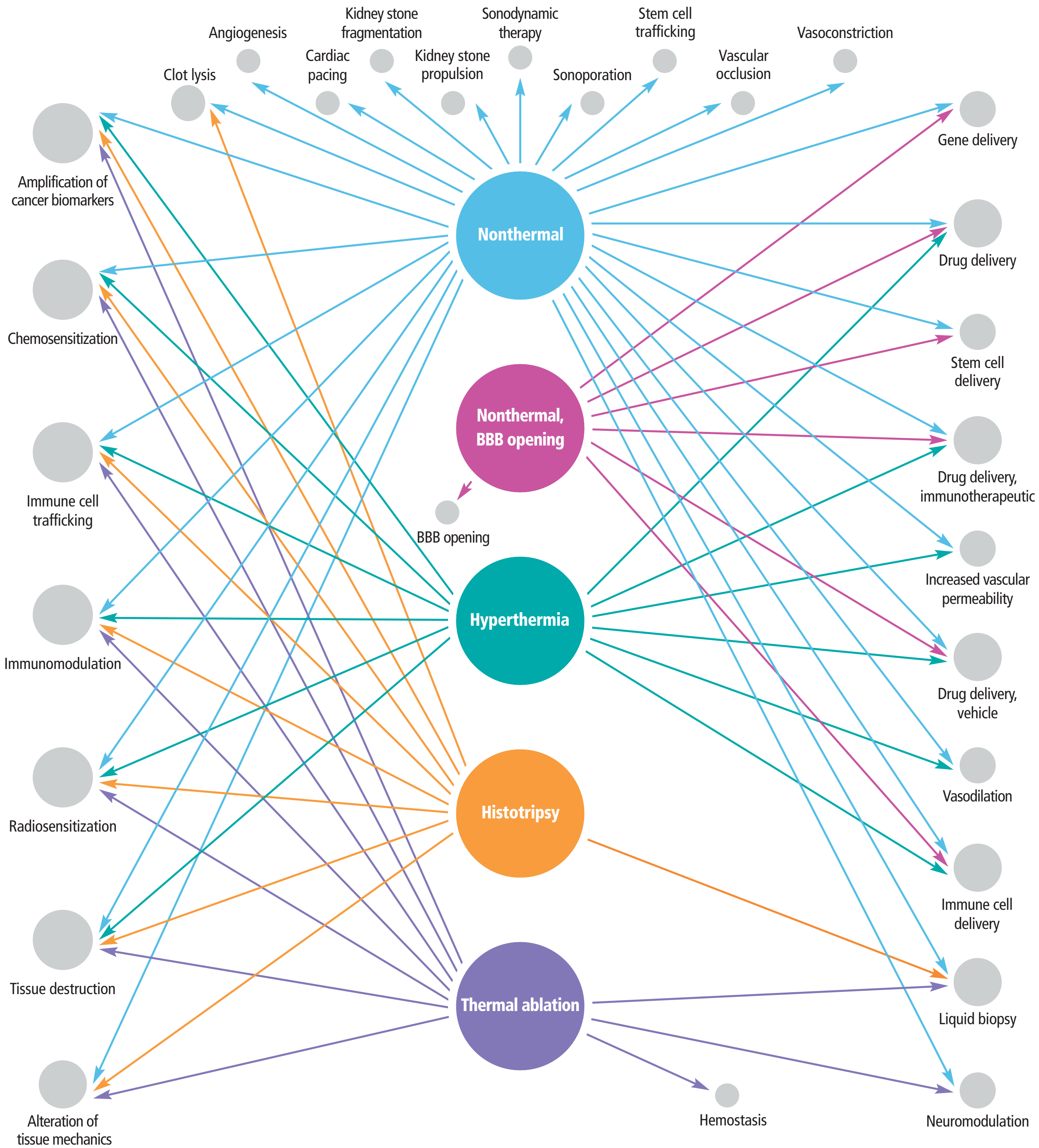
Thermal ablation | 92 sites
- Amplification of cancer biomarkers
- Chemosensitization
- Hemostasis
- Immune cell trafficking
- Immunomodulation
- Neuromodulation
- Radiosensitization
- Tissue destruction

Ultrasound Applications and Biological Effects*
Table

HISTOTRIPSY **9** **biological effects**	HYPERTHERMIA **12** **biological effects**	NONTHERMAL **27** **biological effects**	NONTHERMAL, BBB OPENING **7** **biological effects**	THERMAL ABLATION **10** **biological effects**
Alteration of tissue mechanics Amplification of cancer biomarkers Chemosensitization Clot lysis Immune cell trafficking Immunomodulation Liquid biopsy Radiosensitization Tissue destruction	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	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	BBB opening Drug delivery Drug delivery, immunotherapeutic Drug delivery, vehicle Gene delivery Immune cell delivery Stem cell delivery	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**

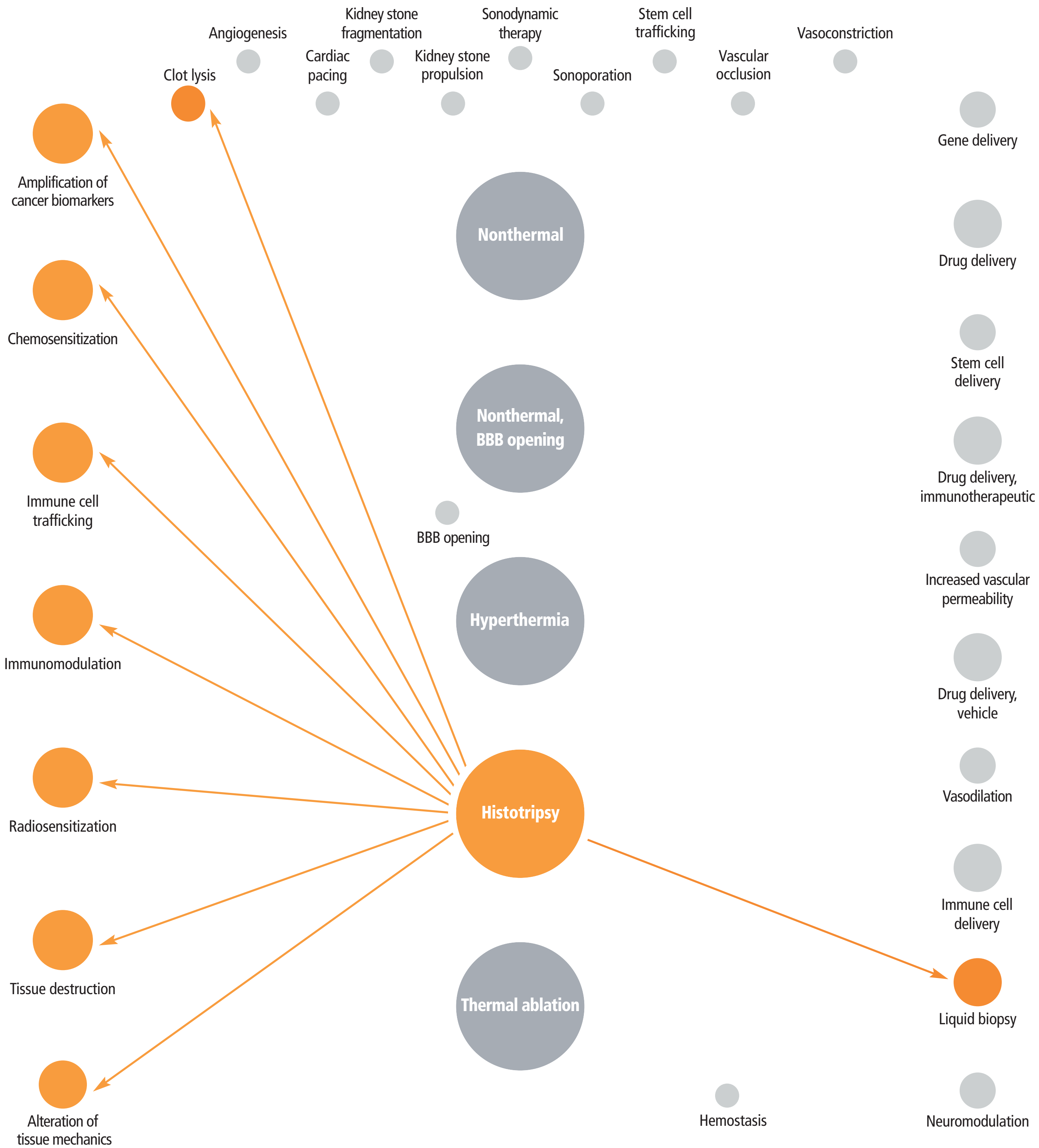
Drug delivery spans three different ultrasound applications—hyperthermia, nonthermal, and nonthermal BBB opening—for a total of 180 sites worldwide working on focused ultrasound-related drug delivery.

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

Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
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

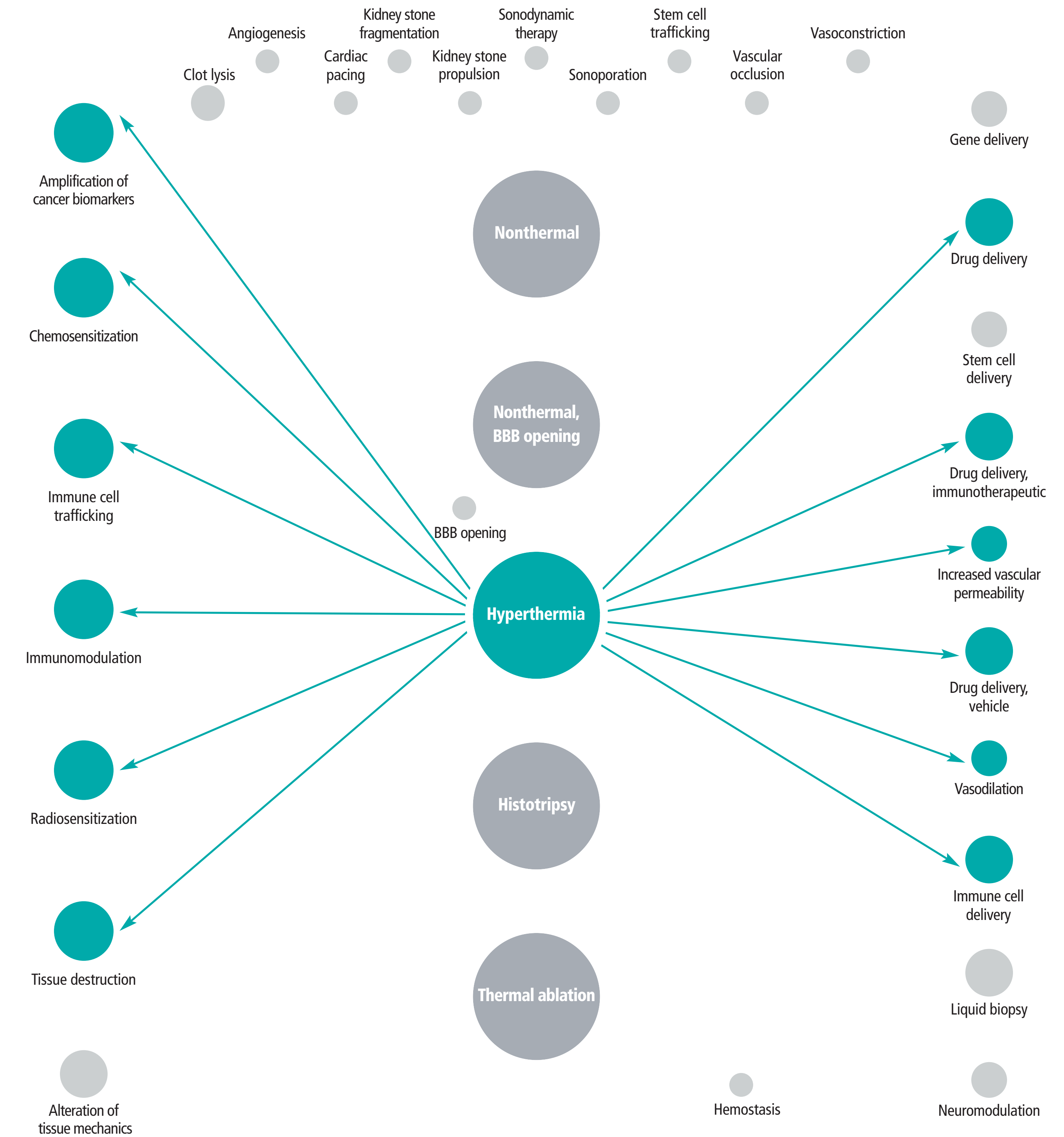
Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
Histotripsy | Tissue destruction continued				
Prostate cancer	1	–	–	**1**
Root canal endodontia	–	1	–	**1**
Rotator cuff injury	1	–	–	**1**
Soft tissue cancer	1	–	–	**1**
Stroke, intracerebral hemorrhage	1	–	–	**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.

Page intentionally left blank

NEW

Ultrasound Applications and Biological Effects
Graphic—Hyperthermia



Hyperthermia—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
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

Hyperthermia—Number of Sites for Biological Effects by Indications continued

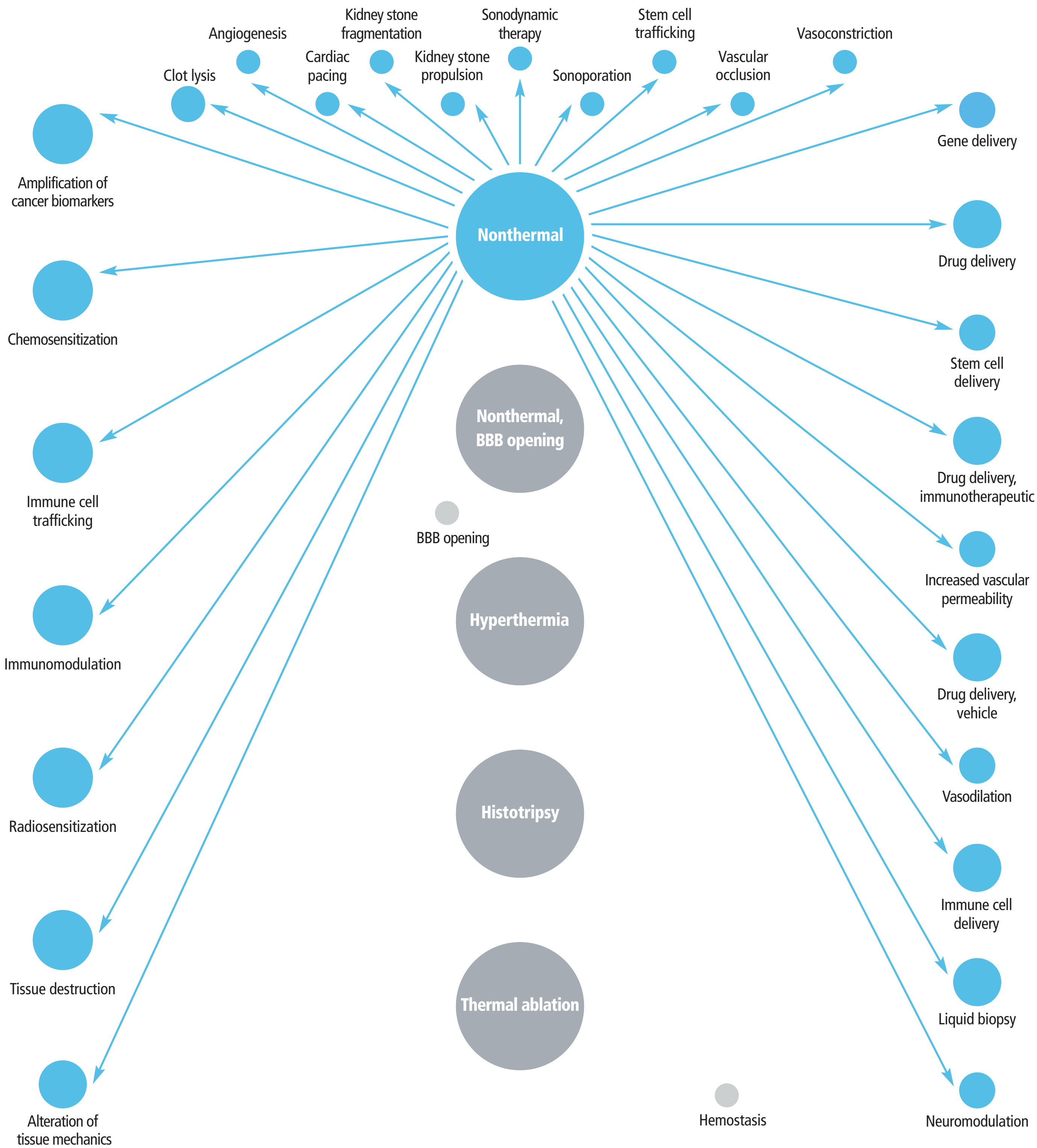
Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
Hyperthermia | Tissue destruction				
Benign prostatic hyperplasia	–	1	–	**1**
Brain tumors, general	1	–	–	**1**
Breast tumors, benign	–	1	–	**1**
Desmoid tumors	–	–	1	**1**
Endometriosis	–	1	–	**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**

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.

Page intentionally left blank

NEW

Ultrasound Applications and Biological Effects
Graphic—Nonthermal



Nonthermal—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
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

Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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**

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

Nontherm al—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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**

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.

Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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.

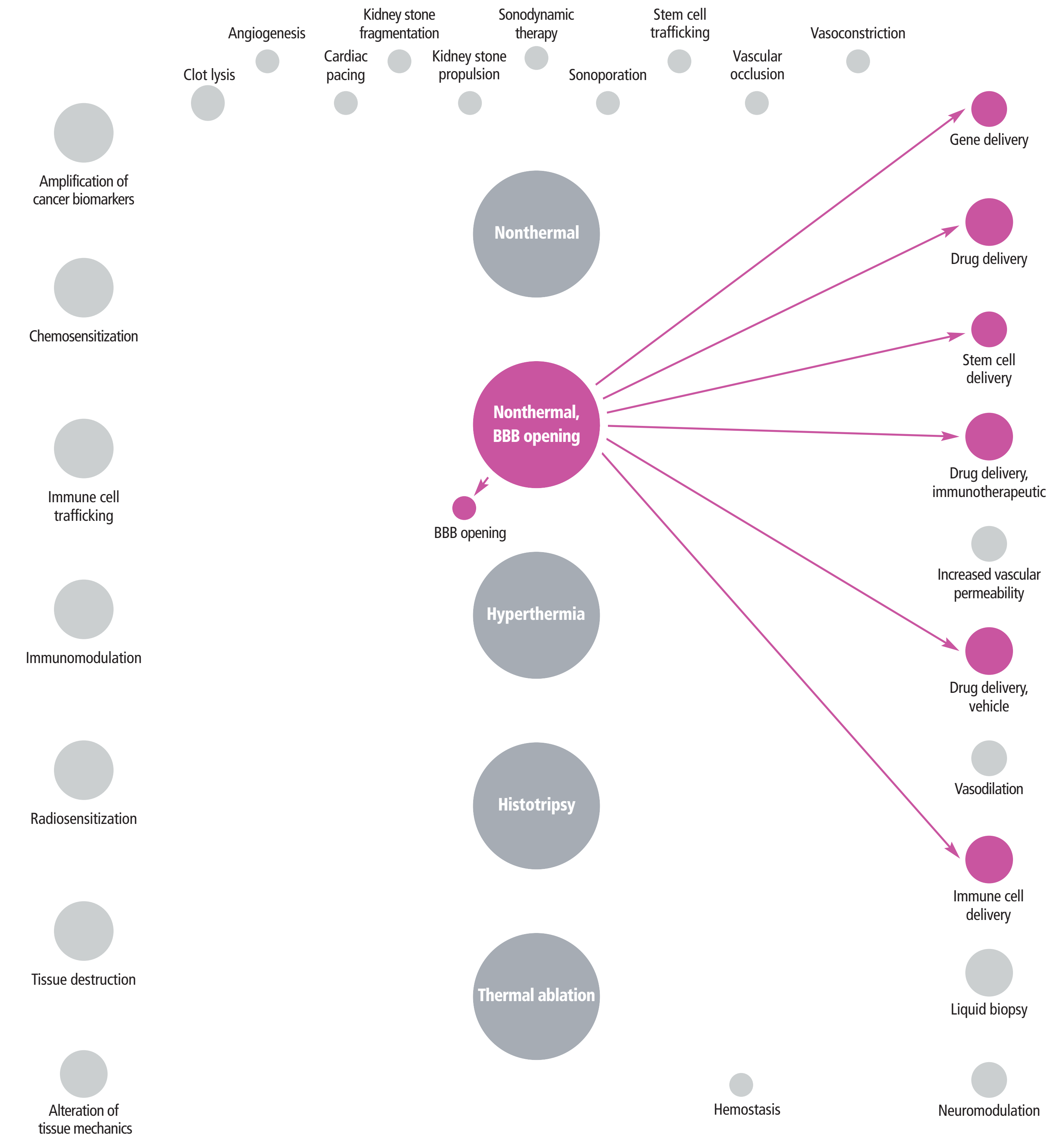
Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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**

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.

NEW

Ultrasound Applications and Biological Effects
Graphic—Nonthermal, BBB opening



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

Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
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**

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.

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

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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**

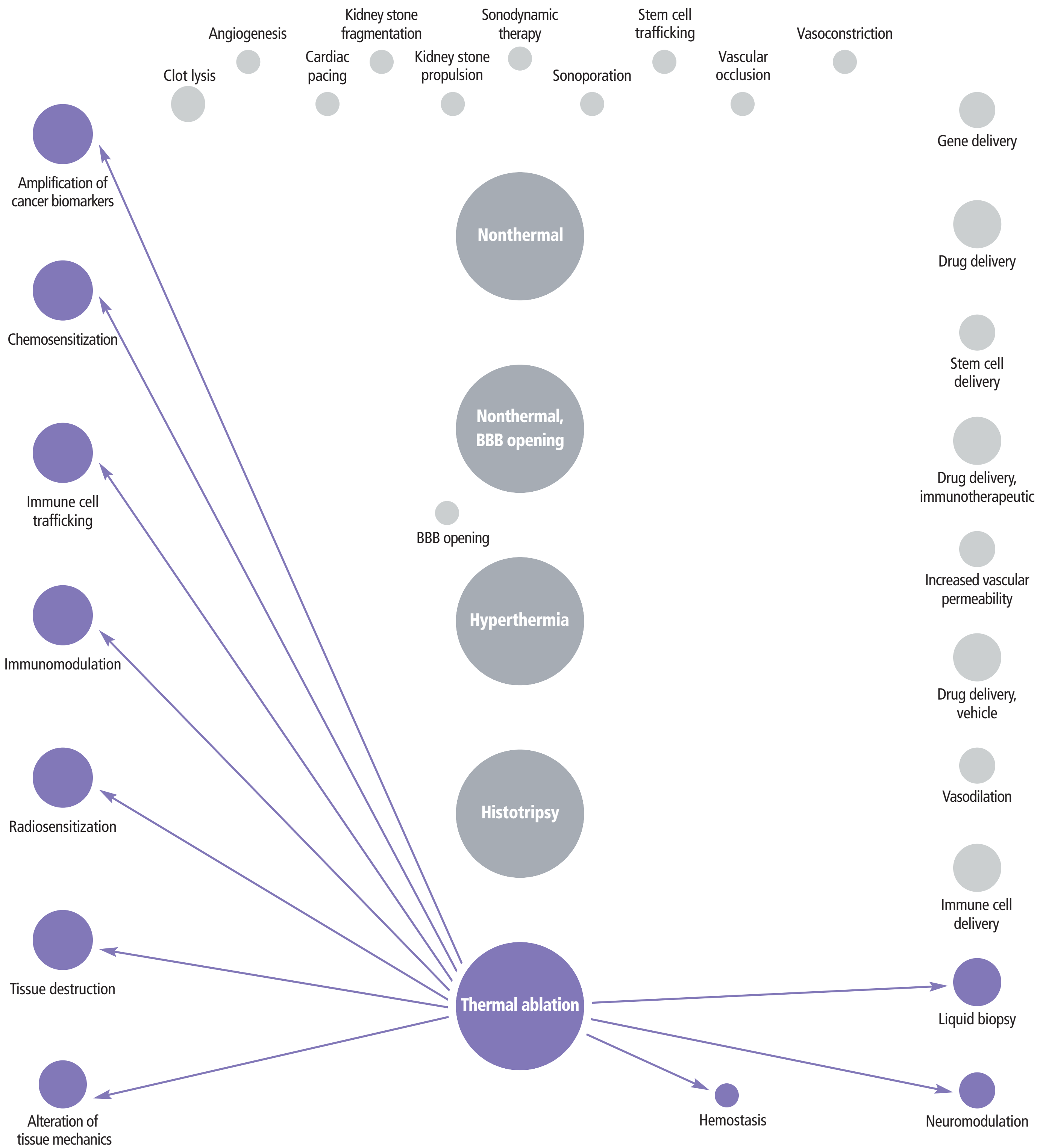
1 A site may use the same mechanism of action to treat or research the same indication across multiple stages. Because of this, the totals may not equal the sum of the three preceding columns.

Page intentionally left blank

NEW

Ultrasound Applications and Biological Effects

Graphic—Thermal ablation



Thermal ablation—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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.

Ultrasound application | Biological effects	Stages			Total[1]
	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**

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.

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

Ultrasound application | Biological effects	Stages			Total[1]
	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**

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

Ultrasound application | Biological effects	Stages: Preclinical	Stages: Clinical	Stages: Commercial	Total[1]
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**

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.

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

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
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.

NEW

Mechanisms of Action by Indication and Stage—Body Systems

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Cardiovascular					
Cardiac					
Atrial fibrillation		✪ Tissue destruction (Thermal ablation)			
Cardiac hypertrophy	▲ Drug delivery, vehicle (Nonthermal)				
Cardiac pacing	▲ Cardiac pacing (Nonthermal)				
Fetal heart anomalies	■ Tissue destruction (Histotripsy)				
Heart valve calcifications		■ Alteration of tissue mechanics (Histotripsy)			
Mitral regurgitation	■ Tissue destruction (Histotripsy)				
Ventricular tachycardia	✪ Tissue destruction (Thermal ablation)				
Peripheral					
Arteriovenous malformations	▲ Tissue destruction (Nonthermal)	▲ Vascular occlusion (Nonthermal)	✪ Tissue destruction (Thermal ablation)[1]		
Atherosclerosis	▲ Drug delivery (Nonthermal); ▲ Sonodynamic therapy (Nonthermal); ▲ Sonoporation (Nonthermal); ▲ Stem cell delivery (Nonthermal)				
Deep vein thrombosis	■ Tissue destruction (Histotripsy); ▲ Clot lysis (Nonthermal); ▲ Drug delivery, vehicle (Nonthermal); ▲ Increased vascular permeability (Nonthermal); ▲ Sonodynamic therapy (Nonthermal)				
Hematoma	■ Tissue destruction (Histotripsy)				
Hemophilia	▲ Drug delivery (Nonthermal)				
Hypertension		✪ Tissue destruction (Thermal ablation)			
Peripheral artery disease	▲ Drug delivery, vehicle (Nonthermal)		✪ Tissue destruction (Thermal ablation)[1]		
Twin-twin transfusion syndrome	▲ Vasodilation (Nonthermal); ✪ Tissue destruction (Thermal ablation)	✪ Hemostasis (Thermal ablation)			
Varicose veins	✪ Hemostasis (Thermal ablation)		✪ Tissue destruction (Thermal ablation)	✪ Tissue destruction (Thermal ablation)	

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Endocrine disorders					
Diabetes	▲				
Graves' disease		✪			
Thyroid cancer	■				
Thyroid nodules			✪	✪	
Gastrointestinal					
Biliary tract cancer		▲			
Colorectal tumors		▲ ✪			
Esophageal tumors		✪			
Gastric tumors	✪	✪			
Inflammatory bowel disease	▲				
Liver metastases	■ ▲	▲ ▲	✪	✪	
Liver tumors	■ ■ ● ● ▲	■ ▲ ▲	✪	✪	
Pancreatic tumors	▲		✪	✪	
Pancreatic tumors, malignant	■ ● ▲ ▲ ▲ ▲	■ ● ● ▲ ▲ ▲ ✪	✪	✪	
Root canal endodontia		■			

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Miscellaneous					
Actinic keratosis		Thermal ablation: Tissue destruction			
Basal cell carcinoma		Thermal ablation: Tissue destruction			
Dercum's disease		Thermal ablation: Tissue destruction			
Head & neck tumors	Hyperthermia: Drug delivery; Nonthermal: Sonoporation; Nonthermal: Tissue destruction	Hyperthermia: Radiosensitization; Nonthermal: Radiosensitization; Thermal ablation: Tissue destruction			
Heterotopic ossification	Histotripsy: Tissue destruction				
Hypersplenism		Thermal ablation: Tissue destruction			
Infection	Histotripsy: Tissue destruction; Nonthermal - BBB opening: Drug delivery; Thermal ablation: Tissue destruction				
Kaposi's sarcoma		Thermal ablation: Tissue destruction			
Lipoma		Thermal ablation: Tissue destruction			
Melanoma	Histotripsy: Immunomodulation	Thermal ablation: Immunomodulation			
Multiple tumors[2]	Histotripsy: Tissue destruction; Hyperthermia: Drug delivery; Hyperthermia: Immunomodulation; Nonthermal: Drug delivery, immunotherapeutic	Hyperthermia: Chemosensitization; Thermal ablation: Immunomodulation; Thermal ablation: Tissue destruction			
Niemann-Pick disease	Nonthermal - BBB opening: Gene delivery				
Sinonasal disease	Thermal ablation: Tissue destruction				
Wound healing	Histotripsy: Alteration of tissue mechanics; Hyperthermia: Drug delivery; Nonthermal: Drug delivery				

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Indications by body systems	Stages: Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Musculoskeletal					
Arthritis, facetogenic	▲		✪	✪	
Arthritis, knee		✪			
Arthritis, sacroiliac		✪			
Bone cancer			✪	✪	
Bone metastases	●	■ ✪	✪	✪	✪
Bone tumors, benign			✪	✪	
Desmoid tumors			●[1] ✪	✪	
Muscle atrophy	▲ ▲				
Osteoid osteoma			✪	✪	✪
Osteomyelitis	✪				
Osteopenia	●				
Plantar fasciitis		✪			
Rotator cuff injury	■				
Sacral chordoma		✪			
Soft tissue cancer	■ ■ ● ▲	● ● ✪	●[1] ✪	✪	
Soft tissue tumors, benign	●		✪	✪	
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
- ▲ 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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

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		●	✪	✪	✪
Parkinson's disease, dyskinesia	✦		✪	✪	✪
Parkinson's disease, tremor	▲ ✦		✪	✪	✪
Tremor, orthostatic		✪			
Neurodegenerative					
Alzheimer's disease	▲ ▲ ✦ ✦ ✦	▲ ✦ ✦	▲[1]		
Amyotrophic lateral sclerosis	✦	✦			
Dementia	✦	✦			
Huntington's disease	✦				
Multiple sclerosis		✪			
Parkinson's disease, underlying cause	▲ ▲ ▲ ▲ ✦ ✪	✦			
Rett syndrome	✦				

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Other					
Hydrocephalus	▲				
Neuromyelitis optica	✦				
Pain					
Cancer pain	▲	✪			
Headache	▲				
Neuropathic pain	▲ ▲	▲ ✪	✪	✪	
Neuropathy	▲	▲	✪[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

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

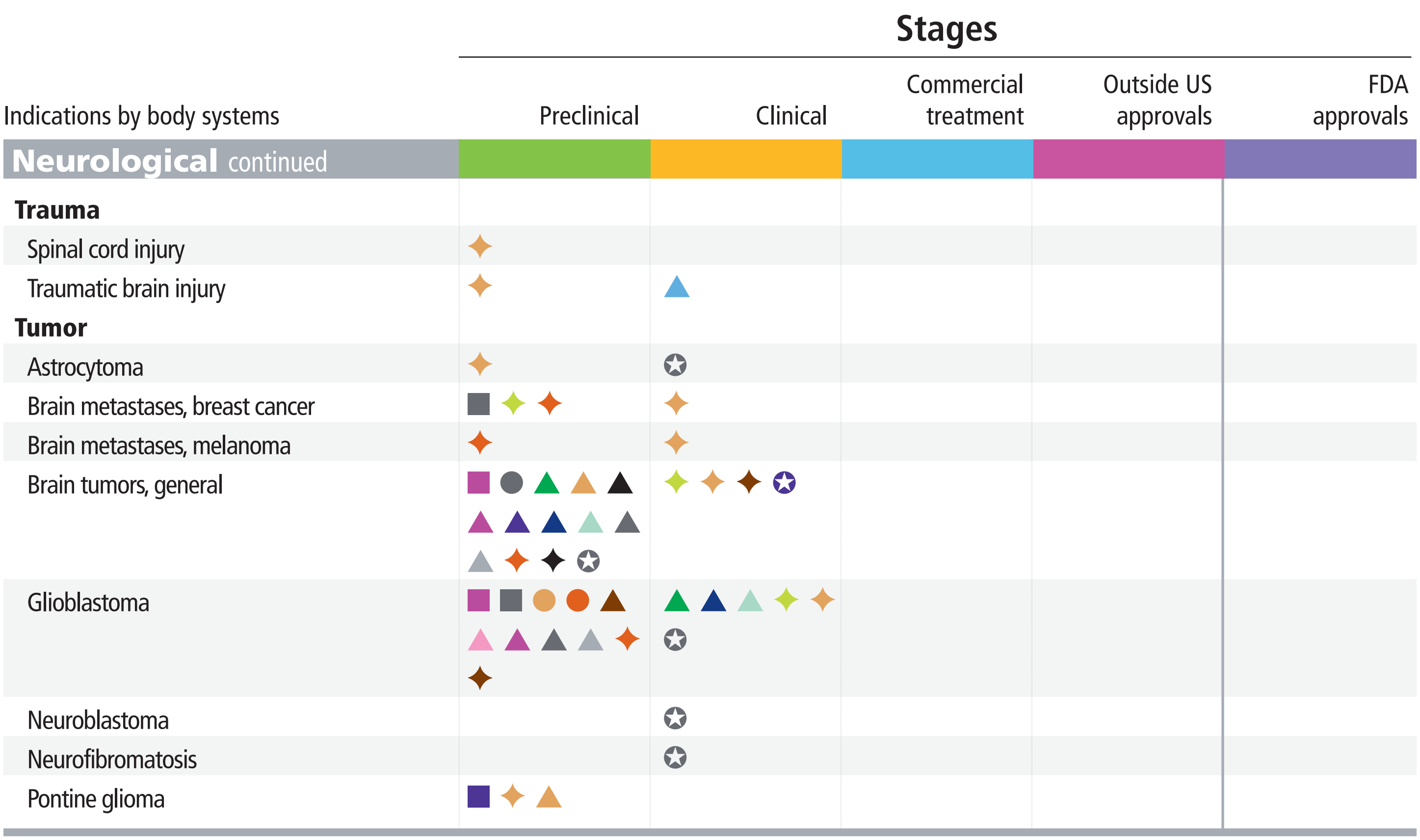
Nonthermal
- ▲ Alteration of tissue mechanics
- ▲ Amplification of cancer biomarkers
- ▲ Angiogenesis
- ▲ Cardiac pacing
- ▲ Clot lysis
- ▲ Drug delivery
- ▲ Drug delivery, immunotherapeutic
- ▲ Drug delivery, vehicle
- ▲ Gene delivery
- ▲ Immune cell trafficking
- ▲ Immunomodulation
- ▲ Increased vascular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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued



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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Indications by body systems	Stages: Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Vascular					
Cavernomas	▲				
Stroke, intracerebral hemorrhage	■ ▲ ▲ ▲ ✦				
Stroke, thromboembolic	▲ ▲ ▲ ▲ ✦	▲			
Ophthalmological					
Glaucoma		▲	✪	✪	
Macular degeneration	▲ ▲				
Presbyopia	✪				
Retinal injury	▲				
Pulmonary					
Lung cancer	● ✪	✪			
Lung metastases	✪				
Rhinitis			✪		
Tuberculosis	✪				

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Indications by body systems	Stages: 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] ✪	✪	✪
Urinary tract infection	▲				

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

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

NEW

Mechanisms of Action by Indication and Stage—Body Systems continued

Indications by body systems	Stages: Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Women's health					
Breast tumors, benign		● Hyperthermia – Tissue destruction	✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	
Breast tumors, malignant	● Hyperthermia – Drug delivery, immunotherapeutic; ● Hyperthermia – Vasodilation; ▲ Nonthermal – Drug delivery, vehicle; ▲ Nonthermal – Gene delivery; ▲ Nonthermal – Immunomodulation; ▲ Nonthermal – Increased vascular permeability; ▲ Nonthermal – Tissue destruction; ✦ Nonthermal - BBB opening – BBB opening; ✪ Thermal ablation – Immunomodulation	● Hyperthermia – Drug delivery; ● Hyperthermia – Radiosensitization; ▲ Nonthermal – Drug delivery; ▲ Nonthermal – Radiosensitization	✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	
Cervical tumors		● Hyperthermia – Radiosensitization; ✪ Thermal ablation – Immunomodulation; ✪ Thermal ablation – Tissue destruction			
Cervicitis			✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	
Ectopic pregnancy		✪ Thermal ablation – Tissue destruction			
Endometrial tumors			✪ Thermal ablation – Tissue destruction[1]		
Endometriosis		● Hyperthermia – Tissue destruction	✪ Thermal ablation – Tissue destruction[1]		
Endometriosis, colorectal		✪ Thermal ablation – Tissue destruction			
Lichen sclerosis			✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	
Ovarian tumors		✪ Thermal ablation – Immunomodulation; ✪ Thermal ablation – Tissue destruction			
Retained placenta		✪ Thermal ablation – Tissue destruction			
Urinary incontinence, stress		✪ Thermal ablation – Alteration of tissue mechanics			
Uterine adenomyosis		● Hyperthermia – Tissue destruction	✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	
Uterine fibroids	■ Histotripsy – Tissue destruction; ▲ Nonthermal – Alteration of tissue mechanics		✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction	✪ Thermal ablation – Tissue destruction
Vaginal tumors		✪ Thermal ablation – Tissue destruction			

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

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

NEW

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	✪				

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

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

NEW

Mechanisms of Action by Indication and Stage—Pain

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Cardiovascular					
Peripheral					
Varicose veins	✪		✪	✪	
Gastrointestinal					
Pancreatic tumors	▲		✪	✪	
Pancreatic tumors, malignant	■ ● ▲ ▲ ▲ ✪	■ ● ● ▲ ▲ ▲ ✪	✪	✪	
Miscellaneous					
Dercum's disease		✪			
Musculoskeletal					
Arthritis, facetogenic	▲		✪	✪	
Arthritis, knee		✪			
Arthritis, sacroiliac		✪			
Bone cancer			✪	✪	
Bone metastases	●	■ ✪	✪	✪	✪
Bone tumors, benign			✪	✪	
Desmoid tumors			●[1] ✪	✪	
Osteoid osteoma			✪	✪	✪

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

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

NEW

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	✪ (Thermal ablation: Tissue destruction)				
Plantar fasciitis		✪ (Thermal ablation: Tissue destruction)			
Rotator cuff injury	■ (Histotripsy: Tissue destruction)				
Neurological					
Pain					
Cancer pain	▲ (Nonthermal: Neuromodulation)	✪ (Thermal ablation: Tissue destruction)			
Headache	▲ (Nonthermal: Neuromodulation)				
Neuropathic pain	▲ (Nonthermal: Alteration of tissue mechanics) ▲ (Nonthermal: Drug delivery, vehicle)	▲ (Nonthermal: Neuromodulation) ✪ (Thermal ablation: Neuromodulation)	✪ (Thermal ablation: Tissue destruction)		
Neuropathy	▲ (Nonthermal: Vasodilation)	▲ (Nonthermal: Neuromodulation)	✪ (Thermal ablation: Tissue destruction) [1]		
Painful amputation neuromas		✪ (Thermal ablation: Tissue destruction)			
Trigeminal neuralgia			✪ (Thermal ablation: Tissue destruction) [1]		

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

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

NEW

Mechanisms of Action by Indication and Stage—Pediatrics

Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Miscellaneous					
Multiple tumors[2]	■ ● ● ▲	● ✪ ✪			
Niemann-Pick disease	✦				
Musculoskeletal					
Bone metastases	●	■ ✪	✪	✪	✪
Desmoid tumors			●[1] ✪	✪	
Osteoid osteoma			✪	✪	✪
Sacral chordoma		✪			
Soft tissue cancer	■ ■ ● ▲	● ● ✪	●[1] ✪	✪	
Soft tissue tumors, benign	●		✪	✪	
Neurological					
Movement disorder					
Epilepsy	■ ▲ ▲ ✦ ✦ ✦ ✪	▲	✪[1]		
Other					
Hydrocephalus	▲				
Psychiatric					
ADHD		▲			

1 Off-label treatment
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

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

NEW

Mechanisms of Action by Indication and Stage—Pediatrics continued

Indications by body systems	Stages: Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Neurological continued					
Tumor					
Astrocytoma	✦	✪			
Brain tumors, general	■ ● ▲ ▲ ▲ ▲ ▲ ▲ ▲ ▲ ▲ ✦ ✦ ✪	✦ ✦ ✦ ✪			
Neuroblastoma		✪			
Neurofibromatosis		✪			
Pontine glioma	■ ▲ ✦				

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

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

NEW

Mechanisms of Action by Indication and Stage—Oncology

Indications by body systems	Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Endocrine disorders					
Thyroid cancer	■				
Gastrointestinal					
Biliary tract cancer		▲			
Colorectal tumors		▲ ✪			
Esophageal tumors		✪			
Gastric tumors	✪	✪			
Liver metastases	■ ▲	▲ ▲	✪	✪	
Liver tumors	■ ■ ● ● ▲	■ ▲ ▲	✪	✪	
Pancreatic tumors	▲		✪	✪	
Pancreatic tumors, malignant	■ ● ▲ ▲ ▲ ▲	■ ● ● ▲ ▲ ▲ ✪	✪	✪	
Miscellaneous					
Basal cell carcinoma		✪			
Head & neck tumors	● ▲ ▲	● ▲ ✪			
Kaposi's sarcoma		✪			
Melanoma	■	✪			
Multiple tumors[2]	■ ● ● ▲	● ✪ ✪			

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

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

NEW

Mechanisms of Action by Indication and Stage—Oncology continued

Indications by body systems	Stages: Preclinical	Clinical	Commercial treatment	Outside US approvals	FDA approvals
Musculoskeletal					
Bone cancer			✪	✪	
Bone metastases	●	■ ✪	✪	✪	✪
Sacral chordoma		✪			
Soft tissue cancer	■ ■ ● ▲	● ● ✪	●[1] ✪	✪	
Neurological					
Pain					
Cancer pain	▲	✪			
Tumor					
Brain metastases, breast cancer	■ ✦ ✦	✦			
Brain metastases, melanoma	✦	✦			
Brain tumors, general	■ ● ▲ ▲ ▲ ▲ ▲ ▲ ▲ ▲ ▲ ✦ ✦ ✪	✦ ✦ ✦ ✪			
Glioblastoma	■ ■ ● ● ▲ ▲ ▲ ▲ ▲ ✦ ✦	▲ ▲ ▲ ✦ ✦ ✪			
Neuroblastoma		✪			
Neurofibromatosis		✪			
Pontine glioma	■ ▲ ✦				

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

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

NEW

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	■ ▲		✪	✪	
Prostate cancer	■ ▲ ▲	▲	●[1] ✪	✪	✪
Women's health					
Breast tumors, malignant	● ● ▲ ▲ ▲ ▲ ▲ ✦ ✪	● ● ▲ ▲	✪	✪	
Cervical tumors		● ✪ ✪			
Endometrial tumors			✪[1]		
Ovarian tumors		✪ ✪			
Vaginal tumors		✪			

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

Thermal ablation
- ✪ 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,[1] where standard treatments include surgery, radiotherapy, hormone therapy, chemotherapy, and targeted therapies, delivered alone or in combination.[2]

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, also know as FUS) ablation is an image-guided procedure, where imaging can be used for treatment planning, targeting, monitoring, and evaluating. The FUS 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 FUS 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 treat-and-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-guided[6] or MRI-guided FUS systems[7] 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 area.[12] 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, FUS 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. Ecancermedicalscience. 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

7 Merckel LG, Knuttel FM, Deckers R, van Dalen T, Schubert G, Peters NHGM, et al. First clinical experience with a dedicated MRI-guided high-intensity focused ultrasound system for breast cancer ablation. Eur Radiol [Internet]. 2016; 26(11):4037–46. Available from: http://dx.doi.org/10.1007/s00330-016-4222-9

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.

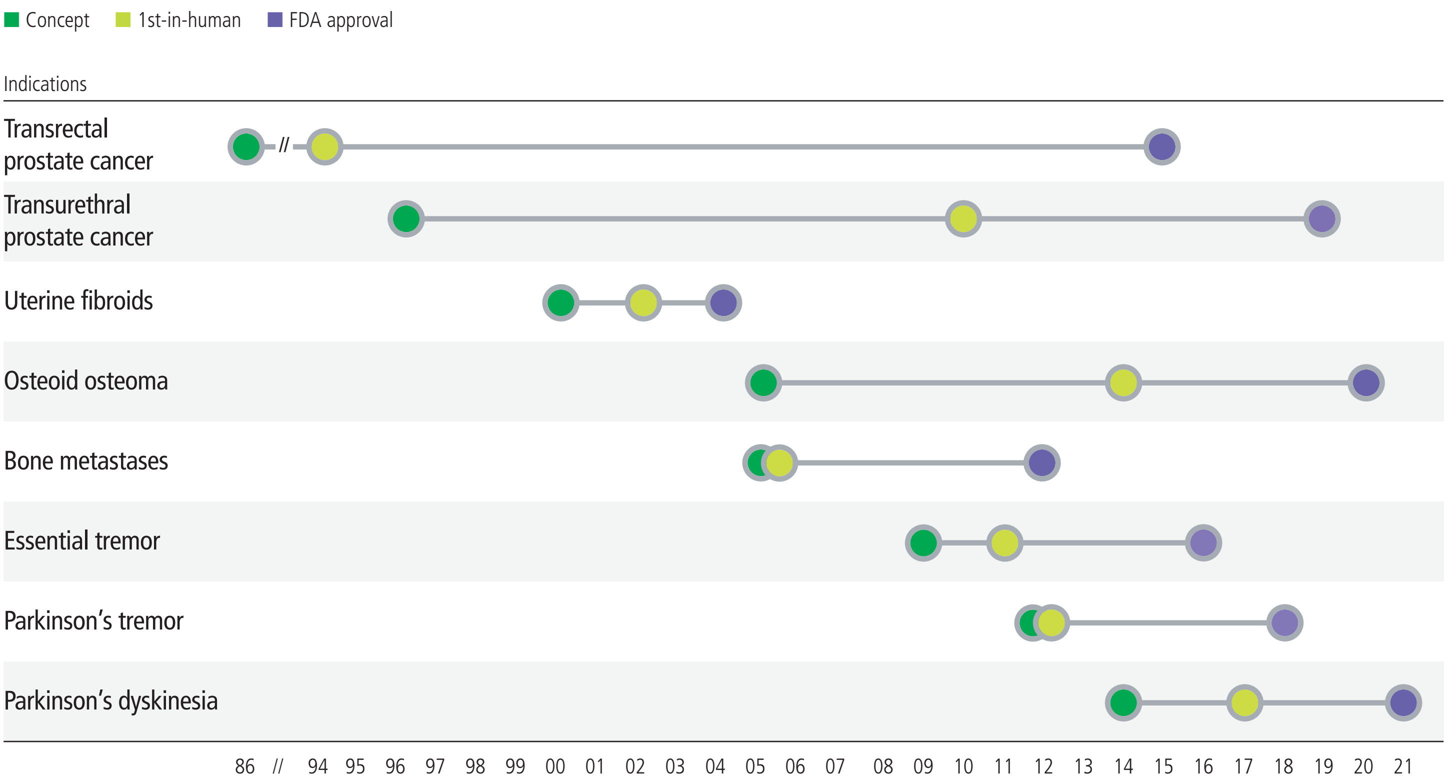
12 Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, et al. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. Breast Cancer Res Treat. 2005;92(1):51–60.

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.

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.

FDA Approved Indications Timeline



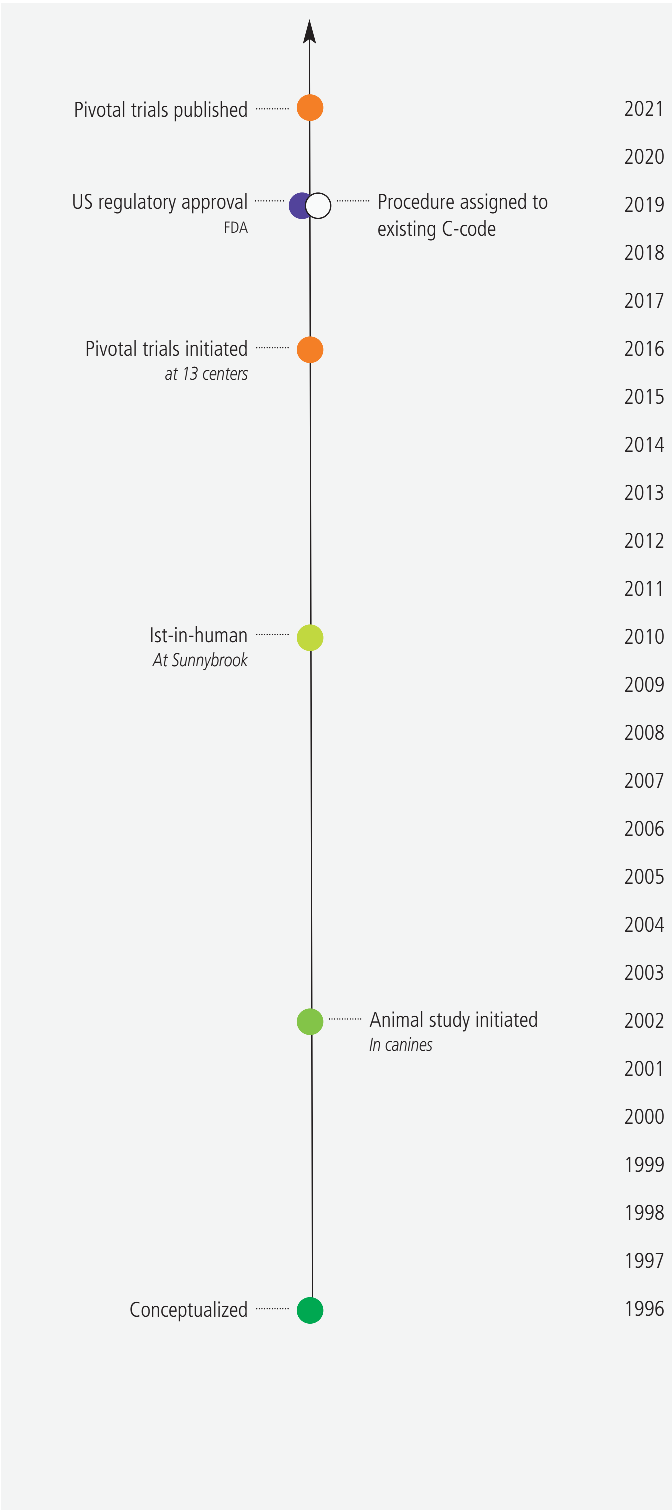
CASE STUDY

Indication Timeline—Transrectal Prostate Cancer

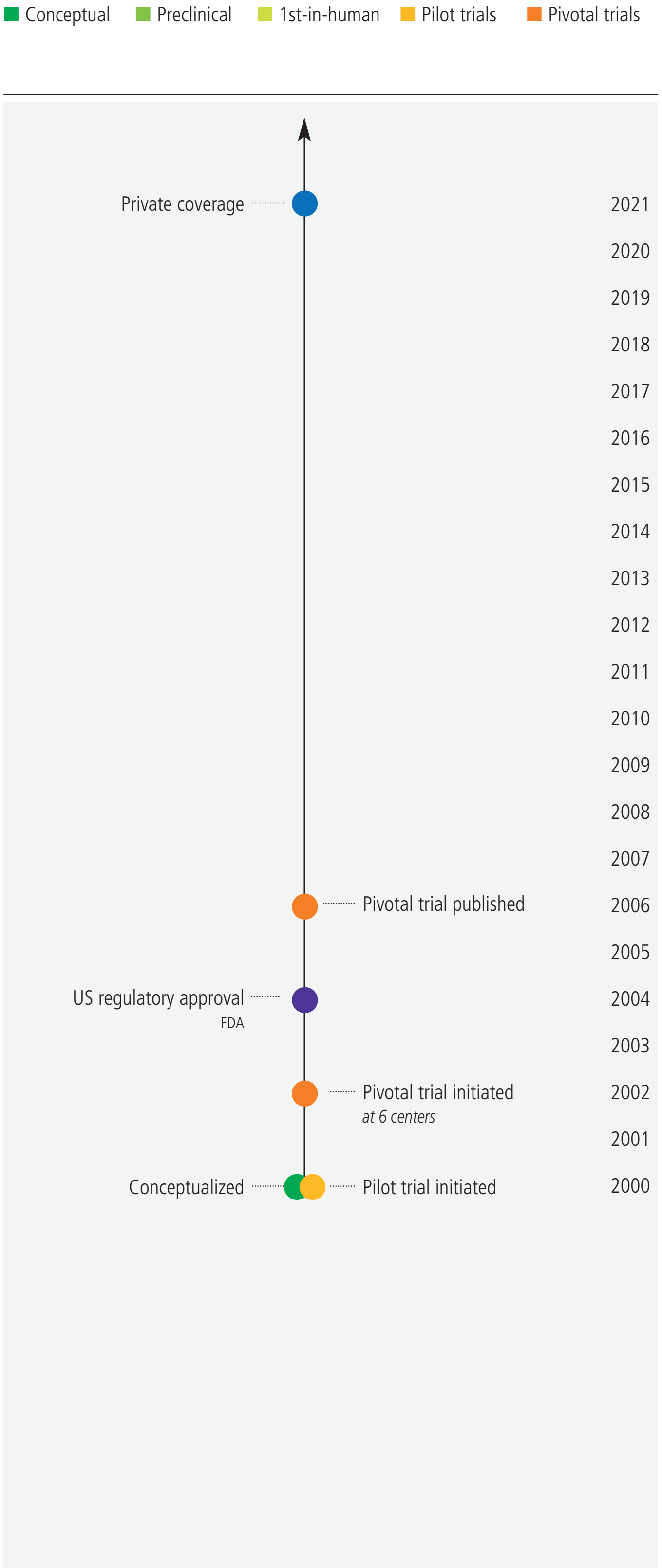
■ Conceptual ■ Preclinical ■ 1st-in-human ■ Pilot trials ■ Pivotal trials ■ FDA approval ■ US reimbursement

Indication Timeline—Transurethral Prostate Cancer

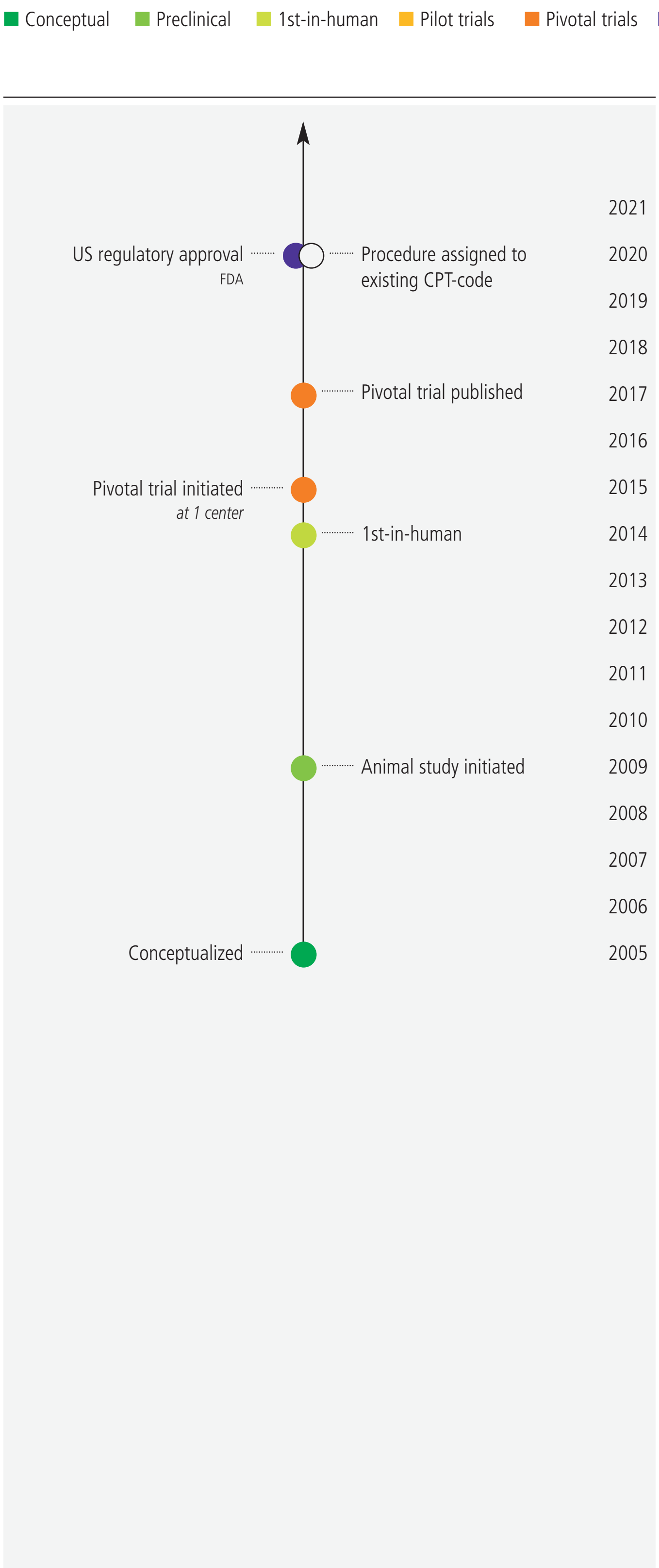
Conceptual · Preclinical · 1st-in-human · Pilot trials · Pivotal trials · FDA approval · US reimbursement



Indication Timeline—Uterine Fibroids



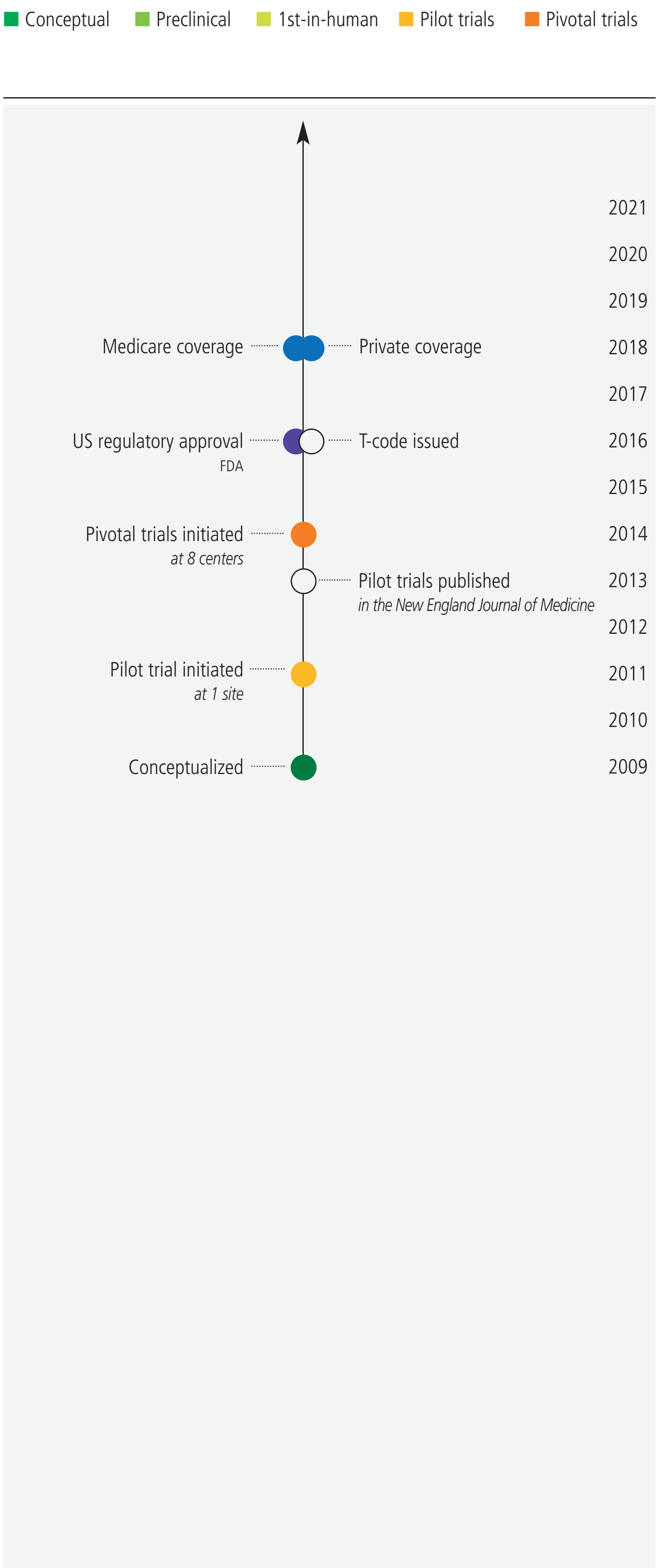
Indication Timeline—Osteoid Osteoma



Indication Timeline—Bone Metastases

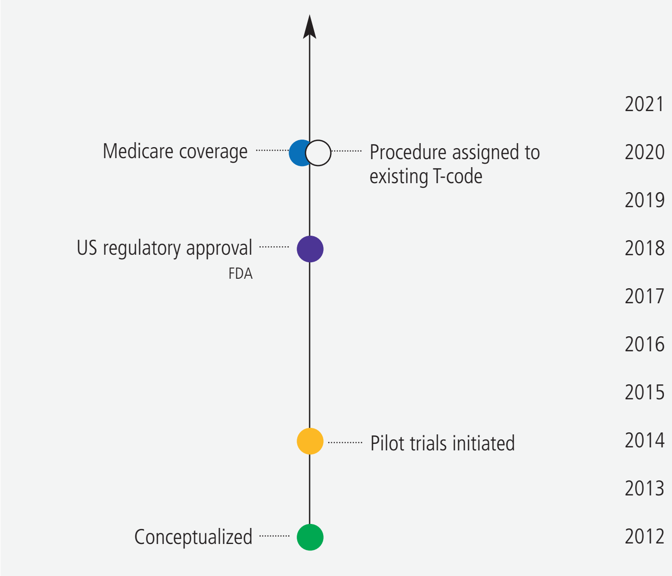
Conceptual · Preclinical · 1st-in-human · Pilot trials · Pivotal trials · FDA approval · US reimbursement

Indication Timeline—Essential Tremor



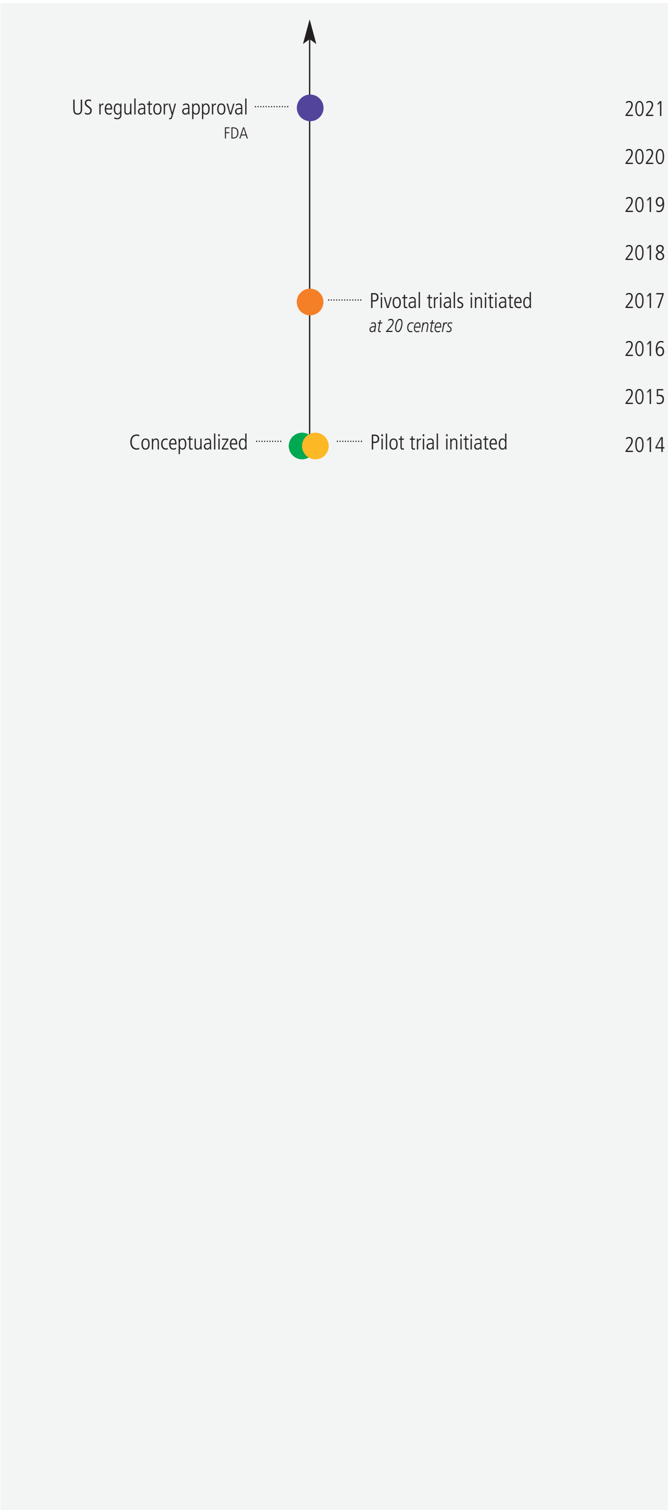
Indication Timeline—Parkinson's Tremor

■ Conceptual ■ Preclinical ■ 1st-in-human ■ Pilot trials ■ Pivotal trials ■ FDA approval ■ US reimbursement



Indication Timeline—Parkinson's Dyskinesia

■ Conceptual ■ Preclinical ■ 1st-in-human ■ Pilot trials ■ Pivotal trials ■ FDA approval ■ US reimbursement



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

5 Commercial Treatments	**5** 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

Chrit T.W. Moonen, PhD, Program Director | c.moonen@umcutrecht.nl

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.

Synthesis, Characterization, and Imaging of Radiopaque Bismuth Beads for Image-guided Transarterial Embolization. Negussie AH, de Ruiter QMB, Britton H, Donahue DR, Boffi Q, Kim YS, Pritchard WF, Moonen C, Storm G, Lewis AL, Wood BJ. Sci Rep. 2021 Jan 12;11(1):533. doi: 10.1038/s41598-020-79900-z. PMID: 33436734; PMCID: PMC7804415.

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 Radio-recurrent 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

Exploring Label Dynamics of Velocity-selective Arterial Spin Labeling in the Kidney. Bones IK, Franklin SL, Harteveld AA, van Osch MJP, Schmid S, Hendrikse J, Moonen C, van Stralen M, Bos C. Magn Reson Med. 2021 Jul;86(1):131-142. doi: 10.1002/mrm.28683. Epub 2021 Feb 4. PMID: 33538350; PMCID: PMC8048977.

Systematic Review of Reproductive Outcomes after High Intensity Focused Ultrasound Treatment of Uterine Fibroids. Anneveldt KJ, van 't Oever HJ, Nijholt IM, Dijkstra JR, Hehenkamp WJ, Veersema S, Huirne JAF, Schutte JM, Boomsma MF. Eur J Radiol. 2021 Aug;141:109801. doi: 10.1016/j.ejrad.2021.109801. Epub 2021 May 27. PMID: 34116454.

Publications—2021 continued

Rapid 2D Variable Flip Angle Method for Accurate and Precise T1 Measurements Over a Wide Range of T1 Values. Lena B, Bos C, Ferrer CJ, Moonen CTW, Viergever MA, Bartels LW. NMR Biomed. 2021 Aug;34(8):e4542. doi: 10.1002/nbm.4542. Epub 2021 May 24. PMID: 34031938; PMCID: PMC8365751.

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.

Ultrasound-Mediated Drug Delivery with a Clinical Ultrasound System: In Vitro Evaluation. de Maar JS, Rousou C, van Elburg B, Vos HJ, Lajoinie GPR, Bos C, Moonen CTW, Deckers R. Front Pharmacol. 2021 Oct 19;12:768436. doi: 10.3389/fphar.2021.768436. PMID: 34737709; PMCID: PMC8560689.

Ultrasound and Microbubbles for the Treatment of Ocular Diseases: From Preclinical Research towards Clinical Application. Rousou C, Schuurmans CCL, Urtti A, Mastrobattista E, Storm G, Moonen C, Kaarniranta K, Deckers R. Pharmaceutics. 2021 Oct 25;13(11):1782. doi: 10.3390/pharmaceutics13111782. PMID: 34834196; PMCID: PMC8624665.

Interleaved Water and Fat MR Thermometry for Monitoring High Intensity Focused Ultrasound Ablation of Bone Lesions. Lena B, Bartels LW, Ferrer CJ, Moonen CTW, Viergever MA, Bos C. Magn Reson Med. 2021 Nov;86(5):2647-2655. doi: 10.1002/mrm.28877. Epub 2021 Jun 1. PMID: 34061390; PMCID: PMC8596687.

Comparison of (Cost-)Effectiveness of Magnetic Resonance Image-Guided High-Intensity-Focused Ultrasound with Standard (Minimally) Invasive Fibroid Treatments: Protocol for a Multicenter Randomized Controlled Trial (MYCHOICE). Anneveldt KJ, Nijholt IM, Schutte JM, Dijkstra JR, Frederix GWJ, Ista E, Verpalen IM, Veersema S, Huirne JAF, Hehenkamp WJK, Boomsma MF. JMIR Res Protoc. 2021 Nov 24;10(11):e29467. doi: 10.2196/29467. PMID: 34821569; PMCID: PMC8663707.

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.

Lessons Learned During Implementation of MR-guided High-Intensity Focused Ultrasound Treatment of Uterine Fibroids. Anneveldt KJ, Verpalen IM, Nijholt IM, Dijkstra JR, van den Hoed RD, Van't Veer-Ten Kate M, de Boer E, van Osch JAC, Heijman E, Naber HR, Ista E, Franx A, Veersema S, Huirne JAF, Schutte JM, Boomsma MF. Insights Imaging. 2021 Dec 18;12(1):188. doi: 10.1186/s13244-021-01128-w. PMID: 34921657; PMCID: PMC8684568.

Workflow for Automatic Renal Perfusion Quantification Using ASL-MRI and Machine Learning. Bones IK, Bos C, Moonen C, Hendrikse J, van Stralen M. Magn Reson Med. 2022 Feb;87(2):800-809. doi: 10.1002/mrm.29016. Epub 2021 Oct 20. PMID: 34672029.

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

Children's National Hospital continued

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

Publications—2021

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.

1 Protocols inclusive of more than one indication

Physics for Medicine Paris

1 Clinical Research

4	5	9	28
Preclinical Research	Mechanisms of Action Research	Technical Research	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

Mickael Tanter, **PhD** | Program Director | mickael.tanter@espci.fr

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, underlying cause	Nonthermal - Neuromodulation

Physics for Medicine Paris continued

Publications—2021

Introduction to the Special Issue on Histotripsy: Approaches, Mechanisms, Hardware, and Applications. Xu Z, Khokhlova VA, Wear KA, Aubry J-F, Bigelow TA. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control 2021;68:2834–6. https://doi.org/10.1109/TUFFC.2021.3102092.

New Mechanistic Insights, Novel Treatment Paradigms, and Clinical Progress in Cerebrovascular Diseases. Boltze J, Aronowski JA, Badaut J, Buckwalter MS, Caleo M, Chopp M, Dave KR, Didwischus N, Dijkhuizen RM, Doeppner TR, Dreier JP, Fouad K, Gelderblom M, Gertz K, Golubczyk D, Gregson BA, Hamel E, Hanley DF, Härtig W, Hummel FC, Ikhsan M, Janowski M, Jolkkonen J, Karuppagounder SS, Keep RF, Koerte IK, Kokaia Z, Li P, Liu F, Lizasoain I, Ludewig P, Metz GAS, Montagne A, Obenaus A, Palumbo A, Pearl M, Perez-Pinzon M, Planas AM, Plesnila N, Raval AP, Rueger MA, Sansing LH, Sohrabji F, Stagg CJ, Stetler RA, Stowe AM, Sun D, Taguchi A, Tanter M, Vay SU, Vemuganti R, Vivien D, Walczak P, Wang J, Xiong Y, Zille M. Front Aging Neurosci. 2021 Jan 28;13:623751. doi: 10.3389/fnagi.2021.623751. PMID: 33584250; PMCID: PMC7876251.

Publications—2021 continued

A simple novel approach for detecting blood-brain barrier permeability using GPCR internalization. Csaba Z, Vitalis T, Charriaut-Marlangue C, Margaill I, Coqueran B, Leger PL, Parente I, Jacquens A, Titomanlio L, Constans C, Demene C, Santin MD, Lehericy S, Perrière N, Glacial F, Auvin S, Tanter M, Ghersi-Egea JF, Adle-Biassette H, Aubry JF, Gressens P, Dournaud P. Neuropathol Appl Neurobiol. 2021 Feb;47(2):297-315. doi: 10.1111/nan.12665. Epub 2020 Sep 27. PMID: 32898926; PMCID: PMC7891648.

Bedside functional monitoring of the dynamic brain connectivity in human neonates. Baranger J, Demene C, Frerot A, Faure F, Delanoë C, Serroune H, Houdouin A, Mairesse J, Biran V, Baud O, Tanter M. Nat Commun. 2021 Feb 17;12(1):1080. doi: 10.1038/s41467-021-21387-x. PMID: 33597538; PMCID: PMC7889933.

Whole-Brain 3D Activation and Functional Connectivity Mapping in Mice using Transcranial Functional Ultrasound Imaging. Bertolo A, Nouhoum M, Cazzanelli S, Ferrier J, Mariani JC, Kliewer A, Belliard B, Osmanski BF, Deffieux T, Pezet S, Lenkei Z, Tanter M. J Vis Exp. 2021 Feb 24;(168). doi: 10.3791/62267. PMID: 33720137.

Tolerability and Feasibility of X-ray Guided Non-Invasive Ablation of the Medial Branch Nerve with Focused Ultrasound: Preliminary Proof of Concept in a Pre- clinical Model. Aginsky R, LeBlang S, Hananel A, Chen J, Gofeld M, Perez J, Shir Y, Aubry JF. Ultrasound Med Biol. 2021 Mar;47(3):640-650. doi: 10.1016/j.ultrasmedbio.2020.10.019. Epub 2020 Nov 28. PMID: 33261908.

Transcranial ultrafast ultrasound localization microscopy of brain vasculature in patients. Demené C, Robin J, Dizeux A, Heiles B, Pernot M, Tanter M, Perren F. Nat Biomed Eng. 2021 Mar;5(3):219-228. doi: 10.1038/s41551-021-00697-x. Epub 2021 Mar 15. PMID: 33723412; PMCID: PMC7610356.

Feasibility and Performance of Noninvasive Ultrasound Therapy in Patients With Severe Symptomatic Aortic Valve Stenosis: A First-in-Human Study. Messas E, IJsselmuiden A, Goudot G, Vlieger S, Zarka S, Puymirat E, Cholley B, Spaulding C, Hagège AA, Marijon E, Tanter M, Bertrand B, Rémond MC, Penot R, Ren B, den Heijer P, Pernot M, Spaargaren R. Circulation. 2021 Mar 2;143(9):968-970. doi: 10.1161/CIRCULATIONAHA.120.050672. Epub 2021 Jan 25. PMID: 33486971.

Large-scale functional ultrasound imaging of the spinal cord reveals in-depth spatiotemporal responses of spinal nociceptive circuits in both normal and inflammatory states. Claron J, Hingot V, Rivals I, Rahal L, Couture O, Deffieux T, Tanter M, Pezet S. Pain. 2021 Apr 1;162(4):1047-1059. doi: 10.1097/j.pain.0000000000002078. PMID: 32947542; PMCID: PMC7977620.

Single-trial decoding of movement intentions using functional ultrasound neuroimaging. Norman SL, Maresca D, Christopoulos VN, Griggs WS, Demene C, Tanter M, Shapiro MG, Andersen RA. Neuron. 2021 May 5;109(9):1554-1566.e4. doi: 10.1016/j.neuron.2021.03.003. Epub 2021 Mar 22. PMID: 33756104; PMCID: PMC8105283.

Imaging the Renal Microcirculation in Cell Therapy. Apelt K, Bijkerk R, Lebrin F, Rabelink TJ. Cells. 2021 May 2;10(5):1087. doi: 10.3390/cells10051087. PMID: 34063200; PMCID: PMC8147454.

Publications—2021 continued

In vitro Three-Dimensional Sprouting Assay of Angiogenesis using Mouse Embryonic Stem Cells for Vascular Disease Modeling and Drug Testing. Galaris G, Thalgott JH, Teston E, Lebrin FPG. J Vis Exp. 2021 May 11;(171). doi: 10.3791/62554. PMID: 34057453.

Wall Shear Stress Measurement by Ultrafast Vector Flow Imaging for Atherosclerotic Carotid Stenosis. Goudot G, Poree J, Pedreira O, Khider L, Julia P, Alsac JM, Laborie E, Mirault T, Tanter M, Messas E, Pernot M. Ultraschall Med. 2021 Jun;42(3):297-305. English. doi: 10.1055/a-1060-0529. Epub 2019 Dec 19. PMID: 31856281.

Dealiasing High-Frame-Rate Color Doppler Using Dual-Wavelength Processing. Poree J, Goudot G, Pedreira O, Laborie E, Khider L, Mirault T, Messas E, Julia P, Alsac JM, Tanter M, Pernot M. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Jun;68(6):2117-2128. doi: 10.1109/TUFFC.2021.3056932. Epub 2021 May 25. PMID: 33534706.

Functional ultrasound imaging of the spreading activity following optogenetic stimulation of the rat visual cortex. Provansal M, Labernède G, Joffrois C, Rizkallah A, Goulet R, Valet M, Deschamps W, Ferrari U, Chaffiol A, Dalkara D, Sahel JA, Tanter M, Picaud S, Gauvain G, Arcizet F. Sci Rep. 2021 Jun 15;11(1):12603. doi: 10.1038/s41598-021-91972-z. PMID: 34131223; PMCID: PMC8206208.

Comparison Between Ray-Tracing and Full-Wave Simulation for Transcranial Ultrasound Focusing on a Clinical System Using the Transfer Matrix Formalism. Bancel T, Houdouin A, Annic P, Rachmilevitch I, Shapira Y, Tanter M, Aubry JF. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Jul;68(7):2554-2565. doi: 10.1109/TUFFC.2021.3063055. Epub 2021 Jun 29. PMID: 33651688.

Combining brain perturbation and neuroimaging in non-human primates. Klink PC, Aubry JF, Ferrera VP, Fox AS, Froudist-Walsh S, Jarraya B, Konofagou EE, Krauzlis RJ, Messinger A, Mitchell AS, Ortiz-Rios M, Oya H, Roberts AC, Roe AW, Rushworth MFS, Sallet J, Schmid MC, Schroeder CE, Tasserie J, Tsao DY, Uhrig L, Vanduffel W, Wilke M, Kagan I, Petkov CI. Neuroimage. 2021 Jul 15;235:118017. doi: 10.1016/j.neuroimage.2021.118017. Epub 2021 Mar 29. PMID: 33794355.

A functional ultrasound brain GPS for automatic vascular-based neuronavigation. Nouhoum M, Ferrier J, Osmanski BF, Ialy-Radio N, Pezet S, Tanter M, Deffieux T. Sci Rep. 2021 Jul 26;11(1):15197. doi: 10.1038/s41598-021-94764-7. PMID: 34312477; PMCID: PMC8313708.

The SVD beamformer with diverging waves: a proof-of-concept for fast aberration correction. Bendjador H, Décombas-Deschamps S, Dioguardi Burgio M, Sartoris R, Van Beers B, Vilgrain V, Deffieux T, Tanter M. Phys Med Biol. 2021 Sep 17;66(18). doi: 10.1088/1361-6560/ac2129. PMID: 34433145.

Functional Ultrasound Imaging: A New Imaging Modality for Neuroscience. Deffieux T, Demené C, Tanter M. Neuroscience. 2021 Oct 15;474:110-121. doi: 10.1016/j.neuroscience.2021.03.005. Epub 2021 Mar 13. PMID: 33727073.

Von Willebrand factor multimers during non-invasive ultrasound therapy for aortic valve stenosis. Smadja DM, Goudot G, Gendron N, Zarka S, Puymirat E, Philippe A, Spaulding C, Peronino C, Tanter M, Pernot M, Messas E. Angiogenesis. 2021 Nov;24(4):715-717. doi: 10.1007/s10456-021-09803-8. Epub 2021 Jun 8. PMID: 34101096.

Publications—2021 continued

Megalencephalic leukoencephalopathy with subcortical cysts is a developmental disorder of the gliovascular unit. Gilbert A, Elorza-Vidal X, Rancillac A, Chagnot A, Yetim M, Hingot V, Deffieux T, Boulay AC, Alvear-Perez R, Cisternino S, Martin S, Taïb S, Gelot A, Mignon V, Favier M, Brunet I, Declèves X, Tanter M, Estevez R, Vivien D, Saubaméa B, Cohen-Salmon M. Elife. 2021 Nov 1;10:e71379. doi: 10.7554/eLife.71379. PMID: 34723793; PMCID: PMC8598235.

Distinct higher-order representations of natural sounds in human and ferret auditory cortex. Landemard A, Bimbard C, Demené C, Shamma S, Norman-Haignere S, Boubenec Y. Elife. 2021 Nov 18;10:e65566. doi: 10.7554/eLife.65566. PMID: 34792467; PMCID: PMC8601661.

Cross-Correlation of Orthogonal Apertures for 3D Blood Flow Imaging. Bertolo A, Sauvage J, Tanter M, Pernot M, Deffieux T. XDoppler: IEEE Trans Med Imaging. 2021 Dec;40(12):3358-3368. doi: 10.1109/TMI.2021.3084865. Epub 2021 Nov 30. PMID: 34048341.

Ultrasound modulation of macaque prefrontal cortex selectively alters credit assignment-related activity and behavior. Folloni D, Fouragnan E, Wittmann MK, Roumazeilles L, Tankelevitch L, Verhagen L, Attali D, Aubry JF, Sallet J, Rushworth MFS. Sci Adv. 2021 Dec 17;7(51):eabg7700. doi: 10.1126/sciadv.abg7700. Epub 2021 Dec 15. PMID: 34910510; PMCID: PMC8673758.

Smart Ultrasound Device for Non-Invasive Real-Time Myocardial Stiffness Quantification of the Human Heart. Pedreira O, Correia M, Chatelin S, Villemain O, Goudot G, Thiebaut S, Bassan G, Messas E, Tanter M, Papadacci C, Pernot M. IEEE Trans Biomed Eng. 2022 Jan;69(1):42-52. doi: 10.1109/TBME.2021.3087039. Epub 2021 Dec 23. PMID: 34097602.

Assessing cardiac stiffness using ultrasound shear wave elastography. Caenen A, Pernot M, Nightingale KR, Voigt JU, Vos HJ, Segers P, D'hooge J. Phys Med Biol. 2022 Jan 17;67(2). doi: 10.1088/1361-6560/ac404d. PMID: 34874312.

Carotid Plaque Vulnerability Assessed by Combined Shear Wave Elastography and Ultrafast Doppler Compared to Histology. Goudot G, Sitruk J, Jimenez A, Julia P, Khider L, Alsac JM, El Batti S, Bruneval P, Amemyia K, Pedreira O, Mortelette H, Calvet D, Tanter M, Mirault T, Pernot M, Messas E. Transl Stroke Res. 2022 Feb;13(1):100-111. doi: 10.1007/s12975-021-00920-6. Epub 2021 Jun 28. PMID: 34181190.

.

Inserm - LabTAU

1 Commercial Treatment	**5** Clinical Research		
20 Preclinical Research	**13** Mechanisms of Action Research	**7** Technical Research	**24** 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

Cyril Lafon, PhD | Program Director | cyril.lafon@inserm.fr

Commercial treatment

Urological	Prostate cancer, *Hôpital Edouard Herriot*

Clinical research

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	
Pancreatic tumors, malignant	Nonthermal - Sonodynamic therapy Nonthermal - Tissue destruction Thermal ablation - Immunomodulation
Preclinical research - Neurological	
Cancer pain	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - drug delivery
Stroke, thromboembolic	Nonthermal, BBB opening - drug delivery
Preclinical research - Women's health	
Breast tumors, malignant	Nonthermal - Immunomodulation Nonthermal - Tissue destruction

Publications—2021

Micro-elastography: Towards Ultrasonic Shear Waves in Soft Solids. Catheline S, Laloy-Borgna G, Zorgani A. Appl. Phys. Lett. 2021; 118, 113701. doi: 10.1063/5.0039816.

Development of a Simple In Vitro Artery Model and an Evaluation of the Impact of Pulsed Flow on High-intensity Focused Ultrasound Ablation. Cilleros C, Dupre A, Vincenot J, Melodelima D. IRBM. 2021;42(2): 112-9. doi: 10.1016/j.irbm.2020.11.004.

IRBM: Trends for 2021. Melodelima D, Frouin F. 2021. IRBM. 42. 1. 10.1016/j.irbm.2021.01.005.

Spatio-temporal Characterization of Causal Electrophysiological Activity Stimulated by Single Pulse Focused Ultrasound: an Ex Vivo Study on Hippocampal Brain Slices. Suarez-Castellanos IM, Dossi E, Vion-Bailly J, Salette L, Chapelon JY, Carpentier A, Huberfeld G, N'Djin WA. J Neural Eng. 2021 Jan 25. doi: 10.1088/1741-2552/abdfb1. Epub ahead of print. PMID: 33494078.

Stimulation of Oral Mucosal Regeneration by Low Intensity Pulsed Ultrasound: an In Vivo Study in a Porcine Model. Chauvel-Picard J, Korn P, Corbin S, Brosset S, Bera JC, Gleizal A. J Prosthodont Res. 2021 Feb 24;65(1):46-51. doi: 10.2186/jpr.JPOR_2019_345. Epub 2020 Oct 27. PMID: 32938859.

Cavitation Emissions Nucleated by Definity Infused through an EkoSonic Catheter in a Flow Phantom. Lafond M, Salido NG, Haworth KJ, Hannah AS, Macke GP, Genstler C, Holland CK. Ultrasound Med Biol. 2021 Mar;47(3):693-709. doi: 10.1016/j.ultrasmedbio.2020.10.010. Epub 2021 Jan 7. PMID: 33349516

Use of the Cross-Spectral Density Matrix for Enhanced Passive Ultrasound Imaging of Cavitation. Polichetti M, Varray F, Gilles B, Bera JC, Nicolas B. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Apr;68(4):910-925. doi: 10.1109/TUFFC.2020.3032345. Epub 2021 Mar 26. PMID: 33079648.

Publications—2021 continued

Evaluation of Pseudorandom Sonications for Reducing Cavitation with a Clinical Neurosurgery HIFU Device. Lafon C, Moore D, Eames MDC, Snell J, Drainville RA, Padilla F. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Apr;68(4):1224-1233. doi: 10.1109/TUFFC.2020.3036774. Epub 2021 Mar 26. PMID: 33166253.

Induction of Microstreaming by Nonspherical Bubble Oscillations in an Acoustic Levitation System. Inserra C, Regnault G, Cleve S, Mauger C, Blanc-Benon P. J Vis Exp. 2021 May 9;(171). doi: 10.3791/62044. PMID: 34028449.

Evaluation of Ultrasonic Attenuation in Primary and Secondary Human Liver Tumors and Its Potential Effect on High-Intensity Focused Ultrasound Treatment. Barrere V, Sanchez M, Cambronero S, Dupré A, Rivoire M, Melodelima D. Ultrasound Med Biol. 2021 Jul;47(7):1761-1774. doi: 10.1016/j.ultrasmedbio.2021.03.014. Epub 2021 Apr 22. PMID: 33895037.

Shear Wave Generation by Remotely Stimulating Aluminum Patches with a Transient Magnetic Field and Its Preliminary Application in Elastography. Sun Z, Giammarinaro B, Birer A, Liu G, Catheline S. IEEE Trans Biomed Eng. 2021 Jul;68(7):2129-2139. doi: 10.1109/TBME.2020.3028098. Epub 2021 Jun 17. PMID: 33001796.

DNA Double-Strand Breaks in Murine Mammary Tumor Cells Induced by Combined Treatment with Doxorubicin and Controlled Stable Cavitation. Fant C, Granzotto A, Mestas JL, Ngo J, Lafond M, Lafon C, Foray N, Padilla F. Ultrasound Med. 2021 Jul 24. PMID: 34315620.

Development of a Noninvasive HIFU Treatment for Breast Adenocarcinomas Using a Toroidal Transducer Based on Preliminary Attenuation Measurements. Sanchez M, Barrere V, Treilleux I, Chopin N, Melodelima D. Ultrasonics. 2021 Aug;115:106459. doi: 10.1016/j.ultras.2021.106459. Epub 2021 May 9. PMID: 33990009.

Inserm – LabTAU continued

Publications—2021 continued

Time-of-flight and Noise-correlation-inspired Algorithms for Full-field Shear-wave Elastography using Digital Holography. Marmin A, Laloy-Borgna G, Facca S, Gioux S, Catheline S, Nahas A. J Biomed Opt. 2021 Aug;26(8):086006. doi: 10.1117/1.JBO.26.8.086006. PMID: 34414704; PMCID: PMC8374320.

Salvage High-Intensity Focused Ultrasound for Local Recurrence in the Prostatic Bed after Prostatectomy and Adjuvant or Salvage Radiotherapy: Preliminary Results. Khedime S, Gelet A, Rouvière O, Lafon C, Badet L, Crouzet S, Hostiou T. J Urol. 2021 Aug;206(2):325-337. doi: 10.1097/JU.0000000000001771. Epub 2021 Apr 9. PMID: 33835863.

Signatures of Microstreaming Patterns Induced by Non-spherically Oscillating Bubbles. Regnault G, Mauger C, Blanc-Benon P, Doinikov AA, Inserra C. J Acoust Soc Am. 2021 Aug;150(2):1188. doi: 10.1121/10.0005821. PMID: 34470320.

Focal HIFU Treatment of Apical Lesion: Safety and Oncological Results. Crouzet S, Gelet A, Hostiou T, Rouviere O, Badet L, Regusci S, Martins M. JUrology. 2021 Sep 12;206(3S):e816. doi: 10.1097/JU.0000000000002067.09.

Fluids Alter Elasticity Measurements: Porous Wave Propagation Accounts for Shear Wave Dispersion in Elastography. Aichele J, Stefan C. Front. Phys. 2021 Sep 22. doi: 10.3389/fphy.2021.697990.

Passive Elastography of the Esophagus: From Model to Preliminary In-vivo Experiments Using Diameter Measurements. Delattre V, Catheline S, Laloy-Borgna G, Zorgani A, Roman S. Biomed Phys Eng Express. 2021 Oct 14; 7(6). doi: 10.1088/2057-1976/ac277d. PMID: 34530409.

Ultrasound Molecular Imaging for the Guidance of Ultrasound-Triggered Release of Liposomal Doxorubicin and Its Treatment Monitoring in an Orthotopic Prostatic Tumor Model in Rat. Helbert A, von Wronski M, Mestas JL, Tardy I, Bettinger T, Lafon C, Hyvelin JM, Padilla F. Ultrasound Med Biol. 2021 Dec;47(12):3420-3434. doi: 10.1016/j.ultrasmedbio.2021.07.022. Epub 2021 Sep 6. PMID: 34503895.

Publications—2021 continued

Neurostimulation Success Rate of Repetitive-pulse Focused Ultrasound in an In Vivo Giant Axon Model: An Acoustic Parametric Study. Vion-Bailly J, Suarez-Castellanos IM, Chapelon JY, Carpentier A, N'Djin WA. Med Phys. 2022 Jan;49(1):682-701. doi: 10.1002/mp.15358. Epub 2021 Dec 7. PMID: 34796512.

Intraoperative HIFU Ablation of the Pancreas Using a Toroidal Transducer in a Porcine Model. The First Step towards a Clinical Treatment of Locally Advanced Pancreatic Cancer. Cilleros C, Dupré A, Chen Y, Vincenot J, Rivoire M, Melodelima D. Cancers (Basel). 2021 Dec 20;13(24):6381. doi: 10.3390/cancers13246381. PMID: 34945001; PMCID: PMC8699564.

Spectral Analysis of Tissue Displacement for Cardiac Activation Mapping: Ex-vivo Working Heart and In-vivo Study. Robert J, Bessiere F, Cao E, Loyer V, Abell E, Vaillant F, Quesson B, Catheline S, Lafon C. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Dec 23;PP. doi: 10.1109/TUFFC.2021.3137989. Epub ahead of print. PMID: 34941506.

High Intensity Focused Ultrasound: A Future Alternative to Surgery for the Treatment of Localized Pancreatic Tumors? Fabritius M, Lambin T, Cao E, Robert J, Milot L, Lafon C, Pioche M. Endoscopy. 2022 Jan;54(1):E17-E18. doi: 10.1055/a-1338-0293. Epub 2021 Feb 16. Erratum in: Endoscopy. 2021 Feb 22; PMID: 33592643.

Stanford University School of Medicine

		12 Commercial Treatments	9 Clinical Research
9 Preclinical Research	17 Mechanisms of Action 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
Pejman Ghanouni, MD, PhD | Program Co-Director | ghanouni@stanford.edu
Kim Butts Pauly, PhD | Program Co-Director | kbpauly@stanford.edu

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

Stanford University School of Medicine continued

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 research
Drug delivery technology
FUS Image guidance, MR
FUS Physics
FUS Simulation & treatment planning
FUS Transducer technology, Nonthermal
FUS Transducer technology, Thermal ablation
FUS Treatment evaluation
FUS Treatment monitoring

Research not involving thermal ablation, tissue destruction	
Clinical research - Gastrointestinal	
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Clinical research - Neurological	
Glioblastoma	Nonthermal, BBB opening - drug delivery
Preclinical research - Gastrointestinal	
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Preclinical research - Miscellaneous	
Melanoma	Thermal ablation - Immunomodulation
Preclinical research - Neurological	
Epilepsy	Nonthermal, BBB opening - drug delivery
Glioblastoma	Nonthermal, BBB opening - drug delivery
Neuropathic pain	Nonthermal - Drug delivery, vehicle
Preclinical research - Urological	
Acute kidney injury	Nonthermal - Stem cell delivery
Preclinical research - Women's health	
Breast tumors, malignant	Nonthermal - Gene delivery Thermal ablation - Immunomodulation
Ovarian tumors	Thermal ablation - Immunomodulation
Veterinary research - Gastrointestinal	
Liver tumors	Nonthermal - Drug delivery, vehicle Nonthermal - Gene delivery Nonthermal - Immunomodulation

Publications—2021

Evaluation of an MRI Receive Head Coil for Use in Transcranial MR Guided Focused Ultrasound for Functional Neurosurgery. Bitton RR, Sheingaouz E, Assif B, Kelm N, Dayan M, Butts Pauly K, Ghanouni P. Int J Hyperthermia. 2021;38(1):22-29. doi: 10.1080/02656736.2020.1867242. PMID: 33459092.

Design and Evaluation of an Open-source, Conformable Skin-cooling System for Body Magnetic Resonance Guided Focused Ultrasound Treatments. Merrill R, Odéen H, Dillon C, Bitton R, Ghanouni P, Payne A. Int J Hyperthermia. 2021;38(1):679-690. doi: 10.1080/02656736.2021.1914872. PMID: 33899653.

Immune Modulation Resulting from MR-guided High Intensity Focused Ultrasound in a Model of Murine Breast Cancer. Fite BZ, Wang J, Kare AJ, Ilovitsh A, Chavez M, Ilovitsh T, Zhang N, Chen W, Robinson E, Zhang H, Kheirolomoom A, Silvestrini MT, Ingham ES, Mahakian LM, Tam SM, Davis RR, Tepper CG, Borowsky AD, Ferrara KW. Sci Rep. 2021 Jan 13;11(1):927. doi: 10.1038/s41598-020-80135-1. PMID: 33441763; PMCID: PMC7806949.

Stanford University School of Medicine continued

Publications—2021 continued

ProsRegNet: A Deep Learning Framework for Registration of MRI and Histopathology Images of the Prostate. Shao W, Banh L, Kunder CA, Fan RE, Soerensen SJC, Wang JB, Teslovich NC, Madhuripan N, Jawahar A, Ghanouni P, Brooks JD, Sonn GA, Rusu M. Med Image Anal. 2021 Feb;68:101919. doi: 10.1016/j.media.2020.101919. Epub 2020 Dec 17. PMID: 33385701; PMCID: PMC7856244.

Therapeutic Ultrasound Parameter Optimization for Drug Delivery Applied to a Murine Model of Hepatocellular Carcinoma. Telichko AV, Wang H, Bachawal S, Kumar SU, Bose JC, Paulmurugan R, Dahl JJ. Ultrasound Med Biol. 2021 Feb;47(2):309-322. doi: 10.1016/j.ultrasmedbio.2020.09.009. Epub 2020 Nov 3. PMID: 33153807; PMCID: PMC8489309.

Development of Thermosensitive Resiquimod-loaded Liposomes for Enhanced Cancer Immunotherapy. Zhang H, Tang WL, Kheirolomoom A, Fite BZ, Wu B, Lau K, Baikoghli M, Raie MN, Tumbale SK, Foiret J,

Ingham ES, Mahakian LM, Tam SM, Cheng RH, Borowsky AD, Ferrara KW. J Control Release. 2021 Feb 10;330:1080-1094. doi: 10.1016/j.jconrel.2020.11.013. Epub 2020 Nov 13. PMID: 33189786; PMCID: PMC7906914.

Bilateral Deep Brain Stimulation is the Procedure to Beat for Advanced Parkinson Disease: A Meta-Analytic, Cost- Effective Threshold Analysis for Focused Ultrasound. Mahajan UV, Ravikumar VK, Kumar KK, Ku S, Ojukwu DI, Kilbane C, Ghanouni P, Rosenow JM, Stein SC, Halpern CH. Neurosurgery. 2021 Feb 16;88(3):487-496. doi: 10.1093/neuros/nyaa485. PMID: 33295629; PMCID: PMC8190460.

Improved Survival and Disease Control Following Pembrolizumab-induced Immune-related Adverse Events in High PD-L1 Expressing Non-small Cell Lung Cancer with Brain Metastases. Zhang M, Rodrigues AJ, Pollom EL, Gibbs IC, Soltys SG, Hancock SL, Neal JW, Padda SK, Ramchandran KJ, Wakelee HA, Chang SD, Lim M, Hayden Gephart M, Li G. J Neurooncol. 2021 Mar;152(1):125-134. doi: 10.1007/s11060-020-03686-3. Epub 2021 Jan 7. PMID: 33415659; PMCID: PMC8214448.

MRI-Guided Focused Ultrasound of Osseous Metastases: Treatment Parameters Associated with Successful Pain Reduction. Bitton RR, Rosenberg J, LeBlang S, Napoli A, Meyer J, Butts Pauly K, Hurwitz M, Ghanouni P. Invest Radiol. 2021 Mar 1;56(3):141-146. doi: 10.1097/RLI.0000000000000721. PMID: 32858582.

Transcranial Focused Ultrasound Phase Correction Using the Hybrid Angular Spectrum Method. Leung SA, Moore D, Webb TD, Snell J, Ghanouni P, Butts Pauly K. Sci Rep. 2021 Mar 22;11(1):6532. doi: 10.1038/s41598-021-85535-5. PMID: 33753771; PMCID: PMC7985511.

A Preclinical Study of Diffusion-weighted MRI Contrast as an Early Indicator of Thermal Ablation. Allen SP, Prada F, Xu Z, Gatesman J, Feng X, Sporkin H, Gilbo Y, DeCleene S, Pauly KB, Meyer CH. Magn Reson Med. 2021 Apr;85(4):2145-2159. doi: 10.1002/mrm.28537. Epub 2020 Nov 11. PMID: 33174639.

3D Registration of Pre-surgical Prostate MRI and Histopathology Images via Super-resolution Volume Reconstruction. Sood RR, Shao W, Kunder C, Teslovich NC, Wang JB, Soerensen SJC, Madhuripan N, Jawahar A, Brooks JD, Ghanouni P, Fan RE, Sonn GA, Rusu M. Med Image Anal. 2021 Apr;69:101957. doi: 10.1016/j.media.2021.101957. Epub 2021 Jan 23. PMID: 33550008; PMCID: PMC7933126.

Publications—2021 continued

Estimation of Tissue Attenuation from Ultrasonic B-Mode Images-Spectral-Log-Difference and Method-of- Moments Algorithms Compared. Brandner DM, Cai X, Foiret J, Ferrara KW, Zagar BG. Sensors (Basel). 2021 Apr 5;21(7):2548. doi: 10.3390/s21072548. PMID: 33916496; PMCID: PMC8038607.

Pre-clinical Evaluation of ImmunoPET Imaging Using Agonist CD40 Monoclonal Antibody in Pancreatic Tumor-bearing Mice. Aghevlian S, Wu B, Raie MN, Tumbale SK, Kare AJ, Seo JW, Ferrara KW. Nucl Med Biol. 2021 Jul-Aug;98-99:8-17. doi: 10.1016/j.nucmedbio.2021.04.001. Epub 2021 Apr 21. PMID: 33962357; PMCID: PMC8486004.

Systemic Immunotherapy with Micellar Resiquimod-Polymer Conjugates Triggers a Robust Antitumor Response in a Breast Cancer Model. Kakwere H, Zhang H, Ingham ES, Nura-Raie M, Tumbale SK, Allen R, Tam SM, Wu B, Liu C, Kheirolomoom A, Fite BZ, Ilovitsh A, Lewis JS, Ferrara KW. Adv Healthc Mater. 2021 May;10(10):e2100008. doi: 10.1002/adhm.202100008. Epub 2021 Mar 1. PMID: 33646600; PMCID: PMC8153207.

Acoustic Attenuation: Multifrequency Measurement and Relationship to CT and MR Imaging. Webb TD, Leung SA, Ghanouni P, Dahl JJ, Pelc NJ, Pauly KB. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 May;68(5):1532-1545. doi: 10.1109/TUFFC.2020.3039743. Epub 2021 Apr 26. PMID: 33226938; PMCID: PMC8580404.

Closed-loop Trans-skull Ultrasound Hyperthermia Leads to Improved Drug Delivery from Thermosensitive Drugs and Promotes Changes in Vascular Transport Dynamics in Brain Tumors. Kim C, Guo Y, Velalopoulou A, Leisen J, Motamarry A, Ramajayam K, Aryal M, Haemmerich D, Arvanitis CD. Theranostics. 2021 May 24;11(15):7276-7293. doi: 10.7150/thno.54630. PMID: 34158850; PMCID: PMC8210606.

Stanford University School of Medicine continued

Publications—2021 continued

Enhancing Proteasomal Processing Improves Survival for a Peptide Vaccine Used to Treat Glioblastoma. Fidanza M, Gupta P, Sayana A, Shanker V, Pahlke SM, Vu B, Krantz F, Azameera A, Wong N, Anne N, Xia Y, Rong J, Anne A, Skirboll S, Lim M, Wong AJ. Sci Transl Med. 2021 Jun 16;13(598):eaax4100. doi: 10.1126/scitranslmed.aax4100. PMID: 34135109.

Intracranial Sonodynamic Therapy With 5-Aminolevulinic Acid and Sodium Fluorescein: Safety Study in a Porcine Model. Raspagliesi L, D'Ammando A, Gionso M, Sheybani ND, Lopes MB, Moore D, Allen S, Gatesman J, Porto E, Timbie K, Franzini A, Di Meco F, Sheehan J, Xu Z, Prada F. Front Oncol. 2021 Jun 21;11:679989. doi: 10.3389/fonc.2021.679989. PMID: 34235081; PMCID: PMC8256685.

Minicircles for a Two-step Blood Biomarker and PET Imaging Early Cancer Detection Strategy. Robinson ER, Gowrishankar G, D'Souza AL, Kheirolomoom A, Haywood T, Hori SS, Chuang HY, Zeng Y, Tumbale SK, Aalipour A, Beinat C, Alam IS, Sathirachinda A, Kanada M, Paulmurugan R, Ferrara KW, Gambhir SS. J Control Release. 2021 Jul 10;335:281-289. doi: 10.1016/j.jconrel.2021.05.026. Epub 2021 May 21. PMID: 34029631; PMCID: PMC8262353.

Automated Detection of Aggressive and Indolent Prostate Cancer on Magnetic Resonance Imaging. Seetharaman A, Bhattacharya I, Chen LC, Kunder CA, Shao W, Soerensen SJC, Wang JB, Teslovich NC, Fan RE, Ghanouni P, Brooks JD, Too KJ, Sonn GA, Rusu M. Med Phys. 2021 Jun;48(6):2960-2972. doi: 10.1002/mp.14855. Epub 2021 May 3. PMID: 33760269; PMCID: PMC8360053.

Systematic Review of Combinations of Targeted or Immunotherapy in Advanced Solid Tumors. Tan AC, Bagley SJ, Wen PY, Lim M, Platten M, Colman H, Ashley DM, Wick W, Chang SM, Galanis E, Mansouri A, Khagi S, Mehta MP, Heimberger AB, Puduvalli VK, Reardon DA, Sahebjam S, Simes J, Antonia SJ, Berry D, Khasraw M. J Immunother Cancer. 2021 Jul;9(7):e002459. doi: 10.1136/jitc-2021-002459. PMID: 34215688; PMCID: PMC8256733.

Emerging Technologies for Non-invasive Monitoring of Treatment Response to Immunotherapy for Brain Tumors. Mathios D, Srivastava S, Kim T, Bettegowda C, Lim M. Neuromolecular Med. 2021 Jul 23. doi: 10.1007/s12017-021-08677-9. Epub ahead of print. PMID: 34297308.

Focused Ultrasound: Growth Potential and Future Directions in Neurosurgery. Zhang M, Rodrigues A, Zhou Q, Li G. J Neurooncol. 2022 Jan;156(1):23-32. doi: 10.1007/s11060-021-03820-9. Epub 2021 Aug 19. PMID: 34410576.

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.

Publications—2021 continued

Optimization of Microbubble-based DNA Vaccination with Low-frequency Ultrasound for Enhanced Cancer Immunotherapy. Zhang N, Foiret J, Kheirolomoom A, Liu P, Feng Y, Tumbale S, Raie M, Wu B, Wang J, Fite BZ, Dai Z, Ferrara KW. Adv Ther (Weinh). 2021 Sep;4(9):2100033. doi: 10.1002/adtp.202100033. Epub 2021 Jun 4. PMID: 34632048; PMCID: PMC8494128.

Non-invasive, Neurotoxic Surgery Reduces Seizures in a Rat Model of Temporal Lobe Epilepsy. Zhang Y, Buckmaster PS, Qiu L, Wang J, Keunen O, Ghobadi SN, Huang A, Hou Q, Li N, Narang S, Habte FG, Bertram EH, Lee KS, Wintermark M. Exp Neurol. 2021 Sep;343:113761. doi: 10.1016/j.expneurol.2021.113761. Epub 2021 May 12. PMID: 33991523.

A Crowdsourced Consensus on Supratotal Resection Versus Gross Total Resection for Anatomically Distinct Primary Glioblastoma. Khalafallah AM, Rakovec M, Bettegowda C, Jackson CM, Gallia GL, Weingart JD, Lim M, Esquenazi Y, Zacharia BE, Goldschmidt E, Ziu M, Ivan ME, Venteicher AS, Nduom EK, Mamelak AN, Chu RM, Yu JS, Sheehan JP, Nahed BV, Carter BS, Berger MS, Sawaya R, Mukherjee D. Neurosurgery. 2021 Sep 15;89(4):712-719. doi: 10.1093/neuros/nyab257. PMID: 34320218; PMCID: PMC8440068.

Designing Clinical Trials for Combination Immunotherapy: A Framework for Glioblastoma. Singh K, Batich KA, Wen PY, Tan AC, Bagley SJ, Lim M, Platten M, Colman H, Ashley DM, Chang SM, Rahman R, Galanis E, Mansouri A, Puduvalli VK, Reardon DA, Sahebjam S, Sampson JH, Simes J, Berry DA, Zadeh G, Cloughesy TF, Mehta MP, Piantadosi S, Weller M, Heimberger AB, Khasraw M. Clin Cancer Res. 2021 Sep 24. doi: 10.1158/1078-0432.CCR-21-2681. Epub ahead of print. PMID: 34561270.

The Challenges and Future of Immunotherapy for Gliomas. Wu A, Lim M. Cancer J. 2021 Sep-Oct 01;27(5):371-378. doi: 10.1097/PPO.0000000000000544. PMID: 34570451.

Gold-Nanostar-Chitosan-Mediated Delivery of SARS-CoV-2 DNA Vaccine for Respiratory Mucosal Immunization: Development and Proof-of-Principle. Kumar US, Afjei R, Ferrara K, Massoud TF, Paulmurugan R. ACS Nano. 2021 Oct 27:acsnano.1c05002. doi: 10.1021/acsnano.1c05002. Epub ahead of print. PMID: 34705425; PMCID: PMC8565460.

Synergies Between Therapeutic Ultrasound, Gene Therapy and Immunotherapy in Cancer Treatment. Zhang N, Wang J, Foiret J, Dai Z, Ferrara KW. Adv Drug Deliv Rev. 2021 Nov;178:113906. doi: 10.1016/j.addr.2021.113906. Epub 2021 Jul 30. PMID: 34333075; PMCID: PMC8556319.

Noninvasive Disconnection of Targeted Neuronal Circuitry Sparing Axons of Passage and Nonneuronal Cells. Wang Y, Anzivino MJ, Zhang Y, Bertram EH, Woznak J, Klibanov AL, Dumont E, Wintermark M, Lee KS. J Neurosurg. 2021 Nov 19:1-11. doi: 10.3171/2021.7.JNS21123. Epub ahead of print. PMID: 34798617.

The Stanford Prostate Cancer Calculator: Development and External Validation of Online Nomograms Incorporating PIRADS Scores to Predict Clinically Significant Prostate Cancer. Wang NN, Zhou SR, Chen L, Tibshirani R, Fan RE, Ghanouni P, Thong AE, To'o KJ, Ghabili K, Nix JW, Gordetsky JB, Sprenkle P, Rais-Bahrami S, Sonn GA. Urol Oncol. 2021 Dec;39(12):831.e19-831.e27. doi: 10.1016/j.urolonc.2021.06.004. Epub 2021 Jul 8. PMID: 34247909.

Stanford University School of Medicine continued

Publications—2021 continued

Patterned Interference Radiation Force for Transcranial Neuromodulation. Kim YH, Kang KC, Kim JN, Pai CN, Zhang Y, Ghanouni P, Park KK, Firouzi K, Khuri-Yakub BT. Ultrasound Med Biol. 2021 Dec 23:S0301-5629(21)00485-3. doi: 10.1016/j.ultrasmedbio.2021.11.006. Epub ahead of print. PMID: 34955292.

Focused Ultrasound for Functional Neurosurgery. Lev-Tov L, Barbosa DAN, Ghanouni P, Halpern CH, Buch VP. J Neurooncol. 2022 Jan;156(1):17-22. doi: 10.1007/s11060-021-03818-3. Epub 2021 Aug 12. PMID: 34383232.

Selective Identification and Localization of Indolent and Aggressive Prostate Cancers via CorrSigNIA: an MRI-pathology Correlation and Deep Learning Framework. Bhattacharya I, Seetharaman A, Kunder C, Shao W, Chen LC, Soerensen SJC, Wang JB, Teslovich NC, Fan RE, Ghanouni P, Brooks JD, Sonn GA, Rusu M. Med Image Anal. 2022 Jan;75:102288. doi: 10.1016/j.media.2021.102288. Epub 2021 Nov 6. PMID: 34784540; PMCID: PMC8678366.

Sunnybrook Health Sciences Centre

1 Commercial Treatment

19 Clinical Research

17 Preclinical Research

14 Mechanisms of Action Research

12 Technical Research

42 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.

Contacts

Nir Lipsman, MD, PhD | Clinical Research Director | nir.lipsman@utoronto.ca
Kullervo Hynynen, PhD | Scientific Director | khynynen@sri.utoronto.ca

Commercial treatment

Neurological	Essential tremor

Clinical 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

Sunnybrook Health Sciences Centre continued

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

Research not involving thermal ablation, tissue destruction

Clinical research - Gastrointestinal	
Pancreatic tumors, malignant	Nonthermal - Drug delivery Nonthermal - Immunomodulation
Clinical research - Miscellaneous	
Head & neck tumors	Hyperthermia - Radiosensitization Nonthermal - Radiosensitization
Clinical research - Neurological	
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 health	
Breast tumors, malignant	Hyperthermia - Radiosensitization Nonthermal - Radiosensitization
Preclinical research - Cardiovascular	
Deep vein thrombosis	Histotripsy - Tissue destruction
Preclinical research - Neurological	
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 - Ophthalmological	
Retinal injury	Nonthermal - Gene delivery

Sunnybrook Health Sciences Centre continued

Publications—2021

Technical Principles and Clinical Workflow of Transcranial MR-Guided Focused Ultrasound. Meng Y, Jones RM, Davidson B, Huang Y, Pople CB, Surendrakumar S, Hamani C, Hynynen K, Lipsman N. Stereotact Funct Neurosurg. 2021;99(4):329-342. doi: 10.1159/000512111. Epub 2020 Dec 10. PMID: 33302282.

Focused Ultrasound Neuromodulation. Meng Y, Pople CB, Lea-Banks H, Hynynen K, Lipsman N, Hamani C. Int Rev Neurobiol. 2021;159:221-240. doi: 10.1016/bs.irn.2021.06.004. Epub 2021 Aug 7. PMID: 34446247.

Applications of Focused Ultrasound in the Brain: From Thermoablation to Drug Delivery. Meng Y, Hynynen K, Lipsman N. Nat Rev Neurol. 2021 Jan;17(1):7-22. doi: 10.1038/s41582-020-00418-z. Epub 2020 Oct 26. PMID: 33106619.

A High-Frequency Phased Array System for Transcranial Ultrasound Delivery in Small Animals. Rahimi S, Jones RM, Hynynen K. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Jan;68(1):127-135. doi: 10.1109/TUFFC.2020.3012868. Epub 2020 Dec 23. PMID: 32746231; PMCID: PMC7863589.

Neutrophil Recruitment and Leukocyte Response Following Focused Ultrasound and Microbubble Mediated Blood-Brain Barrier Treatments. Poon C, Pellow C, Hynynen K. Theranostics. 2021 Jan 1;11(4):1655-1671. doi: 10.7150/thno.52710. PMID: 33408773; PMCID: PMC7778596.

Vasculotide Restores the Blood-brain Barrier after Focused Ultrasound-induced Permeability in a Mouse Model of Alzheimer's Disease. Lynch M, Heinen S, Markham-Coultes K, O'Reilly M, Van Slyke P, Dumont DJ, Hynynen K, Aubert I. Int J Med Sci. 2021 Jan 1;18(2):482-493. doi: 10.7150/ijms.36775. PMID: 33390817; PMCID: PMC7757142.

Comparing Rapid Short-pulse to Tone Burst Sonication Sequences for Focused Ultrasound and Microbubble-mediated Blood-brain barrier Permeability Enhancement. McMahon D, Deng L, Hynynen K. J Control Release. 2021 Jan 10;329:696-705. doi: 10.1016/j.jconrel.2020.10.004. Epub 2020 Oct 3. PMID: 33022327.

Perfusion Fixation Methods for Preclinical Biodistribution Studies: A Comparative Assessment Using Automated Image Processing. Belhadjhamida R, Lea-Banks H, Hynynen K. Methods Appl Fluoresc. 2021 Jan 11;9(1). doi: 10.1088/2050-6120/abd37b. Erratum in: Methods Appl Fluoresc. 2021 Jun 10;9(3): PMID: 33316782.

International Legal Approaches to Neurosurgery for Psychiatric Disorders. Chandler JA, Cabrera LY, Doshi P, Fecteau S, Fins JJ, Guinjoan S, Hamani C, Herrera-Ferrá K, Honey CM, Illes J, Kopell BH, Lipsman N, McDonald PJ, Mayberg HS, Nadler R, Nuttin B, Oliveira-Maia AJ, Rangel C, Ribeiro R, Salles A, Wu H. Front Hum Neurosci. 2021 Jan 13;14:588458. doi: 10.3389/fnhum.2020.588458. PMID: 33519399; PMCID: PMC7838635.

Three-Tesla Magnetic Resonance Imaging of Patients with Deep Brain Stimulators: Results from a Phantom Study and a Pilot Study in Patients. Davidson B, Tam F, Yang B, Meng Y, Hamani C, Graham SJ, Lipsman N. Neurosurgery. 2021 Jan 13;88(2):349-355. doi: 10.1093/neuros/nyaa439. PMID: 33045736; PMCID: PMC7803432.

Novel Treatment Approaches for Brain Tumour from a Blood-Brain Barrier Perspective. Wu SK, Tsai CL, Hynynen K. Handb Exp Pharmacol. 2021 Jan 17. doi: 10.1007/164_2020_408. Epub ahead of print. PMID: 33454856.

Sunnybrook Health Sciences Centre continued

Publications—2021 continued

Systemic AAV6-synapsin-GFP Administration Results in Lower Liver Biodistribution, Compared to AAV1&2 and AAV9, with Neuronal Expression Following Ultrasound-mediated Brain Delivery. Weber-Adrian D, Kofoed RH, Silburt J, Noroozian Z, Shah K, Burgess A, Rideout S, Kügler S, Hynynen K, Aubert I. Sci Rep. 2021 Jan 21;11(1):1934. doi: 10.1038/s41598-021-81046-5. PMID: 33479314; PMCID: PMC7820310.

Psychiatric Neuromodulation: The Underappreciated Importance of Pre- and Post-treatment Care. Davidson B, Li DZ, Meng Y, Hamani C, Lipsman N. Mol Psychiatry. 2021 Feb;26(2):366-369. doi: 10.1038/s41380-020-0851-0. Epub 2020 Jul 28. PMID: 32724198.

Technology of Deep Brain Stimulation: Current Status and Future Directions. Krauss JK, Lipsman N, Aziz T, Boutet A, Brown P, Chang JW, Davidson B, Grill WM, Hariz MI, Horn A, Schulder M, Mammis A, Tass PA, Volkmann J, Lozano AM. Nat Rev Neurol. 2021 Feb;17(2):75-87. doi: 10.1038/s41582-020-00426-z. Epub 2020 Nov 26. PMID: 33244188; PMCID: PMC7116699.

MRI-guided Focused Ultrasound Enhances Drug Delivery in Experimental Diffuse Intrinsic Pontine Glioma. Ishida J, Alli S, Bondoc A, Golbourn B, Sabha N, Mikloska K, Krumholtz S, Srikanthan D, Fujita N, Luck A, Maslink C, Smith C, Hynynen K, Rutka J. J Control Release. 2021 Feb 10;330:1034-1045. doi: 10.1016/j.jconrel.2020.11.010. Epub 2020 Nov 11. PMID: 33188825.

Characterization of Ultrasound-mediated Delivery of Trastuzumab to Normal and Pathologic Spinal Cord Tissue. Smith P, Ogrodnik N, Satkunarajah J, O'Reilly MA. Sci Rep. 2021 Feb 24;11(1):4412. doi: 10.1038/s41598-021-83874-x. PMID: 33627726; PMCID: PMC7904756.

Interventional Psychiatry: An Idea Whose Time has Come? Giacobbe P, Ng E, Blumberger DM, Daskalakis ZJ, Downar J, Garcia C, Hamani C, Lipsman N, Vila-Rodriguez F, Watling M. Can J Psychiatry. 2021 Mar;66(3):316-318. doi: 10.1177/0706743720963887. Epub 2020 Oct 5. PMID: 33016106; PMCID: PMC7958196.

Investigating the Role of CB1 Endocannabinoid Transmission in the Anti-fear and Anxiolytic-like Effects of Ventromedial Prefrontal Cortex Deep Brain Stimulation. Gidyk DC, Diwan M, Gouveia FV, Giacobbe P, Lipsman N, Hamani C. J Psychiatr Res. 2021 Mar;135:264-269. doi: 10.1016/j.jpsychires.2021.01.029. Epub 2021 Jan 21. PMID: 33513472.

Ultrasound-sensitive Nanodroplets Achieve Targeted Neuromodulation. Lea-Banks H, Meng Y, Wu SK, Belhadjhamida R, Hamani C, Hynynen K. J Control Release. 2021 Apr 10;332:30-39. doi: 10.1016/j.jconrel.2021.02.010. Epub 2021 Feb 16. PMID: 33600879; PMCID: PMC8089063.

The Mechanical Potential of Ultrasound on Nervous Tissue. O'Reilly MA, Hynynen K. J Acoust Soc Am. 2021 Jun;149(6):R11. doi: 10.1121/10.0005066. PMID: 34241452.

Intravenous and Non-invasive Drug Delivery to the Mouse Basal Forebrain Using MRI-guided Focused Ultrasound. Xhima K, McMahon D, Ntiri E, Goubran M, Hynynen K, Aubert I. Bio Protoc. 2021 Jun 20;11(12):e4056. doi: 10.21769/BioProtoc.4056. PMID: 34262999; PMCID: PMC8260260.

Focused Ultrasound-Induced Blood-Spinal Cord Barrier Opening Using Short-Burst Phase-Keying Exposures in Rats: A Parameter Study. Fletcher SP, Choi M, Ramesh R, O'Reilly MA. Ultrasound Med Biol. 2021 Jul;47(7):1747-1760. doi: 10.1016/j.ultrasmedbio.2021.03.007. Epub 2021 Apr 18. PMID: 33879388.

Publications—2021 continued

Transcranial Magnetic Stimulation for the Treatment of Concussion: A Systematic Review. Mollica A, Safavifar F, Fralick M, Giacobbe P, Lipsman N, Burke MJ. Neuromodulation. 2021 Jul;24(5):803-812. doi: 10.1111/ner.13319. Epub 2020 Nov 12. PMID: 33184973.

Therapeutic Agent Delivery Across the Blood-Brain Barrier Using Focused Ultrasound. McMahon D, O'Reilly MA, Hynynen K. Annu Rev Biomed Eng. 2021 Jul 13;23:89-113. doi: 10.1146/annurev-bioeng-062117-121238. Epub 2021 Mar 22. PMID: 33752471

Role of Perivascular and Meningeal Macrophages in Outcome Following Experimental Subarachnoid Hemorrhage. Wan H, Brathwaite S, Ai J, Hynynen K, Macdonald RL. J Cereb Blood Flow Metab. 2021 Aug;41(8):1842-1857. doi: 10.1177/0271678X20980296. Epub 2021 Jan 14. PMID: 33444089; PMCID: PMC8327101.

The Therapeutic Potential of Nerve Growth Factor Combined with Blood-Brain Barrier Modulation by Focused Ultrasound for Neurodegenerative Disorders. Xhima K, Aubert I. Neural Regen Res. 2021 Sep;16(9):1783-1785. doi: 10.4103/1673-5374.306076. PMID: 33510076; PMCID: PMC8328756.

A Systematic Review on Neuromodulation Therapies for Reducing Body Weight in Patients with Obesity. Gouveia FV, Silk E, Davidson B, Pople CB, Abrahao A, Hamilton J, Ibrahim GM, Müller DJ, Giacobbe P, Lipsman N, Hamani C. Obes Rev. 2021 Oct;22(10):e13309. doi: 10.1111/obr.13309. Epub 2021 Aug 1. PMID: 34337843.

MR-guided Focused Ultrasound Liquid Biopsy Enriches Circulating Biomarkers in Patients with Brain Tumors. Meng Y, Pople CB, Suppiah S, Llinas M, Huang Y, Sahgal A, Perry J, Keith J, Davidson B, Hamani C, Amemiya Y, Seth A, Leong H, Heyn CC, Aubert I, Hynynen K, Lipsman N. Neuro Oncol. 2021 Oct 1;23(10):1789-1797. doi: 10.1093/neuonc/noab057. PMID: 33693781; PMCID: PMC8485448.

Sunnybrook Health Sciences Centre continued

Publications—2021 continued

Comparison of Computer Simulations and Clinical Treatment Results of Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS) of Uterine Fibroids. Hyvärinen M, Huang Y, David E, Hynynen K. Med Phys. 2021 Oct 3. doi: 10.1002/mp.15263. Epub ahead of print. PMID: 34601729.

Transgene Distribution and Immune Response after Ultrasound Delivery of rAAV9 and PHP.B to the Brain in a Mouse Model of Amyloidosis. Kofoed RH, Heinen S, Silburt J, Dubey S, Dibia CL, Maes M, Simpson EM, Hynynen K, Aubert I. Mol Ther Methods Clin Dev. 2021 Oct 8;23:390-405. doi: 10.1016/j.omtm.2021.10.001. PMID: 34761053; PMCID: PMC8560718.

Sub-millimetre Precision of Drug Delivery in the Brain from Ultrasound-triggered Nanodroplets. Lea-Banks H, Hynynen K. J Control Release. 2021 Oct 10;338:731-741. doi: 10.1016/j.jconrel.2021.09.014. Epub 2021 Sep 14. PMID: 34530050

MR-guided Focused Ultrasound Enhances Delivery of Trastuzumab to Her2-positive Brain Metastases. Meng Y, Reilly RM, Pezo RC, Trudeau M, Sahgal A, Singnurkar A, Perry J, Myrehaug S, Pople CB, Davidson B, Llinas M, Hyen C, Huang Y, Hamani C, Suppiah S, Hynynen K, Lipsman N. Sci Transl Med. 2021 Oct 13;13(615):eabj4011. doi: 10.1126/scitranslmed.abj4011. Epub 2021 Oct 13. PMID: 34644145

Viral Alpha-synuclein Knockdown Prevents Spreading Synucleinopathy. Menon S, Kofoed RH, Nabbouh F, Xhima K, Al-Fahoum Y, Langman T, Mount HTJ, Shihabuddin LS, Sardi SP, Fraser PE, Watts JC, Aubert I, Tandon A. Brain Commun. 2021 Oct 22;3(4):fcab247. doi: 10.1093/braincomms/fcab247. PMID: 34761222; PMCID: PMC8576194.

Implementation of a Skull-Conformal Phased Array for Transcranial Focused Ultrasound Therapy. Adams C, Jones RM, Yang SD, Kan WM, Leung K, Zhou Y, Lee KU, Huang Y, Hynynen K. IEEE Trans Biomed Eng. 2021 Nov;68(11):3457-3468. doi: 10.1109/TBME.2021.3077802. Epub 2021 Oct 19. PMID: 33950835.

Magnetic Resonance-Guided Focused Ultrasound Capsulotomy for Musical Obsessions. Davidson B, Hamani C, Rabin JS, Meng Y, Richter MA, Giacobbe P, Lipsman N. Biol Psychiatry. 2021 Nov 15;90(10):e49-e50. doi: 10.1016/j.biopsych.2020.07.005. Epub 2020 Aug 27. PMID: 32862969.

Publications—2021 continued

Brain Structure and Function in People Recovering from COVID-19 after Hospital Discharge or Self-isolation: A Longitudinal Observational Study Protocol. MacIntosh BJ, Ji X, Chen JJ, Gilboa A, Roudaia E, Sekuler AB, Gao F, Chad JA, Jegatheesan A, Masellis M, Goubran M, Rabin J, Lam B, Cheng I, Fowler R, Heyn C, Black SE, Graham SJ. CMAJ Open. 2021 Nov 30;9(4):E1114-E1119. doi: 10.9778/cmajo.20210023. PMID: 34848552; PMCID: PMC8648350.

An Ultrasound-Guided Hemispherical Phased Array for Microbubble-Mediated Ultrasound Therapy. Deng L, Yang SD, O'Reilly MA, Jones RM, Hynynen K. IEEE Trans Biomed Eng. 2021 Dec 2;PP. doi: 10.1109/TBME.2021.3132014. Epub ahead of print. PMID: 34855582.

Ultrasound Delivery of a TrkA Agonist Confers Neuroprotection to Alzheimer-associated Pathologies. Xhima K, Markham-Coultes K, Kofoed RH, Saragovi HU, Hynynen K, Aubert I. Brain. 2021 Dec 17:awab460. doi: 10.1093/brain/awab460. Epub ahead of print. PMID: 34919633.

An Acoustic Measurement Library for Non- Invasive Trans-Rodent Skull Ultrasonic Focusing at High Frequency. Rahimi S, Jones RM, Hynynen K. IEEE Trans Biomed Eng. 2021 Dec 24;PP. doi: 10.1109/TBME.2021.3138352. Epub ahead of print. PMID: 34951839.

An Unusual Case of Deep Brain Stimulation Wound Infection Secondary to COVID-19 Mask-Related Friction. Malhotra AK, Davidson B, Giacobbe P, Hamani C, Lipsman N. Stereotact Funct Neurosurg. 2022;100(1):67-69. doi: 10.1159/000518068. Epub 2021 Aug 17. PMID: 34515238; PMCID: PMC8450836.

Current State of Therapeutic Focused Ultrasound Applications in Neuro-oncology. Meng Y, Pople CB, Budiansky D, Li D, Suppiah S, Lim-Fat MJ, Perry J, Sahgal A, Lipsman N. J Neurooncol. 2022 Jan;156(1):49-59. doi: 10.1007/s11060-021-03861-0. Epub 2021 Oct 18. PMID: 34661791.

Lesional Psychiatric Neurosurgery: Meta-analysis of Clinical Outcomes Using a Transdiagnostic Approach. Davidson B, Eapen-John D, Mithani K, Rabin JS, Meng Y, Cao X, Pople CB, Giacobbe P, Hamani C, Lipsman N. J Neurol Neurosurg Psychiatry. 2022 Feb;93(2):207-215. doi: 10.1136/jnnp-2020-325308. Epub 2021 Jul 14. PMID: 34261748.

University of Maryland School of Medicine

1	Commercial Treatment		5	Clinical Research
14	Preclinical Research	11	Mechanisms of Action 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.

Contacts

Howard M. Eisenberg, MD | Program Co-Director | heisenberg@som.umaryland.edu

Elias R. Melhem, MD | Program Co-Director | emelhem@umm.edu

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

Research not involving thermal ablation, tissue destruction	
Clinical research - Neurological	
Glioblastoma	Nonthermal, BBB opening - Drug delivery
Neuropathic pain	Thermal ablation - Neuromodulation
Preclinical research - Miscellaneous	
Infection	Nonthermal, BBB opening - Drug delivery
Preclinical research - Neurological	
Brain tumors, general	Nonthermal - Amplification of cancer biomarkers Nonthermal, BBB opening Nonthermal, BBB opening - Drug delivery Nonthermal, BBB opening - Drug delivery; 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

Publications—2021

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.

Localized Blood-brain Barrier Opening in Infiltrating Gliomas with MRI-guided Acoustic Emissions-controlled Focused Ultrasound. Anastasiadis P, Gandhi D, Guo Y, Ahmed AK, Bentzen SM, Arvanitis C, Woodworth GF. Proc Natl Acad Sci U S A. 2021 Sep 14;118(37):e2103280118. doi: 10.1073/pnas.2103280118. PMID: 34504017; PMCID: PMC8449371.

Focused Ultrasound Mediated Opening of the Blood- Brain Barrier for Neurodegenerative Diseases. Fishman PS, Fischell JM. Front Neurol. 2021 Nov 4;12:749047. doi: 10.3389/fneur.2021.749047. PMID: 34803886; PMCID: PMC8599441.

Brigham and Women's Hospital

3 Commercial Treatments

5 Clinical Research

7 Preclinical Research

12 Mechanisms of Action 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

Nathan J. McDannold, PhD | Program Co-Director | njm@bwh.harvard.edu

Clare M. Tempany, MD | Program Co-Director | ctempany@bwh.harvard.edu

Commercial treatments

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 action 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

Technical research

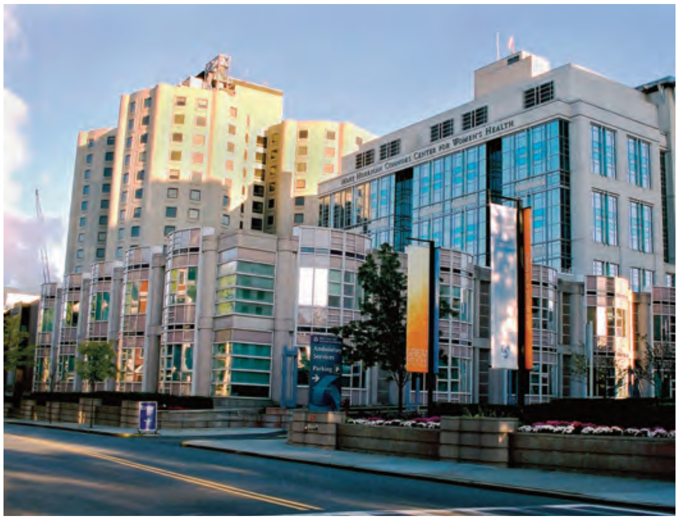
- FUS Image guidance, MR
- FUS Image guidance, Ultrasound
- FUS Physics
- FUS Simulation & treatment planning
- FUS Treatment evaluation
- FUS Treatment monitoring

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

Brigham and Women's Hospital continued



Research not involving thermal ablation, tissue destruction

Clinical research - Neurological	
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal, BBB opening - Drug delivery
Preclinical research - Miscellaneous	
Niemann-Pick disease	Nonthermal, BBB opening - Gene delivery
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 - Drug delivery
Parkinson's disease, tremor	Nonthermal - Neuromodulation

Publications—2020

Engineering Caged Microbubbles for Controlled Acoustic Cavitation and Pressure Sensing. Peng Y, Peng C, Nguyen T, Sun T, Porter T, McDannold N, Kheir JN, Polizzotti BD. ACS Materials Lett. 2021; 3(7), 978–987. doi: 10.1021/acsmaterialslett.1c00296.

Targeted Blood Brain Barrier Opening with Focused Ultrasound Induces Focal Macrophage/Microglial Activation in Experimental Autoimmune Encephalomyelitis. Schregel K, Baufeld C, Palotai M, Meroni R, Fiorina P, Wuerfel J, Sinkus R, Zhang YZ, McDannold N, White PJ, Guttmann CRG. Front Neurosci. 2021 May 12;15:665722. doi: 10.3389/fnins.2021.665722. PMID: 34054415; PMCID: PMC8149750.

Focused Ultrasound Enhances the Anesthetic Effects of Topical Lidocaine in Rats. Kim HC, Lee W, Böhlke M, Yoon K, Yoo SS. BMC Anesthesiol. 2021 May 21;21(1):158. doi: 10.1186/s12871-021-01381-y. PMID: 34020595; PMCID: PMC8138995.

Focused Ultrasound with Anti-pGlu3 Aß Enhances Efficacy in Alzheimer's Disease-like Mice via Recruitment of Peripheral Immune Cells. Sun T, Shi Q, Zhang Y, Power C, Hoesch C, Antonelli S, Schroeder MK, Caldarone BJ, Taudte N, Schenk M, Hettmann T, Schilling S, McDannold NJ, Lemere CA. J Control Release. 2021 Aug 10;336:443-456. doi: 10.1016/j.jconrel.2021.06.037. Epub 2021 Jun 26. PMID: 34186148; PMCID: PMC8373822.

Transcranial Focused Ultrasound Modulates Cortical and Thalamic Motor Activity in Awake Sheep. Kim HC, Lee W, Kunes J, Yoon K, Lee JE, Foley L, Kowsari K, Yoo SS. Sci Rep. 2021 Sep 29;11(1):19274. doi: 10.1038/s41598-021-98920-x. PMID: 34588588; PMCID: PMC8481295.

A Pilot Clinical Study of Low-intensity Transcranial Focused Ultrasound in Alzheimer's Disease. Jeong H, Im JJ, Park JS, Na SH, Lee W, Yoo SS, Song IU, Chung YA. Ultrasonography. 2021 Oct;40(4):512-519. doi: 10.14366/usg.20138. Epub 2021 Jan 16. PMID: 33730775; PMCID: PMC8446491.

Targeting Neurological Abnormalities in Lysosomal Storage Diseases. van Gool R, Tucker-Bartley A, Yang E, Todd N, Guenther F, Goodlett B, Al- Hertani W, Bodamer OA, Upadhyay J. Trends Pharmacol Sci. 2021 Nov 27:S0165-6147(21)00222-4. doi: 10.1016/j.tips.2021.11.005. Epub ahead of print. PMID: 34844772.

Lesion Location and Lesion Creation Affect Outcomes After Focused Ultrasound Thalamotomy. Segar DJ, Lak AM, Lee S, Harary M, Chavakula V, Lauro P, McDannold N, White J, Cosgrove GR. Brain. 2021 Nov 29;144(10):3089-3100. doi: 10.1093/brain/awab176. PMID: 34750621.

Focus Ultrasound-Induced Blood-Brain Barrier Opening Enhances Anti-pGlu3 Aß mAb Delivery and Amyloid-beta Plaque Clearance. Bathini P, Sun T, Shi Q, Zhang Y, Taudte N, Schenk M, Hettmann T, Schilling S, McDannold N, Lemere CA. Alzheimers Dement. 2021 Dec;17 Suppl 2:e058725. doi: 10.1002/alz.058725. PMID: 34971185.

ICR and The Royal Marsden

1 Commercial Treatment

3 Clinical Research

6 Preclinical Research

11 Mechanisms of Action Research

8 Technical 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.

1 Veterinary Research

Contact

Gail R. ter Haar, PhD, DSc | Program Director | gail.terhaar@icr.ac.uk

Commercial treatment

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 - Cardiovascular	
Twin-twin transfusion syndrome	Nonthermal - Vascular occlusion
Preclinical research - Gastrointestinal	
Pancreatic tumors	Nonthermal - Immunomodulation
Preclinical research - Neurological	
Glioblastoma	Nonthermal - Drug delivery, vehicle
Veterinary research - Urological	
Bladder tumors	Thermal ablation - Immunomodulation

Publications—2021

HSP90 Inhibition Acts Synergistically with Heat to Induce a Pro-immunogenic Form of Cell Death in Colon Cancer Cells. Mouratidis PXE, ter Haar G. Int J Hyperthermia. 2021;38(1):1443-1456. doi: 10.1080/02656736.2021.198303 PMID: 34612127.

Quantitative Prediction of the Extent of Pelvic Tumour Ablation by Magnetic Resonance-guided High Intensity Focused Ultrasound. Lam NFD, Rivens I, Giles SL, Harris E, deSouza NM, ter Haar G. Int J Hyperthermia. 2021;38(1):1111-1125. doi: 10.1080/02656736.2021.1959658. PMID: 34325608.

Feasibility of Palliating Recurrent Gynecological Tumors with MRGHIFU: Comparison of Symptom, Quality-of-Life, and Imaging Response in Intra and Extra-pelvic Disease. Imseeh G, Giles SL, Taylor A, Brown MRD, Rivens I, Gordon-Williams R, ter Haar G, deSouza NM. Int J Hyperthermia. 2021;38(1):623-632. doi: 10.1080/02656736.2021.1904154. PMID: 33882792.

A History of High Intensity Focused Ultrasound (HIFU) Therapy. ter Haar GR. Medical Physics International 2021 6, 643-659.

Ultrasound-Responsive Nanocarriers in Cancer Treatment: A Review. Awad NS, Paul V, AlSawaftah NM, ter Haar G, Allen TM, Pitt WG, Husseini GA. ACS Pharmacol Transl Sci. 2021 Mar 3;4(2):589-612. doi: 10.1021/acsptsci.0c00212. PMID: 33860189; PMCID: PMC8033618.

Pulsed Focused Ultrasound Can Improve the Anti-cancer Effects of Immune Checkpoint Inhibitors in Murine Pancreatic Cancer. Mouratidis PXE, Costa M, Rivens I, Repasky EE, ter Haar G. J R Soc Interface. 2021 Jul;18(180):20210266. doi: 10.1098/rsif.2021.0266. Epub 2021 Jul 7. PMID: 34229458; PMCID: PMC8261215.

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.

Inertial Cavitation Behaviors Induced by Nonlinear Focused Ultrasound Pulses. Bawiec CR, Rosnitskiy PB, Peek AT, Maxwell AD, Kreider W, ter Haar GR, Sapozhnikov OA, Khokhlova VA, Khokhlova TD. IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Sep;68(9):2884-2895. doi: 10.1109/TUFFC.2021.3073347. Epub 2021 Aug 27. PMID: 33861702; PMCID: PMC8500614.

A Review of High-Intensity Focused Ultrasound in Urology. Cranston D, Leslie T, ter Haar G. Cancers (Basel). 2021 Nov 14;13(22):5696. doi: 10.3390/cancers13225696. PMID: 34830852; PMCID: PMC8616438.

Methods of Monitoring Thermal Ablation of Soft Tissue Tumors - A Comprehensive Review. Geoghegan R, ter Haar G, Nightingale K, Marks L, Natarajan S. Med Phys. 2021 Dec 29. doi: 10.1002/mp.15439. Epub ahead of print. PMID: 34965307.

University of Virginia Health System

2 Commercial Treatments

13 Clinical Research

20 Preclinical Research

19 Mechanisms of Action 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

Richard J. Price, PhD | Program Co-Director | rprice@virginia.edu

Alan H. Matsumoto, MD | Program Co-Director | ahm4d@virginia.edu

Commercial treatments

Neurological	Essential tremor
Women's health	Uterine fibroids

Clinical research

Gastrointestinal	Esophageal tumors, Gastric tumors
Miscellaneous	Melanoma, Multiple tumors[1]
Neurological	Cancer pain, Epilepsy, Glioblastoma
Pulmonary	Lung cancer
Women's health	Breast tumors, benign; Breast tumors, malignant; Cervical tumors, Ovarian tumors

Preclinical research

Cardiovascular	Arteriovenous malformations, Peripheral artery disease
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 action 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

Research not involving thermal ablation, tissue destruction	
Clinical research - Gastrointestinal	
Esophageal tumors	Thermal ablation - Immunomodulation
Gastric tumors	Thermal ablation - Immunomodulation
Clinical research - Miscellaneous	
Melanoma	Thermal ablation - Immunomodulation
Multiple tumors[1]	Thermal ablation - Immunomodulation
Clinical research - Neurological	
Glioblastoma	Nonthermal, BBB opening - drug delivery
Clinical research - Pulmonary	
Lung cancer	Thermal ablation - Immunomodulation
Clinical research - Women's health	
Cervical tumors	Thermal ablation - Immunomodulation
Ovarian tumors	Thermal ablation - Immunomodulation
Preclinical research - Cardiovascular	
Arteriovenous malformations	Nonthermal - Tissue destruction
Peripheral artery disease	Nonthermal - Drug delivery, vehicle
Preclinical research - Gastrointestinal	
Pancreatic tumors	Thermal ablation - Immunomodulation
Preclinical research - Miscellaneous	
Melanoma	Thermal ablation - Immunomodulation
Preclinical research - Neurological	
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
Preclinical research - Women's health	
Breast tumors, malignant	Thermal ablation - Immunomodulation

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.

Focused Ultrasound in Neuroscience. State of the Art and Future Perspectives. Giammalva GR, Gagliardo C, Marrone S, Paolini F, Gerardi RM, Umana GE, Yagmurlu K, Chaurasia B, Scalia G, Midiri F, La Grutta L, Basile L, Gulì C, Messina D, Pino MA, Graziano F, Tumbiolo S, Iacopino DG, Maugeri R. Brain Sci. 2021 Jan 10;11(1):84. doi: 10.3390/brainsci11010084. PMID: 33435152; PMCID: PMC7827488.

Single-cell Mapping of Focused Ultrasound-transfected Brain. Mathew AS, Gorick CM, Price RJ. Gene Ther. 2021 Feb 1:10.1038/s41434-021-00226-0. doi: 10.1038/s41434-021-00226-0. Epub ahead of print. PMID: 33526842; PMCID: PMC8325700.

Bubble Cloud Behavior and Ablation Capacity for Histotripsy Generated from Intrinsic or Artificial Cavitation Nuclei. Edsall C, Khan ZM, Mancia L, Hall S, Mustafa W, Johnsen E, Klibanov AL, Durmaz YY, Vlaisavljevich E. Ultrasound Med Biol. 2021 Mar;47(3):620-639. doi: 10.1016/j.ultrasmedbio.2020.10.020. Epub 2020 Dec 10. PMID: 33309443; PMCID: PMC8514340.

Pulsed Ultrasound of the Spleen Prolongs Survival of Rats with Severe Intra-abdominal Sepsis. Zhang A, Charles EJ, Xing J, Sawyer RG, Yang Z. J Surg Res. 2021 Mar;259:97-105. doi: 10.1016/j.jss.2020.11.005. Epub 2020 Dec 3. PMID: 33279849; PMCID: PMC7897287.

Contrast-Enhanced Ultrasound Assisted Surgery of Intramedullary Spinal Cord Tumors: Analysis of Technical Benefits and Intra-operative Microbubble Distribution Characteristics. Vetrano IG, Gennari AG, Erbetta A, Acerbi F, Nazzi V, DiMeco F, Prada F. Ultrasound Med Biol. 2021 Mar;47(3):398-407. doi: 10.1016/j.ultrasmedbio.2020.10.017. Epub 2020 Dec 19. PMID: 33349517.

Sonodynamic Therapy for the Treatment of Intracranial Gliomas. D'Ammando A, Raspagliesi L, Gionso M, Franzini A, Porto E, Di Meco F, Durando G, Pellegatta S, Prada F. J Clin Med. 2021 Mar 6;10(5):1101. doi: 10.3390/jcm10051101. PMID: 33800821; PMCID: PMC7961476.

ImmunoPET-informed Sequence for Focused Ultrasound-targeted mCD47 Blockade Controls Glioma. Sheybani ND, Breza VR, Paul S, McCauley KS, Berr SS, Miller GW, Neumann KD, Price RJ. J Control Release. 2021 Mar 10;331:19-29. doi: 10.1016/j.jconrel.2021.01.023. Epub 2021 Jan 18. PMID: 33476735; PMCID: PMC7946780.

Transcranial Focused Ultrasound Phase Correction Using the Hybrid Angular Spectrum Method. Leung SA, Moore D, Webb TD, Snell J, Ghanouni P, Butts Pauly K. Sci Rep. 2021 Mar 22;11(1):6532. doi: 10.1038/s41598-021-85535-5. PMID: 33753771; PMCID: PMC7985511.

Anterior Insula Stimulation Increases Pain Threshold in Humans: A Pilot Study. Liu CC, Moosa S, Quigg M, Elias WJ. J Neurosurg. 2021 Apr 2:1-6. doi: 10.3171/2020.10.JNS203323. Epub ahead of print. PMID: 33799301.

Pulsed Ultrasound Attenuates the Hyperglycemic Exacerbation of Myocardial Ischemia-reperfusion Injury. Charles EJ, Tian Y, Zhang A, Wu D, Mehaffey JH, Gigliotti JC, Klibanov AL, Kron IL, Yang Z. J Thorac Cardiovasc Surg. 2021 Apr;161(4):e297-e306. doi: 10.1016/j.jtcvs.2019.10.096. Epub 2019 Nov 2. PMID: 31839230; PMCID: PMC7195241.

Publications—2021 continued

A Preclinical Study of Diffusion-weighted MRI Contrast as an Early Indicator of Thermal Ablation. Allen SP, Prada F, Xu Z, Gatesman J, Feng X, Sporkin H, Gilbo Y, DeCleene S, Pauly KB, Meyer CH. Magn Reson Med. 2021 Apr;85(4):2145-2159. doi: 10.1002/mrm.28537. Epub 2020 Nov 11. PMID: 33174639.

The Inhibitory Thermal Effects of Focused Ultrasound on an Identified, Single Motoneuron. Collins MN, Legon W, Mesce KA. eNeuro. 2021 Apr 30;8(2):ENEURO.0514-20.2021. doi: 10.1523/ENEURO.0514-20.2021. PMID: 33853851; PMCID: PMC8174046.

High-Precision Assessment of Chemoradiotherapy of Rectal Cancer with Near-Infrared Photoacoustic Microscopy and Deep Learning. Klibanov AL. Radiology. 2021 May;299(2):359-361. doi: 10.1148/radiol.2021210261. Epub 2021 Mar 23. PMID: 33759582; PMCID: PMC8103911.

Comparison of Contrast-Enhanced Ultrasound Versus Magnetic Resonance Imaging in the Detection and Characterization of Uterine Leiomyomas. Chhabra P, Daugherty R, LeNoir AM, Grilli C, Makai G, Patel N, DeMauro C. J Ultrasound Med. 2021 Jun;40(6):1147-1153. doi: 10.1002/jum.15495. Epub 2020 Sep 15. PMID: 32930416.

Sonodynamic Therapy for Metastatic Melanoma to the Brain. Sheehan D, Sheehan K, Sheehan J. J Neurooncol. 2021 Jun;153(2):373-374. doi: 10.1007/s11060-021-03768-w. Epub 2021 May 10. PMID: 33970404.

Quantitative Analysis of In-vivo Microbubble Distribution in the Human Brain. Prada F, Gennari AG, Linville IM, Mutersbaugh ME, Chen Z, Sheybani N, DiMeco F, Padilla F, Hossack JA. Sci Rep. 2021 Jun 3;11(1):11797. doi: 10.1038/s41598-021-91252-w. PMID: 34083642; PMCID: PMC8175375.

Intracranial Sonodynamic Therapy With 5-Aminolevulinic Acid and Sodium Fluorescein: Safety Study in a Porcine Model. Raspagliesi L, D'Ammando A, Gionso M, Sheybani ND, Lopes MB, Moore D, Allen S, Gatesman J, Porto E, Timbie K, Franzini A, Di Meco F, Sheehan J, Xu Z, Prada F. Front Oncol. 2021 Jun 21;11:679989. doi: 10.3389/fonc.2021.679989. PMID: 34235081; PMCID: PMC8256685.

Can Low-Intensity Pulsed Ultrasound Treat Discrete Pulmonary Lesions in Patients With COVID-19? Prada F, Cogliati C, Wu MA, Durando G, Montano N, Gaspare Vetrano I, Calliada F, Bastianello S, Pichiecchio A, Padilla F. J Ultrasound Med. 2021 Jul;40(7):1445-1450. doi: 10.1002/jum.15522. Epub 2020 Oct 19. PMID: 33073873.

How to Perform Intra-Operative Contrast-Enhanced Ultrasound of the Brain-A WFUMB Position Paper. Prada F, Vetrano IG, Gennari AG, Mauri G, Martegani A, Solbiati L, Sconfienza LM, Quaia E, Kearns KN, Kalani MYS, Park MS, DiMeco F, Dietrich C. Ultrasound Med Biol. 2021 Aug;47(8):2006-2016. doi: 10.1016/j.ultrasmedbio.2021.04.016. Epub 2021 May 24. Erratum in: Ultrasound Med Biol. 2021 Jul 12;: PMID: 34045096.

Non-invasive, Neurotoxic Surgery Reduces Seizures in a Rat Model of Temporal Lobe Epilepsy. Zhang Y, Buckmaster PS, Qiu L, Wang J, Keunen O, Ghobadi SN, Huang A, Hou Q, Li N, Narang S, Habte FG, Bertram EH, Lee KS, Wintermark M. Exp Neurol. 2021 Sep;343:113761. doi: 10.1016/j.expneurol.2021.113761. Epub 2021 May 12. PMID: 33991523.

University of Virginia Health System continued

Publications—2021 continued

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.

Preparation and Characterization of Targeted Microbubbles. Diakova GB, Wang M, Unnikrishnan S, Klibanov AL. J Vis Exp. 2021 Sep 4;(175). doi: 10.3791/62370. PMID: 34542531.

Thermal Neuromodulation with Focused Ultrasound: Implications for the Technique of Subthreshold Testing. Neurosurgery. Sammartino F, Snell J, Eames M, Krishna V. 2021 Sep 15;89(4):610-616. doi: 10.1093/neuros/nyab238. PMID: 34245158

DNA Double-Strand Breaks in Murine Mammary Tumor Cells Induced by Combined Treatment with Doxorubicin and Controlled Stable Cavitation. Fant C, Granzotto A, Mestas JL, Ngo J, Lafond M, Lafon C, Foray N, Padilla F. Ultrasound Med Biol. 2021 Oct;47(10):2941-2957. doi: 10.1016/j.ultrasmedbio.2021.05.028. Epub 2021 Jul 24. PMID: 34315620.

Pulsed Ultrasound for Bone Regeneration - Outcomes and Hurdles in the Clinical Application: A Systematic Review. Puts R, Vico R, Beilfuß N, Shaka M, Padilla F, Raum K. Eur Cell Mater. 2021 Oct 14;42:281-311. doi: 10.22203/eCM.v042a20. PMID: 34647316.

Multiple Regression Analysis of a Comprehensive Transcriptomic Data Assembly Elucidates Mechanically-and Biochemically Driven Responses to Focused Ultrasound Blood-brain Barrier Disruption. Mathew AS, Gorick CM, Price RJ. Theranostics. 2021 Oct 11;11(20):9847-9858. doi: 10.7150/thno.65064. PMID: 34815790; PMCID: PMC8581408.\

Dynamic Filtering of Adherent and Non-adherent Microbubble Signals Using Singular Value Thresholding and Normalized Singular Spectrum Area Techniques. Herbst EB, Klibanov AL, Hossack JA, Mauldin FW Jr. Ultrasound Med Biol. 2021 Nov;47(11):3240-3252. doi: 10.1016/j.ultrasmedbio.2021.06.019. Epub 2021 Aug 8. PMID: 34376299; PMCID: PMC8691388.

Contrast-enhanced Ultrasound of the Pediatric Brain. Hwang M, Barnewolt CE, Jüngert J, Prada F, Sridharan A, Didier RA. Pediatr Radiol. 2021 Nov;51(12):2270-2283. doi: 10.1007/s00247-021-04974-4. Epub 2021 Feb 18. PMID: 33599780

Functional Intersections Between Extracellular Vesicles and Oncolytic Therapies. Clark RA, Garman ZG, Price RJ, Sheybani ND. Trends Pharmacol Sci. 2021 Nov;42(11):883-896. doi: 10.1016/j.tips.2021.09.001. Epub 2021 Sep 28. PMID: 34598797; PMCID: PMC8526420.

From Focused Ultrasound Tumor Ablation to Brain Blood Barrier Opening for High Grade Glioma: A Systematic Review. Paun L, Moiraghi A, Jannelli G, Nouri A, DiMeco F, Pallud J, Meling TR, Momjian S, Schaller K, Prada F, Migliorini D. Cancers (Basel). 2021 Nov 10;13(22):5614. doi: 10.3390/cancers13225614. PMID: 34830769; PMCID: PMC8615744.

Ultrasound-targeted Nucleic Acid Delivery for Solid Tumor Therapy. Schwartz MR, Debski AC, Price RJ. J Control Release. 2021 Nov 10;339:531-546. doi: 10.1016/j.jconrel.2021.10.010. Epub 2021 Oct 14. PMID: 34655678; PMCID: PMC8599656.

Publications—2021 continued

Computational Model of Brain Endothelial Cell Signaling Pathways Predicts Therapeutic Targets for Cerebral Pathologies. Gorick CM, Saucerman JJ, Price RJ. J Mol Cell Cardiol. 2021 Nov 16;164:17-28. doi: 10.1016/j.yjmcc.2021.11.005. Epub ahead of print. PMID: 34798125.

Noninvasive Disconnection of Targeted Neuronal Circuitry Sparing Axons of Passage and Nonneuronal Cells. Wang Y, Anzivino MJ, Zhang Y, Bertram EH, Woznak J, Klibanov AL, Dumont E, Wintermark M, Lee KS. J Neurosurg. 2021 Nov 19:1-11. doi: 10.3171/2021.7.JNS21123. Epub ahead of print. PMID: 34798617.

Vancomycin-decorated Microbubbles as a Theranostic Agent for Staphylococcus Aureus Biofilms. Kouijzer JJP, Lattwein KR, Beekers I, Langeveld SAG, Leon-Grooters M, Strub JM, Oliva E, Mislin GLA, de Jong N, van der Steen AFW, Klibanov AL, van Wamel WJB, Kooiman K. Int J Pharm. 2021 Nov 20;609:121154. doi: 10.1016/j.ijpharm.2021.121154. Epub 2021 Oct 6. PMID: 34624449.

Ultrasound Molecular Imaging for the Guidance of Ultrasound-Triggered Release of Liposomal Doxorubicin and Its Treatment Monitoring in an Orthotopic Prostatic Tumor Model in Rat. Helbert A, von Wronski M, Mestas JL, Tardy I, Bettinger T, Lafon C, Hyvelin JM, Padilla F. Ultrasound Med Biol. 2021 Dec;47(12):3420-3434. doi: 10.1016/j.ultrasmedbio.2021.07.022.

Profiling of the Immune Landscape in Murine Glioblastoma Following Blood Brain/Tumor Barrier Disruption with MR Image-guided Focused Ultrasound. Sheybani ND, Witter AR, Garrison WJ, Miller GW, Price RJ, Bullock TNJ. J Neurooncol. 2022 Jan;156(1):109-122. doi: 10.1007/s11060-021-03887-4. Epub 2021 Nov 3. PMID: 34734364; PMCID: PMC8714701.

Sonodynamic Therapy for Gliomas. Bunevicius A, Pikis S, Padilla F, Prada F, Sheehan J. J Neurooncol. 2022 Jan;156(1):1-10. doi: 10.1007/s11060-021-03807-6. Epub 2021 Jul 12. PMID: 34251601.

Low-Cost 3-D Hydrophone Scanning Tank with MATLAB GUI Control. Clinard S, Wettstone E, Moore D, Snell J, Padilla F, Eames M. Ultrasound Med Biol. 2022 Jan;48(1):157-163. doi: 10.1016/j.ultrasmedbio.2021.09.022. Epub 2021 Oct 23. PMID: 34702638.

Transcranial Magnetic Resonance-Guided Histotripsy for Brain Surgery: Pre-clinical Investigation. Lu N, Gupta D, Daou BJ, Fox A, Choi D, Sukovich JR, Hall TL, Camelo-Piragua S, Chaudhary N, Snell J, Pandey AS, Noll DC, Xu Z. Ultrasound Med Biol. 2022 Jan;48(1):98-110. doi: 10.1016/j.ultrasmedbio.2021.09.008. Epub 2021 Oct 4. PMID: 34615611.

Pilot Study of Focused Ultrasound for Drug-resistant Epilepsy. Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, Peng SJ, Liu HL, Yu HY. Epilepsia. 2022 Jan;63(1):162-175. doi: 10.1111/epi.17105. Epub 2021 Nov 2. PMID: 34729772.

Development of and Gathering Validity Evidence for a Theoretical Test in Contrast-Enhanced Ultrasound. Jacobsen N, Nolsøe CP, Konge L, Graumann O, Dietrich CF, Sidhu PS, Gilja OH, Meloni MF, Berzigotti A, Harvey CJ, Deganello A, Prada F, Lerchbaumer MH, Laursen CB. Ultrasound Med Biol. 2022 Feb;48(2):248-256. doi: 10.1016/j.ultrasmedbio.2021.10.016. Epub 2021 Nov 21. PMID: 34815128.

Page intentionally left blank

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.

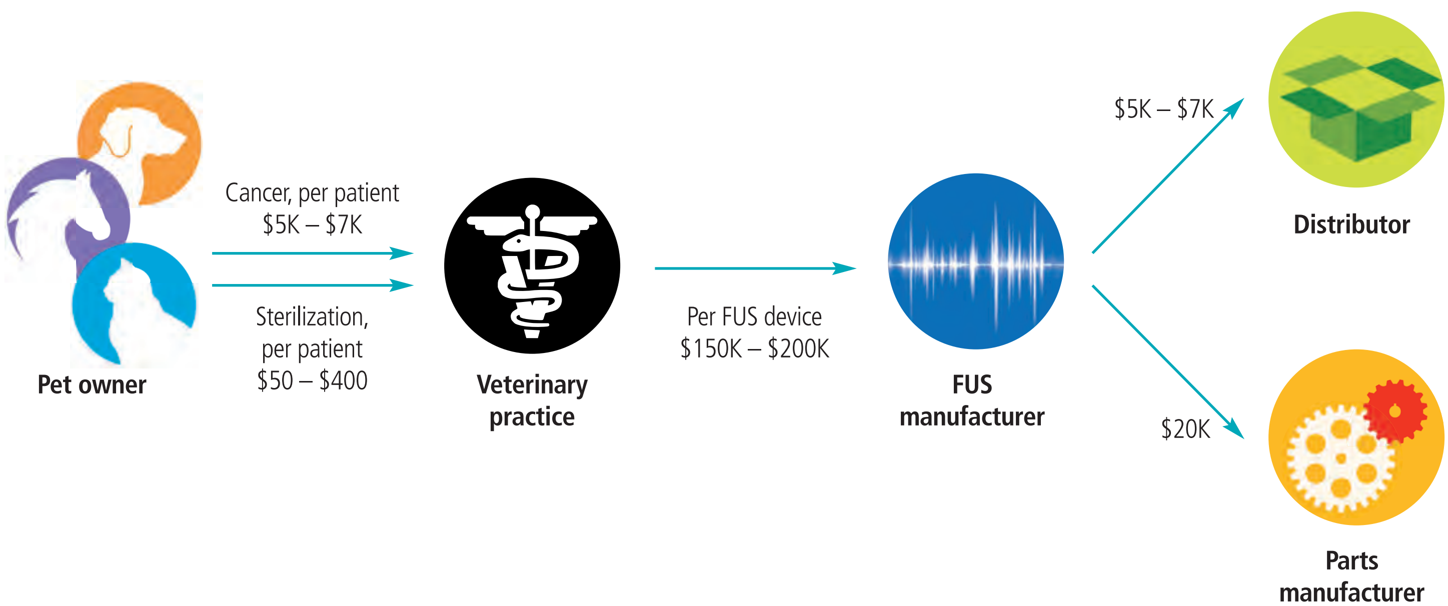
Focused ultrasound's ability to noninvasively treat tissue and enhance the efficacy of some therapies, thus reducing the length of hospital stays and total cost, is a crucial benefit for pet owners who pay out of pocket.

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-priority-research-areas/veterinary-program.

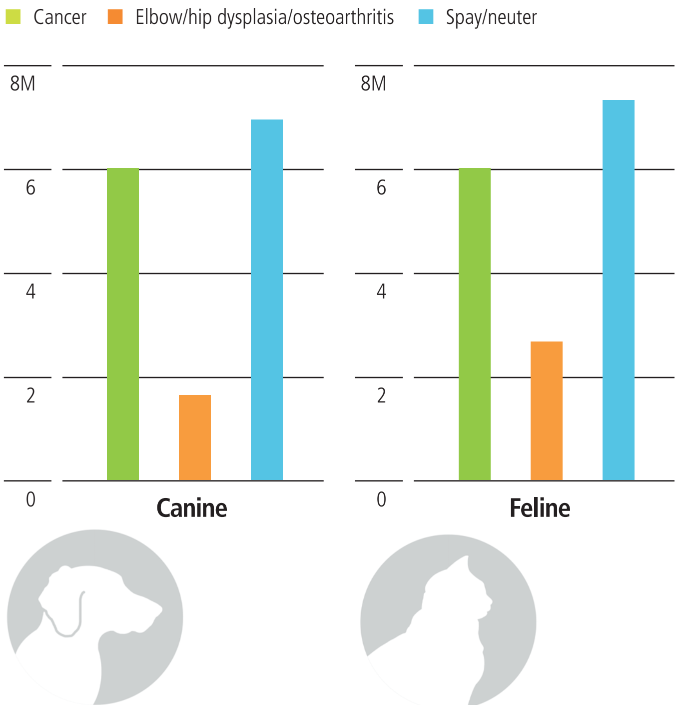
Value Chain



Proposed Market

Projected Patient Base

Millions per year in US



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

Adopters Market

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 stage: Proposed, Clinical trial, Clinical practice

Species: Canine, Feline, Equine

MOAs: Histotripsy, Hyperthermia, Nonthermal, Nonthermal, BBB opening, Thermal ablation

Oncology

	Development stage	Species	MOAs
Soft tissue tumors*	Clinical practice (2018)	Canine, Feline	Thermal ablation - immunomodulation
	Clinical trial (2018)	Canine, Feline	Nonthermal - drug delivery
	Clinical trial (2020)	Canine, Feline	Histotripsy - immunomodulation
	Clinical trial (2021)	Canine	Nonthermal - sonodynamic therapy
Bladder cancer	Clinical trial (2020)	Canine	Thermal - ablation, tissue destruction
Brain tumors	Clinical trial (2021)	Canine	Histotripsy - tissue destruction
Chronic wound	Clinical trial (2018)	Canine	Nonthermal - drug delivery
Hepatocellular carcinoma	Clinical trial (2016)	Canine	Nonthermal - gene delivery
	Proposed (2021)	Canine	Histotripsy - tissue destruction
Oral tumors**	Clinical trial (2019)	Canine	Thermal ablation -immunomodulation
Osteosarcoma	Clinical trial (2020)	Canine	Histotripsy - immunomodulation
Sarcomas	Clinical trial (2021)	Feline	Histotripsy - immunomodulation
Lung cancer	Proposed (2018)	Canine	Thermal ablation - tissue destruction
Sarcoids	Proposed (2018)	Equine	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 stage: Proposed, Clinical trial, Clinical practice
Species: Canine, Feline, Equine
MOAs: Histotripsy, Hyperthermia, Nonthermal, Nonthermal, BBB opening, Thermal ablation

Indication	Development stage	Species	MOAs
Pain			
Elbow/hip dysplasia	Clinical trial 2018	Canine	Nonthermal
Osteoarthritis	Clinical trial 2018	Canine, Feline, Equine	Nonthermal
Soft tissue injuries	Clinical trial 2018	Canine, Equine	Nonthermal
Miscellaneous			
Diabetes	Proposed 2021	Feline	Nonthermal - neuromodulation
Epilepsy	Proposed 2020	Canine	Thermal ablation - tissue destruction
Kidney stones	Proposed 2020	Feline	Nonthermal - kidney stone fragmentation
Spay/neuter	Proposed 2018	Feline, Equine	Thermal ablation - tissue destruction

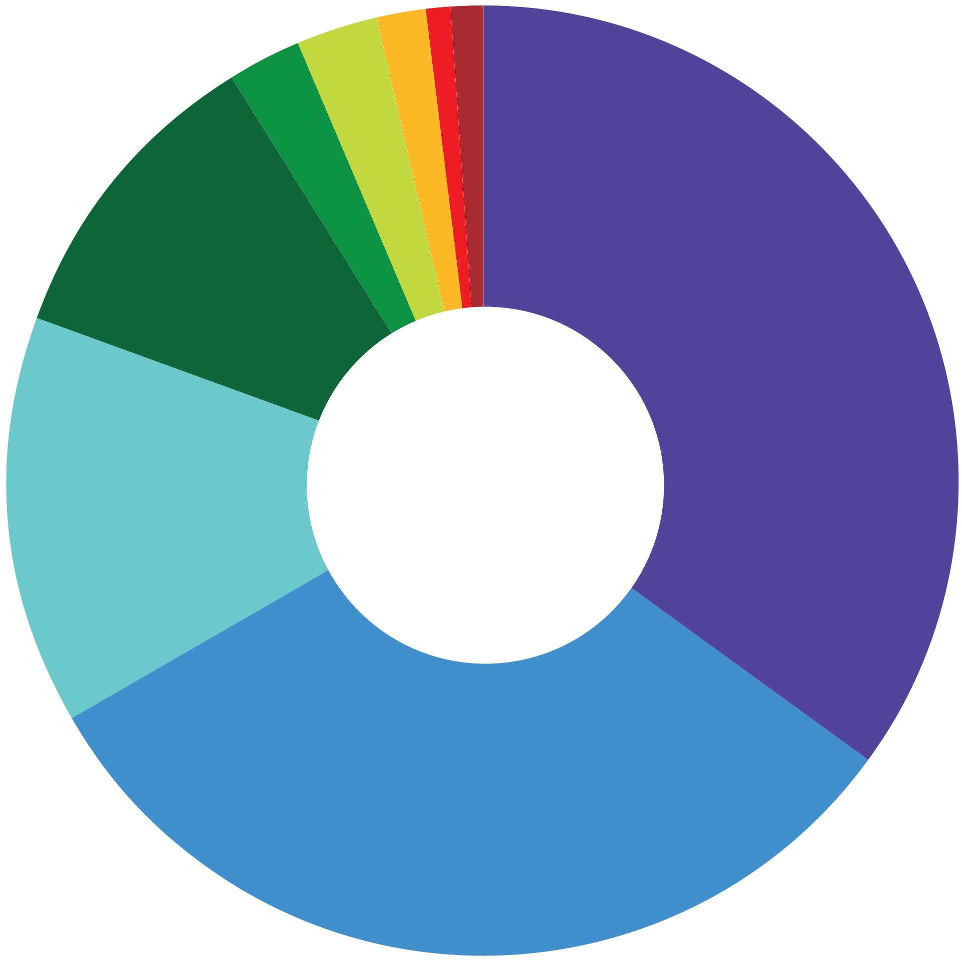
Veterinary advances in 2021

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

114 total treatments

- 40 Osteoarthritis
- 36 Soft tissue tumors
- 16 Osteosarcoma
- 12 Oral tumors**
- 3 Chronic wound
- 3 Hepatocellular carcinoma
- 2 Soft tissue injuries
- 1 Nasal chondrosarcoma
- 1 Thyroid carcinoma



*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).

NEW

Common Diseases in Popular Breeds

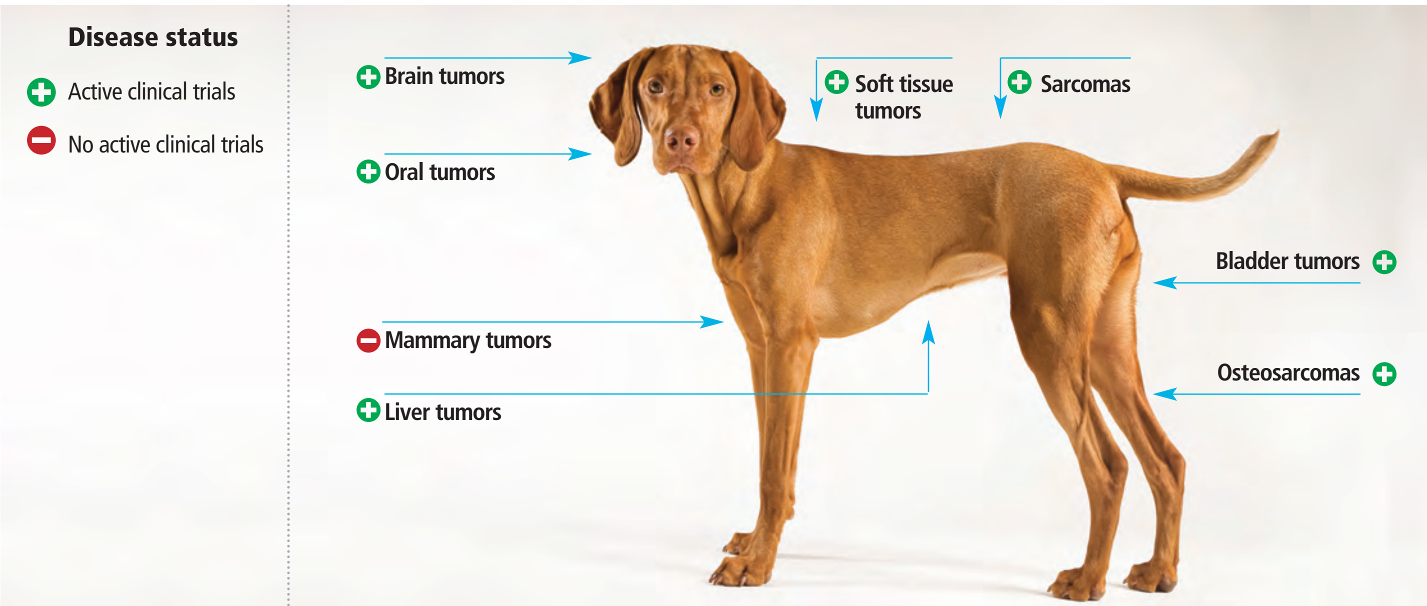
Most popular breeds	Common ailments	Common cancers	Cancer caused mortality
Labrador Retriever	Elbow and hip dysplasia, Obesity, Heart disorders, Hereditary myopathy, Eye conditions, Bloat	Lymphoma, Mast cell tumor, Melanoma, Osteosarcoma, Hemangiosarcoma	31%
German Shepherd	Degenerative myelopathy, Hip 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	Dogs and cats— 6,000+ cases per year	Systemic chemotherapy
Hyperthyroid	Cats over age 10— 12.5%	Radioiodine therapy
Oral tumors	Dogs— 15,000+ cases per year	Aggressive resection
Osteosarcomas	Dogs— 10,000+ cases per year	Amputation, chemotherapy, radiation
Sarcomas	Dogs and cats— 80,000+ cases per years	Surgery and radiation, amputation often required

In the News

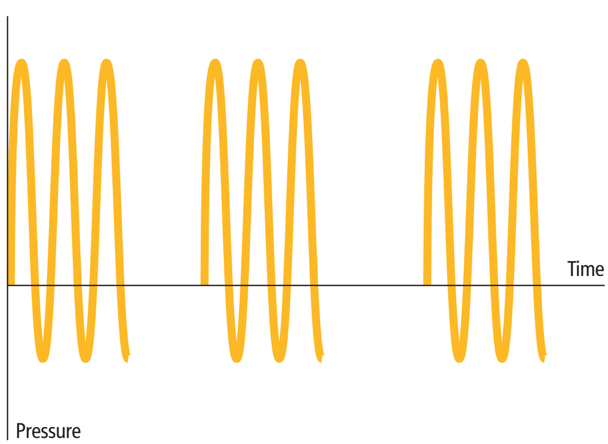
New Center

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

NEW

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.

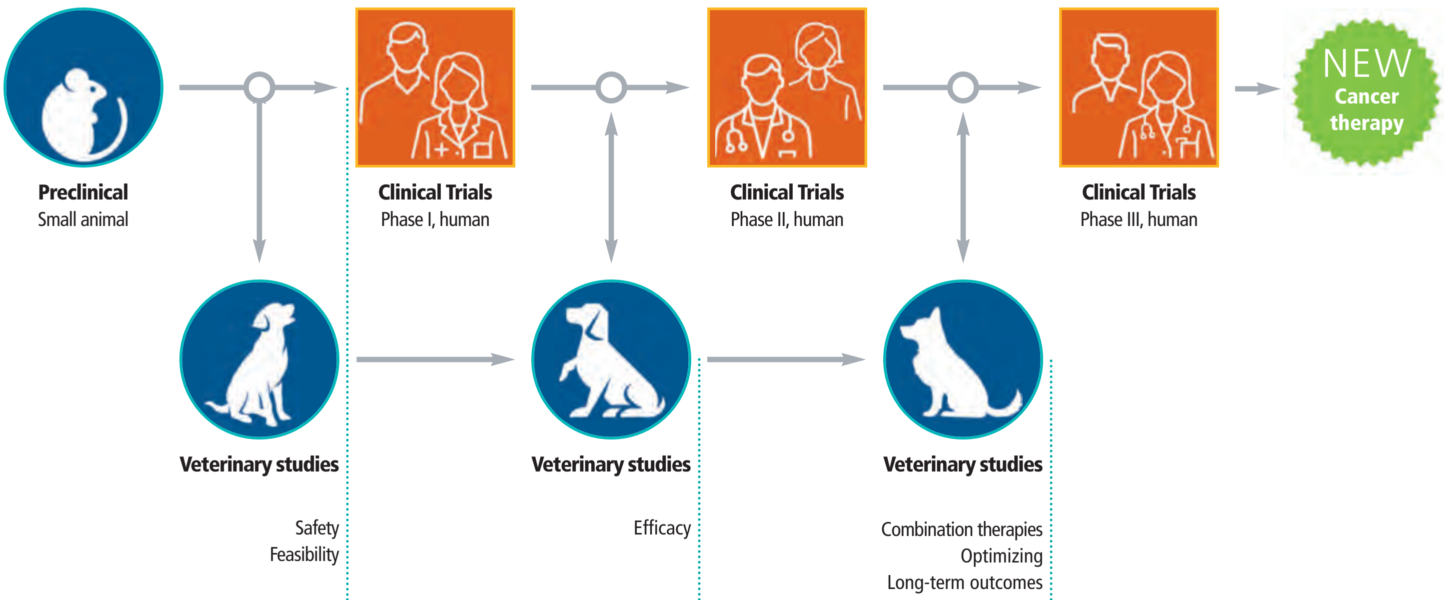
Osteosarcoma presents the perfect example of the potential for synergy between veterinary and human medicine. In humans, osteosarcoma is a rare disease typically found in the pediatric population. While the 5-year survival rate is 60%, curative treatment requires removal of the affected bone. This often 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 50,000 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

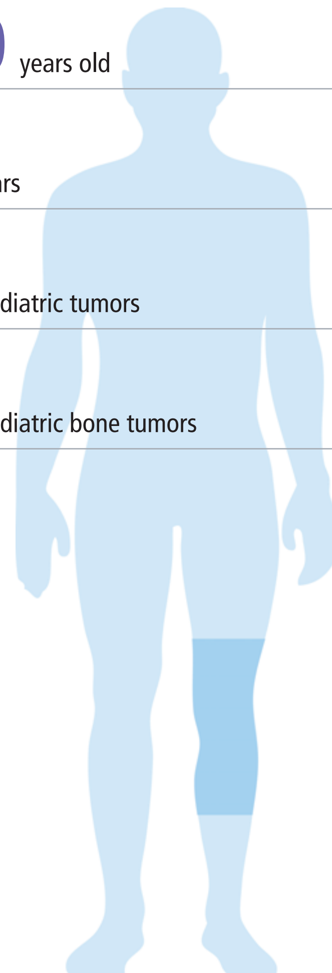
Comparative oncology
Integrated and comparative drug development plan



Case Study continued
Osteosarcoma

Canine and human population comparison

Characteristics	Canines	Humans
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



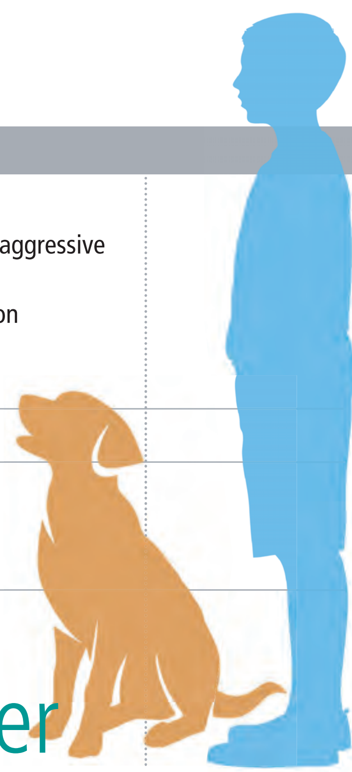
Case Study continued
Osteosarcoma

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 50,000 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	✓ **10**x 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

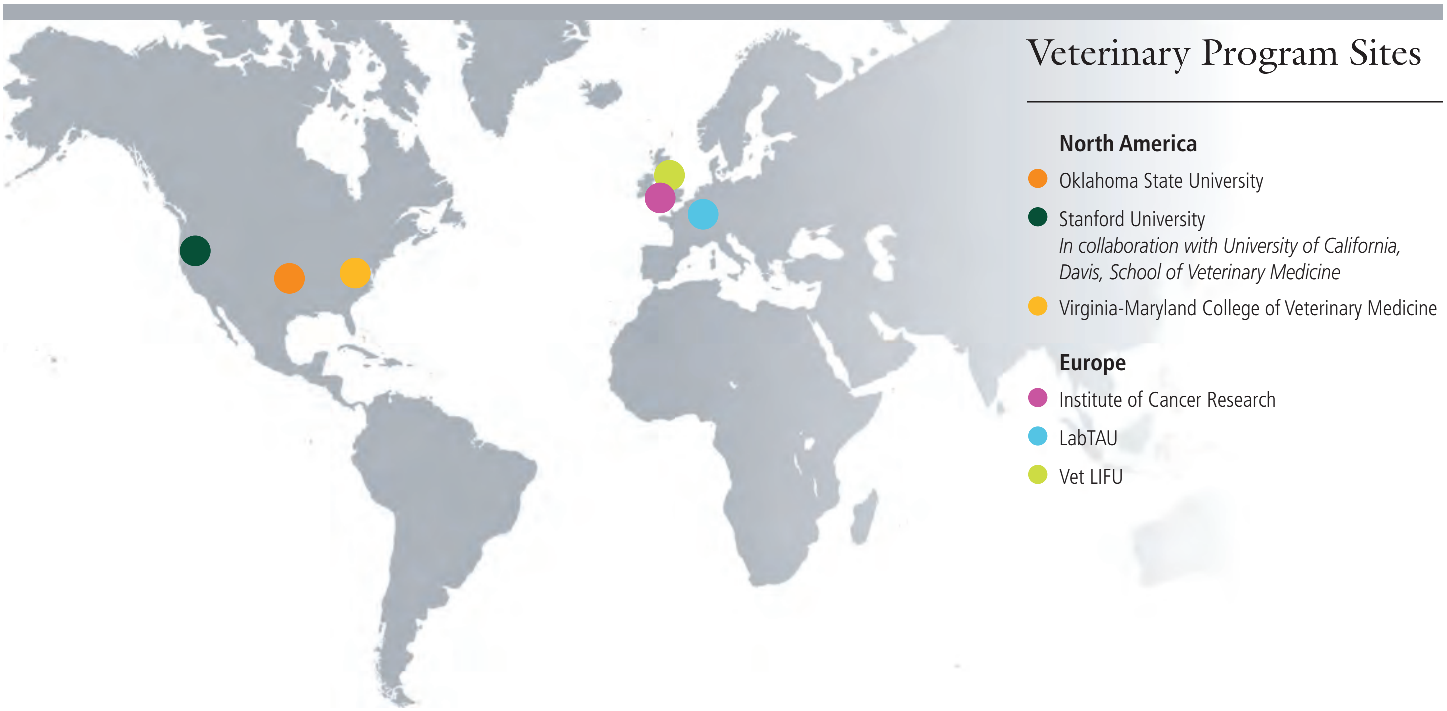
Latifi M, Hay A, Carroll J, et al. Focused ultrasound tumour ablation in small animal oncology. Vet Comp Oncol. 2021;19(3):411-419. doi:10.1111/vco.12742

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

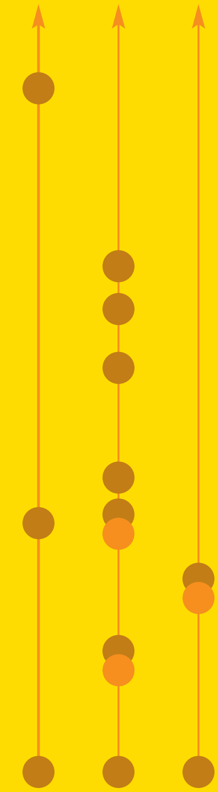


2022

State of Commercialization

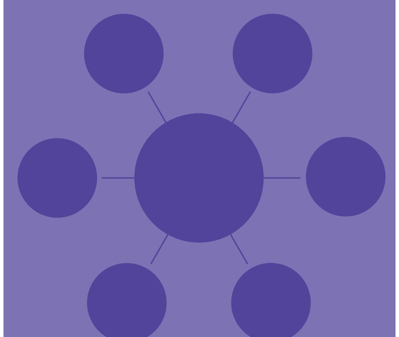
Focused Ultrasound Foundation

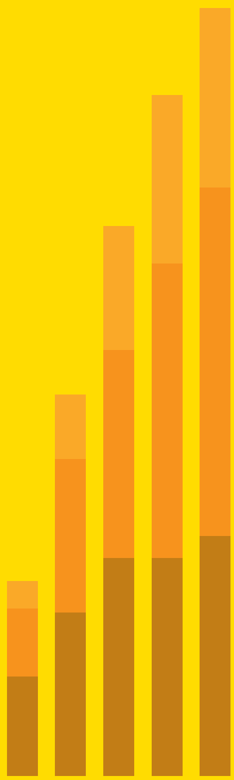
11
new FUS
industry companies



32
indications with
regulatory approvals

5
indications with
US reimbursement





59
FUS device manufacturers

1,654
employees
in the FUS industry

$393M
invested 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.

12
companies
with regulatory approvals

35
regulatory agencies
have approved
FUS indications

Contents

III. State of Commercialization

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

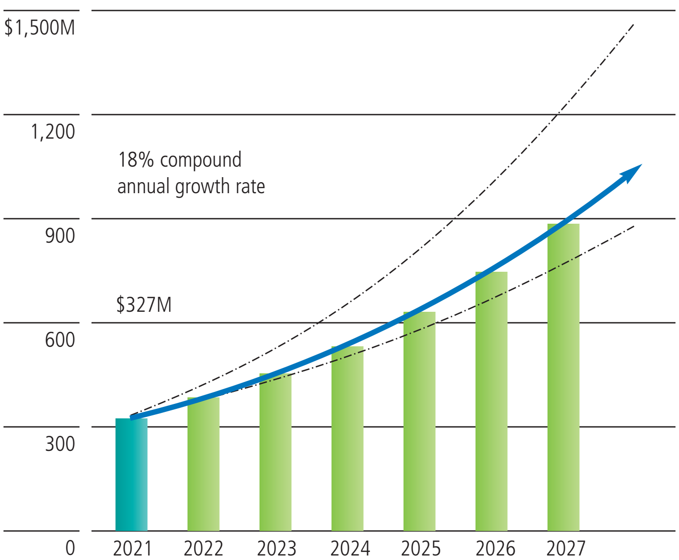
- Inform regulatory agencies, payers, and MedTech advocacy organizations about focused ultrasound
- Monitor clinical trials and potentially decrease cost of care while improving quality
- Connect and engage focused ultrasound manufacturers with advocacy organizations

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

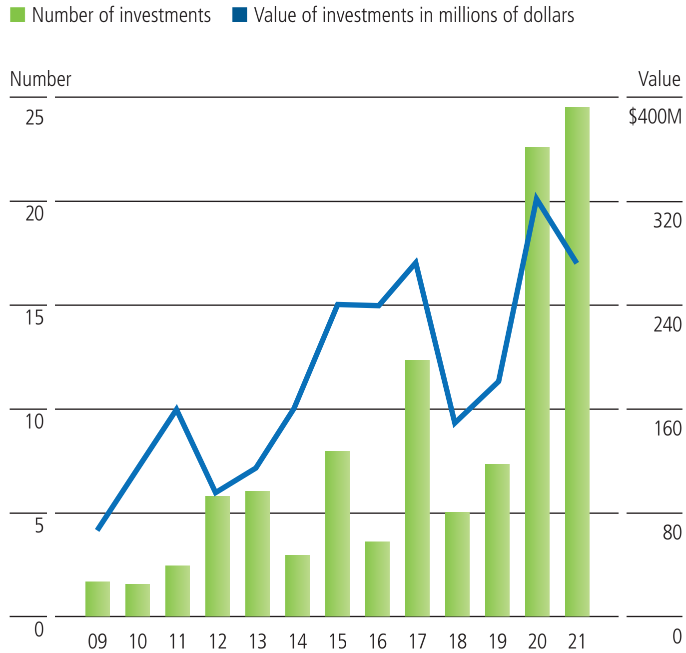
https://www.qyresearch.com/index/detail/2634979/global-high-intensity-focused-ultrasound-system-market

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

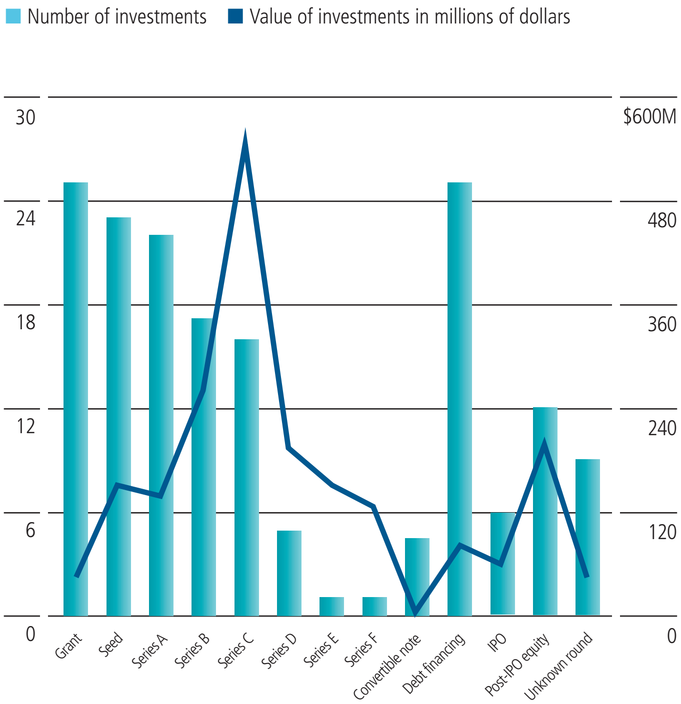
https://www.qyresearch.com/index/detail/4108833/global-high-intensity-focused-ultrasound-hifu-market

FUS Industry Investments Over Time



Source: www.crunchbase.com and industry press releases

FUS Industry Investments by Stage



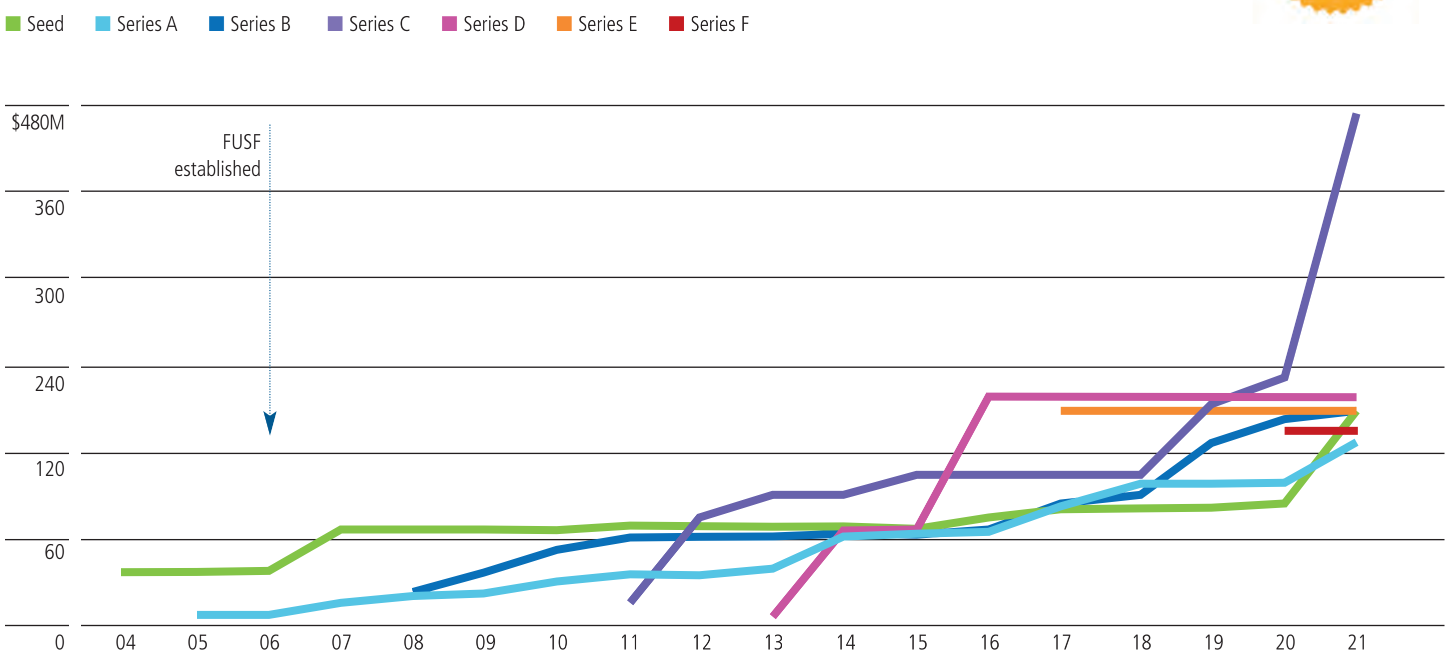
www.crunchbase.com and industry press releases

Focused ultrasound Industry Investments

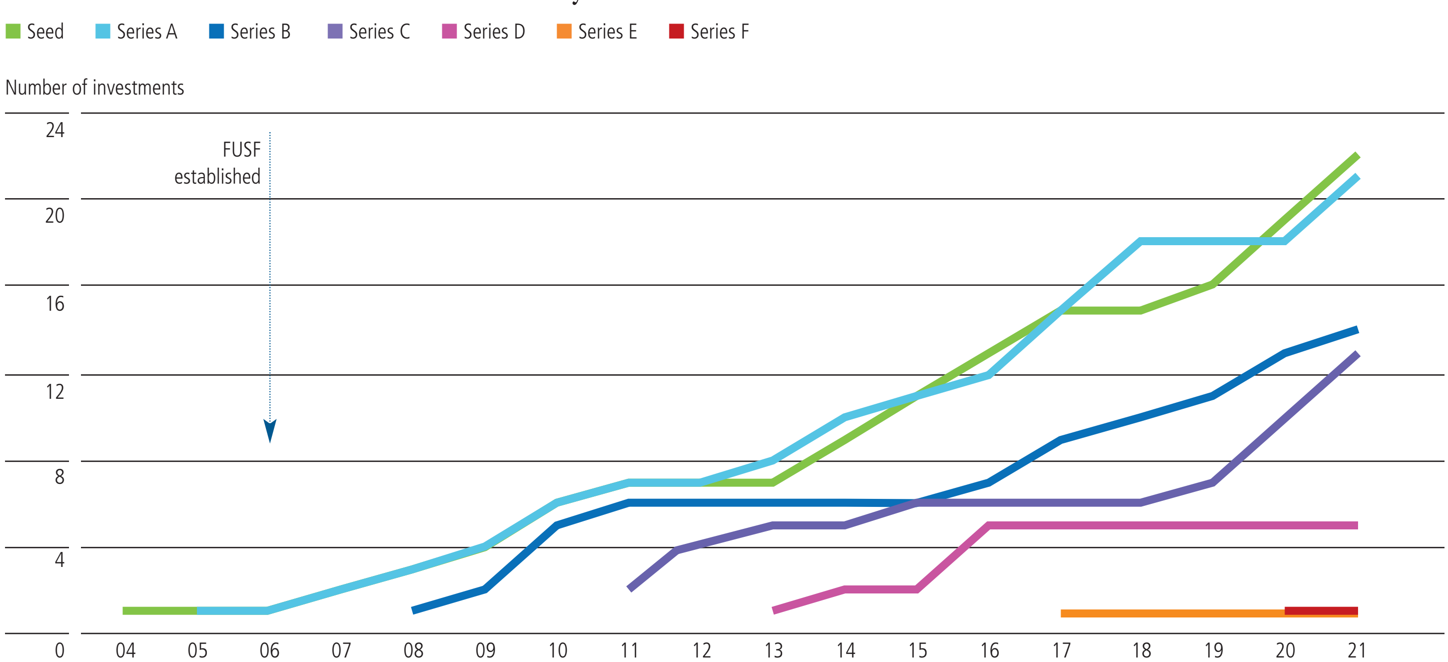
As is demonstrated by the graphs on the previous and following pages, most of the investments in this field are still early stage. 2021 included Series C financing for three different companies and comprised the bulk of the total money invested last year. New in this year's report on page III.9 is focused 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.

NEW

Cumulative Value of Investments by Series



Cumulative Number of Investments by Series



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

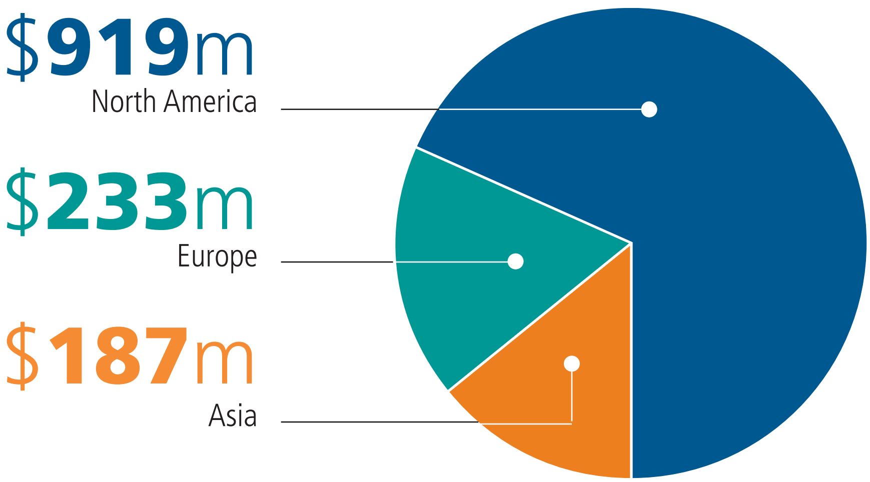
New for the 2022 report on the following page, we examined both geographic origin of the money invested, and which geographic regions were the recipients of said monies. The majority of the money is invested in North American companies, with a 3x increase over other regions. Money originating in North 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

NEW

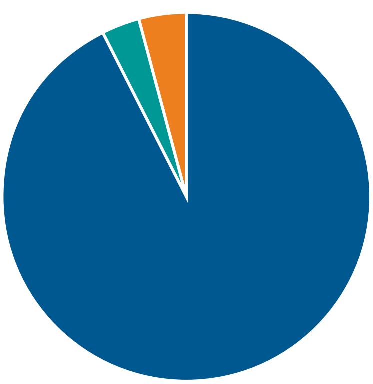
Flow of Investments

Investments by region



Disbursement to FUS Companies

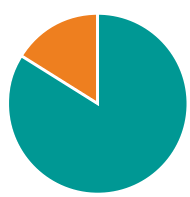
$707m
North America



Source

North America	$655.1m
Europe	$ 22.0m
Asia	$ 29.4m
Total	$706.5m

$170m
Europe



Source

North America	$ — m
Europe	$142.9m
Asia	$ 27.1m
Total	$170.0m

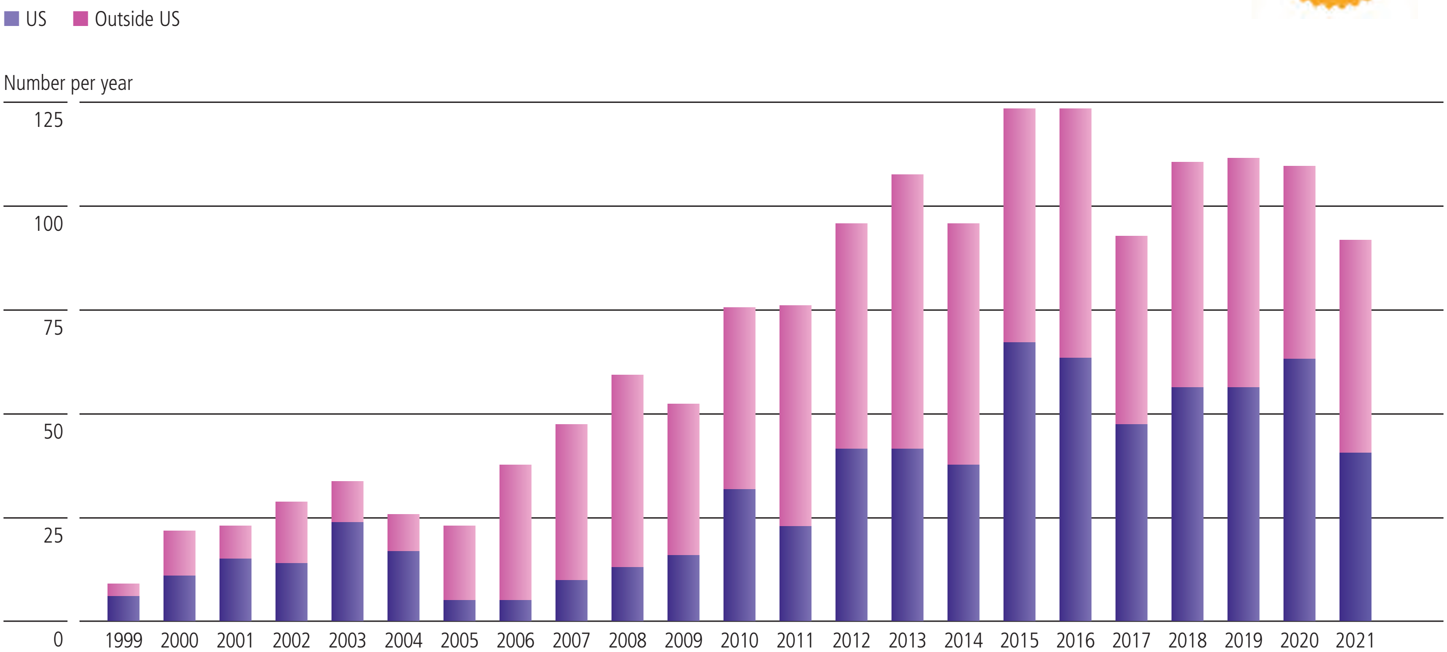
$461m
Asia

Source

North America	$263.4m
Europe	$ 67.7m
Asia	$ 130.2m
Total	$461.3m

NEW

Focused Ultrasound Industry Patents



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.

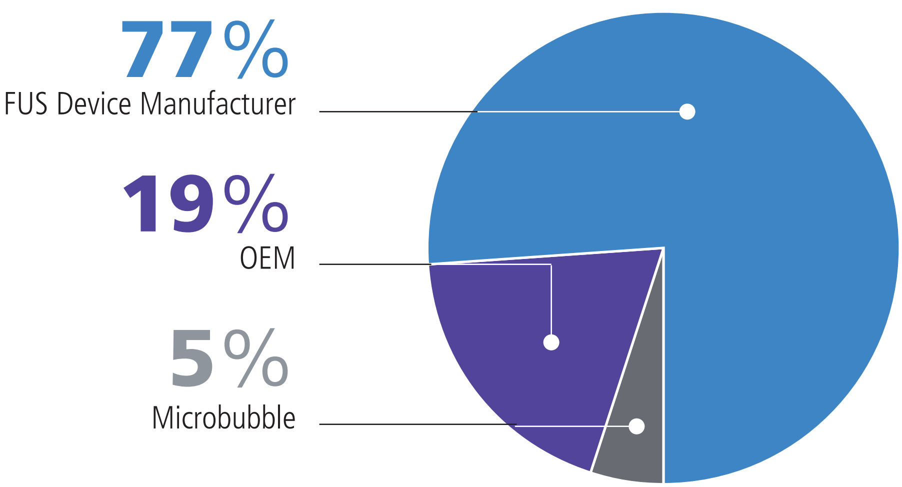
Seventy percent of USPTO patents were awarded to corporate assignees, compared to 57 percent of those from WIPO. The high ratio of corporate applicants is from companies who are likely protecting their internally derived technology improvements. This indicates that proportionally more WIPO IP was derived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

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

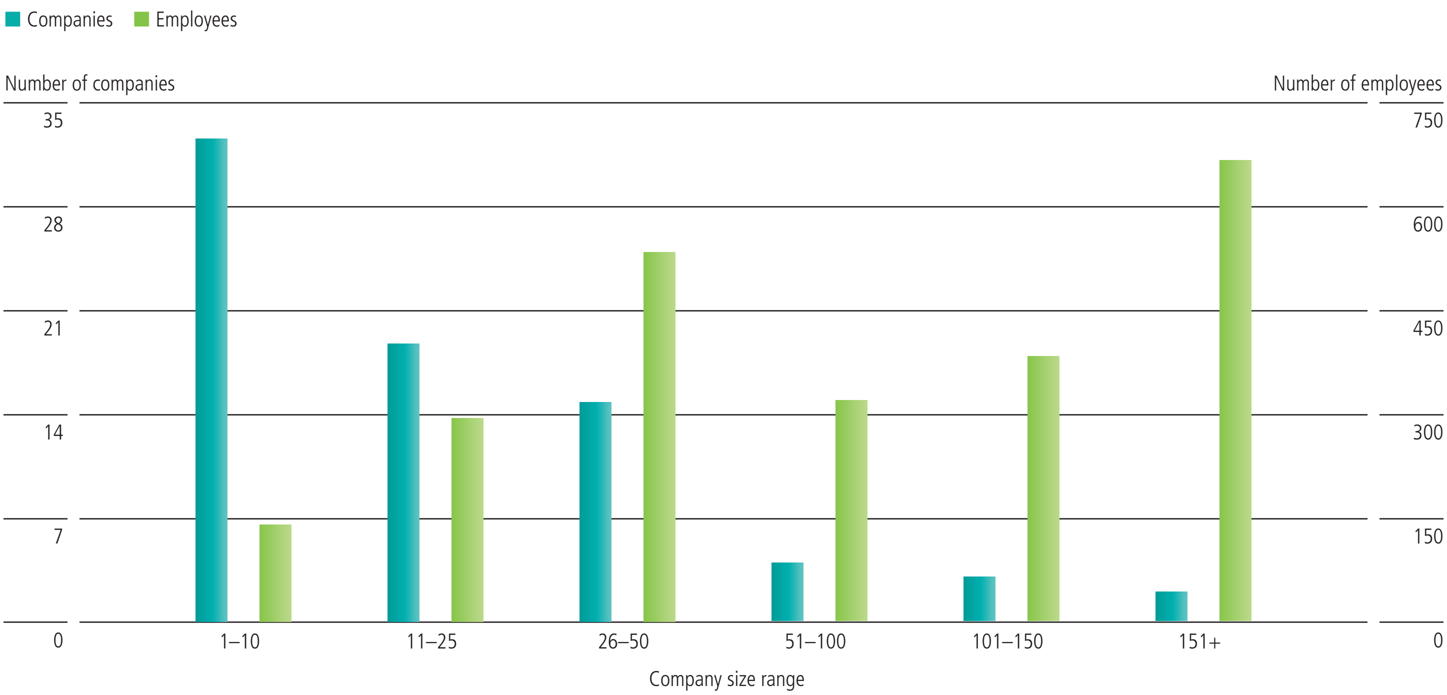
10%
of the total workforce is employed by the
41 smallest companies

68%
of companies have
25 or fewer employees

51%
of the total workforce is employed by the
7 largest companies

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

Numbers Employed by FUS Companies*

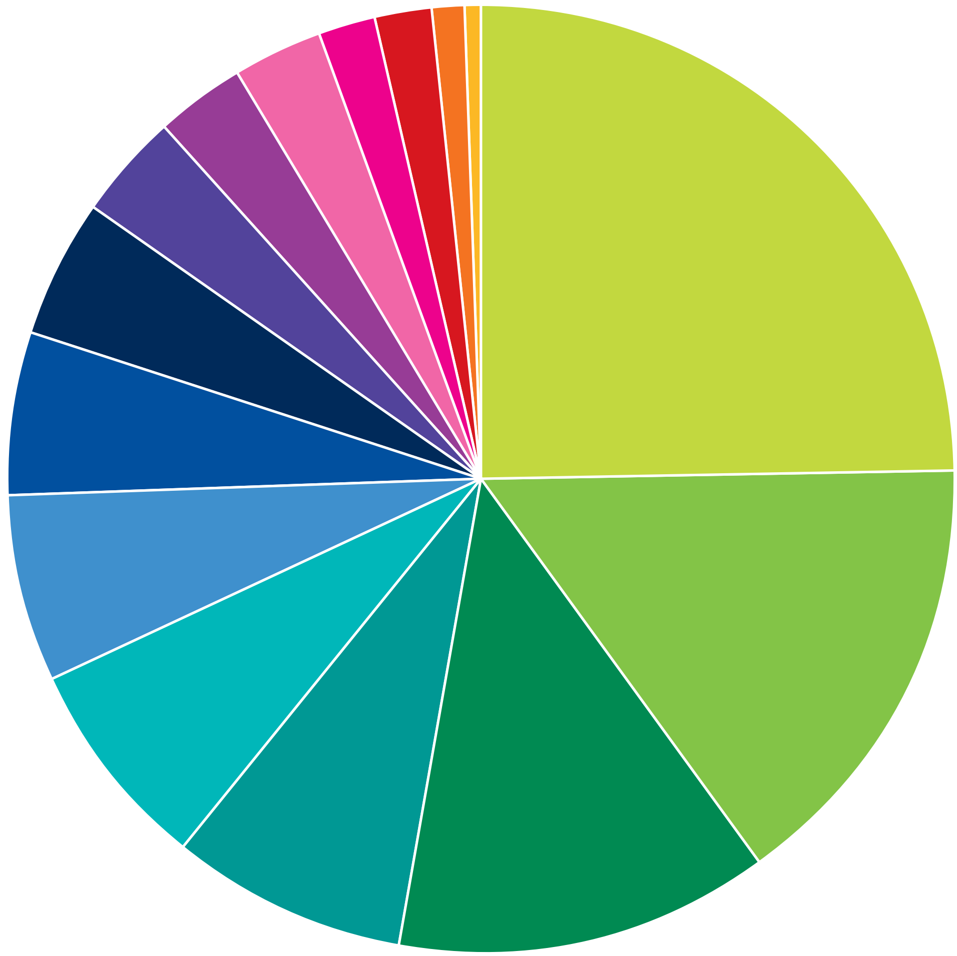


NEW

FUS Employee Locations

1,654 employees*

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



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

Page intentionally left blank

NEW

FUS Devices in Use

Number and Growth

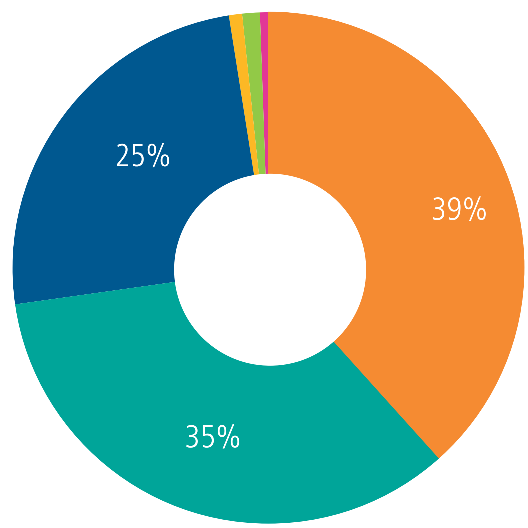
2021

1,143
FUS Devices

11%
Growth
2021 over 2020

Worldwide Distribution

2021



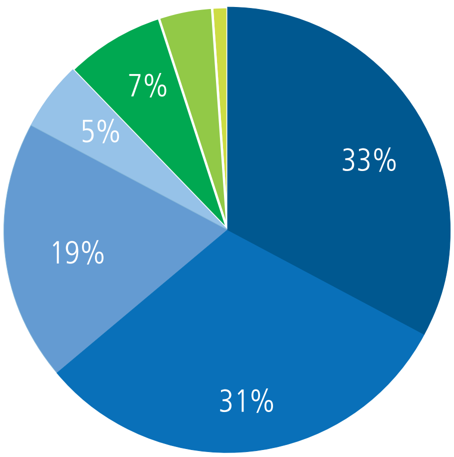
North America	25%
Europe	35%
Asia	39%
South America	1%
Oceania	1%
Africa	>1%

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.

NEW

FUS Device Use by Region

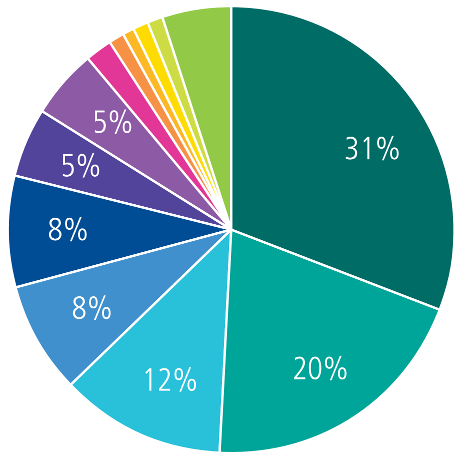
North America



US,	Central	33%
	Eastern	31%
	Pacific	19%
	Mountain	5%
Canada		7%
Mexico		4%
Other*		1%

*Cayman Islands, Cuba, and Dominican Republic

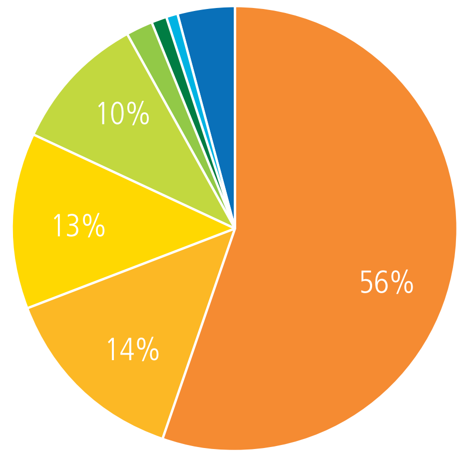
Europe



France	31%
Germany	20%
Italy	12%
Russian Federation	8%
United Kingdom	8%
Spain	5%
Switzerland	5%
Netherlands	2%
Austria	1%
Norway	1%
Poland	1%
Romania	1%
Other*	5%

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

Asia



China	56%
South Korea	14%
Japan	13%
Taiwan	10%
India	2%
Israel	1%
Singapore	1%
Other*	4%

*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 Germany	Saudi Arabia Singapore	Australia
Bone metastases	United States[1]	Germany Italy[3]	Israel Malaysia Saudi Arabia South Korea	Australia
Breast tumors, benign		Germany[4]		
Breast tumors, malignant		Germany[4]		
Desmoid tumors		Germany[4]		
Essential tremor	Canada[2] United States[1]	Germany Italy[3] Switzerland United Kingdom	Israel Japan	
Neuropathic pain		Germany Italy[3] Switzerland	Israel	
Osteoid osteoma		Germany Italy[3]		
Pancreatic tumors		Germany[4]		
Parkinson's disease, tremor	United States[1]	Germany Italy[3] Switzerland	Israel Japan	
Prostate cancer	United States[1]	France Germany United Kingdom	Japan Saudi Arabia Singapore South Korea	Australia

* 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] United States[1]	Germany Italy[3]	China Israel Malaysia Saudi Arabia South Korea Vietnam	Australia
Varicose veins		Germany[4]		

Reimbursement

NEW

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

NEW

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

20

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.

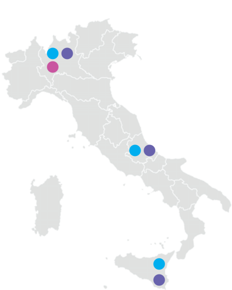
The codification system for hospital care is the International Classification of Diseases ICD-9-CM for the main diagnosis and a catalog of codes for procedures. Assigned codes are collated and linked to a Diagnostic-Related Group (DRG), in addition to the related reimbursement tariff for the procedure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

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).

Case Study
FUS and Reimbursement in Italy

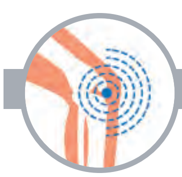
The autonomous Regions have each implemented their own HTA programs, with various degrees of sophistication and respective agencies and authorities.

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.

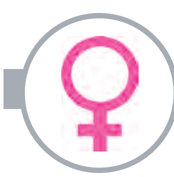


Musculoskeletal

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.

● Bone metastases
● Osteoid osteoma



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.

● 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*

	BPH	Bone metastases	Breast tumors, benign	Breast tumors, malignant	Desmoid tumors	Essential tremor	Neuropathic pain	Osteoid osteoma	Pancreatic tumors	Parkinson's tremor	Prostate cancer
North America											
Canada[2]						●					
United States[1]		●				●				●	●
Europe											
France	●										●
Germany	●	●	●[4]	●[4]	●[4]	●	●	●	●[4]	●	●
Italy[3]		●				●	●	●		●	
Switzerland						●	●			●	
United Kingdom						●					●
Asia											
China											
Israel		●				●	●			●	
Japan						●				●	●
Malaysia		●									
Saudi Arabia	●	●									●
Singapore	●										●
South Korea		●									●
Vietnam											
Oceania											
Australia	●	●									●

* 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

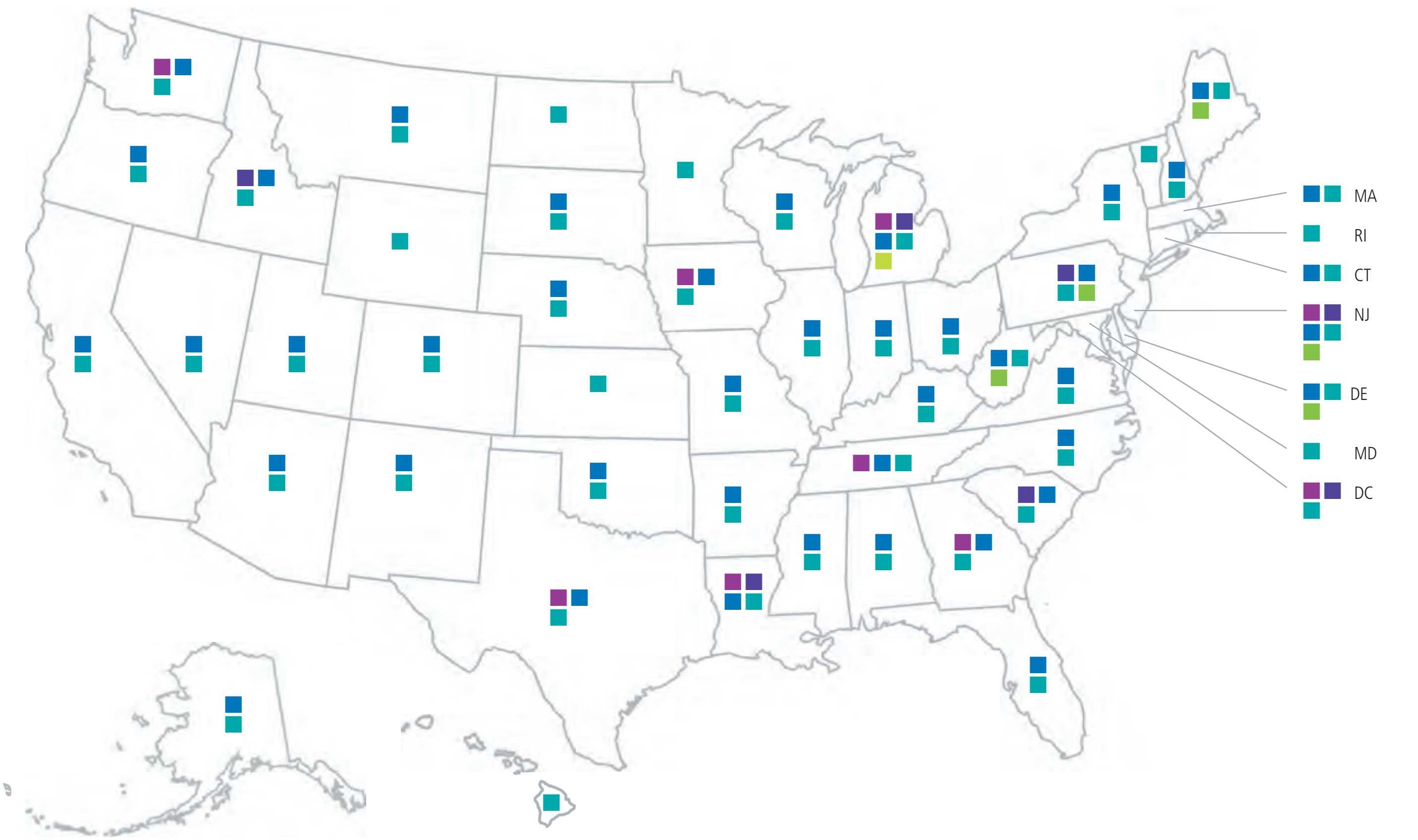
Insurance Coverage by Country* continued

	Thyroid nodules	Uterine fibroids	Varicose veins
North America			
Canada[2]		●	
United States[1]		●	
Europe			
France			
Germany	●[4]	●	●[4]
Italy[3]		●	
Switzerland			
United Kingdom			
Asia			
China		●	
Israel		●	
Japan			
Malaysia		●	
Saudi Arabia		●	
Singapore			
South Korea		●	
Vietnam		●	
Oceania			
Australia		●	

* 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*

Bone metastases | Pain palliation



Bone metastases | Pain palliation

Private carrier

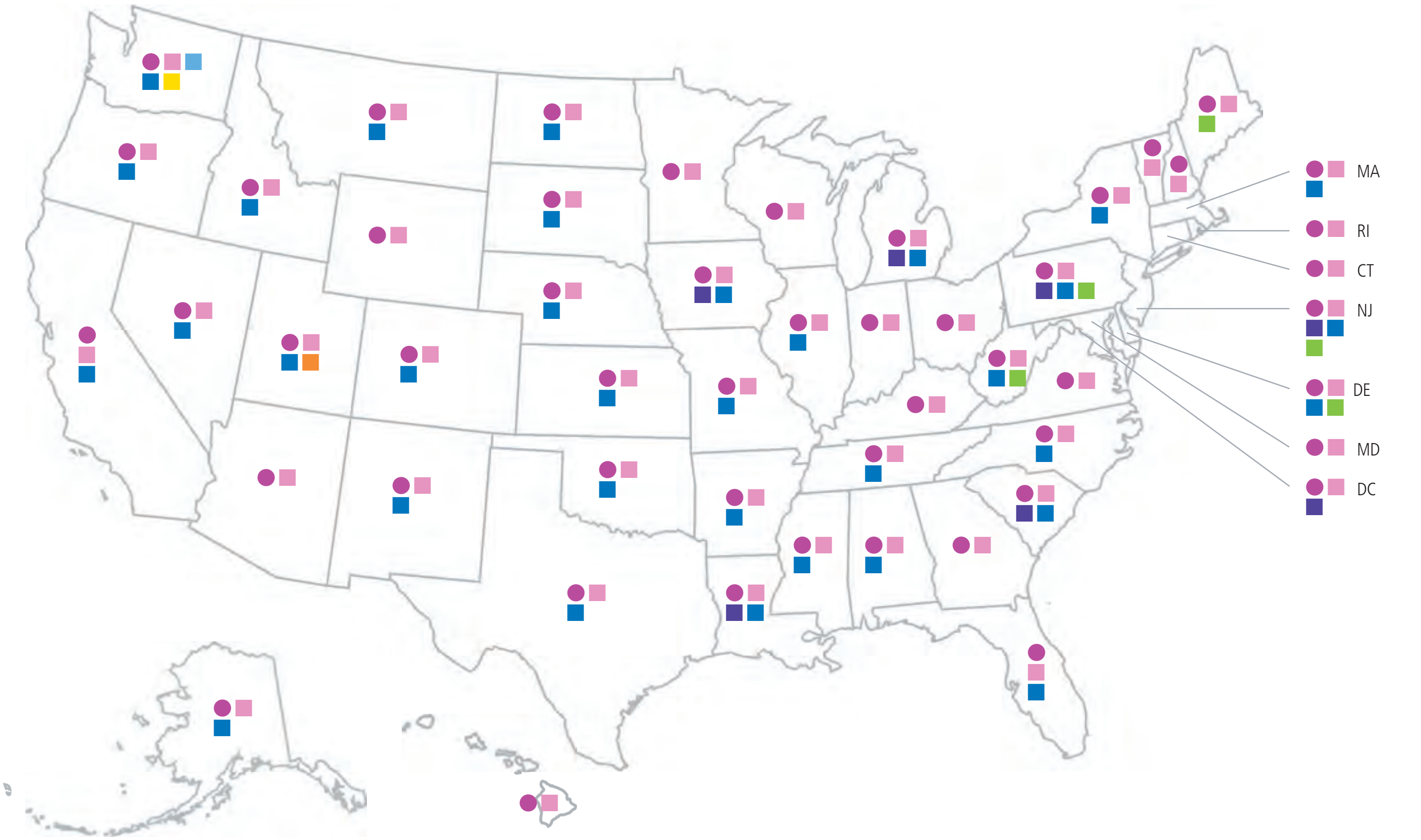
- Amerigroup Healthcare
  DC, GA, IA, LA, MI, NJ, TN, TX, WA
- AmeriHealth
  DC, ID, LA, MI, NJ, PA, SC
- Blue Cross Blue Shield
  AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, IA, ID, IL, IN, KY, LA, MA, ME, MI, MO, MS, MT, NC, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, SD, TN, TX, UT, VA, WA, WI, WV
- CIGNA
  ALL STATES AND DC
- Geisinger Health Plan
  DE, ME, NJ, PA, WV
- HAP Health Alliance Plan
  MI

Covered lives	Medicare	—
	Private	99.0
		99.0 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.

Insurance Coverage in the United States* continued

Essential tremor



Essential tremor

Public carrier

- Medicare
  ALL STATES AND DC

Private carriers

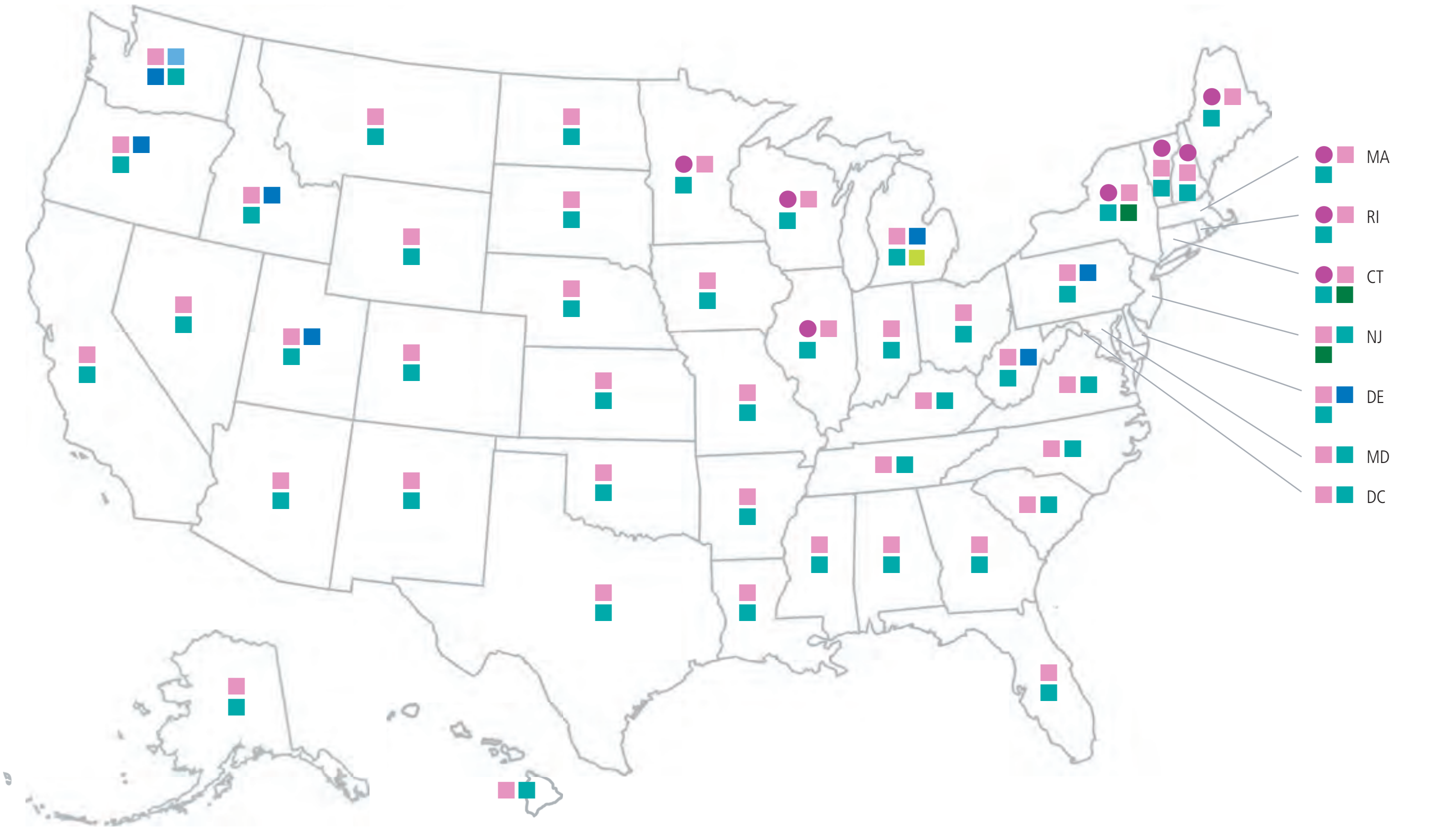
- Aetna
  ALL STATES AND DC
- AmeriHealth
  DC, IA, LA, MI, NJ, PA, SC
- Asuris Northwest Health
  WA
- Blue Cross Blue Shield
  AK, AL, AR, CA, DE, FL, IA, ID, IL, KS, LA, MA, MI, MO, MS, MT, NC, ND, NE, NJ, NM, NY, OK, OR, PA, SC, SD, TN, TX, UT, WA, WV
- Geisinger Health Plan
  DE, ME, NJ, PA, WV
- Lifewise
  WA
- University of Utah Health Plans
  UT

Covered lives		
	Medicare	63.0
	Private	76.3
		139.3 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.

Insurance Coverage in the United States* continued

Prostate cancer | Salvage therapy[1]



Prostate cancer | Salvage therapy[1]

Public carrier

● Medicare
CT, IL, MA, ME, MN, NH, NY, RI, VT, WI

Private carriers

■ Aetna
ALL STATES AND DC

■ Asuris Northwest Health
WA

■ Blue Cross Blue Shield
DE, ID, MI, PA, OR, UT, WA, WV

■ CIGNA
ALL STATES AND DC

■ Emblem Health
CT, NJ, NY

■ HAP Health Alliance Plan
MI

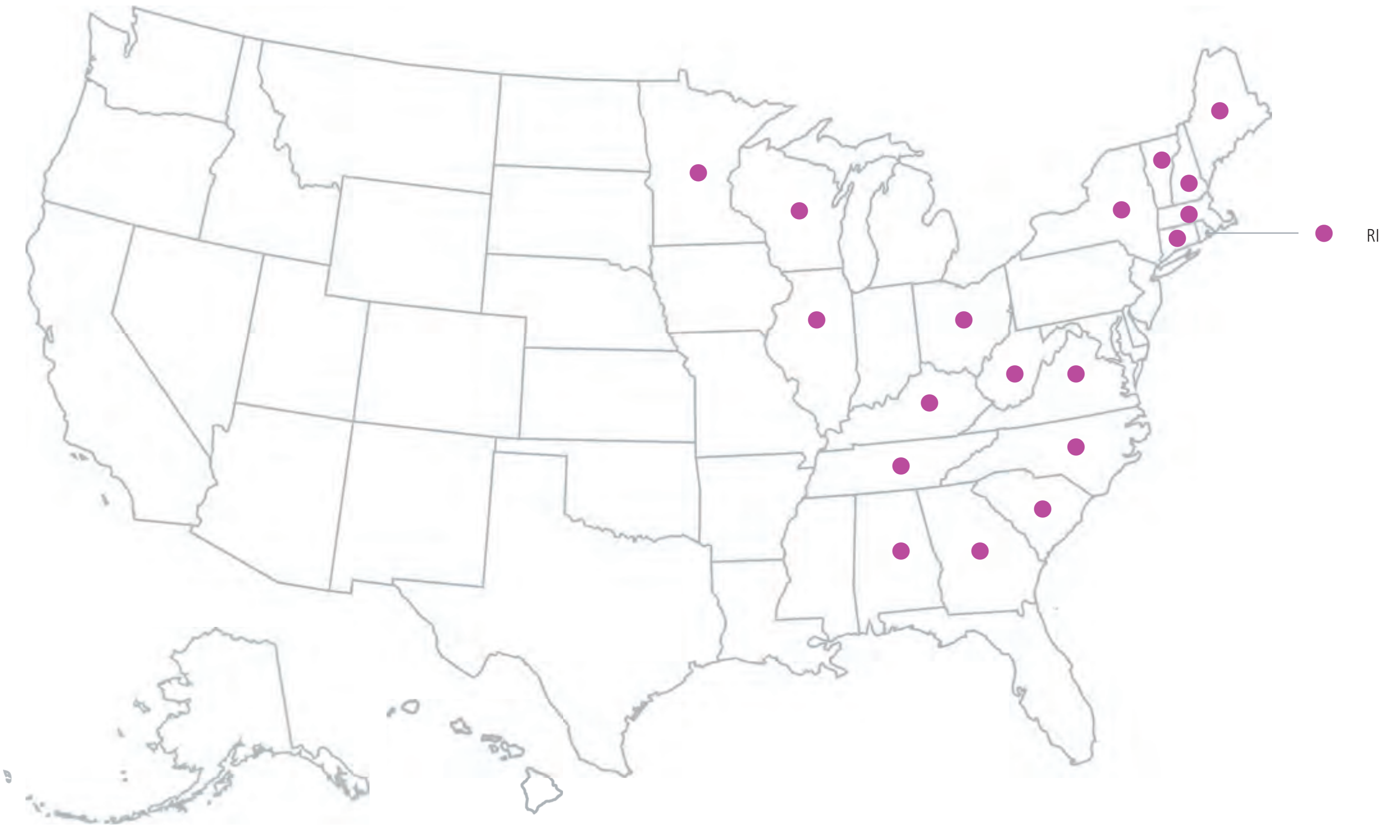
Covered lives	Medicare	11.5
	Private	44.6
		56.1 million

* 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.

1 Local treatment for recurrent prostate cancer following radiation therapy

Insurance Coverage in the United States* continued

Parkinson's disease, tremor



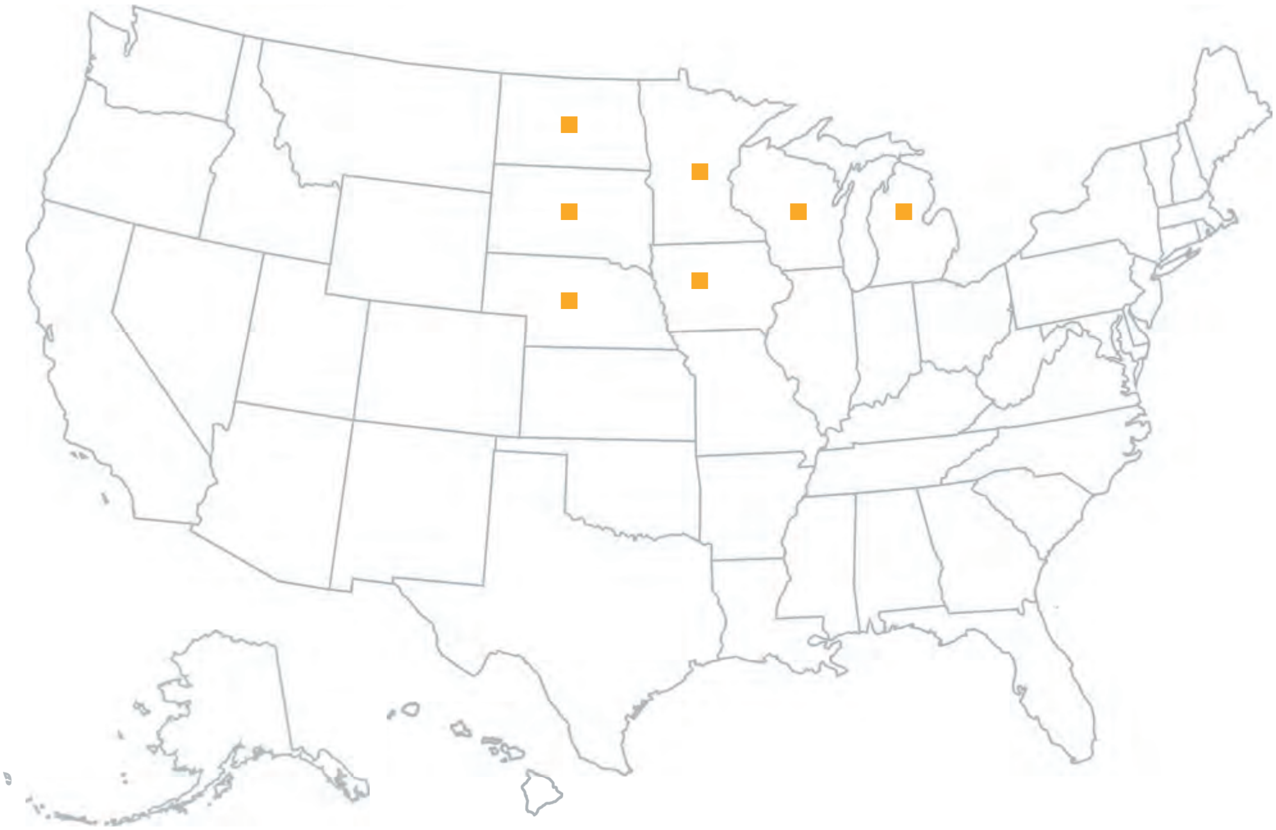
Parkinson's disease, tremor

Public carrier	● Medicare AL, CT, GA, IL, KY, MA, ME, MN, NC, NH, NY, OH, RI, SC, TN, VA, 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.

Insurance Coverage in the United States* continued

Uterine fibroids



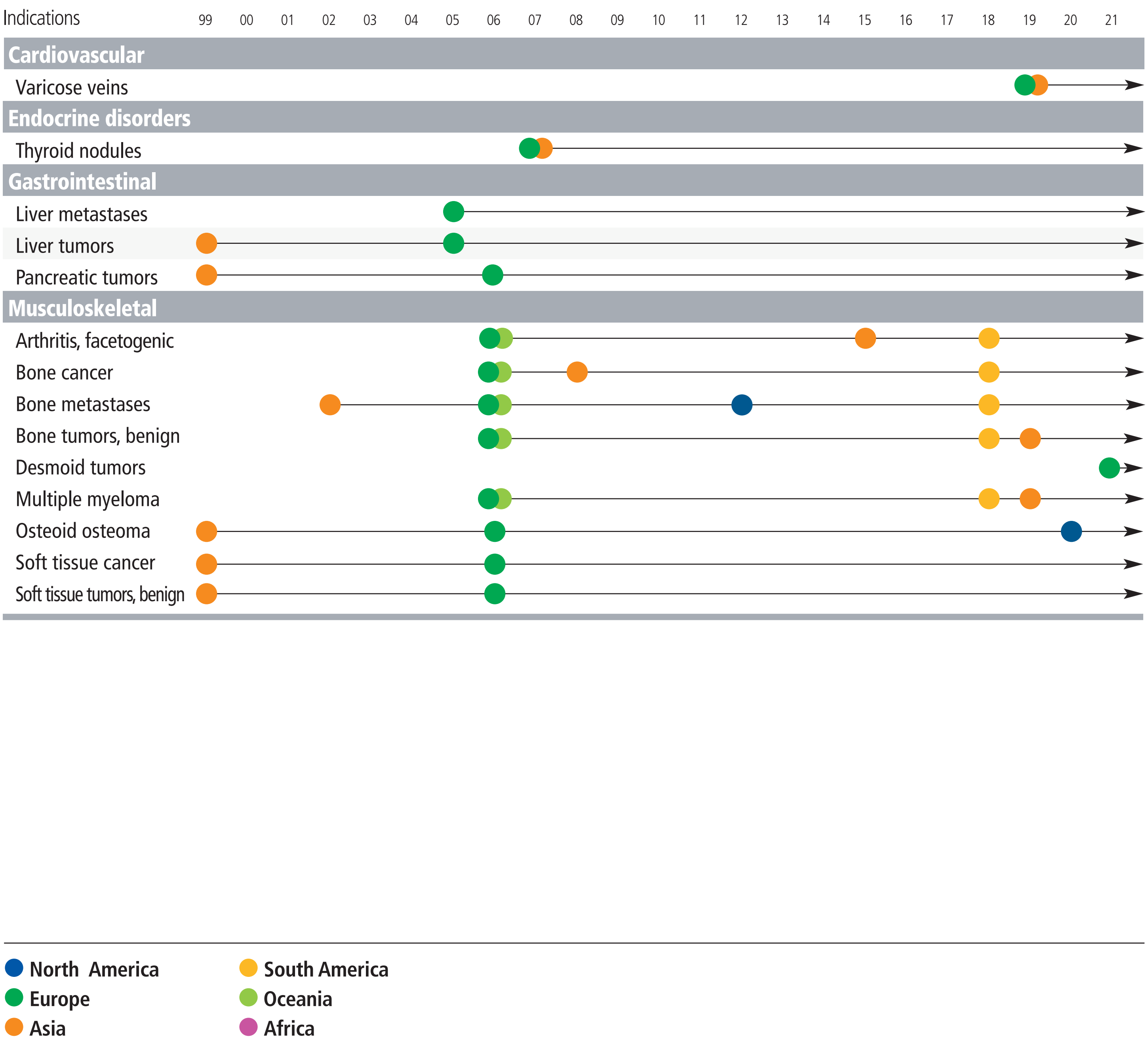
Uterine fibroids

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

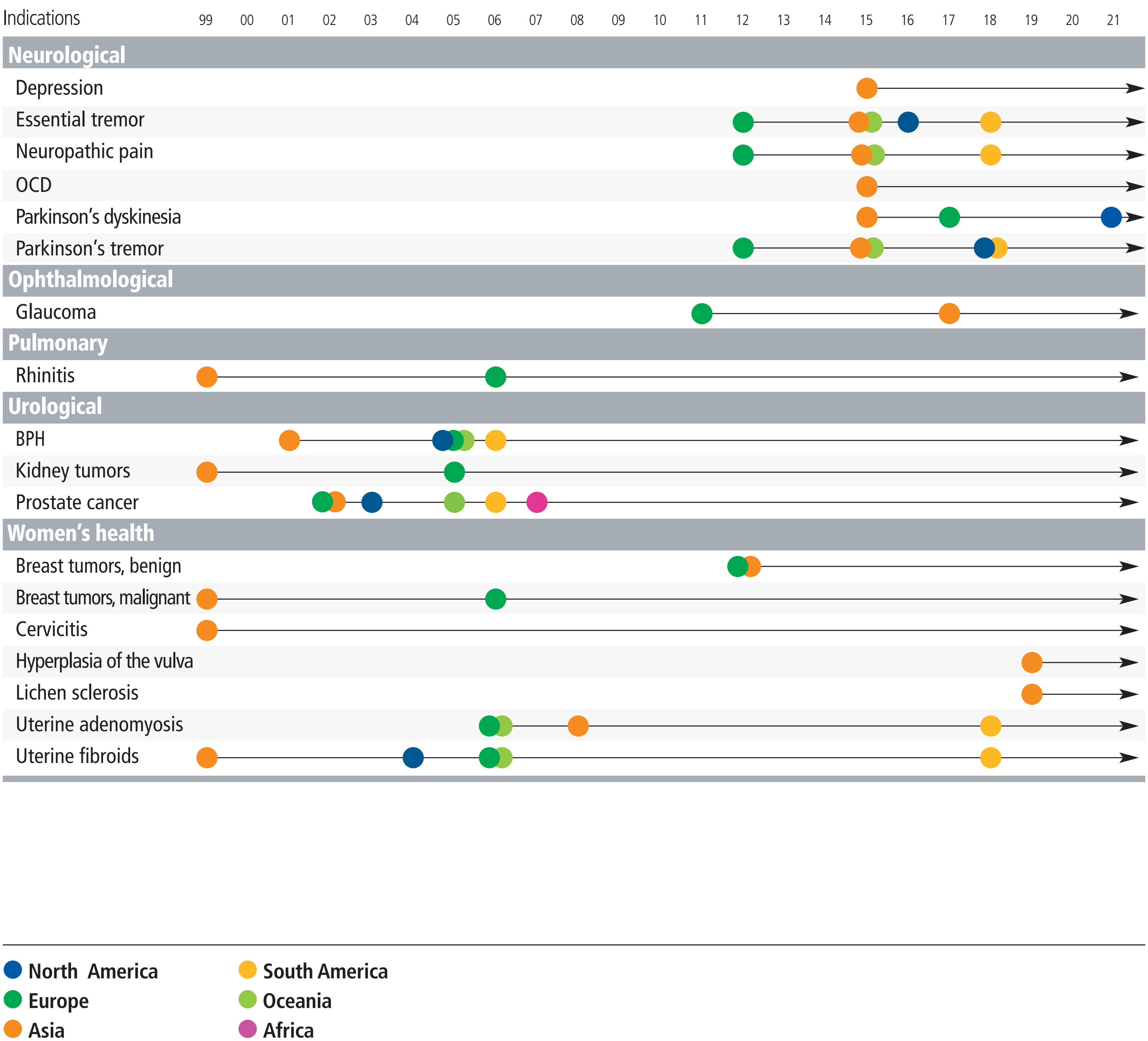
* All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

Page intentionally left blank

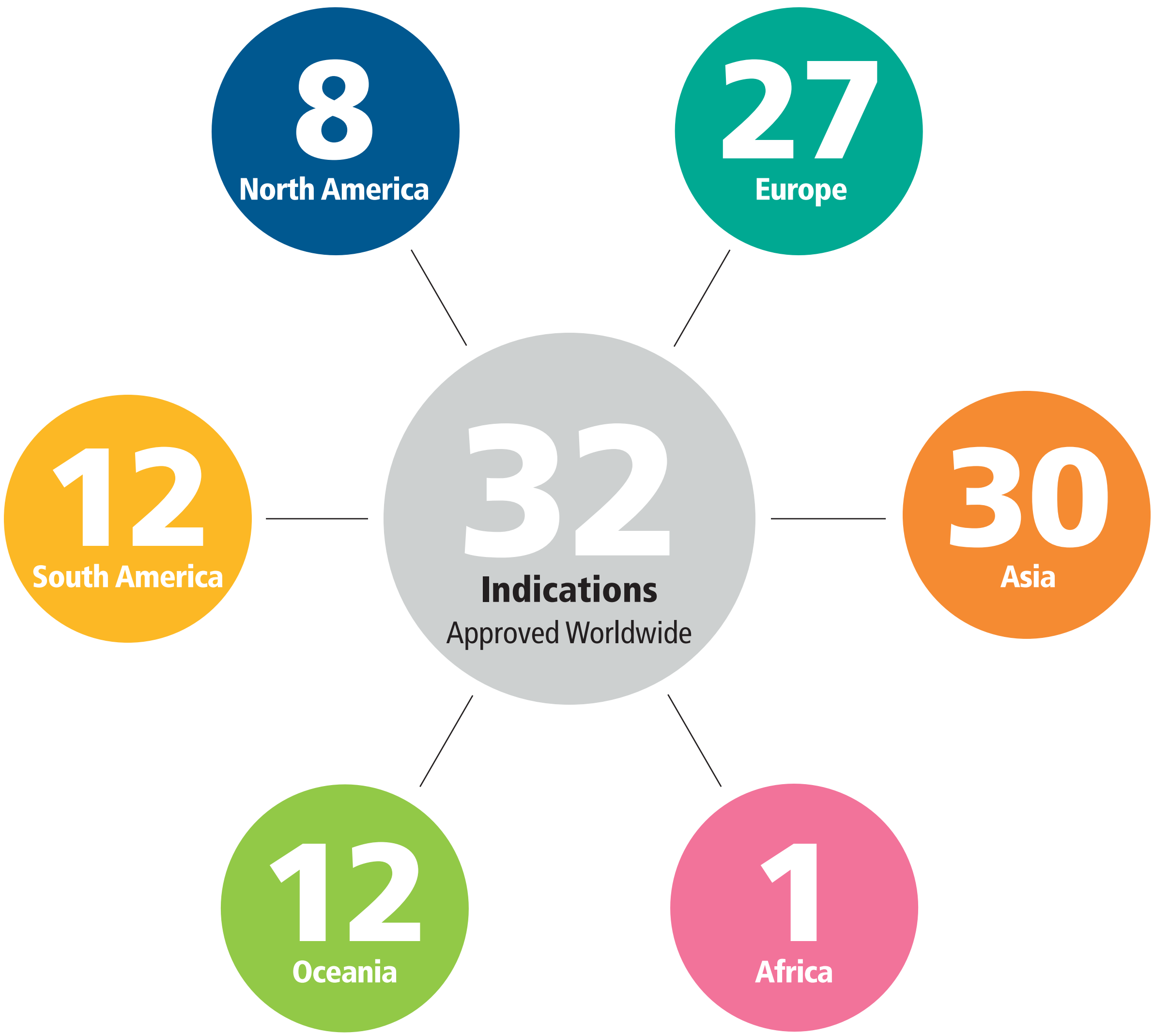
FUS Regulatory Approvals by Indication and Region



FUS Regulatory Approvals by Indication and Region continued



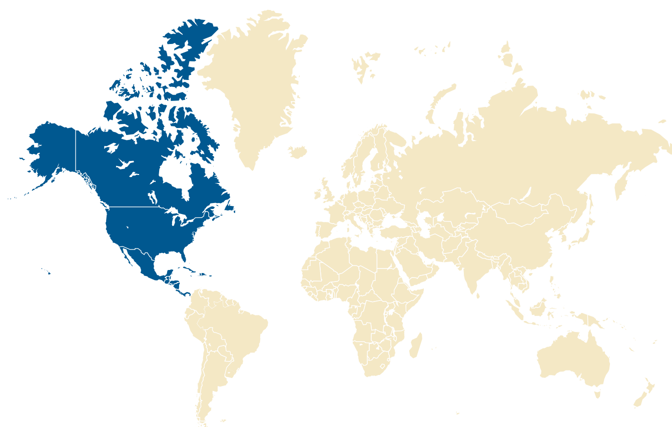
FUS Regulatory Approvals by Indication and Region
Graphic



North America

FUS Regulatory Approvals by Indication

8 Approvals



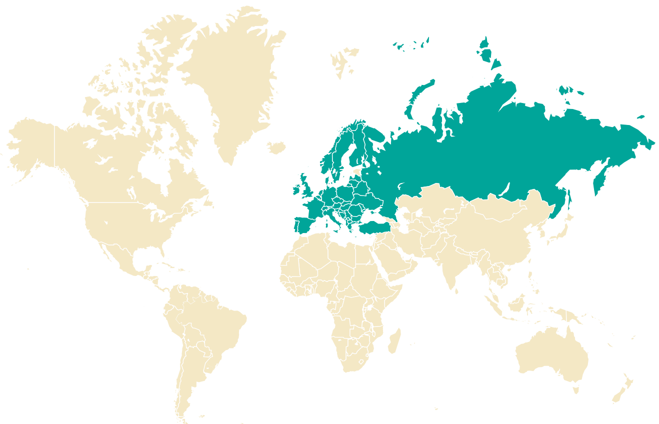
Approval
- Approval begin date
- Approval end date

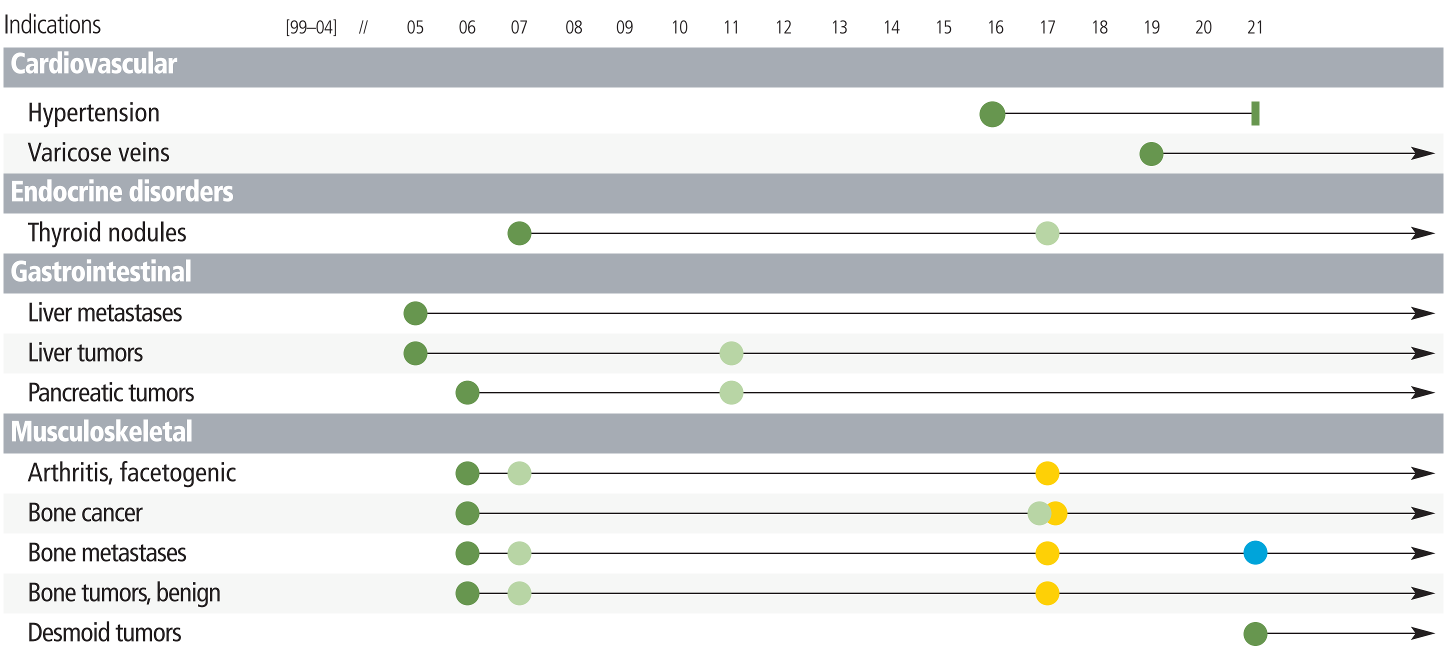
North America
- Bahamas, *Ministry of Health*
- Barbados, *Ministry of Health and Wellness*
- Costa Rica, *Ministerio de Salud*
- Dominican Republic, *MISPAS*
- United States, *FDA, Center for Devices & Radiological Health*
- Canada, *Health Canada, Medical Devices Bureau*
- Mexico, *COFEPRIS*

Europe

FUS Regulatory Approvals by Indication

27 Approvals





Approval

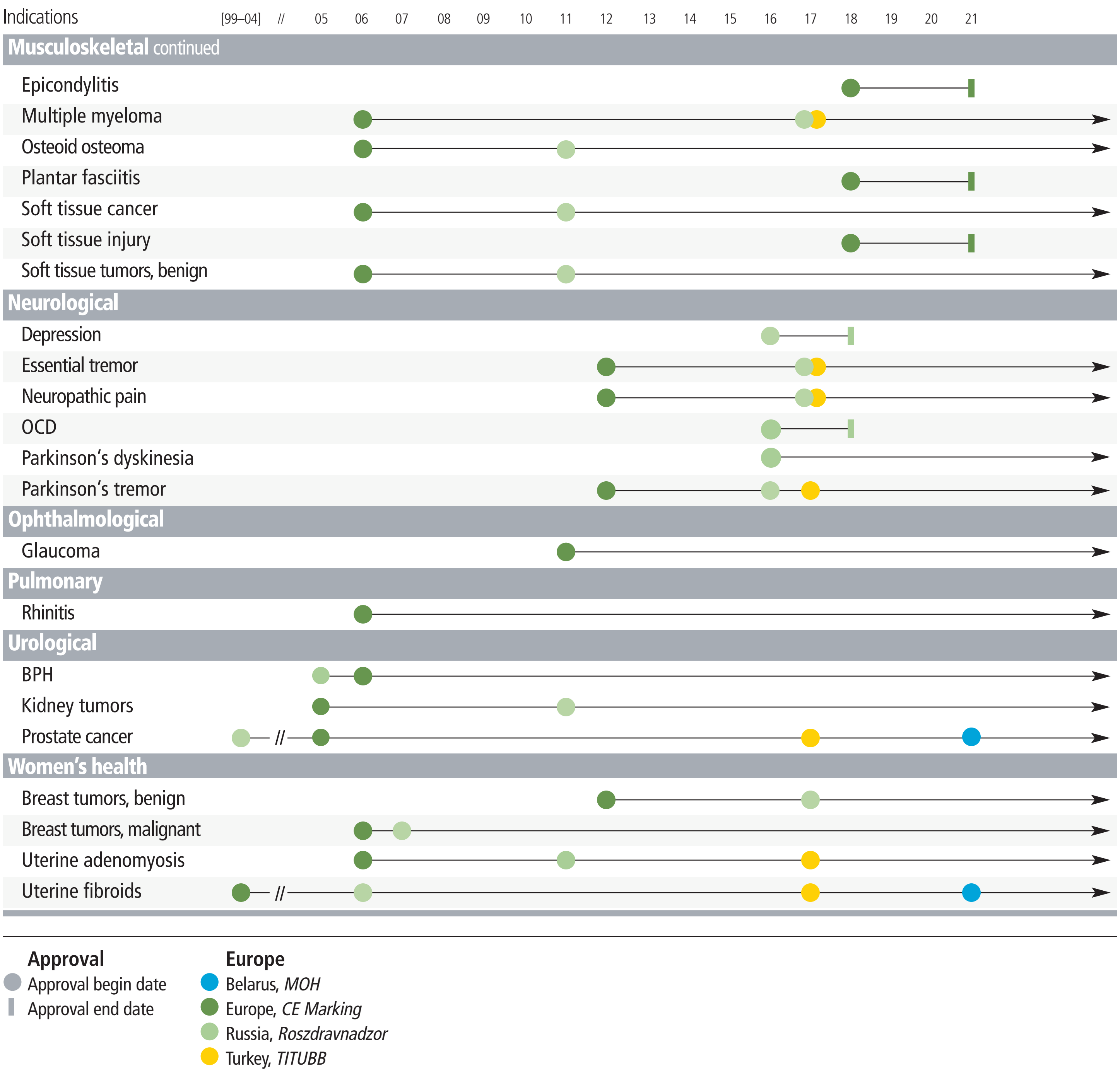
- Approval begin date
- Approval end date

Europe

- Belarus, *MOH*
- Europe, *CE Marking*
- Russia, *Roszdravnadzor*
- Turkey, *TITUBB*

Europe

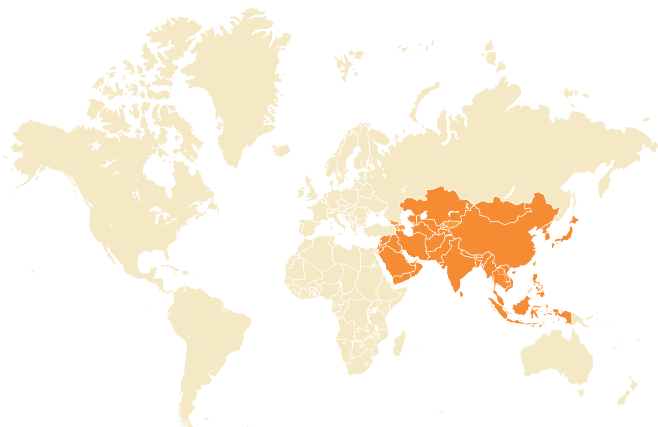
FUS Regulatory Approvals by Indication continued

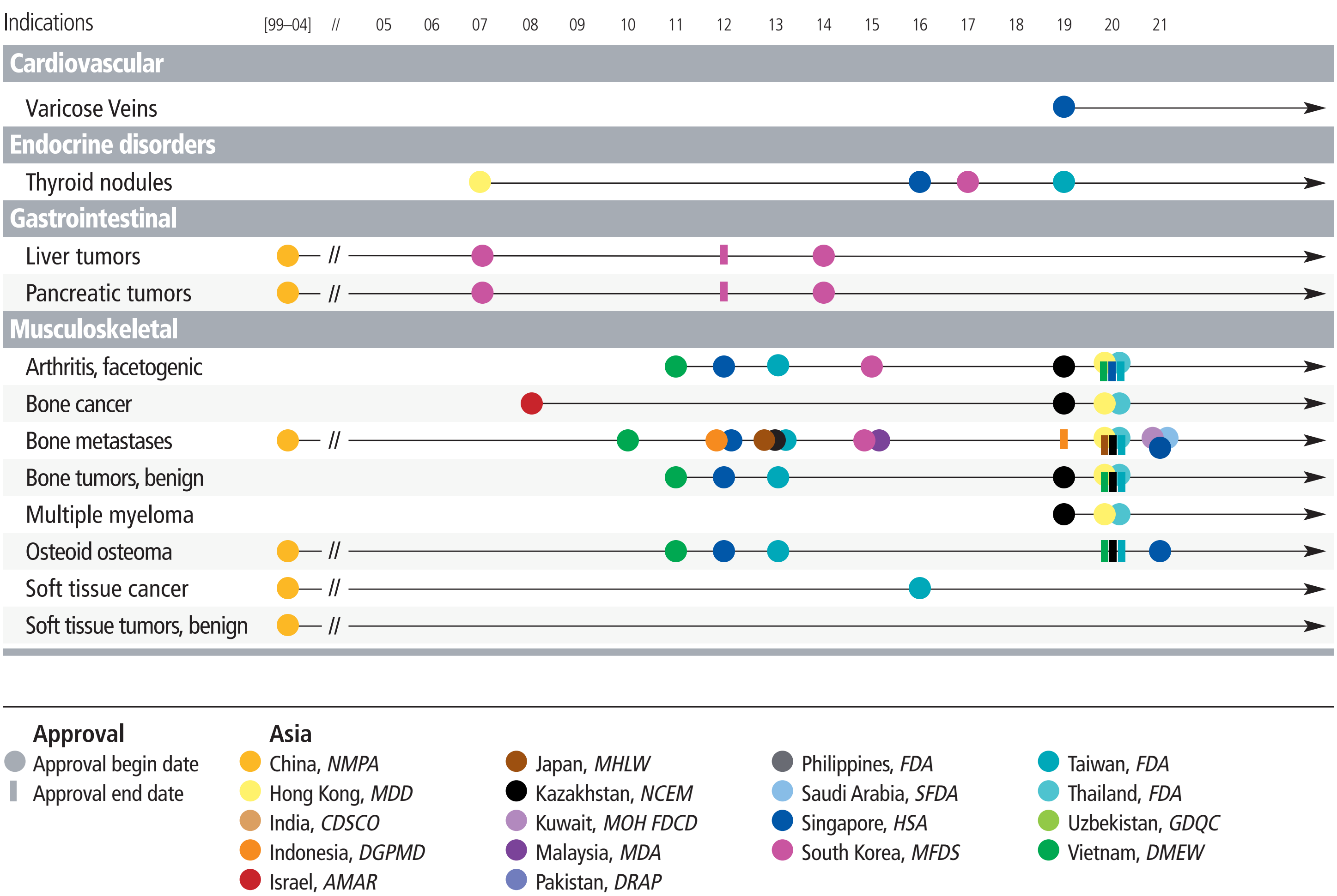


Asia

FUS Regulatory Approvals by Indication

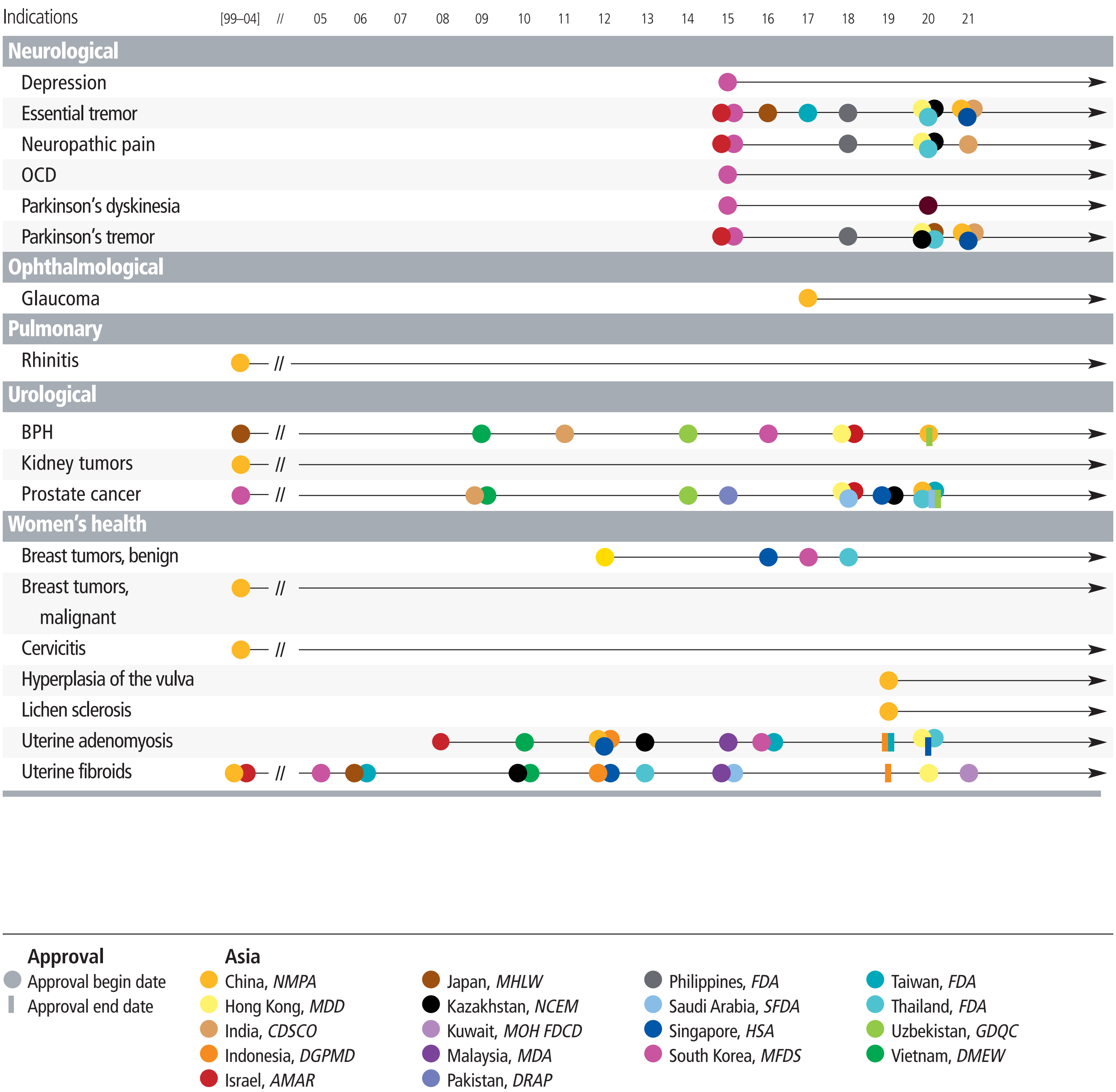
30 Approvals





Asia

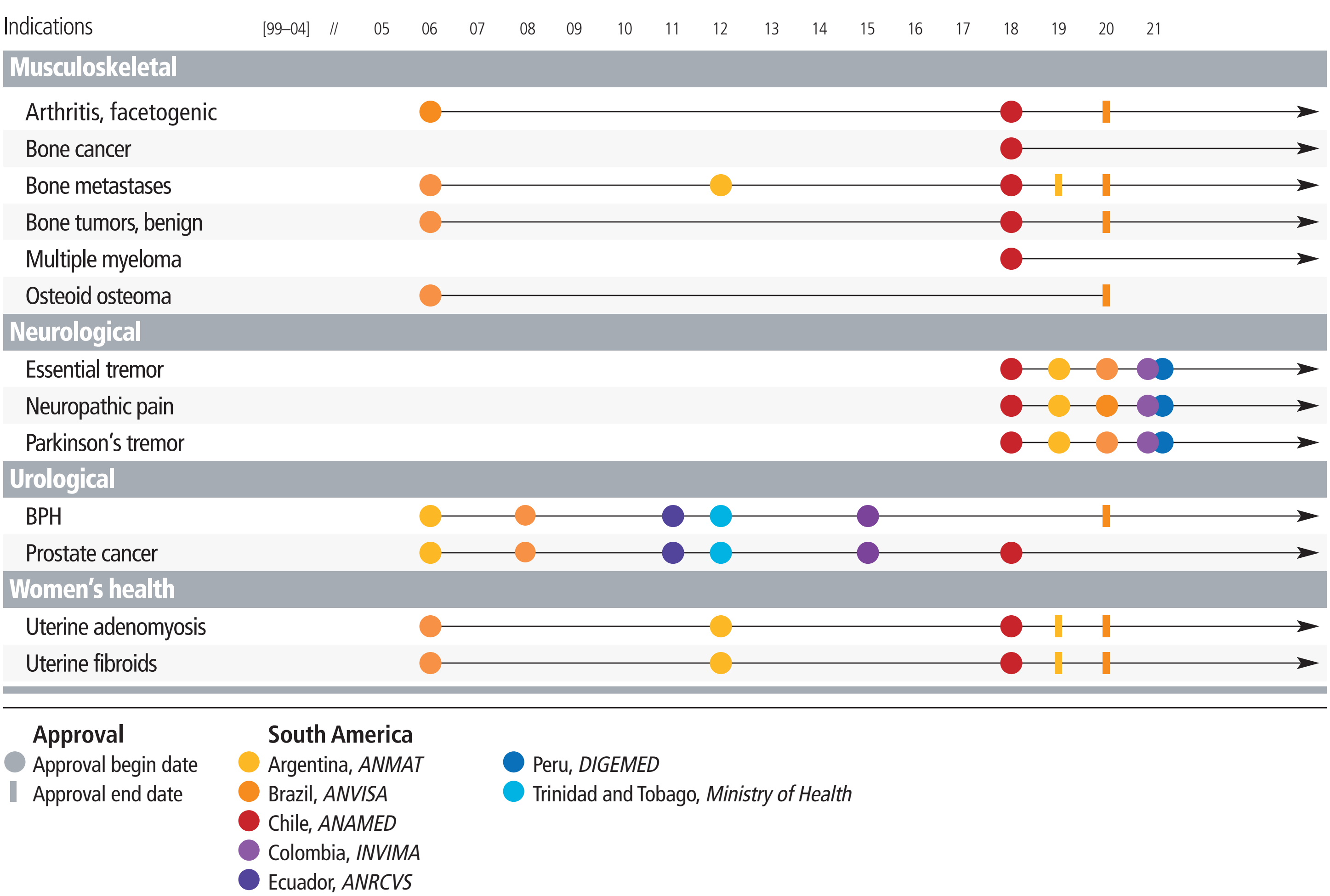
FUS Regulatory Approvals by Indication continued



South America

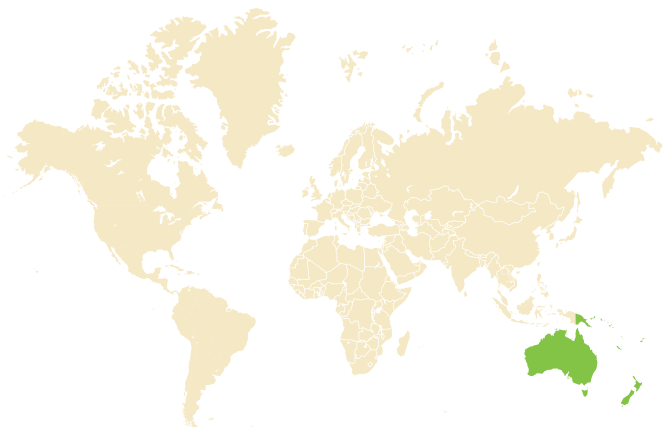
FUS Regulatory Approvals by Indication

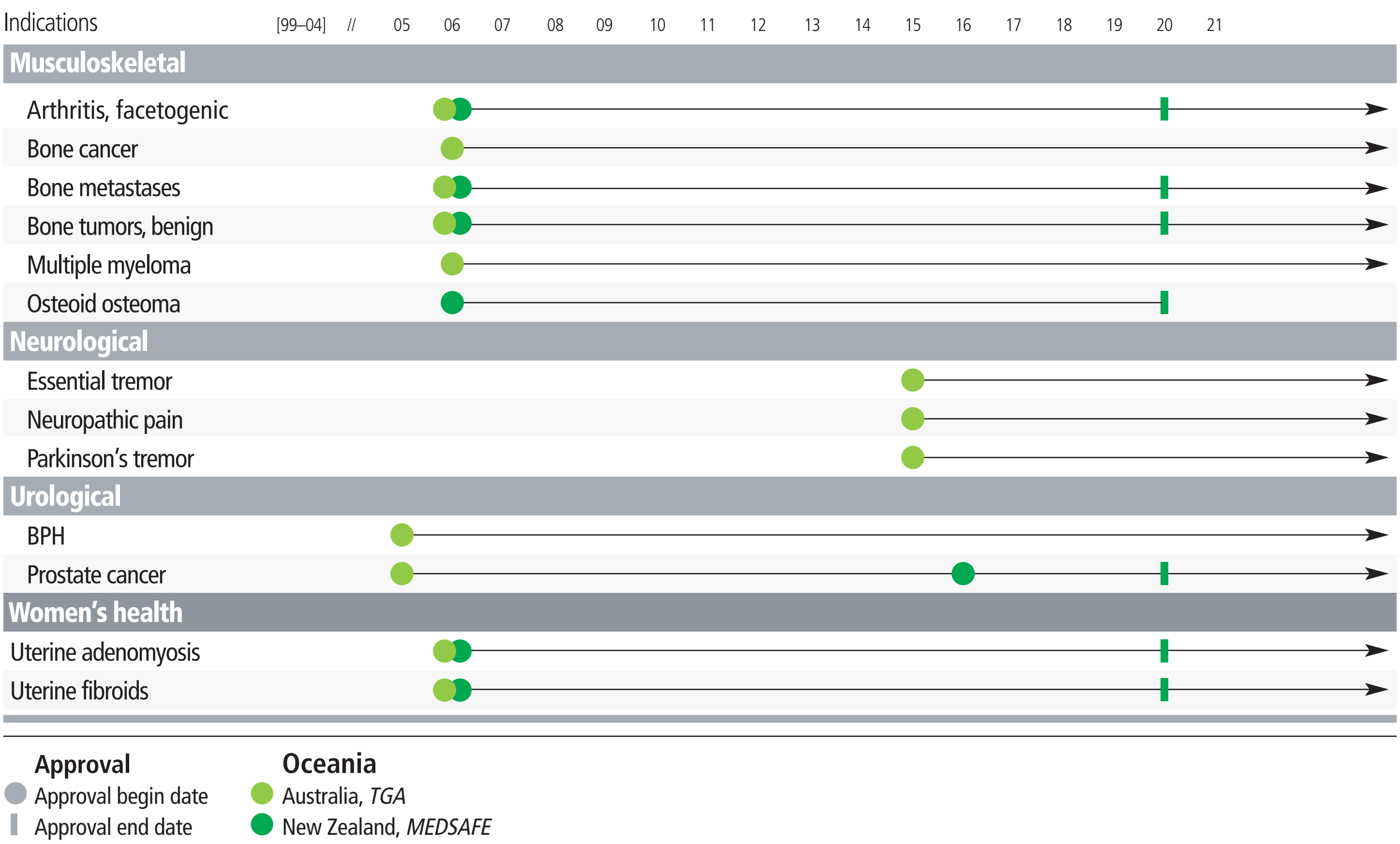
12 Approvals



Oceania
FUS Regulatory Approvals by Indication

12 Approvals

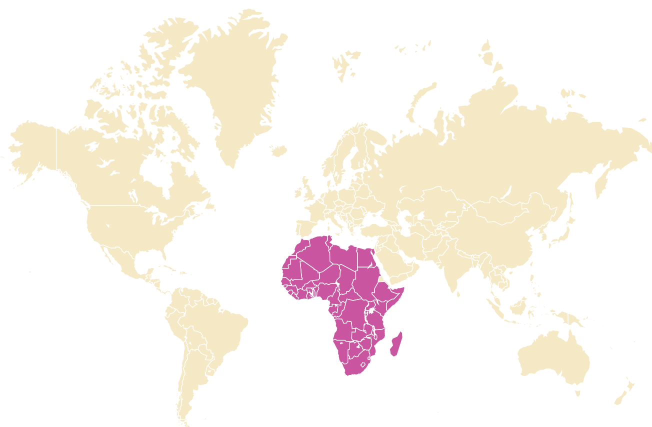


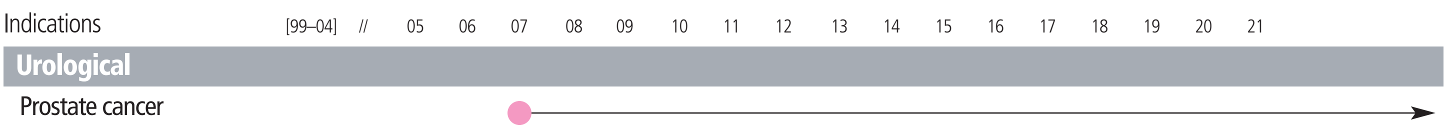


Africa

FUS Regulatory Approvals by Indication

1 Approval





Approval
- Approval begin date
- Approval end date

Africa
- South Africa, *MCC*

NEW

Focused Ultrasound Industry Geographic Overview

2021

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

Indication Approvals by Manufacturer

Manufacturer	North America	Europe	Asia	South America	Oceania	Africa
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

NEW

12

Companies

with approved indications

32

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
- Glaucoma

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

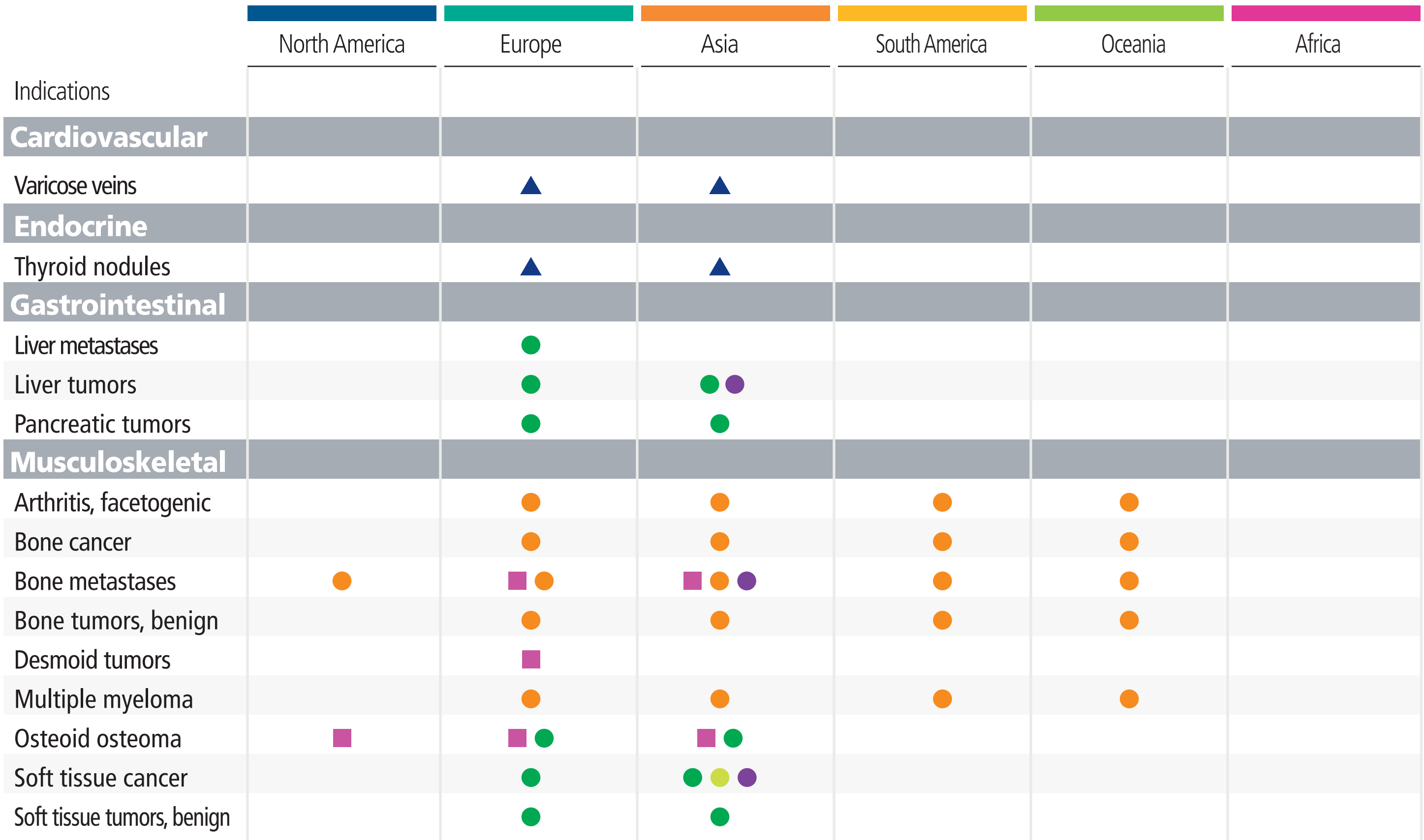
Insightec
- Arthritis, facetogenic
- Bone cancer
- Bone metastases
- Bone tumors, benign
- Essential tremor
- Multiple myeloma
- Neuropathic pain
- Parkinson's disease, tremor
- Prostate cancer
- Uterine adenomyosis
- Uterine fibroids

Sonablate
- Benign prostatic hyperplasia
- Prostate cancer

Africa

Sonablate
- Prostate cancer

FUS Regulatory Approvals by Region and Manufacturer



Manufacturers

North America

- Profound Medical, *Canada*
- Sonablate, *US*

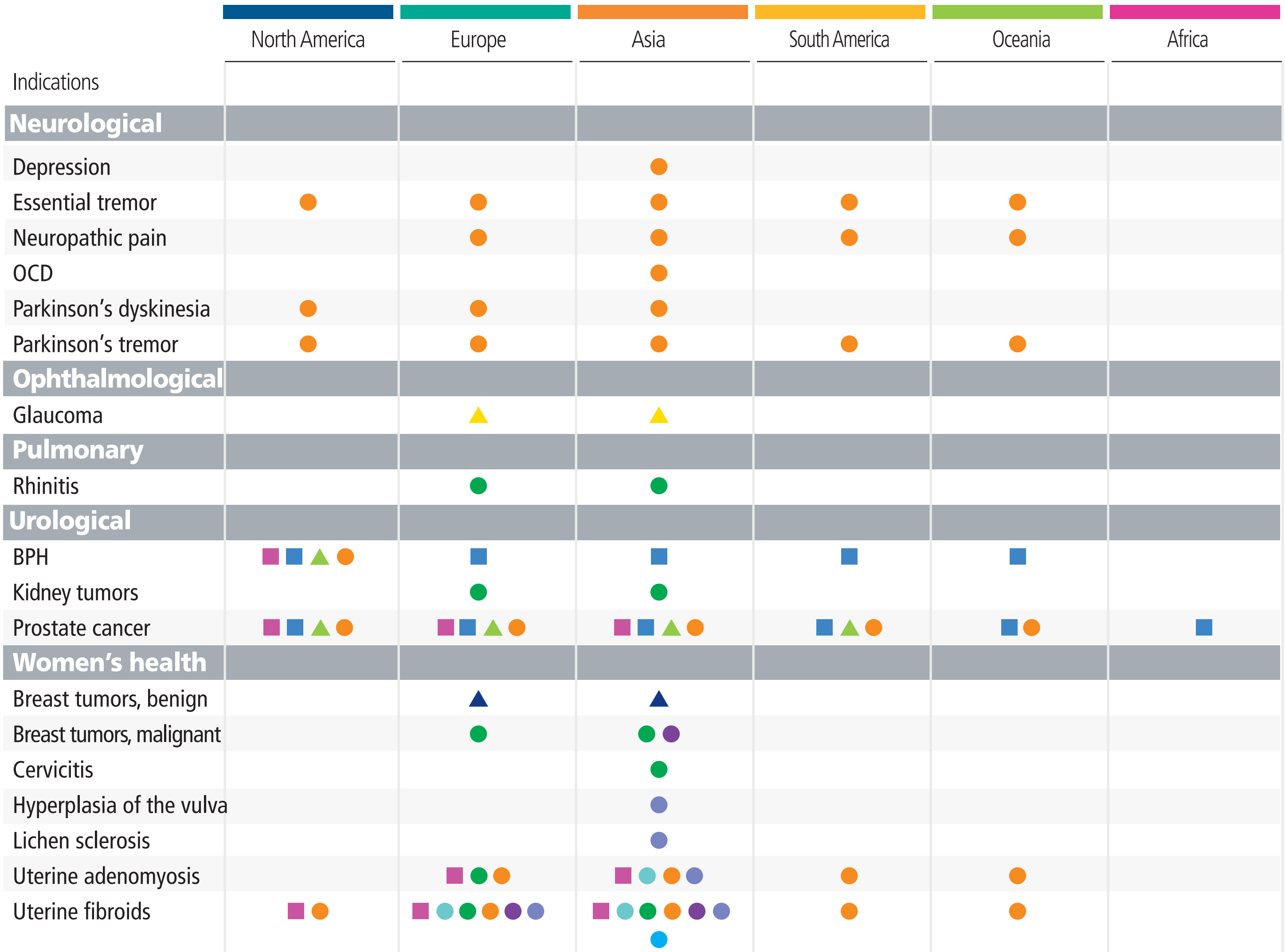
Europe

- EDAP TMS, *France*
- EyeTechCare, *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*

FUS Regulatory Approvals by Region and Manufacturer continued



Manufacturers

North America

- Profound Medical, *Canada*
- Sonablate, *US*

Europe

- EDAP TMS, *France*
- EyeTechCare, *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

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

Manufacturers

North America
- Profound Medical, *Canada*
- Sonablate, *US*

Europe
- EDAP TMS, *France*
- EyeTechCare, *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*

Europe
FUS Regulatory Approvals by Country and Manufacturer

Indications	Belarus MOH	Europe CE Marking	Russia Roszdravnadzor	Turkey TITUBB
Cardiovascular				
Varicose veins		▲ Theraclion		
Endocrine				
Thyroid nodules		▲ Theraclion	▲ Theraclion	
Gastrointestinal				
Liver metastases		● Chongqing Haifu		
Liver tumors		● Chongqing Haifu	● Chongqing Haifu	
Pancreatic tumors		● Chongqing Haifu	● Chongqing Haifu	
Musculoskeletal				
Arthritis, facetogenic		● Insightec	● Insightec	● Insightec
Bone cancer		● Insightec	● Insightec	● Insightec
Bone metastases	● Insightec	■ Profound Medical, ● Insightec	● Insightec	● Insightec
Bone tumors, benign		● Insightec	● Insightec	● Insightec
Desmoid tumors		■ Profound Medical		
Multiple myeloma		● Insightec	● Insightec	● Insightec
Osteoid osteoma		■ Profound Medical, ● Chongqing Haifu	● Chongqing Haifu	
Soft tissue cancer		● Chongqing Haifu	● Chongqing Haifu	
Soft tissue tumors, benign		● Chongqing Haifu	● Chongqing Haifu	

Manufacturers

North America
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Europe

FUS Regulatory Approvals by Country and Manufacturer continued

Indications	Belarus (MOH)	Europe (CE Marking)	Russia (Roszdravnadzor)	Turkey (TITUBB)
Neurological				
Essential tremor		● Insightec	● Insightec	● Insightec
Neuropathic pain		● Insightec	● Insightec	● Insightec
Parkinson's dyskinesia			● Insightec	
Parkinson's tremor		● Insightec	● Insightec	● Insightec
Ophthalmological				
Glaucoma		▲ EyeTechCare		
Pulmonary				
Rhinitis		● Chongqing Haifu		
Urological				
BPH		■ Sonablate	■ Sonablate	
Kidney tumors		● Chongqing Haifu	● Chongqing Haifu	
Prostate cancer	● Insightec	■ Profound Medical, ■ Sonablate, ▲ EDAP TMS, ● Insightec	■ Sonablate, ▲ EDAP TMS, ● Insightec	● Insightec
Women's health				
Breast tumors, benign		▲ Theraclion	▲ Theraclion	
Breast tumors, malignant		● Chongqing Haifu	● Chongqing Haifu	
Uterine adenomyosis		■ Profound Medical, ● Chongqing Haifu, ● Insightec	● Chongqing Haifu	● Insightec
Uterine fibroids	● Insightec	■ Profound Medical, ● Alpinion, ● Chongqing Haifu, ● Insightec, ● Shanghai A&S, ● Shenzhen PRO-HITU	● Chongqing Haifu, ● Insightec	● Insightec

Manufacturers

North America
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Page intentionally left blank

Asia

FUS Regulatory Approvals by Country and Manufacturer

Indications	China NMPA	Hong Kong MDD	India CDSCO	Israel AMAR	Japan MHLW	Kazakhstan NCEM	Kuwait MOH FDCD	Malaysia MDA
Cardiovascular								
Varicose veins								
Endocrine								
Thyroid nodules		🔺						
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
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Asia

FUS Regulatory Approvals by Country and Manufacturer continued

Indications	Pakistan DRAP	Philippines FDA	Saudi Arabia SFDA	Singapore HSA	South Korea MFDS	Taiwan FDA	Thailand FDA	Vietnam DMEW
Cardiovascular								
Varicose veins				▲				
Endocrine								
Thyroid nodules				▲	▲	▲		
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
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Asia

FUS Regulatory Approvals by Country and Manufacturer continued

Indications	China NMPA	Hong Kong MDD	India CDSCO	Israel AMAR	Japan MHLW	Kazakhstan NCEM	Kuwait MOH FDCD	Malaysia MDA
Ophthalmological								
Glaucoma	EyeTechCare							
Pulmonary								
Rhinitis	Chongqing Haifu							
Urological								
BPH	Sonablate	Sonablate	Sonablate	Sonablate	Sonablate			
Kidney tumors	Chongqing Haifu							
Prostate cancer	Sonablate	Sonablate, Insightec	Sonablate	Sonablate		Insightec		
Women's health								
Breast tumors, benign		Theraclion						
Breast tumors, malignant	Chongqing Haifu, Shanghai A&S							
Cervicitis	Chongqing Haifu							
Hyperplasia of the vulva	Shenzhen PRO-HITU							
Lichen sclerosis	Shenzhen PRO-HITU							
Uterine adenomyosis	Shenzhen PRO-HITU	Insightec		Insightec		Insightec		Profound Medical
Uterine fibroids	Profound Medical, Chongqing Haifu, Insightec, Shanghai A&S, Shenzhen PRO-HITU, Wuxi Haiying	Insightec		Insightec	Insightec	Insightec	Insightec	Profound Medical

Manufacturers

North America
- Profound Medical, *Canada*
- Sonablate, *US*

Europe
- EDAP TMS, *France*
- EyeTechCare, *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*

Asia

FUS Regulatory Approvals by Country and Manufacturer continued

Indications	Pakistan DRAP	Philippines FDA	Saudi Arabia SFDA	Singapore HSA	South Korea MFDS	Taiwan FDA	Thailand FDA	Vietnam DMEW
Ophthalmological								
Glaucoma								
Pulmonary								
Rhinitis								
Urological								
BPH					Sonablate			Sonablate
Kidney tumors								
Prostate cancer	Sonablate			Profound Medical	Sonablate, EDAP TMS	Sonablate	Insightec	Sonablate
Women's health								
Breast tumors, benign				Theraclion	Theraclion	Theraclion		
Breast tumors, malignant								
Cervicitis								
Hyperplasia of the vulva								
Lichen sclerosis								
Uterine adenomyosis					Alpinion Medical Systems, Shenzhen PRO-HITU Medical		Insightec	Profound Medical
Uterine fibroids			Profound Medical, Insightec	Profound Medical, Insightec	Profound Medical, Alpinion Medical Systems, Chongqing Haifu Medical Technology, Shanghai A&S	Insightec, Shenzhen PRO-HITU Medical	Insightec, Shanghai A&S	Profound Medical

Manufacturers

North America
- Profound Medical, *Canada*
- Sonablate, *US*

Europe
- EDAP TMS, *France*
- EyeTechCare, *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*

South America

FUS Regulatory Approvals by Country and Manufacturer

Indications	Argentina ANMAT	Brazil ANVISA	Chile ANAMED	Colombia INVIMA	Ecuador ANRCVS	Peru DIGEMED
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

- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe

- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

South America

FUS Regulatory Approvals by Country and Manufacturer continued

Indications	Trinidad and Tobago Ministry of Health
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

- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe

- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Oceania
FUS Regulatory Approvals by Country and Manufacturer

Indications	Australia 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
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Africa
FUS Regulatory Approvals by Country and Manufacturer

	South Africa
Indications	MCC
Urological	
Prostate cancer	■ (Sonablate)

Manufacturers

North America
- ■ Profound Medical, *Canada*
- ■ Sonablate, *US*

Europe
- ▲ EDAP TMS, *France*
- ▲ EyeTechCare, *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*

Global Landscape of Approved Indications and Manufacturers

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

Approval regions

- North America
- Europe
- Asia
- South America
- Oceania
- Africa

Global Landscape of Approved Indications and Manufacturers continued

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

Approval regions

- North America
- Europe
- Asia
- South America
- Oceania
- Africa

Global Landscape of Approved Indications and Manufacturers continued

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

Approval regions

- North America
- Europe
- Asia
- South America
- Oceania
- Africa

Page intentionally left blank

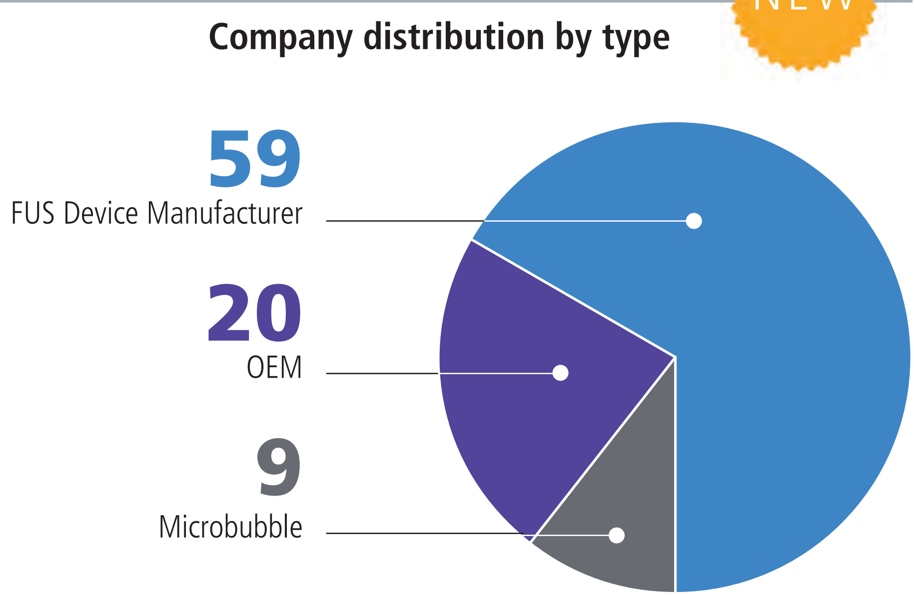
FUS Industry Timelines

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.

NEW

88

FUS companies*



*Includes device manufacturers, OEM, and microbubble companies

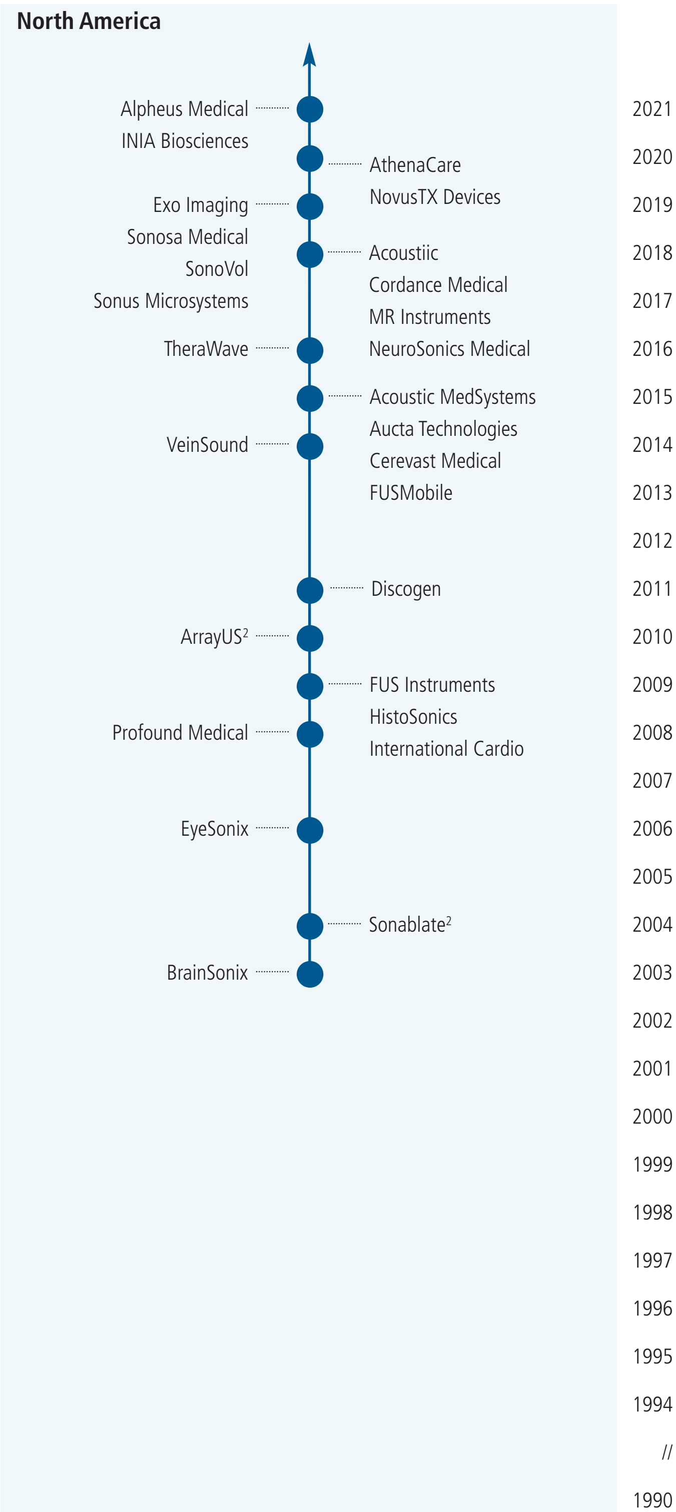
North America—Timelines of Companies, p.III.67

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.

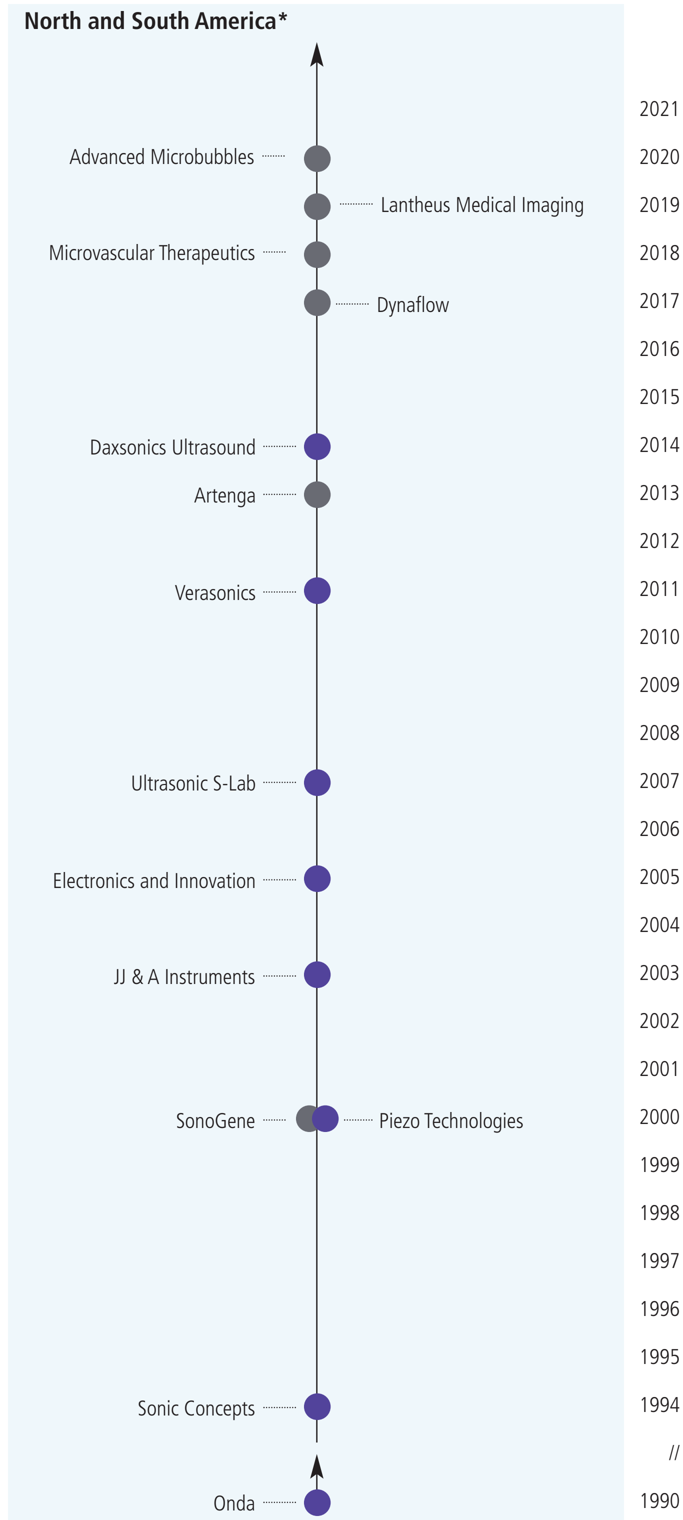
North America—Timelines of Companies

Clinical Device Manufacturers



Other FUS Companies

Microbubble OEM

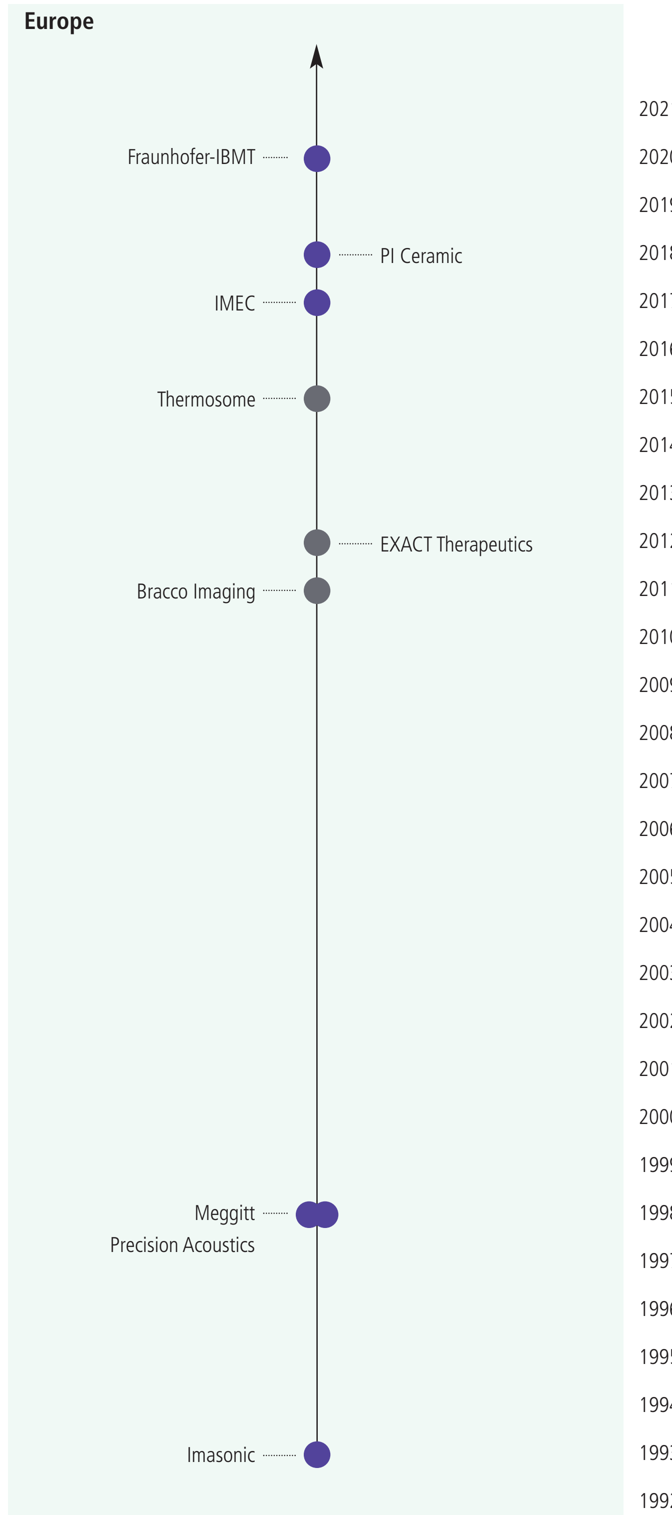


Europe—Timelines of Companies

Clinical Device Manufacturers

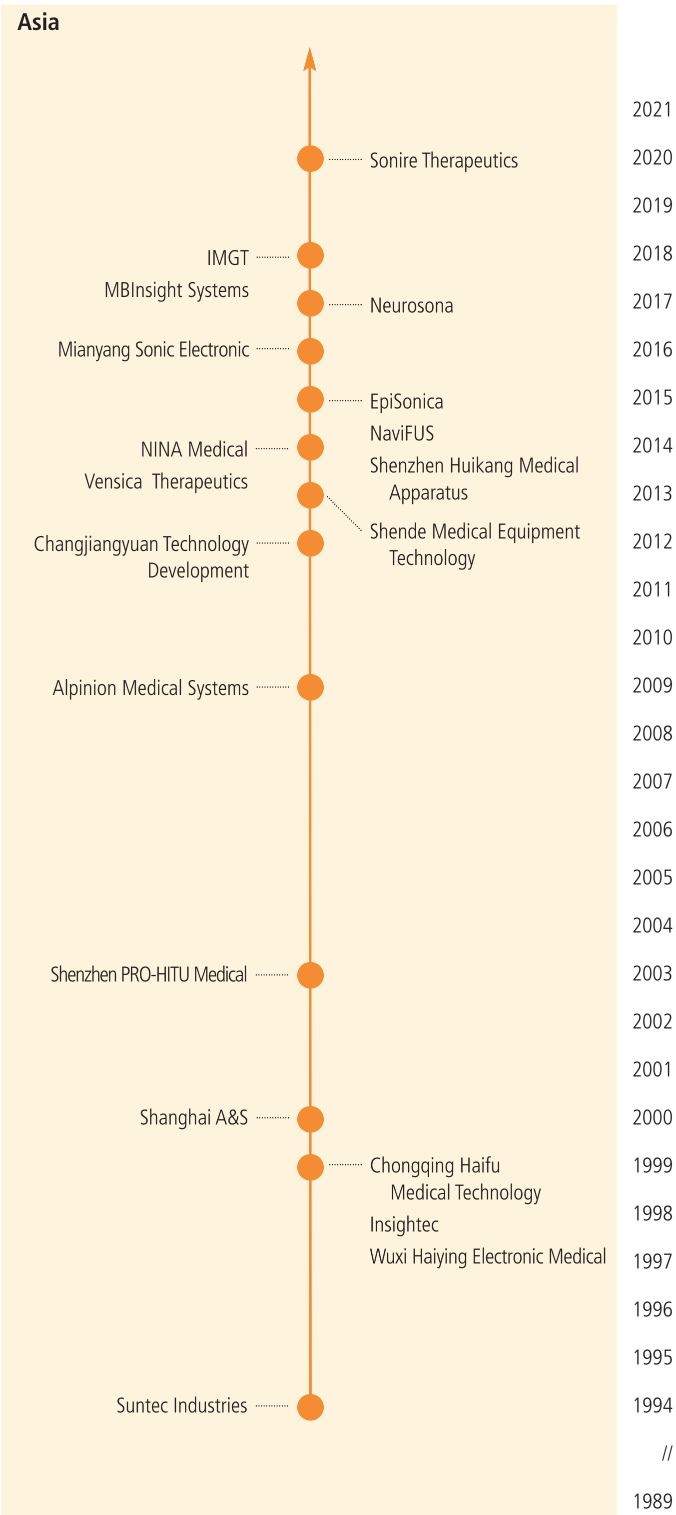
Other FUS Companies

Microbubble OEM



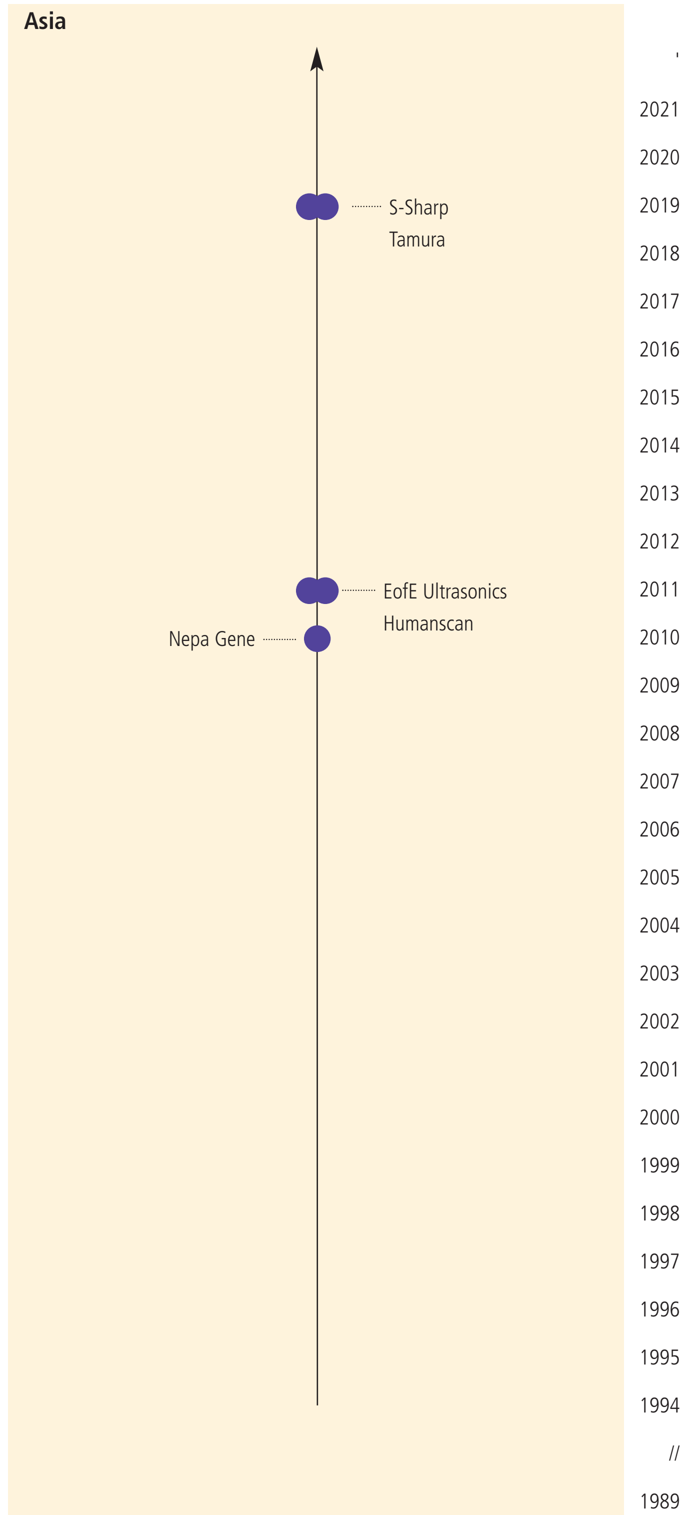
Asia—Timelines of Companies

Clinical Device Manufacturers



Other FUS Companies

Microbubble OEM

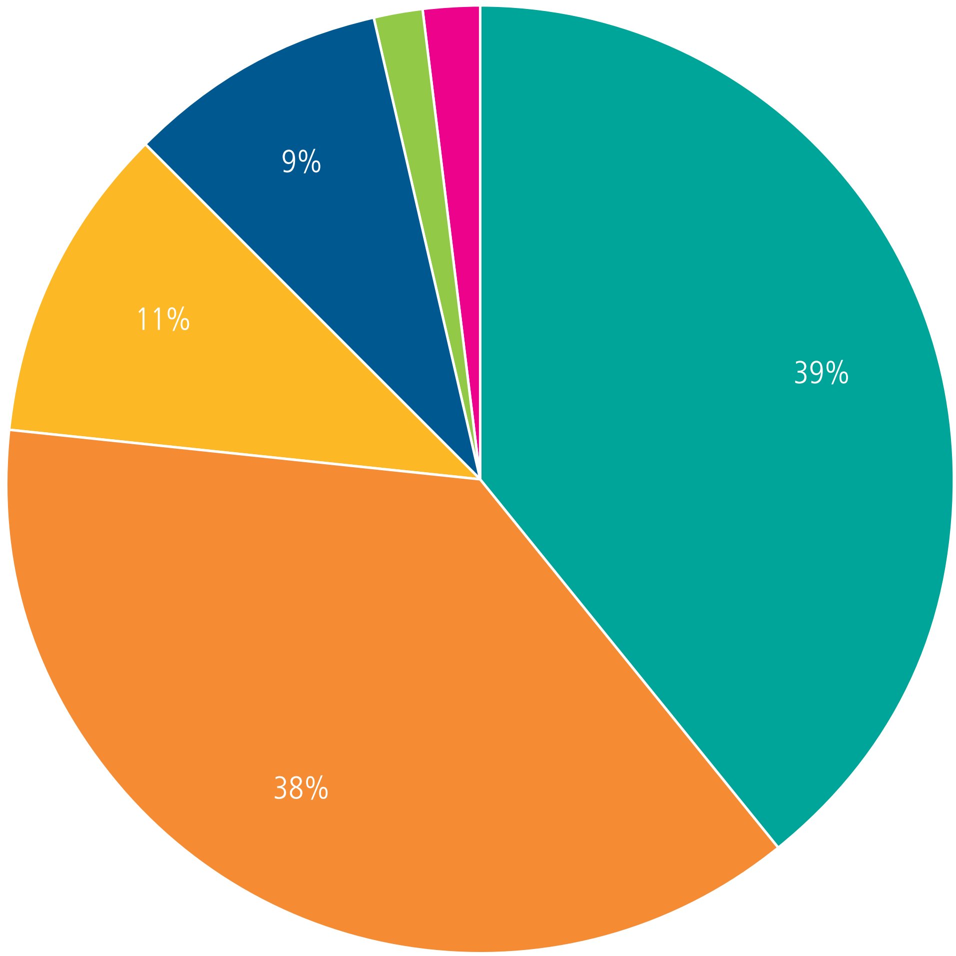


NEW

FUS Device Distributors by Region

56 distributors

North America	5	9%
Europe	22	39%
Asia	21	38%
South America	6	11%
Oceania	1	2%
Africa	1	2%



NEW

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 SRO
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 CO LTD
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

North America

American HIFU LLC
Cyber Robotic Solutions SA de CV
HIFU Prostate Services LLC
Soluciones Medicas Avanzadas SAS
Vituro Health LLC

Oceania

Strattner & Cia LTDA

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.

FUS Industry by Region continued

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

FUS Industry by Region continued

Europe

22

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.

FUS Industry by Region continued

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

FUS Industry by Region continued

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 CO 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.

FUS Industry by Region continued

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	Ultrasound, CT-fluoroscopy, MRI, and 3D targeting	–	
	TheraVision	–	–	
Acoustiic	AcuFUSS	MR guidance	MR guidance	
ArrayUS	Symphony	US & MR guidance	–	
Aucta Technologies	DECIMA	Unguided	–	
BrainSonix	BXPulsar 1001 LIFUP	MR guidance	MR guidance	
	BXPulsar 1002 LIFUP	MR guidance	MR guidance	
Cerevast Medical	Aureva Pulse	US guidance	–	
	Reflow RVO	US guidance	–	
Exo Imaging	Performance Ultrasound Platform	–	–	
EyeSonix	TUG - Therapeutic Ultrasound for Glaucoma	Unguided	Visual guidance	
FUS Instruments	DS-50	–	–	
	LP-100	MR guidance	–	
	RK-100	–	–	
	RK-20	Other guidance	–	
	RK-300	MR guidance	–	
	RK-50	Other 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 guidance	MR guidance	
	MR-guided TRUST (Transcranial Ultrasound Stimulation)	MR guidance	MR guidance	
NeuroSonics Medical	NeuroSonics (prototype)	US guidance	MR guidance	
Profound Medical	Sonalleve	MR guidance	MR guidance	+
	TULSA-PRO	MR guidance	MR guidance	+
Sonablate Corp.	Sonablate	US guidance	MR/US fusion	+
	Sonatherm	US guidance	US guidance	+
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	

FUS Devices with Treatment and Planning Guidance continued

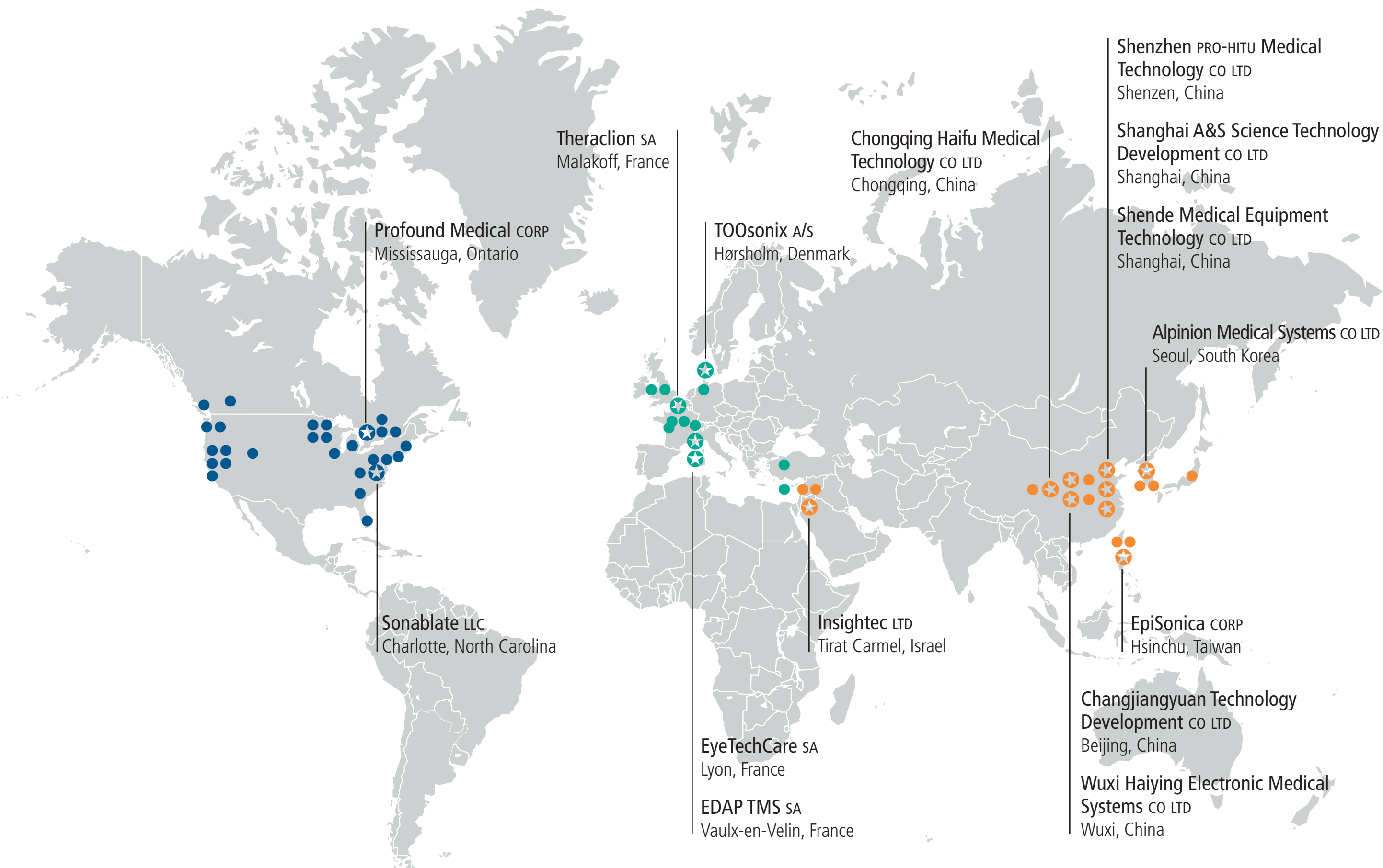
Manufacturer	Device	Treatment guidance	Planning guidance	Approval
Asia				
Alpinion Medical Systems	Alpius 900	US guidance	–	✚
	VIFU2000	US guidance	–	
Changjiangyuan Technology Development	NUTAS – Non-invasive Ultrasound Tumor Ablation System	US guidance	US guidance	✚
	SUPER Knife-Focused Beam Therapy 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	–	✚

NEW

Clinical Device Manufacturers with Regulatory Approvals



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.

Clinical Device Manufacturers with Regulatory Approvals continued

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

NEW

289
Approvals
worldwide

35
Regulatory agencies

Clinical Device Manufacturers with Regulatory Approvals

NEW

Alpinion Medical Systems CO LTD

Devices

2	1		
Total devices	Approved device		

Name	Status	Treatment guidance	Planning guidance
Alpius 900	✚	Ultrasound	—
VIFU2000	—	Ultrasound	—

Approvals

2	2	2	3
Approved indications	Regions	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.

Clinical Device Manufacturers with Regulatory Approvals continued

Alpinion Medical Systems CO LTD continued

Clinical research

2 Indications	1 Region	1 Country	2 Sites

Indication	Region	Country	Site
Gastrointestinal			
Pancreatic tumors, malignant	1	1	1
Women's health			
Uterine fibroids	1	1	1

NEW

Clinical Device Manufacturers with Regulatory Approvals

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	Region	Country	Agency and date
Gastrointestinal			
Liver metastases	Europe	Europe	CE Marking, 2005
Liver tumors	Europe Europe Asia Asia	Europe Russia China South Korea	CE Marking, 2005 Roszdravnadzor, 2011 NMPA, 1999 MFDS, 2014

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

Chongqing Haifu Medical Technology CO LTD continued

Approvals continued

Indication	Region	Country	Agency and date
Gaatrointestinal continued			
Pancreatic tumors	Europe Europe Asia Asia	Europe Russia China South Korea	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999 MFDS, 2014
Musculoskeletal			
Osteoid osteoma	Europe Europe Asia	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	Europe Europe Asia	Europe Russia China	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999
Pulmonary			
Rhinitis	Europe Asia	Europe China	CE Marking, 2006 NMPA, 1999
Urological			
Kidney tumors	Europe Europe Asia	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

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 Asia Asia	Europe Russia China South Korea	CE Marking, 2006 Roszdravnadzor, 2011 NMPA, 1999 MFDS, 2014

Clinical research

15	2	4	12
Indications	Regions	Countries	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.

Clinical Device Manufacturers with Regulatory Approvals continued

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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

EDAP TMS SA

Devices

3	2		
Total devices	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	4	6	14
Approved indications	Regions	Countries	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.

Clinical Device Manufacturers with Regulatory Approvals continued

EDAP TMS SA continued

Clinical research

5	2	6	28
Indications	Regions	Countries	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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

EpiSonica CORP

Devices

1 Total device	1 Approved device		
Name	**Status**	**Treatment guidance**	**Planning guidance**
ArcBLATE (ARC-100M)	✚	MR	MR

Approvals

1 Approved indication	1 Region	1 Country	1 Total approvals
Indication	**Region**	**Country**	**Agency and date**
Musculoskeletal			
Soft tissue cancer	Asia	Taiwan	FDA, 2016

✚ Devices with regulatory approvals.

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

EyeTechCare SA

Devices

1	1		
Total device	Approved device		

Name	Status	Treatment guidance	Planning guidance
EyeOP1	✚	Unguided	—

Approvals

1	2	2	3
Approved indication	Regions	Countries	Total approvals

Indication	Region	Country	Agency and date
Ophthalmological			
Glaucoma	Europe	Europe	CE Marking, 2011
	Asia	China	NMPA, 2017

Clinical research

1	2	4	6
Indication	Regions	Countries	Sites

Indication	Region	Country	Site
Ophthalmological			
Glaucoma	2	4	6

✚ Devices with regulatory approvals.

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC

Devices

3 Total devices

3 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.

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Approvals continued

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

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Approvals continued

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

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Approvals continued

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

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Approvals continued

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

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Approvals continued

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

“**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 INC

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec INC continued

Clinical research

40	5	16	67
Indications	Regions	Countries	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

Clinical Device Manufacturers with Regulatory Approvals continued

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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

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	Europe Asia Asia Asia	Europe Malaysia Singapore Vietnam	CE Marking, 2011 MDA, 2015 HSA, 2021 DMEW, 2010
Desmoid tumors	Europe	Europe	CE Marking, 2021
Osteoid osteoma	North America Europe Asia	United States Europe Singapore	FDA, 2020 CE Marking, 2020 HSA, 2021

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

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 America	Canada	Health Canada, 2019
	North America	United States	FDA, 2019
	Europe	Europe	CE Marking, 2016
	Asia	Singapore	HSA, 2019
Women's health			
Uterine adenomyosis	Europe	Europe	CE Marking, 2010
	Asia	Malaysia	MDA, 2015
	Asia	Vietnam	DMEW, 2010
Uterine fibroids	North America	Canada	Health Canada, 2013
	Europe	Europe	CE Marking, 2009
	Asia	China	NMPA, 2018
	Asia	Malaysia	MDA, 2015
	Asia	Saudi Arabia	SFDA, 2015
	Asia	Singapore	HSA, 2021
	Asia	South Korea	MFDS, 2012
	Asia	Vietnam	DMEW, 2010

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

Clinical Device Manufacturers with Regulatory Approvals continued

Profound Medical CORP continued

Clinical research continued

Indication	Region	Country	Site
Women's health			
Breast tumors, malignant	2	2	2
Cervical tumors	1	1	1
Uterine adenomyosis	2	2	2
Uterine fibroids	2	6	7
Vaginal tumors	1	1	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."

— Profound Medical CORP

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

Shanghai A&S Science Technology Development CO, LTD

Devices

1 Total device

1 Approved devices

Name	Status	Treatment guidance	Planning guidance
HIFUNIT9000	✚	Ultrasound	MR

Approvals

5 Approved indications

2 Regions

4 Countries

8 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	Europe Asia Asia Asia	Europe China South Korea Thailand	CE Marking, 2008 NMPA, 2002 MFDS, 2007 FDA, 2013

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

Shanghai A&S Science Technology Development CO, LTD continued

Clinical research

1 Indication	1 Region	1 Country	1 Site

Indication	Region	Country	Site
Gastrointestinal			
Liver tumors	1	1	1

> “**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 CO LTD

Clinical Device Manufacturers with Regulatory Approvals continued

NEW

Shenzhen PRO-HITU Medical Technology CO, LTD

Devices

5 Total devices

3 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	Europe Asia Asia	Europe China Taiwan	CE Marking, 2012 MDA, 2012 FDA, 2018

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

Shenzhen PRO-HITU Medical Technology CO, LTD continued

Clinical research

2	1	1	4
Indications	Region	Country	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 CO, LTD

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

Sonablate CORP

Devices

2	2		
Total devices	Approved devices		

Name	Status	Treatment guidance	Planning guidance
Sonablate	✚	Ultrasound	MR/US fusion
Sonatherm	✚	Ultrasound	Ultrasound

Approvals

2	6	23	39
Approved indications	Regions	Countries	Total approvals

Indication	Region	Country	Agency and date
Urological			
Benign prostatic hyperplasia	North America	Canada	Health Canada, 2005
	North America	Costa Rica	Ministerio de Salud, 2005
	North America	Dominican Republic	MISPAS, 2005
	North America	United States	FDA, 2006
	Europe	Russia	Roszdravnadzor, 2005
	Asia	China	NMPA, 2020``
	Asia	Hong Kong	MDD, 2018
	Asia	India	CDSCO, 2011
	Asia	Israel	AMAR, 2018
	Asia	Japan	MHLW, 2001
	Asia	South Korea	MFDS, 2016
	Asia	Vietnam	DMEW, 2009

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

Sonablate CORP continued

Approvals continued

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

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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

Theraclion SA

Devices

2 Total devices | **2** 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	Europe	CE Marking, 2019
	Asia	Singapore	HSA, 2019
Endocrine disorders			
Thyroid nodules	Europe	Europe	CE Marking, 2007
	Europe	Russia	Roszdravnadzor, 2017
	Asia	Hong Kong	MDD, 2007
	Asia	South Korea	MFDS, 2017
	Asia	Singapore	HSA, 2016
	Asia	Taiwan	FDA, 2019

✚ Devices with regulatory approvals.

Clinical Device Manufacturers with Regulatory Approvals continued

Theraclion SA continued

Approvals continued

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

Clinical research

13	3	6	10
Indications	Regions	Countries	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

Clinical Device Manufacturers with Regulatory Approvals continued

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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

TOOsonix A/S

Devices

2 Total devices

1 Approved device

Name	Status	Treatment guidance	Planning guidance
System ONE-M	✚	Image fusion	Visual guidance
System ONE-R	—	Image fusion	Visual guidance

Approvals

0 Approved indications[1]

1 Region

1 Country

0 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.

Clinical Device Manufacturers with Regulatory Approvals continued

TOOsonix S/A continued

Clinical research

3 Indications	1 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

NEW

Clinical Device Manufacturers with Regulatory Approvals continued

Wuxi Haiying Electronic Medical Systems CO, LTD

Devices

1
Total device

1
Approved device

Name	Status	Treatment guidance	Planning guidance
HY2900	✚	Ultrasound	—

Approvals

1
Approved indication

1
Region

1
Country

1
Total approval

Indication	Region	Country	Agency and date
Women's health			
Uterine fibroids	Asia	China	NMPA, 2016

✚ Devices with regulatory approvals.

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.

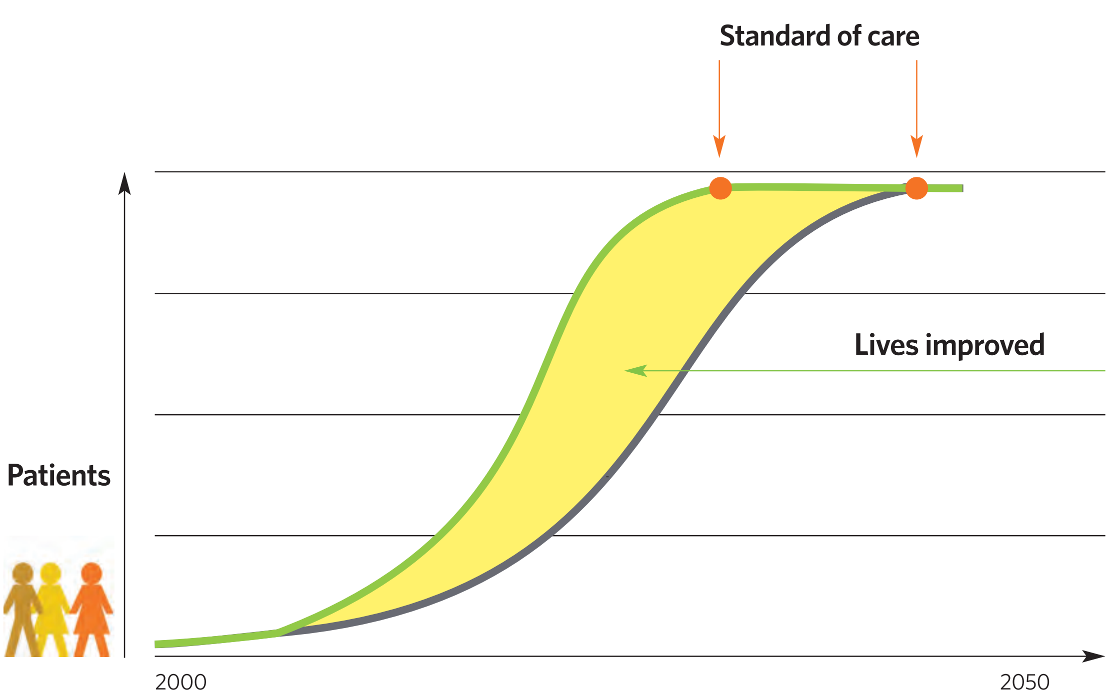
Major initiatives include

- 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.

The Focused Ultrasound Foundation encourages widespread distribution of the *2022 State of the Field Report* in part or its entirety. Inquiries for reproduction can be directed to Emily White at ewhite@fusfoundation.org.

Focused Ultrasound Foundation

FOCUSED ULTRASOUND FOUNDATION

1230 Cedars Court, Suite 206
Charlottesville, VA 22903
434.220.4993 MAIN LINE

www.fusfoundation.org

Contact
Emily White, MD
Editor in Chief
ewhite@fusfoundation.org EMAIL
434.277.1274 DIRECT LINE