Gadolinium Toxicity
A Survey of the Chronic Effects of Retained Gadolinium from Contrast MRIs

Plus Updated Gadolinium Retention Information

This is a follow-up to *Gadolinium Toxicity: A Group Self-Study of Retained Gadolinium from Contrast MRIs* which provided evidence of retained Gadolinium from Contrast MRIs in study participants with no history of renal impairment. Readers of the aforementioned Study wanted to know what symptoms the participants were experiencing. The results of our Symptom Survey show high levels of commonality in the participants' chronic symptoms of Gadolinium Toxicity.

Updated Gadolinium Retention test result information is also presented. The updated graphs show an even stronger pattern of Gadolinium urine levels based on the number of months since the participant's last Contrast MRI.

Information and conclusions presented here should not be interpreted as medical advice.

The conclusions are based on a small sample and suggest that a larger study should be conducted. Symptoms presented were obtained from a survey completed by respondents. The urine test results are as reported by participants normalized to a common measuring unit. No attempt is made to determine what, if any, level of Gadolinium, is safe to remain in the body.

All participants consented to inclusion of their test results and survey responses. The authors, two of the participants, take sole responsibility for the content of this document.

Sharon Williams and Hubbs Grimm

Team of Patient Advocates
April 2, 2014

We would first like to thank the people who responded to the original Study for their questions and insight into the best approach to illuminate this medical issue. The authors would also like to thank the participants for sharing their test results and completing the Symptom Survey. Without their participation, this report would not have been possible.

Background

Gadolinium-Based Contrast Agents (GBCAs) are administered intravenously to enhance images of abnormal tissue on MRI and MRA. GBCAs are generally thought to be safe to use; however, retention of Gadolinium is known to have serious consequences. The medical community and government agencies have recognized the toxicity of retained Gadolinium from GBCAs as the primary contributor to the development of Nephrogenic Systemic Fibrosis (NSF) in patients with compromised renal function.

While much has been written about the evidence and effects of retained Gadolinium in the renally impaired, very little has been published regarding findings in patients with normal renal function. Consequently, clinicians believe that patients with normal renal function do not retain Gadolinium. Retained Gadolinium is not normally considered as a possible cause of patients' symptoms, and it is not tested for when making medical diagnoses, which can result in underreporting of Gadolinium-related health issues.

As members of a support group comprised of people who have suspected Gadolinium Toxicity, we personally know others with normal renal function that have both evidence of retained Gadolinium and unexplained symptoms after contrast procedures. In an attempt to bring attention to the issues related to Gadolinium retention in patients without severe renal disease, two self-study efforts were undertaken.

The original *Group Self-Study of Retained Gadolinium from Contrast MRIs* (Study), released on October 1, 2013 showed urinary levels of retained Gadolinium from GBCAs well beyond expectations in patients with no history of renal impairment. An update to the results of the Study reflecting new data points is contained in Appendix 1 - Gadolinium Retention Study Update. While the Study provided new insight into Gadolinium retention, its results are consistent with other published works as described in Appendix 2 - Related Research.

This second self-study effort reports on the Chronic Effects of Retained Gadolinium from Contrast MRIs in patients with normal renal function and whose urinary Gadolinium levels are reported in the Gadolinium Retention Study Update (Appendix 1).

Scope of Effort

The original *Group Self-Study of Retained Gadolinium from Contrast MRIs* (Study) was received by many across the medical industry with keen interest. Questions from those professionals focused on the symptoms reported by the participants, timetables for onset of symptoms, duration of symptoms, and dosage. Recognizing the retrospective nature of this study and the dependence on patient reported information, we provide some answers to these questions. By way of a survey, we report on the chronic symptoms experienced by patients exposed to Gadolinium-Based Contrast Agents (GBCAs) and whose urine test results are also reported.

The passage of time has resulted in changes to the database of urine test results for Gadolinium retention. Most notably, new results mapped closely to the trend line established in the original Study. A new trend line developed based on all current test results is even more accurate, now explaining 79% of the distribution of test results. Updated graphs of Gadolinium Retention Test Results are provided in Appendix 1.

Symptom Survey Methodology

The Symptom Survey was developed and administered using Survey Monkey. Questions in the survey were constructed to formalize and quantify symptoms discussed by people represented in the database. Most of the questions were of a multiple choice, multiple selection nature, always providing "None" as a choice and "Other", which allowed participants to describe additional symptoms. Questions were also included to determine the onset of symptoms and to allow participants to prioritize their symptoms. A listing of the Survey questions is in Appendix 3.

The Survey was completed between January 14, 2014 and February 1, 2014 by 17 people whose urine test results are presented in Appendix 1. Their Survey responses are presented here in a manner that will preserve the privacy of individual health information.

Symptom Survey Results

We present below the findings of the Symptom Survey.

Symptom Start

- For 100% of the patients, the symptoms started within the first month following contrast MRI. 59% reported their symptoms started almost immediately or on the same day. In some cases the onset of symptoms was subtle.

Symptom Duration

- The time from last contrast administration to completion of the survey ranged from 2 months to 6 years, with an average of 28 months.
- All respondents continue to have chronic symptoms. For 6 of the respondents, symptoms continue more than 3 years after their last contrast MRI.

Symptom Severity

- 65% sought emergency care for their symptoms reported here.

Pain

- All 17 patients cited "Pain" as a Chronic Symptom with 13 identifying "Ache (dull, continuous pain)". 11 identified "Burning, numbness, tingling, or prickling sensations (Paresthesia)". "Deep Bone Pain" and "Electric-like feelings" were each identified by 10 patients.
- For location of the pain, 14 identified their Extremities, 11 identified Hips, and 11 identified Joints. Interestingly, 8 people identified pain in their Ribs, and 7 of the 8 had multiple Contrast MRIs
- For all patients, the pain began within a month of their last contrast MRI and for 14 of the patients, this early pain included "Burning, numbness, tingling, or prickling sensations (Paresthesia)".
- 14 people identified Pain as one of their top 3 priorities; of these, 10 cited Pain as their 1st priority.

Dermal Changes

- 12 of the patients identified Dermal Changes as a Chronic Symptom, with 11 of these patients locating Dermal Changes on their Extremities.
- Of the 12 patients identifying Dermal Changes, 8 cited "Tight Skin", 7 cited "Skin Lesions (ulcers, papules, macules, nodules or other lesions)" and 7 identified "Discoloration (hyperpigmented, mottled, blotchy)" as Chronic Symptoms.
- Of the 12 patients identifying Dermal Changes as a Chronic Symptom, 11 had Dermal Changes appearing within one month of their last contrast MRI.
- Of the 5 patients who did not identify any Dermal Changes as a Chronic Symptom, 3 had a rash initially.
- "Dermal Changes" was the 3rd highest Prioritized Symptom with 6 identifying Dermal Changes as their 2nd highest priority Chronic Symptom.

Muscle Symptoms

- 15 of the 17 patients identified Muscle Symptoms as a Chronic Symptom. More specifically, 11 identified "Twitching - Small, local, rapid contractions" while 9 of those with Muscle Symptoms identified "Weakness - major loss of strength" as a Chronic Symptom.
- For 14 of the patients with Chronic Muscle Symptoms, their muscle problems began within one month of their last contrast MRI.

Other Symptoms

- 13 patients experience Chronic Ocular Symptoms (Worsening Vision - 8, Dry Eyes - 8, Bloodshot eyes - 8)
- 11 report Cognitive Symptoms - It was the Second highest Prioritized Symptom, with 3 selecting it as their highest Priority.
- 11 patients identified Chronic, new onset ENT Symptoms (Ringing in ears - 8, Swallowing Problems - 6, Voice Problems - 5)
- 10 report Low Body Temperature
- 10 report Hair Loss
- 10 report Itchy Skin
- 9 report Balance Problems
- 9 report Swelling of Extremities

Write-in Symptoms

The "Other" selection in multiple choice questions and "Comment Boxes" allowed participants to describe symptoms not provided for in the selections. The results for these questions were examined carefully to determine if a common symptom would appear that was not otherwise covered. Only one write-in symptom was mentioned repeatedly.

- Fatigue, often described as chronic fatigue, was mentioned by 8 people in the free-form "Other" and "Comment Box" areas.

Symptom Progress

In looking at the onset and progress of specific symptoms, we found a significantly higher number of people citing the following symptoms as Chronic as compared to the number citing them as Initial Symptoms:

- Tight Skin went up 100%, from 4 to 8 patients
- Low Body Temperature went up 67%, from 6 to 10 patients
- Ringing in Ears went up 60%, from 5 to 8 patients
- Worsening Vision went up 60%, from 5 to 8 patients

Number of Contrast Administrations

The number of contrast MRI administrations was chosen as the only metric that was available to address the dosage question. The participants broke down into two groups as follows:

- Of the 17 respondents, 7 had only a single contrast administration, with 4 having had that contrast administration within the last year.
- Of the 10 respondents with multiple contrast MRIs, the number of contrast administrations ranged from 2 to 8, with 6 patients having had 5 or more contrast MRIs. The length of time since the last contrast administration ranged from 2 months to 6 years, with an average of 3 years.

- While the chronic symptoms reported are occurring after respondents' latest contrast MRI, 9 of the 10 who have had multiple contrast administrations believe they began to experience milder versions of their symptoms after prior contrast MRIs.

We looked at the difference in the percentage of patients in each group selecting a particular response. The following bullets describe those chronic conditions in which there was a difference of at least 40 percentage points between the two groups. We do not know whether these differences between the response rates of each group are significant.

- 80% in the Multiple Contrast MRI group rated their Pain as their highest priority chronic symptom compared to 29% of those with a single contrast administration.
- 70% in the Multiple Contrast MRI group have Dry Eyes, compared to 14% of those with a single contrast MRI.
- 70% in the Multiple Contrast MRI group developed Tinnitus, compared to 14% of those with a single contrast MRI.
- 70% in the Multiple Contrast MRI group identified Pain in their Ribs, compared to 14% of those with a single contrast MRI.

In their own words

After having the respondents prioritize their symptoms, we asked them to describe their symptoms in their own words. Excerpts from some of their descriptions are provided here to show the impact these chronic symptoms have on their daily lives.

My highest priority is daily pain and the twisting/squeezing tightness of craniofacial tendons and ligaments. The skin on my scalp feels like an open, gaping wound at the slightest touch. The neuropathy and not having a sense of where my arms and hands are, is just as painful.

The pain is burning and tingling. Constant in feet but most impacting in ribs, abdomen and diaphragm. Burning impacts muscle operation.

Constant pain and pressure inside my head. Short-term memory and concentration is getting worse. My low body temperature causes me to feel like I am freezing from inside my bones outward. It affects my ability to function normally and disrupts my daily life.

Pain = Hip bones, leg muscles. Weak arms & legs, abnormal sensations. Effect is debilitating to daily life & what I can do.

The ringing in ears is constant.

Both the fatigue and reduced cognitive function affect my job. My life has changed dramatically.

I have bilateral dependent pedal paresthesias; the sensations are burning, tingling, numbness and sometimes a scintillating paroxysm. Standing still is difficult, walking is better.

My twitching seems to cause atrophy more and more. All functioning is almost at a standstill.

Pain in my hands, legs is 24 hr. Stiffness, drop things, can't do anything repetitive, can't sit long either. I had a career, that's gone! I can't even squeeze a cloth too much or else my hand pain increases and hands freeze.

Hand joint stiffness (namely thumb) and an overall inflammation in the body have given me a continued fatigued feeling , red eyes constantly, and sensitivity to specific foods that was not present prior.

Cognitive issues have changed and gotten worse - inability to concentrate, impaired reasoning ability, inability to crunch numbers as I did prior to MRI with great ability.

My lower legs, from mid calf down have a tight feeling, they burn off and on, my left ankle aches some. My left arm, wrist area burns, and overall my skin feels hypersensitive.

My life seems to have been permanently altered by my exposure to gadolinium. Though I continue to function as well as possible, my symptoms are too severe to ignore, and they have been a "game changer."

Summary of Survey Results

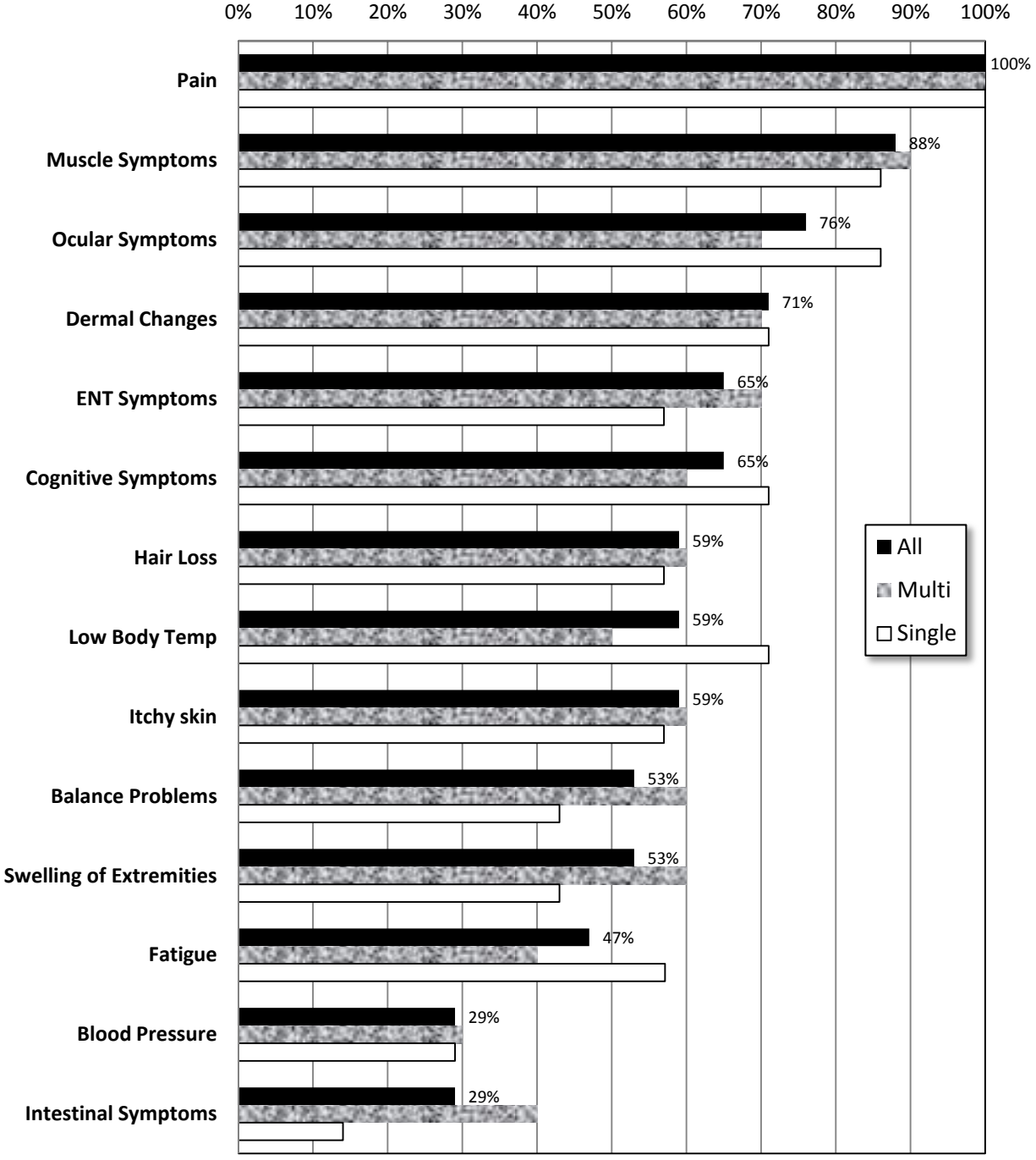
The Survey results demonstrate the following commonality of symptoms from GBCA exposure:

- Patients' symptoms are not going away; they are chronic.
- In all cases, symptom onset was within one month of the last contrast MRI. In some cases the symptoms were subtle at the time.
- Pain is present for 100% of patients and was reported as the highest priority chronic symptom by 59% of patients.
- Muscle Symptoms were reported by 88% of the patients.
- Ocular Symptoms were reported by 76% of the patients.
- Dermal Changes were reported by 71% of the patients.
- Cognitive Symptoms were reported by 65% of patients
- ENT Symptoms were reported by 65% of the patients.
- Low Body Temperature, Hair Loss, and Itchy Skin were each reported by 59% of the patients.
- Balance Problems and Swelling of Extremities were each reported by 53% of the patients.

The graph on the following page shows the percentage of patients reporting each symptom. It shows responses of all respondents, both as a group and separately for those who had a single contrast MRI and those who had multiple contrast MRIs.

Percentage of Symptoms Reported

Showing Single and Multiple Contrast MRI Differentiation



	Pain	Muscle Symp.	Ocular Symp.	Dermal Changes	ENT Symp.	Cognitive Symp.	Hair Loss	Low Body Temp	Itchy Skin	Balance Prob.	Swelling of Extremities	Fatigue	Blood Pressure	Intestinal Symp.
All	100%	88%	76%	71%	65%	65%	59%	59%	59%	53%	53%	47%	29%	29%
Multi Contrast	100%	90%	70%	70%	70%	60%	60%	50%	60%	60%	60%	40%	30%	40%
Single Contrast	100%	86%	86%	71%	57%	71%	57%	71%	57%	43%	43%	57%	29%	14%

Questions we could not answer

As with most research, there are questions and topics that could not be answered within the scope of this effort but deserve to be presented for consideration by others.

> **What other possible causes for each person's symptoms have been ruled out by their medical care providers?** All of the Survey participants have pursued medical answers that could lead to treatment of their symptoms. A comprehensive catalogue of the related medical opinions ruling out known potential medical causes was not pursued because each participant set their own course of evaluation, and this would have provided nothing more than anecdotal information.
>
> **What other co-factors may have contributed to the symptom patterns reported?** Although there is great commonality of symptoms demonstrated by the Survey, minor differences remain in the symptom patterns. Without a complete medical history of each patient along with a consistent medical examination, we could not address the co-factors that may be involved in the clinical presentation of each patient's symptoms.
>
> **What success has been found from treatment modalities used by the Survey participants?** Each person in the Survey has had to make their own decisions for dealing with their Gadolinium Toxicity and related symptoms. Some are following traditional approaches of medical diagnosis and symptomatic relief while others are following either chelation or naturopathic methods. We are unable to address the relative success of these modalities due to their patient-controlled nature.

Combining these questions, we can report that no one has reached a level of symptom improvement or condition understanding that has caused them to stop searching, regardless of causes that have been ruled out, their personal co-factors, or the treatment approaches they have taken.

Discussions

While some might say that the symptoms reported are not specific symptoms that can be associated with a "known disease", that is precisely the point. Doctors hearing about these symptoms from a patient typically look for some known cause, and finding none, revert to treating only the symptoms, leaving the patient with the anxiety of an "unknown cause".

Others may observe that these symptoms are described on the GBCA product labeling as possible "Adverse Reactions" which, except for NSF, are thought to be temporary. However, the survey results describe chronic problems that have a major impact on people's lives, not short-term or temporary reactions. The fact that the symptoms experienced are similar to those associated with GBCAs warrants further investigation.

We have reviewed the published literature for studies relevant to our findings. Articles pertaining to finding Gadolinium from GBCAs in patients with normal renal function, symptoms of NSF patients, and toxic effects of retained Gadolinium are documented in Appendix 2 - Related Research, giving the reader the opportunity to quickly locate other related works.

To our knowledge, there has never been a published, long-term study of non-renally impaired patients to determine the possible chronic effects of Gadolinium retention after contrast MRI. If this is true, then our survey is the first to report such chronic symptoms. Until a larger study is published, these findings stand as the most and best information regarding the possible Chronic Effects of Retained Gadolinium.

Conclusion

The results of the Symptom Survey and Gadolinium Retention Update presented here should stimulate further professional investigation into Gadolinium retention in all patient populations including those with normal renal function.

Declaration of Interests

The authors are also Study participants. Our only motivation is to bring attention to the effects of Gadolinium retention in patients with normal renal function. Neither author has anything else to declare.

Appendix 1

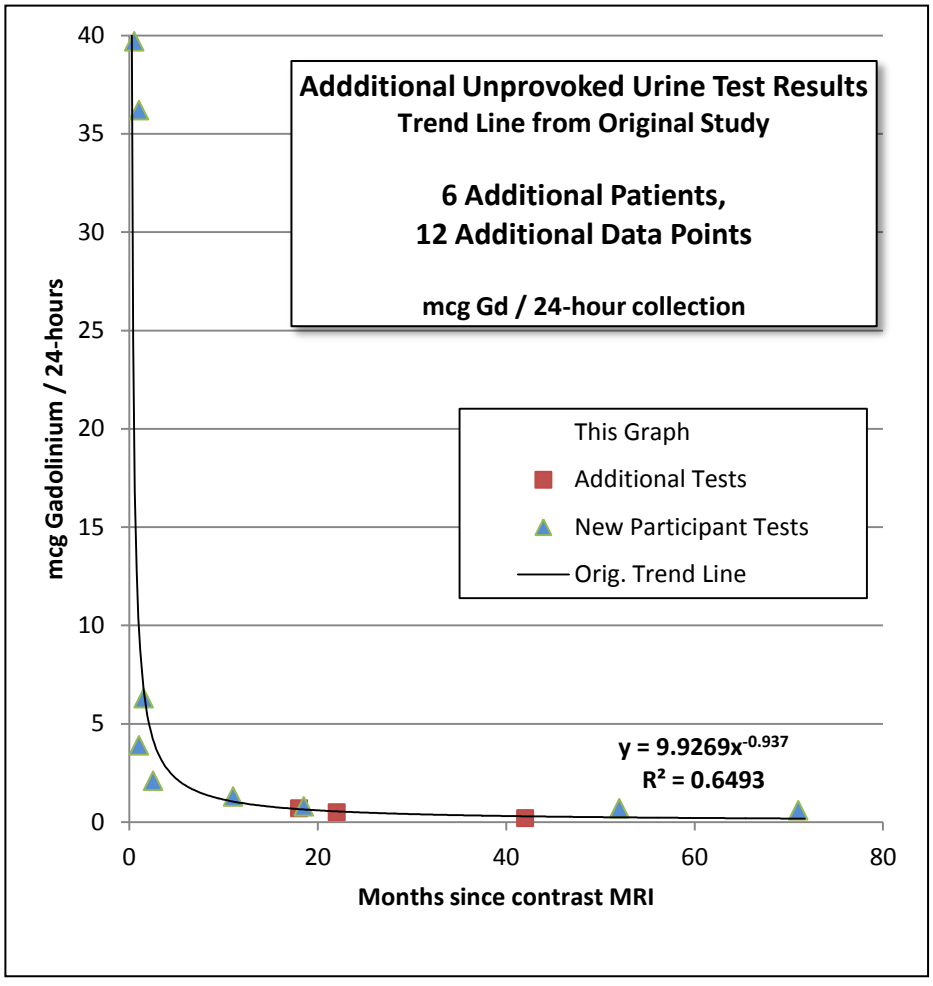
The background for this Appendix starts on October 1, 2013 when we released *Gadolinium Toxicity: A Group Self-Study of Retained Gadolinium from Contrast MRIs* (Study). This small group retrospective Self-Study of Gadolinium Toxicity examined urine test results which showed long-term retention of Gadolinium occurs in patients with normal kidney function who had contrast MRI/MRA procedures. Unprovoked and Provoked urine testing results were presented documenting the retention of Gadolinium at toxic levels long after the patient's most recent contrast procedure as compared with the expectation that all of the Gadolinium clears the body within several days. The conclusion of the Study called for medical research that would document the amount of Gadolinium being retained by patients with normal renal function and review their unexplained symptoms for possible connection to Gadolinium Toxicity.

We present the latest database of urine testing results in the same manner that the information was presented in the Study. We were unable to find any published literature showing a reference range for Gadolinium in urine for patients with normal kidney function. For purposes of comparison, we will use Mayo Clinic Labs' reference range. Its 24-hour urine test has a range of 0.0 to 0.4 mcg Gd/24-hour specimen that is collected more than 4 days after exposure to a Gadolinium-based contrast agent.

Gadolinium Retention Study Update

Since releasing the original Study, there have been several changes to our database of test results, with updated graphs shown here. The updated test results follow strongly the patterns described in the original Study, strengthening the Trend Line of test results as a function of months since last contrast administration.

Six additional people have become participants in the testing results database, and their nine test results are shown in the graph to the right. The Trend Line is from the original Study; note how close the new participants' test results are to the Trend Line, validating the prior work. Also shown on the graph are three additional test results from the original group of participants. Here too, they map nicely to the previously established Trend Line.



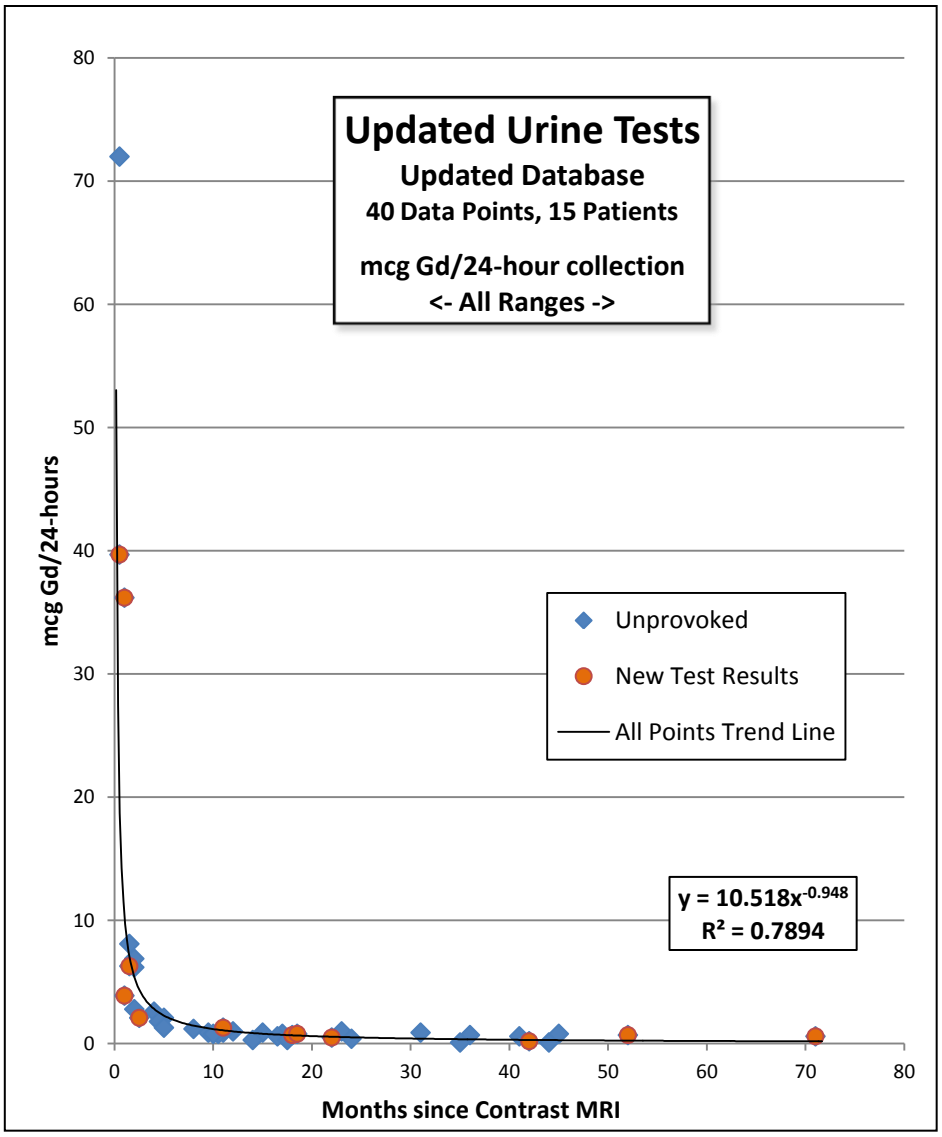
In addition to the six people with unprovoked tests who were added to the database, one person with only provoked test results was added and 3 participants left the database project (they were unresponsive to follow-up emails). Presently, the database has 40 Unprovoked test results from 15 people and 16 Provoked results from 7 people. In total, the database has 56 results from 17 different people; two of whom only have Provoked test results.

We now present briefly the updated graphs and new Trend Lines based on the updated database. The new test results are highlighted on the graphs.

The first thing to notice is that the Trend Line now has a 79% coefficient of determination as compared to 65% in the original Study. Presumably this is due to the additional test results that mapped so closely to the original Trend Line.

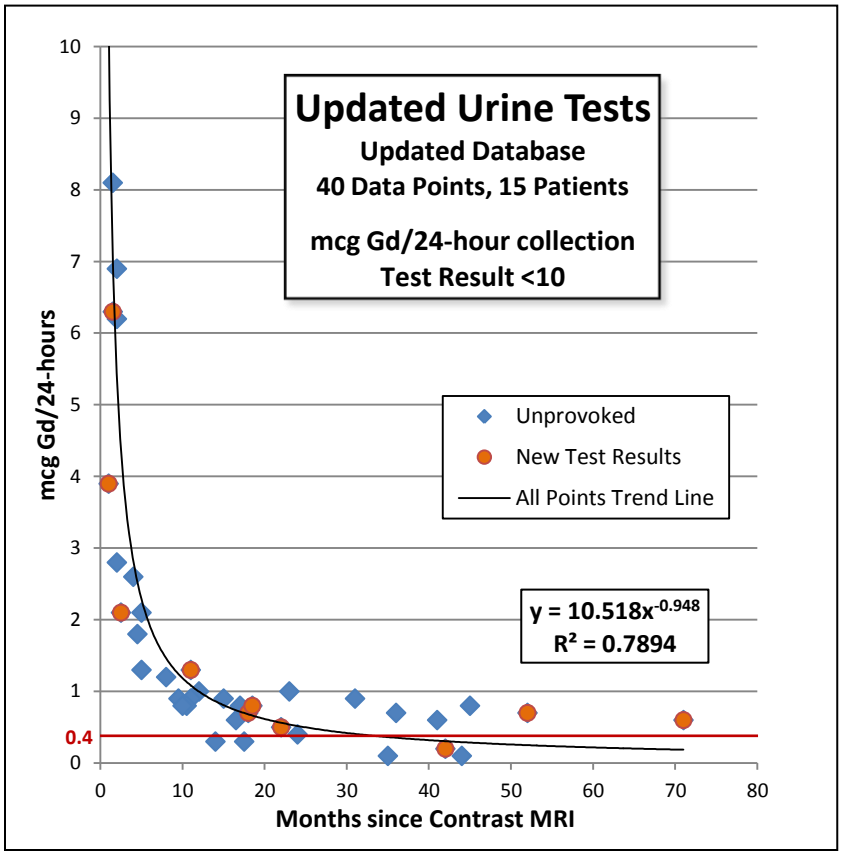
We believe this closeness of fit provides even stronger evidence that the Gadolinium is not eliminated within a few days as most presently believe.

Since the data points are so close to the axes, graphs are presented on the following page that provide more visual differentiation.

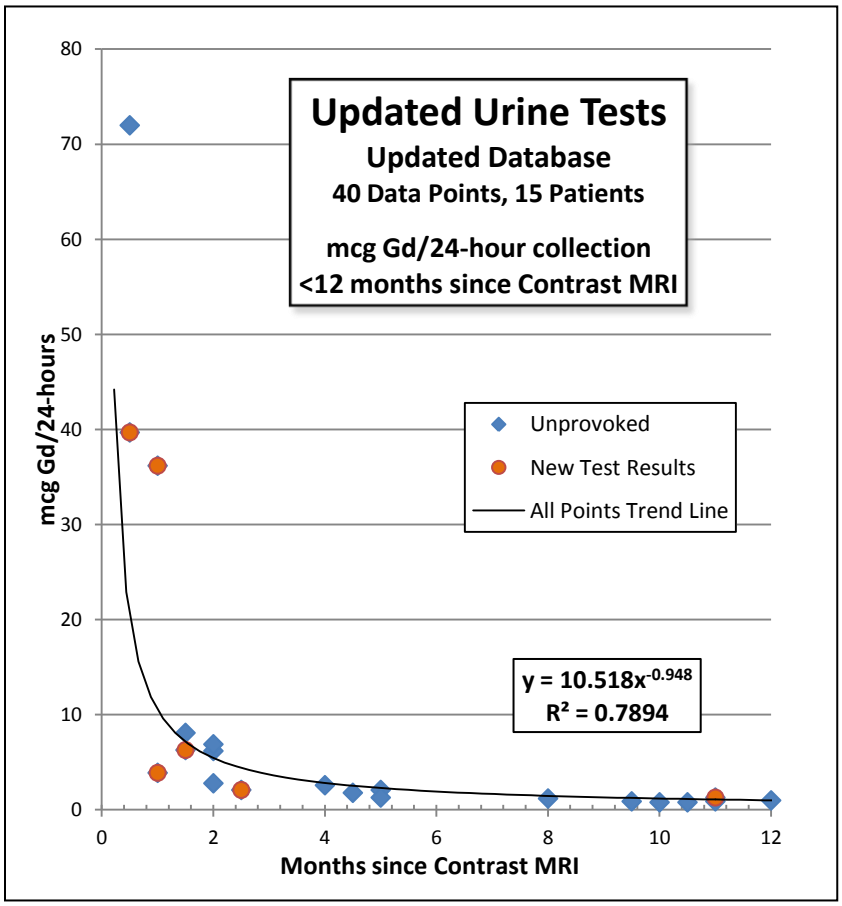


These visual expansions look more closely at the test results less than 10 mcg Gd/24-hours in the upper graph, and those results within the first 12 months in the lower graph. Both demonstrate a clear pattern of test results along the Trend Line.

Looking at these two graphs, you will see that there are no test results between 0.0 and 0.4 mcg Gd/24-hours during the first year following contrast with the lowest value being 0.8 mcg Gd/24 hours.



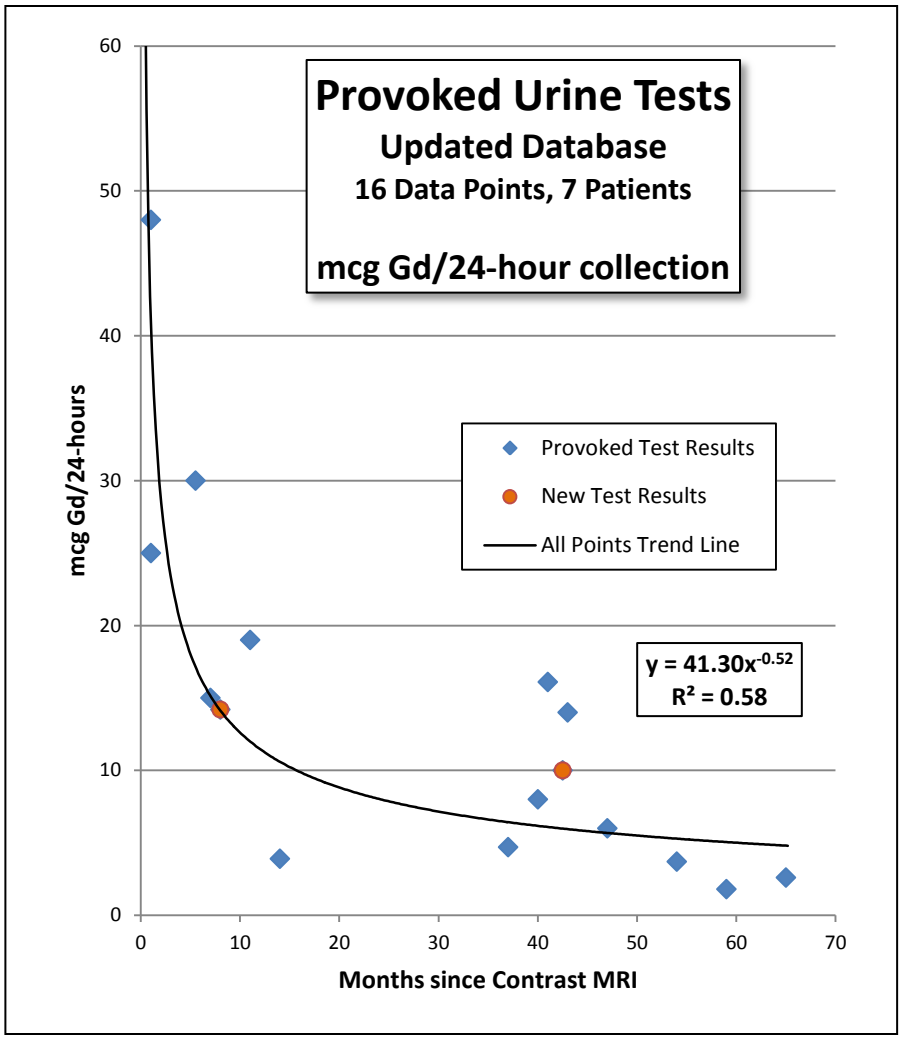
Updated graphs for Provoked test results are shown on the next page.



The graph for Provoked Urine Test results in the updated database is shown at the right. As noted in the original Study, these results show a much more dispersed pattern because of the different chelation protocols used in the tests for individual people.

The Trend Line now has a 58% coefficient of determination as compared to 33% in the original Study.

Although Gadolinium levels are generally much higher for provoked tests, they should not be compared to the Mayo [unprovoked] Reference Range. Provoked tests involve the administration of a chelating agent which has the ability to extract elements from tissue in much higher quantity than would normally be excreted in urine. We have included the Provoked graph to show that Gadolinium can be removed at higher levels long after administration of a Gadolinium-based contrast agent.



Gadolinium Retention Update Summary

Taken together, the updated Gadolinium Urine Retention Database information presented here demonstrates the following:

- The results presented in the original *Gadolinium Toxicity: A Group Self-Study of Retained Gadolinium from Contrast MRIs* were not an anomaly. Additional test results from six new people along with additional test results from people in the original Study not only mapped to the trend line of the original Study, they served to improve the goodness of fit for a new trend line including these data points.
- Urinary Gadolinium test results presented do not fit the expected low level after a few days, but instead register at significantly higher levels for extended periods of time.

In summary, the additions to the Gadolinium retention database further demonstrate that a larger study is called for.

Appendix - 2

Related Research

We believe our Survey Report is "new information" and that the Updated Gadolinium Retention Study information contained in Appendix 1 provides new evidence that Gadolinium from GBCAs is retained for long periods of time in patients with no history of renal disease. While our paper is the first to report Gadolinium Retention in 17 patients with normal renal function, previously published studies also describe patients without severe renal impairment who retained Gadolinium, some for long periods of time. Based on published literature, the symptoms reported by Survey participants are consistent with what is known about Gadolinium Toxicity. The long-term effects of retained Gadolinium are unknown.

We have summarized information from related research below.

Gadolinium in Patients with Normal Renal Function

The following published studies found evidence of Gadolinium in brain, bone and skin tissues of patients without severe renal disease:

Gibby (2004) confirmed deposition of Gadolinium in bone tissue from patients with normal renal function 4 days after exposure to a GBCA.[1]

Darrah et al (2009) confirmed that Gadolinium, introduced in chelated form, incorporates into bone and is retained for longer than 8 years post-exposure.[2]

A Mayo Clinic study by Christensen et al (2011) found detectable concentrations of Gadolinium in fresh tissue specimens taken from two control subjects with normal renal function; both patients had previous GBCA exposure, one 8 months and the other 16 months before biopsy.[3]

Xia et al (2010) found Gadolinium-containing deposits present in brain tumor biopsies of patients without severe renal disease. Insoluble deposits containing Gadolinium were found in 7 biopsies from 5 patients whose estimated GFRs were above 53 ml/min. In two cases in which more than one biopsy from the same patient was analyzed, the later biopsies after more scans had higher amounts of Gadolinium than the earlier biopsies.[4]

Kanda et al (2013) found that abnormally high signal intensity detected in two regions of the brain on unenhanced T1-weighted images was related to the number of previous Gadolinium-based contrast enhanced MRIs that had been undergone by the population of patients with normal renal function.[5]

Symptoms of NSF Patients

While we could not find a comprehensive catalogue of NSF patient symptoms, articles regarding NFD/NSF describe both symptoms and affected body systems that are similar to those reported in this paper.

Cowper SE [ICNSFR Website on March 13, 2014] reports symptoms and signs of NSF that include swelling and tightening of skin, joint contractures, and skin changes described as reddened or darkened patches, papules, or plaques. Skin may feel “woody” and resemble the texture of the peel of an orange. There may be burning, itching, or severe sharp pains in involved areas. Muscle weakness often occurs. Radiography may reveal calcification of the soft tissue. Deep “bone pain” has been described in the hips and ribs. Hand and foot swelling with blister-like lesions has been reported. Some patients have yellow papules or plaques on or near the eyes. Rapid, new onset fluctuating hypertension of unknown cause has been described prior to onset of the skin lesions.[6]

Ting et al (2003) report the first case of NFD with systemic involvement. Autopsy revealed extensive fibrosis and calcification of the diaphragm, psoas muscle, renal tubules, and rete testes. Also affected were the esophagus, lungs, kidneys, and myocardium of the left ventricle.[7]

Levine et al (2004) report 5 cases of NFD. Patients had progressive induration and stiffening of limbs. All had skin changes over affected muscles variably consisting of hyperpigmentation, erythematous patches, thickening, and tightening with a dimpled or furrowed appearance. Lower limbs were affected in all patients, with pain reported as joint pain, and burning pain in legs and/or feet. One patient had hardening of the muscles of the neck, back, arms, forearms, thighs and legs. Jaw opening was affected in two patients. All had chronic scleral injection (bloodshot eyes).[8]

Mendoza et al (2006) describe symptoms of 12 NFD patients that include: skin sclerosis and puckering, pruritus and burning, extremity swelling, difficulty swallowing, muscle induration, paresthesias or burning pain, aching or cramping, and joint flexion contractures.[9]

Kucher et al (2006) presented an NFD/NSF autopsy with fibrosis of the diaphragm and esophagus.[10]

Swaminathan et al (2008) reported unique cardiac and vascular events in NSF including sudden monocular blindness secondary to posterior ischemic optic neuropathy, limb ischemia, and recurrent cardiac arrhythmias. They presented the first evidence that NSF is associated with systemic deposition of metals including gadolinium, iron, and aluminum, with the highest quantity of gadolinium deposited in the heart, blood vessels, and skin.[11]

Mayr et al (2009), in describing the clinical spectrum of NSF, write: "In summary, the involvement of subcutaneous structures such as fascia, muscle, tendons, periarticular tissue, and joints by NSF is well established by clinical and histopathology data." [12]

Koreishi et al (2009) conducted a review of 4 NSF autopsy cases. Besides cutaneous manifestations of NSF, some had calcification and fibrosis of the dura, thyroid, and heart including cardiac conduction system. Fibrosis of the thyroid manifested clinically as hypothyroidism.[13]

Kanamalla and Boyko (2002) described progressive gadolinium diffusion into the vitreous and aqueous humors of the ocular globes, perivascular spaces, and the ventricles of the brain seen on fluid-attenuated inversion-recovery (FLAIR) MR imaging in patients with chronic renal failure.[14]

Barker-Griffith et al (2011) evaluated the previously unreported ophthalmic pathologic feature of two autopsy cases of NSF including Gadolinium deposition in the eye.[15]

Edgar et al (2010) report a case of NSF presenting as a progressive myopathy with minimal skin findings. The patient developed limb stiffness, proximal weakness, and woody muscle texture.[16]

Sanyal et al (2011) conducted an autopsy-based review of one NSF case along with a review of published literature. Insoluble Gd-phosphate deposits were detected in the skin, liver, lungs, intestinal wall, kidney, lymph node, skeletal muscle, dura mater and cerebellum of the NSF autopsy case, primarily in vascular walls. The authors believed this to be the first case to document Gadolinium deposition in brain parenchyma in NSF.[17]

Zou and Ma (2011) reviewed 408 biopsy-confirmed cases of NSF. Clinical features noted include: dermal pain, thickening and hardening, especially in lower extremities; sharp pains, burning or itching in affected areas; joint contractures or limited range of motion; “stiffness” without contractures; scleral plaque or injection. Over one-third of patients were without contractures or limited range of motion; the authors felt this suggests that these patients had a mild form of NSF.[18]

Toxic Effects of Retained Gadolinium

It is widely recognized that NSF is essentially the manifestation of toxicity of Gadolinium released from Gd-containing contrast agents.[19]

Beyond NSF, little has been published about the toxic effects of Gadolinium retention in the human body. Most of what is known about Gadolinium Toxicity comes from testing on animals.

Although the free Gadolinium ion is known to be toxic, Gadolinium is not listed as a toxic element by the CDC's Agency for Toxic Substances & Disease Registry (ATSDR). However, the symptoms reported in this paper are similar to those known to occur from exposure to other toxic metals.

Gabbiani et al (1966) found that all Rare Earth Elements (REEs) induce connective-tissue calcification at the site of subcutaneous injection. "The induction of splenic calcification after intravenous administration appears to be typical of lanthanides".[20] (Gadolinium is a lanthanide).

Spencer et al (1997) report on the toxicity of Gadolinium Chloride ($GdCl_3$) in the rat. After administration, major lesions consisted of mineral deposition in capillary beds (particularly lung and kidney). Major toxic effects were also evident in the hematopoietic and lymphoid tissues, liver, and stomach. Electron microscopy and x-ray microanalysis of the spleen and liver revealed electron-dense deposits in splenic macrophages, Kupffer cells, and hepatocytes composed of gadolinium, calcium, and phosphate.[21]

Adding et al (2001) noted in their review article that the non-complexed gadolinium ion is retained for long periods in the body. They also note that toxicity studies have indicated that gadolinium can cause several "deleterious effects".[22]

From *A Primer on Gadolinium Chemistry (2009)* – Gd^{3+} (gadolinium) has an ionic radius very nearly equal to that of Ca^{2+} (calcium). This is one of the reasons why Gd^{3+} is so toxic in biological systems – Gd^{3+} can compete with Ca^{2+} in all biological systems that require Ca^{2+} for proper function and, in doing so, Gd^{3+} binds with much higher affinity.[23]

Vassallo et al (2011) found that mercury, lead and gadolinium, even at low doses or concentrations, affect vascular reactivity.[24]

Feng et al (2010) offered new insights into the mechanism of Gd-induced neurotoxicity. The results suggest that Gadolinium causes neuron cell apoptosis primarily by inhibiting mitochondrial function and inducing oxidative stress.[25]

Xia et al (2011) demonstrated that Gadolinium-induced cytotoxicity in neurons occurs via oxidative injury and endoplasmic reticulum (ER) stress-related signal transduction.[26]

Ibrahim et al (2006) present a review of heavy metal poisoning including clinical presentation. The most commonly involved organ systems include central nervous, gastrointestinal (GI), cardiovascular, hematopoietic, renal, and peripheral nervous systems.[27]

Medscape (2013) provides information on the clinical presentation of Mercury Toxicity including many of the symptoms reported in this paper.[28]

Liu et al (2013) review the neurotoxicity and biomarkers of lead.[29]

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Appendix - 3

Survey Questions

Question	Response Choices (where applicable)
Date of last Contrast MRI: Enter the date of your last contrast MRI. If you only know the month, you can guess at the day of the month.	
Start of Initial Symptoms: Select the timeframe after your last contrast MRI that your initial symptoms started. Note that there are questions later to have you identify your specific symptoms.	Almost immediately the same day or the next day Within 1 week Within 1 month Within 6 months Within 1 year Longer than 1 year
Immediate acute symptoms following your last MRI: If you experienced acute problems within a day or two of their last contrast MRI and sought medical attention, please select the symptoms you experienced. If you did not, select "None of the Above".	Cognitive Issues Extreme Fatigue Flu-like Symptoms (fever, nausea, stomach or intestinal problems) Headache Shortness of breath None of the Above Visited Emergency Room or Urgent Care Other (please specify)
INITIAL SYMPTOMS - Pain Like Symptoms: Please select those pain-like symptoms that you experienced during the Initial Symptoms Timeframe. Select only those from your notes or reported to a medical professional.	Ache (dull continuous pain) Burning, numbness, tingling, or prickling sensations (Paresthesia) Deep Bone Pain Electric-like feelings Pain was severe enough to visit the Emergency Room or seek Urgent Care None of the Above Other (please specify)
INITIAL SYMPTOMS - Location of Pain: Select the locations of any pains you experienced initially.	Chest Extremities (Feet, Legs, Hands, Arms) Head Hips Joints Ribs None of the Above Other (please specify)
INITIAL SYMPTOMS - Dermal Changes: Select from the following all changes to your skin during the Initial Symptoms timeframe. If you did not have any skin changes, select "None".	None Discoloration (hyperpigmented, mottled, blotchy) Rash Skin Lesions (ulcers, papules, macules, nodules or other lesions) Tight Skin Thickened Tissue (Includes Induration or Tethering) Other (please specify)

INITIAL SYMPTOMS - Location of Dermal Changes: Select the locations of any skin issues you experienced initially.	Extremities (Feet, Legs, Hands, Arms) Head (Face, Scalp) Torso None of the above Other (please specify)
INITIAL SYMPTOMS - Muscle Issues: Select from the following if you had Muscle issues initially. Select "None" if appropriate.	None Spasms - sudden, involuntary contraction Twitching - Small, local, rapid contractions Weakness - major loss of strength Other (please specify)
INITIAL SYMPTOMS - ENT (Ear, Nose and Throat) Problems: Select from the following if you had ENT issues initially. Select "None" if appropriate.	None Ringing in Ears (Tinnitus) Swallowing Problems (Dysphagia) Voice Problems including hoarseness Worsening of Hearing Other (please specify)
INITIAL SYMPTOMS - Ocular Issues (eyes): Select from the following if you had Ocular issues initially. Select "None" if appropriate.	None Dry Eyes Eye Redness (Sclera/white of the eye) Scleral Plaques/Yellowing Worsening Vision Other (please specify)
INITIAL SYMPTOMS - Other Initial Symptoms: Select all the symptoms below that you experienced during the Initial Symptoms timeframe.	Balance Issues Blood Pressure Issues (High, Low, Labile) Cognitive Issues (brain fog, difficulty concentrating, etc.) Hair Loss Itchy skin Intestinal Problems Low Body Temperature Swelling of Extremities (Edema) None of the Above Other (please specify)
INITIAL SYMPTOMS - Emergency Treatment: Did you require treatment at an Emergency Room at any time during the Initial Symptoms timeframe? If so, please explain. If not, enter "No"	Open-Ended Response
INITIAL SYMPTOMS: Progress of Initial Symptoms: How have the symptoms you experienced in the Initial Symptoms Timeframe progressed up to today. You may check more than one box.	Some Initial Symptoms continue to get worse Some Initial Symptoms have gone away Some Initial Symptoms continue at the same level Some Initial Symptoms happen sporadically All Initial Symptoms have gone away All Initial Symptoms are worse Other (please specify)
OTHER COMMENTS REGARDING INITIAL SYMPTOMS A response is not required for this question. Use only if you believe you have a significant INITIAL SYMPTOM that was not covered in the above questions.	Open-Ended Response

CHRONIC SYMPTOMS - Pain Like Symptoms: Please select those pain-like symptoms that you presently experience. Select only those from your notes or reported to a medical professional.	Ache (dull continuous pain) Burning, numbness, tingling, or prickling sensations (Paresthesia) Deep Bone Pain Electric-like feelings Pain was severe enough to visit the Emergency Room or seek Urgent Care None of the Above Other (please specify)
CHRONIC SYMPTOMS - Location of Pain: Select the locations of your pains.	Chest Extremities (Feet, Legs, Hands, Arms) Head Hips Joints Ribs None of the Above Other (please specify)
CHRONIC SYMPTOMS - Dermal Changes: Select all the changes to your skin you are experiencing now. If you have not had any skin changes, select "None".	None Discoloration (hyperpigmented, mottled, blotchy) Rash Skin Lesions (ulcers, papules, macules, nodules or other lesions) Tight Skin Thickened Tissue (Includes Induration or Tethering) Other (please specify)
CHRONIC SYMPTOMS - Location of Dermal Changes: Select the locations of your skin issues today.	Extremities (Feet, Legs, Hands, Arms) Head (Face, Scalp) Torso None of the above Other (please specify)
CHRONIC SYMPTOMS - Muscle Issues: Select all the Muscle issues you presently experience. Select "None" if appropriate.	None Spasms - sudden, involuntary contraction Twitching - Small, local, rapid contractions Weakness - major loss of strength Other (please specify)
CHRONIC SYMPTOMS - ENT (Ear, Nose and Throat) Problems: Select all the ENT issues you presently experience. Select "None" if appropriate.	None Ringing in Ears (Tinnitus) Swallowing Problems (Dysphagia) Voice Problems including hoarseness Worsening of Hearing Other (please specify)
CHRONIC SYMPTOMS - Ocular Issues (eyes): Select all the Ocular issues you presently experience. Select "None" if appropriate.	None Dry Eyes Eye Redness (Sclera/white of the eye) Scleral Plaques/Yellowing Worsening Vision Other (please specify)

CHRONIC SYMPTOMS - Other Chronic Symptoms: Select all the symptoms below that you presently experience.	Balance Issues Blood Pressure Issues (High, Low, Labile) Cognitive Issues (brain fog, difficulty concentrating, etc.) Hair Loss Itchy skin Intestinal Problems Low Body Temperature Swelling of Extremities (Edema) None of the Above Other (please specify)
CHRONIC SYMPTOMS - Emergency Treatment: Did you require treatment at an Emergency Room at any time following the Initial Symptoms timeframe? If so, please explain. If not, enter "No"	Open-Ended Response
RECENT SYMPTOMS PROGRESS: How have your symptoms progressed in the last 12 months? You may check more than one box.	All symptoms have gotten worse All symptoms are stable but still affecting quality of life Some symptoms continue to get worse Some symptoms have gone away Some symptoms continue at the same level Some symptoms are new Some symptoms happen sporadically Other (please specify)
OTHER COMMENTS REGARDING CHRONIC SYMPTOMS A response is not required for this question. Use only if you believe you have a significant CHRONIC SYMPTOM that was not covered in the above questions.	Open-Ended Response
NEW DIAGNOSES: After your last Contrast MRI: If a medical professional has diagnosed you with a named condition that relates to the Symptoms you have identified in either the Initial or Chronic Symptoms Sections, please list those diagnoses here. If none, enter "None"	Open-Ended Response
Number of contrast MRIs: How many total Contrast MRIs have you had, including the last contrast MRI?	Total Contrast MRIs
Symptoms from earlier MRIs: Enter "NA" if you have only had 1 MRI. Otherwise, now that you understand your present symptoms from your "last contrast MRI", have you identified symptoms experienced earlier that you now attribute to previous Contrast MRI administrations? If so, please explain, being as specific as possible with dates and symptom/MRI relationships.	Open-Ended Response
PRIORITIZE YOUR SYMPTOMS Select the symptom descriptor that fits for your 1st, 2nd, 3rd and 4th priority. Use "Other" as necessary and then explain the Other in the following question. Select "None" if appropriate.	Symptoms to prioritize were: Pain Dermal Issues Twitching/spasms ENT Ocular Low Temp Cognitive None Other

FINAL QUESTION: Please write a few words that describe your high priority symptoms. Briefly describe how they feel, look, or change your functioning.	Open-Ended Response
FINAL COMMENT BOX: You must click the "Done" button below to complete your Survey. We will send you an email after we have reviewed your responses. You may provide any additional comments about your responses to the Survey in the box below.	Open-Ended Response