2021

State of the Field

Focused Ultrasound Foundation

State of the Field Team

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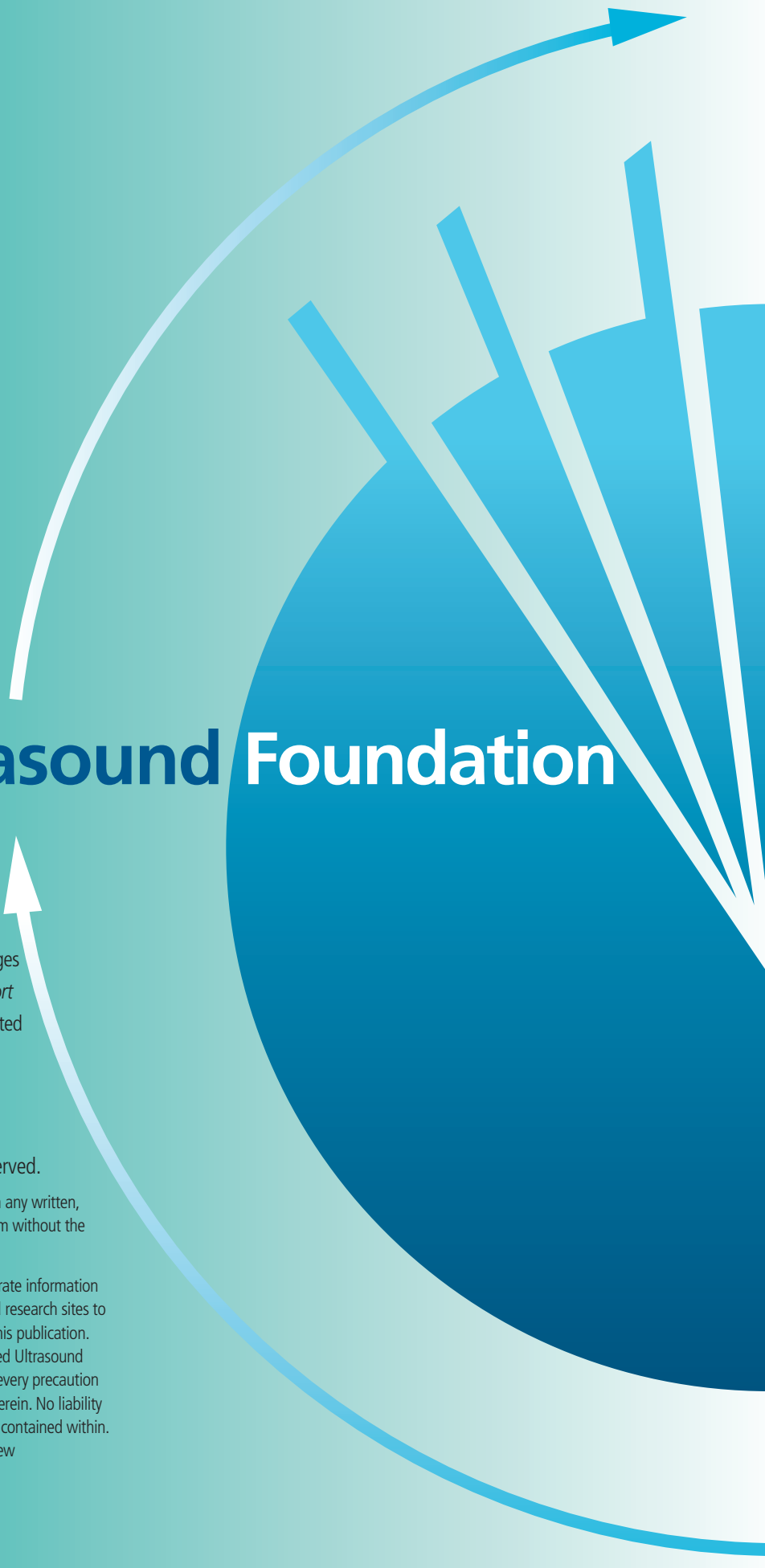

Focused Ultrasound Foundation

Date 7.15.2021

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, 2020. 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 If you note something out of date or inaccurate, please submit the new information/updates to: info@fusfoundation.org.

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Focused Ultrasound Foundation

FOCUSED ULTRASOUND FOUNDATION

Dear Friends,

As we look back at the accomplishments of the field in 2020, despite the COVID 19 worldwide pandemic we continue to be impressed with the depth and breadth of progress in the field of focused ultrasound. The bench researchers and clinicians working in this field were undaunted by the shutdowns and temporary suspensions of clinical trials due to COVID constraints. When they could not be in their labs conducting research or in their clinics treating patients, this community was busy drafting manuscripts for publications, dreaming up new projects, and writing statements of work or clinical trial protocols. Our scientific team was just as busy as in any other year with new funding applications—in addition to handling all the project modifications resulting from the COVID shut-downs.

We saw many groundbreaking discoveries in the technology's mechanisms of action and clinical indications as well as successes in regulatory approvals and reimbursement, including the technology's seventh US FDA approval, for the treatment of osteoid osteoma.

The vast majority of data contained in this document is self-reported and comes from our annual surveys sent to members of the focused ultrasound community every January.

Additionally, the Foundation actively collects data from various publicly available sources and reports, and gains invaluable personal knowledge gleaned through the phone calls and site visits of our 40+ staff members located around the globe. These folks are tireless in their efforts to reach out to sites within their respective geographic regions and to validate the work of those sites. They have sought to re-engage those who have gotten lost in the annual survey process and assist with the unglamorous job of cleaning up our database, the source of information from which this extensive annual report is generated. We are more confident in the accuracy of this year's report because of their efforts.

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 their contributions to this report.

Be well,

Emily White, MD
Editor in Chief
2021 State of the Field

Focused Ultrasound in Brief

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

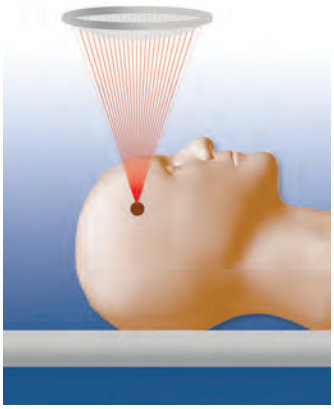
This revolutionary technology has the potential to increase the quality and longevity of life and decrease the cost of care by transforming the treatment of a range of indications.

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

Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver—thermal or mechanical—and whether the effects of treatment are permanent or transient. When focused ultrasound produces a high-power, continuous pressure wave, thermal energy accumulates rapidly at the focal point. This technique, termed thermal ablation, is currently used most frequently in the clinic and produces permanent effects. However, additional ultrasound treatment regimens are currently under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications currently in clinical trials is a low-power, pulsed treatment that produces mild mechanical forces capable of enhancing drug delivery to the brain. 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 altered immune response is dependent on the nature of the focused ultrasound treatment parameters, although most treatments do induce a response.

There are currently 152 clinical indications or disorders in various stages of development, and the number is increasing rapidly. Most are early stage. Worldwide, 34 indications have regulatory approval; in the US, 7 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.

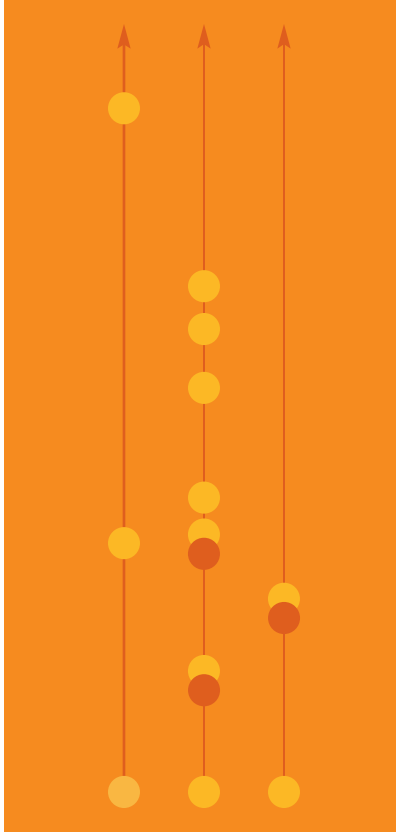


2021 Field Overview

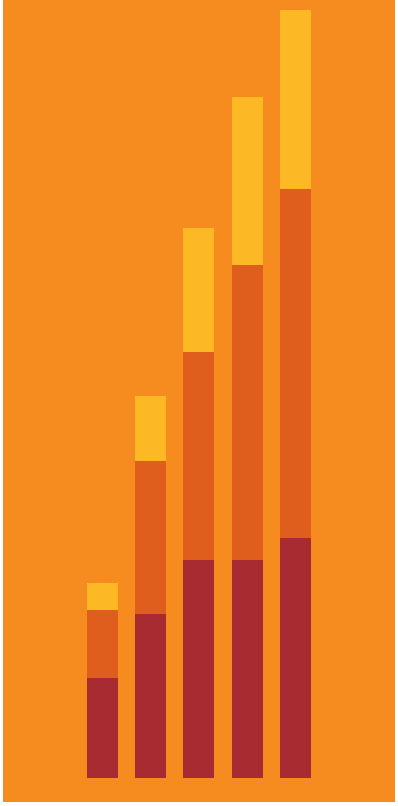
Focused Ultrasound Foundation

81,332
patient treatments
in 2020

152
distinct indications
in 2020

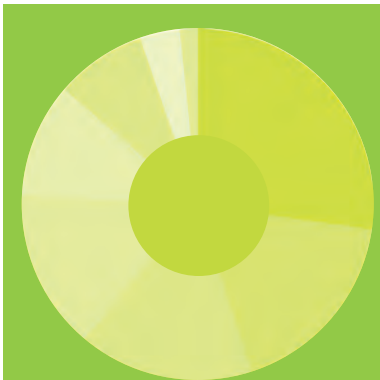


32
regulatory approvals
in new geographic regions



1,883
brain treatments
in 2020

10
Centers of Excellence



47,506
oncology treatments
in 2020

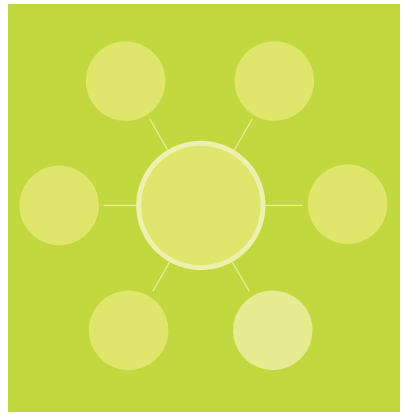
Field Overview

The Field Overview is designed to give the "big picture" of the state of the field for focused ultrasound. It highlights the cumulative growth of focused ultrasound as well as the annual growth in 2020. Six indications transitioned from bench research to first-in-human clinical trials. Eleven new indications were identified in 2020, further confirming the continuing growth and expansion of the focused ultrasound field.

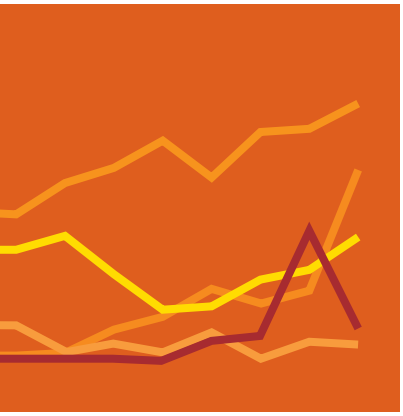
New this year is a one-page summary of all types of research and treatment, with sites broken down by region. This summary format provides a succinct overview of how big the field of focused ultrasound is on a global scale.

As was discussed at the beginning of this report (p iii), part of the appeal of focused ultrasound as a technology platform is the depth and breadth of the way a sound wave can affect the body. In 2020, for the first time, we are reporting on the cumulative number of mechanisms of action by indication and stage of research.

We hope you find the 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.



11
new indications
in 2020



$62m
federal funding
for FUS research

Contents

I. Field Overview

Development Stage Advancements and New Indications

2020

11

New indications

Gastrointestinal	Inflammatory bowel disease (Preclinical) Irritable bowel syndrome (Preclinical)
Miscellaneous	Heterotopic ossification (Preclinical) Infection (Preclinical) Kaposi's sarcoma (Clinical)
Musculoskeletal	Osteopenia (Preclinical)
Neurological	Mood disorder (Clinical)
Ophthalmological	Retinal impairment (Preclinical) Retinal injury (Preclinical)
Women's Health	Hyperplasia of the vulva (Clinical) Lichen sclerosis (Clinical)

Development stage

● Preclinical ● Clinical

2020

6

Indications advanced to first-in-human clinical trials

Cardiovascular	Twin-twin transfusion syndrome
Miscellaneous	Kaposi's sarcoma†
Neurological	Mood disorder† Parkinson's disease, underlying cause
Women's health	Hyperplasia of the vulva† Lichen sclerosis†

† New Indication for 2020

Development stage advancements

2020 saw an addition of 11 new indications to the focused ultrasound landscape. Four of these new indications were identified for the first time at the clinical trial stage. Six indications advanced to first-in-human clinical trials. Details on where this research is taking place can be found in Section II of this report.

No new indications were granted regulatory approval in 2020, but many indications were granted regulatory approval in new geographic regions, further expanding the global nature of focused ultrasound technology.

NEW

Development Stage Advancements and New Indications continued

2020

32

New global regulatory approvals

Brazil | ANVISA

Essential tremor
Neuropathic pain
Parkinson's disease, tremor

China | NMPA

Benign prostatic hyperplasia
Prostate cancer

Hong Kong | MDD

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

Japan | MHLW

Parkinson's disease, dyskinesia
Parkinson's disease, tremor

Kazakhstan | NCEM

Essential tremor
Neuropathic pain
Parkinson's disease, tremor

Taiwan | FDA

Prostate cancer

Thailand | FDA

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

United States | FDA, Center for Devices

Osteoid osteoma

Industry Highlights

NEW

2020

$326m

Invested in

9

FUS industry companies

CarThera SA
EXACT Therapeutics AS
Exo Imaging INC
HistoSonics INC
Insightec LTD
Microvascular Therapeutics LLC
NeuroSonics Medica INC
Profound Medical CORP
Theraclion SA

2020

6

New FUS industry companies

4 Distributors

1 Microbubble company

1 Clinical device manufacturer

Industry growth

2020 saw nearly triple the amount of investment dollars in the field compared to 2019. Details on this incredible level of investment and the names and details of the new companies started in 2020 can all be found in Section III of this report.

The addition of 214 commercial treatment sites in the past year is further proof of transition of the field from "if" the technology will be adopted to "when" it will occur. In 2020 there were 15 focused ultrasound manufacturers in full-scale commercialization efforts through their partnerships with 15 distributors.

NEW

Industry Highlights continued

2020

214

New focused ultrasound commercial treatment sites worldwide

North America	Europe	Asia	South America	Oceania	Africa
51	90	66	5	1	1

An increase over 2019 of

36%

bringing the total number of focused ultrasound commercial treatment sites to

799

State of Research and Regulatory Approvals by Body System

Cardiovascular

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

Endocrine disorders

- Thyroid nodules
- Graves' disease
- Hyperparathyroidism
- Thyroid cancer
- Diabetes

Gastrointestinal

- Liver metastases
- Liver tumors
- Pancreatic tumors, malignant
- Biliary tract cancer
- Colorectal tumors
- Esophageal tumors
- Gastric tumors
- Malignant obstructive jaundice
- Pancreatic tumors, benign
- Root canal endodontia
- Inflammatory bowel disease†
- Irritable bowel syndrome†
- Liver fibrosis

Miscellaneous

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

There are 152 distinct indications for 2020.

1 Protocols inclusive of more than one indication

† New in 2020

State of Research and Regulatory Approvals by Body System continued

Musculoskeletal

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

Neurological

- Essential tremor
- Parkinson's disease, tremor
- Depression
- Neuropathic pain
- Obsessive-compulsive disorder
- Parkinson's disease, dyskinesia
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Astrocytoma
- Brain tumors, general
- Cancer pain
- Dementia
- Dystonia
- Dystonia, hand
- Epilepsy
- Glioblastoma
- Holmes tremor
- Huntington's disease
- Migraine
- Mood disorder†
- Multiple sclerosis
- Neuroblastoma
- Neuropathy
- Opioid and other addictions
- Painful amputation neuromas
- Parkinson's disease, other[3]
- Pontine glioma
- Traumatic brain injury
- Cavernomas
- Hydrocephalus
- Neuromyelitis optica
- Rett syndrome
- Spinal cord injury
- Stroke, intracerebral hemorrhage
- Stroke, thromboembolic
- Trigeminal neuralgia
- Anorexia

There are 152 distinct indications for 2020.

2 Multiple myeloma approval is based on bone metastases.
3 Treatment of the underlying cause of the disease
† New in 2020

State of Research and Regulatory Approvals by Body System continued

Ophthalmological

- Glaucoma
- Keratoplasty
- Macular degeneration
- Retinal impairment†
- Retinal injury†

Pulmonary

- Rhinitis
- Lung cancer
- Lung metastases
- Tuberculosis

Urological

- Prostate cancer[4, 5]
- Benign prostatic hyperplasia[4]
- Kidney tumors
- Bladder tumors
- Chyluria
- Kidney stones
- Acute kidney injury
- Acute tubular necrosis
- Fetal bladder obstruction
- Ureterocele
- Urinary tract infection
- Vasectomy

Women's health

- Uterine fibroids
- Breast tumors, benign
- Breast tumors, malignant
- Cervicitis
- Lichen sclerosis†
- Uterine adenomyosis
- Brain metastases, breast cancer
- Cervical tumors
- Ectopic pregnancy
- Endometrial tumors
- Endometriosis
- Endometriosis, colorectal
- Hyperplasia of the vulva†
- Ovarian tumors
- Retained placenta
- Vaginal tumors
- Vulvar dystrophy
- Polycystic ovary syndrome

There are 152 distinct indications for 2020.

4 FDA approval is for prostate tissue ablation.
5 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
† New in 2020

Indications with Anecdotal Case Reports

Indications	Date	Mechanism of action	Reference
Cardiovascular			
Arteriovenous malformations	2015	Thermal ablation, Tissue destruction	https://doi.org/10.1186/s40349-015-0042-7 https://doi.org/10.1111/1471-0528.14749
Fetal heart anomalies	2012	Thermal ablation, Tissue destruction	https://doi.org/10.1002/uog.11114 https://doi.org/10.1002/uog.20101
Endocrine disorders			
Insulinoma	2010	Thermal ablation, Tissue destruction	https://doi.org/10.1007/s00270-010-9884-0
Gastrointestinal			
Liver alveococcosis	2015	Thermal ablation, Tissue destruction	https://doi.org/10.1016/j.ultsonch.2015.05.022 https://doi.org/10.1007/s10396-018-0914-x

Areas of Interest

A note on multiple listings

The preceding chart's categories are body systems, comprising a group of tissues structured to perform specific functions. All indications in development for focused ultrasound treatment appear on this chart, in the body system category to which they belong. Thus, bone metastases is in the Musculoskeletal category, but nowhere else. A chart arranged solely by body system can skew the assessment of focused ultrasound's impact on diseases with wide-ranging effects.

In an effort to see the data through a different lens, four "Areas of Interest"—Fetal, Oncology, Pain, and Pediatrics—have been identified and make up the categories in the chart that follows. Indications that do not match with any of the Areas of Interest will not appear in this chart, but those that do may appear in multiple categories; bone metastases, for example, appears in Oncology, Pain, and Pediatrics. Looking at the indications by "Area of Interest" reveals patterns and trends over time that might otherwise be difficult to discern.

State of Research and Regulatory Approvals by Area of Interest

Fetal

- Twin-twin transfusion syndrome
- Fetal bladder obstruction
- Fetal heart anomalies

Pediatrics

- Bone metastases
- Osteoid osteoma
- Soft tissue cancer
- Soft tissue tumors, benign
- Astrocytoma
- Brain tumors, general
- Desmoid tumors
- Epilepsy
- Multiple tumors[1]
- Neuroblastoma
- Pontine glioma
- Sacral chordoma
- Coarctation of the aorta
- Hydrocephalus
- Hypoplastic left heart syndrome
- Septal perforation
- Ureterocele
- Anorexia

1 Protocols inclusive of more than one indication

State of Research and Regulatory Approvals by Area of Interest continued

Oncology

- Bone metastases
- Prostate cancer[4,5]
- Bone cancer
- Breast tumors, malignant
- Kidney tumors
- Liver metastases
- Liver tumors
- Multiple myeloma[2]
- Pancreatic tumors, malignant
- Soft tissue cancer
- Astrocytoma
- Basal cell carcinoma
- Biliary tract cancer
- Bladder tumors
- Brain metastases, breast cancer
- Brain tumors, general
- Cancer pain
- Cervical tumors
- Colorectal tumors
- Endometrial tumors
- Esophageal tumors
- Gastric tumors
- Glioblastoma
- Head & neck tumors
- Kaposi's sarcoma†
- Lung cancer
- Lung metastases
- Melanoma
- Multiple tumors[1]
- Neuroblastoma
- Ovarian tumors
- Pontine glioma
- Sacral chordoma
- Thyroid cancer
- Vaginal tumors

Pain

- Bone metastases
- Osteoid osteoma
- Arthritis, facetogenic
- Bone cancer
- Bone tumors, benign
- Multiple myeloma[2]
- Neuropathic pain
- Pancreatic tumors, malignant
- Soft tissue injury
- Arthritis
- Arthritis, ankle
- Arthritis, hand
- Arthritis, hip
- Arthritis, knee
- Arthritis, sacroiliac
- Cancer pain
- Dercum's disease
- Desmoid tumors
- Migraine
- Neuropathy
- Painful amputation neuromas
- Pancreatic tumors, benign
- Osteomyelitis
- Trigeminal neuralgia

1 Protocols inclusive of more than one indication
2 Multiple myeloma approval is based on bone metastases.
4 FDA approval is for prostate tissue ablation.
5 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
† New in 2020

Global Development Landscape by Body System

Cardiovascular

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

Endocrine disorders

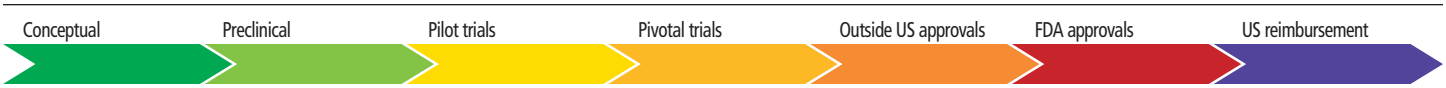
Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Diabetes	Grave's disease Hyperparathyroidism Thyroid cancer		Thyroid nodules		

Gastrointestinal

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

† New in 2020

Global Development Landscape by Body System continued



Miscellaneous

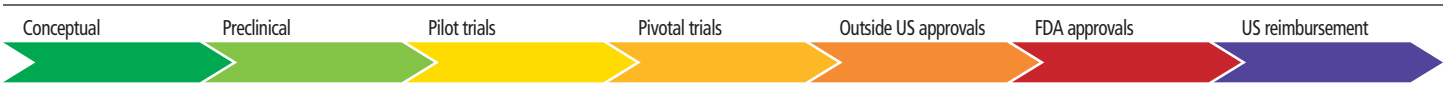
Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Heterotopic ossification† Infection† Wound healing	Actinic keratosis Basal cell carcinoma Dercum's disease Head & neck tumors Hypersplenism Kaposi's sarcoma† Lipoma Melanoma Multiple tumors[1] Obesity				

Musculoskeletal

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Muscle atrophy Osteomyelitis Osteopenia† 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 Osteoid osteoma	Bone metastases

1 Protocols inclusive of more than one indication
2 Multiple myeloma approval is based on bone metastases.
† New in 2020

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 Rett syndrome Spinal cord injury Stroke, intracerebral hemorrhage Stroke, thromboembolic Trigeminal neuralgia	Alzheimer's disease Amyotrophic lateral sclerosis Astrocytoma Brain tumors, general Cancer pain Dementia Dystonia Dystonia, hand Epilepsy Glioblastoma Holmes tremor Huntington's disease Migraine Mood disorder† Multiple sclerosis Neuroblastoma Neuropathy Opioid and other addictions Painful amputation neuromas Parkinson's disease, other[3] 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 Parkinson's disease, tremor

Ophthalmological

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Keratoplasty Macular degeneration Retinal impairment† Retinal injury†			Glaucoma		

3 Treatment of the underlying cause of the disease
† New in 2020

Global Development Landscape by Body System continued

Pulmonary

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Tuberculosis	Lung cancer Lung metastases		Rhinitis		

Urological

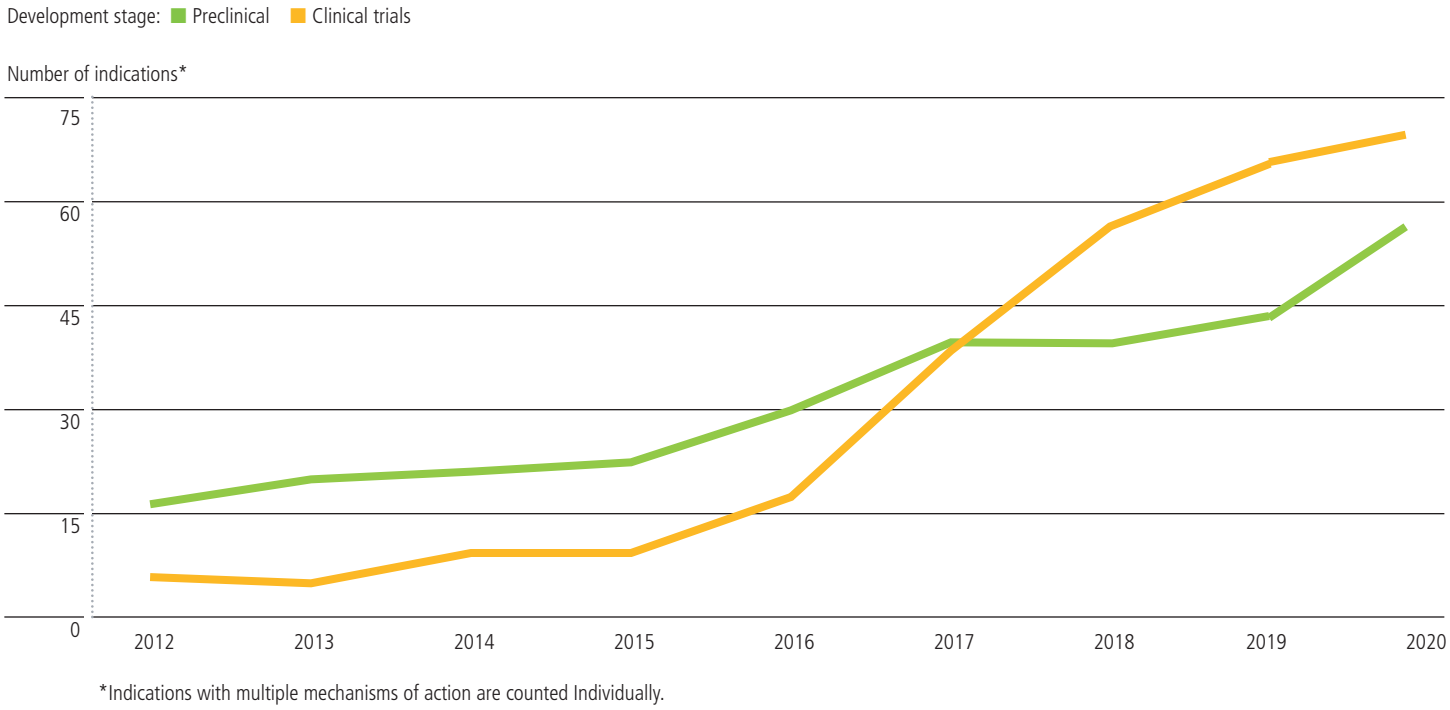
Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Acute kidney injury Acute tubular necrosis Fetal bladder obstruction Ureterocele Urinary tract infection Vasectomy	Bladder tumors Chyluria Kidney stones		Benign prostatic hyperplasia[4] Kidney tumors Prostate cancer[4,5]	Benign prostatic hyperplasia[4] Prostate cancer	Prostate cancer[4,5]

Women's health

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
	Polycystic ovary syndrome	Brain metastases, breast cancer Cervical tumors Ectopic pregnancy Endometrial tumors Endometriosis Endometriosis, colorectal Hyperplasia of the vulva† Ovarian tumors Retained placenta Vaginal tumors Vulvar dystrophy		Breast tumors, benign Breast tumors, malignant Cervicitis Lichen sclerosis† Uterine adenomyosis Uterine fibroids	Uterine fibroids	

4 FDA approval is for prostate tissue ablation.
5 Reimbursement is for salvage therapy in radiorecurrent prostate cancer.
† New in 2020

Development Stages of FUS Research

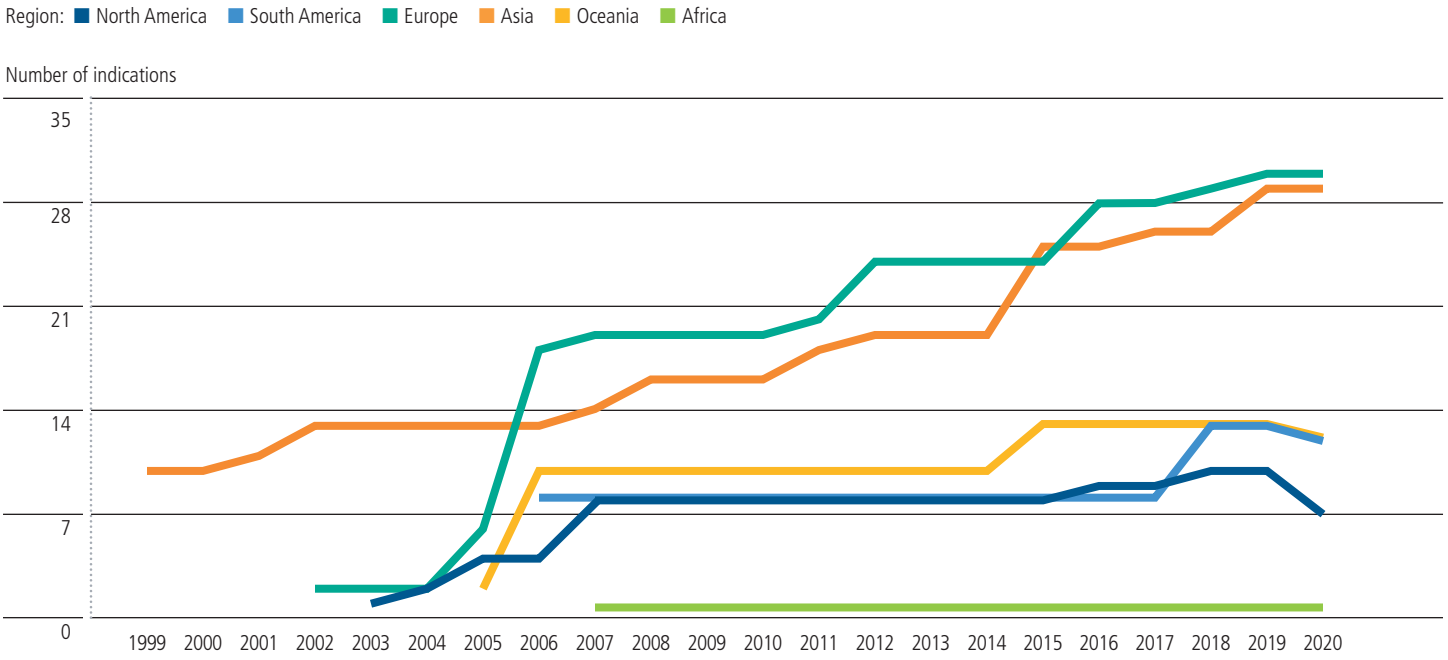


*Indications with multiple mechanisms of action are counted Individually.

Development stages of focused ultrasound research

The intersection of the preclinical and clinical research lines in 2017 is an inflection point in the field of focused ultrasound. It marks the transition of the field away from an early-stage, bench research-and-development proof of concept to first-in-human clinical trials. The 11 new indications in 2020, discussed earlier in this document, are reflected in the steeper upward trend in the slope of the preclinical line between 2019 and 2020.

Cumulative Approved Indications by Region*



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

Cumulative approved indications by region

European and Asian regulatory approvals have increased at a steady rate since the early 2000s, leading the rest of the world. This is likely attributable to the age and geographic locations of many companies in the focused ultrasound space and to an overall maturation of the industry in these regions; see Timeline of Clinical Device Manufacturers by Region on pages III.50–51. Regulatory agencies in these areas do not have the efficacy standard that others do in the regulatory landscape. Their concern is primarily proof of safety standard, thus leaving the market to sort out efficacy. 2020 marks the first year that regulatory approvals were dropped by manufacturers—likely due to lack of uptake in a particular geographic market. For more details on specific indications and countries, please see Section III.22–III.30.

NEW

Summary of Types of Research and Treatment Sites by Region

Number of sites

	Total	North America	Europe	Asia	South America	Oceania	Africa
Commercial treatments	**799**	181	278	318	14	4	4
Clinical research	**235**	55	98	75	2	5	–
Preclinical research	**148**	68	39	38	–	3	–
Mechanisms of action research	**173**	76	41	54	–	2	–
Technical research	**145**	57	48	39	–	1	–

Number of Research Sites and Mechanisms of Action under Investigation

Mechanisms of action research

The table that follows is the first attempt to highlight the depth and breadth of how many different mechanisms of action are currently being investigated for each indication. Our hope is that in future years this table might become interactive on our website, linking our database of content to a graphical representation of the data, which can be drilled down to specific institutions conducting the research, as we currently do for other research types. The table shows that the highest numbers of mechanisms under investigation closely align with those indications where current standard of therapy is far from ideal, that are lethal very soon after diagnosis, and/or that have a very poor quality of life.

NEW

Number of Research Sites and Mechanisms of Action under Investigation

Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Cardiovascular					
Arteriovenous malformations	2	1	–	2	**3**
Atherosclerosis	4	7	–	–	**6**
Atrial fibrillation	1	3	1	–	**4**
Cardiac hypertrophy	1	1	–	–	**1**
Cardiac pacing	1	1	–	–	**1**
Coarctation of the aorta	1	1	–	–	**1**
Congestive heart failure	*	2	–	–	**2**
Deep vein thrombosis	5	9	–	–	**7**
Fetal heart anomalies	1	1	–	–	**1**
Heart valve calcifications	1	1	5	–	**6**
Hematoma	1	1	–	–	**1**
Hemophilia	1	1	–	–	**1**
Hypertension	1	2	13	–	**14**
Mitral regurgitation	1	1	–	–	**1**
Peripheral artery disease	1	2	–	1	**3**
Twin-twin transfusion syndrome	2	6	1	–	**6**
Varicose veins	2	1	1	6	**8**
Ventricular tachycardia	1	2	–	–	**2**
Endocrine disorders					
Diabetes	*	1	–	–	**1**
Graves' disease	1	1	1	–	**2**
Thyroid cancer	2	3	1	–	**4**
Thyroid nodules	1	1	4	19	**24**
Gastrointestinal					
Biliary tract cancer	1	–	1	–	**1**
Colorectal tumors	3	2	3	–	**5**
Esophageal tumors	1	–	1	–	**1**
Gastric tumors	1	1	1	–	**2**
Inflammatory bowel disease	1	1	–	–	**1**

1 Mechanisms of action

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

* No mechanism of action was provided.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Gastrointestinal continued					
Liver metastases	5	6	4	2	**10**
Liver tumors	9	30	24	99	**130**
Malignant obstructive jaundice	*	–	1	–	**1**
Pancreatic tumors, unspecified	12	32	16	6	**40**
Pancreatic tumors, benign	1	–	1	–	**1**
Pancreatic tumors, malignant	4	3	3	2	**6**
Root canal endodontia	*	–	1	–	**1**
Miscellaneous					
Actinic keratosis	1	–	1	–	**1**
Basal cell carcinoma	1	–	2	–	**2**
Dercum's disease	1	–	1	–	**1**
Head & neck tumors	6	4	3	–	**6**
Heterotopic ossification	1	1	–	–	**1**
Hypersplenism	*	–	1	–	**1**
Infection	1	1	–	–	**1**
Kaposi's sarcoma	1	–	1	–	**1**
Lipoma	1	–	1	–	**1**
Melanoma	3	2	2	–	**3**
Multiple tumors	4	5	1	–	**6**
Obesity	*	1	–	–	**1**
Wound healing	2	2	–	–	**2**
Musculoskeletal					
Arthritis, facetogenic	1	5	9	10	**20**
Arthritis, knee	1	1	1	–	**2**
Arthritis, sacroiliac	1	–	1	–	**1**
Bone cancer	1	1	5	5	**11**
Bone metastases	5	13	21	25	**46**
Bone tumors, benign	1	2	3	1	**6**
Desmoid tumors	2	–	4	9	**12**

1 Mechanisms of action

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* No mechanism of action was provided.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Musculoskeletal continued					
Disc degeneration	*	1	–	–	**1**
Muscle atrophy	2	2	–	–	**2**
Osteoid osteoma	1	4	25	106	**111**
Osteomyelitis	1	1	–	–	**1**
Osteopenia	1	1	–	–	**1**
Plantar fasciitis	1	–	1	–	**1**
Rotator cuff injury	1	1	–	–	**1**
Sacral chordoma	1	–	1	–	**1**
Soft tissue cancer	7	8	6	2	**13**
Soft tissue tumors, benign	2	6	25	97	**107**
Tendon contracture	2	2	–	–	**1**
Neurological					
Alzheimer's disease	7	19	12	1	**21**
Amyotrophic lateral sclerosis	2	2	–	–	**2**
Astrocytoma	5	15	2	1	**14**
Brain tumors, general	6	7	1	–	**8**
Cancer pain	2	4	–	1	**4**
Cavernomas	1	1	–	–	**1**
Dementia	2	1	1	–	**2**
Depression	2	5	6	1	**9**
Dystonia	1	–	1	1	**2**
Dystonia, hand	1	–	1	1	**1**
Epilepsy	7	21	8	2	**24**
Essential tremor	2	3	21	66	**70**
Glioblastoma	17	50	21	–	**48**
Huntington's disease	1	1	–	–	**1**
Hydrocephalus	1	1	–	–	**1**
Mood disorder	1	–	1	–	**1**
Multiple sclerosis	1	–	1	–	**1**

1 Mechanisms of action

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

* No mechanism of action was provided.

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Neurological continued					
Neuroblastoma	2	1	1	–	**2**
Neuromyelitis optica	1	1	–	–	**1**
Neuropathic pain	4	5	5	3	**12**
Neuropathy	3	1	2	1	**4**
Obsessive-compulsive disorder	1	–	2	1	**3**
Opioid and other addictions	2	3	2	–	**5**
Painful amputation neuromas	1	–	1	–	**1**
Parkinson's disease, dyskinesia	2	1	17	3	**20**
Parkinson's disease, tremor	3	2	7	18	**27**
Parkinson's disease, underlying cause	6	13	2	–	**11**
Pontine glioma	3	3	–	–	**3**
Rett syndrome	1	1	–	–	**1**
Spinal cord injury	1	4	–	–	**4**
Stroke, intracerebral hemorrhage	5	12	–	–	**12**
Stroke, thromboembolic	6	8	1	–	**9**
Traumatic brain injury	2	3	1	–	**4**
Tremor, orthostatic	1	–	1	–	**1**
Trigeminal neuralgia	1	–	1	1	**2**
Ophthalmological					
Glaucoma	2	4	7	14	**22**
Keratoplasty	1	1	–	–	**1**
Macular degeneration	2	2	–	–	**2**
Retinal injury	1	1	–	–	**1**
Pulmonary					
Lung cancer	1	4	–	–	**4**
Lung metastases	1	1	–	–	**1**
Rhinitis	1	–	1	–	**1**
Tuberculosis	1	1	–	–	**1**

1 Mechanisms of action

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

* No mechanism of action was provided..

Number of Research Sites and Mechanisms of Action under Investigation continued

Indications	MOAs[1]	Sites			Total[2]
		Preclinical	Clinical	Commercial	
Urological					
Acute kidney injury	1	1	1	–	**2**
Acute tubular necrosis	1	1	–	–	**1**
Benign prostatic hyperplasia	4	2	3	62	**66**
Bladder tumors	1	2	–	–	**2**
Chyluria	1	–	1	–	**1**
Fetal bladder obstruction	1	1	–	–	**1**
Kidney stones	2	3	1	–	**2**
Kidney tumors	4	10	17	95	**103**
Prostate cancer	6	26	53	402	**444**
Urinary tract infection	1	1	–	–	**1**
Women's Health					
Brain metastases, breast cancer	3	4	1	–	**4**
Breast tumors, benign	2	2	10	12	**22**
Breast tumors, malignant	9	27	25	96	**122**
Cervical tumors	1	1	2	–	**3**
Cervicitis	1	–	–	1	**1**
Ectopic pregnancy	*	–	1	–	**1**
Endometrial tumors	1	2	1	1	**4**
Endometriosis	2	1	3	2	**5**
Lichen sclerosis	*	–	–	1	**1**
Ovarian tumors	1	2	1	–	**3**
Retained placenta	1	–	1	–	**1**
Uterine adenomyosis	2	3	19	88	**101**
Uterine fibroids	3	19	62	292	**316**
Vaginal tumors	1	–	3	–	**3**
Vulvar dystrophy	1	–	1	–	**1**

1 Mechanisms of action

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

* No mechanism of action was provided.

Patient Treatments

Manufacturer supplied data

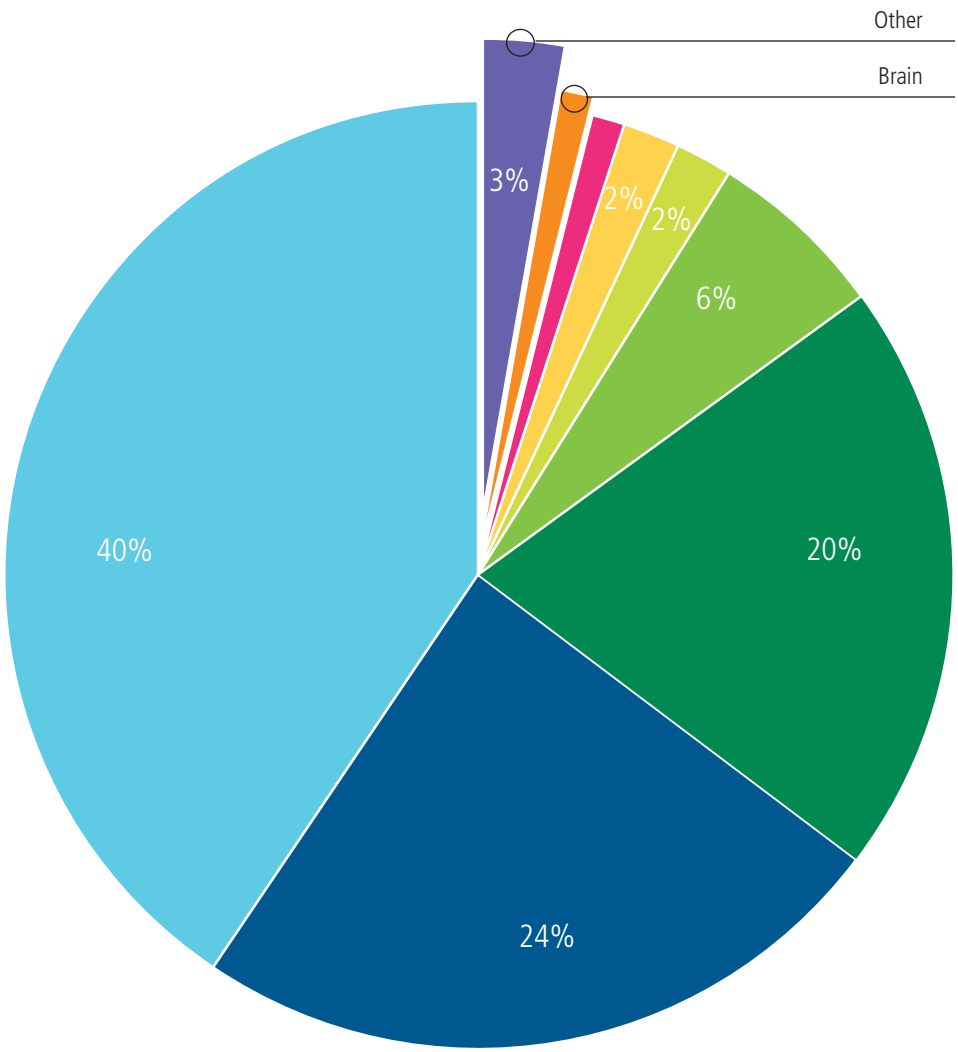
As we have mentioned previously, this report contains mostly self-reported data. The information that follows is an accumulation of data provided by the manufacturers in the industry. If we have companies with large numbers of treatment sites that do not submit data for a particular year, it can significantly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

Patient Treatments by Indication—Cumulative

All indications

374,812 total treatments[1]

Uterine fibroids	151,637	40%
Prostate diseases	88,288	24%
Liver tumors	75,687	20%
Pancreatic tumors[2]	22,723	6%
Uterine adenomyosis	8,570	2%
Glaucoma	6,164	2%
Cancer, unspecified	5,560	1%
Brain	5,519	1%
Other[3]	10,664	3%



Historically, the annual patient treatment numbers by indication tracked alongside the cumulative treatment numbers. 2019 marked the first divergence drom this historical trend, with an annual uptick in liver tumor treatments.

In 2020, liver treatments continued to trend similarly, 25 percent. Also in 2020, patient treatments of pancreatic tumor, 27 percent, and uterine adenomyosis, 9 percent, dominated the annual treatment numbers compared to their status within the cumulative treatment pie chart.

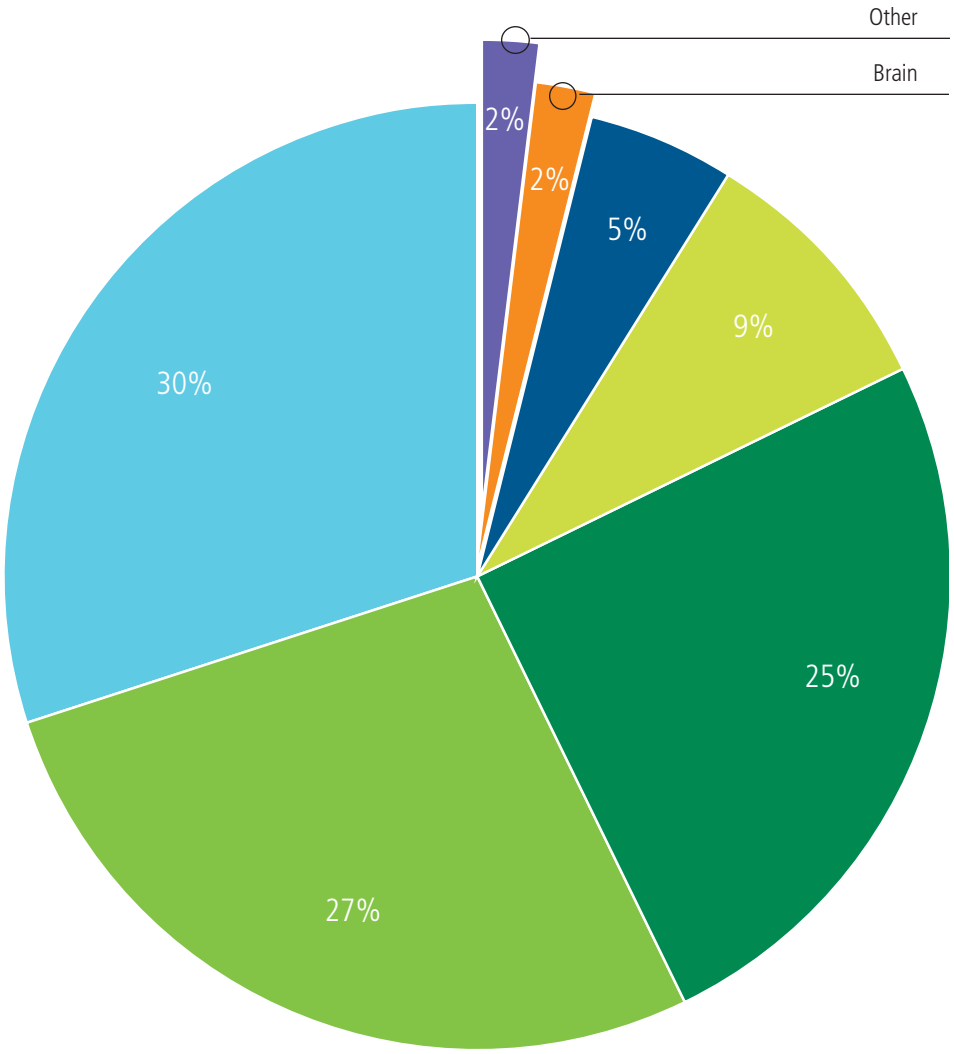
1 The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites. Companies reporting patient treatment values were: Cardiawave, EDAP TMS SA, EyeSonix, FUSMobile INC, Harmonic Medical, HistoSonics INC, Image Guided Therapy, INSIGHTEC LTD, NaviFUS, Neurosona CO LTD, Profound Medical CORP, Shanghai A&S Science Technology Development CO LTD, Shenzhen PRO-HITU Medical Tech. CO LTD, SonaCare Medical LLC, TheraWave LLC, and TOOsonix.
2 Unspecified
3 For an expanded list of these indications, please refer to Cumulative Other Treatments by Indication, on p. I.36.

Patient Treatments by Indication—2020

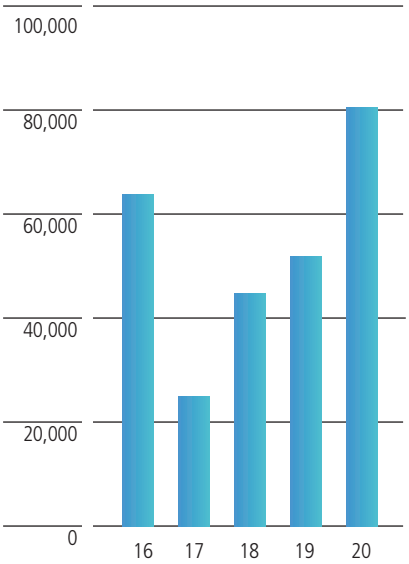
81,332 total treatments[1]

Uterine fibroids	24,101	30%
Pancreatic tumors[2]	22,005	27%
Liver tumors	20,170	25%
Uterine adenomyosis	7,638	9%
Prostate diseases	3,830	5%
Brain	1,883	2%
Other[3]	1,683	2%
– Glaucoma	22	—

All indications



Annual Patient Treatments



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2 Unspecified
3 For an expanded list of these indications, please refer to Cumulative Other Treatments by Indication, on p. I.36.

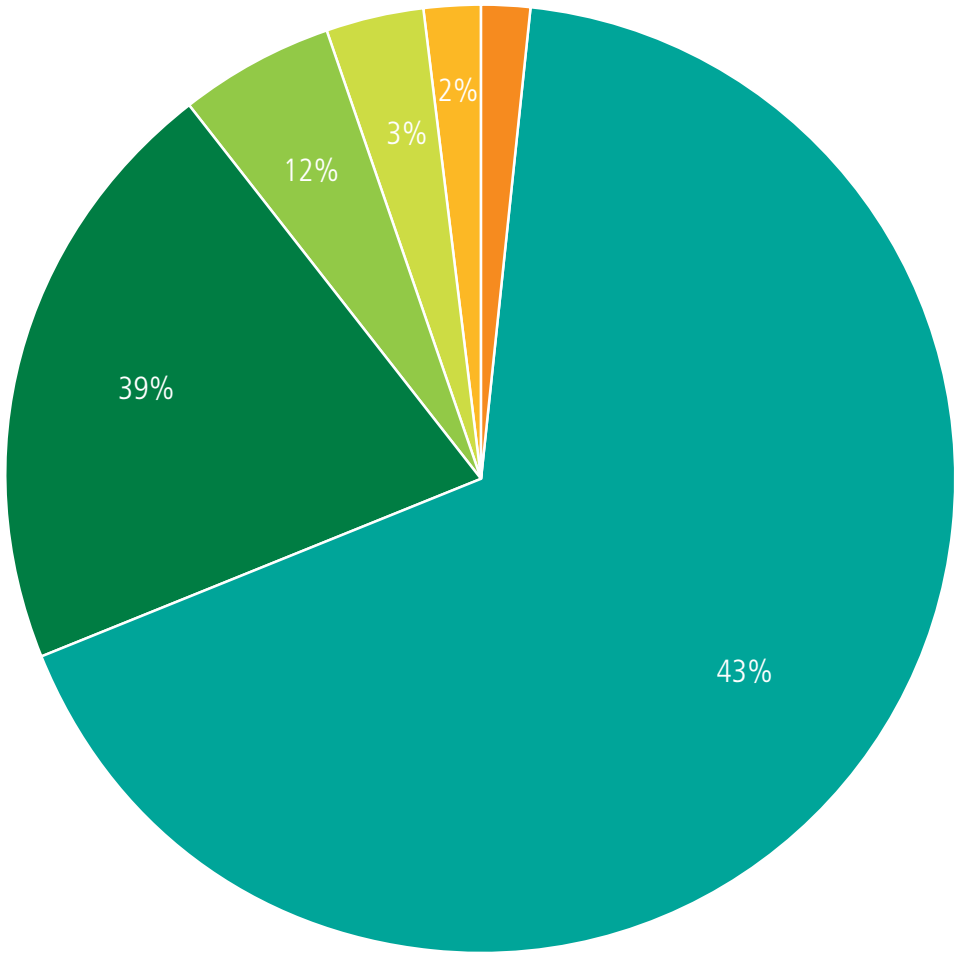
Oncology Treatments by Indication—Cumulative

194,106 total treatments

Prostate cancer	83,083	43%
Liver tumors	75,687	39%
Pancreatic tumors[2]	22,723	12%
Cancer, unspecified	5,560	3%
Bone metastases	3,154	2%
Soft tissue cancer	2,607	1%
– Breast tumors, malignant	890	—
– Other[1]	402	—

In 2020, pancreatic and liver tumors dominated the annual oncology patient treatment numbers. These two indications alone represent 88 percent of the patient treatments in 2020.

Oncology indications



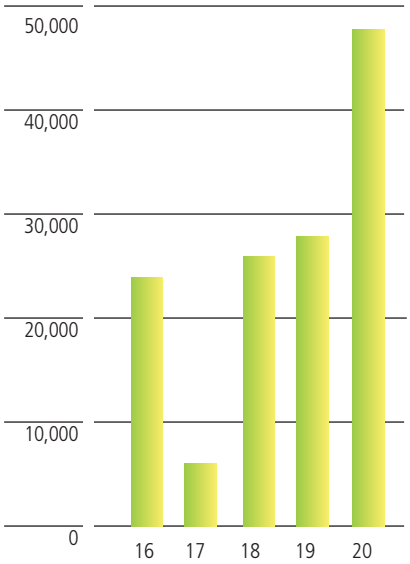
1 Includes, in descending order of patient treatments: glioblastoma; endometrial tumors; brain tumors, general; kidney tumors; bone cancer; abdominal paraganglioma; hemangioma;' abdominal tumor; astrocytoma; basal cell carcinoma; granular cell tumor of the gluteals; cervical tumors; Kaposi's sarcoma; sacral chordoma; schwannoma; spleen tumors; ganglioglioma; and neurofibroma
2 Unspecified

Oncology Treatments by Indication—2020

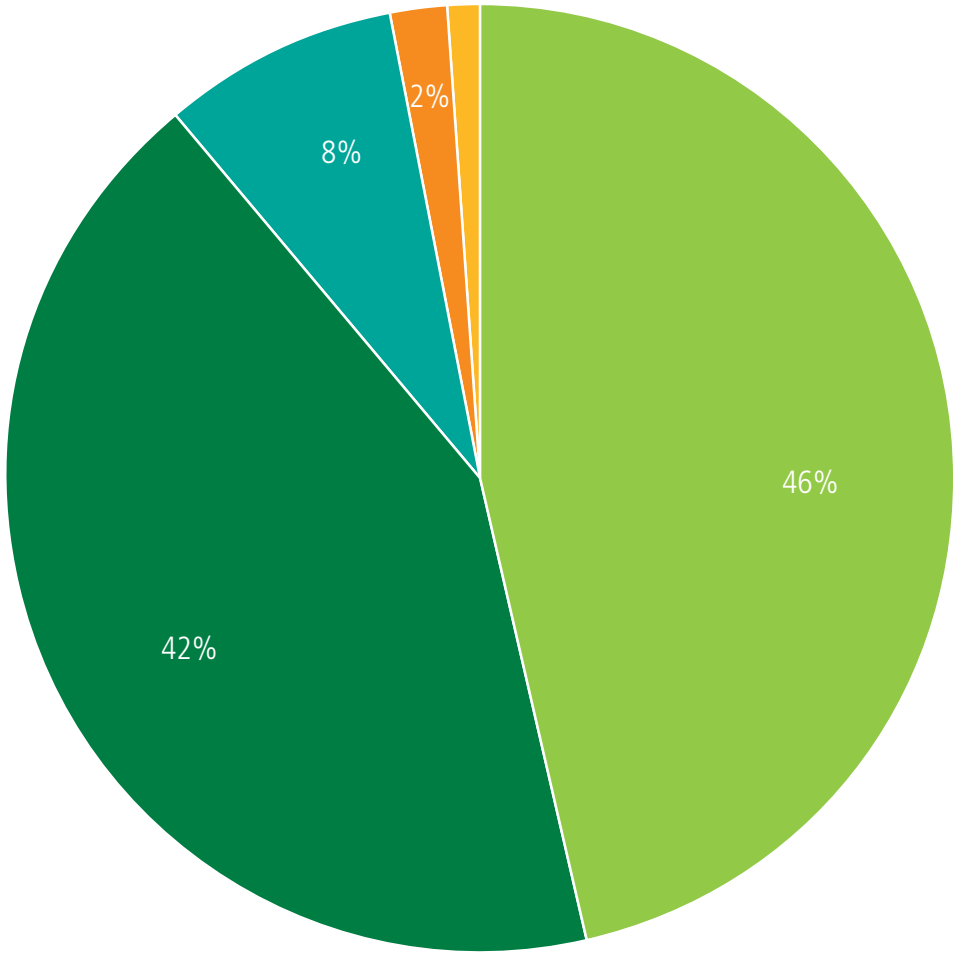
47,506 total treatments

Pancreatic tumors[2]	22,005	46%
Liver tumors	20,170	42%
Prostate cancer	3,715	8%
Soft tissue cancer	1,100	2%
Bone metastases	376	1%
– Other[1]	137	—
– Breast tumors, malignant	3	—

Annual Oncology Treatments



Oncology indications



1 Includes, in descending order of patient treatments: endometrial tumors; glioblastoma; brain tumors, general; bone cancer; basal cell carcinoma; and Kaposi's sarcoma
2 Unspecified

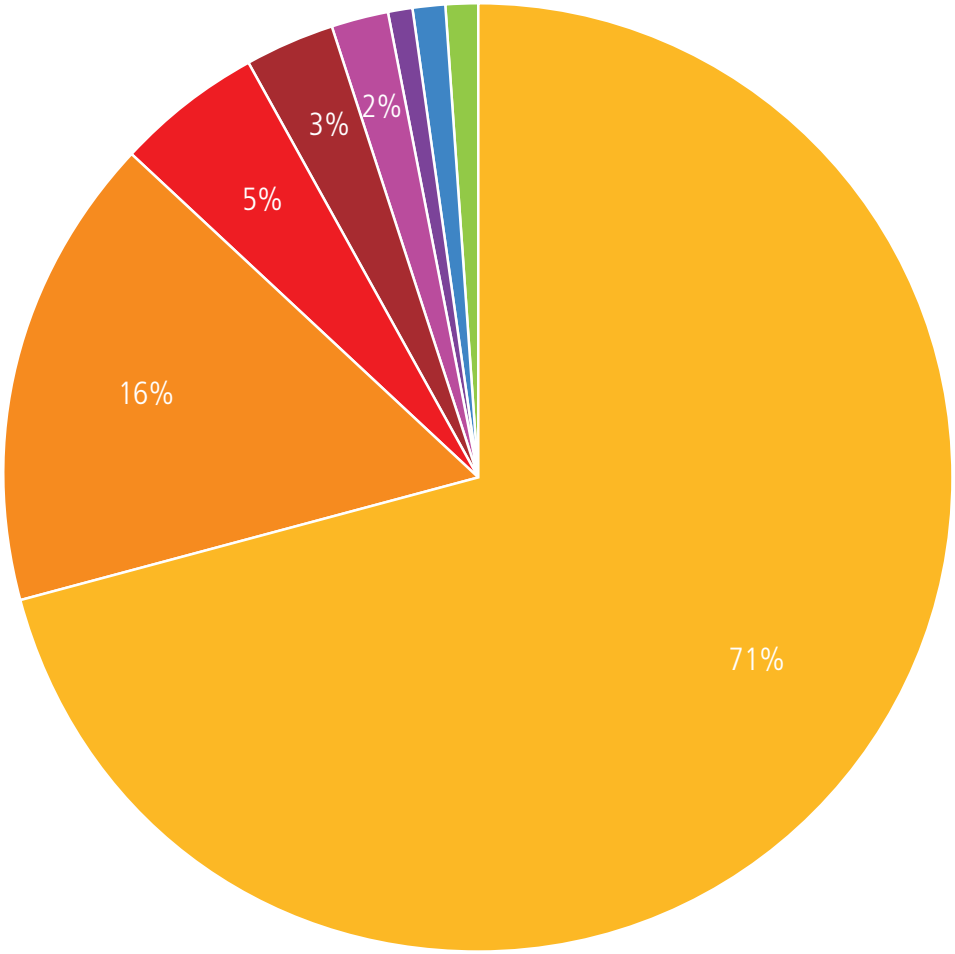
Brain Treatments by Indication—Cumulative

5,519 total brain treatments

Essential tremor	3,908	71%
Parkinson's disease	869	16%
Brain tumors[1]	258	5%
Neuropathic pain	193	3%
Alzheimer's disease	118	2%
Other movement disorders[2]	65	1%
Mental health[3]	79	1%
Other brain[4]	29	1%

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

Brain indications



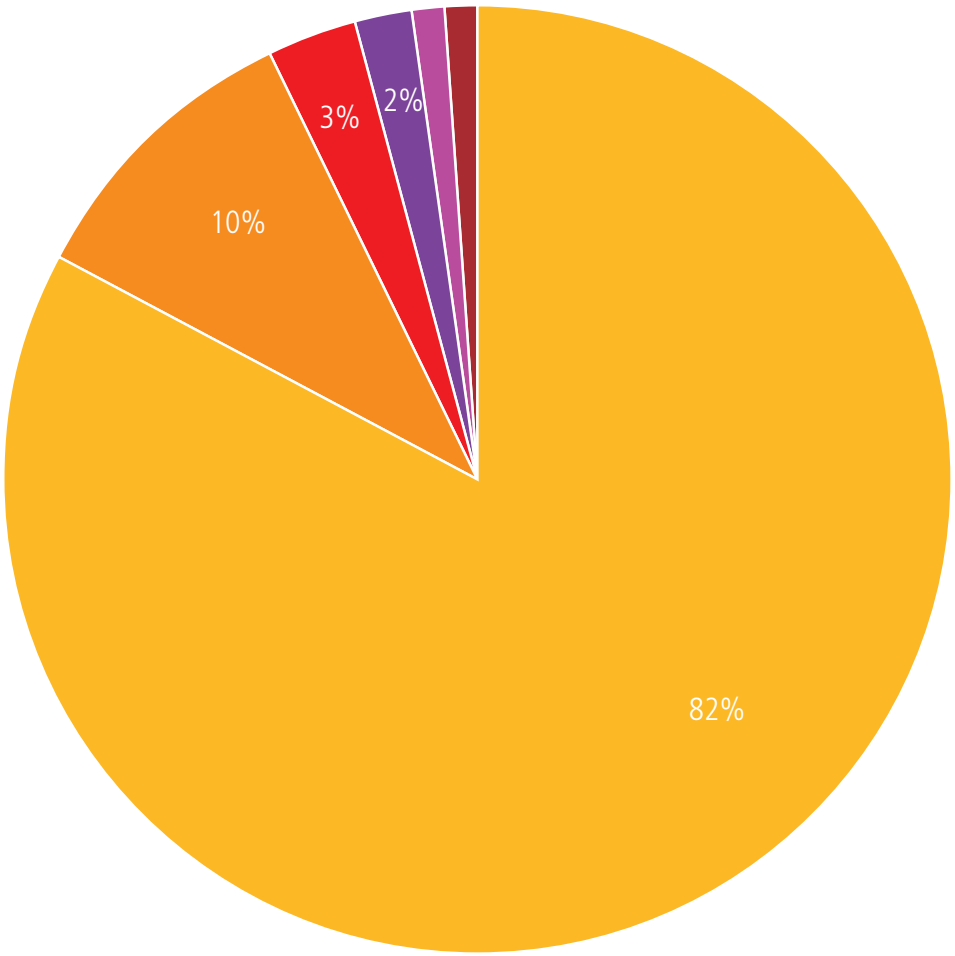
1 Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; astrocytoma; and ganglioglioma
2 Includes, in descending order of patient treatments: epilepsy and dystonia
3 Includes, in descending order of patient treatments: obsessive-compulsive disorder, depression, and anxiety
4 Includes, in descending order of patient treatments: blood-brain barrier opening and traumatic brain injury

Brain Treatments by Indication—2020

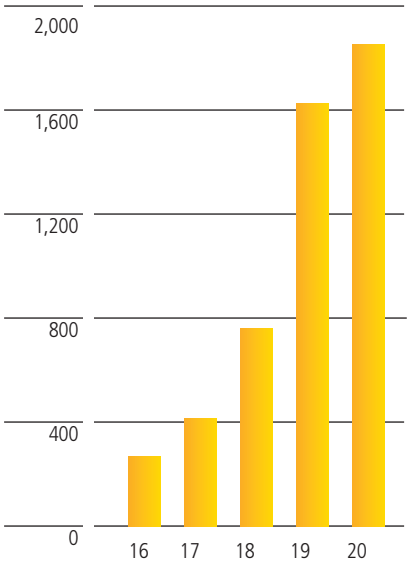
1,883 total brain treatments

Essential Tremor	1,540	82%
Parkinson's disease	194	10%
Brain tumors[1]	52	3%
Alzheimer's disease	43	2%
Mental health[3]	26	1%
Neuropathic pain	16	1%
– Other movement disorders[2]	8	—
– Other brain[4]	4	—

Brain indications



Annual Brain Treatments



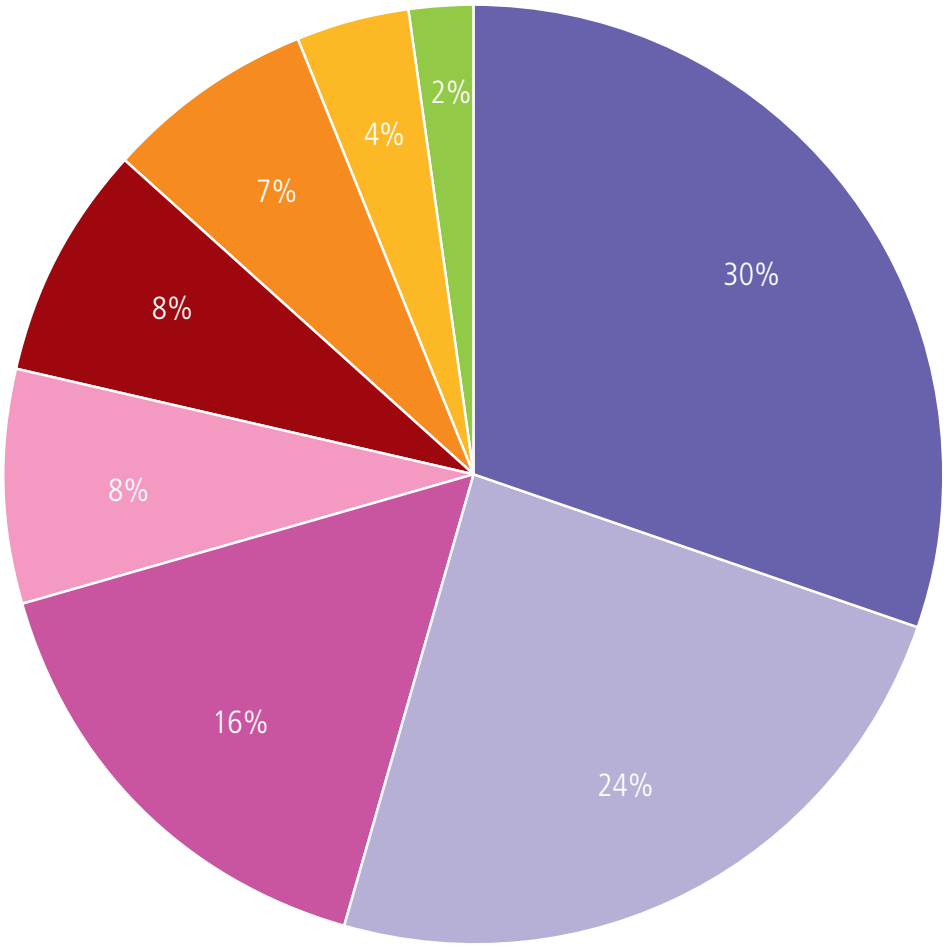
1 Includes, in descending order of patient treatments: glioblastoma; brain tumors, general; astrocytoma; and ganglioglioma
2 Includes, in descending order of patient treatments: epilepsy and dystonia
3 Includes, in descending order of patient treatments: obsessive-compulsive disorder, depression, and anxiety
4 Includes, in descending order of patient treatments: blood-brain barrier opening and traumatic brain injury

Other Treatments by Indication—Cumulative

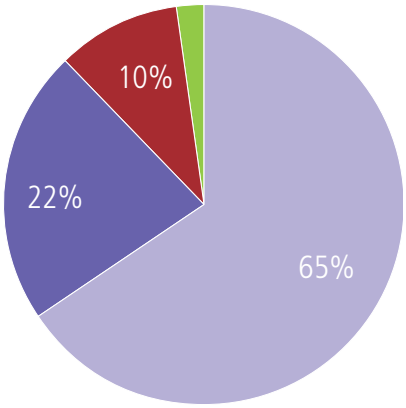
Other indications

10,664 total treatments

Bone metastases	3,154	30%
Soft tissue cancer	2,607	24%
Thyroid nodules	1,759	16%
Breast tumors, malignant	890	8%
Other[1]	824	8%
Breast fibroadenoma	795	7%
Arthritis, facetogenic	375	4%
Osteoid osteoma	260	2%



Other Treatments—2020



1,683 total treatments

Bone metastases	376	22%
Soft tissue cancer	1,100	65%
Other[2]	162	10%
Osteoid osteoma	34	2%
– Arthritis, facetogenic	8	—
– Breast tumors, malignant	3	—

1 Includes, in descending order of patient treatments: varicose veins; desmoid tumors; endometrial tumors; hypertension; hyperparathyroidism; arthritis; dermatology, unspecified; actinic keratosis; heart valve calcifications; tattoo removal; endometriosis; bone tumors, benign; kidney tumors; bone cancer; painful amputation neuromas; abdominal paraganglioma; hemangioma; abdominal tumor; amyotrophic lateral sclerosis; arteriovenous malformations; basal cell carcinoma; granular cell tumor of the gluteals; cervical tumors; Kaposi's sarcoma; sacral chormdoma; schwannoma; soft tissue tumors, benign; spleen tumors; and neurofibroma

2 Includes, in descending order of patient treatments: endometrial tumors; endometriosis; bone tumors, benign; actinic keratosis; desmoid tumors; heart valve calcifications; bone cancer; basal cell carcinoma; and Kaposi's sarcoma

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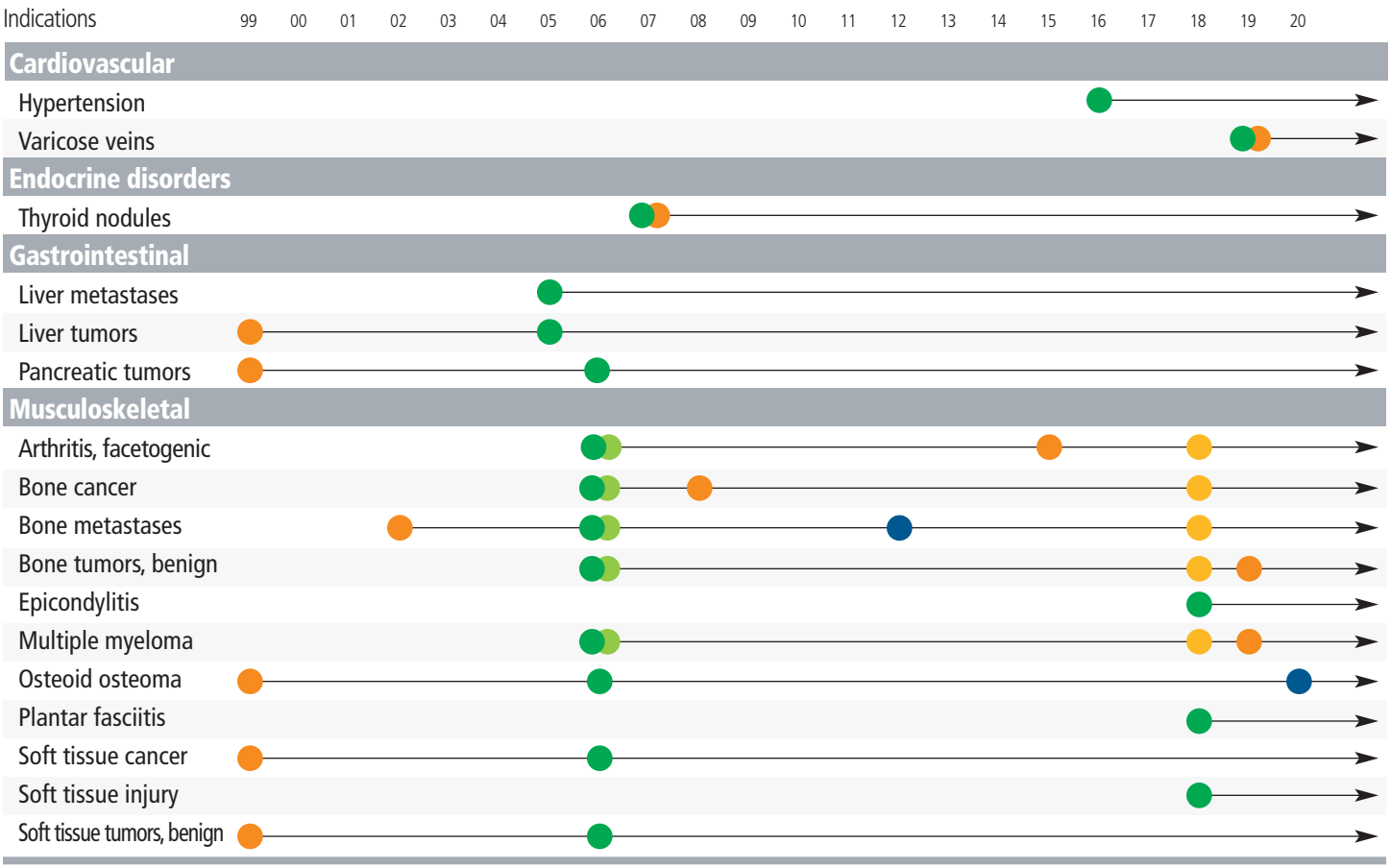
FUS Regulatory Approvals by Indication and Region
Graphic

FUS Regulatory Approvals by Indication and Region continued

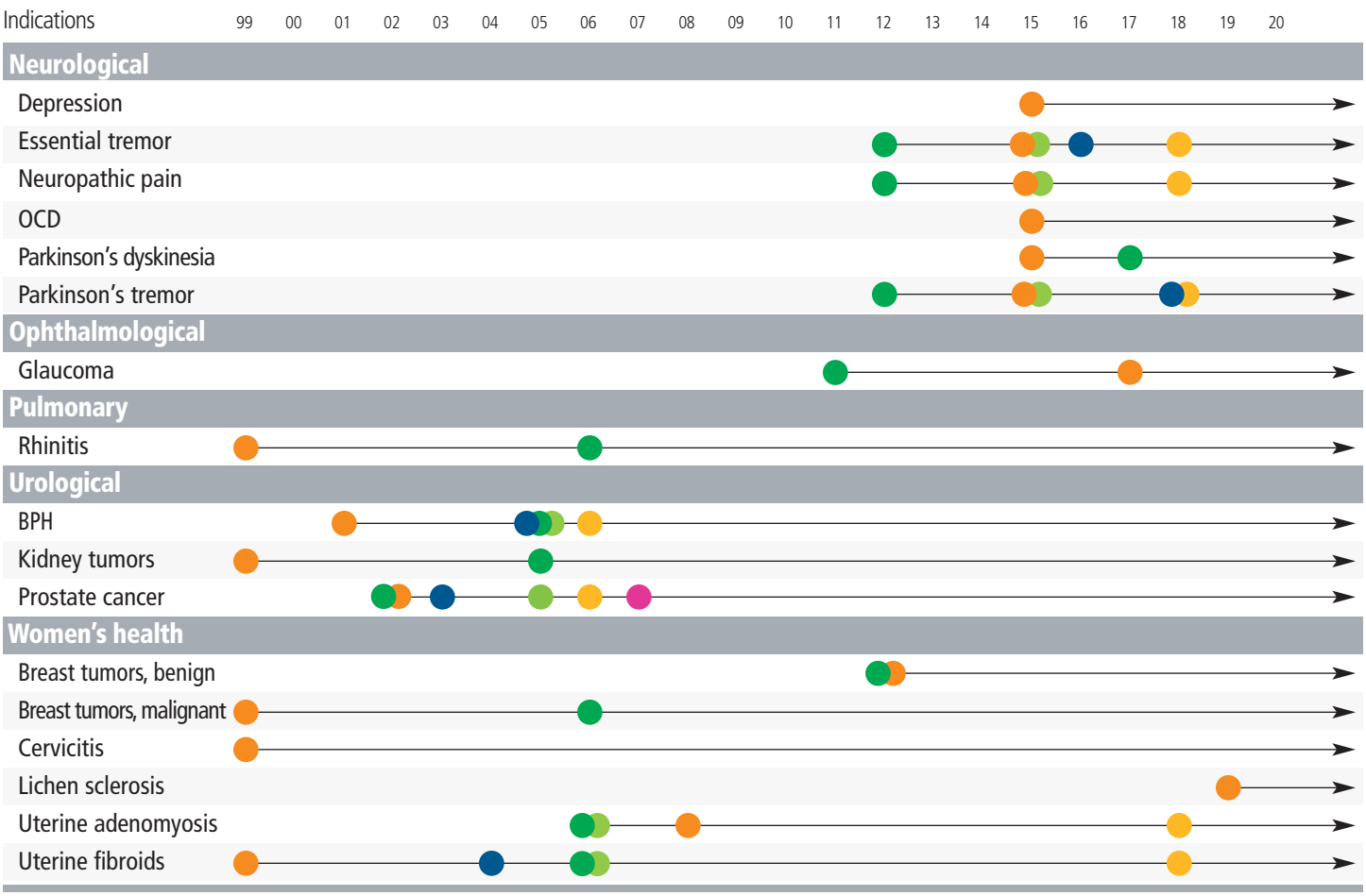
Table

North America	Europe	Asia	South America	Oceania	Africa
Benign prostatic hyperplasia	Arthritis, facetogenic	Arthritis, facetogenic	Arthritis, facetogenic	Arthritis, facetogenic	Prostate cancer
Bone metastases	Benign prostatic hyperplasia	Benign prostatic hyperplasia	Benign prostatic hyperplasia	Benign prostatic hyperplasia	
Essential tremor	Bone cancer	Bone cancer	Bone cancer	Bone cancer	
Osteoid osteoma	Bone metastases	Bone metastases	Bone metastases	Bone metastases	
Parkinson's disease, tremor	Bone tumors, benign	Bone tumors, benign	Bone tumors, benign	Bone tumors, benign	
Prostate cancer	Breast tumors, benign	Breast tumors, benign	Essential tremor	Essential tremor	
Uterine fibroids	Breast tumors, malignant	Breast tumors, malignant	Multiple myeloma	Multiple myeloma	
	Epicondylitis	Cervicitis	Neuropathic pain	Neuropathic pain	
	Essential tremor	Depression	Parkinson's disease, tremor	Parkinson's disease, tremor	
	Glaucoma	Essential tremor	Prostate cancer	Prostate cancer	
	Hypertension	Glaucoma	Uterine adenomyosis	Uterine adenomyosis	
	Kidney tumors	Kidney tumors	Uterine fibroids	Uterine fibroids	
	Liver metastases	Lichen sclerosis			
	Liver tumors	Liver tumors			
	Multiple myeloma	Multiple myeloma			
	Neuropathic pain	Neuropathic pain			
	Osteoid osteoma	Obsessive-compulsive disorder			
	Pancreatic tumors	Osteoid osteoma			
	Parkinson's disease, dyskinesia	Pancreatic tumors			
	Parkinson's disease, tremor	Parkinson's disease, dyskinesia			
	Plantar fasciitis	Parkinson's disease, tremor			
	Prostate cancer	Prostate cancer			
	Rhinitis	Rhinitis			
	Soft tissue cancer	Soft tissue cancer			
	Soft tissue injury	Soft tissue tumors, benign			
	Soft tissue tumors, benign	Thyroid nodules			
	Thyroid nodules	Uterine adenomyosis			
	Uterine adenomyosis	Uterine fibroids			
	Uterine fibroids	Varicose veins			
	Varicose veins				

FUS Regulatory Approvals by Indication and Region



FUS Regulatory Approvals by Indication and Region continued



North America
Europe
Asia
South America
Oceania
Africa

Global Landscape of Approved Indications and Manufacturers

NEW

Indication regional approvals	Indications	Manufacturers
	Cardiovascular	
	Hypertension	Kona Medical
	Varicose veins	Theraclion
	Endocrine disorders	
	Thyroid nodules	Theraclion
	Gastrointestinal	
	Liver tumors	Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
		Shanghai A&S
	Pancreatic tumors	Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
	Musculoskeletal	
	Arthritis, facetogenic	Insightec
	Bone cancer	Insightec
	Bone metastases	Insightec
		Profound Medical
		Shanghai A&S
	Bone tumors, benign	Insightec
	Epicondylitis	Guided Therapy Systems
	Multiple myeloma	Insightec
	Osteoid osteoma	Chongqing Haifu Medical Technology
		Profound Medical
	Plantar fasciitis	Guided Therapy Systems
	Soft tissue cancer	Chongqing Haifu Medical Technology
		EpiSonica
		Shanghai A&S
	Soft tissue injury	Guided Therapy Systems
	Soft tissue tumors, benign	Chongqing Haifu Medical Technology

Approval regions

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

Global Landscape of Approved Indications and Manufacturers continued

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

Approval regions

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

Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Women's health continued	
	Lichen sclerosis	Shenzhen PRO-HITU Medical
	Liver metastases	Chongqing Haifu Medical Technology
	Uterine adenomyosis	Alpinion Medical Systems
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shenzhen PRO-HITU Medical
	Uterine fibroids	Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shanghai A&S
		Shenzhen PRO-HITU Medical
		Wuxi Haiying Electronic Medical

Approval regions

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

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Abstracts Presented at FUS Symposia

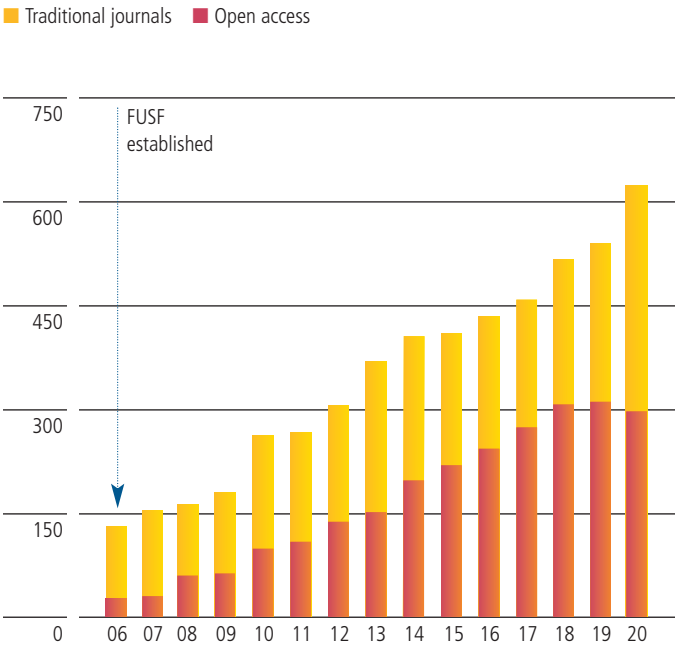
Symposium	2015	2016	2017	2018	2019	2020
Focused Ultrasound Foundation Symposium, FUSF[1]	–	200	–	250	–	257
European Symposium on Focused Ultrasound, EUFUS[2]	75	–	54	–	197[2]	*
International Symposium on Therapeutic Ultrasound, ISTU	177	152	207	257		
Totals	**252**	**352**	**261**	**507**	**197**	**257**

FUS Abstracts Presented at Other Symposia

Symposium	2015	2016	2017	2018	2019	2020
Acoustical Society of America	19	64	48	39	22	13
American Association for Cancer Research, AACR	–	–	–	–	–	7
American Association of Physicists in Medicine, AAPM	14	8	16	5	7	6
American Institute of Ultrasound in Medicine, AIUM	4	2	–	9	6	*
American Society for Radiation Oncology	–	2	5	3	–	2
American Society for Stereotactic and Functional Neurosurgery	–	3	–	6	–	*
American Society of Clinical Oncology, ASCO	–	–	–	–	–	4
American Urological Association, AUA	4	11	7	4	16	*
Biomedical Engineering Society	13	12	16	14	26	9
Cardiovascular and Interventional Radiology Society of Europe, CIRSE	–	–	–	–	–	10
European Association of Urology, EAU	–	–	–	–	–	5
European Congress of Radiology	7	7	13	22	10	15
IEEE International Engineering in Medicine and Biology	11	9	5	11	11	2
IEEE International Ultrasonics Symposium	42	26	71	19	49	57
International Society for Magnetic Resonance in Medicine, ISMRM	–	–	–	–	–	33
Japanese Society for Therapeutic Ultrasound	37	39	35	48	52	*
Korean Society for Therapeutic Ultrasound	10	14	15	17	22	6
Radiological Society of North America, RSNA	18	21	17	14	26	7
Society for Thermal Medicine, STM	4	22	10	10	9	*
Society of Interventional Radiology	–	3	2	1	5	*
TAITU	–	–	–	–	12	5
Totals	**183**	**243**	**260**	**222**	**273**	**181**

1 Held biennially
2 EUFUS and ISTU held jointly in 2019.
* Cancelled due to COVID-19 pandemic.

FUS Publications



Source: Data from Web of Knowledge as of January 18, 2021

FUS Citations

Cumulative

5,233
FUS publications

153,824
Citations of FUS publications

2020

624
FUS publications

18,705
Citations of FUS publications

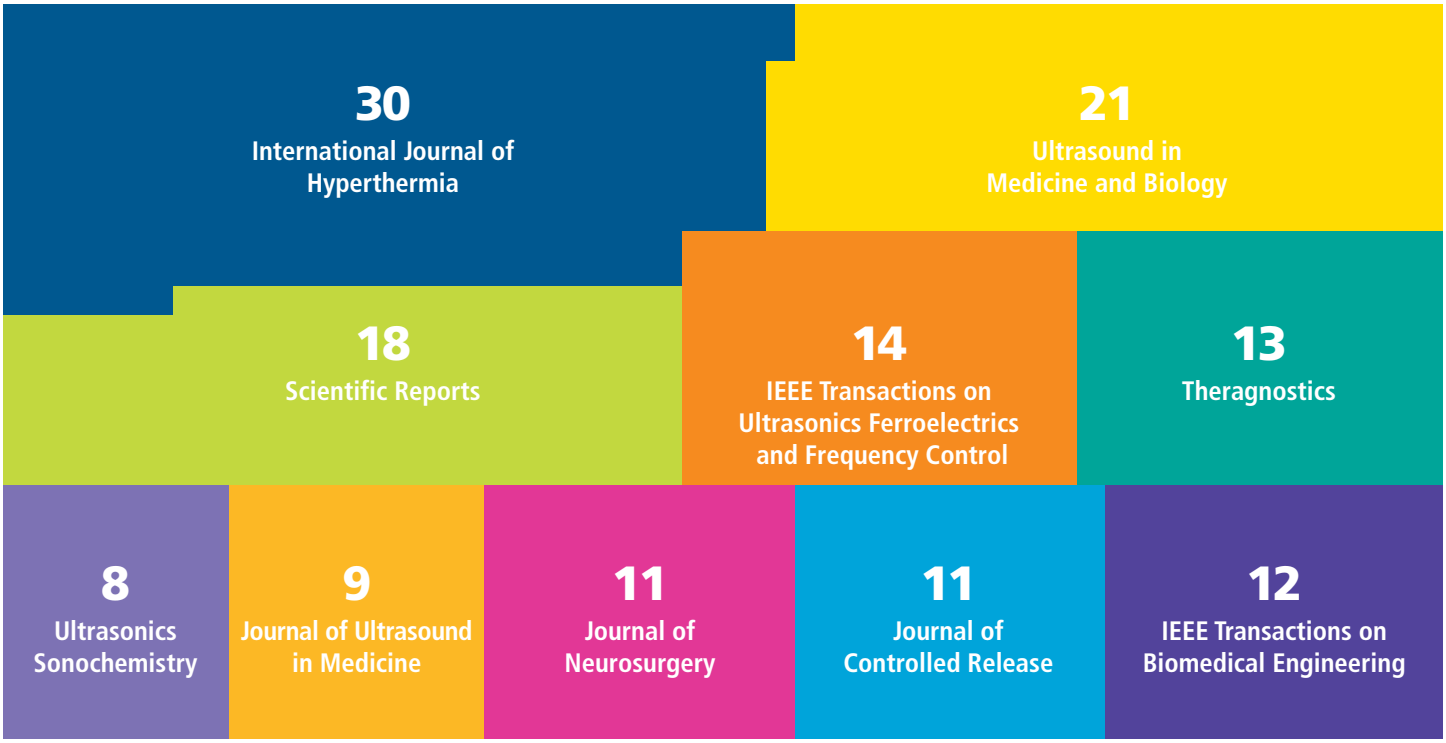
In 2020, there was an uptick in publications compared to 2019. One explanation of this increase could be that while research labs and clinical trials around the globe shut down for various lengths of time due to COVID-19 issues, researchers and clinicians who were working from home finally had the time and capacity to write up previously completed research into publication-ready manuscripts.

New in 2020, on page I.49 we are reporting on the impact factor and TOP score, Transparency and Openness Promotion for each of the journals on our list of 2020 top ten source titles.

Publications—Cumulative Top Twenty-five Source Titles

Records	Scientific publication titles
427	Ultrasound in Medicine and Biology
214	International Journal of Hyperthermia
197	Physics in Medicine and Biology
177	IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control
116	Journal of the Acoustical Society of America
110	Medical Physics
106	Journal of Therapeutic Ultrasound
100	Ultrasonics
96	Magnetic Resonance in Medicine
89	Journal of Controlled Release
87	Scientific Reports
86	Ultrasonics Sonochemistry
69	Plos One
68	Radiology
66	IEEE Transactions on Biomedical Engineering
65	Annual International Conference of the IEEE Engineering in Medicine and Biology Society, *Proceedings*
65	European Urology
63	Journal of Urology
56	Journal of Neurosurgery
56	Journal of Ultrasound in Medicine
55	BJU International
54	European Radiology
53	Theranostics
52	Journal of Magnetic Resonance Imaging JMRI
37	Journal of Endourology

Publications—2020 Top Ten Source Titles



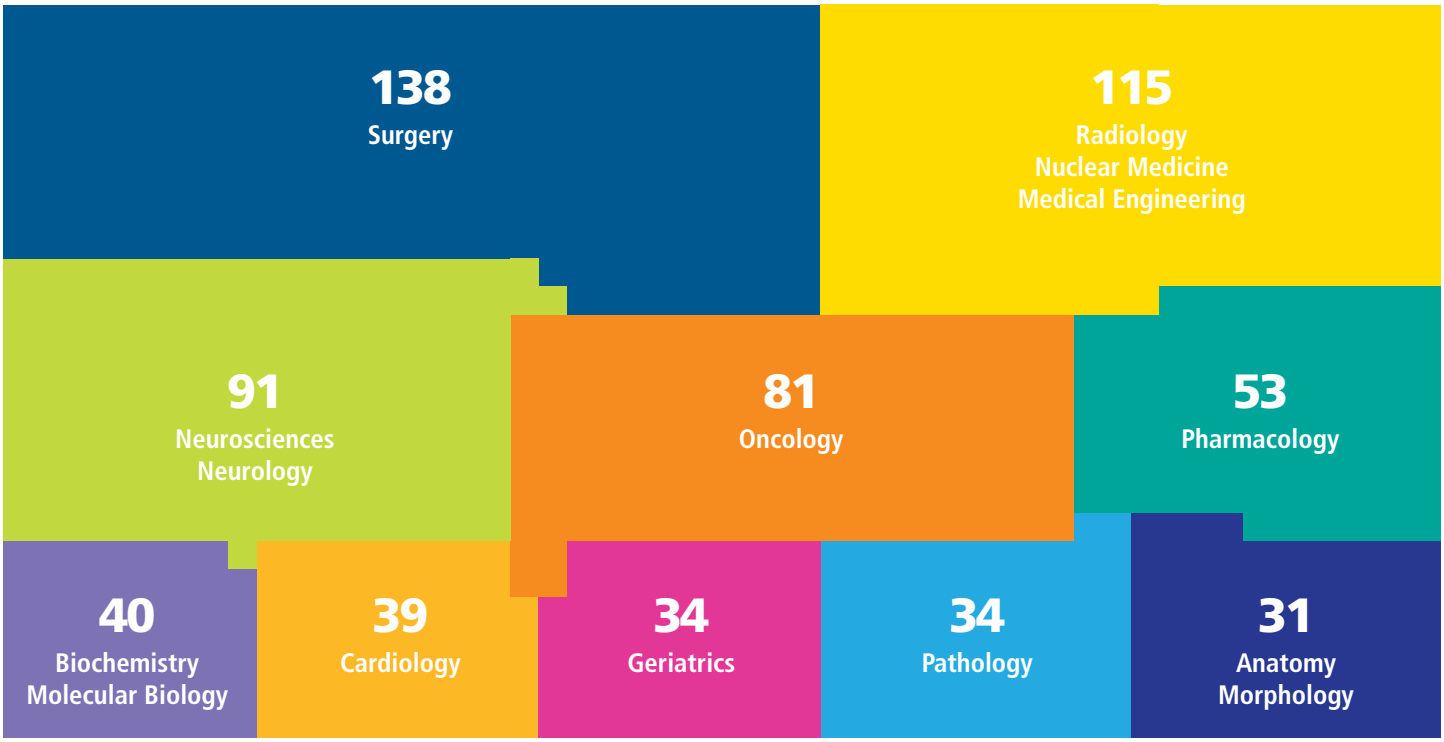
Publications—2020 Top Ten Source Titles

Records	Impact factor	TOP score	Scientific publication titles
30	3.6	1	International Journal of Hyperthermia
21	2.5	0	Ultrasound in Medicine and Biology
18	4.0	6	Scientific Reports
14	2.8	0	IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control
13	8.1	0	Theranostics
12	4.4	0	IEEE Transactions on Biomedical Engineering
11	7.7	1	Journal of Controlled Release
11	4.0	1	Journal of Neurosurgery
9	1.8	0	Journal of Ultrasound in Medicine
8	6.5	1	Ultrasonics Sonochemistry

Publications—Cumulative Top Twenty-five Research Areas

Records	Scientific research areas
2651	Radiology, Nuclear Medicine, Medical Engineering
2481	Surgery
1966	Oncology
1464	Pathology
1076	Neurosciences, Neurology
984	Pharmacology
915	Medical Laboratory Technology
893	Cardiology
830	Acoustics
786	Urology, Nephrology
762	Biochemistry, Molecular Biology
651	Gastroenterology, Hepatology
628	Mathematics
612	Anatomy, Morphology
573	Geriatrics
522	Physics
519	Cell Biology
502	Computer Science
464	Obstetrics, Gynecology
350	General Internal Medicine
316	Medical Informatics
312	Immunology
299	Hematology
297	Imaging Science, Photographic Technology
271	Dermatology } tie
271	Physiology } tie

Publications—2020 Top Ten Research Areas

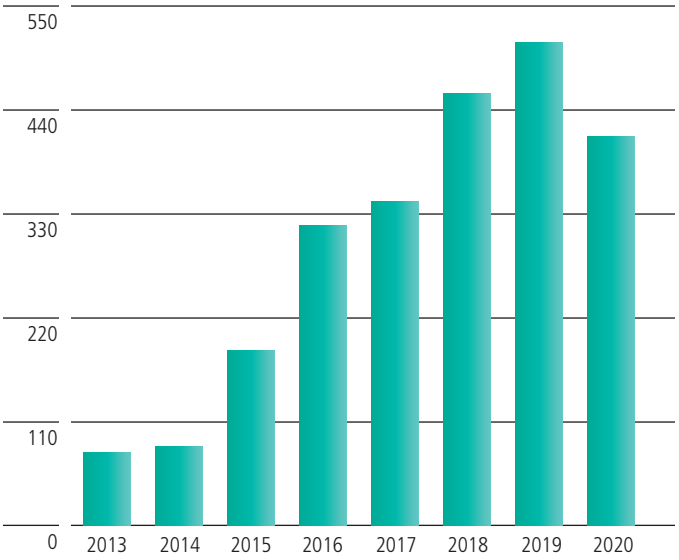


Publications—2020 Top Ten Research Areas

Records	Scientific research areas
138	Surgery
115	Radiology, Nuclear Medicine, Medical Engineering
91	Neurosciences, Neurology
81	Oncology
53	Pharmacology
40	Biochemistry, Molecular Biology
39	Cardiology
34	Geriatrics
34	Pathology
31	Anatomy, Morphology

United States FUS Media Placements

Per year



FUSF began tracking US FUS media placements in 2013

2,389

Media placements, 2013–2020

418

Media placements, 2020

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

> "Each dose of sound applied to the brain can be tested first with a lower intensity, to check for reduced tremor, before the intensity is increased, and the lesion is made permanent."
>
> — Washington Post
> March 1, 2020

> "Scientists say they've developed a low-intensity ultrasound technique that kills cancer cells without damaging healthy cells."
>
> — WebMD
> January 10, 2020

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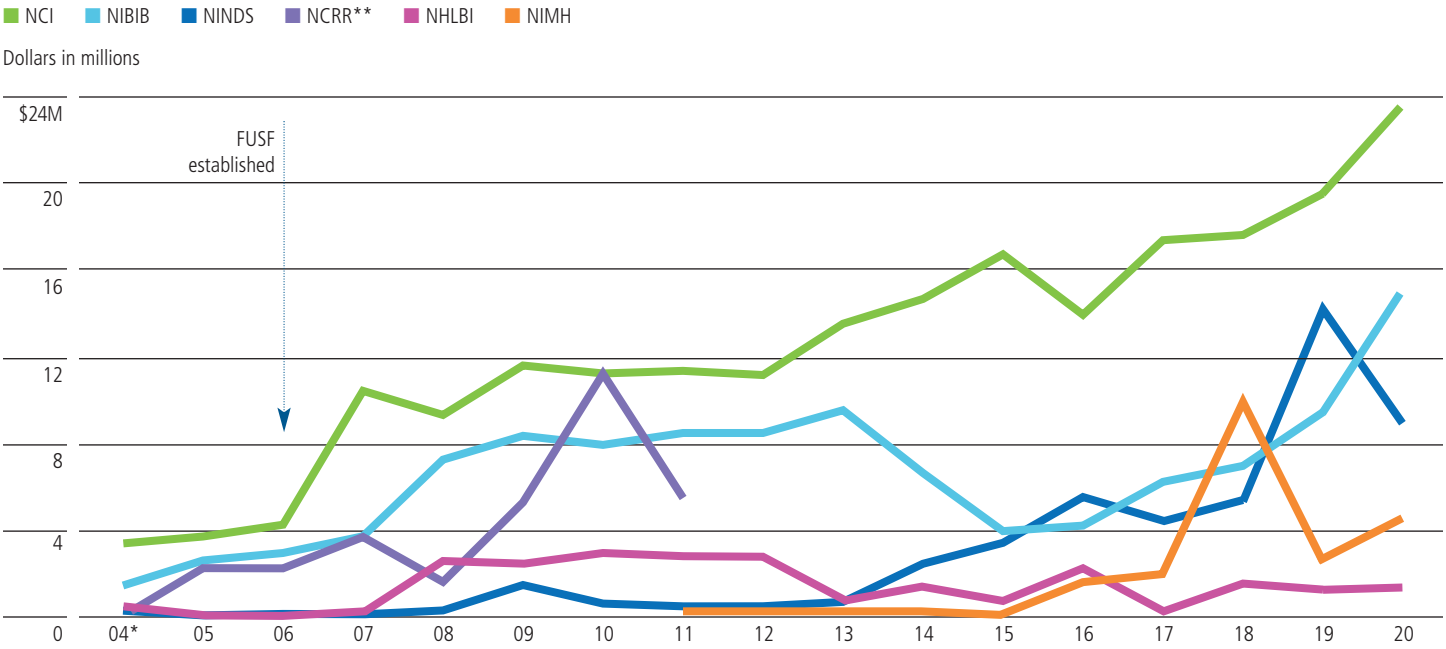
United States Top Federal Government Funders



*The first record of funded focused ultrasound research by the United States Federal Government was in 2004.
**Agency dissolved in 2012.
Addtional gorvernment funders are: CDMRP, CLC, CNRM, FIC, NIMHD, 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
Note terms searched: "focused ultrasound", MRgFUS, HIFU, LIFU

United States federal government focused ultrasound grants

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

Total FUS Funding by United States Government Agencies

2020 FUS funding[1]	Total FUS funding[2] 2004–2020	Granting agency
$23,383,209	**$215,115,380**	**NCI**	National Cancer Institute
$15,515,034	**$113,297,750**	**NIBIB**	National Institute of Biomedical Imaging and Bioengineering
$9,075,363	**$50,329,103**	**NINDS**	National Institute of Neurological Disorders and Stroke
—	**$32,924,533**	**NCRR**[3]	National Center for Research Resources
$1,409,120	**$23,626,496**	**NHLBI**	National Heart, Lung, and Blood Institute
$4,817,958	**$22,906,168**	**NIMH**	National Institute of Mental Health
$1,226,029	**$11,632,944**	**NIDDK**	National Institute of Diabetes and Digestive and Kidney Diseases
$782,568	**$11,089,061**	**OD**	Office of the Director, NIH
$1,890,612	**$10,358,402**	**NIA**	National Institute on Aging
—	**$7,264,005**	**CDMRP**	Congressionally Directed Medical Research Programs
—	**$7,066,696**	**NSF**	National Science Foundation
$276,786	**$6,988,469**	**NICHD**	National Institute of Child Health and Human Development
$1,157,422	**$6,915,181**	**NIGMS**	National Institute of General Medical Sciences
—	**$5,349,795**	**NIDA**	National Institute on Drug Abuse
$1,325,953	**$5,137,246**	**NEI**	National Eye Institute
—	**$1,858,361**	**CNRM**	Center For Neuroscience and Regenerative Medicine
$361,877	**$1,428,533**	**NIDCR**	National Institute of Dental and Craniofacial Research
—	**$1,316,497**	**NIDCD**	National Institute on Deafness and Other Communication Disorders
—	**$909,727**	**NIMHD**	National Institute on Minority Health and Health Disparities
—	**$749,990**	**NIAMS**	National Institute of Arthritis and Musculoskeletal and Skin Diseases
$968,750	**$576,760**	**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
$62,190,681	**$537,291,002**	**TOTAL**

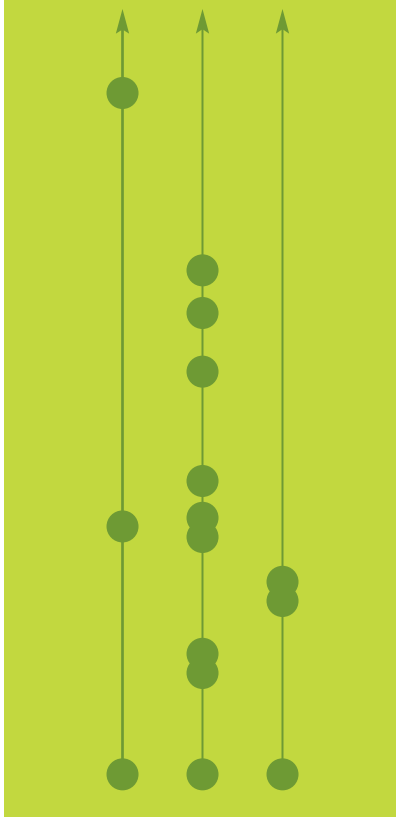
1 Overall 2020 NIH funding was $34,963,147,380.
2 The first record of funding for focused ultrasound research by the US Federal Government was in 2004.
3 Agency dissolved in 2012.

Sources
Site: NIH RePORTER projectreporter.nih.gov/reporter.cfm
Site: Federal RePORTER federalreporter.nih.gov
Note terms searched: "focused ultrasound", MRgFUS, HIFU, LIFU

2021 State of Research and Treatment

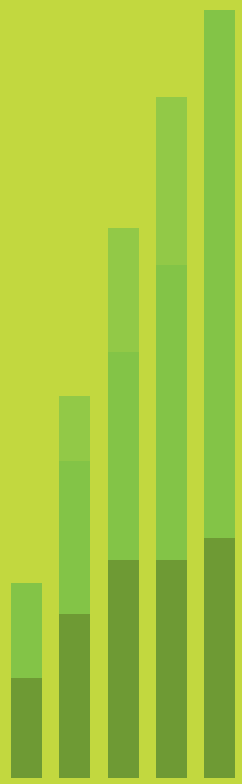
Focused Ultrasound Foundation

165
sites researching
drug delivery



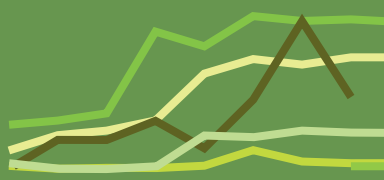
235
clinical research sites

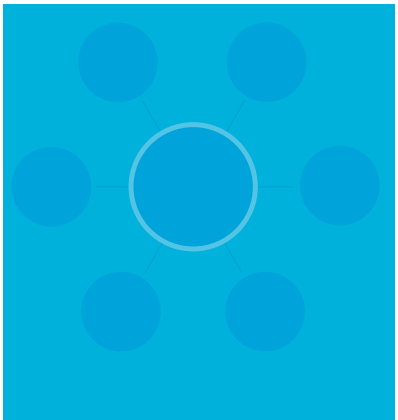
214
new commercial treatment sites



193
COE publications
in 2020

10
sites researching
opening the BBB





148
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.

2020 was a big year for commercialization in focused ultrasound. The field saw gains of 214 new treatment sites worldwide, 90 new sites in Europe, 66 new sites in Asia, and 51 new sites in North America.

Clinical trial sites in 2020 were up by 27. The largest gains were in Europe, with 13 new trial sites, followed by 8 new sites in North America, 5 new sites in Asia, and one new site in Oceania.

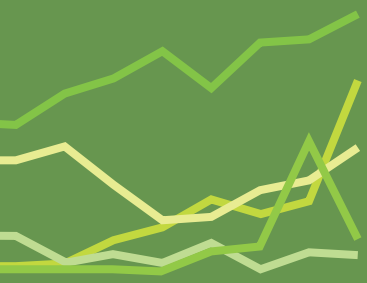
Worldwide, there are 166 sites conducting preclinical research on 27 unique indications.

New this year, we are reporting further detail on both focused ultrasound transducer technology and focused ultrasound image guidance as part of our technical research section.

Two new sites were designated as Centers of Excellence in 2020. Ten sites worldwide are Centers of Excellence, with four located in Europe, five in the United States, and one in Canada.

2020 also saw the official formation of a Veterinary Advisory Board for focused ultrasound. One of their accomplishments is a list of recommendations where focused ultrasound could best help the veterinary community, specifically identifying areas where current standards of care provide opportunities for innovation.

2
new in 2020
Centers of Excellence



17
MOAs
in glioblastoma research

Contents

II. State of the Research and Treatment

Commercial Treatment Sites by Region

799 Commercial treatment sites worldwide

181 North America	**278** Europe	**318** Asia
14 South America	**4** Africa	**4** Oceania

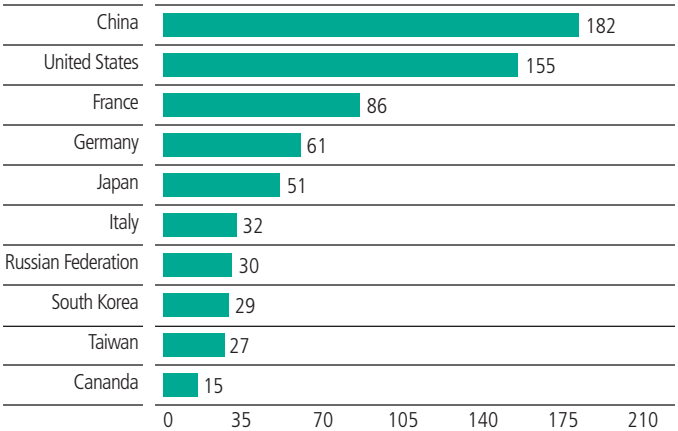
China continues to lead the world with 182 treatment sites, including 29 new sites added in 2020, and 28 unique approved indications. The United States, in second place, has 155 treatment, including 48 new sites in 2020, but with only 7 indications. This trend is indicative of just a few companies in the US, with technology that's heavily commercialization or specific indications—a different commercialization strategy than what is happening in China.

Commercial treatment additional content

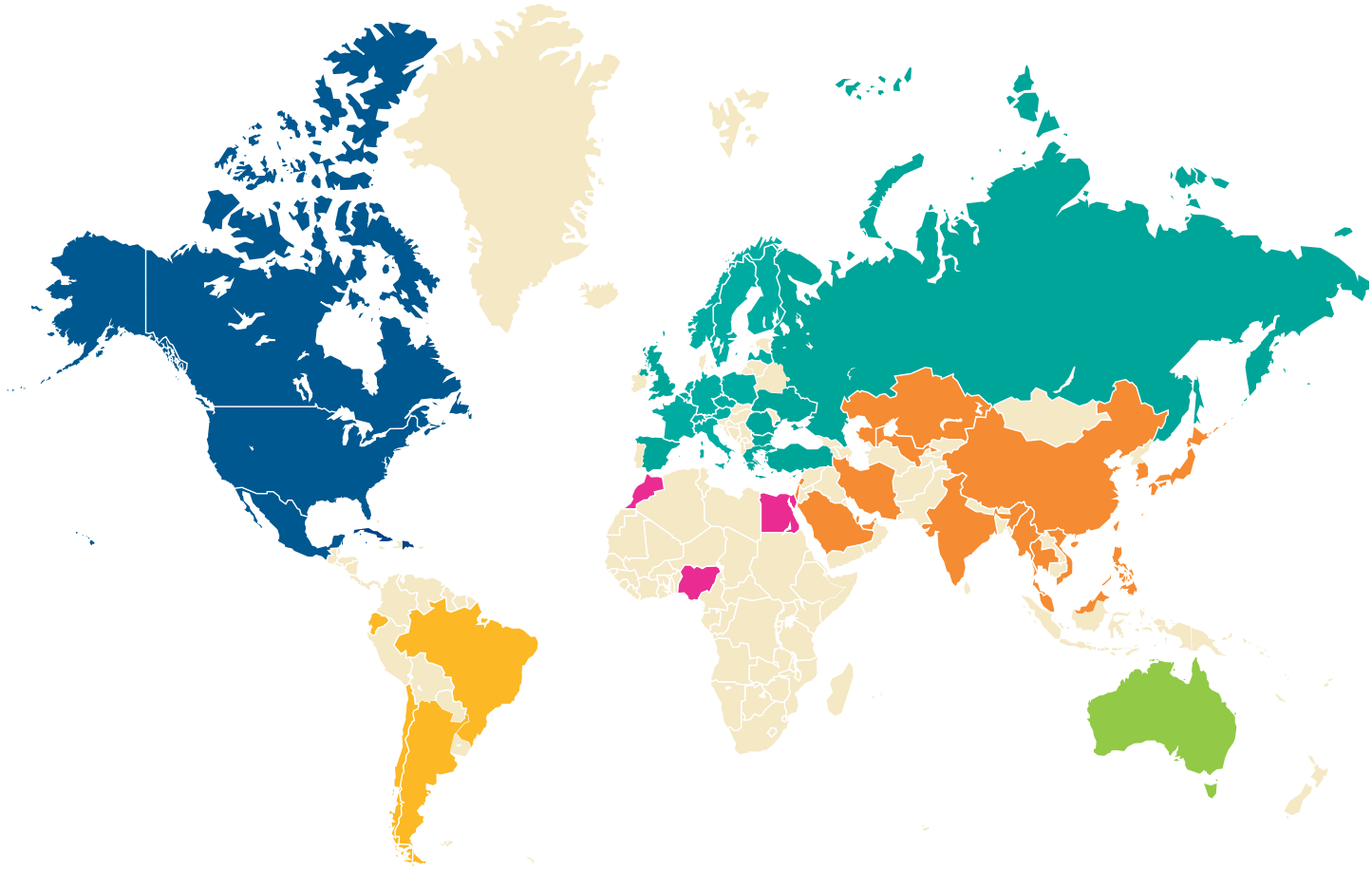
For more information about specific commercial treatment sites and indications, please visit:
www.fusfoundation.org/the-technology/treatment-sites

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

Top Countries for Commercial Treatment



Commercial Treatment Sites by Country



North America

15 Canada
1 Cayman Islands
1 Cuba
1 Dominican Republic
8 Mexico
155 United States

South America

1 Argentina
9 Brazil
2 Chile
2 Ecuador

Europe

3 Austria
1 Belgium
1 Bulgaria
1 Finland
86 France
61 Germany
2 Greece
32 Italy
1 Latvia
1 Monaco
5 The Netherlands
3 Norway
5 Poland
1 Romania
30 Russian Federation
13 Spain
1 Sweden
13 Switzerland
3 Turkey
1 Ukraine
14 United Kingdom

Asia

182 China
6 India
1 Iran
3 Israel
51 Japan
2 Kazakhstan
2 Lebanon
1 Malaysia
1 Myanmar
1 Philippines
2 Qatar
2 Saudi Arabia
3 Singapore
29 South Korea
27 Taiwan
2 Thailand
1 Arab Emirates
1 Uzbekistan
1 Vietnam

Oceania

4 Australia

Africa

2 Egypt
1 Morocco
1 Nigeria

Commercial Treatment Sites by Indication and Region*

9 Cardiovascular sites — 3 indications

19 Endocrine disorders sites — 1 indication

109 Gastrointestinal sites — 4 indications

255 Musculoskeletal sites — 8 indications

101 Neurological sites — 14 indications

14 Ophthalmological sites — 1 indication

559 Urological sites — 3 indications

493 Women's health sites — 8 indications

	Regions						Totals
Indications	N. America	Europe	Asia	S. America	Africa	Oceania	
Cardiovascular							
Arteriovenous malformations	***1***	***1***	–	–	–	–	**2**
Peripheral artery disease	***1***	–	–	–	–	–	**1**
Varicose veins	–	5	***1***	–	–	–	**6**
Endocrine disorders							
Thyroid nodules	–	17	2	–	–	–	**19**
Gastrointestinal							
Liver metastases	–	–	***1***	–	***1***	–	**2**
Liver tumors	***1***	8	89	–	***1***	–	**99**
Pancreatic tumors, unspecified	–	1	***4***	–	***1***	–	**6**
Pancreatic tumors, malignant	–	***2***	–	–	–	–	**2**
Musculoskeletal							
Arthritis, facetogenic	***6***	1	***2***	–	–	1	**10**
Bone cancer	***2***	***2***	***1***	–	–	–	**5**
Bone metastases	6	11	***6***	–	***1***	1	**25**
Bone tumors, benign	***1***	–	–	–	–	–	**1**
Desmoid tumors	***3***	***5***	–	–	–	***1***	**9**
Osteoid osteoma	***4***	13	88	–	–	***1***	**106**
Soft tissue cancer	***1***	***1***	–	–	–	–	**2**
Soft tissue tumors, benign	***1***	7	88	–	–	***1***	**97**

*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: N. America	Europe	Asia	S. America	Africa	Oceania	Totals
Neurological							
Alzheimer's disease	–	–	***1***	–	–	–	**1**
Astrocytoma	***1***	–	–	–	–	–	**1**
Cancer pain	–	***1***	–	–	–	–	**1**
Depression	–	–	1	–	–	–	**1**
Dystonia	–	***1***	–	–	–	–	**1**
Dystonia, hand	–	–	***1***	–	–	–	**1**
Epilepsy	–	***1***	***1***	–	–	–	**2**
Essential tremor	29	15	19	1	–	2	**66**
Neuropathic pain	–	2	–	–	–	1	**3**
Neuropathy	–	***1***	–	–	–	–	**1**
Obsessive-compulsive disorder	–	–	1	–	–	–	**1**
Parkinson's disease, dyskinesia	–	***2***	1	–	–	–	**3**
Parkinson's disease, tremor	6	6	4	1	–	1	**18**
Trigeminal neuralgia	–	***1***	–	–	–	–	**1**
Ophthalmological							
Glaucoma	–	14	–	–	–	–	**14**
Urological							
Benign prostatic hyperplasia	29	8	24	***1***	–	–	**62**
Kidney tumors	***1***	5	88	–	***1***	–	**95**
Prostate cancer	142	206	38	12	***3***	1	**402**
Women's health							
Breast tumors, benign	–	11	–	–	***1***	–	**12**
Breast tumors, malignant	–	7	89	–	–	–	**96**
Cervicitis	–	***1***	–	–	–	–	**1**
Endometrial tumors	–	–	***1***	–	–	–	**1**
Endometriosis	–	***2***	–	–	–	–	**2**
Lichen sclerosis	–	–	1	–	–	–	**1**
Uterine adenomyosis	***2***	8	76	–	–	2	**88**
Uterine fibroids	12	35	241	1	***1***	2	**292**

*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*

235 Clinical research sites worldwide

55 North America

98 Europe

75 Asia

2 South America

5 Oceania

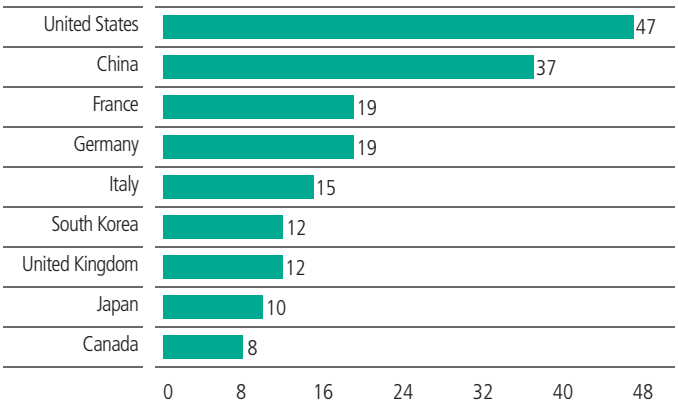
*Clinical research sites treat patients as part of a clinical study.

Clinical research additional content

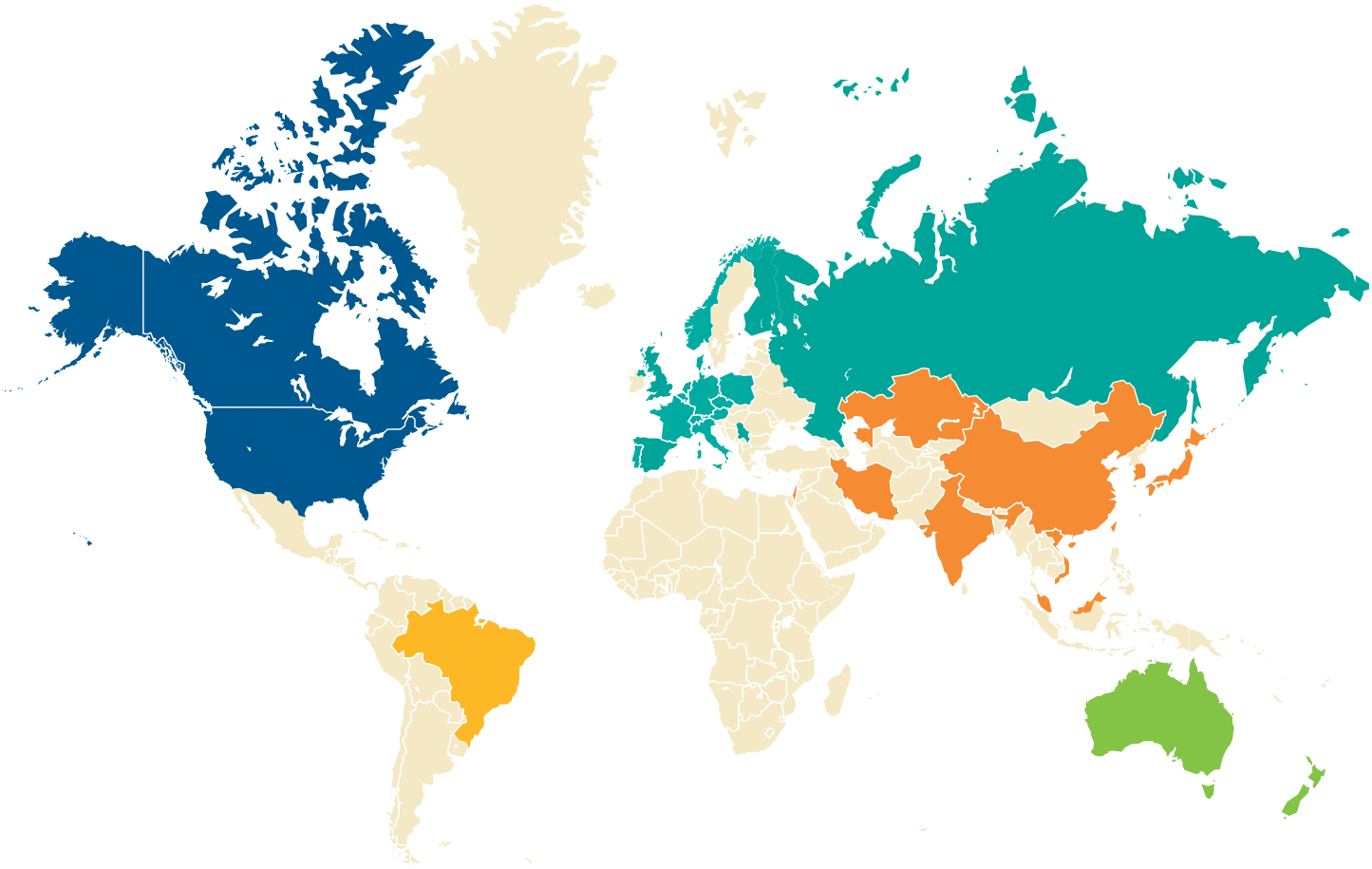
For more information about specific clinical research sites and indications, please visit:
www.fusfoundation.org/the-technology/research-sites

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

Top Countries for Clinical Research



Clinical Research Sites by Country



North America
- 8 Canada
- 47 United States

South America
- 2 Brazil

Europe
- 1 Austria
- 1 Belgium
- 3 Czech Republic
- 2 Denmark
- 1 Finland
- 19 France
- 19 Germany
- 15 Italy
- 4 The Netherlands
- 3 Norway
- 1 Poland
- 1 Portugal
- 5 Russian Federation
- 1 Serbia
- 7 Spain
- 3 Switzerland
- 12 United Kingdom

Asia
- 37 China
- 2 India
- 1 Iran
- 3 Israel
- 10 Japan
- 1 Kazakhstan
- 1 Malaysia
- 12 South Korea
- 7 Taiwan
- 1 Vietnam

Oceania
- 4 Australia
- 1 New Zealand

Clinical Research Sites by Indication and Region

86 indications are being researched at clinical sites worldwide.

21 Cardiovascular sites — 5 indications

6 Endocrine disorders sites — 3 indications

50 Gastrointestinal sites — 11 indications

102 Musculoskeletal sites — 12 indications

112 Neurological sites — 24 indications

7 Ophthalmological sites — 1 indication

1 Pulmonary site — 1 indication

75 Urological sites — 6 indications

129 Women's health sites — 14 indications

	Regions					Totals
Indications	N. America	Europe	Asia	S. America	Oceania	
Cardiovascular						
Atrial fibrillation	–	1	–	–	–	**1**
Heart valve calcifications	–	5	–	–	–	**5**
Hypertension	–	10	2	–	1	**13**
Twin-twin transfusion syndrome	–	1	–	–	–	**1**
Varicose veins	–	1	–	–	–	**1**
Endocrine disorders						
Graves' disease	–	–	1	–	–	**1**
Thyroid cancer	–	1	–	–	–	**1**
Thyroid nodules	–	2	2	–	–	**4**
Gastrointestinal						
Biliary tract cancer	–	–	1	–	–	**1**
Colorectal tumors	–	3	–	–	–	**3**
Esophageal tumors	1	–	–	–	–	**1**
Gastric tumors	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

86 indications are being researched at clinical sites worldwide.

	Regions					Totals
Indications	N. America	Europe	Asia	S. America	Oceania	
Gastrointestinal continued						
Liver metastases	–	3	–	–	–	**3**
Liver tumors	–	9	14	–	–	**23**
Malignant obstructive jaundice	–	–	1	–	–	**1**
Pancreatic tumors, unspecified	–	6	7	–	–	**13**
Pancreatic tumors, benign	–	1	–	–	–	**1**
Pancreatic tumors, malignant	1	–	1	–	–	**2**
Root canal endodontia	1	–	–	–	–	**1**
Miscellaneous						
Actinic keratosis	–	1	–	–	–	**1**
Basal cell carcinoma	–	2	–	–	–	**2**
Dercum's disease	–	–	1	–	–	**1**
Head & neck tumors	2	1	–	–	–	**3**
Hypersplenism	–	–	1	–	–	**1**
Kaposi's sarcoma	–	1	–	–	–	**1**
Lipoma	–	–	1	–	–	**1**
Melanoma	1	1	–	–	–	**2**
Multiple tumors[1]	1	–	–	–	–	**1**
Musculoskeletal						
Arthritis, facetogenic	2	4	2	1	–	**9**
Arthritis, knee	–	–	1	–	–	**1**
Arthritis, sacroiliac	–	1	–	–	–	**1**
Bone cancer	3	2	–	–	–	**5**
Bone metastases	2	11	7	1	–	**21**
Bone tumors, benign	–	3	–	–	–	**3**
Desmoid tumors	3	1	–	–	–	**4**
Osteoid osteoma	5	6	13	1	–	**25**
Plantar fasciitis	–	1	–	–	–	**1**
Sacral chordoma	–	1	–	–	–	**1**
Soft tissue cancer	3	3	–	–	–	**6**
Soft tissue tumors, benign	4	6	14	–	1	**25**

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

86 indications are being researched at clinical sites worldwide.

	Regions					Totals
Indications	N. America	Europe	Asia	S. America	Oceania	
Neurological						
Alzheimer's disease	5	2	1	–	2	**10**
Astrocytoma	2	–	–	–	–	**2**
Brain tumors, general	1	–	–	–	–	**1**
Dementia	–	1	–	–	–	**1**
Depression	1	–	4	–	–	**5**
Dystonia	–	–	1	–	–	**1**
Dystonia, hand	–	–	1	–	–	**1**
Epilepsy	4	–	4	–	–	**8**
Essential tremor	10	6	5	–	–	**21**
Glioblastoma	8	7	4	–	–	**19**
Mood disorder	1	–	–	–	–	**1**
Multiple sclerosis	1	–	–	–	–	**1**
Neuroblastoma	1	–	–	–	–	**1**
Neuropathic pain	3	–	1	–	–	**4**
Neuropathy	2	–	–	–	–	**2**
Obsessive-compulsive disorder	2	–	–	–	–	**2**
Opioid and other addictions	1	1	–	–	–	**2**
Painful amputation neuromas	–	–	1	–	–	**1**
Parkinson's disease, dyskinesia	10	3	4	–	–	**17**
Parkinson's disease, tremor	3	3	1	–	–	**7**
Parkinson's disease, underlying cause	1	1	–	–	–	**2**
Stroke, thromboembolic	1	–	–	–	–	**1**
Traumatic brain injury	1	–	–	–	–	**1**
Trigeminal neuralgia	1	–	–	–	–	**1**
Ophthalmological						
Glaucoma	1	6	–	–	–	**7**
Pulmonary						
Rhinitis	–	–	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

86 indications are being researched at clinical sites worldwide.

	Regions					Totals
Indications	N. America	Europe	Asia	S. America	Oceania	
Urological						
Acute kidney injury	–	–	1	–	–	**1**
Benign prostatic hyperplasia	–	3	–	–	–	**3**
Chyluria	–	–	1	–	–	**1**
Kidney stones	1	–	–	–	–	**1**
Kidney tumors	–	4	13	–	–	**17**
Prostate cancer	23	23	5	1	–	**52**
Women's health						
Brain metastases, breast cancer	1	–	–	–	–	**1**
Breast tumors, benign	5	2	3	–	–	**10**
Breast tumors, malignant	1	9	14	–	–	**24**
Cervical tumors	–	2	–	–	–	**2**
Ectopic pregnancy	–	–	1	–	–	**1**
Endometrial tumors	–	1	–	–	–	**1**
Endometriosis	–	1	1	–	–	**2**
Endometriosis, colorectal	–	1	–	–	–	**1**
Ovarian tumors	–	1	–	–	–	**1**
Retained placenta	–	–	1	–	–	**1**
Uterine adenomyosis	–	7	10	–	2	**19**
Uterine fibroids	1	24	34	1	2	**62**
Vaginal tumors	–	3	–	–	–	**3**
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*

148 Preclinical research sites worldwide

68 North America

39 Europe

38 Asia

3 Oceania

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

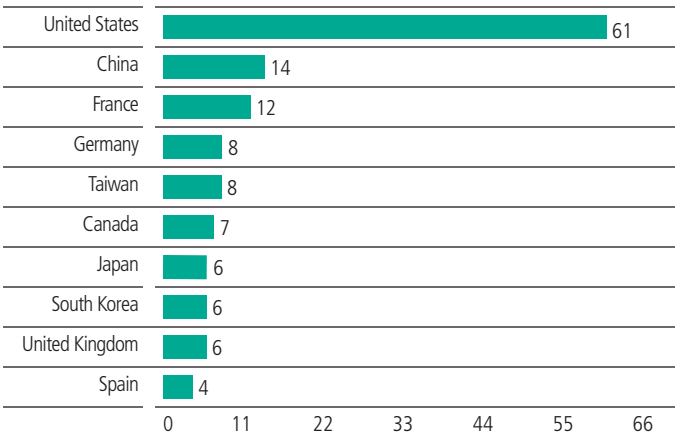
The United States leads the world in preclinical focused ultrasound research with over four-fold more research sites than the next closest country. This is likely a reflection of the US leading the world in medical research and the robust research infrastructure that exists in institutions of higher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

Preclinical research additional content

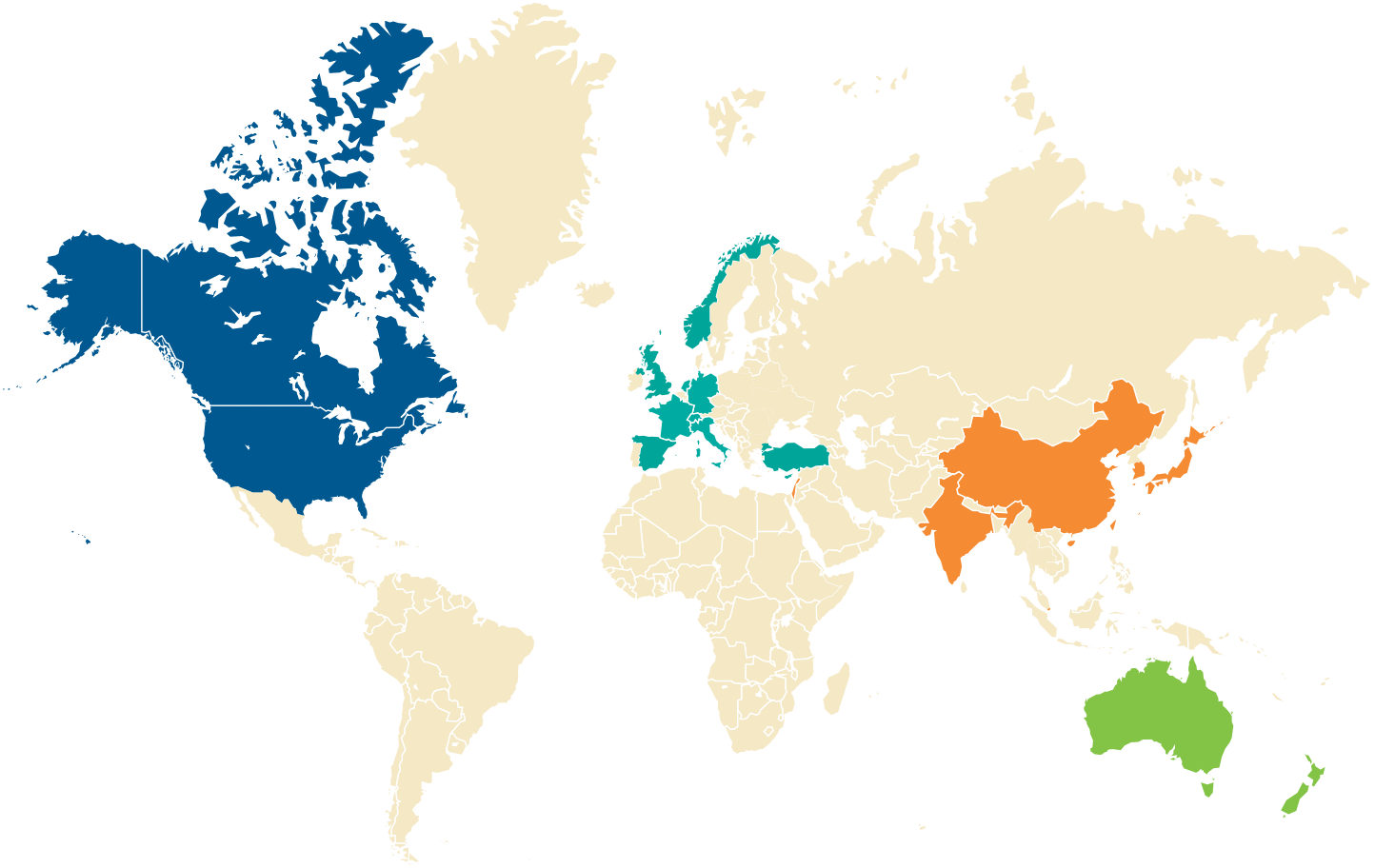
For more information about specific preclinical research sites and indications, please visit:
www.fusfoundation.org/the-technology/research-sites

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

Top Countries for Preclinical Research



Preclinical Research Sites by Country



North America

7 Canada
61 United States

Europe

1 Cyprus
12 France
8 Germany
2 Italy
1 The Netherlands
1 Norway
4 Spain
3 Switzerland
1 Turkey
6 United Kingdom

Asia

14 China
1 India
2 Israel
6 Japan
1 Singapore
6 South Korea
8 Taiwan

Oceania

2 Australia
1 New Zealand

Preclinical Research Sites by Indication and Region

101 indications are being researched at preclinical sites worldwide.

39 Cardiovascular sites — 18 indications

6 Endocrine disorders sites — 4 indications

61 Gastrointestinal sites — 7 indications

46 Musculoskeletal sites — 14 indications

166 Neurological sites — 26 indications

8 Ophthalmological sites — 4 indications

6 Pulmonary sites — 3 indications

44 Urological sites — 9 indications

56 Women's health sites — 9 indications

	Regions				Totals
Indications	N. America	Europe	Asia	Oceania	
Cardiovascular					
Arteriovenous malformations	1	–	–	–	**1**
Atherosclerosis	4	1	1	–	**6**
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	7	–	–	–	**7**
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

101 indications are being researched at preclinical sites worldwide.

	Regions				Totals
Indications	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	–	1	–	**3**
Thyroid nodules	1	–	–	–	**1**
Gastrointestinal					
Colorectal tumors	1	1	–	–	**2**
Gastric tumors	–	1	–	–	**1**
Inflammatory bowel disease	–	1	–	–	**1**
Liver metastases	3	3	–	–	**6**
Liver tumors	12	10	5	–	**27**
Pancreatic tumors, unspecified	8	10	4	–	**22**
Pancreatic tumors, malignant	1	1	–	–	**2**
Miscellaneous					
Head & neck tumors	1	2	1	–	**4**
Infection	1	–	–	–	**1**
Melanoma	2	–	–	–	**2**
Multiple tumors[1]	3	2	–	–	**5**
Obesity	1	–	–	–	**1**
Wound healing	2	–	–	–	**2**
Musculoskeletal					
Arthritis, facetogenic	2	2	1	–	**5**
Arthritis, knee	–	–	1	–	**1**
Bone cancer	1	–	–	–	**1**
Bone metastases	5	3	3	1	**12**
Bone tumors, benign	1	1	–	–	**2**
Disc degeneration	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

101 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Musculoskeletal continued					
Muscle atrophy	2	–	–	–	**2**
Osteoid osteoma	1	1	2	–	**4**
Osteomyelitis	1	–	–	–	**1**
Osteopenia	1	–	–	–	**1**
Rotator cuff injury	1	–	–	–	**1**
Soft tissue cancer	7	1	–	–	**8**
Soft tissue tumors, benign	3	1	2	–	**6**
Tendon contracture	1	–	–	–	**1**
Neurological					
Alzheimer's disease	8	4	3	1	**16**
Amyotrophic lateral sclerosis	1	1	–	–	**2**
Astrocytoma	7	2	3	–	**12**
Brain tumors, general	5	1	1	–	**7**
Cancer pain	1	3	–	–	**4**
Cavernomas	1	–	–	–	**1**
Dementia	–	–	1	–	**1**
Depression	3	2	–	–	**5**
Epilepsy	13	3	3	–	**19**
Essential tremor	1	1	1	–	**3**
Glioblastoma	20	9	9	–	**38**
Huntington's disease	1	–	–	–	**1**
Hydrocephalus	1	–	–	–	**1**
Neuroblastoma	–	1	–	–	**1**
Neuromyelitis optica	1	–	–	–	**1**
Neuropathic pain	4	–	1	–	**5**
Neuropathy	–	–	1	–	**1**
Opioid and other addictions	1	1	1	–	**3**
Parkinson' disease, dyskinesia	–	–	1	–	**1**
Parkinson's disease, tremor	1	–	1	–	**2**
Parkinson's disease, underlying cause	5	2	4	–	**11**
Pontine glioma	1	2	–	–	**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

101 indications are being researched at preclinical sites worldwide.

Indications	Regions: N. America	Europe	Asia	Oceania	Totals
Neurological continued					
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**
Ophthalmological					
Glaucoma	–	4	–	–	**4**
Keratoplasty	–	–	1	–	**1**
Macular degeneration	1	1	–	–	**2**
Retinal injury	1	–	–	–	**1**
Pulmonary					
Lung cancer	2	1	1	–	**4**
Lung metastases	–	1	–	–	**1**
Tuberculosis	–	–	1	–	**1**
Urological					
Acute kidney injury	1	–	–	–	**1**
Acute tubular necrosis	1	–	–	–	**1**
Benign prostatic hyperplasia	1	–	1	–	**2**
Bladder tumors	2	–	–	–	**2**
Fetal bladder obstruction	–	–	1	–	**1**
Kidney stones	2	–	–	–	**2**
Kidney tumors	5	2	2	–	**9**
Prostate cancer	13	8	4	–	**25**
Urinary tract infection	–	1	–	–	**1**
Women's health					
Brain metastases, breast cancer	3	–	1	–	**4**
Breast tumors, benign	1	–	1	–	**2**
Breast tumors, malignant	15	1	6	–	**22**
Cervical tumors	–	–	1	–	**1**
Endometrial tumors	1	–	1	–	**2**

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

101 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
Women's health continued					
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

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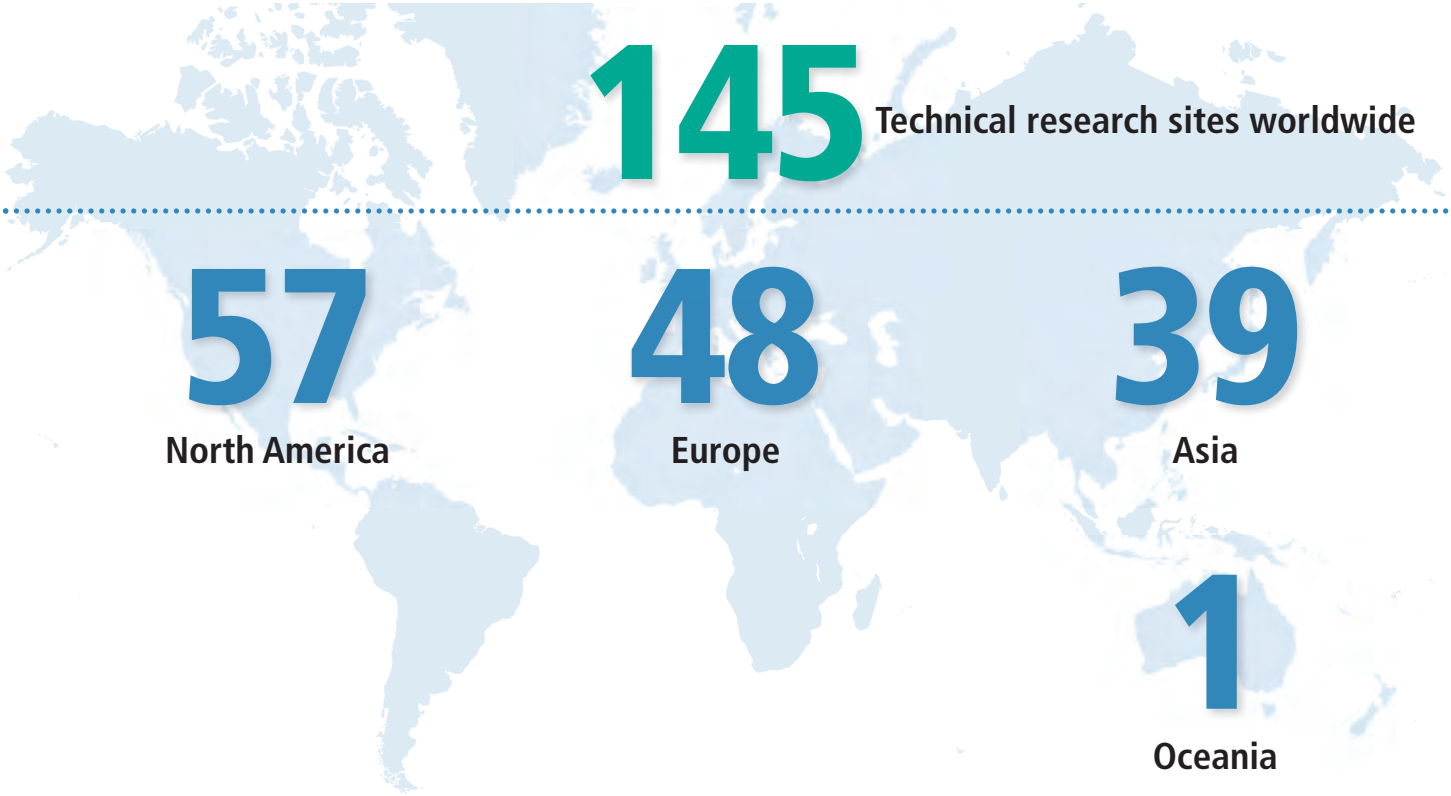
Technical Research Sites by Region

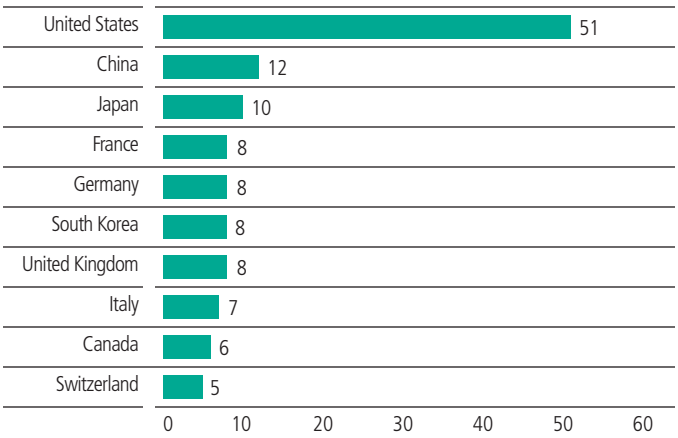


Technical research additional content

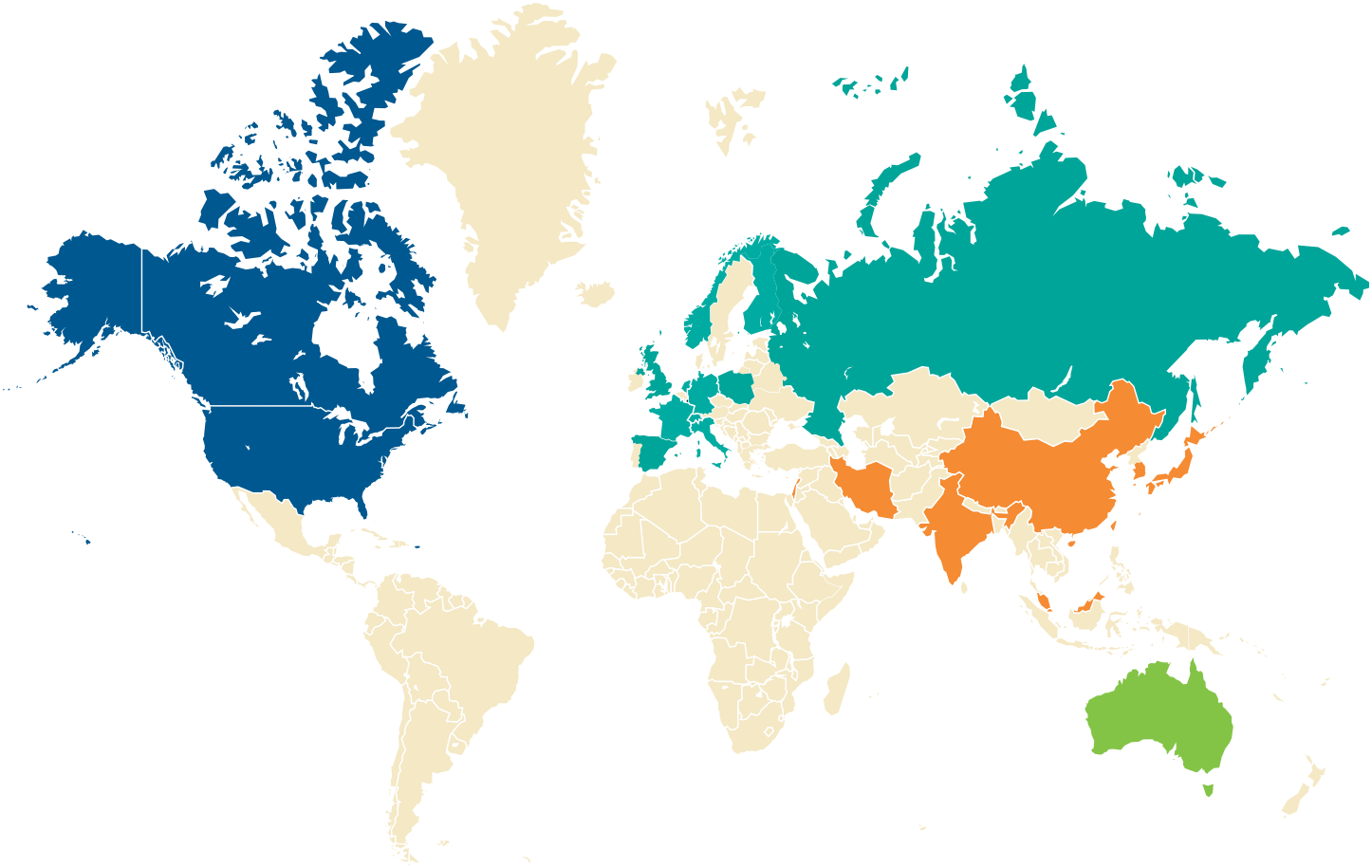
For more information about specific technical research sites, please visit:
www.fusfoundation.org/the-technology/research-sites

Use the "search by technical research" dropdown menu.

Top Countries for Technical Research



Technical Research Sites by Country



North America
- 6 Canada
- 51 United States

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

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

Oceania
- 1 Australia

NEW

Technical Research Sites*

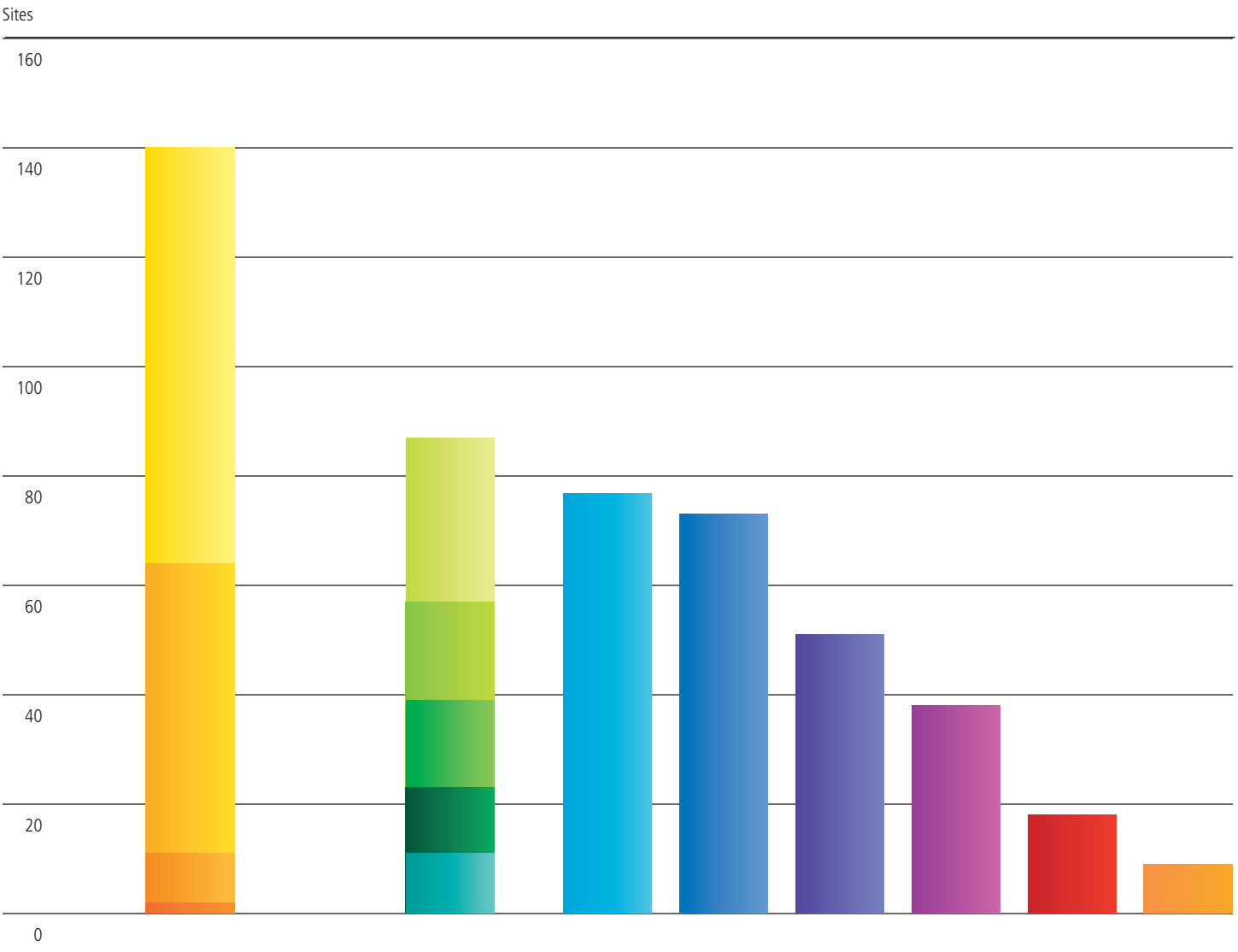
	Sites				Totals
	North America	Europe	Asia	Oceania	
FUS Transducer technology					
Thermal ablation	10	13	7	–	**30**
Hyperthermia	7	8	3	–	**18**
Nonthermal	9	3	4	–	**16**
Histotripsy	7	2	2	–	**11**
Other	6	6	–	–	**12**
FUS Image guidance					
MR	30	27	19	–	**76**
Ultrasound	28	16	9	–	**53**
Navigation	1	6	2	–	**9**
Other	–	–	2	–	**2**
Drug delivery technology	21	12	4	1	**38**
FUS Physics	38	24	15	–	**77**
FUS Simulation & treatment planning	23	20	8	–	**51**
FUS Treatment monitoring	31	27	15	–	**73**
FUS Treatment evaluation	2	6	1	–	**9**
Standards & quality assurance	8	7	3	–	**18**

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

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

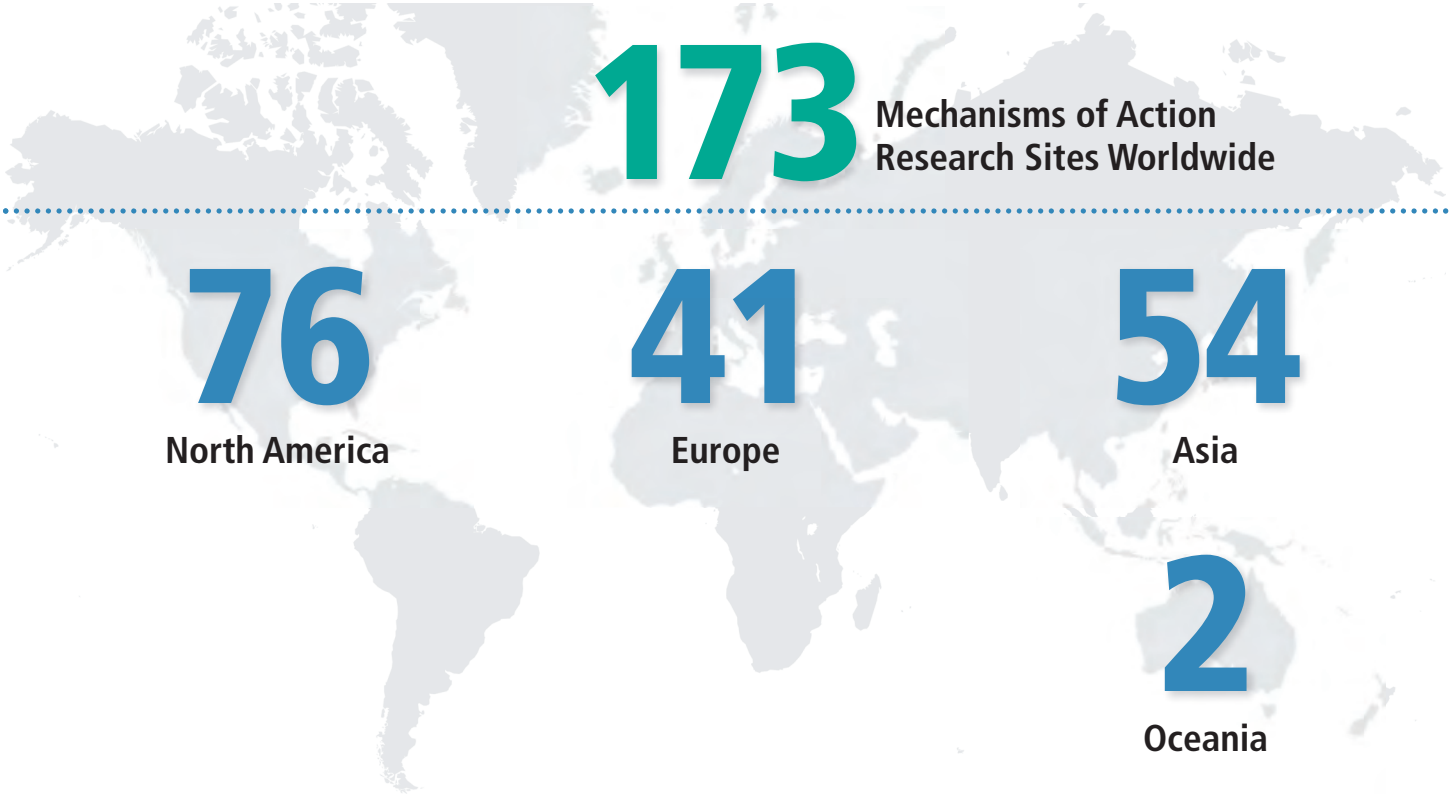
NEW

Technical Research Types*



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

Mechanisms of Action Research Sites by Region*



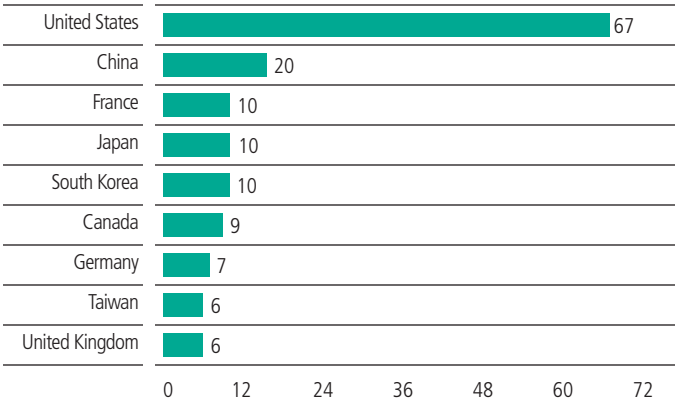
*Mechanisms of action research sites conduct basic science research to understand how focused ultrasound affects the body.

Mechanisms of action (MOA)

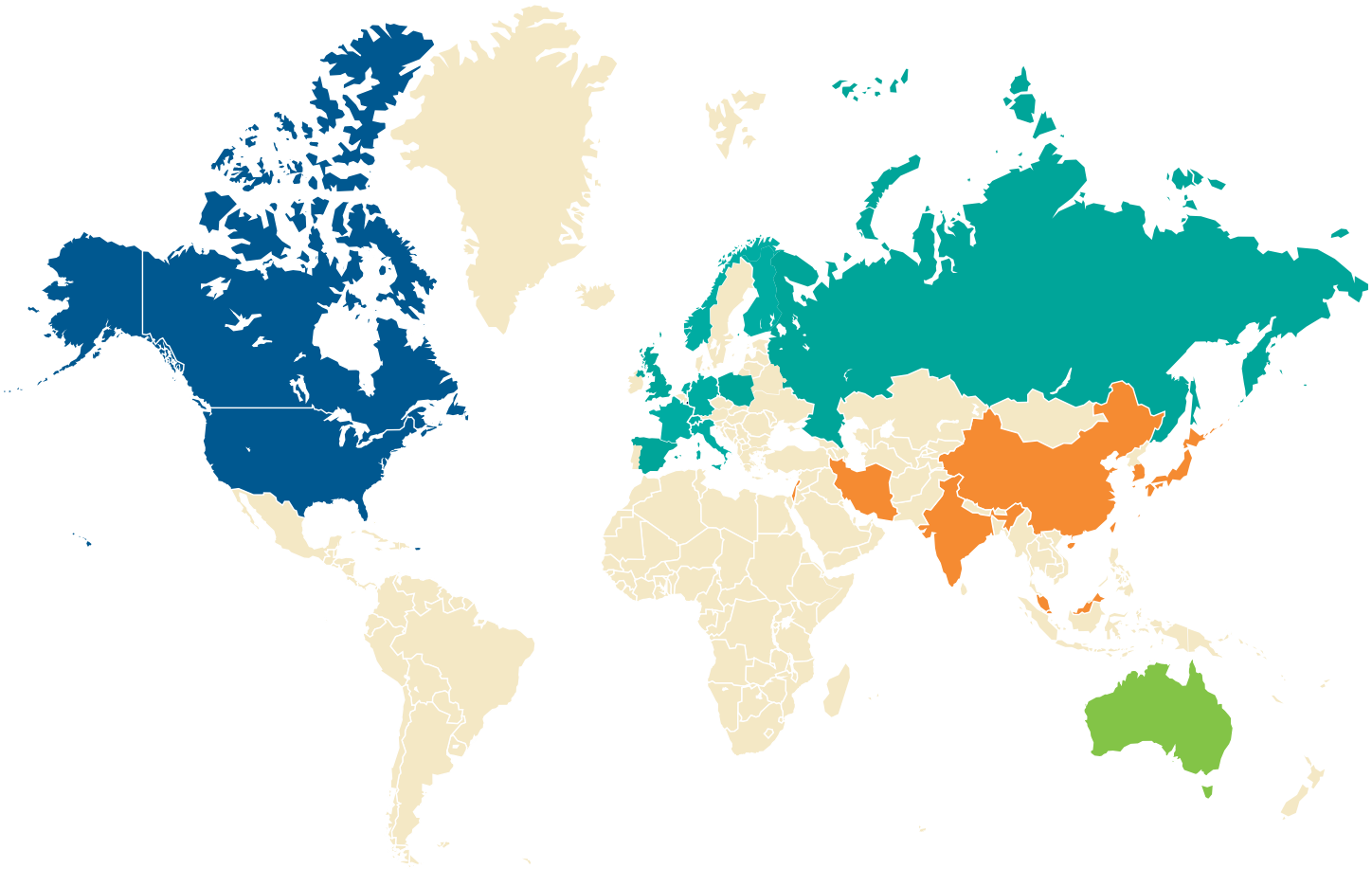
For more information about specific mechanisms of action research sites, please visit:
www.fusfoundation.org/the-technology/research-sites

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

Top Countries for MOA Research



Mechanisms of Action Research Sites by Country



North America

9 Canada
67 United States

Europe

1 Cyprus
10 France
7 Germany
5 Italy
2 The Netherlands
2 Norway
1 Russian Federation
2 Spain
5 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.

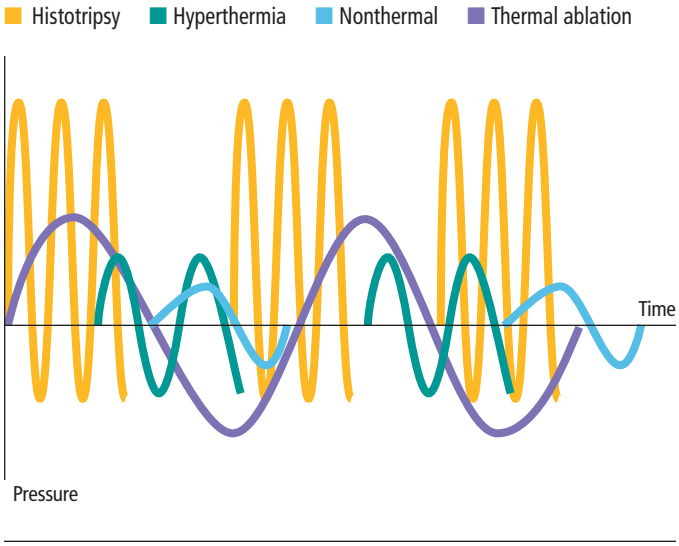
Focused ultrasound is a medical technology that provides a uniquely flexible treatment platform applicable to a wide range of diseases and conditions. It can produce treatments across the spectrum of thermal to mechanical effects, and these various treatments elicit a multitude of responses in biological 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 currently used most frequently in the clinic, and produces permanent effects, but additional ultrasound treatment regimens are under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications being tested in clinical trials is a low-power, pulsed treatment that produces mild mechanical forces capable of enhancing drug delivery to the brain. This effect is transient, and treated tissue reverts to normal function within a few hours.

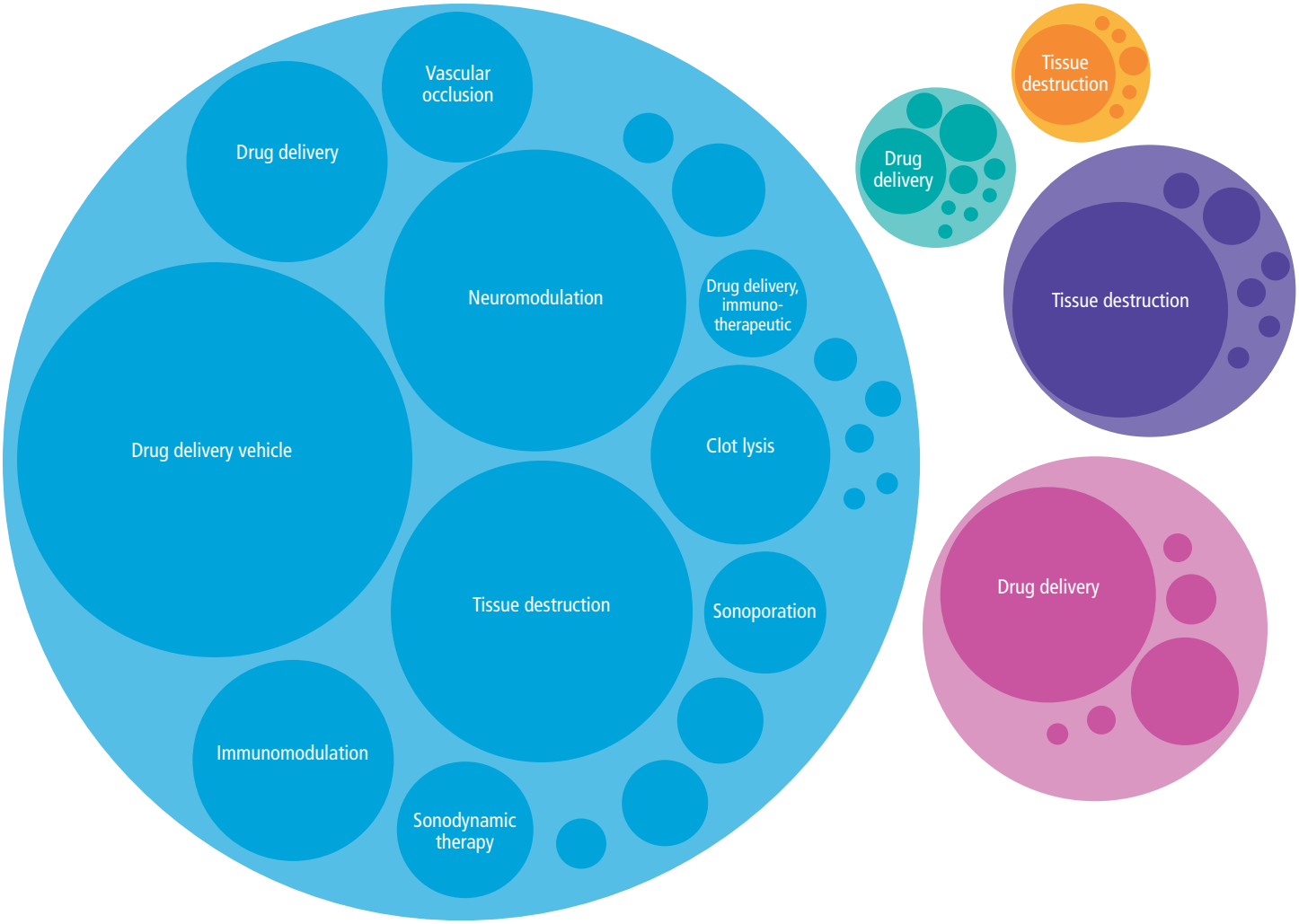
The effects induced by focused ultrasound can vary greatly depending on the ultrasound application and the type of tissue targeted. These biological effects are sometimes uniquely paired to a set of ultrasound parameters, as is the case with blood-brain barrier disruption, but others may be induced by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

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

What do sound waves look like?



Mechanisms of Action Research Sites



Ultrasound applications and biological effects

Histotripsy | 44 sites
- Amplification of cancer biomarkers
- Immune cell trafficking
- Immunomodulation
- Liquid biopsy
- Radiosensitization
- Tissue destruction

Hyperthermia | 48 sites
- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Immune cell trafficking
- Immunomodulation
- Radiosensitization
- Tissue destruction
- Vasodilation

Nonthermal | 315 sites
- Amplification of cancer biomarkers
- Angiogenesis
- Cardiac pacing
- Chemosensitization
- Clot lysis
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Gene delivery
- Immune cell trafficking
- Immunomodulation
- Liquid biopsy
- Neuromodulation
- Radiosensitization
- Sonodynamic therapy
- Sonoporation
- Stem cell delivery
- Stem cell trafficking
- Tissue destruction
- Vascular occlusion

Nonthermal - BBB opening | 101 sites
- Blood-brain barrier opening
- Drug delivery
- Drug delivery, immunotherapeutic
- Gene delivery
- Immune cell delivery
- Stem cell delivery

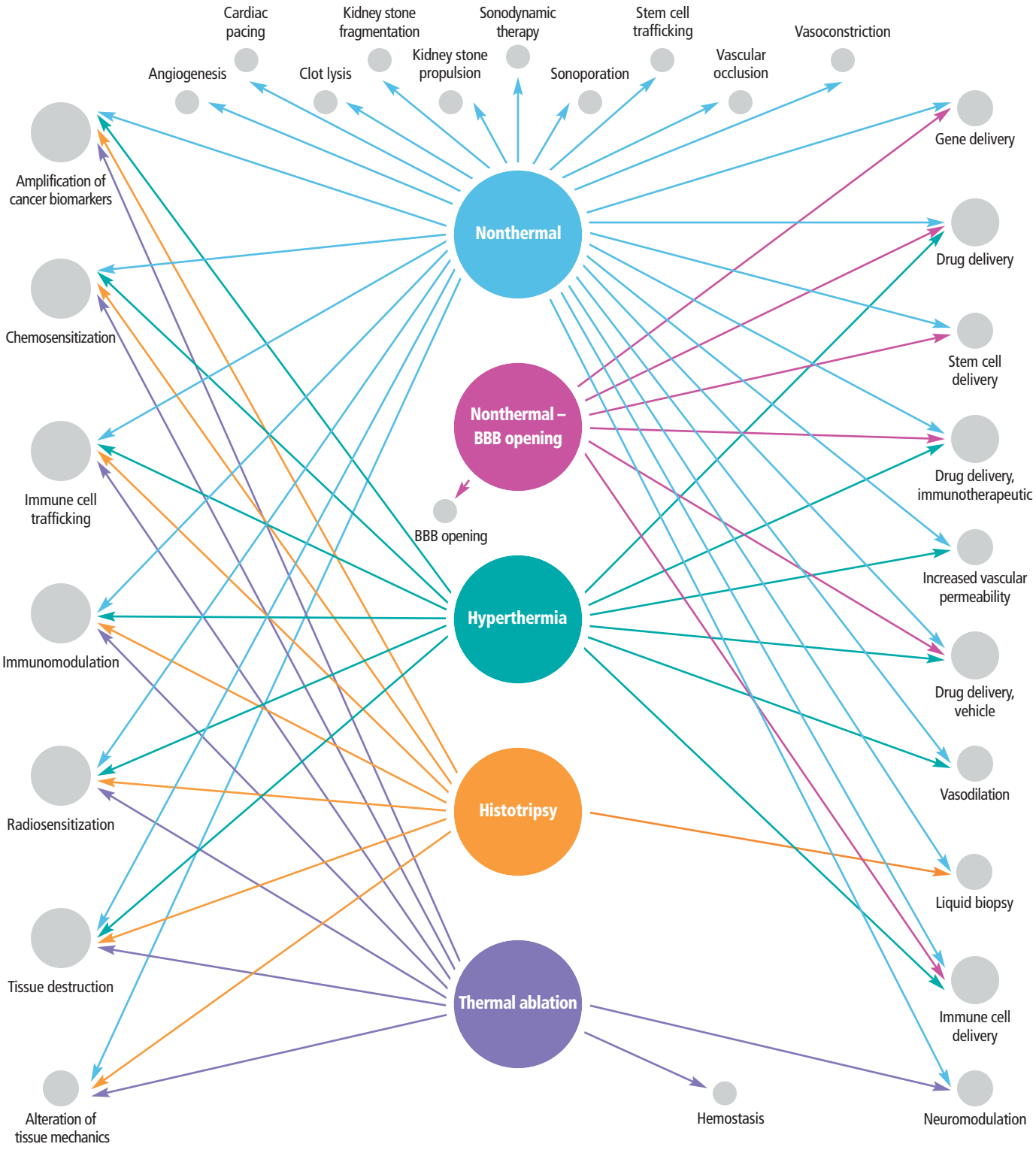
Thermal ablation | 92 sites
- Amplification of cancer biomarkers
- Chemosensitization
- Hemostasis
- Immune cell trafficking
- Immunomodulation
- Neuromodulation
- Radiosensitization
- Tissue destruction

Ultrasound Applications and Biological Effects

Table

HISTOTRIPSY	HYPERTHERMIA	NONTHERMAL	NONTHERMAL-BBB OPENING	THERMAL ABLATION
8 biological effects	**12** biological effects	**26** biological effects	**7** biological effects	**9** biological effects
Alteration of tissue mechanics	Amplification of cancer biomarkers	Amplification of cancer biomarkers	BBB opening	Alteration of tissue mechanics
Amplification of cancer biomarkers	Chemosensitization	Angiogenesis	Drug delivery	Amplification of cancer biomarkers
Chemosensitization	Drug delivery	Cardiac pacing	Drug delivery, immunotherapeutic	Chemosensitization
Immune cell trafficking	Drug delivery, immunotherapeutic	Chemosensitization	Drug delivery, vehicle	Hemostasis
Immunomodulation	Drug delivery, vehicle	Clot lysis	Gene delivery	Immune cell trafficking
Liquid biopsy	Immune cell delivery	Drug delivery	Immune cell delivery	Immunomodulation
Radiosensitization	Immune cell trafficking	Drug delivery, immunotherapeutic	Stem cell delivery	Neuromodulation
Tissue destruction	Immunomodulation	Drug delivery, vehicle		Radiosensitization
	Increased vascular permeability	Gene delivery		Tissue destruction
	Radiosensitization	Immune cell delivery		
	Tissue destruction	Immune cell trafficking		
	Vasodilation	Immunomodulation		
		Increased vascular permeability		
		Kidney stone fragmentation		
		Kidney stone propulsion		
		Liquid biopsy		
		Neuromodulation		
		Radiosensitization		
		Sonodynamic therapy		
		Sonoporation		
		Stem cell delivery		
		Stem cell trafficking		
		Tissue destruction		
		Vascular occlusion		
		Vasoconstriction		
		Vasodilation		

Ultrasound Applications and Biological Effects
Graphic



Mechanisms of Action Research Sites by Region

	Regions				Total
	N. America	Europe	Asia	Oceania	
Histotripsy | 44 sites					
Amplification of cancer biomarkers	1	–	–	–	**1**
Immune cell trafficking	1	–	–	–	**1**
Immunomodulation	6	3	–	–	**9**
Liquid biopsy	1	–	–	–	**1**
Radiosensitization	–	1	–	–	**1**
Tissue destruction	21	7	3	–	**31**
Hyperthermia | 48 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	2	3	1	–	**6**
Tissue destruction	6	2	3	–	**11**
Vasodilation	–	1	–	–	**1**
Nonthermal | 315 sites					
Amplification of cancer biomarkers	6	–	1	–	**7**
Angiogenesis	2	1	2	–	**5**
Cardiac pacing	–	–	1	–	**1**
Chemosensitization	5	2	–	–	**7**
Clot lysis	14	3	3	–	**20**
Drug delivery	14	5	2	–	**21**
Drug delivery, immunotherapeutic	7	2	–	1	**10**
Drug delivery, vehicle	31	12	20	–	**63**
Gene delivery	1	–	–	–	**1**
Immune cell trafficking	2	–	–	–	**2**
Immunomodulation	13	4	4	–	**21**
Liquid biopsy	3	1	–	–	**4**
Neuromodulation	28	5	15	1	**49**
Radiosensitization	5	–	–	–	**5**

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

Mechanisms of Action Research Sites by Region continued

	Regions				Total
	N. America	Europe	Asia	Oceania	
Nonthermal continued					
Sonodynamic therapy	5	3	6	–	**14**
Sonoporation	8	2	2	–	**12**
Stem cell delivery	7	–	1	–	**8**
Stem cell trafficking	3	–	–	–	**3**
Tissue destruction	20	13	12	–	**45**
Vascular occlusion	10	3	4	–	**17**
Nonthermal - BBB opening | 101 sites					
Blood-brain barrier opening	18	8	4	–	**30**
Drug delivery	24	17	20	1	**62**
Drug delivery, immunotherapeutic	2	2	–	–	**4**
Gene delivery	1	1	–	–	**2**
Immune cell delivery	1	–	–	–	**1**
Stem cell delivery	1	–	1	–	**2**
Thermal ablation | 92 sites					
Amplification of cancer biomarkers	3	1	–	–	**4**
Chemosensitization	1	1	–	–	**2**
Hemostasis	2	–	–	–	**2**
Immune cell trafficking	2	1	–	–	**3**
Immunomodulation	5	4	2	–	**11**
Neuromodulation	1	–	–	–	**1**
Radiosensitization	1	–	–	–	**1**
Tissue destruction	32	20	15	1	**68**

Drug delivery spans three different ultrasound applications—hyperthermia, nonthermal, and nonthermal BBB opening—for a total of 185 sites worldwide working on focused ultrasound-related drug delivery.

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

Histotripsy—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Histotripsy | Alteration of tissue mechanics				
Heart valve calcifications	1	5	–	**6**
Histotripsy | Immunomodulation				
Brain tumors, general	1	–	–	**1**
Glioblastoma	1	–	–	**1**
Liver tumors	1	–	–	**1**
Melanoma	1	–	–	**1**
Pancreatic tumors, unspecified	1	–	–	**1**
Soft tissue cancer	1	–	–	**1**
Histotripsy | Liquid biopsy				
Pontine glioma	1	–	–	**1**
Histotripsy | Tissue destruction				
Benign prostatic hyperplasia	1	–	–	**1**
Bone metastases	–	1	–	**1**
Brain metastases, breast cancer	1	–	–	**1**
Coarctation of the aorta	1	–	–	**1**
Deep vein thrombosis	3	–	–	**3**
Epilepsy	1	–	–	**1**
Fetal heart anomalies	1	–	–	**1**
Glioblastoma	2	–	–	**2**
Hematoma	1	–	–	**1**
Heterotopic ossification	1	–	–	**1**
Infection	1	–	–	**1**
Kidney tumors	2	–	–	**2**
Liver metastases	1	–	–	**1**
Liver tumors	3	1	–	**4**
Mitral regurgitation	1	–	–	**1**
Multiple tumors[2]	1	–	–	**1**
Pancreatic tumors, unspecified	3	1	–	**4**

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

Histotripsy—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Histotripsy | Tissue destruction continued				
Parkinson's disease, tremor	1	–	–	**1**
Prostate cancer	1	–	–	**1**
Rotator cuff injury	1	–	–	**1**
Soft tissue cancer	1	–	–	**1**
Stroke, intracerebral hemorrhage	1	–	–	**1**
Tendon contracture	1	–	–	**1**
Thyroid cancer	1	–	–	**1**
Uterine fibroids	1	–	–	**1**

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

Hyperthermia—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Hyperthermia | Chemosensitization				
Pancreatic tumors, unspecified	–	1	–	**1**
Hyperthermia | Drug delivery				
Brain metastases, breast cancer	1	–	–	**1**
Breast tumors, malignant	–	1	–	**1**
Glioblastoma	1	–	–	**1**
Head & neck tumors	1	–	–	**1**
Multiple tumors[2]	2	–	–	**2**
Osteopenia	1	–	–	**1**
Pancreatic tumors, unspecified	2	2	–	**4**
Soft tissue cancer	1	1	1	**3**
Wound healing	1	–	–	**1**
Hyperthermia | Drug delivery, immunotherapeutic				
Glioblastoma	1	–	–	**1**
Pancreatic tumors, malignant	1	–	–	**1**
Soft tissue cance	1	–	–	**1**
Hyperthermia | Drug delivery, vehicle				
Bone metastases	1	–	–	**1**
Colorectal tumors	1	–	–	**1**
Soft tissue tumors, benign	1	–	–	**1**
Hyperthermia | Radiosensitization				
Glioblastoma	1	–	–	**1**
Head & neck tumors	1	–	–	**1**
Liver tumors	1	–	–	**1**
Prostate cancer	1	–	–	**1**
Hyperthermia | Tissue destruction				
Benign prostatic hyperplasia	–	1	–	**1**
Bone metastases	1	–	–	**1**
Brain tumors, general	1	–	–	**1**
Breast tumors, benign	–	1	–	**1**

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

Hyperthermia—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Hyperthermia | Tissue destruction continued				
Desmoid tumors	–	–	1	**1**
Endometriosis	–	1	–	**1**
Essential tremor	–	1	–	**1**
Kidney tumors	1	–	–	**1**
Liver tumors	2	–	–	**2**
Prostate cancer	3	1	1	**5**
Thyroid cancer	1	–	–	**1**
Uterine adenomyosis	–	1	–	**1**

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

Nonthermal—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Nonthermal | Angiogenesis				
Muscle atrophy	1	–	–	**1**
Nonthermal | Cardiac pacing				
Cardiac pacing	1	–	–	**1**
Nonthermal | Clot lysis				
Deep vein thrombosis	1	–	–	**1**
Hydrocephalus	1	–	–	**1**
Nonthermal | Drug delivery				
Alzheimer's disease	1	–	–	**1**
Atherosclerosis	3	–	–	**3**
Bladder tumors	1	–	–	**1**
Colorectal tumors	–	1	–	**1**
Hemophilia	1	–	–	**1**
Inflammatory bowel disease	1	–	–	**1**
Liver metastases	1	1	–	**1**
Liver tumors	1	–	–	**1**
Macular degeneration	1	–	–	**1**
Pancreatic tumors, malignant	–	1	–	**1**
Pontine glioma	1	–	–	**1**
Stroke, intracerebral hemorrhage	1	–	–	**1**
Stroke, thromboembolic	2	–	–	**2**
Wound healing	1	–	–	**1**
Nonthermal | Drug delivery, immunotherapeutic				
Pancreatic tumors, unspecified	1	–	–	**1**
Nonthermal | Drug delivery, vehicle				
Breast tumors, malignant	2	–	–	**2**
Cardiac hypertrophy	1	–	–	**1**
Deep vein thrombosis	1	–	–	**1**
Glioblastoma	2	–	–	**2**
Kidney tumors	1	–	–	**1**
Liver tumors	–	1	–	**1**

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

Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Nonthermal | Drug delivery, vehicle continued				
Neuropathic pain	1	–	–	**1**
Pancreatic tumors, unspecified	3	1	–	**4**
Parkinson's disease, underlying cause	1	–	–	**1**
Peripheral artery disease	1	–	–	**1**
Prostate cancer	1	–	–	**1**
Stroke, intracerebral hemorrhage	2	–	–	**2**
Stroke, thromboembolic	1	–	–	**1**
Urinary tract infection	1	–	–	**1**
Nonthermal | Gene delivery				
Breast tumors, malignant	1	–	–	**1**
Retinal injury	1	–	–	**1**
Nonthermal | Immune cell trafficking				
Glioblastoma	1	–	–	**1**
Nonthermal | Immunomodulation				
Astrocytoma	1	–	–	**1**
Breast tumors, malignant	1	–	–	**1**
Epilepsy	1	–	–	**1**
Glaucoma	–	1	–	**1**
Glioblastoma	3	–	–	**3**
Pancreatic tumors, unspecified	1	–	–	**1**
Nonthermal | Increased vascular permeability				
Alzheimer's disease	–	1	–	**1**
Breast tumors, malignant	1	–	–	**1**
Deep vein thrombosis	1	–	–	**1**
Nonthermal | Kidney stone fragmentation				
Kidney stones	2	–	–	**2**
Nonthermal | Kidney stone propulsion				
Kidney stones	1	1	–	**1**

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

Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Nonthermal | Neuromodulation				
Alzheimer's disease	1	–	1	**2**
Cancer pain	1	–	–	**1**
Depression	4	4	–	**8**
Epilepsy	9	3	–	**12**
Mood disorder	–	1	–	**1**
Neuropathic pain	2	2	–	**4**
Neuropathy	–	2	–	**2**
Opioid and other addictions	2	2	–	**4**
Parkinson's disease, tremor	1	–	–	**1**
Parkinson's disease, underlying cause	1	–	–	**1**
Stroke, intracerebral hemorrhage	1	–	–	**1**
Stroke, thromboembolic	1	1	–	**2**
Traumatic brain injury	1	1	–	**2**
Nonthermal | Radiosensitization				
Astrocytoma	1	–	–	**1**
Glioblastoma	2	–	–	**2**
Nonthermal | Sonodynamic therapy				
Atherosclerosis	1	–	–	**1**
Biliary tract cancer	–	1	–	**1**
Brain tumors, general	1	–	–	**1**
Cavernomas	1	–	–	**1**
Deep vein thrombosis	1	–	–	**1**
Glioblastoma	2	–	–	**2**
Pancreatic tumors, unspecified	2	–	–	**2**

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

Nonthermal—Number of Sites for Biological Effects by Indications continued

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

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

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

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Nonthermal - BBB opening | BBB opening				
Alzheimer's disease	7	6	–	**10**
Amyotrophic lateral sclerosis	1	–	–	**1**
Brain tumors, general	2	–	–	**2**
Breast tumors, malignant	1	–	–	**1**
Dementia	1	–	–	**1**
Epilepsy	1	–	–	**1**
Glioblastoma	–	7	–	**7**
Opioid and other addictions	1	–	–	**1**
Parkinson's disease, underlying cause	–	1	–	**1**
Nonthermal - BBB opening | Drug delivery				
Alzheimer's disease	7	5	–	**11**
Amyotrophic lateral sclerosis	1	–	–	**1**
Astrocytoma	2	–	–	**2**
Brain metastases, breast cancer	2	1	–	**2**
Brain tumors, general	1	1	–	**2**
Dementia	–	1	–	**1**
Epilepsy	2	–	–	**2**
Glioblastoma	14	5	–	**16**
Neuromyelitis optica	1	–	–	**1**
Parkinson's disease, underlying cause	6	1	–	**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**

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

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

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Nonthermal - BBB opening | Drug delivery, vehicle				
Glioblastoma	1	–	–	**1**
Nonthermal - BBB opening | Gene delivery				
Huntington's disease	1	–	–	**1**
Parkinson's disease, tremor	1	–	–	**1**
Parkinson's disease, underlying cause	4	–	–	**4**
Rett syndrome	1	–	–	**1**
Nonthermal - BBB opening | Stem cell delivery				
Alzheimer's disease	1	–	–	**1**

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

Thermal ablation—Number of Sites for Biological Effects by Indications

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Thermal ablation | Chemosensitization				
Bone metastases	–	1	–	**1**
Thermal ablation | Hemostasis				
Varicose veins	1	–	–	**1**
Thermal ablation | Immunomodulation				
Breast tumors, malignant	4	–	–	**4**
Melanoma	1	–	–	**1**
Multiple tumors[2]	1	1	–	**2**
Neuroblastoma	1	–	–	**1**
Pancreatic tumors, unspecified	4	–	–	**4**
Pancreatic tumors, malignant	–	1	–	**1**
Soft tissue cancer	1	1	–	**2**
Thermal ablation | Neuromodulation				
Epilepsy	1	–	–	**1**
Neuropathic pain	–	1	–	**1**
Tremor, orthostatic	–	1	–	**1**
Thermal ablation | Radiosensitization				
Head & neck tumors	–	1	–	**1**

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

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

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

	Stages			Total[1]
Ultrasound application | Biological effects	Preclinical	Clinical	Commercial	
Thermal ablation | Tissue destruction				
Cardiovascular				
Arteriovenous malformations	–	–	2	**2**
Atrial fibrillation	–	1	–	**1**
Hypertension	–	11	–	**11**
Twin-twin transfusion syndrome	1	1	–	**2**
Varicose veins	–	1	6	**7**
Ventricular tachycardia	2	–	–	**2**
Endocrine disorders				
Graves' disease	–	1	–	**1**
Thyroid nodules	–	2	19	**21**
Gastrointestinal				
Colorectal tumors	–	2	–	**2**
Esophageal tumors	–	1	–	**1**
Gastric tumors	1	1	–	**2**
Liver tumors	4	5	99	**106**
Pancreatic tumors, unspecified	4	5	6	**15**
Pancreatic tumors, benign	–	1	–	**1**
Pancreatic tumors, malignant	2	–	2	**5**
Miscellaneous				
Actinic keratosis	–	1	–	**1**
Basal cell carcinoma	–	2	–	**2**

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

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

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Thermal ablation | Tissue destruction continued				
Miscellaneous continued				
Dercum's disease	–	1	–	**1**
Head & neck tumors	–	2	–	**2**
Kaposi's sarcoma	–	1	–	**1**
Lipoma	–	1	–	**1**
Melanoma	–	1	–	**1**
Multiple tumors[2]	1	–	–	**1**
Musculoskeletal				
Arthritis, facetogenic	1	7	10	**16**
Arthritis, knee	–	1	–	**1**
Arthritis, sacroiliac	–	1	–	**1**
Bone cancer	–	5	5	**10**
Bone metastases	2	16	25	**36**
Bone tumors, benign	1	3	1	**5**
Desmoid tumors	–	4	8	**11**
Osteoid osteoma	1	25	106	**110**
Osteomyelitis	1	–	–	**1**
Plantar fasciitis	–	1	–	**1**
Sacral chordoma	–	1	–	**1**
Soft tissue cancer	–	3	1	**4**
Soft tissue tumors, benign	–	9	97	**102**
Tendon contracture	1	–	–	**1**
Neurological				
Astrocytoma	–	2	1	**2**
Brain tumors, general	1	–	–	**1**
Cancer pain	1	–	1	**1**
Depression	1	2	1	**2**
Dystonia	–	1	1	**2**
Dystonia, hand	–	1	1	**1**

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

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

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Thermal ablation | Tissue destruction continued				
Neurological continued				
Epilepsy	4	5	2	**9**
Essential tremor	3	20	66	**69**
Glioblastoma	2	7	–	**9**
Multiple sclerosis	–	1	–	**1**
Neuroblastoma	–	1	–	**1**
Neuropathic pain	1	2	3	**6**
Neuropathy	–	–	1	**1**
Obsessive-compulsive disorder	–	2	1	**3**
Painful amputation neuromas	–	1	–	**1**
Parkinson's disease, dyskinesia	–	17	3	**19**
Parkinson's disease, tremor	–	7	18	**25**
Parkinson's disease, underlying cause	1	–	–	**1**
Trigeminal neuralgia	–	1	1	**2**
Ophthalmological				
Glaucoma	1	6	14	**20**
Keratoplasty	1	–	–	**1**
Pulmonary				
Lung cancer	3	–	–	**3**
Lung metastases	1	–	–	**1**
Rhinitis	–	1	–	**1**
Tuberculosis	1	–	–	**1**
Urological				
Benign prostatic hyperplasia	–	2	62	**64**
Chyluria	–	1	–	**1**
Fetal bladder obstruction	1	–	–	**1**
Kidney tumors	2	2	95	**98**
Prostate cancer	4	46	401	**428**

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

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

Ultrasound application | Biological effects	Stages			Total[1]
	Preclinical	Clinical	Commercial	
Thermal ablation | Tissue destruction continued				
Women's Health				
Breast tumors, benign	1	8	12	**19**
Breast tumors, malignant	3	8	96	**106**
Cervical tumors	1	2	–	**3**
Cervicitis	–	–	1	**1**
Endometrial tumors	–	2	1	**2**
Endometriosis	1	1	2	**3**
Endometriosis, colorectal	–	1	–	**1**
Liver metastases	2	1	2	**4**
Ovarian tumors	–	1	–	**1**
Retained placenta	–	1	–	**1**
Uterine adenomyosis	–	13	88	**94**
Uterine fibroids	2	53	292	**307**
Vaginal tumors	–	3	–	**3**
Vulvar dystrophy	–	1	–	**1**

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

Neurological—Mechanisms of Action Global Development Landscape

Development stage: ● Preclinical studies ● Clinical trials ● Commercial treatments

	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	–	–	●[1]	–	●
Radiosensitization	–	●	●	–	–
Sonodynamic therapy	–	–	●	–	–
Sonoporation	–	–	●	–	–
Stem cell delivery	–	–	–	●	–
Tissue destruction	●	●	●	–	●
Vascular occlusion	–	–	●	–	–
Vasodilation	–	–	●	–	–

1 Alzheimer's disease (Asia, off label)

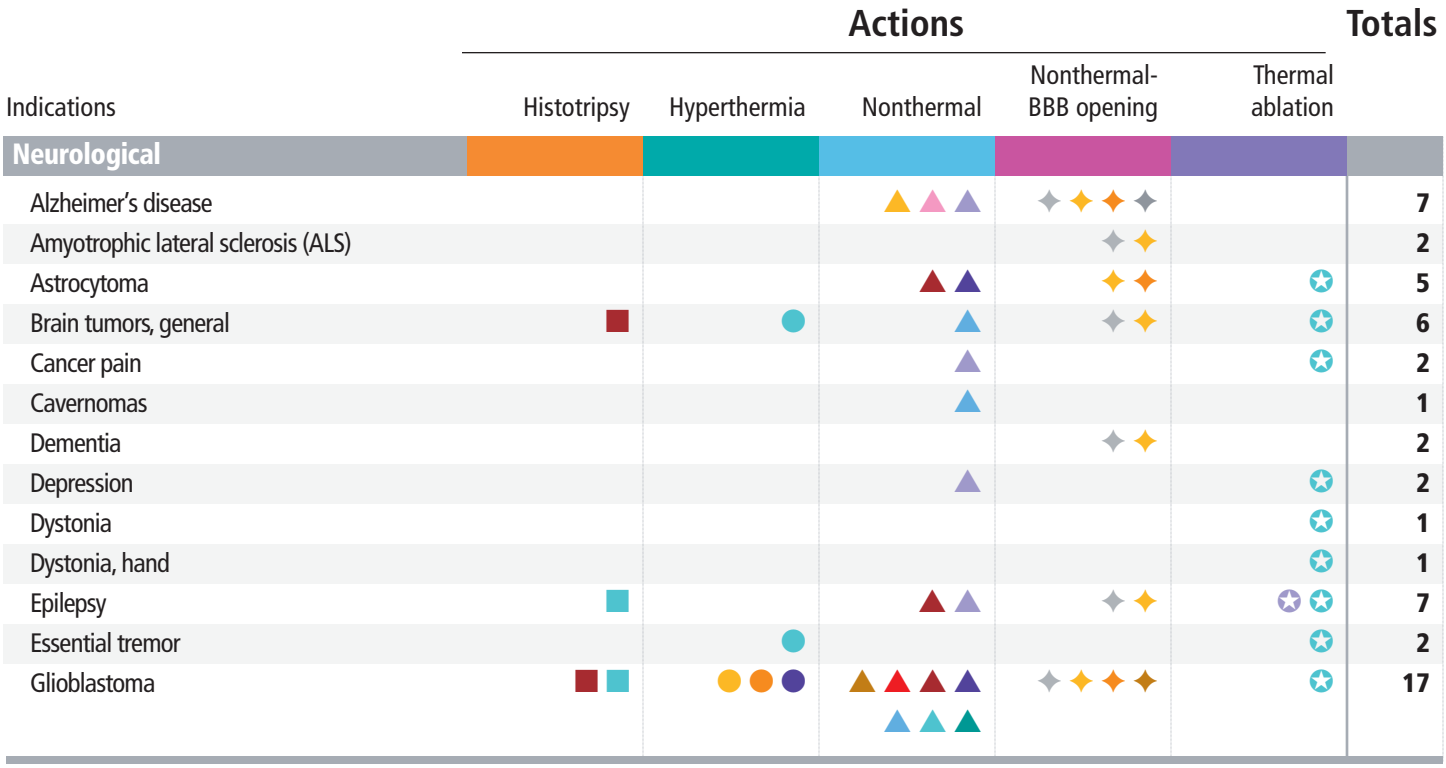
Emerging mechanisms of action for neurological indications

In addition to the significant changes in the methods by which the Foundation is tracking mechanisms of action, the 2021 report goes into greater detail on pages II.52–II.57 in examining the development stage of ultrasound applications and biological effects for specific indications in two areas—neurological and oncology. The table above reveals 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.

Neurological—Ultrasound Application by Indication

Mechanisms of action for glioblastoma

Glioblastoma, even with the best standard-of-care treatment available, remains a devastating diagnosis. Glioblastoma patients are in great need of better treatment options, and the data on this chart speaks to the efforts by focused ultrasound scientists around the globe to identify them, evidenced by the various mechanisms of action currently under investigation.



Histotripsy
- Immunomodulation
- Liquid biopsy
- Tissue destruction

Hyperthermia
- Drug delivery
- Drug delivery, immunotherapeutic
- Radiosensitization
- Tissue destruction

Nonthermal
- Clot lysis
- Drug delivery
- Drug delivery, vehicle
- Immune cell trafficking
- Immunomodulation
- Increased vascular permeability
- Neuromodulation
- Radiosensitization
- Sonodynamic therapy
- Sonoporation
- Tissue destruction
- Vascular occlusion
- Vasodilation

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

Thermal ablation
- Immunomodulation
- Neuromodulation
- Tissue destruction

Neurological—Ultrasound Application by Indication continued

Histotripsy
- Immunomodulation
- Liquid biopsy
- Tissue destruction

Hyperthermia
- Drug delivery
- Drug delivery, immunotherapeutic
- Radiosensitization
- Tissue destruction

Nonthermal
- Clot lysis
- Drug delivery
- Drug delivery, vehicle
- Immune cell trafficking
- Immunomodulation
- Increased vascular permeability
- Neuromodulation
- Radiosensitization
- Sonodynamic therapy
- Sonoporation
- Tissue destruction
- Vascular occlusion
- Vasodilation

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

Thermal ablation
- Immunomodulation
- Neuromodulation
- Tissue destruction

Oncology—Mechanisms of Action Global Development Landscape

Development stage: ● Preclinical studies ● Clinical trials ● Commercial treatments

Biological effects	Ultrasound Applications: 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	●	–	●	–	●
Increased vascular permeability	–	–	●	–	–
Liquid biopsy	●	–	–	–	–
Neuromodulation	–	–	●	–	–
Radiosensitization	–	●	●	–	●
Sonodynamic therapy	–	–	●	–	–
Sonoporation	–	–	●	–	–
Tissue destruction	●	● [1]	●	–	●
Vascular occlusion	–	–	●	–	–

1 Desmoid tumors (North America, off label), Prostate tumors (North America & Asia, off label)

Emerging mechanisms of action for oncology

When we turn from the neurological field, with its preponderance of preclinical research, page II.51 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 farther along, and much of this work is already in the clinical space. But here again, despite this increased clinical activity, there remain few mechanisms of action with regulatory approval.

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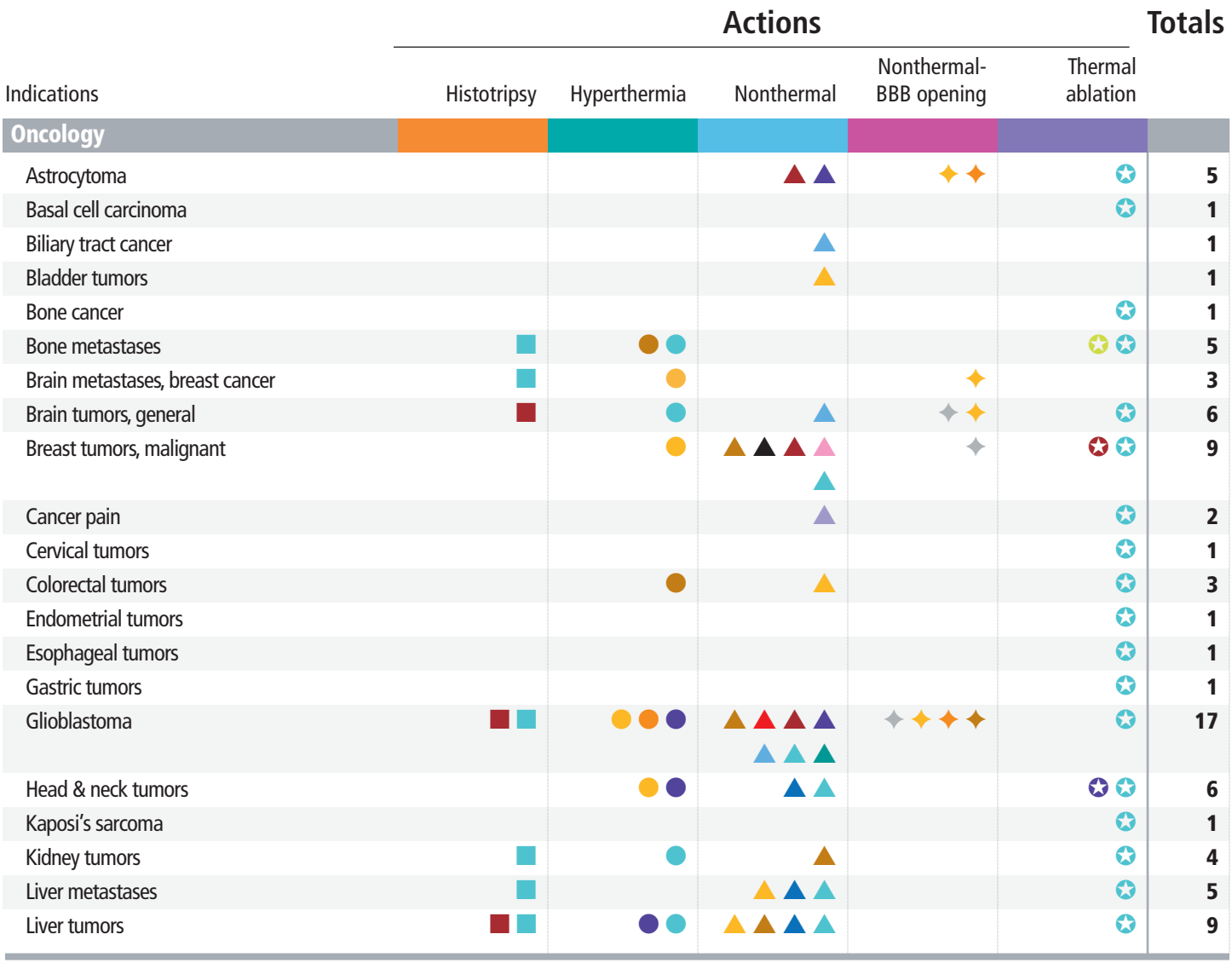
Oncology—Ultrasound Application by Indication



Histotripsy
- Immunomodulation
- Liquid biopsy
- Tissue destruction

Hyperthermia
- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Radiosensitization
- Tissue destruction

Nonthermal
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Gene delivery
- Immune cell trafficking
- Immunomodulation
- Increased vascular permeability
- Neuromodulation
- Radiosensitization
- Sonodynamic therapy
- Sonoporation
- Tissue destruction
- Vascular occlusion

Nonthermal - BBB opening
- BBB opening
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle

Thermal ablation
- Chemosensitization
- Immunomodulation
- Neuromodulation
- Radiosensitization
- Tissue destruction

Oncology—Ultrasound Application by Indication continued

Indications	Actions: Histotripsy	Hyperthermia	Nonthermal	Nonthermal-BBB opening	Thermal ablation	Totals
Oncology continued						
Lung cancer					Tissue destruction	1
Lung metastases					Tissue destruction	1
Melanoma	Immunomodulation				Immunomodulation, Tissue destruction	3
Multiple tumors	Tissue destruction	Drug delivery			Immunomodulation, Tissue destruction	4
Neuroblastoma					Immunomodulation, Tissue destruction	2
Ovarian tumors					Tissue destruction	1
Pancreatic tumors, unspecified	Immunomodulation, Tissue destruction	Chemosensitization, Drug delivery	Drug delivery, Drug delivery, immunotherapeutic, Immunomodulation, Sonoporation, Sonodynamic therapy, Radiosensitization		Immunomodulation, Tissue destruction	12
Pancreatic tumors, malignant		Drug delivery, immunotherapeutic	Drug delivery, immunotherapeutic		Immunomodulation, Tissue destruction	4
Pontine glioma	Liquid biopsy		Drug delivery, immunotherapeutic	BBB opening		3
Prostate cancer	Tissue destruction	Radiosensitization, Tissue destruction	Drug delivery, vehicle, Sonoporation		Tissue destruction	6
Sacral chordoma					Tissue destruction	1
Soft tissue cancer	Immunomodulation, Tissue destruction	Drug delivery, Drug delivery, immunotherapeutic	Drug delivery, immunotherapeutic		Immunomodulation, Tissue destruction	7
Thyroid cancer	Tissue destruction	Tissue destruction				2
Vaginal tumors					Tissue destruction	1

Mechanisms of action for pancreatic cancer

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

Histotripsy
- Immunomodulation
- Liquid biopsy
- Tissue destruction

Hyperthermia
- Chemosensitization
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Radiosensitization
- Tissue destruction

Nonthermal
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle
- Gene delivery
- Immune cell trafficking
- Immunomodulation
- Increased vascular permeability
- Neuromodulation
- Radiosensitization
- Sonodynamic therapy
- Sonoporation
- Tissue destruction
- Vascular occlusion

Nonthermal - BBB opening
- BBB opening
- Drug delivery
- Drug delivery, immunotherapeutic
- Drug delivery, vehicle

Thermal ablation
- Chemosensitization
- Immunomodulation
- Neuromodulation
- Radiosensitization
- Tissue destruction

Case Study—Prostate Cancer

This year, we're taking a closer look at several aspects of focused ultrasound, FUS, as it compares to current standards of care, in the treatment for prostate cancer. Included in the analysis: disease control, side effects, economics and a brief analysis of the market opportunity.

Disease control

Two recent studies were used to compare the effectiveness of FUS to the current standards of care for the treatment of prostate cancer:

- A UK Multicenter, prospective study of **focused ultrasound** that included 625 patients.[1]
- The ProtecT trial, in which 553 men were treated with **radical prostatectomy** and 545 with external beam radiation therapy, or referred to simply as **radiotherapy**.[2]

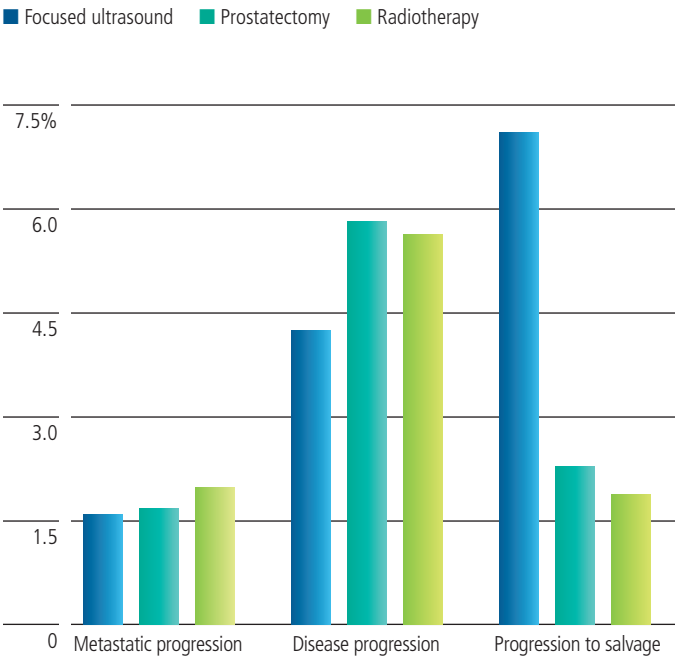
Despite an advanced cancer progression for patients enrolled in the UK study,[3] FUS was found to be equivalent to prostatectomy and radiotherapy, with a 100 percent rate of five-year prostate cancer-specific survival. Beyond this, there are other metrics that can be used to evaluate the effectiveness of prostate cancer treatment.

FUS led to better outcomes than prostatectomy and radiotherapy for both metastatic progression and disease progression. Where FUS did not perform as well was in the progression to salvage therapy, which is the need for follow-up treatment after disease recurrence. This outcome is not unexpected given that, prior to treatment, a reasonable proportion of patients in the UK study were diagnosed with cancer that had spread outside of their prostate (Stage T3: 14 percent), while none of the patients in the ProtecT trial had this issue.[3]

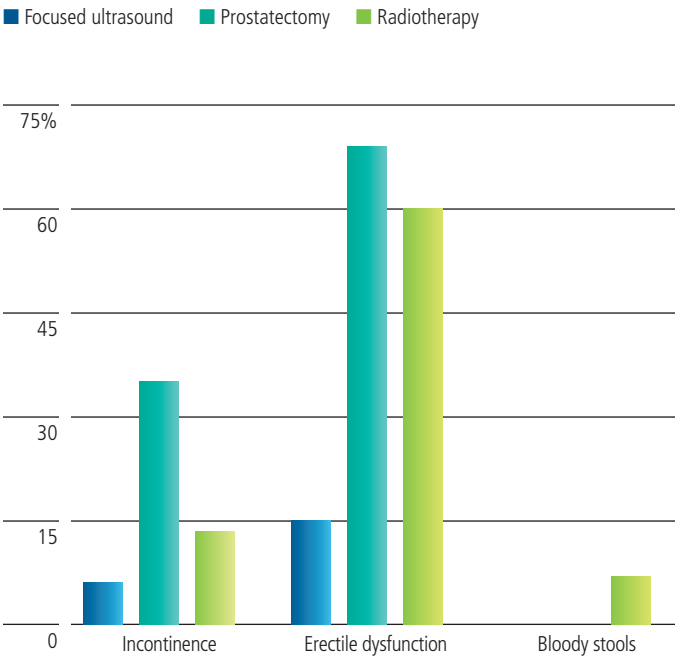
Side effects and their impacts

Four key studies were used to compare the side-effect profile of treatment with FUS to that using prostatectomy or radiotherapy, with a total of 7,675 patients.[1, 4, 5, 6]

Disease Progression



Side Effects



Case Study—Prostate Cancer continued

By comparing reported side effects from each treatment, FUS was shown to have a substantially lower overall side-effect profile as compared to prostatectomy and radiotherapy. In addition, the recommended time for returning to activities of daily living following FUS treatment—including driving, vigorous activity, and resuming work functions—is two days. In contrast, a return to all normal daily activities was shown to take up to 10 weeks following prostatectomy.[7, 8] In another study, surgery or radiotherapy for the treatment of prostate cancer led to 46 and 44 days of sick leave, respectively.[9]

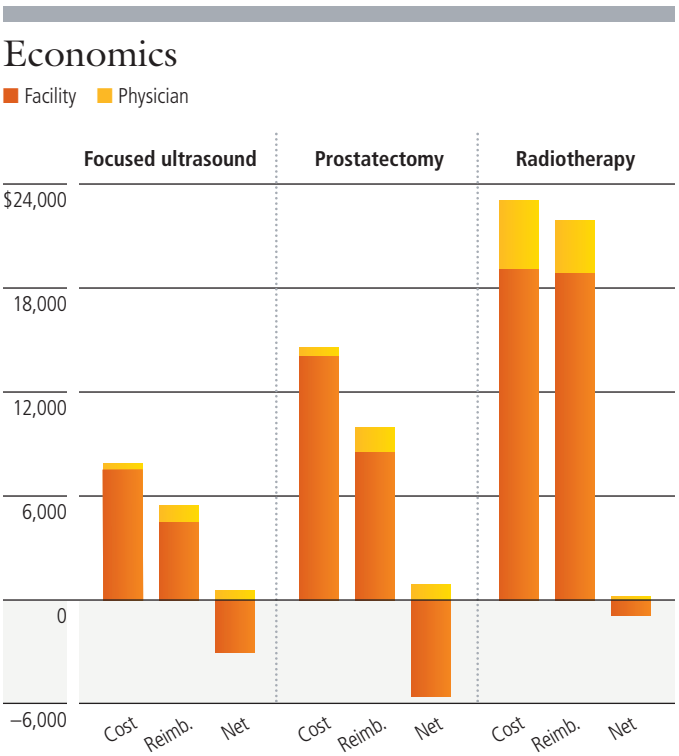
Economics[10]

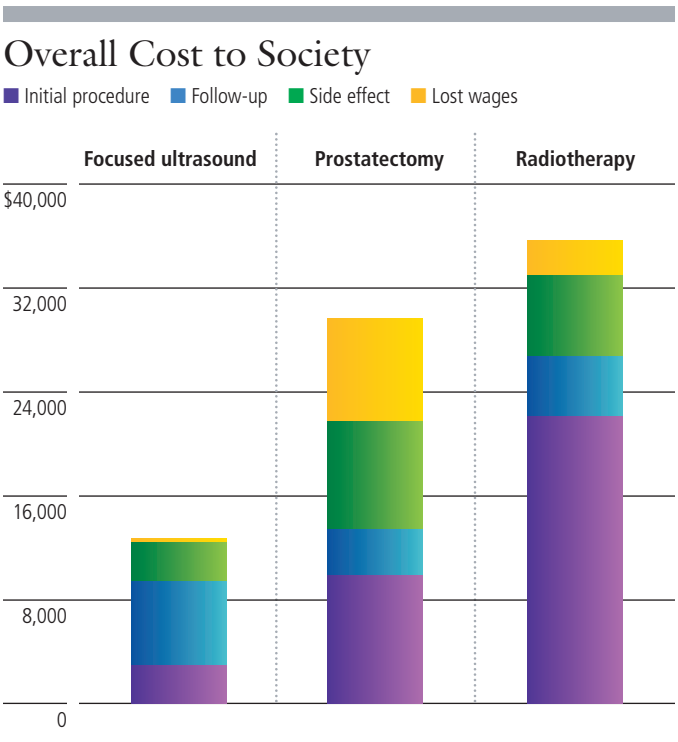
The economics of a procedure can be evaluated based on **costs**, **reimbursement** rates, and reimbursement **net** of costs.

The overall cost of FUS to the facility (primary facility costs plus the cost of the device) and to the physician are substantially lower than that for competing technologies. However, because of differences in Medicare payment levels, net physician reimbursement is positive only for those treating with FUS or prostatectomy. In contrast, net facility reimbursement is only positive when radiotherapy is used as the treatment method.

Economics also can be gauged by the overall cost to society. These costs include: payment for the primary procedure, follow up-office visits (including testing and follow-up procedures), costs associated with side effects, and wages lost due to missed time from work.

Based on the overall economic impact to society, FUS is substantially more cost-effective than either prostatectomy or radiotherapy. This is largely the result of substantially less time lost from work, reduced costs of treating side effects, and a significantly lower payment for the primary procedure.





Case Study—Prostate Cancer continued

Market opportunity

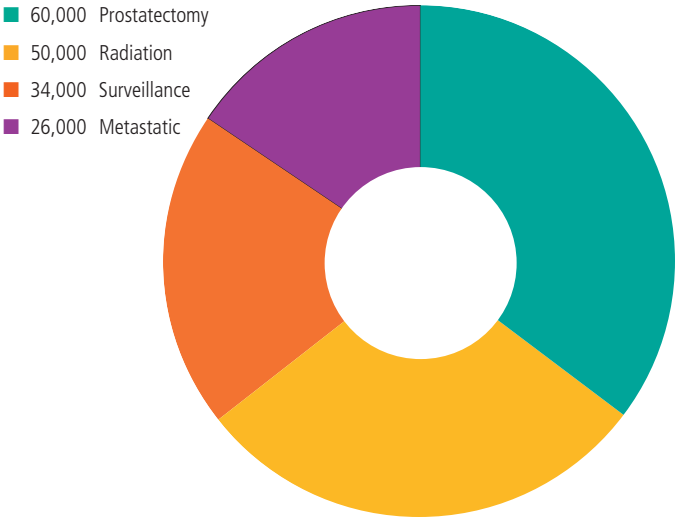
In 2020, there were 1,414,259 cases of prostate cancer globally.[11] In the US, the annual number of cases is thought to range from 170,000[12] to 240,000[9, 13]. To be conservative in our market estimates, we used the lower of these values.

Based on conversations with urologists as well as publicly available data,[14, 10, 15] we've parsed the overall US market into the estimated segments shown in the pie chart below. Despite there being 170,000 annual prostate cancer cases in the US, data in the accompanying table demonstrates that the number of patients for which FUS treatment is clinically recommmended, the total US market, is closer to 148,000. Not all of these patients will have access to FUS as a treatment option; patients cannot get access to FUS treatment if their medical center does not offer it. To calculate the US FUS market, we factored the total US market by the ratio of FUS treatment sites to all prostate cancer sites. Our records indicate that, in 2020, there were 126 FUS prostate cancer sites in the US, whereas there were approximately 2,000 total US medical centers treating prostate cancer. Accordingly, the US FUS market is approximately six percent of the total US market.

In all, we estimate that the US market for FUS is about 9,200 patients annually. If this value is extrapolated to all global prostate cancer patients, we project a global FUS market of over 76,000 prostate cancer patients.

Data from our annual survey of device manufacturers indicate that 6,529 global FUS treatments for prostate cancer took place in 2019 (to exclude the potential impact of COVID-related restriction on 2020 data). This suggests that the use of FUS for the treatment of prostate cancer has yet to acheive its full market potential.

Market Opportunity



	Total US market	US FUS market
Primary therapy		
Low to intermediate risk*	94,000	5,849
Surveillance	34,000	2,116
Total primary	128,000	7,964
Salvage therapy		
	20,000	1,244
Total		
	148,000	**9,208**

*Gleason 7 or high-volume Gleason 6

Case Study—Prostate Cancer continued

Conclusions

Focused Ultrasound has been used to treat prostate cancer for almost two decades, but has not gained the expected market traction in light of the overall advantanges that FUS treatment provides to patients.

Overall, FUS-based prostate cancer treatment offers patients a means of disease control that is mostly equivalent to prostatectomy and radiotherapy, yet with a side-effect profile that is more attractive than that of the current standards of care. FUS also enables a quicker return to activities of daily living, with reduced costs to physicians, facilities, and society as a whole. The only real downside to the use of FUS is the low reimbursement rate for treatment facilities.

Since the treatment facilities—not physicians—are the ultimate decision-makers of device purchases, it is incumbent on the entire focused ultrasound field to ensure that reimbursement rates are improved, to the point that the economics of FUS become more advantageous.

1 http://dx.doi.org/10.1016/j.eururo.2018.06.006
2 https://www.nejm.org/doi/full/10.1056/nejmoa1606220
3 Compared to the ProtecT trial, the average patient in the UK Multicenter study had a higher T Stage and Gleason Score , as well as higher PSA levels. As such, we would expect a poorer prognosis for patients in the UK Multicenter than we would for those in the ProtecT trial.
4 https://doi.org/10.1016/j.euo.2018.04.012
5 https://doi.org/10.1016/j.juro.2018.02.1755 4S, Supplement: e739
6 https://doi.org/10.1016/j.eururo.2018.02.012
7 https://doi.org/10.1001/jamasurg.2013.131
8 https://doi.org/10.1016/j.jval.2015.12.019
9 https://doi.org/10.1136/bmjopen-2019-032914
10 Data in this section are based on internal calculations
11 https://gco.iarc.fr/tomorrow/en/dataviz/tables?cancers=27
12 https://www.urologytimes.com/view/cdc-warns-incidence-of-metastatic-prostate-cancer-on-the-rise
13 https://seer.cancer.gov/statfacts/html/prost.html
14 https://www.pcf.org/about-prostate-cancer/prostate-cancer-treatment/active-surveillance/
15 https://doi.org/10.1038/s41585-020-0287-y

Overview

2020 saw the addition of two new Centers of Excellence—University Medical Center in Utrecht, The Netherlands; and Children's National Hospital in Washington, DC.

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

Established in 2009, the COE program brings together the best people and technical resources at luminary sites across the globe. The Centers are created through partnerships of academia, industry, and the Foundation to showcase focused ultrasound technology and serve as hubs for collaboration. They are the powerhouses of focused ultrasound research; in 2020, they collectively published 184 scientific journal articles on their accomplishments. These sites, which include some of the most influential leaders in the field, are cultivators of the next generation of researchers and physicians for focused ultrasound and are creating the intellectual property that will likely spur the next iteration of commercialization efforts. We encourage you to review these pages in detail, look up the publications that might interest you, and reach out to the contacts we list for each site, if you are interested in a potential collaboration.

This portion of the 2021State of the Field Report contains a summary of self-reported data from the COEs.

Centers of Excellence

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

Overview continued

University Medical Center Utrecht

4 Commercial Treatments

5 Clinical Research

4 Preclinical Research

12 Mechanisms of Action Research

6 Technical Research

12 Publications

University Medical Center Utrecht | The Netherlands

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

Contact

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

Commerical treatments

Musculoskeletal	Bone metastases, Desmoid tumors
Women's health	Endometriosis, Uterine fibroids

Clinical research

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

Preclinical research

Miscellaneous	Head & neck tumors
Neurological	Neuroblastoma, Pontine glioma
Ophthalmological	Macular degeneration

Mechanisms of action research

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

Technical research

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

University Medical Center Utrecht continued

Research not involving thermal ablation, tissue destruction

Clinical Research - Women's health	
Breast tumors, malignant	Hyperthermia - Drug delivery
Preclinical Research - Miscellaneous	
Head & neck tumors	Nonthermal - Sonoporation
Preclinical Research - Neurological	
Neuroblastoma	Thermal ablation - Immunomodulation
Pontine glioma	Nonthermal - Drug delivery
Preclinical Research - Ophthalmological	
Macular degeneration	Nonthermal - Drug delivery

Publications—2020

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High-Intensity Focused Ultrasound (HIFU) Triggers Immune Sensitization of Refractory Murine Neuroblastoma to Checkpoint Inhibitor Therapy. Eranki A, Srinivasan P, Ries M, Kim AR, Lazarski CA, Rossi CT, Khokhlova TD, Wilson E, Knoblach SM, Sharma KV, Wood BJ, Moonen C, Sandler AD, Kim PCW. Clin Cancer Res. 2020 Mar 1;26(5):1152-1161. doi: 10.1158/1078-0432.CCR-19-1604. Epub 2019 Oct 15. PMID: 31615935.

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The Focused Ultrasound Myoma Outcome Study (FUMOS); a retrospective cohort study on long-term outcomes of MR-HIFU therapy. Verpalen IM, de Boer JP, Linstra M, Pol RLI, Nijholt IM, Moonen CTW, Bartels LW, Franx A, Boomsma MF. Eur Radiol. 2020 May;30(5):2473-2482. doi: 10.1007/s00330-019-06641-7. Epub 2020 Feb 10. PMID: 32040725.

A Doxorubicin-Glucuronide Prodrug Released from Nanogels Activated by High-Intensity Focused Ultrasound Liberated β-Glucuronidase. Besse HC, Chen Y, Scheeren HW, Metselaar JM, Lammers T, Moonen CTW, Hennink WE, Deckers R. Pharmaceutics. 2020 Jun 10;12(6):536. doi: 10.3390/pharmaceutics12060536. PMID: 32532061; PMCID: PMC7355552.

Publications—2020 continued

Development and clinical evaluation of a 3-step modified manipulation protocol for MRI-guided high-intensity focused ultrasound of uterine fibroids. Verpalen IM, van 't Veer-Ten Kate M, de Boer E, van den Hoed RD, Schutte JM, Dijkstra JR, Franx A, Bartels LW, Moonen CTW, Boomsma MF. Eur Radiol. 2020 Jul;30(7):3869-3878. doi: 10.1007/s00330-020-06780-2. Epub 2020 Mar 12. PMID: 32166489.

Use of multiparametric MRI to characterize uterine fibroid tissue types. Verpalen IM, Anneveldt KJ, Vos PC, Edens MA, Heijman E, Nijholt IM, Dijkstra JR, Schutte JM, Franx A, Bartels LW, Moonen CTW, Boomsma MF. MAGMA. 2020 Oct;33(5):689-700. doi: 10.1007/s10334-020-00841-9. Epub 2020 Mar 26. PMID: 32219676.

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Deep ction of breathing-related artifacts in real-time MR-thermometry. de Senneville BD, Coupé P, Ries M, Facq L, Moonen CTW. Comput Med Imaging Graph. 2021 Jan;87:101834. doi: 10.1016/j.compmedimag.2020.101834. Epub 2020 Dec 8. PMID: 33352524.

Children's National Hospital

6
Clinical Research

7
Preclinical Research

7
Mechanisms of Action Research

4
Technical Research

3
Publications

Children's National Hospital | Washington, DC

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

Contacts

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Clinical research

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

Preclinical research

Musculoskeletal	Bone metastases; Osteoid osteoma; Soft tissue cancer; Soft tissue tumors, benign
Neurological	Epilepsy, Essential tremor
Urological	Kidney tumors

Mechanisms of action research

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

Technical research

FUS Image guidance, MR

FUS Simulation & treatment planning

FUS Transducer technology, Histotripsy

FUS Treatment monitoring

Research not involving thermal ablation, tissue destruction

Clinical research - Musculoskeletal	
Bone metastases	Thermal ablation - Chemosensitization
Preclinical research - Musculoskeletal	
Bone metastases	Hyperthermia - Drug delivery, vehicle
Soft tissue cancer	Histotripsy - Immunomodulation
Soft tissue tumors, benign	Hyperthermia - Drug delivery, vehicle

Children's National Hospital continued

Publications—2020

Emerging hyperthermia applications for pediatric oncology. Tydings C, Sharma KV, Kim A, Yarmolenko PS. Adv Drug Deliv Rev. 2020;163-164:157-167. doi: 10.1016/j.addr.2020.10.016. Epub 2020 Oct 24. PMID: 33203538.

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Physics for Medicine Paris

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Physics for Medicine Paris | France

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

Contacts

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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 - Alteration of tssue mechanics
Preclinical research - Neurological	
Depression	Nonthermal - Neuromodulation

Physics for Medicine Paris continued

Publications—2020

Efficacy and safety assessment of an ultrasound-based thermal treatment of varicose veins in a sheep model. Barnat N, Grisey A, Gerold B, Yon S, Anquez J, Aubry JF. Int J Hyperthermia. 2020;37(1):231-244. doi: 10.1080/02656736.2020.1734672. PMID: 32133898.

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Publications—2020 continued

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Inserm - LabTAU

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INSERM - LabTAU | Lyon, France

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

Contact

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Commercial treatment

Urological	Prostate cancer, *Hôpital Edouard Herriot*

Clinical research

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

Preclinical research

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

Mechanisms of action research

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

Technical research

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

Inserm – LabTAU continued

Research not involving thermal ablation, tissue destruction

Clinical research - Neurological	
Glioblastoma	Nonthermal - BBB opening
Preclinical research - Cardiovascular	
Twin-twin transfusion syndrome	Nonthermal - Vascular occlusion
Varicose veins	Thermal ablation - Hemostasis
Preclinical research - Gastrointestinal	
Pancreatic tumors, malignant	Nonthermal - Sonodynamic therapy Nonthermal - Tissue destruction Thermal ablation - Immunomodulation
Preclinical research - Neurological	
Cancer pain	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal - BBB opening, drug delivery
Stroke, thromboembolic	Nonthermal - BBB opening, drug delivery
Preclinical research - Women's health	
Breast tumors, malignant	Nonthermal - Immunomodulation Nonthermal - Tissue destruction

Publications—2020

Super-resolution limit of shear wave elastography. Zemzemi C, Zorgani A, Daunizeau L, Belabar S, Catheline S. European Physics Letter, Volume 129 (3): 34002, 2020 https://doi.org/10.1209/0295-5075/129/34002.

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Publications—2020 continued

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Robot-assisted ultrasound navigation platform for 3D HIFU treatment planning: Initial evaluation for conformal interstitial ablation. Daunizeau L, Nguyen A, Le Garrec M, Chapelon JY, N'Djin WA. Comput Biol Med. 2020 Sep;124:103941. doi: 10.1016/j.compbiomed.2020.103941. Epub 2020 Aug 1. PMID: 32818742

Inserm – LabTAU continued

Publications—2020 continued

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Publications—2020 continued

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Stanford University School of Medicine

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Stanford University School of Medicine | California

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

Stanford University | California
University of California Davis | California

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

2
Veterinary Research

Contacts

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Commercial treatments

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

Stanford University School of Medicine continued

Clinical research

Gastrointestinal	Pancreatic tumors, malignant
Musculoskeletal	Desmoid tumors, Osteoid osteoma
Neurological	Epilepsy
Urological	Prostate cancer

Preclinical research

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

Mechanisms of action research

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

Technical research

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

Research not involving thermal ablation, tissue destruction

Clinical research - Gastrointestinal	
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Preclinical research - Gastrointestinal	
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Preclinical research - Neurological	
Epilepsy	Nonthermal - BBB opening, drug delivery
Glioblastoma	Nonthermal - BBB opening, drug delivery
Neuropathic pain	Nonthermal - Drug delivery, vehicle
Preclinical research - Urological	
Acute kidney injury	Nonthermal - Stem cell delivery
Preclinical research - Women's health	
Breast tumors, malignant	Nonthermal - Gene delivery
	Thermal ablation - Immunomodulation
Veterinary research - Gastrointestinal	
Liver tumors	Nonthermal - Drug delivery, vehicle

Publications—2020

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Stanford University School of Medicine continued

Publications—2020 continued

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Sunnybrook Health Sciences Centre

18	14	1	11
Preclinical Research	Mechanisms of Action Research	Commercial Treatment	Clinical Research
		12	39
		Technical Research	Publications

Sunnybrook Health Sciences Centre | Toronto, Canada

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

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Commercial treatment

Neurological	Essential tremor

Clinical research

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

Preclinical research

Cardiovascular	Atrial fibrillation, Deep vein thrombosis
Gastrointestinal	Colorectal tumors, 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, thromboembolicic
Ophthalmological	Retinal injury
Women's health	Brain metastases, breast cancer; Breast tumors, malignant

Mechanisms of action research

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

Sunnybrook Health Sciences Centre 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
Parkinson's disease, underlying cause	Nonthermal - BBB opening, drug delivery
Clinical research - Women's health	
Brain metastases, breast cancer	Nonthermal - BBB opening, drug delivery
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 - Ophthalmological	
Retinal injury	Nonthermal - Gene delivery
Preclinical research - Women's health	
Brain metastases, breast cancer	Nonthermal - BBB opening, drug delivery

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University of Maryland School of Medicine

8	11	1	7
Preclinical Research	Mechanisms of Action Research	Commercial Treatment	Clinical Research
		7	7
		Technical Research	Publications

University of Maryland School of Medicine | Baltimore, MD

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

Contacts

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Commercial treatment

Neurological	Essential tremor

Clinical research

Neurological	Essential tremor, Glioblastoma, Neuropathic pain, Trigeminal neuralgia

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

University of Maryland School of Medicine continued

Research not involving thermal ablation, tissue destruction

Clinical research - Neurological	
Glioblastoma	Nonthermal - BBB opening Nonthermal - BBB opening, drug delivery
Neuropathic pain	Thermal ablation - Neuromodulation
Preclinical research - Neurological	
Astrocytoma	Nonthermal - BBB opening, drug delivery Nonthermal - BBB opening, drug delivery, immunotherapeutic Nonthermal - Immunomodulation Nonthermal - Radiosensitization
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal - Immune cell trafficking Nonthermal - Immunomodulation
Traumatic brain injury	Nonthermal - Neuromodulation

Publications—2020

Radiosensitization of high-grade gliomas through induced hyperthermia: Review of clinical experience and the potential role of MR-guided focused ultrasound. Schneider CS, Woodworth GF, Vujaskovic Z, Mishra MV. Radiother Oncol. 2020 Jan;142:43-51. doi: 10.1016/j.radonc.2019.07.017. Epub 2019 Aug 17. PMID: 31431370.

Reply to: Comment on "the role of high-intensity focused ultrasound as a symptomatic treatment for Parkinson's disease". Moosa S, Martínez-Fernández R, Elias WJ, Del Alamo M, Eisenberg HM, Fishman PS. Mov Disord. 2020 Mar;35(3):521-522. doi: 10.1002/mds.27972. PMID: 32166804.

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Publications—2020 continued

Predictors of Outcomes After Focused Ultrasound Thalamotomy. Krishna V, Sammartino F, Cosgrove R, Ghanouni P, Schwartz M, Gwinn R, Eisenberg H, Fishman P, Chang JW, Taira T, Kaplitt M, Rezai A, Rumià J, Gedroyc W, Igase K, Kishima H, Yamada K, Ohnishi H, Halpern C. Neurosurgery. 2020 Aug 1;87(2):229-237. doi: 10.1093/neuros/nyz417. Erratum in: Neurosurgery. 2020 Apr 1;86(4):604. PMID: 31690945.

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Brigham and Women's Hospital

3	3
Commercial Treatments	Clinical Research
6	**12**
Preclinical Research	Mechanisms of Action Research
6	**15**
Technical Research	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

Mechanisms of action research

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

Technical research

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

Research not involving thermal ablation, tissue destruction

Preclinical research - Neurological

Alzheimer's disease	Nonthermal - BBB opening, drug delivery
Epilepsy	Nonthermal - Neuromodulation
Glioblastoma	Nonthermal - BBB opening, drug delivery Nonthermal - Tissue destruction
Huntington's disease	Nonthermal - BBB opening, gene delivery
Parkinson's disease, tremor	Nonthermal - Neuromodulation

Brigham and Women's Hospital continued

Publications—2020

Therapeutic Potentials of Localized Blood-Brain Barrier Disruption by Noninvasive Transcranial Focused Ultrasound: A Technical Review. Cammalleri A, Croce P, Lee W, Yoon K, Yoo SS. J Clin Neurophysiol. 2020 Mar;37(2):104-117. doi: 10.1097/WNP.0000000000000488. PMID: 32142021; PMCID: PMC7080303.

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Localized Disruption of Blood Albumin-Phenytoin Binding Using Transcranial Focused Ultrasound. Xu L, Lee W, Rotenberg A, Böhlke M, Yoon K, Yoo SS. Ultrasound Med Biol. 2020 Aug;46(8):1986-1997. doi: 10.1016/j.ultrasmedbio.2020.04.011. Epub 2020 May 10. PMID: 32402673.

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Publications—2020 continued

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Using phase data from MR temperature imaging to visualize anatomy during MRI-guided focused ultrasound neurosurgery. McDannold N, White PJ, Cosgrove GR. IEEE Trans Med Imaging. 2020 Dec;39(12):3821-3830. doi: 10.1109/TMI.2020.3005631. Epub 2020 Nov 30. PMID: 32746127 PMCID: PMC7749411

ICR and The Royal Marsden

6 Preclinical Research

11 Mechanisms of Action Research

1 Commercial Treatment

8 Technical Research

10 Publications

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

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

1 Veterinary Research

Contact

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Commercial treatment

Neurological	Cancer pain

Preclinical research

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

Mechanisms of action research

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

Technical research

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

Research not involving thermal ablation, tissue destruction

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

ICR and The Royal Marsden continued

Publications—2020

Heating technology for malignant tumors: a review. Kok HP, Cressman ENK, Ceelen W, Brace CL, Ivkov R, Grüll H, ter Haar G, Wust P, Crezee J. Int J Hyperthermia. 2020;37(1):711-741. doi: 10.1080/02656736.2020.1779357. PMID: 32579419; PMCID: PMC7781160.

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ISUOG Safety Committee Position Statement on use of personal protective equipment and hazard mitigation in relation to SARS-CoV-2 for practitioners undertaking obstetric and gynecological ultrasound. Abramowicz JS, Basseal JM, Brezinka C, Dall'Asta A, Deng J, Harrison G, Lee JC, Lim A, Maršal K, Miloro P, Poon LC. Ultrasound Obstet Gynecol. 2020 Jun;55(6): 886-891. doi: 10.1002/uog.22035. PMID: 32255535 PMCID: PMC7262197.

World Federation for Ultrasound in Medicine and Biology Position Statement: How to Perform a Safe Ultrasound Examination and Clean Equipment in the Context of COVID-19. World Federation for Ultrasound in Medicine and

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Therapeutic ultrasound experiments in vitro: Review of factors influencing outcomes and reproducibility. Snehota M, Vachutka J, ter Haar G, Dolezal L, Kolarova H. Ultrasonics. 2020 Sep;107:106167. doi: 10.1016/j.ultras.2020.106167. Epub 2020 Apr 29. PMID: 32402858.

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A Polyvinyl Alcohol-Based Thermochromic Material for Ultrasound Therapy Phantoms. Ambrogio S, Baêsso RM, Gomis A, Rivens I, ter Haar G, Zeqiri B, Ramnarine KV, Fedele F, Miloro P. Ultrasound Med Biol. 2020 Nov; 46(11):3135-3144. doi: 10.1016/j.ultrasmedbio.2020.07.032. Epub 2020 Aug 29. PMID: 32873445.

University of Virginia Health System

2	10
Commercial Treatments	Clinical Research
18	**19**
Preclinical Research	Mechanisms of Action Research
4	**29**
Technical Research	Publications

University of Virginia Health System | Charlottesville, VA

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

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Commercial treatments

Neurological	Essential tremor
Women's health	Uterine fibroids

Clinical research

Gastrointestinal	Esophageal tumors, Gastric tumors
Miscellaneous	Melanoma, Multiple tumors[1]
Neurological	Epilepsy; Essential tremor; Neuropathic pain; Parkinson's disease, dyskinesia
Women's health	Breast tumors, benign; Breast tumors, malignant

Preclinical research

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

Mechanisms of action research

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

Technical research

Drug delivery technology
FUS Image guidance, MR
FUS Image guidance, Ultrasound
FUS Treatment monitoring
Standards & quality assurance

1 Protocols inclusive of more than one indication.

University of Virginia Health System continued

Research not involving thermal ablation, tissue destruction

Clinical research - Miscellaneous	
Multiple tumors[1]	Thermal ablation - Immunomodulation
Preclinical research - Cardiovascular	
Arteriovenous malformations	Nonthermal - Tissue destruction
Peripheral artery disease	Nonthermal - Drug delivery, vehicle
Preclinical research - Gastrointestinal	
Pancreatic tumors, malignant	Thermal ablation - Immunomodulation
Preclinical research - Miscellaneous	
Melanoma	Thermal ablation - Immunomodulation
Preclinical research - Neurological	
Cavernomas	Nonthermal - Sonodynamic therapy
Epilepsy	Nonthermal - BBB opening, drug delivery Nonthermal - Neuromodulation
Glioblastoma	Nonthermal - BBB opening, drug delivery Nonthermal - Drug delivery, vehicle Nonthermal - Immunomodulation Nonthermal - Radiosensitization Nonthermal - Sonodynamic therapy Nonthermal - Vascular occlusion
Parkinson's disease, underlying cause	Nonthermal - BBB opening, drug delivery
Stroke, thromboembolic	Nonthermal - Sonoporation
Preclinical research - Women's health	
Breast tumors, malignant	Thermal ablation - Immunomodulation

Publications—2020

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Ultrasound Molecular Imaging With BR55, a Predictive Tool of Anti-Angiogenic Treatment Efficacy in a Chemo-Induced Mammary Tumor Model. A. Helbert, M. von Wronski, D. Colevret, C. Botteron, F. Padilla, T. Bettinger, I. Tardy, and J.-M. Hyvelin. Accepted on Jan 19 2020 for publication in Investigative Radiology. Investigative radiology 55(10), 657 – 665 (2020). https://dx.doi.org/10.1097/rli.0000000000000661

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Publications—2020 continued

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Investigation of the tumoricidal effects of sonodynamic therapy in malignant glioblastoma brain tumors. Sheehan K, Sheehan D, Sulaiman M, Padilla F, Moore D, Sheehan J, Xu Z. J Neurooncol. 2020 May;148(1):9-16. doi: 10.1007/s11060-020-03504-w. Epub 2020 May 2. PMID: 32361864.

Effects of Non-invasive, Targeted, Neuronal Lesions on Seizures in a Mouse Model of Temporal Lobe Epilepsy. Zhang Y, Zhou H, Qu H, Liao C, Jiang H, Huang S, Ghobadi SN, Telichko A, Li N, Habte FG, Doyle T, Woznak JP, Bertram EH, Lee KS, Wintermark M. Ultrasound Med Biol. 2020 May;46(5):1224-1234. doi: 10.1016/j.ultrasmedbio.2020.01.008. Epub 2020 Feb 17. PMID: 32081583.

Augmentation of brain tumor interstitial flow via focused ultrasound promotes brain- penetrating nanoparticle dispersion and transfection. Curley CT, Mead BP, Negron K, Kim N, Garrison WJ, Miller GW, Kingsmore KM, Thim EA, Song J, Munson JM, Klibanov AL, Suk JS, Hanes J, Price RJ. Sci Adv. 2020 May 1;6(18):eaay1344. doi: 10.1126/sciadv.aay1344. PMID: 32494662; PMCID: PMC7195188.

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1 Protocols inclusive of more than one indication.

University of Virginia Health System continued

Publications—2020 continued

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From Anatomy to Functional and Molecular Biomarker Imaging and Therapy: Ultrasound Is Safe, Ultrafast, Portable, and Inexpensive. Wang S, Hossack JA, Klibanov AL. Invest Radiol. 2020 Sep;55(9):559-572. doi: 10.1097/RLI.0000000000000675. PMID: 32776766.

Preparation of perfluorocarbon emulsions by premix membrane emulsification for Acoustic Droplet Vaporization (ADV) in biomedical applications. Melich R, Zorgani A, Padilla F, Charcosset C. Biomed Microdevices. 2020 Sep 3;22(3):62. doi: 10.1007/s10544-020-00504-5. PMID: 32880712.

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

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Mitochondrial dysfunction in neurological disorders: Exploring mitochondrial transplantation. Norat P, Soldozy S, Sokolowski JD, Gorick CM, Kumar JS, Chae Y, Yağmurlu K, Prada F, Walker M, Levitt MR, Price RJ, Tvrdik P, Kalani MYS. NPJ Regen Med. 2020 Nov 23;5(1):22. doi: 10.1038/s41536-020-00107-x. PMID: 33298971; PMCID: PMC7683736.

Contrast-Enhanced Ultrasound Assisted Surgery of Intramedullary Spinal Cord Tumors: Analysis of Technical Benefits and Intra-operative Microbubble Distribution Characteristics. Vetrano IG, Gennari AG, Erbetta A, Acerbi F, Nazzi V, DiMeco F, Prada F. Ultrasound Med Biol. 2020 Dec 18:S0301-5629(20)30481-6. doi: 10.1016/j.ultrasmedbio.2020.10.017. Epub ahead of print. PMID: 33349517.

Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease. Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, Del Álamo M, Shah BB, Hernández-Fernández F, Pineda-Pardo JA, Monje MHG, Fernández-Rodríguez B, Sperling SA, Mata-Marín D, Guida P, Alonso-Frech F, Obeso I, Gasca-Salas C, Vela-Desojo L, Elias WJ, Obeso JA. N Engl J Med. 2020 Dec 24;383(26):2501-2513. doi: 10.1056/NEJMoa2016311. PMID: 33369354.

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FUS Veterinary Applications

Introduction

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

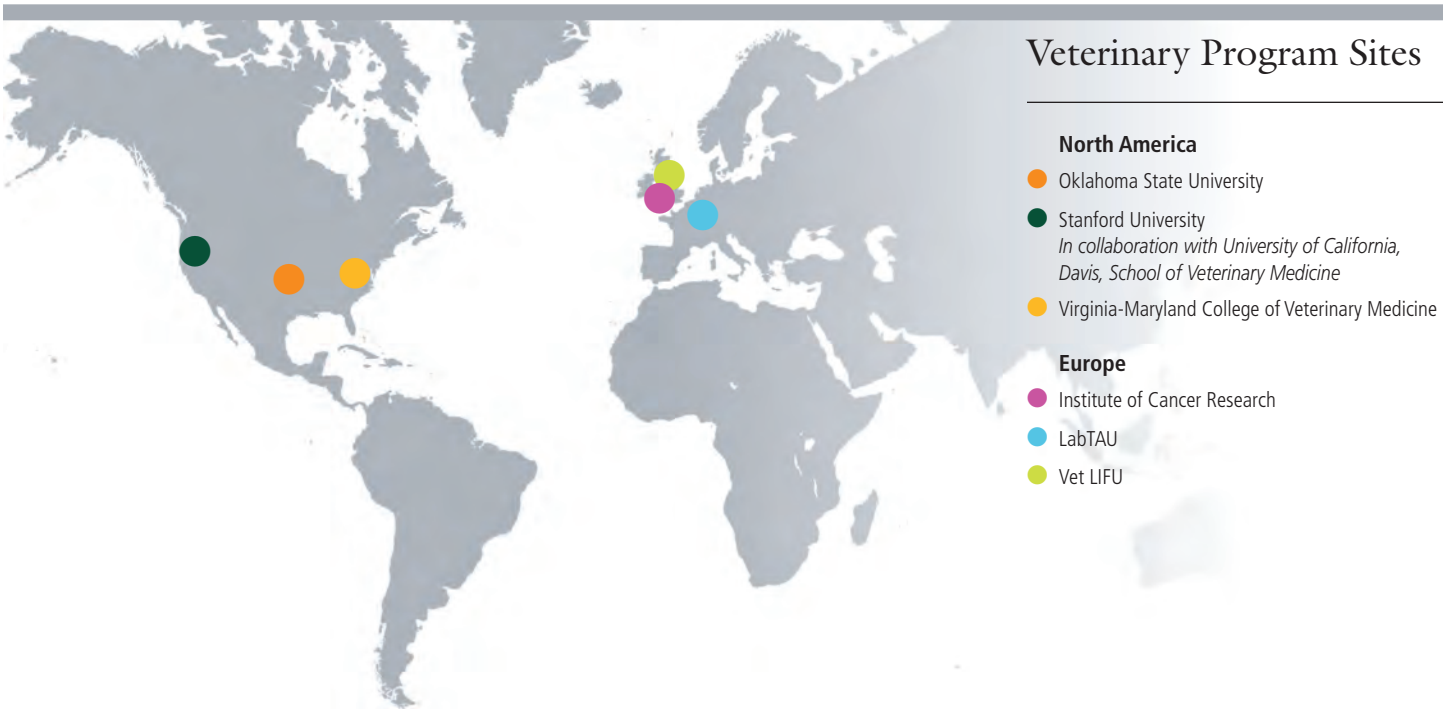
Focused ultrasound's ability to noninvasively treat tissue and enhance the efficacy of some therapies, thus reducing the length of hospital stays and total cost, is a crucial benefit for pet owners who pay out of pocket.

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

In addition to ablating tumor tissue and enhancing the efficacy of chemo- and immunotherapeutics, preclinical and human clinical data suggest that focused ultrasound can induce a potent anti-tumor immune response. This is of particular interest for 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 increase blood flow to the damaged tissue, enhancing healing and reducing scar formation. Focused ultrasound can also be used to noninvasively ablate nerve tissue, relieving pain in advanced arthritis.

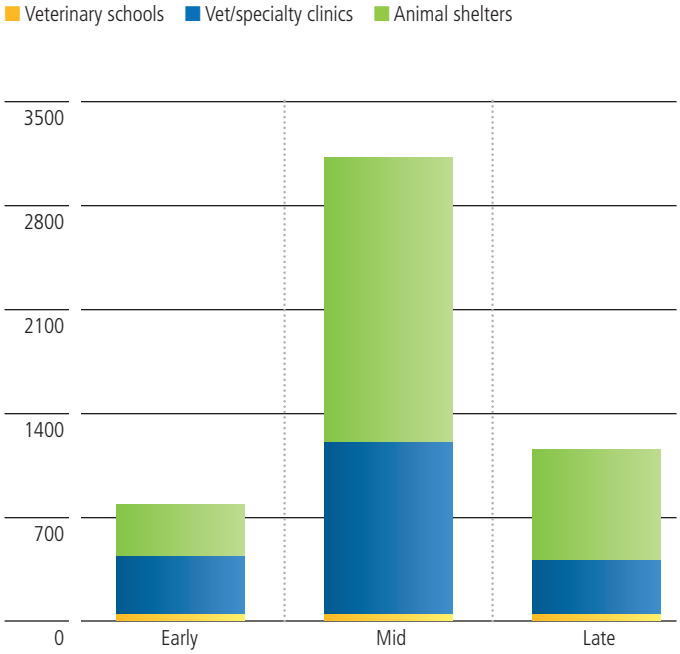
For more information, please visit: www.fusfoundation.org/for-researchers/high-priority-research-areas/veterinary-program.



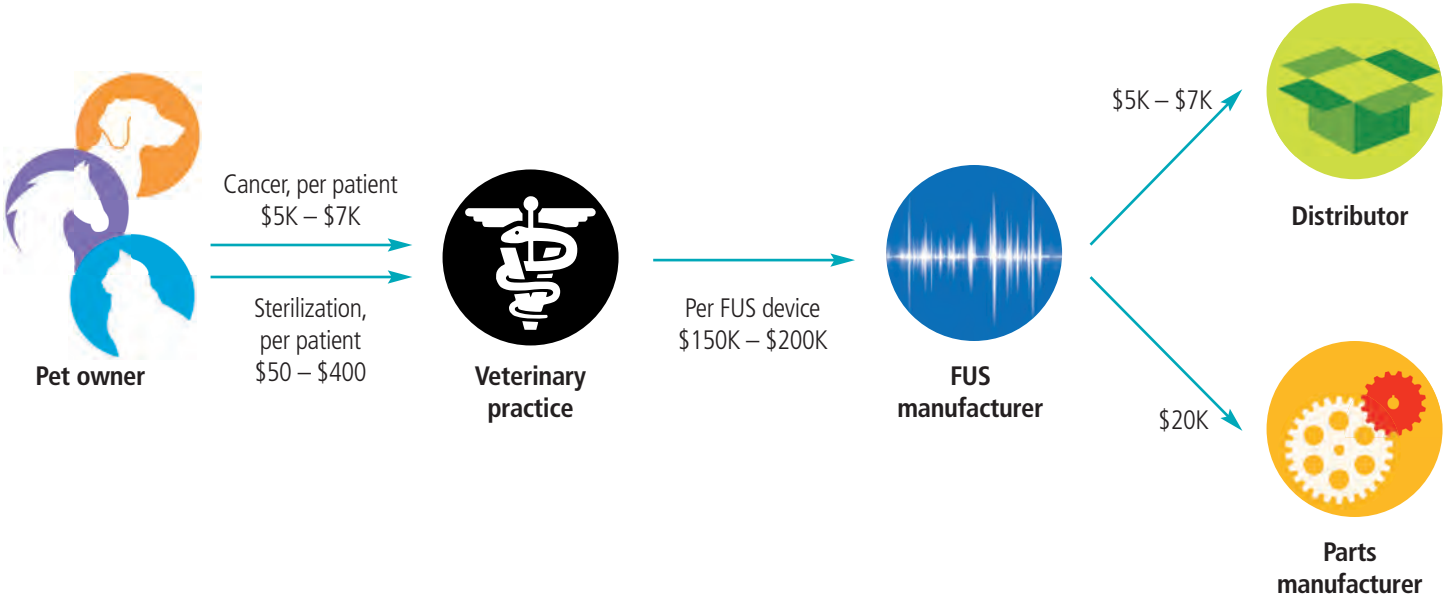
Proposed Market and Value Chain

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

Development stage Proposed | Clinical trial | Clinical practice

Species Canine | Feline | Equine

Oncology

Soft tissue tumors*	2018
Bladder cancer	2020
Brain tumors	2020
Hepatocellular carcinoma	2019
Hygroma	2018
Oral tumors**	2018
Osteosarcoma	2020
Lung cancer	2018
Sarcoids	2018

Pain

Elbow/hip dysplasia	2018
Osteoarthritis	2018
Soft tissue injuries	2018

Miscellaneous

Epilepsy	2020
Kidney stones	2020
Spay/neuter	2018

*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

Development stage Proposed | Clinical trial | Clinical practice

Species Canine | Feline | Equine

Oncology

Proposed	Clinical trial	Clinical practice
Lung cancer Sarcoids	Bladder cancer Brain tumors Hepatocellular carcinoma Hygroma Oral tumors** Osteosarcoma	Soft tissue tumors*

Pain

Proposed	Clinical trial	Clinical practice
		Elbow/hip dysplasia Osteoarthritis Soft tissue injuries

Miscellaneous

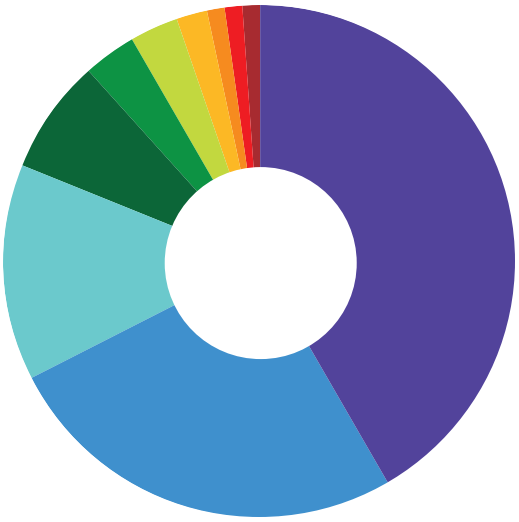
Proposed	Clinical trial	Clinical practice
Epilepsy Kidney stones Spay/neuter		

Treated Patients by Indication

Cummulative

96 total treatments

- 40 Osteoarthritis
- 25 Soft tissue sarcoma
- 13 Oral tumors**
- 7 Mast cell tumor
- 3 Chronic wound
- 3 Hepatocellular carcinoma
- 2 Soft tissue injuries
- 1 Osteosarcoma
- 1 Thyroid carcinoma
- 1 Nasal chondrosarcoma



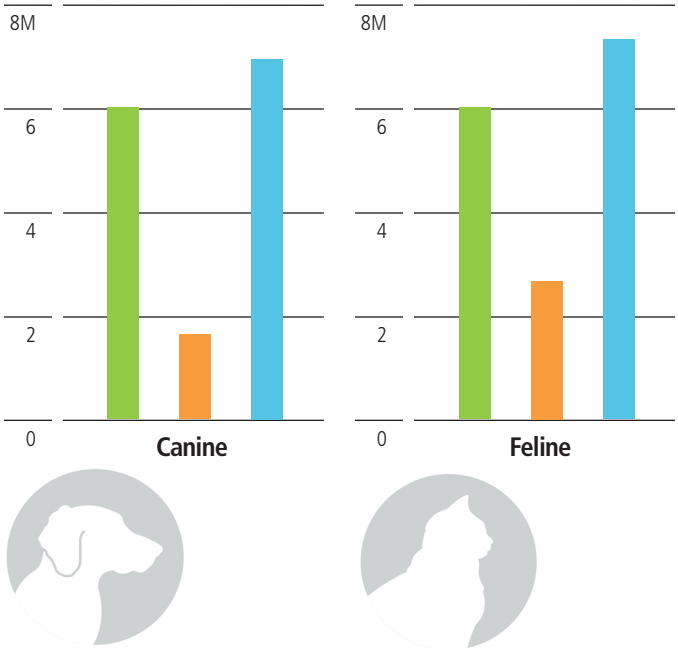
*Soft tissue tumors includes soft tissue sarcoma and mast cell tumors.

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

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

Scientific Advisory Board

Membership and mission

The Focused Ultrasound Foundation has established an advisory board to aid in the advancement and adoption of focused ultrasound in the veterinary space.

The Scientific Advisory Board is composed of experts in small animal practice, with a concentration in oncology; they come from a range of different fields, including academic research, clinical practice, and business and device development.

The main purpose of the advisory board is to provide advice regarding the direction and scope of the Veterinary Program. Specific goals include identifying the greatest clinical needs in the veterinary space, defining functional specifications for a focused ultrasound device, developing a better understanding of the likely client base, and outlining a potential business model.

Chair

Gregory B Daniel, DVM
Chair, Professor of Radiology, Department of Small Animal Clinical Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA

Board

Cynthia Cole, DVM, PhD
Technical Partner, Digitalis Ventures

Richard Hawkin, DVM
Founder, Colony Park Animal Hospital

Craig Clifford, DVM, MS
Oncologist, Hope Veterinary Specialists, Malvern, PA

Ashish Ranjan, BVSc, PhD
Professor, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK

Ruth Rose, DVM
Research Scientist, Flint Animal Cancer Center, Colorado State University College of Veterinary Medicine & Biomedical Sciences, Fort Collins, CO

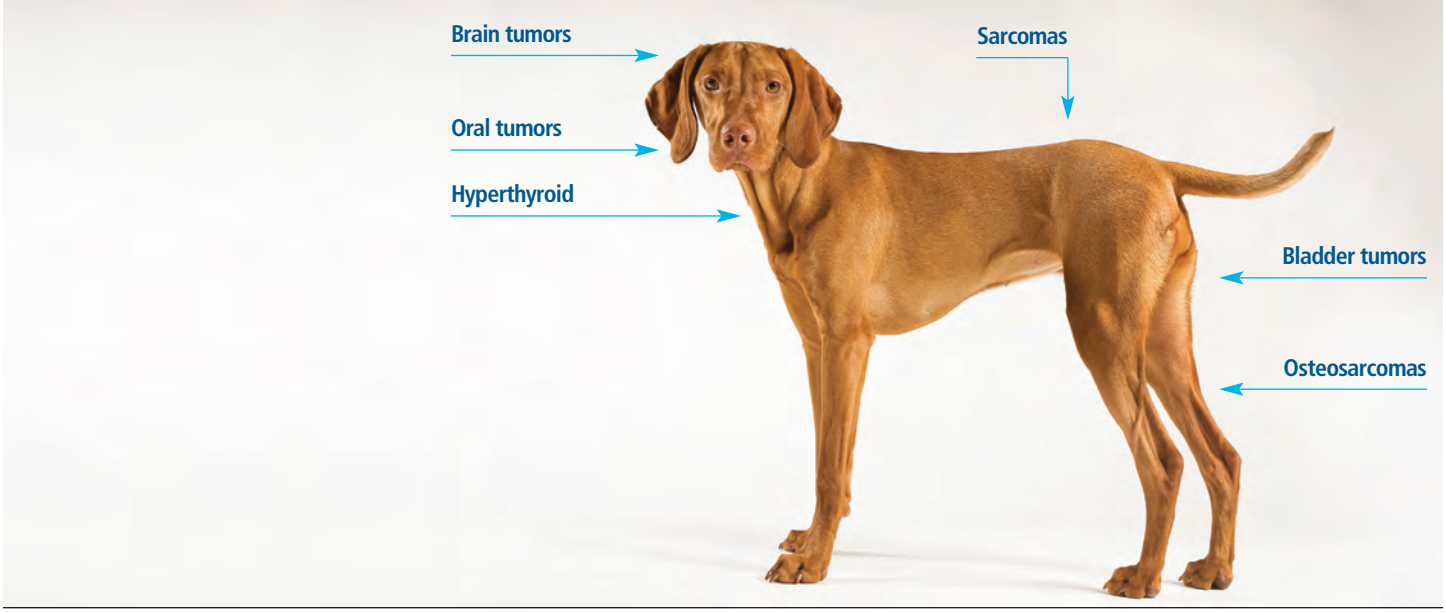
Identified Critical Unmet Needs

The Scientific Advisory Board identified several critical unmet needs in the veterinary space that focused ultrasound could address. Current treatment options for these indications are limited or undesirable, requiring long hospital stays and life-altering surgical procedures such as amputation.

- **Brain tumors** in clinical trials as of 2020, a jump from being proposed in 2014. Dogs are the only mammalian species other than humans in which brain tumors frequently arise. Even with aggressive therapy, expected survival time for dogs with gliomas is around a year. Side effects from treatment can be severe.
- **Bladder tumors** in dogs and cats are very difficult to treat surgically and cause significant quality-of-life difficulties for both the pet and the owner. Only 20 percent of patients respond to systemic chemotherapy and prognosis is poor.
- **Hyperthyroidism** is the most common form of endocrinopathy in cats, and affects more than 1 in 10 senior cats. Standard-of-care therapy requires a five-day stay in isolation in a special radiotherapy center.
- **Oral tumors** are generally locally aggressive and difficult to treat surgically. Surgical resection often requires the removal of large sections of the upper or lower jaw, significantly impacting quality of life.
- **Osteosarcomas** are the most common form of bone cancer in dogs, and are highly aggressive tumors. Most arise in the limbs, and even with immediate amputation, survival beyond a year is rare.
- **Sarcomas** are very common, both on the trunk and the extremities. Metastatic cancer is virtually impossible to treat.

Diseases Where Focused Ultrasound Could Have Biggest Impact

Identified Critical Unmet Needs



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

Media and Publications

New Center

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

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

Choosing a Treatment

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

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

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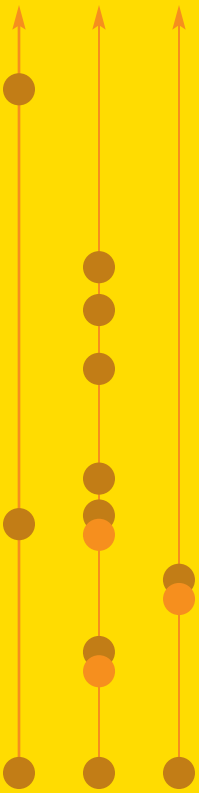
2021

State of Commercialization

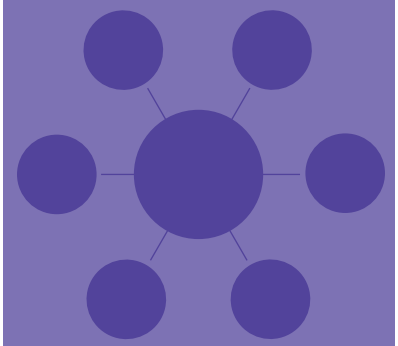
Focused Ultrasound Foundation

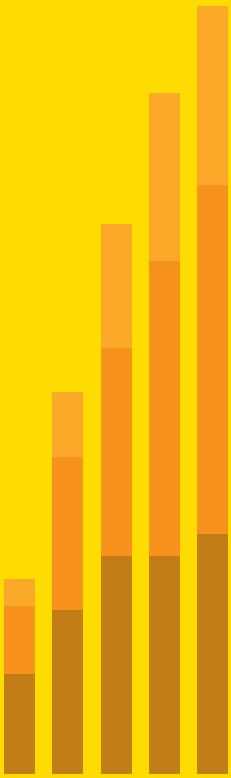
6
new FUS
industry companies
in 2020

34
indications with
regulatory approvals



14
indications with
insurance coverage
in Europe





54
clinical device
manufacturers

302.4m
have insurance coverage for
FUS treatment
in the US

$326m
invested in
FUS manufacturers
in 2020

State of Commercialization

15
companies
with regulatory approvals

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 data points and metrics needed to understand and evaluate this global commercialization 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.

New this year, we are including a global landscape of insurance coverage by country. This work is in large part thanks to our regional focused ultrasound ambassadors in Europe and Asia. Also new in 2020 is detailed insurance coverage for focused ultrasound in the United States, broken down by state, indication, and private carriers.

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

4
indications
with
US reimbursement

Contents

III. State of Commercialization

FUS Partners Role in the Industry

To help accelerate the transition of the field from a primarily science-based research environment to a 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 advance the field significantly and effectively by identifying commercial opportunities, making connections between stakeholders, and enhancing the flow of information between strategic and financial investors and focused ultrasound companies. The program has grown from two employees in 2016 to a team of five core team members.

Goals

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

Activities

Regulatory & Reimbursement

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

Financial & Human Capital

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

Strategic Partnerships & Technology Transfer

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

Advocacy

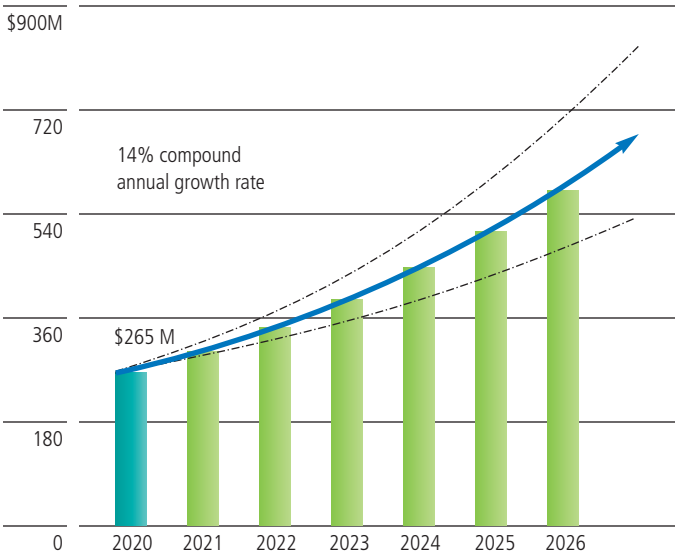
- Inform regulatory agencies, payers, and MedTech advocacy organizations about focused ultrasound
- Monitor clinical trials and potentially decrease cost of care while improving quality
- Connect and engage focused ultrasound manufacturers with advocacy organizations

Intellectual Property

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

FUS Market Projection

Revenue in millions of dollars



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

www.a2zmarketresearch.com/data/Global-High-Intensity-Focused-Ultrasound-(HIFU)-Market-Report-2020/317267

www.industryresearch.biz/global-high-intensity-focused-ultrasound-hifu-market-15962486

www.marketsandresearch.biz/report/115710/global-high-intensity-focused-ultrasound-system-market-2020-by-manufacturers-regions-type-and-application-forecast-to-2025

www.marketstudyreport.com/reports/global-high-intensity-focused-ultrasound-hifu-market-2020-by-manufacturers-regions-type-and-application-forecast-to-2025

www.marketstudyreport.com/reports/global-high-intensity-focused-ultrasound-hifu-market-growth-2020-2025

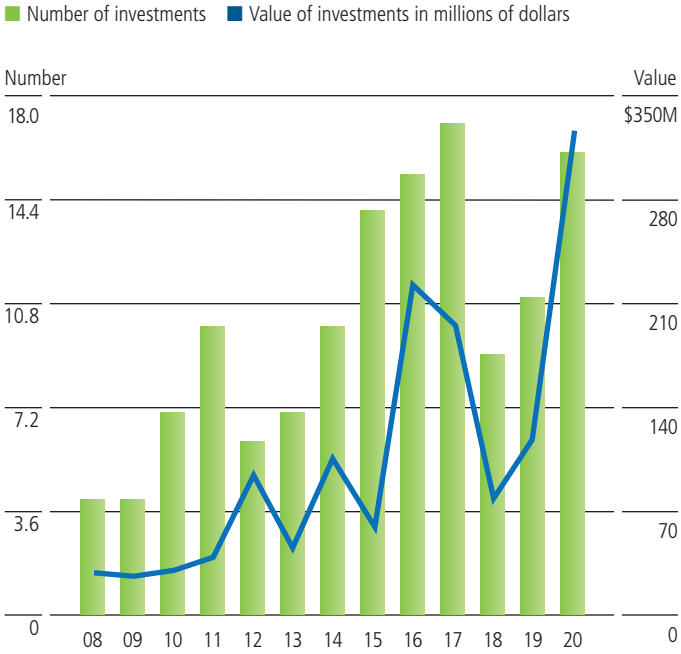
www.mrinsights.biz/report-detail/232522/request-sample#description

www.persistencemarketresearch.com/market-research/mri-guided-focused-ultrasound-devices-market.asp

www.pixionmarketresearch.com/report/global-high-intensity-focused-ultrasound-hifu-market/7406/

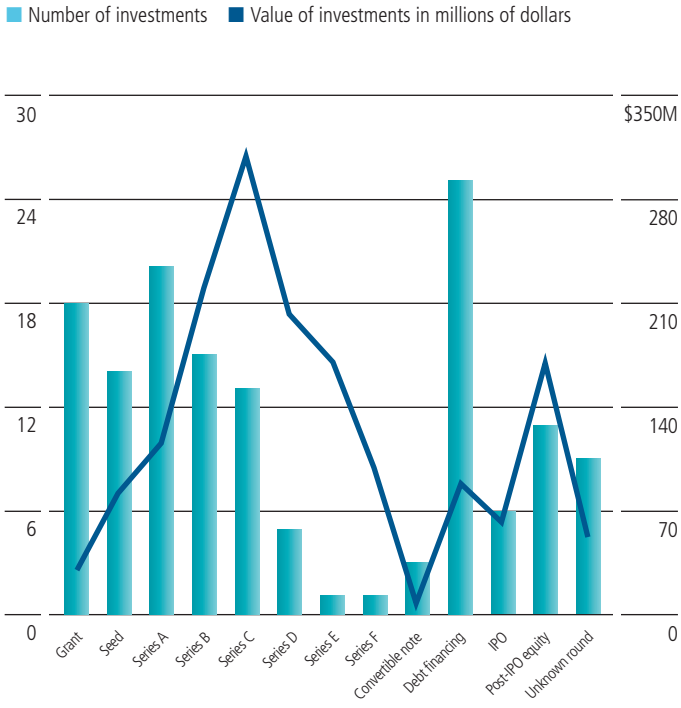
www.worldwidemarketreports.com/market-insights/global-high-intensity-focused-ultrasound-hifu-market

FUS Industry Investments Over Time



Source: www.crunchbase.com and company press releases

FUS Industry Investments by Stage



www.crunchbase.com and company press releases

2020 FUS Industry Investments*

Manufacturer	Funding type	Investors	Funding date	Money raised, millions $US
Insightec LTD				
	Series F	Koch Disruptive Technologies Investments, LLC	3.6.2020	$100M
Profound Medical CORP				
	Post-IPO Equity	—	1.22.2020	$34.4M
	Post-IPO Equity	—	7.21.2020	$46.0M
Exo Imaging INC				
	Series B	Action Potential Venture Capital, Ltd. Applied Ventures, LLC Bold Capital Partners Fiscus Ventures Intel Capital Corp. Reimagined Ventures, LLC Rising Tide Fund Solasta Ventures, Inc. TDK Ventures, Inc. Wanxiang Healthcare Investments	8.20.2020	$40.0M
HistoSonics INC				
	Series C	Yonjin Venture Johnson & Johnson Lumira Ventures State of Wisconsin Investment Board Varian Medical Systems, Inc. Venture Investors, LLC	5.29.2020	$40.0M
	Debt	Signature Bank	11.25.2020	$15.0M
EXACT Therapeutics AS				
	IPO	Canica, AS Investinor, AS Nordea Bank, AB Sundt, AS TD Veen, AS	7.14.2020	$16.2M
OxSonics LTD				
	Series C	Longwall Venture Partners Perivoli Innovations Winton Group, Ltd.	7.1.2020	$13.1M
CarThera SA				
	Series C	European Innovation Council	9.14.2020	$12.5M
	Grant	European Innovation Council	9.14.2020	$ 2.4M

*Source: www.crunchbase as reported by Crunchbase and industry press releases

2020 FUS Industry Investments* continued

Manufacturer	Funding type	Investors	Funding date	Money raised, millions $US
Theraclion SA				
	Post-IPO Equity	—	—	$ 3.7M
	Debt	Bpifrance Crédit Industriel et Commercial		$ 1.8M
Microvascular Therapeutics LLC				
	Grant	National Institute on Aging	8.1.2020	$ 0.4M
	Grant	National Institutes of Health	7.17.2020	$ 0.4M
Acoustiic INC				
	Seed	Angel investor	7.1.2020	$ 0.7M
NeuroSonics Medical INC				
	Grant	National Science Foundation	2.1.2020	$ 0.2M
				$326.8M USD Total

2020 marks a first for the field of focused ultrasound commercialization. In 2020, we saw the introduction of two strategic investors in the space: Both Johnson & Johnson and Varian Medical Systems invested in Histosonics, Inc.

*As reported by Crunchbase and industry press releases

Reimbursement

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

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

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

What follows on the next few pages is our first attempt to report on reimbursement on a global scale. We hope in the coming years to greatly expand on this, providing more detail.

NEW

Insurance Coverage by Region*

Indications	North America	Europe	Asia	Oceania
Benign prostatic hyperplasia		France Germany	Saudia Arabia Singapore	Australia
Bone metastases	United States[1]	Germany Italy[2]	Israel Malaysia Saudi Arabia South Korea	Australia
Breast tumors, benign		Germany		
Breast tumors, malignant		Germany		
Desmoid tumors		Germany		
Essential tremor	Canada United States[1]	Germany Italy[2] Switzerland United Kingdom[3]	Israel Japan	
Neuropathic pain		Germany Italy[2] Switzerland	Israel	
Osteoid osteoma		Germany Italy[2]		
Pancreatic tumors		Germany		
Parkinson's disease, tremor	United States[1]	Germany Italy[2] Switzerland	Japan Israel	
Prostate cancer	United States[1]	France Germany United Kingdom[3]	Saudia Arabia Singapore	Australia
Thyroid nodules		Germany		
Uterine fibroids		Germany Italy[2]	China Israel Malaysia Saudi Arabia South Korea Vietnam	Australia
Varicose veins		Germany		

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

2 In Italy: Essential tremor and TDPD are only covered in Sicily, Abruzzo, and Lombardia. Neuropathic pain is only covered in Milan. Bone metastases and osteoid osteoma are only covered in Lombardia, Emilia Romagna, Lazio, and Abruzzo.

3 Coverage determination was made in 2020, to take effect on April 1, 2021.

NEW

Insurance Coverage by Country*

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

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3 Coverage determination was made in 2020, to take effect on April 1, 2021.

Insurance Coverage by Country* continued

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

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

2 In Italy: Essential tremor and TDPD are only covered in Sicily, Abruzzo, and Lombardia. Neuropathic pain is only covered in Milan. Bone metastases and osteoid osteoma are only covered in Lombardia, Emilia Romagna, Lazio, and Abruzzo.

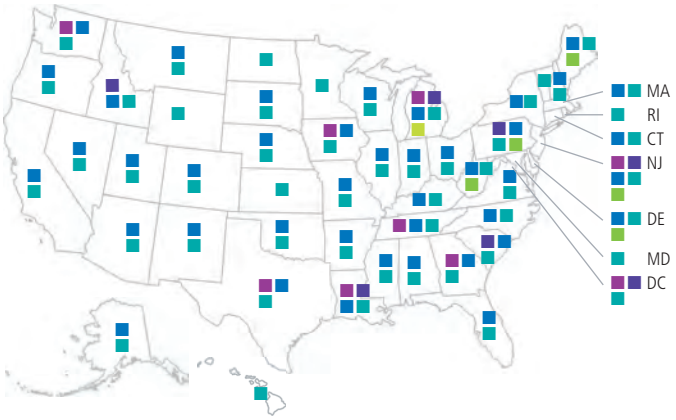
Coverage in the United States*

Bone metastases | Pain palliation

Private carrier

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

Covered lives 116.6 million



Essential tremor

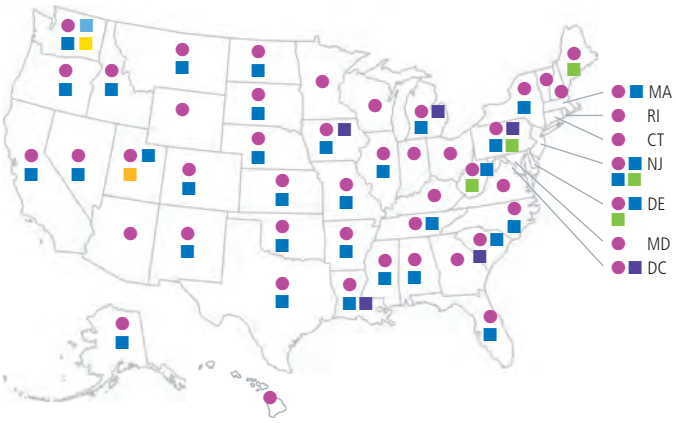
Public carrier

- Medicare
  ALL STATES

Private carriers

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

Covered lives 121.2 million

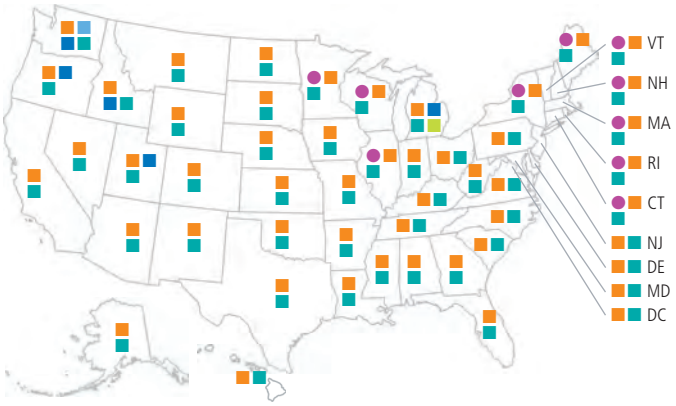


* All coverage decisions are conditional, requiring that patients meet specific inclusion and exclusion criteria. The most current policy documents from the individual insurers should be referenced for a complete description.

Insurance Coverage in the United States* continued

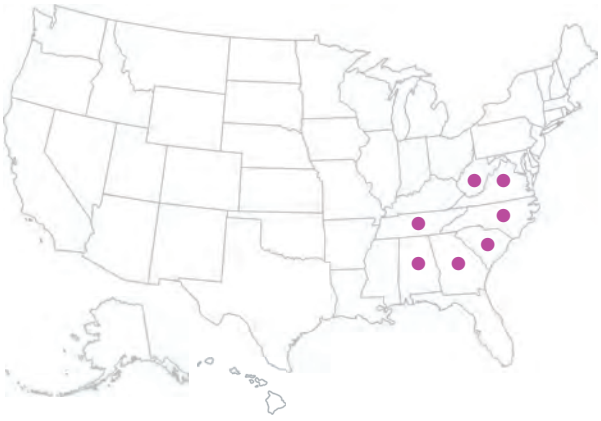
Prostate cancer | Salvage therapy[1]

Public carrier	● Medicare CT, IL, MA, ME, MN, NH, NY, RI, VT, WI
Private carriers	■ Aetna ALL STATES ■ Asuris Northwest Health WA ■ Blue Shield Regence ID, MI, OR, UT, WA ■ CIGNA ALL STATES ■ HAP Health Alliance Plan MI
Covered lives	57.5 million



Parkinson's disease, tremor

Public carrier	● Medicare AL, GA, NC, SC, TN, VA, WV
Covered lives	7.1 million



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

1 Local treatment for recurrent prostate cancer following radiation therapy

Essential Tremor Market Study

Clinical trials for focused ultrasound, FUS, treatment of essential tremor, ET, began in 2011. As a result, we have a decade of information that is worthy of analysis. Below, we take a closer look at what drives the adoption of this technology.

Timelines of the factors that drive adoption

When we compare the relative number of treatment sites that have adopted FUS to the relative number of patients treated with the technology, it is clear that the increase in treatment sites precedes the increase in number of patient treatments.

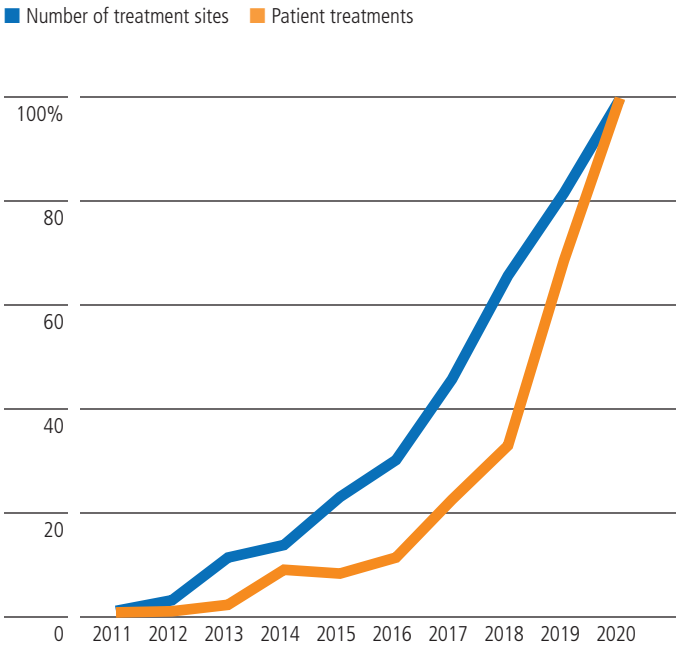
In 2016, when reimbursement—also referred to as insurance coverage—for the procedure was first granted, there were one-third the number of sites that there are today. In contrast, only one-tenth the number of patients were being treated in 2016, as compared to current treatment volumes.

There are two main factors that potentially drive site adoption and patient treatment volume. Regulatory approval is critical, since physicians cannot utilize a technology unless it is approved in their country. Reimbursement by government health agencies or private insurers is also a vital factor, since patients often cannot—or will not—pay out-of-pocket for medical treatment.

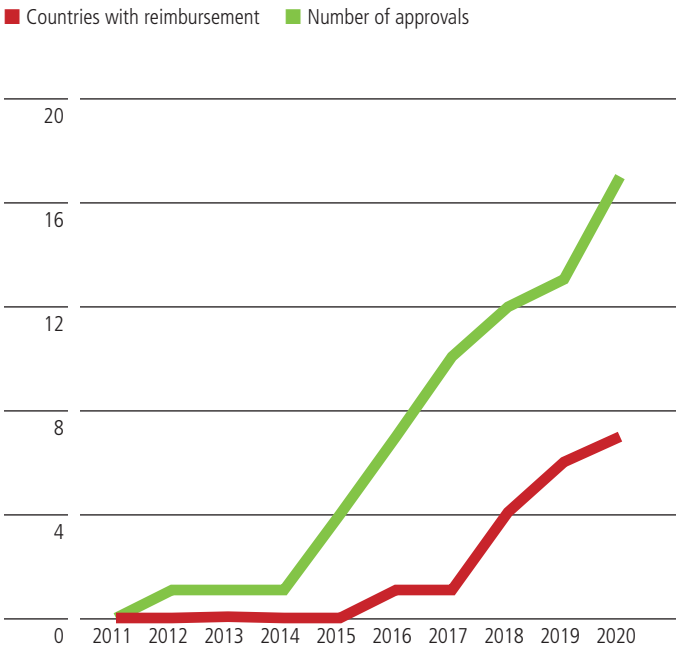
When the number of global regulatory approvals is compared to the number of countries granting insurance coverage, we see that approvals lead reimbursement, in the later years by a healthy margin.

This is not surprising, since regulatory approval is a prerequisite of reimbursement. Although regulatory approval and insurance coverage both require data about patient safety and efficacy, those for reimbursement are of greater rigor than these required for approval. Reimbursement also requires information on utilization (how many cases are being performed) and cost-effectiveness. Data for the last two factors can only be obtained after the device has been in commercial use for a certain period of time, creating a lag in reimbursement relative to approvals.

Treatment Sites vs. Patient Treatments



Approvals vs. Reimbursement



Essential Tremor Market Study continued

Correlating the factors

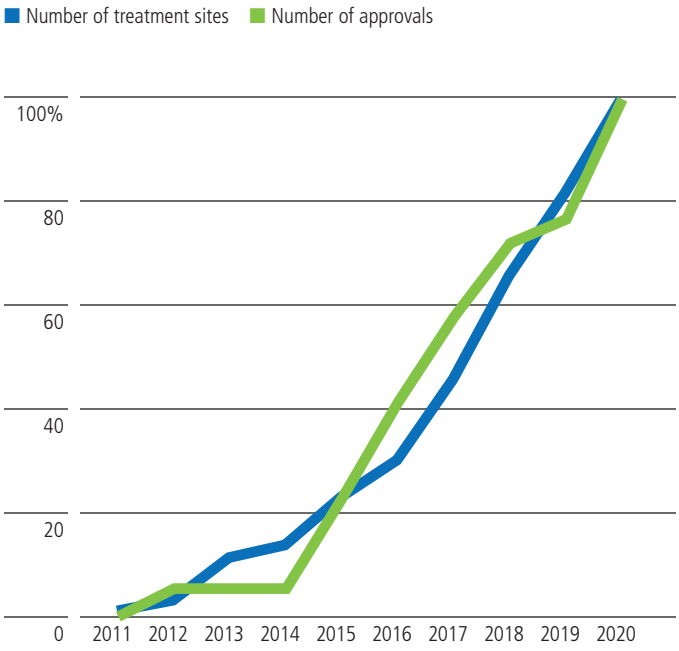
So which factor drives site adoption, and which drives patient treatments? The graph to the right demonstrates that the relative rate of site adoption tracks very closely with that of regulatory approvals. In fact, the correlation coefficient between the two (the degree to which the number of approvals predicts the number of sites adopting FUS, and vice-versa) is 0.96. In other words, using one to predict the other will be accurate 96 percent of the time.

In addition, the relative number of patient treatments tracks most closely with the relative number of countries that reimburse the procedure, although reimbursement does lead patient treatments to an extent. The correlation coefficient in this case is 0.94.

Interpreting the correlations

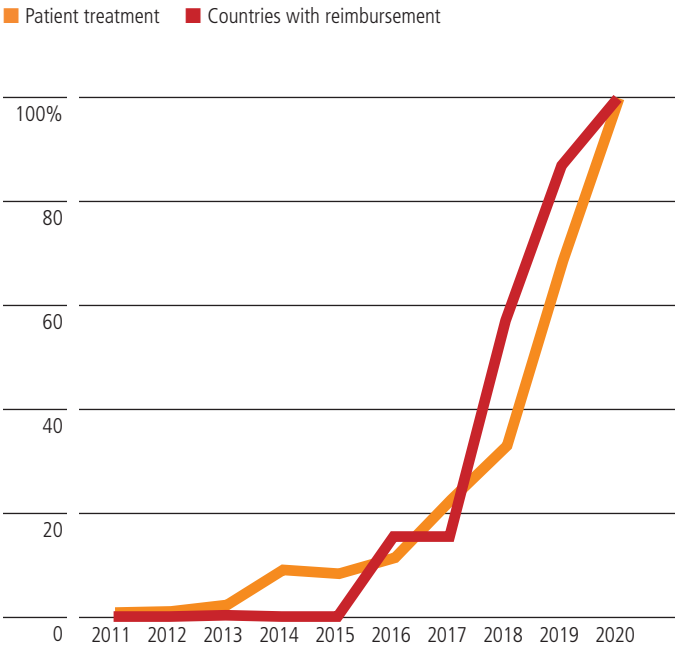
The close alignment between reimbursement and patient treatments was not unexpected. As mentioned above, patients are often unable or unwilling to pay for a medical procedure out-of-pocket. This is especially true in the many countries with socialized medicine, where the concept of a patient paying directly for a procedure is largely unheard of. Essential tremor is a debilitating, but not a life-threatening, disease. In addition, there are alternative ET treatment procedures that are covered by insurance in most countries. Because of this, patients who wish to have their ET treated specifically with FUS, in countries that don't currently offer insurance coverage are likely to assume a wait-and-see position, with the anticipation that their country will soon offer reimbursement.

Treatment Sites vs. Approvals



Essential Tremor Market Study continued

Patient Treatments vs. Reimbursement



The graph above shows reimbursement somewhat leading patient treatments. This likely results from two factors.

- Most essential tremor patients are not aware of new insurance coverage immediately after the decision is announced, often finding out about this only after consultation with their neurologist or neurosurgeon.
- There is almost always more demand for the procedure than there are treatment times available to perform it. As a result, it takes some time for patient treatments to catch up with new coverage.

Both of these factors cause a lag between coverage being granted and the patient treatment numbers reflecting this fact.

The one remaining question is: why does site adoption track most closely with regulatory approvals and not reimbursement? Reimbursement of FUS-based ET treatments began in 2016, with the number of countries reimbursing the procedure increasing rapidly since then. Even though the rate of treatment sites adopting the technology increased after 2016, we have certainly not seen the exponential growth that you would expect if reimbursement drove site adoption. We propose two theories to explain this close relationship between site adoption and regulatory approvals.

It is not uncommon for medical centers to choose to purchase the equipment "on spec" after approval is granted, with the expectation that coverage will soon be forthcoming. In the US, 80 percent of new medical technologies that obtain FDA approval are later granted Medicare coverage. Because of this, future prospects for insurance coverage likely offset the financial risk of purchasing the equipment.

A less economic rationale we've heard while in discussion with many ET treatment sites—academic and for-profit institutions alike—is based on the medical industry concept of "compassionate care." Medical centers are willing to purchase medical equipment, regardless of potential profitability, as long as it provides a clear improvement in patient outcomes.

Based on this information, we view the consistently robust growth in the number of treatment sites as evidence that FUS for the treatment of ET is seen as an attractive alternative to competing technologies, and one that may be worth acquiring, even if the odds of future insurance coverage are not absolute.

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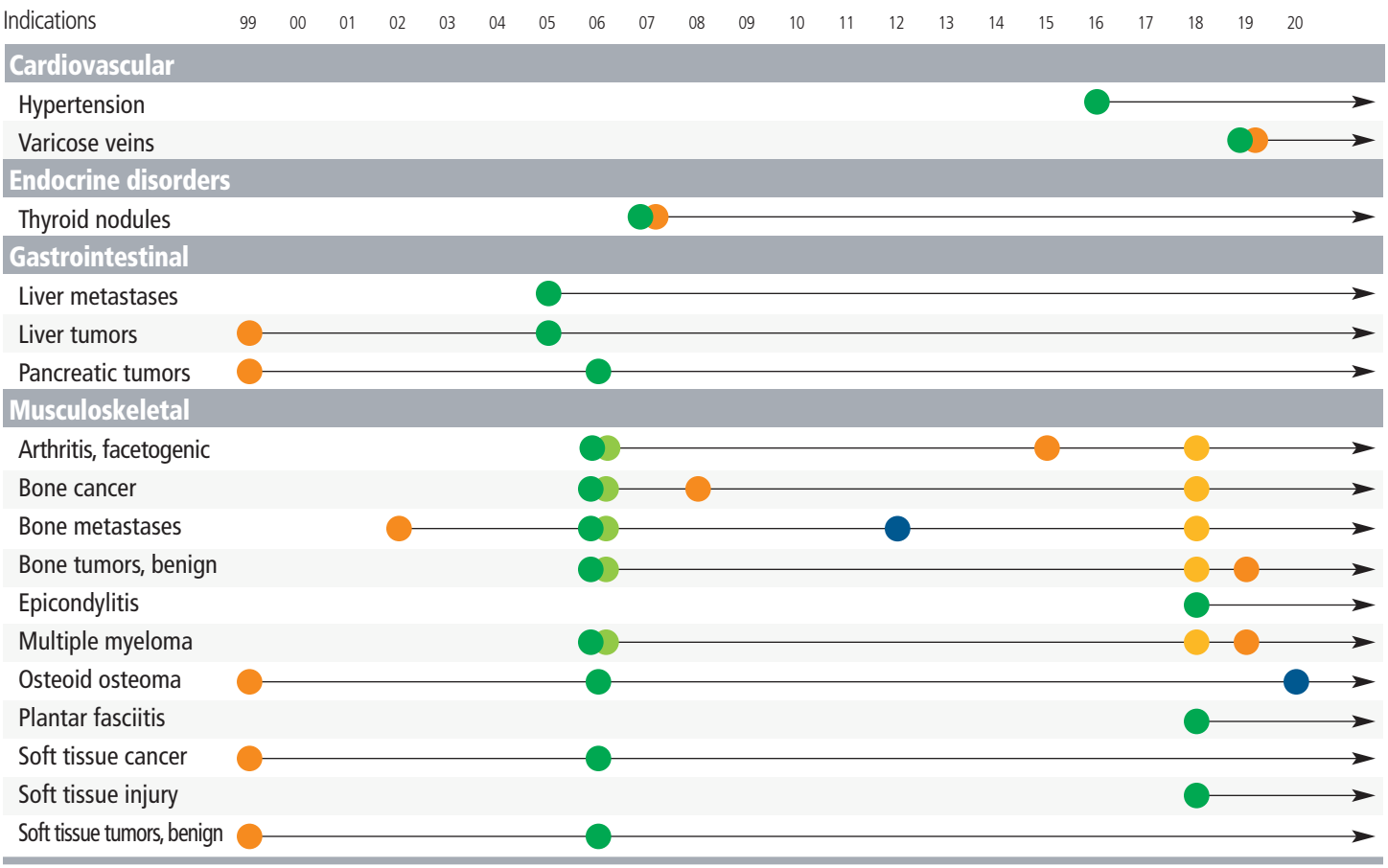
FUS Regulatory Approvals by Indication and Region
Graphic

FUS Regulatory Approvals by Indication and Region continued

Table

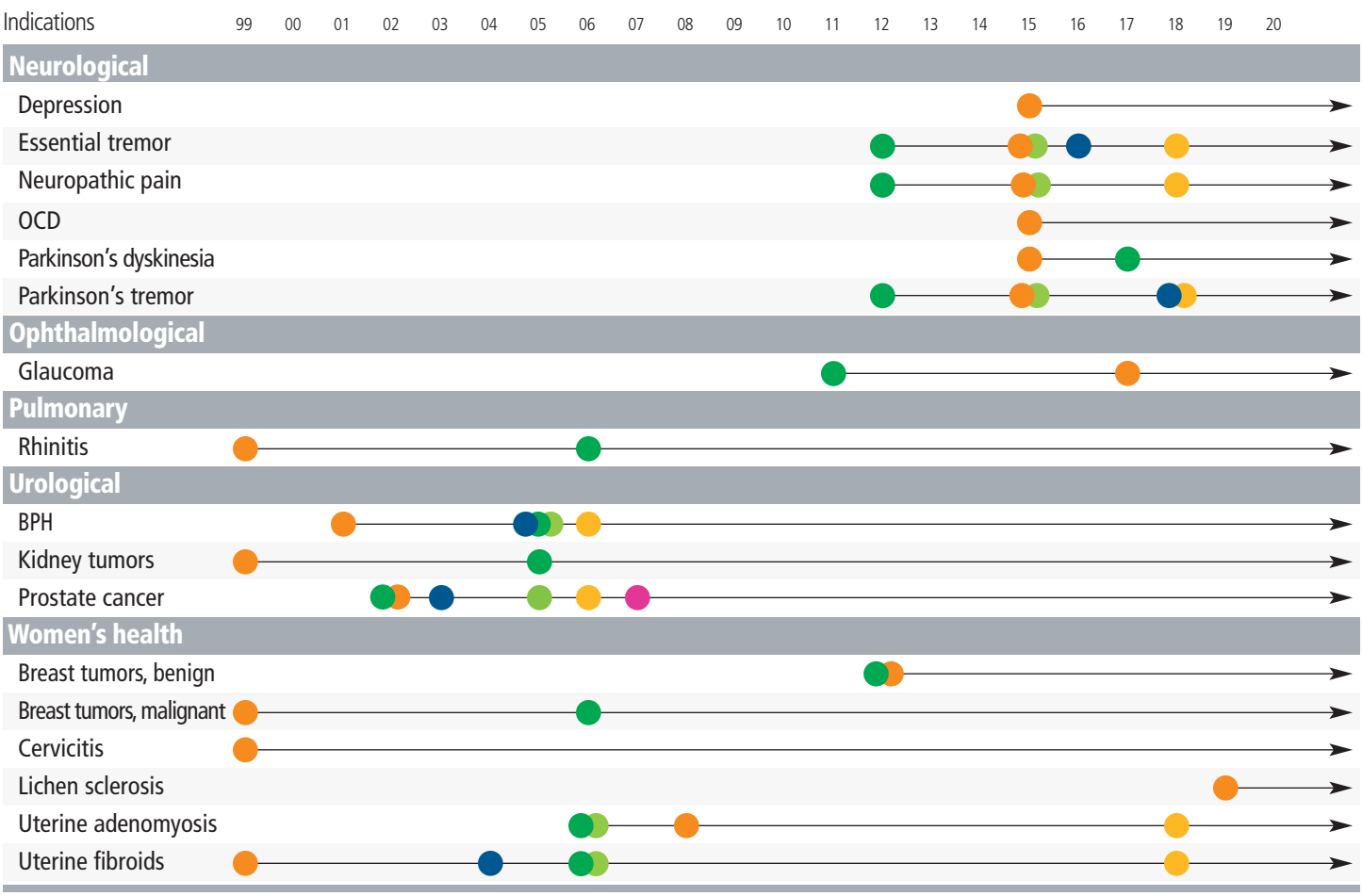
North America	Europe	Asia	South America	Oceania	Africa
Benign prostatic hyperplasia	Arthritis, facetogenic	Arthritis, facetogenic	Arthritis, facetogenic	Arthritis, facetogenic	Prostate cancer
Bone metastases	Benign prostatic hyperplasia	Benign prostatic hyperplasia	Benign prostatic hyperplasia	Benign prostatic hyperplasia	
Essential tremor	Bone cancer	Bone cancer	Bone cancer	Bone cancer	
Osteoid osteoma	Bone metastases	Bone metastases	Bone metastases	Bone metastases	
Parkinson's disease, tremor	Bone tumors, benign	Bone tumors, benign	Bone tumors, benign	Bone tumors, benign	
Prostate cancer	Breast tumors, benign	Breast tumors, benign	Essential tremor	Essential tremor	
Uterine fibroids	Breast tumors, malignant	Breast tumors, malignant	Multiple myeloma	Multiple myeloma	
	Epicondylitis	Cervicitis	Neuropathic pain	Neuropathic pain	
	Essential tremor	Depression	Parkinson's disease, tremor	Parkinson's disease, tremor	
	Glaucoma	Essential tremor	Prostate cancer	Prostate cancer	
	Hypertension	Glaucoma	Uterine adenomyosis	Uterine adenomyosis	
	Kidney tumors	Kidney tumors	Uterine fibroids	Uterine fibroids	
	Liver metastases	Lichen sclerosis			
	Liver tumors	Liver tumors			
	Multiple myeloma	Multiple myeloma			
	Neuropathic pain	Neuropathic pain			
	Osteoid osteoma	Obsessive-compulsive disorder			
	Pancreatic tumors	Osteoid osteoma			
	Parkinson's disease, dyskinesia	Pancreatic tumors			
	Parkinson's disease, tremor	Parkinson's disease, dyskinesia			
	Plantar fasciitis	Parkinson's disease, tremor			
	Prostate cancer	Prostate cancer			
	Rhinitis	Rhinitis			
	Soft tissue cancer	Soft tissue cancer			
	Soft tissue injury	Soft tissue tumors, benign			
	Soft tissue tumors, benign	Thyroid nodules			
	Thyroid nodules	Uterine adenomyosis			
	Uterine adenomyosis	Uterine fibroids			
	Uterine fibroids	Varicose veins			
	Varicose veins				

FUS Regulatory Approvals by Indication and Region



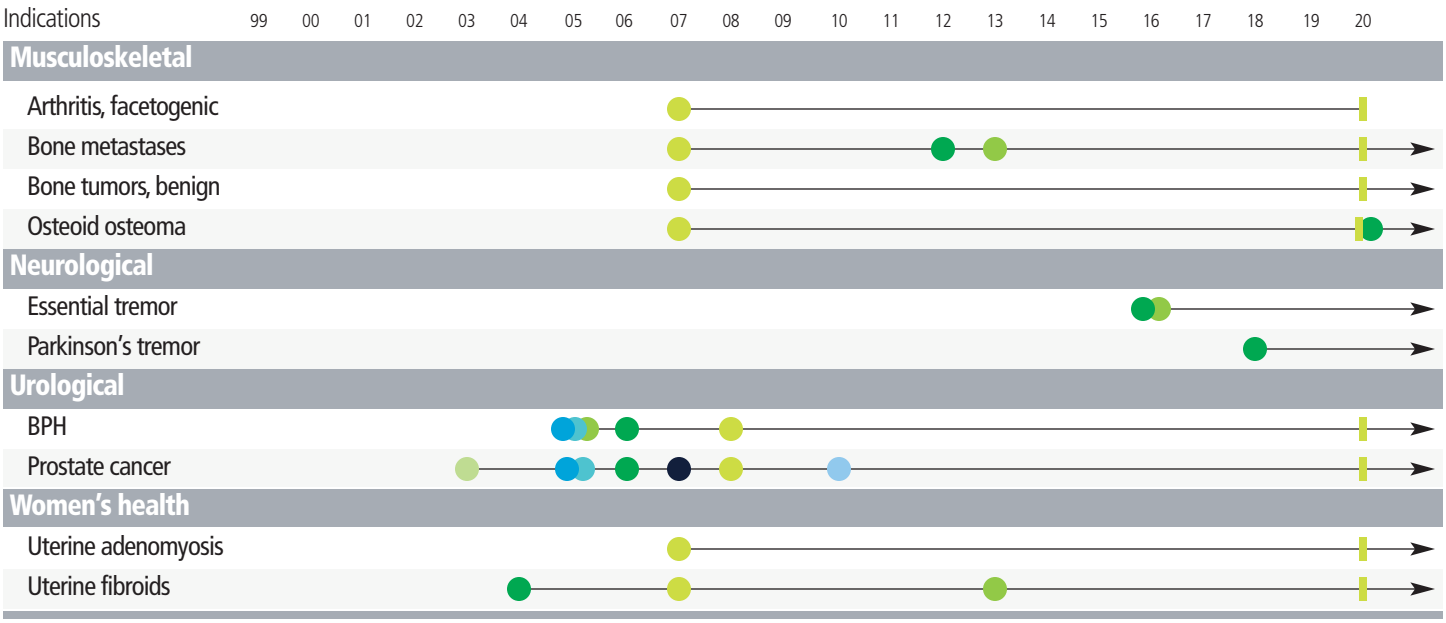
North America
Europe
Asia
South America
Oceania
Africa

FUS Regulatory Approvals by Indication and Region continued



North America
Europe
Asia
South America
Oceania
Africa

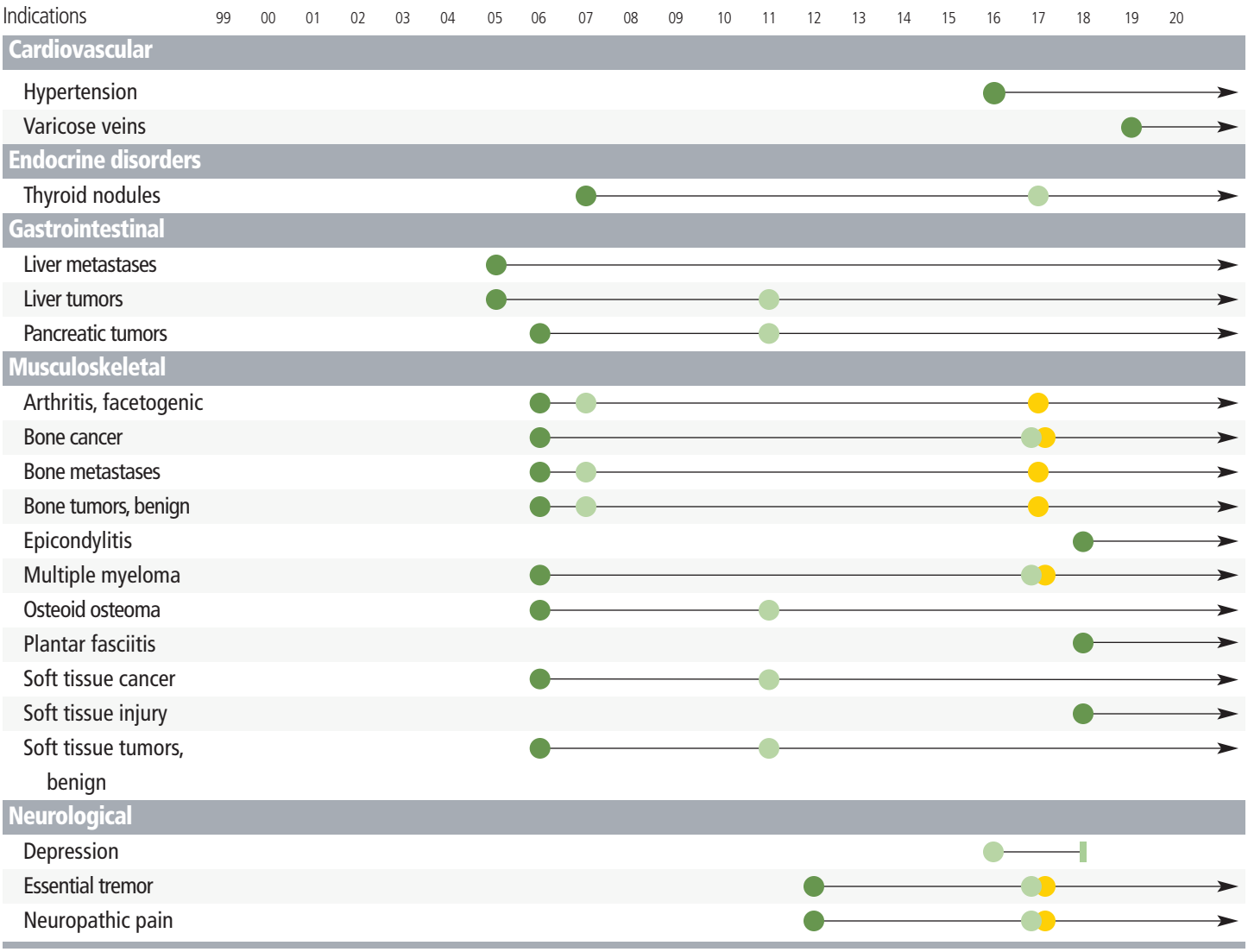
North America—FUS Regulatory Approvals by Indication



Approval
- Approval begin date
- Approval end date

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

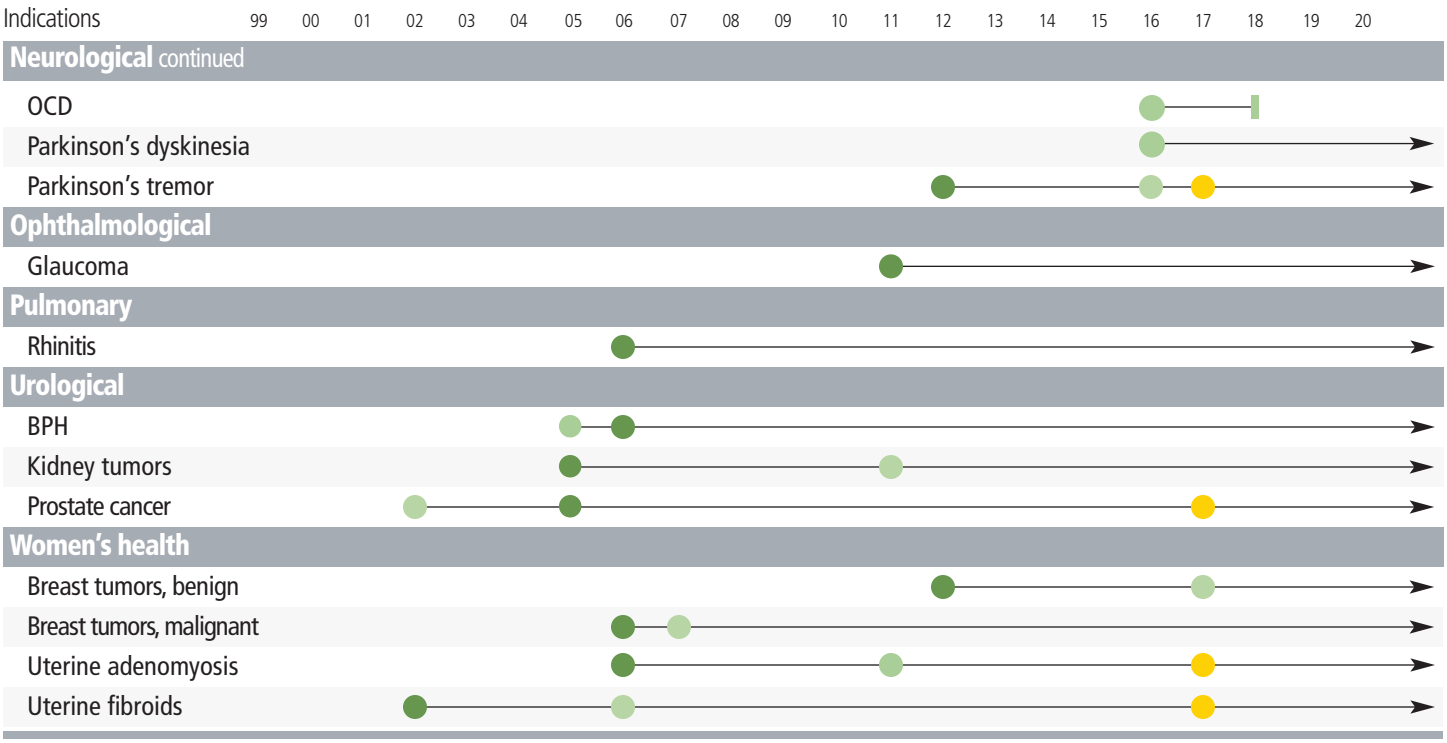
Europe—FUS Regulatory Approvals by Indication



Approval
- Approval begin date
- Approval end date

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

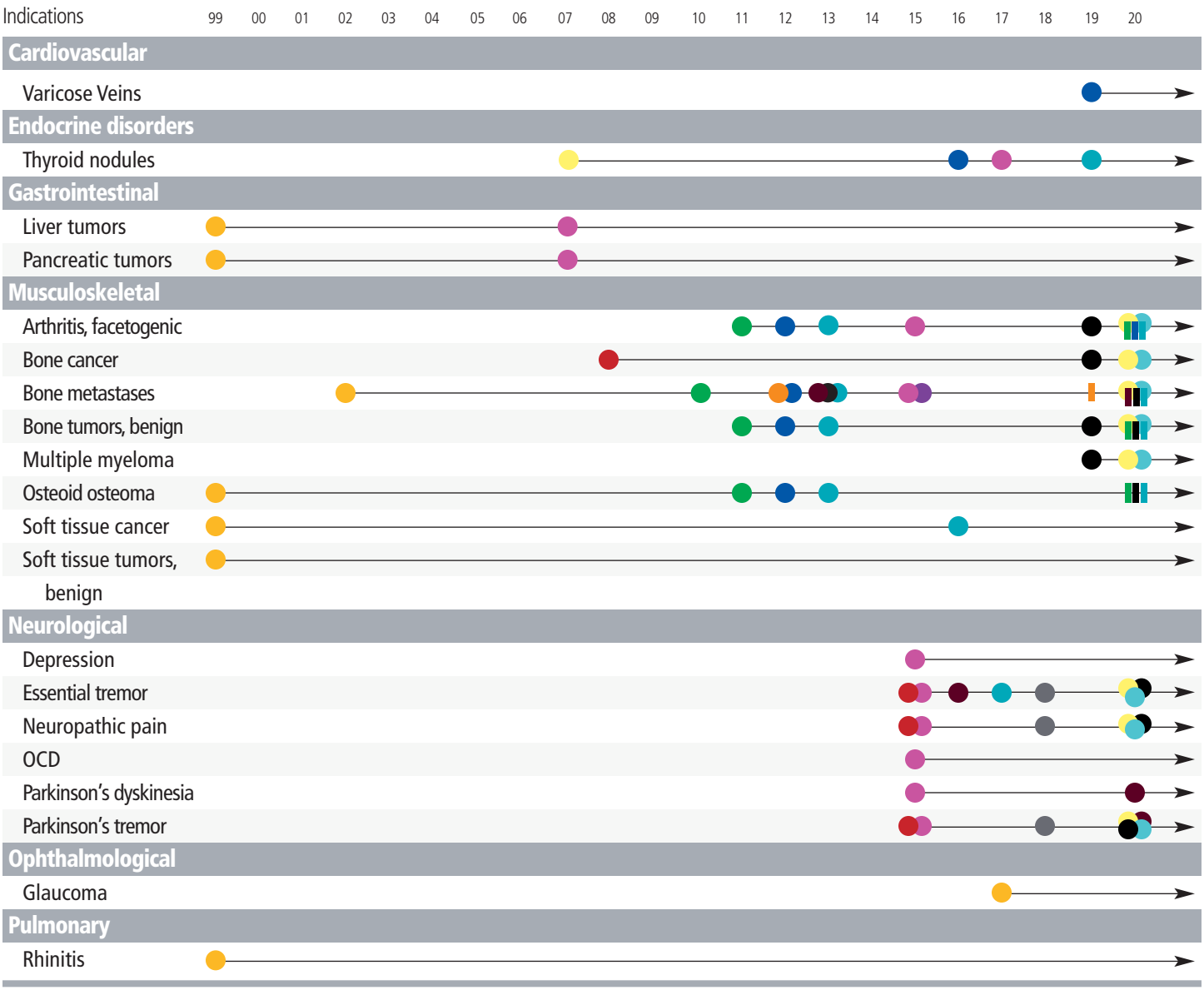
Europe—FUS Regulatory Approvals by Indication continued



Approval
- Approval begin date
- Approval end date

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

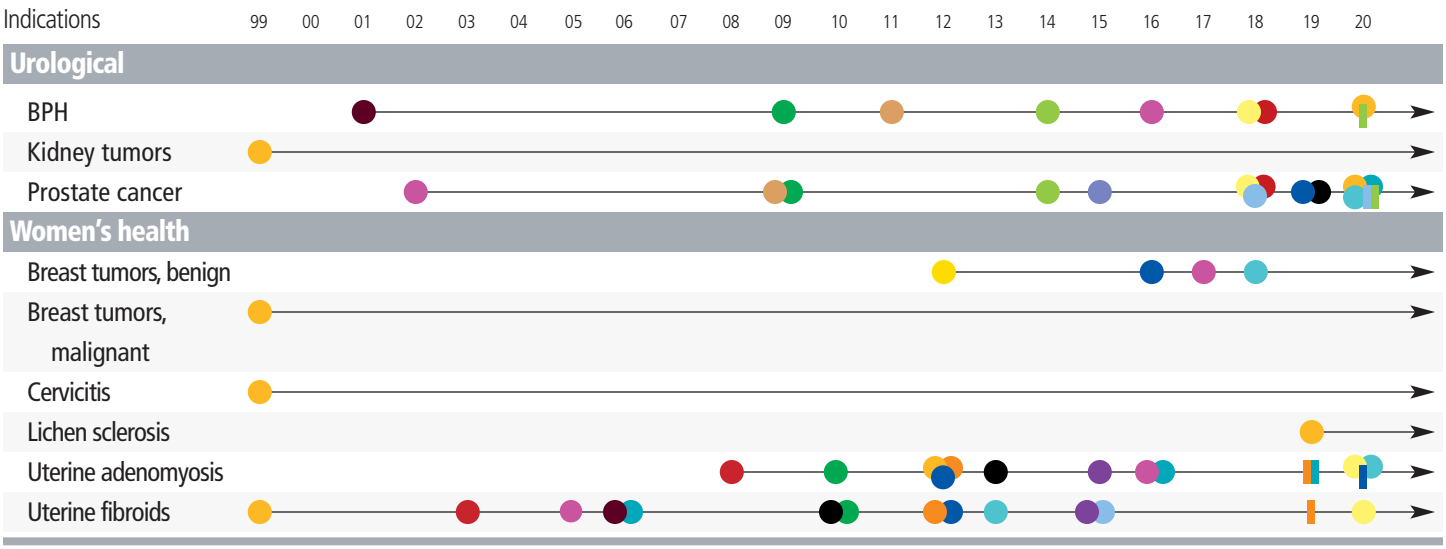
Asia—FUS Regulatory Approvals by Indication



Approval
- Approval begin date
- Approval end date

Asia
- China, *NMPA*
- Hong Kong, *MDD*
- India, *CDSCO*
- Indonesia, *DGPMD*
- Israel, *AMAR*
- Japan, *MHLW*
- Kazakhstan, *NCEM*
- Malaysia, *MDA*
- Pakistan, *DRAP*
- Philippines, *FDA*
- Saudi Arabia, *SFDA*
- Singapore, *HSA*
- South Korea, *MFDS*
- Taiwan, *FDA*
- Thailand, *FDA*
- Uzbekistan, *GDQC*
- Vietnam, *DMEW*

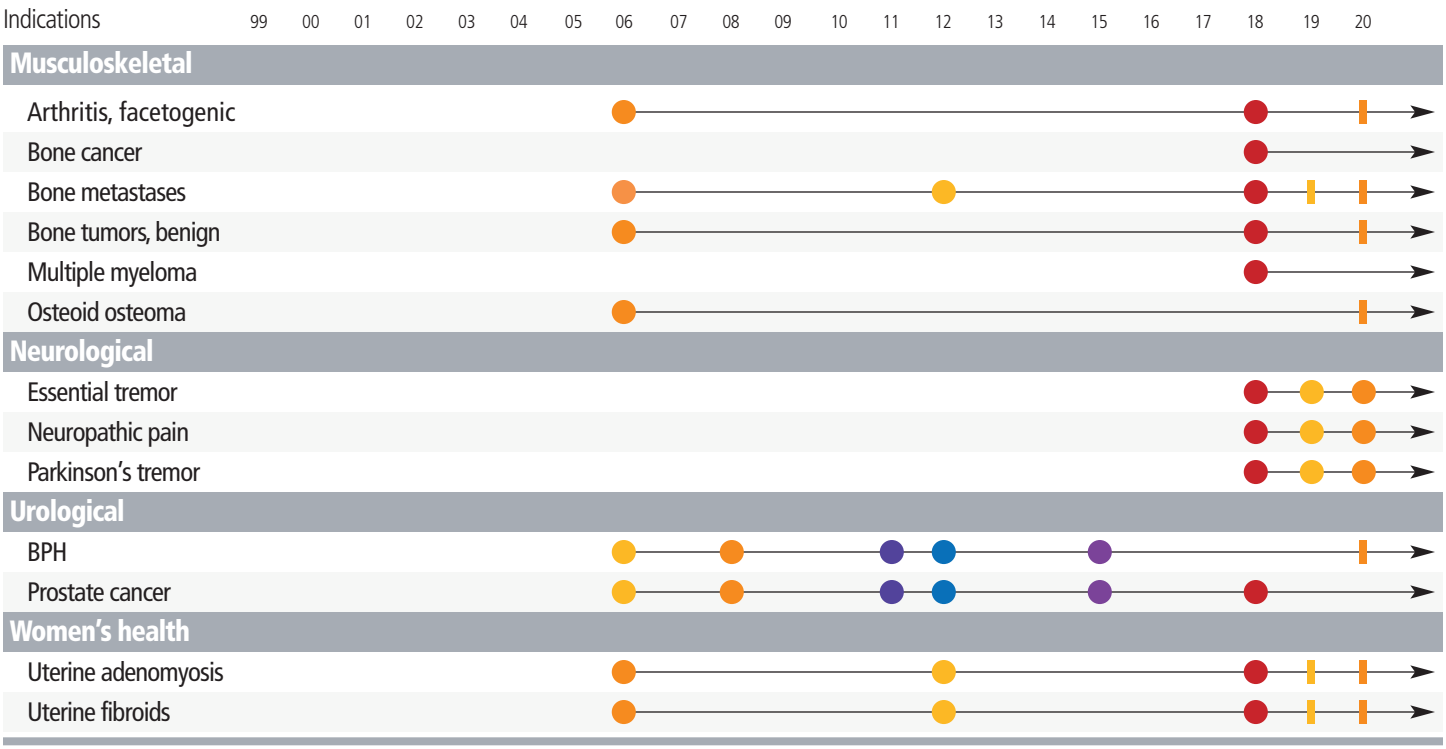
Asia—FUS Regulatory Approvals by Indication continued



Approval
- Approval begin date
- Approval end date

Asia
- China, *NMPA*
- Hong Kong, *MDD*
- India, *CDSCO*
- Indonesia, *DGPMD*
- Israel, *AMAR*
- Japan, *MHLW*
- Kazakhstan, *NCEM*
- Malaysia, *MDA*
- Pakistan, *DRAP*
- Philippines, *FDA*
- Saudi Arabia, *SFDA*
- Singapore, *HSA*
- South Korea, *MFDS*
- Taiwan, *FDA*
- Thailand, *FDA*
- Uzbekistan, *GDQC*
- Vietnam, *DMEW*

South America—FUS Regulatory Approvals by Indication

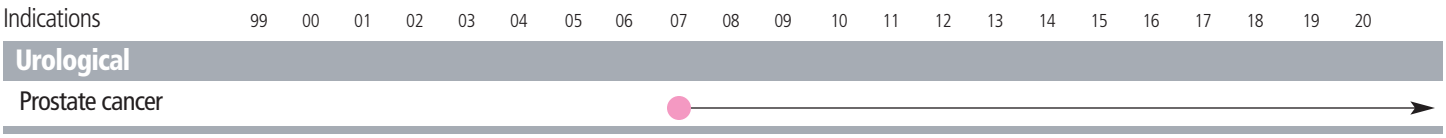


Approval
- Approval begin date
- Approval end date

South America
- Argentina, *ANMAT*
- Brazil, *ANVISA*
- Chile, *ANAMED*
- Colombia, *INVIMA*
- Ecuador, *ANRCVS*
- Trinidad and Tobago, *Ministry of Health*

Oceania—FUS Regulatory Approvals by Indication

Africa—FUS Regulatory Approvals by Indication



Approval
- Approval begin date
- Approval end date

Oceania
- Australia, *TGA*
- New Zealand, *MEDSAFE*

Africa
- South Africa, *MCC*

NEW

Global Landscape of Approved Indications and Manufacturers

Indication regional approvals	Indications	Manufacturers
	Cardiovascular	
	Hypertension	Kona Medical
	Varicose veins	Theraclion
	Endocrine disorders	
	Thyroid nodules	Theraclion
	Gastrointestinal	
	Liver tumors	Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
		Shanghai A&S
	Pancreatic tumors	Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
	Musculoskeletal	
	Arthritis, facetogenic	Insightec
	Bone cancer	Insightec
	Bone metastases	Insightec
		Profound Medical
		Shanghai A&S
	Bone tumors, benign	Insightec
	Epicondylitis	Guided Therapy Systems
	Multiple myeloma	Insightec
	Osteoid osteoma	Chongqing Haifu Medical Technology
		Profound Medical
	Plantar fasciitis	Guided Therapy Systems
	Soft tissue cancer	Chongqing Haifu Medical Technology
		EpiSonica
		Shanghai A&S
	Soft tissue injury	Guided Therapy Systems
	Soft tissue tumors, benign	Chongqing Haifu Medical Technology

Approval regions

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

Global Landscape of Approved Indications and Manufacturers continued

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

Approval regions

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

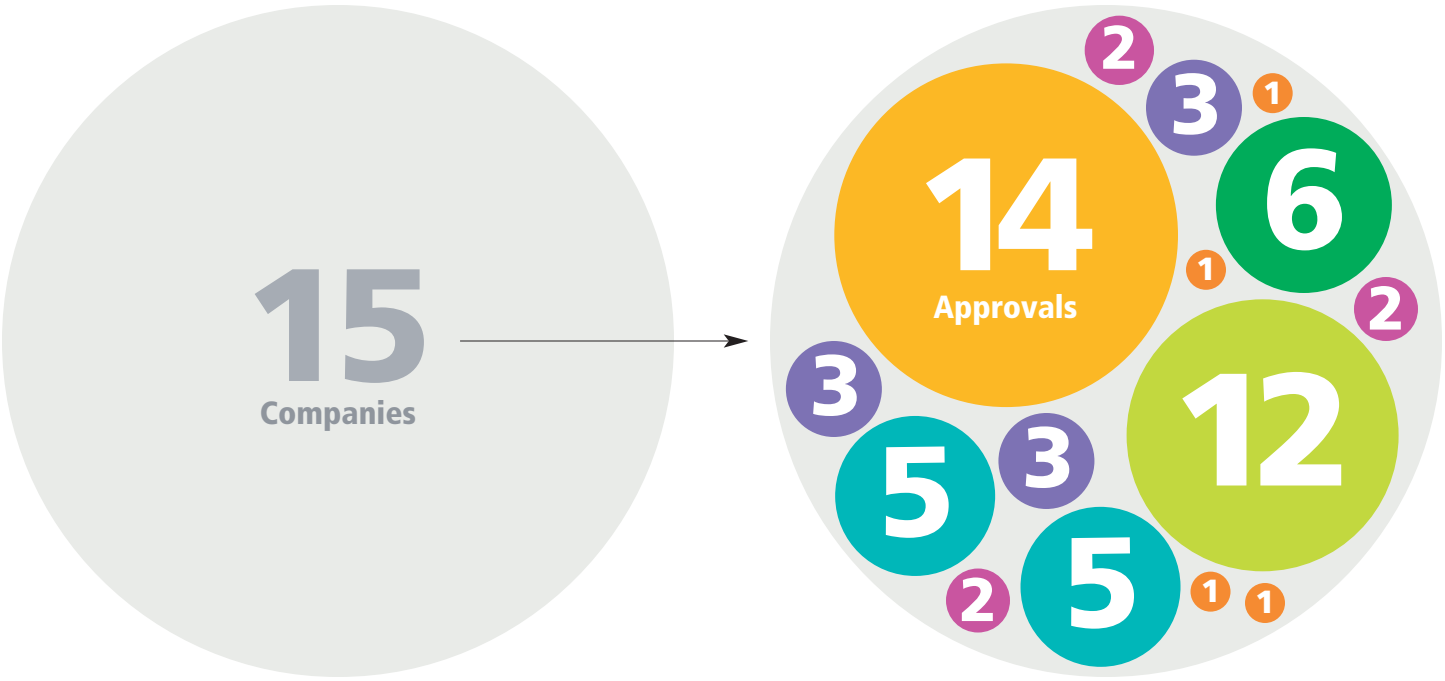
Global Landscape of Approved Indications and Manufacturers continued

Indication regional approvals	Indications	Manufacturers
	Women's health continued	
	Lichen sclerosis	Shenzhen PRO-HITU Medical
	Liver metastases, breast cancer	Chongqing Haifu Medical Technology
	Uterine adenomyosis	Alpinion Medical Systems
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shenzhen PRO-HITU Medical
	Uterine fibroids	Alpinion Medical Systems
		Beijing Yuande Bio-Medical Engineering
		Chongqing Haifu Medical Technology
		Insightec
		Profound Medical
		Shanghai A&S
		Shenzhen PRO-HITU Medical
		Wuxi Haiying Electronic Medical

Approval regions

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

Number of Indication Approvals by Company



Manufacturer Indication Approvals

One approval

EpiSonica
EyeTechCare
Kona Medical
Wuxi Haiying Electronic Medical

Two approvals

Alpinion Medical Systems
EDAP TMS
SonaCare Medical

Three approvals

Guided Therapy Systems
Shenzhen PRO-HITU Medical
Theraclion

Five approvals

Beijing Yuande Bio-Medical Engineering
Shanghai A&S

Six approvals

Profound Medical

Twelve approvals

Chongqing Haifu Medical Technology

Fourteen approvals

Insightec

Regulatory Approvals for Companies by Region and Indication

North America

EDAP TMS
- Benign prostatic hyperplasia
- Prostate cancer

Insightec
- Bone metastases
- Essential tremor
- Parkinson's disease, tremor
- Uterine fibroids

Profound Medical
- Benign prostatic hyperplasia
- Osteoid osteoma
- Prostate cancer
- Uterine fibroids

SonaCare Medical
- Benign prostatic hyperplasia
- Prostate cancer

Europe

Alpinion Medical Systems
- Uterine fibroids

Chongqing Haifu Medical Technology
- Breast tumors, malignant
- Kidney tumors
- Liver metastases
- Liver tumors
- Osteoid osteoma
- Pancreatic tumors
- Rhinitis
- Soft tissue cancer
- Soft tissue tumors, benign
- Uterine adenomyosis
- Uterine fibroids

EDAP TMS
- Prostate cancer

EyeTechCare
- Glaucoma

Guided Therapy Systems
- Epicondylitis
- Plantar fasciitis
- Soft tissue injury

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

Kona Medical
- Hypertension

Profound Medical
- Bone metastases
- Osteoid osteoma
- Prostate cancer
- Uterine adenomyosis
- Uterine fibroids

Shanghai A&S
- Uterine fibroids

Shenzhen PRO-HITU Medical
- Uterine fibroids

SonaCare Medical
- Benign prostatic hyperplasia
- Prostate cancer

Theraclion
- Breast tumors, benign
- Thyroid nodules
- Varicose veins

Asia

Alpinion Medical Systems
- Uterine adenomyosis
- Uterine fibroids

Beijing Yuande Bio-Medical Engineering
- Breast tumors, malignant
- Kidney tumors
- Liver tumors
- Pancreatic tumors
- Uterine fibroids

Chongqing Haifu Medical Technology
- Breast tumors, malignant
- Cervicitis
- Kidney tumors
- Liver tumors
- Osteoid osteoma
- Pancreatic tumors
- Rhinitis
- Soft tissue cancer
- Soft tissue tumors, benign
- Uterine fibroids

EDAP TMS
- Prostate cancer

EpiSonica
- Soft tissue cancer

EyeTechCare
- Glaucoma

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

Profound Medical
- Bone metastases
- Prostate cancer
- Uterine adenomyosis
- Uterine fibroids

Shanghai A&S
- Bone metastases
- Breast tumors, malignant
- Liver tumors
- Soft tissue cancer
- Uterine fibroids

Shenzhen PRO-HITU Medical
- Lichen sclerosis
- Uterine adenomyosis
- Uterine fibroids

SonaCare Medical
- Benign prostatic hyperplasia
- Prostate cancer

Theraclion
- Breast tumors, benign
- Thyroid nodules
- Varicose veins

Wuxi Haiying Electronic Medical
- Uterine fibroids

South America

EDAP TMS
- Prostate cancer

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

SonaCare Medical
- Benign prostatic hyperplasia
- Prostate cancer

Oceania

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

SonaCare Medical
- Benign prostatic hyperplasia
- Prostate cancer

Africa

SonaCare Medical
- Prostate cancer

FUS Regulatory Approvals by Region and Manufacturer

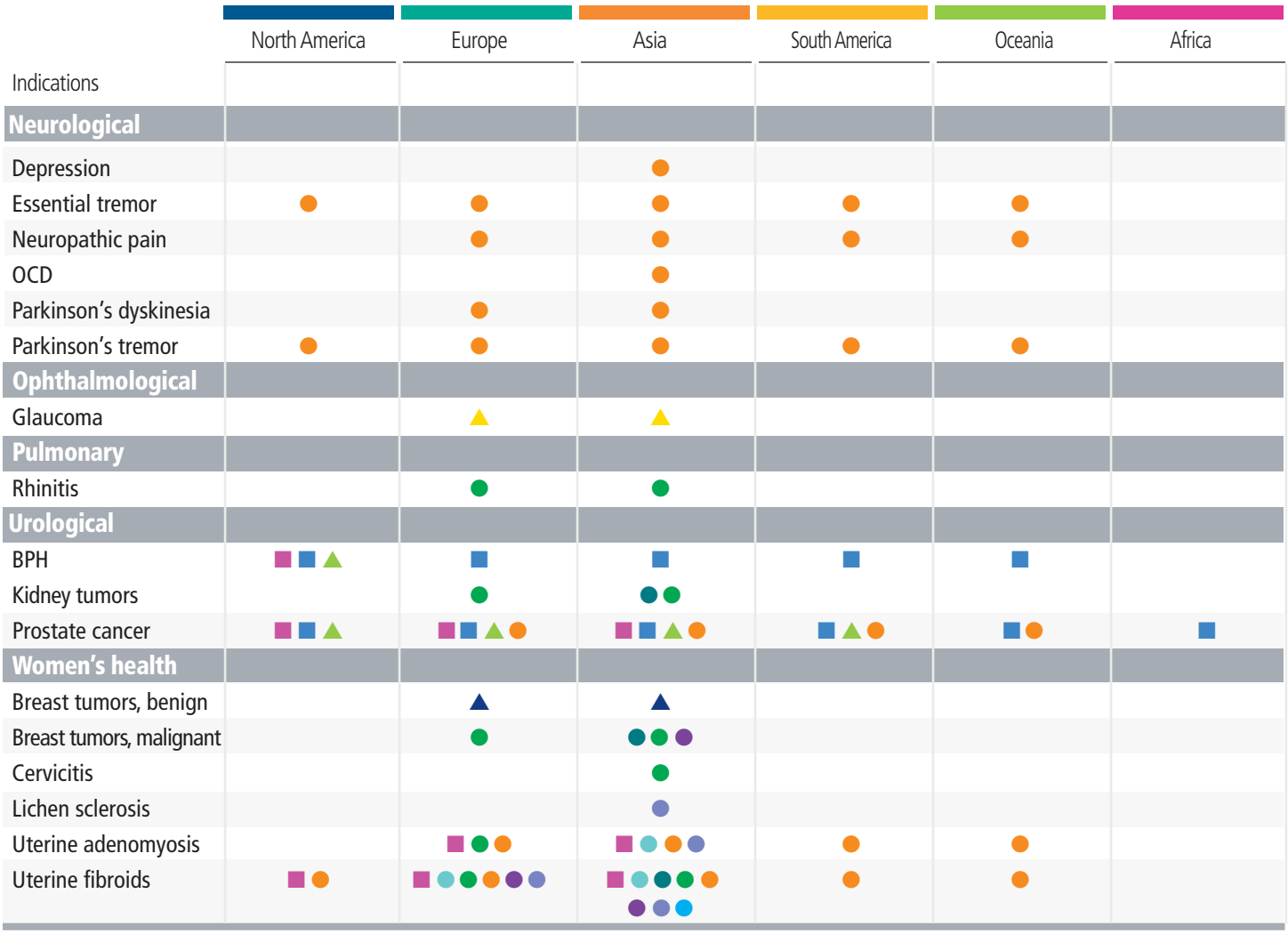
Manufacturers

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

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

FUS Regulatory Approvals by Region and Manufacturer continued



Manufacturers

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

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

North America—FUS Regulatory Approvals by Country and Manufacturer

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

Manufacturers

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

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

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

Europe—FUS Regulatory Approvals by Country and Manufacturer

Indications	Europe CE Marking	Russia Roszdravnadzor	Turkey TITUBB
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*
- Profound Medical, *Canada*
- SonaCare Medical, *US*

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

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- 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*

Europe—FUS Regulatory Approvals by Country and Manufacturer continued

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

Manufacturers

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

Europe
- EDAP TMS, *France*
- EyeTechCare, *France*
- Theraclion, *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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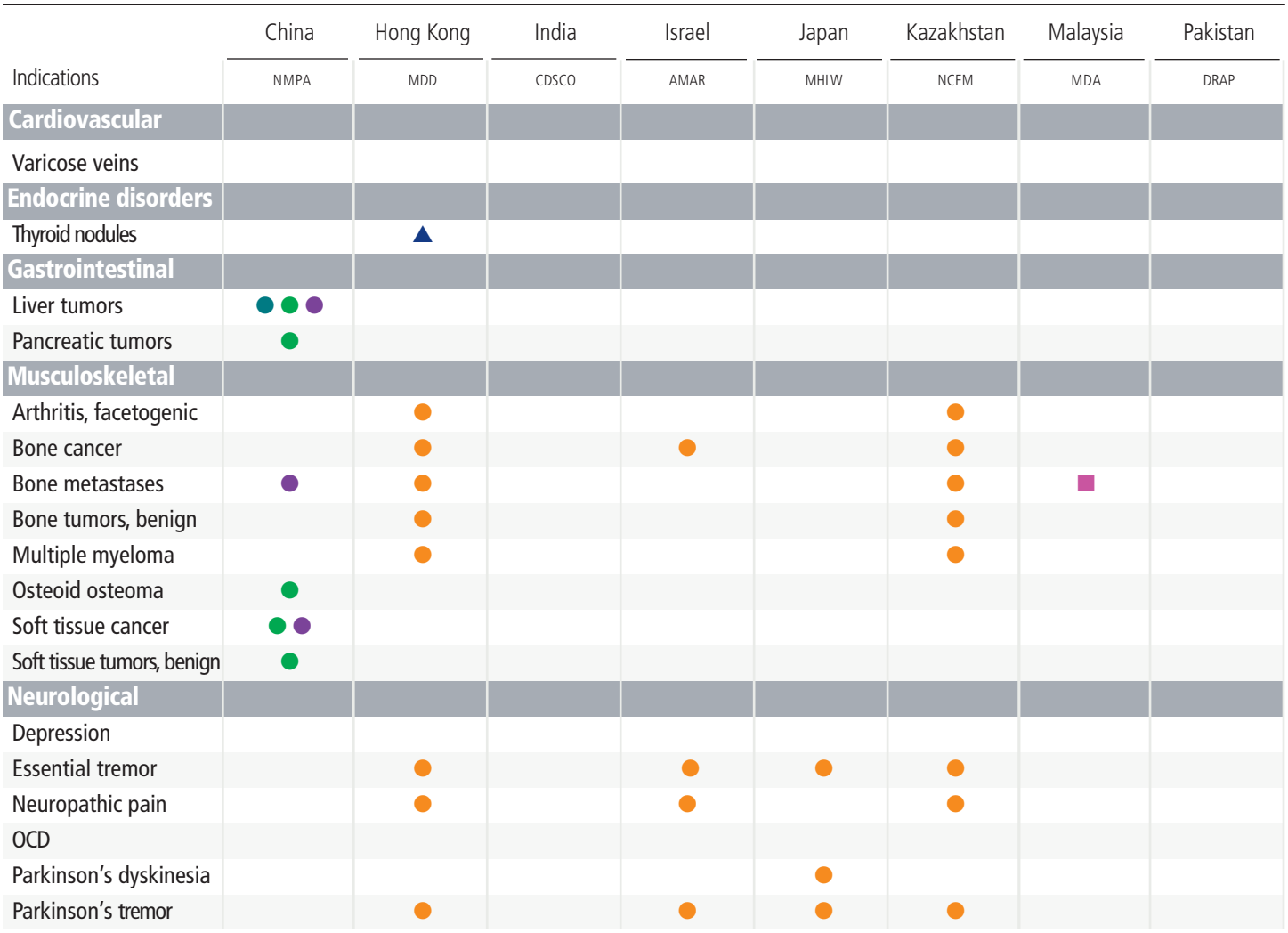
Asia—FUS Regulatory Approvals by Country and Manufacturer



Manufacturers

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

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

Asia—FUS Regulatory Approvals by Country and Manufacturer continued

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

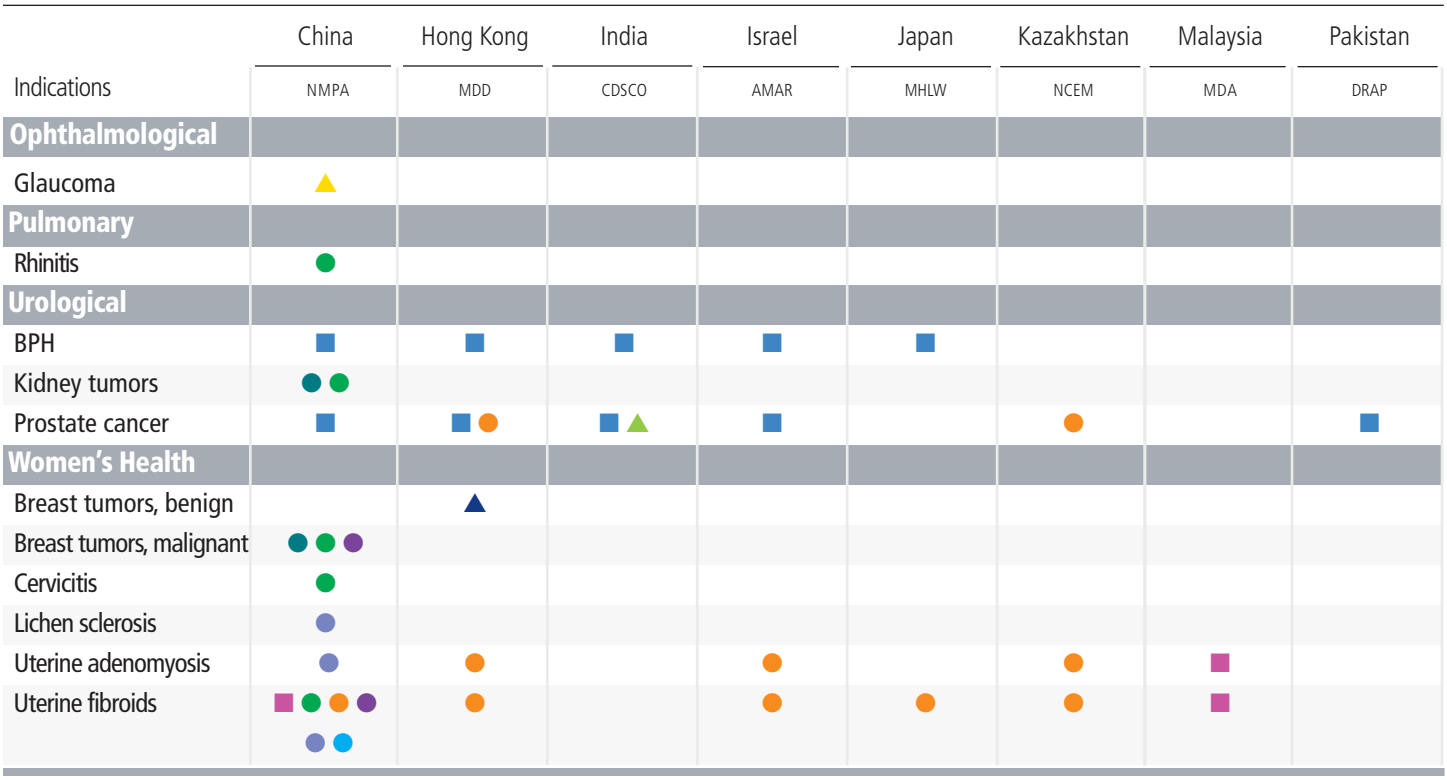
Manufacturers

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

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

Asia—FUS Regulatory Approvals by Country and Manufacturer continued



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*
- Theraclion, *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*

Asia—FUS Regulatory Approvals by Country and Manufacturer continued

Indications	Philippines FDA	Saudi Arabia SFDA	Singapore HSA	South Korea MFDS	Taiwan FDA	Thailand FDA	Vietnam DMEW	
Ophthalmological								
Glaucoma								
Pulmonary								
Rhinitis								
Urological								
BPH				■			■	
Kidney tumors								
Prostate cancer			■	■ ▲	■	●	■	
Women's health								
Breast tumors, benign			▲	▲	▲			
Breast tumors, malignant								
Cervicitis								
Lichen sclerosis								
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*
- Theraclion, *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*

South America—FUS Regulatory Approvals by Country and Manufacturer

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

Manufacturers

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

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

Oceania—FUS Regulatory Approvals by Country and Manufacturer

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

Manufacturers

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

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

Africa—FUS Regulatory Approvals by Region and FUS Manufacturer

	South Africa
Indications	MCC
Urological	
Prostate cancer	■

Manufacturers

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

Europe
- EDAP TMS, *France*
- EyeTechCare, *France*
- Theraclion, *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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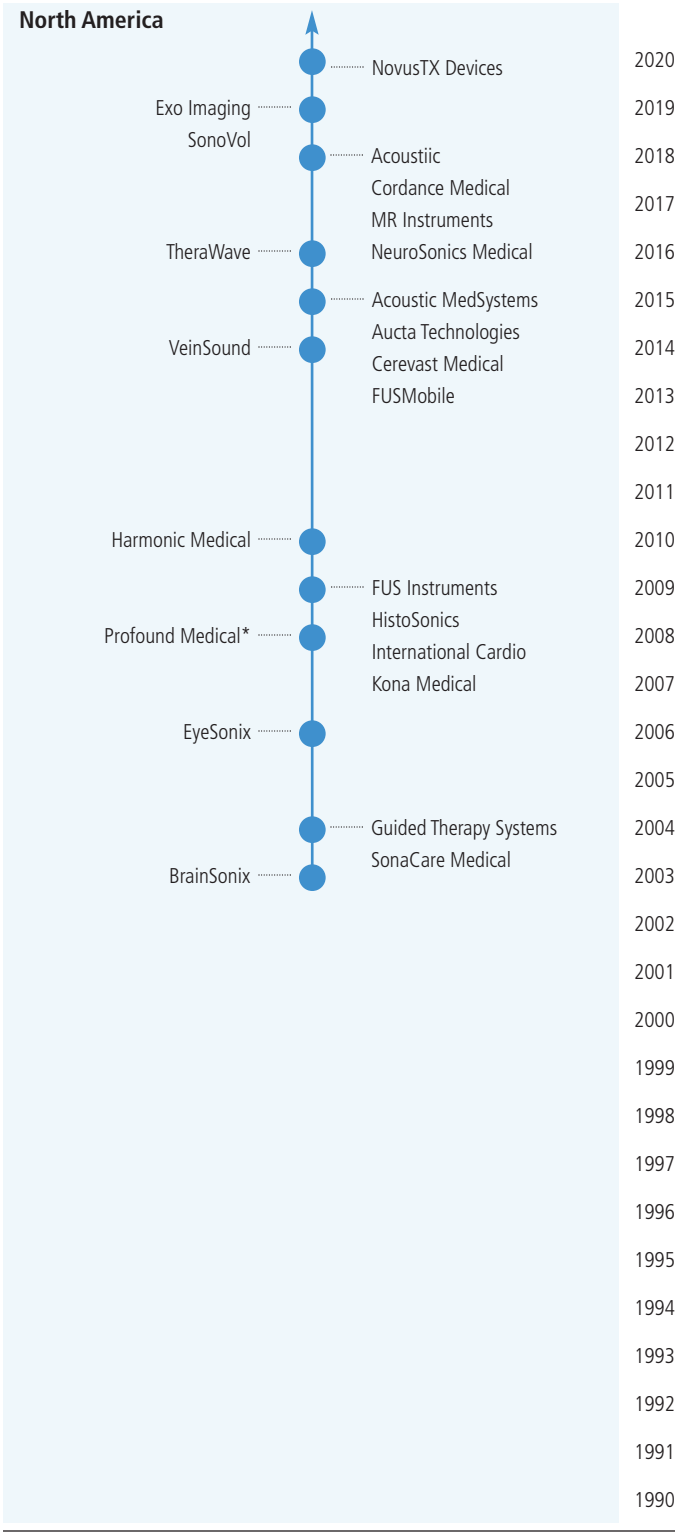
Timeline of Clinical Device Manufacturers by Region

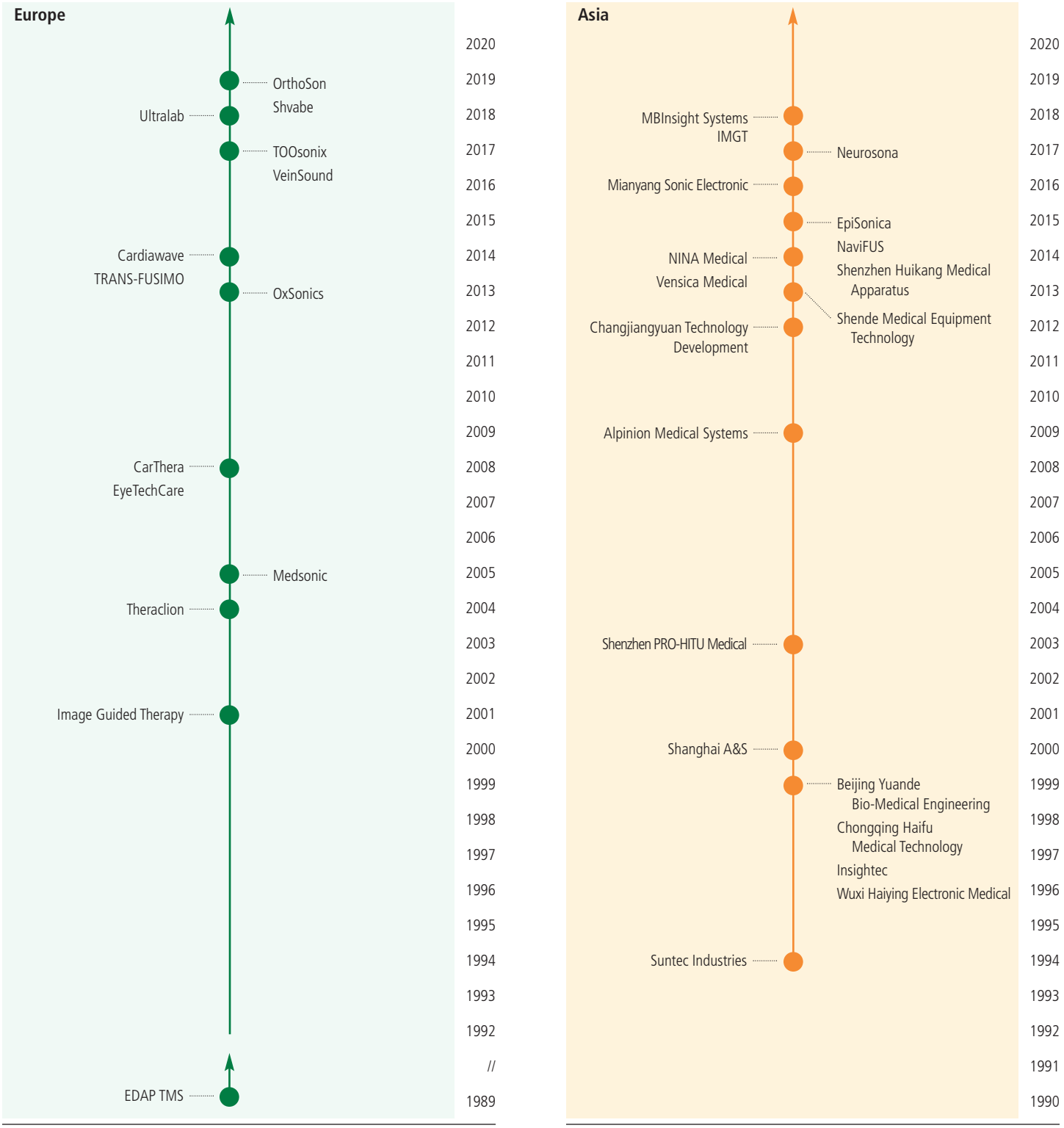
In past State of the Field reports, the company timelines were based upon date of company formation. Last year we transitioned. Instead of the date of incorporation, we are reporting on the year the company became involved in the focused ultrasound industry. For many early-stage focused ultrasound manufacturing companies, this date is one and the same; however, for the OEM manufacturers and/or microbubble companies, this is a difference from previous years.

Please note, 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.62–III.65.

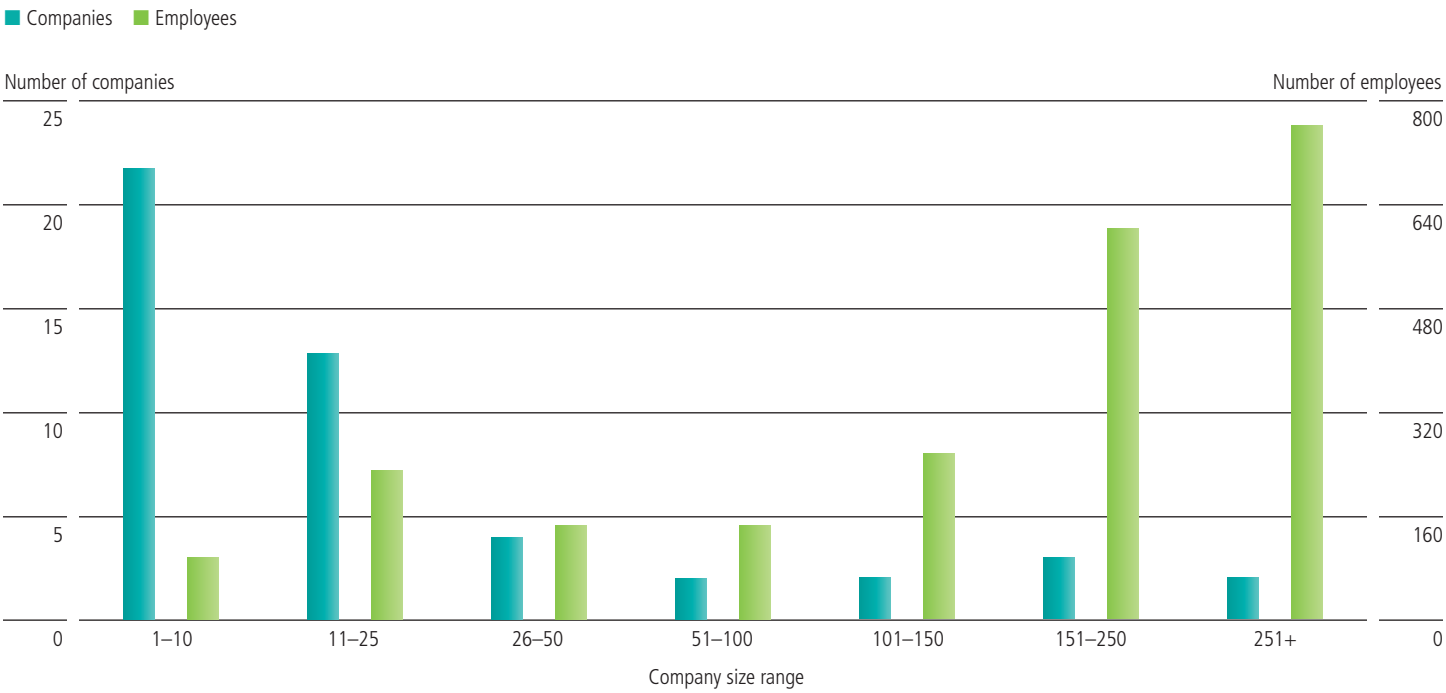


*Profound Medical acquired the HIFU assets of Philips in July, 2017.

Timeline of Clinical Device Manufacturers by Region continued



Numbers Employed by FUS Companies



FUS Company Size

19

employees

is the median company size

10%

of the total workforce is employed by the

32 smallest companies

70%

of companies have

25 or fewer employees

47%

of the total workforce is employed by the

6 largest companies

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

FUS Devices in Use

2020 Growth

703 Devices, 1 January 2020 + (103 Added* − 26 Decommissioned) = **780** Devices, 31 December 2020

* May include replacement units

2020 Growth Rate

11%

FUS Industry by Region

Clinical Device Manufacturers

North America

23

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

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

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

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

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

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

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

FUS Mobile INC | Alpharetta, Georgia, United Sates, www.fusmobile.com

● Guided Therapy Systems LLC | Scottsdale, 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

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

NeuroSonics Medical INC | Baltimore, Maryland, United States

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

● Profound Medical CORP | Mississauga, Ontario, Canada, 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 Sates

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

FUS Industry by Region continued

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, eyetechcare.com

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

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

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

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

Shvabe OJSC Holding | Moscow, Russian Federation, shvabe.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. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

FUS Industry by Region continued

Clinical Device Manufacturers

Asia

19

- 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.cjykj.com
- Chongqing Haifu Medical Technology CO LTD | Chongqing, China, www.haifumedical.com
- EpiSonica CORP | Hsinchu, Taiwan, www.episonica.com

IMGT CO LTD | Seongnam, South Korea, www.nanoimgt.com

- Insightec LTD | Tirat Carmel, Israel, www.insightec.com

MBInsight Systems INC | Taiwan

Mianyang Sonic Electronic LTD | Mianyang City, China, www.ultrasound.cn

NaviFUS CORP | New Taipei City, Taiwan, www.navi-fus.com

Neurosona CO LTD | Seoul, South Korea | www.neurosona.com

NINA Medical LTD | Israel | ninamed.com

- Shanghai A&S Science Technology Development CO LTD | Shanghai, China, www.aishen.com.cn
- Shende Medical Equipment Technology CO LTD | Shanghai, China, shendehc.com

Shenzhen Huikang Medical Apparatus CO LTD | Shenzhen, China, www.eswl.cn

- Shenzhen PRO-HITU Medical Technology CO LTD | Shenzhen, China, pro-hifu.com

Suntec Industries CO LTD | Shanghai, China

Vensica Medical | Misgav, Israel, vensica.com

- Wuxi Haiying Electronic Medical Systems CO LTD | Wuxi, China, www.haiyingmedical.com.cn

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

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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, malignant Uterine fibroids
Devices	Alpius 900 VIFU2000
Treatment guidance	Ultrasound

Beijing Yuande Bio-Medical Engineering CO LTD

Regulatory approvals	Breast tumors, malignant, 1999 Kidney tumors, 1999 Liver tumors, 1999 Pancreatic tumors, 2007 Uterine fibroids, 2007
Commercial treatments	Bone metastases Breast tumors, malignant Kidney tumors Liver tumors Pancreatic tumors Prostate cancer Soft tissue tumors, benign Uterine fibroids
Device	FEP-BY02
Treatment guidance	Ultrasound

Companies in this section currently have regulatory approval in at least one global region. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

Chongqing Haifu Medical Technology CO LTD

Regulatory approvals	Breast tumors, malignant, 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, 1999
Commercial treatments	Bone metastases Breast tumors, benign Breast tumors, malignant Cervicitis Desmoid tumors Kidney tumors Liver metastases Liver tumors Osteoid osteoma Pancreatic tumors Pancreatic tumors, malignant Soft tissue tumors, benign Uterine adenomyosis Uterine fibroids
Clinical research	Breast tumors, malignant Kidney tumors Liver tumors Osteoid osteoma Pancreatic tumors Retained placenta Rhinitis Sacral chordoma Soft tissue cancer Soft tissue tumors, benign Uterine adenomyosis Uterine fibroids
Devices	CZB CZF CZG300 JC JC200 JC200D JC300
Treatment guidance	Ultrasound

Clinical Device Manufacturers with Regulatory Approvals continued

EDAP TMS SA

Regulatory approvals	Benign prostatic hyperplasia, 2015 Prostate cancer, 2002
Commercial treatments	Benign prostatic hyperplasia Prostate cancer
Clinical research	Endometriosis Liver metastases Prostate cancer
Devices	Ablatherm EDAP Prototype Focal One
Treatment guidance	Image fusion
Planning guidance	MR, Ultrasound, Biopsies

EpiSonica CORP

Regulatory approvals	Soft tissue cancer, 2016
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

Companies in this section currently have regulatory approval in at least one global region. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

Insightec LTD

Regulatory approvals	Arthritis, facetogenic, 2006 Bone cancer, 2006 Bone metastases, 2006 Bone tumors, benign, 2006 Depression, 2015 Essential tremor, 2012 Multiple myeloma, 2006 Neuropathic pain, 2012 Obsessive-compulsive disorder, 2015 Parkinson's disease, dyskinesia, 2015 Parkinson's disease, tremor, 2012
Commercial treatments	Arteriovenous malformations Arthritis, facetogenic Astrocytoma Bone cancer Bone metastases Breast tumors, malignant Depression Desmoid tumors Dystonia Dystonia, hand Epilepsy Essential tremor Neuropathic pain Neuropathy Obsessive-compulsive disorder Osteoid osteoma
Clinical research	Alzheimer's disease Arthritis, facetogenic Arthritis, knee Astrocytoma Bone cancer Bone metastases Bone tumors, benign Brain metastases, breast cancer Dementia Depression Desmoid tumors Dystonia Dystonia, hand Endometriosis Epilepsy Essential tremor Glioblastoma
Devices	Exablate Body System Exablate Neuro Exablate Prostate
Treatment guidance	MR
Planning guidance	MR MR/CT Fusion

Clinical Device Manufacturers with Regulatory Approvals continued

Kona Medical INC

Regulatory approvals	Hypertension, 2016
Clinical research	Hypertension
Device	Surround Sound Prototype
Treatment guidance	Ultrasound

Profound Medical CORP

Regulatory approvals	Benign prostatic hyperplasia, 2019 Bone metastases, 2010 Osteoid osteoma, 2020 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	Arthritis, sacroiliac Benign prostatic hyperplasia Bone cancer Bone metastases Bone tumors, benign Breast tumors, malignant Desmoid tumors Head & neck tumors Neuroblastoma Osteoid osteoma Pancreatic tumors Plantar fasciitis Prostate cancer Soft tissue cancer
Devices	Sonalleve TULSA-PRO
Treatment guidance	MR
Planning guidance	MR

Shanghai A&S Science Technology Development CO LTD

Regulatory approvals	Bone metastases, 2002 Breast tumors, malignant, 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
Clinical research	Liver tumors
Device	HIFUNIT9000
Treatment guidance	Ultrasound

Shenzhen PRO-HITU Medical Tech CO LTD

Regulatory approvals	Lichen sclerosis, 2019 Uterine adenomyosis. 2012 Uterine fibroids, 2012
Commercial treatments	Pancreatic tumors Uterine adenomyosis Uterine fibroids
Clinical research	Uterine adenomyosis Uterine fibroids
Devices	PRO2008 PRO300 PRO3008 PRO5G
Treatment guidance	Ultrasound
Planning guidance	Ultrasound Visual Guidance

Companies in this section currently have regulatory approval in at least one global region. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

Clinical Device Manufacturers with Regulatory Approvals continued

SonaCare Medical LLC

Regulatory approvals	Benign prostatic hyperplasia, 2001 Prostate cancer, 2005
Commercial treatments	Benign prostatic hyperplasia Peripheral artery disease Prostate cancer
Clinical research	Cervical tumors Colorectal tumors Endometrial tumors Ovarian tumors Prostate cancer Vaginal tumors
Devices	Sonablate Sonatherm
Treatment guidance	Ultrasound
Planning guidance	MR/US Fusion Ultrasound

Theraclion SA

Regulatory approvals	Breast tumors, benign, 2012 Thyroid nodules, 2007 Varicose veins, 2019
Commercial treatments	Breast tumors, benign Breast tumors, malignant Thyroid nodules Varicose veins
Clinical research	Breast tumors, benign Breast tumors, malignant Esophageal tumors Gastric tumors Graves' disease Head & neck tumors Melanoma 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
Device	HY2900
Treatment guidance	Ultrasound

Companies in this section currently have regulatory approval in at least one global region. To see a detailed breakdown of regional and country approvals, see charts starting on p.III.36.

FUS Devices with Treatment and Planning Guidance

NEW

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
North America				
Acoustic MedSystems	TheraVision	–	–	
Acoustiic	AcuFUSS	MR guidance	–	
Aucta Technologies	DECIMA	Unguided	–	
BrainSonix	BrainSonix (prototype)	MR guidance	–	
	BXPulsar 1001 LIFUP	MR guidance	–	
	BXPulsar 1002 LIFUP	MR guidance	–	
Cerevast Medical	Aureva Pulse	US guidance	–	
	Neuros	Unguided	–	
	Reflow RVO	US guidance	–	
Exo Imaging	Performance Ultrasound Platform	–	–	
EyeSonix	TUG - Therapeutic Ultrasound for Glaucoma	Unguided	–	
FUS Instruments	DS-50	–	–	
	LP-100	MR guidance	–	
	RK-100	–	–	
	RK-20	Other guidance	–	
	RK-300	MR guidance	–	
	RK-50	Other guidance	–	
FUSMobile	Neurolyser	Other guidance	Not used	
Guided Therapy Systems	Actisound	US guidance	–	●
Harmonic Medical	Symphony	US & MR guidance	–	
HistoSonics	Edison	US guidance	US guidance	
	RAST - Robot Assisted Sonic Therapy System	US guidance	–	
International Cardio	HIFU Synthesizer	US guidance	–	
Kona Medical	Surround Sound (prototype)	US guidance	–	●
MR Instruments	DuoFLEX ACCESS Coil	MR guidance	MR guidance	
	MR-guided TRUST (Transcranial Ultrasound Stimulation)	MR guidance	MR guidance	
NeuroSonics Medical	NeuroSonics (prototype)	US guidance	–	
Profound Medical	Sonalleve	MR guidance	MR guidance	●
	TULSA-PRO	MR guidance	MR guidance	●

FUS Devices with Treatment and Planning Guidance continued

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
North America continued				
SonaCare Medical	Sonablate	US guidance	MR/US fusion	●
	Sonatherm	US guidance	US guidance	●
TheraWave	Ultranav (prototype)	Image fusion	Neuronavigation	
VeinSound, Inc.	Veinotriptor	US guidance	–	
	VeinSound (prototype)	US guidance	–	
Europe				
Cardiawave	Cardiawave (prototype)	US guidance	US guidance	
	Valvopulse	US guidance	US guidance	
	Valvosoft	US guidance	US guidance	
CarThera	SonoCloud	Unguided	Not used	
	SonoCloud 9	Unguided	Not used	
	SonoProbe	MR guidance	MR guidance	
EDAP TMS	Ablatherm	Image fusion	US guidance	●
	EDAP (prototype)	US guidance	US guidance	
	Focal One	Image fusion	MR & US guidance, Biopsies	●
EyeTechCare	EyeOP1	Unguided	–	●
Image Guided Therapy	3Bop	Stereotactic frame	–	
	LabFUS	MR guidance	–	
	TargetedFUS	MR guidance	–	
Medsonic	Bone phantoms	MR guidance	–	
	MR-Compatible Transducers	MR guidance	–	
	Robotic Systems	MR guidance	–	
	Shinsei motor electronic system	MR guidance	–	
	Skull phantoms	MR guidance	–	
OxSonics	SonoTran System	US guidance	US guidance	
Theraclion	Echopulse	US guidance	–	●
	SONOVEIN	US guidance	–	●
TOOsonix	System ONE-M	Image fusion	Visual guidance	●
	System ONE-R	Image fusion	Visual guidance	
TRANS-FUSIMO	TransFUSIMO Treatment System	MR guidance	MR guidance	

FUS Devices with Treatment and Planning Guidance continued

Manufacturer	Device	Treatment guidance	Planning guidance	Approval
Asia				
Alpinion Medical Systems	Alpius 900	US guidance	–	●
	VIFU2000	US guidance	–	
Beijing Yuande Bio-Medical Engineering	FEP-BY02	US guidance	–	●
Changjiangyuan Technology Development	NUTAS – Non-invasive Ultrasound Tumor Ablation System	US guidance	US guidance	●
	SUPER Knife-Focused Beam Therapy System	MR & US guidance	–	
Chongqing Haifu Medical Technology	CZB	US guidance	–	●
	CZF	US guidance	–	●
	CZG300	US guidance	–	
	JC	US guidance	–	●
	JC200	US guidance	–	●
	JC200D	US guidance	–	
	JC300	US guidance	–	
EpiSonica	ArcBLATE (ARC-100M)	MR guidance	MR guidance	●
IMGT	IMD10	US guidance	US Guidance	
Insightec	Exablate MRgFUS	MR guidance	MR guidance	●
	Exablate Neuro	MR guidance	MR/CT fusion	●
	Exablate Prostate	MR guidance	MR guidance	●
Mianyang Sonic Electronic	CZ901	US guidance	–	
NaviFUS	NaviFUS System (prototype)	Neuronavigation	–	
	NaviFUS System 101	Neuronavigation	MR/CT fusion	
Neurosona	Neurosona NS-US100	Other guidance	–	
NINA Medical	NINA	US guidance	US guidance	
Shanghai A&S	HIFUNIT9000	US guidance	–	●
Shende Medical Equipment Technology	Aceso	MR guidance	–	●
Shenzhen Huikang Medical Apparatus	HIFU 2001	US guidance	–	
Shenzhen PRO-HITU Medical	PRO2008	US guidance	US guidance	●
	PRO300	US guidance	US guidance	●
	PRO3008	US guidance	US guidance	
	PRO5G	Other guidance	Visual guidance	●
Suntec Industries	Suntec System	US guidance	–	
Vensica Medical	Vensica (prototype)	US guidance	–	
Wuxi Haiying Electronic Medical	HY2900	US guidance	–	

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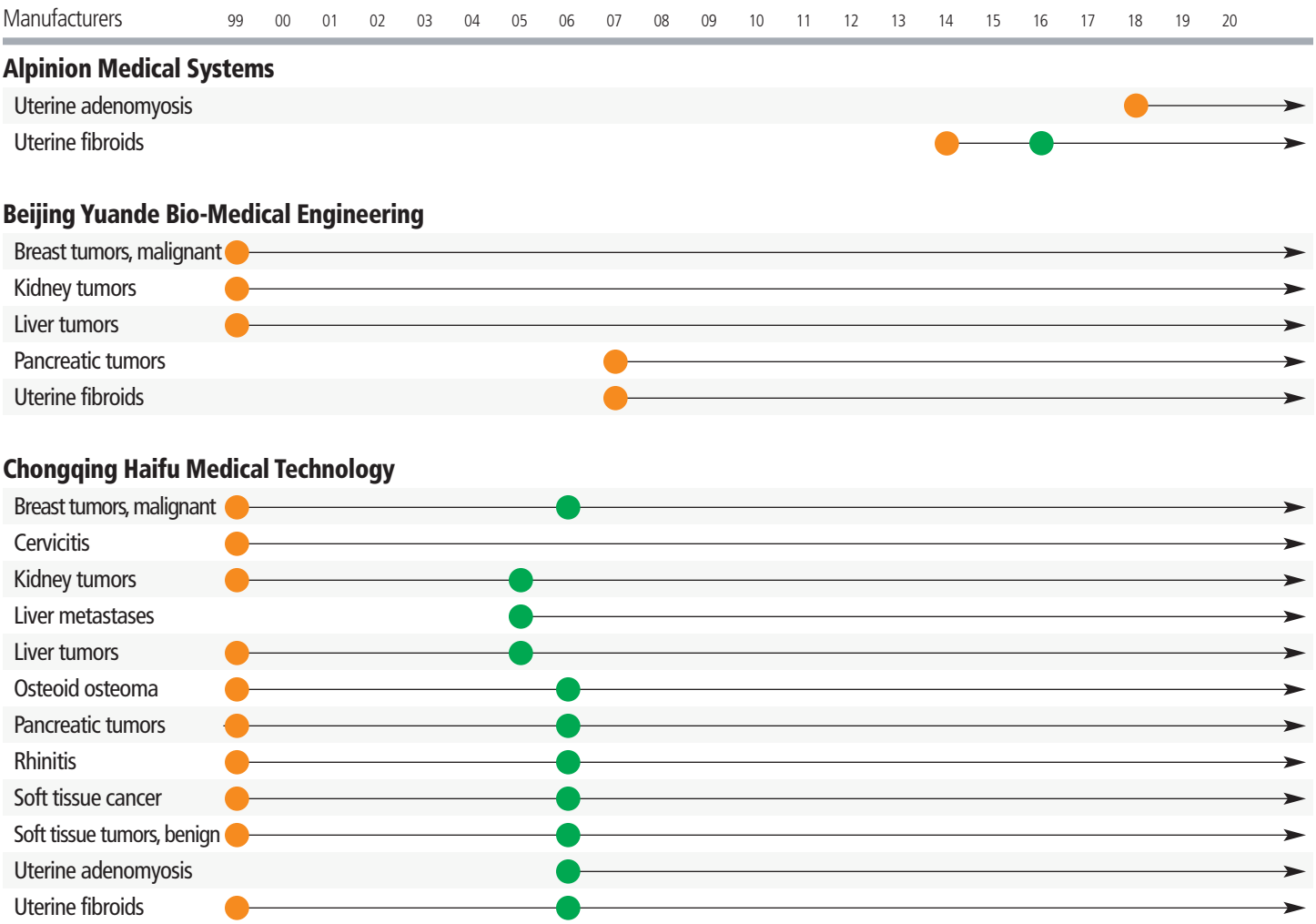
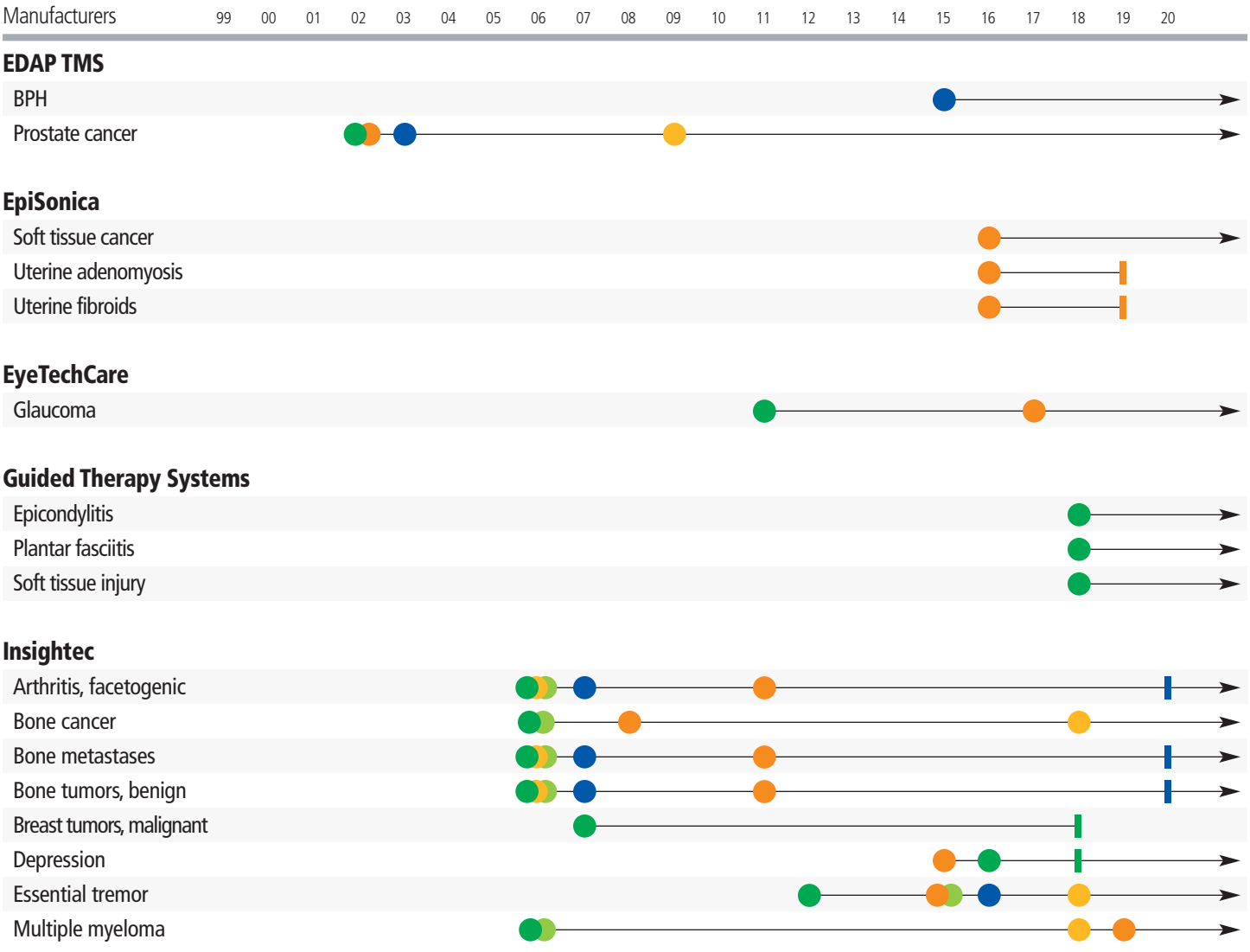
First Global Regulatory Approvals for Companies by Indication



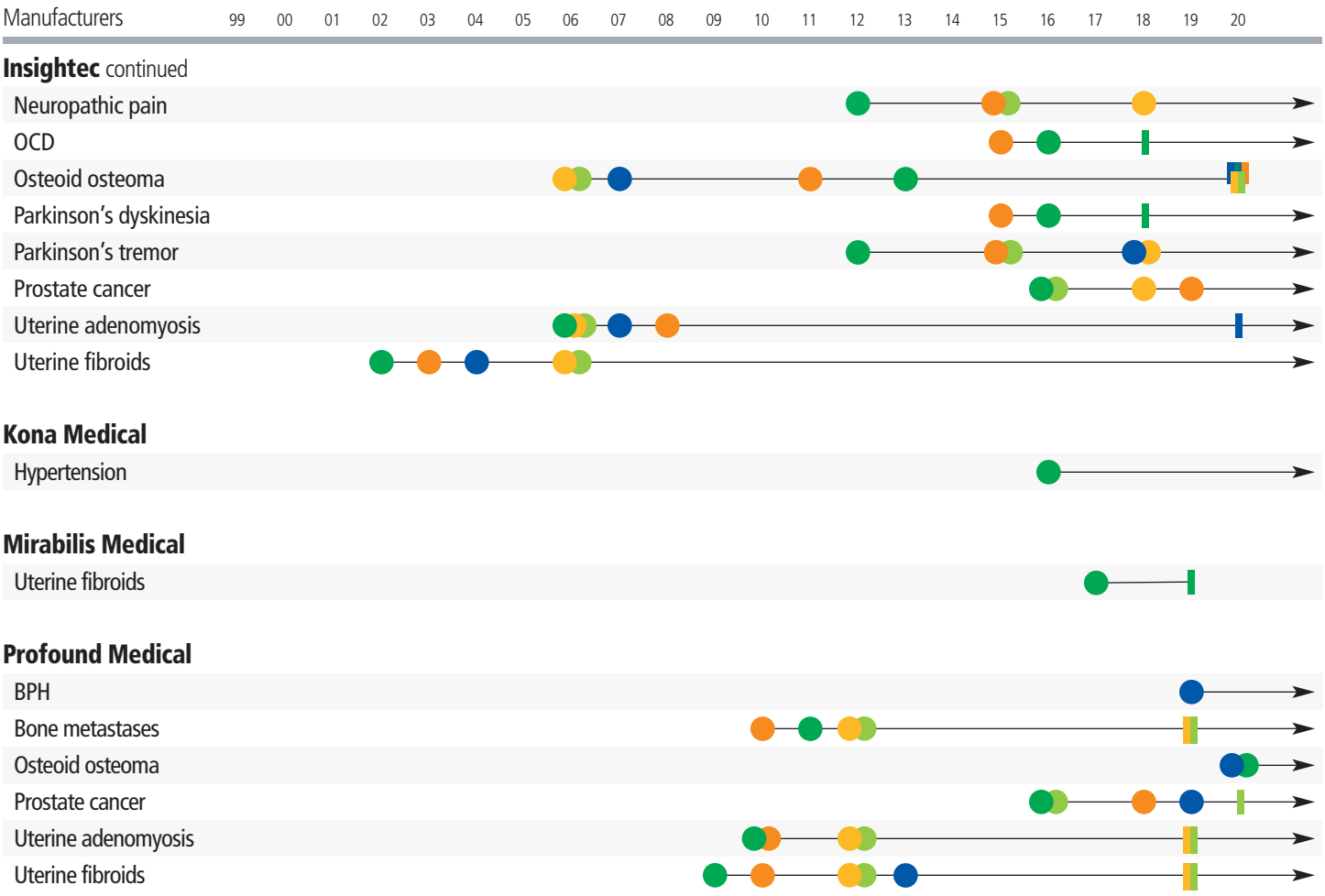
Approval
- Approval begin date
- Approval end date

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

First Global Regulatory Approvals for Companies by Indication continued



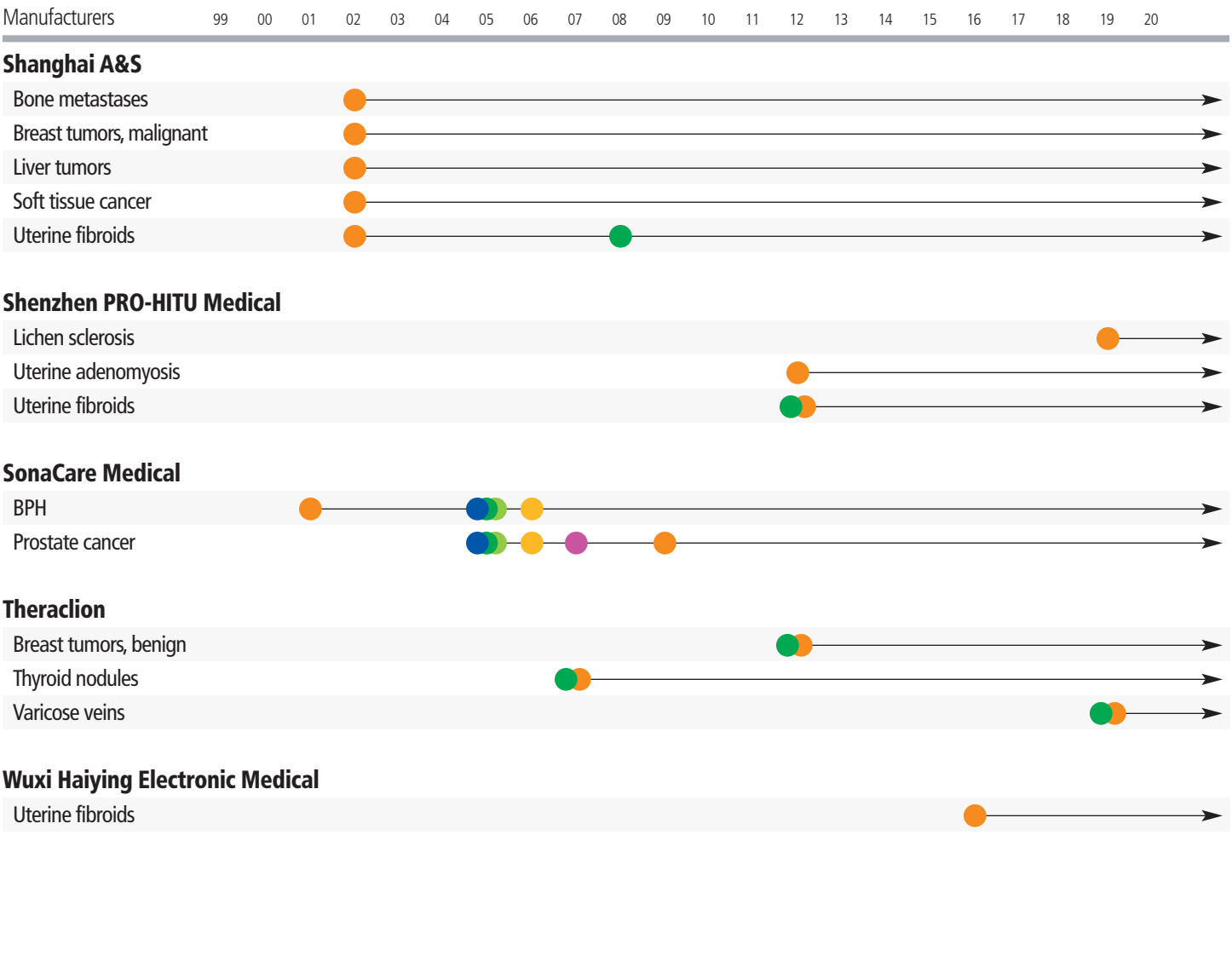
First Global Regulatory Approvals for Companies by Indication continued



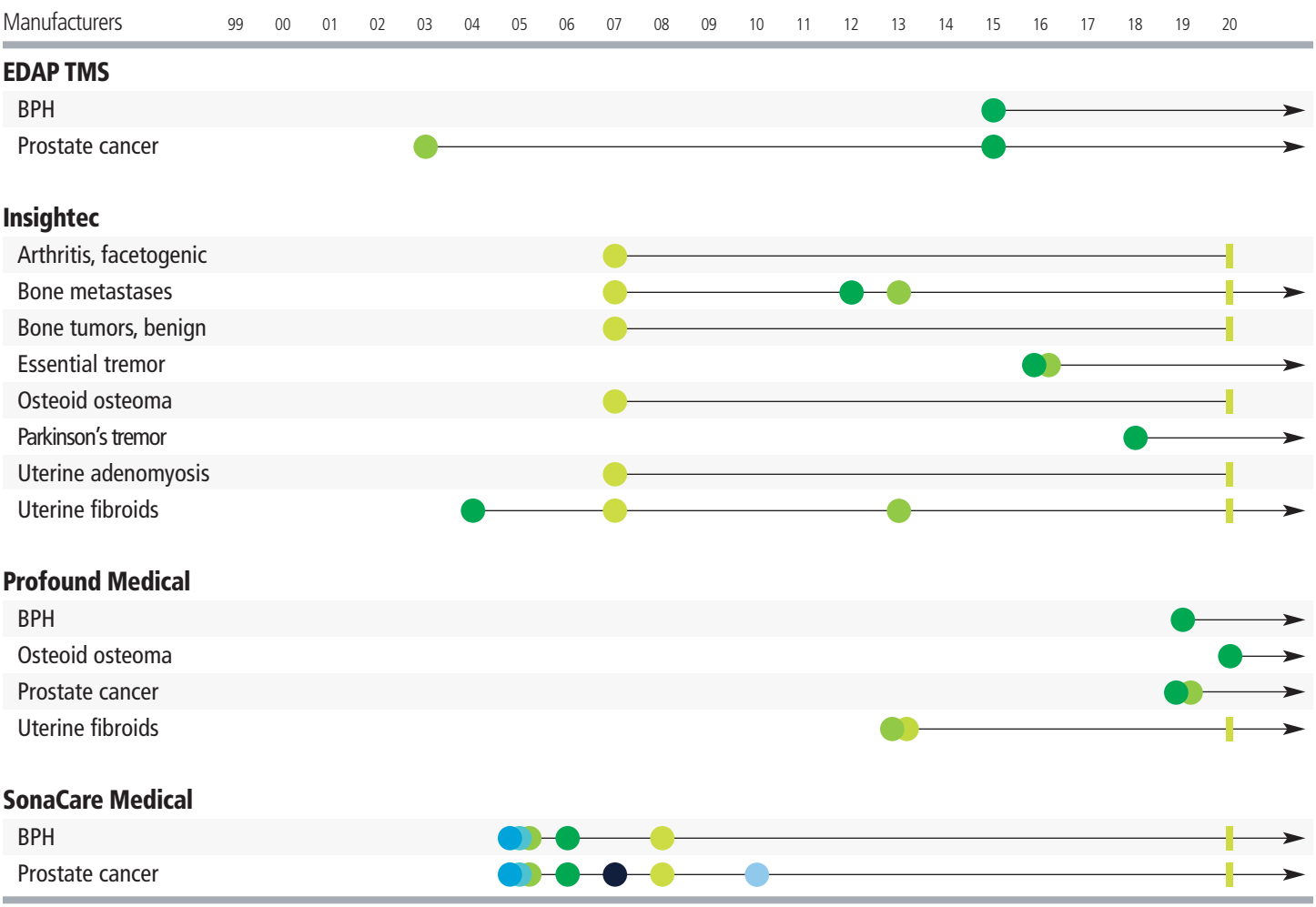
Approval
- Approval begin date
- Approval end date

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

First Global Regulatory Approvals for Companies by Indication continued



North America—FUS Regulatory Approvals by Company and Indication



Approval
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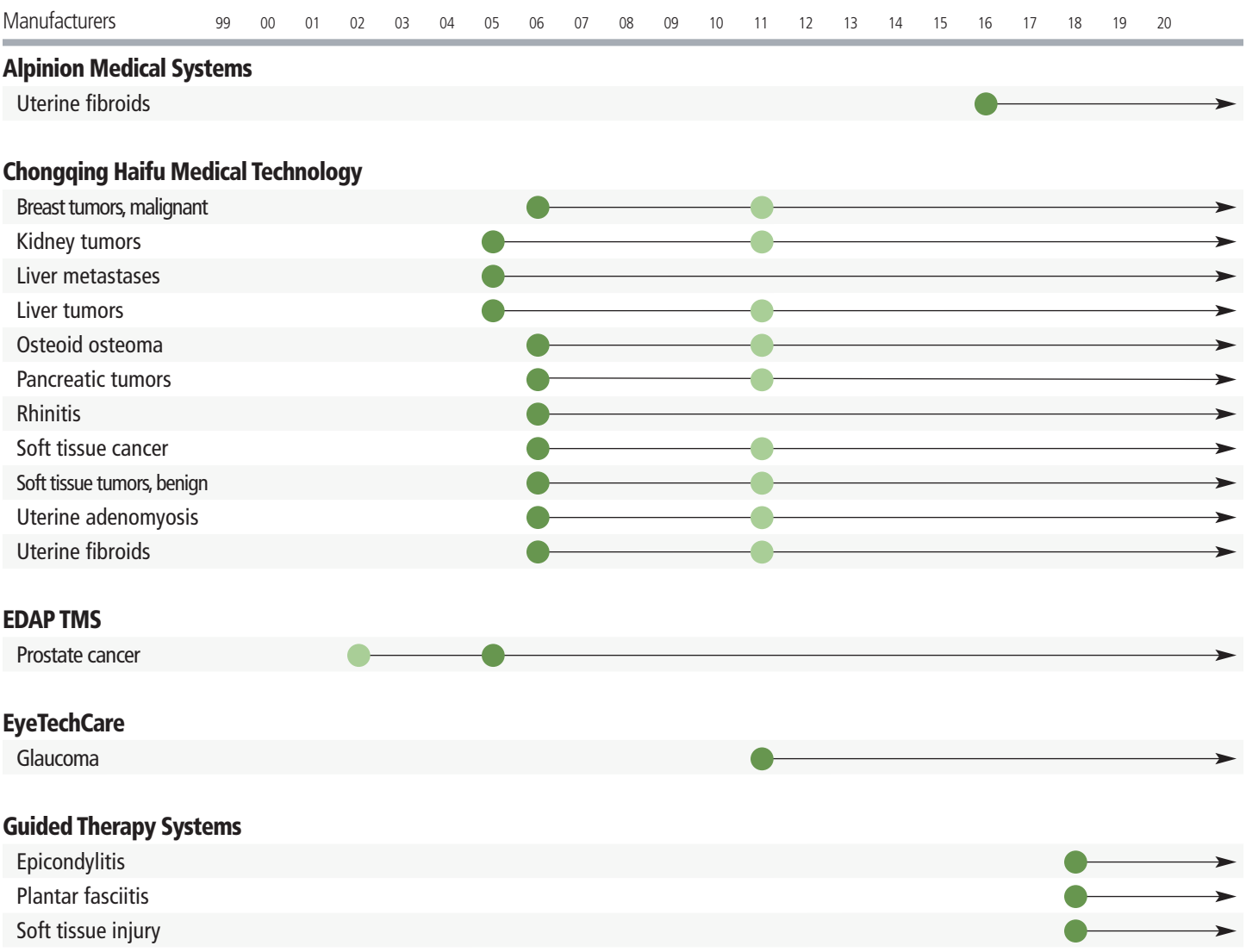
- Approval end date

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

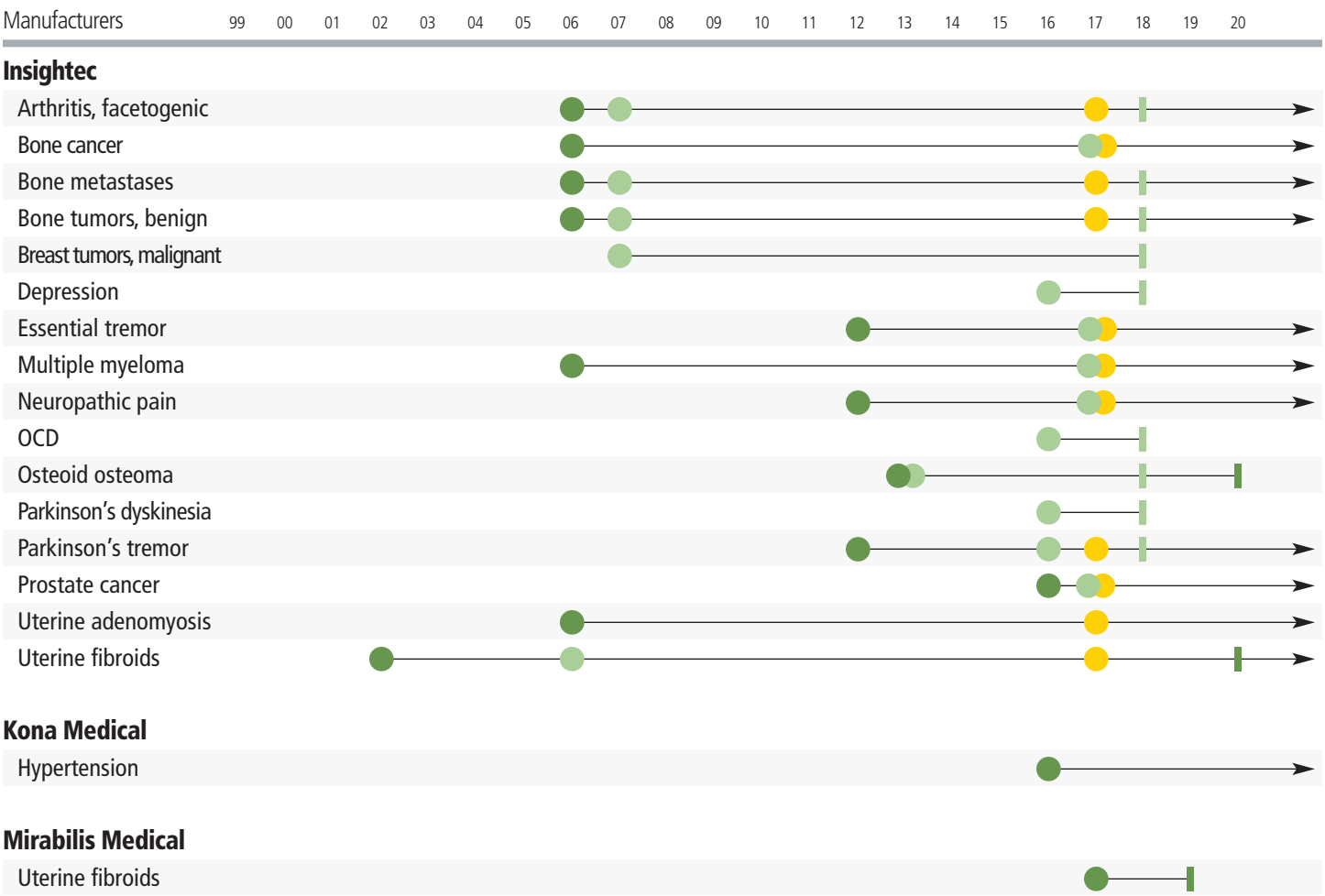
Europe—FUS Regulatory Approvals by Company and Indication



Approval
- Approval begin date
- Approval end date

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

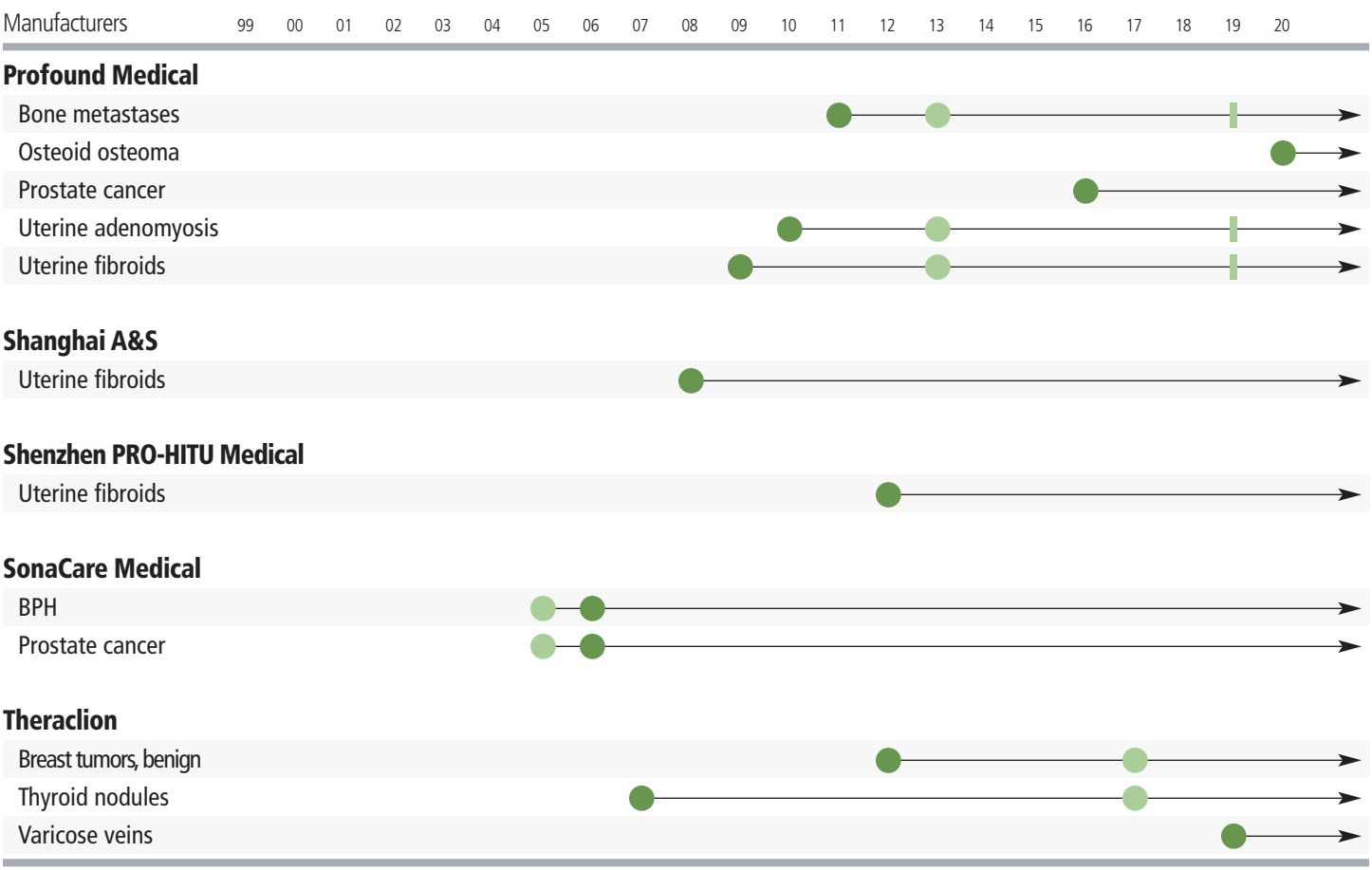
Europe—FUS Regulatory Approvals by Company and Indication continued



Approval
- Approval begin date
- Approval end date

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

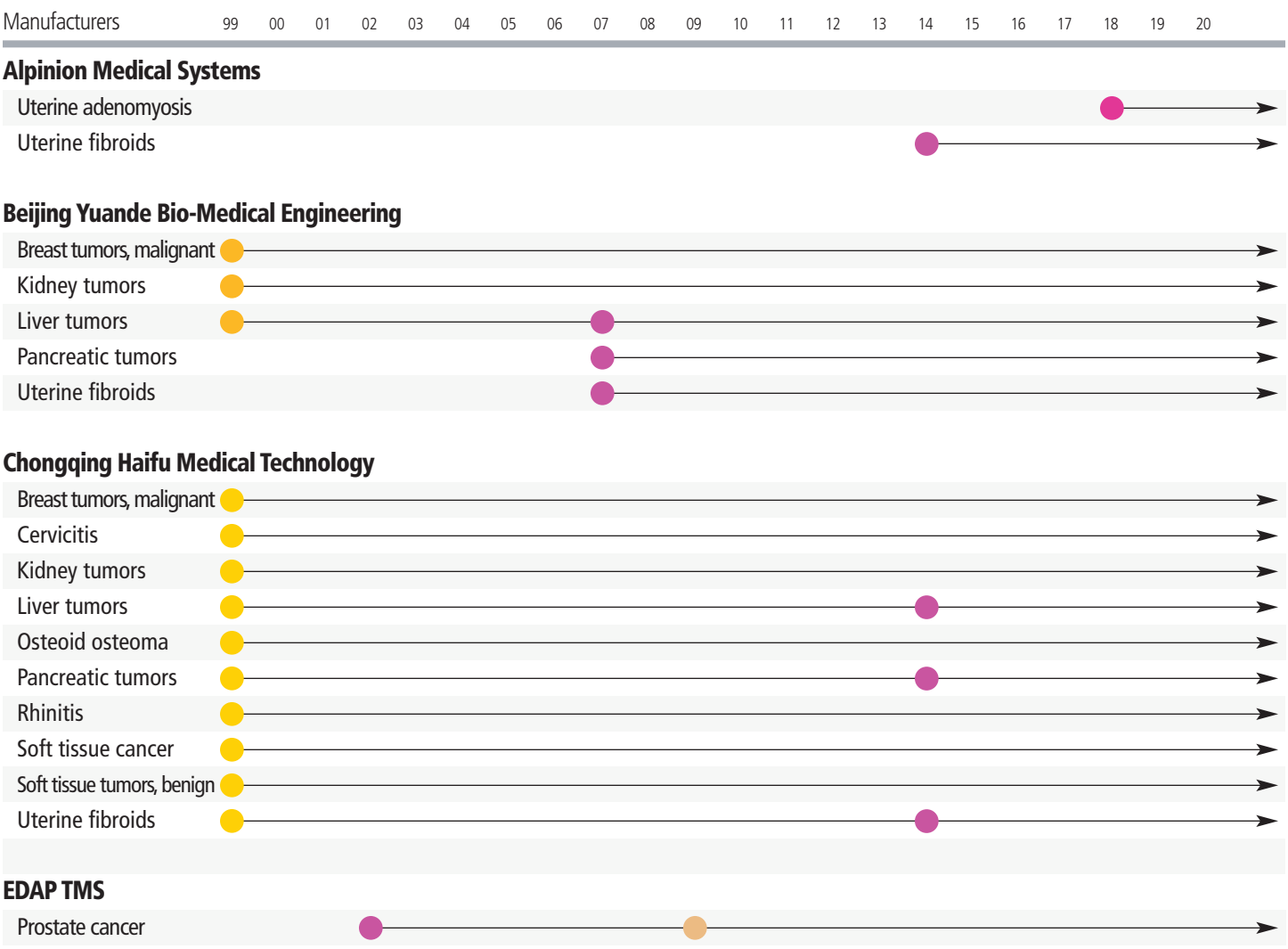
Europe—FUS Regulatory Approvals by Company and Indication continued



Approval
- Approval begin date
- Approval end date

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

Asia—FUS Regulatory Approvals by Company and Indication



Approval
- Approval begin date
- Approval end date

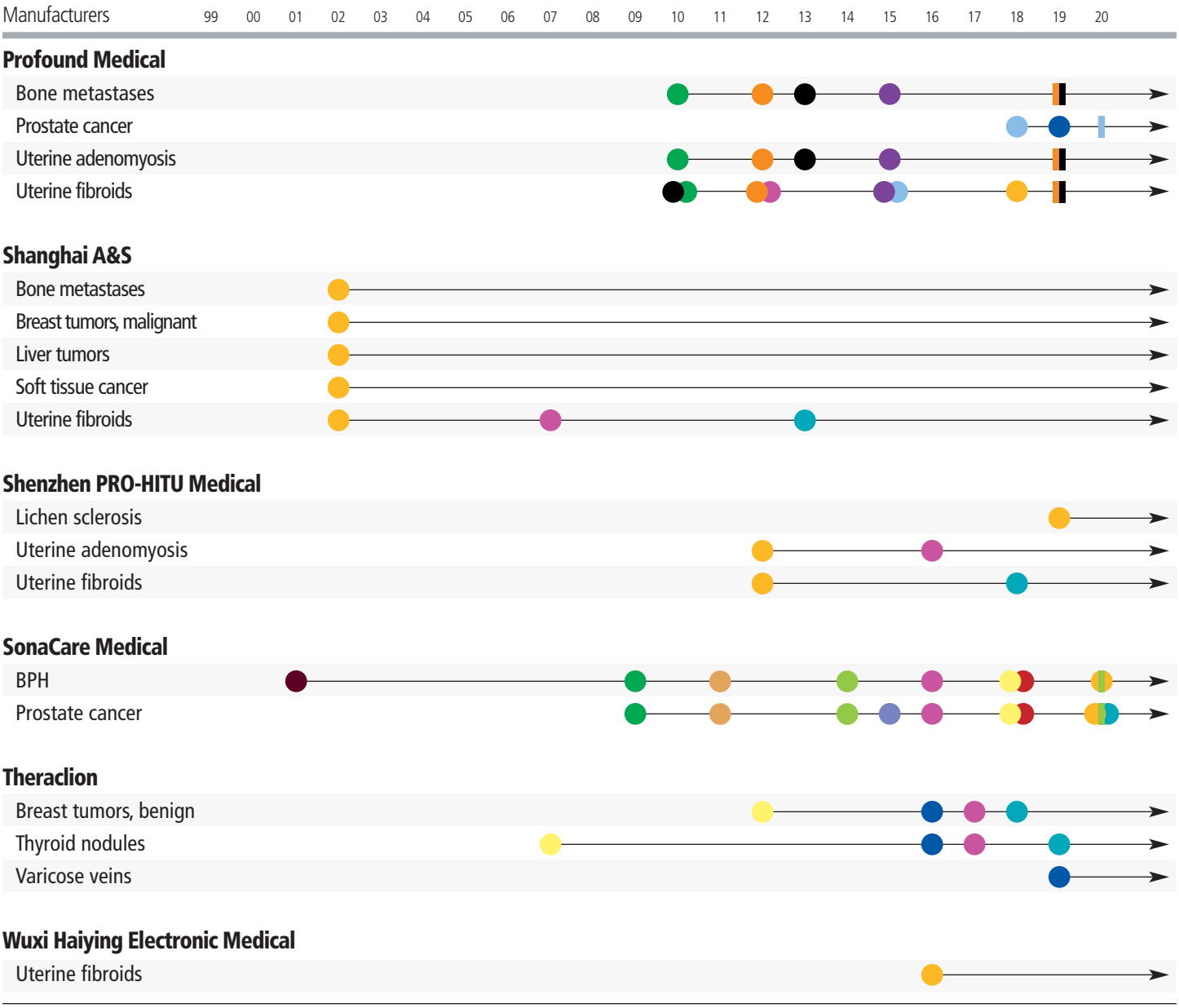
Asia
- China, *NMPA*
- Hong Kong, *MDD*
- India, *CDSCO*
- Indonesia, *DGPMD*
- Israel, *AMAR*
- Japan, *MHLW*
- Kazakhstan, *NCEM*
- Malaysia, *MDA*
- Pakistan, *DRAP*
- Philippines, *FDA*
- Saudi Arabia, *SFDA*
- Singapore, *HSA*
- South Korea, *MFDS*
- Taiwan, *FDA*
- Thailand, *FDA*
- Uzbekistan, *GDQC*
- Vietnam, *DMEW*

Asia—FUS Regulatory Approvals by Company and Indication continued

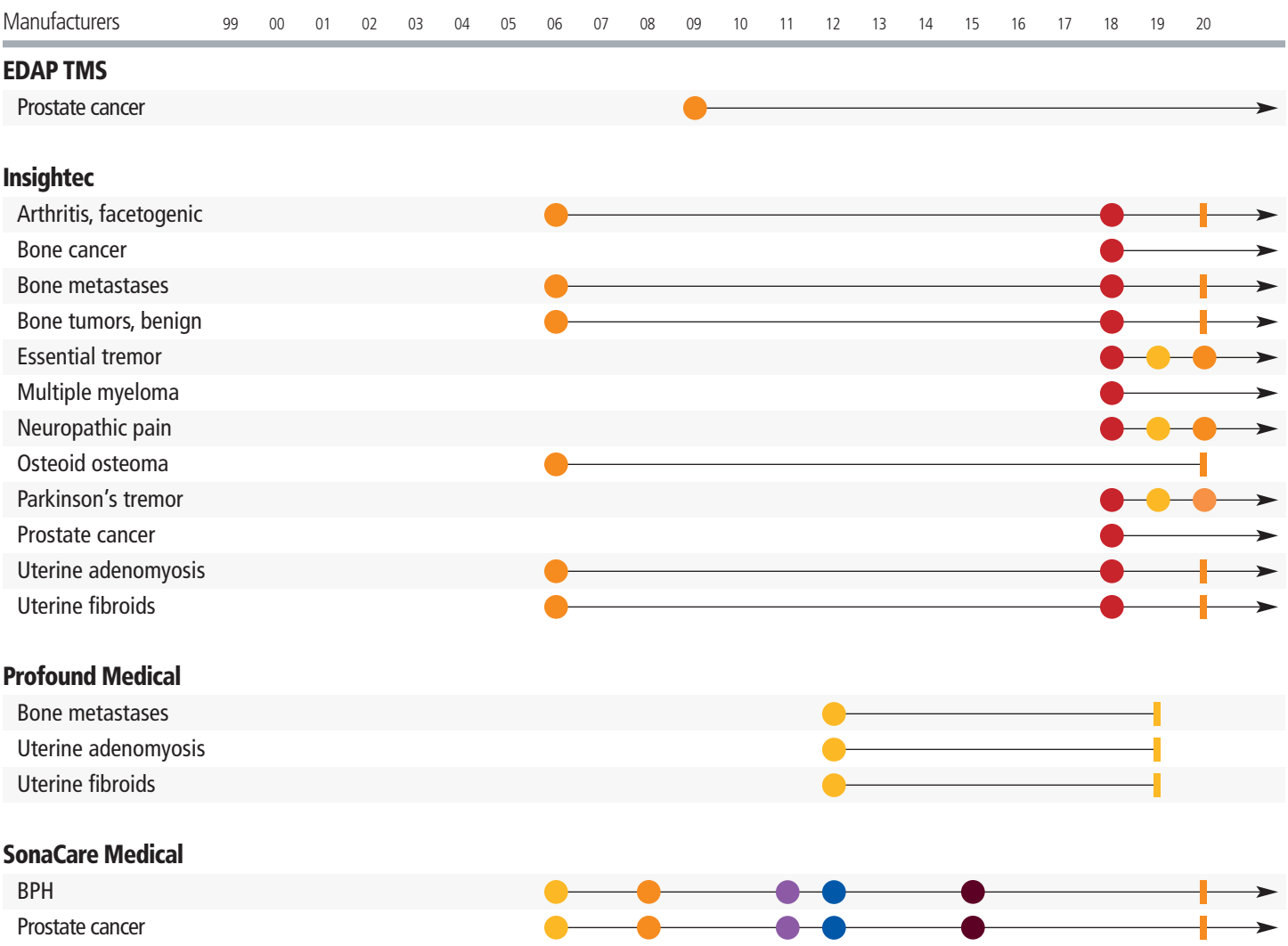
Approval
- Approval begin date
- Approval end date

Asia
- China, *NMPA*
- Hong Kong, *MDD*
- India, *CDSCO*
- Indonesia, *DGPMD*
- Israel, *AMAR*
- Japan, *MHLW*
- Kazakhstan, *NCEM*
- Malaysia, *MDA*
- Pakistan, *DRAP*
- Philippines, *FDA*
- Saudi Arabia, *SFDA*
- Singapore, *HSA*
- South Korea, *MFDS*
- Taiwan, *FDA*
- Thailand, *FDA*
- Uzbekistan, *GDQC*
- Vietnam, *DMEW*

Asia—FUS Regulatory Approvals by Company and Indication continued



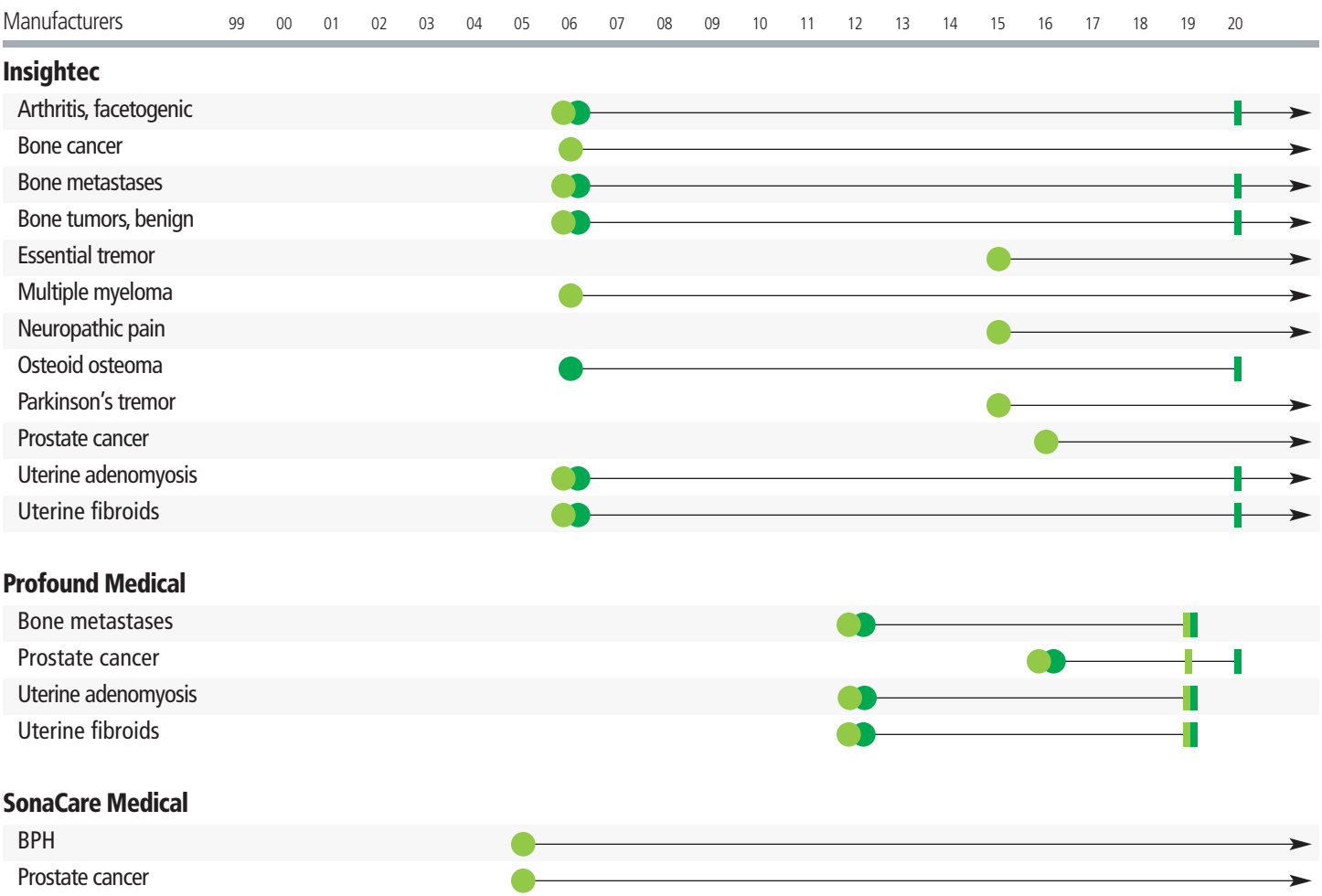
South America—FUS Regulatory Approvals by Company and Indication



Approval
- Approval begin date
- Approval end date

South America
- Argentina, *ANMAT*
- Brazil, *ANVISA*
- Chile, *ANAMED*
- Colombia, *INVIMA*
- Ecuador, *ANRCVS*
- Trinidad and Tobago, *Ministry of Health*

Oceania—FUS Regulatory Approvals by Company and Indication



Approval
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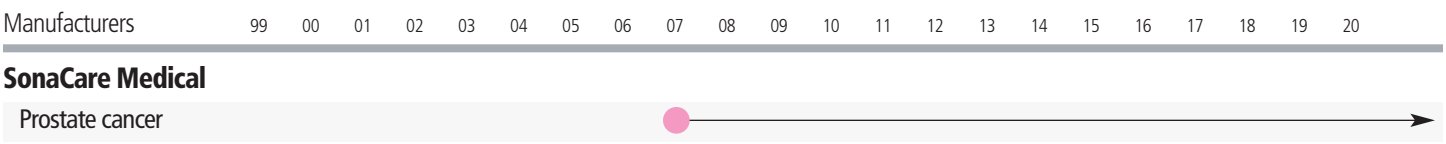
Oceania
- Australia, *TGA*
- New Zealand, *MEDSAFE*

Africa—FUS Regulatory Approvals by Company and Indication



Approval
- Approval begin date
- Approval end date

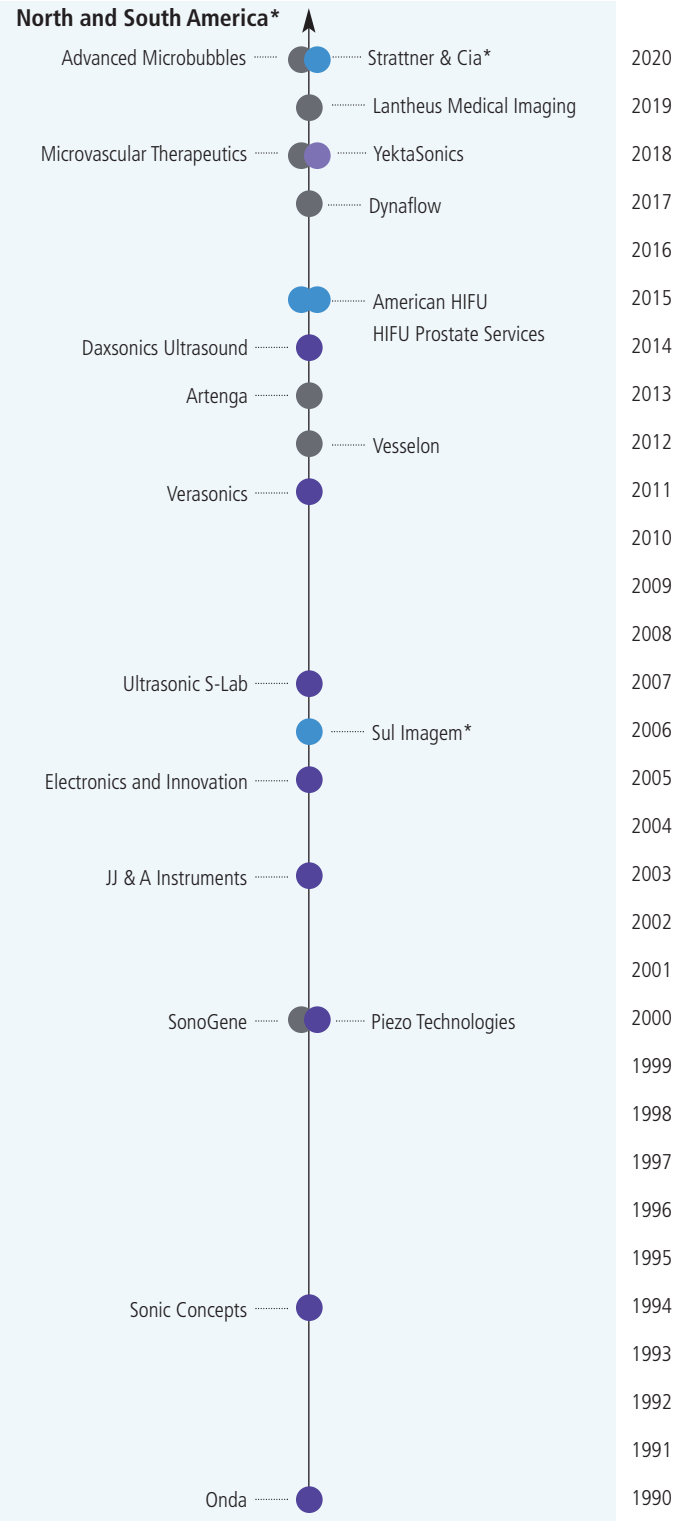
Africa
- South Africa, *MCC*

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. Last year we transitioned. Instead of the date of incorporation we are reporting on the year the company became involved in the focused ultrasound industry. For many early-stage 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.

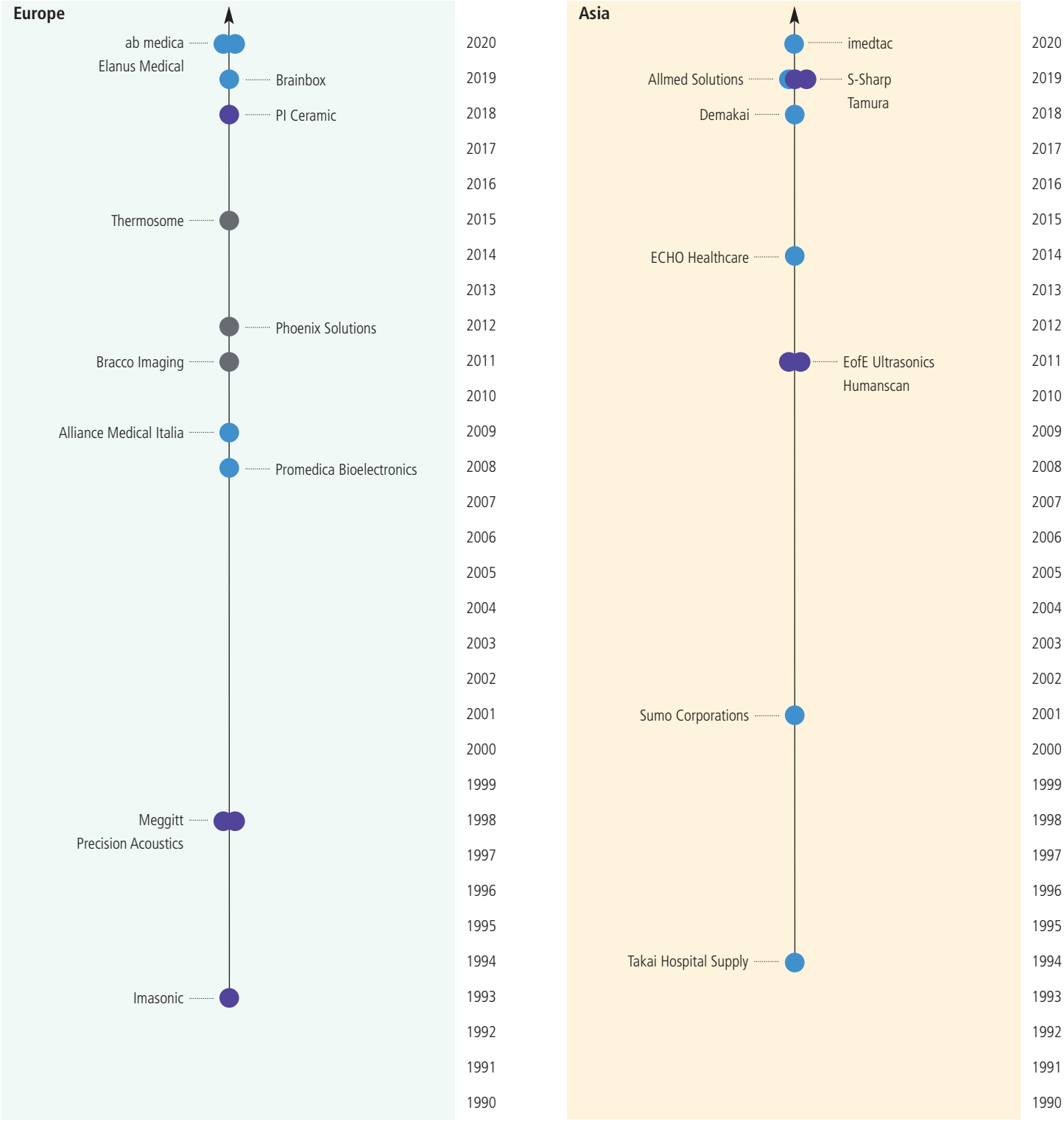
Please note, we are sorting the timelines by geographic regions instead of by image guidance. Image, treatment, and planning guidance for companies/devices can be found on pages III.62–III.64.



*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

MICROBUBBLE

Advanced Microbubbles INC | Newark, California, United States, www.advancedmicrobubbles.com

Artenga INC | Ottawa, Ontario, Canada, www.artenga.com

Dynaflow INC | Jessup, Maryland, United States, www.dynaflow-inc.com

Lantheus Medical Imaging INC | North Billerica, Massachusetts, United States, www.lantheus.com

Microvascular Therapeutics LLC | Tucson, Arizona, United States, www.mvtpharma.com

SonoGene LLC | Glen Ellyn, Illinois, United States

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.sonicconcepts.com

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

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

YektaSonics INC | Santa Cruz, California, United States, www.yektasonics.com

Europe

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ab medica SpA | Cerro Maggiore, Italy, www.abmedica.it

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

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

Elanus Medical AG | Gipf-Oberfrick, Switzerland, www.elanus-medical.com

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

FUS Industry by Region continued

Other FUS Companies

Europe continued

MICROBUBBLE

Bracco Imaging SPA | Milano, Italy, www.braccoimaging.com
EXACT Therapeutics SA | Oslo, Norway, www.exact-tx.com
Thermosome GMBH | Planegg/Martinsried, Germany, www.thermosome.com

OEM

Imasonic SA | Voray-sur-l'Ognon, France, www.imasonic.com
Meggitt A/S | Kvistgård, Denmark, www.meggittferroperm.com
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Asia

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imedtac CO LTD | Taipei City, Taiwan, www.imedtac.com
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Yangde Instrument CO LTD | Taipei City, Taiwan, www.yang-der.com.tw

OEM

EofE Ultrasonics CO LTD | Seoul, South Korea, ultrasonics.co.kr
Humanscan CO LTD | Ansan, South Korea, www.humanscan.co.kr
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FUS Industry by Region continued

Other FUS Companies

South America

2

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Sul Imagem | São José, Brazil

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Focused Ultrasound Foundation Overview

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

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

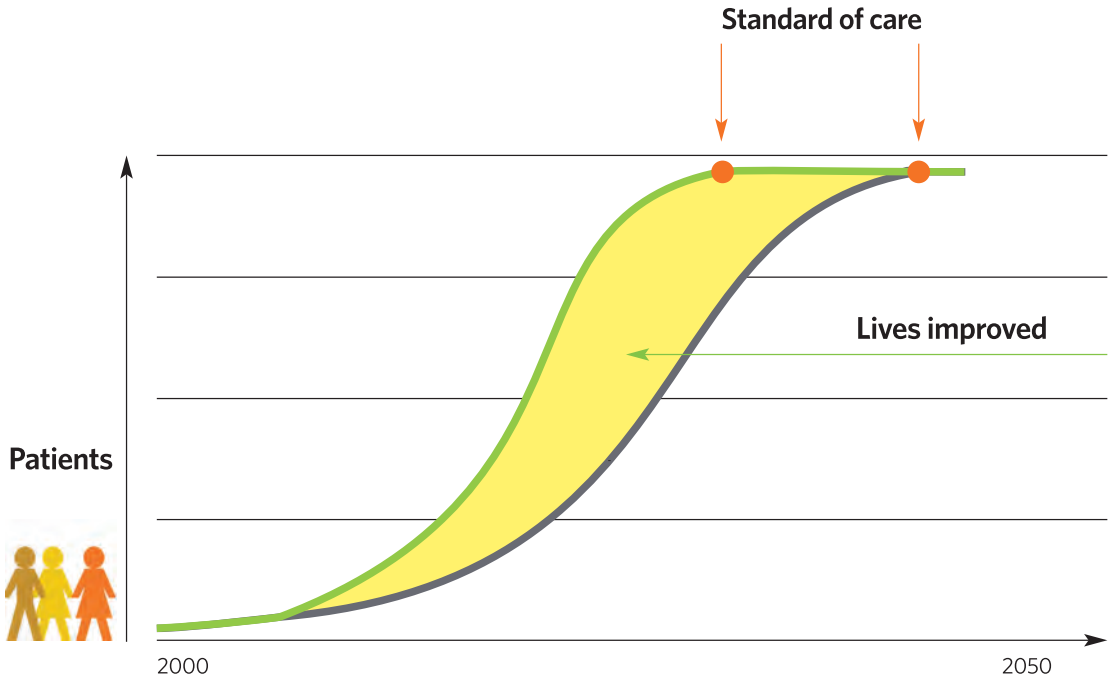
Major initiatives include

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

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

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

fusfoundation.org



Saving time = Saving lives

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

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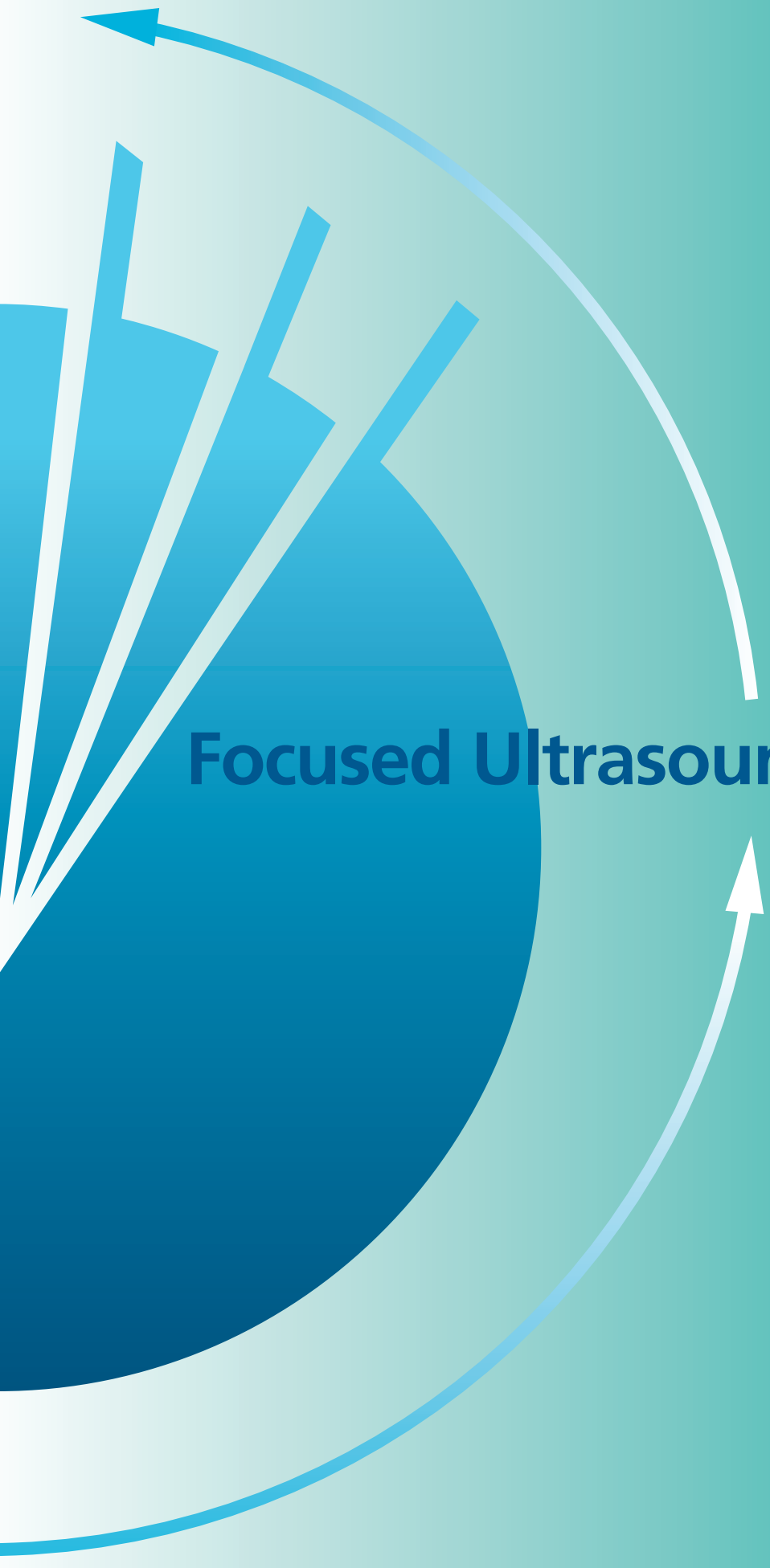
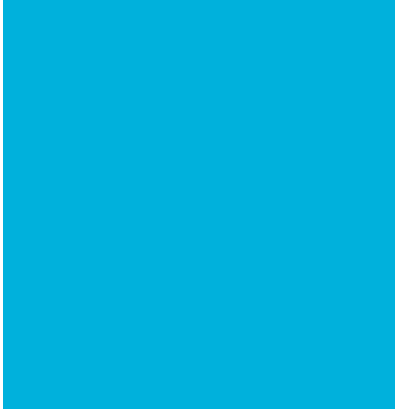
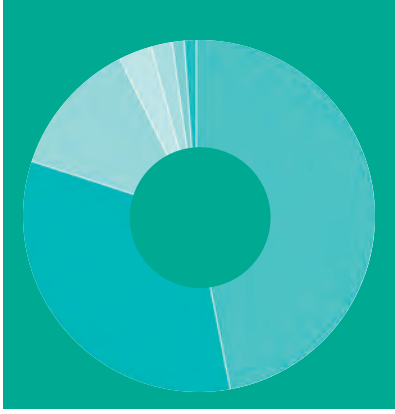
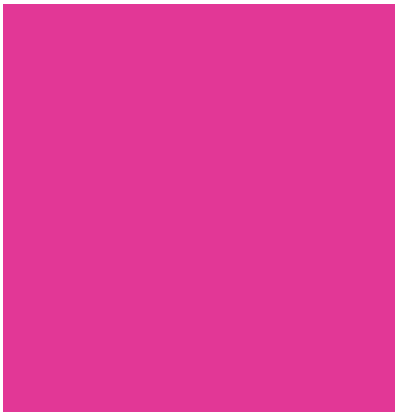
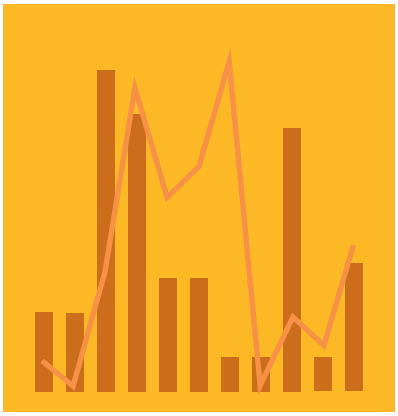
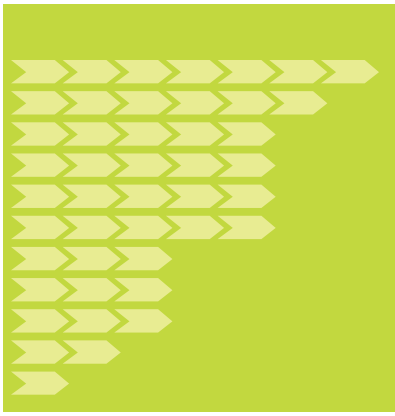
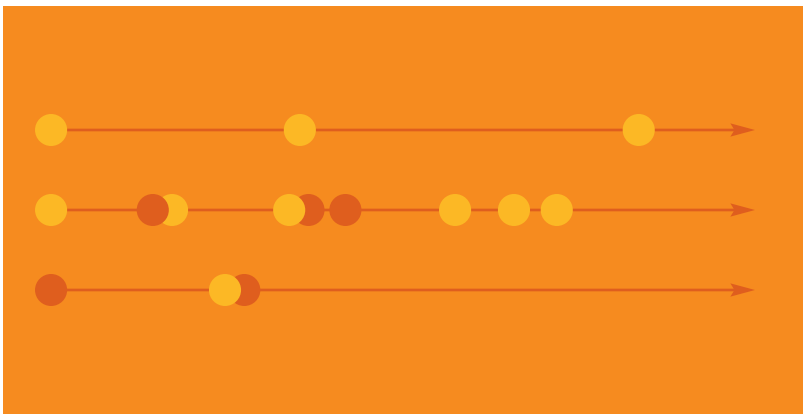
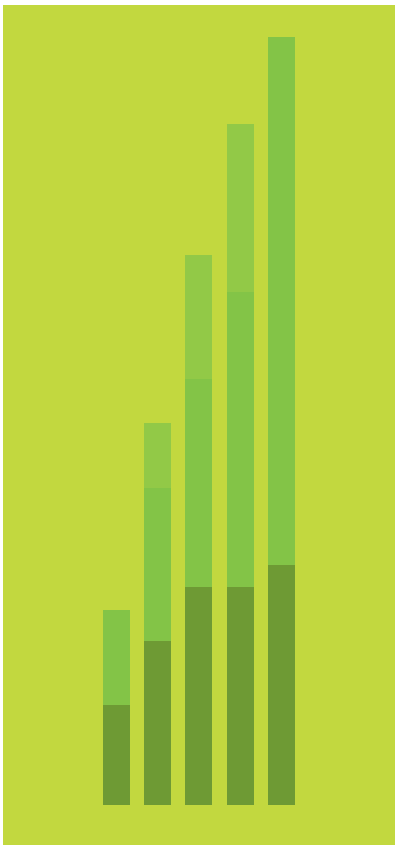
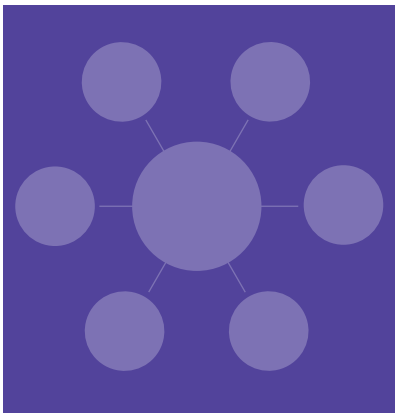
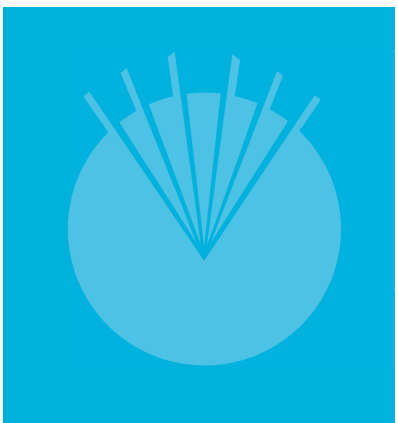
Date 7.15.2021

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, 2020. 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.



Focused Ultrasound Foundation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