

# 2019

State of  
the Field

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## Focused Ultrasound



FOCUSED  
ULTRASOUND  
FOUNDATION



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Date 8.6.0019

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The Focused Ultrasound Foundation strives to provide the most accurate information possible and therefore works proactively with the manufacturers and research sites to collect the most current data available in advance of the release of this publication. This report is based on data through December 31, 2018. 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 If you note something out of date or inaccurate, please submit the new information/updates to: [info@fusfoundation.org](mailto:info@fusfoundation.org).

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## Dear Friends,

The field of focused ultrasound (FUS) is growing more rapidly and having more of an impact than we could have imagined even a mere decade ago. The 2018 data included in this 2019 State of the Field Report reflects many first-in-the-world and first-in-human studies—evidence of how the field is both expanding in scope and marching toward widespread clinical adoption. Other highlights include:

- FUS commercial treatment sites in the USA doubled
- FDA approval for tremor-dominant Parkinson’s disease
- CE Mark approval for epicondylitis and plantar fasciitis
- Expansion of FUS for veterinary usage
- 126 unique indications in various stages of development
- \$218M invested in 6 FUS manufacturers

Our mission to accelerate the development and clinical adoption of FUS continues in force. With the rapid increase in the potential numbers of indications and mechanisms of action, the work required to translate our vision to reality becomes both more rewarding and more challenging.

As the field continues to expand and mature, keeping pace with information gathering and reporting gets more complicated. We have added staff members based in Europe and Asia to help maintain a global perspective, assist with regional relationship building, and validate/expand our knowledge of FUS research and treatment sites around the world. Our hope is to increase data accuracy and decrease the time from data collection to data analysis and availability.

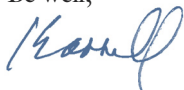
For 2019, the State of the Field Report includes additional graphics focusing on trends over time. We are working to convert the report to a digital format over the next several years, with interactive graphics and links to our database providing readers easy access to the most current information.

In the year ahead, the Foundation plans to increase our emphasis on advancing both the clinical applications of FUS and the commercial success of manufacturers—key pieces to making this technology readily available to patients worldwide. Toward this end, we are beginning to expand this report to more closely resemble a FUS-sector market report, as is typically created by financial analysts and used by med tech investors. Unparalleled access to all global stakeholders will allow us to create a report that makes the most comprehensive and up-to-date information accessible.

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, are all working toward a common goal of making this technology widely available as a standard of care in the shortest time possible. We appreciate all of their contributions to this report.

Thank you for your support, and we look forward to sharing many more milestones with you in 2019.

Be well,



Neal F. Kassell, MD, *Chairman*

## Focused Ultrasound in Brief

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

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

- Benign and malignant tumors of the brain, breast, prostate, liver, and pancreas
- Parkinson's and Alzheimer's diseases and epilepsy
- Depression and obsessive-compulsive disorder
- Arthritis and hypertension
- Uterine fibroids

Focused ultrasound treats tissue with multiple intersecting beams of high-frequency sound 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. Currently there are 19 mechanisms of action under study, including:

### TISSUE DESTRUCTION

- **Thermal Ablation:** coagulative cell death
- **Histotripsy:** mechanical cell disruption
- **Microvascular disruption:** ischemic cell death
- **Sonodynamic therapy:** activation of cell-toxic drugs

### IMMUNOMODULATION

- **Tumor cell disruption:** increased immune cell trafficking; exposure of tumor antigens and release of cytokines
- **Augmentation of immunotherapy drugs**
- **Enhanced drug delivery**

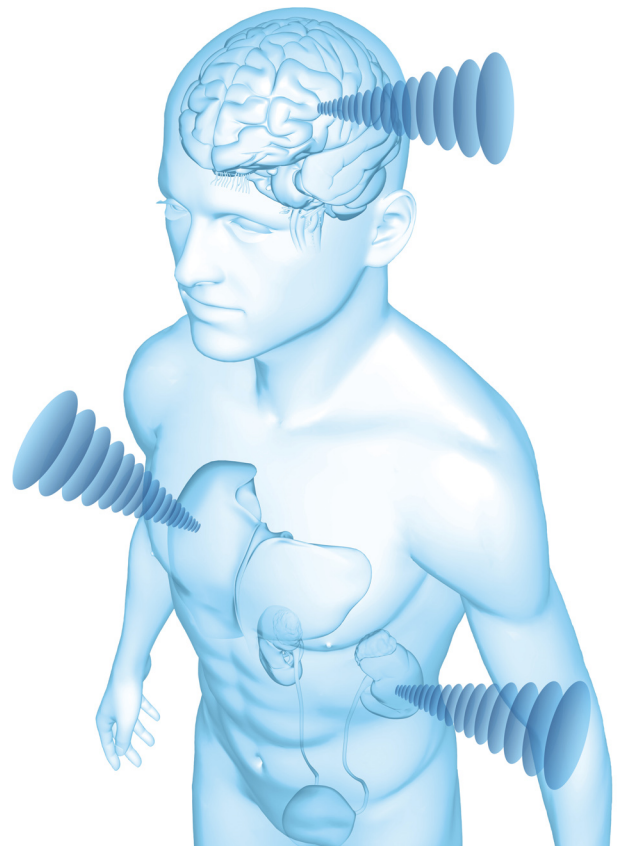
### DRUG DELIVERY

- **Focal delivery of therapeutic agents**
- **Increased vascular permeability and blood-brain barrier opening**
- **Increased cell membrane permeability**

### RADIATION

- **Alternative to ionizing radiation**
- **Decreased radiation dose:** tumor preconditioning and sensitization

There are currently more than 125 clinical indications or disorders in various stages of development, and the number is increasing rapidly. Most are early stage. Worldwide, 31 indications have regulatory approval; in the US, six have been approved by the FDA. Focused ultrasound is not for every patient or every disorder. Much work remains to be done to determine where this technology provides therapeutic and cost-effective value.



State of Research and Regulatory Approvals by Indication



1 Protocols inclusive of more than one indication  
 2 Multiple myeloma approval is based on bone metastases.  
 † New in 2018

State of Research and Regulatory Approvals by Indication continued



<sup>3</sup> FDA approval is for prostate tissue ablation.

† New in 2018

## A Note on Multiple Listings

We often are asked why some of the indications listed on this chart are listed more than once. This is the explanation:

The human body is made up of multiple systems that all work together. Each body system is a group of tissue organized to perform a specific function. We organize the State of Research and Regulatory Approvals by Indication according to body systems for ease of identification. (This is also how the medical community organizes medical specialties and how a patient is referred to a particular specialist when needed.) However, when we organize the chart solely by body system, we lose the impact and the ability of seeing different ways of identifying diseases that can occur in a patient across multiple body systems.

In an effort to correct for this, we have created three additional categories of interest (oncology, pain, and pediatrics) that we believe are important enough to look at grouped together regardless of their body system. These indications are represented in the chart in multiple places—in the body system to which they belong and again in the relevant categories we have identified. This helps us to ascertain patterns and trends over time that might otherwise be difficult to discern.

In 2018 there are 126 distinct indications.



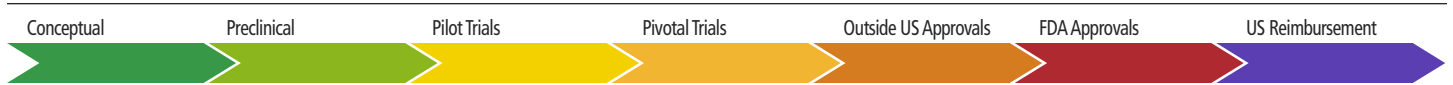
State of Research and Regulatory Approvals by Indication continued



1 Protocols inclusive of more than one indication  
 2 Multiple myeloma approval is based on bone metastases.  
 3 FDA approval is for prostate tissue ablation.  
 † New in 2018

# OVERVIEW

## Global Development Landscape



Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement
<b>Cardiovascular</b>						
	Arteriovenous malformations Atherosclerosis Cardiac hypertrophy† Cardiac pacing Congestive heart failure Coarctation of the aorta† Deep vein thrombosis Fetal heart anomalies Heart valve calcifications Hematoma† Hemophilia B† Hypoplastic left heart syndrome Mitral regurgitation† Septal perforation Ventricular tachycardia†	Atrial fibrillation Peripheral artery disease Varicose veins		Hypertension		
<b>Endocrine Disorders</b>						
	Diabetes	Grave's disease Hyperparathyroidism Thyroid cancer		Thyroid nodules		
<b>Gastrointestinal</b>						
	Esophageal tumors Liver fibrosis	Biliary tract cancer Colorectal tumors Malignant obstructive jaundice		Liver metastases Liver tumors Pancreatic tumors		

† New in 2018

Global Development Landscape continued



Miscellaneous

	<ul style="list-style-type: none"> <li>Ultrasound-induced local anesthesia</li> <li>Wound healing†</li> </ul>	<ul style="list-style-type: none"> <li>Dercum's disease†</li> <li>Head &amp; neck tumors</li> <li>Hypersplenism</li> <li>Lipoma†</li> <li>Melanoma</li> <li>Multiple tumors<sup>1</sup></li> <li>Obesity</li> <li>Root canal endodontia</li> </ul>				
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Musculoskeletal

	<ul style="list-style-type: none"> <li>Muscle atrophy</li> <li>Osteomyelitis†</li> </ul>	<ul style="list-style-type: none"> <li>Arthritis</li> <li>Arthritis - ankle†</li> <li>Arthritis - hand</li> <li>Arthritis - hip</li> <li>Arthritis - knee</li> <li>Arthritis - sacroiliac</li> <li>Desmoid tumors</li> <li>Disc degeneration</li> <li>Sacral chordoma</li> </ul>		<ul style="list-style-type: none"> <li>Arthritis - facetogenic</li> <li>Bone cancer</li> <li>Bone metastases</li> <li>Bone tumors, benign</li> <li>Epicondylitis</li> <li>Multiple myeloma<sup>2</sup></li> <li>Osteoid osteoma</li> <li>Plantar fasciitis</li> <li>Soft tissue cancer</li> <li>Soft tissue injury</li> <li>Soft tissue tumor, benign</li> </ul>	<ul style="list-style-type: none"> <li>Bone metastases</li> </ul>	<ul style="list-style-type: none"> <li>Bone metastases</li> </ul>
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1 Protocols inclusive of more than one indication

2 Multiple myeloma approval is based on bone metastases.

† New in 2018

Global Development Landscape continued



Neurological

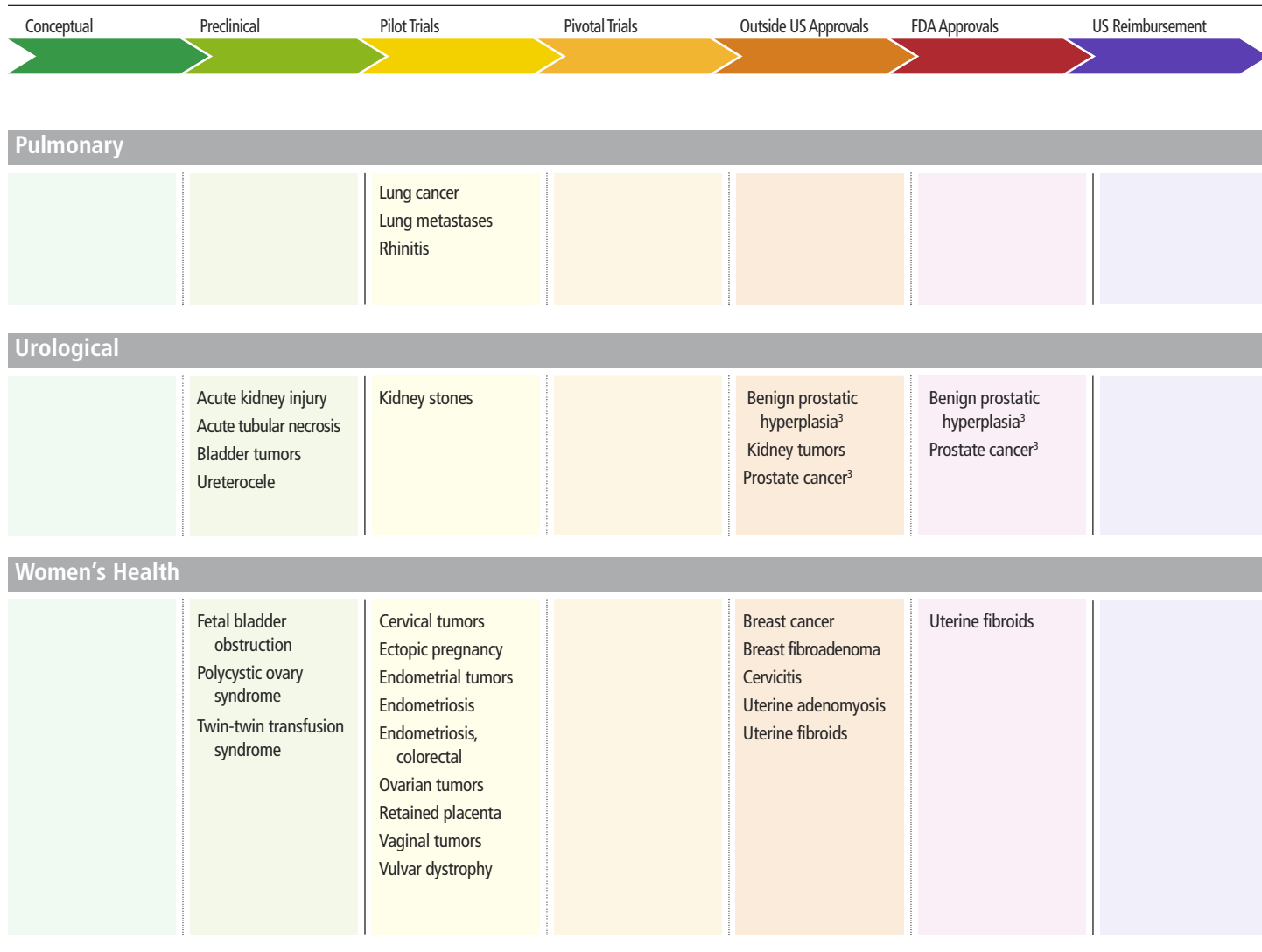
Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement	
Anorexia	Addiction Cavernomas Hydrocephalus Intracerebral hemorrhage Migraine† Multiple sclerosis Spinal cord injury Thromboembolic stroke Trigeminal neuralgia	Alzheimer's disease Amyotrophic lateral sclerosis Astrocytoma (SEGA) Brain metastases Cancer pain Dementia Dystonia Epilepsy Glioblastoma Holmes tremor Huntington's disease Neuroblastoma, pediatric Painful amputation neuromas Pontine glioma Traumatic brain injury			Depression Essential tremor Neuropathic pain Obsessive-compulsive disorder Parkinson's disease, dyskinesia Parkinson's disease, tremor dominant	Essential tremor Parkinson's disease, tremor dominant	Essential tremor

Ophthalmological

Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement
	Keratoplasty Macular degeneration				Glaucoma	

† New in 2018

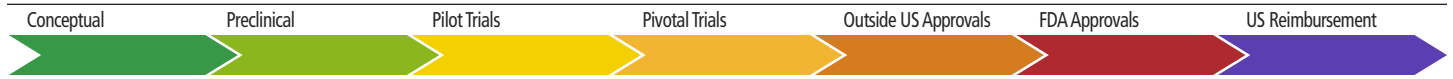
Global Development Landscape continued



<sup>3</sup> FDA approval is for prostate tissue ablation.

# OVERVIEW

## Global Development Landscape continued



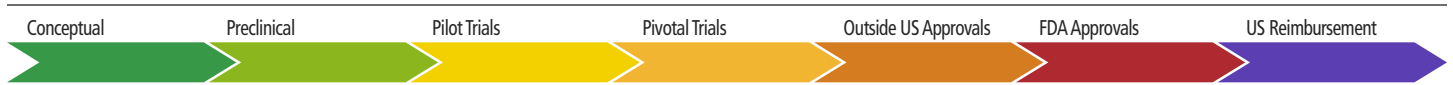
Oncological						
Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement
	Bladder tumors Esophageal tumors	Biliary tract cancer Brain metastases Cancer pain Cervical tumors Colorectal tumors Endometrial tumors Glioblastoma Head & neck tumors Lung cancer Lung metastases Malignant obstructive jaundice Melanoma Multiple tumors <sup>1</sup> Neuroblastoma, pediatric Ovarian tumors Pontine glioma Sacral chordoma Thyroid cancer Vaginal tumors		Bone cancer Bone metastases Breast cancer Kidney tumors Liver metastases Liver tumors Multiple myeloma <sup>2</sup> Pancreatic tumors Prostate cancer <sup>3</sup> Soft tissue cancer	Bone metastases Prostate cancer <sup>3</sup>	Bone metastases

1 Protocols inclusive of more than one indication

2 Multiple myeloma approval is based on bone metastases.

3 FDA approval is for prostate tissue ablation.

Global Development Landscape continued



Pain						
Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement
	Migraine† Osteomyelitis† Trigeminal neuralgia	Arthritis Arthritis - ankle† Arthritis - hand Arthritis - hip Arthritis - knee Arthritis - sacroiliac Cancer pain Decrum's disease† Desmoid tumors Painful amputation neuromas		Arthritis - facetogenic Bone cancer Bone metastases Bone tumors, benign Multiple myeloma <sup>2</sup> Neuropathic pain Osteoid osteoma Pancreatic tumors Soft tissue injury	Bone metastases	Bone metastases

Pediatrics						
Conceptual	Preclinical	Pilot Trials	Pivotal Trials	Outside US Approvals	FDA Approvals	US Reimbursement
	Arteriovenous malformations Coarctation of the aorta† Hydrocephalus Hypoplastic left heart syndrome Septal perforation	Astrocytoma (SEGA) Desmoid tumors Epilepsy Multiple tumors <sup>1</sup> Neuroblastoma, pediatric Sacral chordoma		Bone metastases Osteoid osteoma Soft tissue cancer Soft tissue tumor, benign	Bone metastases	Bone metastases

1 Protocols inclusive of more than one indication  
 2 Multiple myeloma approval is based on bone metastases.  
 † New in 2018

## Indications with Anecdotal Case Reports

Indications	Date	Region					Reference Report
		Europe	N. America	Asia	S. America	Oceania	
<b>Cardiovascular</b>							
Arteriovenous malformations	2015	●	●	●			<a href="http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4696245/">www.ncbi.nlm.nih.gov/pmc/articles/PMC4696245/</a>
Fetal heart anomalies	2013	●		●			<a href="http://www.ncbi.nlm.nih.gov/pubmed/30136326">www.ncbi.nlm.nih.gov/pubmed/30136326</a>
<b>Endocrine</b>							
Insulinoma	2011	●					<a href="http://link.springer.com/article/10.1007/s00270-010-9884-0">link.springer.com/article/10.1007/s00270-010-9884-0</a>
<b>Gastrointestinal</b>							
Liver alveococcosis	2018			●			<a href="http://www.ncbi.nlm.nih.gov/pubmed/30353443">www.ncbi.nlm.nih.gov/pubmed/30353443</a>
<b>Women's Health</b>							
Twin-twin transfusion syndrome	2013	●		●			<a href="http://www.ncbi.nlm.nih.gov/pubmed/23533101">www.ncbi.nlm.nih.gov/pubmed/23533101</a>
<b>Oncological</b>							
Lung metastases	2016	●	●				<a href="http://www.youtube.com/watch?v=Wtr25ypcQIU">www.youtube.com/watch?v=Wtr25ypcQIU</a>

### Anecdotal Cases

Anecdotal case reports are publications that describe instances wherein a clinician used focused ultrasound technology to treat a patient, or a very small number of patients, outside of a clinical trial. Many of these indications are extremely rare, making it difficult to recruit enough patients for a clinical trial, or are too early stage for clinical trial. However, we believe it is worth including these anecdotal cases to show the many ways in which clinicians are using focused ultrasound around the world to help patients in need.

### Clinical Indications

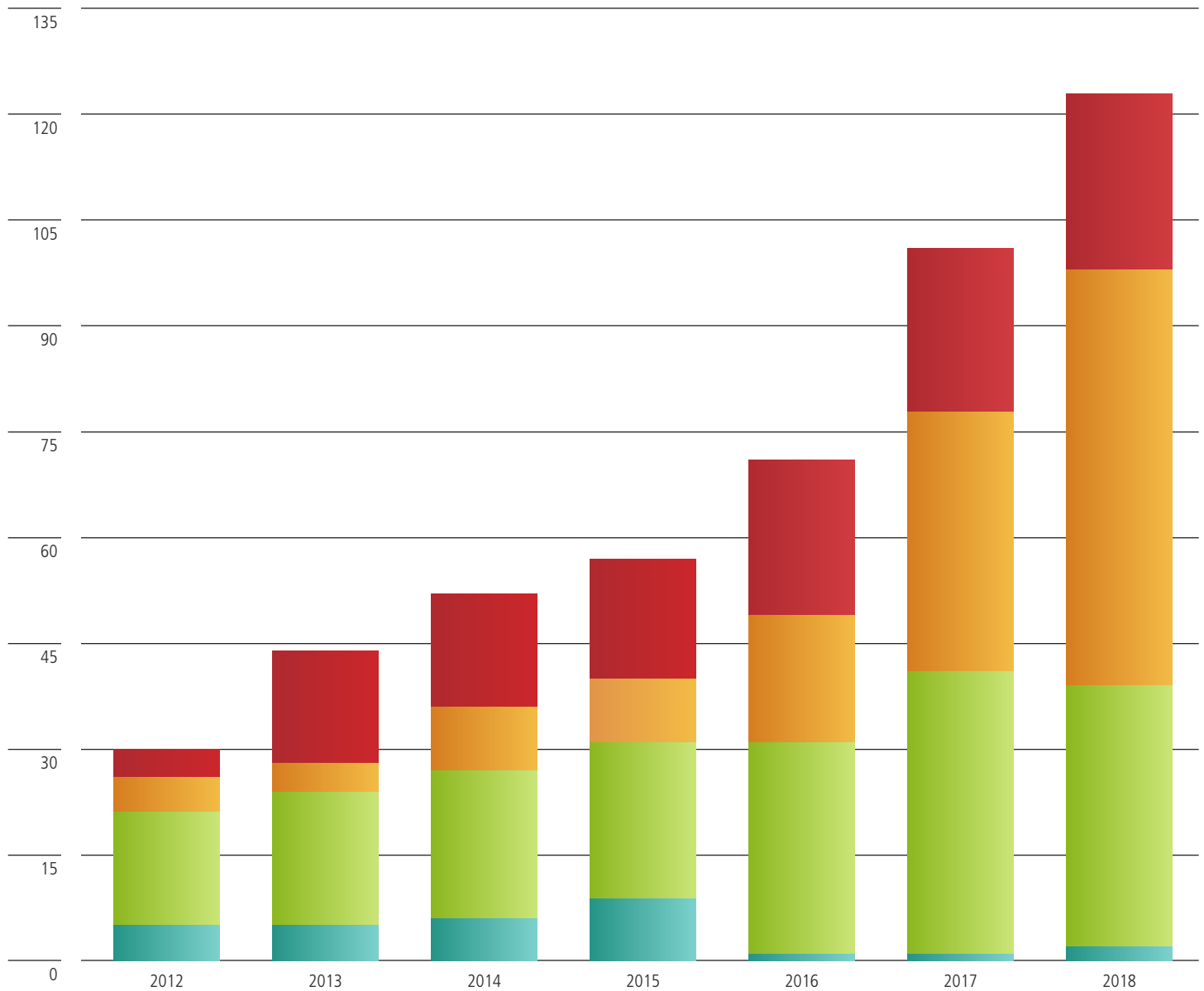
The number of indications progressing to clinical trial status has grown significantly over the last four years, while the number of indications in the preclinical stages has also grown. This indicates two interesting trends: 1) indications are progressing along the development and regulatory pathway over time, and 2) new indications for research and development are increasing as well.



## Developmental Stages of Clinical Indications

Developmental stage: ■ Conceptual ■ Preclinical ■ Clinical trials ■ Regulatory approvals

Indications

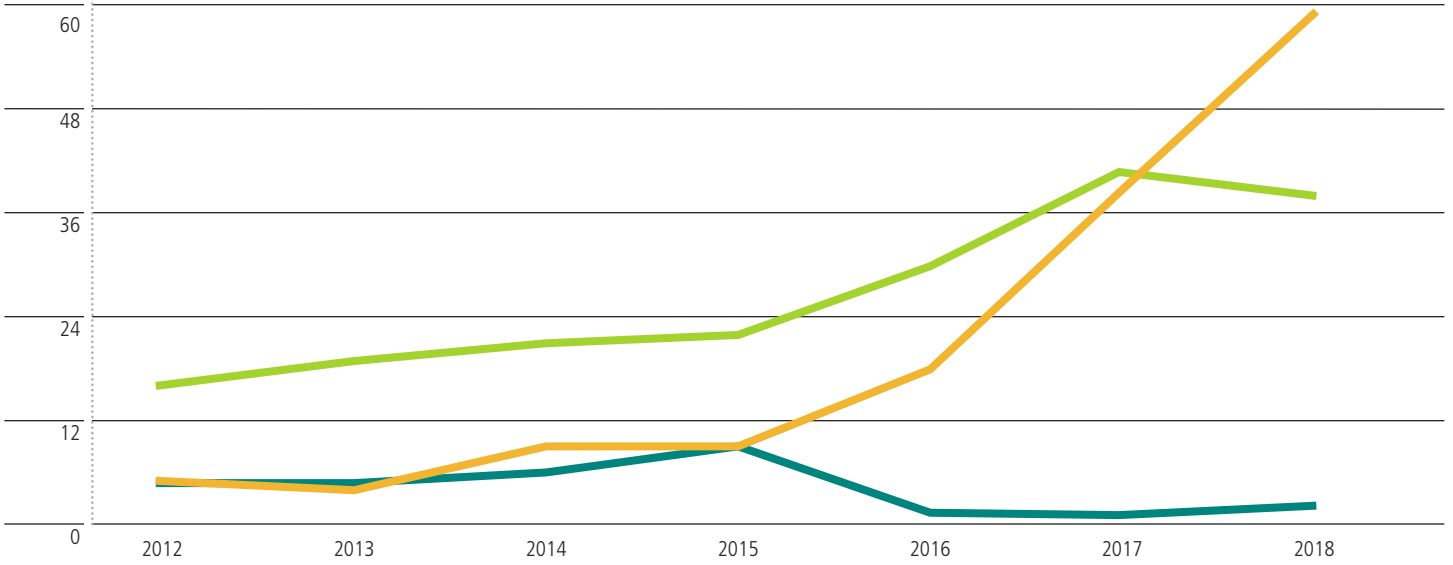


There are 126 distinct indications for 2018.

## Developmental Stages of FUS Research

Developmental stage: ■ Conceptual ■ Preclinical ■ Clinical trials

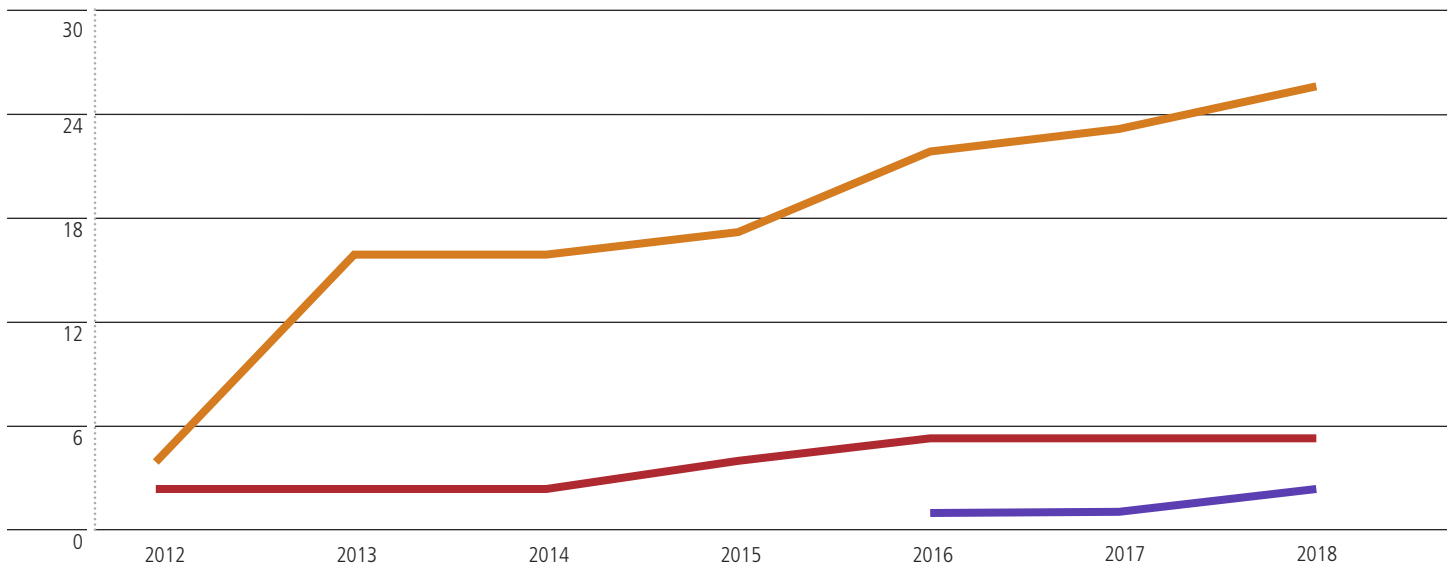
Number of indications



## Developmental Stages of FUS Commercialization

Developmental stage: ■ Outside US approval ■ FDA approval ■ US Reimbursement

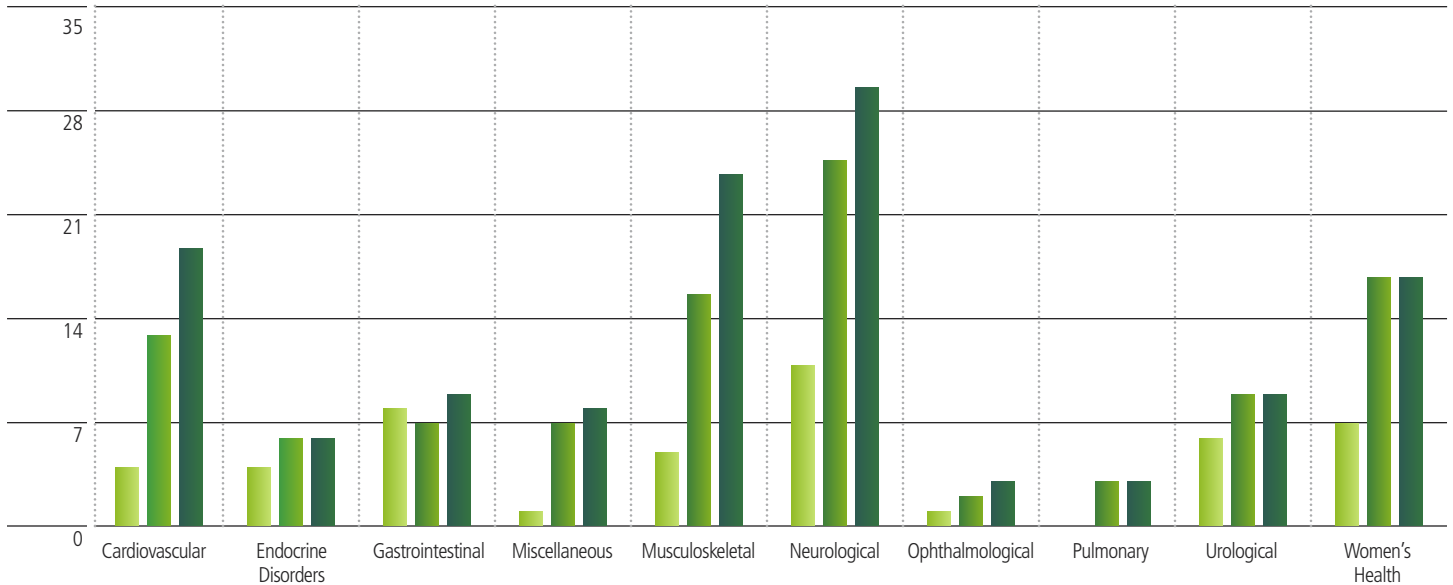
Number of indications



## Expansion of Indications by Body Systems

■ 2012 | ■ 2017 | ■ 2018

Number of indications



### Developmental Stages of FUS Research

Note the slope of the line of clinical trials from 2015 to 2018. This represents a five-fold increase in the number of indications in clinical trials compared to three years ago.

### Developmental Stages of FUS Commercialization

The rest of the world continues to lead the way in regulatory approvals compared to the US. FDA approval criteria are currently more stringent than those in other countries. Reimbursement in the US continues to be a challenge. Please see page 79 for further details on the status of reimbursement.

### Expansion of Indications

Cardiovascular, musculoskeletal, and neurological researchers and clinicians have tremendous interest in expanding the number of indications for which focused ultrasound might be a viable future treatment option. This is evidenced by the growth in the number of indications over the past six years as seen above.

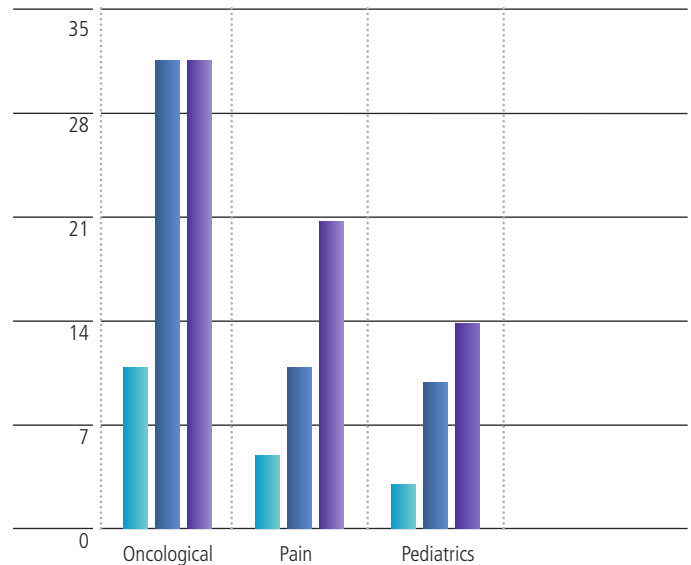
### Areas of Interest

Additionally, the graphs of the three areas of particular interest to the Foundation—oncology, pain, and pediatrics—also demonstrate a significant growth trend.

### Areas of Interest

■ 2012 | ■ 2017 | ■ 2018

Number of indications

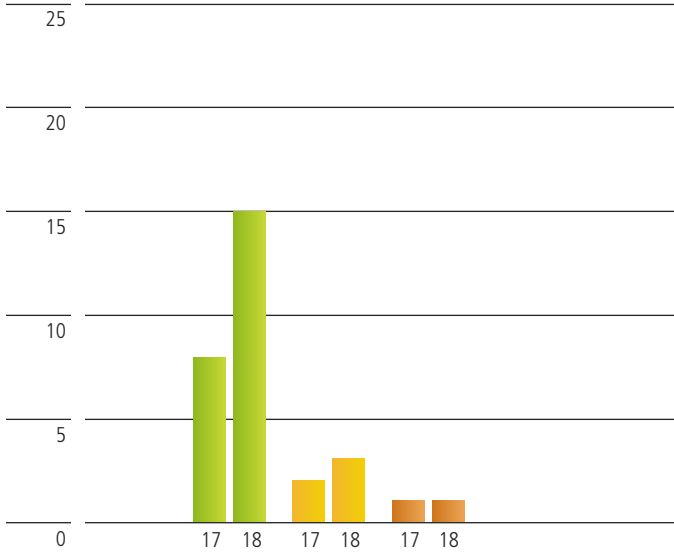


## Expanding Areas of Research

Developmental stage: ■ Conceptual ■ Preclinical ■ Clinical Trials ■ Outside US Approvals ■ FDA Approvals ■ US Reimbursement

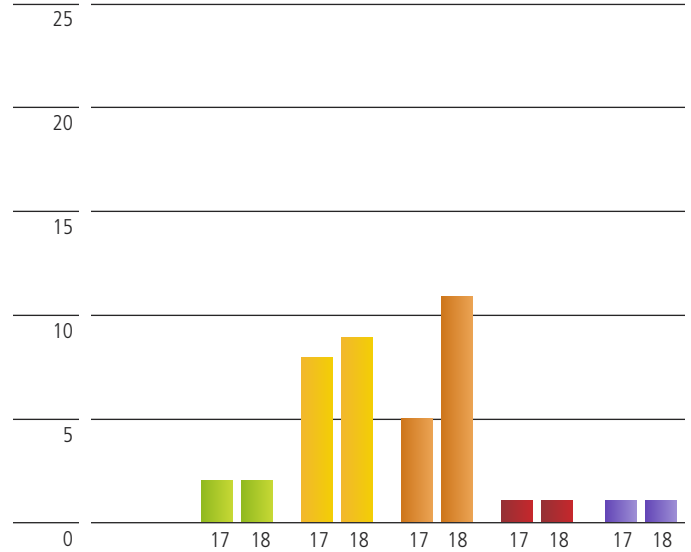
### Cardiovascular

Number of indications



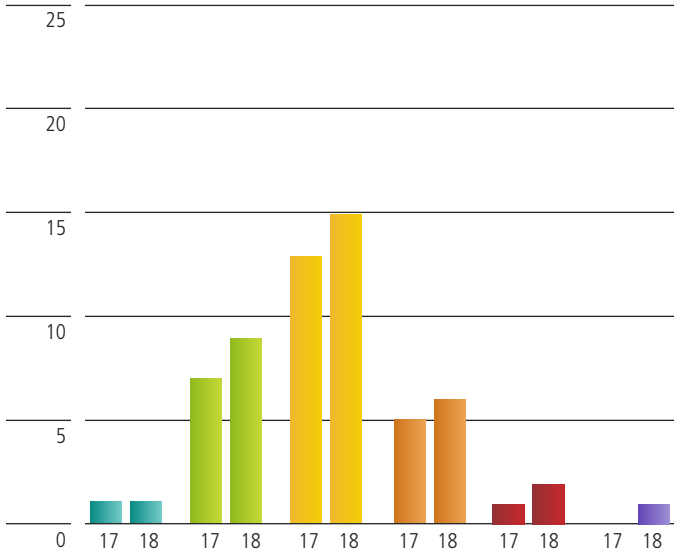
### Musculoskeletal

Number of indications



### Neurological

Number of indications



#### Cardiovascular Research

Research in this body system remains early stage despite the number of increasing indications within the field.

#### Musculoskeletal Research

Predominantly in the clinical research stage right now, this body system also has FDA approval and US insurance reimbursement for one indication, bone metastases.

#### Neurological Research

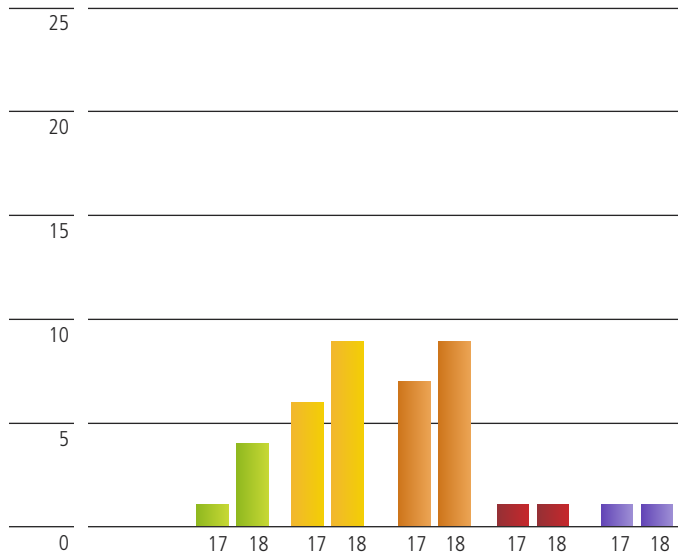
The largest body system of research and growth, progress in neurological research and FDA approvals is matched only by oncological.

## Expanding Areas of Research continued

Developmental stage: ■ Preclinical ■ Clinical Trials ■ Outside US Approvals ■ FDA Approvals ■ US Reimbursement

### Pain

Number of indications

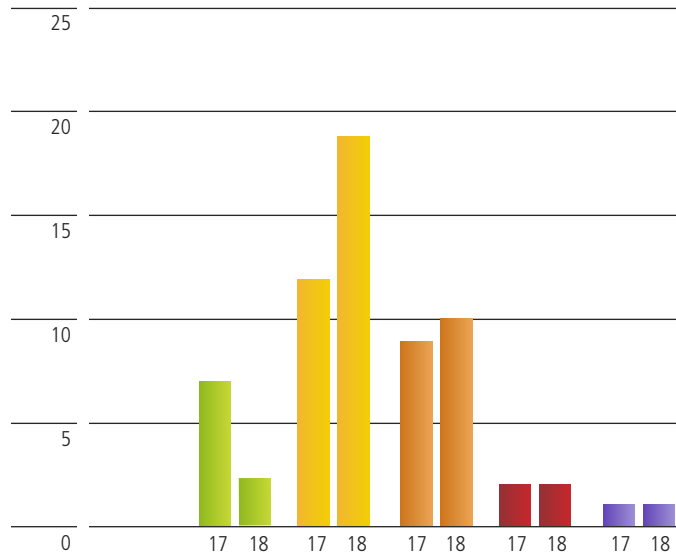


### Pain

In just one year, 2017–2018, the number of clinical trials related to pain indications has almost doubled. Please see page 6 for more information about pain as a category of interest.

### Oncological

Number of indications



### Oncological

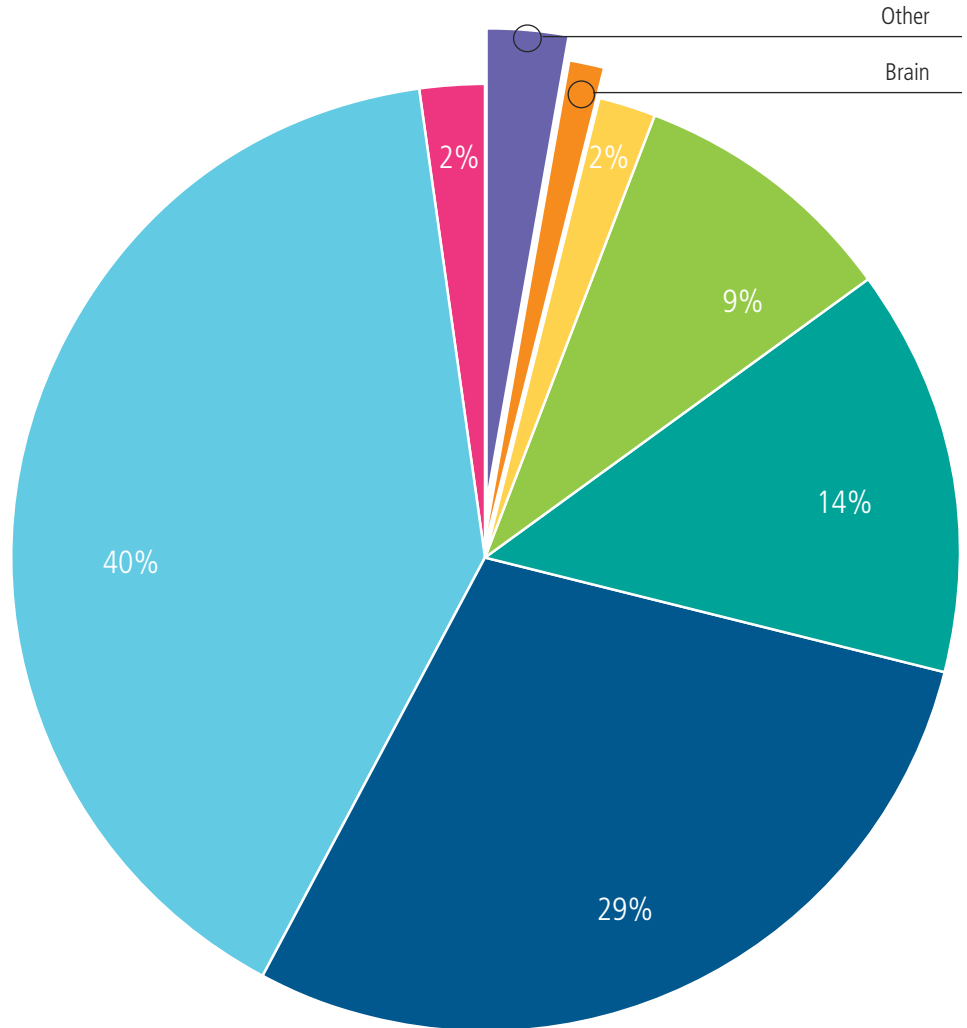
In 2018 there were more clinical trials related to oncology indications than any other area of interest or single body system. Please see page 6 for more information about oncology as a category of interest.

Cumulative Patient Treatments by Indication

All Indications

250,994 Total Treatments<sup>1</sup>

Uterine fibroids	99,304	40%
Prostate diseases	73,685	29%
Liver tumors	35,517	14%
Breast tumors	22,042	9%
Glaucoma	6,142	2%
Brain	1,999	>1%
Cancer, unspecified <sup>2</sup>	5,560	2%
Other	6,745	3%



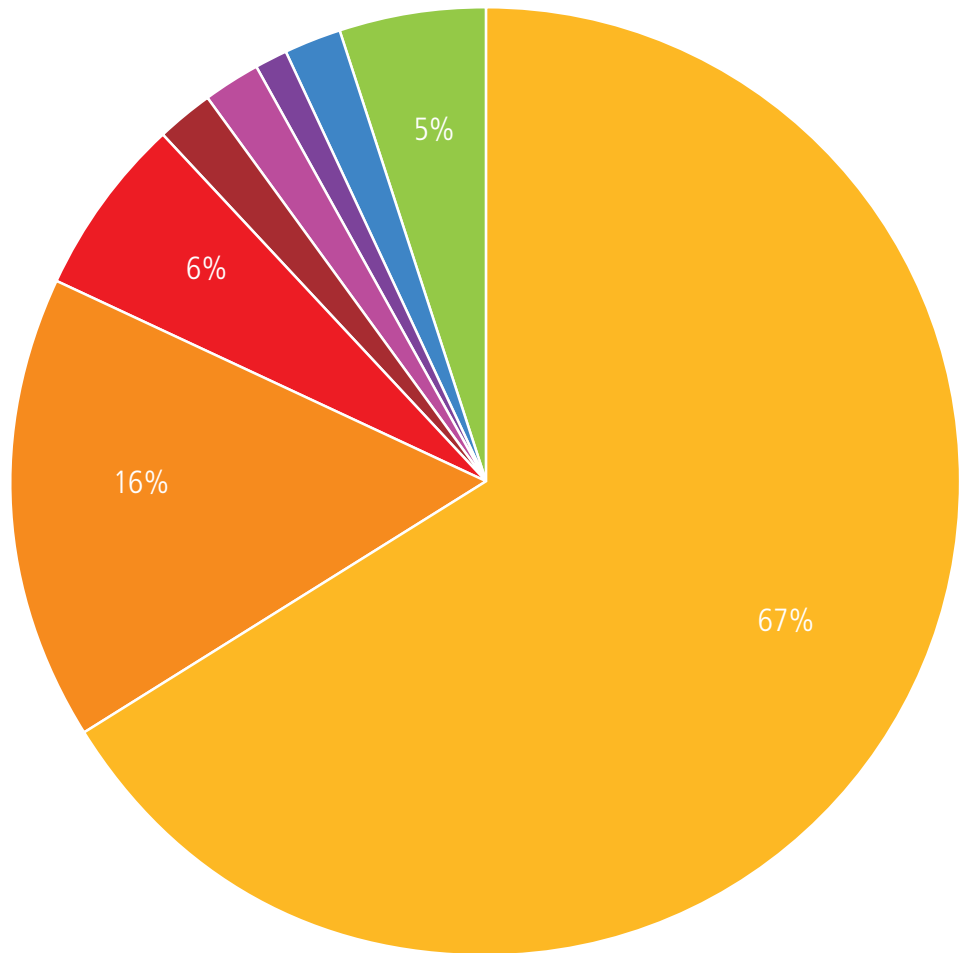
1 Manufacturer-supplied data. The number of patient treatments reported is lower than the actual number of procedures because of incomplete reporting from manufacturers and treatment sites.  
 2 Not all manufacturers are providing specific cancer indications. The Foundation is working to clarify this for future State of the Field Reports.

## Cumulative Brain Treatments by Indication

Brain Indications

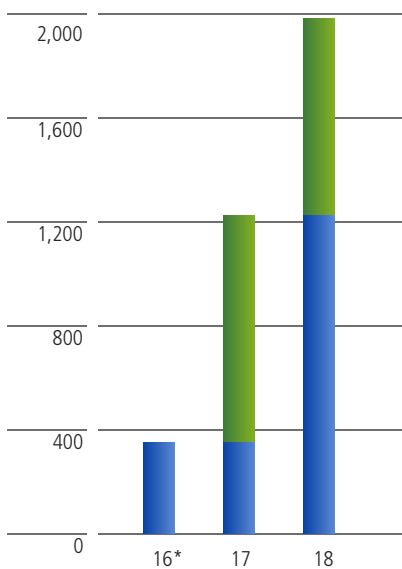
### 1,999 Total Brain Treatments

Essential Tremor	1,342	67%
Parkinson's disease	323	16%
Neuropathic pain	113	6%
Brain tumors	41	2%
Mental health <sup>1</sup>	35	2%
Alzheimer's disease	14	>1%
Other movement disorders <sup>2</sup>	37	2%
Other brain <sup>3</sup>	94	5%



### Total Brain Treatments

■ Cumulative | ■ Reported yearly addition



\*Report in 2016 and prior years

1 Includes Obsessive-compulsive disorder and Depression

2 Includes Epilepsy and Dystonia

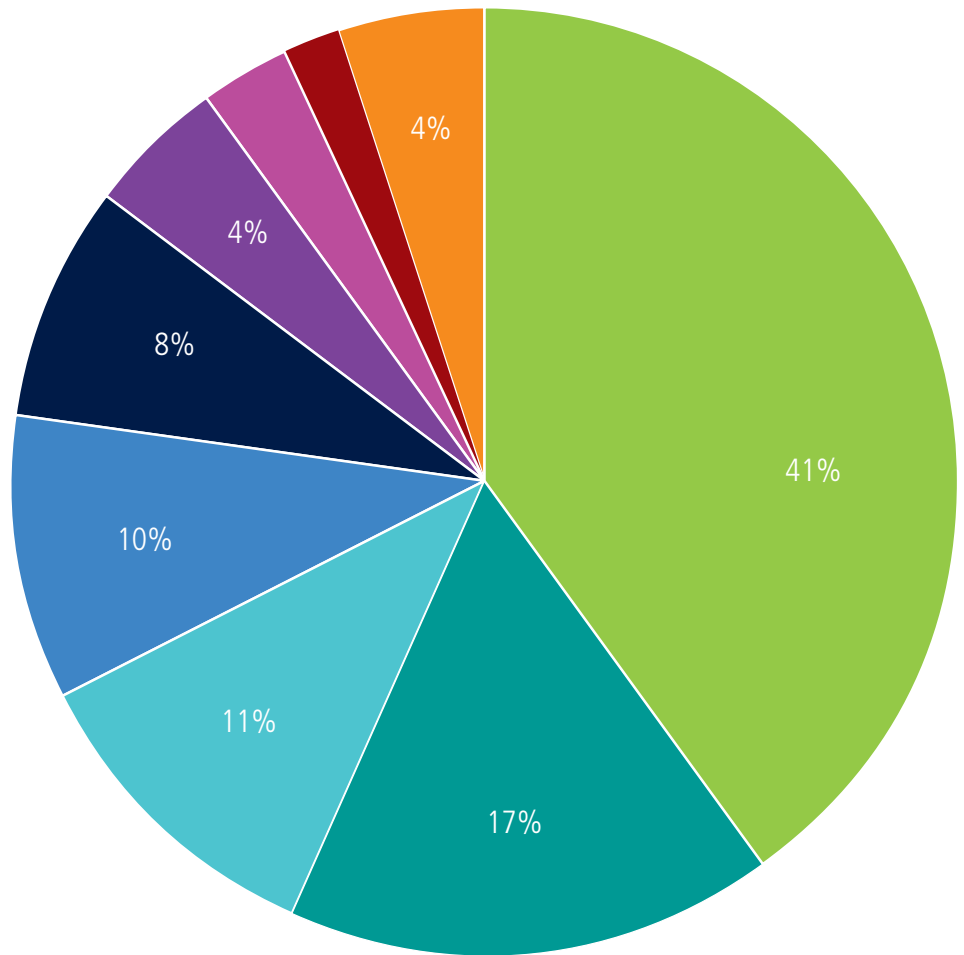
3 Composed of Blood-brain barrier opening

Cumulative Other Treatments by Indication

Other Treatments

6,745 Total Other Treatments

Bone metastases <sup>1</sup>	2,732	41%
Thyroid nodules	1,130	17%
Pancreatic tumors	718	11%
Uterine adenomyosis	668	10%
Soft tissue cancer	510	8%
Arthritis - facetogenic	325	4%
Osteoid osteoma	190	3%
Desmoid tumors	121	2%
Other <sup>2</sup>	351	4%



1 Multiple myeloma approval based on bone metastases.

2 Other indications are treatments less than 100 and include: Abdominal paraglioma; Abdominal tumor; Amyotrophic lateral sclerosis; Arteriovenous malformations; Biliary tract cancer; Bone cancer; Bone tumors, benign; Brain indications, unspecified; Cervical tumors; Dermatology research; Ganglioma; Granular cell tumors of the gluteals; Hemangioma; Kidney tumors; Neurofibroma; Osteoarthritis; Painful amputation neuromas; Sacral chordoma; Schwannoma; Soft tissue cancer; Soft tissue tumors, benign; Varicose veins.



## FUS Regulatory Approvals by Region and FUS Manufacturer

Indications	North America			Europe			Asia					S.Amer. <sup>4</sup>	Oceania <sup>5</sup>	Africa
	US FDA	Canada Health Canada	Other <sup>1</sup>	Europe CE Mark	Russia Roszdravnadzor	China CFDA	India CDSCO	Japan MHLW	Korea MFDS	Mid East <sup>2</sup>	Taiwan Taiwan FDA	Other <sup>3</sup>	SA MCC	
<b>Cardiovascular</b>														
Hypertension				■										
<b>Endocrine</b>														
Thyroid nodules				▲	▲				▲					
<b>Gastrointestinal</b>														
Liver tumors				●	●	●●●			●●					
Pancreatic tumors				●	●	●			●●					
<b>Musculoskeletal</b>														
Arthritis - facetogenic			●	●					●		●	●	●	●
Bone cancer				●										
Bone metastases	●	●	●	●■	■	●		●	●	●■	●	●■	●■	●■
Bone tumors, benign			●	●					●		●	●	●	●
Epicondylitis				■										
Osteoid osteoma			●	●●	●	●			●		●	●	●	●
Plantar fasciitis				■										
Soft tissue cancer				●	●	●●								
Soft tissue tumors, benign				●	●	●					●			
<b>Neurological</b>														
Depression									●					
Essential tremor	●	●		●	●			●	●	●	●			
Neuropathic pain				●	●				●					
OCD									●					
Parkinson's disease	●			●	●				●	●				

### Manufacturers

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

1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE

# OVERVIEW

## FUS Regulatory Approvals by Region and FUS Manufacturer continued

Indications	North America			Europe			Asia					S.Amer. <sup>4</sup>	Oceania <sup>5</sup>	Africa
	US FDA	Canada Health Canada	Other <sup>1</sup>	Europe CE Mark	Russia Roszdravnadzor	China CFDA	India CDSCO	Japan MHLW	Korea MFDS	Mid East <sup>2</sup>	Taiwan Taiwan FDA	Other <sup>3</sup>	SA MCC	
<b>Oncological</b>														
Bone cancer				●										
Bone metastases	●	●	●	●■	■	●		●	●	●■	●	●■	●■	●■
Breast cancer				●	●	●●								
Kidney tumors				●	●	●●								
Liver tumors				●	●	●●●		●●						
Pancreatic tumors				●	●	●		●●						
Prostate cancer	▲■	▲■	■	▲●■	▲■	■	▲■	■	▲■	▲■	▲■	▲■	■	■
Soft tissue cancer				●	●	●●								
<b>Ophthalmological</b>														
Glaucoma				▲		▲								
<b>Pain</b>														
Arthritis - facetogenic			●	●				●	●	●	●	●	●	●
Bone metastases	●	●	●	●■	■	●		●	●	●■	●	●■	●■	●■
Bone tumors, benign			●	●				●		●	●	●	●	●
Neuropathic pain				●				●						
Osteoid osteoma			●	●●	●	●		●		●	●	●	●	●
Pancreatic tumors				●	●	●		●●						

### Manufacturers

<p><b>North America</b></p> <ul style="list-style-type: none"> <li>■ Guided Therapy Systems, US</li> <li>■ Kona Medical, US</li> <li>■ Mirabilis Medical, US</li> <li>■ Profound Medical, Canada</li> <li>■ SonaCare Medical, US</li> </ul>	<p><b>Europe</b></p> <ul style="list-style-type: none"> <li>▲ EDAP TMS, France</li> <li>▲ EyeTechCare, France</li> <li>▲ Theraclion, France</li> </ul> <p><b>Asia</b></p> <ul style="list-style-type: none"> <li>● Alpinion Medical Systems, Korea</li> <li>● Beijing Yuande Bio-Medical Engineering, China</li> </ul>	<ul style="list-style-type: none"> <li>● Chongqing Haifu Medical Technology Co., China</li> <li>● EpiSonica, Taiwan</li> <li>● INSIGHTEC, Israel</li> <li>● Shanghai A&amp;S, China</li> <li>● Shenzhen PRO-HITU Medical, China</li> <li>● Wuxi Haiying Electronic Medical, China</li> </ul>
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1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
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 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE

FUS Regulatory Approvals by Region and FUS Manufacturer continued

Indications	North America			Europe			Asia					S.Amer. <sup>4</sup>	Oceania <sup>5</sup>	Africa
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<b>Pediatrics</b>														
Bone metastases	●	●	●	●■	■	●		●	●	●■	●	●■	●■	●■
Osteoid osteoma			●	●●	●	●			●		●	●	●	●
Soft tissue cancer				●	●	●●								
Soft tissue tumors, benign				●	●	●					●			
<b>Urological</b>														
Kidney tumors				●	●	●●								
Prostate diseases	▲■	▲■	■	▲●■	▲■	■	▲■	■	▲■	■		■	▲■	■
<b>Women's Health</b>														
Breast cancer				●	●	●●●								
Breast fibroadenoma				▲	▲				▲					
Uterine adenomyosis			●	●●■	●●■	●		●●●	●●■	●●■	●●■	●●■	●●■	●●■
Uterine fibroids	●	●■	●■	●●●■	●●●■	●●■		●●●	●●■	●●■	●●■	●●■	●●■	●●■

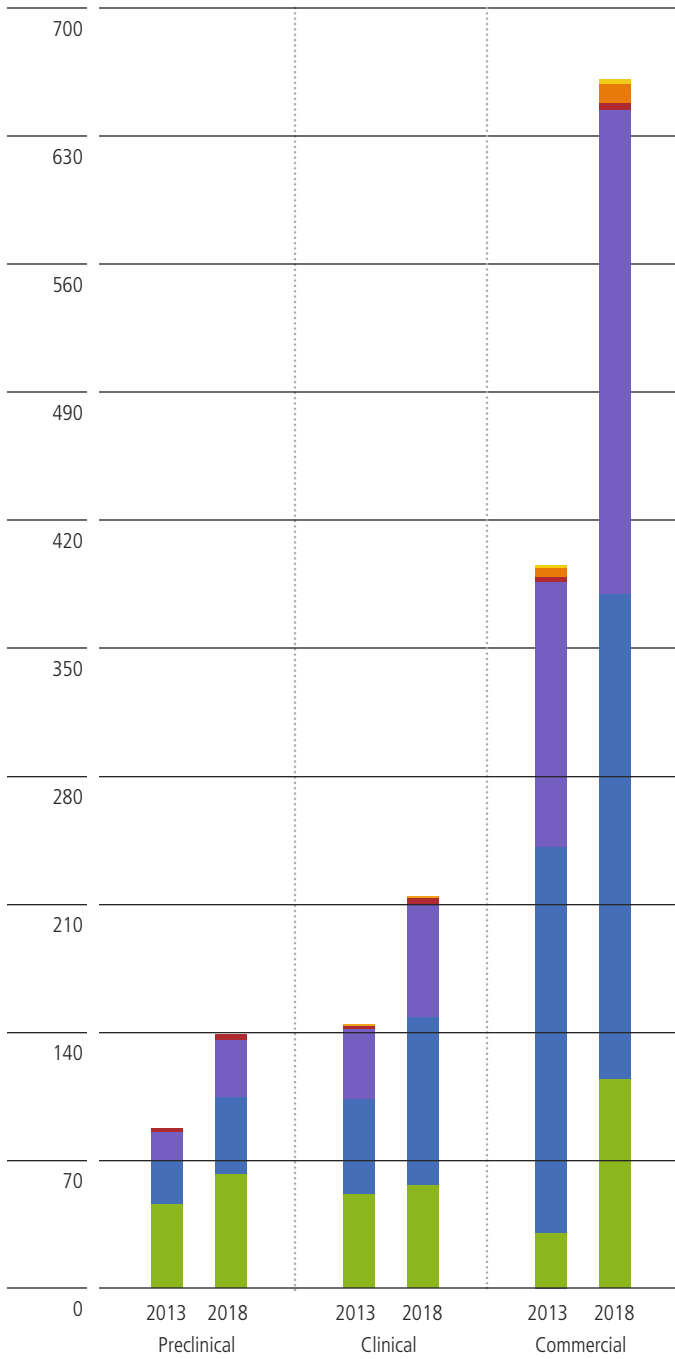
Manufacturers

- |   |  |  |
|---|--|--|
| <p><b>North America</b></p> <ul style="list-style-type: none"> <li>■ Guided Therapy Systems, US</li> <li>■ Kona Medical, US</li> <li>■ Mirabilis Medical, US</li> <li>■ Profound Medical, Canada</li> <li>■ SonaCare Medical, US</li> </ul> | <p><b>Europe</b></p> <ul style="list-style-type: none"> <li>▲ EDAP TMS, France</li> <li>▲ EyeTechCare, France</li> <li>▲ Theraclion, France</li> </ul> <p><b>Asia</b></p> <ul style="list-style-type: none"> <li>● Alpinion Medical Systems, Korea</li> <li>● Beijing Yuande Bio-Medical Engineering, China</li> </ul> | <ul style="list-style-type: none"> <li>● Chongqing Haifu Medical Technology Co., China</li> <li>● EpiSonica, Taiwan</li> <li>● INSIGHTEC, Israel</li> <li>● Shanghai A&amp;S, China</li> <li>● Shenzhen PRO-HITU Medical, China</li> <li>● Wuxi Haiying Electronic Medical, China</li> </ul> |
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1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
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 5 Oceania - Australia, TGA; New Zealand, MEDSAFE

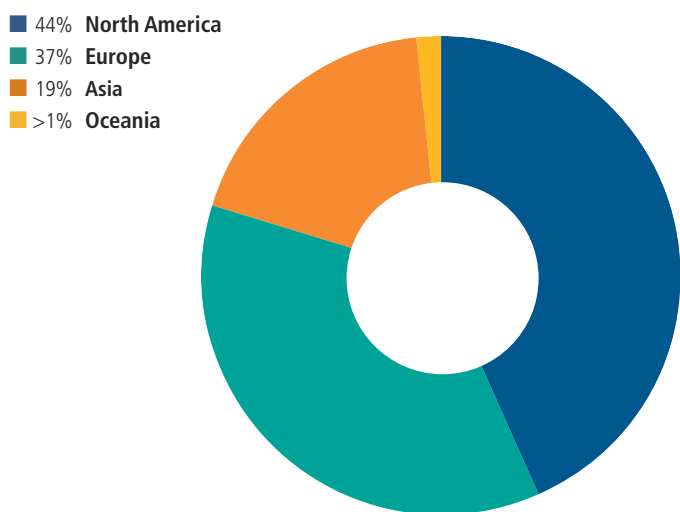
## Growth in Number of Sites Over Time

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



Technical Research Sites\*

	Sites				Totals
	North America	Europe	Asia	Oceania	
<b>Drug Delivery Technology</b>	21	12	4	1	<b>38</b>
<b>FUS Physics</b>	39	28	16	–	<b>83</b>
<b>FUS Simulation and Treatment Planning</b>	20	19	6	–	<b>45</b>
<b>FUS Transducer Technology</b>	16	19	10	–	<b>45</b>
<b>FUS Treatment Monitoring</b>	30	28	15	–	<b>73</b>
<b>MR Imaging for FUS Guidance</b>	31	35	20	–	<b>86</b>
<b>Standards &amp; Quality Assurance</b>	8	6	3	–	<b>17</b>
<b>Ultrasound Imaging for FUS Guidance</b>	29	16	9	–	<b>54</b>
	194	163	83	1	<b>441</b>



Technical research programs are designed to address high-priority scientific and engineering problems. Solutions developed by technical sites help to make clinical treatments faster, safer, less expensive, and available to the widest patient population possible.

Asian research sites may be underrepresented here due to language and cultural barriers. The Foundation is working on this issue and has hired an employee based in Asia and created a team of employees and volunteers to help with outreach to the Asian FUS community.

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

## Mechanisms of Action

TISSUE DESTRUCTION	DRUG DELIVERY	INCREASED VASCULAR PERMEABILITY	IMMUNOMODULATION	OTHER
<b>6</b> mechanisms	<b>6</b> mechanisms	<b>5</b> mechanisms	<b>3</b> mechanisms	<b>13</b> mechanisms
Histotripsy Hyperthermia Mechanical ablation Other <sup>1</sup> Thermal ablation Vascular disruption	Blood-brain barrier opening Drug delivery vehicles Hyperthermia Sonoporation Therapeutic delivery (unencapsulated) Vasodilation	Blood-brain barrier opening Drug delivery Hyperthermia Stem cell delivery Therapeutic delivery (unencapsulated)	Immune cell delivery <b>Immunomodulation</b> <sup>2</sup> Immunotherapeutic delivery	Amplification of cancer biomarkers Angiogenesis Cardiac pacing Clot lysis Hemostasis <b>Liquid biopsy</b> <sup>2</sup> Neuromodulation Radiosensitization Sensitization to chemotherapy Sonodynamic therapy Stem cell homing Vasoconstriction Vasodilation

### Research Sites Investigating Mechanisms of Action

Focused ultrasound is a platform technology that can produce multiple biological effects, either through thermal or mechanical means, that act therapeutically on the target. These effects are dependent on the nature of the tissue (e.g. muscle vs. bone) and the ultrasound parameters (power, duration, and mode—continuous vs. pulsed).

The availability of a variety of mechanisms of action creates the possibility of treating a variety of disorders. While this report highlights the number of research sites working in these areas and identifies geographic locations, it is not an in-depth overview of how the various mechanisms work. An overview of focused ultrasound’s biological effects is

available on the Foundation’s website as a white paper, *An Overview of the Biological Effects of Focused Ultrasound*.

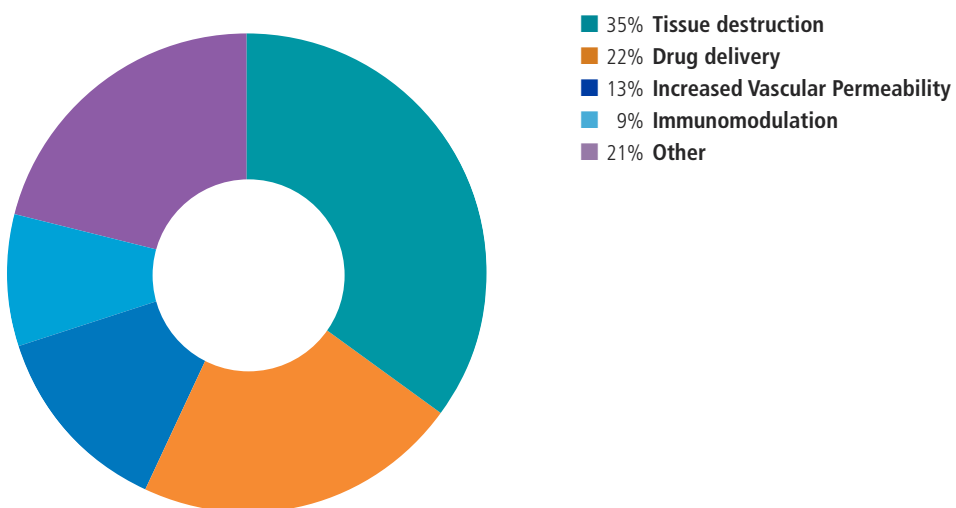
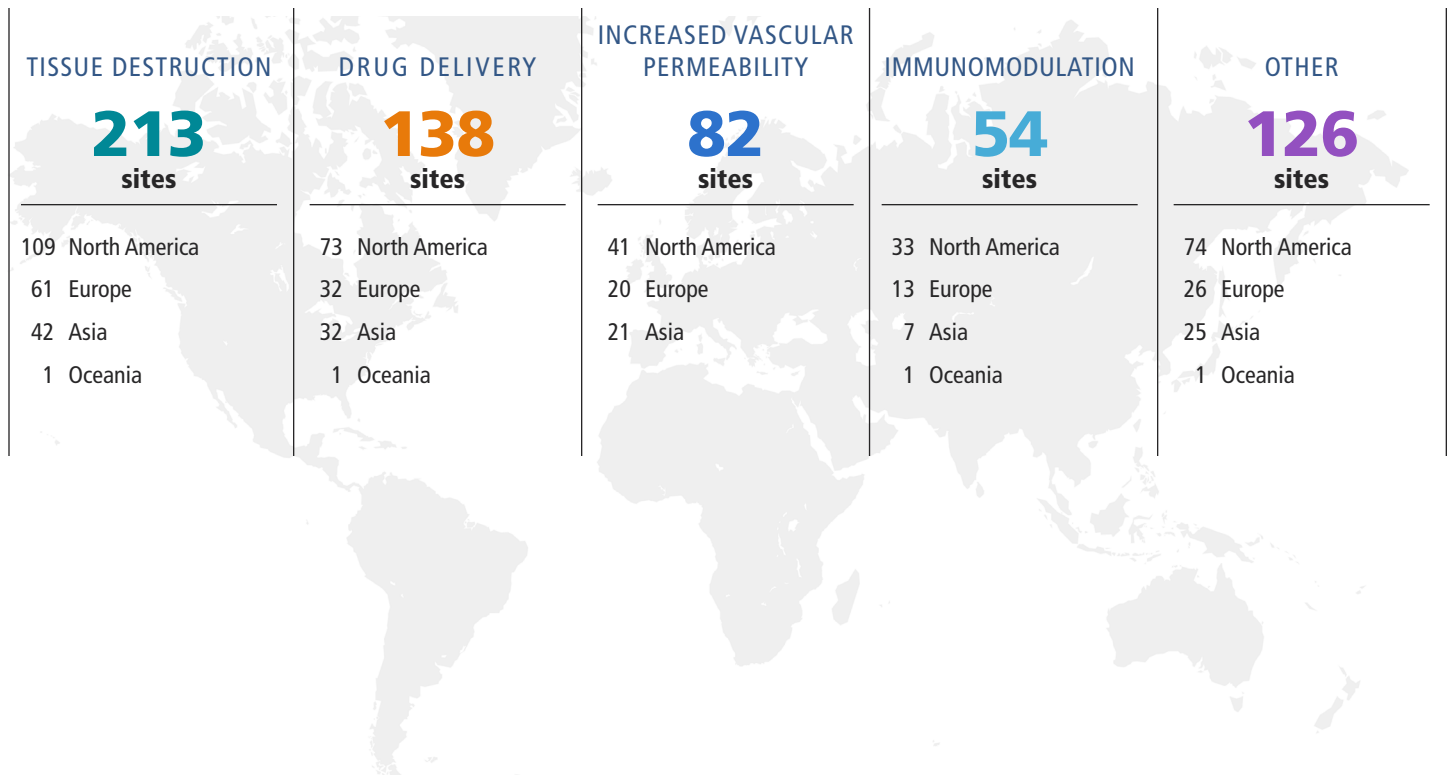
To date, all of the focused ultrasound regulatory approvals for the various indications listed use thermal ablation as the mechanism of action, see pages 23–25. However, given the number of research sites interested in alternate mechanisms of action and the number of clinical trials underway using these alternatives, we predict this regulatory approval landscape will change dramatically over the next few years.

There are 19 distinct mechanisms of action.

<sup>1</sup> Includes multiple mechanisms of denervation and kidney stone propulsion

<sup>2</sup> Mechanisms of Action in bold are new in 2018.

Research Sites Investigating Mechanisms of Action\*

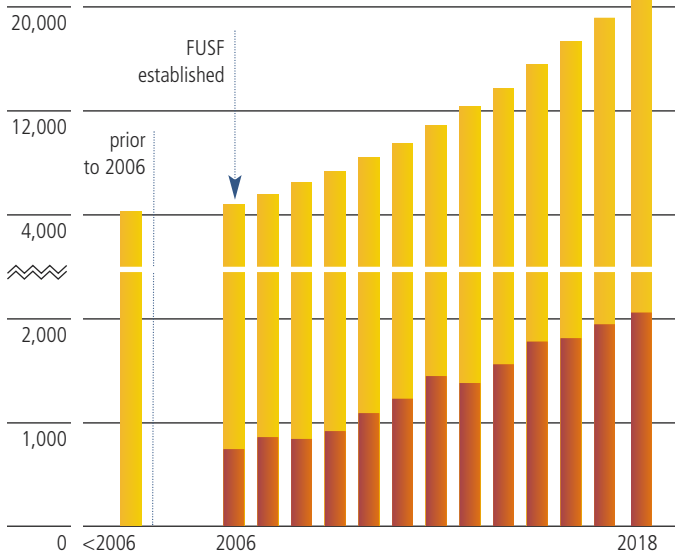


\*Sites researching more than one mechanism of action are counted in each area of active study.

# OVERVIEW

## FUS Publications

■ Per year ■ Cumulative total



Source: Data from Web of Knowledge as of March 5, 2019

## FUS Citations

Cumulative

**20,327**

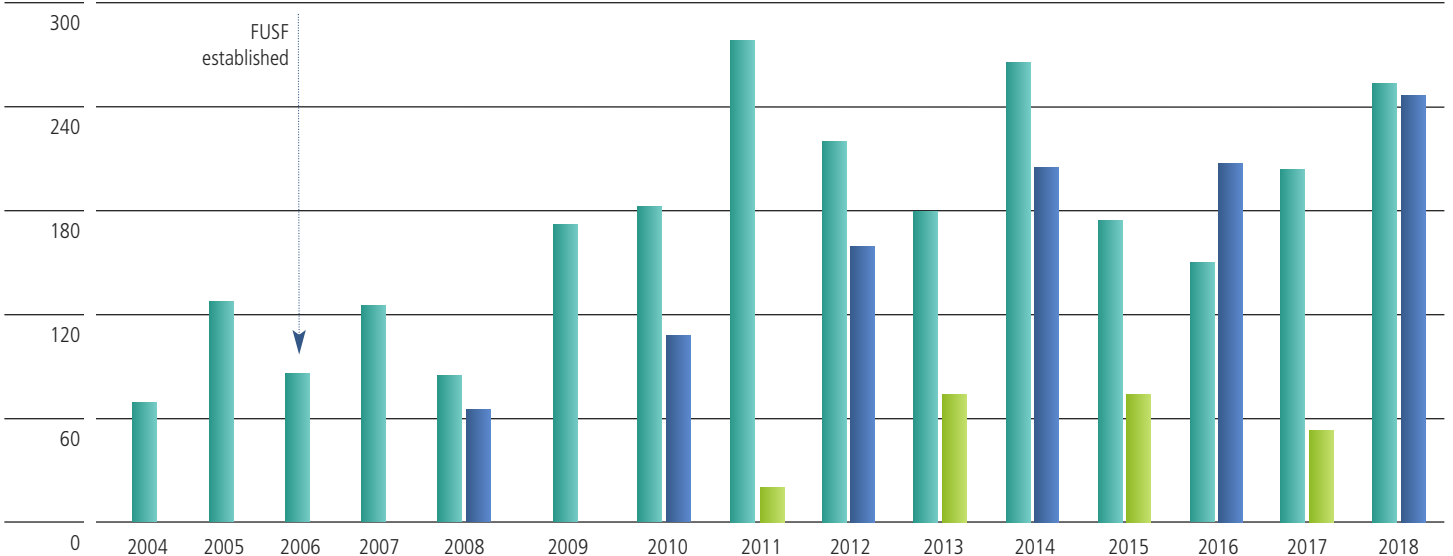
FUS publications

**363,282**

Citations of FUS publications

## Abstracts Presented at FUS Symposia

■ Focused Ultrasound Foundation Symposium (FUSF)\* ■ European Symposium on Focused Ultrasound Therapy (EUFUS)\* ■ International Symposium on Therapeutic Ultrasound (ISTU)



\*Held biennially



## FUS Abstracts Presented at Other Symposia

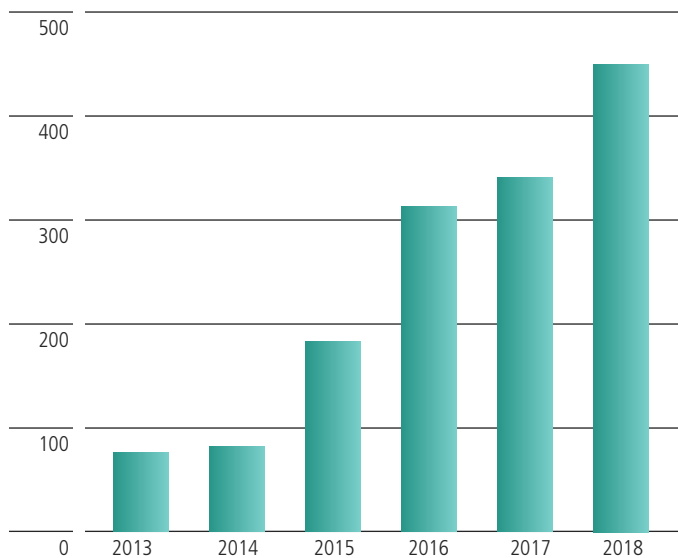
Symposium	2015	2016	2017	2018
Acoustical Society of America	19	64	48	39
American Association of Physicists in Medicine (AAPM)	14	8	16	5
American Institute of Ultrasound in Medicine (AIUM)	4	2	–	9
American Society for Radiation Oncology	–	2	5	3
American Society for Stereotactic and Functional Neurosurgery	–	3	–	6
American Urological Association (AUA)	4	11	7	4
Biomedical Engineering Society	13	12	16	14
European Congress of Radiology	7	7	13	22
IEEE International Engineering in Medicine and Biology	11	9	5	11
IEEE International Ultrasonics Symposium	42	26	71	19
Japanese Society for Therapeutic Ultrasound	37	39	35	48
Korean Society for Therapeutic Ultrasound	10	14	15	17
Radiological Society of North America (RSNA)	18	21	17	14
Society for Thermal Medicine (STM)	4	22	10	10
Society of Interventional Radiology	15	69	55	86
<b>Totals</b>	<b>198</b>	<b>309</b>	<b>313</b>	<b>307</b>

### FUS Abstracts

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

## FUS Media Placements in the US

Per year



# 1,461

Media placements in last 6 years

### News Outlets

- ABC News Australia
- AP Wire
- Associated Press
- Baltimore Sun
- BBC News
- Boston Globe
- CBC
- CBS Miami
- CBS New York
- Chicago Evening Post
- CNBC
- Colorado Springs Gazette
- Daily Mail
- Daily Telescope

- The Edge Singapore
- GlobeNewswire
- The Hill
- Houston Chronicle
- Huffington Post
- KING-5 TV Seattle
- KSAT San Antonio
- Medgadget
- Miami Herald
- Nashville Post
- NBC News
- New York Times
- Newswise
- NPR
- Oregon Live

- Penn State News
- PRNewswire
- Pulse
- Roanoke Times
- South China Morning Post
- Sound & Vision
- Tech Nation
- Telegraph Herald
- Telegraph UK
- The Oklahoman
- The Times
- Toronto Star
- University of Queensland News
- WBZ CBS Boston
- WINA News Radio
- WIRED

### Business Coverage

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

### Science Coverage

- Acoustical Society of America
- Alzheimer's News Today
- American Veterinarian
- Being Patient
- Cancer Therapy Advisor
- DOTmed
- EurekAlert
- Genetic Engineering & Biotech News
- Health Imaging
- Healthline
- Institute of Cancer Research Blog
- Journal of Therapeutic Ultrasound

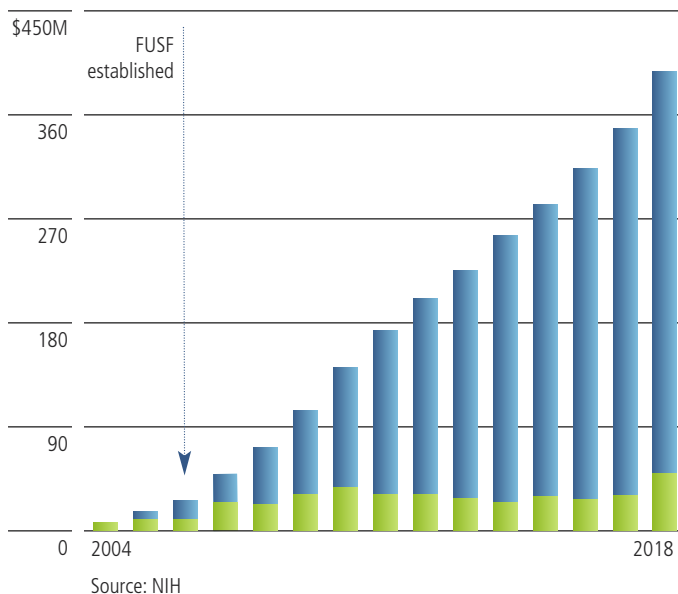
- Journal of Clinical Pathways
- Life Science Daily
- Mass Device
- MD Magazine
- MedCity News
- Med Page Today
- Medical Daily Times
- Medical Physics Web
- Medscape
- Nature
- News-Medical.net
- Neurology Advisor
- Oxford Journals
- Parkinson's News Today
- PharmWeb.com
- Physics World
- Radio MD
- Radiology Business
- R&D Magazine
- Science 2.0
- Science Daily
- Scientific American
- STAT
- UCLA Urology
- UroToday
- Veterinary Practice News

### Commercial Television

- Grey's Anatomy
- New Amsterdam
- The Doctors

## Total Awards for All FUS NIH Research Grants

Dollars in millions ■ Annual funding ■ Cumulative funding



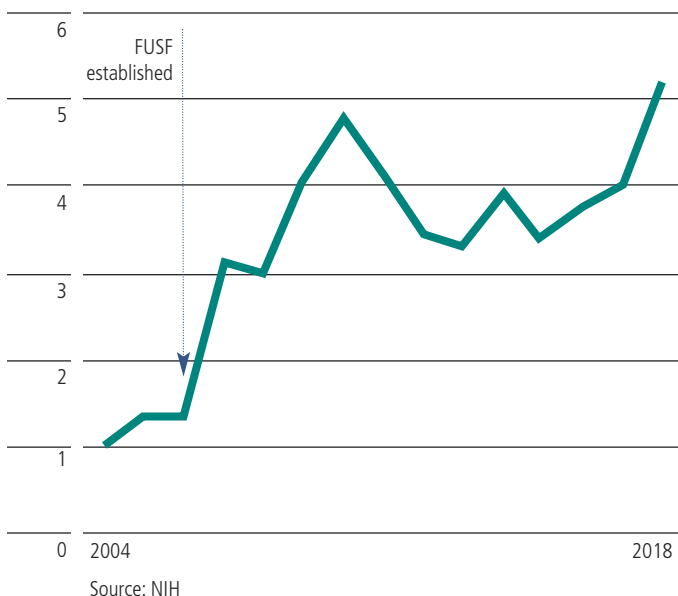
### Total Awards for All FUS NIH Research Grants\*

Focused ultrasound research funding by the National Institutes of Health (NIH) remains robust. Funding has grown nearly 15 percent year-over-year since 2004. In contrast, total NIH funding since 2004 has only grown at 2.1 percent. Overall, the NIH has invested more than \$400 million in 971 FUS-related research projects during the past 15 years.

\* <https://projectreporter.nih.gov/>, search term "focused ultrasound"

## FUS Funding Relative to NIH Total Budget

Relative funding of focused ultrasound



### FUS Funding Relative to NIH Total Budget\*\*

The compound annual growth rate of FUS funding has outpaced total NIH funding. Relative FUS funding has increased over the years, to the point that it was five times more in 2018 as compared to 2004. This is a 12.6 percent compound growth rate in proportional NIH funding. Even though the NIH budget has been somewhat stagnant over the last 15 years, the portion allocated to focused ultrasound research has grown considerably. Funding increases of this nature are typical for medical areas that have the most potential for improving patient health.

\*\* <https://projectreporter.nih.gov/>, search term "focused ultrasound" and <https://fas.org/sgp/crs/misc/R43341.pdf>. The ratio of funding for FUS research to overall NIH funding in 2004 was 0.026%. This value was set at 1, and ratios for subsequent years were calculated relative to that of 2004.

Commercial Treatment Sites by Region\*



\*Commercial treatment sites provide focused ultrasound treatment with a regulatory-approved device.

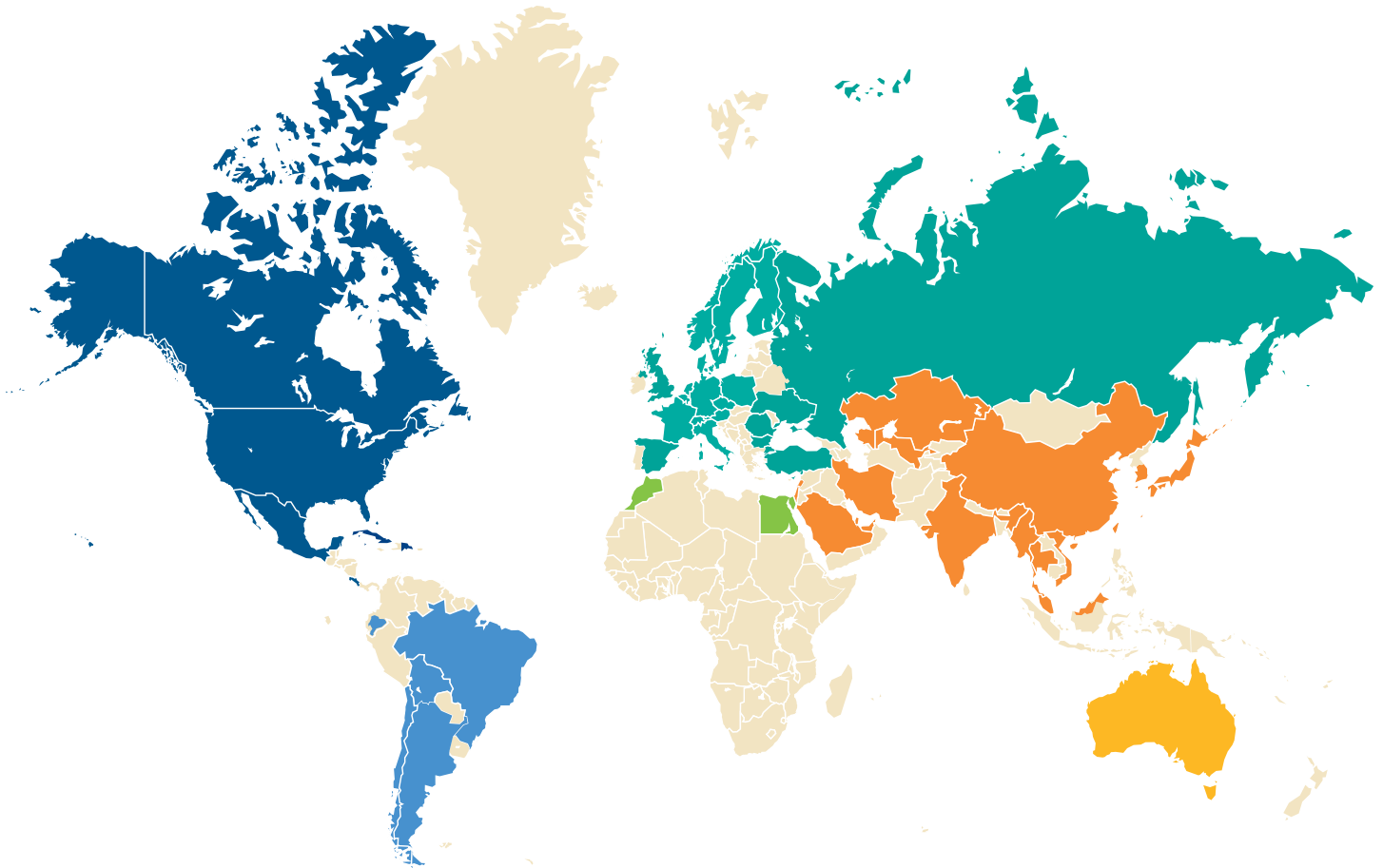
**Commercial Treatment Additional Content**

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

[www.fusfoundation.org/the-technology/treatment-sites](http://www.fusfoundation.org/the-technology/treatment-sites)

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

34 indications are being treated commercially at sites worldwide



**North America**

- 1 Bahamas
- 8 Canada
- 1 Cayman Islands
- 1 Costa Rica
- 1 Cuba
- 2 Dominican Republic
- 9 Mexico
- 91 United States

**South America**

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

**Europe**

- 4 Austria
- 2 Belgium
- 2 Bulgaria
- 1 Denmark
- 1 Finland
- 73 France
- 57 Germany
- 42 Italy
- 1 Monaco
- 2 The Netherlands
- 2 Norway
- 4 Poland
- 2 Romania

**29 Russia Federation**

- 11 Spain
- 2 Sweden
- 13 Switzerland
- 1 Turkey
- 1 Ukraine
- 15 United Kingdom

**Asia**

- 153 China
- 8 India
- 1 Iran
- 4 Israel
- 40 Japan
- 1 Kazakhstan
- 1 Lebanon
- 1 Malaysia
- 1 Myanmar
- 2 Qatar
- 23 South Korea
- 2 Saudi Arabia
- 1 Singapore
- 21 Taiwan
- 2 Thailand

**1 United Arab Emirates**

- 1 Uzbekistan
- 2 Vietnam

**Oceania**

- 3 Australia

**Africa**

- 2 Egypt
- 1 Morocco

# COMMERCIAL TREATMENT

## Commercial Treatment Sites by Indication and Region

34 indications are being treated commercially at sites worldwide.\*

Indications	Regions						Totals
	N. America	Europe	Asia	S. America	Africa	Oceania	
<b>Cardiovascular</b>							
Arteriovenous malformations	1	2	–	–	–	–	<b>3</b>
<b>Endocrine Disorders</b>							
Thyroid nodules	–	11	1	–	–	–	<b>12</b>
<b>Gastrointestinal</b>							
Liver metastases	–	1	1	–	–	–	<b>2</b>
Liver metastases, Breast cancer	–	1	–	–	–	–	<b>1</b>
Liver tumors	1	11	89	–	–	–	<b>101</b>
Pancreatic tumors	–	4	2	–	–	–	<b>6</b>
<b>Miscellaneous</b>							
Multiple tumors	–	1	–	–	–	–	<b>1</b>
<b>Musculoskeletal</b>							
Arthritis - facetogenic	2	1	1	–	–	1	<b>5</b>
Arthritis - sacroiliac	1	–	–	–	–	–	<b>1</b>
Bone cancer	2	3	1	–	–	1	<b>7</b>
Bone metastases	6	18	6	–	–	1	<b>31</b>
Bone tumors, benign	1	–	–	–	–	–	<b>1</b>
Desmoid tumors	2	–	–	–	–	–	<b>2</b>
Osteoid osteoma	3	12	88	–	–	1	<b>104</b>
Soft tissue tumors, benign	2	11	88	–	–	1	<b>102</b>
<b>Neurological</b>							
Dystonia	–	1	–	–	–	–	<b>1</b>
Epilepsy	–	1	–	–	–	–	<b>1</b>
Essential tremor	13	9	9	–	–	1	<b>32</b>
Holmes tremor	–	1	–	–	–	–	<b>1</b>
Multiple sclerosis	–	1	–	–	–	–	<b>1</b>
Neuropathic pain	–	4	–	–	–	–	<b>4</b>
Parkinson's disease	2	7	1	–	–	–	<b>10</b>
Trigeminal neuralgia	–	1	–	–	–	–	<b>1</b>
<b>Ophthalmological</b>							
Glaucoma	–	16	–	–	–	–	<b>16</b>

\*Some indications listed do not have specific regulatory approval for commercial treatment. However, sites have treated patients off label and are reporting those treatments. For more information about specific commercial treatment sites and indications, please visit: [www.fusfoundation.org/the-technology/treatment-sites](http://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

34 indications are being treated commercially at sites worldwide.\*

Indications	Regions						Totals
	N. America	Europe	Asia	S. America	Africa	Oceania	
<b>Pain</b>							
Arthritis - facetogenic	2	1	1	–	–	1	5
Arthritis - sacroiliac	1	–	–	–	–	–	1
Bone cancer	2	3	1	–	–	1	7
Bone metastases	6	18	6	–	–	1	31
Bone tumors, benign	1	–	–	–	–	–	1
Desmoid tumors	2	–	–	–	–	–	2
Neuropathic pain	–	4	–	–	–	–	4
Osteoid osteoma	3	12	88	–	–	1	104
Pancreatic tumors	–	4	2	–	–	–	6
<b>Pediatrics</b>							
Bone metastases	6	18	6	–	–	1	31
Desmoid tumors	2	–	–	–	–	–	2
Epilepsy	–	1	–	–	–	–	1
Multiple tumors	–	1	–	–	–	–	1
Osteoid osteoma	3	12	88	–	–	1	104
Soft tissue tumor, benign	2	11	88	–	–	1	102
<b>Pulmonary</b>							
—							
<b>Urological</b>							
Benign prostatic hyperplasia	32	6	27	1	–	–	66
Kidney stone fragmentation	–	1	–	–	–	–	1
Kidney stone propulsion	1	–	–	–	–	–	1
Kidney tumors	1	9	88	–	–	–	98
Prostate diseases	93	183	33	9	2	–	320
<b>Women's Health</b>							
Breast cancer	1	11	89	–	–	–	101
Breast fibroadenoma	–	16	1	–	1	–	18
Endometrial tumors	–	–	1	–	–	–	1
Uterine adenomyosis	2	4	81	–	–	1	88
Uterine fibroids	12	45	201	1	–	2	261

\*Some indications listed do not have specific regulatory approval for commercial treatment. However, sites have treated patients off label and are reporting those treatments. For more information about specific commercial treatment sites and indications, please visit: [www.fusfoundation.org/the-technology/treatment-sites](http://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

34 indications are being treated commercially at sites worldwide.\*

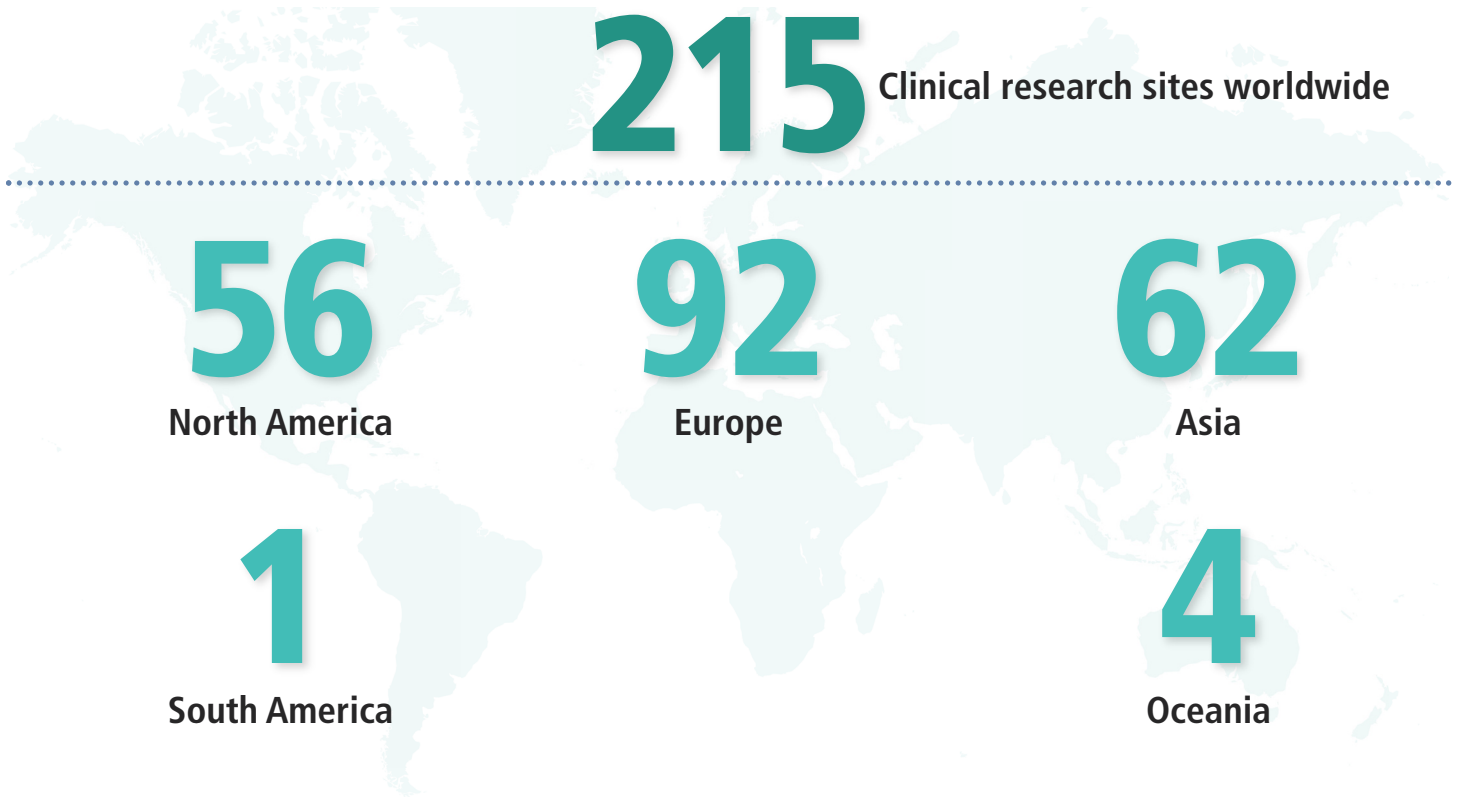
Indications	Regions						Totals
	N. America	Europe	Asia	S. America	Africa	Oceania	
<b>Oncological</b>							
Bone cancer	2	3	1	–	–	1	<b>7</b>
Bone metastases	6	18	6	–	–	1	<b>31</b>
Breast cancer	1	11	89	–	–	–	<b>101</b>
Endometrial tumors	–	–	1	–	–	–	<b>1</b>
Kidney tumors	1	9	88	–	–	–	<b>98</b>
Liver metastases	–	1	1	–	–	–	<b>2</b>
Liver metastases, Breast cancer	–	1	–	–	–	–	<b>1</b>
Liver tumors	1	11	89	–	–	–	<b>101</b>
Multiple tumors	–	1	–	–	–	–	<b>1</b>
Pancreatic tumors	–	4	2	–	–	–	<b>6</b>
Prostate cancer	93	183	33	9	2	–	<b>320</b>

\*Some indications listed do not have specific regulatory approval for commercial treatment. However, sites have treated patients off label and are reporting those treatments. For more information about specific commercial treatment sites and indications, please visit: [www.fusfoundation.org/the-technology/treatment-sites](http://www.fusfoundation.org/the-technology/treatment-sites). Use the "search by disease" dropdown menu and/or location.



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Clinical Research Sites by Region\*



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

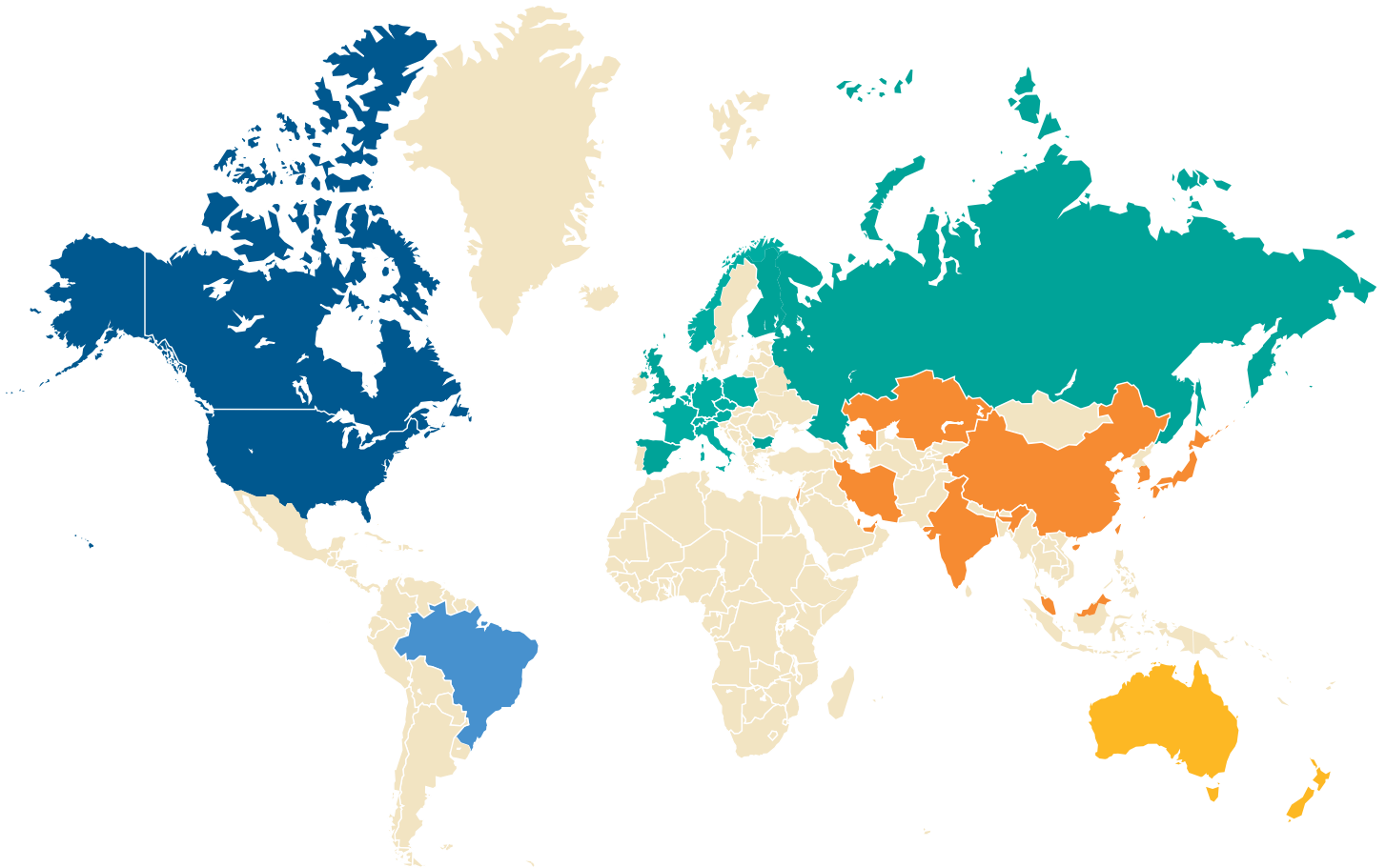
**Clinical Research Additional Content**

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

[www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites)

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

62 indications are being researched at clinical sites worldwide



**North America**

- 10 Canada
- 46 United States

**South America**

- 1 Brazil

**Europe**

- 3 Austria
- 1 Belgium
- 1 Bulgaria
- 5 Czech Republic
- 1 Finland
- 13 France
- 20 Germany
- 16 Italy
- 3 The Netherlands
- 3 Norway
- 1 Poland
- 5 Russia Federation
- 5 Spain
- 3 Switzerland
- 12 United Kingdom

**Asia**

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

**Oceania**

- 3 Australia
- 1 New Zealand

## Clinical Research Sites by Indication and Region

62 indications are being treated commercially at sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
<b>Cardiovascular</b>						
Arteriovenous malformations	–	1	–	–	–	1
Hypertension	–	16	2	–	1	19
Peripheral artery disease	1	–	–	–	–	1
Varicose veins	–	2	–	–	–	2
<b>Endocrine Disorders</b>						
Graves' disease	–	–	1	–	–	1
Hyperparathyroidism	–	1	–	–	–	1
Thyroid cancer	–	1	–	–	–	1
Thyroid nodules	–	3	1	–	–	4
<b>Gastrointestinal</b>						
Colorectal tumors	1	–	–	–	–	1
Liver metastases	–	5	–	–	–	5
Liver tumors	1	8	13	–	–	22
Malignant obstructive jaundice	–	–	1	–	–	1
Pancreatic tumors	–	9	7	–	–	16
<b>Miscellaneous</b>						
Head & neck tumors	1	1	–	–	–	2
Hypersplenism	–	–	1	–	–	1
Melanoma	–	1	–	–	–	1
Multiple tumors	1	–	–	–	–	1
<b>Musculoskeletal</b>						
Arthritis	–	1	–	–	–	1
Arthritis - facetogenic	1	4	1	1	–	7
Arthritis - knee	–	1	–	–	–	1
Arthritis - sacroiliac	–	1	–	–	–	1
Bone cancer	2	7	–	–	–	9
Bone metastases	1	15	6	1	1	24
Bone tumors, benign	–	1	–	–	–	1
Desmoid tumors	–	2	–	–	–	2
Multiple myeloma	–	1	–	–	–	1
Osteoid osteoma	5	7	13	1	–	26
Sacral chordoma	–	1	–	–	–	1

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

62 indications are being treated commercially at sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
<b>Musculoskeletal</b> continued						
Soft tissue cancer	2	5	–	–	–	<b>7</b>
Soft tissue tumors, benign	4	8	14	–	1	<b>27</b>
<b>Neurological</b>						
Addiction	–	1	–	–	–	<b>1</b>
Alzheimer's disease	3	1	1	–	–	<b>5</b>
Amyotrophic lateral sclerosis	1	–	–	–	–	<b>1</b>
Astrocytoma (SEGA)	3	2	–	–	–	<b>5</b>
Brain metastases, Breast cancer	1	–	–	–	–	<b>1</b>
Cancer pain	–	1	–	–	–	<b>1</b>
Dementia	–	1	–	–	–	<b>1</b>
Depression	1	–	1	–	–	<b>2</b>
Dystonia	1	–	1	–	–	<b>2</b>
Epilepsy	2	–	1	–	–	<b>3</b>
Essential tremor	7	3	3	–	–	<b>13</b>
Glioblastoma	3	5	2	–	–	<b>10</b>
Holmes tremor	1	–	–	–	–	<b>1</b>
Neuropathic pain	2	2	–	–	–	<b>4</b>
Obsessive-compulsive disorder	1	–	–	–	–	<b>1</b>
Painful amputation neuromas	–	1	1	–	–	<b>2</b>
Parkinson's disease	11	3	1	–	–	<b>15</b>
Stroke	–	1	–	–	–	<b>1</b>
<b>Ophthalmological</b>						
Glaucoma	1	7	–	–	–	<b>8</b>
<b>Pain</b>						
Arthritis	–	1	–	–	–	<b>1</b>
Arthritis - facetogenic	1	4	1	1	–	<b>7</b>
Arthritis - knee	–	–	1	–	–	<b>1</b>
Arthritis - sacroiliac	–	1	–	–	–	<b>1</b>
Bone cancer	2	7	–	–	–	<b>9</b>
Bone metastases	1	15	6	1	1	<b>24</b>
Bone tumors, benign	–	1	–	–	–	<b>1</b>
Cancer pain	–	1	–	–	–	<b>1</b>

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

62 indications are being treated commercially at sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
<b>Pain continued</b>						
Desmoid tumors	–	2	–	–	–	<b>2</b>
Multiple myeloma	–	1	–	–	–	<b>1</b>
Neuropathic pain	2	2	–	–	–	<b>4</b>
Osteoid osteoma	5	7	13	1	–	<b>26</b>
Painful amputation neuromas	–	1	1	–	–	<b>2</b>
Pancreatic tumors	–	9	7	–	–	<b>16</b>
<b>Pediatrics</b>						
Astrocytoma (SEGA)	3	2	–	–	–	<b>5</b>
Bone metastases	1	15	6	1	1	<b>24</b>
Desmoid tumors	–	2	–	–	–	<b>2</b>
Epilepsy	2	–	1	–	–	<b>3</b>
Multiple tumors	1	–	–	–	–	<b>1</b>
Osteoid osteoma	5	7	13	1	–	<b>26</b>
Sacral chordoma	–	1	–	–	–	<b>1</b>
Soft tissue cancer	2	5	–	–	–	<b>7</b>
Soft tissue tumors, benign	4	8	14	–	1	<b>27</b>
<b>Pulmonary</b>						
Lung metastases	–	1	–	–	–	<b>1</b>
<b>Urological</b>						
Acute kidney injury	–	–	1	–	–	<b>1</b>
Benign prostatic hyperplasia	1	2	–	–	–	<b>3</b>
Kidney tumors	–	5	13	–	–	<b>18</b>
Prostate diseases	34	21	6	–	–	<b>61</b>
<b>Women's Health</b>						
Breast cancer	1	9	14	–	–	<b>24</b>
Breast fibroadenoma	5	3	2	–	–	<b>10</b>
Ectopic pregnancy	–	–	1	–	–	<b>1</b>
Endometrial tumors	–	1	–	–	–	<b>1</b>
Endometriosis	–	2	1	–	–	<b>3</b>
Retained placenta	–	–	1	–	–	<b>1</b>
Uterine adenomyosis	–	6	9	–	2	<b>17</b>
Uterine fibroids	1	26	36	1	2	<b>66</b>

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

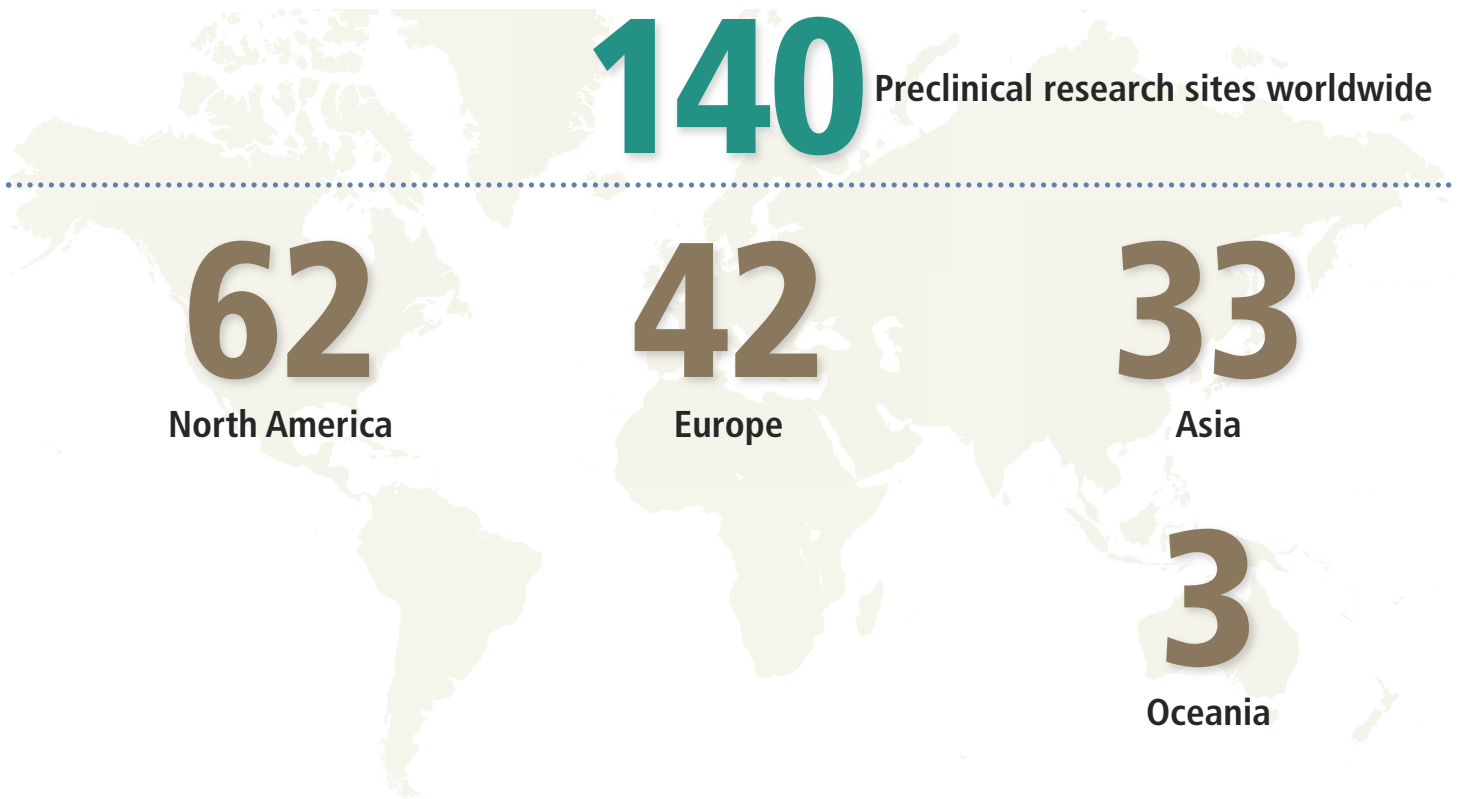
## Clinical Research Sites by Indication and Region continued

62 indications are being treated commercially at sites worldwide.

Indications	Regions					Totals
	N. America	Europe	Asia	S. America	Oceania	
<b>Oncological</b>						
Bone cancer	2	7	–	–	–	<b>9</b>
Bone metastases	1	15	6	1	1	<b>24</b>
Brain metastases, Breast cancer	1	–	–	–	–	<b>1</b>
Breast cancer	1	9	14	–	–	<b>24</b>
Cancer pain	–	1	–	–	–	<b>1</b>
Colorectal tumors	1	–	–	–	–	<b>1</b>
Endometrial tumors	–	1	–	–	–	<b>1</b>
Glioblastoma	3	5	2	–	–	<b>10</b>
Head & neck tumors	1	1	–	–	–	<b>2</b>
Kidney tumors	–	5	13	–	–	<b>18</b>
Liver metastases	–	5	–	–	–	<b>5</b>
Liver tumors	1	8	13	–	–	<b>22</b>
Lung metastases	–	1	–	–	–	<b>1</b>
Malignant obstructive jaundice	–	–	1	–	–	<b>1</b>
Melanoma	–	1	–	–	–	<b>1</b>
Multiple myeloma	–	1	–	–	–	<b>1</b>
Multiple tumors	1	–	–	–	–	<b>1</b>
Pancreatic tumors	–	9	7	–	–	<b>16</b>
Prostate cancer	34	21	6	–	–	<b>61</b>
Sacral chordoma	–	1	–	–	–	<b>1</b>
Soft tissue cancer	2	5	–	–	–	<b>7</b>
Thyroid cancer	–	1	–	–	–	<b>1</b>

For more information about specific clinical research sites and indications, please visit: [www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites).  
Use the “search by disease research” and/or “search by research stage” dropdown menu.

Preclinical Research Sites by Region\*



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

**Preclinical Research Additional Content**

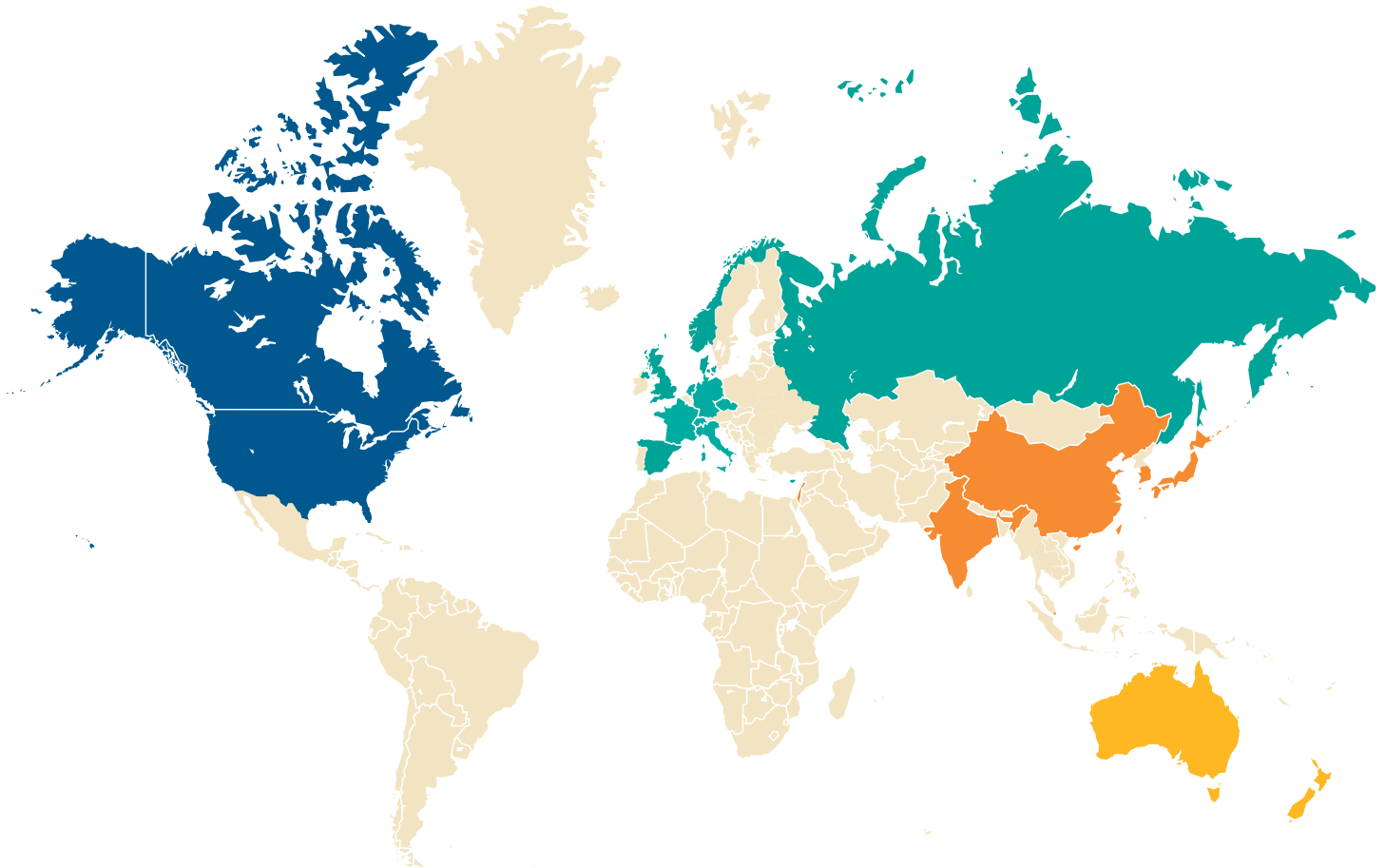
For more information about specific preclinical research sites and indications, please visit :

[www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites)

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



77 indications are being researched at preclinical sites worldwide



#### ■ North America

7 Canada  
55 United States

#### ■ Europe

1 Cyprus  
1 Czech Republic  
1 Denmark  
9 France  
9 Germany  
5 Italy  
2 The Netherlands  
1 Norway  
1 Russia Federation  
4 Spain  
3 Switzerland  
5 United Kingdom

#### ■ Asia

12 China  
1 India  
2 Israel  
6 Japan  
1 Singapore  
5 South Korea  
6 Taiwan

#### ■ Oceania

2 Australia  
1 New Zealand

## Preclinical Research Sites by Indication and Region

77 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
<b>Cardiovascular</b>					
Arteriovenous malformations	1	–	–	–	1
Atherosclerosis	5	4	1	–	10
Atrial fibrillation	1	2	–	–	3
Cardiac pacing	–	2	–	–	2
Congestive heart failure	1	–	1	–	2
Deep vein thrombosis	5	1	–	–	6
Fetal heart anomalies	1	–	–	–	1
Heart valve calcifications	–	1	–	–	1
Hypertension	3	2	–	1	6
Peripheral artery disease	2	1	–	–	3
Septal perforation	–	1	–	–	1
Varicose veins	–	1	–	–	1
<b>Endocrine Disorders</b>					
Diabetes	2	1	–	–	3
Graves' disease	1	–	–	–	1
Thyroid cancer	2	1	–	–	3
Thyroid nodules	1	1	–	–	2
<b>Gastrointestinal</b>					
Biliary tract tumors	–	2	–	–	2
Colorectal tumors	1	2	–	–	3
Esophageal tumors	–	1	–	–	1
Liver metastases	3	5	–	–	8
Liver tumors	16	16	5	–	34
Pancreatic tumors	11	18	4	–	33
<b>Miscellaneous</b>					
Head & neck tumors	–	3	1	–	4
Multiple tumors	4	1	–	–	5
Obesity	1	1	–	–	2
<b>Musculoskeletal</b>					
Arthritis	1	1	–	–	2
Arthritis - facetogenic	2	2	1	–	5
Arthritis - knee	–	1	1	–	2

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

77 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
<b>Musculoskeletal</b> continued					
Bone cancer	1	4	–	–	5
Bone metastases	6	7	3	1	17
Bone tumors, benign	2	1	–	–	3
Disc degeneration	1	–	–	–	1
Muscle atrophy	1	–	–	–	1
Osteoid osteoma	1	1	2	–	4
Soft tissue cancer	6	2	–	–	8
Soft tissue tumors, benign	4	3	2	–	9
<b>Neurological</b>					
Addiction	–	–	1	–	1
Alzheimer's disease	7	6	–	2	15
Amyotrophic lateral sclerosis	1	1	–	–	2
Astrocytoma (SEGA)	9	5	3	–	17
Brain metastases, Breast cancer	2	–	–	–	2
Cancer pain	3	6	–	–	9
Depression	1	2	–	–	3
Epilepsy	10	4	–	–	14
Essential tremor	1	3	1	–	5
Glioblastoma	19	12	8	–	39
Hydrocephalus	1	1	–	–	2
Multiple sclerosis	2	–	–	–	2
Neuroblastoma, pediatric	1	1	–	–	2
Neuropathic pain	4	1	1	–	6
Obsessive-compulsive disorder	–	1	–	–	1
Parkinson's disease	6	3	3	–	12
Spinal cord injury	2	–	1	–	3
Stroke	10	7	1	–	18
Traumatic brain injury	5	1	–	–	6
Trigeminal neuralgia	–	1	–	–	1
<b>Ophthalmological</b>					
Glaucoma	–	5	–	–	5
Macular degeneration	1	–	–	–	1

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

77 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
<b>Pain</b>					
Bone cancer	1	4	–	–	5
Bone metastases	6	7	3	1	17
Cancer pain	3	6	–	–	9
Pancreatic tumors	11	18	4	–	33
<b>Pediatrics</b>					
Astrocytoma (SEGA)	9	5	3	–	17
Bone metastases	6	7	3	1	17
Epilepsy	10	4	–	–	14
Hydrocephalus	1	1	–	–	2
Multiple tumors	4	1	–	–	5
Neuroblastoma, pediatric	1	1	–	–	2
Osteoid osteoma	1	1	2	–	4
Soft tissue cancer	6	2	–	–	8
Soft tissue tumor, benign	4	3	2	–	9
<b>Pulmonary</b>					
Lung tumors	1	1	1	–	3
<b>Urological</b>					
Acute kidney injury	1	–	–	–	1
Acute tubular necrosis	1	–	1	–	2
Benign prostatic hyperplasia	2	–	–	–	2
Bladder tumors	2	1	–	–	3
Kidney stone fragmentation	2	1	–	–	3
Kidney stone propulsion	1	–	–	–	1
Kidney tumors	4	6	2	–	12
Prostate diseases	14	8	3	–	25
<b>Women's Health</b>					
Breast cancer	17	4	6	–	27
Breast fibroadenoma	2	–	1	–	3
Cervical tumors	–	1	1	–	2
Endometrial tumors	1	–	1	–	2
Endometriosis	–	2	–	–	2

For more information about specific preclinical research sites and indications, please visit: [www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites). Use the “search by disease research” and/or “search by research stage” dropdown menu.

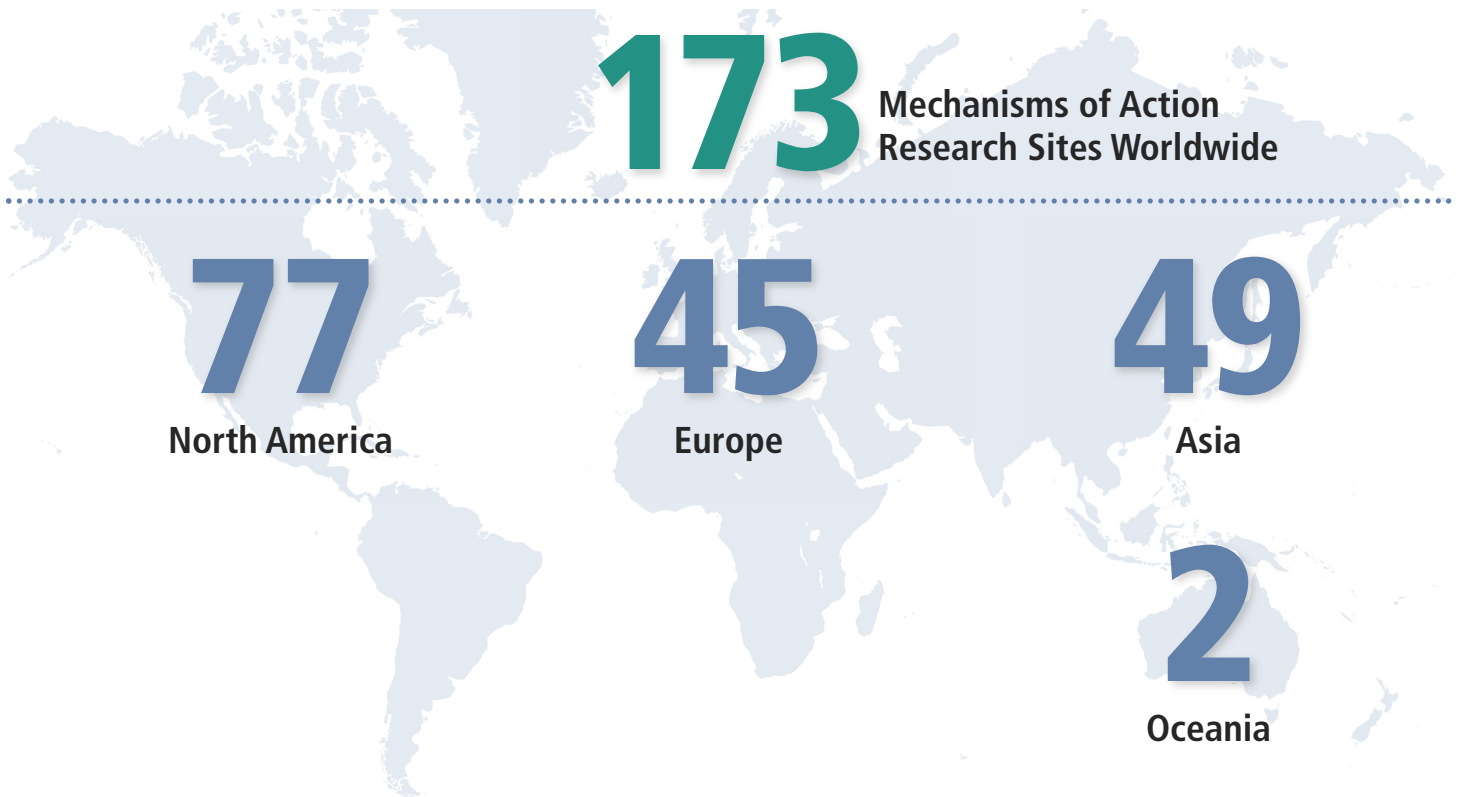
## Preclinical Research Sites by Indication and Region continued

77 indications are being researched at preclinical sites worldwide.

Indications	Regions				Totals
	N. America	Europe	Asia	Oceania	
<b>Women's Health</b> continued					
Fetal bladder obstruction	–	–	1	–	<b>1</b>
Ovarian tumors	–	–	1	1	<b>2</b>
Twin-twin transfusion syndrome	1	4	1	–	<b>6</b>
Uterine adenomyosis	–	1	2	1	<b>4</b>
Uterine fibroids	7	7	8	1	<b>23</b>
<b>Oncological</b>					
Biliary tract tumors	–	2	–	–	<b>2</b>
Bladder tumors	2	1	–	–	<b>3</b>
Bone cancer	1	4	–	–	<b>5</b>
Bone metastases	6	7	3	1	<b>17</b>
Brain metastases, Breast cancer	2	–	–	–	<b>2</b>
Breast cancer	17	4	6	–	<b>27</b>
Cancer pain	3	6	–	–	<b>9</b>
Cervical tumors	–	1	1	–	<b>2</b>
Colorectal tumors	1	2	–	–	<b>3</b>
Endometrial tumors	1	–	1	–	<b>2</b>
Esophageal tumors	–	1	–	–	<b>1</b>
Glioblastoma	19	12	8	–	<b>39</b>
Head & neck tumors	–	3	1	–	<b>4</b>
Kidney tumors	4	6	2	–	<b>12</b>
Liver metastases	3	5	–	–	<b>8</b>
Liver tumors	13	16	5	–	<b>34</b>
Lung tumors	1	1	1	–	<b>3</b>
Multiple tumors	4	1	–	–	<b>5</b>
Neuroblastoma, pediatric	1	1	–	–	<b>2</b>
Ovarian tumors	–	–	1	1	<b>2</b>
Pancreatic tumors	11	18	4	–	<b>33</b>
Prostate cancer	14	8	3	–	<b>25</b>
Soft tissue cancer	6	2	–	–	<b>8</b>
Thyroid cancer	2	1	–	–	<b>3</b>

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

### Mechanisms of Action Research Sites by Region\*



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

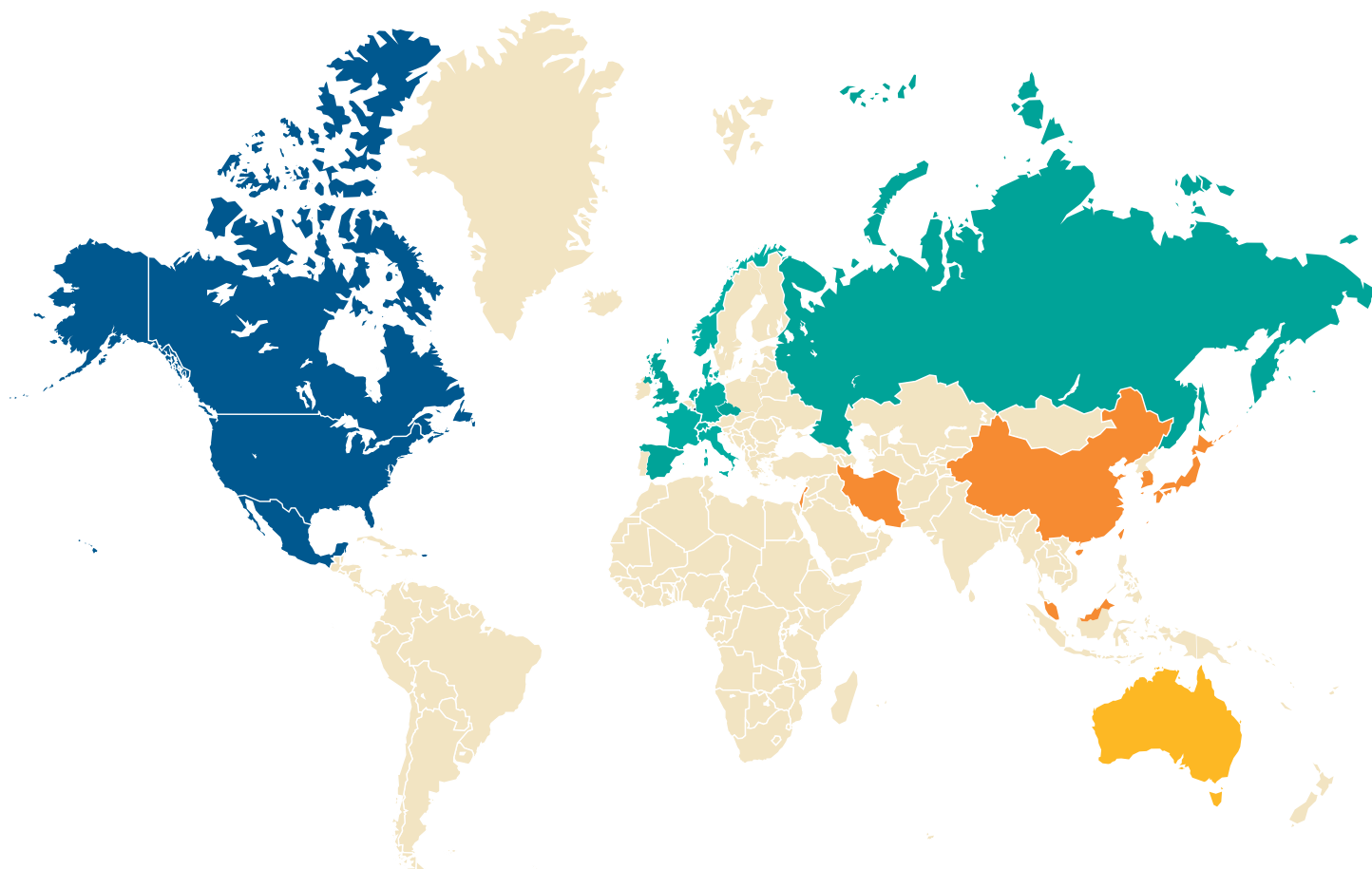
#### Mechanism of Action Additional Content

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

[www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites)

Use the “search by bioeffect research” dropdown menu.

Mechanisms of Action Research Sites Worldwide



■ North America

- 8 Canada
- 69 United States

■ Europe

- 1 Cyprus
- 1 Czech Republic
- 1 Denmark
- 7 France
- 9 Germany
- 6 Italy
- 3 The Netherlands
- 3 Norway
- 2 Russia Federation
- 2 Spain
- 2 Switzerland
- 8 United Kingdom

■ Asia

- 18 China
- 2 Iran
- 3 Israel
- 10 Japan
- 1 Malaysia
- 1 Singapore
- 8 South Korea
- 6 Taiwan

■ Oceania

- 2 Australia

## Mechanisms of Action Research Sites by Action and Region

Actions	Regions				Totals		
	N. America	Europe	Asia	Oceania			
<b>Drug Delivery</b>							
Blood-brain barrier opening			24	12	20	1	<b>57</b>
Drug delivery vehicles			14	5	5	–	<b>24</b>
Hyperthermia			11	6	3	–	<b>20</b>
Sonoporation			8	4	2	–	<b>14</b>
Therapeutic delivery (unencapsulated)			14	5	2	–	<b>21</b>
Vasodilation			2	–	–	–	<b>2</b>
<b>Immunomodulation</b>							
Immune cell delivery			3	1	–	–	<b>4</b>
Immunomodulation			24	10	6	–	<b>40</b>
Immunotherapeutic delivery			6	1	–	1	<b>8</b>
<b>Increased Vascular Permeability</b>							
Blood-brain barrier opening			15	7	4	–	<b>26</b>
Drug delivery vehicles <sup>1</sup>			18	12	15	–	<b>45</b>
Hyperthermia			–	1	–	–	<b>1</b>
Stem cell delivery			7	–	1	–	<b>8</b>
Therapeutic delivery (unencapsulated)			1	–	–	–	<b>1</b>
<b>Tissue Destruction</b>							
Histotripsy			22	7	3	–	<b>32</b>
Hyperthermia			6	6	2	–	<b>14</b>
Mechanical ablation			20	12	11	–	<b>43</b>
Other			11	3	–	–	<b>14</b>
Thermal ablation			35	25	15	1	<b>76</b>
Vascular disruption			11	4	4	–	<b>19</b>

<sup>1</sup> Includes multiple mechanisms of denervation and kidney stone propulsion

For more information about specific mechanisms of action research sites, please visit: [www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites). Use the “search by bioeffect research” dropdown menu.

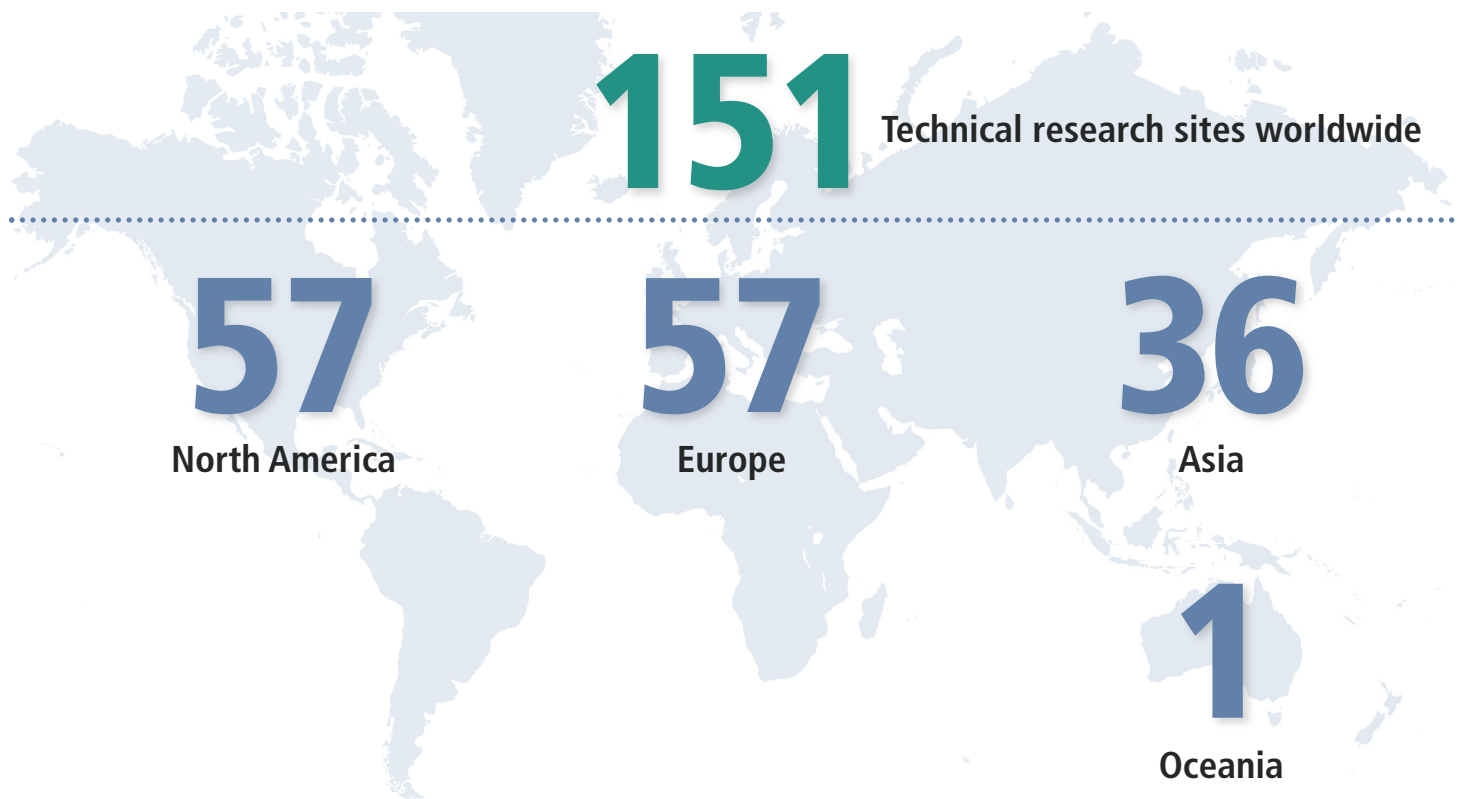


Mechanisms of Action Research Sites by Action and Region *continued*

Actions	Regions				Totals		
	N. America	Europe	Asia	Oceania			
<b>Other</b>							
Amplification of cancer biomarkers			11	1	1	–	<b>13</b>
Angiogenesis			2	1	12	–	<b>5</b>
Cardiac pacing			–	–	1	–	<b>1</b>
Clot lysis			14	4	3	–	<b>21</b>
Hemostasis			2	–	–	–	<b>2</b>
Liquid biopsy			1	–	–	–	<b>1</b>
Neuromodulation			22	7	12	1	<b>42</b>
Radiosensitization			6	8	1	–	<b>15</b>
Sensitization to chemotherapy			5	3	–	–	<b>8</b>
Sonodynamic therapy			6	1	5	–	<b>12</b>
Stem cell homing			3	–	–	–	<b>3</b>

For more information about specific mechanisms of action research sites, please visit: [www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites).  
Use the “search by bioeffect research” dropdown menu.

## Technical Research Sites by Region\*



\*Technical research sites investigate hardware or software solutions related to focused ultrasound.  
No technical research sites in Africa and South America.

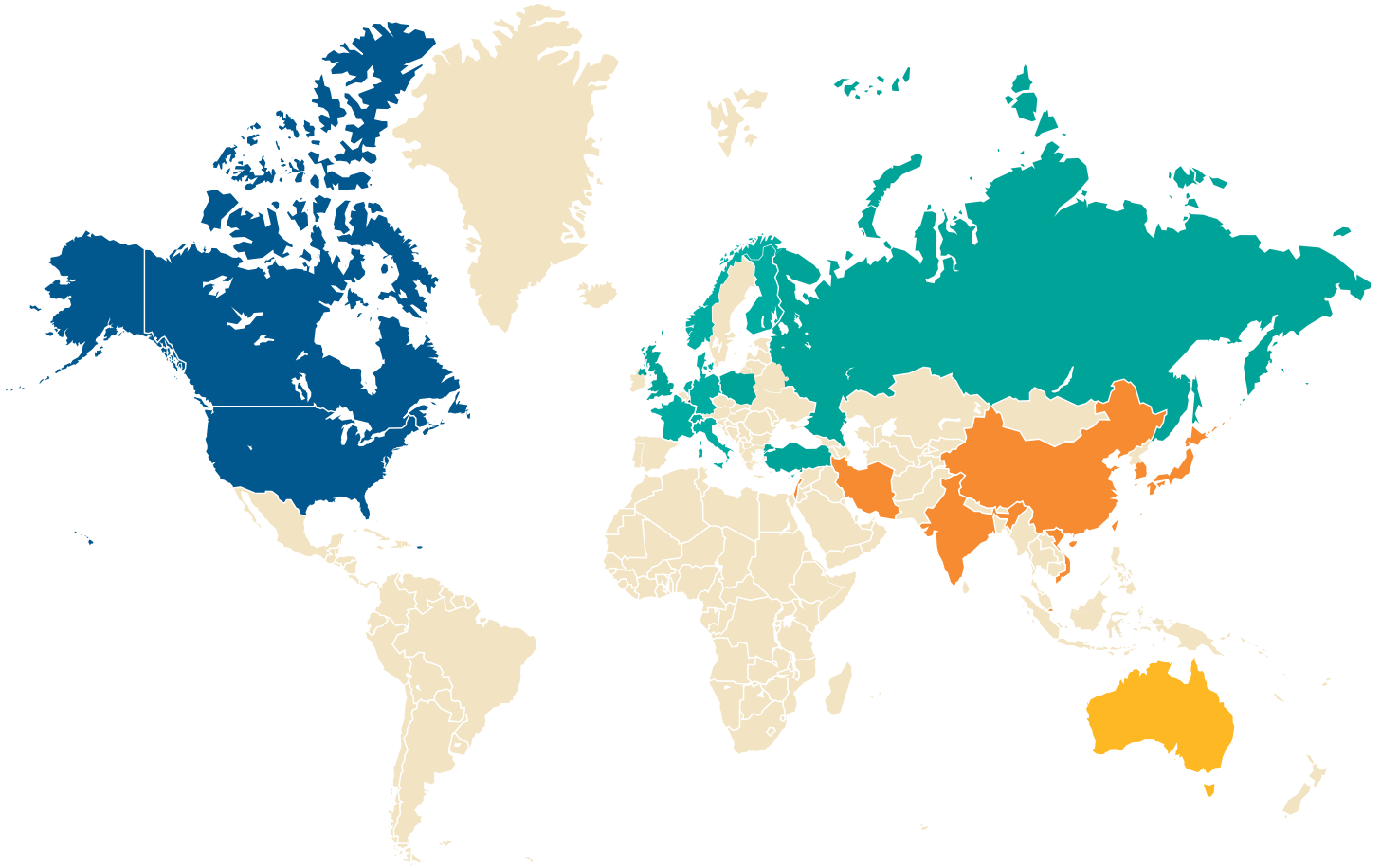
### Technical Research Additional Content

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

[www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites)

Use the “search by technical research” dropdown menu.

Technical Research Sites by Country



■ North America

- 5 Canada
- 52 United States

■ Europe

- 1 Cyprus
- 1 Denmark
- 2 Finland
- 8 France
- 11 Germany
- 8 Italy
- 4 The Netherlands
- 2 Norway
- 2 Poland
- 2 Russia Federation
- 1 Spain
- 4 Switzerland
- 1 Turkey
- 10 United Kingdom

■ Asia

- 13 China
- 1 India
- 1 Iran
- 1 Israel
- 8 Japan
- 1 Singapore
- 6 South Korea
- 4 Taiwan
- 1 Vietnam

■ Oceania

- 1 Australia

Technical Research Sites by Region

	Regions				Totals
	N. America	Europe	Asia	Oceania	
Drug Delivery Technology	21	12	4	1	<b>38</b>
FUS Physics	38	26	14	–	<b>78</b>
FUS Simulation and Treatment Planning	20	18	5	–	<b>43</b>
FUS Transducer Technology	15	18	8	–	<b>41</b>
FUS Treatment Monitoring	30	26	14	–	<b>70</b>
MR Imaging for FUS Guidance	31	32	19	–	<b>82</b>
Standards & Quality Assurance	8	6	3	–	<b>17</b>
Ultrasound Imaging for FUS Guidance	27	15	8	–	<b>50</b>

For more information about specific technical research sites, please visit: [www.fusfoundation.org/the-technology/research-sites](http://www.fusfoundation.org/the-technology/research-sites).  
Use the “search by technical research” dropdown menu.

## FUS Veterinary Applications

### Overview

The Foundation's veterinary program provides a unique opportunity for focused ultrasound to benefit both companion animals and their owners. Veterinary medicine has often lagged behind human medicine, but that is changing as we recognize the benefits of performing clinical trials in companion animals. Our dogs and cats are exposed to the same environmental stimuli that we are, and develop many of the same diseases in a far more natural way than laboratory animals. Veterinary trials make new, innovative therapies available for family pets, while simultaneously collecting data that can be used to advance human medicine, creating a virtuous cycle where humans help animals help humans.

### Benefits

Focused ultrasound offers several advantages over traditional treatments like surgery and radiation. It is noninvasive, reducing the risk of infection and eliminating the need for stitches and the Elizabethan collar. Focused ultrasound can be used to ablate tissue or enhance the local delivery of therapeutic drugs. Because there is no ionizing radiation involved, treatments can be repeated if needed. Focused ultrasound has many potential applications in veterinary medicine, including but not limited to tumor destruction, drug delivery (chemotherapy and immunotherapy), pain relief for arthritis and hip dysplasia, and noninvasive spaying/neutering.

- Noninvasive: no stitches, infections, or scars
- Repeatable: no limiting dose
- Flexible: drug delivery, ablation, immunomodulation
- Adaptable: various lesion sizes and treatment depths

### New for 2018

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

In addition to ablating tumor tissue and enhancing the delivery of chemotherapeutics, 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.

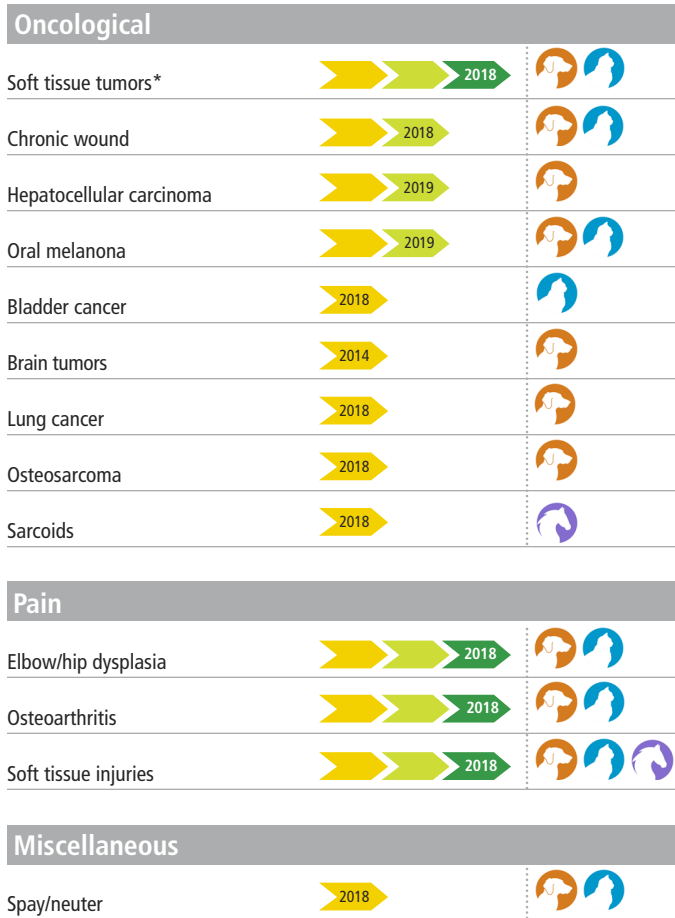
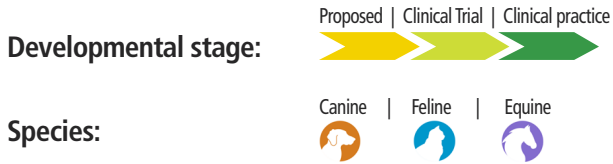
Focused ultrasound also shows great promise in the management of osteoarthritis, soft tissue injury, and elbow/hip dysplasia. Treatment can enhance blood flow to the damaged tissue, enhancing healing.

Focused ultrasound can also be used to noninvasively ablate nerve tissue, relieving pain in advanced arthritis.

For more information visit:

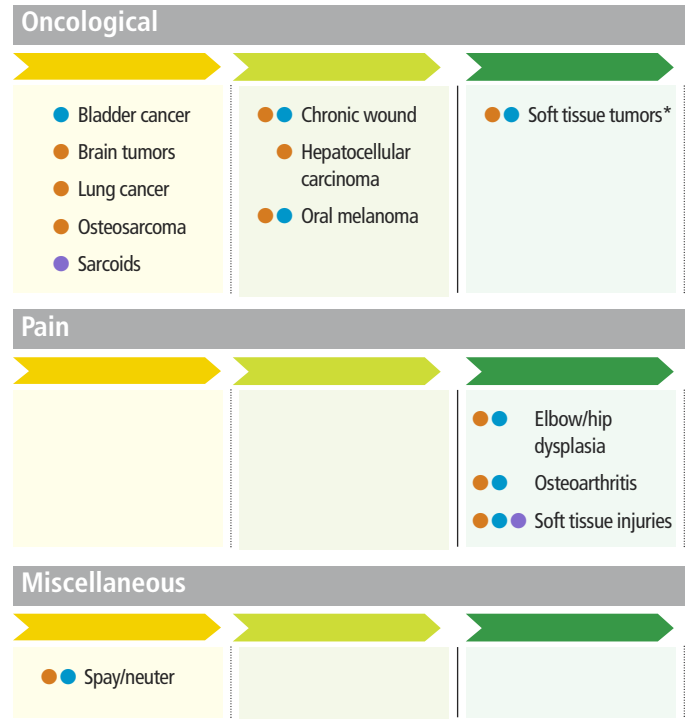
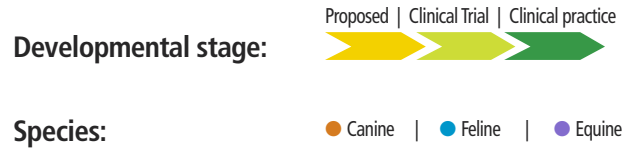
[www.fusfoundation.org/for-researchers/high-priority-research-areas/veterinary-program](http://www.fusfoundation.org/for-researchers/high-priority-research-areas/veterinary-program).

## State of Research by Indication



\*Soft tissue tumors include Ameloblastoma, Mast cell tumors, Oral plasmacytoma, Squamous cell carcinoma, and Salivary gland tumors

## Developmental Landscape

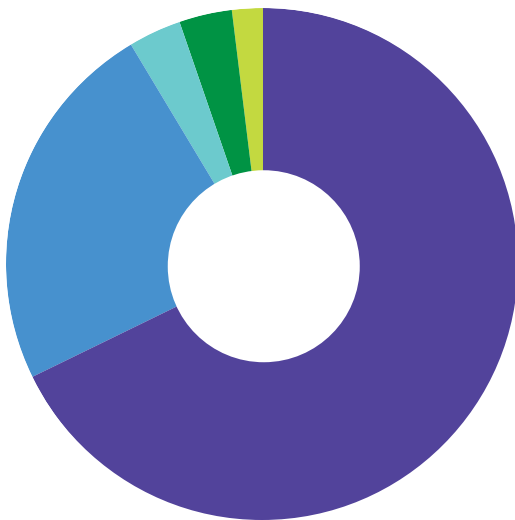


## Treated Patients by Indication

2018

### 59 Total Treatments

- 40 Elbow/hip dysplasia/osteoarthritis
- 14 Soft tissue tumors\*
- 2 Chronic wound
- 2 Soft tissue injury
- 1 Oral melanoma

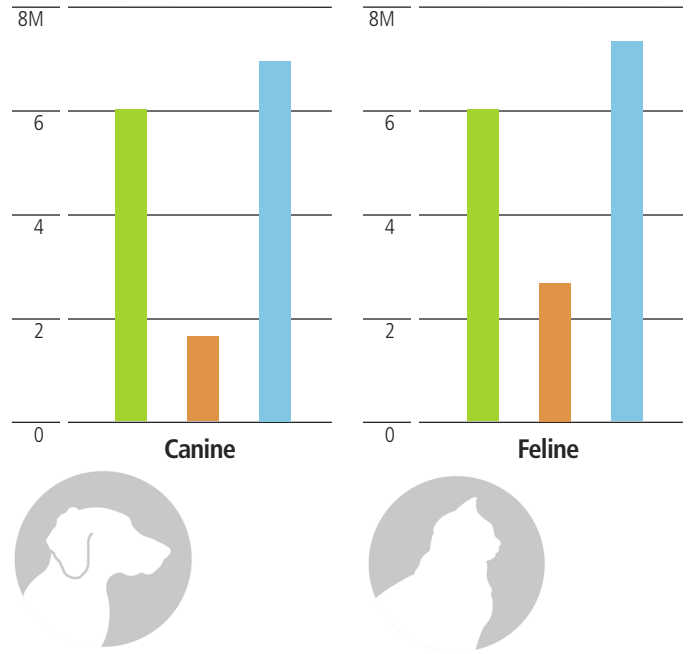


\*Soft tissue tumors include Ameloblastoma, Mast cell tumors, Oral plasmacytoma, Squamous cell carcinoma, and Salivary gland tumors

## Projected Patient Base

Millions per year in US

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



Source: Potential patient populations were calculated from multiple websites:  
[www.acfoundation.org/faqs/](http://www.acfoundation.org/faqs/)  
[www.fda.gov/animalveterinary/resourcesforyou/animalhealthliteracy/ucm382772.htm#endnote8](http://www.fda.gov/animalveterinary/resourcesforyou/animalhealthliteracy/ucm382772.htm#endnote8)  
[www.animalsheltering.org/page/pets-by-the-numbers](http://www.animalsheltering.org/page/pets-by-the-numbers)

Veterinary Program Sites



**North America**

- ★ Oklahoma State University
- ★ Stanford University  
*In collaboration with University of California, Davis, School of Veterinary Medicine*
- ★ Virginia-Maryland College of Veterinary Medicine

**Europe**

- Vet LIFU

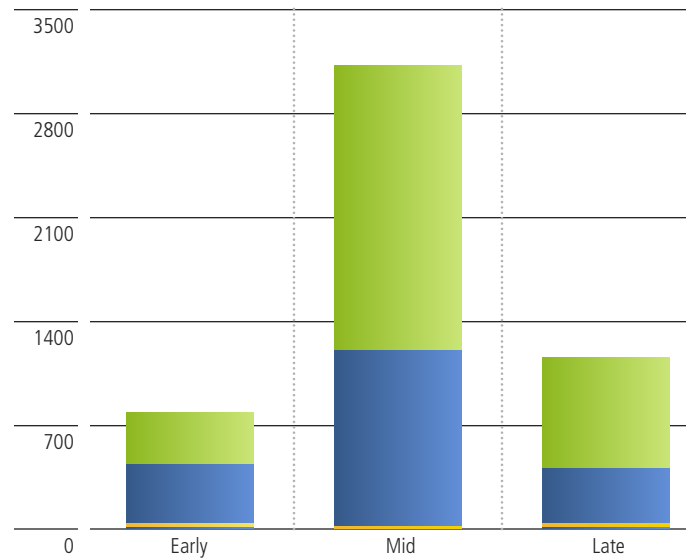


## Proposed Market and Value Chain

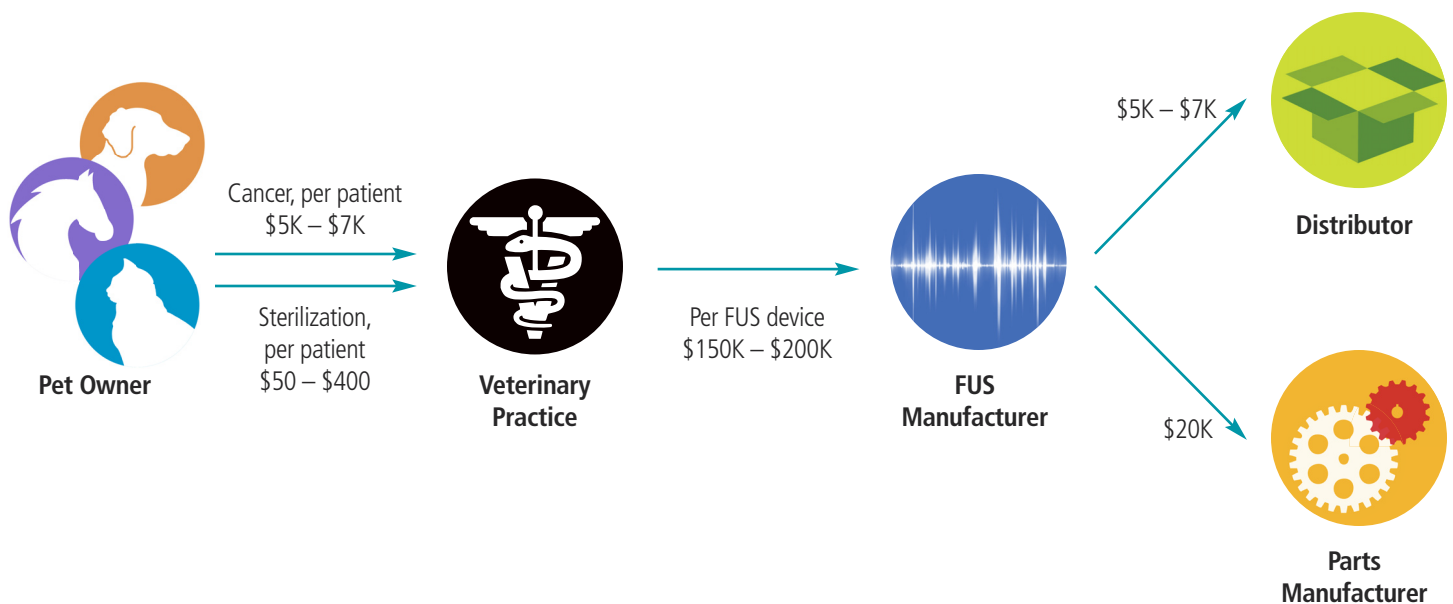
We project that the market is capable of absorbing just under 5,000 focused ultrasound device units at a retail value of between \$150,000 and \$250,000. Early adopters are likely to consist of veterinary schools, large specialty clinics (e.g. oncology and rehabilitation centers), and high-volume animal 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

■ Veterinary Schools 
 ■ Vet/Specialty Clinics 
 ■ Animal Shelters

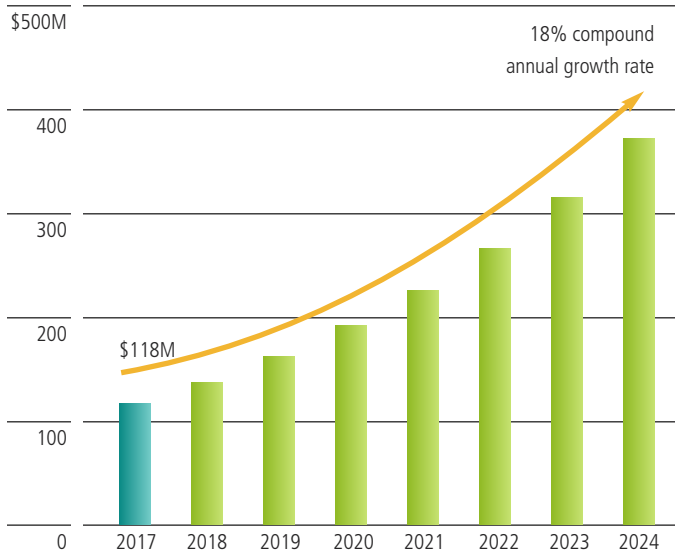


## Value Chain



## FUS Market Projection

Revenue in millions of dollars



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

[www.marketinsightsreports.com/reports/0718708138/global-high-intensity-focused-ultrasound-system-market-professional-survey-report-2018?source=faircolumnist&Mode=12](http://www.marketinsightsreports.com/reports/0718708138/global-high-intensity-focused-ultrasound-system-market-professional-survey-report-2018?source=faircolumnist&Mode=12)

[www.marketreportsworld.com/global-high-intensity-focused-ultrasound-system-market-report-2017-10565236](http://www.marketreportsworld.com/global-high-intensity-focused-ultrasound-system-market-report-2017-10565236)

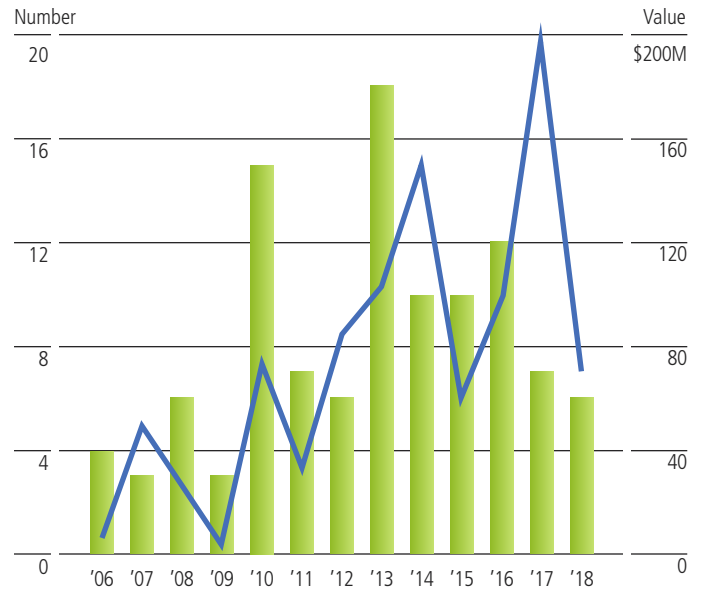
[www.marketresearchfuture.com/reports/high-intensity-focused-ultrasound-therapy-market-885](http://www.marketresearchfuture.com/reports/high-intensity-focused-ultrasound-therapy-market-885)

[www.360marketupdates.com/global-north-america-europe-asia-pacific-south-america-middle-east-and-africa-high-intensity-focused-ultrasound-system-market-2018-forecast-to-2023-12463692](http://www.360marketupdates.com/global-north-america-europe-asia-pacific-south-america-middle-east-and-africa-high-intensity-focused-ultrasound-system-market-2018-forecast-to-2023-12463692)

[www.futureindustryinsight.com/product/high-intensity-focused-ultrasound-hifu-therapy-market/](http://www.futureindustryinsight.com/product/high-intensity-focused-ultrasound-hifu-therapy-market/)

## FUS Industry Investments Over Time

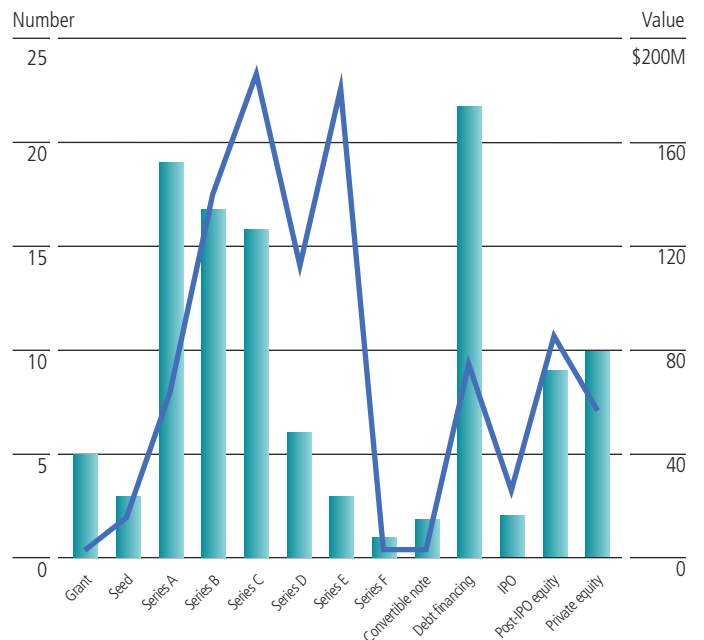
■ Number of investments ■ Value of investments in millions of dollars



Source: www.crunchbase.com

## FUS Industry Investments by Stage

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



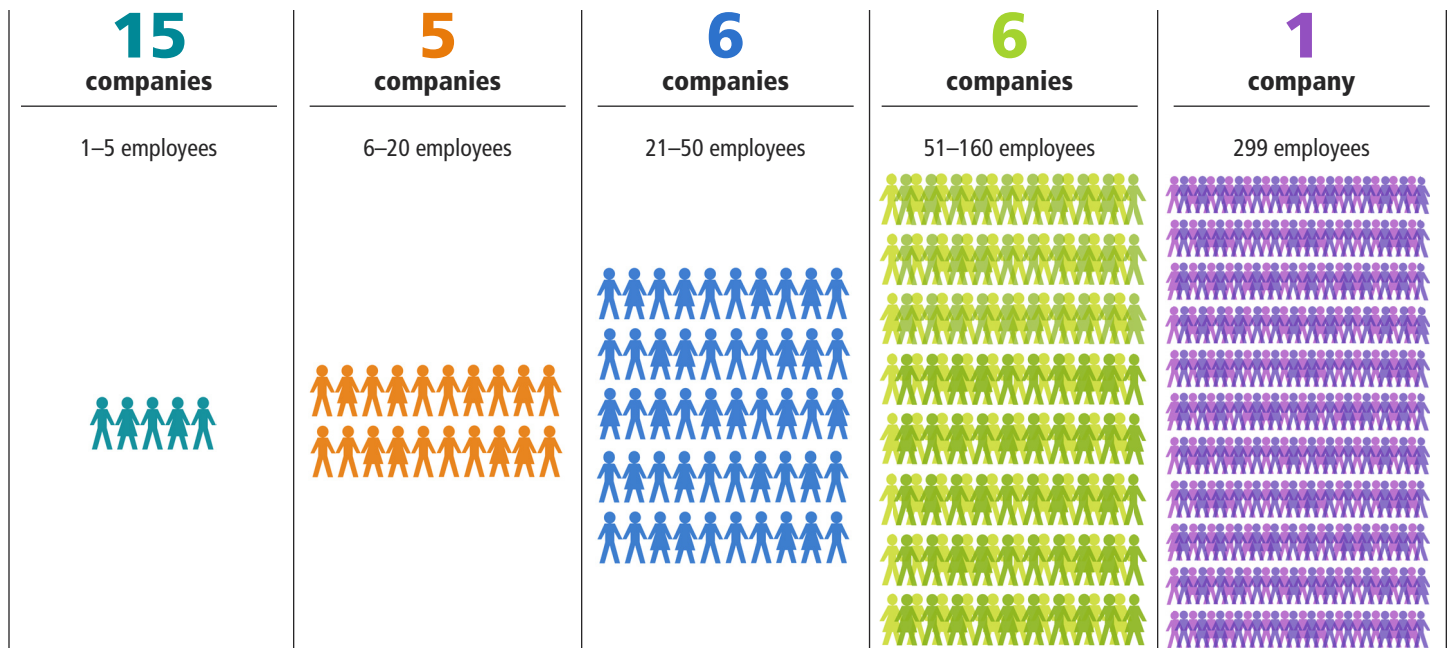
Source: www.crunchbase.com

## 2018 FUS Industry Investments\*

Organization name	Funding type	Investor name	Money raised, millions \$US
<b>INSIGHTEC</b>			
	Series E	Koch Disruptive Technologies GE Healthcare GEOC Focus Holdings York Capital Management Elbit Imaging Ltd.	\$150M
<b>Profound Medical</b>			
	Post-IPO Equity	—	\$34.5M
<b>CarThera</b>			
	Series B	Groupe Arnault Panakès Partners Sham Innovation Santé Supernova Invest	\$10.2M
<b>Cardiawave</b>			
	Series D	Angels Santé Angels' Bay Invest Business Angels des Grandes Ecoles European Program Instrument PME Paris Business Angels Sofimac Innovation	\$8.2M
<b>Verasonics</b>			
	Grant	—	\$5.6M
<b>HistoSonics</b>			
	Series C	—	\$4.8M
<b>Cardiawave</b>			
	Series C	—	\$4.7M
			<b>\$218M Total</b>

\*As reported by Crunchbase and industry press releases.

FUS Company Size



FUS Company Size

**52%**  
of FUS companies have 10 or fewer employees

**79%**  
of FUS companies have fewer than 50 employees

**58%**  
of employees in the FUS industry are employed by the 4 largest companies

Source: Data collected from Foundation survey of manufacturers, LinkedIn, company websites, and Hoover's.

## FUSF Role in the Industry

### FUS Partners

In April of 2018 the Foundation formally launched **FUS Partners**, a new program aimed at fostering relationships among focused ultrasound community members seeking assistance with FUS-related activities, including:

- Financing
- Strategic partnerships
- Technology transfer
- Academic research opportunities

The program aims to systematize and formalize activities in which the Foundation has already been engaging—on an increasingly ad hoc basis—related to connecting the focused ultrasound start-up community with investors and collaborators around the world.

We are at the beginning of the inflection point of the adoption curve for focused ultrasound. For this technology to continue transitioning from research to commercial activity and mainstream use, four crucial needs must be met:

- Evidence/research
- Increased awareness
- Collaboration among stakeholders within the FUS community
- Hundreds of millions of dollars in capital

We expect FUS Partners to help us address these unmet needs at an accelerated pace, catapulting the field of focused ultrasound to a new level.

The primary goals of FUS Partners include:

- Producing a quantum change in the rate of FUS adoption as a mainstream standard of care
- Growing and rationalizing the device manufacturers segment of the FUS community by providing capital and expertise and facilitating the consolidation of the industry

Services provided by FUS Partners include:

- Understanding the current landscape of manufacturers and investors
- Connecting manufacturers with both investors and other manufacturers
- Connecting academic research laboratories with manufacturers
- Assisting with due diligence

FUS Partners is a logical extension of the Foundation's activities and success to date. The Foundation brings to the table its brand and reputation as a trusted, independent, and unbiased third party; its knowledge base, information, and data; its network and community based on strong stakeholder relationships; its organization, including the team, board of directors, council, and donors; and its ability to connect, convene, and influence stakeholders—making FUS Partners well positioned to alter the trajectory of the FUS adoption path and get us closer to achieving the Foundation's goal of decreasing death, disability, and suffering.

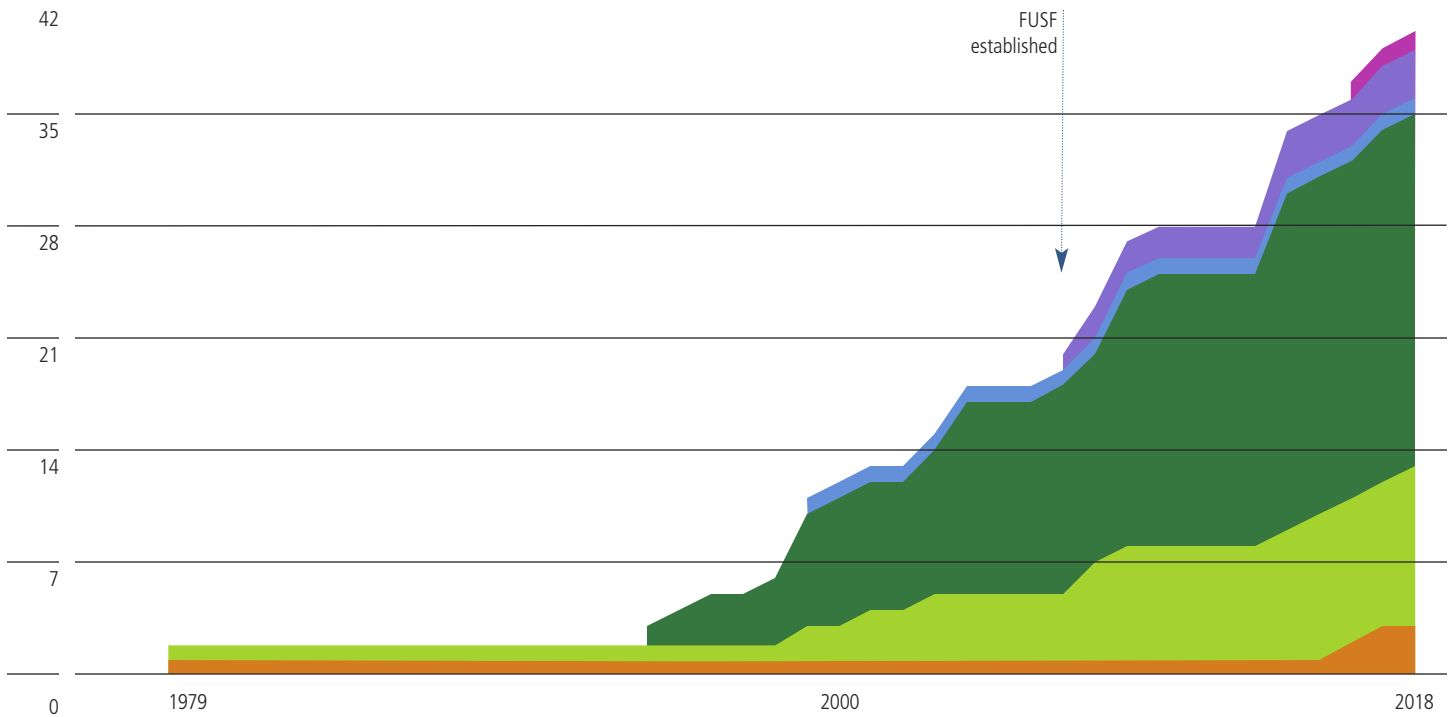
FUS Partners does not make investments or provide investment advice and does not serve as a broker or otherwise receive any compensation for services. Parties to successful transactions will, however, be solicited for donations to the Foundation as a way to grow the field and de-risk investment.

For more information, please contact Emily White, Managing Director, FUS Partners at [ewhite@fusfoundation.org](mailto:ewhite@fusfoundation.org).

## Clinical Device Manufacturers

MR guidance US guidance MR & US guidance Image fusion Other guidance\* Unguided

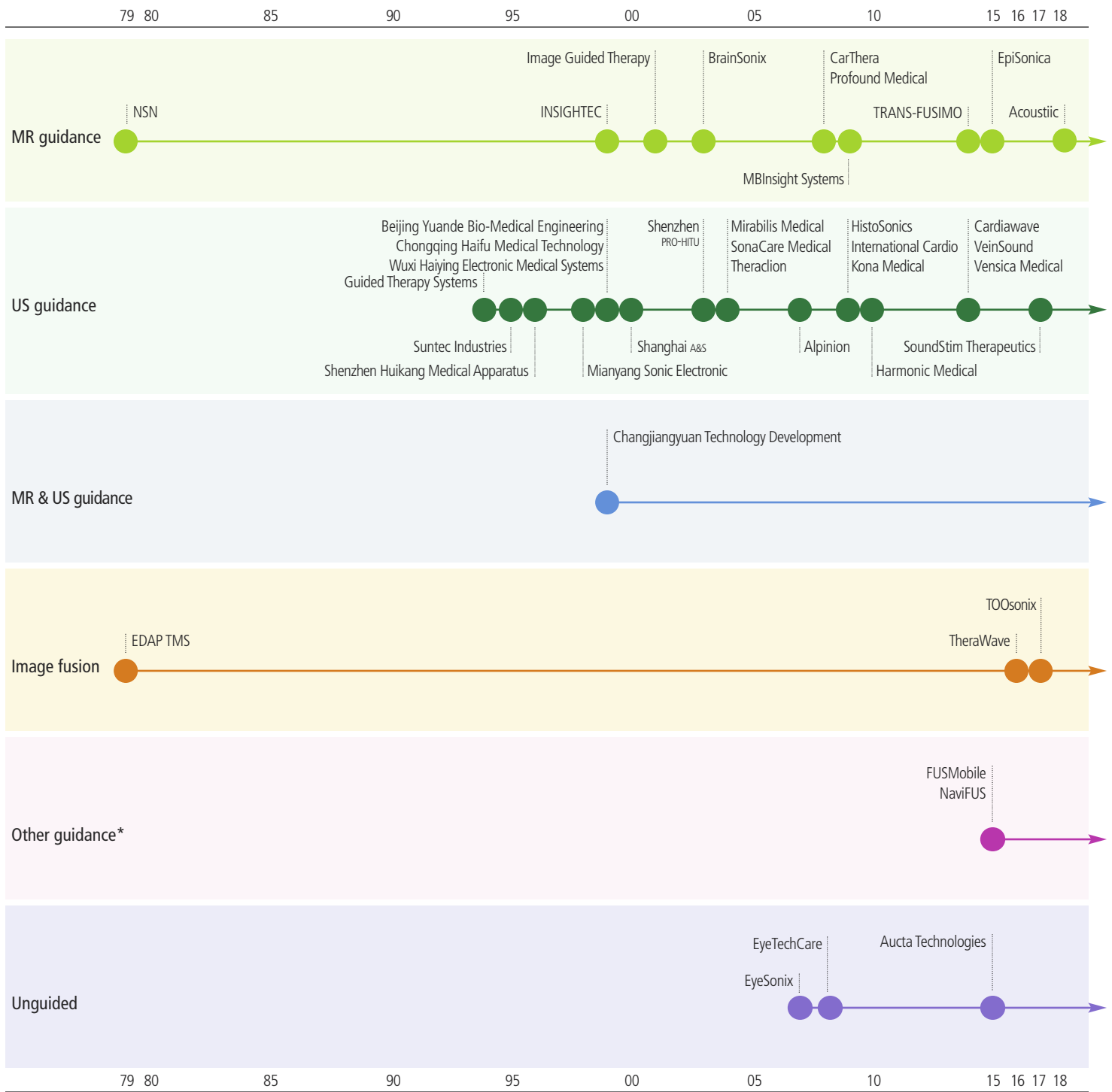
Number of manufacturers



Source: Manufacturer-supplied data

\*Other guidance includes NaviFUS: neuronavigation guidance and FUSMobile: x-ray guidance

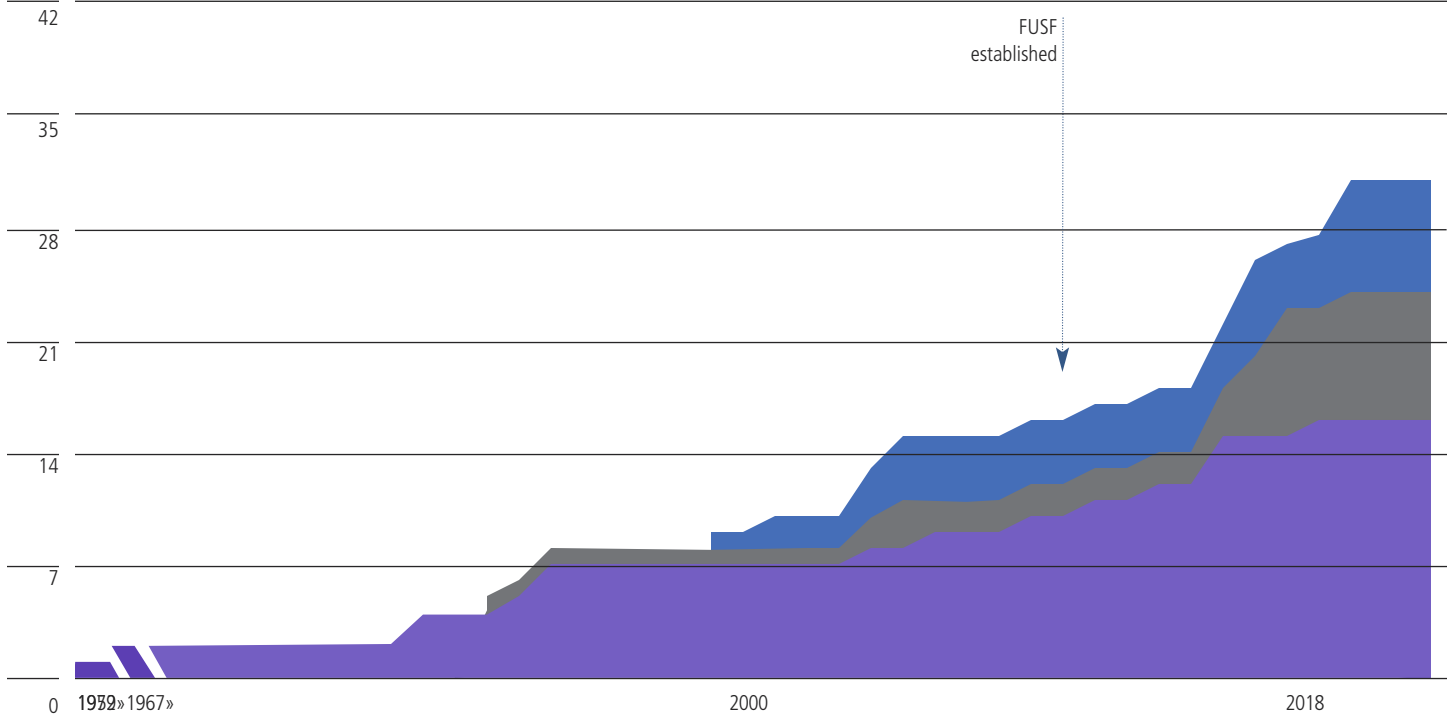
Timeline of Clinical Device Manufacturers



\*Other guidance includes NaviFUS: neuronavigation guidance; and FUSMobile: x-ray guidance.

### Other FUS Manufacturers

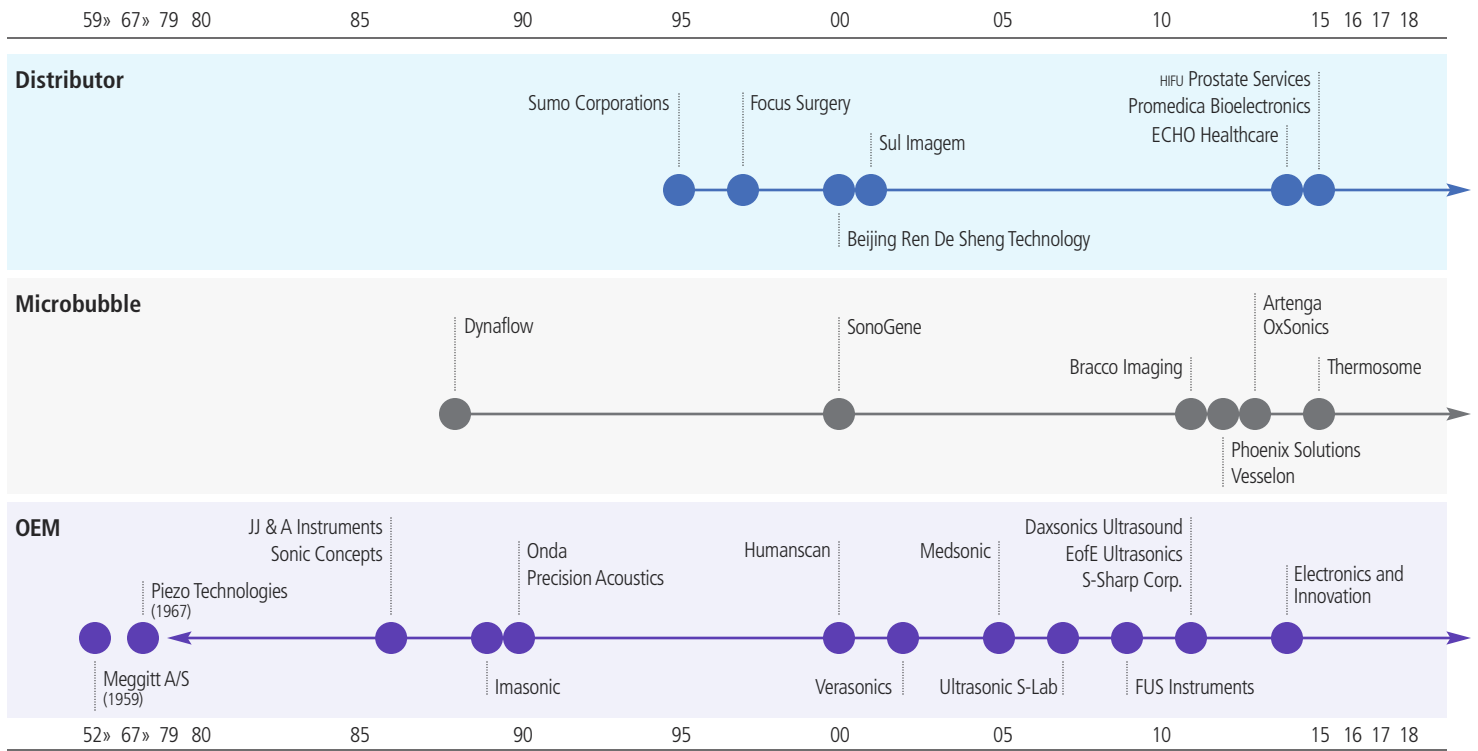
■ Distributor ■ Microbubble ■ OEM  
Number of manufacturers



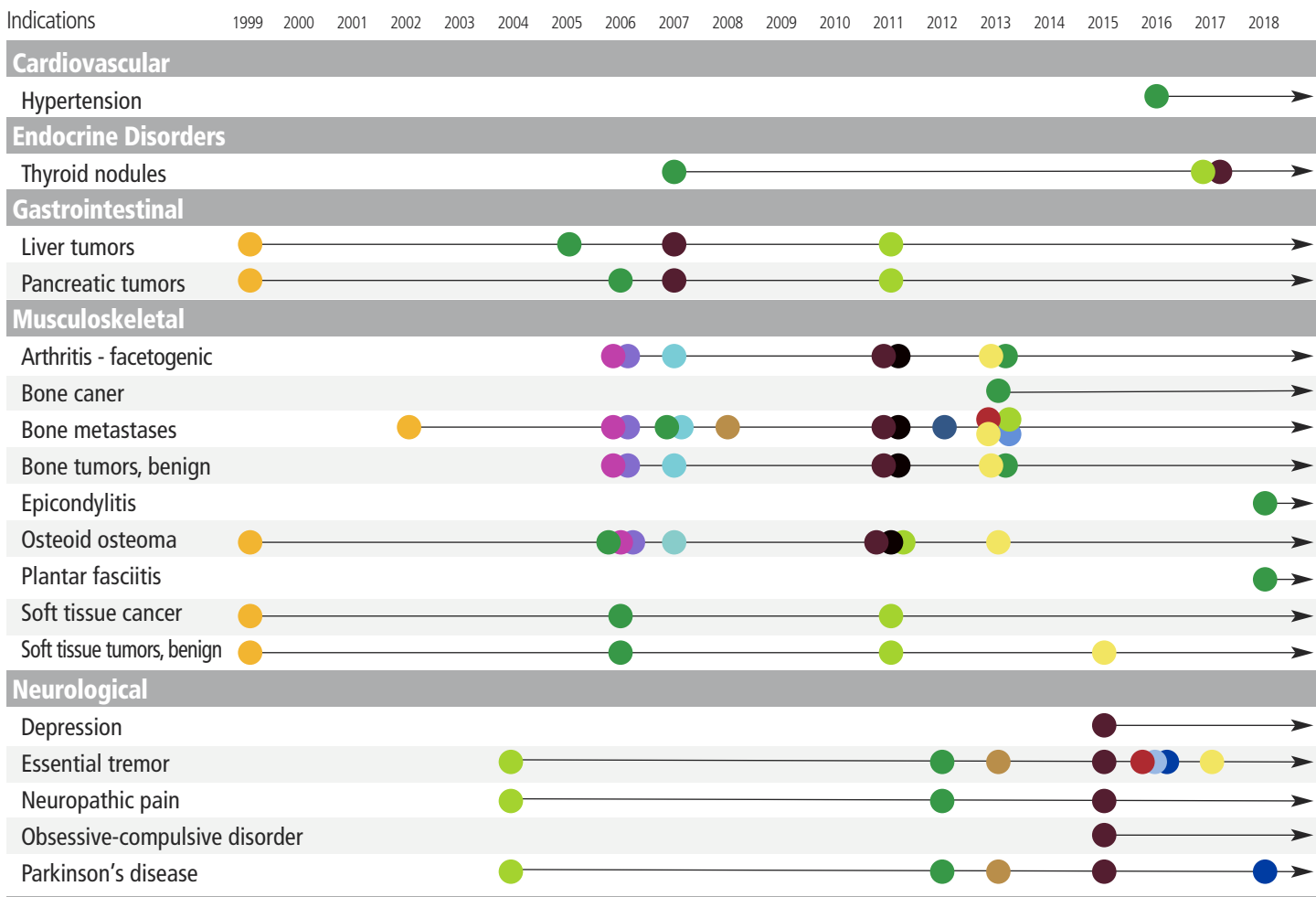
Source: Manufacturer-supplied data



Timeline of Other FUS Manufacturers

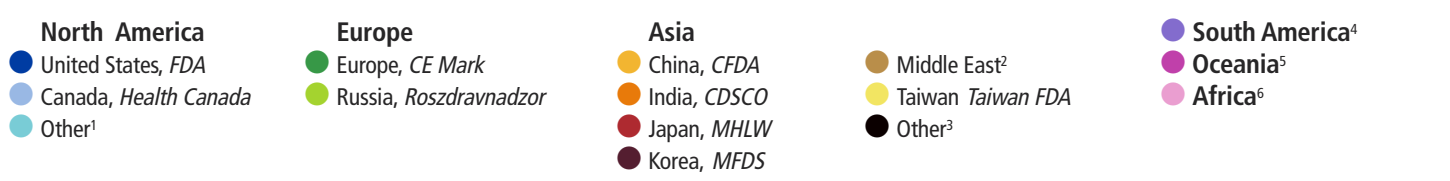
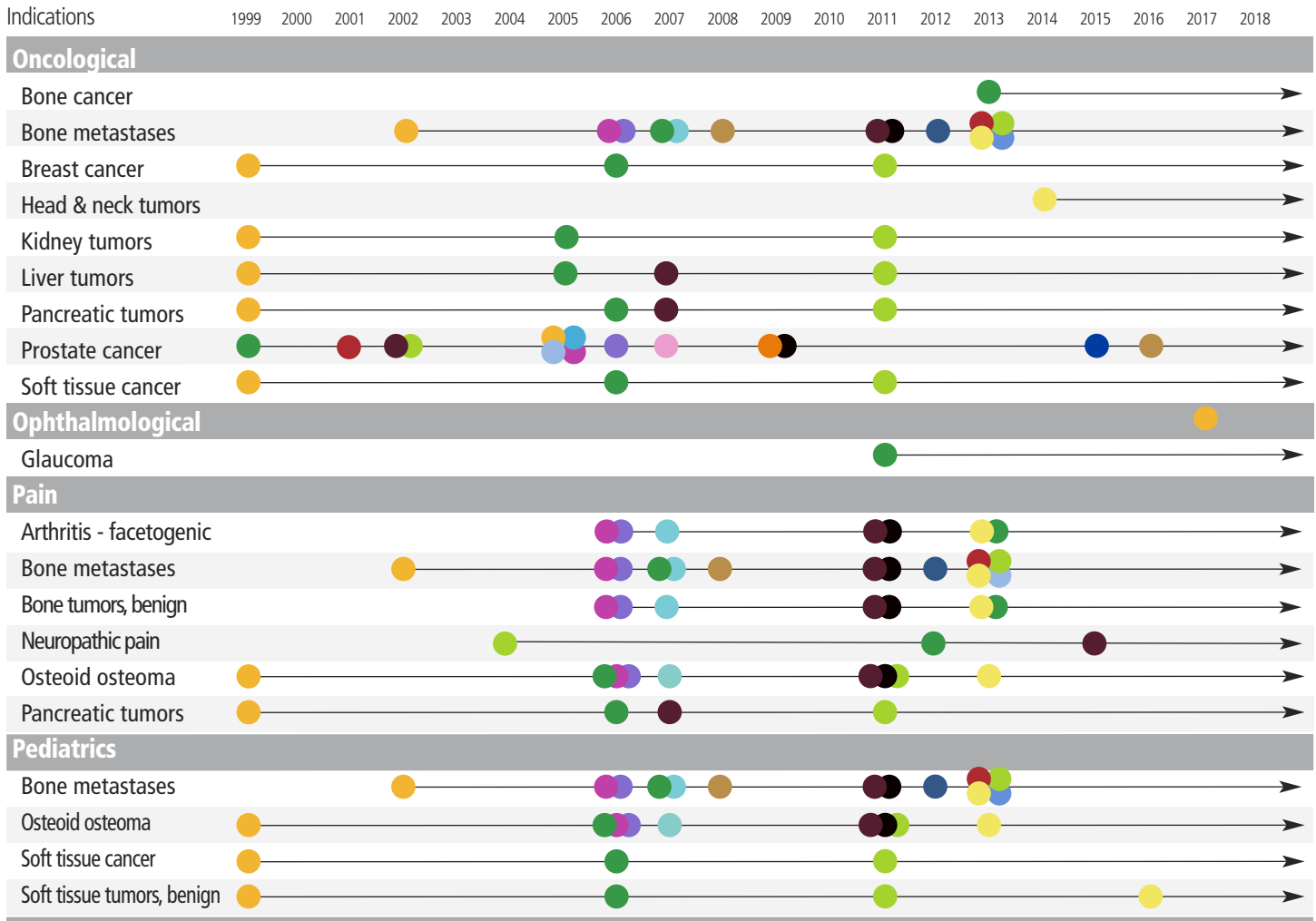


## FUS Regulatory Approvals by Indication and Region



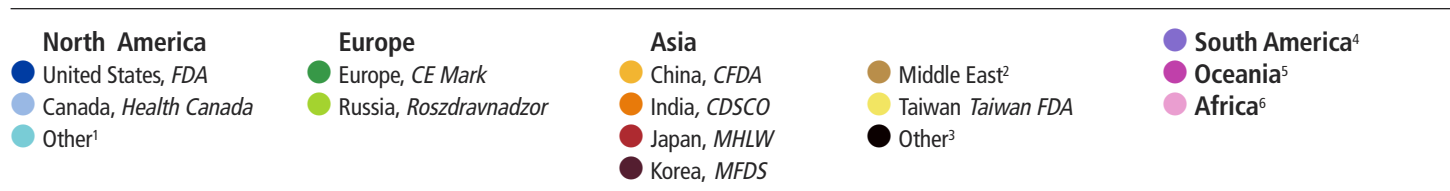
1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPMD; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

FUS Regulatory Approvals by Indication and Region continued



1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

## FUS Regulatory Approvals by Indication and Region continued



1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

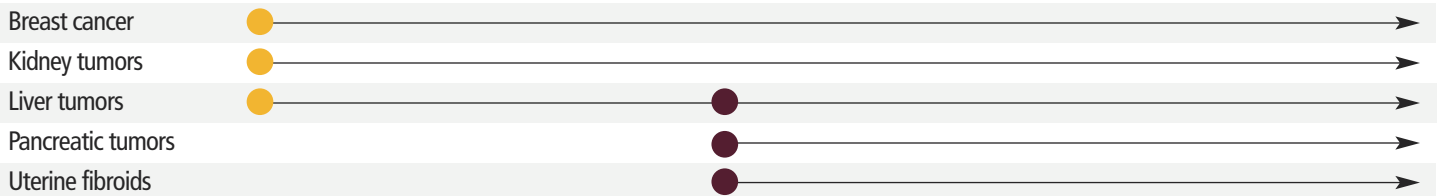
First Global Regulatory Approvals for Companies by Indication

Manufacturers 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

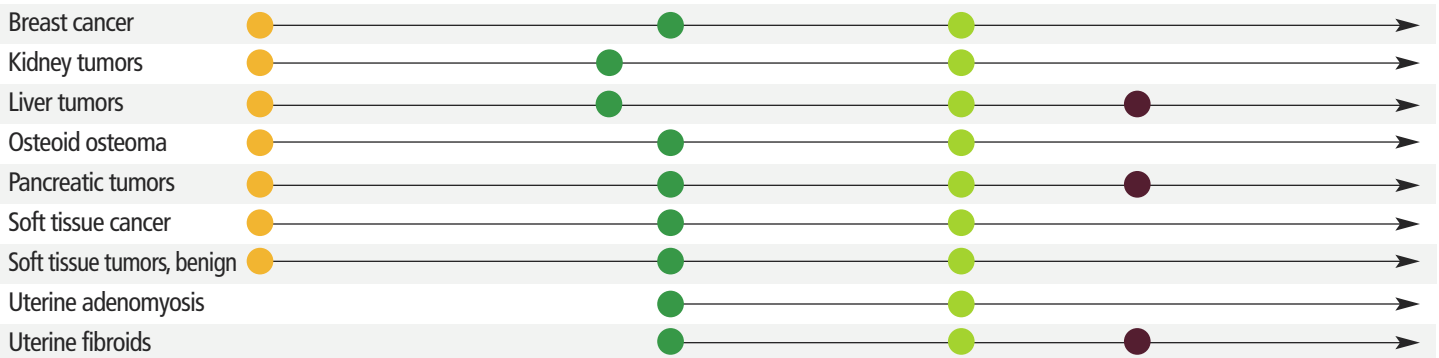
**Alpinion**



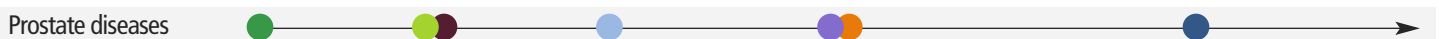
**Beijing Yuande Bio-Medical Engineering**



**Chongqing Haifu Medical Technology**

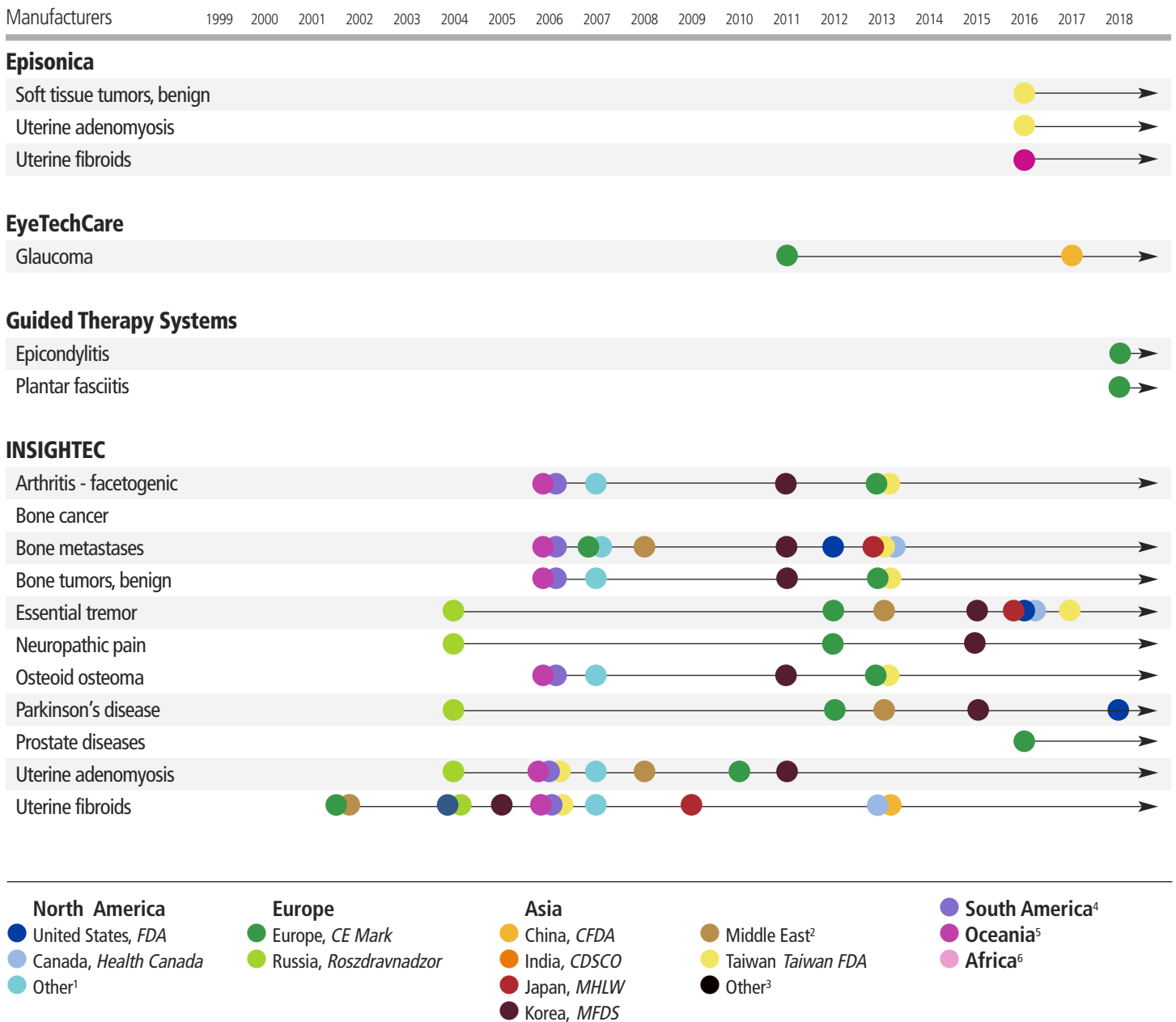


**EDAP TMS**



1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

## First Global Regulatory Approvals for Companies by Indication continued

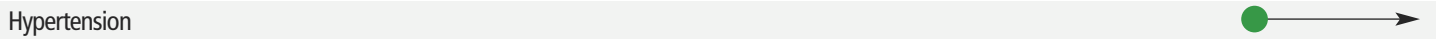


1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

First Global Regulatory Approvals for Companies by Indication continued

Manufacturers 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

**Kona Medical**



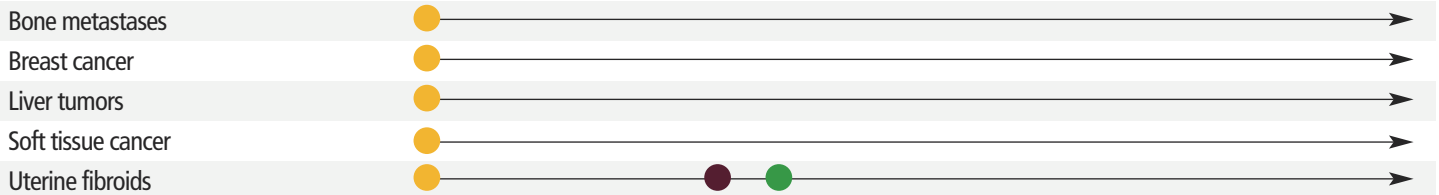
**Mirabilis Medical**



**Profound Medical** formerly Phillips



**Shanghai A&S**

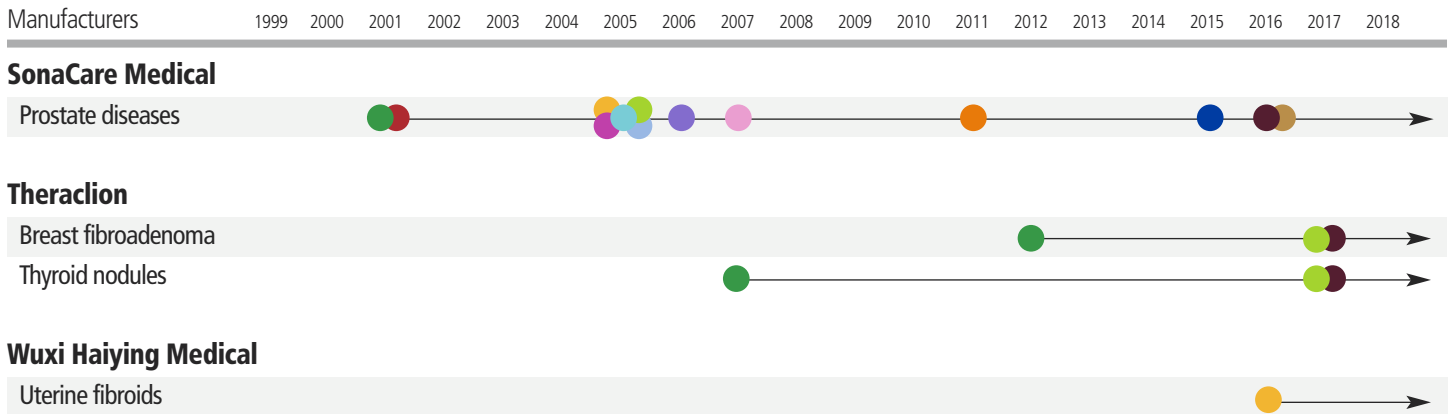


**Shenzhen PRO-HITU Medical**



1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS  
 2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA  
 3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW  
 4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health  
 5 Oceania - Australia, TGA; New Zealand, MEDSAFE  
 6 Africa - Republic of South Africa, Medicines Control Council

## First Global Regulatory Approvals for Companies by Indication continued



1 North America, Other – Bahamas, Ministry of Health; Barbados, Ministry of Health and Wellness; Costa Rica, Ministerio de Salud; Dominican Republic, MISPAS; Mexico, COFEPRIS

2 Asia, Middle East - Israel, AMAR; Jordan, FDA; Saudi Arabia, SFDA

3 Asia, Other - Indonesia, DGPM; Kazakhstan, NCEM; Malaysia, MDA; Pakistan, DRAP; Singapore, HSA; Uzbekistan, GDQC; Vietnam, DMEW

4 South America - Argentina, ANMAT; Brazil, ANVISA; Colombia, INVIMA; Ecuador, ANRCVS; Trinidad and Tobago, Ministry of Health

5 Oceania - Australia, TGA; New Zealand, MEDSAFE

6 Africa - Republic of South Africa, Medicines Control Council



## Insurance Coverage in the US\*

### Prostate cancer, Benign prostatic hyperplasia (prostate tissue ablation)

**Private insurers** Asuris Northwest Health  
CIGNA  
HAP Health Alliance Plan, MI

**Covered enrollees** 15.3 million people

### Essential tremor

**Private insurers** AmeriHealth  
Asuris Northwest Health  
Blue Cross Blue Shield Plans, in 25 states  
Lifewise, WA  
HAP Health Alliance Plan, MI  
Medicare, in 36 states  
United Healthcare, in 36 states, Medicare Advantage patients only

**Covered enrollees** 110 million people

### Bone metastases

**Private insurers** Amerigroup Healthcare  
AmeriHealth  
Anthem, Blue Cross Blue Shield Plans, in 40 states  
CIGNA  
Geisinger Health Plan  
HAP Health Alliance Plan, MI, Medicare Advantage patients only  
Lifewise, WA

**Covered enrollees** 102 million people

## Medicare Coverage

The Foundation is striving to expand Medicare coverage for all FDA-approved indications. Our advocacy efforts with the Medical Imaging Technology Alliance (MITA) aim to address the lag between FDA approval of FUS treatment and Centers for Medicare and Medicaid Services coverage. Additionally, with the help of MITA, we are working to establish and foster focused ultrasound champions within the US Congress who thoroughly understand both the promise of the technology and the challenges that are limiting widespread patient access.

\* 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.

## FUS Industry by Region

### Clinical Device Manufacturers

#### North America

16

##### MR GUIDANCE

Acoustiic INC | Seattle, Washington, United States, [www.acoustiic.com](http://www.acoustiic.com)

BrainSonix CORP | Sherman Oaks, California, United States, [www.brainsonix.com](http://www.brainsonix.com)

Profound Medical CORP | Mississauga, Ontario, Canada, [www.profoundmedical.com](http://www.profoundmedical.com)

##### US GUIDANCE

Guided Therapy Systems | Mesa, Arizona, United States, [www.guidedtherapy.com](http://www.guidedtherapy.com)

Harmonic Medical INC | Toronto, Ontario, Canada, [www.harmonicmedical.com](http://www.harmonicmedical.com)

HistoSonics INC | Ann Arbor, Michigan, United States, [www.histosonics.com](http://www.histosonics.com)

International Cardio CORP, LLC | Minnetonka, Minnesota, United States, [www.hifu-rx.com](http://www.hifu-rx.com)

Kona Medical INC | Bellevue, Washington, United States, [www.konamedical.com](http://www.konamedical.com)

Mirabilis Medical INC | Bothell, Washington, United States, [www.mirabilismedical.com](http://www.mirabilismedical.com)

SonaCare Medical LLC | Charlotte, North Carolina, United States, [www.sonacaremedical.com](http://www.sonacaremedical.com)

Soundstim Therapeutics INC | Encino, California, United States, [www.ssthera.com](http://www.ssthera.com)

VeinSound INC | Sunnyvale, California, United States

##### IMAGE FUSION

TheraWave LLC | New York, New York, United States

##### OTHER GUIDANCE

FUS Mobile INC | Alpharetta, Georgia, United States, [www.fusmobile.com](http://www.fusmobile.com)

##### UNGUIDED

Aucta Technologies INC | Minneapolis, Minnesota, United States, [www.auctatechnologies.com](http://www.auctatechnologies.com)

EyeSonix | Long Beach, California, United States, [eyesonix.com](http://eyesonix.com)

#### Europe

8

##### MR GUIDANCE

CarThera SA | Paris, France, [www.carthera.eu](http://www.carthera.eu)

Image Guided Therapy SA | Pessac, France, [www.imageguidedtherapy.com](http://www.imageguidedtherapy.com)

TRANS-FUSIMO | Bremen, Germany, [www.trans-fusimo.eu](http://www.trans-fusimo.eu)

##### US GUIDANCE

Cardiawave SA | Paris, France, [www.cardiawave.com](http://www.cardiawave.com)

Theraclion SA | Malakoff, France, [www.theraclion.com](http://www.theraclion.com)

## FUS Industry by Region continued

## Clinical Device Manufacturers

## Europe continued

- **IMAGE FUSION**  
EDAP TMS SA | Vaulx-en-Velin, France, [www.edap-tms.com](http://www.edap-tms.com)  
TOOsonix A/S | Hoersholm, Denmark, [www.toosonix.com](http://www.toosonix.com)
- **UNGUIDED**  
EyeTechCare SA | Lyon, France, [www.eyetechcare.com](http://www.eyetechcare.com)

## Asia

16

- **MR GUIDANCE**  
EpiSonica CORP | Hsichu City, Taiwan, [www.episonica.com](http://www.episonica.com)  
INSIGHTEC LTD | Tirat Carmel, Israel, [www.insightec.com](http://www.insightec.com)  
MBInsight Systems INC | Taipei, Taiwan  
NSN CO LTD | Seoul, Korea | [www.neurosona.com](http://www.neurosona.com)
- **US GUIDANCE**  
Alpinion Medical Systems CO LTD | Seoul, South Korea, [www.alpinion.com](http://www.alpinion.com)  
Beijing Yuande Bio-Medical Engineering CO LTD | Beijing, China, [www.yuande.com](http://www.yuande.com)  
Chongqing Haifu Medical Technology CO LTD | Chongqing, China  
Mianyang Sonic Electronic | Mianyang City, China, [www.ultrasound.cn/en](http://www.ultrasound.cn/en)  
Shanghai A&S Science Technology Development CO LTD | Shanghai, China, [www.aishen.com.cn](http://www.aishen.com.cn)  
Shenzhen Huikang Medical Apparatus CO LTD | Shenzhen, China, [www.eswl.cn](http://www.eswl.cn)  
Shenzhen PRO-HITU Medical Technology CO LTD | Shenzhen, China, [en.pro-hifu.com](http://en.pro-hifu.com)  
Suntec Industries CO LTD | Shanghai, China  
Vensica Medical | Misgav, Israel, [www.vensica.com](http://www.vensica.com)  
Wuxi Haiying Electronic Medical Systems CO LTD | Wuxi, China, [www.haiyingmedical.com](http://www.haiyingmedical.com)
- **MR & US GUIDANCE**  
Changjiangyuan Technology Development CO LTD | Beijing, China, [www.cjyjk.com/en](http://www.cjyjk.com/en)
- **OTHER GUIDANCE**  
NaviFUS CORP | New Taipei City, Taiwan, [www.navi-fus.com](http://www.navi-fus.com)

## FUS Industry by Region continued

### Other FUS Companies

#### North America

15

##### ■ DISTRIBUTOR

Focus Surgery INC | Indianapolis, Indiana, United States

HIFU Prostate Services LLC | Charlotte, North Carolina, United States, [www.hifuprostateservices.com](http://www.hifuprostateservices.com)

##### ■ MICROBUBBLE

Artenga INC | Ottawa, Ontario, Canada, [www.artenga.com](http://www.artenga.com)

Dynaflow INC | Jessup, Maryland, United States, [www.dynaflow-inc.com](http://www.dynaflow-inc.com)

SonoGene LLC | Glen Ellyn, Illinois, United States

Vesselon INC | Norwalk, Connecticut, United States, [www.vesselon.com](http://www.vesselon.com)

##### ■ OEM

Daxsonics Ultrasound INC | Halifax, Nova Scotia, Canada, [www.daxsonics.com](http://www.daxsonics.com)

Electronics and Innovation LTD | Rochester, New York, United States, [www.eandiltd.com](http://www.eandiltd.com)

FUS Instruments INC | Toronto, Ontario, Canada, [www.fusinstruments.com](http://www.fusinstruments.com)

JJ & A Instruments LLC | Duvall, Washington, United States, [jja-instruments.com](http://jja-instruments.com)

Onda INC | Sunnyvale, California, United States, [www.ondacorp.com](http://www.ondacorp.com)

Piezo Technologies | Bothell, Washington, United States, [www.piezotechnologies.com](http://www.piezotechnologies.com)

Sonic Concepts LLC | Concord, California, United States, [www.sonicconcpets.com](http://www.sonicconcpets.com)

Ultrasonic S-Lab LLC | Concord, California, United States, [www.ultrasonic-s-lab.com](http://www.ultrasonic-s-lab.com)

Verasonics INC | Kirkland, Washington, United States, [www.verasonics.com](http://www.verasonics.com)

#### Europe

9

##### ■ DISTRIBUTOR

Promedica Bioelectronics SRL | Rome, Italy, [www.promedicasrl.eu](http://www.promedicasrl.eu)

##### ■ MICROBUBBLE

Bracco Imaging SPA | Milan, Italy, [www.braccoimaging.com](http://www.braccoimaging.com)

OxSonics LTD | Oxford, United Kingdom, [www.oxsonics.com](http://www.oxsonics.com)

Phoenix Solutions AS | Moss, Norway, [www.phoenixsolutions.no](http://www.phoenixsolutions.no)

Thermosome, GMBH | Planegg/Martinsried, Germany, [www.thermosome.com](http://www.thermosome.com)

## FUS Industry by Region continued

## Other FUS Companies

## Europe continued

## ■ OEM

Imasonic SA | Voray-sur-l'Ognon, France, [www.imasonic.com](http://www.imasonic.com)

Medsonic LTD | Limassol, Cyprus, [www.medsonic.com.cy](http://www.medsonic.com.cy)

Meggitt A/S | Kvistgård, Denmark, [www.meggittferroperm.com](http://www.meggittferroperm.com)

Precision Acoustics LTD | Higher Bockhampton, Dorchester, United Kingdom, [www.acoustics.co.uk](http://www.acoustics.co.uk)

## Asia

6

## ■ DISTRIBUTOR

Beijing Ren De Sheng Technology | Beijing, China

ECHO Healthcare INC | Seoul, South Korea, [www.hifu.kr](http://www.hifu.kr)

Sumo Corporations LTD | Shanghai, China, [www.sumo.com.hk/Partners.html](http://www.sumo.com.hk/Partners.html)

## ■ OEM

EofE Ultrasonics CO LTD | Hanggongdaehak-ro, South Korea, [www.ultrasonics.co.kr](http://www.ultrasonics.co.kr)

Humanscan CO LTD | Ansan, South Korea, [www.humanscan.co.kr](http://www.humanscan.co.kr)

S-Sharp CORP | New Taipei City, Taiwan, [www.s-sharp.com](http://www.s-sharp.com)

## South America

1

## ■ DISTRIBUTOR

Sul Imagem | São José, Brazil, [www.sul-imagem.com.br](http://www.sul-imagem.com.br)

Contact Information for Commercially Approved Manufacturers\*

**Alpinion Medical Systems Co., Ltd.**

Seoul, South Korea  
www.alpinion.com

**Beijing Yuande Bio-Medical Engineering Co., Ltd.**

Beijing, China  
www.yuande.com

**Chongqing Haifu Medical Technology Co., Ltd.**

Chongqing, China

**EDAP TMS, SA**

Vaulx-en-Velin, France  
www.edap-tms.com

**EpiSonica Corp.**

Hsichu City, Taiwan  
www.episonica.com

**EyeTechCare, SA**

Lyon, France  
www.eyetechcare.com

**Guided Therapy System**

Mesa, Arizona, United States  
www.guidedtherapy.com

**INSIGHTEC, Ltd.**

Tirat Carmel, Israel  
www.insightec.com

**Kona Medical, Inc.**

Bellevue, Washington, United States  
www.konamedical.com

**Mirabilis Medical, Inc**

Bothell, Washington, United States  
www.mirabilismedical.com

**Profound Medical Corp.**

Mississauga, Ontario, Canada  
www.profoundmedical.com

**Shanghai A&S Science**

**Technology Development Co., Ltd.**  
Shanghai, China  
www.aishen.com.cn

**Shenzhen PRO-HITU Medical Technology Co., Ltd.**

Shenzhen, China  
en.pro-hifu.com

**SonaCare Medical, LLC**

Charlotte, North Carolina, United States  
www.sonacaremedical.com

**Theraclion, SA**

Malakoff, France  
www.theraclion.com

**Wuxi Haiying Electronic Medical Systems Co., Ltd.**

Wuxi, China  
www.haiyingmedical.com

\*See pages 23–25.

## About the Focused Ultrasound Foundation

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.

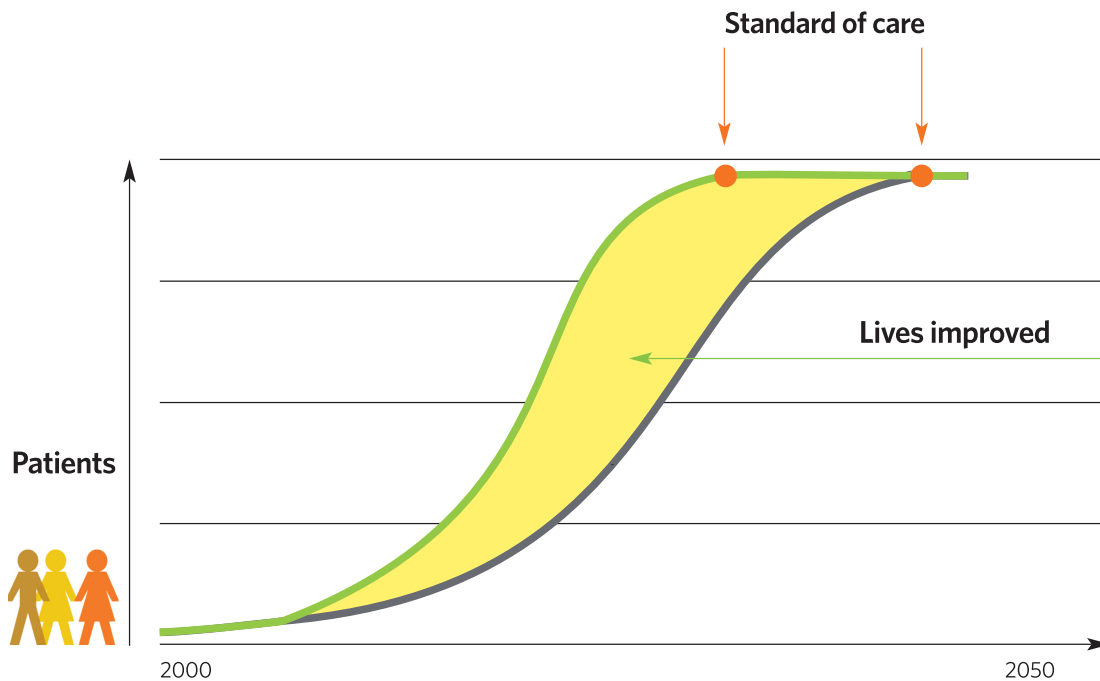
By identifying opportunities and overcoming barriers, the Foundation is shortening the time from laboratory research to widespread treatment.

### 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

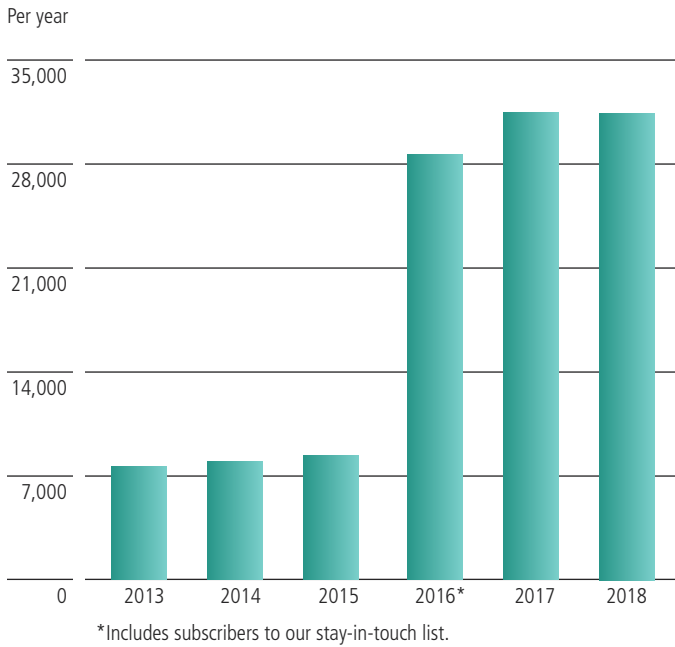
The Foundation has a robust research program and organizes, conducts, and supports clinical trials and preclinical laboratory studies with an emphasis on brain disorders, oncology, and immunotherapy. It is the largest nongovernmental source of focused ultrasound research funding in the world.

The 2019 State of the Field to this point has been a summary of the field as a whole. What follows is a summary of the Foundation’s activities and programs, highlighting accomplishments of the past year. Our mission is to accelerate the timeline of clinical adoption of the technology to treat more patients and relieve more suffering.

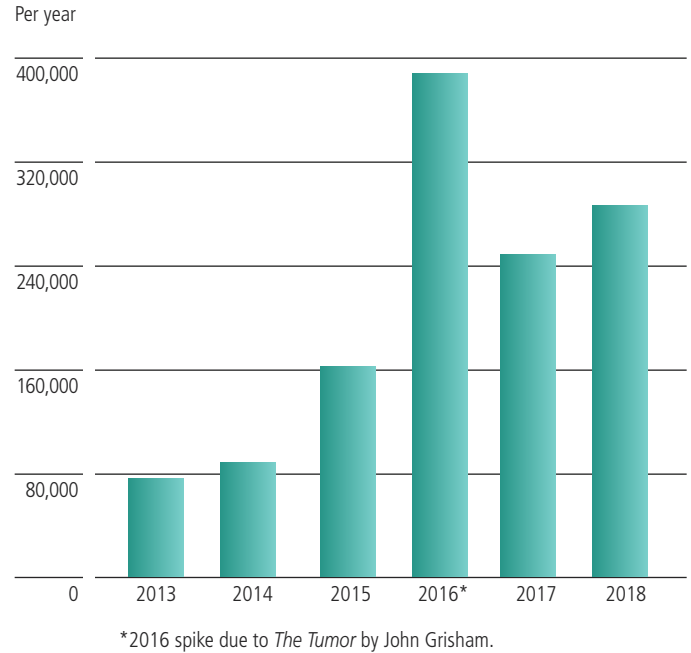


**Saving time = Saving lives**

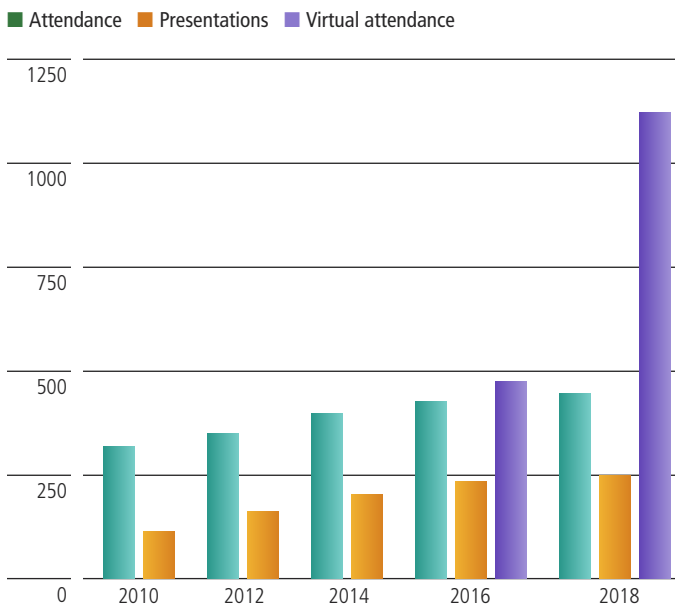
### Focused Ultrasound Foundation Newsletter Distribution



### Focused Ultrasound Foundation Website Visits



### Focused Ultrasound Foundation Symposium Attendance and Presentations



### Increasing Knowledge and Awareness

*The Tumor*, written by board member John Grisham and released in 2016, remains the Foundation’s most successful awareness tool. Our newsletter distribution list quadrupled the year following its release and continues to enjoy high numbers of subscribers, maintaining consistent open rates years later. In addition, 2016 visits to our website skyrocketed threefold as compared to 2015. Website visits have not sustained those record-setting levels, but are still nearly double the number prior to *The Tumor*’s release.

Live webcast registrations and viewership of our biennial symposia doubled from 2016 to 2018. We were unsure of the response when we first proposed live-streaming, but interest in this option has been overwhelming. While funding for symposium attendance is often limited to researchers whose posters or presentations have been accepted, clearly many more researchers would like to attend in whatever way possible. Live-streaming allows virtual attendance for all interested individuals, increasing the dissemination of knowledge.



Focused Ultrasound Foundation Activities

CREATE KNOWLEDGE

**356**

**patients**

treated in FUSF-funded trials  
cumulative

**43**

**Foundation-funded  
clinical trials**

cumulative

**25**

**publications  
by FUSF staff**

cumulative

FOSTER  
COLLABORATION

**6**

**symposia**

cumulative

**25**

**workshops**

cumulative

**18**

**webinars**

cumulative

**16,308**

**webinar attendees**

as of March 1, 2019

to engage stakeholders  
and build communities

INCREASE AWARENESS

**1,461**

**media placements**

cumulative

AGGREGATE & SHARE  
KNOWLEDGE

**32,000**

**newsletter subscribers**

current

**290,000**

**website visits**

2018

OVERCOME BARRIERS

**3**

**reimbursement workshops**

cumulative

CULTIVATE THE  
NEXT GENERATION

**148**

**interns**

cumulative

**17**

**fellows**

cumulative

Social Media



**352,000**

**Twitter impressions**

2018



**229,000**

**Facebook reach**

2018



**49,000**

**LinkedIn impressions**

2018



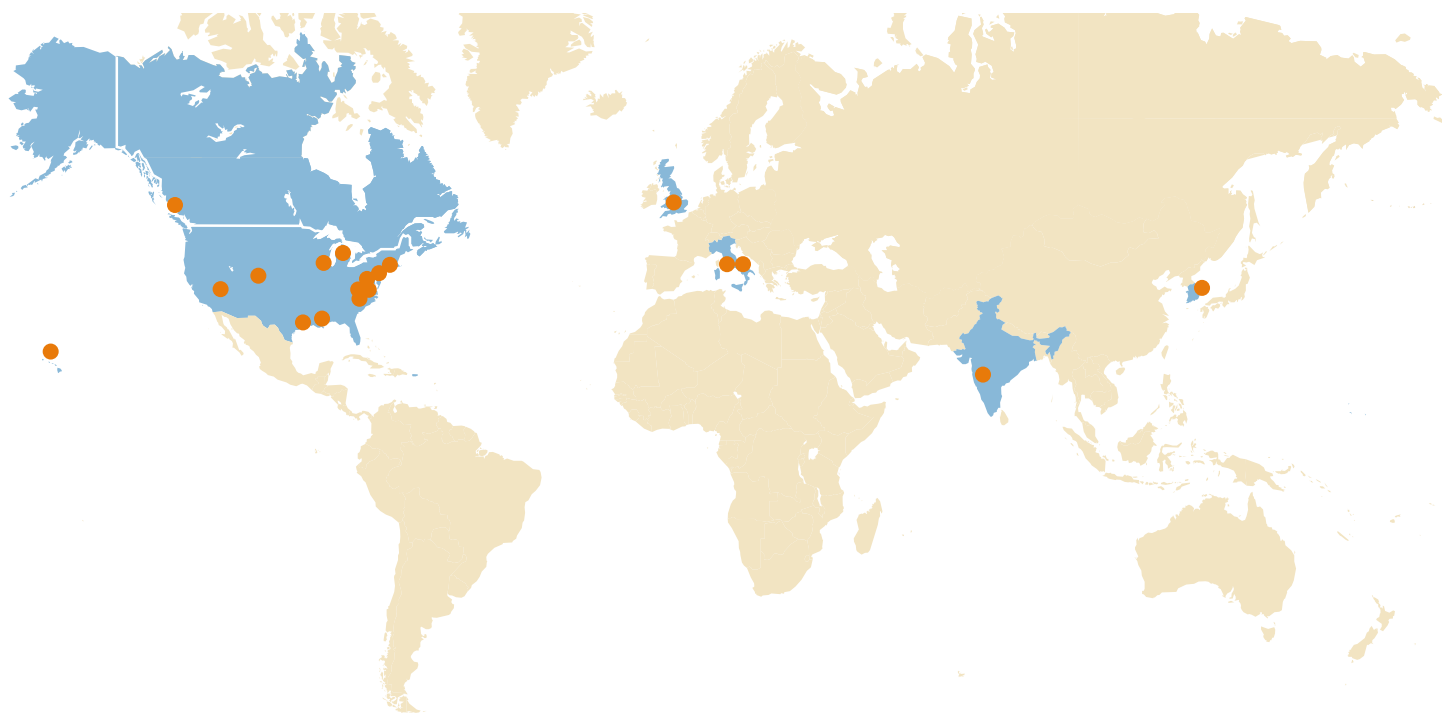
**47,800**

**Views on the Foundation  
YouTube channel**

2018

## Invited Talks

2018

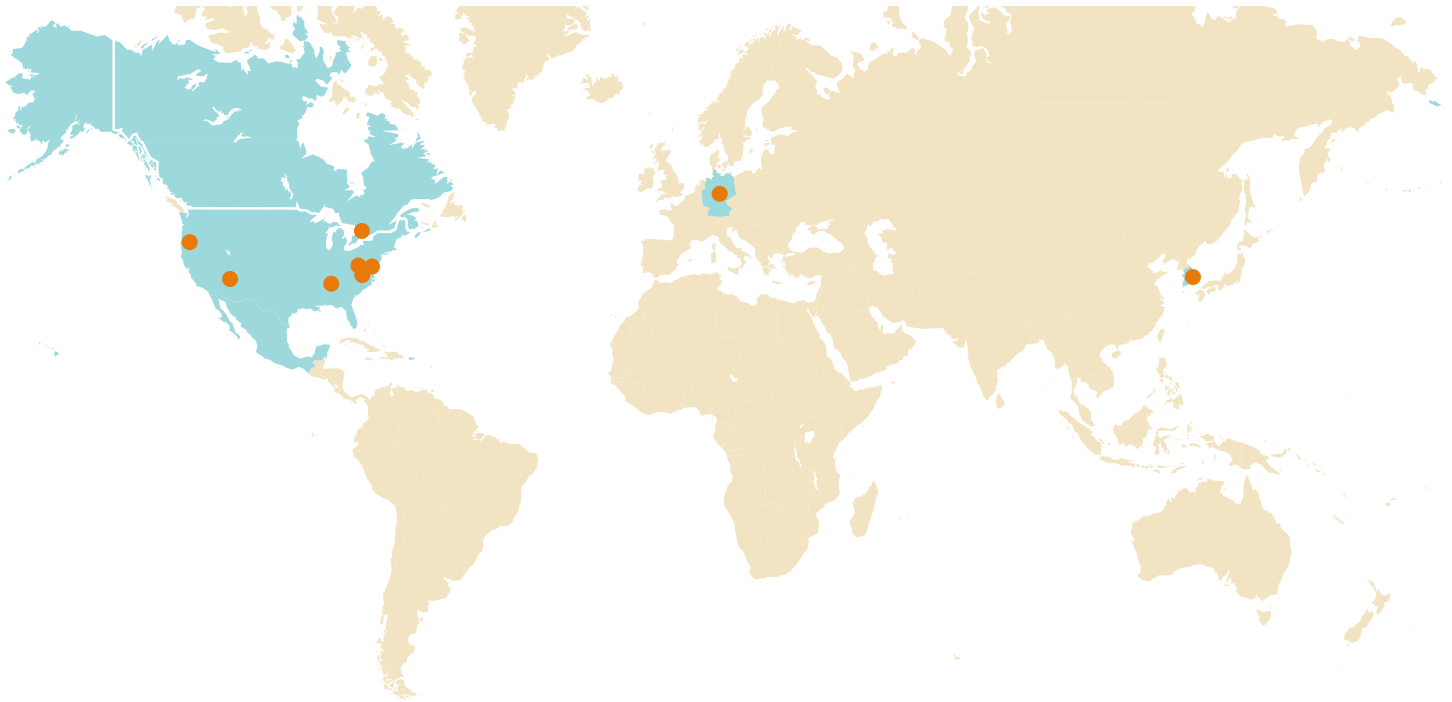


## Invited Talks

Institution or event by chronological order	Location
Consumer Electronics Show (CES™)	Las Vegas, NV
University of Virginia Frank Batten School of Leadership and Public Policy	Charlottesville, VA
Tata Memorial Centre, Masterclass in Neurosurgical Oncology	Mumbai, India
University of Oxford, HIFU Users Group	Oxford, England
Peninsula Engineers Council (PEC)	Richmond, VA
Path North	New Orleans, LA
George Washington University	Washington, DC
Military Officers Association	Charlottesville, VA
American Institute of Ultrasound in Medicine (AIUM)	New York, NY
Senior Statesmen of Virginia	Charlottesville, VA
Duke University	Durham, NC
Bohemian Grove	Washington, DC
American Society for Stereotactic and Functional Neurosurgery (ASSFN)	Denver, CO
40th International Conference of the IEEE Engineering in Medicine and Biology Society	Honolulu, HI
Alzheimer's Association International Conference (AAIC)	Chicago, IL
University of Michigan	Ann Arbor, MI
Korean Society of Therapeutic Ultrasound (KSTU)	Jeju-do, South Korea
Desmoid Tumor Research Foundation (DTRF)	Philadelphia, PA
Congress of Neurological Surgeons (CNS)	Houston, TX
Virginia Bio, Women Building Bio	Fairfax, VA
49 <sup>o</sup> Congress of the Italian Society of Neurology	Rome, Italy
Acoustical Society of America (ASA)	Victoria, BC, Canada
Bambino Gesù Children's Hospital, Lesional Procedures in Focused Ultrasound, Workshop & Course	Rome, Italy

## Meeting Sponsorships

2018



### Meeting Sponsorships

Events by chronological order	Location
9th Annual Neuroanatomy Fellows Course, Seattle Science Foundation	Seattle, WA
Tom Tom Founders Festival	Charlottesville, VA
Society for Thermal Medicine (STM)	Tucson, AZ
International Society for Therapeutic Ultrasound (ISTU)	Nashville, TN
University of Virginia Darden School of Business, Healthcare Conference	Charlottesville, VA
40th Post-Graduate Course of the European Society for Paediatric Radiology HIFU Symposium	Berlin, Germany
Korean Society for Therapeutic Ultrasound 4th Annual Meeting	Jeju City, South Korea
Pancakes for Parkinson's – University of Virginia	Charlottesville, VA
2018 Ontario Gairdner International Symposium	Toronto, ON, Canada

### Invited Talks

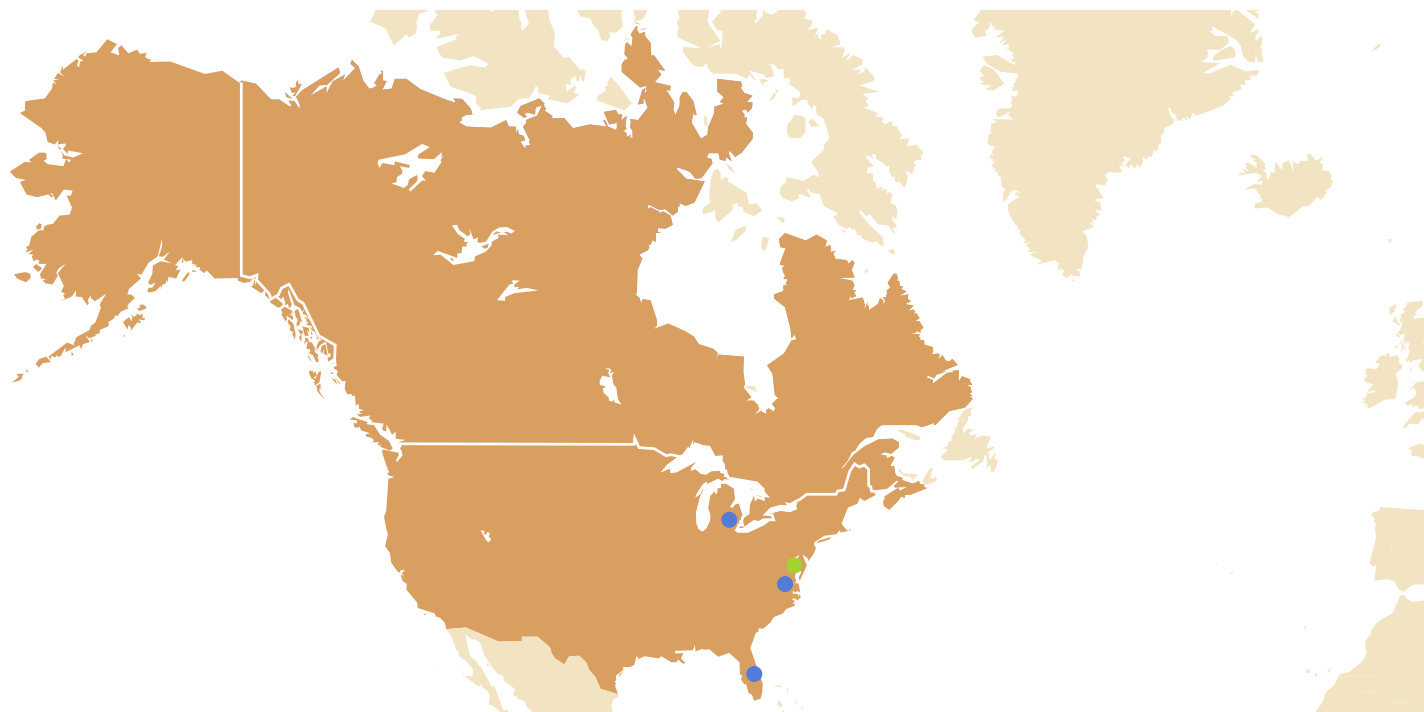
Invited talks are given around the globe by various members of our in-house scientific team.

### Meeting Sponsorships

The Foundation's sponsorship initiative increases focused ultrasound awareness and connects FUSF-funded researchers, FUS industry, and other potential collaborators to further our mission.

## Workshops and Webinars

2018



### ● Workshops

Topic	Location
Focused Ultrasound Opening of the Blood-Brain Barrier for the Treatment of Parkinson's Disease	Reston, VA

### Workshops

For more information on the participants and results of FUSF workshops, please visit:  
[www.fusfoundation.org/for-researchers/resources/white-papers](http://www.fusfoundation.org/for-researchers/resources/white-papers).

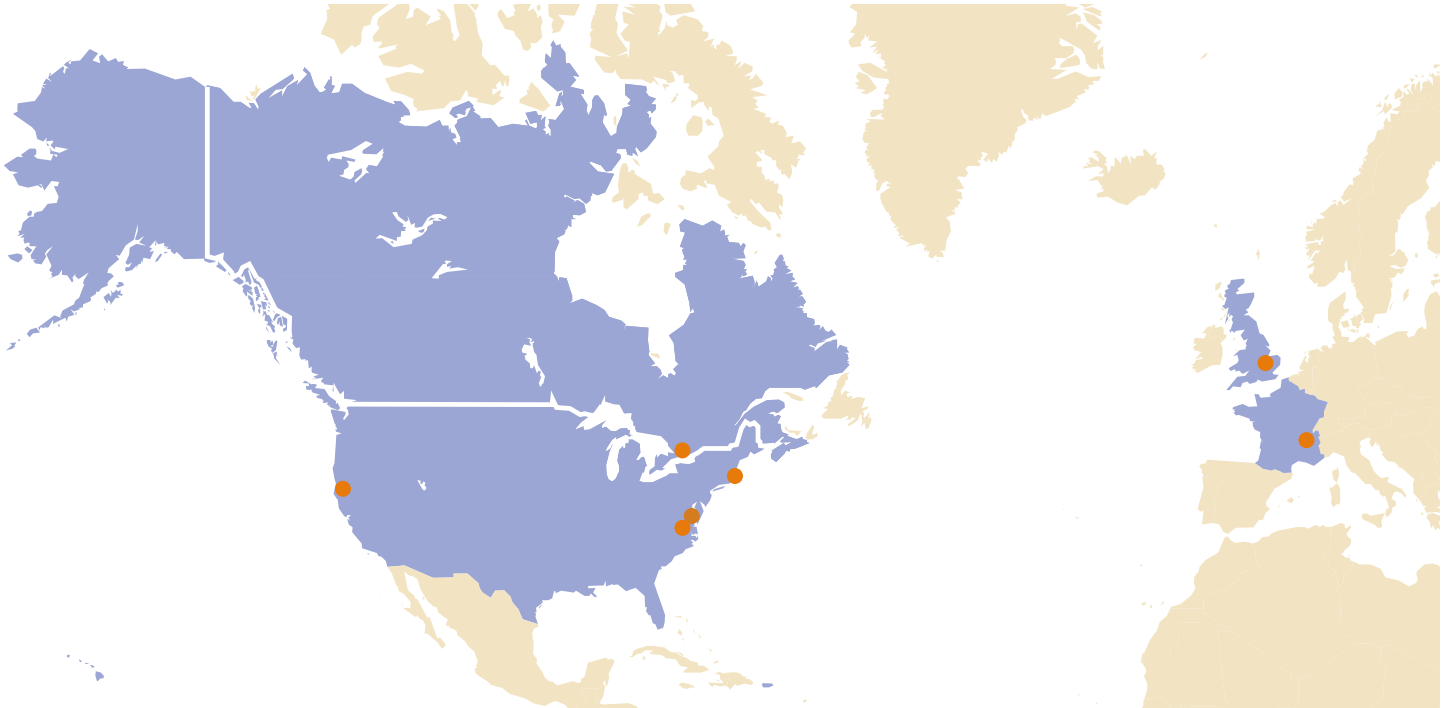
To view webinars, please visit:  
[www.fusfoundation.org/the-foundation/programs/webinars](http://www.fusfoundation.org/the-foundation/programs/webinars).

### ● Webinars

Topic	Speaker and affiliation
Blockchain: A Healthcare-Focused Introduction 690 views	Rick Hamilton Optum, Inc. Detroit, MI
Data Science in Biomedicine 437 views	Philip Bourne University of Virginia Charlottesville, VA
Accelerating Adoption of New Technologies 941 views	Salim Ismail ExO Foundation Miami, FL

## Centers of Excellence

2018



### Centers of Excellence

Institution	Location	Named a COE
French National Institute of Health and Medical Research (INSERM) LabTAU	Lyon, France	2017
Stanford University School of Medicine	Stanford, CA	2016
Sunnybrook Health Sciences Centre	Toronto, ON, Canada	2016
University of Maryland School of Medicine	Baltimore, MD	2016
Brigham and Women's Hospital	Boston, MA	2015
The Institute of Cancer Research and the Royal Marsden	London, England	2013
University of Virginia Health System	Charlottesville, VA	2009

### Centers of Excellence

The Centers of Excellence, COE, program brings together the best people and technical resources at luminary research sites around the globe. In order to earn this designation, an institution must have active technical, preclinical, and clinical research projects underway as well as a focused ultrasound education component to cultivate the next generation of researchers.

## Centers of Excellence Research

### INSERM - LabTAU | Lyon, France

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

#### Program Manager/contact info

**Cyril Lafon, PhD** | [cyril.lafon@inserm.fr](mailto:cyril.lafon@inserm.fr)

#### Commercial Treatment

<b>Ophthalmological</b>	Glaucoma
<b>Urological</b>	Kidney stone fragmentation, Prostate tumors

#### Clinical Research

<b>Gastrointestinal</b>	Liver metastases
<b>Neurological</b>	Glioblastoma
<b>Ophthalmological</b>	Glaucoma
<b>Urological</b>	Prostate tumors
<b>Women's Health</b>	Endometriosis

#### Preclinical Research

<b>Cardiovascular</b>	Atrial fibrillation, Varicose veins
<b>Gastrointestinal</b>	Liver metastases, Liver tumors, Pancreatic tumors
<b>Musculoskeletal</b>	Osteoradionecrosis
<b>Neurological</b>	Cancer pain, Glioblastoma, Stroke
<b>Ophthalmological</b>	Glaucoma
<b>Urological</b>	Kidney stone fragmentation, Prostate tumors
<b>Women's Health</b>	Breast cancer, Endometriosis, Fetal surgery: Twin-twin transfusion syndrome

#### Mechanisms of Action

<b>Drug delivery</b>	Blood-brain barrier opening, Sonoporation, Therapeutic delivery (unencapsulated)
<b>Immunomodulation</b>	Immunomodulation
<b>Increased vascular permeability</b>	Blood-brain barrier opening
<b>Tissue destruction</b>	Histotripsy, Mechanical ablation, Thermal ablation, Vascular disruption
<b>Other</b>	Clot lysis, Lithotripsy, Low-intensity pulsed ultrasound, Neuromodulation, Sensitization to chemotherapy, Sonodynamic therapy

#### Technical Research

Drug delivery technology
FUS physics
FUS simulation and treatment planning
FUS transducer technology
FUS treatment monitoring
MR imaging for FUS guidance
Ultrasound imaging for FUS guidance

#### Publications

Safety evaluation of frequent application of microbubble-enhanced focused ultrasound blood-brain-barrier opening. Tsai HC, Tsai CH, Chen WS, Inserra C, Wei KC, Liu HL. *Sci Rep*. 2018 Dec 7;8(1):17720. doi: 10.1038/s41598-018-35677-w. PubMed PMID: 30531863; PubMed Central PMCID: PMC6286368.

Myocardial Thermal Ablation with a Transesophageal High-Intensity Focused Ultrasound Probe: Experiments on Beating Heart Models. Greillier P, Ankou B, Bour P, Zorgani A, Abell E, Lacoste R, Bessière F, Pernot M, Catheline S, Quesson B, Chevalier P, Lafon C. *Ultrasound Med Biol*. 2018 Dec;44(12):2625-2636. doi: 10.1016/j.ultrasmedbio.2018.06.013. Epub 2018 Sep 9. PubMed PMID: 30205993.

Bone-conducted sound in a dolphin's mandible: Experimental investigation of elastic waves mediating information on sound source position. Reinwald M, Grimal Q, Marchal J, Catheline S, Boschi L. *J Acoust Soc Am*. 2018 Oct;144(4):2213. doi: 10.1121/1.5063356. PubMed PMID: 30404511.

Ultrasound molecular imaging as a non-invasive companion diagnostic for netrin-1 interference therapy in breast cancer. Wischhusen J, Wilson KE, Delcros JG, Molina-Peña R, Gibert B, Jiang S, Ngo J, Goldschneider D, Mehlen P, Willmann JK, Padilla F. *Theranostics*. 2018 Oct 6;8(18):5126-5142. doi: 10.7150/thno.27221. eCollection 2018. PubMed PMID: 30429890 PubMed Central PMCID: PMC6217066.

## Centers of Excellence Research continued

## Publications continued

- Weighting the Passive Acoustic Mapping Technique with the Phase Coherence Factor for Passive Ultrasound Imaging of Ultrasound-Induced Cavitation. Boulos P, Varray F, Poizat A, Poizat A, Ramalli A, Gilles B, Bera JC, Cachard C. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2018 Sep 24. doi: 10.1109/TUFFC.2018.2871983. [Epub ahead of print]. PubMed PMID: 30273149.
- Surface modes with controlled axisymmetry triggered by bubble coalescence in a high-amplitude acoustic field. Cleve S, Guedra M, Inserra C, Mauger C, Blanc-Benon P. *Phys Rev E*. 2018 Sep 24; 98:033115. doi: 10.1103/PhysRevE.98.033115.
- Multiple sources array controls shear-wave field in soft tissue using time reversal. Zemzemi C, Aichele J, Catheline S. *Phys Med Biol*. 2018 Sep 19;63(18):18NT02. doi: 10.1088/1361-6560/aadd3f. PubMed PMID: 30152787
- Review on biomedical techniques for imaging electrical impedance. Grasland-Mongrain P, Lafon C. *IRBM*. 2018 Aug;39(4):243-250. doi: 10.1016/j.irbm.2018.06.001.
- Shear-wave sources for soft tissues in ultrasound elastography. Giammarinaro B, Zorgani A, Catheline S. *IRBM*. 2018 Aug;39(4):236-242. doi: 10.1016/j.irbm.2018.01.002.
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Centers of Excellence Research continued

**Stanford University School of Medicine | Stanford, CA**

Directed by Pejman Ghanouni, MD, PhD, and Kim Butts Pauly, PhD, Stanford’s COE was established in 2016 and focuses on a number of clinical and preclinical projects. These include industry-sponsored trials using focused ultrasound to treat osseous metastases, uterine fibroids, essential tremor, and prostate cancer, as well as investigator-initiated trials to treat soft tissue tumors and facet joint arthritis. Preclinical projects have included the development of referenceless methods for MR thermometry in the brain, as well as respiratory-compensated focused ultrasound in treatment of porcine liver during free-breathing. These clinical and preclinical projects involve close collaboration with clinical colleagues in radiology, obstetrics and gynecology, medical oncology, radiation oncology, neurosurgery, neurology, orthopedic surgery, urology, pathology, immunology, and electrical and mechanical engineering.

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**Commerical Treatments**

<b>Cardiovascular</b>	Arteriovenous malformations
<b>Musculoskeletal</b>	Bone cancer; Bone metastases; Osteoid osteoma; Soft tissue tumors, benign; Desmoid tumors
<b>Neurological</b>	Essential tremor, Parkinson’s disease
<b>Urological</b>	Prostate tumors
<b>Women’s Health</b>	Uterine adenomyosis, Uterine fibroids

**Clinical Research**

<b>Musculoskeletal</b>	Osteoid osteoma
<b>Neurological</b>	Parkinson’s disease
<b>Urological</b>	Prostate tumors

**Preclinical Research**

<b>Gastrointestinal</b>	Pancreatic tumors, Liver tumors
<b>Neurological</b>	Epilepsy, Glioblastoma
<b>Urological</b>	Acute kidney injury

**Veterinary Research**

<b>Gastrointestinal</b>	Liver tumors
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**Mechanisms of Action**

<b>Drug delivery</b>	Blood-brain barrier opening, Drug delivery vehicles, Hyperthermia, Sonoporation, Therapeutic delivery (unencapsulated)
<b>Immunomodulation</b>	Immune cell delivery, Immunomodulation, Immunotherapeutic delivery
<b>Increased vascular permeability</b>	Blood-brain barrier opening, Stem cell delivery
<b>Tissue destruction</b>	Mechanical ablation, Thermal ablation
<b>Other</b>	Amplification of cancer biomarkers, Neuromodulation, Sensitization to chemotherapy, Stem cell homing

**Technical Research**

Drug delivery technology
FUS physics
FUS simulation and treatment planning
FUS treatment monitoring
MR imaging for FUS guidance
Ultrasound imaging for FUS guidance

**Publications**

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Centers of Excellence Research continued

**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, and others. Kullervo Hynynen PhD, is the scientific director of the COE, and Nir Lipsman, MD, PhD, is the center’s clinical director.

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**Commerical Treatments**

**Neurological** Essential tremor

**Clinical Research**

**Gastrointestinal** Colorectal tumors, Liver tumors

**Miscellaneous** Head & neck tumors

**Musculoskeletal** Bone cancer, Bone metastases

**Neurological** Alzheimer’s disease, Amyotrophic lateral sclerosis, Depression, Essential tremor, Glioblastoma, Obsessive-compulsive disorder, Parkinson’s disease

**Women’s Health** Brain metastases, breast cancer; Uterine fibroids

**Preclinical Research**

**Cardiovascular** Atrial fibrillation, Deep vein thrombosis, Hypertension

**Gastrointestinal** Colorectal tumors, Liver metastases, Liver tumors

**Musculoskeletal** Bone metastases

**Neurological** Alzheimer’s disease, Amyotrophic lateral sclerosis, Depression, Epilepsy, Glioblastoma, Parkinson’s disease, Stroke

**Women’s Health** Brain metastases, Beast cancer; Breast cancer

**Mechanisms of Action**

**Drug delivery** Blood-brain barrier opening, Hyperthermia, Sonoporation, Therapeutic delivery (unencapsulated), Vasodilation

**Immunomodulation** Immune cell delivery, Immunotherapeutic delivery

**Increased vascular permeability** Blood-brain barrier opening, Stem cell delivery

**Tissue destruction** Thermal ablation, Vascular disruption

**Other** Clot lysis, Neuromodulation, Radiosensitization, Sensitization to chemotherapy

**Technical Research**

Drug delivery technology

FUS physics

FUS simulation and treatment planning

FUS transducer technology

FUS treatment monitoring

MR imaging for FUS guidance

Standards & QA

Ultrasound imaging for FUS guidance

**Publications**

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Publications continued

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Antidepressant effects of focused ultrasound induced blood-brain-barrier opening. Mooney SJ, Nobrega JN, Levitt AJ, Hynynen K. *Behav Brain Res.* 2018 Apr 16;342:57-61. doi: 10.1016/j.bbr.2018.01.004. Epub 2018 Jan 8. PubMed PMID: 29326057; PubMed Central PMCID: PMC6207941.

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Centers of Excellence Research continued

**University of Maryland School of Medicine | Baltimore, MD**

The COE at the University of Maryland (UMD) was established in 2016. At present, the UMD departments of neurosurgery, radiology, and neurology are collaborating to study treatment of movement disorders, chronic neuropathic pain, brain tumors, and the use of enhanced drug delivery. In addition, their immunomodulation studies range from investigation of cell systems to animal models to human clinical trials. Elias R. Melham, MD, and Howard M. Eisenberg, MD, co-direct this COE.

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**Commercial Treatment**  
**Neurological** Essential tremor

**Clinical Research**  
**Neurological** Astrocytoma (SEGA), Essential tremor, Glioblastoma, Neuropathic pain, Parkinson’s disease

**Preclinical Research**  
**Neurological** Astrocytoma (SEGA), Epilepsy, Glioblastoma, Parkinson’s disease, Traumatic brain injury

**Mechanisms of Action**  
**Drug delivery** Blood-brain barrier opening  
**Immunomodulation** Immunomodulation  
**Increased vascular permeability** —  
**Tissue destruction** Mechanical ablation, Thermal ablation  
**Other** Neuromodulation

**Technical Research**  
 Drug delivery technology  
 FUS physics  
 FUS simulation and treatment planning  
 FUS treatment monitoring  
 MR imaging for FUS guidance  
 Standards & QA  
 Ultrasound imaging for FUS guidance

**Publications**

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Centers of Excellence Research continued

**Brigham and Women’s Hospital | Boston, MA**

Brigham and Women’s Hospital was named a Foundation 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.

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**Commerical Treatments**

- Neurological**      Essential tremor
- Women’s Health**    Uterine fibroids

**Clinical Research**

- Musculoskeletal**    Bone metastases
- Neurological**        Glioblastoma, Parkinson’s disease
- Urological**            Prostate tumors

**Preclinical Research**

- Neurological**        Epilepsy, Glioblastoma

**Mechanisms of Action**

- Drug delivery**        Blood-brain barrier opening
- Immunomodulation**   Immunomodulation
- Increased vascular permeability**    Drug delivery vehicles, Stem cell delivery
- Tissue destruction**    Hyperthermia, Mechanical ablation, Thermal ablation
- Other**                    Amplification of cancer biomarkers, Neuromodulation

**Technical Research**

- FUS physics
- FUS simulation and treatment planning
- FUS treatment monitoring
- MR imaging for FUS guidance
- Ultrasound imaging for FUS guidance

**Publications**

Focused ultrasound transiently increases membrane conductance in isolated crayfish axon. Lin JW, Yu F, Müller WS, Ehnholm G, Okada Y. *J Neurophysiol.* 2018 Dec 19. doi: 10.1152/jn.00541.2018. [Epub ahead of print] PubMed PMID: 30565960

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Centers of Excellence Research continued

Publications continued

Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. Fishman PS, Elias WJ, Ghanouni P, Gwinn R, Lipsman N, Schwartz M, Chang JW, Taira T, Krishna V, Rezai A, Yamada K, Igase K, Cosgrove R, Kashima H, Kaplitt MG, Tierney TS, Eisenberg HM. *Mov Disord.* 2018 May;33(5):843-847. doi: 10.1002/mds.27401. Epub 2018 Apr 27. PubMed PMID: 29701263.

Multi-resolution simulation of focused ultrasound propagation through ovine skull from a single-element transducer. Yoon K, Lee W, Croce P, Cammalleri A, Yoo SS. *Phys Med Biol.* 2018 May 10;63(10):105001. doi: 10.1088/1361-6560/aabe37. PubMed PMID: 29658494; PubMed Central PMCID: PMC5990022.

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

In 2013, the Focused Ultrasound Foundation and Philips entered into an innovative public-private collaboration with the Institute of Cancer Research (ICR) and The Royal Marsden NHS (National Health Service) Foundation Trust to create a COE in London. The Center created a state-of-the-art resource for clinicians and scientists working on focused ultrasound therapy, developing clinical evidence in oncology, and establishing best practices, treatment standards, and protocols. The COE is led by Scientific Director Gail ter Haar, professor of physics at the ICR, and Clinical Director Nandita deSouza, professor of translational imaging at the ICR and honorary consultant at The Royal Marsden.

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Clinical Research

<b>Musculoskeletal</b>	Bone cancer, Soft tissue cancer
<b>Neurological</b>	Cancer pain

Preclinical Research

<b>Gastrointestinal</b>	Liver metastases, Liver tumors, Pancreatic tumors
<b>Neurological</b>	Cancer pain, Glioblastoma
<b>Women's Health</b>	Fetal surgery: Twin-twin transfusion syndrome

Mechanisms of Action

<b>Drug delivery</b>	Dyperthermia, Therapeutic delivery (unencapsulated)
<b>Immunomodulation</b>	Immune cell delievery, Immunomodulation, Immunotherapeutic delivery
<b>Increased vascular permeability</b>	Blood-brain barrier opening
<b>Tissue destruction</b>	Histotripsy, Mechanical ablation, Thermal ablation, Vascular disruption, Other
<b>Other</b>	Radiosensitization, Sensitization to chemotherapy

Centers of Excellence Research continued

Technical Research

- Drug delivery technology
- FUS physics
- FUS simulation and treatment planning
- FUS transducer technology
- FUS treatment monitoring
- MR imaging for FUS guidance
- Standards & QA
- Ultrasound imaging for FUS guidance

Publications

- Quantitative photoacoustic imaging study of tumours in vivo: Baseline variations in quantitative measurements. MM Costa, A Shah, I Rivens, C Box, T O'Shea, E Papaevangelou, J Bamber, G ter Haar. *Photoacoustics* 13:53-65 Mar 2019. doi: 10.1016/j.pacs.2018.12.002. PubMed PMID: 30581729; PubMed Central PMCID: PMC6297191.
- Photoacoustic imaging for the prediction and assessment of response to radiotherapy in vivo. MM Costa, A Shah, I Rivens, C Box, T O'Shea, J Bamber, G ter Haar. *bioRxiv*, 329516. doi: 10.1101/329516
- Dependence of inertial cavitation induced by high intensity focused ultrasound on transducer F-number and nonlinear waveform distortion. Khokhlova T, Rosnitskiy P, Hunter C, Maxwell A, Kreider W, Ter Haar G, Costa M, Sapozhnikov O, Khokhlova V. *J Acoust Soc Am*. 2018 Sep;144(3):1160. doi: 10.1121/1.5052260. PubMed PMID: 30424663; PubMed Central PMCID: PMC6125138.
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- Value of diffusion-weighted imaging for monitoring tissue change during magnetic resonance-guided high-intensity focused ultrasound therapy in bone applications: an ex-vivo study. Giles SL, Winfield JM, Collins DJ, Rivens I, Civalo J, Ter Haar GR, deSouza NM. *Eur Radiol Exp*. 2018;2(1):10. doi: 10.1186/s41747-018-0041-x. Epub 2018 May 10. PubMed PMID: 29774894; PubMed Central PMCID: PMC5945713.
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- Evaluation of Quality of Life Outcomes Following Palliative Treatment of Bone Metastases with Magnetic Resonance-guided High Intensity Focused Ultrasound: An International Multicentre Study. Harding D, Giles SL, Brown MRD, Ter Haar GR, van den Bosch M, Bartels LW, Kim YS, Deppe M, deSouza NM. *Clin Oncol (R Coll Radiol)*. 2018 Apr;30(4):233-242. doi: 10.1016/j.clon.2017.12.023. Epub 2018 Jan 6. PubMed PMID: 29317145; PubMed Central PMCID: PMC5842401.

Publications continued

- Combining radiation with hyperthermia: a multiscale model informed by in vitro experiments. Brueningk SC, Powathil GG, Ziegenhein P, Ijaz J, Rivens I, Chaplain M, Oelfke U, ter Haar GR. *J. R. Soc. Interface* 15: 20170681. doi: 10.1098/rsif.2017.0681. PubMed PMID: 29343635, PubMed Central PMCID: PMC5805969.
- Response to comment by G. Borasi. SC Brüningk, I Rivens, S Nill, G ter Haar, U Oelfke. *International Journal of Hyperthermia* 34 (4), 404-406. doi: 10.1080/02656736.2017.1362117. PubMed PMID: 28812390; PubMed Central PMCID: PMC5989158.



Centers of Excellence Research continued

**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. Led by Clinical Director James Larner, MD, and Research Director Richard Price, PhD, the COE is a leading site for brain research, having pioneered clinical trials for essential tremor and Parkinsonian tremor, as well as technical and preclinical studies for neurological disorders. The center also conducts cancer research and treats uterine fibroids and bone metastases.

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**Commercial Treatment**  
**Neurological** Essential tremor  
**Women’s Health** Uterine fibroids

**Clinical Research**  
**Neurological** Epilepsy, Essential tremor, Neuropathic pain, Parkinson’s disease  
**Women’s Health** Breast cancer, Breast fibroadenoma, Uterine fibroids

**Preclinical Research**  
**Cardiovascular** Arteriovenous malformations, Peripheral artery disease  
**Gastrointestinal** Pancreatic tumors  
**Integumentary** Melanoma  
**Neurological** Glioblastoma, Parkinson’s disease, Stroke  
**Women’s Health** Breast cancer

**Mechanisms of Action**

<b>Drug delivery</b>	Blood-brain barrier opening, Drug delivery vehicles, Hyperthermia, Sonoporation, Therapeutic delivery (unencapsulated), Vasodilation
<b>Immunomodulation</b>	Immune cell delivery, Immunomodulation, Immunotherapeutic delivery
<b>Increased vascular permeability</b>	Blood-brain barrier opening, Stem cell delivery
<b>Tissue destruction</b>	Histotripsy, Mechanical ablation, Thermal ablation, Vascular disruption
<b>Other</b>	Angiogenesis, Clot lysis, Neuromodulation, Sonodynamic therapy, Stem cell homing

**Technical Research**  
 Drug delivery technology  
 FUS treatment monitoring  
 MR imaging for FUS guidance  
 Ultrasound imaging for FUS guidance

**Publications**

Preparation and characterization of perfluorocarbon microbubbles using Shirasu Porous Glass (SPG) membranes. R. Melich, F. Padilla, C. Charcosset. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 560:233-243, 2019. doi.org/10.1016/j.colsurfa.2018.09.058

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Applications of Focused Ultrasound in Cerebrovascular Diseases and Brain Tumors. Prada F, Kalani MYS, Yagmurlu K, Norat P, Del Bene M, DiMeco F, Kassell NF. *Neurotherapeutics*. 2018 Nov 7. doi: 10.1007/s13311-018-00683-3. [Epub ahead of print] Review. PubMed PMID: 30406382.

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Centers of Excellence Research continued

Publications continued

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Transcranial focused ultrasound neuromodulation of the human primary motor cortex. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. *Sci Rep.* 2018 Jul 3;8(1):10007. doi: 10.1038/s41598-018-28320-1. PubMed PMID: 29968768; PubMed Central PMCID: PMC6030101.

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