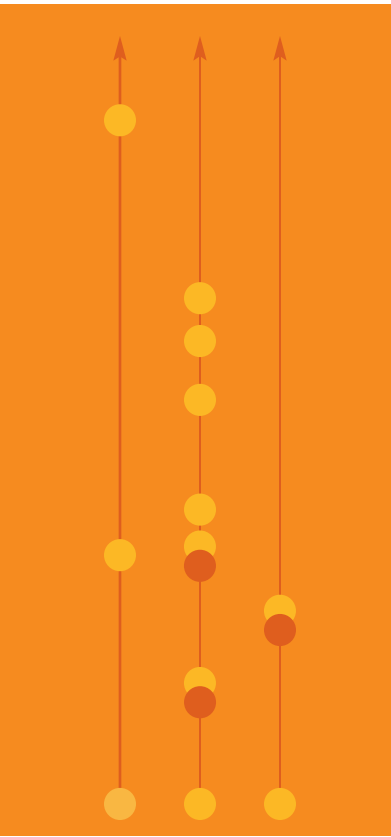


2020



State of the Field

FOCUSED
ULTRASOUND
FOUNDATION





Focused Ultrasound Foundation

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Date 9.8.2020

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The Focused Ultrasound Foundation strives to provide the most accurate information possible and therefore works proactively with the manufacturers and research sites to collect the most current data available in advance of the release of this publication. This report is based on data through December 31, 2019. The Focused Ultrasound Foundation assumes no responsibility for any errors or omissions as every precaution has been taken to verify the accuracy of the information contained herein. No liability is assumed for damages that may result from the use of information contained within. If you note something out of date or inaccurate, please submit the new information/updates to: info@fusfoundation.org.

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Dear Friends,

As we look back at the accomplishments of the field in 2019, we are gratified and amazed by the progress to date. With the rapid increase in the potential numbers of indications and mechanisms of action the past several years, the work required to translate research to commercialization reality becomes both more rewarding and more challenging. In the current landscape of focused ultrasound, these are the most critical questions to ask:

- Which of the 48 identified mechanisms of action are most likely to translate into effective treatment options?
- Which of the 136 indications currently under investigation are going to provide unique value in terms of outcome and cost?
- Which of the 88 companies in the focused ultrasound ecosystem are going to achieve global success?
- How are advances in imaging technology in general going to influence the future of focused ultrasound?
- What new and different stakeholders and audiences do we need to engage and educate as the field transitions from exclusively research based to include an expanding focus on commercialization?

These questions and their eventual answers will guide and determine the future of the field of focused ultrasound. Our hope is that the information contained in this report will provide glimpses into what that future might look like and how it might unfold over time.

As for the most significant achievements and milestones that occurred in 2019? I invite you to review the report and determine for yourself!

In closing, I would like to extend a special thanks to the Foundation's team, Board of Directors, Council members, and generous donors, as well as the growing number of manufacturers, scientists, and clinicians around the world, who are all working toward a common goal of making this technology widely available as a standard of care in the shortest time possible. We appreciate all of their contributions to this report.

Be well,



Neal F. Kassell, MD, *Chairman*

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, including:

- Benign and malignant tumors of the brain, breast, prostate, liver, and pancreas
- Movement disorders such as Parkinson’s disease and epilepsy
- Depression and obsessive-compulsive disorder
- Arthritis
- Hypertension
- Uterine fibroids

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.

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 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. 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 that is 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.

There are currently 136 clinical indications or disorders in various stages of development, and the number is increasing rapidly. Most are early stage. Worldwide, 33 indications have regulatory approval; in the US, six 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.

2020

Field Overview



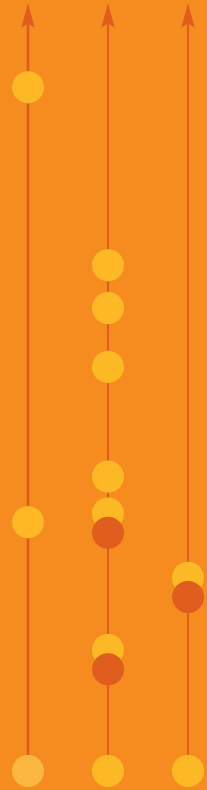
61,190

patient treatments
in 2019



136

distinct indications



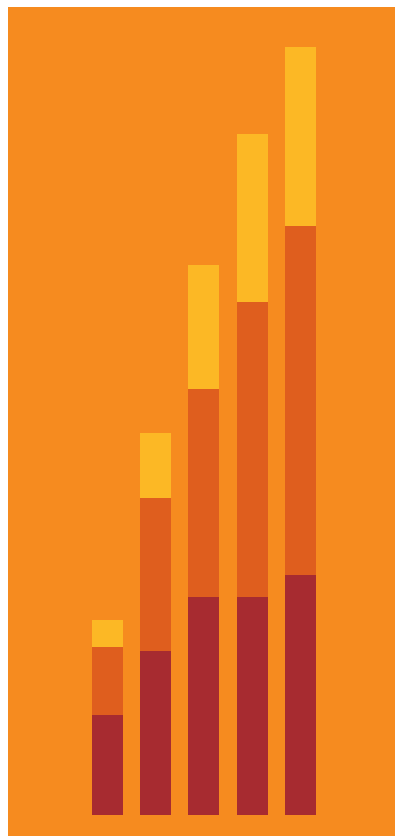
2

new indication approvals



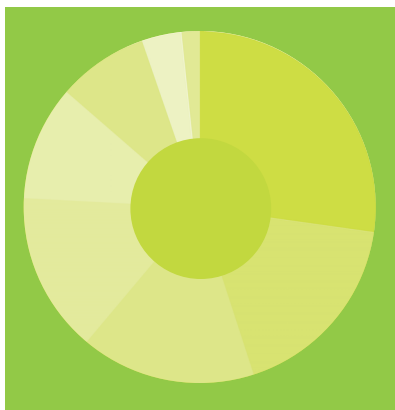
1,971

media placements
in the last 7 years



60

mechanisms of action



315,665
cumulative
patient treatments



Field Overview

The Field Overview is designed to give you 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 2019. Varicose veins received CE Mark approval and Rhinitis received CE Mark and CFDA approval in 2019. Seven indications transitioned from bench research to first in-human clinical trials. Nine new indications were identified in 2019, further confirming the continuing growth and expansion of the focused ultrasound field.

While this report is global in scope, we do break out many of the tables and graphs by geographic region. New for 2019, we examine cumulative regulatory approvals by region as tracked over the past 20 years.

Patient treatment data this year is different from years past. This year we are tracking cumulative treatments by indication as well as isolating the treatment numbers for 2019 and are reporting oncology patient treatments as a separate set of data.

Our State of the Field survey for 2019 expanded types of technical research to include further detail on transducer design and image guidance.

Similarly, the Foundation has revamped the way it reports on mechanisms of action in the 2019 report to further highlight and elucidate the expansion of this area of research.

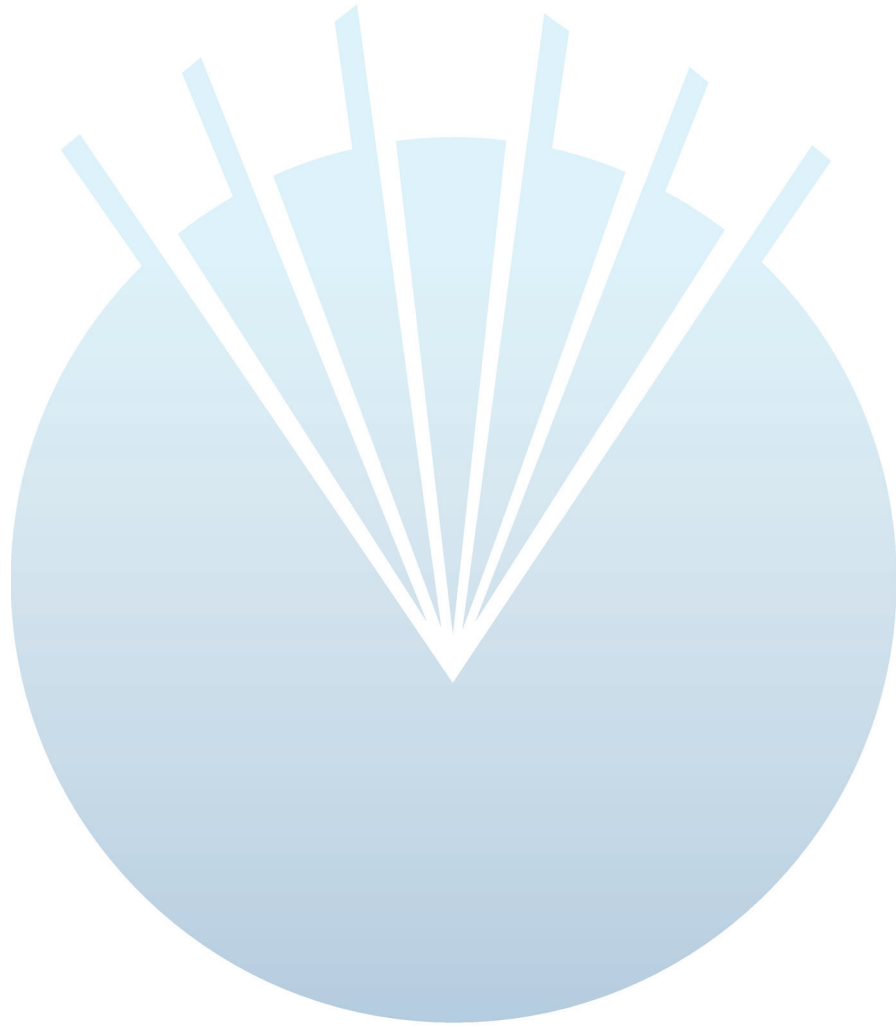
While we have always reported on publications by number of articles and citations, this year we expanded to include topical areas of research as well as identifying the top journals publishing focused ultrasound research.

Lastly, in 2019 we decided to break out United States Government funding by agency/institution. We look at both cumulative totals and annual awards for the past 15 years.

We hope you find all of these additions and changes to this year’s report to be an enhancement over previous reports that will further your understanding of the field as a whole.

9
new indications

7
indications
move to clinical trials



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Development Stage Advancements and New Indications

2019

Development stage advancements

In 2019, nine new indications were identified as possible candidates for treatment with focused ultrasound.

In 2019 Theraclion (France) received a European CE mark for its SONOVEIN device for the treatment of varicose veins. Chongqing Haifu Medical Technology (China) received Chinese and European regulatory approval to treat rhinitis, an inflammation of the nasal passages causing stuffiness and runny nose.

In 2019, the first in-human clinical trials began for seven disorders—including opioid and other addictions, multiple sclerosis, and migraine—all of which currently have standard-of-care treatment options that are suboptimal. Hopefully, these trials will be successful and these challenging conditions may soon have more attractive and effective treatment options.

9

New Indications

Gastrointestinal	● Gastric tumors
Musculoskeletal	● Rotator cuff injury ● Tendon contracture
Neurological	● Neuromyelitis optica ● Parkinson’s disease, other ¹ ● Rett syndrome
Pulmonary	● Tuberculosis
Urological	● Urinary tract infection ● Vasectomy

Development stage

● Preclinical ● Clinical

¹ Treatment of the underlying cause of the disease

Development Stage Advancements and New Indications continued

2019

7

Indications advanced to first in-human clinical trials

Cardiovascular	Heart valve calcifications
Gastrointestinal	Esophageal tumors Gastric tumors†
Neurological	Migraine Multiple sclerosis Opioid and other addictions*
Urological	Bladder tumors

† New Indication for 2019
* Clinical trial is specifically for opioid addiction

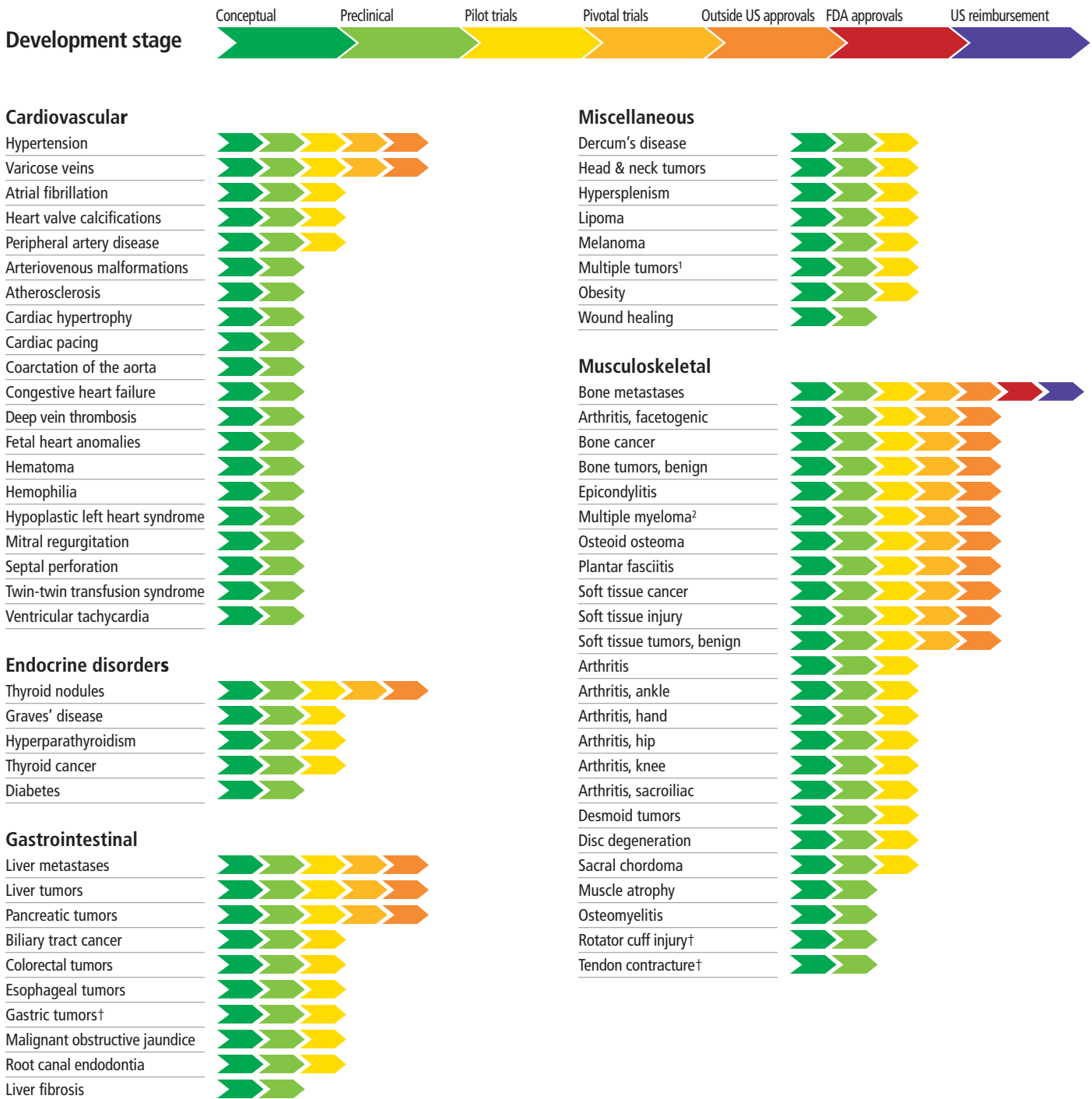
2019

2

Indications granted regulatory approval

Cardiovascular	Varicose veins
Pulmonary	Rhinitis

State of Research and Regulatory Approvals by Body System



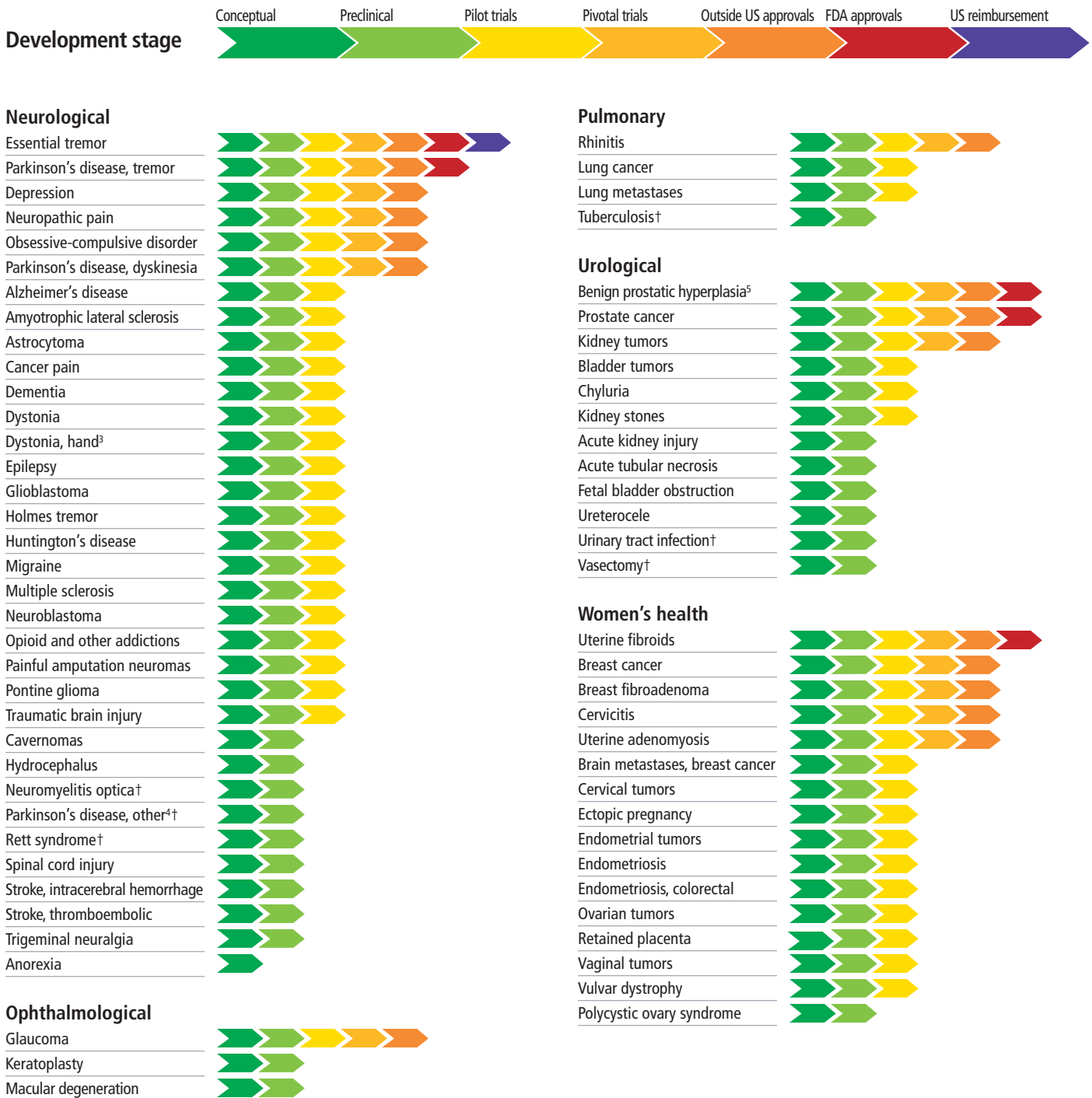
There are 136 distinct indications for 2019.

¹ Protocols inclusive of more than one indication

² Multiple myeloma approval is based on bone metastases.

† New in 2019

State of Research and Regulatory Approvals by Body System continued



There are 136 distinct indications for 2019.

3 In 2019 subcategories for dystonia were established.

4 Treatment of the underlying cause of the disease

5 FDA approval is for prostate tissue ablation.

† New in 2019

FIELD OVERVIEW

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 Twin-twin transfusion syndrome Ventricular tachycardia	Atrial fibrillation Heart valve calcifications Peripheral artery disease		Hypertension Varicose veins		
Endocrine disorders						
	Diabetes	Grave's disease Hyperparathyroidism Thyroid cancer		Thyroid nodules		
Gastrointestinal						
	Liver fibrosis	Biliary tract cancer Colorectal tumors Esophageal tumors Gastric tumors† Malignant obstructive jaundice Root canal endodontia		Liver metastases Liver tumors Pancreatic tumors		

† New in 2019

Global Development Landscape by Body System continued



Miscellaneous

	Wound healing	Dercum's disease Head & neck tumors Hypersplenism Lipoma Melanoma Multiple tumors ¹ Obesity				
--	---------------	--	--	--	--	--

Musculoskeletal

	Muscle atrophy Osteomyelitis Rotator cuff injury† Tendon contracture†	Arthritis Arthritis, ankle Arthritis, hand Arthritis, hip Arthritis, knee Arthritis, sacroiliac Desmoid tumors Disc degeneration Sacral chordoma		Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Epicondylitis Multiple myeloma ² Osteoid osteoma Plantar fasciitis Soft tissue cancer Soft tissue injury Soft tissue tumors, benign	Bone metastases	Bone metastases
--	--	--	--	---	-----------------	-----------------

¹ Protocols inclusive of more than one indication

² Multiple myeloma approval is based on bone metastases.

† New in 2019

FIELD OVERVIEW

Global Development Landscape by Body System continued



Neurological

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Anorexia	Cavernomas Hydrocephalus Neuromyelitis optica† Parkinson's disease, other ⁴ Rett syndrome† Spinal cord injury Stroke, intracerebral hemorrhage Stroke, thromboembolic Trigeminal neuralgia	Alzheimer's disease Amyotrophic lateral sclerosis Astrocytoma Cancer pain Dementia Dystonia Dystonia, hand ³ Epilepsy Glioblastoma Holmes tremor Huntington's disease Migraine Multiple sclerosis Neuroblastoma Opioid and other addictions Painful amputation neuromas Pontine glioma Traumatic brain injury		Depression Essential tremor Neuropathic pain Obsessive-compulsive disorder Parkinson's disease, dyskinesia Parkinson's disease, tremor	Essential tremor Parkinson's disease, tremor	Essential tremor

Ophthalmological

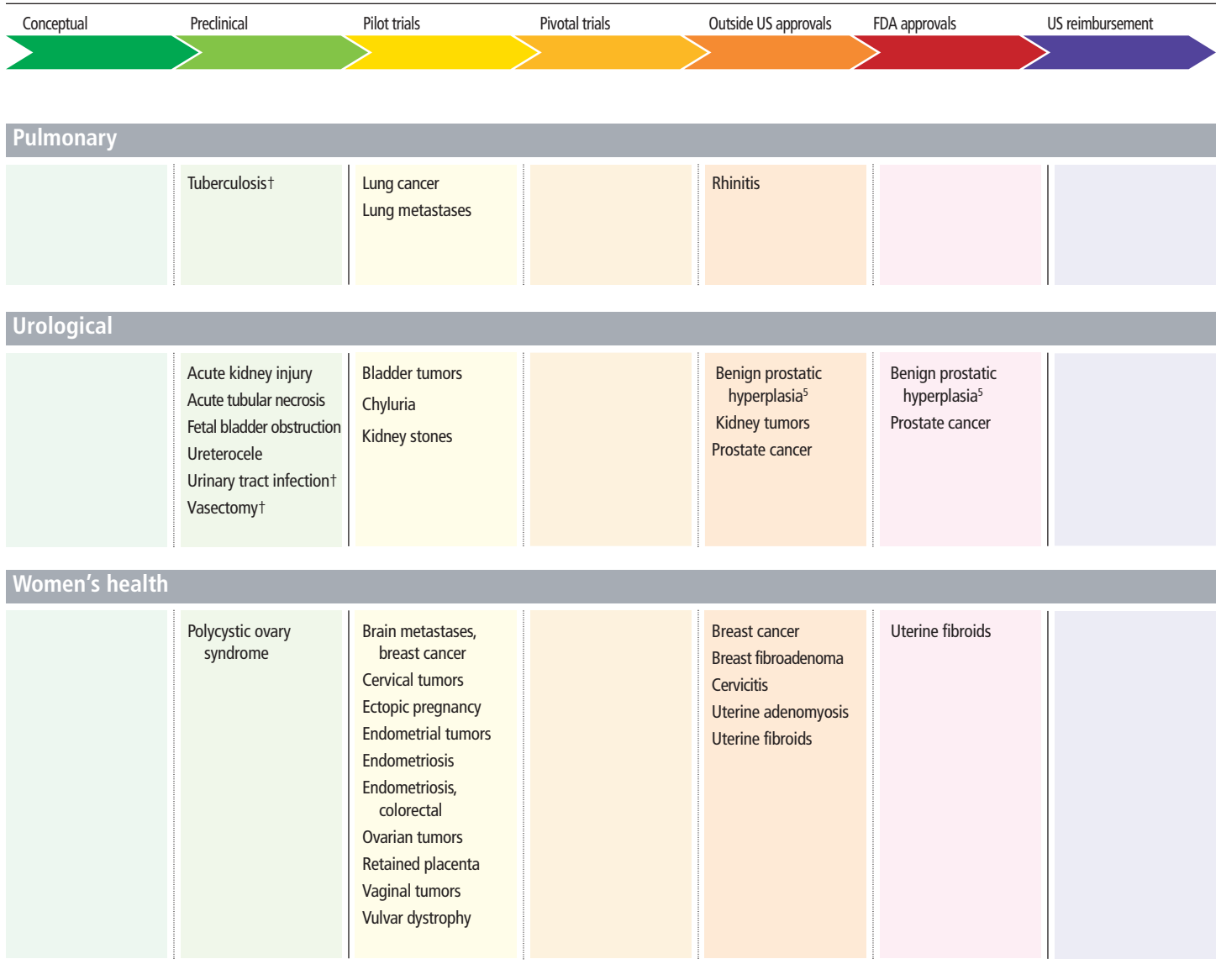
Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Keratoplasty Macular degeneration			Glaucoma		

³ In 2019 subcategories for dystonia were established.

⁴ Treatment of the underlying cause of the disease

† New in 2019

Global Development Landscape by Body System continued



⁵ FDA approval is for prostate tissue ablation.

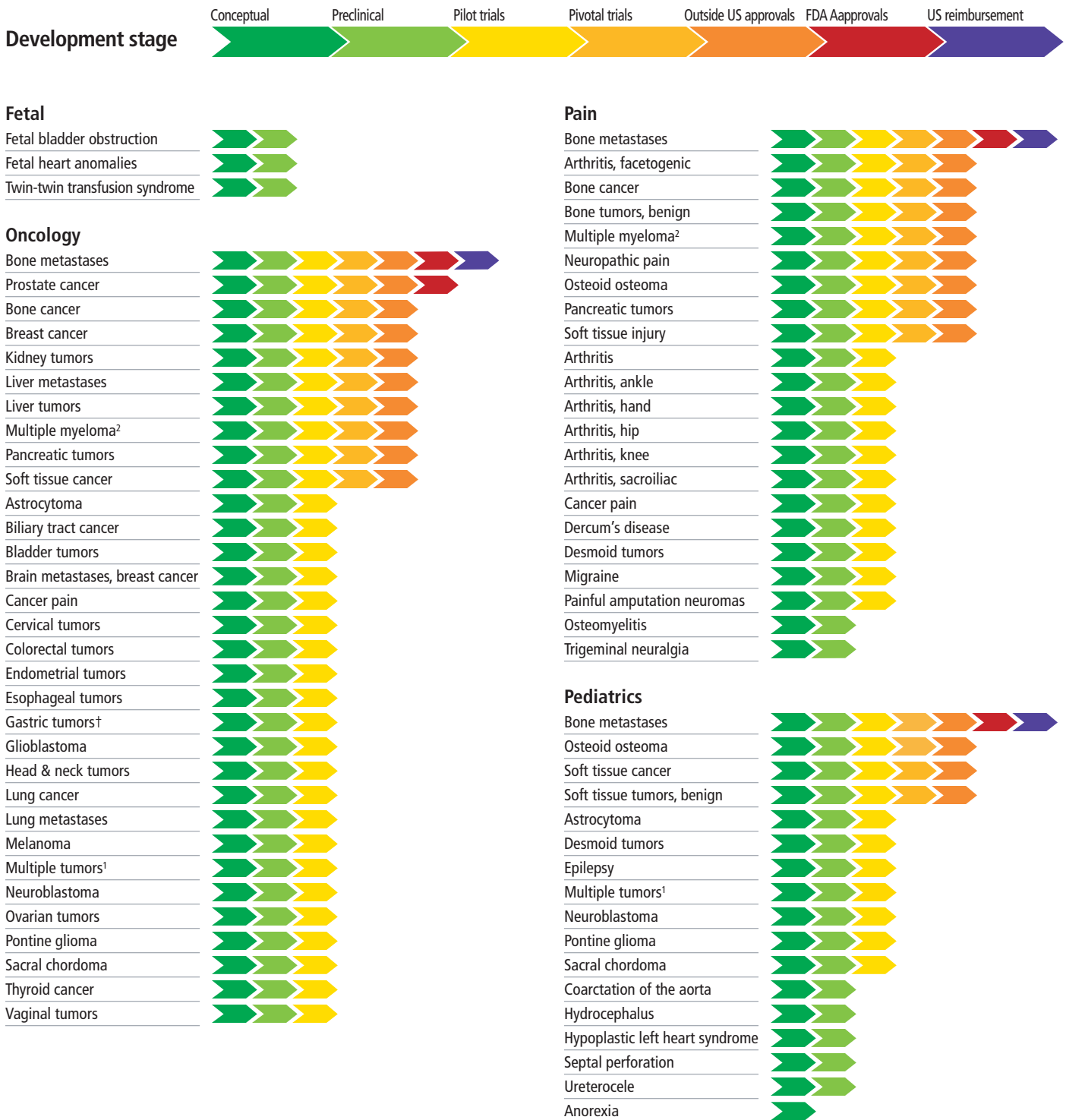
† New in 2019

A note on multiple listings

The human body contains multiple body systems that work together. Each system comprises a group of tissue structured to perform specific functions. The state of research and regulatory approvals are organized by indication according to body systems for case identification. However, when the chart is arranged solely by body system, the assessment of focused ultrasound's impact on diseases that affect multiple body systems can be undermined.

In an effort to see the data through a different lens, four “Areas of Interest”—fetal, oncology, pain, and pediatrics—are identified in this report on the following pages. These indications are represented in the chart in multiple places, in the body system to which they belong and again within the established areas of interest. This helps reveal patterns and trends over time that might otherwise be difficult to discern.

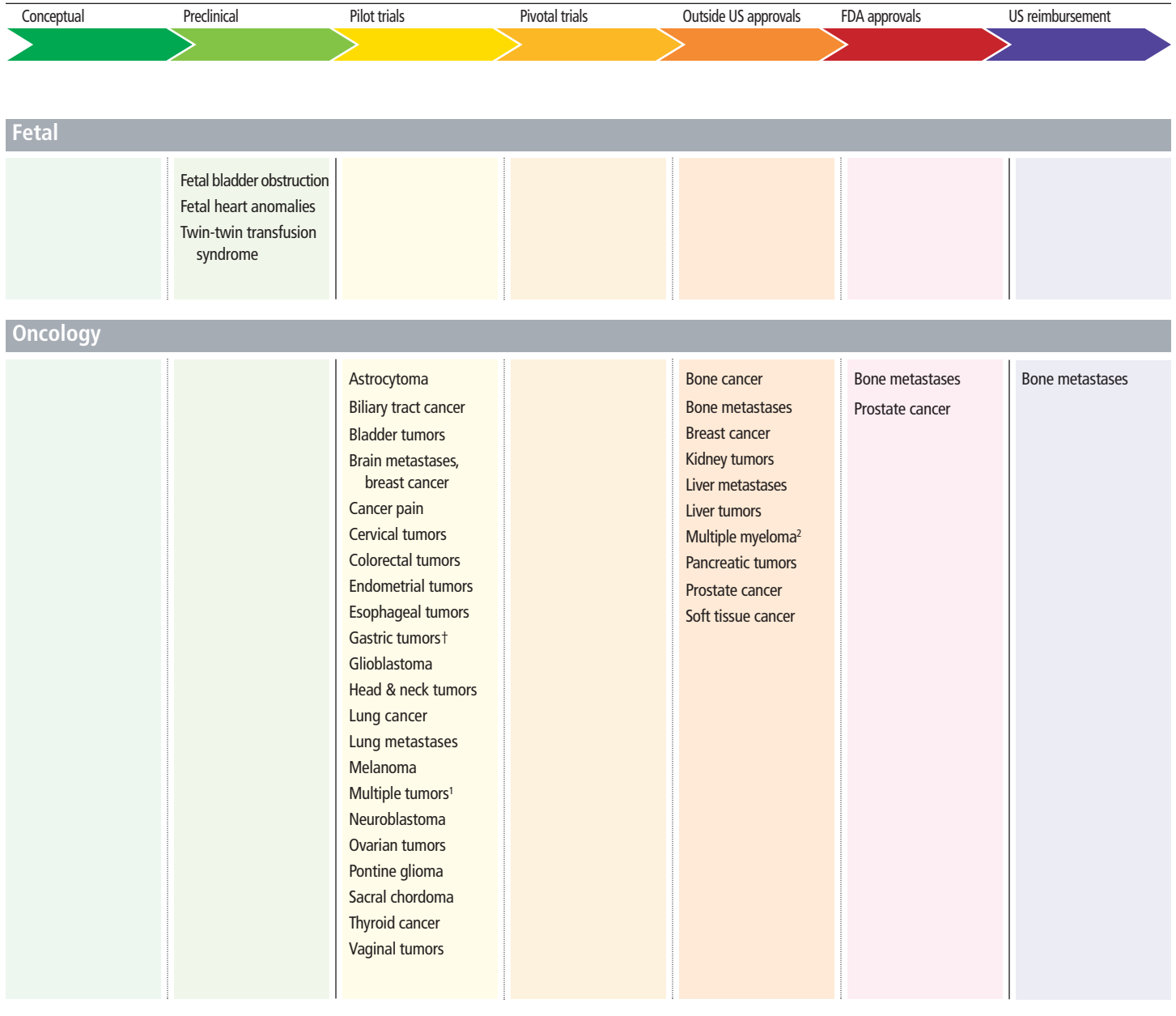
State of Research and Regulatory Approvals by Area of Interest



1 Protocols inclusive of more than one indication
 2 Multiple myeloma approval is based on bone metastases.
 † New in 2019

FIELD OVERVIEW

Global Development Landscape by Area of Interest



1 Protocols inclusive of more than one indication

2 Multiple myeloma approval is based on bone metastases.

† New in 2019

Global Development Landscape by Area of Interest continued



Pain						
Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Osteomyelitis Trigeminal neuralgia	Arthritis Arthritis, ankle Arthritis, hand Arthritis, hip Arthritis, knee Arthritis, sacroiliac Cancer pain Dercum's disease Desmoid tumors Migraine Painful amputation neuromas		Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Multiple myeloma ² Neuropathic pain Osteoid osteoma Pancreatic tumors Soft tissue injury	Bone metastases	Bone metastases
Pediatrics						
Anorexia	Coarctation of the aorta Hydrocephalus Hypoplastic left heart syndrome Septal perforation Ureterocele	Astrocytoma Desmoid tumors Epilepsy Multiple tumors ¹ Neuroblastoma Pontine glioma Sacral chordoma		Bone metastases Osteoid osteoma Soft tissue cancer Soft tissue tumors, benign	Bone metastases	Bone metastases

1 Protocols inclusive of more than one indication

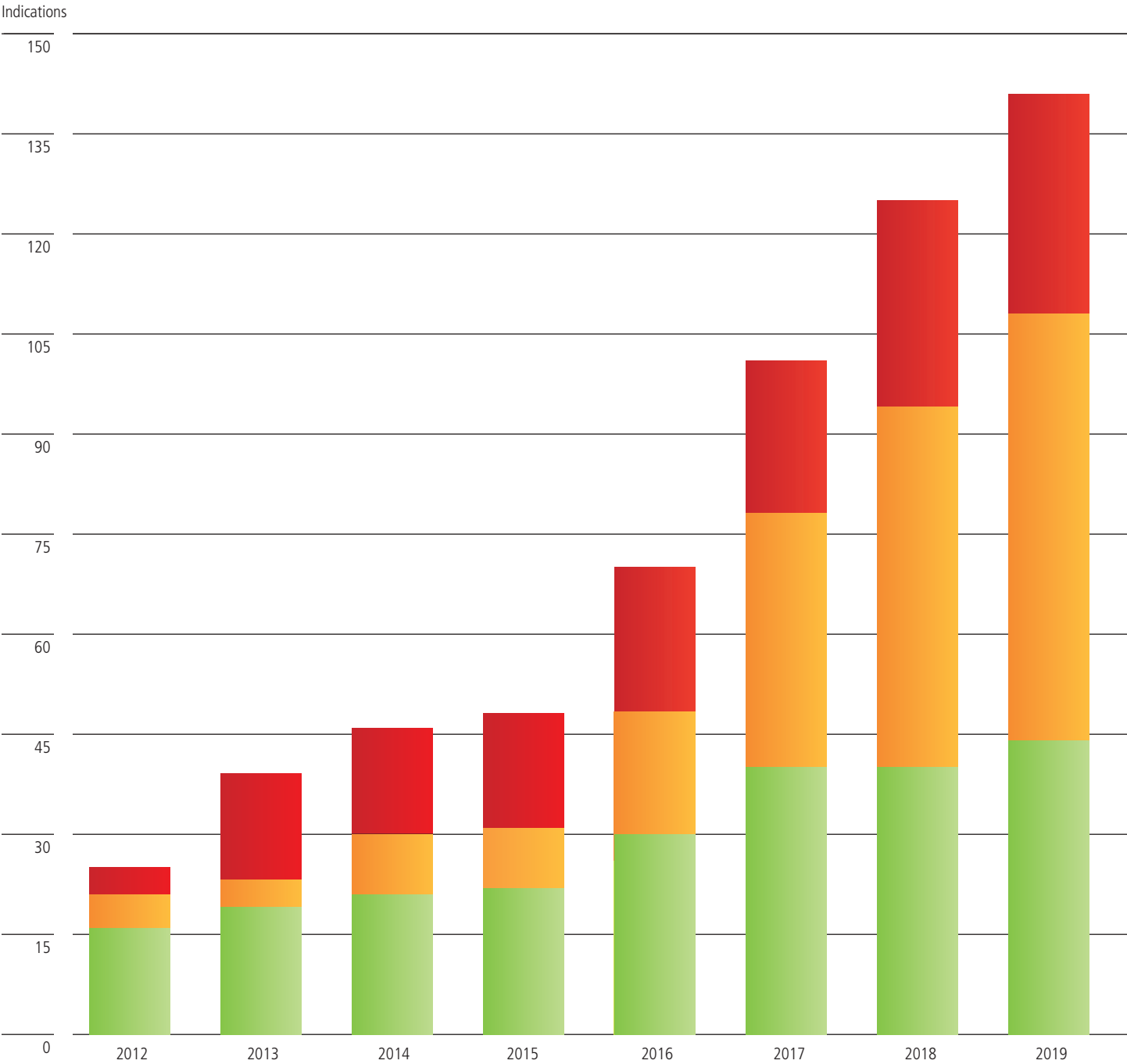
2 Multiple myeloma approval is based on bone metastases.

Indications with Anecdotal Case Reports

Indications	Date	Reference
Cardiovascular		
Arteriovenous malformations	2015	https://doi.org/10.1186/s40349-015-0042-7 https://doi.org/10.1111/1471-0528.14749
Fetal heart anomalies	2012	https://doi.org/10.1002/uog.11114 https://doi.org/10.1002/uog.20101
Twin-twin transfusion syndrome	2013	https://doi.org/10.1002/uog.12466
Endocrine disorders		
Insulinoma	2011	https://doi.org/10.1007/s00270-010-9884-0
Gastrointestinal		
Liver alveococcosis	2015	https://doi.org/10.1016/j.ultsonch.2015.05.022 https://doi.org/10.1007/s10396-018-0914-x
Miscellaneous		
Actinic keratosis	2020	https://doi.org/10.1111/srt.12883
Basal cell carcinoma	2020	https://doi.org/10.1111/srt.12883

Development Stages of Clinical Indications

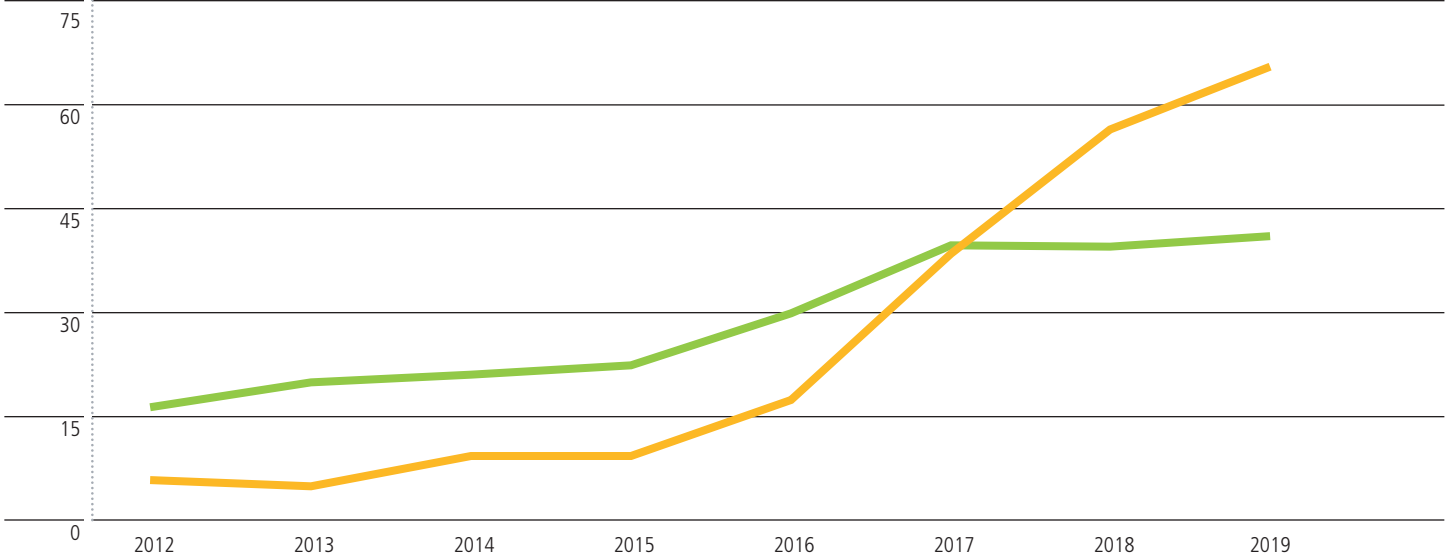
Development stage: ■ Preclinical ■ Clinical trials ■ Regulatory approvals



Development Stages of FUS Research

Development stage: ■ Preclinical ■ Clinical trials

Number of indications



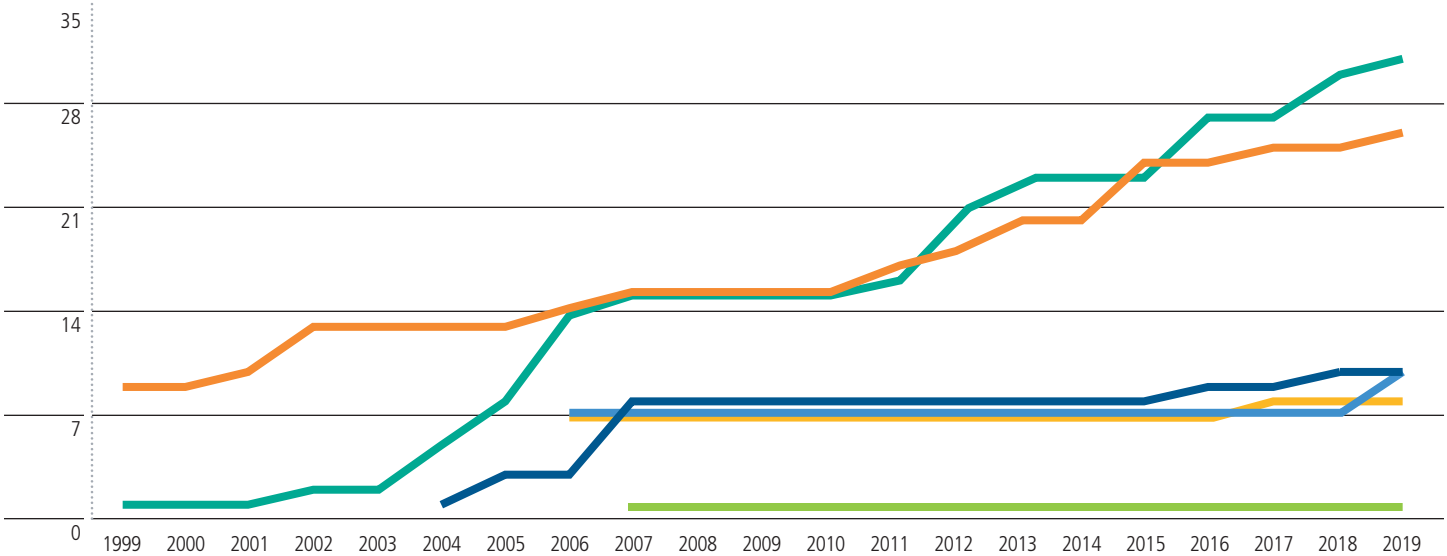
Indications with multiple mechanisms of action are counted Individually.

In 2019, growth in the number of indications progressing to clinical trials was consistent with the upward trend which began in 2016. It is also worth noting that this graph and the graph on the previous page demonstrate that FUS research is maturing through the various development stages and, at the same time, is also continuing to expand to include new indications.

Cumulative Approved Indications by Region

Region: ■ North America ■ South America ■ Europe ■ Asia ■ Oceania ■ Africa

Number of indications



As noted in the above graph, European and Asian regulatory bodies have approved indications for focused ultrasound at a steady rate since the early 2000s, and these regions lead the rest of the world. Some of this can be attributed 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.34–35.). Another cause is the varying criteria for regulatory approval in different geographic regions.

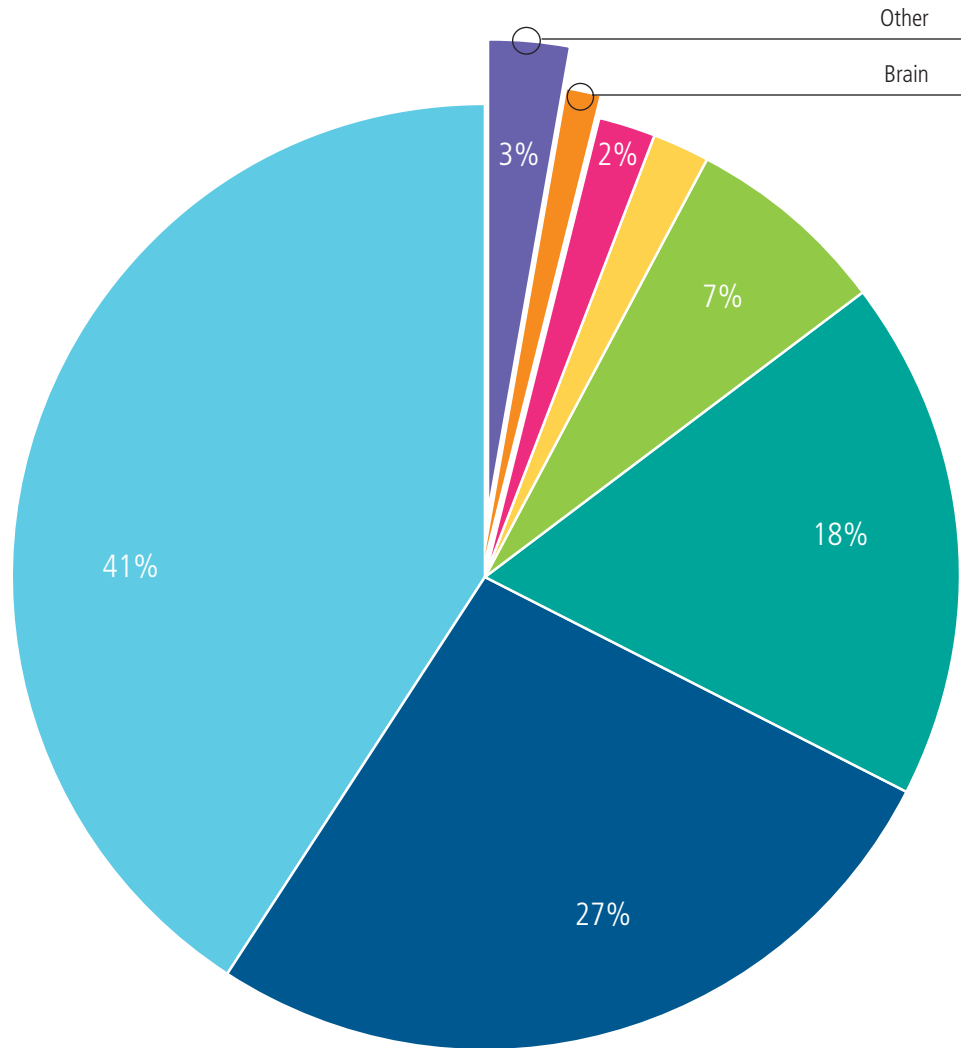
Cumulative Patient Treatments by Indication

315,665 total treatments¹

Uterine fibroids	128,443	41%
Prostate diseases	84,458	27%
Liver tumors	55,517	18%
Breast tumors	22,554	7%
Glaucoma	6,142	2%
Cancer, unspecified	5,560	2%
Brain	3,724	1%
Other	9,267	3%

Uterine fibroids remain the most commonly treated condition using focused ultrasound thermal ablation. A majority of these treatments occur in Asia. It is worth noting both the cumulative number of liver tumor treatments, and the number of liver tumor treatments in 2019 (pages I.28–29). Nearly half of all treatments occurred in 2019, indicating a huge area of growth in the field.

All indications



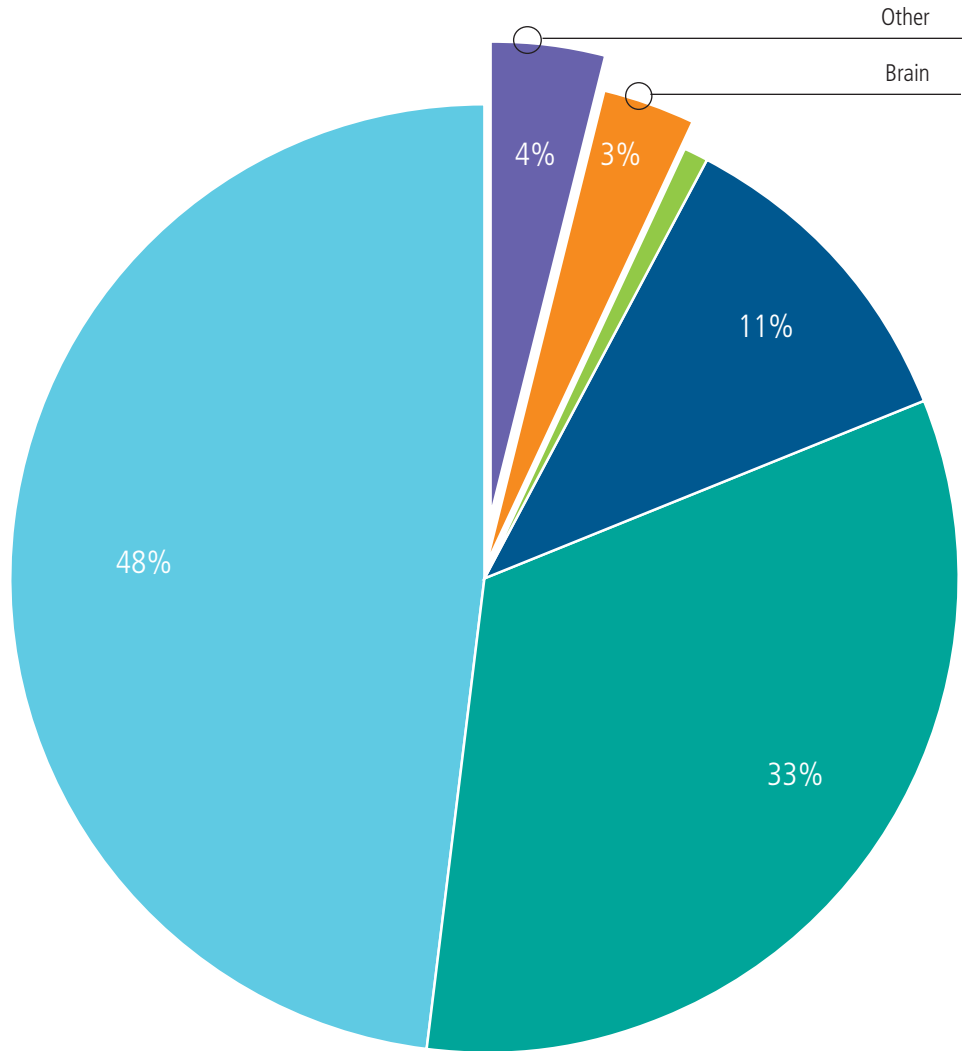
¹ Manufacturer-supplied data. The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites. Companies reporting patient treatment values in 2019 were: BrainSonix, Cardiawave, EDAP TMS, FUSMobile, Image Guided Therapy, Insightec, Mirabilis Medical, NaviFUS, Profound Medical, Shanghai A&S, Shenzhen PRO-HITU Medical, Sonacare Medical, Theraclion, and TOOsonix.

2019 Patient Treatments by Indication

All indications

60,460 total treatments¹

Uterine fibroids	29,137	48%
Liver tumors	20,000	33%
Prostate diseases	6,549	11%
Brain	1,725	3%
Breast tumors	512	1%
Other	2,537	4%



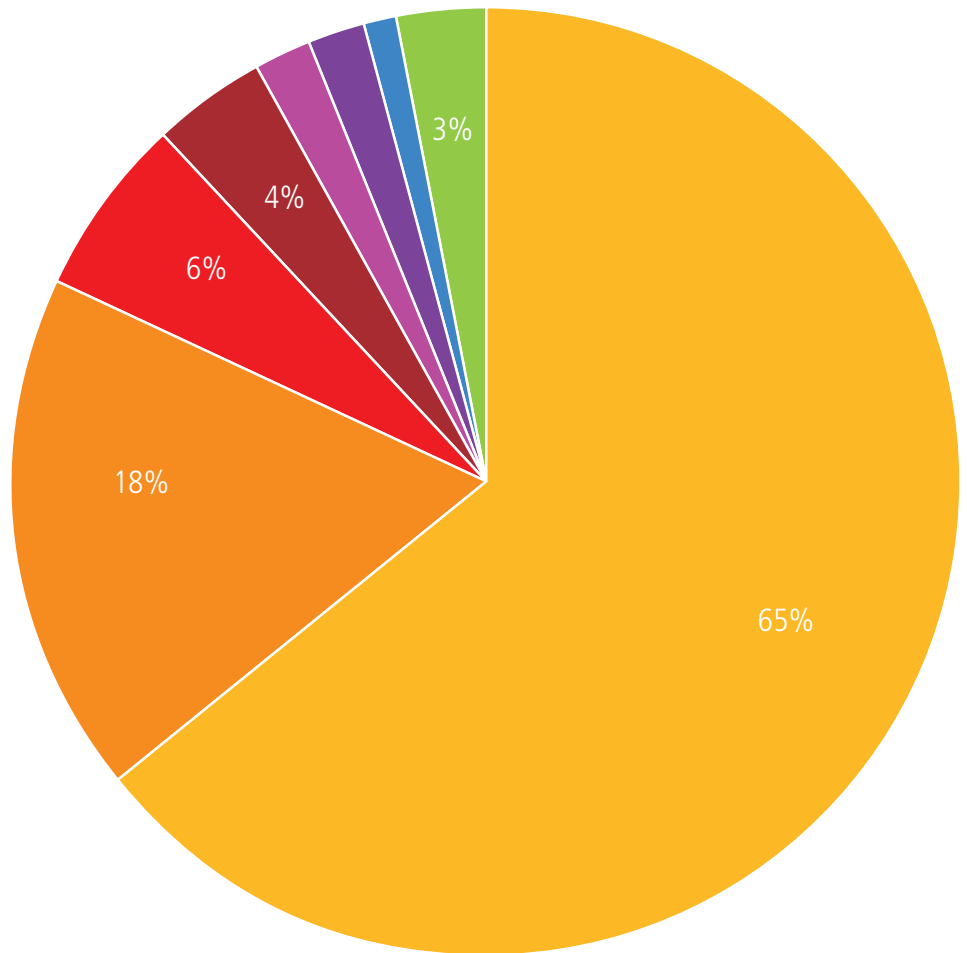
¹ Manufacturer-supplied data. The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites. Companies reporting patient treatment values in 2019 were: BrainSonix, Cardiawave, EDAP TMS, FUSMobile, Image Guided Therapy, Insightec, Mirabilis Medical, NaviFUS, Profound Medical, Shanghai A&S, Shenzhen PRO-HITU Medical, SonaCare Medical, Theraclion, and TOOsonix.

Cumulative Brain Treatments by Indication

Brain indications

3,724 total brain treatments

Essential Tremor	2,408	65%
Parkinson's disease	656	18%
Brain tumors	212	6%
Neuropathic pain	156	4%
Alzheimer's disease	75	2%
Other movement disorders ¹	57	2%
Mental health ²	50	1%
Other brain ³	110	3%



Brain treatments dramatically increased in 2019, with almost half of all cumulative treatments occurring last year. The majority (88 percent) were for essential tremor and Parkinson's disease, pointing to a more widespread acceptance of focused ultrasound as a treatment for neurological conditions.

1 Includes, in descending order of patient treatments: epilepsy and dystonia

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

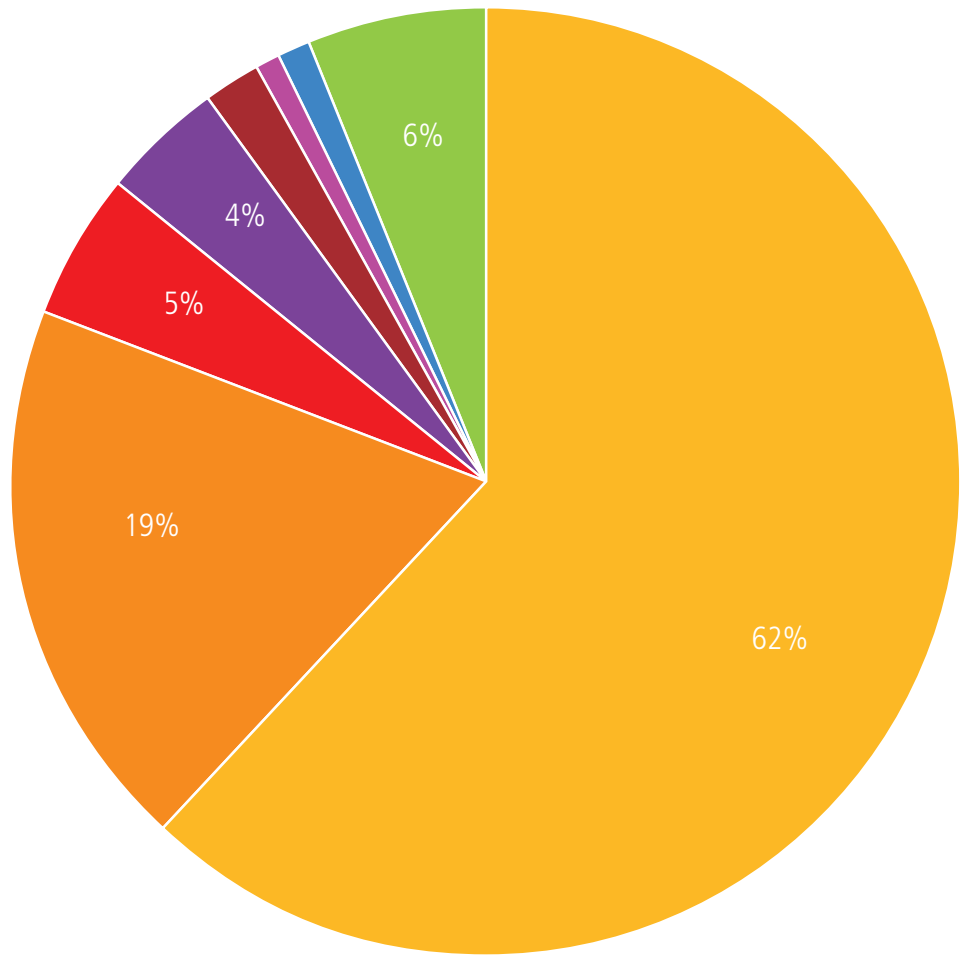
3 Includes, in descending order of patient treatments: blood-brain barrier opening and traumatic brain injury

2019 Brain Treatments by Indication

Brain indications

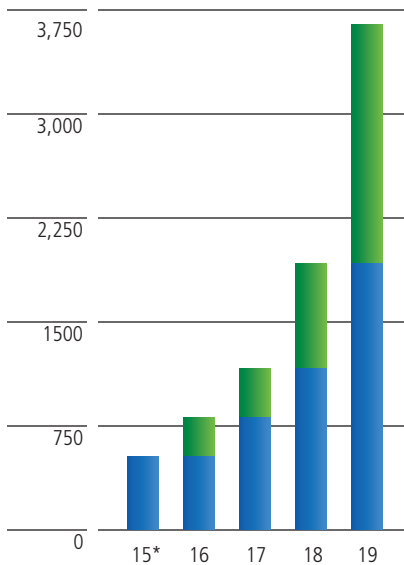
1,725 total brain treatments

Essential Tremor	1,066	62%
Parkinson's disease	333	19%
Brain tumors	82	5%
Alzheimer's disease	61	4%
Neuropathic pain	43	3%
Mental health ¹	15	1%
Other movement disorders ²	20	1%
Other brain ³	105	6%



Total Brain Treatments

■ Cumulative | ■ Reported yearly addition



*Reported in 2015 and prior years

1 Includes, in descending order of patient treatments: obsessive-compulsive disorder, depression, and anxiety

2 Includes, in descending order of patient treatments: epilepsy and dystonia

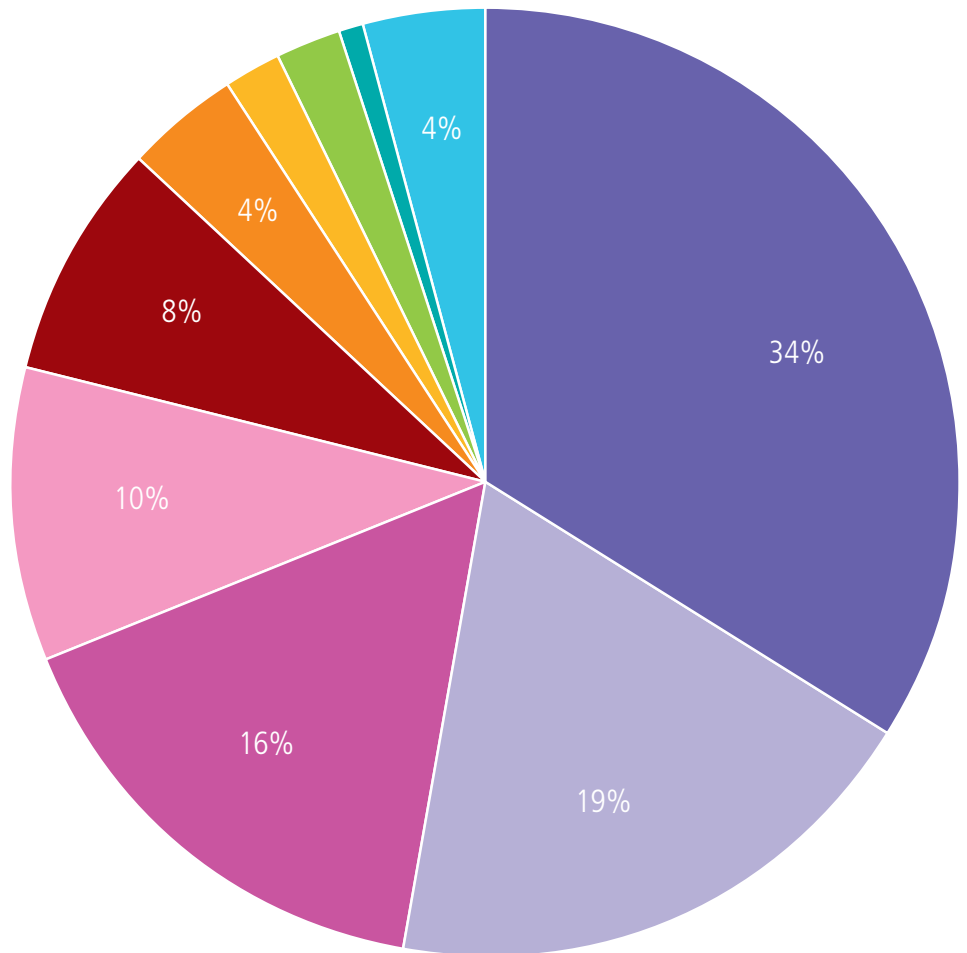
3 Includes, in descending order of patient treatments: blood-brain barrier opening and traumatic brain injury

Cumulative Other Treatments by Indication

Other indications

9,267 total treatments

Bone metastases	3,149	34%
Thyroid nodules	1,759	19%
Soft tissue cancer	1,510	16%
Uterine adenomyosis	932	10%
Pancreatic tumors	718	8%
Arthritis, facetogenic	335	4%
Varicose veins	211	2%
Osteoid osteoma	190	2%
Desmoid tumors	122	1%
Other ¹	341	4%



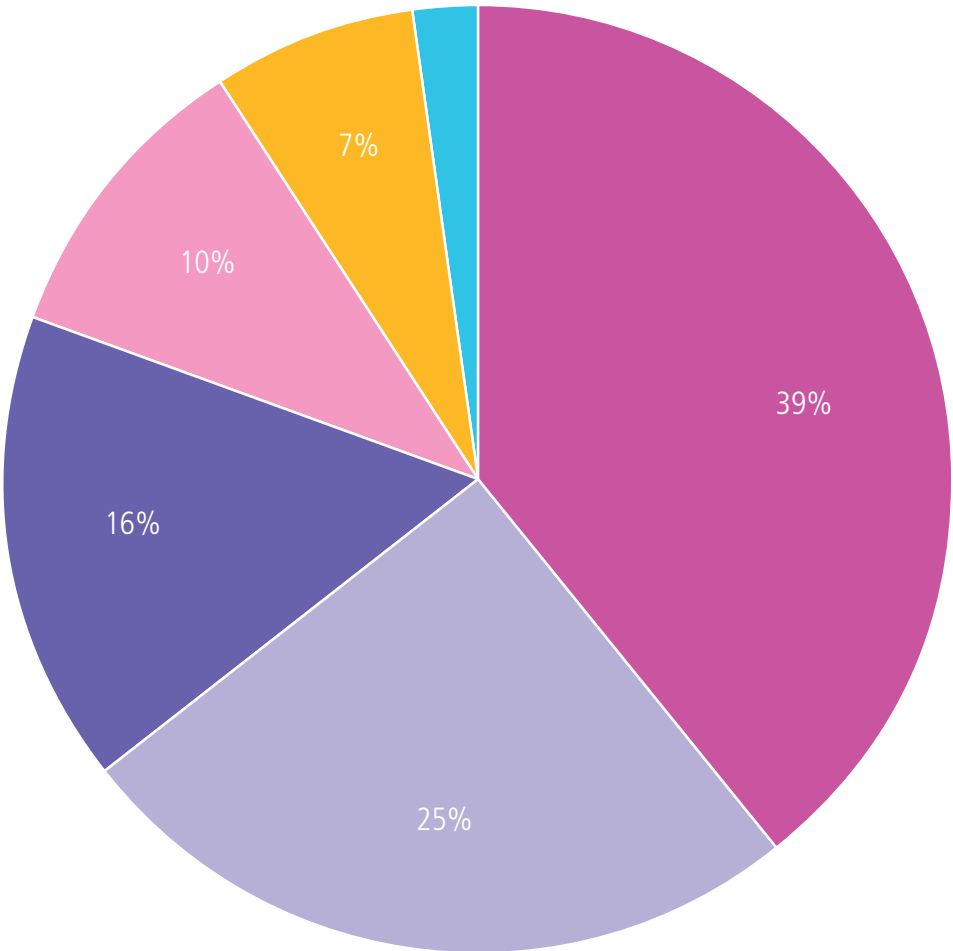
¹ Includes, in descending order of patient treatments: hypertension, hyperparathyroidism, osteoarthritis, dermatology research, tattoo removal, kidney tumors, heart valve calcifications, painful amputation neuromas, abdominal paraganglioma, actinic keratosis, osteosarcoma, hemangioma, abdominal tumors, amyotrophic lateral sclerosis, arteriovenous malformations, granular cell tumors of the gluteals, benign soft tissue cancer, cervical tumors, sacral chordoma, schwannoma, spleen tumors, basal cell carcinoma, benign bone tumors, Kaposi's sarcoma, and neurofibroma

2019 Other Treatments by Indication

Other indications

2,537 total treatments

Soft tissue cancer	1,000	39%
Thyroid nodules	629	25%
Bone metastases	417	16%
Uterine adenomyosis	264	10%
Varicose veins	173	7%
Arthritis, facetogenic	10	—
Desmoid tumors	1	—
Other ¹	43	2%



Note the growth in 2019 in soft tissue cancer and thyroid nodules treatments, with approximately two thirds of the cumulative soft tissue cancer treatments occurring in 2019.

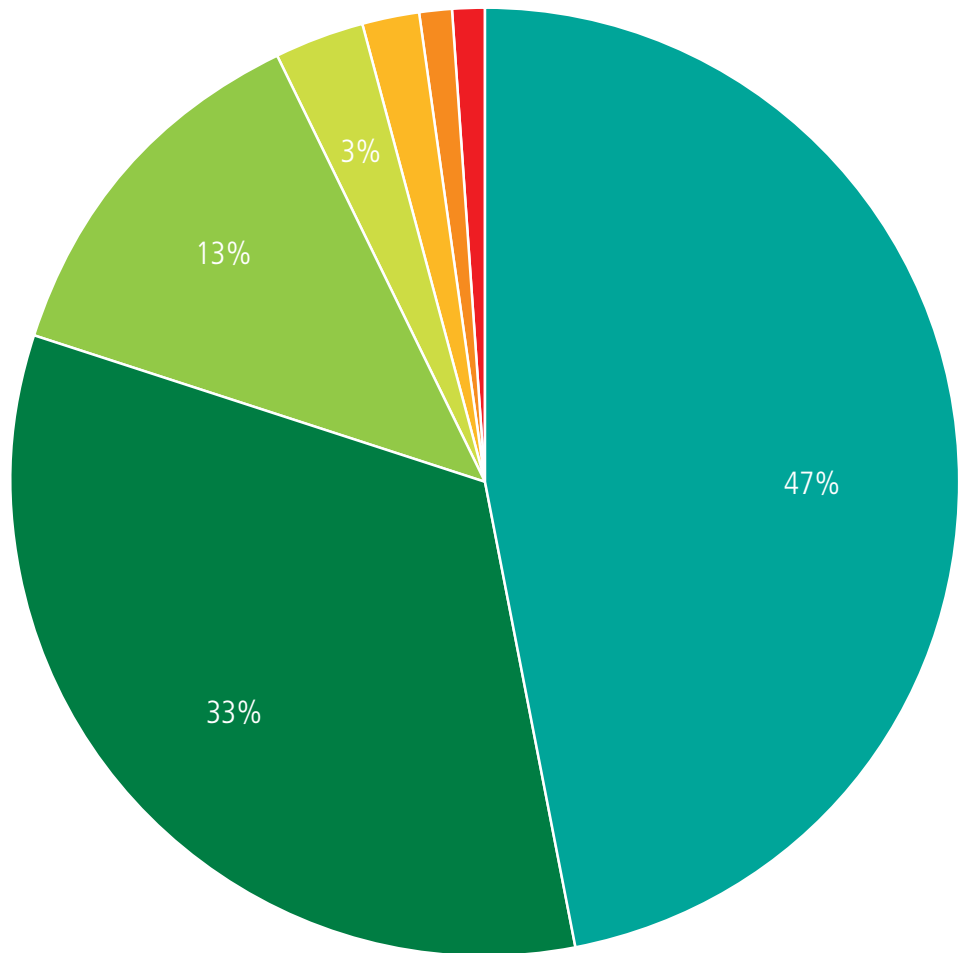
¹ Includes, in descending order of patient treatments: tattoo removal, heart valve calcifications, actinic keratosis, basal cell carcinoma, and Kaposi's sarcoma

Cumulative Oncology Treatments by Indication

Oncology indications

167,809 total treatments

Prostate cancer	79,368	47%
Liver tumors	55,517	33%
Breast cancer	21,719	13%
Cancer unspecified	5,560	3%
Bone metastases	3,149	2%
Soft tissue cancer	1,510	1%
Other ¹	986	1%



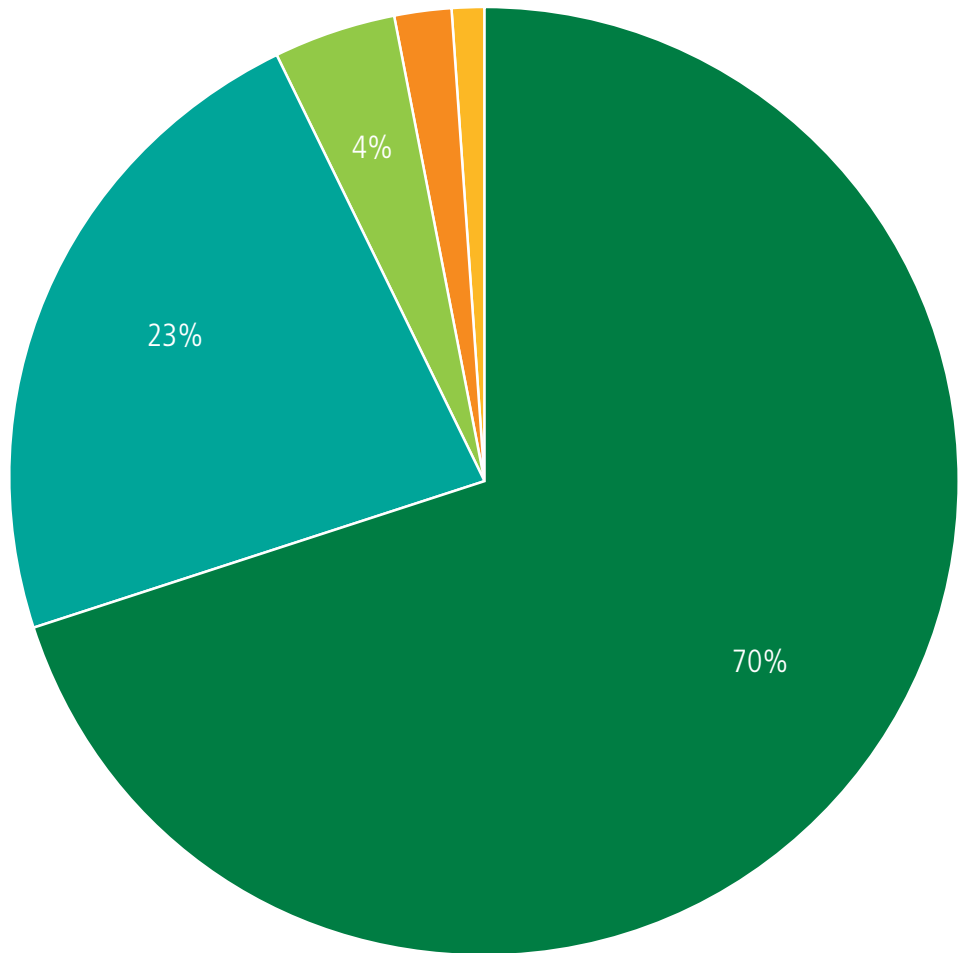
¹ Includes, in descending order of patient treatments: pancreatic tumors, glioblastoma, kidney tumors, brain tumors, abdominal paraganglioma, osteosarcoma, hemangioma, abdominal tumors, astrocytoma, granular cell tumors of the gluteals, cervical tumors, sacral chordoma, schwannoma, spleen tumors, ganglioglioma, Kaposi's sarcoma, and neurofibroma

2019 Oncology Treatments by Indication

Oncology indications

28,484 total treatments

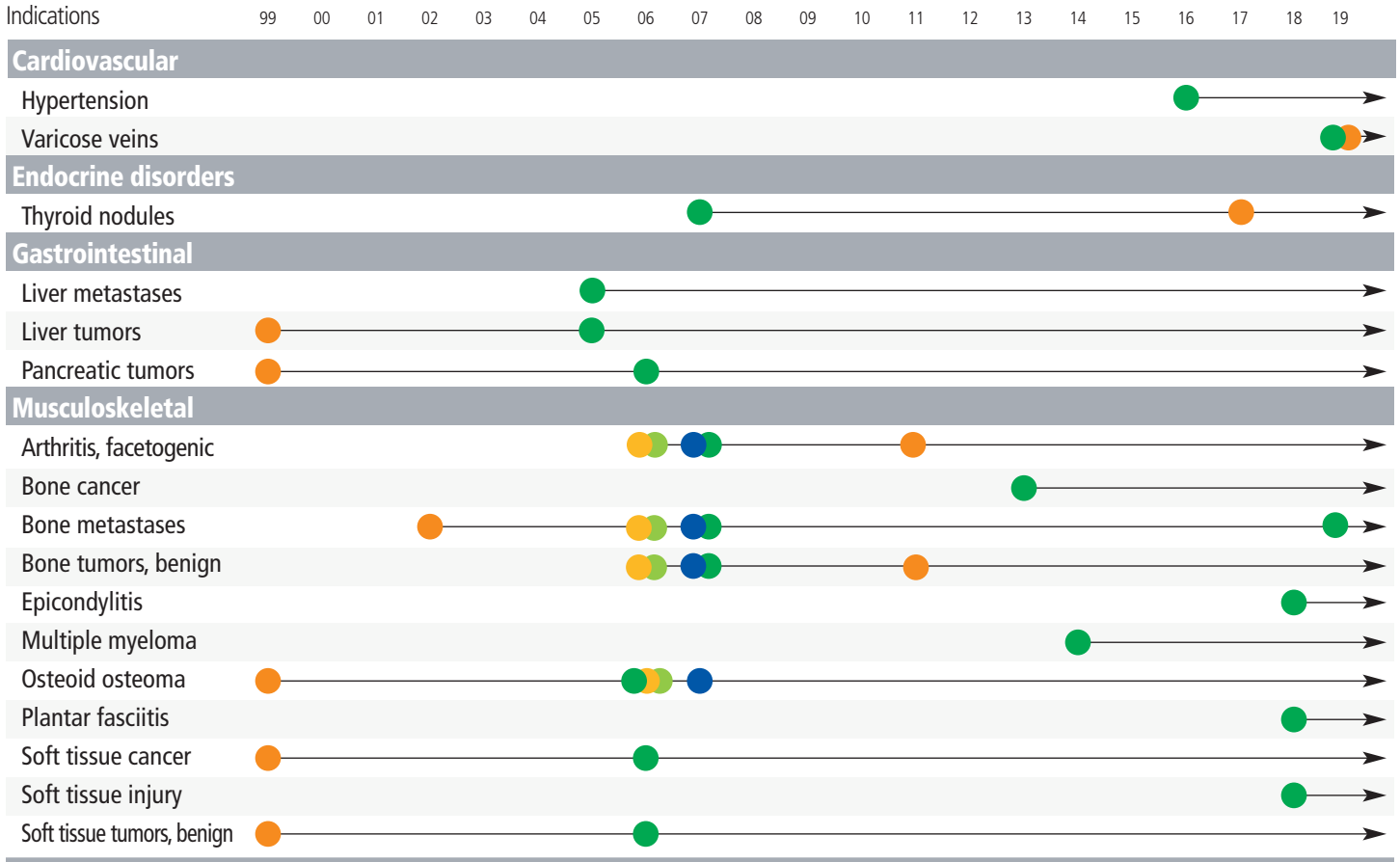
Liver tumors	20,000	70%
Prostate cancer	6,529	23%
Breast cancer	1,000	4%
Soft tissue cancer	455	2%
Bone metastases	417	1%
Other ¹	83	—



¹ Includes, in descending order of patient treatments: glioblastoma, brain tumors, and Kaposi's sarcoma

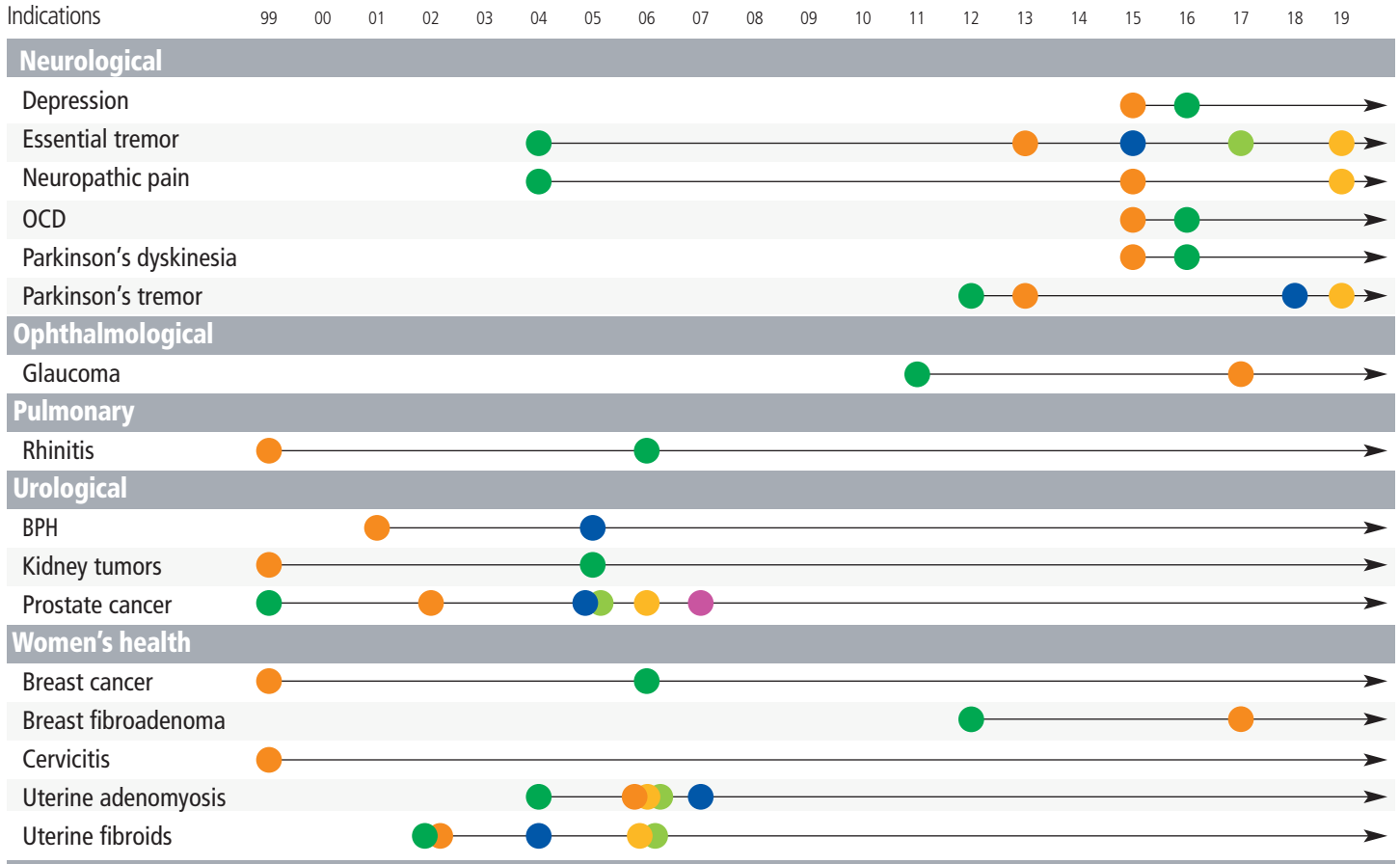
FIELD OVERVIEW

FUS Regulatory Approvals by Indication and Region

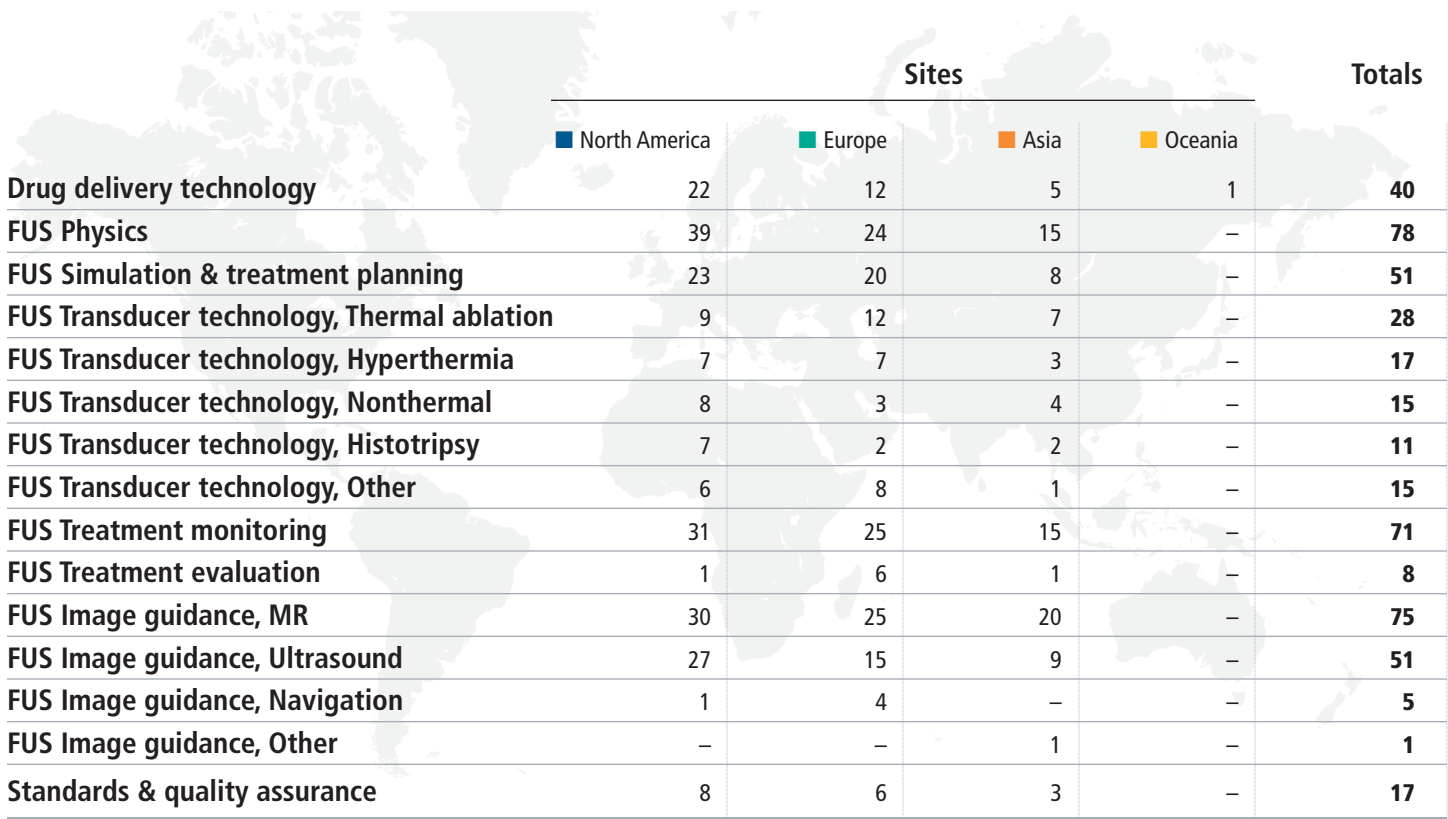


- North America
- Europe
- Asia
- South America
- Oceania
- Africa

FUS Regulatory Approvals by Indication and Region continued



Technical Research Sites*



	Sites				Totals
	■ North America	■ Europe	■ Asia	■ Oceania	
Drug delivery technology	22	12	5	1	40
FUS Physics	39	24	15	–	78
FUS Simulation & treatment planning	23	20	8	–	51
FUS Transducer technology, Thermal ablation	9	12	7	–	28
FUS Transducer technology, Hyperthermia	7	7	3	–	17
FUS Transducer technology, Nonthermal	8	3	4	–	15
FUS Transducer technology, Histotripsy	7	2	2	–	11
FUS Transducer technology, Other	6	8	1	–	15
FUS Treatment monitoring	31	25	15	–	71
FUS Treatment evaluation	1	6	1	–	8
FUS Image guidance, MR	30	25	20	–	75
FUS Image guidance, Ultrasound	27	15	9	–	51
FUS Image guidance, Navigation	1	4	–	–	5
FUS Image guidance, Other	–	–	1	–	1
Standards & quality assurance	8	6	3	–	17

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 faster, safer, less expensive, and available to a wider patient population.

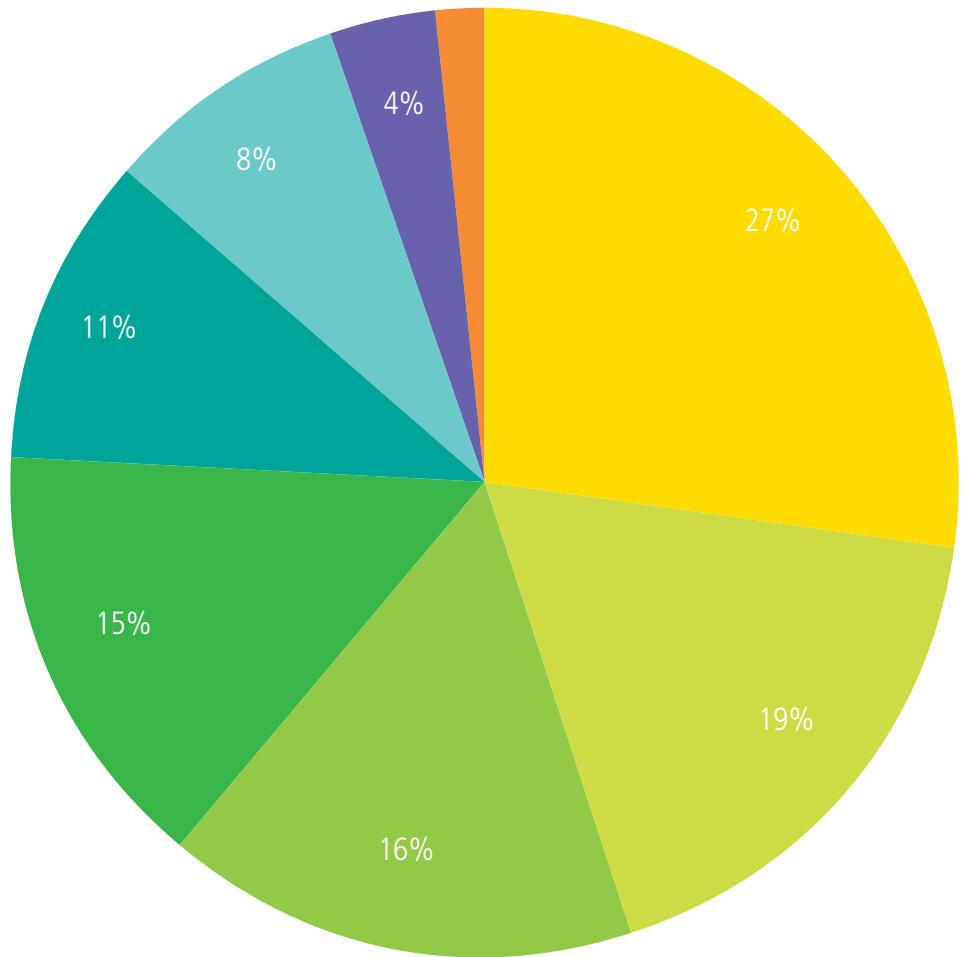
*Technical research sites may be working in more than one technical research area.
No technical sites in South America or Africa

Technical Research Types*

Technical research types

Totals

132	FUS Image guidance
86	FUS Transducer technology
78	FUS Physics
71	FUS Treatment monitoring
51	FUS Simulation & treatment planning
40	Drug delivery technology
17	Standards & quality assurance
8	FUS Treatment evaluation



*Technical research sites may be working in more than one technical research area.
No technical sites in South America or Africa

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.

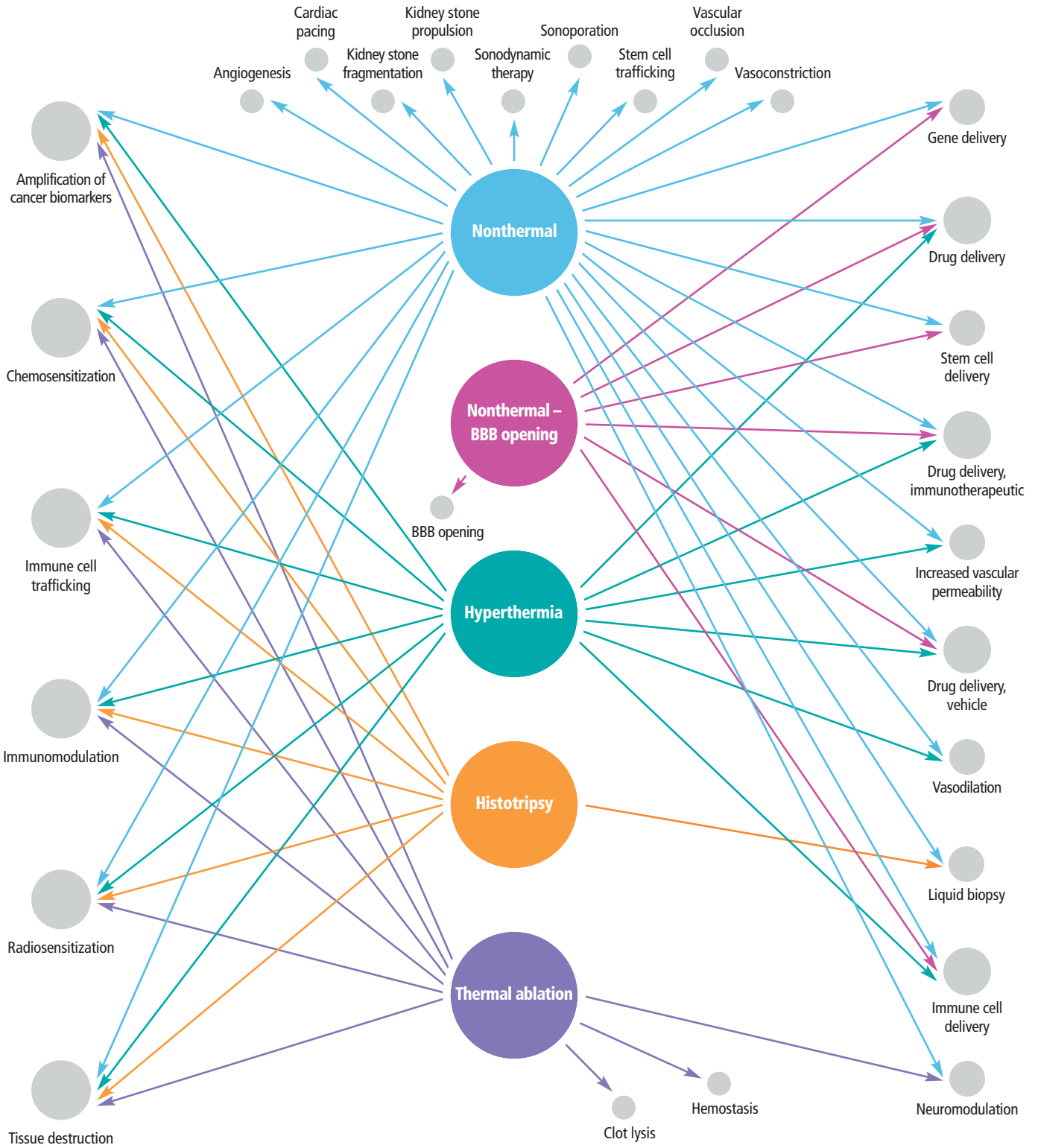
Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver (thermal or mechanical), and whether the effects of treatment are permanent 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 used most frequently in the clinic and produces permanent effects, but additional ultrasound treatment regimens are currently under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications currently 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 that is 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.

Ultrasound Applications and Biological Effects
Graphic



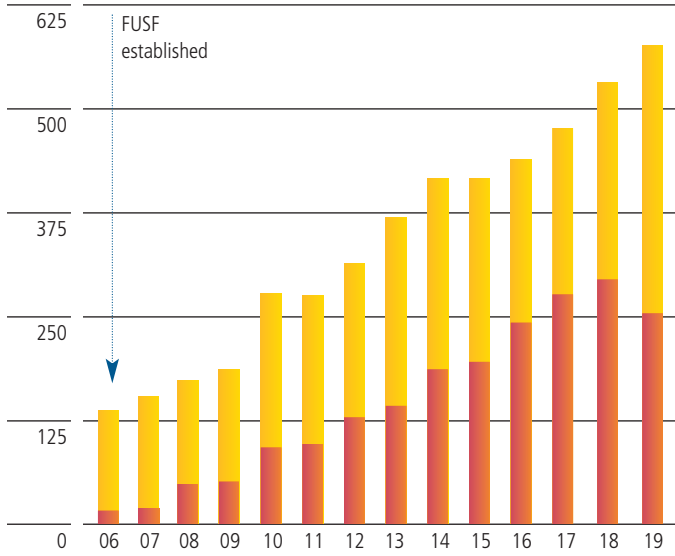
Ultrasound Applications and Biological Effects

Table

<p>HISTOTRIPSY</p> <p>7</p> <p>biological effects</p>	<p>HYPERTHERMIA</p> <p>12</p> <p>biological effects</p>	<p>NONTHERMAL</p> <p>25</p> <p>biological effects</p>	<p>NONTHERMAL BBB OPENING</p> <p>7</p> <p>biological effects</p>	<p>THERMAL ABLATION</p> <p>9</p> <p>biological effects</p>
<p>Amplification of cancer biomarkers</p> <p>Chemosenitization</p> <p>Immune cell trafficking</p> <p>Immunomodulation</p> <p>Liquid biopsy</p> <p>Radiosensitization</p> <p>Tissue destruction</p>	<p>Amplification of cancer biomarkers</p> <p>Chemosenitization</p> <p>Drug delivery</p> <p>Drug delivery, immunotherapeutic</p> <p>Drug delivery, vehicle</p> <p>Immune cell delivery</p> <p>Immune cell trafficking</p> <p>Immunomodulation</p> <p>Increased vascular permeability</p> <p>Radiosensitization</p> <p>Tissue destruction</p> <p>Vasodilation</p>	<p>Amplification of cancer biomarkers</p> <p>Angiogenesis</p> <p>Cardiac pacing</p> <p>Chemosenitization</p> <p>Drug delivery</p> <p>Drug delivery, immunotherapeutic</p> <p>Drug delivery, vehicle</p> <p>Gene delivery</p> <p>Immune cell delivery</p> <p>Immune cell trafficking</p> <p>Immunomodulation</p> <p>Increased vascular permeability</p> <p>Kidney stone fragmentation</p> <p>Kidney stone propulsion</p> <p>Liquid biopsy</p> <p>Neuromodulation</p> <p>Radiosensitization</p> <p>Sonodynamic therapy</p> <p>Sonoporation</p> <p>Stem cell delivery</p> <p>Stem cell trafficking</p> <p>Tissue destruction</p> <p>Vascular occlusion</p> <p>Vasoconstriction</p> <p>Vasodilation</p>	<p>BBB opening</p> <p>Drug delivery</p> <p>Drug delivery, immunotherapeutic</p> <p>Drug delivery, vehicle</p> <p>Gene delivery</p> <p>Immune cell delivery</p> <p>Stem cell delivery</p>	<p>Amplification of cancer biomarkers</p> <p>Chemosenitization</p> <p>Clot lysis</p> <p>Hemostasis</p> <p>Immune cell trafficking</p> <p>Immunomodulation</p> <p>Neuromodulation</p> <p>Radiosensitization</p> <p>Tissue destruction</p>

FUS Publications

Traditional journals Open access



Source: Data from Web of Knowledge as of March 31, 2020

FUS Citations

Cumulative

5,393
FUS publications

139,375
Citations of FUS publications

2019

575
FUS publications

17,608
Citations of FUS publications

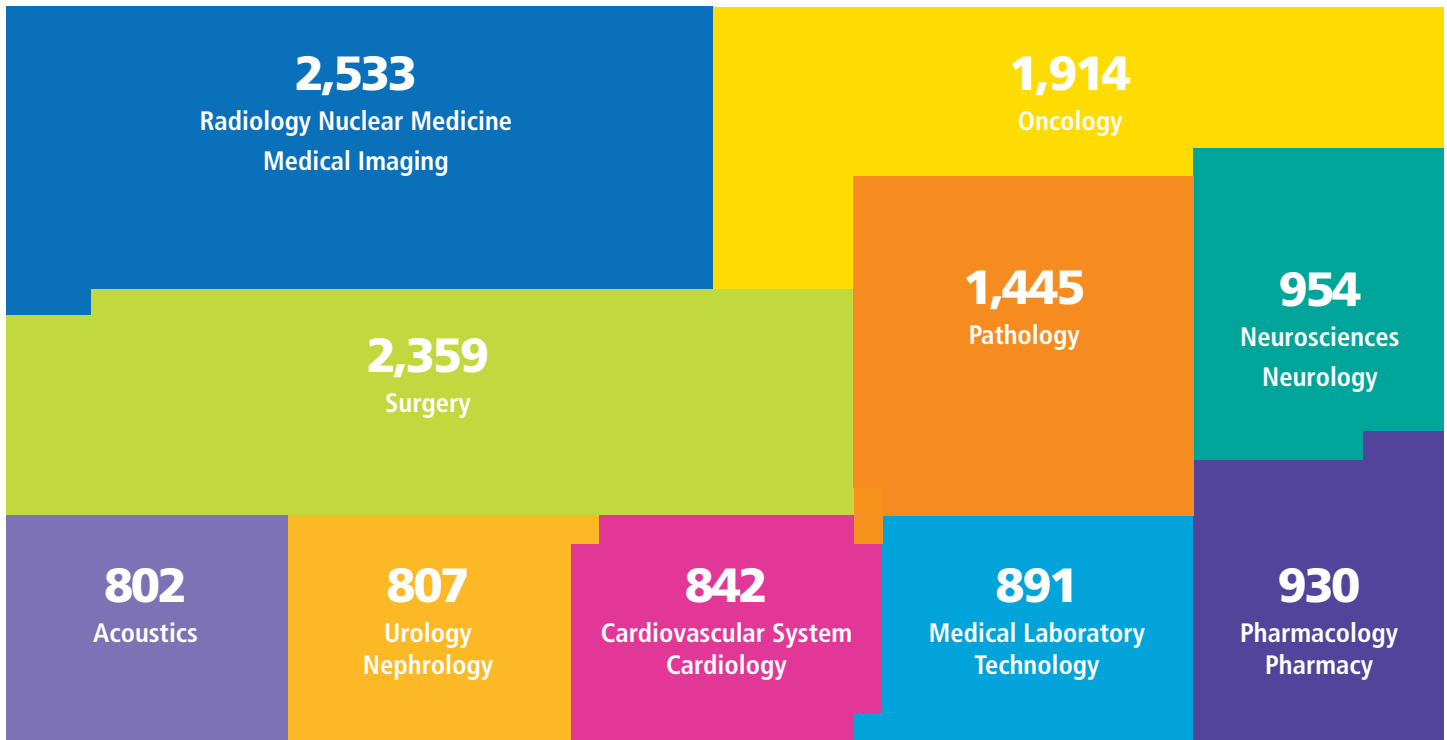
Publications—Top Twenty-Five Source Titles

Cumulative

Records	Medical Journal Title
414	Ultrasound in Medicine Biology
195	International Journal of Hyperthermia, Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group
193	Physics in Medicine and Biology
157	IEEE Transactions on Ultrasonics Ferroelectrics, and Frequency Control
113	The Journal of the Acoustical Society of America
111	Medical Physics
106	Journal of Therapeutic Ultrasound
98	Ultrasonics
96	Magnetic Resonance in Medicine
80	Ultrasonics Sonochemistry
77	Journal of Controlled Release, Official Journal of the Controlled Release Society
74	Conference Proceedings, IEEE Engineering in Medicine and Biology Society Annual International Conference
68	Scientific Reports
67	European Urology
67	PLOS One, published by Public Library of Science
66	Radiology
61	IEEE Transactions on Biomedical Engineering
60	The Journal of Urology
59	BJU International, formerly the British Journal of Urology
54	Journal of Ultrasound in Medicine, Official Journal of the American Institute of Ultrasound in Medicine
52	Journal of Magnetic Resonance Imaging, JMRI
50	European Radiology
50	Journal of Neurosurgery
38	Journal of Endourology
38	Theranostics

Publications—Top Ten Research Areas

Cumulative

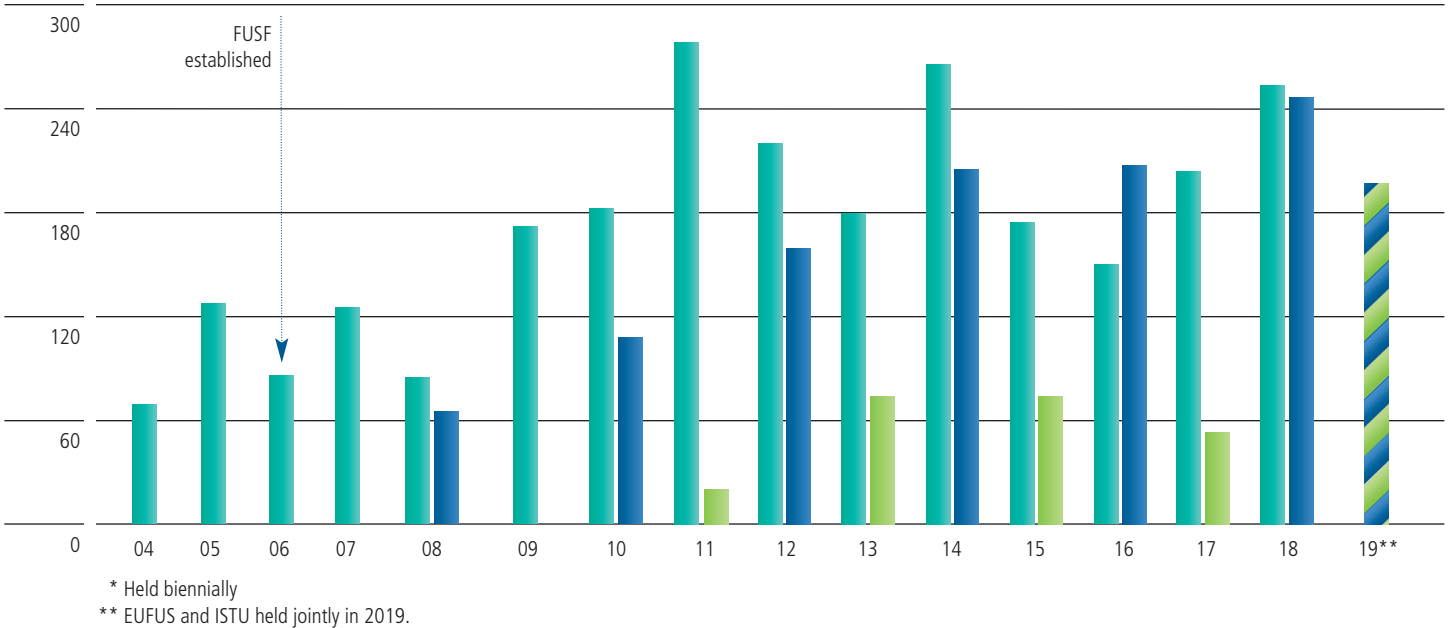


Publications—2019 Top Ten Source Titles

Records	Medical Journal Title
33	International Journal of Hyperthermia, Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group
28	Ultrasound in Medicine Biology
22	Scientific Reports
11	Movement Disorders, Official Journal of the International Parkinson and Movement Disorder Society
10	Journal of Neurosurgery
10	Theranostics
10	Ultrasonics Sonochemistry
9	IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control
9	Journal of Ultrasound in Medicine, Official Journal of the American Institute of Ultrasound in Medicine
9	Physics in Medicine and Biology

Abstracts Presented at FUS Symposia

■ Focused Ultrasound Foundation Symposium, FUSF* ■ European Symposium on Focused Ultrasound, EUFUS* ■ International Symposium on Therapeutic Ultrasound, ISTU



While the number of abstracts presented at FUS Symposia has remained strong over the last few years, this year we decided to also look at FUS abstracts presented at other professional meetings. We predict that as this technology continues to translate to additional clinical trials and commercial adoption, the clinicians and researchers involved will present their work/experiences at various medical specialty conferences and/or to patient advocacy groups. We are already beginning to see evidence that bears out this prediction.

Abstracts Presented at FUS Symposia

Symposium	2015	2016	2017	2018	2019
Focused Ultrasound Foundation Symposium, FUSF*	–	200	–	250	–
European Symposium on Focused Ultrasound, EUFUS*	75	–	54	–	} 197**
International Symposium on Therapeutic Ultrasound, ISTU	177	152	207	257	
Totals	252	352	262	507	197

* Held biennially

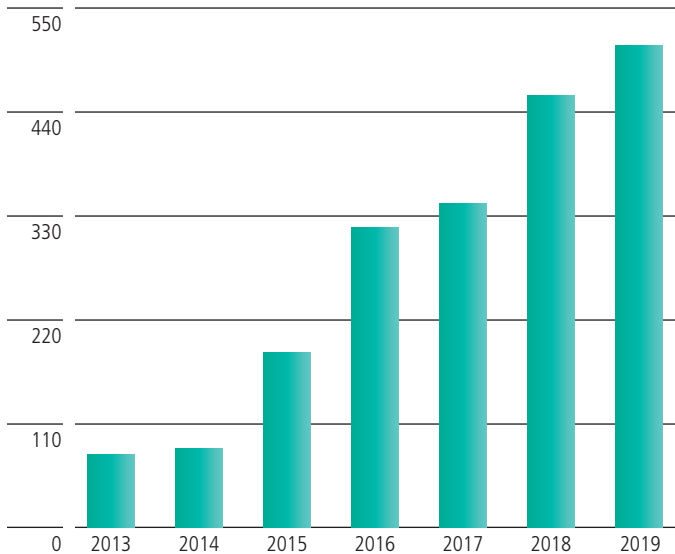
** EUFUS and ISTU held jointly in 2019.

FUS Abstracts Presented at Other Symposia

Symposium	2015	2016	2017	2018	2019
Acoustical Society of America	19	64	48	39	22
American Association of Physicists in Medicine, AAPM	14	8	16	5	7
American Institute of Ultrasound in Medicine, AIUM	4	2	–	9	6
American Society for Radiation Oncology	–	2	5	3	–
American Society for Stereotactic and Functional Neurosurgery	–	3	–	6	–
American Urological Association, AUA	4	11	7	4	16
Biomedical Engineering Society	13	12	16	14	26
European Congress of Radiology	7	7	13	22	10
IEEE International Engineering in Medicine and Biology	11	9	5	11	11
IEEE International Ultrasonics Symposium	42	26	71	19	49
Japanese Society for Therapeutic Ultrasound	37	39	35	48	52
Korean Society for Therapeutic Ultrasound	10	14	15	17	22
Radiological Society of North America, RSNA	18	21	17	14	26
Society for Thermal Medicine, STM	4	22	10	10	9
Society of Interventional Radiology	–	3	2	1	5
Totals	183	243	260	222	261

United States FUS Media Placements

Per year



1,971

Media placements in last 7 years

News Outlets

- AARP The Magazine
- ABC News Australia
- AP Wire
- Associated Press
- Baltimore Sun
- BBC News
- Boston Globe
- CBC
- CBS Miami
- CBS New York
- Chicago Evening Post
- The Chronicle of Higher Education
- CNBC
- Colorado Springs Gazette

- Daily Mail
- Daily Telescope
- Discover Magazine
- The Edge Singapore
- Globe and Mail
- GlobeNewswire
- The Hill
- Houston Chronicle
- Huffington Post
- KING-5 TV Seattle
- KSAT San Antonio
- Los Angeles Times
- Medgadget
- Miami Herald
- Nashville Post
- NBC News
- Newswise

- New York Times
- NPR
- The Oklahoman
- Oregon Live
- PBS NewsHour
- Penn State News
- Philadelphia Tribune
- The Plain Dealer
- PRNewswire
- Pulse
- Roanoke Times
- Sound & Vision
- South China Morning Post
- Tech Nation
- Telegraph Herald
- Telegraph UK
- The Times (London)
- Toronto Star
- University of Queensland News
- US News & World Report
- Washington Examiner
- WBZ CBS Boston
- WINA News Radio
- WIRED

Business Coverage

- Business Wire
- Crain's Detroit Business
- Financial Times
- Forbes
- Fortune
- Markets Insider
- Nasdaq
- Pittsburgh Business Times
- S&P Global
- South Florida Business Journal
- Virginia Business

Science Coverage

- Acoustical Society of America
- Alzheimer's News Today
- American Veterinarian
- Being Patient
- Cancer Therapy Advisor
- DOTmed
- EurekAlert

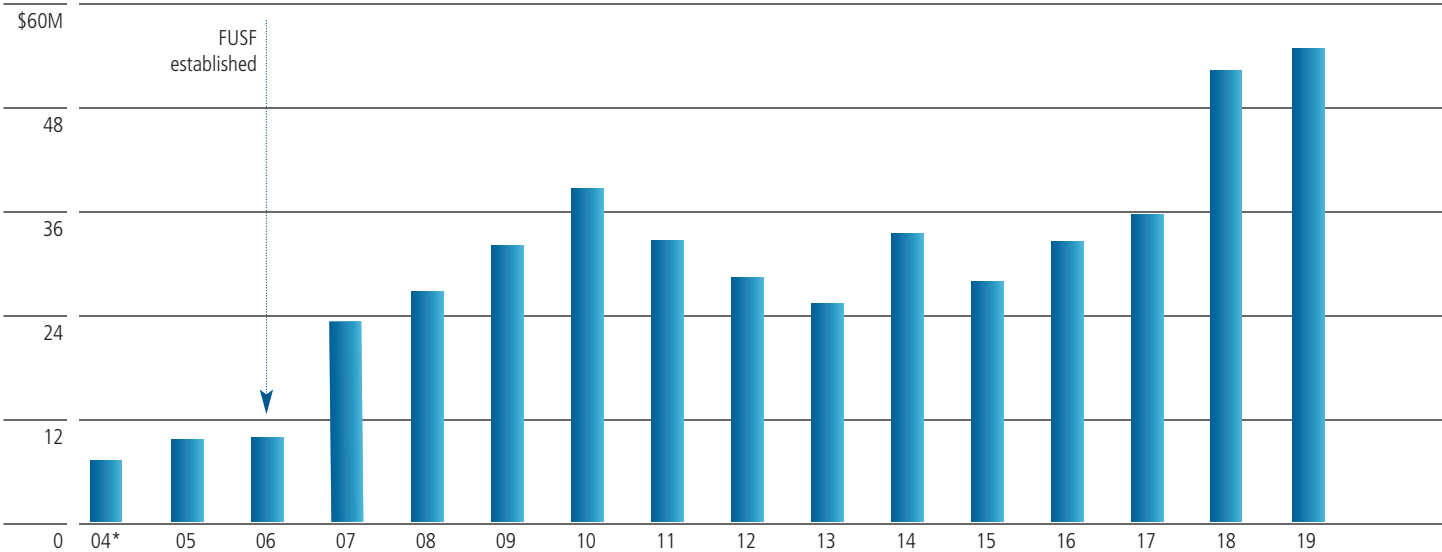
- Genetic Engineering & Biotech News
- Health Imaging
- Healthline
- Institute of Cancer Research Blog
- Journal of Clinical Pathways
- Journal of Therapeutic Ultrasound
- Life Science Daily
- Mass Device
- MD Magazine
- MedCity News
- Medical Daily Times
- Medical Physics Web
- Med Page Today
- Medscape
- Nature
- Neurology Advisor
- News-Medical.net
- Oxford Journals
- Parkinson's News Today
- PharmWeb.com
- Physics Today
- Physics World
- Psychology Today
- Radiology Business
- Radio MD
- R&D Magazine
- Science 2.0
- Science Daily
- Scientific American
- STAT
- UCLA Urology
- UroToday
- Veterinary Practice News
- WebMD

Commercial Television

- The Doctors
- Grey's Anatomy
- Holby City (BBC)
- New Amsterdam

United States Federal Government FUS Grants

Dollars in millions ■ Annual funding



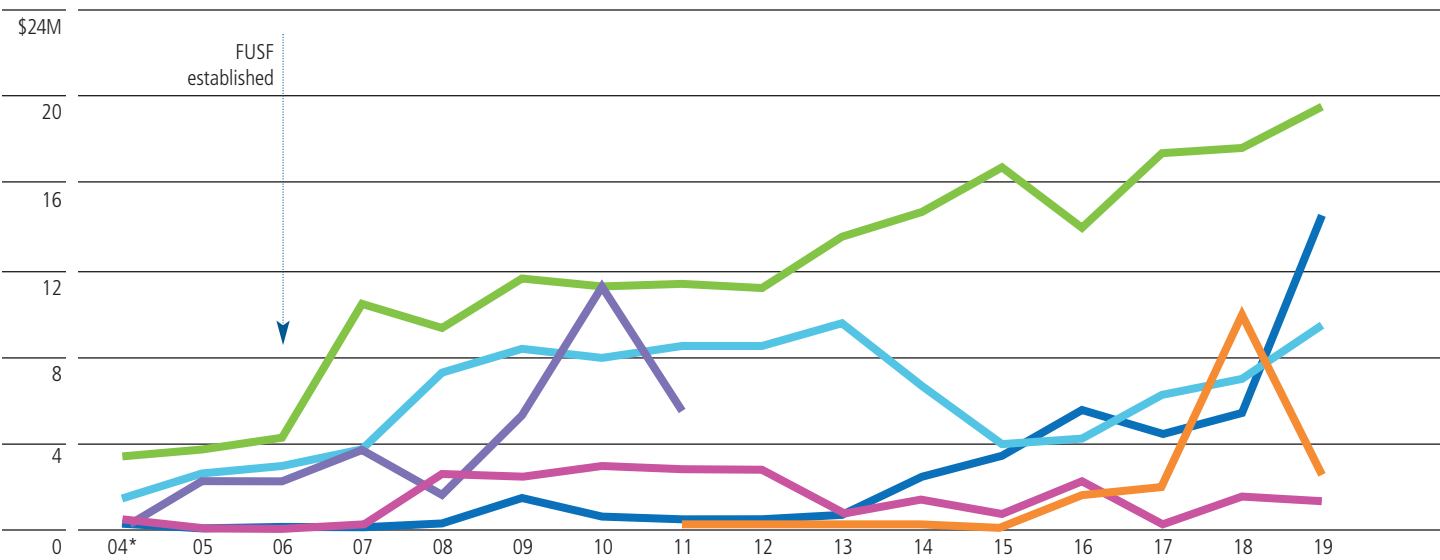
Encouragingly, there continues to be an increase in federal funding for focused ultrasound-related projects in the United States. Even though the National Institutes of Health, NIH, budget has been somewhat stagnant over the last 15 years, the portion of funding allocated to focused ultrasound research is growing. Funding increases of this nature are typical for medical innovations that have shown the most potential for improving patient health.

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

United States Top Federal Government Funders

■ NCI ■ NIBIB ■ NINDS ■ NCRR** ■ NHLBI ■ NIMH

Dollars in millions



*The first record of funded focused ultrasound 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: NIH RePORTER projectreporter.nih.gov/reporter.cfm
 Site: Federal RePORTER federalreporter.nih.gov
 Terms searched: "focused ultrasound", MRgFUS, HIFU

Financial support for focused ultrasound research from federal government funders remains robust. In addition to National Cancer Institute (NCI) funding, which has historically been very good, there was a significant increase in 2019 funding from the National Institute of Neurological Disorders and Stroke (NINDS). This was in large part due to the awarding of over \$8M in NIH HEAL (Helping to End Addiction Long Term) grants to investigators who are using focused ultrasound to find new ways to treat chronic pain and combat the opioid epidemic.

Note the sharp, one-year increase in funding from the National Institute of Mental Health (NIMH) in 2018. This funding was related to focused ultrasound-induced neuromodulation studies—a newer area of research inquiry for the field. Neuromodulation occurs when focused ultrasound is used to stimulate or suppress neural activity, depending on the parameters of the energy applied to neural tissue.

Total Funding by United States Government Agencies

Total funding	Granting agency
\$191,732,171	■ NCI National Cancer Institute
\$97,782,716	■ NIBIB National Institute of Biomedical Imaging and Bioengineering
\$41,253,740	■ NINDS National Institute of Neurological Disorders and Stroke
\$32,924,533	■ NCRR* National Center for Research Resources
\$22,217,376	■ NHLBI National Heart, Lung, and Blood Institute
\$18,088,210	■ NIMH National Institute of Mental Health
\$10,406,915	NIDDK National Institute of Diabetes and Digestive and Kidney Diseases
\$9,575,834	OD Office of the Director, NIH
\$9,198,449	NIA National Institute on Aging
\$6,988,469	CDMRP Congressionally Directed Medical Research Programs
\$6,915,181	NSF National Science Foundation
\$6,789,910	NICHD National Institute of Child Health and Human Development
\$6,106,583	NIGMS National Institute of General Medical Sciences
\$5,349,795	NIDA National Institute on Drug Abuse
\$3,811,293	NEI National Eye Institute
\$1,858,361	CNRM Center For Neuroscience and Regenerative Medicine
\$1,066,656	NIDCR National Institute of Dental and Craniofacial Research
\$909,727	NIDCD National Institute on Deafness and Other Communication Disorders
\$749,990	NIMHD National Institute on Minority Health and Health Disparities
\$576,760	NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases
\$347,747	NIAAA National Institute on Alcohol Abuse and Alcoholism
\$223,196	NHGRI National Human Genome Research Institute
\$158,851	CLC Clinical Center
\$67,858	FIC John E. Fogarty International Center
\$475,100,321	TOTAL

*Agency dissolved in 2012.

2020

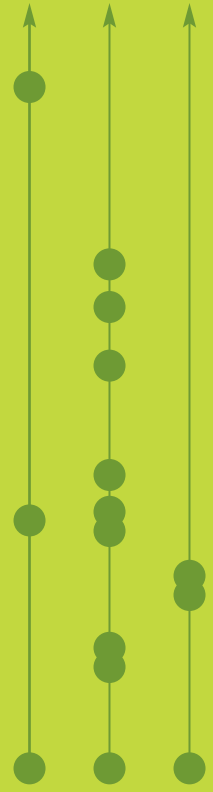
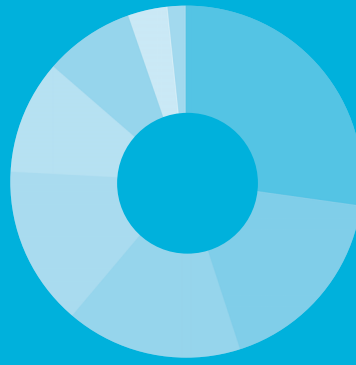
State of Research and Treatment



FOCUSED
ULTRASOUND
FOUNDATION

94

indications
are being researched at
preclinical sites

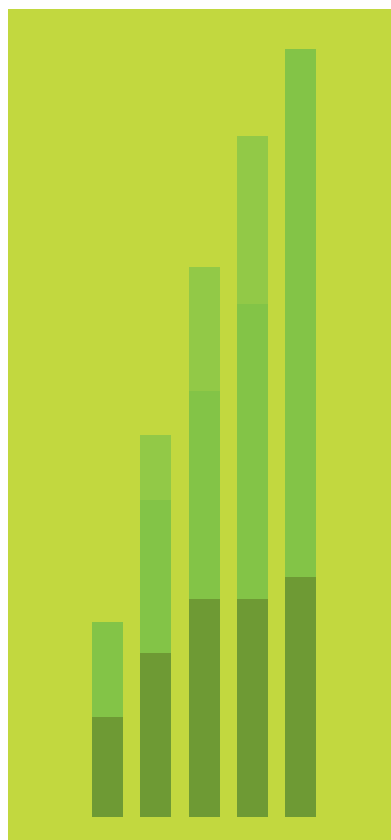


208

clinical research sites

585

commercial
treatment sites



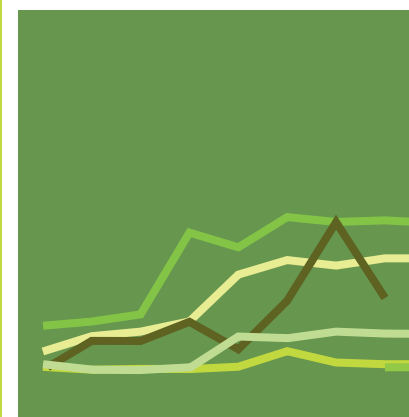
71

indications
in
clinical trials



150

technical research sites



138

preclinical research sites



State of Research and Treatment

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

The section on technical research this year is a bit different. By teasing out more detail on transducer technology and image guidance, we hope to provide information that will be useful to both the research community at large and the companies interested in further developing their existing technology and/or expanding their offerings.

This year we have greatly expanded the section on mechanisms of action. We hope you will spend some extra time in this section; trust us, it is well worth your time. Pages II.26 through II.47 present all sorts of new data that folks familiar with the field are aware of but that the Foundation has never tracked in this fashion. We will let you in on a little secret: This revamp has been in the works for several years now, and we are excited that it is finally time to reveal it. Please let us know what you think.

A further note to those detail-oriented readers who study this report year after year, have amazing memories, and possess sharp skills at comparing various data points: This report has inconsistencies. We work diligently to identify these inconsistencies, attempting to ensure they are not errors but are in fact discrepancies that we can explain. The data in this section is self-reported and comes from our annual surveys sent to members of the focused ultrasound community every January. However, the data in the Field Overview is data that the Foundation actively collects from various sources and reports, including personal knowledge gleaned through phone calls and site visits. Therefore, the Field Overview has some differences with the State of Research and Treatment and the State of Commercialization.

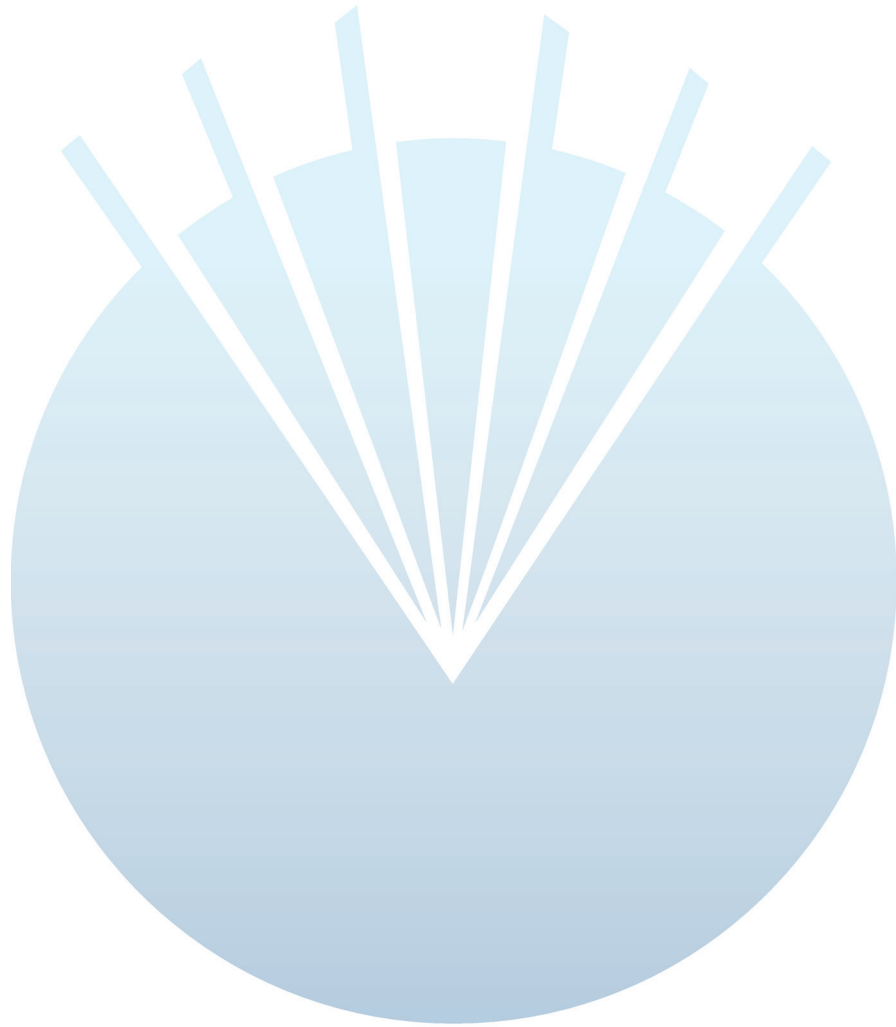
Lastly, a very special thank you to our new global ambassadors who are working hard to extend the reach of the Foundation in Europe and Asia. In the past year, they have been tireless in their efforts to reach out to sites within their respective regions and validate the work of those sites. They have sought to re-engage those who have gotten lost in the annual survey process, and just otherwise assist with the unglamorous job of cleaning up our database—the source of information from which this extensive annual report is generated. They have been an essential addition to our team, and we are more confident in the accuracy of this year's report than in years past because of their efforts.

8

Centers of Excellence

6

veterinary
programs sites



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- II. 6 Top Countries for Commercial Treatment
- II. 7 Sites by Country
- II. 8 Sites by Indication and Region

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Commercial Treatment Sites by Region



It is worth noting that while China leads the world in treatment sites and has 26 unique approved indications, the United States follows with the second largest number of treatment sites, but with only 6 indications. This trend is representative of only a few companies in the United States market heavily commercializing their technology for specific indications—signifying a different commercialization strategy than what is happening in China.

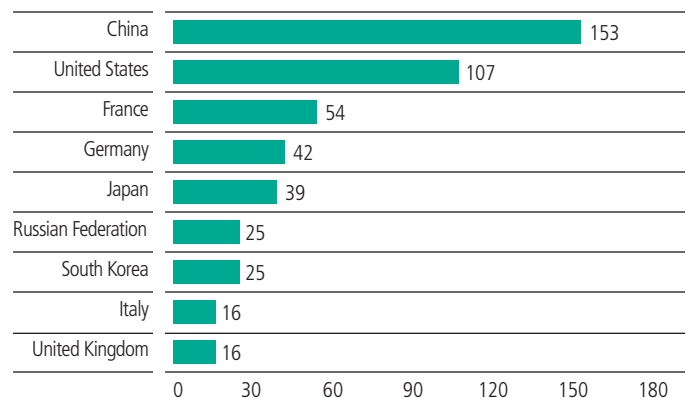
Commercial treatment additional content

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

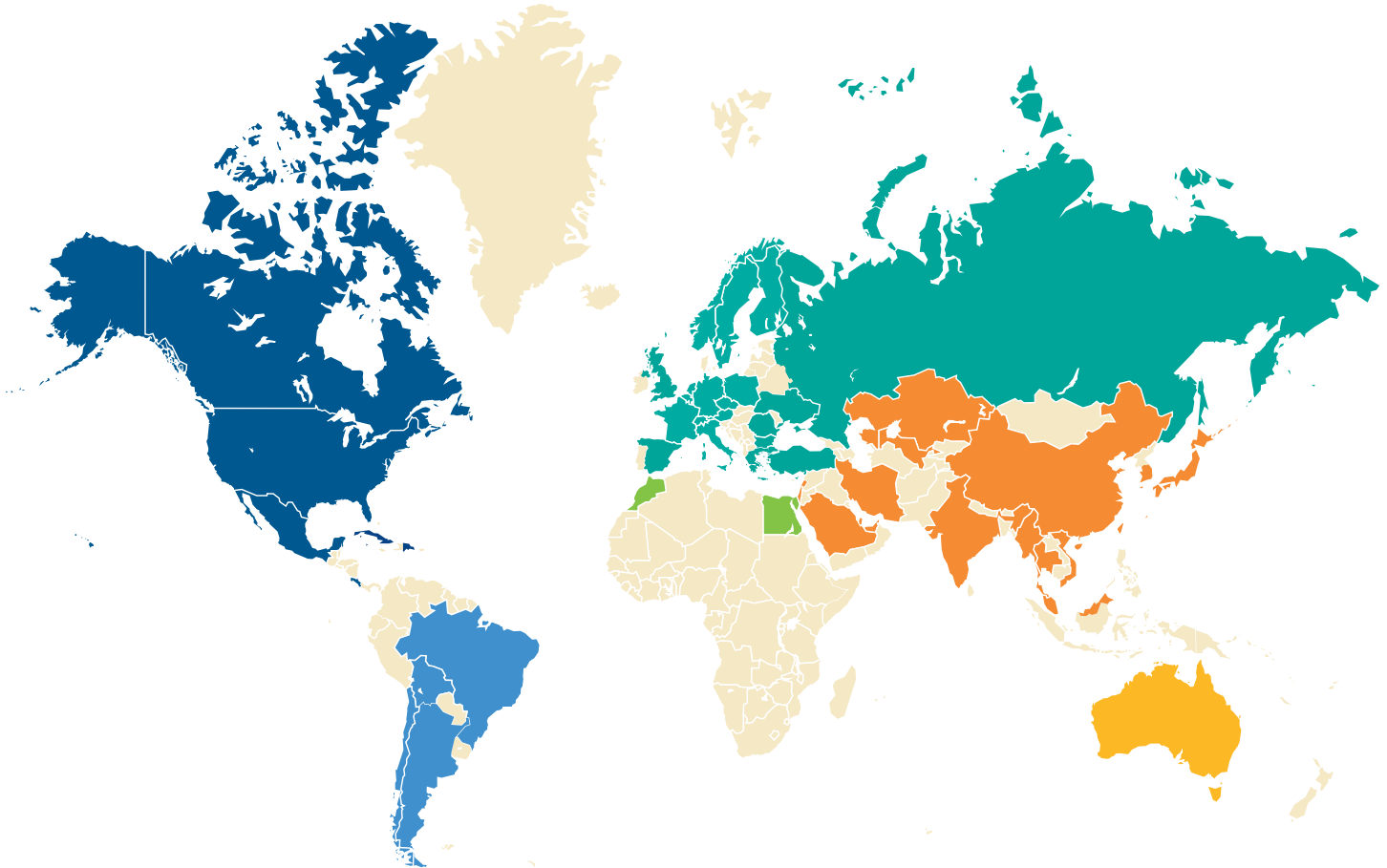
www.fusfoundation.org/the-technology/treatment-sites

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

Top Countries for Commercial Treatment



Commercial Treatment Sites by Country



■ North America

- 9 Canada
- 1 Cayman Islands
- 1 Costa Rica
- 1 Cuba
- 2 Dominican Republic
- 9 Mexico
- 107 United States

■ South America

- 1 Argentina
- 4 Brazil
- 1 Chile
- 3 Ecuador

■ Europe

- 2 Austria
- 2 Belgium
- 1 Bulgaria
- 1 Finland
- 54 France
- 42 Germany
- 1 Greece
- 16 Italy
- 4 The Netherlands
- 2 Norway
- 3 Poland
- 1 Romania
- 25 Russian Federation

- 4 Spain
- 1 Sweden
- 11 Switzerland
- 1 Turkey
- 1 Ukraine
- 16 United Kingdom

■ Asia

- 153 China
- 6 India
- 1 Iran
- 3 Israel
- 39 Japan
- 1 Kazakhstan
- 1 Lebanon
- 1 Malaysia
- 2 Qatar
- 2 Saudi Arabia
- 2 Singapore
- 25 South Korea
- 13 Taiwan

- 1 Thailand
- 1 Uzbekistan
- 1 Vietnam

■ Oceania

- 3 Australia

■ Africa

- 2 Egypt
- 1 Morocco

COMMERCIAL TREATMENT

Commercial Treatment Sites by Indication and Region*

6 Cardiovascular sites 3 indications	9 Endocrine disorders sites 1 indication	111 Gastrointestinal sites 3 indications	251 Musculoskeletal sites 8 indications
66 Neurological sites 9 indications	14 Ophthalmological sites 1 indication	414 Urological sites 3 indications	455 Women's health sites 8 indications

Indications	Regions						Totals
	N. America	Europe	Asia	S. America	Africa	Oceania	
Cardiovascular							
Arteriovenous malformations	1	2	–	–	–	–	3
Peripheral artery disease	1	–	–	–	–	–	1
Varicose veins	–	2	–	–	–	–	2
Endocrine disorders							
Thyroid nodules	–	9	–	–	–	–	9
Gastrointestinal							
Liver metastases	–	1	1	–	–	1	3
Liver tumors	1	9	89	–	–	1	100
Pancreatic tumors	–	4	3	–	–	1	8
Musculoskeletal							
Arthritis, facetogenic	2	1	1	–	1	–	5
Bone cancer	2	2	1	–	–	1	6
Bone metastases	6	15	6	–	1	1	29
Bone tumors, benign	1	–	–	–	–	–	1
Desmoid tumors	2	4	–	–	–	–	6
Osteoid osteoma	3	11	88	–	1	–	103
Soft tissue cancer	1	2	–	–	–	–	3
Soft tissue tumors, benign	2	7	88	–	1	–	98

*Indications being performed off label in a region are shown in bold italic.

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

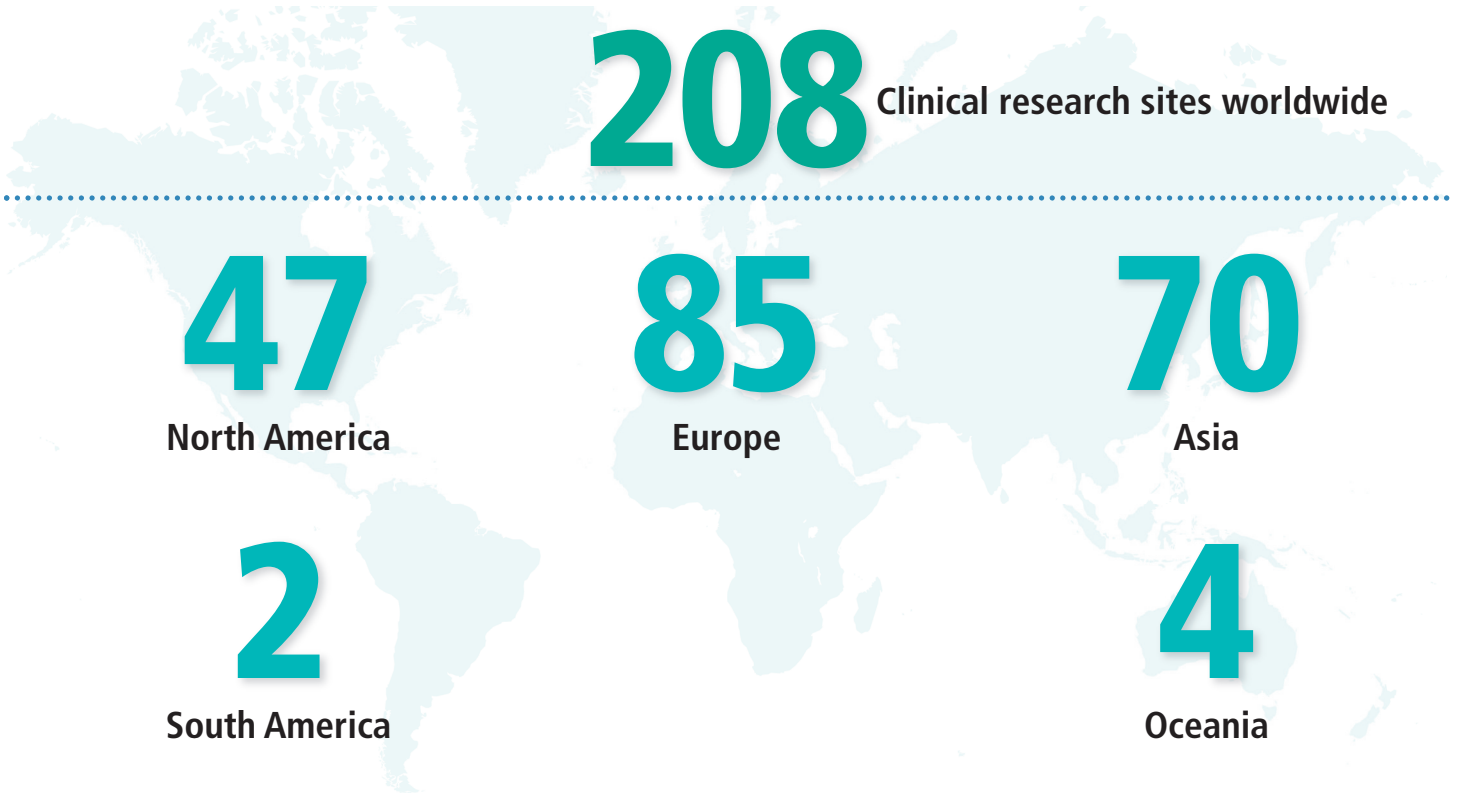
Use the "search by disease" dropdown menu and/or location.

Commercial Treatment Sites by Indication and Region* continued

Indications	Regions						Totals
	N. America	Europe	Asia	S. America	Africa	Oceania	
Neurological							
Astrocytoma	2	–	–	–	–	–	2
Cancer pain	–	1	–	–	–	–	1
Dystonia	–	1	–	–	–	–	1
Epilepsy	–	1	1	–	–	–	2
Essential tremor	22	11	9	–	1	–	43
Neuropathic pain	–	2	–	–	–	–	2
Parkinson’s disease, dyskinesia	–	1	–	–	–	–	1
Parkinson’s disease, tremor	5	6	2	–	–	–	13
Trigeminal neuralgia	–	1	–	–	–	–	1
Ophthalmological							
Glaucoma	–	14	–	–	–	–	14
Urological							
Benign prostatic hyperplasia	27	8	24	1	–	–	60
Kidney tumors	1	6	88	–	–	–	96
Prostate cancer	103	122	23	8	–	2	258
Women’s health							
Breast cancer	–	7	89	–	–	–	96
Breast fibroadenoma	–	11	–	–	–	1	12
Cervicitis	–	1	–	–	–	–	1
Endometrial tumors	–	–	1	–	–	–	1
Endometriosis	–	1	–	–	–	–	1
Liver metastases, breast cancer	–	1	–	–	–	–	1
Uterine adenomyosis	2	6	82	–	2	–	92
Uterine fibroids	11	34	202	1	2	1	251

*Indications being performed off label in a region are shown in bold italic.
 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.

Clinical Research Sites by Region*



*Clinical research sites treat patients as part of a clinical study. No clinical research sites in Africa.

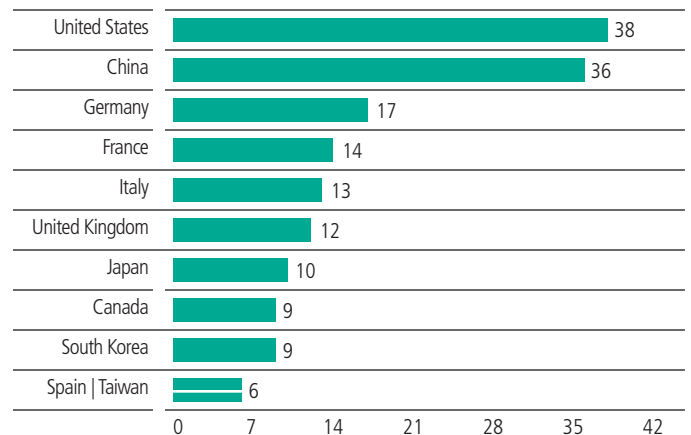
Clinical research additional content

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

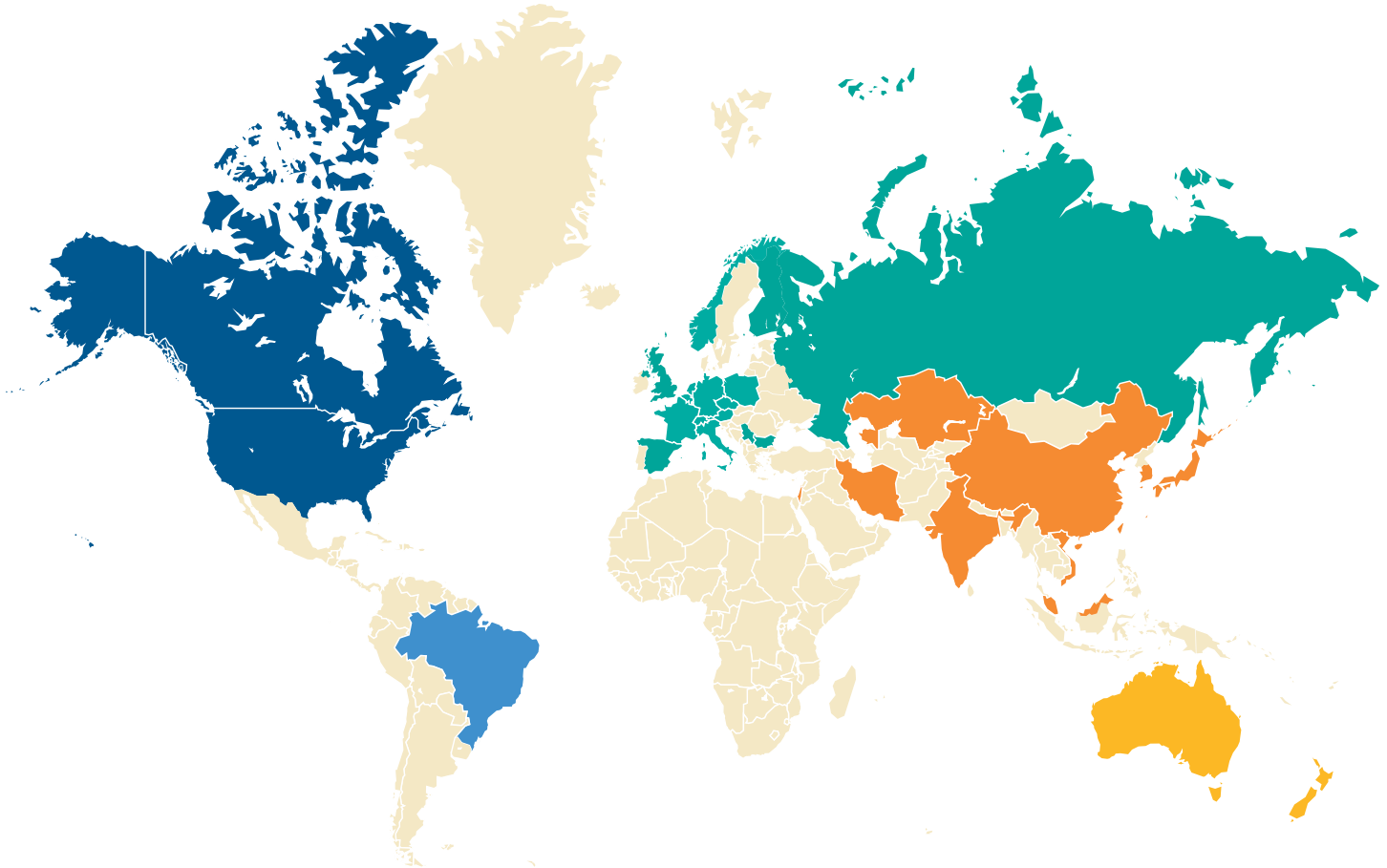
www.fusfoundation.org/the-technology/research-sites

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

Top Countries for Clinical Research



Clinical Research Sites by Country



North America

- 9 Canada
- 38 United States

South America

- 2 Brazil

Europe

- 1 Austria
- 1 Belgium
- 1 Bulgaria
- 3 Czech Republic
- 1 Finland
- 14 France
- 17 Germany
- 13 Italy
- 4 The Netherlands
- 3 Norway
- 1 Poland
- 4 Russian Federation

- 1 Serbia
- 6 Spain
- 3 Switzerland
- 12 United Kingdom

Asia

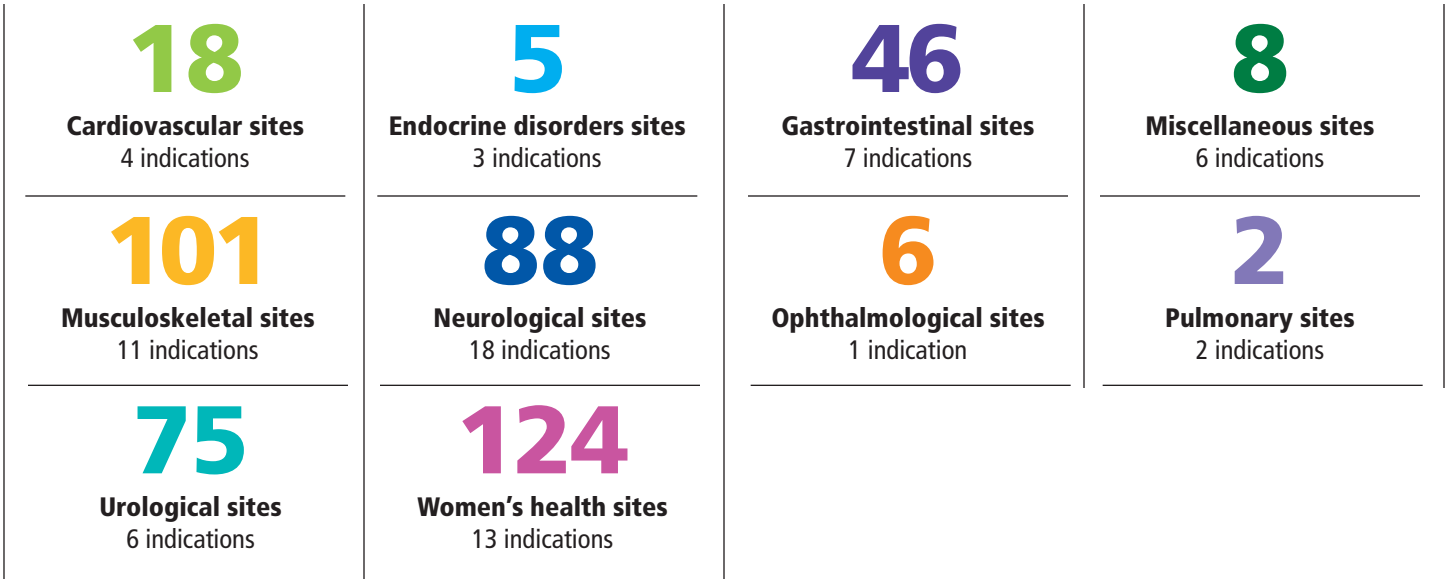
- 36 China
- 2 India
- 1 Iran
- 3 Israel
- 10 Japan
- 1 Kazakhstan
- 1 Malaysia
- 9 South Korea
- 6 Taiwan
- 1 Vietnam

Oceania

- 3 Australia
- 1 New Zealand

Clinical Research Sites by Indication and Region

71 indications are being researched at clinical sites worldwide.



Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
Cardiovascular						
Atrial fibrillation	–	1	–	–	–	1
Heart valve calcifications	–	3	–	–	–	3
Hypertension	–	10	2	–	1	13
Varicose veins	–	1	–	–	–	1
Endocrine disorders						
Graves' disease	–	–	1	–	–	1
Thyroid cancer	–	1	–	–	–	1
Thyroid nodules	–	2	1	–	–	3
Gastrointestinal						
Biliary tract cancer	–	–	1	–	–	1
Colorectal tumors	–	1	–	–	–	1
Liver metastases	–	4	–	–	–	4
Liver tumors	–	9	13	–	–	22
Malignant obstructive jaundice	–	–	1	–	–	1

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

71 indications are being researched at clinical sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
Gastrointestinal continued						
Pancreatic tumors	–	8	8	–	–	16
Root canal endodontia	1	–	–	–	–	1
Miscellaneous						
Dercum's disease	–	–	1	–	–	1
Head & neck tumors	2	1	–	–	–	3
Hypersplenism	–	–	1	–	–	1
Lipoma	–	–	1	–	–	1
Melanoma	–	1	–	–	–	1
Multiple tumors ¹	1	–	–	–	–	1
Musculoskeletal						
Arthritis, facetogenic	2	3	2	1	–	8
Arthritis, knee	–	–	1	–	–	1
Arthritis, sacroiliac	–	1	–	–	–	1
Bone cancer	3	3	–	–	–	6
Bone metastases	2	11	6	1	1	21
Bone tumors, benign	–	2	–	–	–	2
Desmoid tumors	1	1	–	–	–	2
Osteoid osteoma	5	6	13	1	–	25
Sacral chordoma	–	2	–	–	–	2
Soft tissue cancer	3	5	–	–	–	8
Soft tissue tumors, benign	4	6	14	–	1	25
Neurological						
Alzheimer's disease	4	2	1	–	1	8
Astrocytoma	3	2	–	–	–	5
Cancer pain	–	1	–	–	–	1
Dementia	–	1	–	–	–	1
Depression	1	–	2	–	–	3
Dystonia	1	–	2	–	–	3
Epilepsy	3	–	2	–	–	5
Essential tremor	7	6	6	–	–	19

¹ Protocols inclusive of more than one indication.

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

71 indications are being researched at clinical sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
Neurological continued						
Glioblastoma	4	5	3	–	–	12
Holmes tremor	1	–	–	–	–	1
Huntington’s disease	1	–	–	–	–	1
Neuroblastoma	1	–	–	–	–	1
Neuropathic pain	3	–	–	–	–	3
Obsessive-compulsive disorder	2	–	–	–	–	2
Opioid and other addictions	1	1	–	–	–	2
Painful amputation neuromas	–	–	1	–	–	1
Parkinson’s disease, dyskinesia	11	2	3	–	–	16
Parkinson’s disease, tremor	1	2	1	–	–	4
Ophthalmological						
Glaucoma	1	5	–	–	–	6
Pulmonary						
Lung metastases	–	1	–	–	–	1
Rhinitis	–	–	1	–	–	1
Urological						
Acute kidney injury	–	–	1	–	–	1
Benign prostatic hyperplasia	2	3	–	–	–	5
Chyluria	–	–	1	–	–	1
Kidney stones	1	–	–	–	–	1
Kidney tumors	–	5	13	–	–	18
Prostate cancer	23	20	5	1	–	49

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.

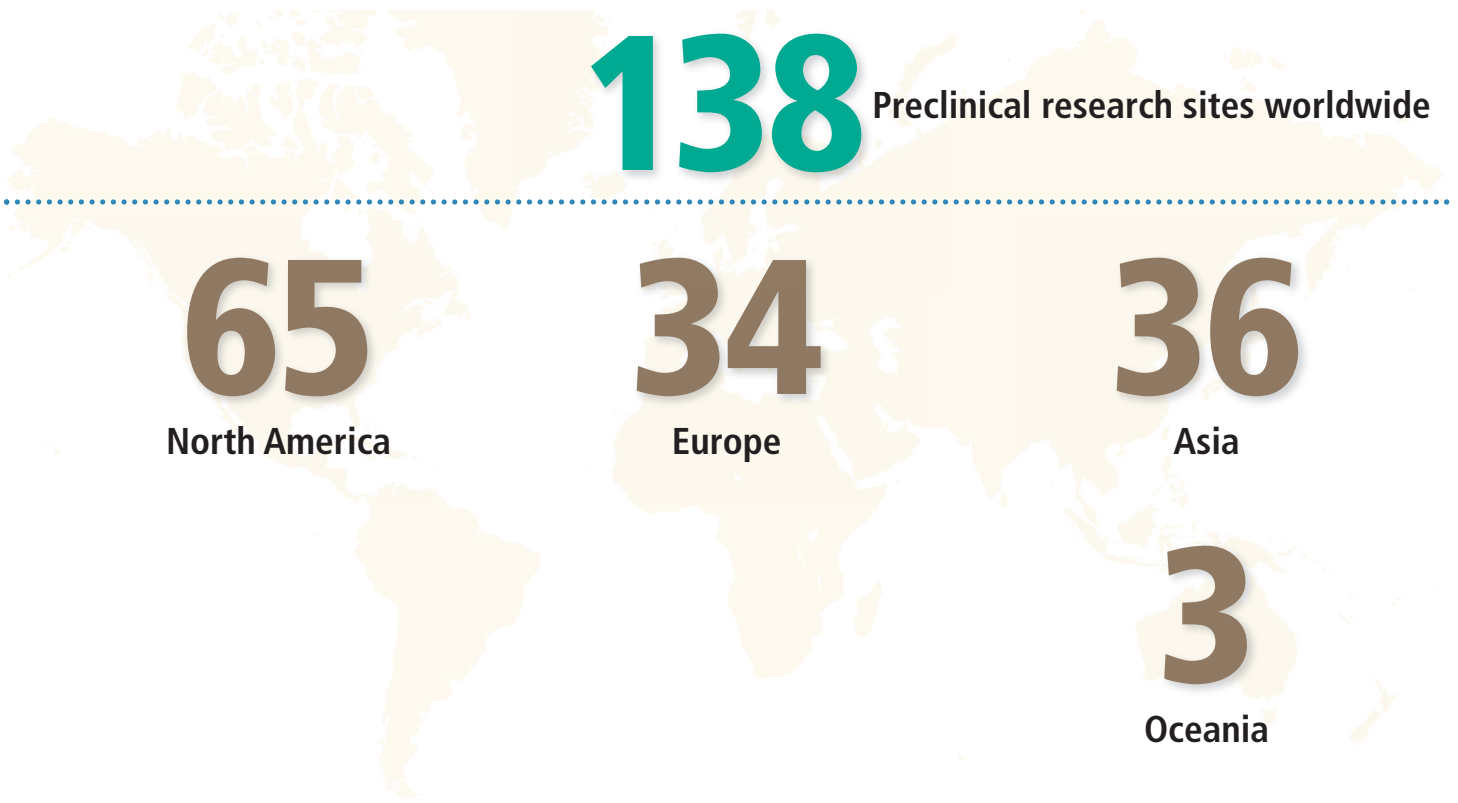
Clinical Research Sites by Indication and Region continued

71 indications are being researched at clinical sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
Women's health						
Brain metastases, breast cancer	1	–	–	–	–	1
Breast cancer	1	9	14	–	–	24
Breast fibroadenoma	5	3	2	–	–	10
Cervical tumors	–	2	–	–	–	2
Ectopic pregnancy	–	–	1	–	–	1
Endometrial tumors	–	1	–	–	–	1
Endometriosis	–	–	1	–	–	1
Ovarian tumors	–	1	–	–	–	1
Retained placenta	–	–	1	–	–	1
Uterine adenomyosis	–	6	10	–	2	18
Uterine fibroids	1	22	35	1	2	61
Vaginal tumors	–	2	–	–	–	2
Vulvar dystrophy	–	–	1	–	–	1

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 Region*



*Preclinical research sites conduct non-human FUS research to collect data in support of the safety or feasibility of clinical applications. No preclinical research sites in South America and Africa.

The United States leads the world in preclinical focused ultrasound research. This is likely a reflection of the United States leading the world in medical research in general and the robust research infrastructure that exists in institutions of higher learning throughout the country.

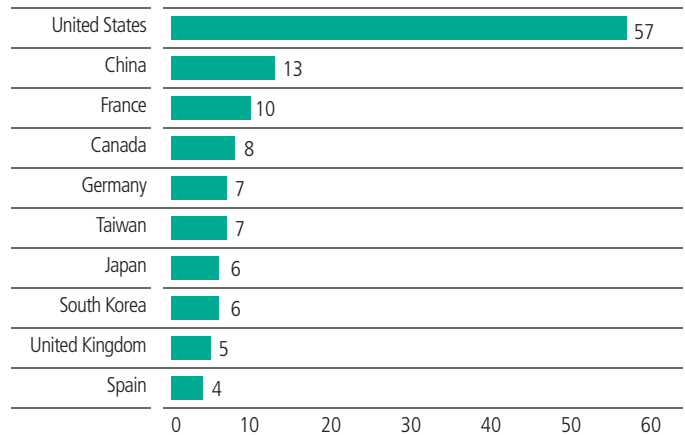
Preclinical research additional content

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

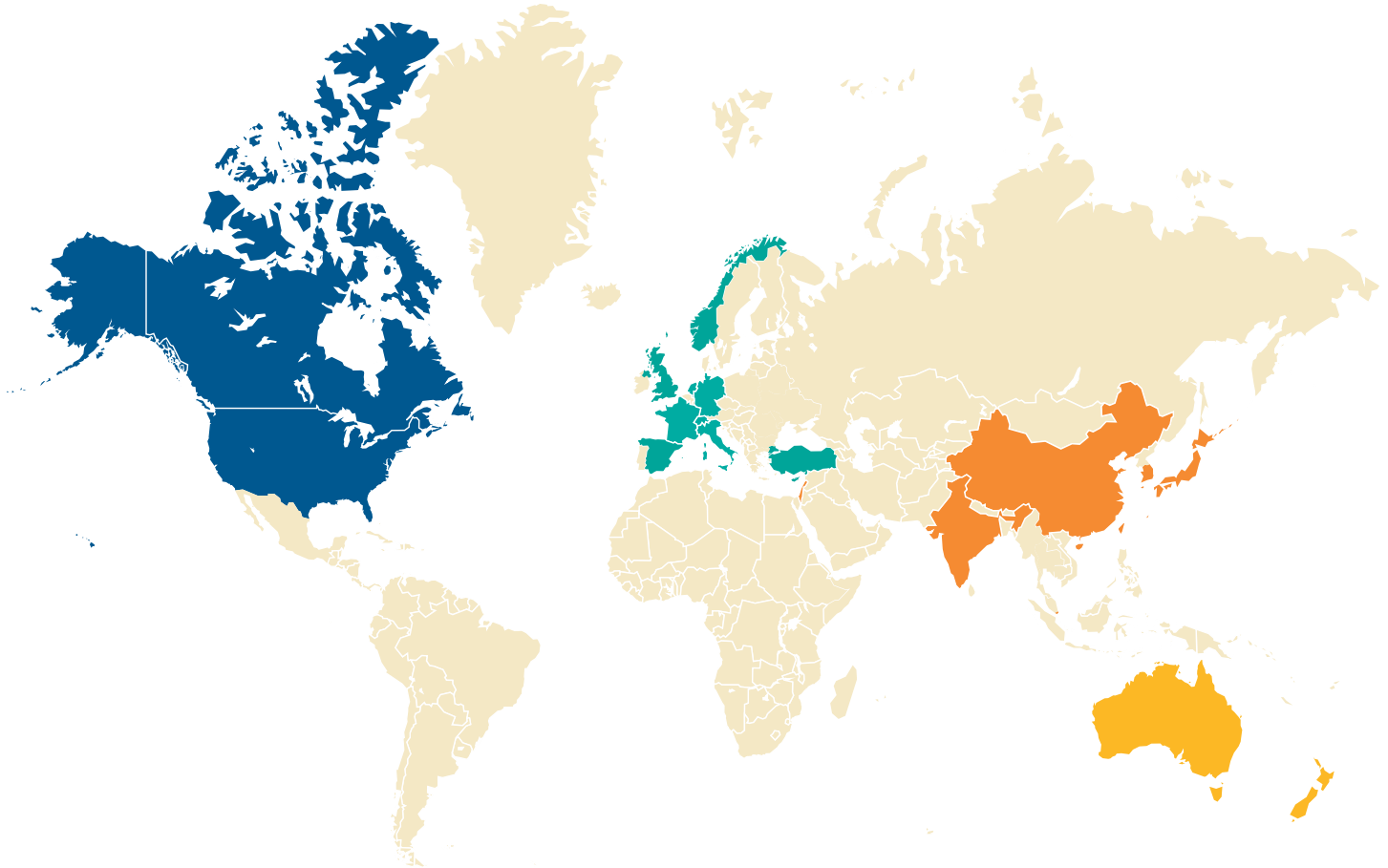
www.fusfoundation.org/the-technology/research-sites

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

Top Countries for Preclinical Research



Preclinical Research Sites by Country



■ North America

- 8 Canada
- 57 United States

■ Europe

- 1 Cyprus
- 10 France
- 7 Germany
- 1 Italy
- 1 The Netherlands
- 1 Norway
- 4 Spain
- 3 Switzerland
- 1 Turkey
- 5 United Kingdom

■ Asia

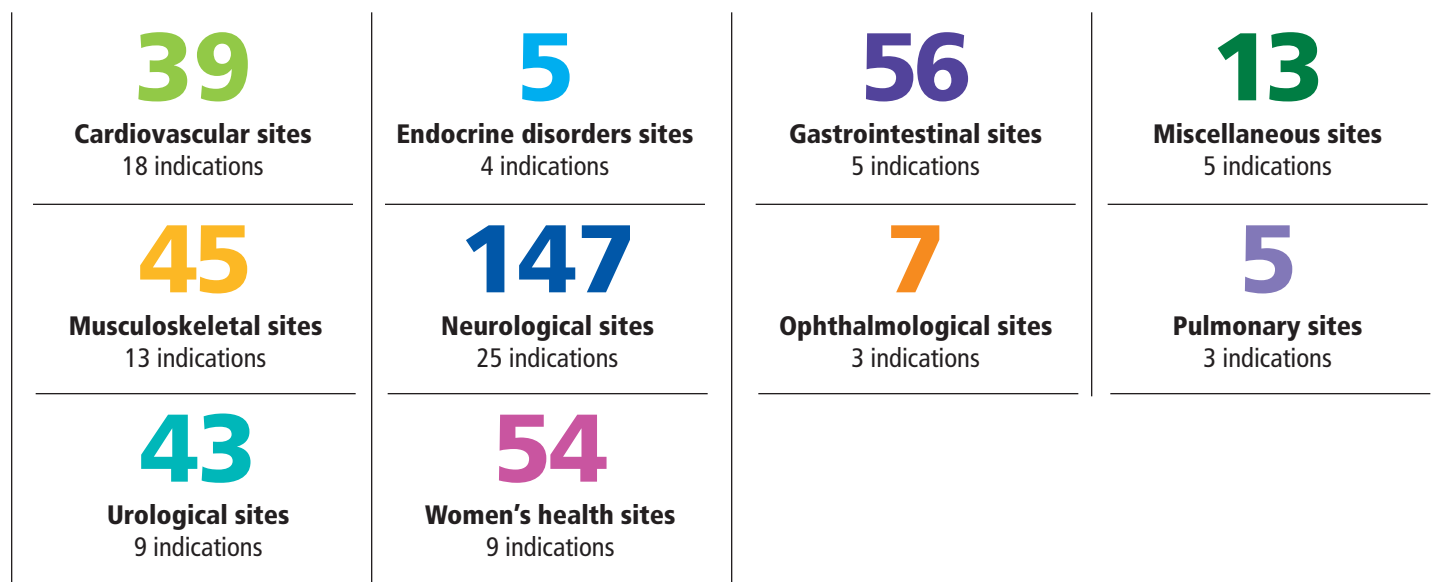
- 13 China
- 1 India
- 2 Israel
- 6 Japan
- 1 Singapore
- 6 South Korea
- 7 Taiwan

■ Oceania

- 2 Australia
- 1 New Zealand

Preclinical Research Sites by Indication and Region

94 indications are being researched at preclinical sites worldwide.



Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Cardiovascular					
Arteriovenous malformations	1	–	–	–	1
Atherosclerosis	5	1	1	–	7
Atrial fibrillation	1	1	1	–	3
Cardiac hypertrophy	–	–	1	–	1
Cardiac pacing	–	1	–	–	1
Coarctation of the aorta	1	–	–	–	1
Congestive heart failure	1	–	1	–	2
Deep vein thrombosis	6	–	–	–	6
Fetal heart anomalies	1	–	–	–	1
Heart valve calcifications	–	1	–	–	1
Hematoma	1	–	–	–	1
Hemophilia	1	–	–	–	1
Hypertension	1	–	–	1	2
Mitral regurgitation	–	1	–	–	1

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 Indication and Region continued

94 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Cardiovascular continued					
Peripheral artery disease	2	–	–	–	2
Twin-twin transfusion syndrome	1	3	1	–	5
Varicose veins	–	1	–	–	1
Ventricular tachycardia	1	1	–	–	2
Endocrine disorders					
Diabetes	1	–	–	–	1
Graves' disease	1	–	–	–	1
Thyroid cancer	2	–	–	–	2
Thyroid nodules	1	–	–	–	1
Gastrointestinal					
Biliary tract tumors	–	1	–	–	1
Colorectal tumors	1	1	–	–	2
Liver metastases	3	3	–	–	6
Liver tumors	13	8	5	–	26
Pancreatic tumors	8	9	4	–	21
Miscellaneous					
Head & neck tumors	1	2	1	–	4
Melanoma	2	–	–	–	2
Multiple tumors ¹	3	2	–	–	5
Obesity	1	–	–	–	1
Wound healing	1	–	–	–	1
Musculoskeletal					
Arthritis, facetogenic	2	2	1	–	5
Arthritis, knee	–	–	1	–	1
Bone cancer	1	–	–	–	1
Bone metastases	6	2	3	1	12
Bone tumors, benign	2	–	–	–	2
Disc degeneration	1	–	–	–	1
Muscle atrophy	1	–	–	–	1
Osteoid osteoma	1	1	2	–	4
Osteomyelitis	1	–	–	–	1

¹ Protocols inclusive of more than one indication.

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

94 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Musculoskeletal continued					
Rotator cuff injury	1	–	–	–	1
Soft tissue cancer	7	1	–	–	8
Soft tissue tumors, benign	4	1	2	–	7
Tendon contracture	1	–	–	–	1
Neurological					
Alzheimer’s disease	7	3	2	1	13
Amyotrophic lateral sclerosis	1	1	–	–	2
Astrocytoma	7	2	3	–	12
Cancer pain	2	3	–	–	5
Dementia	–	–	1	–	1
Depression	2	1	–	–	3
Epilepsy	11	1	–	–	12
Essential tremor	1	1	1	–	3
Glioblastoma	20	9	10	–	39
Huntington’s disease	1	–	–	–	1
Hydrocephalus	1	–	–	–	1
Migraine	1	–	–	–	1
Multiple sclerosis	1	–	–	–	1
Neuroblastoma	1	1	–	–	2
Neuromyelitis optica	1	–	–	–	1
Neuropathic pain	3	–	1	–	4
Opioid and other addictions	1	1	1	–	3
Parkinson’s disease, tremor	1	–	–	–	1
Parkinson’s disease, underlying cause	6	2	3	–	11
Pontine glioma	1	2	–	–	3
Rett syndrome	–	1	–	–	1
Spinal cord injury	3	–	1	–	4
Stroke, intracerebral hemorrhage	9	2	1	–	12
Stroke, thromboembolic	4	3	1	–	8
Traumatic brain injury	3	–	–	–	3

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.

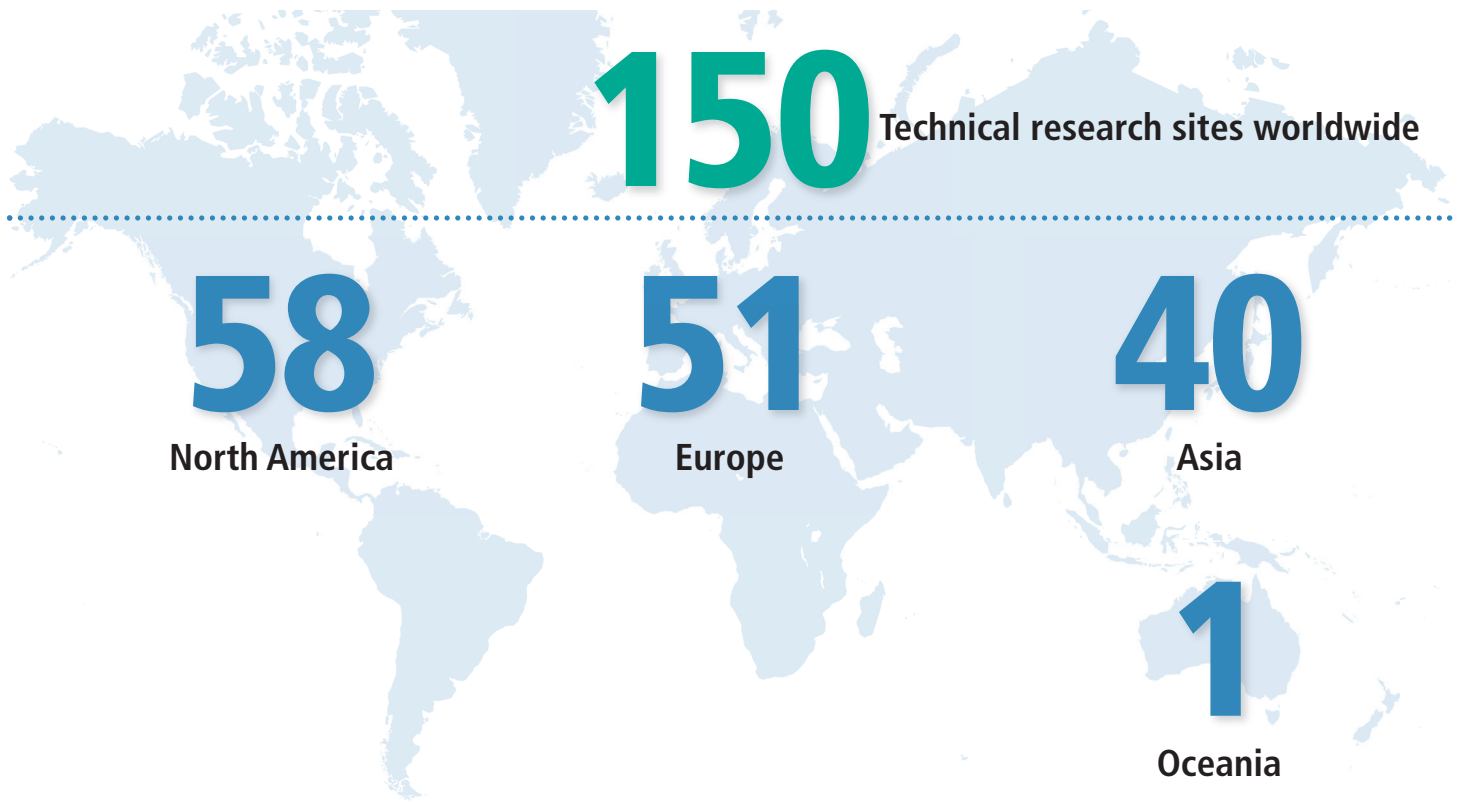
Preclinical Research Sites by Indication and Region continued

94 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Ophthalmological					
Glaucoma	–	4	–	–	4
Keratoplasty	–	–	1	–	1
Macular degeneration	1	1	–	–	2
Pulmonary					
Lung cancer	1	1	1	–	3
Lung metastases	–	1	–	–	1
Tuberculosis	–	–	1	–	1
Urological					
Acute kidney injury	1	–	–	–	1
Acute tubular necrosis	1	–	1	–	2
Benign prostatic hyperplasia	2	–	–	–	2
Bladder tumors	2	–	–	–	2
Fetal bladder obstruction	–	–	1	–	1
Kidney stones	2	–	–	–	2
Kidney tumors	5	2	2	–	9
Prostate cancer	13	7	3	–	23
Urinary tract infection	–	1	–	–	1
Women's health					
Brain metastases, breast cancer	2	–	–	–	2
Breast cancer	15	1	6	–	22
Breast fibroadenoma	1	–	1	–	2
Cervical tumors	–	–	1	–	1
Endometrial tumors	1	–	1	–	2
Endometriosis	–	1	–	–	1
Ovarian tumors	–	–	1	1	2
Uterine adenomyosis	–	1	2	1	4
Uterine fibroids	6	3	8	1	18

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

Technical Research Sites by Region



New for the 2020 report, we have broken down both transducer design and image guidance into greater detail. These new categories can be found on page II.24.

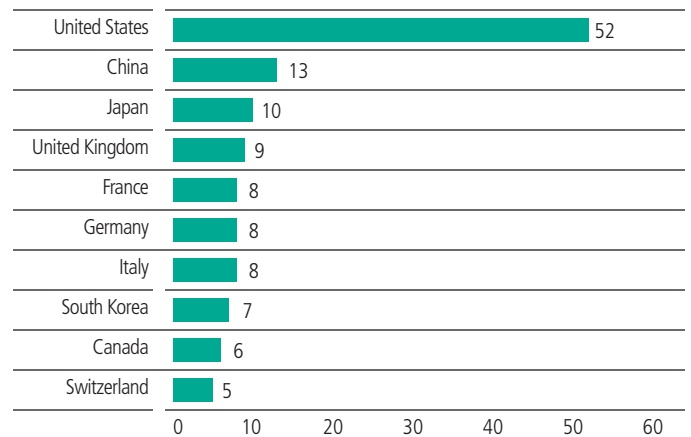
Technical research additional content

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

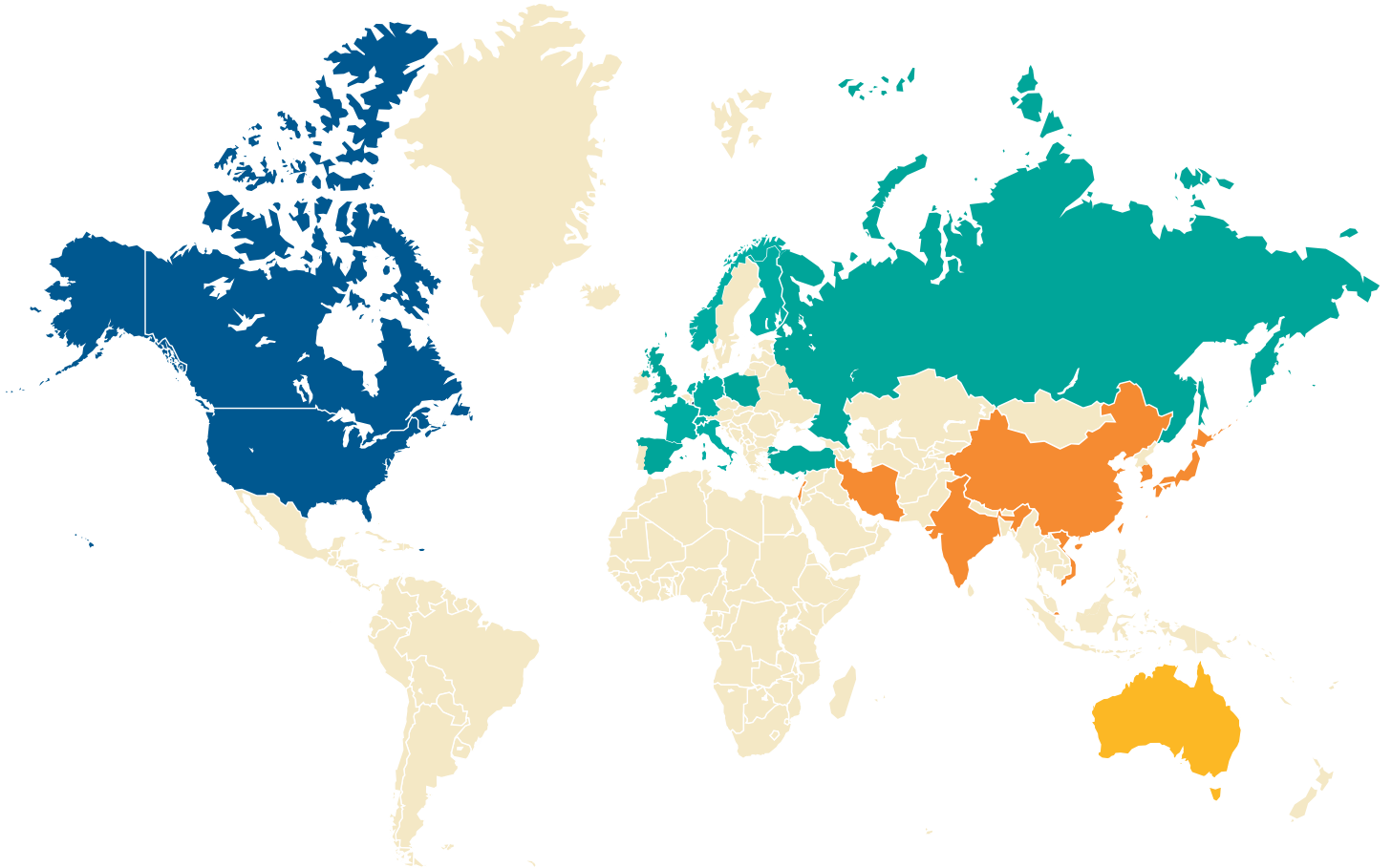
www.fusfoundation.org/the-technology/research-sites

Use the “search by technical research” dropdown menu.

Top Countries for Technical Research



Technical Research Sites by Country



■ North America

- 6 Canada
- 52 United States

■ Europe

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

■ Asia

- 13 China
- 1 India
- 1 Iran
- 2 Israel
- 10 Japan
- 1 Singapore
- 7 South Korea
- 4 Taiwan
- 1 Vietnam

■ Oceania

- 1 Australia

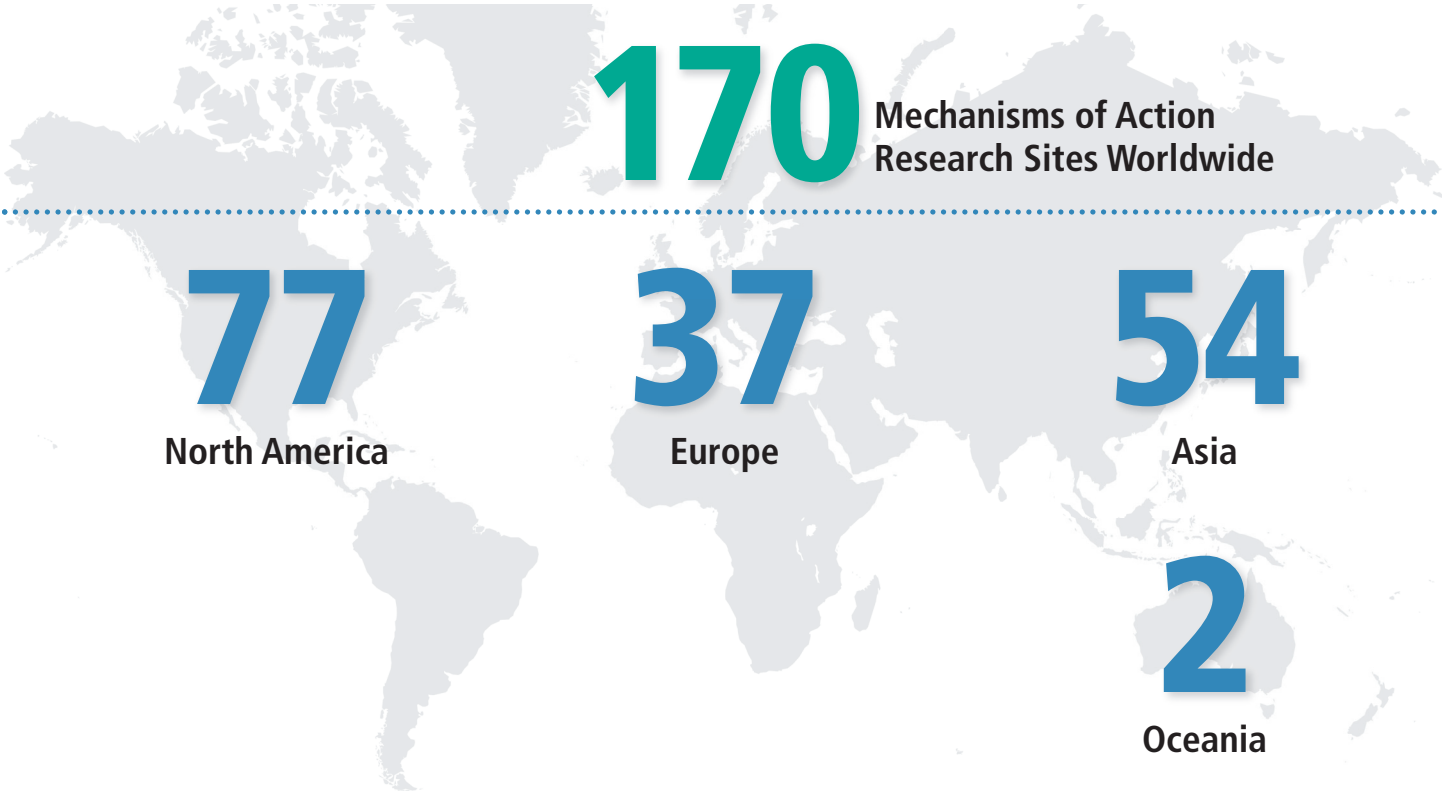
Technical Sites by Research Type and Region

	Regions				Totals
	N. America	Europe	Asia	Oceania	
Drug delivery technology	22	12	5	1	40
FUS Simulation & treatment planning	23	20	8	–	51
FUS Physics	39	24	15	–	78
FUS Transducer technology, Thermal ablation	9	12	7	–	28
FUS Transducer technology, Hyperthermia	7	7	3	–	17
FUS Transducer technology, Nonthermal	8	3	4	–	15
FUS Transducer technology, Histotripsy	7	2	2	–	11
FUS Transducer technology, Other	6	8	1	–	15
FUS Treatment monitoring	31	25	15	–	71
FUS Treatment evaluation	1	6	1	–	8
FUS Image guidance, MR	30	25	20	–	75
FUS Image guidance, Ultrasound	27	15	9	–	51
FUS Image guidance, Navigation	1	4	–	–	5
FUS Image guidance, Other	–	–	1	–	1
Standards & quality assurance	8	6	3	–	17

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.

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Mechanisms of Action Research Sites by Region*



*Mechanisms of action research sites conduct basic science research to understand how focused ultrasound affects the body. No mechanisms of action research sites in South America and Africa.

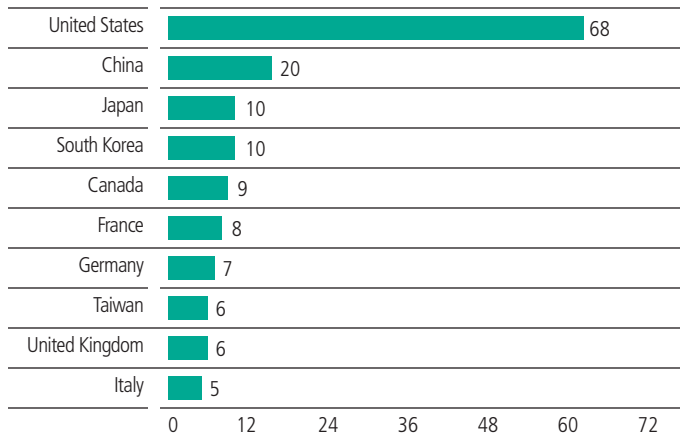
Mechanisms of action (MOA)

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

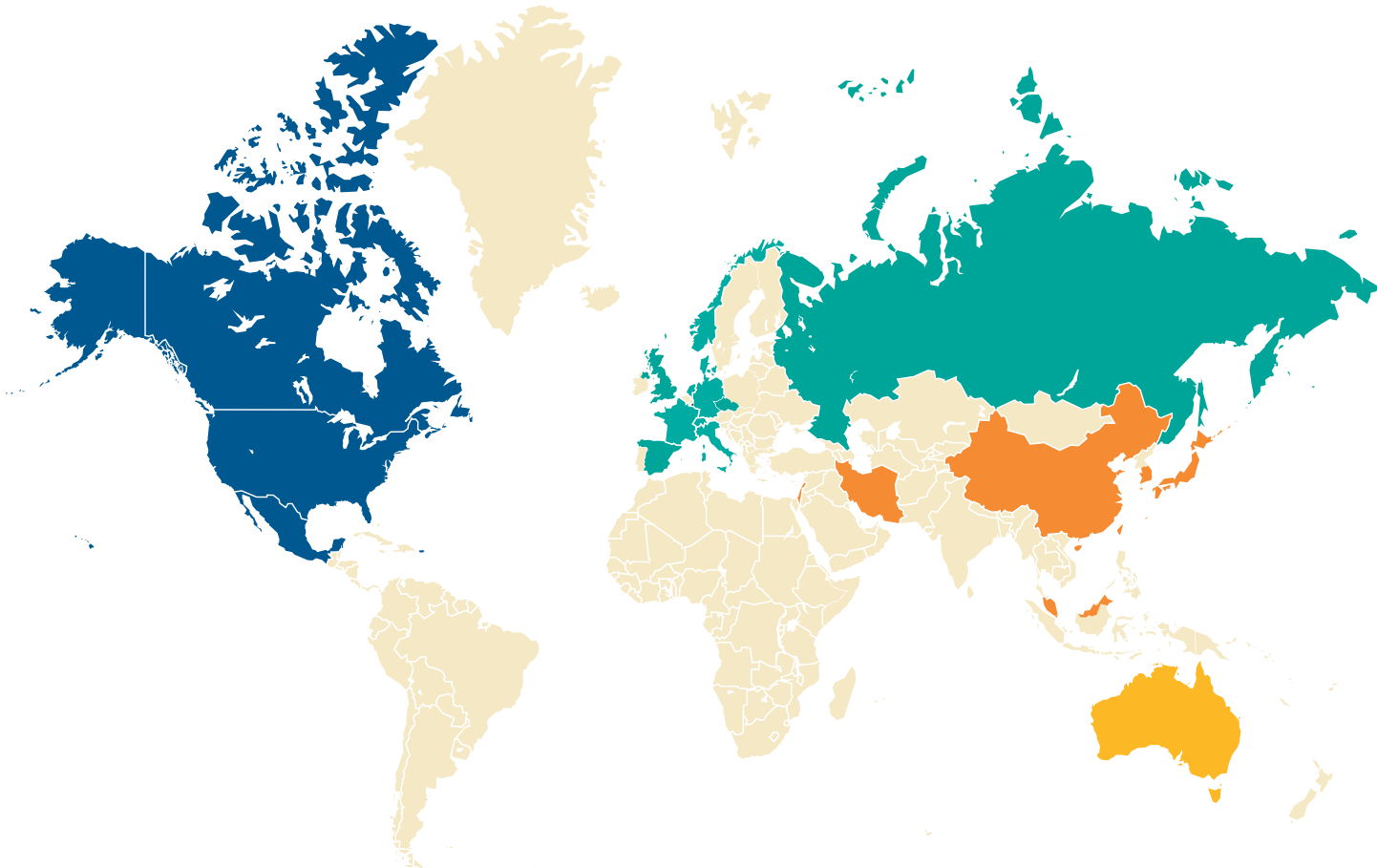
www.fusfoundation.org/the-technology/research-sites

Use the “search by biological effects research” dropdown menu.

Top Countries for MOA Research



Mechanisms of Action Research Sites by Country



■ North America

- 9 Canada
- 68 United States

■ Europe

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

■ Asia

- 20 China
- 2 Iran
- 4 Israel
- 10 Japan
- 1 Malaysia
- 1 Singapore
- 10 South Korea
- 6 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.

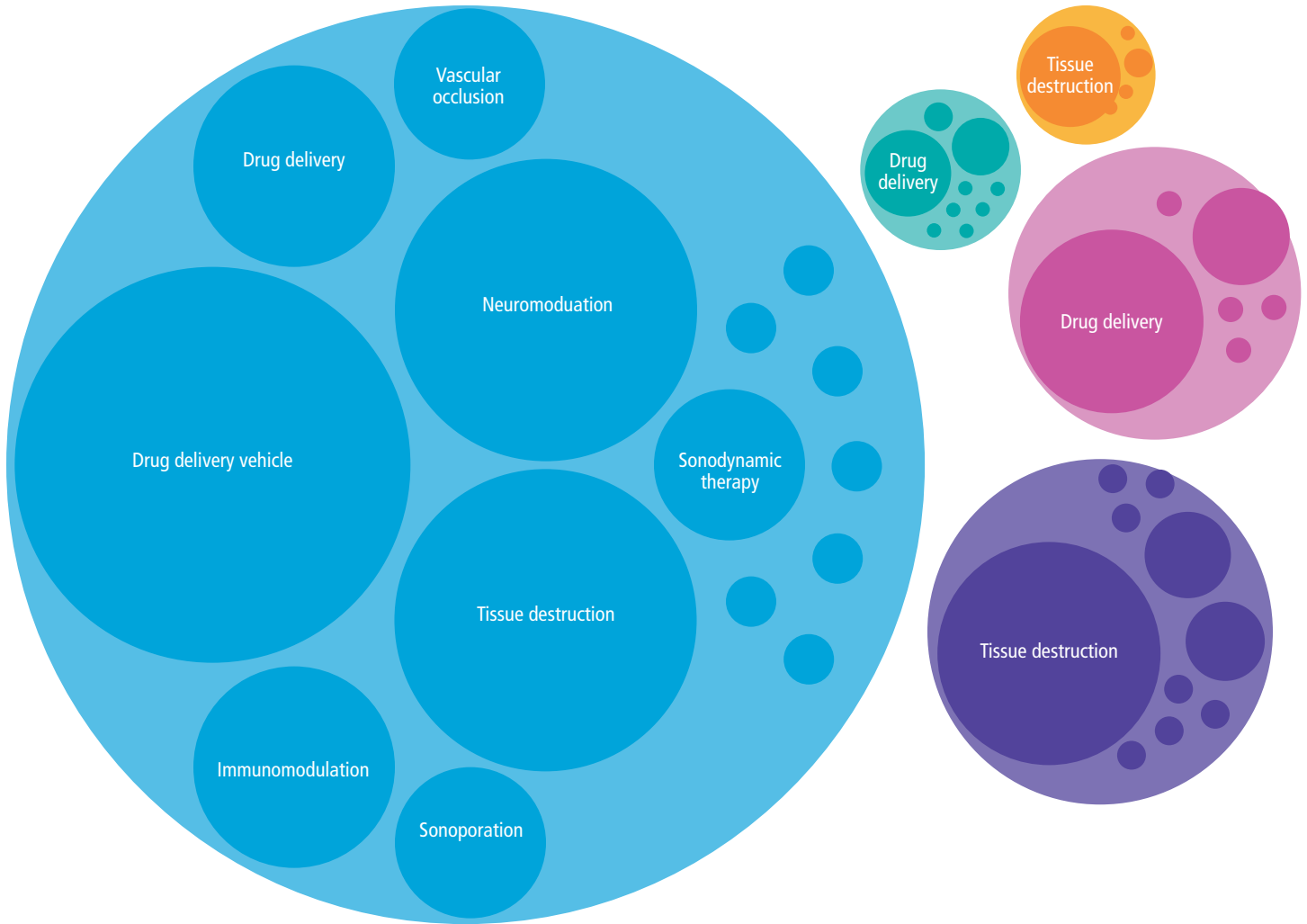
Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver (thermal or mechanical), and whether the effects of treatment are permanent 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 used most frequently in the clinic and produces permanent effects, but additional ultrasound treatment regimens are currently under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications currently 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 that is 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.

Mechanisms of Action Research Sites



Ultrasound applications and biological effects

Histotripsy | 45 sites

- Amplification of cancer biomarkers
- Immune cell trafficking
- Immunomodulation
- Liquid biopsy
- Tissue destruction

Hyperthermia | 52 sites

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

Nonthermal | 298 sites

- Amplification of cancer biomarkers
- Angiogenesis
- Cardiac pacing
- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Gene delivery
- Immune cell trafficking
- Immunomodulation
- Liquid biopsy
- Neuromodulation
- Radiosensitization

- Sonodynamic therapy
 - Sonoporation
 - Stem cell delivery
 - Stem cell trafficking
 - Tissue destruction
 - Vascular occlusion
- Nonthermal - BBB opening** | 95 sites

- Blood-brain barrier opening
- Drug delivery
- Drug delivery, immunotherapeutic
- Gene delivery
- Immune cell delivery
- Stem cell delivery

Thermal ablation | 112 sites

- Amplification of cancer biomarkers
- Chemosensitization
- Clot lysis
- Hemostasis
- Immune cell trafficking
- Immunomodulation
- Neuromodulation
- Radiosensitization
- Tissue destruction

MECHANISMS OF ACTION

Mechanisms of Action Research Sites by Region

	Regions				Totals
	N. America	Europe	Asia	Oceania	
Histotripsy 45 sites					
Amplification of cancer biomarkers	1	–	–	–	1
Immune cell trafficking	1	–	–	–	1
Immunomodulation	6	3	–	–	9
Liquid biopsy	1	–	–	–	1
Tissue destruction	22	7	4	–	33
Hyperthermia 52 sites					
Chemosensitization	1	–	–	–	1
Drug delivery	12	7	3	–	22
Drug delivery, immunotherapeutic	–	2	–	–	2
Drug delivery, vehicle	–	1	–	–	1
Immune cell trafficking	1	–	–	–	1
Immunomodulation	1	2	–	–	3
Radiosensitization	3	5	1	–	9
Tissue destruction	6	3	3	–	12
Vasodilation	–	1	–	–	1
Nonthermal 298 sites					
Amplification of cancer biomarkers	6	–	1	–	7
Angiogenesis	2	1	2	–	5
Cardiac pacing	–	–	1	–	1
Chemosensitization	5	2	–	–	7
Drug delivery	16	5	2	–	23
Drug delivery, immunotherapeutic	6	2	–	1	9
Drug delivery, vehicle	32	12	20	–	64
Gene delivery	1	–	–	–	1
Immune cell trafficking	2	–	–	–	2
Immunomodulation	13	4	4	–	21
Liquid biopsy	4	–	–	–	4
Neuromodulation	26	6	14	1	47
Radiosensitization	4	–	–	–	4
Sonodynamic therapy	7	2	6	–	15

Mechanisms of Action Research Sites by Region continued

	Regions				Totals
	N. America	Europe	Asia	Oceania	
Nonthermal continued					
Sonoporation	9	2	2	–	13
Stem cell delivery	7	–	1	–	8
Stem cell trafficking	3	–	–	–	3
Tissue destruction	21	13	12	–	46
Vascular occlusion	11	3	4	–	18
Nonthermal - BBB opening 95 sites					
Blood-brain barrier opening	18	6	4	–	28
Drug delivery	24	13	21	1	59
Drug delivery, immunotherapeutic	2	1	–	–	3
Gene delivery	1	1	–	–	2
Immune cell delivery	1	–	–	–	1
Stem cell delivery	1	–	1	–	2
Thermal ablation 112 sites					
Amplification of cancer biomarkers	3	1	–	–	4
Chemosensitization	1	1	–	–	2
Clot lysis	14	3	3	–	20
Hemostasis	2	–	–	–	2
Immune cell trafficking	2	1	–	–	3
Immunomodulation	5	4	2	–	11
Neuromodulation	1	–	–	–	1
Radiosensitization	1	–	–	–	1
Tissue destruction	32	19	16	1	68

Neurological—Mechanisms of Action Global Development Landscape

Development stage: ● Preclinical ● Clinical ● Regulatory approval

Ultrasound Applications

Biological effects	Histotripsy	Hyperthermia	Nonthermal	Nonthermal - BBB opening	Thermal ablation
BBB opening	—	—	—	●	—
Clot lysis	—	—	—	—	●
Drug delivery	—	●	●	●	—
Drug delivery, immunotherapeutic	—	●	—	●	—
Drug delivery, vehicle	—	—	●	●	—
Gene delivery	—	—	—	●	—
Immune cell trafficking	—	—	●	—	—
Immodulation	●	—	●	—	●
Increased vascular permeability	—	—	●	—	—
Liquid biopsy	●	—	—	—	—
Neuromodulation	—	—	●	—	●
Radiosensitization	—	●	●	—	—
Sonodynamic therapy	—	—	●	—	—
Sonoporation	—	—	●	—	—
Stem cell delivery	—	—	—	●	—
Tissue destruction	●	●	●	—	●
Vascular occlusion	—	—	●	—	—
Vasodilation	—	—	●	—	—

Emerging mechanisms of action for neurological

In addition to the significant changes in the methods by which the Foundation is tracking mechanisms of action, the 2020 report goes into greater detail on pages II.33–II.47 in examining the development stage of ultrasound applications and biological effects for specific indications in two areas—neurological and oncology. The table above reveals at a glance the predominance of preclinical studies occurring in the neurological research space, making it abundantly clear that, within this body system, the research on mechanisms of action is early stage for the majority of indications. Notably, there is only one mechanism of action—thermal ablation resulting in tissue destruction—with regulatory approval to date.

Neurological—Research by Mechanism of Action, Indication, and Stage

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Histotripsy Immunomodulation				
Glioblastoma	1	–	–	1
Histotripsy Liquid biopsy				
Pontine glioma	1	–	–	1
Histotripsy Tissue destruction				
Epilepsy	1	–	–	1
Glioblastoma	2	–	–	2
Stroke, intracerebral hemorrhage	1	–	–	1
Hyperthermia Drug delivery				
Glioblastoma	1	–	–	1
Neuroblastoma	1	–	–	1
Hyperthermia Drug delivery, immunotherapeutic				
Glioblastoma	1	–	–	1
Hyperthermia Radiosensitization				
Glioblastoma	1	–	–	1
Hyperthermia Tissue destruction				
Essential tremor	–	1	–	1
Nonthermal Drug delivery				
Alzheimer's disease	1	–	–	1
Pontine glioma	1	–	–	1
Stroke, intracerebral hemorrhage	1	–	–	1
Stroke, thromboembolic	2	–	–	2
Nonthermal Drug delivery, vehicle				
Glioblastoma	2	–	–	2
Neuropathic pain	1	–	–	1
Parkinson's disease, underlying cause	1	–	–	1
Neuropathic pain	1	–	–	1
Stroke, intracerebral hemorrhage	2	–	–	2
Stroke, thromboembolic	1	–	–	1

MECHANISMS OF ACTION

Neurological—Research by Mechanism of Action, Indication, and Stage continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Nonthermal Immune cell trafficking				
Glioblastoma	1	–	–	1
Nonthermal Immunomodulation				
Astrocytoma	1	–	–	1
Glioblastoma	4	–	–	4
Multiple sclerosis	1	–	–	1
Nonthermal Increased vascular permeability				
Alzheimer's disease	–	1	–	1
Nonthermal Neuromodulation				
Alzheimer's disease	1	–	–	1
Cancer pain	1	–	–	1
Depression	2	1	–	3
Epilepsy	6	1	–	7
Neuropathic pain	1	1	–	2
Opioid and other addictions	2	2	–	4
Parkinson's disease, tremor	1	–	–	1
Stroke, intracerebral hemorrhage	1	–	–	1
Stroke, thromboembolic	1	–	–	1
Traumatic brain injury	1	–	–	1
Nonthermal Radiosensitization				
Astrocytoma	1	–	–	1
Glioblastoma	2	–	–	2
Nonthermal Sonodynamic therapy				
Glioblastoma	3	–	–	3
Nonthermal Sonoporation				
Stroke, thromboembolic	1	–	–	1
Nonthermal Tissue destruction				
Glioblastoma	1	–	–	1
Nonthermal Vascular occlusion				
Glioblastoma	1	–	–	1

Neurological—Research by Mechanism of Action, Indication, and Stage* continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Nonthermal Vasodilation				
Stroke, thromboembolic	1	–	–	1
Nonthermal - BBB opening BBB opening				
Alzheimer's disease	4	5	–	9
Amyotrophic lateral sclerosis	1	–	–	1
Astrocytoma	–	–	1	1
Dementia	1	–	–	1
Epilepsy	1	–	–	1
Glioblastoma	–	1	–	1
Opioid and other addictions	1	–	–	1
Parkinson's disease, underlying cause	–	1	–	1
Nonthermal - BBB opening Drug delivery				
Alzheimer's disease	7	3	–	10
Amyotrophic lateral sclerosis	1	–	–	1
Astrocytoma	2	–	1	3
Dementia	–	1	–	1
Epilepsy	2	–	–	2
Glioblastoma	13	5	–	18
Multiple sclerosis	1	–	–	1
Neuromyelitis optica	1	–	–	1
Parkinson's disease, underlying cause	6	–	–	6
Pontine glioma	1	–	–	1
Spinal cord injury	2	–	–	2
Stroke, intracerebral hemorrhage	1	–	–	1
Stroke, thromboembolic	2	–	–	2
Traumatic brain injury	1	–	–	1
Nonthermal - BBB opening Drug delivery, immunotherapeutic				
Alzheimer's disease	2	–	–	2
Astrocytoma	1	–	–	1
Glioblastoma	1	–	–	1

*Indications being performed off label in a region are shown in bold italic.

MECHANISMS OF ACTION

Neurological—Research by Mechanism of Action, Indication, and Stage* continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Nonthermal - BBB opening Drug delivery vehicle				
Glioblastoma	1	–	–	1
Nonthermal - BBB opening Gene delivery				
Huntington’s disease	1	–	–	1
Parkinson’s disease, underlying cause	4	–	–	4
Rett syndrome	1	–	–	1
Nonthermal - BBB opening Stem cell delivery				
Alzheimer’s disease	1	–	–	1
Thermal ablation Clot lysis				
Hydrocephalus	1	–	–	1
Thermal ablation Immunomodulation				
Neuroblastoma	1	–	–	1
Thermal ablation Neuromodulation				
Neuropathic pain	–	1	–	1
Parkinson’s disease, dyskinesia	–	1	–	1
Parkinson’s disease, tremor	–	1	–	1
Thermal ablation Tissue destruction				
Alzheimer’s disease	1	–	–	1
Astrocytoma	–	5	1	6
Cancer pain	1	1	1	3
Depression	1	2	–	3
Dystonia	–	3	1	4
Epilepsy	2	5	2	9
Essential tremor	3	17	43	63
Glioblastoma	2	7	–	9
Holmes tremor	–	1	–	1
Huntington’s disease	–	1	–	1
Migraine	1	–	–	1
Neuroblastoma	–	1	–	1
Neuropathic pain	1	2	2	5

*Indications being performed off label in a region are shown in bold italic.

Neurological—Research by Mechanism of Action, Indication, and Stage* continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Thermal ablation Tissue destruction continued				
Obsessive-compulsive disorder	–	1	–	1
Painful amputation neuromas	–	1	–	1
Parkinson’s disease, dyskinesia	–	22	1	23
Parkinson’s disease, tremor	–	3	14	17
Parkinson’s disease, underlying cause	1	–	–	1
Trigeminal neuralgia	–	–	1	1

*Indications being performed off label in a region are shown in bold italic.

Neurological—Ultrasound Application by Indication continued

Indications	Actions					Totals
	Histotripsy	Hyperthermia	Nonthermal	Nonthermal BBB opening	Thermal ablation	
Neurological continued						
Holmes tremor					★	1
Huntington's disease				◆	★	2
Hydrocephalus					★	1
Migraine					★	1
Multiple sclerosis			▲	◆		2
Neuroblastoma		●			★	3
Neuromyelitis optica				◆		1
Neuropathic pain			▲ ▲		★ ★	4
Obsessive-compulsive disorder					★	1
Opioid and other addictions			▲	◆		2
Painful amputation neuromas					★	1
Parkinson's disease, dyskinesia					★ ★	2
Parkinson's disease, tremor			▲		★ ★	3
Parkinson's disease, underlying cause			▲	◆ ◆ ◆	★	5
Pontine glioma	■		▲	◆		3
Rett syndrome				◆		1
Spinal cord injury				◆		1
Stroke, intracerebral hemorrhage	■		▲ ▲ ▲ ▲	◆		5
Stroke, thromboembolic			▲ ▲ ▲ ▲ ▲	◆		6
Traumatic brain injury			▲	◆		2
Trigeminal neuralgia					★	1

- | | | | | |
|--|---|---|--|--|
| <p>Histotripsy</p> <ul style="list-style-type: none"> ■ Immunomodulation ■ Liquid biopsy ■ Tissue destruction <p>Hyperthermia</p> <ul style="list-style-type: none"> ● Drug delivery ● Drug delivery, immunotherapeutic ● Radiosensitization ● Tissue destruction | <p>Nonthermal</p> <ul style="list-style-type: none"> ▲ Drug delivery ▲ Drug delivery, immunotherapeutic ▲ Drug delivery, vehicle ▲ Immune cell trafficking ▲ Immunomodulation ▲ Increased vascular permeability ▲ Neuromodulation | <ul style="list-style-type: none"> ▲ Radiosensitization ▲ Sonodynamic therapy ▲ Sonoporation ▲ Tissue destruction ▲ Vascular occlusion ▲ Vasodilation | <p>Nonthermal - BBB opening</p> <ul style="list-style-type: none"> ◆ BBB opening ◆ Drug delivery ◆ Drug delivery, immunotherapeutic ◆ Drug delivery, vehicle ◆ Gene delivery ◆ Stem cell delivery | <p>Thermal ablation</p> <ul style="list-style-type: none"> ★ Clot lysis ★ Chemosensitization ★ Immunomodulation ★ Neuromodulation ★ Tissue destruction |
|--|---|---|--|--|

Oncology—Mechanisms of Action Global Development Landscape

Development stage: ● Preclinical ● Clinical ● Regulatory approval

Ultrasound Applications

Biological effects	Histotripsy	Hyperthermia	Nonthermal	Nonthermal - BBB opening	Thermal ablation
BBB opening	—	—	—	●	—
Chemosensitization	—	●	—	—	●
Drug delivery	—	●	●	●	—
Drug delivery, immunotherapeutic	—	●	●	●	—
Drug delivery, vehicle	—	●	●	●	—
Gene delivery	—	—	●	—	—
Immune cell trafficking	—	—	●	—	—
Immunomodulation	●	—	●	—	●
Liquid biopsy	●	—	—	—	—
Neuromodulation	—	—	●	—	—
Radiosensitization	—	●	●	—	●
Sonodynamic therapy	—	—	●	—	—
Sonoporation	—	—	●	—	—
Tissue destruction	●	●	●	—	●
Vascular occlusion	—	—	●	—	—

Emerging mechanisms of action for oncology

When we turn from the neurological field, with its preponderance of preclinical studies (page II.32), to the field of oncology, we see a shift to a more even distribution of preclinical studies and clinical trials across a multitude of mechanisms of action. The mechanisms of action research for cancer is developmentally further along, and much of this work is already in the clinical space. But here again, and despite this increased clinical activity, there remains only one mechanism of action with regulatory approval—thermal ablation resulting in tissue destruction.

Oncology—Research by Mechanism of Action, Indication, and Stage*

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Histotripsy Immunomodulation				
Glioblastoma	1	–	–	1
Liver tumors	1	–	–	1
Melanoma	1	–	–	1
Pancreatic tumors	1	–	–	1
Soft tissue cancer	1	–	–	1
Histotripsy Liquid biopsy				
Pontine glioma	1	–	–	1
Histotripsy Tissue destruction				
Biliary tract cancer	2	–	–	2
Glioblastoma	2	–	–	2
Kidney tumors	2	–	–	2
Liver metastases	1	–	–	1
Liver tumors	2	–	–	2
Multiple tumors	1	–	–	1
Pancreatic tumors	2	1	–	3
Prostate cancer	1	–	–	1
Soft tissue cancer	1	–	–	1
Thyroid cancer	1	–	–	1
Hyperthermia Chemosensitization				
Pancreatic tumors	–	1	–	1
Hyperthermia Drug delivery				
Breast cancer	–	1	–	1
Glioblastoma	1	–	–	1
Head & neck tumors	1	–	–	1
Multiple tumors	2	–	–	2
Neuroblastoma	1	–	–	1
Pancreatic tumors	2	2	–	4
Soft tissue cancer	1	1	1	3

*Indications being performed off label in a region are shown in bold italic.

MECHANISMS OF ACTION

Oncology—Research by Mechanism of Action, Indication, and Stage *continued*

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Hyperthermia Drug delivery, immunotherapeutic				
Glioblastoma	1	–	–	1
Hyperthermia Drug delivery, vehicle				
Bone metastases	1	–	–	1
Colorectal tumors	1	–	–	1
Hyperthermia Radiosensitization				
Glioblastoma	1	–	–	1
Head & neck tumors	1	–	–	1
Prostate cancer	1	–	–	1
Hyperthermia Tissue destruction				
Bone metastases	1	–	–	1
Kidney tumors	1	–	–	1
Liver tumors	3	–	–	3
Prostate cancer	1	1	–	2
Nonthermal Drug delivery				
Bladder tumors	1	–	–	1
Bone metastases	1	–	–	1
Liver metastases	1	1	–	2
Liver tumors	1	–	–	1
Pontine glioma	1	–	–	1
Nonthermal Drug delivery, immunotherapeutic				
Pancreatic tumors	1	–	–	1
Nonthermal Drug delivery, vehicle				
Breast cancer	2	–	–	2
Glioblastoma	2	–	–	2
Kidney tumors	1	–	–	1
Liver tumors	–	1	–	1
Pancreatic tumors	2	1	–	3
Prostate cancer	1	–	–	1

Oncology—Research by Mechanism of Action, Indication, and Stage continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Nonthermal Gene delivery				
Breast cancer	1	–	–	1
Prostate cancer	1	–	–	1
Nonthermal Immune cell trafficking				
Glioblastoma	1	–	–	1
Nonthermal Immunomodulation				
Astrocytoma	1	–	–	1
Breast cancer	1	–	–	1
Glioblastoma	4	–	–	4
Pancreatic tumors	1	–	–	1
Nonthermal Neuromodulation				
Cancer pain	1	–	–	1
Nonthermal Radiosensitization				
Astrocytoma	1	–	–	1
Glioblastoma	2	–	–	2
Nonthermal Sonodynamic therapy				
Biliary tract cancer	–	1	–	1
Glioblastoma	3	–	–	3
Pancreatic tumors	2	–	–	2
Nonthermal Sonoporation				
Head & neck tumors	1	–	–	1
Liver metastases	–	1	–	1
Liver tumors	–	1	–	1
Pancreatic tumors	1	2	–	3
Nonthermal Tissue destruction				
Breast cancer	2	–	–	2
Glioblastoma	1	–	–	1
Head & neck tumors	1	–	–	1
Liver metastases	1	–	–	1
Liver tumors	1	–	–	1
Pancreatic tumors	3	–	–	3

MECHANISMS OF ACTION

Oncology—Research by Mechanism of Action, Indication, and Stage* continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Nonthermal Tissue destruction <i>continued</i>				
Prostate cancer		2	–	2
Soft tissue cancer		1	–	1
Nonthermal Vascular occlusion				
Glioblastoma		1	–	1
Nonthermal - BBB opening				
Astrocytoma		–	–	1
Glioblastoma		–	1	1
Nonthermal - BBB opening Drug delivery				
Astrocytoma		2	–	1
Brain metastases, breast cancer		2	1	3
Glioblastoma		13	5	18
Pontine glioma		1	–	1
Nonthermal - BBB opening Drug delivery, immunotherapeutic				
Astrocytoma		1	–	1
Glioblastoma		1	–	1
Nonthermal - BBB opening Drug delivery, vehicle				
Glioblastoma		1	–	1
Thermal ablation Chemosensitization				
Bone metastases		–	1	1
Thermal ablation Immunomodulation				
Breast cancer		4	–	4
Melanoma		1	–	1
Multiple tumors		1	1	2
Neuroblastoma		1	–	1
Pancreatic tumors		4	–	4
Soft tissue cancer		1	1	2
Thermal ablation Radiosensitization				
Head & neck tumors		–	1	1

*Indications being performed off label in a region are shown in bold italic.

Oncology—Research by Mechanism of Action, Indication, and Stage* continued

	Stages			Totals
	Preclinical	Clinical	Commercial	
Ultrasound application Biological effects				
Thermal ablation Tissue destruction				
Astrocytoma	–	5	1	6
Bone cancer	–	6	5	11
Bone metastases	1	17	30	48
Breast cancer	3	8	96	107
Cancer pain	1	1	1	3
Cervical tumors	1	2	–	3
Colorectal tumors	–	1	–	1
Endometrial tumors	–	1	1	2
Glioblastoma	2	7	–	9
Head & neck tumors	–	2	–	2
Kidney tumors	3	3	96	102
Liver metastases	2	2	4	8
Liver tumors	5	5	100	110
Lung cancer	2	–	–	2
Lung metastases	1	1	–	2
Multiple tumors	1	–	–	1
Neuroblastoma	–	1	–	1
Ovarian tumors	–	1	–	1
Pancreatic tumors	5	6	8	19
Prostate cancer	3	45	262	310
Sacral chordoma	–	2	–	2
Soft tissue cancer	–	5	2	7
Vaginal tumors	–	2	–	2

From a commercial standpoint, the most widely utilized mechanism of action in focused ultrasound cancer treatments has been thermal ablation, causing tissue destruction of prostate cancer, liver tumors, breast cancer, and kidney tumors.

*Indications being performed off label in a region are shown in bold italic

MECHANISMS OF ACTION

Oncology—Ultrasound Application by Indication

Indications	Actions					Totals
	Histotripsy	Hyperthermia	Nonthermal	Nonthermal BBB opening	Thermal ablation	
Oncology						
Astrocytoma			▲▲	◆◆◆	★	6
Biliary tract cancer	■		▲			2
Bladder tumors			▲			1
Bone cancer					★	1
Bone metastases		●●	▲		★★	5
Brain metastases, breast cancer				◆		1
Breast cancer		●	▲▲▲▲		★★	7
Cancer pain			▲		★	2
Cervical tumors					★	1
Colorectal tumors		●			★	2
Endometrial tumors					★	1
Glioblastoma	■■	●●●	▲▲▲▲▲ ▲▲▲	◆◆◆◆	★	17
Head & neck tumors		●●	▲▲		★★	6
Kidney tumors	■	●	▲		★	4
Liver metastases	■		▲▲▲		★	5
Liver tumors	■■	●	▲▲▲▲		★	8
Lung cancer					★	1
Lung metastases					★	1
Melanoma	■				★	2
Multiple tumors	■	●			★★	4
Neuroblastoma		●			★★	3
Ovarian tumors					★	1

<p>Histotripsy</p> <ul style="list-style-type: none"> ■ Immunomodulation ■ Liquid biopsy ■ Tissue destruction <p>Hyperthermia</p> <ul style="list-style-type: none"> ● Chemosensitization ● Drug delivery ● Drug delivery, immunotherapeutic ● Drug delivery, vehicle ● Radiosensitization ● Tissue destruction 	<p>Nonthermal</p> <ul style="list-style-type: none"> ▲ Drug delivery ▲ Drug delivery, immunotherapeutic ▲ Drug delivery, vehicle ▲ Gene delivery ▲ Immune cell trafficking ▲ Immunomodulation ▲ Neuromodulation ▲ Radiosensitization ▲ Sonodynamic therapy 	<ul style="list-style-type: none"> ▲ Sonoporation ▲ Tissue destruction ▲ Vascular occlusion 	<p>Nonthermal - BBB opening</p> <ul style="list-style-type: none"> ◆ BBB opening ◆ Drug delivery ◆ Drug delivery, immunotherapeutic ◆ Drug delivery, vehicle 	<p>Thermal ablation</p> <ul style="list-style-type: none"> ★ Chemosensitization ★ Immunomodulation ★ Neuromodulation ★ Radiosensitization ★ Tissue destruction
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Oncology—Ultrasound Application by Indication *continued*

Indications	Actions					Totals
	Histotripsy	Hyperthermia	Nonthermal	Nonthermal BBB opening	Thermal ablation	
Oncology <i>continued</i>						
Pancreatic tumors	■ ■	● ●	▲ ▲ ▲ ▲		★ ★	12
Pontine glioma	■		▲ ▲ ▲	◆		3
Prostate cancer	■	● ●	▲ ▲ ▲		★	7
Sacral chordoma					★	1
Soft tissue cancer	■ ■	●	▲		★ ★	6
Thyroid cancer	■					1
Vaginal tumors					★	1

Mechanisms of action for pancreatic cancer

Pancreatic cancer, like glioblastoma, is a devastating diagnosis with survival generally measured in months after initial diagnosis, even when patients receive the best standard-of-care treatment. It is not surprising to see that, on a global scale, pancreatic tumor research is investigating multiple mechanisms of action, each one representing hopes for a breakthrough in care.

<p>Histotripsy</p> <ul style="list-style-type: none"> ■ Immunomodulation ■ Liquid biopsy ■ Tissue destruction <p>Hyperthermia</p> <ul style="list-style-type: none"> ● Chemosensitization ● Drug delivery ● Drug delivery, immunotherapeutic ● Drug delivery, vehicle ● Gene delivery ● Immune cell trafficking ● Immunomodulation ● Neuromodulation ● Radiosensitization ● Sonodynamic therapy 	<p>Nonthermal</p> <ul style="list-style-type: none"> ▲ Drug delivery ▲ Drug delivery, immunotherapeutic ▲ Drug delivery, vehicle ▲ Gene delivery ▲ Immune cell trafficking ▲ Immunomodulation ▲ Neuromodulation ▲ Radiosensitization ▲ Sonodynamic therapy 	<ul style="list-style-type: none"> ▲ Sonoporation ▲ Tissue destruction ▲ Vascular occlusion 	<p>Nonthermal - BBB opening</p> <ul style="list-style-type: none"> ◆ BBB opening ◆ Drug delivery ◆ Drug delivery, immunotherapeutic ◆ Drug delivery vehicle 	<p>Thermal ablation</p> <ul style="list-style-type: none"> ★ Chemosensitization ★ Immunomodulation ★ Neuromodulation ★ Radiosensitization ★ Tissue destruction
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Centers of Excellence Research

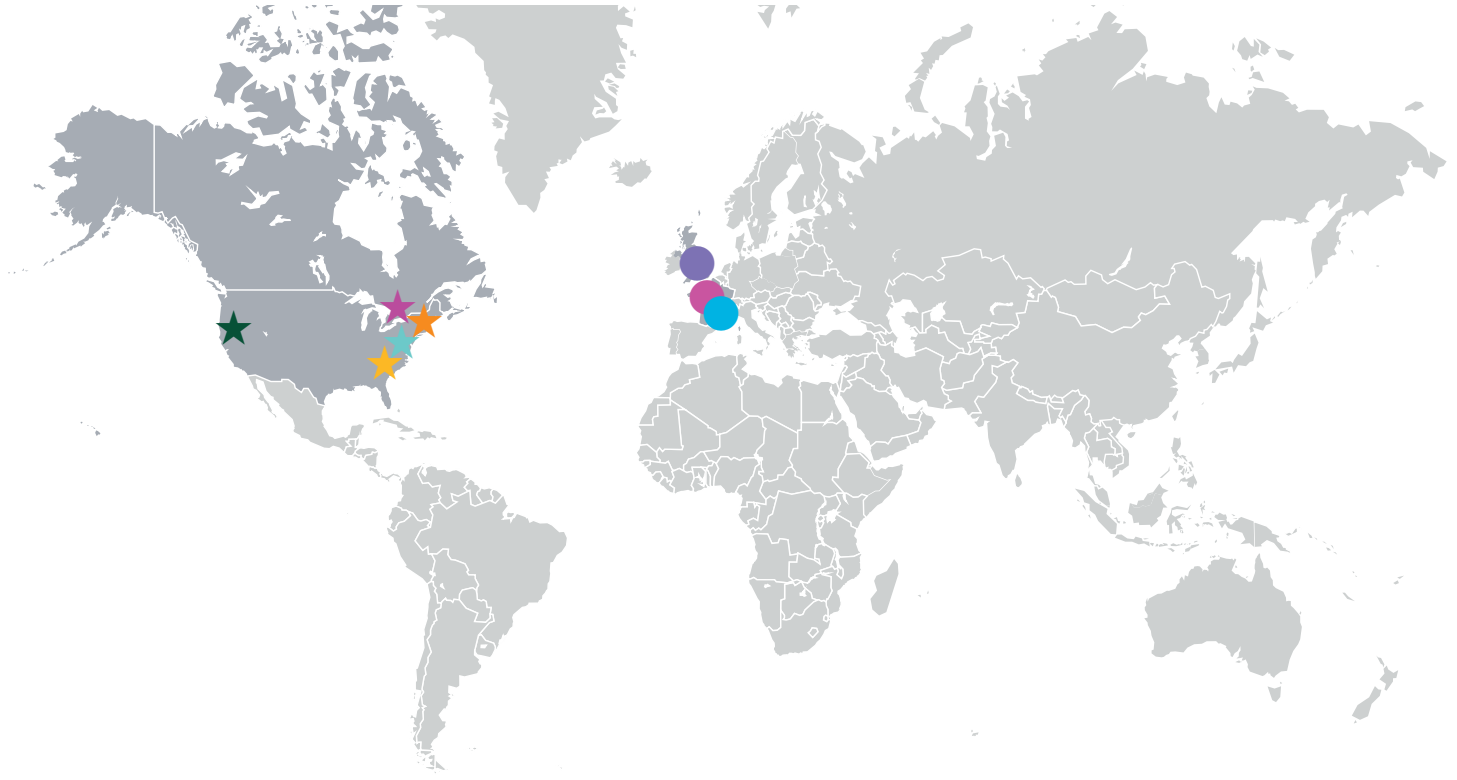
The eight research/treatment sites that we highlight in this report are the Focused Ultrasound Foundation-designated Centers of Excellence (COE). They are also listed on our website for the sake of consistency.

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 2019, they collectively published 156 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 create 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 the sites if you're interested in a potential collaboration.

As stated in the overview, this portion of the *2020 State of the Field Report* contains a summary of self-reported data from the COEs. We no longer include information on individual treatment and/or research sites. This change was made in 2018; interested individuals are now referred to the www.fusfoundation.org website, where all site-specific information is now stored and updated in real time.

Centers of Excellence		
Name	Location	Established
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

Centers of Excellence Research continued

**North America**

- ★ Brigham and Women's Hospital
- ★ Stanford University School of Medicine
- ★ Sunnybrook Health Sciences Centre
- ★ University of Maryland School of Medicine
- ★ University of Virginia Health System

Europe

- Inserm - LabTAU
- The Institute of Cancer Research and The Royal Marsden
- Physics for Medicine Paris

Centers of Excellence Research continued

Physics for Medicine Paris

3

Preclinical Research

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Mechanisms of Action Research

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Technical Research

1

Clinical Research

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Publications

Physics for Medicine Paris | Paris, France

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

Contacts

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Clinical research

Neurological Essential tremor

Preclinical research

Cardiovascular Heart valve calcifications

Neurological Depression, Essential tremor

Mechanisms of action research

Histotripsy Tissue destruction

Nonthermal BBB opening, drug delivery; Drug delivery, vehicle; 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, Tissue destruction

Preclinical research - Neurological

Depression Nonthermal, Neuromodulation

Centers of Excellence Research continued

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Centers of Excellence Research continued

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Centers of Excellence Research continued

Inserm - LabTAU

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Preclinical Research

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Mechanisms of Action
Research

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Commercial Treatment

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Clinical Research

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Technical Research

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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 COE. LabTAU conducts significant translational and clinical research with a multidisciplinary, highly qualified, and complementary team of physicians and scientists. The Center of Excellence has special expertise in commercializing technology and creating strategic interfaces between engineering and medicine.

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Commercial treatment

Urological Prostate cancer, *Hôpital Edouard Herriot*

Clinical research

Gastrointestinal	Liver metastases, <i>Centre Léon Bérard</i>
Neurological	Glioblastoma, <i>Hôpitaux Universitaires Pitié-Salpêtrière & Hôpital Pierre Wertheimer</i>
Urological	Prostate cancer, <i>Hôpital Edouard Herriot</i>
Women's health	Endometriosis, colorectal, <i>Hôpital Croix-Rousse</i>

Preclinical research

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

Mechanisms of action research

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

Centers of Excellence Research continued

Research not involving thermal ablation, tissue destruction

Preclinical research - Neurological

Glioblastoma	Nonthermal, BBB opening, drug delivery
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Preclinical research - Cardiovascular

Twin-twin transfusion syndrome	Nonthermal, Vascular occlusion
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Varicose veins	Thermal ablation, Hemostasis
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Preclinical research - Gastrointestinal

Pancreatic tumors	Nonthermal, Sonodynamic therapy
	Nonthermal, Tissue destruction
	Thermal ablation, Immunomodulation

Preclinical research - Neurological

Cancer pain	Nonthermal, Neuromodulation
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Glioblastoma	Nonthermal, BBB opening, drug delivery
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Stroke, thromboembolic	Nonthermal, BBB opening, drug delivery
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Preclinical research - Women's health

Breast cancer	Nonthermal, Immunomodulation
	Nonthermal, Tissue destruction

Publications

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Centers of Excellence Research continued

Publications continued

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Centers of Excellence Research continued

Stanford University School of Medicine

6

Preclinical Research

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Mechanisms of Action Research

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Commercial Treatment

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Clinical Research

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Technical Research

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Publications

Stanford University School of Medicine | Stanford, CA

Stanford's COE was established in 2016 and focuses on a number of 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 referenceless 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.

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Veterinary Research

Stanford University School of Medicine | Stanford, CA

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.

Contacts

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Commercial treatments

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

Clinical research

Musculoskeletal	Osteoid osteoma
Neurological	Parkinson's disease, dyskinesia
Urological	Prostate cancer

Preclinical research

Gastrointestinal	Pancreatic tumors
Neurological	Epilepsy, Glioblastoma, Neuropathic pain
Urological	Acute kidney injury
Women's health	Breast cancer

Veterinary research

Gastrointestinal	Liver tumors
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Centers of Excellence Research continued

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

Research not involving thermal ablation, tissue destruction

Preclinical research - Gastrointestinal

Pancreatic tumors	Thermal ablation, Immunomodulation
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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
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Preclinical research - Women's health

Breast cancer	Nonthermal, Gene delivery
	Thermal ablation, Immunomodulation

Veterinary research - Gastrointestinal

Liver tumors	Nonthermal, Drug delivery, vehicle
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Centers of Excellence Research continued

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Centers of Excellence Research continued

Sunnybrook Health Sciences Centre

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Preclinical Research

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Mechanisms of Action Research

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Commercial Treatment

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Clinical Research

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Technical Research

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Publications

Sunnybrook Health Sciences Centre | Toronto, Canada

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

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Commercial treatment

Neurological Essential tremor

Clinical research

Miscellaneous Head & neck tumors

Musculoskeletal Bone cancer

Neurological Alzheimer's disease, Depression, Essential tremor, Glioblastoma, Obsessive-compulsive disorder

Women's health Brain metastases, breast cancer; Uterine fibroids

Preclinical research

Cardiovascular Atrial fibrillation, Deep vein thrombosis

Gastrointestinal Colorectal tumors, Liver metastases, Liver tumors

Musculoskeletal Bone metastases

Neurological Alzheimer's disease; Amyotrophic lateral sclerosis; Depression; Epilepsy; Glioblastoma; Parkinson's disease, underlying cause; Spinal cord injury; Stroke, intracerebral hemorrhage; Stroke, thromboembolic

Women's health Brain metastases, breast cancer; Breast cancer

Mechanisms of action research

Hyperthermia Drug delivery, Radiosensitization

Nonthermal BBB opening; BBB opening, drug delivery; Chemosensitization; Drug delivery; Drug delivery, immunotherapeutic; Neuromodulation; Sonoporation; Stem cell delivery; Vascular occlusion

Thermal ablation Clot lysis, Immune cell trafficking, Tissue destruction

Centers of Excellence Research continued

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 - Neurological

Alzheimer's disease	Nonthermal, BBB opening, drug delivery
Glioblastoma	Nonthermal, BBB opening, drug delivery

Clinical research - Women's health

Brain metastases, breast cancer	Nonthermal, BBB opening, drug delivery
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Preclinical research - Gastrointestinal

Liver metastases	Nonthermal, Drug delivery
Liver tumors	Nonthermal, Drug delivery

Preclinical research - Neurological

Alzheimer's disease	Nonthermal, BBB opening, drug delivery
Amyotrophic lateral sclerosis	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 - Women's health

Brain metastases, breast cancer	Nonthermal, BBB opening, drug delivery
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Publications continued

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Centers of Excellence Research continued

Publications continued

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Centers of Excellence Research continued

University of Maryland School of Medicine

4

Preclinical Research

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Mechanisms of Action
Research

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Commercial Treatment

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Clinical Research

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Technical Research

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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 investigation of cell systems to animal models and human clinical trials.

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Commercial treatment

Neurological Astrocytoma, Essential tremor

Clinical research

Neurological Astrocytoma; Essential tremor; Glioblastoma;
Neuropathic pain; Parkinson's disease, dyskinesia

Preclinical research

Neurological Astrocytoma, Epilepsy, Glioblastoma,
Traumatic brain injury

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

Centers of Excellence Research continued

Research not involving thermal ablation, tissue destruction

Commercial treatment - Neurological

Astrocytoma	Nonthermal, BBB opening Nonthermal, BBB opening, drug delivery
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Clinical research - Neurological

Glioblastoma	Nonthermal, BBB opening Nonthermal, BBB opening, drug delivery
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Neuropathic pain	Thermal ablation, Neuromodulation
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Parkinson's disease, dyskinesia	Thermal ablation, Neuromodulation
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Preclinical research - Neurological

Astrocytoma	Nonthermal, BBB opening, drug delivery Nonthermal, BBB opening, drug delivery, immunotherapeutic Nonthermal, Immunomodulation Nonthermal, Radiosensitization
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Epilepsy	Nonthermal, Neuromodulation
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Glioblastoma	Nonthermal, Immune cell trafficking Nonthermal, Immunomodulation
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Traumatic brain injury	Nonthermal, Neuromodulation
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Publications

Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. Halpern CH, Santini V, Lipsman N, Lozano AM, Schwartz ML, Shah BB, Elias WJ, Cosgrove GR, Hayes MT, McDannold N, Aldrich C, Eisenberg HM, Gandhi D, Taira T, Gwinn R, Ro S, Witt J, Jung NY, Chang JW, Rosenberg J, Ghanouni P. *Neurology*. 2019 Dec 10;93(24):e2284-e2293. doi: 10.1212/WNL.0000000000008561. Epub 2019 Nov 20. PubMed PMID: 31748250..

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Centers of Excellence Research continued

Brigham and Women's Hospital

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Preclinical Research

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Mechanisms of Action
Research

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Commercial Treatment

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Clinical Research

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Technical Research

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Publications

Brigham and Women's Hospital | Boston, MA

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

Contacts

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Commercial treatments

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

Clinical research

Neurological	Glioblastoma; Parkinson's disease, dyskinesia
Urological	Prostate cancer

Preclinical research

Neurological	Alzheimer's disease; Epilepsy; Glioblastoma; Huntington's disease; Parkinson's disease, tremor
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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

Centers of Excellence Research continued

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Focused Ultrasound Strategies for Brain Tumor Therapy. Bunevicius A, McDannold NJ, Golby AJ. *Oper Neurosurg* (Hagerstown). 2019 Dec 19. pii: opz374. doi: 10.1093/ons/opz374. [Epub ahead of print] PubMed PMID: 31853548.

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Centers of Excellence Research continued

ICR and The Royal Marsden

6

Preclinical Research

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Mechanisms of Action
Research

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Commercial Treatment

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Clinical Research

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Technical Research

8

Publications

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

In 2013, the Focused Ultrasound Foundation and Philips entered into an innovative public-private collaboration with the Institute of Cancer Research (ICR) and The Royal Marsden NHS (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.

Contact

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Commercial treatment

Neurological Cancer pain

Clinical research

Musculoskeletal Bone cancer, Soft tissue cancer

Neurological Cancer pain

Preclinical research

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

Mechanisms of action research

Histotripsy	Tissue destruction
Hyperthermia	Drug delivery, Radiosensitization
Nonthermal	Chemosensitization; Drug delivery; Drug delivery, immunotherapeutic; issue 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

Centers of Excellence Research 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

Publications

Focused Ultrasound-Mediated Hyperthermia in Vitro: An Experimental Arrangement for Treating Cells under Tissue-Mimicking Conditions. Brüningk SC, Rivens I, Mouratidis P, ter Haar G. *Ultrasound Med Biol.* 2019 Dec;45(12):3290-3297. doi: 10.1016/j.ultrasmedbio.2019.06.410. Epub 2019 Sep 26. PubMed PMID: 31500898; PubMed Central PMCID: PMC6878221.

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Publications continued

MR guided high intensity focused ultrasound (MRgHIFU) for treating recurrent gynaecological tumours: a pilot feasibility study. Giles SL, Imseeh G, Rivens I, ter Haar GR, Taylor A, deSouza NM. *Br J Radiol.* 2019 Jun;92(1098):20181037. doi: 10.1259/bjr.20181037. Epub 2019 May 14. PubMed PMID: 31084495; PubMed Central PMCID: PMC6592075.

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In Memoriam: Peter NT Wells. Halliwell M, ter Haar GR, Holland CK. (1936–2017) Editor in Chief, *Ultrasound in Medicine and Biology* (1994–2006). *Ultrasound in Medicine and Biology.* 2019 May 1;45(5):1023-4.

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Centers of Excellence Research continued

University of Virginia Health System

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Preclinical Research

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Mechanisms of Action Research

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Commercial Treatment

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Clinical Research

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Technical Research

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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 is a leading site for brain research, having pioneered clinical trials for essential tremor and Parkinsonian tremor, as well as technical and preclinical studies for neurological disorders. The center also treats uterine fibroids and bone metastases, conducts cancer research, and is currently spearheading the world's first clinical trial combining focused ultrasound and immunotherapy.

Contacts

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Commercial treatments

Neurological Essential tremor

Women's health Uterine fibroids

Clinical research

Miscellaneous Multiple tumors

Neurological Epilepsy; Neuropathic pain; Parkinson's disease, dyskinesia

Women's health Breast cancer, Breast fibroadenoma

Preclinical research

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

Mechanisms of action research

Histotripsy	Tissue destruction
Hyperthermia	Drug delivery
Nonthermal	Angiogenesis; BBB opening; BBB opening, drug delivery; 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	Clot lysis, Tissue destruction

Technical research

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

Centers of Excellence Research continued

Research not involving thermal ablation, tissue destruction

Clinical research - Miscellaneous

Multiple tumors	Nonthermal, Immunomodulation
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Preclinical research - Cardiovascular

Arteriovenous malformations	Nonthermal, Tissue destruction
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Peripheral artery disease	Nonthermal, Drug delivery, vehicle
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Preclinical research - Gastrointestinal

Pancreatic tumors	Thermal ablation, Immunomodulation
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Preclinical research - Miscellaneous

Melanoma	Thermal ablation, Immunomodulation
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Preclinical research - Neurological

Epilepsy	Nonthermal, BBB opening, drug delivery Nonthermal, Neuromodulation
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Glioblastoma	Nonthermal, Drug delivery, vehicle
	Nonthermal, Immunomodulation
	Nonthermal, Radiosensitization
	Nonthermal, Sonodynamic therapy
	Nonthermal, Vascular occlusion

Parkinson's disease, underlying causes	Nonthermal, BBB opening, drug delivery
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Stroke, thromboembolic	Nonthermal, Sonoporation
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Preclinical research - Women's health

Breast cancer	Thermal ablation, Immunomodulation
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Publications

American Society for Stereotactic and Functional Neurosurgery Position Statement on Magnetic Resonance-Guided Focused Ultrasound for the Management of Essential Tremor. Pouratian N, Baltuch G, Elias WJ, Gross R. *Neurosurgery*. 2019 Dec 12. pii: nyz510. doi: 10.1093/neuros/nyz510. [Epub ahead of print] PubMed PMID: 31832649.

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Centers of Excellence Research continued

Publications continued

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FUS Veterinary Applications

Introduction

Veterinary medicine offers a unique opportunity to expand research and commercial applications of focused ultrasound 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 treat tissue noninvasively and enhance the efficacy of some therapies, thus reducing the length of hospital stays and total cost of treatment, is a crucial benefit for pet owners who pay out of pocket.

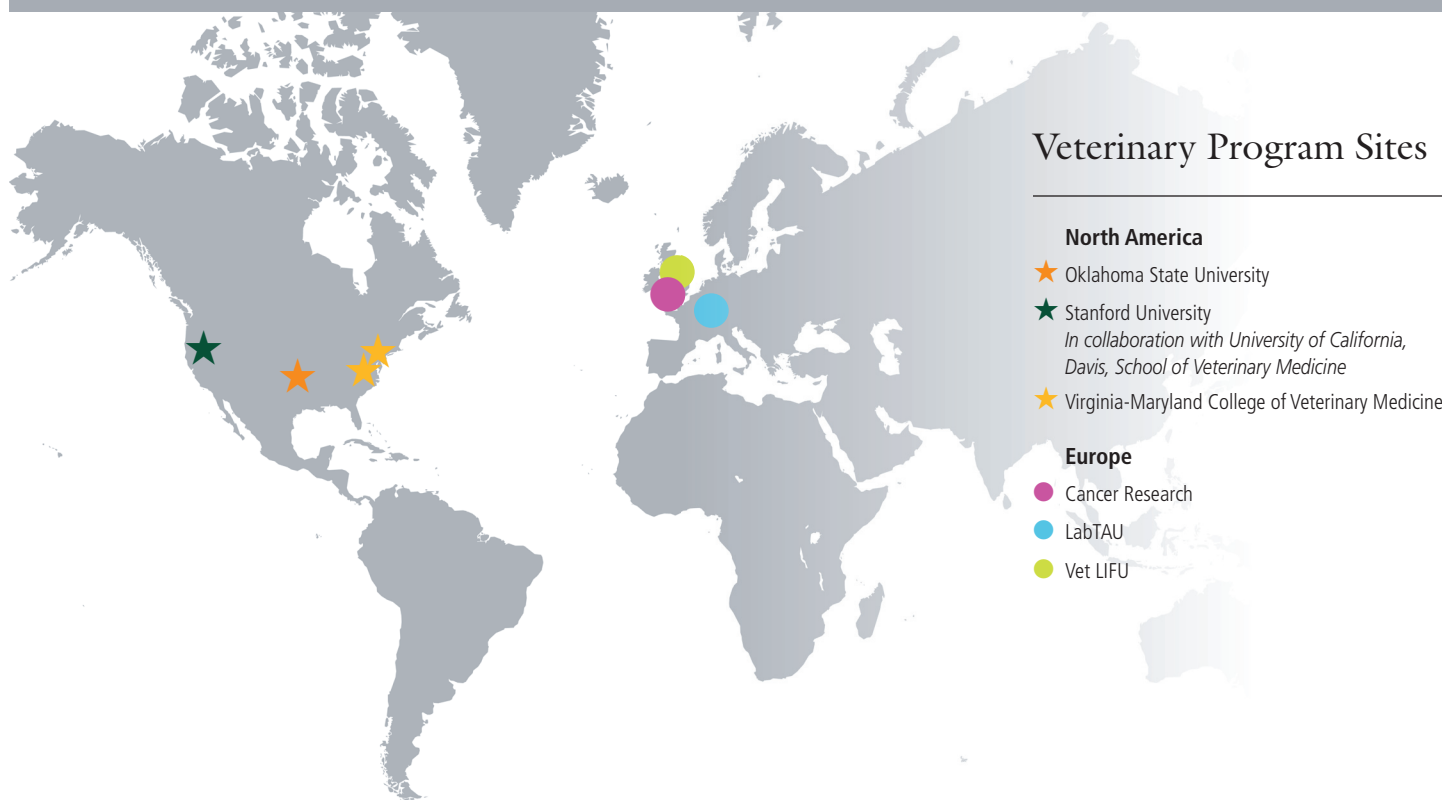
Currently, the most promising focused ultrasound applications in veterinary medicine are in the fields of oncology and pain management.

In addition to ablating tumor tissue and enhancing the efficacy of chemo- and immunotherapies, preclinical and human

clinical data suggest that focused ultrasound can induce a potent antitumor immune response. This is of particular interest in the case of animals with metastatic disease or those who are not good surgical candidates. Patients with partially resected, recurrent, or surgically inaccessible tumors are also ideal candidates for treatment with focused ultrasound.

Focused ultrasound also shows great promise in the management of osteoarthritis, soft tissue injury, and elbow/hip dysplasia. Treatment can enhance blood flow to the damaged tissue, enhancing healing and reducing scar formation. Focused ultrasound can also be used to ablate nerve tissue noninvasively, relieving pain in advanced arthritis.

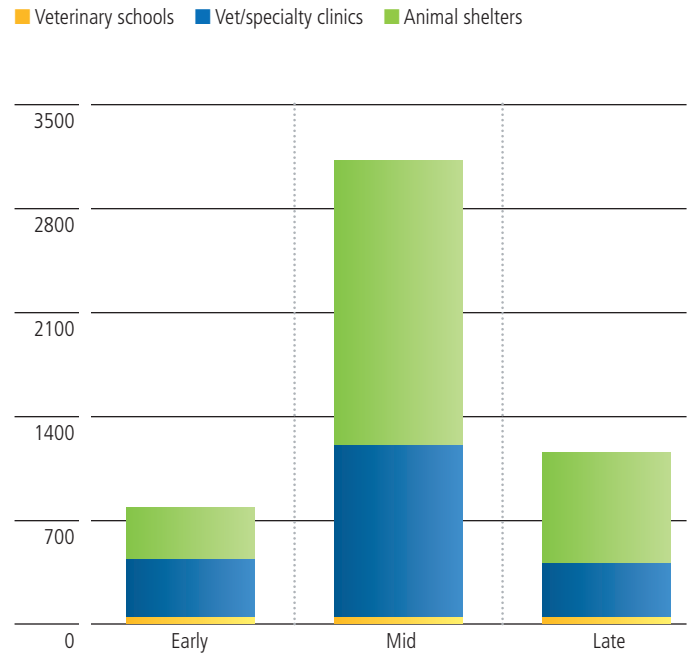
For more information visit:
www.fusfoundation.org/for-researchers/high-priorityresearch-areas/veterinary-program.



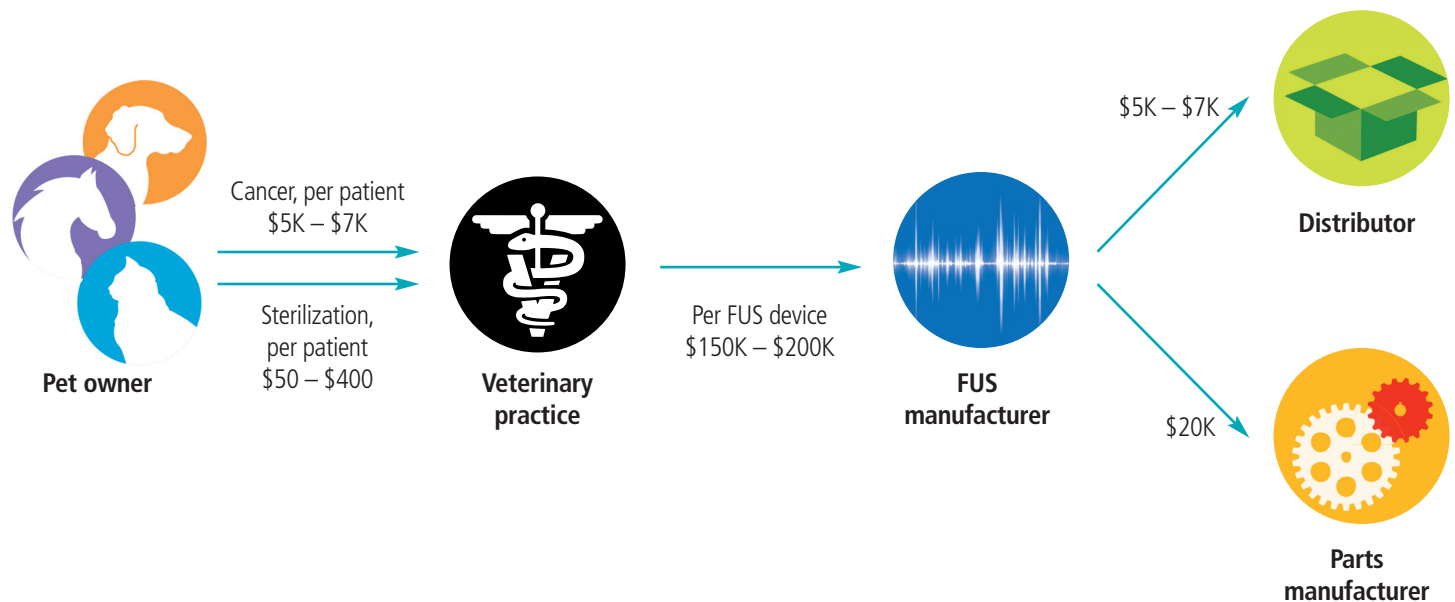
Proposed Market and Value Chain

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.

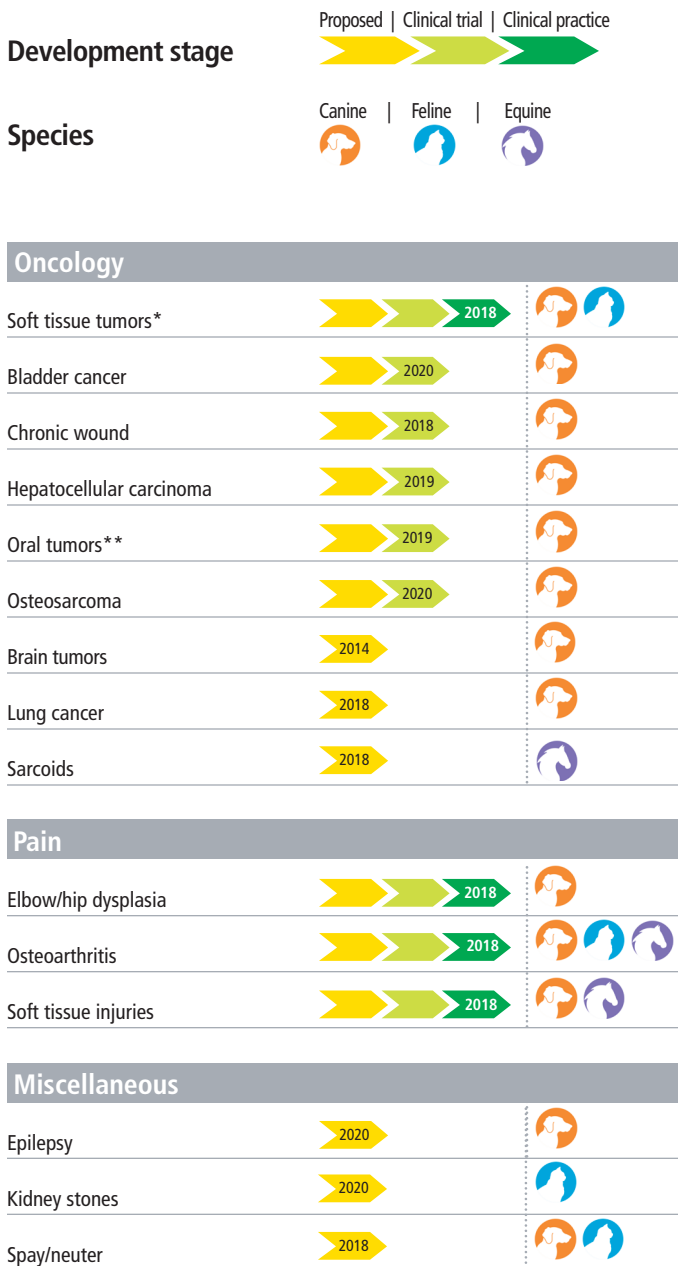
Adopters Market



Value Chain



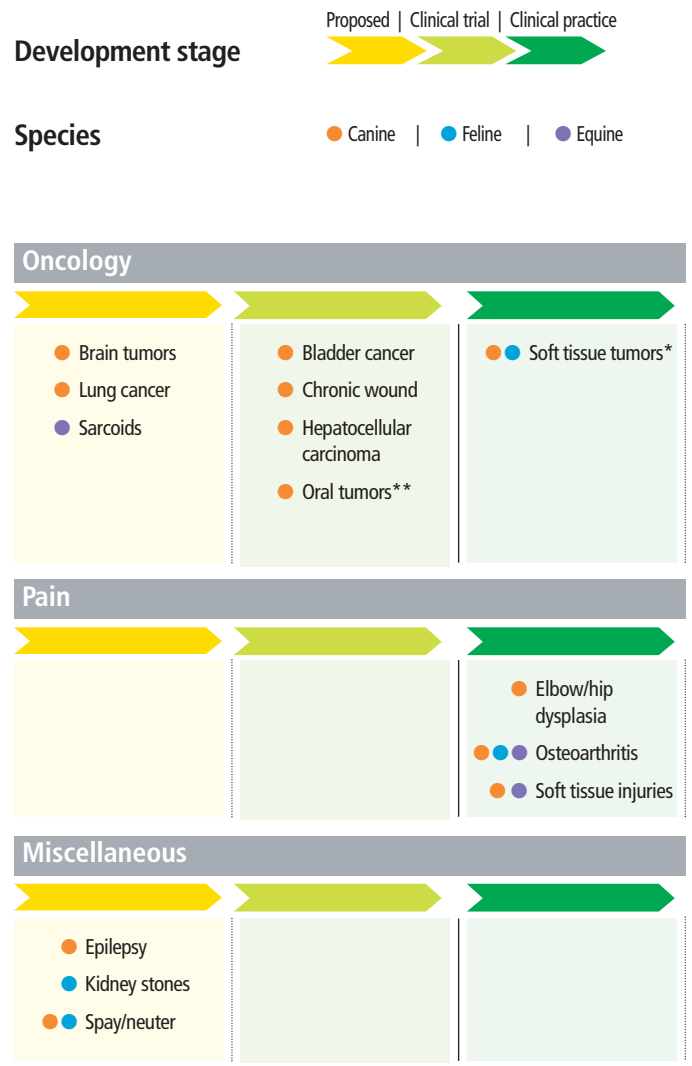
State of Research by Indication



*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).

Development Landscape

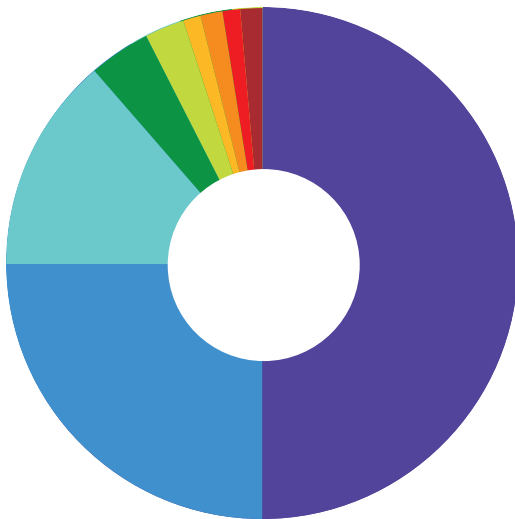


Treated Patients by Indication

Cummulative

81 total treatments

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



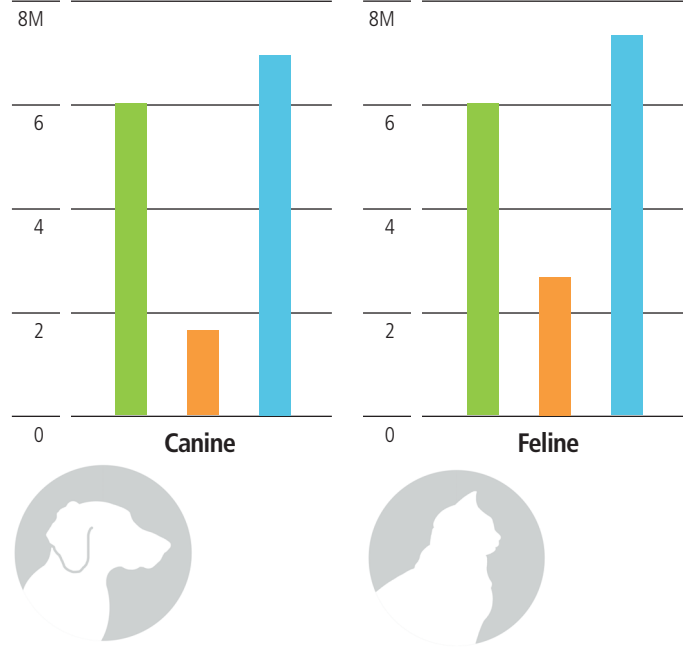
*Soft tissue tumors includes soft tissue sarcoma and mast cell tumors.

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

Projected Patient Base

Millions per year in US

■ Cancer ■ Elbow/hip dysplasia/osteoarthritis ■ Spay/neuter



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

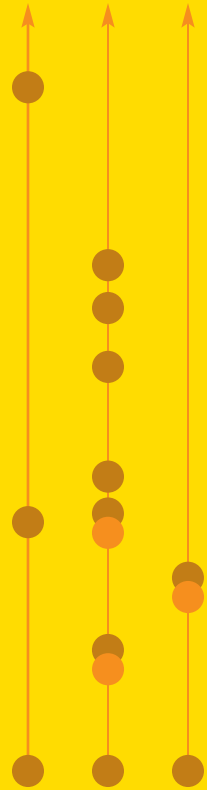
2020

State of Commercialization



76.9m

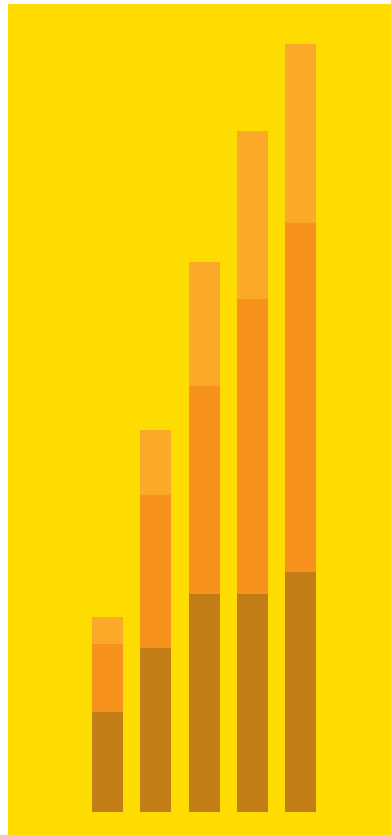
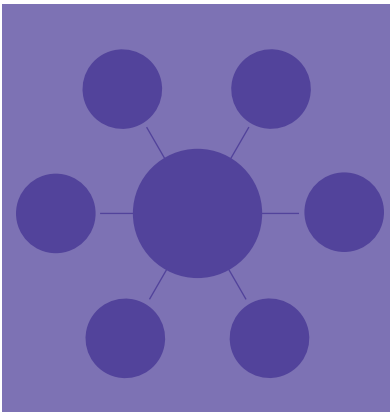
have insurance coverage for
bone metastases
in the US



33

indications with
regulatory approvals

120m
have insurance coverage for
bone metastases
in the US



50
clinical device
manufacturers



22.8m
have insurance coverage for
prostate cancer
in the US



\$112m
FUS industry investment
in 2019



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.

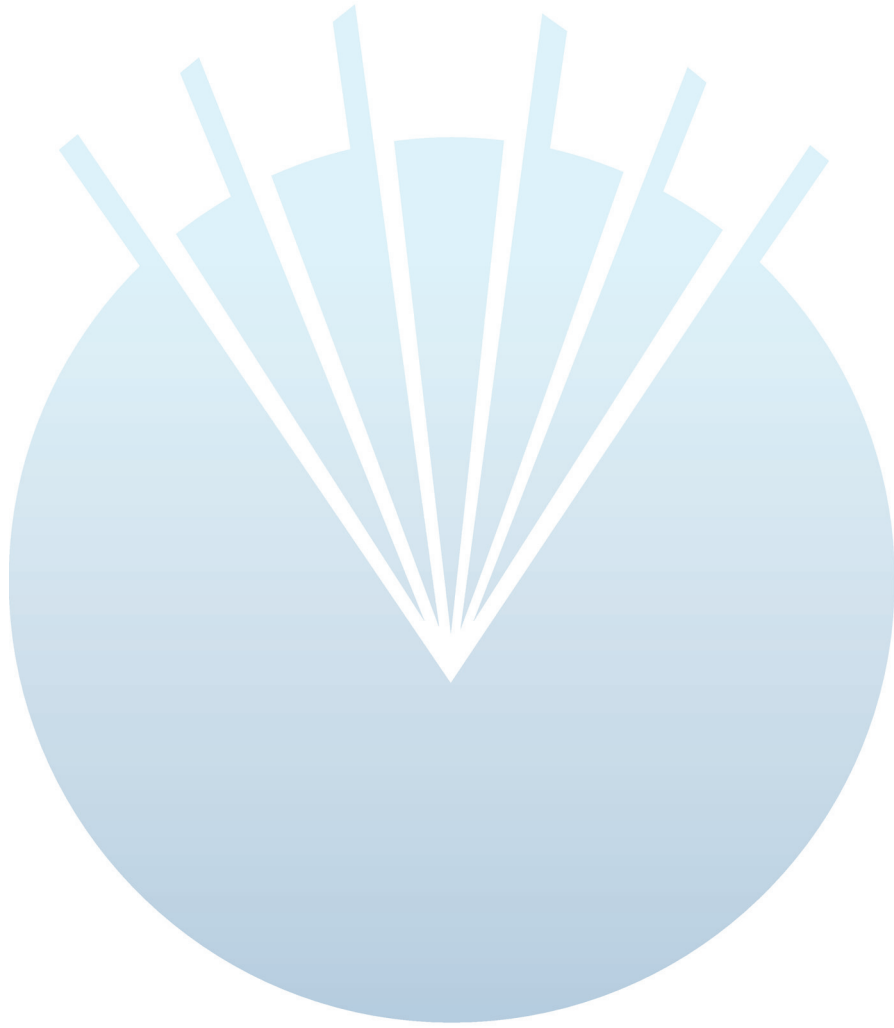
Additionally, we are seeing increasing evidence that the field is now transitioning from primarily a science-based research environment to a commercialization and patient treatment space focused on marketing and sales. As this transition continues to occur, we want to keep pace with the different data points and metrics needed to understand and evaluate this global commercialization in order to accurately analyze the information and disseminate our findings to all stakeholders. This section reflects an expansion from previous years and contains an in-depth analysis of regulatory approvals. We have reorganized previous years' data by geographic regions and provided more detail on each company working in the focused ultrasound space.

16

companies
have regulatory approvals

3

indications
with
US reimbursement



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FUS Partners Role in the Industry

In order to help accelerate the transition of the field from a primarily science-based research environment to a commercialization and patient treatment space 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 significantly and effectively advance the field by identifying commercial opportunities, making connections between stakeholders, and enhancing the flow of information between strategic and financial investors and FUS companies.

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 FUS 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 with respect to 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 preparing investor relations materials
- Support FUS companies in attracting and hiring talent

Strategic Partnerships & Technology Transfer

- Connect manufacturers with other manufacturers of FUS and related equipment and components, academic research laboratories, and strategic sponsors

Advocacy

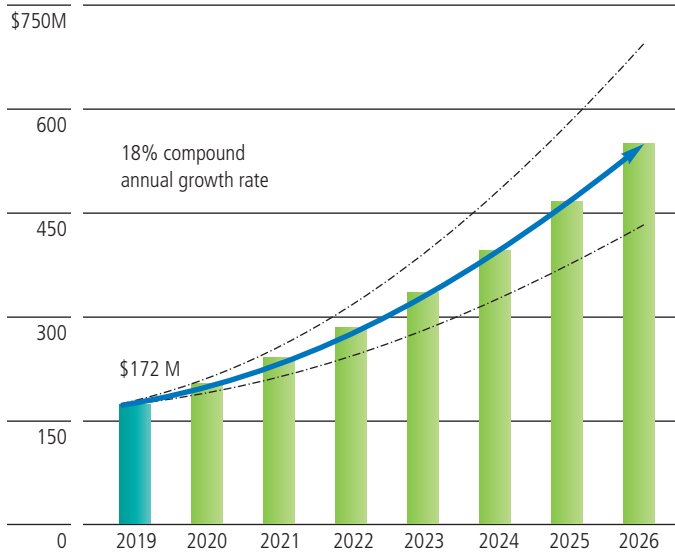
- Inform regulatory agencies, payers, and MedTech advocacy organizations about FUS
- Monitor clinical trials and potentially decrease cost of care while improving quality
- Connect and engage FUS manufacturers with advocacy organizations

Intellectual Property

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

FUS Market Projection

Revenue in millions of dollars

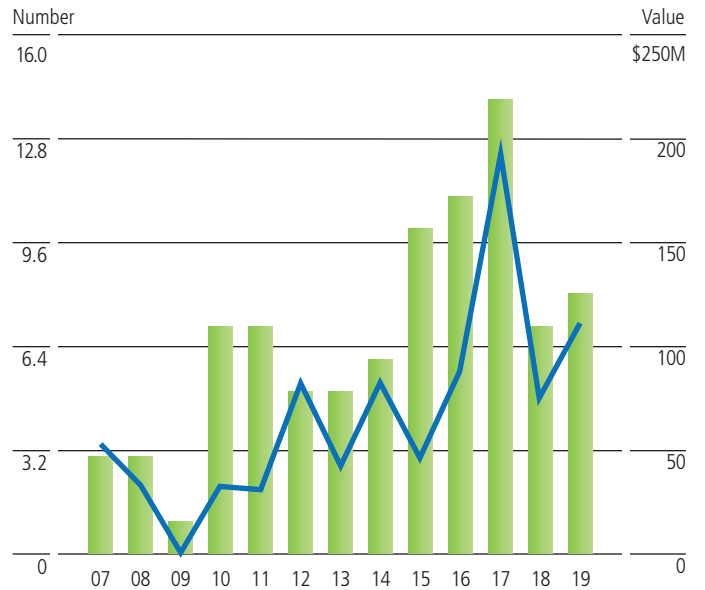


Market value and growth rate estimates were compiled from the following websites:

- [a2zmarketresearch.com/data/Global-High-Intensity-Focused-Ultrasound-\(HIFU\)-Market-Report-2019/72503](https://a2zmarketresearch.com/data/Global-High-Intensity-Focused-Ultrasound-(HIFU)-Market-Report-2019/72503)
- theresearchcorporation.com/semiconductor-electronics/Global-High-Intensity-Focused-Ultrasound-HIFU-Market-Report-2019-43544
- industryresearch.biz/global-high-intensity-focused-ultrasound-system-market-13807202
- intensersearch.com/report/157513
- htfmarketreport.com/reports/1387744-global-high-intensity-focused-ultrasound-10
- 1marketresearch.com/market-reports/high-intensity-focused-ultrasound-hifu-market-industry-report-111594
- kandjmarketresearch.com/reports/124380-global-high-intensity-focused-ultrasound-hifu-sales-marketsalesrevenue-and-competitors-analysis-of-major-marketfrom-2014-2026
- industryandresearch.com/report/Global-High-Intensity-Focused-Ultrasound--HIFU--Market-Report-2019/129641
- marketstudyreport.com/reports/global-high-intensity-focused-ultrasound-hifu-market-growth-2019-2024
- globalinforesearch.com/global-high-intensity-focused-ultrasound-hifu-market_p217443.html
- marketprognosis.com/report/high-intensity-focused-ultrasound-hifu-therapy-market-by-application-and-region-and-forecast-company-profile-product-analysis--recent-development-of-20-hifu-manufacturers---global-analysis-to/pr-20191

FUS Industry Investments Over Time

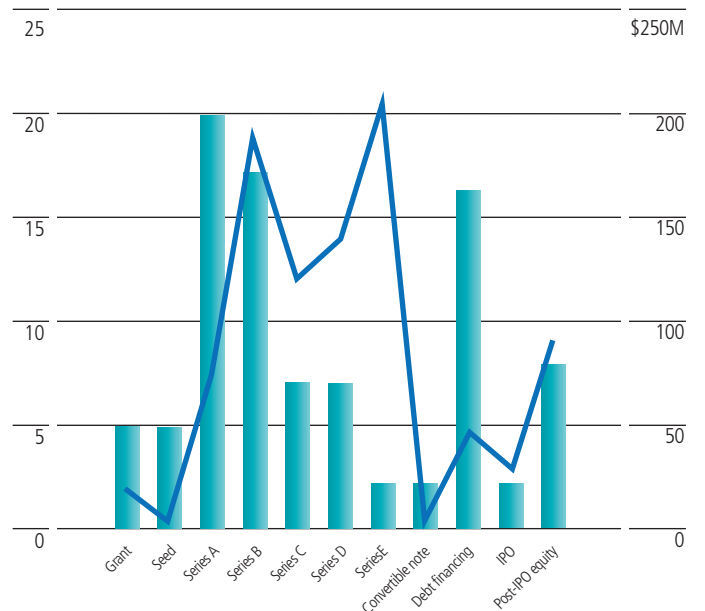
■ Number of investments ■ Value of investments in millions of dollars



Source: www.crunchbase.com and company press releases

FUS Industry Investments by Stage

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



www.crunchbase.com and company press releases

STATE OF COMMERCIALIZATION

2019 FUS Industry Investments*

Manufacturer	Funding type	Investors	Money raised, millions \$US
HistoSonics, Inc.			
	Series C	Varian Medical Systems, Inc. Fred Moll Johnson & Johnson Innovation Lumira Ventures State of Wisconsin Investment Board Venture Investors	\$54.7M
Exo Imaging			
	Series B	Wanxiang Healthcare Investments	\$35.0M
Profound Medical Corp			
	Post-IPO Equity	—	\$11.5M
Theraclion, SA.			
	Post-IPO Equity	Unigestion, SA.	\$5.4M
Cardiawave, SA			
	Grant	EU Executive Agency for SMEs	\$4.1M
Harmonics Medical, Inc.			
	Series A	FedDev Ontario	\$1.6M
			\$112.3M Total

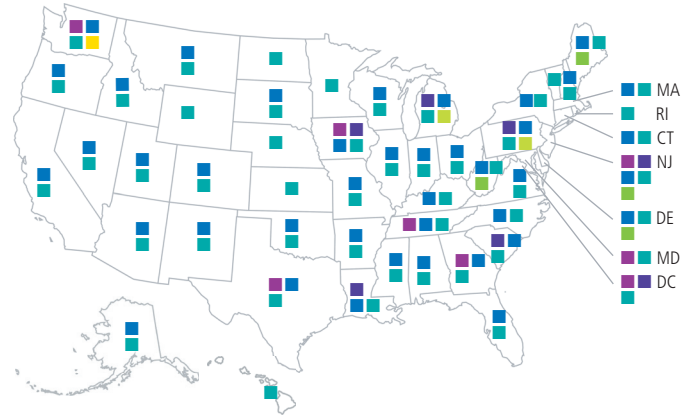
*As reported by Crunchbase and industry press releases

While 2019 investment was about 50 percent of the previous year, it is worth noting that 2019 is the first year that we have seen investment in the field of focused ultrasound by two major stakeholders in the medical device space—Johnson & Johnson Innovation and Varian Medical Systems.

Insurance Coverage in the United States*

Bone metastases | Pain palliation

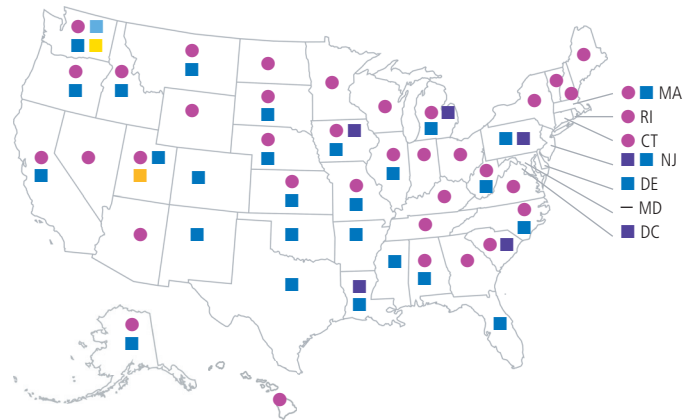
- Private carriers**
- Amerigroup Healthcare
DC, GA, IA, MD, NJ, TN, TX, WA
 - AmeriHealth
DC, IA, LA, MI, NJ, PA, SC
 - Anthem, Blue Cross Blue Shield
AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, IA, ID, IL, IN, KY, LA, MA, ME, MI, MO, MS, MT, NC, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, SD, TN, TX, VA, WA,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



Covered lives 120 million

Essential tremor

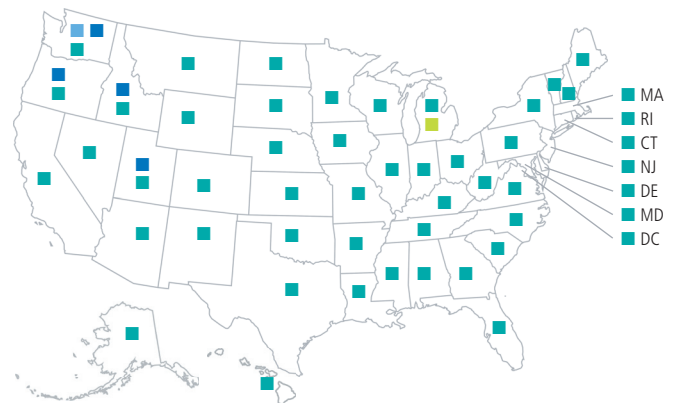
- Public carriers**
- Medicare
AK, AL, AZ, CA, CT, GA, HI, IA, ID, IL, IN, KS, KY, MA, ME, MI, MN, MO, MT, NC, ND, NE, NH, NV, NY, OH, OR, RI, SC, SD, TN, UT, VA, VT, WA, WI, WV, WY
- Private carriers**
- AmeriHealth
DC, IA, LA, MI, NJ, PA, SC
 - Asuris Northwest Health
WA
 - Blue Cross Blue Shield Plan
AK, AL, AR, CA, DE, FL, IA, ID, IL, KS, LA, MA, MI, MO, MS, MT, NC, NJ, NM, OK, OR, PA, SD, TX, UT, WA, WV
 - Lifewise
WA
 - University of Utah Health Plans
UT



Covered lives 76.9 million

Prostate cancer | Salvage therapy¹

- Private carriers**
- Asuris Northwest Health
WA
 - Blue Shield Regence
ID, OR, UT, WA
 - CIGNA
ALL STATES
 - HAP Health Alliance Plan
MI



Covered lives 22.8 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

FUS Regulatory Approvals by Indication and Region



FUS Regulatory Approvals by Indication and Region continued

■ North America

Arthritis, facetogenic
 Benign prostatic hyperplasia
 Bone metastases
 Bone tumors, benign
 Essential tremor
 Osteoid osteoma
 Parkinson's disease, tremor
 Prostate cancer
 Uterine adenomyosis
 Uterine fibroids

■ Europe

Arthritis, facetogenic
 Bone cancer
 Bone metastases
 Bone tumors, benign
 Breast cancer
 Breast fibroadenoma
 Depression
 Epicondylitis
 Essential tremor
 Glaucoma
 Hypertension
 Kidney tumors
 Liver metastases
 Liver tumors
 Multiple myeloma
 Neuropathic pain
 Obsessive-compulsive disorder
 Osteoid osteoma
 Pancreatic tumors
 Parkinson's disease, dyskinesia
 Parkinson's disease, tremor
 Plantar fasciitis
 Prostate cancer
 Rhinitis
 Soft tissue cancer
 Soft tissue injury
 Soft tissue tumors, benign
 Thyroid nodules
 Uterine adenomyosis
 Uterine fibroids
 Varicose veins

■ Asia

Arthritis, facetogenic
 Benign prostatic hyperplasia
 Bone metastases
 Bone tumors, benign
 Breast cancer
 Breast fibroadenoma
 Cervicitis
 Depression
 Essential tremor
 Glaucoma
 Kidney tumors
 Liver tumors
 Neuropathic pain
 Obsessive-compulsive disorder
 Osteoid osteoma
 Pancreatic tumors
 Parkinson's disease, dyskinesia
 Parkinson's disease, tremor
 Prostate cancer
 Rhinitis
 Soft tissue cancer
 Soft tissue tumors, benign
 Thyroid nodules
 Uterine adenomyosis
 Uterine fibroids
 Varicose veins

■ South America

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

■ Oceania

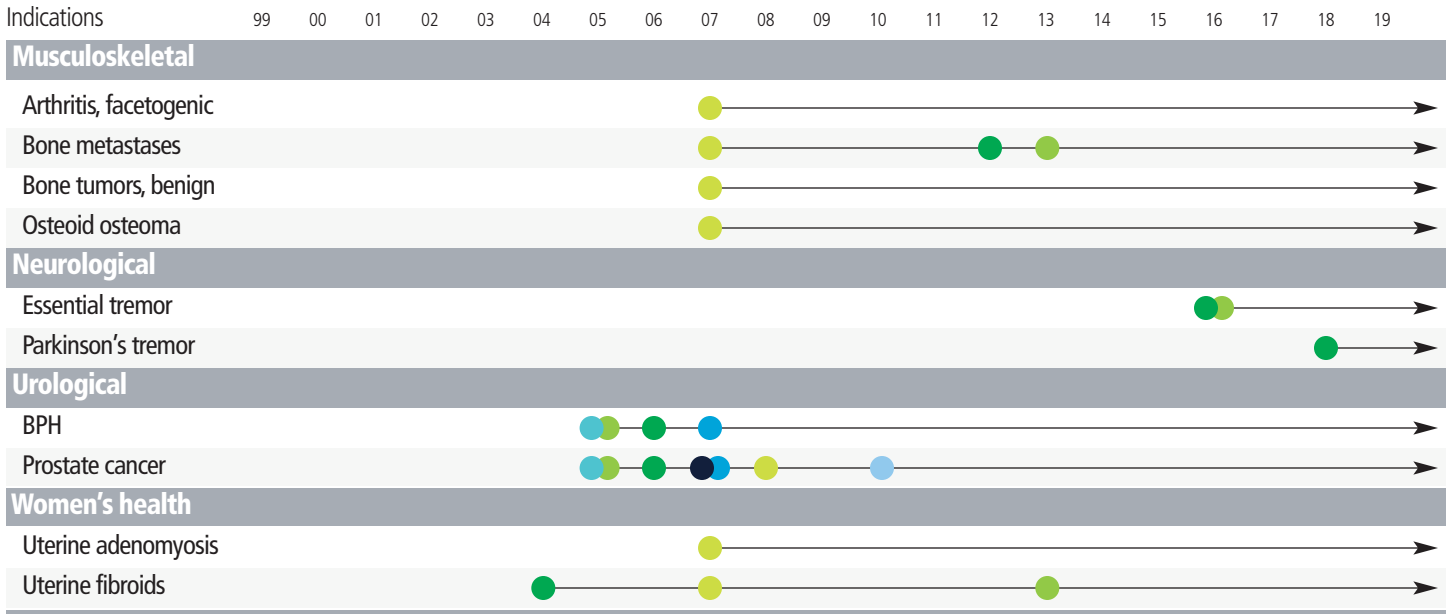
Arthritis, facetogenic
 Bone metastases
 Bone tumors, benign
 Essential tremor
 Osteoid osteoma
 Prostate cancer
 Uterine adenomyosis
 Uterine fibroids

■ Africa

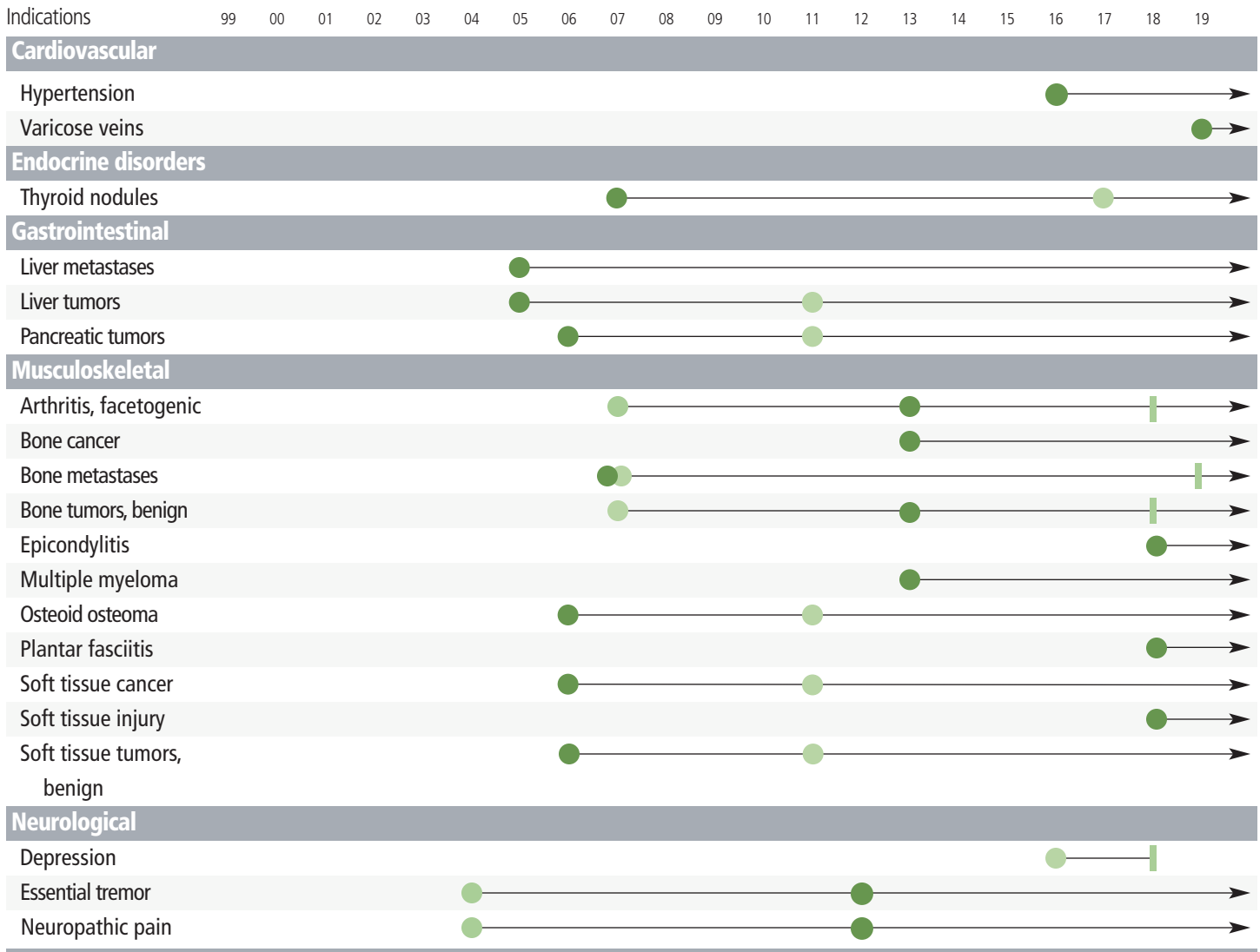
Prostate cancer

STATE OF COMMERCIALIZATION

North America—FUS Regulatory Approvals by Indication

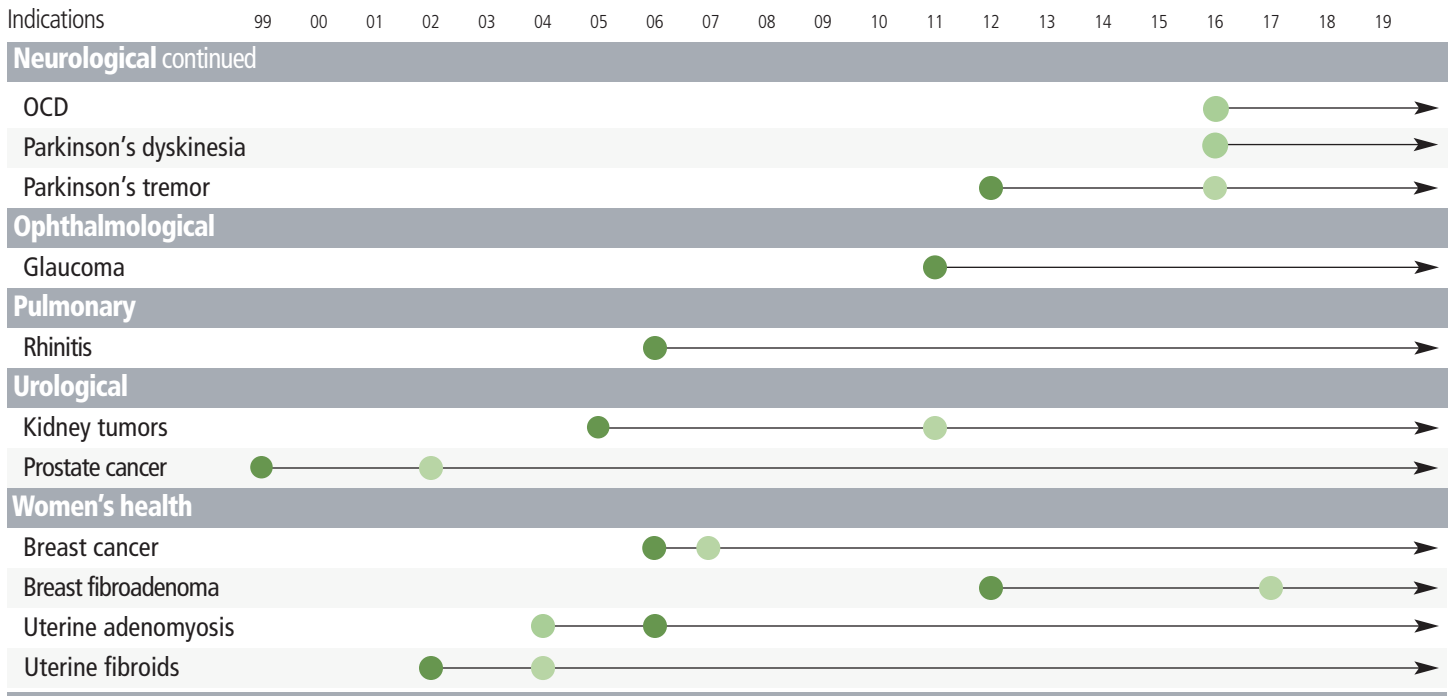


Europe—FUS Regulatory Approvals by Indication

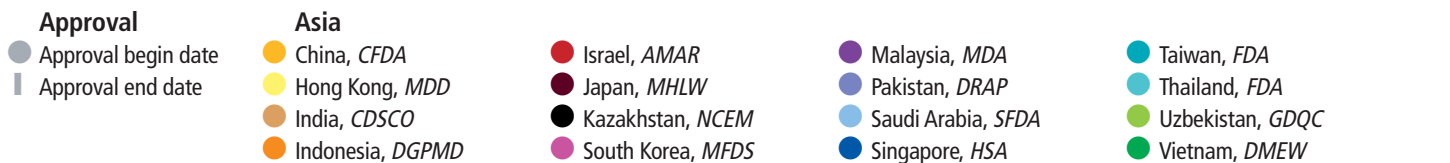
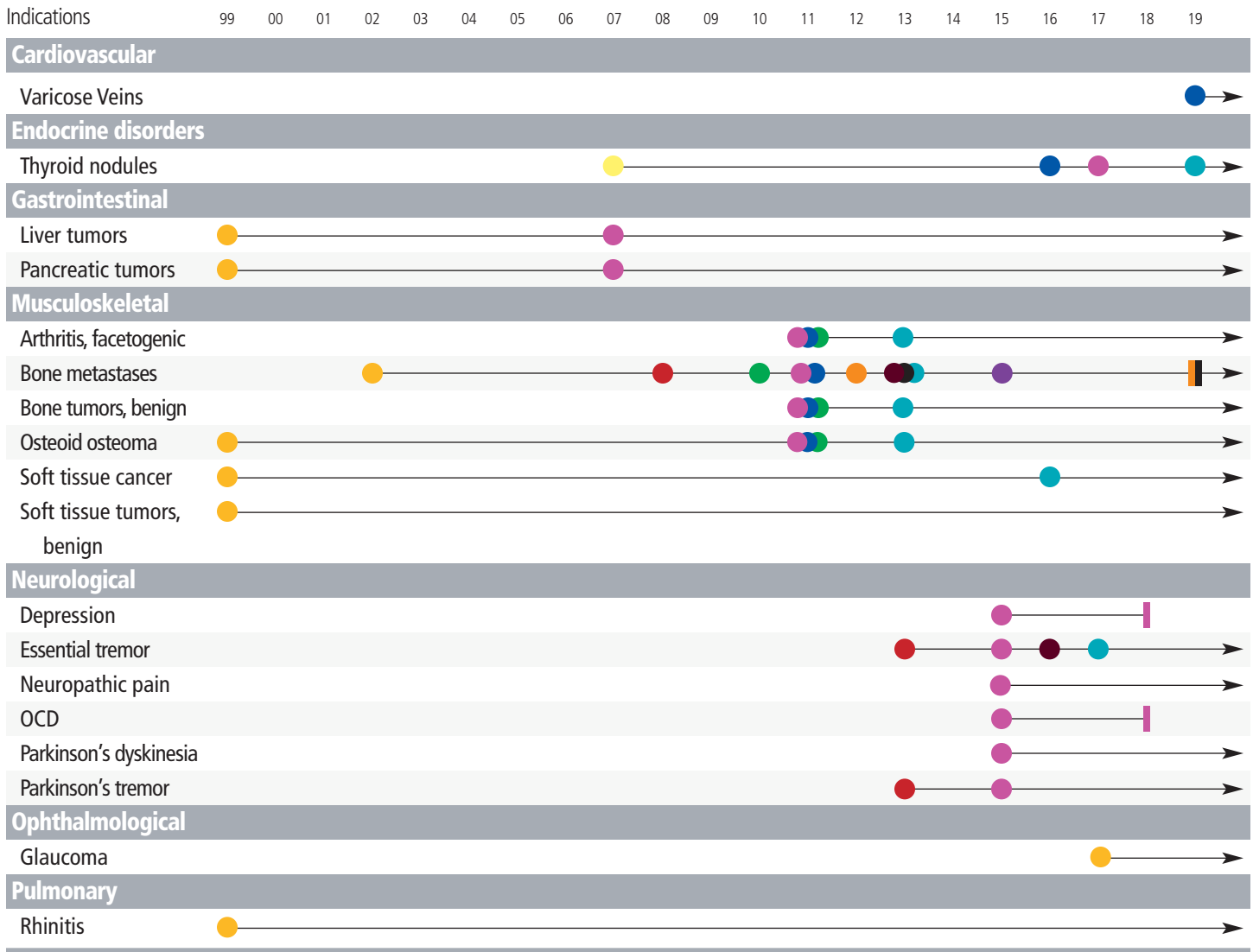


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Europe—FUS Regulatory Approvals by Indication *continued*

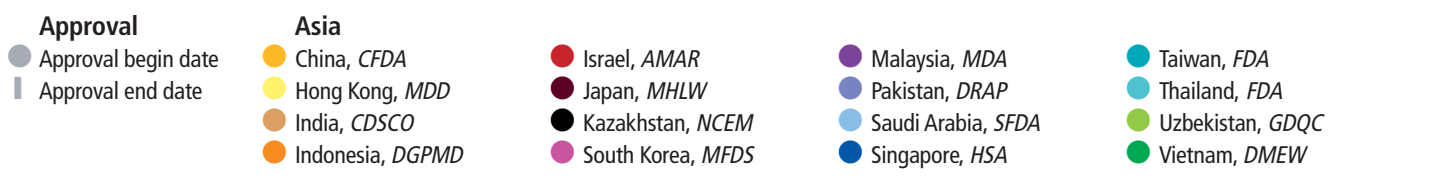
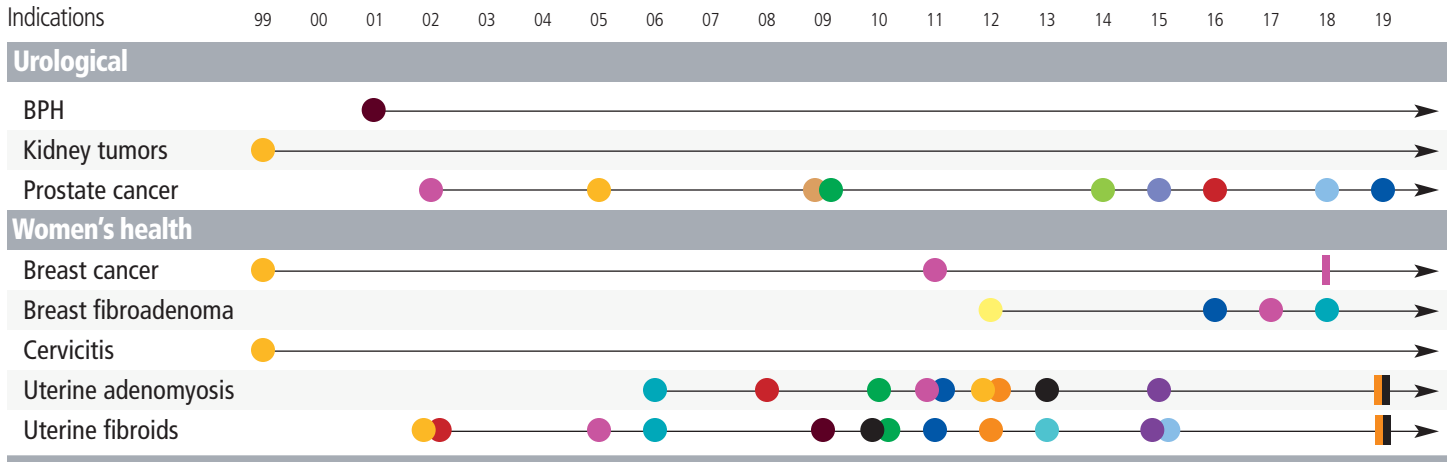


Asia—FUS Regulatory Approvals by Indication

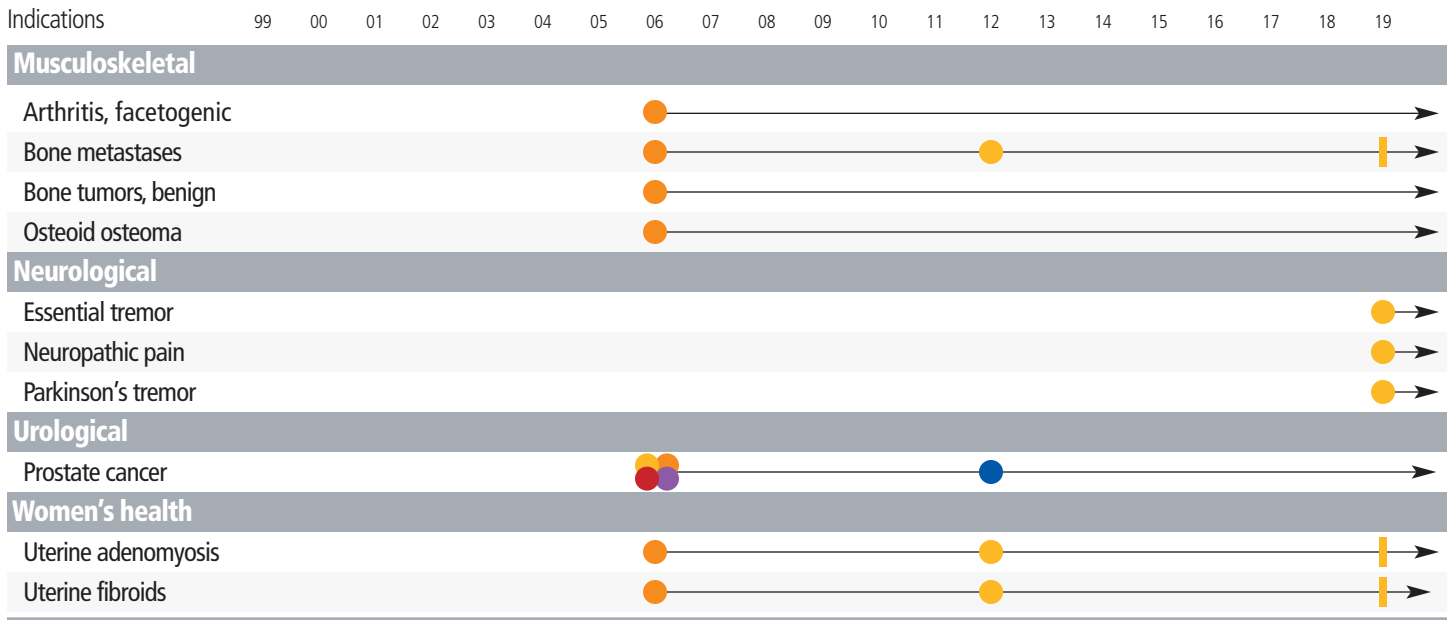


STATE OF COMMERCIALIZATION

Asia—FUS Regulatory Approvals by Indication continued

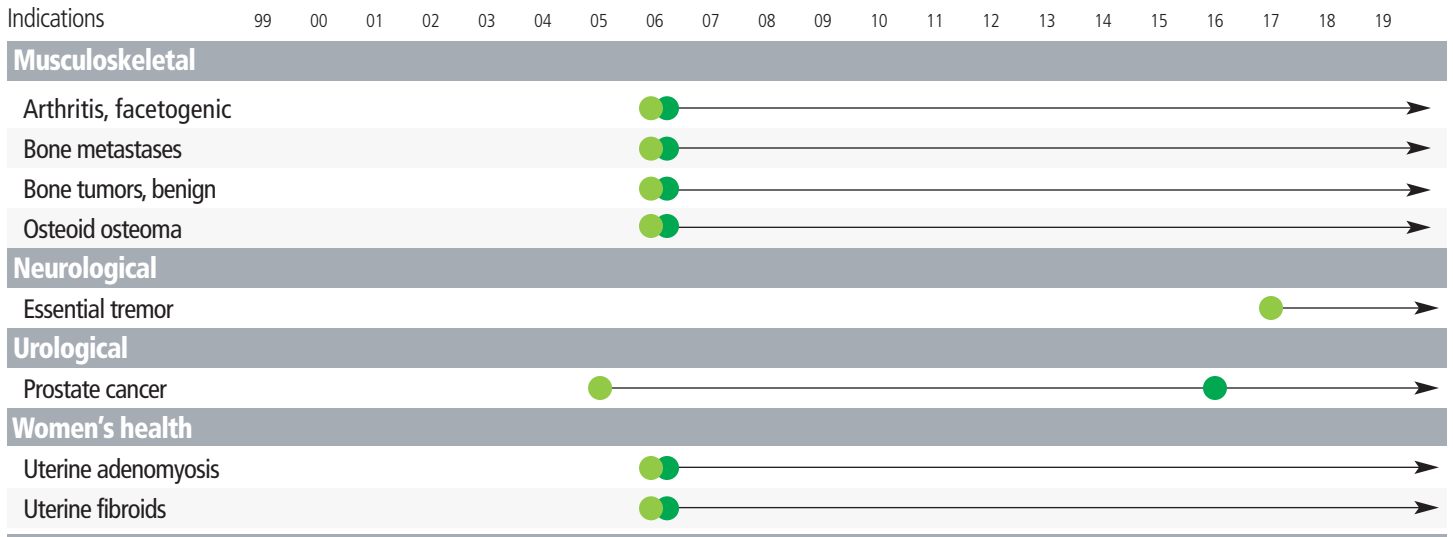


South America—FUS Regulatory Approvals by Indication

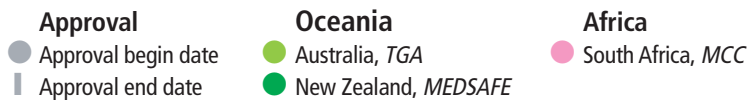
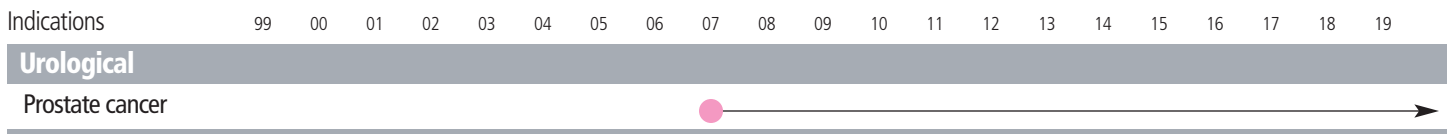


STATE OF COMMERCIALIZATION

Oceania—FUS Regulatory Approvals by Indication



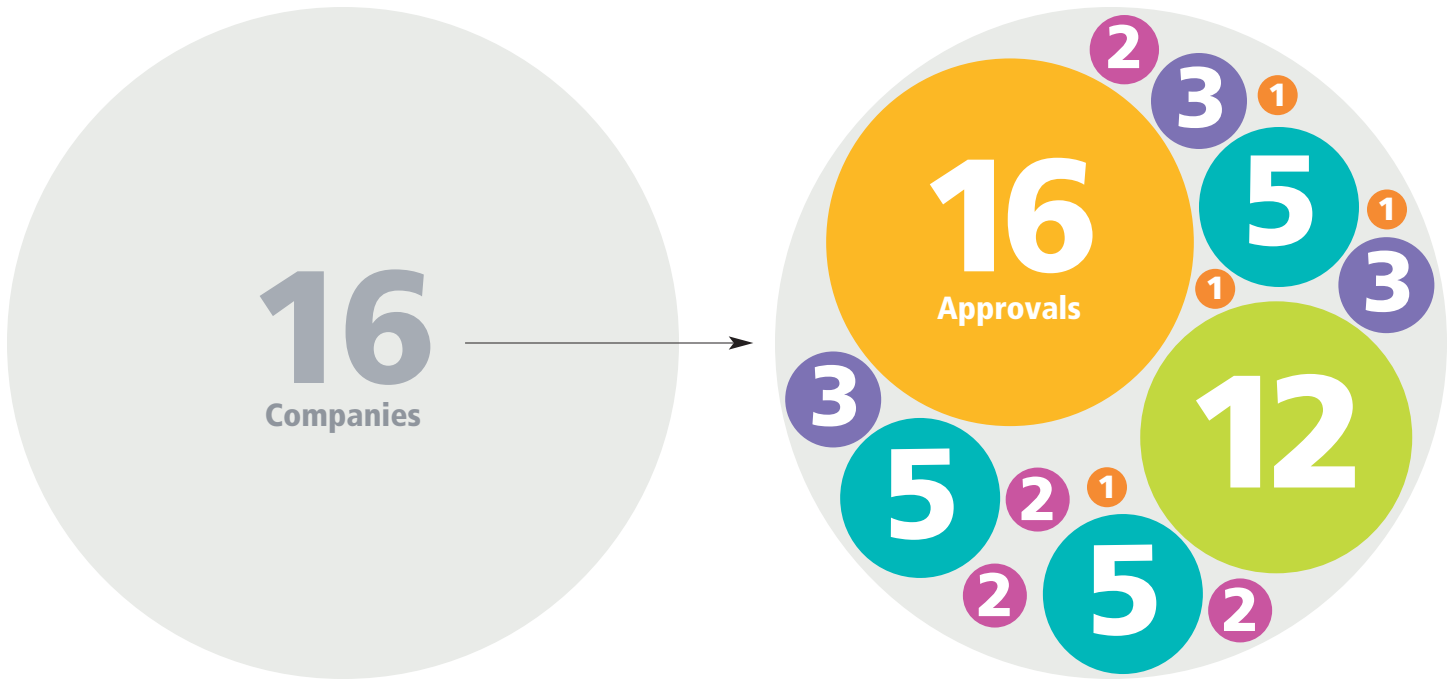
Africa—FUS Regulatory Approvals by Indication



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STATE OF COMMERCIALIZATION

Number of Indication Approvals by Company



Manufacturer Indication Approvals

● One approval

EyeTechCare
Kona Medical
Mirabilis Medical
Wuxi Haiying Electronic Medical

● Two approvals

Alpinion Medical Systems
EDAP TMS
Shenzhen PRO-HITU Medical
SonaCare Medical

● Three approvals

EpiSonica
Guided Therapy Systems
Theraclion

● Five approvals

Beijing Yuande Bio-Medical Engineering
Profound Medical
Shanghai A&S

● Twelve approvals

Chongqing Haifu Medical Technology

● Sixteen approvals

Insightec

Regulatory Approvals for Companies by Region and Indication

■ North America	■ Europe		■ Asia		■ South America
<p>EDAP TMS Benign prostatic hyperplasia Prostate cancer</p> <p>Insightec Arthritis, facetogenic Bone metastases Bone tumors, benign Essential tremor Osteoid osteoma Parkinson's disease, tremor Uterine adenomyosis Uterine fibroids</p> <p>Profound Medical Benign prostatic hyperplasia Prostate cancer Uterine fibroids</p> <p>SonaCare Medical Benign prostatic hyperplasia Prostate cancer</p>	<p>Alpinion Medical Systems Uterine fibroids</p> <p>Chongqing Haifu Medical Technology Breast cancer Kidney tumors Liver metastases Liver tumors Osteoid osteoma Pancreatic tumors Rhinitis Soft tissue cancer Soft tissue tumors, benign Uterine adenomyosis Uterine fibroids</p> <p>EDAP TMS Prostate cancer</p> <p>EyeTechCare Glaucoma</p> <p>Guided Therapy Systems Epicondylitis Plantar fasciitis Soft tissue injury</p> <p>Insightec Arthritis, facetogenic Bone cancer Bone metastases Bone tumors, benign Breast cancer Depression Essential tremor Multiple myeloma Neuropathic pain Obsessive-compulsive disorder Osteoid osteoma Parkinson's disease, dyskinesia Parkinson's disease, tremor</p>	<p>Prostate cancer Uterine adenomyosis Uterine fibroids</p> <p>Kona Medical Hypertension</p> <p>Mirabilis Medical Uterine fibroids</p> <p>Profound Medical Bone metastases Prostate cancer Uterine adenomyosis Uterine fibroids</p> <p>Shanghai A&S Uterine fibroids</p> <p>Shenzhen PRO-HITU Medical Uterine fibroids</p> <p>SonaCare Medical Prostate cancer</p> <p>Theraclion Breast fibroadenoma Thyroid nodules Varicose veins</p>	<p>Alpinion Medical Systems Uterine adenomyosis Uterine fibroids</p> <p>Beijing Yuande Bio-Medical Engineering Breast cancer Kidney tumors Liver tumors Pancreatic tumors Uterine fibroids</p> <p>Chongqing Haifu Medical Technology Breast cancer Cervicitis Kidney tumors Liver tumors Osteoid osteoma Pancreatic tumors Rhinitis Soft tissue cancer Soft tissue tumors, benign Uterine fibroids</p> <p>EDAP TMS Prostate cancer</p> <p>EpiSonica Soft tissue cancer Uterine adenomyosis Uterine fibroids</p> <p>EyeTechCare Glaucoma</p> <p>Insightec Arthritis, facetogenic Bone metastases Bone tumors, benign Breast cancer Depression Essential tremor Neuropathic pain Obsessive-compulsive disorder</p>	<p>Osteoid osteoma Parkinson's disease, dyskinesia Parkinson's disease, tremor Uterine adenomyosis Uterine fibroids</p> <p>Profound Medical Bone metastases Prostate cancer Uterine adenomyosis Uterine fibroids</p> <p>Shanghai A&S Bone metastases Breast cancer Liver tumors Soft tissue cancer Uterine fibroids</p> <p>Shenzhen PRO-HITU Medical Uterine adenomyosis Uterine fibroids</p> <p>SonaCare Medical Benign prostatic hyperplasia Prostate cancer</p> <p>Theraclion Breast fibroadenoma Thyroid nodules Varicose veins</p> <p>Wuxi Haiying Electronic Medical Uterine fibroids</p>	<p>EDAP TMS Prostate cancer</p> <p>Insightec Arthritis, facetogenic Bone metastases Bone tumors, benign Essential tremor Neuropathic pain Osteoid osteoma Parkinson's disease, tremor Uterine adenomyosis Uterine fibroids</p> <p>Profound Medical Bone metastases Uterine adenomyosis Uterine fibroids</p> <p>SonaCare Medical Prostate cancer</p> <p>■ Oceania</p> <p>Insightec Arthritis, facetogenic Bone metastases Bone tumors, benign Essential tremor Osteoid osteoma Uterine adenomyosis Uterine fibroids</p> <p>Profound Medical Bone metastases Prostate cancer Uterine adenomyosis Uterine fibroids</p> <p>SonaCare Medical Prostate cancer</p> <p>■ Africa</p> <p>SonaCare Medical Prostate cancer</p>

STATE OF COMMERCIALIZATION

FUS Regulatory Approvals by Region and Manufacturer

	North America	Europe	Asia	South America	Oceania	Africa
Indications						
Cardiovascular						
Hypertension		■				
Varicose veins		▲	▲			
Endocrine						
Thyroid nodules		▲	▲			
Gastrointestinal						
Liver metastases		●				
Liver tumors		●	● ● ●			
Pancreatic tumors		●	● ●			
Musculoskeletal						
Arthritis, facetogenic	●	●	●	●	●	
Bone cancer		●				
Bone metastases	●	■ ●	■ ● ●	■ ●	■ ●	
Bone tumors, benign	●	●	●	●	●	
Epicondylitis		■				
Multiple myeloma		●				
Osteoid osteoma	●	● ●	● ●	●	●	
Plantar fasciitis		■				
Soft tissue cancer		●	● ● ●			
Soft tissue injury		■				
Soft tissue tumors, benign		●	●			

Manufacturers

<p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, <i>US</i> ■ Kona Medical, <i>US</i> ■ Mirabilis Medical, <i>US</i> ■ Profound Medical, <i>Canada</i> ■ SonaCare Medical, <i>US</i> 	<p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, <i>France</i> ▲ EyeTechCare, <i>France</i> ▲ Theracision, <i>France</i> <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, <i>South Korea</i> ● Beijing Yuande Bio-Medical Engineering, <i>China</i> 	<ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, <i>China</i> ● EpiSonica, <i>Taiwan</i> ● Insightec, <i>Israel</i> ● Shanghai A&S, <i>China</i> ● Shenzhen PRO-HITU Medical, <i>China</i> ● Wuxi Haiying Electronic Medical, <i>China</i>
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FUS Regulatory Approvals by Region and Manufacturer continued

	North America	Europe	Asia	South America	Oceania	Africa
Indications						
Neurological						
Depression		●	●			
Essential tremor	●	●	●	●	●	
Neuropathic pain		●	●	●		
OCD		●	●			
Parkinson's dyskinesia		●	●			
Parkinson's tremor	●	●	●	●		
Ophthalmological						
Glaucoma		▲	▲			
Pulmonary						
Rhinitis		●	●			
Urological						
BPH	■ ■ ▲		■			
Kidney tumors		●	● ●			
Prostate cancer	■ ■ ▲	■ ■ ▲ ●	■ ■ ▲	■ ▲	■ ■	■
Women's health						
Breast cancer		● ●	● ● ● ● ●			
Breast fibroadenoma		▲	▲			
Cervicitis			●			
Uterine adenomyosis	●	■ ● ●	■ ● ● ● ● ●	■ ●	■ ●	
Uterine fibroids	■ ●	■ ■ ● ● ● ● ●	■ ● ● ● ● ● ● ● ● ● ●	■ ●	■ ●	

Manufacturers

- | | | |
|---|--|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, US ■ Kona Medical, US ■ Mirabilis Medical, US ■ Profound Medical, Canada ■ SonaCare Medical, US | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, France ▲ EyeTechCare, France ▲ Theraclion, France <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, South Korea ● Beijing Yuande Bio-Medical Engineering, China | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, China ● EpiSonica, Taiwan ● Insightec, Israel ● Shanghai A&S, China ● Shenzhen PRO-HITU Medical, China ● Wuxi Haiying Electronic Medical, China |
|---|--|--|

STATE OF COMMERCIALIZATION

North America—FUS Regulatory Approvals by Country and Manufacturer

Indications	Bahamas	Barbados	Canada	Costa Rica	Dominican Republic	Mexico	US
	Ministry of Health	Ministry of Health and Wellness	Health Canada, Medical Devices Bureau	Ministerio de Salud	MISPAS	COFEPRIS	FDA, Center for Devices & Radiological Health
Musculoskeletal							
Arthritis, facetogenic						●	
Bone metastases			●			●	●
Bone tumors, benign						●	
Osteoid osteoma						●	
Neurological							
Essential tremor			●				●
Parkinson's tremor							●
Urological							
BPH			■	■	■		■ ■ ▲
Prostate cancer	■	■	■ ▲	■	■	■	■ ■ ▲
Women's health							
Uterine adenomyosis						●	
Uterine fibroids			■ ●			■ ●	●

Manufacturers

- | | | |
|--|--|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, <i>US</i> ■ Kona Medical, <i>US</i> ■ Mirabilis Medical, <i>US</i> ■ Profound Medical, <i>Canada</i> ■ Sonacare Medical, <i>US</i> | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, <i>France</i> ▲ EyeTechCare, <i>France</i> ▲ Theradion, <i>France</i> <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, <i>South Korea</i> ● Beijing Yuande Bio-Medical Engineering, <i>China</i> | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, <i>China</i> ● EpiSonica, <i>Taiwan</i> ● Insightec, <i>Israel</i> ● Shanghai A&S, <i>China</i> ● Shenzhen PRO-HITU Medical, <i>China</i> ● Wuxi Haiying Electronic Medical, <i>China</i> |
|--|--|--|

Europe—FUS Regulatory Approvals by Country and Manufacturer

Indications	Europe	Russia
	CE Marking	Roszdraznadzor
Cardiovascular		
Hypertension	■	
Varicose veins	▲	
Endocrine disorders		
Thyroid nodules	▲	▲
Gastrointestinal		
Liver metastases	●	
Liver tumors	●	●
Pancreatic tumors	●	●
Musculoskeletal		
Arthritis, facetogenic	●	●
Bone cancer	●	
Bone metastases	■ ●	■ ●
Bone tumors, benign	●	●
Epicondylitis	■	
Multiple myeloma	●	
Osteoid osteoma	● ●	● ●
Plantar fasciitis	■	
Soft tissue cancer	●	●
Soft tissue injury	■	
Soft tissue tumors, benign	●	●

Manufacturers

- North America**
- Guided Therapy Systems, *US*
 - Kona Medical, *US*
 - Mirabilis Medical, *US*
 - Profound Medical, *Canada*
 - SonaCare Medical, *US*

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

- Asia**
- Alpinion Medical Systems, *South Korea*
 - Beijing Yuande Bio-Medical Engineering, *China*

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

STATE OF COMMERCIALIZATION

Europe—FUS Regulatory Approvals by Country and Manufacturer *continued*

Indications	Europe	Russia
	CE Marking	Roszdraznadzor
Neurological		
Depression		●
Essential tremor	●	●
Neuropathic pain	●	●
OCD		●
Parkinson's dyskinesia		●
Parkinson's tremor	●	●
Ophthalmological		
Glaucoma	▲	
Pulmonary		
Rhinitis	●	
Urological		
Kidney tumors	●	●
Prostate cancer	■ ▲ ●	■ ▲ ●
Women's health		
Breast cancer	●	● ●
Breast fibroadenoma	▲	▲
Uterine adenomyosis	■ ● ●	■ ● ●
Uterine fibroids	■ ■ ● ● ● ● ● ●	■ ● ●

Manufacturers

- North America**
- Guided Therapy Systems, *US*
 - Kona Medical, *US*
 - Mirabilis Medical, *US*
 - Profound Medical, *Canada*
 - SonaCare Medical, *US*

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

- Asia**
- Alpinion Medical Systems, *South Korea*
 - Beijing Yuande Bio-Medical Engineering, *China*

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

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STATE OF COMMERCIALIZATION

Asia—FUS Regulatory Approvals by Country and Manufacturer

	China	Hong Kong	India	Indonesia	Israel	Japan	Kazakhstan	Malaysia
Indications	CFDA	MDD	CDSKO	DGPMO	AMAR	MHLW	NCEM	MDA
Cardiovascular								
Varicose veins								
Endocrine disorders								
Thyroid nodules		▲						
Gastrointestinal								
Liver tumors	●●●							
Pancreatic tumors	●							
Musculoskeletal								
Arthritis, facetogenic								
Bone metastases	●			■	●	●	■	■
Bone tumors, benign								
Osteoid osteoma	●							
Soft tissue cancer	●●							
Soft tissue tumors, benign	●							
Neurological								
Depression								
Essential tremor				●	●	●		
Neuropathic pain								
OCD								
Parkinson's dyskinesia								
Parkinson's tremor				●	●			

Manufacturers

- | | | |
|--|--|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, <i>US</i> ■ Kona Medical, <i>US</i> ■ Mirabilis Medical, <i>US</i> ■ Profound Medical, <i>Canada</i> ■ SonaCare Medical, <i>US</i> | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, <i>France</i> ▲ EyeTechCare, <i>France</i> ▲ Theracion, <i>France</i> <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, <i>South Korea</i> ● Beijing Yuande Bio-Medical Engineering, <i>China</i> | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, <i>China</i> ● EpiSonica, <i>Taiwan</i> ● Insightec, <i>Israel</i> ● Shanghai A&S, <i>China</i> ● Shenzhen PRO-HITU Medical, <i>China</i> ● Wuxi Haiying Electronic Medical, <i>China</i> |
|--|--|--|

Asia—FUS Regulatory Approvals by Country and Manufacturer continued

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

Manufacturers

- | | | |
|--|---|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, <i>US</i> ■ Kona Medical, <i>US</i> ■ Mirabilis Medical, <i>US</i> ■ Profound Medical, <i>Canada</i> ■ SonaCare Medical, <i>US</i> | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, <i>France</i> ▲ EyeTechCare, <i>France</i> ▲ Theraction, <i>France</i> <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, <i>South Korea</i> ● Beijing Yuande Bio-Medical Engineering, <i>China</i> | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, <i>China</i> ● EpiSonica, <i>Taiwan</i> ● Insightec, <i>Israel</i> ● Shanghai A&S, <i>China</i> ● Shenzhen PRO-HITU Medical, <i>China</i> ● Wuxi Haiying Electronic Medical, <i>China</i> |
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STATE OF COMMERCIALIZATION

Asia—FUS Regulatory Approvals by Country and Manufacturer continued

	China	Hong Kong	India	Indonesia	Israel	Japan	Kazakhstan	Malaysia
Indications	CFDA	MDD	CDSKO	DGPMO	AMAR	MHLW	NCEM	MDA
Ophthalmological								
Glaucoma	▲							
Pulmonary								
Rhinitis	●							
Urological								
BPH						■		
Kidney tumors	● ●							
Prostate cancer	■		■ ▲		■			
Women's Health								
Breast cancer	● ● ●							
Breast fibroadenoma		▲						
Cervicitis	●							
Uterine adenomyosis	●			■	●		■	■
Uterine fibroids	■ ● ● ● ●			■	●	●	■	■

Manufacturers

- | | | |
|---|---|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, US ■ Kona Medical, US ■ Mirabilis Medical, US ■ Profound Medical, Canada ■ SonaCare Medical, US | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, France ▲ EyeTechCare, France ▲ Theracision, France <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, South Korea ● Beijing Yuande Bio-Medical Engineering, China | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, China ● EpiSonica, Taiwan ● Insightec, Israel ● Shanghai A&S, China ● Shenzhen PRO-HITU Medical, China ● Wuxi Haiying Electronic Medical, China |
|---|---|--|

STATE OF COMMERCIALIZATION

South America—FUS Regulatory Approvals by Country and Manufacturer

Indications	Argentina	Brazil	Colombia	Ecuador	Trinidad and Tobago
	ANMAT	ANVISA	INVIMA	ANRCVS	Ministry of Health
Musculoskeletal					
Arthritis, facetogenic		●			
Bone metastases	■	●			
Bone tumors, benign		●			
Osteoid osteoma		●			
Neurological					
Essential tremor	●				
Neuropathic pain	●				
Parkinson's tremor	●				
Urological					
Prostate cancer	■	■▲	■	■	■
Women's Health					
Uterine adenomyosis	■	●			
Uterine fibroids	■	●			

Manufacturers

North America	Europe	● Chongqing Haifu Medical Technology, <i>China</i>
■ Guided Therapy Systems, <i>US</i>	▲ EDAP TMS, <i>France</i>	● EpiSonica, <i>Taiwan</i>
■ Kona Medical, <i>US</i>	▲ EyeTechCare, <i>France</i>	● Insightec, <i>Israel</i>
■ Mirabilis Medical, <i>US</i>	▲ Theraclion, <i>France</i>	● Shanghai A&S, <i>China</i>
■ Profound Medical, <i>Canada</i>	Asia	● Shenzhen PRO-HITU Medical, <i>China</i>
■ SonaCare Medical, <i>US</i>	● Alpinion Medical Systems, <i>South Korea</i>	● Wuxi Haiying Electronic Medical, <i>China</i>
	● Beijing Yuande Bio-Medical Engineering, <i>China</i>	

Oceania—FUS Regulatory Approvals by Country and Manufacturer

Indications	Australia	New Zealand
	TGA	MEDSAFE
Musculoskeletal		
Arthritis, facetogenic	●	●
Bone metastases	■ ●	■ ●
Bone tumors, benign	●	●
Osteoid osteoma	●	●
Neurological		
Essential tremor	●	
Urological		
Prostate cancer	■ ■	■
Women's Health		
Uterine adenomyosis	■ ●	■ ●
Uterine fibroids	■ ●	■ ●

Africa—FUS Regulatory Approvals by Region and FUS Manufacturer

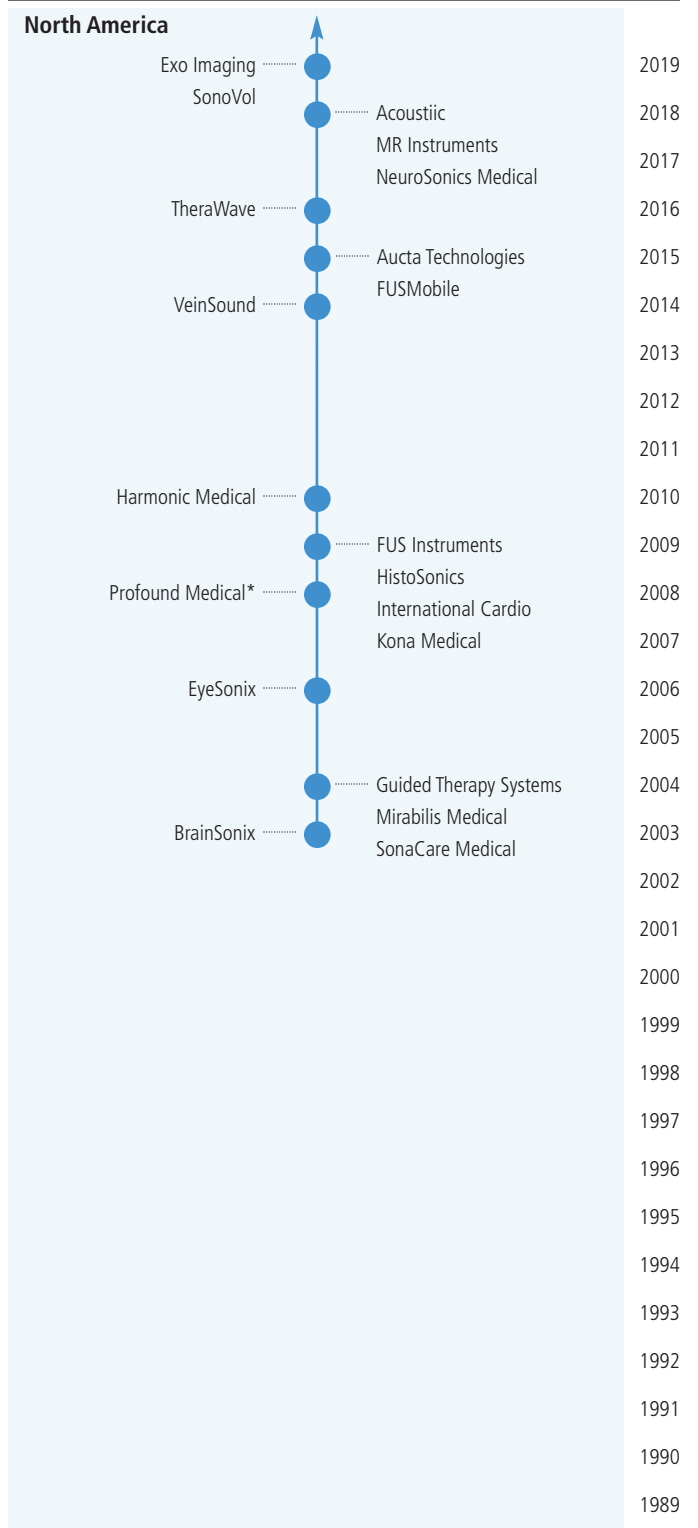
Indications	South Africa
	MCC
Urological	
Prostate cancer	■

Manufacturers

- | | | |
|--|--|--|
| <p>North America</p> <ul style="list-style-type: none"> ■ Guided Therapy Systems, <i>US</i> ■ Kona Medical, <i>US</i> ■ Mirabilis Medical, <i>US</i> ■ Profound Medical, <i>Canada</i> ■ SonaCare Medical, <i>US</i> | <p>Europe</p> <ul style="list-style-type: none"> ▲ EDAP TMS, <i>France</i> ▲ EyeTechCare, <i>France</i> ▲ Theracision, <i>France</i> <p>Asia</p> <ul style="list-style-type: none"> ● Alpinion Medical Systems, <i>South Korea</i> ● Beijing Yuande Bio-Medical Engineering, <i>China</i> | <ul style="list-style-type: none"> ● Chongqing Haifu Medical Technology, <i>China</i> ● EpiSonica, <i>Taiwan</i> ● Insightec, <i>Israel</i> ● Shanghai A&S, <i>China</i> ● Shenzhen PRO-HITU Medical, <i>China</i> ● Wuxi Haiying Electronic Medical, <i>China</i> |
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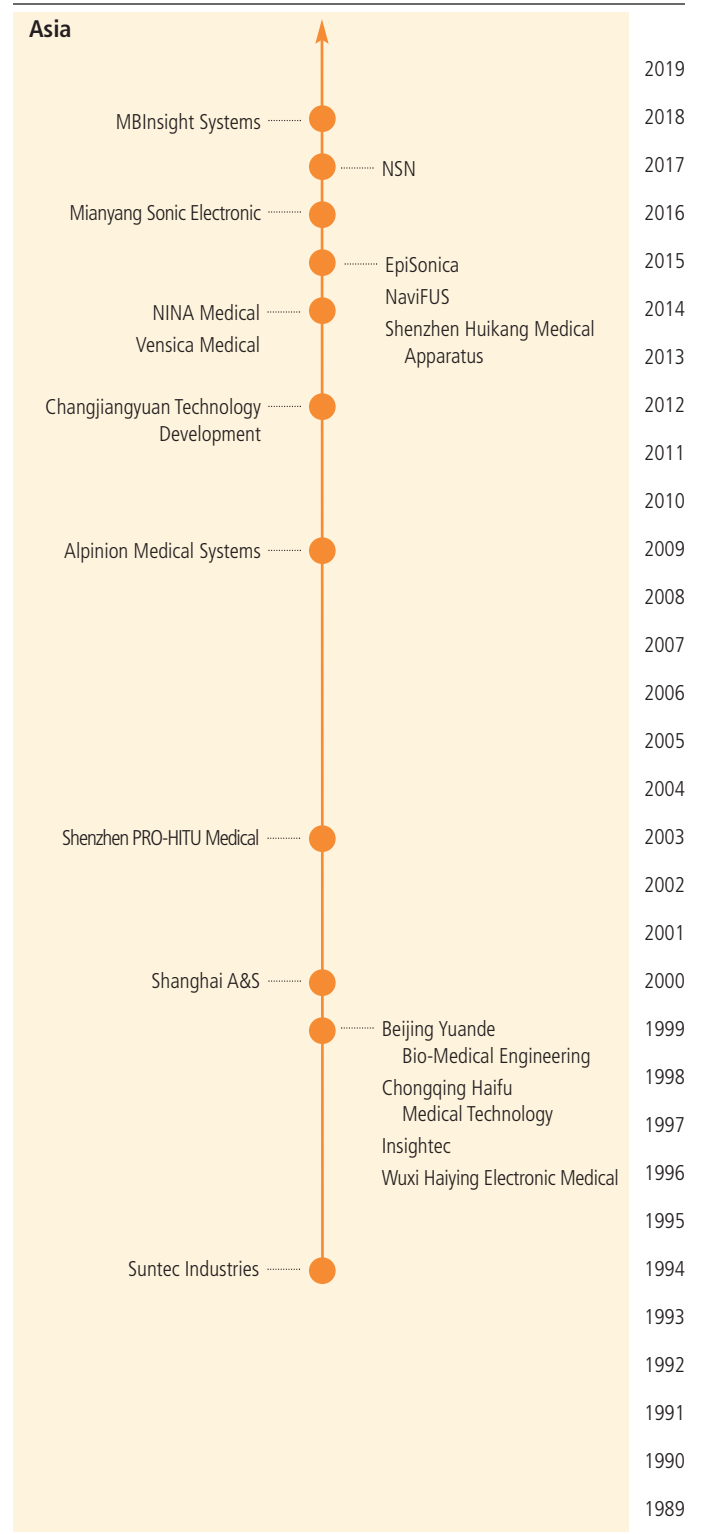
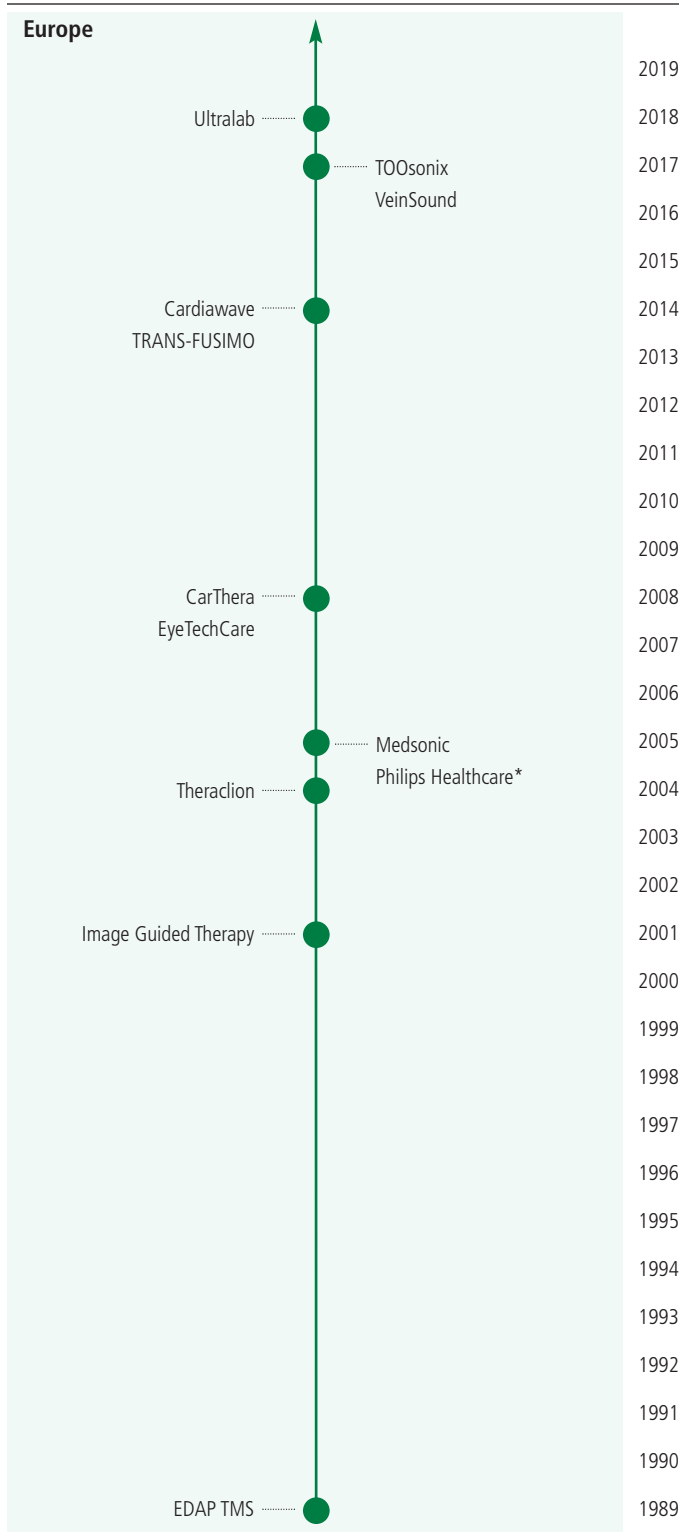
Timeline of Clinical Device Manufacturers by Region

In past State of the Field Reports, the company timelines were based upon date of company formation. This year's reporting is a bit different. Instead of the date of incorporation we are reporting on the year the company became involved in the FUS industry. For many early-stage FUS manufacturing companies this date is one and the same; however, for the OEM manufacturers and/or microbubble companies this is a difference from previous years. Also new for 2020, we are sorting the timelines by geographic regions instead of by image guidance. Image, treatment, and planning guidance for companies/devices can be found on pages III.42–III.47.



*Profound Medical acquired the HIFU assets of Philips in July, 2017.

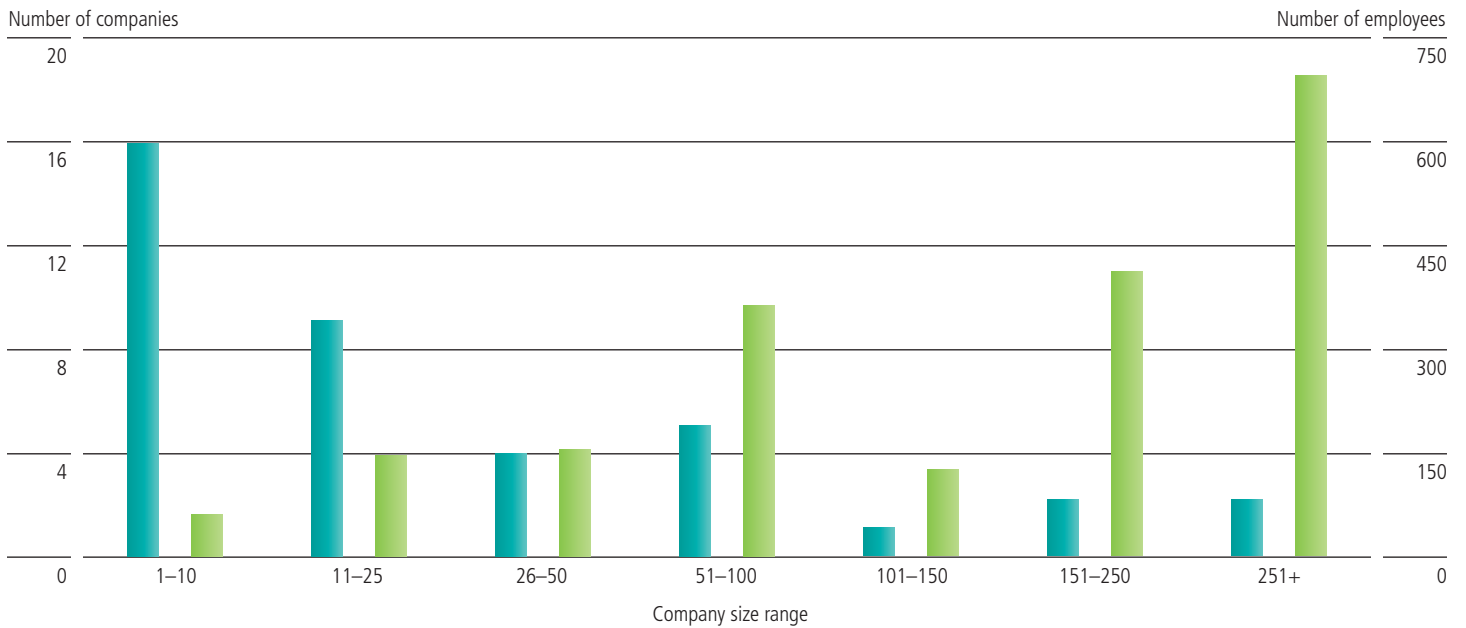
Timeline of Clinical Device Manufacturers by Region continued



STATE OF COMMERCIALIZATION

Numbers Employed by FUS Companies

■ Companies ■ Employees



FUS Company Size

64%

of companies have
25 or fewer employees

74%

of companies have
50 or fewer employees

57%

of the industry is employed by
the four largest companies

This analysis includes all FUS industry companies, including FUS device manufacturers, distributors, microbubble companies and OEM manufacturers.

FUS Industry by Region

Clinical Device Manufacturers

North America

20

- Acoustiic INC | Seattle, Washington, United States, www.acoustiic.com
- Aucta Technologies INC | Minneapolis, Minnesota, United States, auctatechnologies.com
- BrainSonix CORP | Sherman Oaks, California, United States, www.brainsonix.com
- Exo Imaging | Redwood City, California, United States, www.exo-imaging.com
- EyeSonix | Long Beach, California, United States, eyesonix.com
- FUS Instruments INC | Toronto, Ontario, Canada, www.fusinstruments.com
- FUS Mobile INC | Alpharetta, Georgia, United States, www.fusmobile.com
- Guided Therapy Systems LLC | Mesa, Arizona, United States, www.guidedtherapy.com
- Harmonic Medical INC | Burlington, Ontario, Canada, www.harmonicmedical.com
- HistoSonics INC | Ann Arbor, Michigan, United States, www.histosonics.com
- International Cardio CORP, LLC | Edina, Minnesota, United States, www.hifu-rx.com
- Kona Medical INC | Bellevue, Washington, United States, konamedical.com
- Mirabilis Medical INC | Bothell, Washington, United States, mirabilismed.com
- MR Instruments INC | Hopkins, Minnesota, United States, mrinstruments.com
- NeuroSonics Medical INC | Baltimore, Maryland, United States
- Profound Medical CORP* | Mississauga, Ontario, Canada, www.profoundmedical.com
- SonaCare Medical LLC | Charlotte, North Carolina, United States, www.sonacaremedical.com
- SonoVol | Durham, North Carolina, United States, sonovol.com
- TheraWave LLC | New York, New York, United States
- VeinSound INC | Sunnyvale, California, United States

● Manufacturers with regulatory approvals; see page III.21 for approvals.

* Profound Medical acquired the HIFU assets of Philips in July of 2017.

FUS Industry by Region continued

Clinical Device Manufacturers

Europe

13

- 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, www.eyetechcare.com
- Image Guided Therapy SA | Pessac, France, www.imageguidedtherapy.com
- Medsonic LTD | Limassol, Cyprus, www.medsonic.com.cy
- The Philips Healthcare* | Eindhoven, The Netherlands, www.healthcare.philips.com
- PI Ceramic GMBH | Lederhose, Germany, www.piceramic.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

● Manufacturers with regulatory approvals; see page III.21 for approvals.

* Profound Medical acquired the HIFU assets of Philips in July of 2017.

FUS Industry by Region continued

Clinical Device Manufacturers

Asia

17

- Alpinion Medical Systems CO LTD | Seoul, South Korea, www.alpinion.com
- Beijing Yuande Bio-Medical Engineering CO LTD | Daxing, China, www.yuande.com
Changjiangyuan Technology Development CO LTD | Beijing, China, www.cjyjkj.com
- Chongqing Haifu Medical Technology CO LTD | Chongqing, China, www.haifumedical.com
- EpiSonica CORP | Hsinchu, Taiwan, www.episonica.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, Korea | www.neurosona.com
- NINA Medical LTD | Israel | ninamed.com
- Shanghai A&S Science Technology Development CO LTD | Shanghai, China, www.aishen.com.cn
Shenzhen Huikang Medical Apparatus CO LTD | Shenzhen, China, www.eswl.cn
- Shenzhen PRO-HITU Medical Technology CO LTD | Shenzhen, China, en.pro-hifu.com
Suntec Industries CO LTD | Shanghai, China
- Vensica Medical | Misgav, Israel, vensica.com
- Wuxi Haiying Electronic Medical Systems CO LTD | Wuxi, China, www.haiyingmedical.com

● Manufacturers with regulatory approvals; see page III.21 for approvals.

Clinical Device Manufacturers with Regulatory Approvals

Alpinion Medical Systems co LTD

Regulatory approvals

Uterine adenomyosis, 2018
Uterine fibroids, 2014

Commercial treatments

Uterine adenomyosis
Uterine fibroids

Clinical research

Pancreatic tumors
Uterine fibroids

Devices

Alpius 900
VIFU2000

Treatment guidance

Ultrasound

Beijing Yuande Bio-Medical Engineering co LTD

Regulatory approvals

Breast cancer, 1999
Kidney tumors, 1999
Liver tumors, 1999
Pancreatic tumors, 2007
Uterine fibroids, 2007

Commercial treatments

Bone metastases
Breast cancer
Kidney tumors
Liver tumors
Pancreatic tumors
Prostate cancer
Soft tissue tumors, benign
Uterine fibroids

Device

FEP-BY02

Treatment guidance

Ultrasound

Chongqing Haifu Medical Technology co LTD

Regulatory approvals

Breast cancer, 1999
Cervicitis, 1999
Kidney tumors, 1999
Liver metastases, 2005
Liver tumors, 1999
Osteoid osteoma, 1999
Pancreatic tumors, 1999
Rhinitis, 1999
Soft tissue cancer, 1999
Soft tissue tumors, benign, 1999
Uterine adenomyosis, 2006
Uterine fibroids, 2006

Commercial treatments

Bone metastases
Breast cancer
Breast fibroadenoma
Cervicitis
Kidney tumors
Liver metastases
Liver tumors
Osteoid osteoma
Pancreatic tumors
Soft tissue cancer
Soft tissue tumors, benign
Uterine adenomyosis
Uterine fibroids

Clinical research

Breast cancer
Kidney tumors
Liver metastases
Liver tumors
Lung metastases
Osteoid osteoma
Pancreatic tumors
Retained placenta
Rhinitis
Sacral chordoma
Soft tissue cancer
Soft tissue tumors, benign
Uterine adenomyosis
Uterine fibroids

Clinical Device Manufacturers with Regulatory Approvals continued

Devices

CZB
CZF
CZG300
JC
JC200
JC200D

Treatment guidance

Ultrasound

EDAP TMS SA

Regulatory approvals

Benign prostatic hyperplasia, 2015
Prostate cancer, 1999

Commercial treatments

Benign prostatic hyperplasia
Prostate cancer

Clinical research

Benign prostatic hyperplasia
Liver metastases
Prostate cancer

Devices

Ablatherm
Focal One

Treatment guidance

Image fusion

Planning Guidance

Ultrasound

EpiSonica corp

Regulatory approval

Soft tissue cancer, 2016
Uterine Adenomyosis, 2016–2019
Uterine Fibroids, 2016–2019

Device

ArcBLATE (ARC-100M)

Treatment guidance

MR

Planning guidance

MR

EyeTechCare SA

Regulatory approval

Glaucoma, 2011

Commercial treatment

Glaucoma

Clinical research

Glaucoma

Device

EyeOP1

Treatment guidance

Unguided

Guided Therapy Systems LLC

Regulatory approvals

Epicondylitis, 2018
Plantar fasciitis, 2018
Soft tissue injury, 2018

Device

Actisound

Treatment Guidance

Ultrasound

Clinical Device Manufacturers with Regulatory Approvals continued

Insightec LTD

Regulatory approvals

- Arthritis, facetogenic, 2006
- Bone cancer, 2013
- Bone metastases, 2006
- Bone tumors, benign, 2006
- Breast cancer, 2007–2018
- Depression, 2015–2018
- Essential tremor, 2004
- Multiple myeloma, 2013
- Neuropathic pain, 2004
- Obsessive-compulsive disorder, 2015–2018
- Osteoid osteoma, 2006
- Parkinson’s disease, dyskinesia, 2015
- Parkinson’s disease, tremor, 2015
- Prostate cancer, 2016
- Uterine adenomyosis, 2004
- Uterine fibroids, 2002

Commercial treatments

- Arteriovenous malformations
- Arthritis, facetogenic
- Astrocytoma
- Bone cancer
- Bone metastases
- Breast cancer
- Desmoid tumors
- Dystonia
- Epilepsy
- Essential tremor
- Multiple tumors
- Neuropathic pain
- Osteoid osteoma
- Parkinson’s disease, dyskinesia
- Parkinson’s disease, tremor
- Prostate cancer
- Soft tissue tumors, benign
- Trigeminal neuralgia
- Uterine adenomyosis
- Uterine fibroids

Clinical research

- Alzheimer’s disease
- Arthritis, facetogenic
- Arthritis, knee
- Astrocytoma
- Bone cancer
- Bone metastases
- Bone tumors, benign
- Brain metastases, breast cancer
- Dementia
- Depression
- Dystonia
- Endometriosis
- Epilepsy
- Essential tremor
- Glioblastoma
- Head & neck tumors
- Holmes tremor
- Huntington’s disease
- Liver tumors
- Multiple sclerosis
- Neuropathic pain
- Obsessive-compulsive disorder
- Opioid and other addictions
- Osteoid osteoma
- Painful amputation neuromas
- Parkinson’s disease, dyskinesia
- Parkinson’s disease, tremor
- Prostate cancer
- Soft tissue cancer
- Soft tissue tumors, benign
- Uterine adenomyosis
- Uterine fibroids

Devices

- Exablate Body System
- Exablate Neuro
- Exablate Prostate

Treatment guidance

- MR

Clinical Device Manufacturers with Regulatory Approvals continued

Kona Medical inc

Regulatory approval

Hypertension, 2016

Clinical research

Hypertension

Device

Surround Sound (Prototype)

Treatment guidance

Ultrasound

Mirabilis Medical inc

Regulatory approval

Uterine fibroids, 2017

Commercial treatment

Uterine fibroids

Device

Mirabilis System (Prototype)

Treatment guidance

Ultrasound

Profound Medical corp

Regulatory approvals

Benign prostate hyperplasia, 2019

Bone metastases, 2010

Prostate cancer, 2016

Uterine adenomyosis, 2010

Uterine fibroids, 2009

Commercial treatments

Arteriovenous malformations

Benign prostatic hyperplasia

Bone cancer

Bone metastases

Bone tumors, benign

Cancer pain

Desmoid tumors

Endometriosis

Osteoid osteoma

Prostate cancer

Soft tissue cancer

Soft tissue tumors, benign

Uterine adenomyosis

Uterine fibroids

Clinical research

Benign prostatic hyperplasia

Bone cancer

Bone metastases

Bone tumors, benign

Breast cancer

Cancer pain

Desmoid tumors

Osteoid osteoma

Pancreatic tumors

Plantar fasciitis

Prostate cancer

Soft tissue cancer

Soft tissue tumors, benign

Uterine adenomyosis

Uterine fibroids

Vaginal tumors

Devices

Sonalleve

TULSA-PRO

Treatment guidance

MR

Clinical Device Manufacturers with Regulatory Approvals continued

Shanghai A&S Science Technology Development co LTD

Regulatory approvals

- Bone metastases, 2002
- Breast cancer, 2002
- Liver tumors, 2002
- Soft tissue cancer, 2002
- Uterine fibroids, 2002

Commercial treatments

- Endometrial tumors
- Liver metastases
- Liver tumors
- Pancreatic tumors
- Uterine adenomyosis
- Uterine fibroids

Device

- HIFUNIT9000

Treatment guidance

- Ultrasound

Shenzhen PRO-HITU Medical Tech co LTD

Regulatory approvals

- Uterine adenomyosis. 2012
- Uterine fibroids, 2012

Commercial treatments

- Pancreatic tumors
- Uterine adenomyosis
- Uterine fibroids

Devices

- PRO2008
- PRO300

Treatment guidance

- Ultrasound

SonaCare Medical LLC

Regulatory approvals

- Benign prostatic hyperplasia, 2001
- Prostate cancer, 2005

Commercial treatments

- Benign prostatic hyperplasia
- Prostate cancer

Clinical research

- Cervical tumors
- Endometrial tumors
- Ovarian tumors
- Prostate cancer

Devices

- Sonablate
- Sonatherm

Treatment guidance

- Ultrasound

 Clinical Device Manufacturers with Regulatory Approvals continued

Theraclion SA

Regulatory approvals

Breast fibroadenoma, 2012
 Thyroid nodules, 2007
 Varicose veins, 2019

Commercial treatments

Breast cancer
 Breast fibroadenoma
 Thyroid nodules
 Varicose veins

Clinical research

Breast cancer
 Breast fibroadenoma
 Graves' disease
 Head & neck tumors
 Multiple tumors
 Thyroid nodules
 Varicose veins

Devices

Echopulse
 SONOVEIN

Treatment guidance

Ultrasound

Wuxi Haiying Electronic Medical Systems CO LTD

Regulatory approval

Uterine fibroids, 2016

Commercial treatment

Uterine fibroids

Treatment guidance

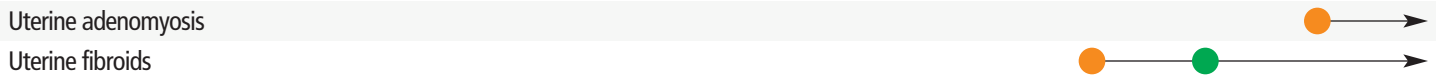
Ultrasound

STATE OF COMMERCIALIZATION

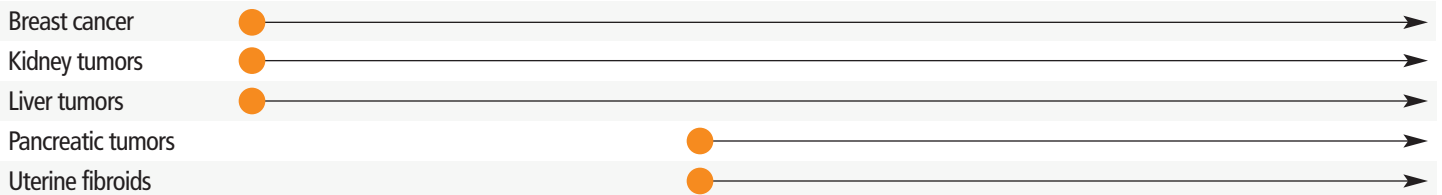
First Global Regulatory Approvals for Companies by Indication

Manufacturers 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19

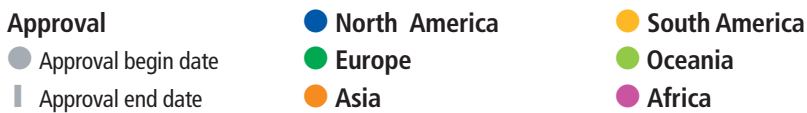
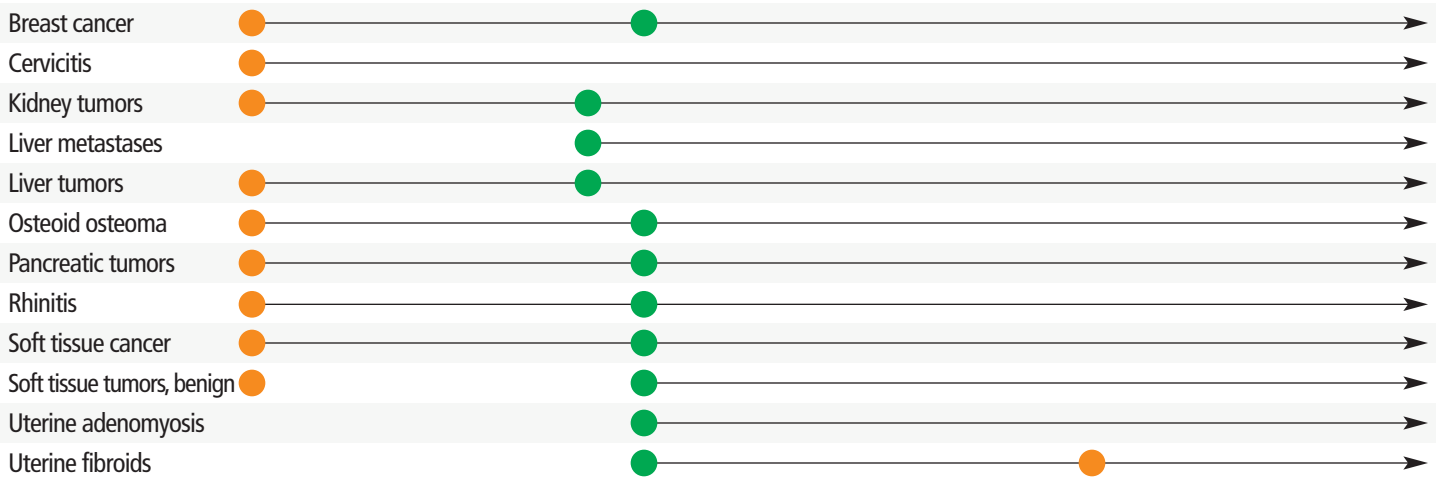
Alpinion Medical Systems



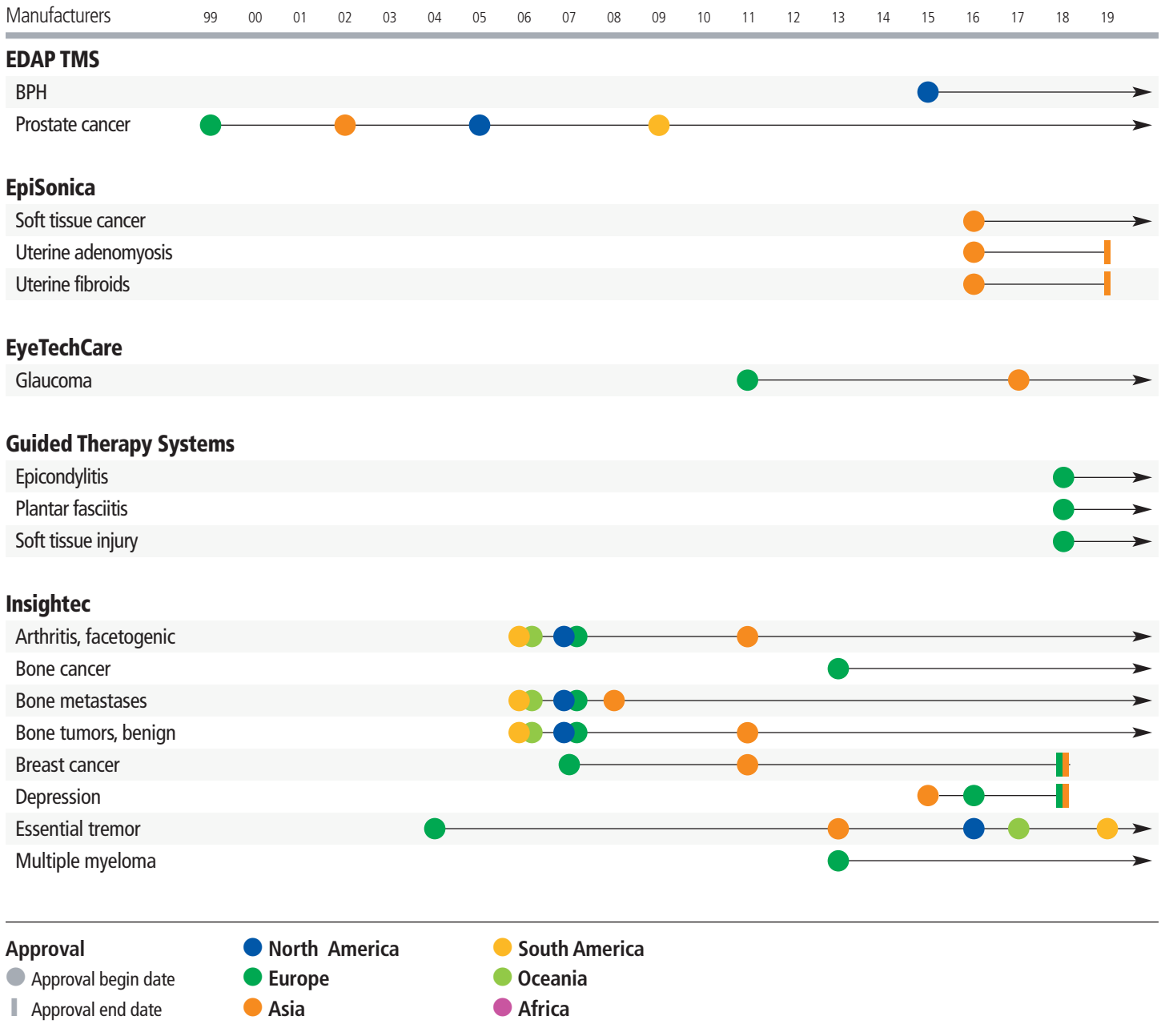
Beijing Yuande Bio-Medical Engineering



Chongqing Haifu Medical Technology

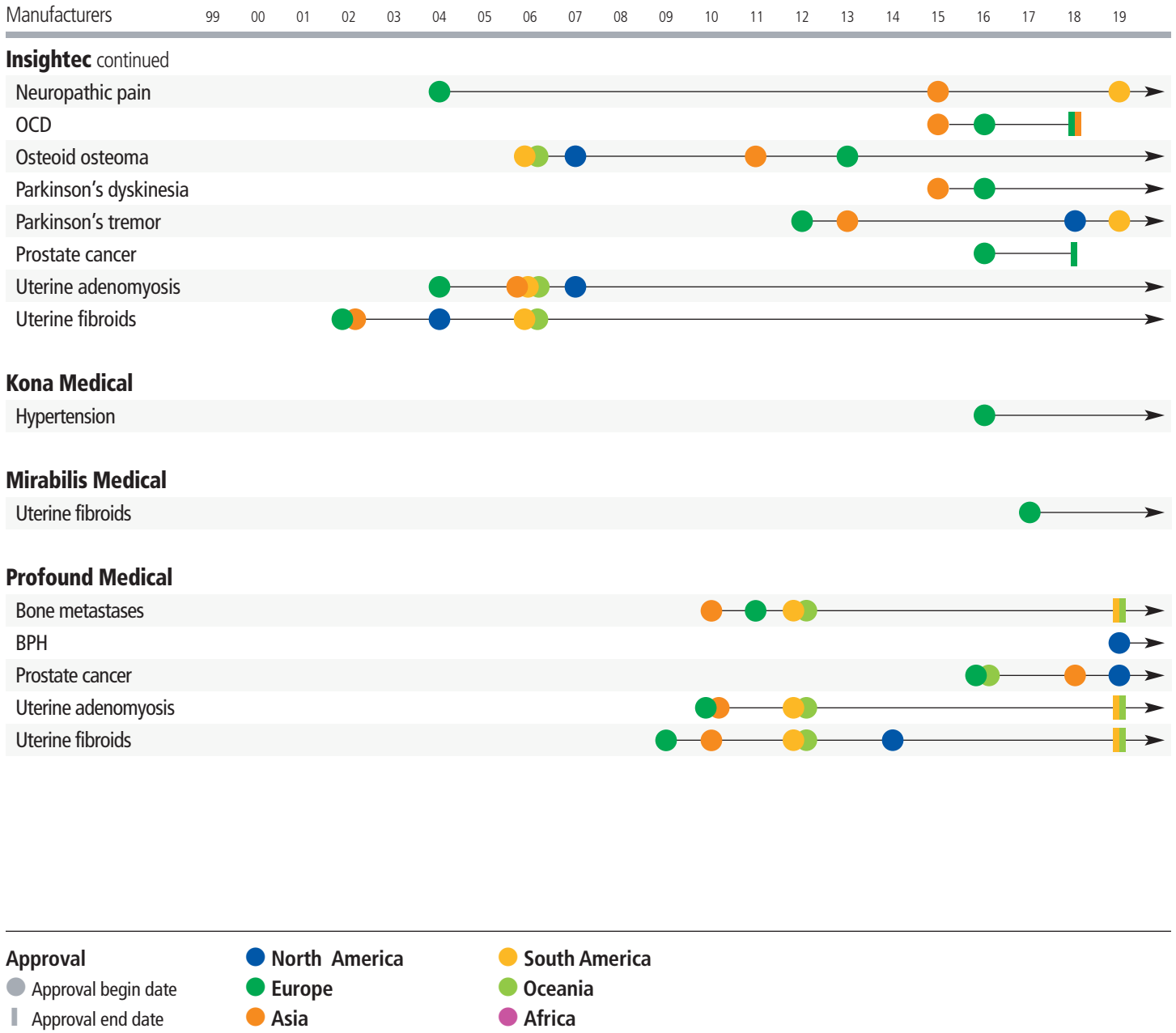


First Global Regulatory Approvals for Companies by Indication continued

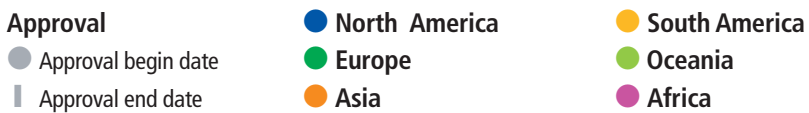
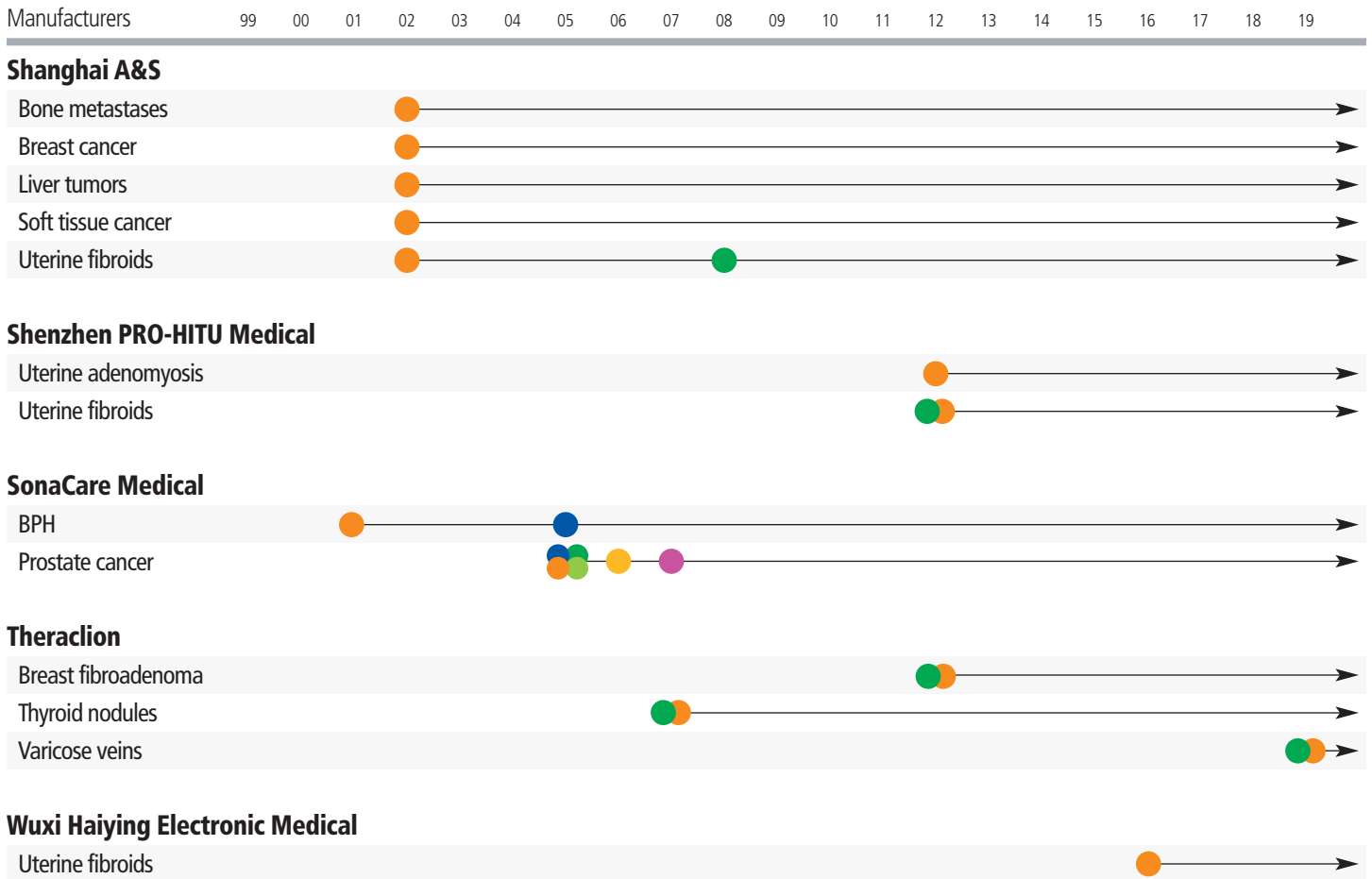


STATE OF COMMERCIALIZATION

First Global Regulatory Approvals for Companies by Indication continued



First Global Regulatory Approvals for Companies by Indication continued



STATE OF COMMERCIALIZATION

North America—FUS Regulatory Approvals by Company and Indication

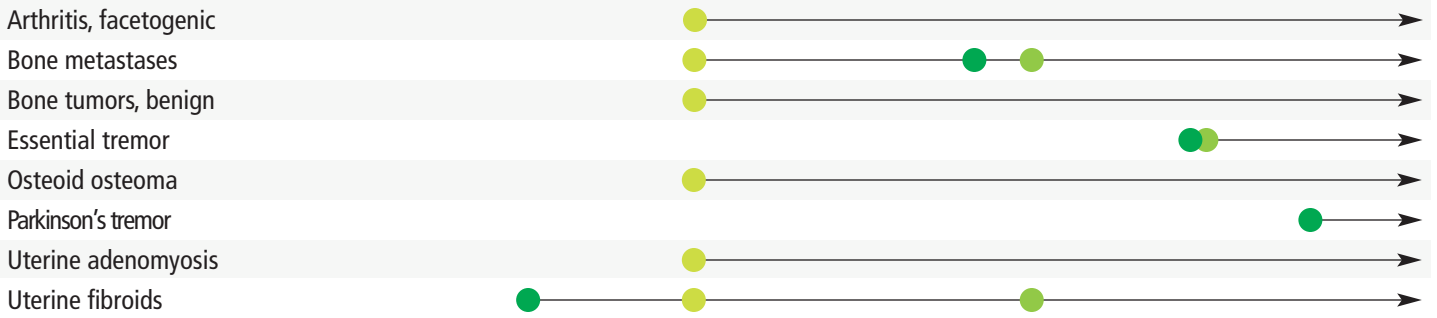
Manufacturers

99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19

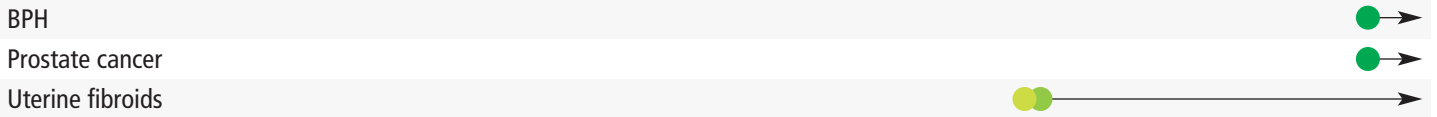
EDAP TMS



Insightec



Profound Medical



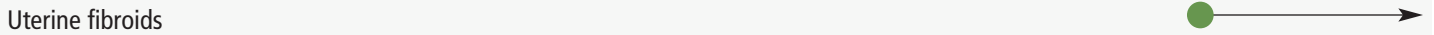
SonaCare Medical



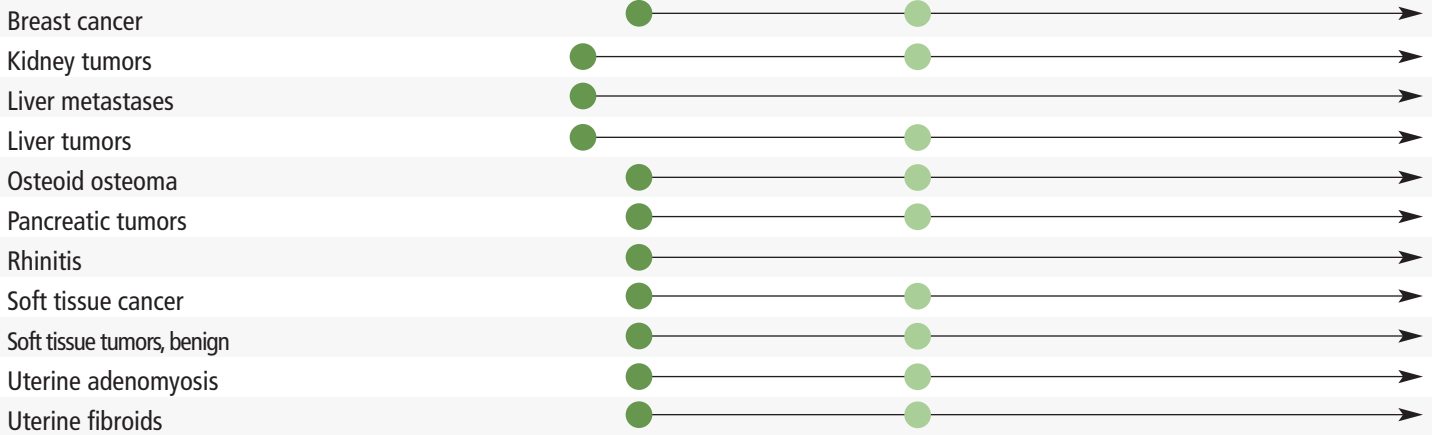
Europe—FUS Regulatory Approvals by Company and Indication

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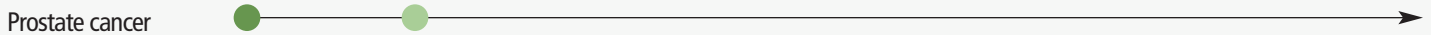
Alpinion Medical Systems



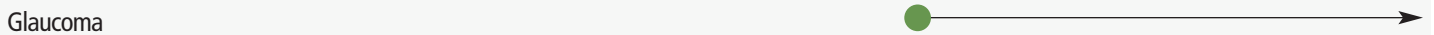
Chongqing Haifu Medical Technology



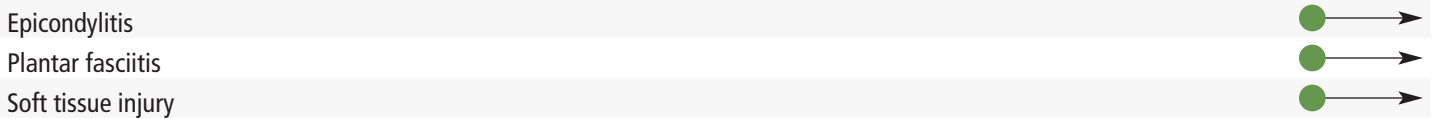
EDAP TMS



EyeTechCare



Guided Therapy Systems

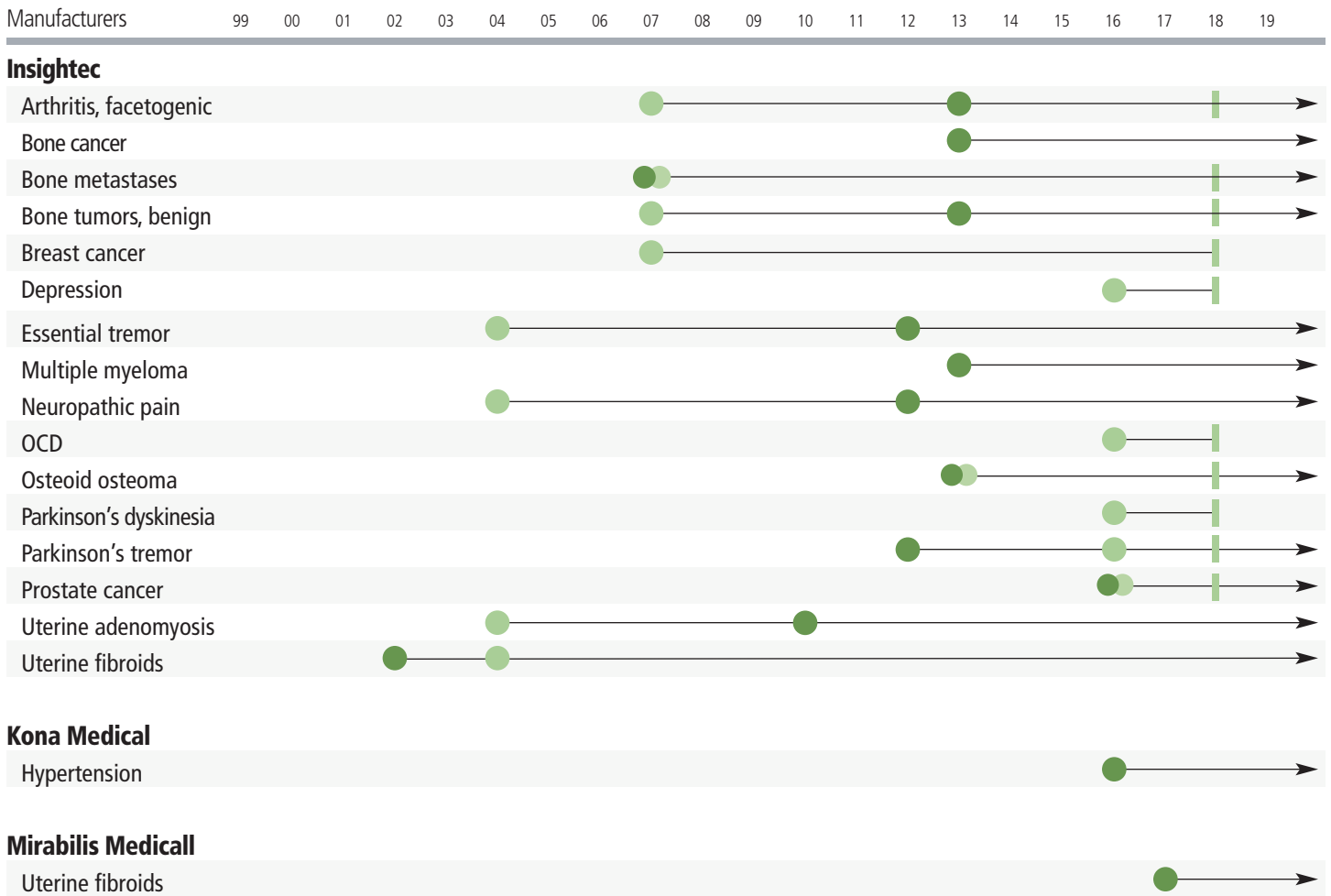


Approval
 ● Approval begin date
 | Approval end date

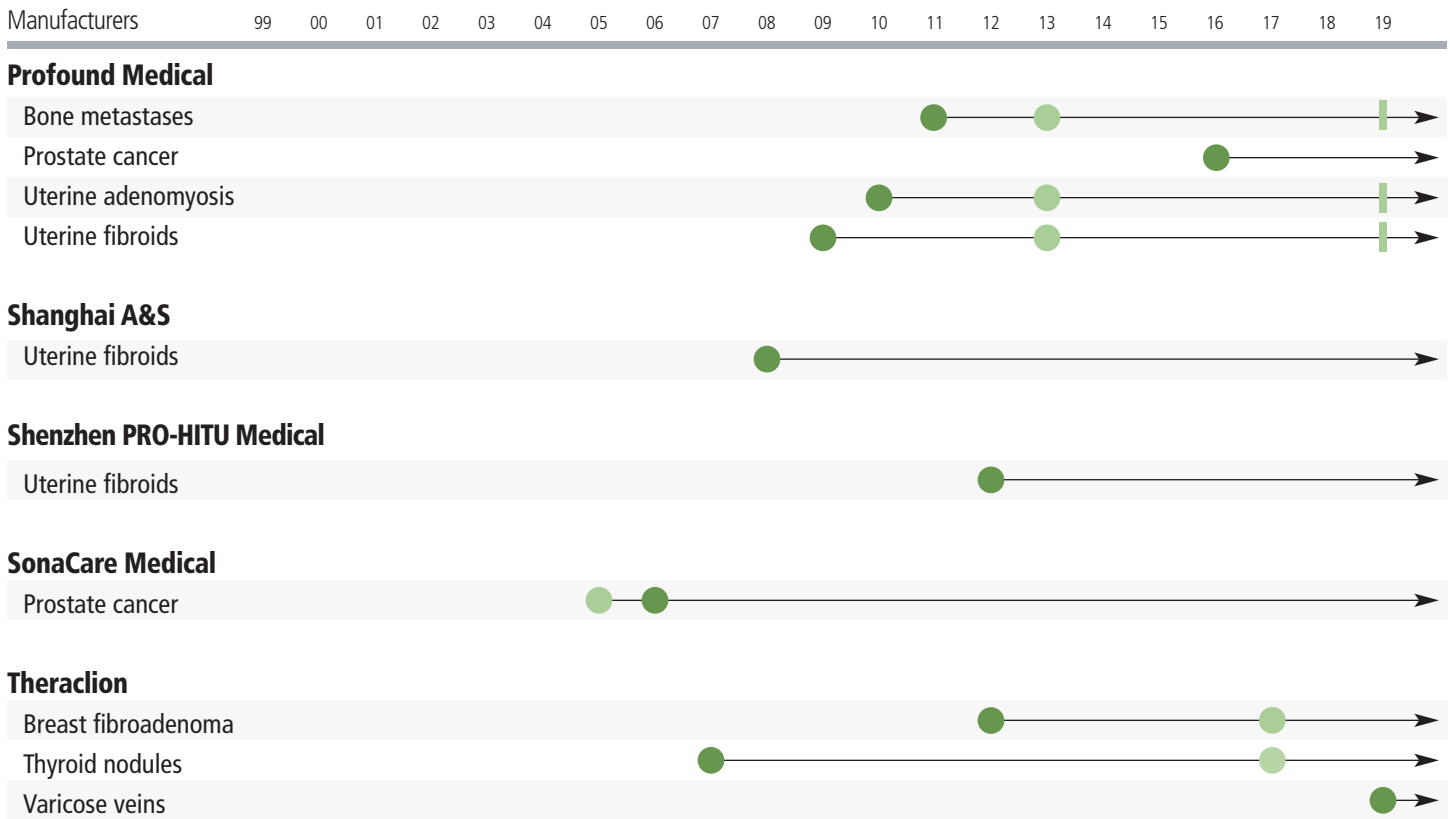
Europe
 ● Europe, CE Marking
 ● Russia, Roszdravnadzor

STATE OF COMMERCIALIZATION

Europe—FUS Regulatory Approvals by Company and Indication continued



Europe—FUS Regulatory Approvals by Company and Indication continued

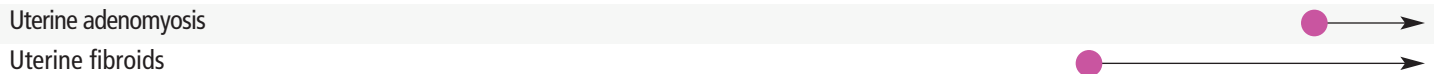


STATE OF COMMERCIALIZATION

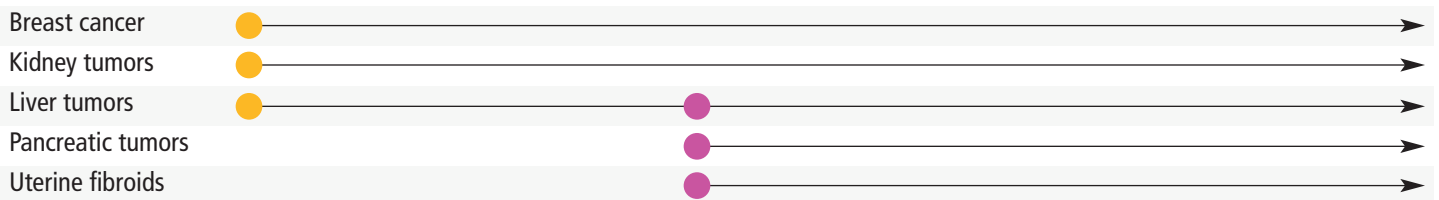
Asia—FUS Regulatory Approvals by Company and Indication

Manufacturers 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19

Alpinion Medical Systems



Beijing Yuande Bio-Medical Engineering



Chongqing Haifu Medical Technology



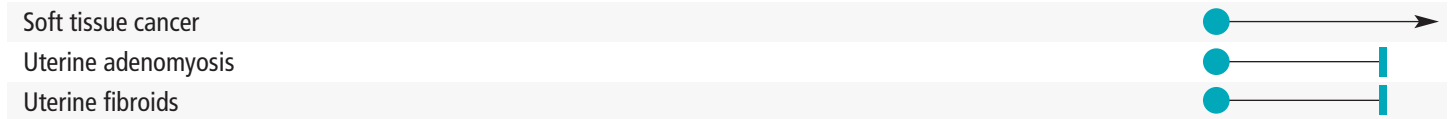
EDAP TMS



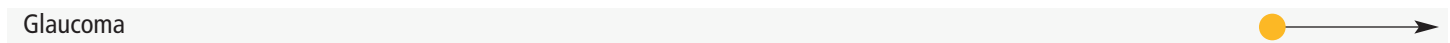
Asia—FUS Regulatory Approvals by Company and Indication continued

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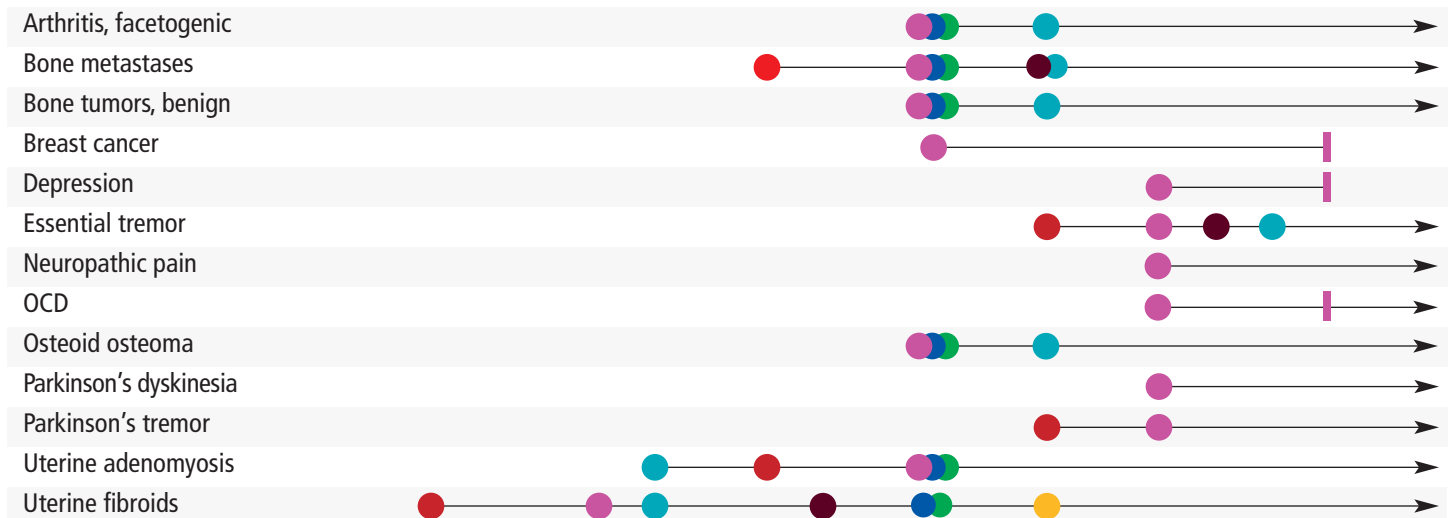
EpiSonica



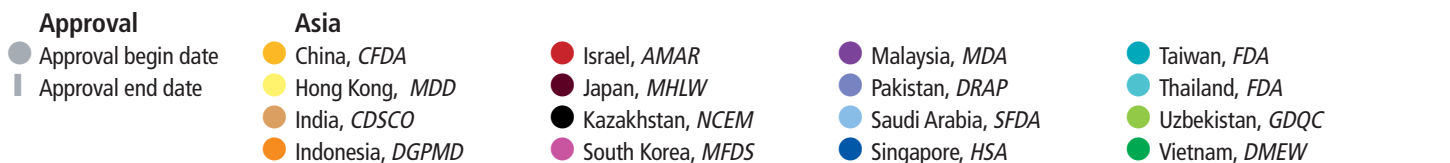
EyeTechCare



Insightec

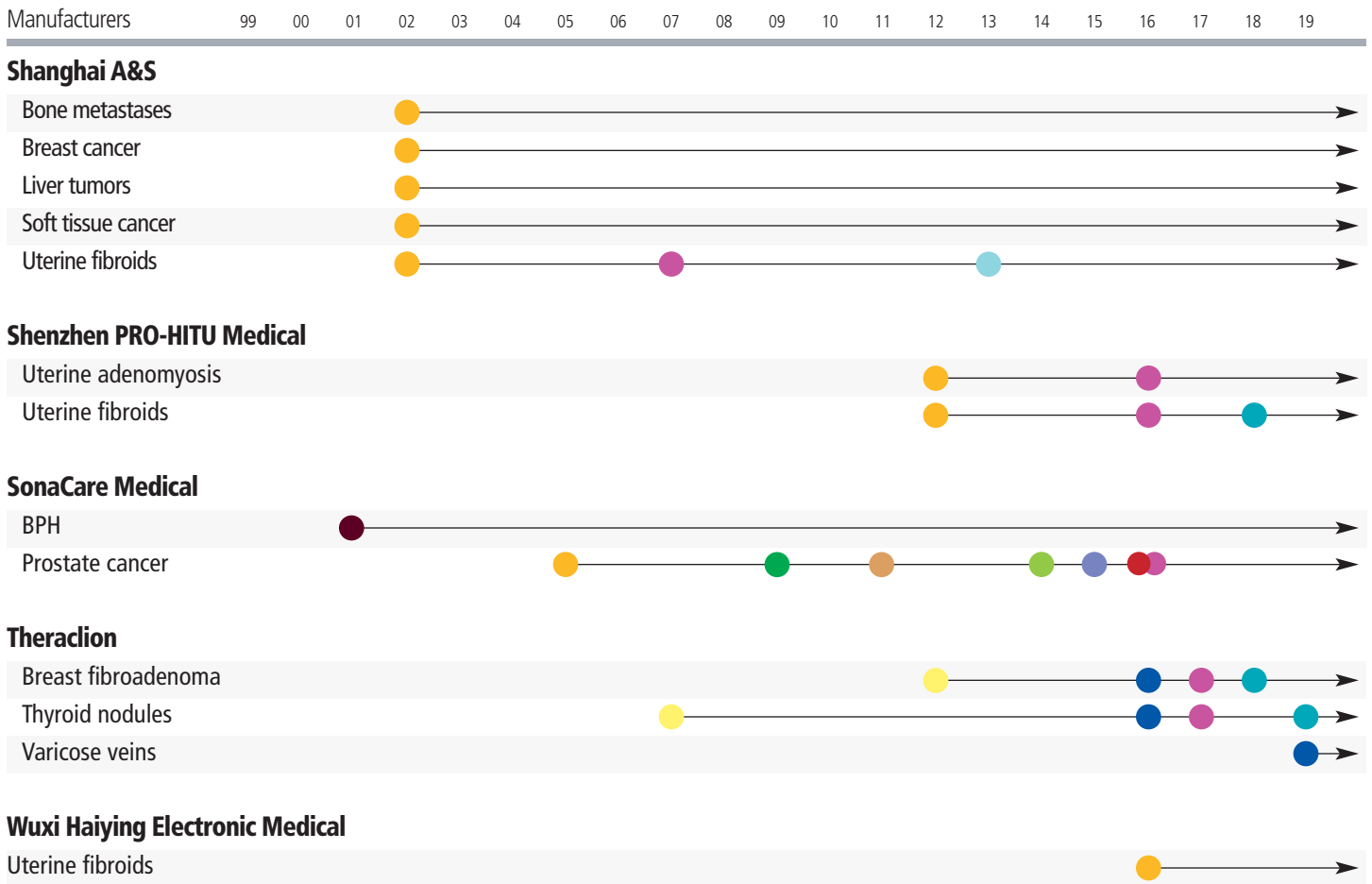


Profound Medical



STATE OF COMMERCIALIZATION

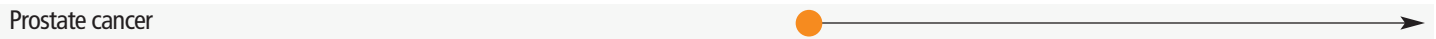
Asia—FUS Regulatory Approvals by Company and Indication *continued*



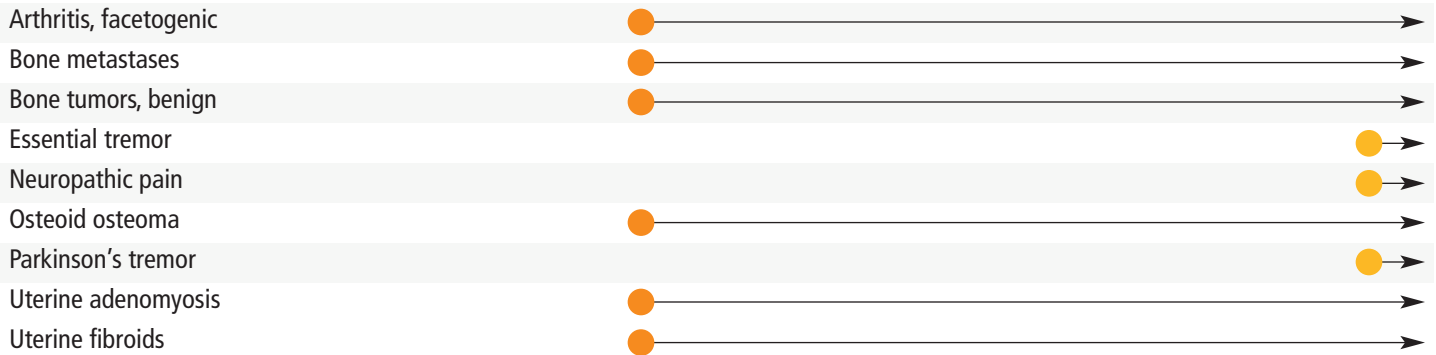
South America—FUS Regulatory Approvals by Company and Indication

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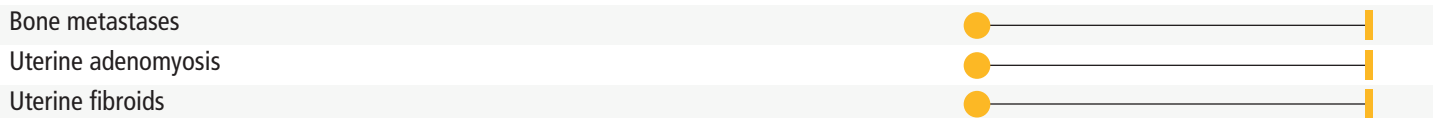
EDAP TMS



Insightec



Profound Medical

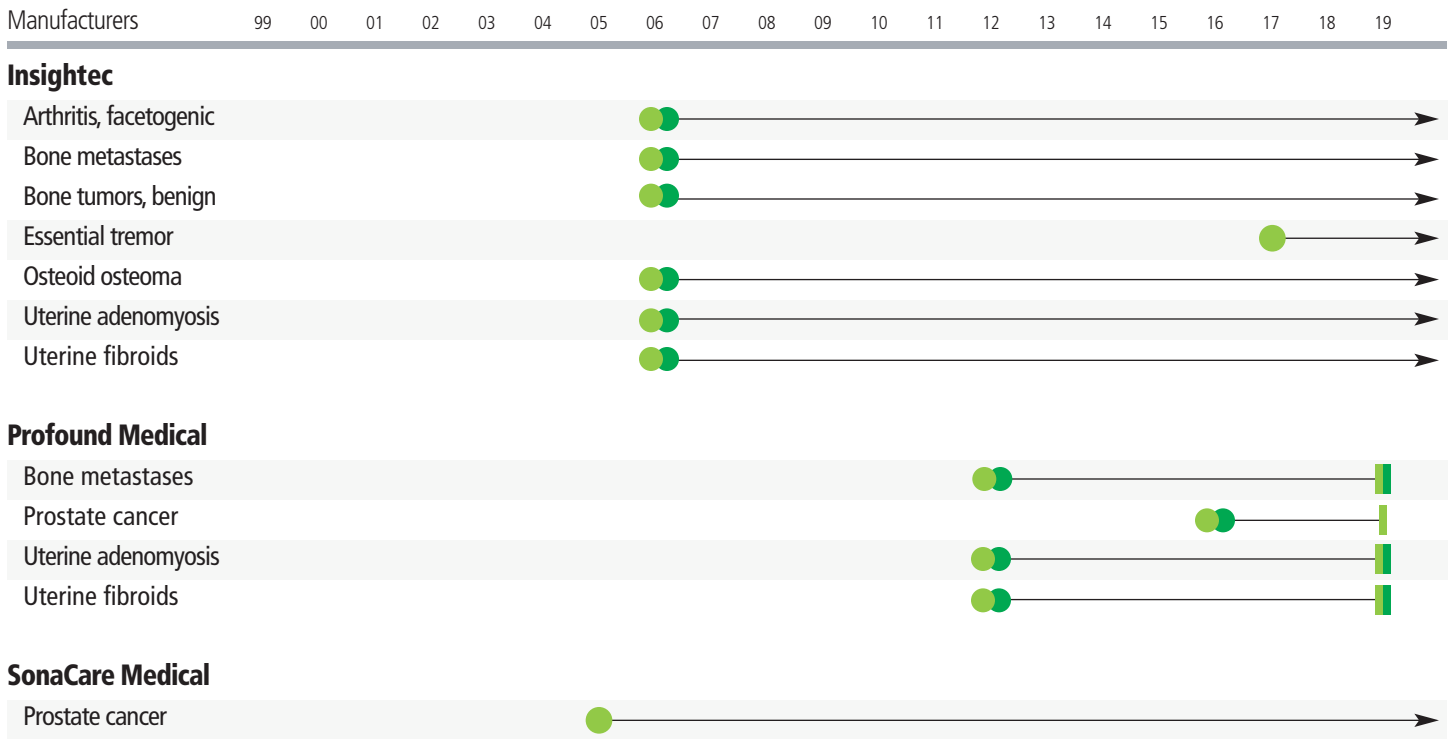


SonaCare Medical

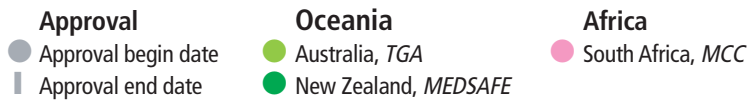
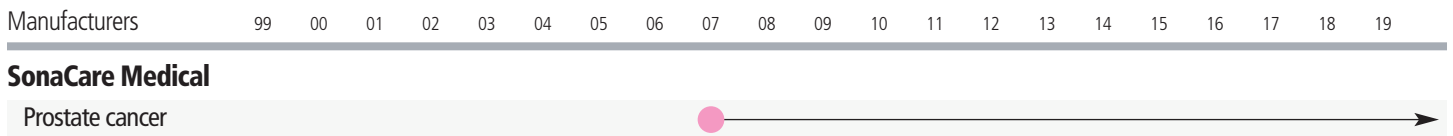


STATE OF COMMERCIALIZATION

Oceania—FUS Regulatory Approvals by Company and Indication



Africa—FUS Regulatory Approvals by Company and Indication

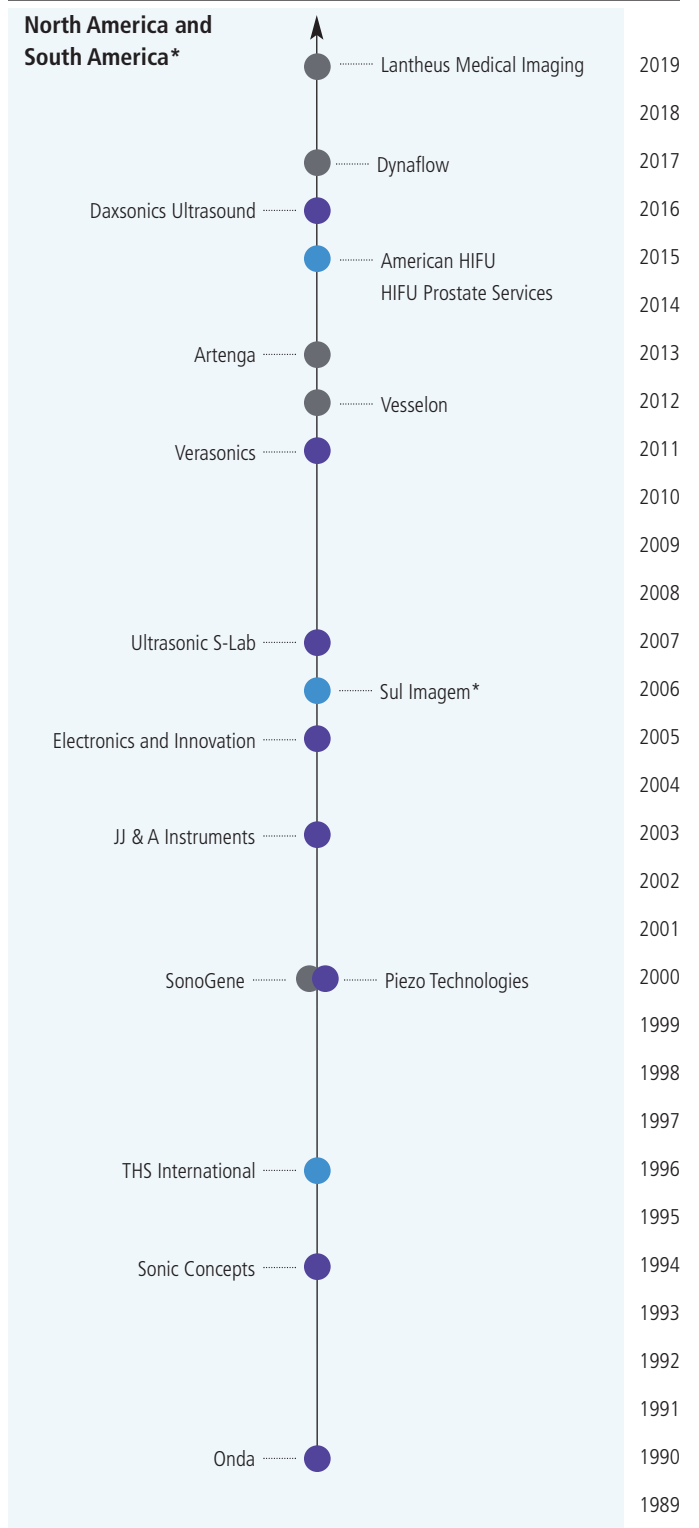


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Timeline of Other FUS Companies by Region

● Distributor ● Microbubble ● OEM

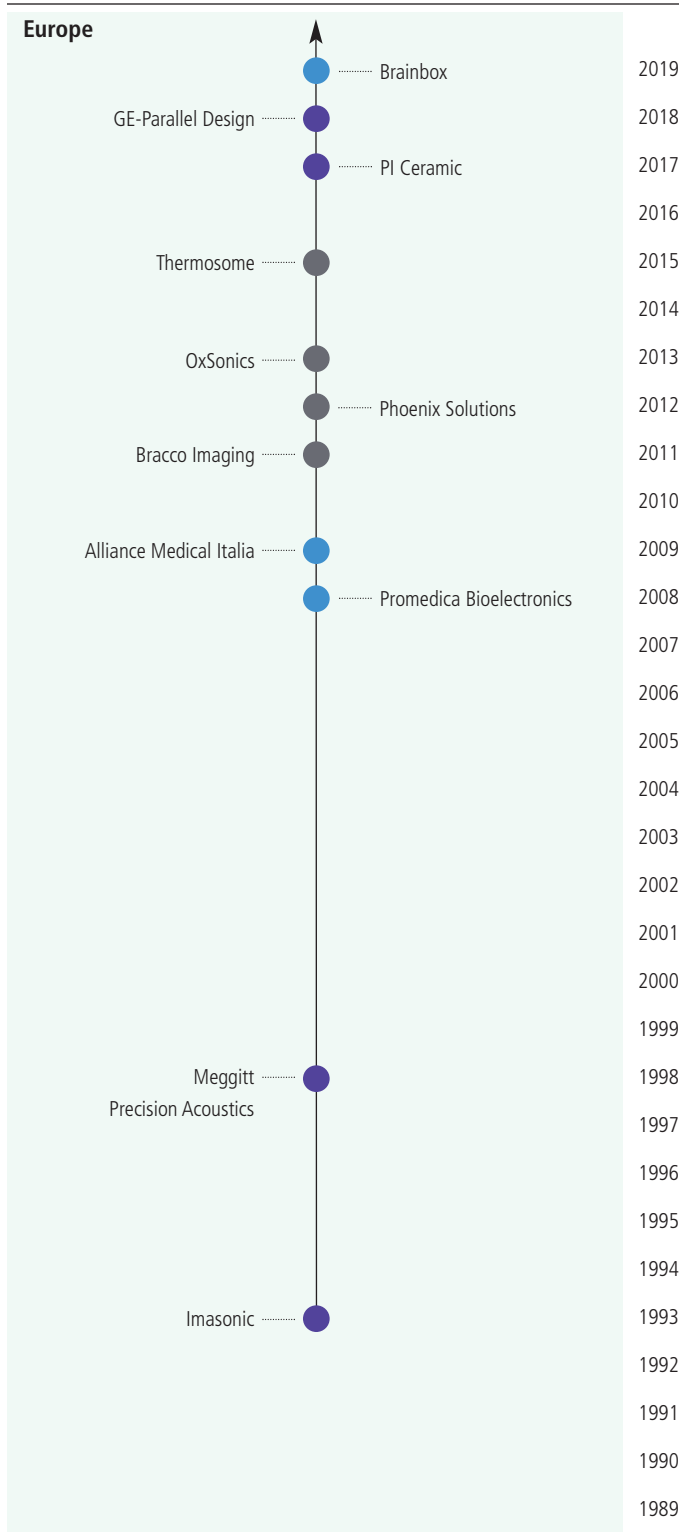
In past State of the Field Reports, the company timelines were based upon date of company formation. This year's reporting is a bit different. Instead of the date of incorporation we are reporting on the year the company became involved in the FUS industry. For many early-stage FUS manufacturing companies this date is one and the same; however, for the OEM manufacturers and/or microbubble companies listed here this is a difference from previous years.



*Located in South America

Timeline of Other FUS Companies by Region continued

● Distributor ● Microbubble ● OEM



FUS Industry by Region

Other FUS Companies

North America

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■ DISTRIBUTOR

American HIFU LLC | Naples, Florida, United States, americanhifu.com

HIFU Prostate Services LLC | Charlotte, North Carolina, United States, www.hifuprostateservices.com

THS International INC | Indianapolis, Indiana, United States, www.thsinternational.com

■ MICROBUBBLE

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

SonoGene LLC | Glen Ellyn, Illinois, United States

Vesselon INC | Norwalk, Connecticut, United States, www.vesselon.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 | Duvall, Washington, United States, jja-instruments.com

Onda INC | Sunnyvale, California, United States, www.ondacorp.com

Piezo Technologies | Indianapolis, Indiana, United States, www.piezotechnologies.com

Sonic Concepts INC | Bothell, Washington, United States, www.sonicconcpets.com

Ultrasonic S-Lab LLC | Concord, California, United States, www.ultrasonic-s-lab.com

Verasonics INC | Kirkland, Washington, United States, www.verasonics.com

Europe

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■ DISTRIBUTOR

Alliance Medical Italia SRL | Milano, Italy, www.alliancemedical.it

Brainbox LTD | Cardiff, Wales, United Kingdom, brainbox-neuro.com

Penta Elektronik Medikal Sistemler AS | Ankara, Turkey, penta-med.com.tr

Promedica Bioelectronics SRL | Roma, Italy, www.promedicasrl.eu

■ MICROBUBBLE

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

OxSonics LTD | Oxford, United Kingdom, www.oxsonics.com

Phoenix Solutions AS | Moss, Norway, www.phoenixsolutions.no

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

FUS Industry by Region continued

Other FUS Companies

Europe continued

■ OEM

GE-Parallel Design SAS | Sophia Antipolis, France

Imasonic SA | Voray-sur-l'Ognon, France, www.imasonic.com

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

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

Asia

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■ DISTRIBUTOR

Beijing Ren De Sheng Technology | Beijing, China

Demakai CO LTD | New Taipei City, Taiwan, www.dermacare.com.tw

ECHO Healthcare INC | Seoul, South Korea, www.hifu.kr

Sumo Corporations LTD | Shanghai, China, www.sumo.com.hk

■ OEM

EofE Ultrasonics CO LTD | Hanggongdaehak-ro, South Korea, ultrasonics.co.kr

Humanscan CO LTD | Ansan, South Korea, www.humanscan.co.kr

S-Sharp CORP | New Taipei City, Taiwan, www.s-sharp.com

Tamura CORP | Tokyo, Japan, www.tamuracorp.com

South America

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■ DISTRIBUTOR

Sul Imagem | São José, Brazil, www.sul-imagem.com.br

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.

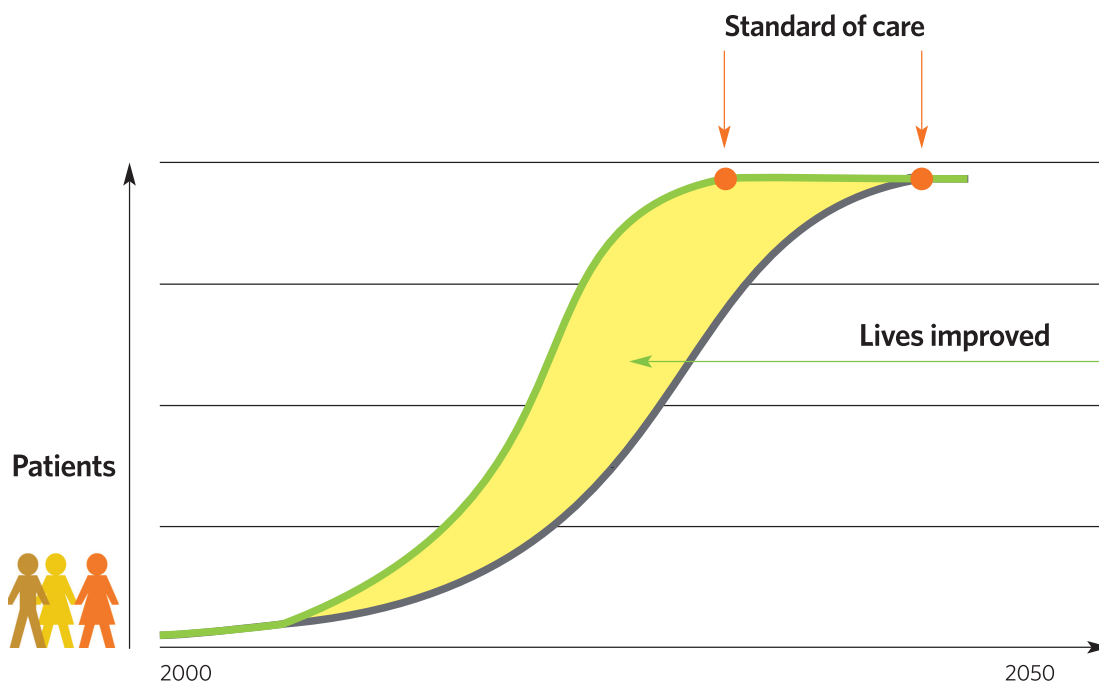
Major initiatives include

- 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 timeline of clinical adoption of the technology to treat more patients and relieve more suffering.

fusfoundation.org



Saving time = Saving lives

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

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*Deceased

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Date 9.8.2020

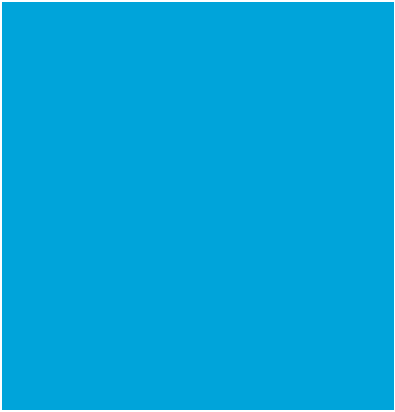
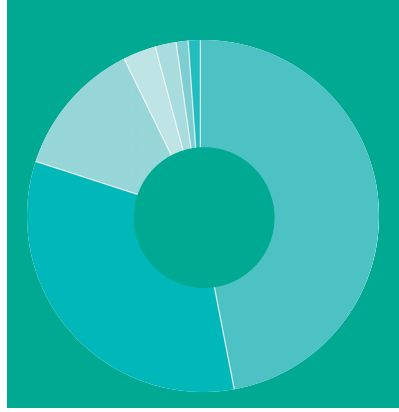
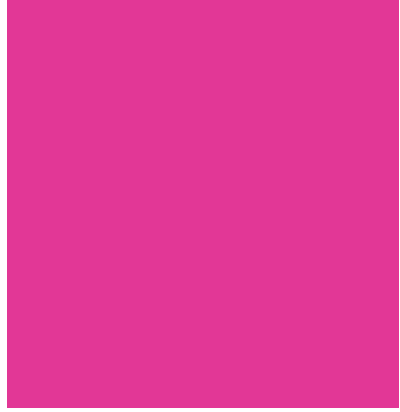
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The Focused Ultrasound Foundation strives to provide the most accurate information possible and therefore works proactively with the manufacturers and research sites to collect the most current data available in advance of the release of this publication. This report is based on data through December 31, 2019. The Focused Ultrasound Foundation assumes no responsibility for any errors or omissions as every precaution has been taken to verify the accuracy of the information contained herein. No liability is assumed for damages that may result from the use of information contained within. If you note something out of date or inaccurate, please submit the new information/updates to: info@fusfoundation.org.

The image features a teal-to-blue gradient background. On the left, a large, dark blue circular shape is partially visible. Overlapping this circle are several curved arrows: a light blue arrow at the top pointing left, and a white arrow at the bottom pointing right. Three white lines radiate from the left edge of the circle towards the center. The text 'Focused Ultrasound Foundation' is centered horizontally across the middle of the image.

Focused Ultrasound Foundation



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www.fusfoundation.org

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