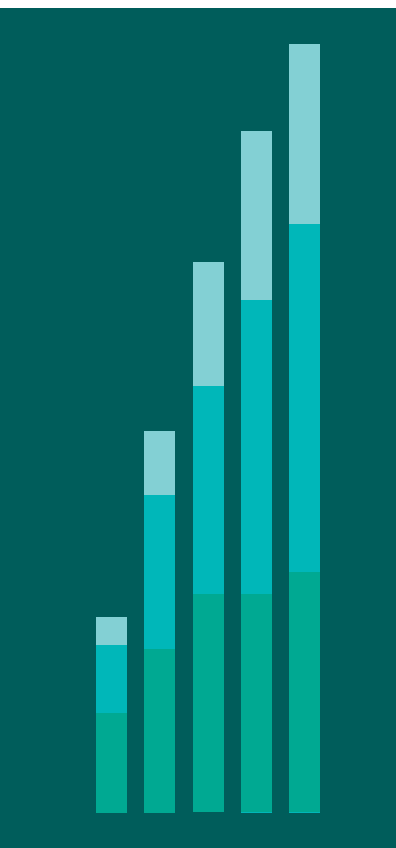


2023

Indication Development Pipeline



FOCUSED
ULTRASOUND
FOUNDATION



Overview

Chapter 2 includes a high-level overview of the indication pipeline and a deep dive for each indication on the various mechanisms of action and their stage of development. In the State of Research and Regulatory Approvals (nicknamed “the rainbow chart”) we list the most advanced stage of research/regulation/reimbursement regardless of geographic location. Further detail on indication status by geographic location can be found later in the report.

New this year we saw the addition of three preclinical indications—periodontal disease, autism, and cerebral palsy. Four indications advanced to first-in-human trials, all of which were neurological—bipolar disorder, lung cancer brain metastases, post traumatic stress disorder, and orthostatic tremor.

II. Indication Development Pipeline

- II. 2 Overview
- II. 3 Development State Advancements and New Indications

State of Research and Regulatory Approvals

- II. 4 By Body System
- II. 8 Neurological Indications
- II. 9 Indications with Anecdotal Case Reports
- II.10 Areas of Interest
- II.13 Oncology Indications

Mechanisms of Action

- II.14 About MOAs
- II.15 By Body System
 - II.15 Cardiovascular
 - II.17 Endocrine disorders
 - II.18 Gastrointestinal
 - II.20 Miscellaneous
 - II.22 Musculoskeletal
 - II.24 Neurological
 - II.33 Ophthalmological
 - II.34 Pulmonary
 - II.35 Urological
 - II.37 Women’s health

Development Stage Advancements and New Indications

2022

7

New indications

Gastrointestinal	● Periodontal disease
Neurological	● Bipolar disorder
	● Brain metastases, lung cancer
	● PTSD
	● Tremor, orthostatic
	● Autism
	● Cerebral palsy

Development stage

● Preclinical ● Clinical trials

2022

4

Indications advanced to first-in-human clinical trials

Neurological	Bipolar disorder†
	Brain metastases, lung cancer†
	PTSD†
	Tremor, orthostatic†

† New Indication for 2021

INDICATION PIPELINE

State of Research and Regulatory Approvals by Body System

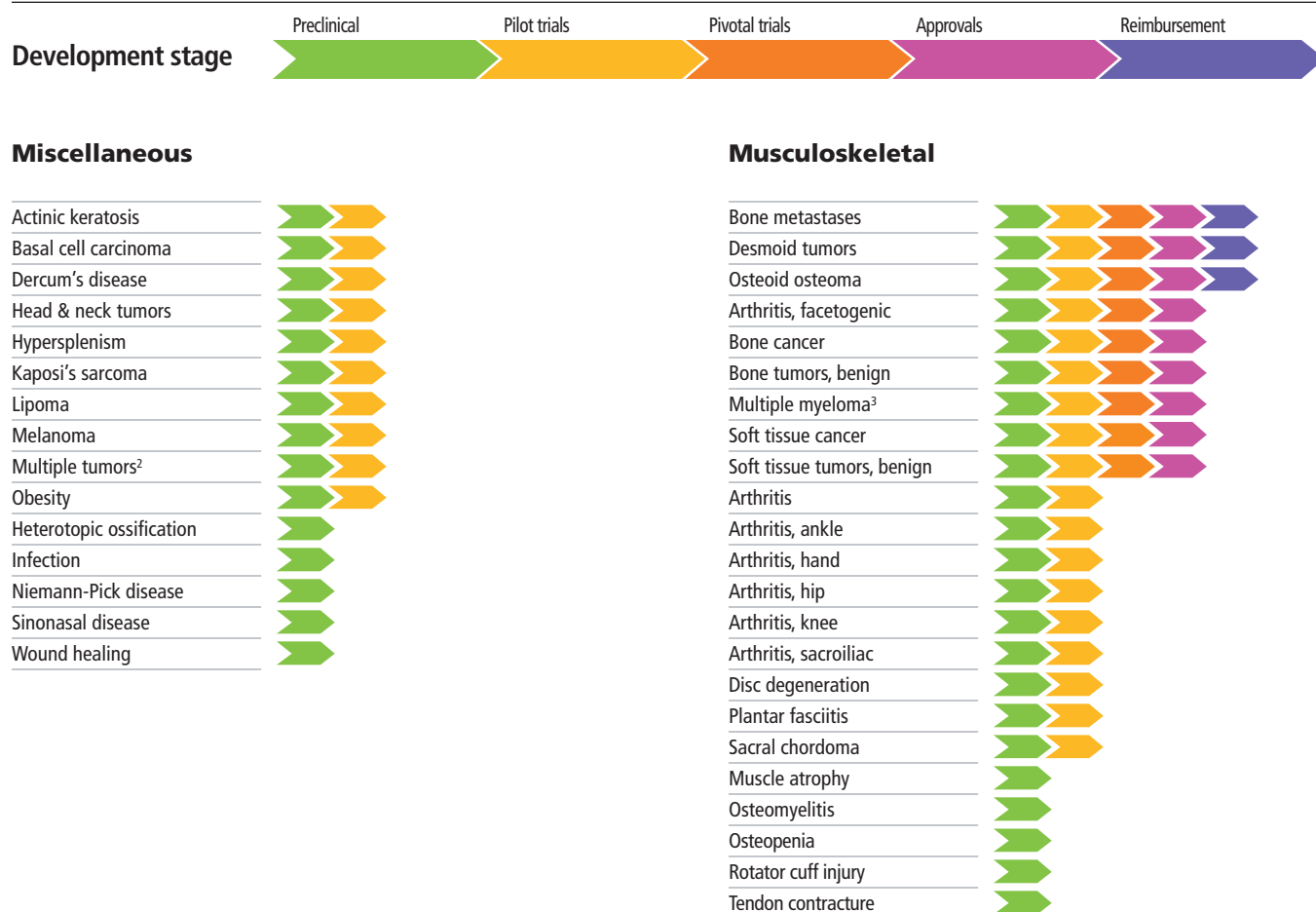


There are 166 distinct indications for 2022.

¹ Indication was listed as root canal endodontia in last year's State of the Field Report.

[†] New in 2022

State of Research and Regulatory Approvals by Body System continued



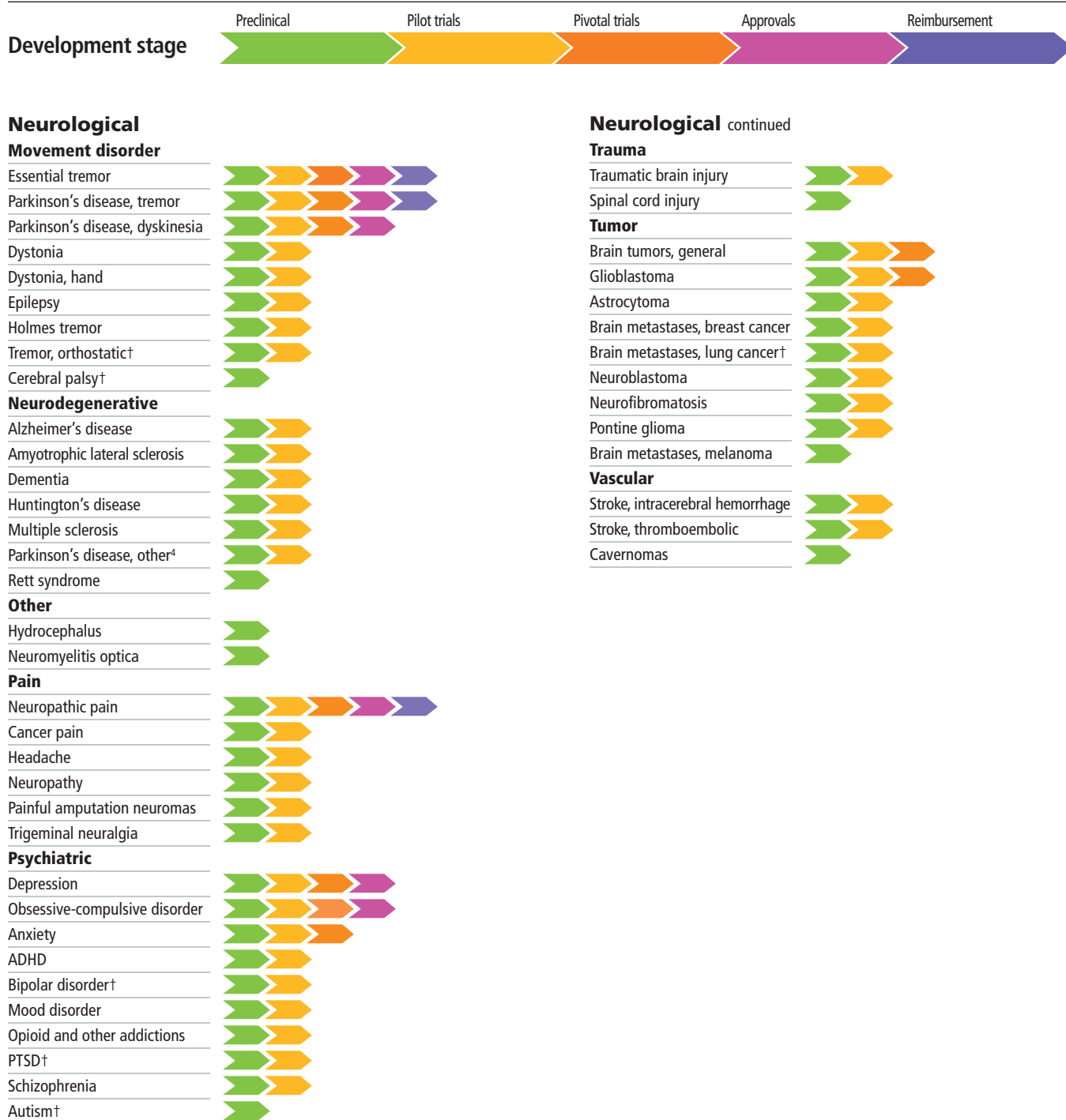
There are 166 distinct indications for 2022.

² Protocols inclusive of more than one indication

³ Multiple myeloma approval is based on bone metastases.

INDICATION PIPELINE

State of Research and Regulatory Approvals by Body System continued



There are 166 distinct indications for 2022.

⁴ Treatment of the underlying cause of the disease

† New in 2022

State of Research and Regulatory Approvals by Body System continued



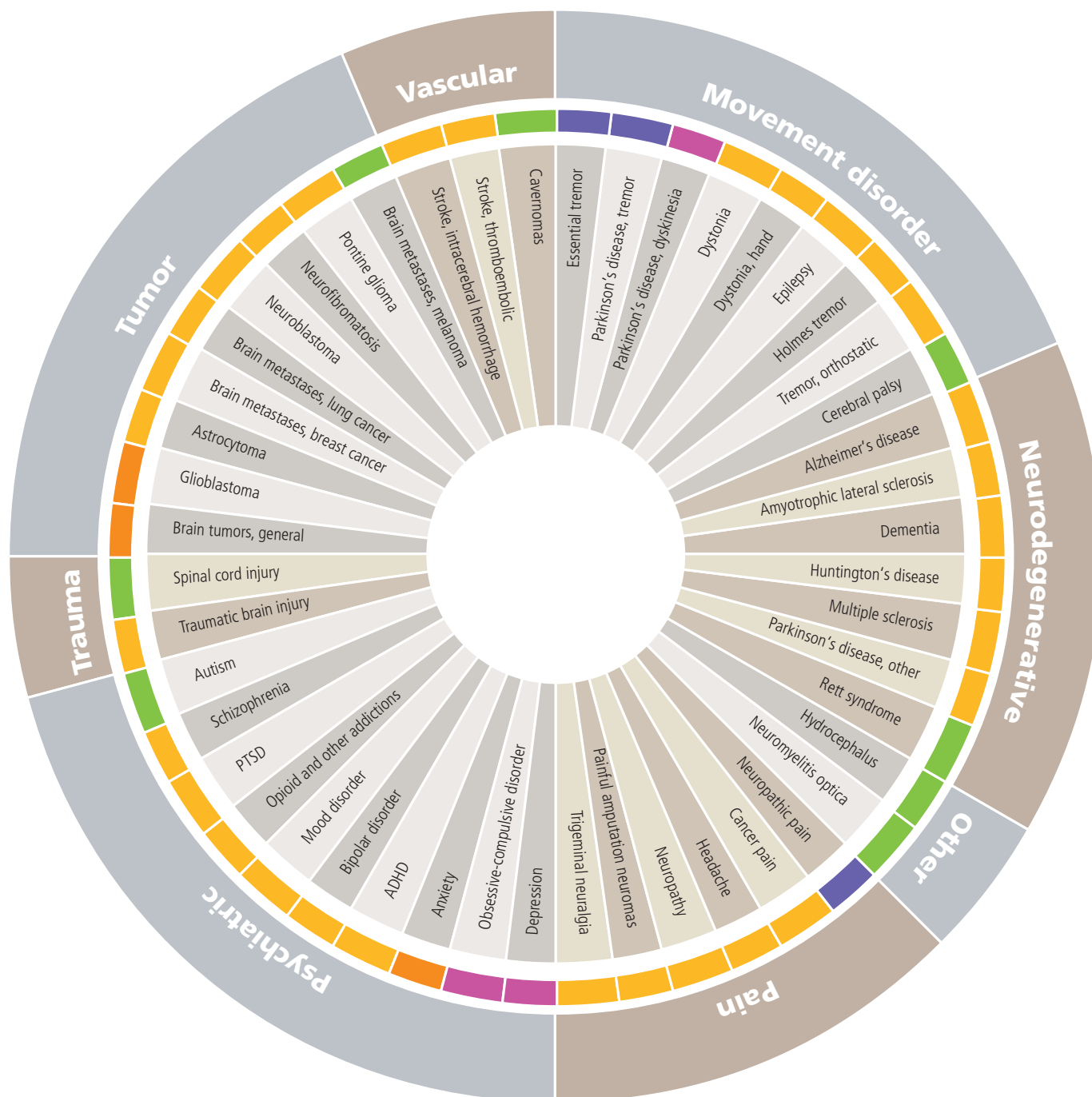
There are 166 distinct indications for 2022.

⁵ Indication was listed as acute kidney injury in last year's State of the Field Report.

Neurological Indications

Out of the 48 neurological indications, only 6 have regulatory approval.

Development stage: ■ Preclinical ■ Pilot trials ■ Pivotal trials ■ Outside US approvals ■ Reimbursement



Indications with Anecdotal Case Reports

Indications	Date	Mechanism of action	Reference
Endocrine disorders			
Insulinoma	2010	Thermal ablation, Tissue destruction	https://doi.org/10.1007/s00270-010-9884-0
Gastrointestinal			
Liver alveococcosis	2015	Thermal ablation, Tissue destruction	https://doi.org/10.1007/s10396-018-0914-x
Miscellaneous			
Warts	2021	Thermal ablation, Tissue destruction	https://doi.org/10.1159/000515075
Neurological			
Ataxia	2022	Thermal ablation, Tissue destruction	https://doi.org/10.1002/mds.28918
Women's health			
Gestational trophoblastic disease	2022	Thermal ablation, Tissue destruction	https://doi.org/10.1186/s12905-022-02114-0

What are anecdotal case reports?

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.

Areas of Interest

A note on multiple listings

In the so-called rainbow chart—see pages II.4–II.7—the categories are body systems, comprising a group of tissues structured to perform specific functions. All indications in development for focused ultrasound treatment appear on this chart, in the body system category to which they belong. Thus, bone metastases is in the Musculoskeletal category, but nowhere else.

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

on pages II.11–II.12. Indications that do not match with any of the Areas of Interest will not appear in this chart, but those that do may appear in multiple categories; bone metastases, for example, appears in Oncology, Pain, and Pediatrics. Looking at the indications by “Area of Interest” reveals patterns and trends over time that might otherwise be difficult to discern.

State of Research and Regulatory Approvals by Area of Interest



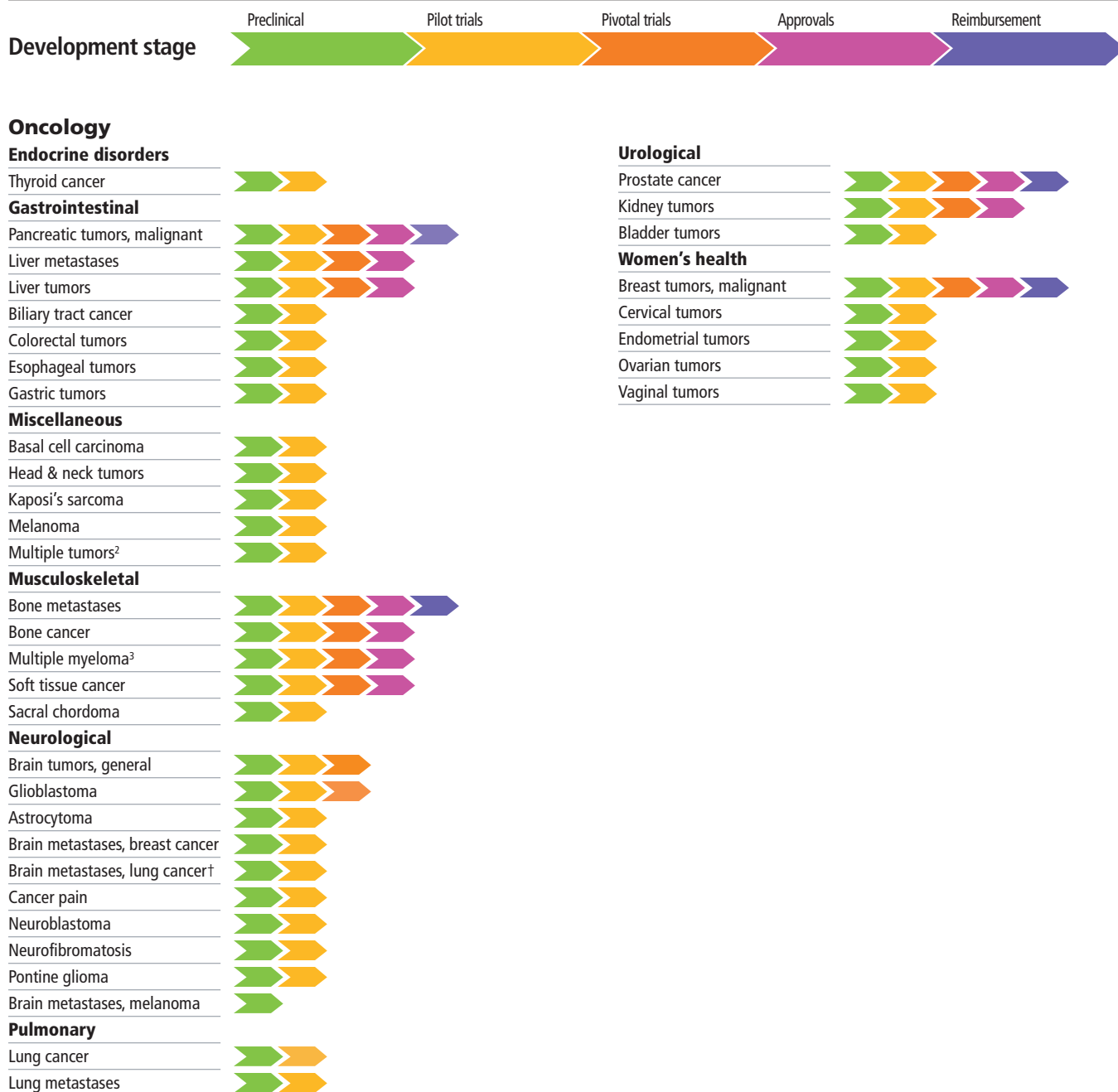
2 Protocols inclusive of more than one indication

3 Multiple myeloma approval is based on bone metastases.

† New in 2022

INDICATION PIPELINE

State of Research and Regulatory Approvals by Area of Interest continued



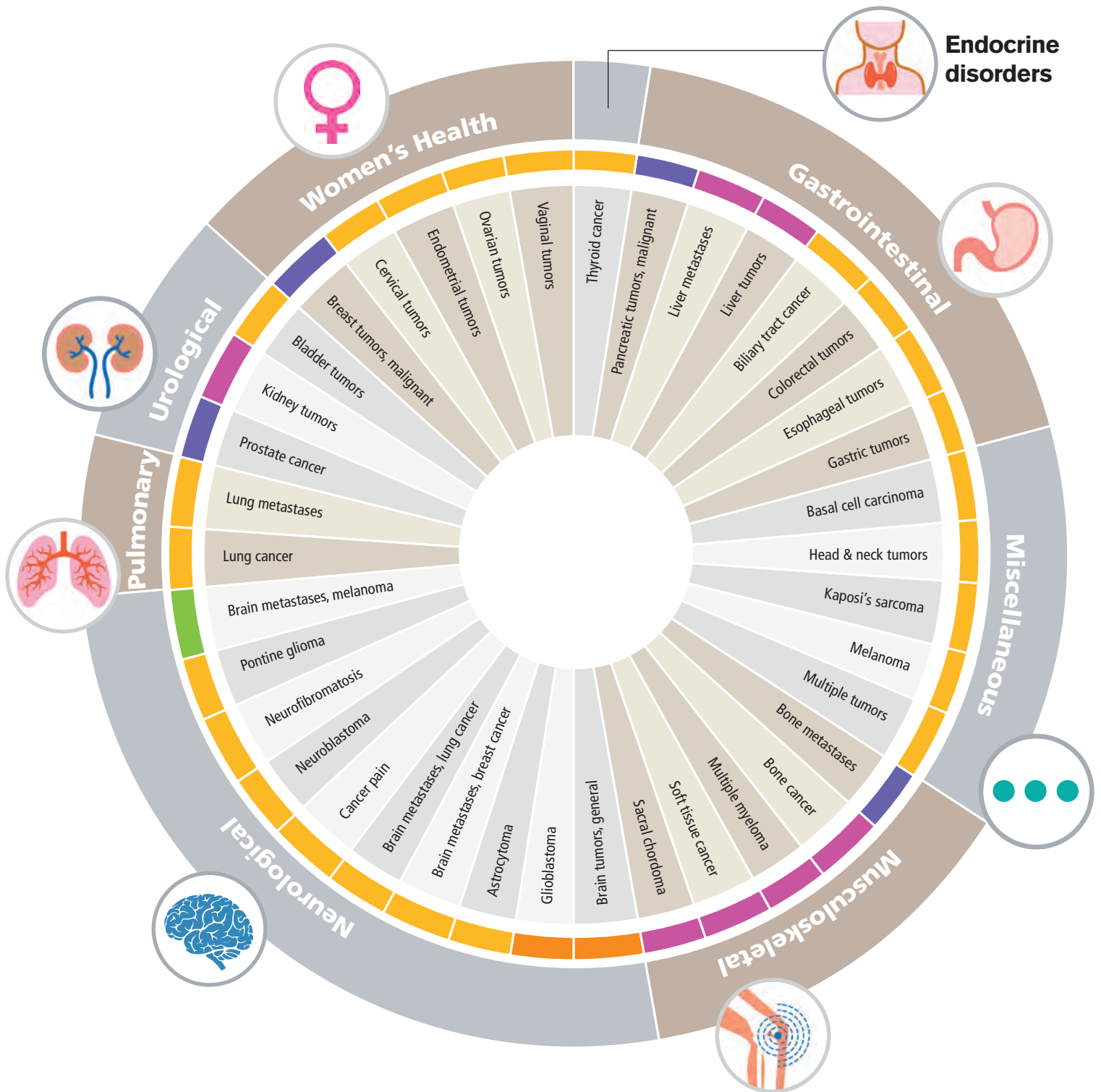
2 Protocols inclusive of more than one indication

3 Multiple myeloma approval is based on bone metastases.

† New in 2022

Oncology Indications

Development stage: ■ Preclinical ■ Clinical trials ■ Pilot trials ■ Outside US approvals ■ Reimbursement



Mechanisms of Action

Ultrasound applications and biological effects

In its most simple form, a Mechanism of Action (MOA) occurs when an ultrasound application produces a biological effect. Please see Chapter Three for a comprehensive overview of the ultrasound applications and biological effects currently under investigation. The following table is the state of development of all the indications by biological effect. This information was presented for the first-time last year, but in a slightly different form. As you review this table notice that the diseases with increased numbers of MOA under investigation trend towards the diseases where

the current standard of care is lacking and where the medical community wants new treatment options. Pay particular attention to both pancreatic cancer and glioblastoma both in the number of MOA's, and, as is evidenced in Chapter 3, the number of research sites performing this type of research.

■ Histotripsy

Alteration of tissue mechanics
Immunomodulation
Liquid biopsy
Tissue destruction

■ Hyperthermia

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

■ Nonthermal

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

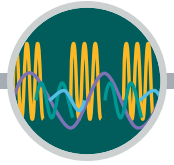
Kidney stone fragmentation
Kidney stone propulsion
Liquid biopsy
Neuromodulation
Radiosensitization
Sonodynamic therapy
Sonoporation
Stem cell delivery
Tissue destruction
Vascular occlusion
Vasodilation

■ Nonthermal - BBB opening

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

■ Thermal ablation

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



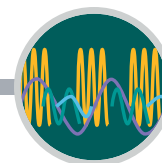
Mechanisms of Action and Indications—Body Systems



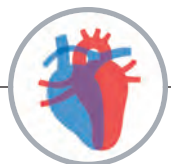
Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Approvals
Cardiovascular				
Cardiac				
Atrial fibrillation	■ Thermal ablation Tissue destruction			
Cardiac hypertrophy	■ Nonthermal Drug delivery, vehicle			
Cardiac pacing	■ Nonthermal Cardiac pacing			
Fetal heart anomalies	■ Histotripsy Tissue destruction			
Heart valve calcifications		■ Histotripsy Alteration of tissue mechanics		
Mitral regurgitation	■ Histotripsy Tissue destruction			
Ventricular tachycardia	■ Thermal ablation Tissue destruction			
Peripheral				
Arteriovenous malformations	■ Nonthermal Tissue destruction	■ Nonthermal Vascular occlusion	■ Thermal ablation Tissue destruction ⁶	
Atherosclerosis	■ Nonthermal Drug delivery Sonodynamic therapy Sonoporation Stem cell delivery			

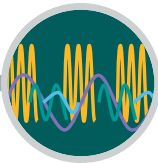
6 Off-label treatment



Mechanisms of Action and Indications—Body Systems continued



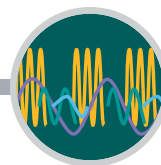
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Cardiovascular continued				
Peripheral continued				
Deep vein thrombosis	<ul style="list-style-type: none"> ■ Histotripsy Alteration of tissue mechanics Tissue destruction ■ Nonthermal Clot lysis Drug delivery, vehicle Increased vascular permeability Sonodynamic therapy 			
Hematoma	<ul style="list-style-type: none"> ■ Histotripsy Tissue destruction ■ Thermal ablation Hemostasis 			
Hemophilia	<ul style="list-style-type: none"> ■ Nonthermal Drug delivery 			
Hypertension		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Peripheral artery disease	<ul style="list-style-type: none"> ■ Nonthermal Drug delivery, vehicle 	<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Twin-twin transfusion syndrome	<ul style="list-style-type: none"> ■ Nonthermal Vascular occlusion ■ Thermal ablation Tissue destruction 	<ul style="list-style-type: none"> ■ Thermal ablation Hemostasis 		
Varicose veins		<ul style="list-style-type: none"> ■ Nonthermal Vascular occlusion 		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction



Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Endocrine disorders				
Diabetes	■ Nonthermal Neuromodulation			
Thyroid cancer	■ Histotripsy Tissue destruction			
Thyroid nodules				■ Thermal ablation Tissue destruction



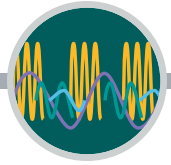
Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Gastrointestinal				
Colorectal tumors	■ Nonthermal Drug delivery, vehicle	■ Nonthermal Drug delivery ■ Thermal ablation Tissue destruction		
Dental infections ¹		■ Histotripsy Tissue destruction		
Esophageal tumors		■ Thermal ablation Immunomodulation		
Gastric tumors		■ Thermal ablation Immunomodulation	■ Thermal ablation Tissue destruction ⁶	
Inflammatory bowel disease	■ Nonthermal Drug delivery			
Liver metastases	■ Histotripsy Tissue destruction ■ Nonthermal Tissue destruction	■ Nonthermal Drug delivery Sonoporation		■ Thermal ablation Tissue destruction
Liver tumors	■ Histotripsy Alteration of tissue mechanics Immunomodulation ■ Hyperthermia Immunomodulation Radiosensitization Tissue destruction ■ Nonthermal Tissue destruction	■ Histotripsy Tissue destruction ■ Nonthermal Drug delivery, vehicle Sonoporation		■ Thermal ablation Tissue destruction

¹ Indication was listed as root canal endodontia in 2022 State of the Field Report.

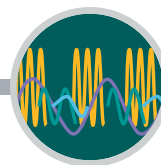
⁶ Off-label treatment



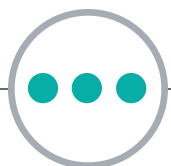
Mechanisms of Action and Indications—Body Systems continued



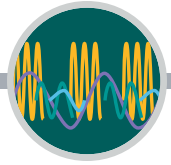
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Gastrointestinal continued				
Pancreatic tumors	■ Nonthermal Drug delivery, vehicle			■ Thermal ablation Tissue destruction
Pancreatic tumors, benign			■ Thermal ablation Tissue destruction	
Pancreatic tumors, malignant	■ Histotripsy Immunomodulation ■ Hyperthermia Drug delivery, immunotherapeutic Immunomodulation ■ Nonthermal Drug delivery, immunotherapeutic Drug delivery, vehicle Immunomodulation Sonodynamic therapy Tissue destruction ■ Thermal ablation Immunomodulation	■ Histotripsy Tissue destruction ■ Hyperthermia Chemosensitization Drug delivery ■ Nonthermal Drug delivery Immunomodulation Sonoporation		
Periodontal disease	■ Histotripsy Tissue destruction ■ Nonthermal Drug delivery, vehicle		■ Thermal ablation Tissue destruction	



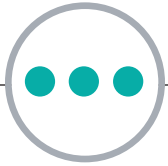
Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Miscellaneous				
Actinic keratosis		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		
Basal cell carcinoma		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		
Dercum's disease		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		
Head & neck tumors	<ul style="list-style-type: none"> Hyperthermia Drug delivery Nonthermal Sonoporation Tissue destruction 	<ul style="list-style-type: none"> Hyperthermia Radiosensitization Nonthermal Radiosensitization Thermal ablation Tissue destruction 		
Heterotopic ossification	<ul style="list-style-type: none"> Histotripsy Tissue destruction 			
Hypersplenism		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		
Infection	<ul style="list-style-type: none"> Histotripsy Tissue destruction Nonthermal - BBB Opening Drug delivery Thermal ablation Tissue destruction 			
Kaposi's sarcoma		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		
Lipoma		<ul style="list-style-type: none"> Thermal ablation Tissue destruction 		

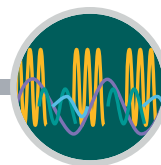


Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Miscellaneous continued				
Melanoma	<ul style="list-style-type: none"> Histotripsy Immunomodulation 	<ul style="list-style-type: none"> Nonthermal Radiosensitization Thermal ablation Immunomodulation 		
Multiple tumors ²	<ul style="list-style-type: none"> Histotripsy Tissue destruction Nonthermal Drug delivery, immunotherapeutic Thermal ablation Tissue destruction 	<ul style="list-style-type: none"> Hyperthermia Chemosensitization Drug delivery Thermal ablation Immunomodulation 		
Niemann-Pick disease	<ul style="list-style-type: none"> Nonthermal - BBB Opening Gene delivery 			
Sinonasal disease	<ul style="list-style-type: none"> Thermal ablation Tissue destruction 			
Wound healing	<ul style="list-style-type: none"> Histotripsy Alteration of tissue mechanics Hyperthermia Drug delivery Nonthermal Alteration of tissue mechanics Drug delivery 			

² Protocols inclusive of more than one indication

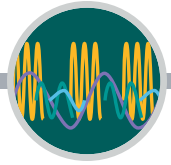


Mechanisms of Action and Indications—Body Systems continued

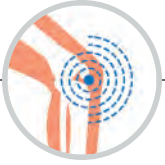


Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Musculoskeletal				
Arthritis, facetogenic	■ Nonthermal Tissue destruction			■ Thermal ablation Tissue destruction
Arthritis, knee		■ Thermal ablation Tissue destruction		
Arthritis, sacroiliac		■ Thermal ablation Tissue destruction		
Bone cancer				■ Thermal ablation Tissue destruction
Bone metastases		■ Histotripsy Tissue destruction ■ Hyperthermia Radiosensitization ■ Thermal ablation Chemosensitization		■ Thermal ablation Tissue destruction
Bone tumors, benign				■ Thermal ablation Tissue destruction
Desmoid tumors				■ Thermal ablation Tissue destruction
Multiple myeloma ³				■ Thermal ablation Tissue destruction
Muscle atrophy	■ Nonthermal Angiogenesis Gene delivery Stem cell delivery			
Osteoid osteoma				■ Thermal ablation Tissue destruction

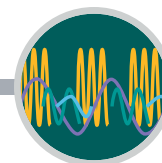
³ Multiple myeloma approval is based on bone metastases.



Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Musculoskeletal continued				
Osteopenia	<ul style="list-style-type: none"> ■ Hyperthermia Drug delivery ■ Nonthermal Alteration of tissue mechanics 			
Plantar fasciitis		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Rotator cuff injury	<ul style="list-style-type: none"> ■ Histotripsy Tissue destruction 			
Sacral chordoma		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Soft tissue cancer	<ul style="list-style-type: none"> ■ Histotripsy Immunomodulation Tissue destruction ■ Hyperthermia Drug delivery Drug delivery, immunotherapeutic ■ Nonthermal Tissue destruction 	<ul style="list-style-type: none"> ■ Thermal ablation Immunomodulation 		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction
Soft tissue tumors, benign				<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction
Tendon contracture	<ul style="list-style-type: none"> ■ Histotripsy Tissue destruction ■ Thermal ablation Tissue destruction 			

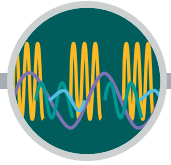


Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological				
Movement disorder				
Dystonia		■ Nonthermal Neuromodulation	■ Thermal ablation Tissue destruction ⁶	
Dystonia, hand			■ Thermal ablation Tissue destruction ⁶	
Epilepsy	■ Histotripsy Tissue destruction ■ Nonthermal Gene delivery Immunomodulation ■ Nonthermal - BBB Opening BBB opening Drug delivery Gene delivery ■ Thermal ablation Neuromodulation	■ Nonthermal Neuromodulation	■ Thermal ablation Tissue destruction ⁶	
Essential tremor		■ Nonthermal Neuromodulation		■ Thermal ablation Tissue destruction
Parkinson's disease, dyskinesia	■ Nonthermal - BBB Opening Gene delivery			■ Thermal ablation Tissue destruction

6 Off-label treatment



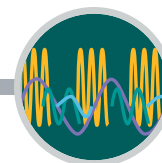
Mechanisms of Action and Indications—Body Systems continued



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Movement disorder continued				
Parkinson's disease, tremor	<p>■ Nonthermal - BBB Opening Drug delivery</p>	<p>■ Nonthermal Neuromodulation</p>		<p>■ Thermal ablation Tissue destruction</p>
Tremor, orthostatic		<p>■ Nonthermal Neuromodulation</p> <p>■ Thermal ablation Tissue destruction</p>		
Neurodegenerative				
Alzheimer's disease	<p>■ Nonthermal Alteration of tissue mechanics Drug delivery</p> <p>■ Nonthermal - BBB Opening Drug delivery, immunotherapeutic Gene delivery Stem cell delivery</p>	<p>■ Nonthermal Increased vascular permeability</p> <p>■ Nonthermal - BBB Opening BBB opening Drug delivery</p>	<p>■ Nonthermal Neuromodulation⁶</p>	
Amyotrophic lateral sclerosis	<p>■ Nonthermal - BBB Opening BBB opening</p>	<p>■ Nonthermal - BBB Opening Drug delivery</p>		
Dementia	<p>■ Nonthermal - BBB Opening BBB opening</p>			
Huntington's disease	<p>■ Nonthermal - BBB Opening Gene delivery</p>			

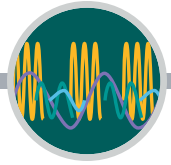
6 Off-label treatment



Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Neurodegenerative continued				
Multiple sclerosis		<div> <div></div> Thermal ablation Tissue destruction </div>		
Parkinson's disease, underlying cause	<div> <div></div> Nonthermal Drug delivery, vehicle Gene delivery Neuromodulation </div> <div> <div></div> Nonthermal - BBB Opening Drug delivery Gene delivery </div> <div> <div></div> Thermal ablation Tissue destruction </div>	<div> <div></div> Nonthermal Liquid biopsy </div>		
Rett syndrome	<div> <div></div> Nonthermal - BBB Opening Gene delivery </div>			
Other				
Hydrocephalus	<div> <div></div> Nonthermal Clot lysis </div>			
Neuromyelitis optica	<div> <div></div> Nonthermal - BBB Opening Drug delivery </div>			
Pain				
Cancer pain	<div> <div></div> Nonthermal Neuromodulation </div>	<div> <div></div> Thermal ablation Tissue destruction </div>		
Headache	<div> <div></div> Nonthermal Neuromodulation </div>			



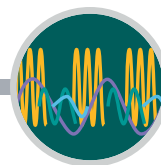
Mechanisms of Action and Indications—Body Systems continued



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Pain continued				
Neuropathic pain	■ Nonthermal Alteration of tissue mechanics Drug delivery, vehicle	■ Nonthermal Neuromodulation		■ Thermal ablation Tissue destruction
Neuropathy	■ Nonthermal Vasodilation	■ Nonthermal Neuromodulation	■ Thermal ablation Tissue destruction ⁶	
Painful amputation neuromas		■ Thermal ablation Tissue destruction		
Trigeminal neuralgia			■ Thermal ablation Tissue destruction ⁶	
Psychiatric				
ADHD		■ Nonthermal Neuromodulation		
Anxiety		■ Nonthermal Neuromodulation		
	■ Nonthermal - BBB Opening Drug delivery			
Autism	■ Nonthermal - BBB Opening Drug delivery			
Bipolar disorder		■ Nonthermal Neuromodulation		

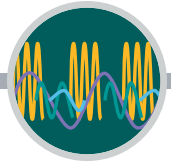
6 Off-label treatment



Mechanisms of Action and Indications—Body Systems continued



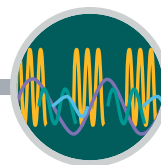
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Psychiatric continued				
Depression		■ Nonthermal Neuromodulation		■ Thermal ablation Tissue destruction
Mood disorder		■ Nonthermal Neuromodulation		
Obsessive-compulsive disorder		■ Nonthermal Neuromodulation		■ Thermal ablation Tissue destruction
Opioid and other addictions		■ Nonthermal Neuromodulation		
PTSD		■ Nonthermal Neuromodulation		
Schizophrenia		■ Nonthermal Neuromodulation		
Trauma				
Spinal cord injury	■ Nonthermal - BBB Opening Drug delivery			
Traumatic brain injury	■ Nonthermal - BBB Opening Drug delivery	■ Nonthermal Neuromodulation		



Mechanisms of Action and Indications—Body Systems continued



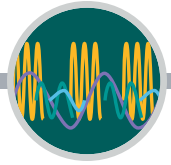
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Tumor				
Astrocytoma	<p>■ Nonthermal - BBB Opening Drug delivery</p>	<p>■ Thermal ablation Tissue destruction</p>		
Brain metastases, breast cancer	<p>■ Histotripsy Tissue destruction</p> <p>■ Nonthermal Immunomodulation</p> <p>■ Nonthermal - BBB Opening BBB opening Drug delivery, immunotherapeutic</p>	<p>■ Nonthermal - BBB Opening Drug delivery</p>		
Brain metastases, lung cancer		<p>■ Nonthermal - BBB Opening Drug delivery, immunotherapeutic</p>		
Brain metastases, melanoma	<p>■ Nonthermal Immunomodulation Sonodynamic therapy</p> <p>■ Nonthermal - BBB Opening Drug delivery, immunotherapeutic</p>	<p>■ Nonthermal - BBB Opening Drug delivery</p>		



Mechanisms of Action and Indications—Body Systems continued



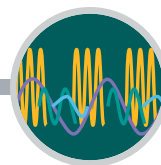
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Tumor continued				
Brain tumors, general	<ul style="list-style-type: none"> ■ Histotripsy Immunomodulation ■ Hyperthermia Immune cell trafficking Radiosensitization Tissue destruction ■ Nonthermal Amplification of cancer biomarkers Drug delivery Gene delivery Immunomodulation Neuromodulation Radiosensitization Sonodynamic therapy Tissue destruction Vascular occlusion ■ Nonthermal - BBB Opening Drug delivery, immunotherapeutic Drug delivery, vehicle Gene delivery 	<ul style="list-style-type: none"> ■ Nonthermal Liquid biopsy ■ Nonthermal - BBB Opening BBB opening Drug delivery ■ Thermal ablation Liquid biopsy Tissue destruction 		



Mechanisms of Action and Indications—Body Systems continued



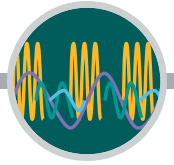
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Tumor continued				
Glioblastoma	<ul style="list-style-type: none"> ■ Histotripsy Immunomodulation Tissue destruction ■ Hyperthermia Drug delivery Drug delivery, immunotherapeutic Immunomodulation ■ Nonthermal Drug delivery, vehicle Immune cell trafficking Immunomodulation Tissue destruction Vascular occlusion ■ Nonthermal - BBB Opening Drug delivery, immunotherapeutic Drug delivery, vehicle Gene delivery 	<ul style="list-style-type: none"> ■ Nonthermal Amplification of cancer biomarkers Liquid biopsy Radiosensitization Sonodynamic therapy ■ Nonthermal - BBB Opening BBB opening Drug delivery ■ Thermal ablation Tissue destruction 		
Neuroblastoma		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Neurofibromatosis	<ul style="list-style-type: none"> ■ Nonthermal - BBB Opening Drug delivery 	<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		



Mechanisms of Action and Indications—Body Systems continued



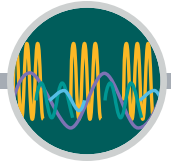
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Neurological continued				
Tumor continued				
Pontine glioma	<ul style="list-style-type: none"> ■ Histotripsy Liquid biopsy ■ Nonthermal Drug delivery 	<ul style="list-style-type: none"> ■ Nonthermal Sonodynamic therapy ■ Nonthermal - BBB Opening Drug delivery Drug delivery, immunotherapeutic 		
Vascular				
Cavernomas	<ul style="list-style-type: none"> ■ Nonthermal Sonodynamic therapy 			
Stroke, intracerebral hemorrhage	<ul style="list-style-type: none"> ■ Histotripsy Tissue destruction ■ Nonthermal Drug delivery Drug delivery, vehicle ■ Nonthermal - BBB Opening Drug delivery 	<ul style="list-style-type: none"> ■ Nonthermal Neuromodulation 		
Stroke, thromboembolic	<ul style="list-style-type: none"> ■ Nonthermal Drug delivery Drug delivery, vehicle Sonoporation Vasodilation ■ Nonthermal - BBB Opening Drug delivery 	<ul style="list-style-type: none"> ■ Nonthermal Angiogenesis Neuromodulation 		



Mechanisms of Action and Indications—Body Systems continued



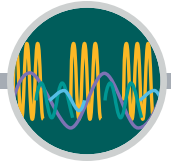
Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Ophthalmological				
Glaucoma		■ Nonthermal Immunomodulation		■ Thermal ablation Tissue destruction
Macular degeneration	■ Nonthermal Vascular occlusion			
Presbyopia	■ Nonthermal Tissue destruction ■ Thermal ablation Tissue destruction			
Retinal injury	■ Nonthermal Gene delivery			



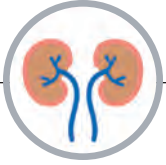
Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Pulmonary				
Lung cancer	<ul style="list-style-type: none"> Histotripsy Tissue destruction Hyperthermia Tissue destruction Thermal ablation Tissue destruction 	<ul style="list-style-type: none"> Thermal ablation Immunomodulation 		
Rhinitis				<ul style="list-style-type: none"> Thermal ablation Tissue destruction
Tuberculosis	<ul style="list-style-type: none"> Thermal ablation Tissue destruction 			

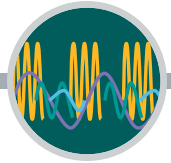


Mechanisms of Action and Indications—Body Systems continued

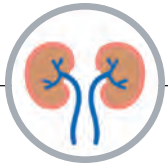


Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Urological				
Acute tubular necrosis	■ Nonthermal Stem cell delivery			
Benign prostatic hyperplasia	■ Histotripsy Tissue destruction ■ Nonthermal Tissue destruction			■ Thermal ablation Tissue destruction
Bladder tumors	■ Nonthermal Drug delivery			
Chyluria		■ Thermal ablation Tissue destruction		
Fetal bladder obstruction	■ Thermal ablation Tissue destruction			
Kidney disease, acute ⁵	■ Nonthermal Stem cell delivery			
Kidney stones		■ Nonthermal Kidney stone fragmentation Kidney stone propulsion		
Kidney tumors	■ Histotripsy Tissue destruction ■ Nonthermal Drug delivery, vehicle			■ Thermal ablation Tissue destruction

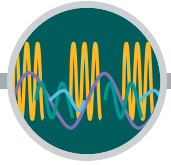
⁵ Indication was listed as acute kidney injury in 2022 State of the Field Report.



Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Urological continued				
Prostate cancer	<ul style="list-style-type: none"> ■ Histotripsy Tissue destruction ■ Hyperthermia Immunomodulation Radiosensitization ■ Nonthermal Drug delivery, vehicle Tissue destruction 	<ul style="list-style-type: none"> ■ Hyperthermia Tissue destruction ■ Nonthermal Immunomodulation 		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction
Urinary tract infection	<ul style="list-style-type: none"> ■ Nonthermal Drug delivery, vehicle 			



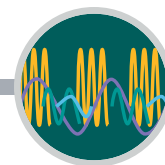
Mechanisms of Action and Indications—Body Systems continued



Stages

Indications by body systems	Preclinical	Clinical	Commercial treatment	Approvals
Women's health				
Breast tumors, benign		<ul style="list-style-type: none"> ■ Hyperthermia Tissue destruction 		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction
Breast tumors, malignant	<ul style="list-style-type: none"> ■ Hyperthermia Drug delivery, immunotherapeutic Immunomodulation Vasodilation ■ Nonthermal Drug delivery Drug delivery, vehicle Gene delivery Increased vascular permeability Tissue destruction ■ Nonthermal - BBB Opening BBB opening 	<ul style="list-style-type: none"> ■ Hyperthermia Drug delivery Radiosensitization ■ Nonthermal Immunomodulation Radiosensitization ■ Thermal ablation Immunomodulation Tissue destruction 		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction ■ Thermal ablation Tissue destruction
Cervical tumors		<ul style="list-style-type: none"> ■ Thermal ablation Immunomodulation Tissue destruction 		
Cervicitis				<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction
Ectopic pregnancy		<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction 		
Endometrial tumors			<ul style="list-style-type: none"> ■ Thermal ablation Tissue destruction⁶ 	

6 Off-label treatment



Mechanisms of Action and Indications—Body Systems continued



Indications by body systems	Stages			
	Preclinical	Clinical	Commercial treatment	Approvals
Women's health continued				
Endometriosis		■ Hyperthermia Tissue destruction	■ Thermal ablation Tissue destruction ⁶	
Hyperplasia of the vulva				■ Thermal ablation Tissue destruction
Lichen sclerosis				■ Thermal ablation Tissue destruction
Ovarian tumors		■ Thermal ablation Immunomodulation Tissue destruction		
Retained placenta		■ Thermal ablation Tissue destruction		
Urinary incontinence, stress			■ Thermal ablation Alteration of tissue mechanics ⁶	
Uterine adenomyosis		■ Hyperthermia Tissue destruction		■ Thermal ablation Tissue destruction
Uterine fibroids	■ Histotripsy Tissue destruction ■ Nonthermal Tissue destruction			■ Thermal ablation Tissue destruction
Vaginal tumors		■ Thermal ablation Tissue destruction		

⁶ Off-label treatment