Gadolinium Retention: A Research Roadmap from the 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates

Robert J. McDonald, MD, PhD • Deborah Levine, MD • Jeffrey Weinreb, MD • Emanuel Kanal, MD • Matthew S. Davenport, MD • James H. Ellis, MD • Paula M. Jacobs, PhD • Robert E. Lenkinski, PhD • Kenneth R. Maravilla, MD • Martin R. Prince, MD, PhD • Howard A. Rowley, MD • Michael F. Tweedle, PhD • Herbert Y. Kressel, MD

From the Division of Neuroradiology, Department of Radiology, Mayo Clinic, Rochester, Minn (R.J.M.); Department of Radiology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (D.L., H.Y.K.); Department of Radiology & Biomedical Imaging, Yale School of Medicine, New Haven, Conn (J.W.); Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pa (E.K.); Department of Radiology, University of Michigan Health System, Ann Arbor, Mich (M.S.D., J.H.E.); Cancer Imaging Program, National Institutes of Health, National Cancer Institute, Bethesda, Md (P.M.J.); Department of Radiology, UT Southwestern Medical Center, Dallas, Tex (R.E.L.); Department of Radiology, University of Washington, Seattle, Wash (K.R.M.); Department of Radiology, Cornell and Columbia Universities, New York, NY (M.R.P.); Department of Radiology, University of Wisconsin, Madison, Wis (H.A.R.); and Department of Radiology, The Ohio State University, Columbus, Ohio (M.F.T.). Received May 14, 2018; revision requested June 5; revision received June 27; accepted July 27. **Address correspondence to** H.Y.K. (e-mail: *hkressel@bidmc.harvard.edu*).

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Gadolinium-based contrast agents (GBCAs) have revolutionized MRI, enabling physicians to obtain crucial life-saving medical information that often cannot be obtained with other imaging modalities. Since initial approval in 1988, over 450 million intravenous GBCA doses have been administered worldwide, with an extremely favorable pharmacologic safety profile; however, recent information has raised new concerns over the safety of GBCAs. Mounting evidence has shown there is long-term retention of gadolinium in human tissues. Further, a small subset of patients have attributed a constellation of symptoms to GBCA exposure, although the association of these symptoms with GBCA administration or gadolinium retention has not been proven by scientific investigation. Despite evidence that macrocyclic GBCAs show less gadolinium retention than linear GBCAs, the safety implications of gadolinium retention are unknown. The mechanism and chemical forms of gadolinium retention, as well as the biologic activity and clinical importance of these retained gadolinium species, remain poorly understood and underscore the need for additional research. In February 2018, an international meeting was held in Bethesda, Md, at the National Institutes of Health to discuss the current literature and knowledge gaps about gadolinium retention, to prioritize future research initiatives to better understand this phenomenon, and to foster collaborative standardized studies. The greatest priorities are to determine *(a)* if gadolinium retention adversely affects the function of human tissues, *(b)* if retention is causally associated with short- or long-term clinical manifestations of disease, and *(c)* if vulnerable populations, such as children, are at greater risk for experiencing clinical disease. The purpose of the research roadmap is to highlight important information that is not known and to identify and prioritize needed research.

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Since initial regulatory approval, over 450 million doses of gadolinium-based contrast agents (GBCAs) have been administered worldwide (1). The historic safety profile of GBCA use has been highly favorable, with very low rates of immediate adverse side effects when compared with other pharmaceuticals, including iodinated contrast agents (2–4). GBCA use in patients with severely compromised renal function has been associated with development of the rare condition nephrogenic systemic fibrosis (NSF), in which fibrotic changes may be seen in many tissues, predominately skin, and muscle contractures may occur (5–9). Fortunately, rapid changes in clinical practice in the use of GBCAs within the renally impaired population have essentially eradicated this clinical entity.

At the time of initial regulatory approval in 1988, it was widely thought that the gadolinium ion remained in the chelated state after intravenous administration of a GBCA and that it was rapidly excreted. However, scientific evidence has been mounting that traces of gadolinium remain in the bone, brain, and other organs in patients with normal renal function (10–21). The extent of tissue retention (defined by our writing group as both short term [beyond 24 hours] and long term [>1 month after exposure]) tends to show an association with cumulative dose. Although tissue retention appears to be highest with linear GBCAs, all agents (linear and macrocyclic) demonstrate some degree of tissue retention of gadolinium in some form, and existing data suggest there may be intraclass variability in this retention (17,22–25). The causal relationship between GBCA exposure, retention, and symptoms remains unclear due to inconsistencies in the timing of symptom onset relative to GBCA administration, dose thresholds, and heterogeneity in presumed associated symptoms (26).

Nine GBCAs have been approved for use in the United States, each with unique chemical and physical properties (Table 1, Figure) (27–32). However, in the European Union, the linear GBCAs have recently been restricted or removed from the market due to concerns regarding gadolinium retention. This difference may, in part, be reflective of the differences in the regulatory approach across countries, and it also attests to the limitations in the available research on these agents, their biodistribution, and the effect of long-term retention in tissues, highlighting the need for stronger evidence regarding the safety of these agents.

Abbreviations

BBB = blood-brain barrier, CNS = central nervous system, CSF = cerebrospinal fluid, GBCA = gadolinium-based contrast agent, ICP-MS = inductively coupled plasma mass spectrometry, NSF = nephrogenic systemic fibrosis

Summary

This research roadmap prioritizes needed research to understand the clinical importance of gadolinium retention.

On February 15, 2018, an international meeting convened by the National Institute of Biomedical Imaging and Bioengineering and cosponsored by the American College of Radiology (ACR), Radiological Society of North America (RSNA), and National Institutes of Health (NIH) was held to discuss current knowledge and knowledge gaps and to identify and prioritize future research initiatives regarding the mechanisms, biological importance, and clinical implications of gadolinium retention. Attendees (Appendix E1 [online]), including an international group of researchers, GBCA manufacturers, and representatives of the Food and Drug Administration, were invited based on their expertise in a diverse set of scientific and clinical disciplines relevant to the study of the chemistry, measurement, clinical manifestations, or health-related effects of retained gadolinium in human tissues. The meeting focused on gadolinium retention; it did not specifically address acute or allergic-like reactions to contrast material, nor did it cover regulatory issues regarding GBCA use. The purpose of this research roadmap is to highlight important information that is not known and to identify and prioritize needed research to understand the clinical importance of this retention for patients receiving a GBCA.

Chemical Properties and Stabilities of GBCA

- Stability of GBCA chelates is governed by their thermodynamic stability at equilibrium and lability (rate of approach to equilibrium or "kinetic stability"). As a class, macrocyclic GBCAs are less labile (greater kinetic stability) than linear GBCAs, accounting for lower amounts of gadolinium tissue retention.
- Although in vitro measurements of GBCA lability are typically performed in nonphysiologic acidic aqueous solutions, their relative values have been shown to be consistent with the results of bone deposition studies of gadolinium in animal models and humans.

GBCAs can be categorized by the identity of the organic polyaminocarboxylate ligand (linear and macrocyclic agent subclasses), overall charge (ionic vs nonionic), thermodynamic stability (the affinity of the ligand for the gadolinium ion at equilibrium defined by the pH independent thermodynamic stability constant, K_{therm} = [GBCA]/[Gd] [ligand], or as adjusted for physiologic pH, by K_{cond}), lability or kinetic stability (the rate at which GBCAs

Table 1: Chemical and Pharmacologic Properties of Gadolinium-based Contrast Agents Approved for Use in the United States

Chemical Name	Structure	Ionicity	Protein Binding	k_{obs} (sec^{-1}); T1/2	Log K_{therm}	Log K_{cond}	Elimination Half-Life (min)	Injected Dose Eliminated within 24 Hours (%)
Gadodiamide	Linear	Nonionic	No	12.7; <5 sec	16.9	14.9	77.8 ± 16	95.4 ± 5.5
Gadoversetamide*	Linear	Nonionic	No	8.6; <1 sec	16.6	15.0	NA	NA
Gadopentetate dimeglumine	Linear	Ionic	No	0.58; <5 sec	22.5	18.4	96 ± 7.8	91 ± 13
Gadoxetate dimeglumine	Linear	Ionic	Yes	0.16; <4 sec	23.5	18.7	54.6–57	Amount remaining was too small to be detected
Gadobenate dimeglumine	Linear	Ionic	Yes	0.41; <5 sec	22.6	18.4	70 ± 16 to 121 ± 36	80–98
Gadofosveset trisodium†	Linear	Ionic	Yes	2.9×10^{-2}; 24 sec	22.1	18.9	NA	NA
Gadoteridol	Macrocyclic	Nonionic	No	2.6×10^{-4}; 3.9 hr	23.8	17.1	94.2 ± 4.8	94.4 ± 4.8
Gadobutrol	Macrocyclic	Nonionic	No	2.8×10^{-5}; 43 hr	21.8	14.7	108 (72–393)	>90
Gadoterate meglumine	Macrocyclic	Ionic	No	$2–8 \times 10^{-6}$; 338 hr	25.6	19.3	84 ± 12 (F), 120 ± 42 (M)	72.9 ± 17.0 (F), 84.4 ± 9.7 (M)

Source.—References 37,114–118.

Note.—Half-life (T1/2) is calculated as $\ln 2/k_{obs}$. Note that K_{therm}, K_{cond}, k_{obs} and T1/2 data were not obtained in identical testing, are not an exhaustive listing, and can be highly dependent on conditions; thus, they are only order of magnitude comparable. F = female, K_{cond} = conditional stability constant, k_{obs} = rate constants characterizing the acid-catalyzed dissociation of Gd^{3+} complexes, K_{therm} = thermodynamic stability constant, M = male, NA = not available.

* Withdrawn from the United States market as of the middle of 2018.

† No longer being manufactured.

approach equilibrium [otherwise known as dechelate; dissociate, defined by a dissociation constant, k_{obs}; or reach their half-life [T1/2]), protein binding, and relaxivity (Table 1). At equilibrium, the thermodynamic stability constant, K_{cond}, can be used to calculate the relative concentration of the intact chelated GBCA, unchelated gadolinium, and unchelated ligand. K_{cond} describes the GBCA system at equilibrium in an aqueous solution at physiologic pH. Once GBCA is injected, however, the system is no longer at equilibrium because of the varied competitive microenvironments that exist in vivo. The system subsequently will reestablish a new equilibrium over a time period defined by the lability of the GBCA at the in vivo conditions.

GBCAs also differ in their tissue uptake and intracellular stability. Central to the current safety concern is the imperfect stability of all gadolinium chelates, a consequence of balancing the need for strong kinetically inert GBCA ligand-gadolinium bonding with one kinetically labile H_2O-Gd bond that is required for effective bulk water proton relaxation—the fundamental basis for contrast enhancement at MRI. Accordingly, all GBCAs exist in chemical equilibrium with free gadolinium and free ligand and are governed by their unique thermodynamic and kinetic properties (Table 1). Macrocyclic GBCAs are more stable than linear GBCAs, but there are differences among the class members as well.

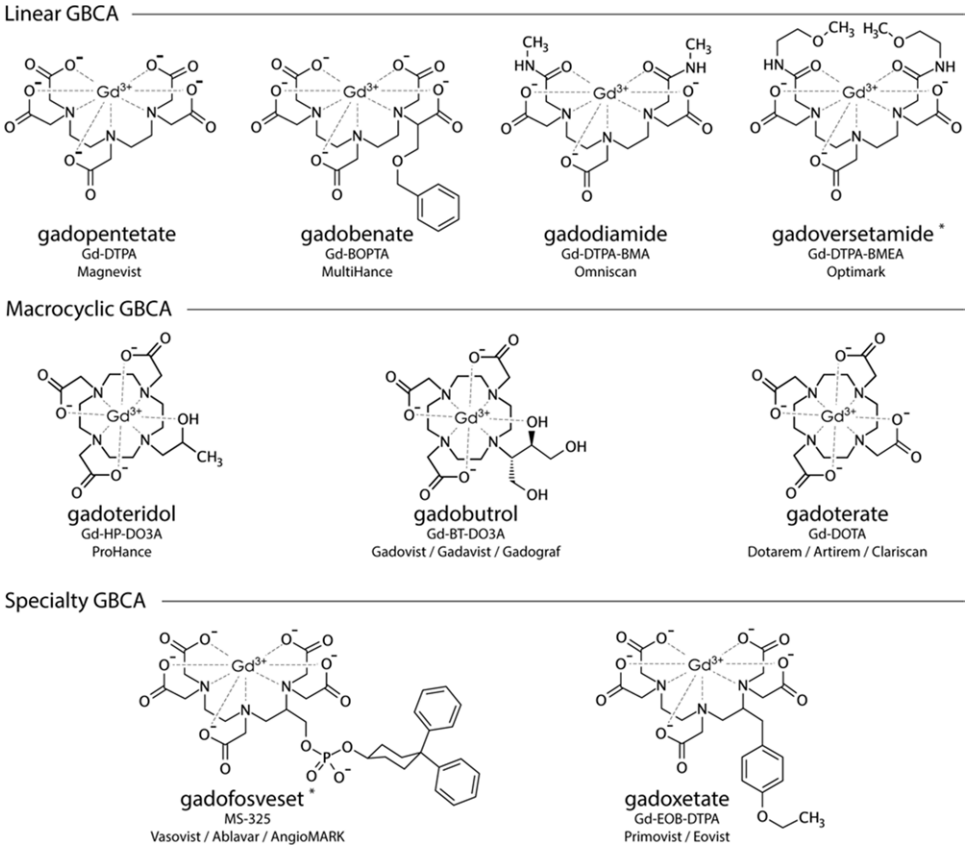

Figure 1: Structures of commercial gadolinium-based contrast agents (GBCAs). Top row GBCAs are the linear agents. Middle row GBCAs are the macrocyclic agents, by virtue of their closed ring *N*-containing backbone. Bottom row: Specialty GBCAs, which are both protein (primarily albumin) binders. Gadoxetate and gadobenate are very weak protein binders, and gadofosveset is a stronger protein binder.
* GBCAs that have been withdrawn from the U.S. market.

Dechelated forms of gadolinium in vivo are potentially myriad and include "free" forms that associate with anionic counter ions (eg, OH^-, PO_4^{3-}), forms that associate with negatively charged biopolymers (eg, protein side chains, nucleic acid phosphate ester backbones), and insoluble precipitates (33). Identification of the form or forms of dechelated gadolinium is critical to understand the biodistribution, potential toxicity, trafficking, long-term stability, and lability of retained gadolinium species. Gadolinium may also be retained long term as an intact GBCA chelate (34,35).

Stability parameters measured in aqueous solutions in vitro are useful only to the extent that they are predictive of in vivo thermodynamic stability and lability. The thermodynamic stability constants are used to differentiate two subclasses of linear agents, and the dissociation kinetics show that macrocyclic GBCAs are overall less labile (more kinetically inert to dissociation) than are linear GBCAs, owing to the macrocycle-enhanced chemical rigidity and reduced conformational freedom. At physiologic pH, macrocyclic GBCA dissociations were undetectable after incubation at 2 weeks in human serum, while all linear GBCAs showed variable degrees of dissociation; this is despite some cases in which thermodynamic constant differences favor linear agents over macrocyclic agents (27,28,36,37).

Biodistribution

- Biodistribution properties of GBCAs are more heterogeneous and complex in humans than in rodents. In humans, 73%–99% of the GBCA is excreted within 24 hours after administration, whereas in mice, more than 98% of the GBCA is excreted in that time period.
- Biodistribution data of GBCA in humans beyond the first 24 hours suggests the presence of a longer lasting phase of residual excretion from deep compartments, from which gadolinium is slowly eliminated.
- There is a need to better understand in vivo tissue distribution, transformation, trafficking, and excretion of a GBCA in normal individuals and in more vulnerable groups, such as children or adults with comorbidities that might affect biodistribution, such as diabetes, osteoporosis, and renal osteodystrophy.

The short-term biodistribution and clearance of an intravenously administered GBCA have been extensively studied both in animals and in humans (38,39) (Table 1). The general-purpose GBCAs are primarily cleared via glomerular excretion, with

a high fraction excreted in urine, without metabolic chemical modification. In mice with normal renal function, over 98% of the initial injected dose of intravenously administered GBCA is excreted in the urine (38) in 24 hours (92%–96% in 1 hour). In humans with normal renal function, only approximately 90% of injected GBCA is excreted within 24 hours, but this varies with the specific GBCA. Hence, the exposure time that allows GBCA time to approach equilibrium is naturally longer in humans than in small animals. The human findings may reflect different experimental conditions and suggest that the biodistribution properties of GBCAs are more heterogeneous and complex in humans than in animals. Further, delayed renal excretion as a result of impaired renal function can significantly increase the amount of circulating GBCA (by as much as a factor of 12), potentially altering the biodistribution of these agents (40–42). Clearance data beyond 24 hours in humans are limited. The existence of a long-lasting residual excretion phase, demonstrated by detection of the GBCA in urine for long periods of time after administration, suggests the presence of one or more deep compartments from which the GBCA is slowly released (43–46). Bone, liver, and other organs are possible reservoirs for the slow-releasing pool of GBCA. Bone retention was detected up to 8 years after injection (34). Among patients undergoing total hip arthroplasty, exposure to the linear agent gadodiamide was associated with four times higher levels of gadolinium measured in resected bone when compared with patients who received the macrocyclic agent gadoteridol (19). Animal biodistribution studies have shown measurable fractions of the administered dose at both intermediate (1–2 weeks after injection) and long-term (34 weeks after injection) time points in multiple tissues; these fractions are generally greater with linear GBCA chelates than with macrocyclic GBCA chelates (38,47).

Several knowledge gaps exist. First, details of in vivo tissue distribution, transformation, trafficking, and excretion are incomplete. Existing biodistribution data are limited by the absence of side-by-side comparisons of all approved GBCAs using standardized animal and human protocols. Second, human biodistribution data are much more limited than animal biodistribution data, and pharmacokinetics in animals differ from those in humans. For example, hepatobiliary excretion of gadobenate dimeglumine is much higher in rat models (about 50%) than in humans (about 5%) (48). Third, much less is known about the potentially more complex biodistribution of the chronically retained gadolinium fraction, including its chemical form or forms, equilibration, and lability, and its propensity to be slowly cleared over time (44).

In addition to defining gadolinium distribution patterns and elimination rates in normal populations, it is also critical to define potentially altered dynamics in potentially vulnerable populations. Fetal, infant, and early childhood populations may be uniquely vulnerable due to ongoing growth and development, and these populations have a long life expectancy, during which retained gadolinium may exert a clinically important effect. Identification of events, comorbid conditions, and clinical therapies that may mobilize gadolinium into the serum and affect elimination rates may help identify other potential vulnerable populations. For example, will gadolinium in bone be mobilized in patients with osteoporosis, renal osteodystrophy, or hyperparathyroidism? Does the immature or treatment-altered blood-brain barrier (BBB) predispose one to gadolinium retention? Are patients who are exposed to higher levels of iron, zinc, manganese, lanthanides, or copper at greater risk for transmetallation effects when exposed to a GBCA (49–54)? Will other chronic diseases, such as diabetes, affect the biodistribution of GBCA?

Improved noninvasive protocols to measure the biodistribution and elimination of retained gadolinium are needed to provide temporal information to understand GBCA kinetics. Although gadolinium can be detected in the urine for months, or possibly even years, after GBCA administration, age- and sex-defined normative ranges have yet to be prospectively defined. Measurement of serum levels is another potential method with which to monitor gadolinium retention, and it should be studied as a possible monitoring technique (55). Each agent needs to be studied, not just one agent from each class. Standardization of specimen collection, storage, and measurement needs to be established to ensure uniform reproducible clinical laboratory testing. Even local environmental water supply concentrations of anthropomorphic gadolinium (56) may need to be considered when establishing normal reference ranges for different regional populations.

Speciation

- Limited information is available on the biologically active and potentially toxic chemical forms of retained gadolinium in tissues. These include intact GBCA; soluble GBCA metabolites; one of many possible inorganic insoluble or matrixed entities (eg, hydroxyapatite); solid hydroxides, oxides, phosphonates, carbonates or combinations of insoluble species; or gadolinium bound into macromolecular or macrostructural forms.
- While this information is essential for evaluating potential toxicity of GBCA, it is largely unknown.
- Appropriate studies to identify these chemical species are technically challenging and require the use of an array of techniques.

Speciation analysis seeks to identify the chemical forms and interactions of gadolinium in tissues and is an essential element of absorption, distribution, metabolism, and excretion (or ADME) studies that are, in turn, required for the interpretation of toxicologic and clinical studies (33). Because unchelated gadolinium ions are considerably more toxic than the gadolinium chelates used in GBCA, the primary focus of speciation is to identify the biologically inactive (presumable gadolinium chelate) versus potentially toxic chemical forms of residual gadolinium within tissues (33,57). These include intact GBCA; soluble GBCA metabolites; one of many possible inorganic insoluble or matrixed entities (eg, hydroxyapatite); solids of hydroxides, oxides, phosphonates, carbonates, or combinations of insoluble species; or gadolinium bound into macromolecular or macrostructural forms. The gadolinium deposits are most likely formed from the various insoluble forms of gadolinium salts. Careful in vivo animal studies of trafficking kinetics are needed to characterize the chemical forms of dissociated

Table 2: Approaches to Speciation

Method	Strengths	Challenges
Field-dependent MRI	In vivo detection	Limited by equipment, few field points, sensitivity, not direct; limited spatial resolution in small animals; no direct speciation
Magnetic methods (ENDOR, NMR, NMRD, ESR)	Direct speciation using model compounds; some quantitation; some are micro and sensitive; can work without separation	Some difficulty to combine with separation methods due to low sensitivity
MSA	Direct speciation; sensitive, can be combined with separation methods	Not directly quantitative due to variable volatilization, which can be overcome by calibration; requires tissue extraction which may alter species
EXAFS	Direct speciation, with model compounds; regional with XRF	Lower sensitivity than MSA; less frequently available equipment
XRF	Sensitive in EM to points of gadolinium	Microscopy fixation can affect speciation or exposure; no direct speciation; depends on gadolinium concentration
ICP in combination techniques (with chromatography, MSA, EM)	Simple and available; quantitative; highly sensitive.	ICP alone does not allow speciation; requires tissue extraction, which may alter species
Radioactive tracers with long-lived isotopes	Sensitive; quantitative; can be combined with separation methods	Animal only, no direct speciation; regulatory burden
Tissue ablation (eg, laser)	Highly regional with small area analysis of ex vivo tissues; can be combined with ICP, MSA, some chromatography	Volatilization can affect gadolinium species and quantitation; requires tissue preparation; no direct speciation
Tissue extraction (eg, into saline from ex vivo tissue)	Separates soluble from insoluble gadolinium for analysis; soluble analytes are a prerequisite for most speciation analyses	Highly method/controls dependent; methods can change gadolinium in vivo species/exposure (eg, destruction of cell membranes); not inherently quantitative
Use of other lanthanides (55)	Optical and other properties of lanthanides can be structure dependent	Indirect information hard to validate

Note.—ENDOR = electron nuclear double resonance, EM = electronic microscopy, ESR = electron spin resonance, EXAFS = extended x-ray absorption fine structure, ICP = inductively coupled plasma, MSA = mass spectral analysis, NMR = nuclear magnetic resonance, NMRD = nuclear magnetic relaxation dispersion, XRF = x-ray fluorescence.

gadolinium produced after presumed gadolinium dissociation from GBCA.

To fully understand the in vivo trafficking of GBCAs and their metabolites, a combination of speciation techniques (Appendix E2 [online]) is needed to accurately determine the chemical speciation of GBCA and gadolinium. All speciation methods require relevant controls, and best practices will depend on combining methods to ameliorate weaknesses and magnify strengths (Table 2).

To interpret absorption, distribution, metabolism, and excretion data on the final small percentage of retained GBCA or gadolinium that is not rapidly excreted, human tissue biodistribution analyses are needed. An ideal approach would be to develop a multiorgan tissue biorepository that is not confounded by multiagent GBCA contamination, with reliable patient history data (eg, date or dates of GBCA administration, estimated glomerular filtration rate at each administration, GBCA dose, and specific GBCA used), that could be preserved for future analysis. Such a tissue biorepository would alleviate one of the greatest hurdles in future speciation studies: the dearth of well-characterized human tissue samples from patients exposed to gadolinium. These tissues could be harvested from formalin-fixed or fresh frozen tissue samples saved at autopsy or surgery. Fresh frozen tissue may be more desirable, since the fixation process may alter gadolinium distribution and speciation. The common practice of choosing to study one member of each GBCA subclass (for example, macrocyclic vs linear) ignores the fact that differences between individual GBCAs (Table 1) exist and may affect results of speciation studies, making generalization among classes and subclasses unreliable in the absence of full data sets using all GBCA moieties.

Additional limitations of these studies lie in the technical issues surrounding the instrumentation and methods used in trace metal and GBCA speciation analyses. Highly sensitive speciation analyses generally involve separating gadolinium from tissue, requiring tight control of variables. Current limitations include *(a)* validation that the methods do not change or favor one chemical form of gadolinium over another; *(b)* movement of retained gadolinium species among tissue compartments during extractions, causing different gadolinium exposure from that which was present in vivo; *(c)* imperfections inherent in substituting animal tissues for human tissues; *(d)* the relative lability of the ligands involved in many biologically relevant forms of dissociated gadolinium, such as gadolinium macromolecules; and *(e)*

exposure of gadolinium to new microenvironments during tissue homogenizations (eg, ones that disrupt cell membranes). The importance of ensuring the benign separation, causing no important change to the tissue or alteration of the gadolinium species extracted, cannot be overemphasized. Analytical methods and controls are imperfect, and multiple complementary methods are recommended to alleviate the weaknesses of individual techniques.

Toxicology

- The acute non–allergic-like toxic effects of gadolinium salts are due to competition with calcium-dependent biologic processes, cytotoxic effects, inducement of cytokine expression, and inhibition of mononuclear phagocytosis. Gadolinium chelates do not show these effects.
- All the general pharmacology, general toxicology (single and repeated doses), organ-specific toxicity, genetic toxicology, reproductive and developmental toxicology, and local tolerance studies expected for any drug have been performed for each GBCA.
- The potential toxicities of the small pool of retained GBCAs, their metabolites, as well as the soluble and insoluble complexes derived from this pool, are largely unknown.

The fate of the small percentage of an administered GBCA that is not rapidly excreted is at the center of current concerns for three reasons. First, gadolinium has no known biologic role in vivo; however, it is known to have adverse biologic effects (5,49,58–61). Second, gadolinium plays a role in the development of NSF, albeit inconsistently, since not all patients with severely compromised renal function who had multiple exposures to a GBCA developed NSF, and some patients with renal failure developed NSF after only one exposure to a GBCA (5–7,62,63). Third, some forms of residual gadolinium from GBCAs have long biologic residence times (10,12). Thus, the small fraction of the retained GBCA or any of the products of its dissociation might have the potential to lead to chronic toxic effects.

The acute toxic effects of gadolinium salts and other rare-earth metals have been extensively studied (30,58,64–66). Acute toxic effects may arise from the ability of gadolinium to interfere with calcium-mediated cellular processes (38,58,59). Gadolinium also has been shown to be a cytotoxic agent and can modulate the immune system via induction of cytokine expression and inhibition of the mononuclear phagocyte system (67,68).

Toxicity in gadolinium chelates also has been studied. Although GBCAs are well tolerated when administered intravenously at clinically relevant doses, at much higher experimental doses, well-defined toxic and lethal nonclinical dose thresholds were observed with all GBCAs (69). Additional acute neurotoxic effects (delayed seizures hours after administration) have been observed in canines with an osmotically disrupted BBB (70). Such effects are attenuated in mammalian species, such as rats, with more primitive brain parenchyma and sulcation (71).

To satisfy regulatory requirements, the safety and toxicologic potential of each GBCA has been evaluated by the respective manufacturers and has been reported in the approved product labeling (26,72–74). Tests included evaluations of the general pharmacology, general toxicology (single and repeated doses), organ-specific toxicities, genetic toxicology, reproductive and developmental toxicology, and local tolerance studies. In central nervous system (CNS) safety studies conducted by the Food and Drug Administration for GBCA approval, adverse effects (histologically or behaviorally) were not detected in single- or repeated-dose studies at high GBCA dose multiples and in multiple animal species. However, the standard test batteries may not be sensitive enough to enable detection of rare or subtle effects, highlighting the need for new approaches, such as sensitive animal models, expansion of nonclinical functional testing, and improved assay sensitivities.

Furthermore, the patient populations that are potentially more vulnerable to GBCA side-effects have not been fully defined. Maximova et al (54) have shown elevated gadolinium levels in the livers of pediatric patients with concomitant iron overload amenable to chelation therapy with deferoxamine mesylate. It is unknown if other potentially vulnerable populations (eg, fetal, pediatric, pregnant) with higher cell turnover are at greater risk for gadolinium-mediated toxicity. Fetuses and children are also potentially vulnerable because of ongoing CNS development, immature renal function, and active bone formation. GBCA administered to pregnant nonhuman primates resulted in measurable gadolinium concentration in the bone, brain, skin, liver, kidney, or spleen of offspring for at least 7 months (75). Although gadolinium retention is lower in the brain than in bones or skin, there are concerns about metal toxicity in the brain and developing organs.

Unlike the known acute toxicities of gadolinium and GBCAs, there is less evidence of chronic GBCA-mediated toxicities after intravenous administration in animal models, even when animals are exposed to supradiagnostic doses that exceed clinical doses by one to two orders of magnitude. However, some evidence of harm from retained gadolinium was reported by Khairinisa et al in pregnant BALB/c mice. Prenatal exposure to intravenous gadoterate meglumine or gadodiamide (embryonic days 15–19) was associated with abnormal behaviors and decreased muscle strength (76).

The following areas of research are suggested to better understand the potential toxic effects of retained gadolinium: *(a)* development of animal models (species, prenatal, juvenile, and adults); *(b)* adoption of uniform study protocols for side-by-side simultaneous comparison of GBCAs; *(c)* standardization of safety (including CNS safety) and toxicology study protocols (dose, multiple doses, dose timing, dose frequency, observational batteries, timing of evaluations, and assay methods, particularly those for gadolinium levels) that go beyond the recommendations for initial regulatory approval, as established by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (74); *(d)* characterization of gadolinium retention; *(e)* development of biomarkers of toxicity; and *(f)* standardization of critical assay elements.

Retention of Gadolinium in CNS Tissues

- Dose-dependent increases in signal intensity in the globus pallidus and dentate nucleus at T1-weighted MRI have been identified in patients receiving a linear GBCA. In a smaller number of studies, researchers have also reported a similar but less pronounced change with macrocyclic GBCAs.
- Autopsy studies using inductively coupled plasma mass spectrometry (ICP-MS) among patients receiving a linear GBCA have shown high T1 signal intensity in the dentate nucleus and globus pallidus is related to the presence of retained gadolinium in these regions.
- ICP-MS studies on brain tissue obtained at autopsy in patients receiving macrocyclic GBCA are limited at this time, but the results confirm the presence of retained gadolinium in these areas.
- Animal studies with ICP-MS and transmission electron microscopy have shown focal retention of linear and macrocyclic GBCAs in brain tissues.
- The identification of compounds associated with retained gadolinium that are visible at MRI, as well as the compounds that are not visible at MRI, represents an important knowledge gap.

In 2014, Kanda and colleagues (21) hypothesized the existence of intracranial gadolinium retention based on the observation of progressive unenhanced T1 signal intensity increases in the dentate and globus pallidus at clinical MRI in human subjects who received gadopentetate dimeglumine or gadodiamide. Subsequent studies have enabled independent confirmation of progressive T1 signal shortening after intravenous administration of linear GBCAs (13–15,77–79). However, there is disagreement in the scientific literature regarding the presence of this signal phenomenon after administration of the macrocyclic GBCA. While most reports have not shown dose-dependent changes in T1 signal with macrocyclic GBCA exposure (15,77,79–83), a weak T1 signal change associated with macrocyclic GBCA has been reported (84–88). The reasons for these disparate findings are unclear, and they may be related to heterogeneity among macrocyclic agents, differences in MRI examination and assessment parameters, heterogeneity in patient factors, inaccuracies in patient data collection, or differences in study methods. In addition, it is unclear what gadolinium-containing species is producing T1 shortening, leading to the possibility that only the MRI visible forms are being selectively detected.

In 2015, two independent human autopsy studies using ICP-MS showed the presence of retained gadolinium in the dentate and globus pallidus (10,89). Subsequent study of human brain tissues demonstrated measurable gadolinium after single-dose intravenous administration of both linear and macrocyclic agents (17). However, significantly less gadolinium retention was observed after macrocyclic agent exposure when compared with linear agent exposure; this finding is in keeping with the greater overall stability of macrocyclic chelates. Although the greatest gadolinium concentrations have been measured in the regions with greatest T1 shortening effects (dentate nucleus and globus pallidus), ICP-MS analysis has served to confirm more widespread low-level retention in all brain parenchyma (89).

This phenomenon of retained brain gadolinium is not limited to patients with potential BBB disruption and has been seen in decedents with normal brains at the time of autopsy without clinical history of an inflammatory, neoplastic, traumatic, or infectious intracranial history (12). Intracranial gadolinium retention also has been identified in the pediatric population after exposure to gadodiamide and gadopentetate dimeglumine (11,25).

An animal model of intracranial gadolinium retention revealed substantially higher gadolinium retention in brain tissues after exposure to gadodiamide relative to gadoterate meglumine (24). In this study, researchers confirmed the superior sensitivity of ICP-MS, as detectable levels of gadolinium after gadoterate meglumine administration at approximately 20 human dose equivalents (0.6 mmol per kilogram of body weight per dose × 20 doses) were observed by using ICP-MS despite the lack of T1 shortening in the cerebellar roof nuclei. Subsequent studies in a rat model revealed significant inter- and intraclass differences in neural tissue gadolinium retention at 80 human dose equivalents (22); at this dose, significant differences in retention, even among macrocyclic agents, were found, and these observations have been confirmed in animal studies by Bussi et al (23) and Gianolio et al (90). It should be noted that these human dose equivalents are based on animal body surface area. These animal studies variously had multiple GBCA or control injections over a 3.5–7.5-week interval and then underwent imaging assessment and/or measurement of gadolinium 3 days to 5 weeks after the final injection. Longer-term retention data are needed to better understand differences in the biodistribution of different GBCAs.

Other human and animal studies have provided potentially useful preliminary data on the biodistribution of intravenously administered GBCA in the context of an intact BBB. Transmission electron microscopy with energy-dispersive x-ray spectroscopy studies of the ultrastructural distribution of retained gadolinium within neural tissues revealed that the majority was localized to the endothelium of capillaries outside of the BBB while a much smaller fraction of gadolinium-enriched foci either circumvented or directly traversed the BBB and was detected in the neural interstitium and cellular organelles (10–12). Animal studies by Jost et al have shown that all GBCAs, regardless of class, enter the cerebrospinal fluid (CSF) from serum, and that neither GBCA structure nor physicochemical properties affect CSF penetration and distribution (91). These findings parallel clinical observations in delayed GBCA-enhanced MRI examinations in which gadolinium has been indirectly detected in the perivascular spaces and CSF through the effects of T1 shortening (92). The presence of gadolinium in CSF has been verified in humans undergoing lumbar puncture after gadobutrol-enhanced MRI. Gadolinium clearance from CSF roughly approximated first-order kinetics, with detectable levels of gadolinium still present up to 30 days after initial GBCA administration (93). Despite the identification of retained gadolinium in neural parenchyma using transmission electron microscopy with energy-dispersive x-ray spectroscopy, there

is no explicit evidence of gadolinium directly transgressing the intact BBB. The mechanisms of transit across the blood-CSF barrier, retention in neural tissues, potential role of concomitant radiation or chemotherapy (94,95), and clearance via the glymphatic tissues are currently poorly understood.

No convincing evidence of chronic toxicity arising from retained gadolinium in neural tissues introduced via intravenous administration has been reported. Studies of human brain tissues and animal studies have consistently failed to demonstrate histopathologic evidence of injury to neurons or the neural interstitium (10,12,22,89,96,97).

Although there is now data that all GBCAs leave trace amounts of residual gadolinium in brain tissues after intravenous GBCA administration, substantial limitations of existing data include the following: *(a)* Small sample sizes and focus on specific patient populations make it difficult to generalize results to the larger and less chronically ill general population. Importantly, T1 signal intensity changes are less sensitive than techniques used in tissue analysis. *(b)* Inconsistent experimental designs with heterogeneity in clinical and animal study methods limiting the comparability of results between studies. In T1 signal analyses, standardization in the pulse sequence parameters and techniques to analyze and report imaging findings is lacking. In tissue studies, standardization is lacking in the quality controls in analytical instrumentation, reference ranges, and dissection techniques. *(c)* Limited human data hinder comparisons between GBCAs. Most human data have been from single center studies with only one or two specific GBCAs in local clinical practice, thereby limiting the comparability of results among GBCAs. *(d)* Generalizability of animal model results to humans is not established. Physiologic and structural differences between humans and animal models may limit the usefulness of animal data. For example, rats are commonly used in toxicology studies, but the lack of substantial sulcation/gyration of the rat brain compared with that in humans limits the generalizability of behavioral and neurologic assessments of these animals to humans, and different species may have differing tolerance to retained gadolinium. In addition, there is abundant evidence that the amount of measured gadolinium in human brain tissue is substantially higher when normalized per unit dose and body surface area when compared with that in rodent models. The mechanisms to account for these differences are unclear, as is whether current human-to-animal dosing conversions are sufficiently accurate to simulate acute or chronic human exposure to retained gadolinium. *(e)* We do not yet fully understand the mechanism of gadolinium retention and washout, nor do we understand the reason for disproportional focal accumulation, such as in the globus pallidus and dentate nucleus. Why gadolinium preferentially localizes to these areas of the brain is unclear, but one untested hypothesis is that gadolinium is being sequestered by the same cellular mechanisms that sequester calcium in the same neuroanatomic regions due to the similar charge and size between gadolinium and calcium. Further, there is a strong correlation between sites of iron and gadolinium retention, potentially due to interactions with iron-containing molecules. *(f)* We also do not understand the discrepancy between T1 signal changes and mass spectrometry results. In general, retained gadolinium from macrocyclic agent exposure shows undetectable or one to two orders of magnitude lower T1 shortening effects when compared with linear GBCA administration, despite ICP-MS data that some long-term CNS gadolinium accumulation occurs with all GBCAs. This discrepancy may well be a manifestation of the inferior detection sensitivity of MRI signal analysis relative to ICP-MS; however, the chemical form of retained gadolinium also may differ between linear and macrocyclic agents. Specifically, T1 shortening effects of retained species associated with macrocyclic agents may be weaker than those from linear GBCA exposure (33,90). In vitro chromatographic data of cellular homogenates appear to support this hypothesis, as retained gadolinium after intravenous administration of linear agents was associated with a greater fraction of insoluble and macromolecule-bound gadolinium complexes than what was observed with macrocyclic agent administration (36,90). However, process controls suggest that the processes used to assess in vitro chromatographic data of cellular homogenates exposed extracellular gadolinium and GBCA to intracellular proteins, which adds uncertainty to the quantitative results. *(g)* A final uncertainty is the relevance of ultrastructural and histopathologic studies to potential gadolinium mediated toxicity. The absence of a priori knowledge of the chronic effects of retained gadolinium makes it difficult to know if investigators are assessing the right location.

Retention of Gadolinium in Non-CNS Tissues

- Gadolinium retention in the skin, bone, liver, and other organs has been reported. Bone tissues are thought to be one of the primary reservoirs of gadolinium in the body, as gadolinium is actively incorporated by osteoblasts into the bone matrix and can replace calcium in hydroxyapatite formation.
- Some fraction of chronically retained tissue gadolinium may be labile or bioconvertable to a more soluble form of gadolinium.
- Although free gadolinium salts have been shown to be profoundly toxic to many tissue types, little is known about the toxicities of retained gadolinium species, including which tissues may be more sensitive to these toxicities.

Biodistribution studies demonstrate gadolinium retention in the skin for months to 1 year after intravenous GBCA administration (47). In 1995, Tweedle et al showed that lability of the GBCA was predictive of the extent of gadolinium detected in tissues at 14 days, suggesting a possible role for dechelation in long-term tissue retention (38). Pietsch et al (47) support this GBCA stability and retention hypothesis by showing an inverse relationship between GBCA thermodynamic stability and GBCA lability in gadolinium skin retention. However, stability alone is not entirely predictive of retention, as the propensity for retention in each organ can differ between GBCAs, as demonstrated in a study of gadolinium retention in rats, in which gadodiamide had its highest retention concentration in skin and gadopentetate dimeglumine had its highest retention concentrations in bone (97).

Skin lesions associated with GBCA administration have been reported both in animal models and in human subjects

(55,97,98). A correlation between gadolinium skin concentration and the presence of skin lesions has been suggested (7,35,55,99). Animal data suggest that skin lesions are an inflammatory response to acute GBCA exposure rather than to chronic gadolinium retention (67). While most skin lesions observed in nonclinical studies have been associated with supradiagnostic gadodiamide exposure, subtle changes in rodent skin occurred, even with more stable GBCAs (100). Both insoluble and soluble forms of gadolinium, including intact GBCA molecules, are retained in the skin of patients with NSF, further complicating our ability to identify what form or forms may be potentially toxic (35,50,63,101).

Skin is the human tissue in which gadolinium retention has been most studied because of efforts to understand the mechanisms underlying NSF. In other human organs and tissues, gadolinium retention is less well-characterized when compared with animal models, but it has been reported in many other tissues, including the musculoskeletal system (muscles, tendons, and bone), nerves, blood vessels, and selected visceral organs in patients with and those without NSF (17,102). Bone tissues are thought to be one of the primary reservoirs of gadolinium in the body, as gadolinium is actively incorporated by osteoblasts into the bone matrix and can replace calcium in hydroxyapatite formation (50). Human autopsy studies have shown trace amounts of gadolinium in bone (and skin) retained up to 2 years after GBCA administration. Gadolinium levels in bone were much higher than those in skin or brain (17). Toxicities may manifest differently between tissues; for example, the brain heals by gliosis, and the skin heals by fibrosis.

Recent nonclinical studies suggest that a certain fraction of chronically retained tissue gadolinium may be labile or bioconvertable to a more soluble form of gadolinium. Smith et al (96), Frenzel et al (103), and Behzadi et al (104) have shown a slow washout of detectable tissue gadolinium over many months after gadodiamide or gadobutrol exposure; this washout appears to be more robust with macrocyclic agents, where the amount of retained gadolinium 52 weeks after supradiagnostic exposure was only 13% of the amount retained, as measured with ICP-MS at 5 weeks (103). In comparison, a more attenuated washout phenomenon was observed after gadodiamide administration, with 50% of the initially measured amount retained at 1 week still present 20 weeks after administration (96). Longer-term washout data are needed at common time points to permit comparability between agents and classes.

Despite considerable accumulated knowledge on gadolinium retention in non-CNS tissues, several knowledge gaps remain. First, although free gadolinium salts have been shown to be profoundly toxic to many tissue types, little is known about the toxicities of retained gadolinium species, including which tissues may be more sensitive to these toxicities. Second, it is unclear if retained gadolinium poses a long-term risk in patients exposed to large GBCA doses early in life and what, if any, physiologic triggers may liberate or convert this retained pool into a more biologically active chemical form.

Clinical Importance of Gadolinium Retention in Humans

- At this time, the clinical importance of gadolinium retention in humans is unknown.
- At the time of this writing, 139 patients with normal or near-normal renal function have been reported to the Food and Drug Administration with non–allergic-like symptoms (eg, joint pain, fatigue, and cognitive changes) and signs they have attributed to GBCA administration; there is insufficient data to confirm that these clinical manifestations are the result of GBCA exposure or gadolinium retention.
- It may be possible to evaluate the clinical importance of gadolinium retention in humans by analyzing pre-existing electronic medical records, databases from prospectively accrued trials, or registries that incorporate neurocognitive studies and patient-reported symptoms.

The central clinical question with respect to gadolinium retention is whether it has clinically meaningful effects and, if so, whether those effects are common or rare or if they are subtle or serious but not recognized. The risks of GBCA administration resulting in NSF or an acute nuisance or life-threatening allergic-like reaction are known and can be addressed with existing risk-mitigation protocols. These quantifiable adverse events can be balanced against the potential benefits of making a diagnosis, excluding a diagnosis, or monitoring a disease when a GBCA-enhanced examination is considered. This risk-benefit assessment is common for all diagnostic procedures and allows the informed provider and patient to make a sound decision regarding the need for a contrast-enhanced examination.

Gadolinium retention complicates this assessment. Although it is known to occur, its clinical importance remains undefined. Relative to the hundreds of millions of doses of GBCA that have been administered in the United States over three decades, there are published reports of only 139 patients, all with normal or minimally impaired renal function, who have reported non–allergic-like effects that they associated with GBCA exposure, with onset often shortly after one dose (105,106). Some of the patients reported joint and cognitive symptoms that overlap with some symptoms of patients with NSF. A small subset (n = 25) of these patients underwent experimental chelation therapy, with a subsequent increased level of gadolinium in the urine, transient worsening of symptoms in 11 patients, and overall symptom improvement in 13 (107); however, there were no control subjects. There are no controlled prospective study data to confirm a causal link between gadolinium retention and symptoms, nor has chelation therapy been performed in a blinded or randomized fashion.

Forslin et al (108) performed a retrospective 18-year longitudinal cohort study in 23 subjects with multiple sclerosis exposed to GBCA and 23 healthy age- and sex-matched control subjects who underwent unenhanced MRI. The results showed that increased signal intensity in the dentate nucleus in the patients with multiple sclerosis was associated with lower verbal fluency scores at neuropsychological testing. The presence of neurologic disease, however, is a major confounder. Ray et al (109) analyzed universal health care databases for the province

of Ontario, Canada, to identify all births of more than 20 weeks gestation from 2003 to 2015. Among the 1 424 105 deliveries, 397 women underwent GBCA-enhanced MRI during pregnancy. When compared with a cohort of women who did not undergo MRI during pregnancy (n = 1 418 451), in utero contrast-enhanced MRI was associated with an increased risk of a heterogeneous array of rheumatologic, inflammatory, and infiltrative skin conditions, as well as an increased adjusted risk of stillbirth and neonatal death (n = 7 in the GBCA group). However, the study was limited by lack of control for the reason GBCA was administered during pregnancy. This information is crucial, since the underlying condition requiring MRI could have affected pregnancy outcome.

Quattrocchi et al (110) studied resting-state functional imaging of the dentate nuclei and basal ganglia among human patients with inflammatory bowel disease and did not find evidence of brain functional changes in patients with visible T1 hyperintensity after exposure to gadodiamide; however, they did identify subtle nonsignificant changes in functional activation that may merit further investigation.

In 2016, Burke et al (106) published observations from 50 patients who previously underwent GBCA-enhanced (both linear and macrocyclic) MRI and who attributed symptoms to GBCA exposure. The symptoms (ie, chronic pain, fatigue, dermal changes, musculoskeletal disturbances, cognitive and visual impairment) manifested within 1 month of exposure, with over 50% of onset within the first 24 hours. All reported persistence of symptoms 2 months to 6 years after GBCA exposure. An association between these symptoms and GBCA exposure was posited by the authors, who termed the constellation of findings "gadolinium deposition disease" (111). However, due to limited data and no control group or blinding, the causative association between these symptoms and chronically retained gadolinium remains speculative. If these symptoms are indeed due to gadolinium, they might be an idiosyncratic acute or semiacute process requiring only exposure to , not long-term retention of gadolinium. If clinical manifestations from gadolinium retention exist, it is unknown if they vary by GBCA type or GBCA class, if they are dose dependent, if they are acute or delayed in onset, or whether any dose-dependent threshold is crossed in clinical use.

At the September 2017 Food and Drug Administration Medical Imaging Drugs Advisory Committee (MIDAC) meeting, a presentation on patients reporting symptoms potentially related to GBCA exposure indicated their MRI examinations were performed for a variety of medical conditions. A total of 132 case reports were identified, with various symptoms often centering around pain; most were self-reported and lacked details, such as the specific GBCA product used, the number of GBCA administrations, and the time to onset of symptoms (26). The MIDAC concluded that no causal relationship between gadolinium retention and patient symptoms could be established at this juncture but that further study was needed (112).

To date, there is no established risk tolerance threshold for chronic gadolinium retention. If gadolinium retention is associated with clinical harm, the harm is likely rare or occult for the vast majority of exposed patients; thus, the clinical effect size will be very small. It is important to establish an acceptable risk tolerance with respect to gadolinium retention so that future studies can be appropriately powered to enable detection of rare or subtle adverse effects, recognizing it is not possible to scientifically prove the absence of harm. The specific signs, symptoms, and diseases to investigate are unclear. Rare at-risk genetic variants and unusual concomitant medical conditions will need to be considered. Early studies have focused on neurocognitive effects due to the retention of gadolinium observed in the deep brain nuclei, but gadolinium retention occurs throughout the body in multiple tissues and organs at much higher concentrations than those in brain tissues. Consultation with toxicologists and interrogation of large population-based exploratory studies (eg, claims-based and "big data"), possibly using artificial intelligence methods, may be helpful to generate hypotheses for future directed study (113).

Studies and experience have established a strong safety profile for all Food and Drug Administration–approved commercially available GBCAs. Since any obvious clinical manifestations of retained gadolinium have escaped clinical detection in the vast majority of exposed patients, the search for effects should focus on two main types of adverse events: *(a)* common and small (eg, a global minute decrement in cognitive performance) or *(b)* rare and severe (eg, debilitating pain). Appropriate power will be critical in any study design, particularly if more than one GBCA is studied. In recognition of this fact, funding agencies and industry need to work cooperatively to study this issue without corporate bias. Study designs should include as many GBCAs as are feasible. Since GBCAs within a class (eg, macrocyclic vs linear, ionic vs nonionic) may behave differently than others within the same class, GBCAs should be studied and reported as a class and individually. Since anecdotal and uncontrolled studies are unlikely to yield results that can withstand scientific scrutiny, suitable controls are necessary and should consider potentially confounding factors, such as pre-existing clinical and laboratory parameters, time from last GBCA administration (due to slow excretion over months), and dosing schedule.

Researchers are encouraged to identify and use pre-existing large databases from prospectively accrued trials or natural history studies that did not investigate a neurologic disease (ie, to avoid confounding) but to include neurocognitive testing as an end point. Phase IV studies analyzing potential subtle, persistent, or delayed manifestations will need to be appropriately powered and should be targeted to plausible symptoms. Registries that incorporate sophisticated neurocognitive testing can be created and informed by retrospective exposure histories, which will minimize the time demands of the study (compared with prospective monitoring of exposure-naïve subjects) but will be limited by recall bias and incomplete histories. Registries also could be considered that avoid expensive neurocognitive testing and instead solicit open-ended self-reported symptoms from exposed and unexposed subjects. Patients who believe they have been adversely affected by gadolinium retention should be approached for possible inclusion in prospective blinded randomized trials of chelation therapy or other future treatment options; a cross-over design might mitigate the stigma of placebo. Given the potential

Table 3: Animal and Basic Science Study Research Roadmap for High-Priority Items

Knowledge Gap	Approach/Methods	Comments	Feasibility/Limitations
	Absorption, Distribution, Metabolism, and Excretion		
What is the long-term biodistribution of intravenously administered GBCA?	Explore the feasibility and safety of using radiolabeled gadolinium 153 for these biodistribution studies. Alternatively, explore the feasibility of using cadaver samples in a multi-institutional program to obtain tissue for these biodistribution studies	There are no data available in this area comparing all agents	Radiolabeled experiments will largely be limited to preclinical studies. Because of concerns over measurement of radioisotopes, nonradioactive gadolinium species could also be used in these preclinical and potentially clinical studies, albeit usually with less detection sensitivity
	Toxicology		
What is the toxic potential of chronically retained amounts of gadolinium in tissues? What are the mechanisms of this toxicity?	Use of molecular, genetic, and proteomic techniques to understand how chronically retained gadolinium can affect cellular function	In vitro and in vivo experiments using standard toxicology methods have already been performed; thus, different tests are needed. Further involvement and collaboration with toxicologists and cell biologists is needed to optimize studies. Studies of juvenile animals could inform risks for pediatric patients	…
What are the best approaches to identification and quantification of gadolinium species in tissues?	See Table 2	May help inform studies of toxicology and clinical manifestations. Appropriate standardized animal studies can assist in this development. Once species are identified, toxicologic and mechanistic studies can be performed to examine the precise pathways, enzymes, etc that will be affected	Many of these techniques cannot be used clinically in living tissues. Ex vivo findings and the manipulation of tissues needed to perform some of these assays may alter the chemical environment of the retained gadolinium species, which may affect the chelation of gadolinium to molecules within the sample
	Clinical Manifestations		
Are there measurable clinical manifestations (neurologic or nonneurologic)? Is there a toxic dose threshold for chronic gadolinium exposure?	Animal studies using both clinically equivalent and supradiagnostic doses to study both neurologic and nonneurologic function and medium-term and long-term symptoms	Animal studies afford us the opportunity to study clinical effects at supradiagnostic doses that cannot be achieved in human subjects for ethical reasons. These studies enable us to better understand if a toxic dose threshold exists, and this can inform clinical efforts with respect to the maximum number of cumulative doses that can be administered in human subjects	Absorption, distribution, metabolism, and excretion parameters in animals often differ from those in humans, which can limit the generalizability of these results. Neurologic and nonneurologic testing of animals can be less sensitive to subtle findings when compared with equivalent clinical tests in humans. Certain mammals (rats) have more primitive brain structures, which may limit the detection sensitivity of some clinical findings
Are there common molecular mechanisms and clinical manifestations between chronic gadolinium retention and NSF?	Animal studies using both clinically equivalent and supradiagnostic doses to study changes in immune function, molecular expression of various architectural proteins associated with NSF, and histopathologic changes in GBCA-exposed animals	Preliminary data may suggest the existence of an NSF-like condition in animals. Follow-up experiments using a large multiagent study are needed to determine if these molecular and cellular changes occur with all or only some GBCA and if these changes have a dose-limiting threshold	Histologic and laboratory analyses may be expensive

Note.—See Table E1 (online) for complete roadmap table. GBCA = gadolinium-based contrast agent, NSF = nephrogenic systemic fibrosis.

Table 4: Clinical Research Roadmap for High-Priority Items

Knowledge Gap	Approach/Methods	Comments	Feasibility/Limitations
	Absorption, Distribution, Metabolism, and Excretion		
What is the long-term biodistribution of intravenously administered GBCA?	Characterize the biodistribution of each GBCA over time in all organs extending well beyond 24 hours to the point when gadolinium tissue levels either stabilize or reach the limits of quantitation. Systematic tissue studies using biopsy and surgical specimens or autopsy samples could be planned and performed to contribute to our knowledge of gadolinium behavior throughout the body. This would be most effectively done as part of a coordinated multicenter study	GBCA pharmacokinetics beyond 24 hours in humans are poorly understood and need to be studied for each GBCA to define normal long-term human quantitation. Disease, age, sex, pregnancy, and drug or dietary interactions may influence GBCA long-term biodistribution	Limited availability of cadaveric tissues, especially from unconfounded samples exposed to only one GBCA and from samples exposed to a wide range of doses, make this challenging. Time between contrast agent exposure and death will be a confounding variable
Define potentially altered dynamics in vulnerable populations	Prospective or retrospective assessment of the long-term concentrations of gadolinium in these populations using ICP-MS (blood, urine, CSF) and/or XRF (bone) and measurement of gadolinium in cadaveric samples with ICP-MS in tissues not easily collected or measured in vivo	Assess vulnerable populations for possible side effects. These include *(a)* infants and children exposed in utero via maternal GBCA administration; *(b)* subjects with increased bone resorption, such as elderly women with osteoporosis and patients with renal osteodystrophy undergoing dialysis; and *(c)* patients with excess cations that can promote transmetallation, including those with iron overload and those taking cation-rich nutritional supplements, including zinc, manganese, iron, copper and lanthanides	Limited availability of cadaveric tissues, especially from unconfounded samples exposed to only one GBCA and from samples exposed to a wide range of doses make this challenging. It may be difficult to find a sufficient number of patients in some vulnerable populations. It may be difficult to extricate the cause of symptoms (disease vs GBCA-driven symptoms) in some vulnerable populations (eg, patients with multiple sclerosis). Prospective studies on smaller vulnerable populations may not be feasible because of sample size limitations and/or assessment of clinical outcomes in some selected populations (eg, pediatric population).
Standardize and validate gadolinium and GBCA tissue measurement methods and quality assurance procedures	Prospective or retrospective collection of body fluids. Perform validation studies (range of test linearity, accuracy, precision, carry-over, etc) on samples for which no current approved values have been determined. Develop normal reference ranges for all human tissues/fluids	Although gadolinium can be detected in the urine in patients for months, or possibly even years, after GBCA administration, the expected range of gadolinium in urine is not known and needs to be systematically studied. Gadolinium in serum, although considerably lower in concentration than gadolinium in urine, is another potential source for gadolinium monitoring that may be easier to obtain than 24-hour urine concentrations and should also be studied as a possible monitoring technique. Specimen collection, storage, and procedures for avoidance of contamination together with standardized measurement protocols need to be established	Number of laboratories currently certified to perform trace metals analysis on human tissues is very limited

Table 4 *(continues)*

Table 4 *(continued)*: Clinical Research Roadmap for High-Priority Items

Knowledge Gap	Approach/Methods	Comments	Feasibility/Limitations
	Speciation		
What chemical forms of gadolinium are found in tissues and body fluids?	Prospective (body fluids) and retrospective cadaveric (organ tissues) studies using multiple speciation techniques (Table 2)	May help inform studies of toxicology or clinical manifestations, as it will enable identification of which forms are potentially toxic to cells and organisms	Fixation and/or homogenization of tissues may alter the stability of the retained forms of gadolinium in tissue samples
	Tissue Retention		
Are all GBCAs retained in human CNS tissue?	Retrospective cadaveric (organ tissues) studies using ICP-MS, electron microscopy, and/or XRF. Retrospective review of prospectively acquired data of existing large study data (eg, Mayo Clinic Study on Aging) or prospective multinational consortium pooling MRI studies	Early data suggest gadolinium is retained in CNS tissue after GBCA exposure, but many of these studies are limited in sample size. Existing data sources (ADNI-like registry, Mayo Clinic Study on Aging) could be used to determine extent of T1 signal changes from retrospective review of prospectively acquired data. Large data sets could be analyzed by using machine learning and automated segmentation methods to automatically calculate regions of interest and identify other areas of gadolinium retention	Limited availability of cadaveric tissues, especially from unconfounded samples exposed to only one GBCA and from samples exposed to a wide range of doses, makes this challenging. MRI techniques and analysis must be standardized so that results between centers are comparable
To what extent does gadolinium accumulate in tissues other than CNS?	Retrospective cadaveric (organ tissues) studies using ICP-MS, electron microscopy, and/or XRF	Early data suggest gadolinium is retained in many tissues after GBCA exposure; however, the scope and extent of this retention phenomenon is still relatively undefined. Such information could aid in understanding the biodistribution of these retained species and toxicologic potential	Limited availability of cadaveric tissues, especially from unconfounded samples exposed to only one GBCA and from samples exposed to a wide range of doses, makes this challenging
Are there clinical or demographic factors that predispose patients to gadolinium retention?	Retrospective review of prospectively acquired data using "big data" from existing data sources, such as Multi-Ethnic Study of Atherosclerosis, Framingham Study, Mayo Clinic Study of Aging, etc	Identify clinical and demographic variables that are associated with greater gadolinium retention vis-á-vis greater T1 signal change	Analysis limited by quality and quantity of existing data
How is gadolinium entering CSF?	Multicenter prospective study of brain MRIs, including standardized protocol of T1 and T2 fluid-attenuated inversion recovery imaging of the brain at multiple time points, as well as short T2 sequences and susceptibility imaging. Imaging study could be paired with measurement of gadolinium in CSF in selected patients who underwent lumbar puncture after MRI. Blood and urine samples could be useful as well to characterize the biodistribution in these patients. Ideally, the study will address multiple GBCAs and in different patient populations (adults, children, vulnerable populations). Retrospective review of already performed studies that had multiple end points for any reason would also be a possible databank for assessment of retention	Preliminary data reveal that gadolinium enters the CSF via the blood CSF barrier; however the biodistribution and persistence of gadolinium within this space long-term remain largely undefined. Sporadic observations of inconsistent T1 shortening of the CSF and vitreous humor of some patients suggest heterogeneity in the magnitude of gadolinium flux into the CSF that could be due to clinical, laboratory, or other factors that could help better define at-risk populations. These data could also help in better defining the mechanisms of how gadolinium agents may potentially transgress the blood-brain barrier	Standardization of MRI protocols and clinical laboratory practices could limit the number of participating institutions. A centralized laboratory will be needed to measure gadolinium level to minimize confounding bias. A centralized biospecimen repository could be helpful in sustaining a long-term research program on these valuable samples

Table 4 *(continues)*

Table 4 *(continued)*: Clinical Research Roadmap for High-Priority Items

Knowledge Gap	Approach/Methods	Comments	Feasibility/Limitations
		Clinical Manifestations	
Are there measurable human clinical manifestations (neurologic or nonneurologic) due to GBCA exposure, retention, or both?	Prospective observational controlled studies adequately powered to uncover uncommon and subtle effects (phase IV studies)	Need to control time from last administration and dosing schedule. Would provide data about frequency, differences in GBCA, whether a dose-dependent threshold exists, and patient factors. Include input from toxicologists to inform study design and to help establish risk tolerance. Identify a normal population for screening (for example, women undergoing breast cancer screening or men undergoing prostate cancer screening without known CNS abnormality) and compare with a healthy unexposed population using standardized neurologic assessments.	Cost and time depend on population and frequency and severity of clinical signals. Consider adaptive study design. Need to define risk threshold a priori to inform power calculation. Use other study designs to inform hypotheses. Use of screening populations could increase their anxiety regarding use of GBCAs in screening. Vulnerable populations, such as children, will need to be specifically studied with long-term outcome analysis.
…	Patient-reported registries (including the already self-identified patients) to identify patients who associate clinical manifestations with GBCA exposure. Can be used to inform hypotheses in other study designs and to identify subjects for possible accrual into prospective blinded randomized trials.	Include input from immunologists to account for possible immune-related interactions with GBCA. Detailed standardized physical examinations of patients are needed.	Study design likely will not inform causality.
…	National registries administered by American College of Radiology or other agency of subjects undergoing MRI with and without GBCA exposure.	Can accrue large numbers of patients. Analysis will need to control for the indications for GBCA exposure. Machine learning could be used to identify unexpected symptoms.	May be difficult to incentivize site participation and adequate follow-up. Need to define risk threshold a priori to inform power calculation. Registries that include GBCA-exposed patients using retrospective exposure histories will increase efficiency but decrease accuracy. Registries of GBCA-naïve subjects will be less biased but may take a decade or more to inform the hypothesis.
What is the risk benefit of each GBCA in clinical use?	In silico risk benefit model created from the most up-to-date clinical and scientific evidence (retrospective and prospective) regarding the use of GBCAs, incidence of adverse events, and quantification of benefits (clinical utility, indications, etc)	The benefit-risk balance of each GBCA remains largely unknown and requires quantification with well-accepted risk-benefit models. These data will help guide clinical and regulatory policies, as they will help us understand the magnitude of the potential risk of retention and juxtapose this to the benefits to help determine when or if risks of retention outweigh benefits. Such a model should be generated for each approved GBCA.	Variables available to these models may be limited for some GBCAs that have less market penetration or more limited clinical use. Risk models might be different for different populations, such as children.

Table 4 *(continues)*

Table 4 *(continued)*: Clinical Research Roadmap for High-Priority Items

Knowledge Gap	Approach/Methods	Comments	Feasibility/Limitations
Are there measurable adverse outcomes from GBCA exposure in vulnerable populations (elderly, pediatric populations, specific disease population)? If so, what risk mitigation strategies are appropriate to minimize the risk in these populations?	Retrospective and prospective studies	Assess vulnerable populations for possible side effects. These include infants and children exposed in utero via maternal GBCA administration. Also subjects with increased bone resorption, such as elderly women with osteoporosis and patients with renal osteodystrophy undergoing dialysis. Additionally, patients with excess cations that can promote transmetallation, including patients with iron overload and those taking cation-rich nutritional supplements, including zinc, manganese, iron, copper, and lanthanides.	May be difficult to find a sufficient number of patients in some vulnerable populations. May be difficult to extricate cause of symptoms (disease vs GBCA-driven symptoms) in some vulnerable populations (eg, patients with multiple sclerosis). Prospective studies on smaller vulnerable populations may not be feasible due to sample size limitations and/or assessment of clinical outcomes in some selected populations (eg, pediatric population).

Note.—See Table E2 (online) for complete roadmap table. ADME = absorption, distribution, metabolism, and excretion; CSF = cerebrospinal fluid; GBCA = gadolinium-based contrast agent; ICP-MS = inductively coupled plasma mass-spectrometry; NSF = nephrogenic systemic fibrosis; XRF = x-ray fluorescence.

immunologic effect of gadolinium exposure and symptoms, immunologists might provide useful insights. Finally, toxicologists with expertise in low-concentration population exposure of a potentially toxic substance should be consulted to better inform these research efforts.

Knowledge Gaps and Prioritized Research Roadmap

Given the importance of the subject matter and the clinical utility of GBCAs, it is important not only to identify the knowledge gaps in this area, but also to guide collaborative research. The participants in the workshop formulated a roadmap to help guide future animal (Table 3, Table E1 [online]) and clinical (Table 4, Table E2 [online]) studies. Standardization and validation of gadolinium and GBCA tissue measurement methods and quality assurance procedures is crucial to these efforts.

Conclusion

The greatest priority for the research roadmap is to understand if gadolinium retention is causally associated with clinical manifestations, as this knowledge will help direct and define the urgency of subsequent research efforts. In spite of more than 30 years of use of GBCAs, important information about the biodistribution and tissue interactions of each GBCA in clinical use remains unknown. It is clear that gadolinium retention in a number of tissues, including bone, skin, and brain, beyond 24 hours may occur with all types of GBCAs, although the magnitude of observed retention is greater with linear GBCAs than with macrocyclic GBCAs. The observed signal intensity changes in the brain account for only some of the retained gadolinium in the brain and other tissues. The research needed must include consideration of the importance of shorter-term retention (<1 month) and longer-term retention in different organs.

Not yet known is the extent, mechanism, chemical form, and clinical implications of chronic gadolinium retention for each GBCA in the general population and in vulnerable populations, such as children and those with relevant comorbidities that may be at higher risk for potential retention. These unknowns call for more systematic research and form the basis of this research roadmap to improve our understanding of gadolinium retention and its clinical importance.

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