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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

Hilary Davis,

Plaintiff,

v.

McKesson Corporation, et al.,

Defendants.

No. CV-18-1157-PHX-DGC
CV-18-1159-PHX-DGC
CV-18-1778-PHX-DGC

ORDER

Plaintiffs Hillary Davis, Srihari Munnuru, and Susan Fischer have sued Defendants Bayer Healthcare Pharmaceuticals, Inc., McKesson Corporation, Guerbet, LLC, and other gadolinium-based contrast agent ("GBCA") manufacturers and distributors. Plaintiffs were administered GBCAs for the medical procedure known as magnetic resonance imaging ("MRI"), and claim they developed various health problems as a result. After conferring with the parties, the Court decided that the issue of general medical causation – whether Plaintiffs can present admissible evidence that GBCAs cause the health problems they claim – should be decided first. Doc. 110, 111, 115. Accordingly, after focused discovery and Plaintiffs' production of expert reports on general causation, Defendants filed motions to exclude the experts' testimony under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 597 (1993), and Rule 702 of the Federal Rules of Evidence. Docs. 153, 157. The motions are fully briefed, and the Court heard oral arguments on July 3, 2019. For the reasons that follow, the Court will

grant Defendants' motions with respect to the medical causation experts and deny them with respect to the chemistry tutorial.[1]

I. Background.

"Gadolinium is a lanthanide element (rare earth metal), which exhibits high paramagnetism, a form of magnetism occurring only in the presence of an externally applied magnetic field." *In re Gadolinium-Based Contrast Agents Prods. Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 1796334, at * 3 (N.D. Ohio May 4, 2010) [hereinafter *In re GBCAs*]. When GBCAs are injected intravenously, they enhance MRI scans, resulting in high quality images that aid in identifying serious health conditions such as cancer, infections, and bleeding. Docs. 154-27 at 2, 154-47 at 2. Since their initial approval in 1988, GBCAs have been used more than 450 million times worldwide. Doc. 154-24 at 2.

Gadolinium in its free state is toxic to humans. *In re GBCAs*, 2010 WL 1796334, at *3. Because of this toxicity, gadolinium must be chemically bound to a chelate (a compound that can be bound to a metal atom) before it is intravenously injected. This binding prevents the gadolinium from interacting with human tissue. *Id*. GBCAs can be chelated in a linear model or a macrocyclic model. Doc. 154-24 at 4. While all GBCAs are mostly eliminated from the body through the kidneys, scientific evidence clearly suggests that linear GBCAs are less stable and tend to dechelate in the body (the gadolinium separates from the chelate) more readily than macrocyclic GBCAs. Doc. 154-47 at 2; *see also* Doc. 154-24 at 5 (92-96% excreted in 1 hour). All of Defendants' products in this case are linear GBCAs.

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[1] Three cases have been consolidated in this action: *Davis v. McKesson Corporation*, 2:18-cv-00157; *Munnuru v. Guerbet, LLC*, No. 2:18-cv-01159-DGC; and *Fischer v. Bayer Healthcare Pharmaceuticals, Inc.*, No 2:18-cv-01778-DGC. Documents cited from the lead case, *Davis*, will be referred to simply as "Doc." Documents cited from the *Fischer* and *Munnuru* cases will be preceded by the Plaintiff's last name. All citations are to public versions of the documents unless otherwise noted, and are to page numbers added at the top of the documents by the Court's electronic filing system.

In 2006, several doctors and researchers noted a strong association between GBCA use in patients with advanced kidney disease and the development of a medical condition known as nephrogenic systemic fibrosis ("NSF"). Doc. 154-14 at 84. Subsequent studies revealed that the elimination of GBCAs from patients with kidney disease takes significantly longer than from patients with healthy kidneys, and that the GBCAs were never entirely eliminated. *In re GBCAs*, 2010 WL 1796334, at *6.

NSF is a disease that primarily involves the skin and subcutaneous tissues, but also may involve other organs such as the lungs, esophagus, heart, and skeletal muscles. *Id.* Symptoms may develop and progress rapidly or appear months or even years after GBCA exposure. *Id.* Once the medical community stopped using GBCAs in renally-impaired patients, NSF was "essentially eradicated." Doc. 154-24 at 2.

Many of the persons who developed NSF brought suit against the manufacturers of GBCAs, and the cases were consolidated in a multi-district litigation in 2010 (the "NSF MDL"). *See In re GBCAs*, 2010 WL 1796334, at *1. Experts in the NSF MDL opined that NSF was caused by dechelation of GBCAs after they were injected into the body, which exposed the body to toxic gadolinium. *Id*. at *6. Although the experts could not identify the precise mechanism by which gadolinium caused NSF, the district court admitted their causation opinions. *Id*. The court found sufficient evidence – including the rapid elimination of NSF when GBCAs were no longer used in renally-impaired patients – that GBCAs caused NSF. *Id*. at *6. One jury trial was held in the NSF MDL, resulting in a verdict for the plaintiff, and the remainder of the MDL cases settled.

This case differs from the NSF MDL in two important respects. Although Plaintiffs in this matter allege that they were exposed to GBCAs when they received MRIs, they do not have impaired kidneys and they have not been diagnosed with NSF. Rather, Plaintiffs and other patients with normal kidney function claim they began to suffer a wide range of symptoms after they received GBCAs. Doc. 191-2 at 2. This range of symptoms has not been recognized as a disease by regulatory authorities or

medical associations, but the collection of symptoms has been referred to in some literature as "gadolinium deposition disease" ("GDD"). *Id*. For the sake of simplicity, the Court will refer to Plaintiffs' alleged illnesses as either GDD or gadolinium toxicity. In doing so, the Court makes no judgment about whether GDD is or should be recognized as a distinct illness, or whether GBCAs are in fact toxic in patients who have healthy kidneys.

Plaintiff Hilary Davis alleges that she contracted GDD after receiving an intravenous GBCA injection. Doc. 1 ¶ 2. In her first and amended complaints, she alleged extreme cognitive impairment; difficult mentation; headaches; swollen, red, thickening, and peeling skin; and pain throughout her body. *Id*. ¶ 39, Doc. 4 ¶ 43. In her second amended complaint, she alleges that the gadolinium from the GBCA deposited indefinitely in her organs and soft tissues and caused fibrosis in her organs, bone, and skin, and crossed the blood-brain barrier to deposit in the neuronal nuclei of her brain. Doc. 142 ¶ 12.

Plaintiff Srihari Munnuru received one or multiple MRIs where he was injected with a GBCA. Munnuru Doc. 1 ¶ 4. He alleges that he developed GDD "soon thereafter," which has caused him severe injury and pain and suffering due to GDD. *Id*. at 8 ¶ 17. In his deposition, he testified to leg stiffness, weakness, bone pain and joint popping, foot pain, brain fog, and eye and teeth pain. Doc. 154-3 at 14.

Plaintiff Susan Fischer alleges that she contracted GDD from intravenous GBCA injections. Fischer Doc. 1 ¶ 2. She alleges the following symptoms: burning sensation; violent shaking; tremors; clouded mentation; confusion; weakness; fatigue; hypoglycemia; difficult, painful movement; low body temperature; inflammation, especially throughout her lymphatic system; muscle cramps; numbness; tingling sensation; aching joints; weight loss; hair loss; lumps and rashes on her body; kidney damage; and osteoporosis. *Id*. ¶ 16. In her amended complaint, Fischer alleges gadolinium retention in multiple organs years after the GBCAs were administered.

Fischer Doc. 10 ¶ 2. She alleges that the gadolinium has caused fibrosis in her organs, bone, and skin, and that it has crossed the blood-brain barrier and deposited in the neuronal nuclei of her brain. *Id*. ¶ 26; *see also* Fischer Doc. 60 ¶ 30.

Plaintiffs' cases are among several actions pending in district courts across the United States. Fischer Doc. 39 at 1. All claim adverse health effects related to GBCA administration. On October 10, 2018, the Judicial Panel on Multidistrict Litigation considered and denied the motion of 17 plaintiffs to centralize pretrial proceedings in an MDL. *Id.* The panel determined that even though there are common issues about gadolinium toxicity and retention, the injuries alleged in each case appear highly specific to each individual plaintiff and the actions involve GBCAs manufactured by four different defendant groups, involving different GBCA formulations. *Id.*

II. Relevant Legal Standards.

Defendants' motions are governed by Rule 702 of the Federal Rules of Evidence. That rule provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702.

Curiously, the parties make few references in their briefs to Rule 702, relying instead almost exclusively on *Daubert* and related cases. The Court notes, however, that *Daubert* applied the then-existing version of Rule 702 and held that it superseded the common law rule in *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923). *See Daubert*, 509 U.S. at 587-89. Rule 702 was amended in 2000, seven years after *Daubert* was decided. Amendment of the rule required approval by the Supreme Court and acceptance by Congress under the Rules Enabling Act, and the amended rule superseded any other law. *See* 28 U.S.C. § 2072(b) ("All laws in conflict with such rules shall be of no further force or effect after such rules have taken effect."). Thus, Rule 702 provides the governing law for this case. Because the 2000 amendment sought to codify and clarify the admissibility of expert testimony in light of *Daubert* and related cases, those cases clearly remain relevant, but the Court will structure its analysis primarily around the requirements of Rule 702. *See* Fed. R. Evid. 702 advisory committee's note to 2000 amendment.

Three legal principles are particularly relevant to the Court's gatekeeping role in this case.

First, the proponent of expert testimony bears the burden of showing that the proposed testimony is admissible under Rule 702. *Cooper v. Brown*, 510 F.3d 870, 942 (9th Cir. 2007); *Lust ex rel. Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996). If Plaintiffs fail to carry this burden, the opinions of their experts are not admissible. *Cooper*, 510 F.3d at 942.

Second, the admissibility of expert testimony under Rule 702 is a preliminary question the Court must decide under Federal Rule of Evidence 104(a), and the Rule 104(a) decision must be made by a preponderance of the evidence. *See Daubert*, 509 U.S. at 592 & n.10; *Bourjaily v. United States*, 483 U.S. 171, 175-76 (1987). Some cases mistakenly suggest that some of the elements in Rule 702 are jury questions – that whether an expert's opinion is based on reliable principles and methods, and whether

those principles and methods have been applied to the facts of the case reliably, go to the weight of the evidence and should be decided by the jury after cross examination and argument at trial. But the requirements of Rule 702 are conditions for admissibility, and the Supreme Court has made clear that "the trial judge must determine at the outset, pursuant to Rule 104(a)," whether the expert's testimony is admissible under Rule 702. *Daubert*, 509 U.S. at 592. Thus, the Court's task in this order is to determine whether Plaintiffs have shown by a preponderance of the evidence that the requirements of Rule 702(a)-(d) have been satisfied with respect to each expert's opinions. *Id*. at 592 n.10; *Bourjaily*, 483 U.S. at 175-76. Both sides agreed with this principle during the hearing on the motions.[2]

Third, experts must explain the basis for their conclusions in a manner that allows the Court to determine whether they are using reliable principles and methods and are applying them to the facts of the case in a reliable manner. Fed. R. Evid. 702(c), (d). Although "[t]rained experts commonly extrapolate from existing data . . . nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

With these legal standards in mind, the Court will discuss the current state of the science with respect to NSF and GDD and the basic approach to causation used by

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[2] The Ninth Circuit has emphasized the statement in *Daubert* that a district court should conduct the admissibility analysis "with a 'liberal thrust' favoring admission." *Messick v. Novartis Pharm. Corp.*, 747 F.3d 1193, 1196 (9th Cir. 2014) (quoting *Daubert*, 509 U.S. at 588). It has stated that the gatekeeping function is meant to "screen the jury from unreliable nonsense opinions, but not to exclude opinions merely because they are impeachable." *Alaska Rent-A-Car, Inc. v. Avis Budget Group, Inc.*, 738 F.3d 960, 969 (9th Cir. 2013). The Court will follow this guidance, but with the understanding, established by the Supreme Court cases cited above, that the Court may admit expert opinions only if it can determine, under Rule 104(a), that Plaintiffs have shown each of the Rule 702 requirements to be satisfied by a preponderance of the evidence.

Plaintiffs' medical causation experts. The Court then will address the individual causation experts, two cases cited heavily by Plaintiffs, and Plaintiffs' chemistry expert.

III. Background Information on NSF and GDD.

A. NSF.

Borrowing liberally from a decision of the district court in the NSF MDL, the Court provides the following description of NSF. *See In re GBCAs*, 2010 WL 1796334, at *3. NSF was first described in the medical literature in 2000, with the first reported cases going back to 1997. NSF causes fibrosis of the skin, connective tissue, and organs throughout the body, and is a painful, progressive, and debilitating disease. While the precise pathogenesis of NSF is unknown, it has been reported only in patients who have severe kidney disease and, with the exception of a few reported cases with inconclusive medical histories, has been found exclusively in kidney patients who have had one or more exposures to GBCAs.

In June 2006, the FDA issued a Public Health Advisory notifying healthcare professionals and the public about the risk of NSF following the administration of GBCAs. In December 2006, the FDA issued an updated Public Health Advisory stating that there was a potential for NSF to occur in at-risk patients following administration of GBCAs. In May 2007, the FDA asked GBCA license holders to issue a warning about the risk of NSF in patients with renal failure. This warning, along with policies and procedures adopted by healthcare facilities and notice to healthcare providers, led to the virtual elimination of new NSF cases. *Id.*

In response to the growing number of NSF cases, medical professionals identified specific diagnostic criteria for identifying the disease. Doc. 154-17. The court in the NSF MDL described NSF as "a singular disease." *In re GBCAs*, 2010 WL 1796334 at *6. Although the plaintiffs' experts in the MDL could not identify with certainty the mechanism by which gadolinium in GBCAs caused NSF, the court found their general causation opinions admissible, providing this explanation:

> The dominant theory is that dechelation occurs through transmetalation (simply, a chemical reaction involving the exchange of ligands between two metal centers), although there are other theories including that dechelated (or, free) gadolinium has a proliferative effect on human dermal fibrosis and gadolinium's propensities as a calcium blocker triggers the fibrotic process. In any event, given the wealth of evidence on causation – that is, the rapid emergence and decline of NSF associated with the rise and fall of its use in renally impaired persons, the presence of gadolinium in the tissue of NSF patients, the known toxicity of gadolinium, and the majority view in the published and peer reviewed studies and articles that dechelated gadolinium causes NSF – the Court concludes that it is not necessary for Plaintiffs' experts to identify the precise mechanism by which dechelated gadolinium causes NSF in order to present the theory to a jury.

Id.

In short, the general medical causation opinions were admissible in the NSF MDL because (1) the increase and decrease of NSF cases tracked the increase and decrease of GBCA use in renally-impaired patients, (2) a majority of published and peer reviewed studies found a causal link between GBCAs and NSF in such patients, (3) gadolinium was found in the tissue of NSF patients, and (4) free gadolinium was known to be toxic. The evidence in this case is less clear.

B. GDD.

Plaintiffs do not argue that GDD has been recognized as a distinct disease by any regulatory body or medical association, but note that it has been proposed as an illness in some published literature. *See* Semelka et al. (2016), Doc. 156-16 (proposing GDD as an illness). Other literature has asserted that labelling symptoms as GDD is too strong a suggestion that it is an actual illness, and has proposed instead that the name be changed to "gadolinium-associated symptoms." *See* Parillo et al. (2018), Doc. 154-26 at 7.

1. MIDAC Review.

In 2017, the FDA convened its Medical Imaging Drugs Advisory Committee ("MIDAC") to consider "the potential risk of gadolinium retention . . . in patients

receiving [GBCAs]." Doc. 154-42 at 2. The committee consisted of 15 voting members, all of whom (with the exception of one patient and one consumer representative) were medical doctors or Ph.D.s. They included seven professors at major universities, laboratory directors, and directors from the National Institutes of Health and the National Cancer Institute. *See* Transcript of September 8, 2017 MIDAC Conference, Doc. 156-7 at 3-9 [hereinafter MIDAC Trans.]. The FDA convened MIDAC because "[t]he evidence indicating retention following the use of GBCAs has led to concerns that gadolinium retention may cause adverse reactions, if not immediately then at some later date." Doc. 154-43 at 4. The focus of MIDAC's inquiry was the connection, if any, between the retention of GBCAs or gadolinium in the body and various symptoms reported in patients with healthy kidneys.

The FDA prepared a lengthy briefing document for the MIDAC inquiry that reviewed all medical literature since 1988, case reports, regulatory decisions, and reports from the FDA's adverse event reporting system ("FAERS"). Doc. 154-43. MIDAC then held a conference on September 8, 2017, where it heard presentations from FDA medical officers, invited scholars, industry representatives, and the public. A 401-page transcript records all of the presentations and discussions, as well as MIDAC's vote on key questions. *See* MIDAC Trans., Doc. 156-7. After considering all of the evidence and hearing presentations from scholars, experts, and patient advocacy groups, MIDAC unanimously concluded that the medical and scientific evidence does not establish that GBCAs cause GDD. *See id.* at 338-56. This does not appear to have been a difficult decision for the committee members – there was no equivocation in their views. *See id.* The chair, Dr. Peter Herscovitch, summarized the committee's views in these words: "I think there is fair uniformity that there is no evidence of a causal relationship between the symptoms and signs in patients with normal renal function and the retention of gadolinium." *Id.* at 356. MIDAC recommended that the FDA revise GBCA warnings to note that retention of gadolinium in some organs, including the brain, is possible

following GBCA use, but otherwise did not recommend that GBCA use be restricted. *Id.* at 377; Doc. 154-45 at 8-9.

2. The FDA and Other Regulatory and Medical Organizations.

Following MIDAC's conference, the FDA approved this revised GBCA product label in April 2018:

> Gadolinium is retained for months and years in several organs. . . . Consequences of gadolinium retention in the brain have not been established. . . . There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention. . . . [C]linical consequences of gadolinium retention have not been established in plaintiffs with normal renal function[.]

Doc. 154-29 at 5.

Due to the retention of gadolinium in the body, other national organizations such as the Australian Department of Health, Health Canada, the European Medicines Agency ("EMA"), the Japanese Pharmaceuticals and Medical Devices Agency, and the New Zealand Ministry of Health have suspended the use of some linear GBCAs. Doc. 153 at 12. But these organizations have also concluded that there is insufficient evidence to show that gadolinium deposition in brain tissues causes harm to patients. *See* Docs. 154-34 at 2, 154-33 at 2, 154-35 at 2, 154-36 at 2, 154-38 at 2. [3]

Additionally, many scientific and medical societies have agreed that no adverse health effects from gadolinium retention in renally-healthy patients have been proven. *See* Doc. 153 at 13. These include 2018 findings by the National Institutes of Health, the

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[3] At the MIDAC conference, an FDA medical officer described EMA's reasons for suspending linear GBCAs: "there's a theoretical risk associated with gadolinium retention in the brain; . . . the clinical consequences could take many years to identify; . . . the concentration of gadolinium in the brain seems to be higher after the linear agents compared to the macrocyclics; gadolinium clearance from the brain occurs at a much faster rate after macrocyclics as compared to linears; . . . there is greater disassociation of gadolinium from the linear GBCAs compared to the macrocyclics; and . . . clinically, the multipurpose GBCAs are interchangeable." MIDAC Trans., Doc. 156-7 at 188.

American College of Radiology, the Radiological Society of North America, and the Canadian Association of Radiologists (Docs. 154-24 at 2, 154-16 at 2), and 2017 findings by the American Society of Neuroradiology and the International Society for Magnetic Resonance in Medicine (Docs. 154-13 at 2, 154-18 at 2, 154-12 at 2).

3. Evidence Supporting GDD and its GBCA Cause.

Although regulators and scientific organizations have not found enough evidence to conclude that GBCAs cause an illness like GDD, there is evidence that some level of GBCAs and gadolinium are retrained in the brain, bone, and other organs of patients who have received GBCAs in connection with an MRI, even when they do not have impaired renal function. *See* Kanda et al. (2014), Doc. 154-24 at 2; 191-5 (hypothesizing the existence of intracranial gadolinium retention based on the observation of unenhanced T1 signal intensity increases in the dentate and globus pallidus); *see also* Semelka et al. (2016), Doc. 187-34 at 2 (describing studies that determined gadolinium was being retained in the brain and bone). No party appears to contest this, but the parties disagree on the form of the retained gadolinium and whether it is toxic in that form and at all doses. And as already noted, research indicates that linear GBCAs deposit in larger amounts or in dechelated forms more often than macrocyclic forms. Doc. 154-24 at 4 (study showed after two weeks in human serum that macrocyclic GBCA disassociations were undetectable but linear GBCAs showed variable degrees of dissociation).

Plaintiffs also point to publications that have drawn a connection between retained GBCAs and various symptoms in renally-healthy patients. These include Burke (2016), where researchers conducted an anonymous online survey of patients who believed that they suffered from gadolinium toxicity. Doc. 187-33 at 2. The researchers received 50 responses, 33 of which described the onset of symptoms immediately following GBCA administration and 16 of which described the onset within six weeks. *Id.* The most commonly reported symptoms were bone and joint pain and head and neck symptoms, including headaches, vision change, and hearing change. *Id.* Skin changes were also

indicated by about 60% of the respondents. *Id*. The authors of the Burke study acknowledged that the "risk of severe adverse reaction to GBCA exposure is extremely small, hence it may be difficult to determine characteristics of individuals that predispose to this type of reaction." *Id*. at 3.

In Semelka (2016), researchers reviewed the medical history and physical examinations of four individuals with normal renal function who reported development of new disease features within hours to four weeks of receiving GBCA injections. Doc. 187-34 at 2. The authors concluded that gadolinium toxicity may occur in subjects with normal renal function. *Id*. Central torso and peripheral arm and leg pain were common features. *Id*. Distal arm and leg pain and rubbery subcutaneous tissue were seen in later stages. *Id*. Clouded mentation was also common. *Id*. The authors noted features that resembled NSF. *Id*. at 4.

In another Semelka article (2016), the authors recruited participants with normal renal function and evidence of gadolinium in their system beyond 30 days from two online gadolinium toxicity support groups. Doc. 156-16 at 2. Participants were asked to answer survey questions about their symptoms. *Id*. The most common symptoms were central pain, peripheral pain, headache, and bone pain. *Id*. Subjects with distal leg and arm distribution described skin thickening. *Id*. Clouded mentation and headaches were described as persistent beyond three months in 29 of the 42 subjects. *Id*. From the results, the authors proposed to call this condition GDD. *Id*. at 4. Many of the reported symptoms appeared to resemble less severe symptoms of NSF. *Id*. The authors theorized that the symptoms may come from an immune system response to these agents. *Id*. They were careful to note the limitations of their study – self reported survey answers, subjectivity, predefined questions, and lack of a control group, noting that "further prospective investigation is needed to verify this condition." *Id*.

C. The Issue.

The history of NSF and GDD frame the issue in this case. On one hand, we have the recognized disease of NSF in renally-impaired patients and its accepted link to GBCAs. On the other hand, we have the broad-ranging proposed illness of GDD in renally-healthy patients and its alleged link to GBCAs. The distinction between the two was captured in this comment by Dr. Jeffrey Brent, a member of the FDA's MIDAC committee, during MIDAC's 2017 conference:

> We know NSF is a disease. It's a very clear-cut unambiguous disease caused by gadolinium retention in patients who have renal failure. It's interesting to contrast that with the gadolinium retention disease we're hearing about today in patients with normal renal function. NSF is an unmistakable, easy to diagnose, clear cut, limited but devastatingly serious clinical condition, limited in the sense of clinical manifestations. What we heard about today is multisystem, multisymptom disease without any unifying presentations that would suggest a physiology that would seem to make sense. So there are a lot of questions here about what this actually is, if it actually is a disease.

MIDAC Trans., Doc. 156-7 at 329-30.

The question to be answered in this case is whether Plaintiffs can present admissible expert opinions that GBCAs cause an illness described as GDD, or whether such causation remains in the realm of reasonable suspicion, unsupported by sufficient scientific and medical evidence to satisfy Rule 702. In resolving this question, the Court must remember that reliable scientific principles and methods, applied reliably, are required by Rule 702. Reasonable suspicions and plausible theories are not enough. As other courts have noted, "an opinion that is an insightful, or even inspired, hunch is not admissible if it lacks scientific rigor." *Anderson v. Bristol Myers Squibb*, No. Civ.A. H-95-0093, 1998 WL 35178199, at *12 (S.D. Tex. Apr. 20, 1998). "The courtroom is not the place for scientific guess work, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

Plaintiffs' counsel argued at the hearing on these *Daubert* motions that the relevant question is whether GBCAs should be included in the list of potential causes to be considered in any differential diagnosis of Plaintiffs' illnesses. There is some vagueness in this argument. On one hand, it could mean that Plaintiffs can clear the *Daubert* hurdle on general causation with expert opinions that GBCAs could potentially cause GDD, even if GBCAs have not been identified as a known cause. On the other hand, it could mean that Plaintiffs must present expert opinions that GBCAs are in fact a cause of GDD, and that GBCAs are therefore a potential cause of Plaintiffs' illnesses when considered with all of the other potential causes in a particular Plaintiff such as, for example, fibromyalgia, other autoimmune illnesses, muscle and bone maladies, or other factors from Plaintiffs' personal medical histories.

The latter formulation is correct. The Court's Case Management Order identified the subject of this order as "*Daubert* motions on general causation." Doc. 115 at 4. Plaintiffs must show that their experts can present admissible opinions that GBCAs cause GDD. Stated differently, the issue to be decided is whether Plaintiffs' experts can present admissible opinions under Rule 702 that GBCAs are in fact a cause of GDD. Whether GBCAs actually caused any particular Plaintiff's illness is an issue of specific causation to be decided later in this litigation.[4]

[4] Plaintiffs' counsel emphasized in their briefing and argument that the Court's Case Management Order identified the issue as "'whether exposure to a substance for which a defendant is responsible . . . is *capable* of causing a particular injury or condition in the general population.'" Doc. 110 at 11 (quoting *Jaros v. E.I. DuPont*, 292 F.3d 1124, 1133 (9th Cir. 2002)) (emphasis added). Plaintiffs focus on the word "capable" in this statement, suggesting that it means the mere potential to cause Plaintiffs' illnesses. The Court does not agree. Plaintiffs must present admissible expert opinions that GBCAs cause GDD. The Court has reviewed the record in this case and is confident that Plaintiffs have understood this to be the relevant inquiry from the outset. *See* Docs. 110, 111. This is confirmed by Plaintiffs' expert reports, each of which opines to a reasonable degree of medical or scientific certainty that GBCAs cause GDD. The Court must now decide whether those opinions are admissible.

IV. Rules 702(a) and (b) – Qualifications and Sufficiency of Facts and Data.

Plaintiffs offer four experts to support their theory of general medical causation: Brent Wagner, M.D., Jody Tversky, M.D., Margert Whittaker, Ph.D., and Kenneth Raymond, Ph.D. The three causation experts – Drs. Wagner, Tversky, and Whittaker – opine that GBCAs cause GDD in patients with healthy kidneys. The fourth expert, Dr. Raymond, is a chemist who explains the nature of GBCAs and how they react in the human body. Plaintiffs assert that Dr. Raymond's chemistry testimony will be essential to the jury's understanding of GBCAs and their fate in the body, but that they will not use him to state a causation opinion.

A. Rule 702(a) – Qualifications.

Dr. Wagner is a board-certified physician in internal medicine and nephrology. Doc. 154-10 at 2. He currently serves as the Director of the Kidney Institute of New Mexico, as the Renal Section Chief of the Medicine Section of the New Mexico Veterans Health Care System, and as an Associate Professor of Medicine at the University of New Mexico Health Science Center. *Id*. He has done research on patients with impaired kidney function exposed to GBCAs and the subsequent development of NSF. *Id*. For nearly two decades, Dr. Wagner's research has focused on renal development and mechanisms implicated in kidney injury. *Id*. at 4. He was the keynote speaker at MIDAC's 2017 conference. *See* MIDAC Trans., Doc. 156-7 at 44-62.

Dr. Tversky is a full-time faculty member and former clinical director of the Division of Allergy and Clinical Immunology at The John Hopkins University School of Medicine. Doc. 154-9 at 2. He is board certified in internal medicine and allergy. *Id.* He is a practicing allergist "with extensive experience managing drug reactions, anaphylaxis, and immunological pathology." *Id*. at 3.

Dr. Whittaker is the managing director and chief toxicologist of ToxServices LLC, a scientific consulting firm headquartered in Washington, D.C. Doc. 154-11 at 5. She is a Diplomate of the American Board of Toxicology and a board-certified toxicologist. *Id.*

She has more than 25 years of experience assessing human health and environmental hazards from substances including inorganic and organic chemicals, microorganisms, and radiological substances. *Id.*

Dr. Raymond is an organic chemist and professor emeritus in chemistry at the University of California, Berkeley. Doc. 154 8 at 2. He has lectured extensively on metal chelate design and has an interest in lanthanide coordination chemistry. *Id.* For many years, he had National Institutes of Health support for the development of GBCAs, which resulted in patents that have been licensed to GBCA providers. *Id.* He has served as a consultant on MRI contrast agents and studies the role of metals in biology and medicine. *Id.*

The Court finds by a preponderance of the evidence that these experts are qualified by training and experience to opine on the subjects each will address, and that their testimony, if admitted, would be helpful to the jury. Rule 702(a) is satisfied.

B. Rule 702(b) – Sufficiency of Facts and Data.

Plaintiffs' experts do not opine on specific causation – whether any Plaintiff's symptoms have in fact been caused by his or her exposure to GBCAs. As a result, they have not focused on Plaintiffs or their medical conditions and histories. The facts and data considered by the experts consist of studies, surveys, and case reports related to the question of gadolinium toxicity in patients with healthy kidneys. The Court finds that their opinions are based on sufficient facts and data. Rule 702(b) is satisfied by a preponderance of the evidence.

V. Rule 702(c) and (d) – General Discussion of the Medical Causation Opinions.

In this section of the order, the Court will engage in a general discussion of the causation experts' opinions, identifying serious flaws in some of the principles and methods they use, as well as a lack of reliability in how they apply some otherwise reliable principles and methods. In the three sections that follow, the Court will address each of the causation experts individually, applying this general discussion.

A. Unproven Hypotheses Are Not Admissible.

As the Supreme Court explained in *Daubert*: "Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry." 509 U.S. at 593 (quotation marks and citations omitted). Merely generating hypotheses – even reasonable ones – is not enough. "[I]n order to qualify as 'scientific knowledge' an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation – i.e., 'good grounds,' based on what is known." *Id.* at 590; *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994) ("[S]cientists whose conviction about the ultimate conclusion of their research is so firm that they are willing to aver under oath that it is correct prior to performing the necessary validating tests could properly be viewed by the district court as lacking the objectivity that is the hallmark of the scientific method."); *see also Nease v. Ford Motor Co.*, 848 F.3d 219, 232 (4th Cir. 2017); *Mitchell v. Gencorp, Inc.*, 165 F.3d 778, 783 (10th Cir. 1999).

Daubert identified several means for determining whether a theory has been reliably validated. "[A] key question to be answered in determining whether a theory or technique is scientific knowledge that will assist the trier of fact will be whether it can be (and has been) tested." 509 U.S. at 593. "Another pertinent consideration is whether the theory or technique has been subjected to peer review and publication." *Id.* "Additionally, in the case of a particular scientific technique, the court ordinarily should consider the known or potential rate of error[.]" *Id.* at 594. Finally, "[w]idespread acceptance can be an important factor in ruling particular evidence admissible, and a known technique which has been able to attract only minimal support within the community may properly be viewed with skepticism." *Id.* (quotation marks and citations omitted). Additional considerations are identified in the Advisory Committee Note to the 2000 amendment of Rule 702 and will be discussed below.

These factors underscore the basic *Daubert* inquiry – whether an expert's theory or hypothesis has been tested and shown to be valid. If not, it is inadmissible.

B. The Common Approach of Plaintiffs' Experts.

Plaintiffs' causation experts offer theories about the existence of GDD and how it is caused, and cite sources which suggest that the theories are worth exploring, but they do not present reliable scientific principles and methods, or apply accepted principles and methods reliably, to show that their theories have been validated. The starting point for the experts' theories consists of several facts Plaintiffs claim to be undisputed: (a) GBCAs are an accepted cause of NSF; (b) GBCAs dechelate in the human body, releasing free gadolinium; (c) some level of GBCAs and free gadolinium is retained in the bodies of patients with healthy kidneys; and (d) free gadolinium is toxic in the human body. *See* Doc. 154-10 at 7-16 (Wagner Report); Doc. 154-9 at 4-5 (Tversky Report); Doc. 154-11 at 15-23 (Whittaker Report); *see also* Doc. 185 at 22.[5] But these facts alone are not enough to establish general causation in this case, as Plaintiffs' experts all seem to concede. These facts suggest that GBCAs can cause adverse symptoms in renally-healthy patients, and they may be enough to raise a reasonable hypothesis that must be tested. But more is needed to conclude reliably that the variety of symptoms associated

[5] Defendants do not dispute these four facts as general propositions but argue that they are not relevant without information about dose. For example, Defendants concede that free gadolinium can be toxic to humans, but argue that dose matters and that Plaintiffs' experts identify no minimum dose for gadolinium toxicity or for the development of GDD. Defendants are correct that dose matters. *See* Federal Judicial Center Reference Manual on Scientific Evidence (3d ed.), 2011 WL 7724262 at *3 ("'the dose makes the poison'; this implies that all chemical agents are intrinsically hazardous – whether they cause harm is only a question of dose"). But dose primarily is relevant to the question of specific causation – whether a particular exposure caused the plaintiff's injury. Courts have placed less emphasis on dose when addressing general causation. *See Clausen v. M/V New Carissa*, 339 F.3d 1049,1059 (9th Cir. 2003). This is especially true in cases like this that do not involve common background levels of exposure to a substance, or where there is no identified benign exposure level. *See In re: Zicam Cold Remedy Mktg, Sales Practices, & Prods. Liab. Litig.*, 797 F. Supp. 2d 940, 944-45 (D. Ariz. 2011); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, (E.D. Wash. 2009). Because dose is not essential to the general causation inquiry, the four facts that form the basis for Plaintiffs' expert opinions will be, for purposes of this order, considered undisputed. The Court notes, however, that dose does matter when the experts seek to apply animal or in vitro studies to humans, as discussed below.

with GDD are in fact an illness, and that the illness is caused by GBCAs. That has been the conclusion of the FDA and every other regulatory and medical body that has considered the question. These bodies are all well aware of Plaintiffs' four foundational facts, and they have found them to be good reasons for further study, but they unanimously have found that there is not enough scientific evidence to conclude that GBCAs cause GDD. *See* Doc. 153 at 11-13.

The key question in this case, therefore, is whether Plaintiffs' experts present reliable principles and methods, applied reliably, to bridge the gap between these foundational facts and the conclusion that GBCAs cause GDD. The gap cannot be bridged merely by the mere *ipse dixit* – the say-so – of the experts. *Joiner*, 522 U.S. at 146. There must be a reliable scientific basis.

Plaintiffs' experts attempt to span the gap by positing that GBCAs cause a "continuum" of symptoms, the most severe of which constitute NSF and the less severe of which are commonly seen in GDD. They rely primarily on four categories of evidence: case reports, surveys, animal studies, and in vitro studies. *See* Doc. 154-10 at 17-31 (Wagner Report); Doc. 154-9 at 5-10 (Tversky Report); Doc. 154-11 at 23-32 (Whittaker Report). The Court will address the experts' proposed continuum, each category of evidence, and other concerns about the experts' principles and methods.[6]

C. The Continuum.

Plaintiffs' causation experts posit that there is a continuum of symptoms caused by GBCAs, with the more severe symptoms commonly seen in patients with renal impairment (NSF) and less severe symptoms commonly seen in patients without renal impairment (GDD). Docs. 154-9 at 3 (Tversky Report); 154-10 at 31 (Wagner Report). If this is true, the continuum essentially establishes the general medical causation Plaintiffs are trying to prove because all of the symptoms on the continuum, including

[6] Wagner also states that he relies on his treatment of patients suffering from gadolinium toxicity. Doc. 154-10 at 2, 4. This factor will be discussed below in the specific review of Dr. Wagner's opinions.

those experienced by Plaintiffs, are caused by GBCAs. The Court will address the continuum evidence cited by Dr. Wagner and Dr. Tversky (Dr. Whittaker provides little discussion of the continuum), and then address a basic question presented by these experts – if GBCAs cause NSF, why doesn't simple logic lead to the conclusion that they also cause the range of symptoms labeled GDD?

1. Dr. Wagner.

After opining that a continuum of symptoms is caused by GBCAs, Dr. Wagner asserts that "[m]any individuals with different backgrounds agree on this point[.]" Doc. 154-10 at 31. He then cites one source: the briefing document from the 2017 MIDAC conference. *Id.* at 38 ¶ 78. But the briefing document, which is part of the record at Doc. 154-43 (and is not available at the website address provided by Dr. Wagner), makes no mention of the three doctors Dr. Wagner names as holding the same opinion – Drs. Pierre Desche, Gene Williams, and Peter Herscovitch. *See* Doc. 154-10 at 31-32.

Because Dr. Wagner's continuum opinion is a very important issue in this case, and the Court could find no mention of these doctors in the FDA briefing document, the Court reviewed the entire transcript of the 2017 MIDAC conference. Sure enough, all three of the named doctors spoke at the conference, and each one mentioned the word "continuum." But contrary to Dr. Wagner's claim, none of them supported his opinion of a continuum of symptoms caused by GBCAs.

Dr. Desche made this statement: "our conclusion is that brain hyperintensities and NSF are, in fact, part of the same continuum from gadolinium retention to gadolinium toxicity, and renal dysfunction acts as a catalyst." *See* MIDAC Trans., Doc. 156-7 at 107; *see also* 113 (same). The continuum Dr. Desche mentions is from gadolinium retention to gadolinium toxicity causing NSF. He does not say there is a continuum that includes a wide range of milder symptoms that encompass GDD, as Dr. Wagner posits.

Indeed, during his deposition Dr. Desche made clear that he was referring to retention that leads to NSF, not some broader continuum. *See* Doc. 202 at 10-15 (sealed).

Dr. Williams made this statement at the MIDAC conference: "if you had information on patients with varying degrees of renal impairment and you could tease out the effect of the renal impairment itself, you might expect it to be a continuum. The idea forwarded by the advisory committee member from a clinical pharmacology standpoint, I think is a reasonable idea." MIDAC Trans., Doc. 156-7 at 222-23. This statement is classic hypothesis. Dr. Williams suggests that there "might" be a continuum detected if the varying degrees of renal impairment could be separated. And he is talking about the universe of patients with renal impairment, not individuals like Plaintiffs who have no renal impairment. Even then, the most he says is that there "might" be a continuum and it is "a reasonable idea." *Id.* at 223. He does not endorse Dr. Wagner's continuum conclusion.

Dr. Herscovitch's statement at the MIDAC meeting was this: "renal function is not either normal or abnormal, but as one of our discussants pointed out, it's a continuum." MIDAC Trans., Doc. 156-7 at 358. This statement has nothing to do with a continuum of symptoms. It concerns a continuum of renal function. And Dr. Herscovitch, who chaired the MIDAC conference, actually made statements that contradict Dr. Wagner's medical causation opinion: "I think there is fair uniformity that there is no evidence of a causal relationship between the symptoms and signs in patients with normal renal function and the retention of gadolinium." *Id.* at 355. He also presciently addressed the kinds of evidence primarily relied on by Plaintiffs' experts, saying: "the FAERS data and other anecdotal reports really perhaps raise questions, but in themselves do not have a scientific foundation for reaching any conclusions." *Id.* at 356.

In short, assuming Dr. Wagner was citing to the MIDAC conference as support for his claim that "[m]any individuals with different backgrounds agree" with his posited

continuum of symptoms caused by GBCAs, he is simply incorrect. That Dr. Wagner would make such a strong but incorrect claim is concerning.

2. Dr. Tversky.

Dr. Tversky does not cite other authorities to support his claim of a continuum. He instead provides this rationale: "it was noted that in patients with NSF there were early signs of the disease that progressed over time to these more characteristic later manifestations. This shows that there is a range or continuum of signs and symptoms caused by gadolinium toxicity exposure." Doc. 154-9 at 3. This assertion – that there is a range of symptoms in NSF patients – is used by Dr. Tversky to conclude that the same range of symptoms must exist in everyone else exposed to GBCAs, including renally-healthy patients. But this leap rests on nothing more than Dr. Tversky's say-so. He cites no other authority to support the continuum. And the Court notes that at least one speaker at MIDAC's conference, Dr. Nicholas Dainiak, characterized this assertion – "that the brain deposits may occur prior to eventual evolution to NSF" – as a mere "hypothesis." MIDAC Trans., Doc. 156-7 at 316.

Later in his report Dr. Tversky notes that case reports suggest milder symptoms for GDD patients than NSF patients, and he compares those milder symptoms to the early stages of NSF, again suggesting it's all one continuum. Doc. 154-9 at 8. This reasoning rests on the reliability of the case reports he cites. As explained in the discussion below, the Court finds the case reports insufficiently reliable to support Dr. Tversky's proposed continuum.

3. If GBCAs Cause NSF, Then Why Not GDD?

Dr. Tversky and Dr. Wagner assert, as do Plaintiffs generally, that NSF is a misnomer – that the use of "nephrogenic" in the name of the disease is incorrect because impaired kidneys don't cause NSF, they simply allow gadolinium to accumulate in the body to a point where it causes NSF. It is the gadolinium, not the kidneys, that causes NSF. Docs. 154-9 at 3-4 (Tversky Report), 154-10 at 16 (Wagner Report). This

rationale leads logically to the conclusion that the accumulation of gadolinium in patients with healthy kidneys will likewise cause the symptoms seen in GDD. But if it were that simple, MIDAC, the FDA, and other organizations would have concluded that GBCAs cause GDD. It is not that simple. As Dr. Anthony Fotenos, an FDA medical officer, noted at the MIDAC conference, the vast majority of patients who receive GBCAs develop no symptoms. "[I]n the postmarketing setting, millions of patients have benefited from GBCAs without reported adverse reactions since the first drug in the class was approved in 1988." MIDAC Trans., Doc. 156-7 at 195; *see also* Endrikat et al. (2016), Doc. 189-20 at 2 (most patients with severe renal impairment who receive even multiple doses of GBCAs do not develop NSF). The mere receipt and even retention of GBCAs clearly does not cause illness in most patients.

And as many comments at the MIDAC conference make clear, the causative mechanism of NSF, although linked to gadolinium, it still not understood. Dr. Wagner himself provided this explanation at the conference:

> In 2006, when [NSF] was clearly linked to gadolinium, we know that gadolinium is the cause, so that the kidney is a risk factor – renal insufficiency is a risk factor – but the kidney per se is not really causing the disease.
>
> There is now evidence that gadolinium is deposited in the central nervous system. I believe that the central nervous deposition *warrants more study*, and I am going to show that gadolinium-based contrast agents are biologically active.
>
> *Very little is known* about the metabolism of these agents, their biologic effects, and the implications of retaining gadolinium in the tissues. The toxic effects and the mechanisms of how they impart their pathophysiology *is a major gap* in our knowledge.
>
> If we understand how the disease processes occur, we are going to know quite a bit more for stratifying patients who are at risk, and it will add to our future knowledge. How these different agents behave once they enter the body *is an active area of investigation*.

MIDAC Trans., Doc. 156-7 at 46-47 (emphasis added). Thus, Plaintiffs' own causation expert stated less than two years ago that much is not known about the effects of GBCA retention and that further investigation is needed. He also told MIDAC that "dechelation of gadolinium is a hypothetical pathologic mechanism," and that "[s]tudies concerning the biologic effects of rare earth minerals in general and their retention in human organs are in the nascent stage, and the science on this topic is at ground zero." *Id.* at 60.

In fact, uncertainty about the precise mechanism by which GBCAs causes NSF is recognized by many sources. Dr. Wagner stated at the MIDAC conference that "there are risk factors out there that have not been defined." *Id*. at 135. One of the FDA medical officers stated: "I also want to note – and this is similar to what Dr. Wagner said – while consideration of the comparative exposure to gadolinium from each GBCA is important, patient factors in addition to renal function are likely to play an important role[.]" *Id.* at 180. Dr. Semelka, the author of several papers cited by Plaintiffs, suggested an entirely different pathology at the MIDAC conference: "My opinion is [that GDD] is a genetic disease of the immune system[.]" *Id.* at 302. Runge (2018) states that NSF is a manifestation of toxicity from gadolinium released by MRI contrast media, but that the illness probably develops in the presence of "cofactors." Doc. 189-17 at 5. Endrikat et al. (2016) notes that multiple cofactors for NSF have been proposed, including metabolic acidosis, vascular surgery, or treatment with erythropoietin. Doc. 189-20 at 2; *see also* Wagner et al. (2016), Doc. 189-21 at 5-6 (noting that many patients with end-stage renal disease on chronic dialysis do not acquire the disease despite several exposures to GBCAs, and some individuals develop NSF without gadolinium exposure). Finally, Dr. Tversky himself asserts that there are other potential contributing factors to NSF, including the activation of free radicals, increased inflammatory chemicals, and the induction of complex immunological cascades. Doc. 154-9 at 7.

If the precise causes of NSF are not yet understood, one cannot simply conclude that if GBCAs contribute to NSF in renally-impaired patients they must also cause GDD

in renally-healthy patients. As MIDAC and other organizations have recognized, causation is more complicated than such a simple proposition.

4. Continuum Conclusion.

Plaintiffs have not shown by a preponderance of the evidence that the continuum theory posited by Drs. Wagner and Tversky is the product of reliable principles and methods applied reliably. The Court will next look to the actual categories of evidence relied on by the causation experts.

D. Individual Case Reports and Surveys.

The most common form of evidence cited by the causation experts consists of individual case reports (descriptions of the experiences of single patients) and surveys of individuals who believe they developed adverse health effects after receiving GBCAs. *See* Docs. 154-10 at 17, 21-26, 28, 30 (Wagner Report); Doc. 154-9 at 8 (Tversky Report); Doc. 154-11 at 25, 30 (Whittaker Report). Some of these reports are from the FDA's FAERS database and others are from published articles, but all of them constitute the experience of single patients, usually as reported by the patients with no complete study of the patients and no control group.

"Such case reports are not reliable scientific evidence of causation, because they simply described reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; do not isolate and exclude potentially alternative causes; and do not investigate or explain the mechanism of causation." *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995). As the Eleventh Circuit has explained:

> [C]ourts must consider that case reports are merely accounts of medical events. They reflect only reported data, not scientific methodology. Some case reports are a very basic form report of symptoms with little or no patient history, description of course of treatment, or reasoning to exclude other possible causes. The contents of these case reports were inadequate, even under the plaintiffs' expert's standards, to demonstrate a relationship between a drug and a potential side effect.

> Some case reports do contain details of the treatment and differential diagnosis. Even these more detailed case reports, however, are not reliable enough, by themselves, to demonstrate the causal link the plaintiffs assert that they do because they report symptoms observed in a single patient in an uncontrolled context. They may rule out other potential causes of the effect, but they do not rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors.

Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1199 (11th Cir. 2002) (citation omitted).

The Federal Judicial Center Reference Manual on Scientific Evidence includes this caution about case reports:

> Anecdotal reports may be of value, but they are ordinarily more helpful in generating lines of inquiry than in proving causation. . . . Anecdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group.

2011 WL 7724256 at *4 [hereinafter Reference Manual].[7]

And the FDA itself has identified these limitations for its FAERS database:

> Yes, FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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[7] The Court will refer frequently in this order to the Reference Manual. The FJC is the research and education arm of the federal judicial system. Established by Congress in 1967, the FJC's duties include conducting and promoting education for federal judges and other court personnel. *Federal Judicial Center*, https://www.fjc.gov/ (last visited July 22, 2019). The Reference Manual is now in its third edition, has been found reliable by many federal courts, and has been cited in hundreds of court decisions. *See e.g.*, *Comcast Corp. v. Behrend*, 569 U.S. 27, 38 (2013); *Elliott v. Google, Inc.*, 860 F.3d 1151, 1160 (9th Cir. 2017).

https://www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers (last visited July 8, 2019); *see also* MIDAC Trans., Doc. 156-7 at 148 (FDA official describing limitations of FAERS database).[8]

"Simply stated, case reports raise questions, they do not answer them." *McLain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005); *see also Cloud v. Pfizer*, 198 F. Supp. 2d 1118, 1133-34 (D. Ariz. 2001); *Jones v. United States*, 933 F. Supp. 894, 899-900 (N.D. Cal. 1996), *affirmed* 127 F.3d 1154 (9th Cir. 1997), *cert. denied* 524 U.S. 946 (1998). Indeed, Dr. Wagner admitted in his deposition that case reports do not provide reliable scientific evidence of causation because they are anecdotal reports of occurrences, without support from the scientific method. Doc. 154-6 at 42.

Surveys are even less reliable. They consist of unscreened answers from people who believe they suffer from GBCA-caused illnesses, often provided anonymously. Unlike case reports, the survey responses generally are not made by physicians. They include statements from medically-untrained individuals, with no verification of exposure to GBCAs or physical symptoms, and certainly no control group. And yet all three causation experts rely on surveys without providing any discussion or acknowledgement of their limitations. *See* Doc. 154-10 at 18, 25, 28-29 (Wagner Report); Doc. 154-9 at 8 (Tversky Report); Doc. 154-11 at 24 (Whittaker Report).

Dr. Brent, a professor at the University of Colorado School of Medicine and a member of MIDAC during the 2017 conference, provided this relevant comment about relying on anecdotal information:

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[8] The Reference Manual provides similar cautions about the FAERS database:

> It is a voluntary system with the following limitations: (1) uncertainty that the drug caused the reported event, (2) no requirement for proof of a causal relationship between product and event, (3) insufficient detail to evaluate events, (4) incomplete reporting of all adverse events, and (5) inability to determine the incidence of an adverse events because the actual number of patients receiving a product and the duration of use of those products are unknown.

2011 WL 7724263 at *28.

> We are in an unfortunate situation here. This is not an easy scientific question. What we do know without any question is that gadolinium is retained, and it's retained in at least some patients irrespective of how good their renal function is.
>
> What we really don't know is whether that has any physiological consequences at all. We have some anecdotal data – some of it is very powerful, some of it is very emotionally concerning – that it may be harmful to some people, but that is fundamentally anecdotal data. Sometimes following our emotions in this kind of data can lead us in unscientific directions.
>
> What we really need to do is to focus our attention on determining what, if any, the adverse consequences are of this gadolinium retention before we decide how we should act on it or to what degree we should be making restrictions, to what degree we should be changing our clinical practice.

MIDAC Trans., Doc. 156-7 at 327-28.

As discussed in more detail below, the Court cannot conclude by a preponderance of the evidence that the causation experts' reliance on individual case reports and surveys, including those in the FAERS database, satisfies the Rule 702 requirements of reliable principles and methods applied reliably.

E. Animal Studies.

Animal studies clearly can be relevant in evaluating the effects of substances on humans, but there are limitations here also.

First, experts must consider the differences between the animals studied and human anatomy and physiology. As the Reference Manual explains: "The expert should review similarities and differences between the animal species in which the compound has been tested and humans. This analysis should form the basis of the expert's opinion regarding whether extrapolation from animals to humans is warranted." 2011 WL 7724262 at *16. Thus, while animal studies are not per se inadmissible, there must be a basis for extrapolating them to the human population. *See Daubert v. Merrell Dow*

Pharm., Inc. (Daubert II), 43 F.3d 1311, 1319 (9th Cir. 1995); *see also Sanderson v. Int'l Flavors & Fragrances, Inc.*, 950 F. Supp. 981, 997 (C.D. Cal. 1996) ("[I]n order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans[.]"). In this case, none of Plaintiffs' experts explains why the animal studies they cite can reliably be extrapolated to humans with normal kidney function.

Second, experts should account for any unique characteristics of the study that might make it less relevant to humans or to the question addressed in the causation analysis. *See Joiner*, 522 U.S. at 144-45 (expert opinions excluded where animal studies were "so dissimilar to the facts presented in . . . litigation"); *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1313-14 (11th Cir. 1999) (expert failed to "explain the correlation of the results . . . of rat studies in which the rats were directly injected with silicone to symptoms in a human patient where [the silicone implants] remained intact"). In this case, Plaintiffs rely on a number of animal studies that included procedures that might make the studies less relevant to whether GBCAs can cause GDD in patients with healthy kidneys. For example, several of the studies involve rodents whose kidneys were removed. Rasschaert, et. al. (2018), Doc. 189-14; Do et. al. (2014), Doc. 191-7; Doc. 154-11 at 30-31 (Whittaker Report). In a study of dogs, the blood-brain barrier was deliberately breached. Doc. 154-10 at 18 (Wagner Report); Doc. 154-11 at 28 (Whittaker Report). In another, GBCAs were injected directly into the animal's brain. Doc. 154-10 at 18 (Wagner Report); *see also* Doc. 154-11 at 28 (Whittaker Report) (discussing negative effects of gadolinium when allowed direct access to the brain). And in another, GBCAs were administered to pregnant mice, and their babies were studied to determine whether gadolinium can affect animals in utero. Doc. 154-10 at 22 (Wagner Report); Doc. 154-11 at 29 (Whittaker Report). Plaintiffs' experts do not address these unique features or explain why, even with these features, the studies are relevant to GBCA exposure in humans with healthy kidneys.

Third, dose matters when extrapolating from animal studies. As the Reference Manual logically explains, "the dose at which mercury causes [an] effect in laboratory animals is modified by many internal factors, and the exact dose-response curve may be different from that for humans." 2011 WL 7724262 at *8; *see also Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 997 (9th Cir. 1997), (expert inappropriately extrapolated data from different dosages, exposures, and chemical compounds without explaining why the extrapolation was scientifically acceptable), *abrogated on other grounds by Weisgram v. Marley Co.*, 528 U.S. 440, 453 (2000); *Turpin v. Merrell Dow Pharm. Inc.*, 959 F.2d 1349, 1360-61 (6th Cir. 1992) (expert failed to clarify why the varying doses of the drug and other chemicals given to rats, rabbits, and in vitro animal cells should be extrapolated to humans). In this case, many of the animal studies cited by Plaintiffs' experts involved very high and continuous doses of GBCAs, gadolinium, or gadolinium chloride (which Defendants' assert is never used in GBCAs). *See, e.g.*, Lohrke et. al. (2017), Doc. 155-13; Doc. 154-9 at 6 (Tversky Report); Doc. 154-10 at 12, 29 (Wagner Report); Doc. 154-11 at 18-19, 30-31 (Whittaker Report). And yet Plaintiffs' experts never address the studies' doses or their use of gadolinium chloride, and never explain why the studies are relevant to the causation question in light of these differences.[9]

Fourth, Plaintiffs' experts cite some studies without acknowledging that the studies' results or the authors' conclusions are inconsistent with the experts' opinions. These will be discussed below in connection with the individual experts.

The Court cannot find that the experts are using reliable principles and methods, or using them reliably, when they fail to say anything about the kinds of animals used in the studies, the unique characteristics of the studies, or the substances and doses used. Without such analysis, the relevancy of the animal studies is connected to the experts' opinions merely by their say-so, which is not sufficient. Plaintiffs have provided no basis

[9] An FDA medical officer explained at the MIDAC conference that "bio-distribution of gadolinium chloride is very different to the GBCAs." MIDAC Trans., Doc. 156-7 at 132

for the Court to conclude by a preponderance of the evidence that use of the animal studies in this case constitutes a reliable principle or method applied reliably.

The Court also notes that all of the animal studies cited by Plaintiffs' experts are known to MIDAC, the FDA, and other regulatory and medical bodies. And yet none of these organizations has found the studies sufficient to conclude that GBCAs cause GDD.

F. In Vitro Studies.

As with animal studies, dose matters when considering in vitro studies. The Reference Manual explains:

> Cellular and tissue culture research can be particularly helpful in identifying mechanisms of toxic action and potential target-organ toxicity. The major barrier to the use of in vitro results is the frequent inability to relate doses that cause cellular toxicity to doses that cause whole-animal toxicity. In many critical areas, knowledge that permits such quantitative extrapolation is lacking.

2011 WL 7724262 at *17; *see also Turpin*, 959 F.2d at 1360-61; *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 428-29 (S.D.N.Y 2005) ("[C]aution must always be used in extrapolating results in tissue culture to effects in live humans."); *In re Bausch & Lomb, Inc. Contact Lens Solution Prods. Liab. Litig.*, No. 2:06-MN-77777-DCN, MDL No. 1785, 2009 WL 2750462, at *12 (D.S.C. Aug. 26, 2009) ("In vitro tests generate hypotheses but lack sufficient reliability, standing alone, to demonstrate causation in humans.").

Plaintiffs' causation experts cite various in vitro studies. Doc. 154-9 at 5-6 (Tversky Report); Doc. 154-10 at 12, 15, 18 (Wagner Report); Doc. 154-11 at 18, 27, 30-31 (Whittaker Report). But none of the experts discusses the doses used in the studies or explains how those doses can reliably be extrapolated to the effects of GBCAs in humans with healthy kidneys. *See Schudel*, 120 F.3d at 997 (finding that expert inappropriately extrapolated data from different dosages, exposures, and chemical compounds without explaining why the extrapolation was scientifically acceptable). In

the absence of such analysis and explanation, the Court cannot find by a preponderance of the evidence that the experts' use of in vitro studies constitutes a reliable principle or method used reliably.

The Court also notes that all of the in vitro studies cited by Plaintiffs' experts are known to MIDAC, the FDA, and other regulatory and medical bodies. And yet none of them has found the studies sufficient to confirm the hypothesis that GBCAs cause GDD.

G. Incorrect Application of the Bradford Hill Criteria.

In order to determine whether a specific compound causes a particular malady, an expert must use valid scientific methodology. *Rains v. PPG Indus., Inc.*, 361 F. Supp. 2d 829, 835 (S.D. Ill. 2004). Many scientists use the Bradford Hill criteria for their causation analysis. *Id.* These criteria were presented in a 1965 lecture by Sir Austin Bradford Hill. Doc. 154-19. All three of Plaintiffs' causation experts mention the Bradford Hill criteria, and two of them – Drs. Tversky and Whittaker – purport to apply the criteria. But as will be explained below, these experts do not apply the criteria correctly. Thus, even though the Bradford Hill criteria represent reliable principles and methods, they have not been applied reliably to the facts of this case as required by Rule 702(d).

H. Other *Daubert* Considerations.

Several other considerations identified in *Daubert* are relevant here. None of the experts' opinions "has been subjected to peer review and publication." *Daubert*, 509 U.S. at 593. None has identified a "known or potential rate of error[.]" *Id.* at 594. And their principles and methods for finding GBCA causation of GDD have not been accepted by other experts, regulatory bodies, or professional associations. As a result, *Daubert* explained, those principles and methods "may properly be viewed with skepticism." *Id.* (quotation marks and citations omitted).

The Advisory Committee Note to Rule 702 identifies additional relevant considerations. One is whether the experts are testifying about matters growing naturally

and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. *See* Fed. R. Evid. advisory committee's note to 2000 amendment (citing *Daubert II*, 43 F.3d at 1317). Dr. Wagner satisfies this criterion, as he has done research on GBCAs and their connection to adverse health effects, but Drs. Tversky and Whittaker have not done such research and their opinions appear to have been prepared solely for this litigation.

I. Conclusion.

These general problems with the causation experts' opinions lead the Court to conclude that they are not admissible under Rule 702. To provide more detail, the Court will address each expert separately.

VI. Rule 702(c) and (d) – Specific Discussion of Dr. Wagner's Opinions.

A. Opinions.

Dr. Wagner begins with the foundational facts described above. He opines first that gadolinium in many free forms is toxic to humans, citing studies of gadolinium dust and gadolinium chloride. Doc. 154-10 at 2. He notes that most GBCAs are eliminated from the body by the kidneys, but that there is always retained gadolinium in the body, even with normal renal function. *Id*. at 10. He identifies various human and animal studies that show GBCA retention, including in patients with and without renal insufficiency. *Id*. at 12. He opines that there is no debate that, in the population of patients with renal impairment, GBCAs cause NSF. *Id*. at 15. He asserts that GBCAs activate fibroblasts, "which are the cells responsible for multiple diseases, including scleroderma and systemic fibrosis." *Id*. Although the severity of systemic fibrosis may increase with repeated GBCA exposure, he states that there does not appear to be a minimum threshold dose for the appearance or occurrence of NSF. *Id*. at 16.

Dr. Wagner then opines that GBCAs cause a variety of health problems. *Id.* Throughout his discussion of these various symptoms, he mixes studies regarding NSF with case reports, surveys, animal data, and in vitro data.

For neurological effects, Dr. Wagner discusses a study involving the direct injection of GBCAs into the brains of rats, noting that the rats developed a number of behavioral and neurologic problems. *Id*. Another study showed that intravenous injection of GBCAs could increase seizures in dogs when the permeability of the blood-brain barrier was altered. *Id.* And one rat study showed detectable metabolic changes from GBCA administration. *Id*. But Dr. Wagner does not explain why the results of these studies can reliably be extrapolated to humans; he does not discuss doses in the studies and how they relate to doses in humans; and he does not explain why direct brain injections in the rats and alteration of the blood-brain barrier in the dogs provide reliable information about the effects of GBCAs in humans with healthy kidneys. *Id*. at 17-18.

Dr. Wagner turns next to "radiographic abnormalities." *Id.* at 19. He cites results from the Burke (2016) anonymous survey where 77.6% of participants noted headaches, vision changes, hearing changes, and other head and neck symptoms that they attributed to GBCA exposure. *Id*. He then cites various human studies showing that gadolinium was retained in the brains of patients who received GBCAs, and that many of the patients had abnormal brain signals. *Id.* at 19-20. He also cites a case report of a 55-year-old woman who had numerous GBCA exposures and normal renal function, and yet developed symptoms of intense pain in her forearms, hands, feet, and toes two to three weeks after the last GBCA dose. *Id*. at 20. From this evidence, Dr, Wagner opines that GBCAs can cause neurological effects in patients with normal kidneys. But he does not explain why reliance on an anonymous survey and a single case report constitutes a reliable scientific method, and he never links the abnormal brain signals observed in some GBCA recipients to any illnesses, whether exhibited in the study patients or in Plaintiffs. *Id.* In fact, the brain signal studies were presented at the MIDAC conference and discussed extensively, and yet MIDAC concluded that they did not establish a causal link between GBCAs and any illnesses. *See* MIDAC Trans., Doc. 156-7 at 2-402 (scores of references to brain studies).

Dr. Wagner then discusses behavioral effects. *Id.* at 21. He notes a study of gadolinium transfer from pregnant mice to developing fetuses which found that the mice pups demonstrated behavioral abnormalities seven to nine weeks after birth. *Id*. at 22. He discusses three case reports where patients were accidentally injected with gadolinium in their spinal canal and experienced seizures, a vegetative state, confusion, nausea, drowsiness, blurred vision, and delirium. *Id*. at 22-23. He details another case of a woman who received multiple doses of GBCAs and experienced "gadolinium encephalopathy" characterized by drowsiness, fluctuating levels of consciousness, and mild left-sided paralysis. *Id*. at 23. In another case report, a 58-year-old woman received one dose of a GBCA and for three months afterward experienced intense, burning pain in her torso, arm, and leg; rashes; nausea; bladder pain; clouded mentation; disorientation; and a metabolic taste. *Id*. at 23. But Dr. Wagner never explains why the transfer of gadolinium from pregnant mice to their pups, or the accidental injection of GBCAs into the spinal canals of patients, or two case reports with their wide and differing range of symptoms can, through reliable scientific principles and methods, be extrapolated to show that GBCAs cause GDD in patients with healthy kidneys. Nor does he explain why this section of his report on behavioral effects has any relevance to Plaintiffs, none of whom claims adverse behavioral effects from GBCAs.

Dr. Wagner addresses "skin diseases" by starting with a discussion of NSF. *Id.* at 22. Symptoms of NSF may include sclerosis, puckering, pruritis, burning, extremity swelling, Raynaud's phenomenon (discoloration of fingers and toes), muscle induration, joint flexion contractures, and neuropathy. *Id*. at 23-24. He then cites two studies where researchers found biological markers of NSF in patients with normal renal function after GBCA exposure and several case reports involving skin issues. Dr. Wagner appears to cite these studies as proof that GBCAs can cause Plaintiffs' skin issues.

Dr. Wagner first notes that gadolinium-associated plaques have been reported in patients without kidney disease, that these plaques are sometimes asymptomatic and

sometimes pruritic and burning, and that specimens taken from these plaques contained specific CD68- and XIIIa-factor spindle-shaped fibrocytes and CD34-postive cells, all of which are distinctive markers for patients with NSF. *Id*. at 24. These markers have also been detected in preclinical models showing that bone marrow-derived fibrocytes are involved in mediating fibrosis. *Id*.

The plaque study involved one patient without kidney failure and one patient who had "chronic renal insufficiency," but not renal disease or NSF. *See* Gathings et al. (2015), Doc. 191-11. The patient with normal kidney function suffered from a pruritic, burning rash on both hands. *Id*. at 2. He had a history of cervical spine disease, prostate carcinoma, hypothyroidism, varicella, and gallstones, and had been exposed to multiple GBCA doses. *Id*. He had six small, red, ring-shaped plaques on the back of his hands. *Id*. at 2-3. The patient with renal insufficiency had a "slowly enlarging, asymptomatic tan-brown plaque on the right anterior lower leg" and had been exposed to "an unknown dose of gadolinium for several contrast-enhanced radiologic procedures." *Id*. at 3. The authors of the study noted that similar plaques had only been described in patients with NSF and that finding them in these patients supported the hypothesis that the plaques were not pathognomonic to NSF. *Id*. As a result, the authors coined a new clinical entity – "gadolinium-associated plaques" ("GAP") – and concluded that gadolinium exposure should be considered in any case of multiple or solitary plaques associated with distinctive histopathologic findings of sclerotic bodies regardless of NSF diagnosis or renal function. *Id*. at 5.

Dr. Wagner's asserts that his second cited case study identified "specific markers for GBCA-induced systemic fibrosis" – NSF – in a patient with normal renal function who underwent 61 contrast-enhanced MRIs over 11 years. Doc. 154-10 at 25. According to Dr. Wagner, a skin biopsy demonstrated the presence of gadolinium, and the patient had joint contractures – a clinical criterion for NSF – in his neck and all four extremities to the point that he was immobilized. *Id*. The study involved a patient with a

history of glioblastoma of the left temporal lobe, seizures, and hypothyroidism. Roberts et. al. (2016), Doc. 187-32 at 4. The authors noted that the patient had "no skin issues, with no complaints of rashes, pruritus, sclerosis of the skin, discoloration, or other changes." *Id*. Skin biopsies revealed normal skin and subcutis with "no evidence of increased dermal cellularity, fibrosis, abnormal collagen bundles, osseous metaplasia, or abnormal numbers of fibroblast like cells or macrophages." *Id*. at 7. But there was increased CD34 reactivity "indicating inflammation and/or tissue injury." *Id*.

The authors concluded that while gadolinium was present in the samples, the "form of the gadolinium retained" was unclear, and it was also unclear which specific gadolinium species deposited in the skin. *Id*. at 10. They noted that the patient's joint contractures were of unknown cause, and "without a joint biopsy, a definite association of the joint contractures with the high levels of gadolinium could not be confirmed or excluded." *Id*. The authors also concluded that, while they found the accumulation or retention of gadolinium in the skin, long-term consequences were unknown. *Id*.

The Court assumes that Dr. Wagner cites these two studies in support of his continuum hypothesis. That is, if distinct biomarkers of NSF are found in patients with normal renal function, it is evidence of a milder GDD-form of NSF due to GBCA retention. The Court finds Dr. Wagner's use of these studies problematic for several reasons.

First, Dr. Wagner does not fully explain what these biomarkers are or how they fit into his opinions. The Court is left to assume their significance. He indicates that CD34 cells have been historically associated with NSF lesions, but the Roberts study stated that CD34 is associated with inflammation or tissue injury, which, the Court can only conclude absent further explanation, may or may not be associated with NSF. The authors of the Roberts study do not mention NSF in connection with CD34. And although Dr. Wagner states that the study demonstrated "specific markers" of NSF, he does not fully explain what the specific markers are, and the authors do not discuss any

specific NSF markers, instead concluding that connection between their patient case study and NSF is indeterminate.

Second, these are single case studies, which, as explained above, are incapable of proving general causation. The plaque study contains only one patient with normal renal function and exposure to cumulative GBCA doses. The Roberts study considered only one patient as well. Both patients had histories of other serious medical issues that were not ruled out as causes for the plaques or joint contractures. The Court finds it troubling that Dr. Wagner represented the Roberts study as concluding that the patient's joint contractures were necessarily gadolinium related, when that was clearly not the case.

Third, assuming the identified markers suggest that gadolinium retention in individuals with normal kidney function mimics a milder form of NSF, these case studies at most support a hypothesis that the myriad skin issues identified by Dr. Wagner – skin changes, burning sensations, thickening, rashes – are caused by gadolinium retention. Doc. 154-10 at 32. As noted above, "case reports raise questions, they do not answer them." *McLain*, 401 F.3d at 1245. What is more, the Roberts study clearly noted that the patient did not actually suffer from any skin changes or skin disorders. And the plaque study was specifically limited to the development of sclerotic bodies associated with gadolinium exposure. The authors did not attempt to use the findings to connect GBCA exposure to any other type of skin issues.

Dr. Wagner then describes the case of a 58-year-old woman with normal renal function who had one GBCA dose and, seven years later, noted skin discoloration, tightness in the webs between her fingers, discoloration of the legs, and a red and rubbery skin texture in the knee regions. *Id.* at 24. Another patient with normal renal function and a history of multiple administrations of GBCAs began to experience symptoms two to three weeks after exposure to a linear GBCA. *Id.* at 25. She experienced erythema and warmth on the bottoms of her feet and the palms of her hands. These symptoms

remained for eight years after the GBCA exposure. *Id.* And Dr. Wagner cites the Burke (2016) survey where over half of the participants noted "skin changes." *Id*.

Again, these are case studies and an informal anonymous survey. They raise questions about possible skin effects, but do not answer them. And Dr. Wagner seems to acknowledge this point in his opinion. He concludes that the fact that GBCAs "are not entirely physiologically inert, and even demonstrate the same disease-inducing traits as witnessed in patients with [NSF] raises concern about the potential problems they pose when retained long-term in any individual." *Id*. Raising concern, of course, is not the same as proving causation.

Dr. Wagner notes additional effects observed in infants exposed to gadolinium in utero. Infants exposed during the first trimester had higher risks for connective tissue diseases, rheumatological, inflammatory, and infiltrative skin conditions. *Id*. Rates of stillbirth and neonatal deaths increased when examining GBCA exposure during any trimester of pregnancy. *Id*. at 25. GBCAs also had an effect on cultured skin cells, causing an increase in growth of human skin cells over one to three days. *Id*. at 26. Dr. Wagner does not explain how the in utero exposure relates to patients with healthy kidneys, nor does he address why the in vitro study of skin growth, and its doses, can be reliably extrapolated to humans with no renal impairment.

Dr. Wagner next turns to joint and bone pain associated with GBCAs. He cites a case report of a 23-year old man with a history of end-stage renal disease who suffered from progressive ankle pain, stiffness, and worsening mobility. *Id*. at 26. Another case report detailed three NSF patients who experienced "diffuse osteopenia, joint contractures, intra-articular and periarticular soft tissue calcification, mature heterotopic bone formation, joint ankylosis, and smooth periosteal reaction along regional long bones." *Id*. at 27. He asserts that other studies have indicated that gadolinium is retained and incorporated into the bone following GBCA exposure, which implies that the metal will only be liberated when the bone undergoes remodeling. *Id*. at 26-27. In the Burke

(2016) survey, 77.6% of respondents noted bone or joint pain, or both. *Id*. at 28. Dr. Wagner does not explain why case reports of specific NSF patients can reliably be extrapolated to GDD, how gadolinium retention in bone leads to a reliable conclusion regarding the effects of GBCAs in patients like Plaintiffs, or why reliance on an anonymous survey is appropriate.

Dr. Wagner also addresses heart, respiratory, kidney, and liver effects, largely relying on NSF data. He notes that gadolinium has been found in the hearts of several NSF patients. *Id*. at 28. Gadolinium was also detected in the lungs, kidneys, and liver of a dog two weeks after GBCA administration. *Id*. at 28-29. Case reports of NSF patients demonstrate experiences with diaphragmatic fibrosis and lung calcifications. *Id*. at 28. In the Burke (2016) survey, 21% of respondents noted difficulty breathing or other chest symptoms. *Id*. at 28-29. Gadolinium and markers of fibrosis were also found in the liver of GBCA-treated rats, and gadolinium chloride irreversibly paralyzed a guinea pig intestine. *Id*. at 30. But Dr. Wagner does not explain why case reports from NSF patients can reliably be applied to reach any conclusions, including conclusions regarding patients who have healthy kidneys and do not have NSF; why the use of a survey or the effects on a dog can be applied reliably to the same patients; or, for that matter, why heart, respiratory, and liver effects have anything to do with Plaintiffs, none of whom claim such ill effects.

In a broad category of "other health effects," Dr. Wagner describes a rat study that showed death of testicular cells and hypogonadism after repeated doses of GBCAs. *Id*. at 30. In another rat study there was evidence of cell death in salivary glands after eight days of daily doses of GBCAs. *Id*. But Dr. Wagner does not explain why these rat studies can reliably be applied to humans, why the effects on testicles and salivary gland cells have anything to do with Plaintiffs in this case, or why the doses received by the animals in these studies are relevant to humans receiving GBCAs.

Based on these sources, Dr. Wagner reaches his conclusions: "There is clear evidence that the phenomena noted in patients with normal renal function and [NSF] are part of the same continuum of disease." *Id*. "And based on what is currently known in the medical and scientific communities, the consequence of long-term retention of a rare earth metal within the cells of multiple critical organs has demonstrable and harmful long-term health effects." *Id*. at 31. The "symptoms known to be caused by these injuries include joint pain, pain with movement, pain in extremities, burning skin sensation, skin changes, skin thickening and rashes, clouded mentation, inflammation, and bone pain." *Id*. These symptoms affect patients with both normal renal function and impaired renal function.

Although he devoted portions of his report to behavioral, heart, respiratory, liver, testicle, and salivary gland effects, he does not include any of these in his final opinions, perhaps because they are not claimed by Plaintiffs. One wonders, then, why they were included in the report at all.

B. Analysis.

As mentioned at various points above, Dr. Wagner never explains how he is using reliable principles and methods, or how he is applying those principles and methods reliably. His connection between GBCAs and the wide range of symptoms characterized as GDD depends on animal studies, but he never explains why they are reliably applied to humans without impaired kidneys, why their dose is analogous, or why they are relevant notwithstanding unique characteristics of the studies such as the removal of kidneys from mice or breaching of the blood-brain barrier in rodents and dogs. He depends on case reports and surveys even though he admitted in his deposition that they do not provide reliable scientific evidence of causation because they are anecdotal, without support from the scientific method. Doc. 154-6 at 42. And he cites some in vitro studies, but never shows why they can be extrapolated to Plaintiffs and the causation issue in this case.

These concerns are compounded by other problems with Dr. Wagner's opinion.

1. Other Studies.

Defendants note that there have been relevant human epidemiologic studies on this issue and that Dr. Wagner never mentions them. Doc. 157 at 12. Defendants identify several such studies.

McDonald (2017) was a published abstract for a study that was presented at multiple medical conferences and at the 2017 MIDAC conference. Doc. 153 at 19. It compared 1,315 patients who received GBCAs to 2,946 patients with no history of GBCA exposure. The authors found no association between GBCA use and cognitive decline, poor neuropsychological performance, or diminished motor performance. *Id*.; *see also* Doc. 154-23.

Welk (2016) compared the risk of new-onset Parkinsonism (stiffness, tremor, imbalance, slowness) between patients who received GBCA-enhanced MRIs and patients who received unenhanced MRIs. The researchers controlled for kidney function and found no association between GBCA exposure and the development of these symptoms. Doc. 153 at 19; *see also* Doc. 154-28.

Parillo (2018) conducted a prospective cohort study of 1,088 MRI patients to test what the authors called "the debated definition of gadolinium deposition disease (GDD)." Doc. 154-26 at 2. Some of the patients received GBCA-enhanced MRIs and others did not. The patients were questioned before and 24 hours after the MRIs. *Id*. at 3. The questions concerned symptoms in the proposed definition of GDD, many of which are claimed by Plaintiffs – central torso pain, arm or leg pain, bone pain, headache, skin redness (any site of the body), fatigue, and mental confusion. *Id*. The study found that most symptoms allegedly related to gadolinium retention manifested at similarly low rates in both the GBCA-enhanced and unenhanced MRIs. The study did find a statistically significant increase of two proposed GDD symptoms – fatigue and mental

confusion – in patients that received GBCAs (about 17%) when compared to those who did not (about 8%). The authors stated this conclusion:

> this study shows that, using a robust methodology with a structured questionnaire administered before and after the MRI scan, and with a reasonable sample size, only 2 (namely, fatigue and mental confusion) of the 7 proposed GDD-like symptoms survived after comparison of [MRI patients that did and did not receive GBCAs]. These results suggest that the proposed term "gadolinium deposition disease" should be revised. Taking into consideration that persistent symptoms may be rarely observed after exposure to GBCAs and that there is not, at least based on currently reported cases and in our population, a dose-dependent relationship with previous exposure to multiple doses of GBCAs, the more conservative term "gadolinium-associated symptoms" could be proposed.

Id. at 7.

Mallio (2019) found no association between imaging evidence of gadolinium retention and resting state brain functional imaging in patients with normal kidney functions and Crohn's disease. Doc. 153 at 20.

Cocozza (2019) found no evidence that gadolinium retention in the brains of patients with multiple sclerosis and normal kidney function affects their clinical status over time. *Id.*

Although it is true, as Plaintiffs claim, that some of these studies focused on narrow populations and examined a narrow set of adverse effects, they are human studies performed by medical professionals, as opposed to case reports, anonymous surveys, animal studies, and in vitro studies, and they certainly are relevant to the general causation question in this case. It is concerning that Dr. Wagner never mentions them.

2. Retention Opinions.

Dr. Wagner fails to connect retained gadolinium in normal kidney patients to the dechelated gadolinium that causes his noted adverse-health effects in NSF cases. He cites evidence from the FDA that gadolinium is retained in the body, and his own studies suggest that GBCAs are not entirely eliminated. Doc. 154-10 at 12-13. But he never

specifies – with reliable evidence – whether the gadolinium that is retained in the body is in a chelated or dechelated form. His report refers to GBCAs, gadolinium, and free gadolinium interchangeably, never specifying the form of the substance he claims causes GDD. And when he cites studies, he seldom if ever identifies the type of gadolinium found in tissues.

The acting chair at the MIDAC conference, Dr. Herscovitch, provided this summary about the state of knowledge regarding how GBCAs are stored in the body: "There is a lot of unknown, not only about the class of agents but the different chemical forms, linear versus macrocyclic classes, but also whether there is free gadolinium or gadolinium as it's originally used in agents or perhaps bound to other macromolecules in the body." MIDAC Trans., Doc. 156-7 at 335. The MIDAC conference also suggested that identifying the form of gadolinium can be very difficult, and that methods for doing so are still being developed. *Id*. at 132-33, 186. This suggests that such identification rarely is done, which would explain why it does not appear to be addressed in the studies. And yet Dr. Wagner and the other causation experts readily opine that free gadolinium is retained in the bodies of patients with healthy kidneys and causes GDD.

Dr. Wagner cites animal studies showing that linear GBCAs are more prone to dechelate than macrocyclic GBCAs and discussing the nanoparticles in the kidney and the skin in his rodent model. Doc. 154-10 at 15. But he does not explain how these experiments relate to the method of gadolinium retention in patients with normal kidneys, or what symptoms, if any, are associated with appearance of the nanoparticles. And an FDA medical officer who reviewed the emerging science on gadolinium retention at the MIDAC conference stated that although linear GBCAs appear to dechelate more readily, "we don't know the clinical significance of this." MIDAC Trans., Doc. 156-7 at 187.

Further, even if Dr. Wagner could show that retained gadolinium is dechelated, he does not explain how retention of small amounts of gadolinium can cause the adverse-health effects he attributes to the gadolinium retention. He notes that GBCAs are the

essential cause of NSF, and that NSF symptoms can occur after even small doses of GBCAs. Doc. 154-10 at 16. He then extrapolates from these facts that the small amounts of reported gadolinium retention in patients without renal failure must cause less severe adverse effects on a continuum with NSF. But he never explains how NSF patients retain gadolinium and whether renally-impaired retention is the same as normal-kidney retention. *Id*. at 10-11.

He also offers no clear guidance on the quantifiable differences in gadolinium retention. The chart he inserts in his report, but barely mentions, demonstrates that in the same timeframe an individual with stage-IV kidney disease may retain nearly 25% of gadolinium, an individual with stage-III would be closer to 8% and a patient with normal renal function would be closer to 5%. *See id*. at 10. He does not connect those retention levels to his underlying theory, which is essentially a proportional relationship between retention and adverse-health effects on an NSF continuum.

Dr. Wagner simply presents what is known of NSF and what is known about gadolinium toxicity in a free form and assumes that this would be the explanation for any symptoms reported by patients with normal kidney function after GBCA administration. *See id*. at 19 (assuming, because GBCAs are retained in multiple and vital brain areas, any neurologic symptoms manifested soon after GBCA exposure are caused by gadolinium until proven otherwise), 28 (assuming, based on NSF research, that GBCAs are the cause of bone and joint pain reported in patients). In a complex area of evolving science, where regulatory agencies and medical researchers uniformly acknowledge many unknowns, Dr. Wagner's assumptions simply do not fill the gaps. Under Rule 702, an expert's *ipse dixit* cannot be used to connect existing data to an unproven conclusion. *Joiner*, 522 U.S. at 146; *see also Turpin*, 959 F.2d at 1360-61 ("a jury should not be asked to speculate on the issue of causation.").

3. Dr. Wagner's MIDAC Testimony.

Dr. Wagner was the keynote speaker during the 2017 MIDAC conference. In that setting, he made several statements quite inconsistent with his current opinions. He stated that (1) central nervous system gadolinium toxicity warrants more study; (2) little is known about the metabolism of GBCAs, their biologic effects, and the implications of retained gadolinium; (3) the toxic effects and mechanisms of GBCAs are a major gap in current knowledge; (4) experiments show that renal insufficiency is not required for fibrosis to occur; (5) dechelation of gadolinium is a hypothetical pathologic mechanism; (6) studies concerning the effects of gadolinium retention in human organs are in the "nascent stage"; and (7) the science on this topic is at "ground zero." Doc. 154-48 at 4-21. Referring to brain retention of gadolinium, Dr. Wagner also said: "We don't know what the toxic effects are of this retention, if there are any." MIDAC Trans., Doc. 156-7 at 135.

The Supreme Court has instructed that an expert must "employ in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999). During his deposition, Defendants asked Dr. Wagner what changed from his 2017 MIDAC presentation, where dechelation of gadolinium was a hypothetical pathologic mechanism, to his expert report in January 2019, where GBCAs are proven to cause disease through gadolinium dechelation. Doc. 158-3 at 27. Defendants also asked why Dr. Wagner told MIDAC that it was not known what health effects gadolinium retention had on patients, and yet opined in his report that several injuries are caused by gadolinium retention. *Id.*

Dr. Wagner responded that, after the 2017 presentation, he took research results showing that nanoparticles were forming in the skin and kidneys in his animal models to a new colleague at the University of New Mexico. *Id.* at 27-28. The colleague pointed out that the animals' skins and kidneys were forming gadolinium-rich structures that appeared similar to what happens when a lanthanide is in a phosphate free solution, and

as the particle attached to bacteria it would leach phosphate out of the cell membrane. *Id.* at 28. Dr. Wagner explained that after seeing the nanoparticles in that light, he did not know how the gadolinium could exist in that form and still be chelated. *Id.* But he did not identify any study he undertook on the basis of his colleague's apparently casual observation, or how, if at all, he sought to validate the hypothesis.

Dr. Wagner also discussed 2018 papers which determined that gadolinium was being liberated from linear chelates, and his own unpublished working papers that showed GBCAs caused fibrocytes to infiltrate the kidneys and that the nanostructures apparent in the cells are damaging the lysosomes, which is causing a cell signal that can cause fibrosis. *Id.* at 30. But if these studies were pivotal in Dr. Wagner's formation of the causation opinions expressed in his expert report, it is curious that they are never mentioned in his report. *Id.*

He also noted that he observed symptoms while treating patients. *See* Docs. 188 at 7, 154-6 at 30. But again, if patient observations are important to his current opinion, it is odd that Dr. Wagner does not describe any of those observations in his report. Defendants also note that (1) the images of the nanoparticles showing dechelation were the same images he presented to the MIDAC conference, and (2) the studies he pointed to were animal studies that merely showed that more gadolinium was retained after linear GBCA administration than macrocyclic administration. Doc. 157 at 11-12.

The Court finds the stark inconsistencies between Dr. Wagner's MIDAC statements and his expert report to be very concerning, particularly since the data he cited in his deposition as having changed his opinions are not mentioned in his report on those opinions. While these inconsistencies alone are not sufficient to find his opinions inadmissible, they do suggest that he has not employed the same level of intellectual rigor to his opinions as he does in practice. *Kumho Tire*, 526 U.S. at 152.

4. General Acceptance in the Scientific Community.

Defendants argue that Dr. Wagner's opinions are not generally accepted by the regulatory and scientific communities. Doc. 157 at 8. As noted above, general acceptance is a factor the Court may consider in deciding whether an expert's opinion is sufficiently reliable to be admitted in evidence. *Daubert*, 509 U.S. at 594. The general acceptance must be of the expert's methodologies, not his conclusions. *Id.* But the Advisory Committee Note to Rule 702 provides this important explanation:

> Under the amendment [to Rule 702], as under *Daubert*, when an expert purports to apply principles and methods in accordance with professional standards, and yet reaches a conclusion that other experts in the field would not reach, the trial court may fairly suspect that the principles and methods have not been faithfully applied.

Fed. R. Evid. 702 advisory committee's note to 2000 amendment; *see also Lust*, 89 F.3d at 598 (same).

Dr. Wagner's causation conclusions are not shared by regulatory and medical organizations that have examined the same evidence, including MIDAC, the FDA and government regulators in Canada, Europe, Australia, Japan, and New Zealand, as well as the National Institutes of Health, the American College of Radiology, the Radiological Society of North America, the American Society of Neuroradiology, the Canadian Association of Radiologists, and the International Society for Magnetic Resonance in Medicine. Such a broad consensus permits the Court to suspect that Dr Wagner has not applied reliable principles and methods reliably, a suspicion confirmed by the close examination of his opinions described above.

5. Patient Experience.

Finally, Dr. Wagner states that he bases his opinions in part on his experience treating patients suffering from gadolinium toxicity. Doc. 154-10 at 2. As explained in the Advisory Committee Note to Rule 702:

> If the witness is relying solely or primarily on experience, then the witness must explain how that experience leads to the conclusion reached, why that experience is a sufficient basis for the opinion, and how that experience is reliably applied to the facts. The trial court's gatekeeping function requires more than simply "taking the expert's word for it."

Fed. R. Evid. 702 advisory committee's note to 2000 amendment (citing *Daubert II*, 43 F.3d at 1319).

As already noted, Dr. Wagner says nothing in his report about his patient-treatment experience or what he has learned from it. He does not describe the conditions of patients he has treated, whether they had impaired or healthy kidneys, the severity or cause of their symptoms, the nature of their exposures to GBCAs, or anything else that might help the Court evaluate whether his patient experience constitutes a reliable basis for rendering opinions in this case.

6. Bradford Hill Criteria.

As noted above, the Bradford Hill criteria provide a well-recognized method for evaluating general causation. Dr. Wagner makes only one passing reference to the criteria: "The methodology I employed here is consistent with the sound deductive and inferential reasoning principles that I employ as a physician in both clinical practice and research, including the Bradford Hill Criteria for evaluating causal connections." Doc. 154-10 at 3. That's it. No further explanation is provided of how the nine-factor Bradford Hill analysis was performed or supports his causation opinion. Dr. Wagner's passing reference to the criteria does nothing to show that he has applied them reliably as required by Rule 702(d).

7. Conclusion.

Considering all of the factors outlined above, Plaintiffs have not shown by a preponderance of the evidence that Dr. Wagner's testimony is based on reliable principles and methods that have been applied to the facts of this case reliably. His opinions therefore are not admissible under Rule 702(c) and (d).

C. Plaintiffs' Motion to File Supplemental References.

Plaintiffs filed a motion for leave to file supplemental references to support Dr. Wagner's opinion. Doc. 209. They seek to file two recently published studies. Plaintiffs assert that the articles are directly relevant to the general causation inquiry. *Id*. Plaintiffs offer only that the studies will help provide the Court a "complete picture of the current state of the scientific evidence." *Id*. at 3.

The first study – "Gadolinium-Based Contrast Agents: Stimulators of Myeloid-Induced Renal Fibrosis and Major Metabolic Disruptors" – involved a rodent experiment on obesity and GBCA-induced disease. Doc. 209-1 at 6. The test mice underwent 5/6 nephrectomies to model chronic kidney disease. *Id*. at 7. Then they were split into two groups: one received a 60% saturated fat diet for 22 weeks and one received a control diet for 22 weeks. *Id*. at 8. At 18 weeks, each group was subdivided into untreated and GBCA-treated groups. *Id*. The GBCA-treated group received 20 doses of GBCAs over the final four weeks. *Id*.

The authors noted that serum chemistries collected at the endpoint revealed increased creatinine and decreased inverse creatinine in the gadolinium-treated group. *Id*. They concluded that these parameters are highly specific for impaired glomerular filtration rates and these data, along with additional findings, demonstrated that GBCAs have a profound impact on renal function and histology. *Id*. The authors go on to discuss the effect of GBCA treatment on the metabolic profile of the kidney in contrast-treated mice with "normal renal function." *Id*. at 10. They state: "This allowed determination of whether pre-existing chronic kidney disease was requisite for gadolinium-based contrast agent-induced systemic fibrosis or not *and* provided a baseline to gauge the similarity with high fat diet-induced kidney fibrosis with that induced by gadolinium and the impact of the combination." *Id*.

It is unclear to the Court how the authors draw conclusions for individuals with normal renal functions when the mice in this experiment were all given 5/6

nephrectomies to simulate chronic kidney disease. The Court guesses that based on the metrics cited above, the authors distinguished between individuals with chronic kidney disease and renal insufficiency. But distinctions on that basis are not consistent with the discussion of NSF. *See* Doc. 154-10 at 16 (Wagner Report) (noting that there is no specific degree of kidney impairment that "plays a causal role in the pathogenesis of the disease"). And Dr. Wagner has failed to provide any other sort of explanation for why the Court should consider these results in relation to his opinions about patients with normal renal function. Doc. 209-1 at 2. Moreover, like with the studies discussed above, Dr. Wagner has not explained why the use of the mice, the dose, and other unique aspects of this study can be extrapolated to humans with healthy kidneys who receive GBCAs.

In the second in vitro study, "Gadolinium-Based MRI Contrast Agents Induce Mitochondrial Toxicity and Cell Death in Human Neurons, and Toxicity Increases with Reduced Kinetic Stability of the Agent," the authors considered whether "GBCAs are toxic to the cellular function of differentiated human neurons that are representative of those found in one of the brain regions with high T1-dependent MRI signal intensity changes." Doc. 209-1 at 21. The authors used dopaminergic neurons and exposed them to increasing concentrations of eight GBCAs for seven days. *Id*. The concentrations ranged from "clinically relevant concentrations measured in some autopsy patients who had received repeated injections of contrast for MRI to higher concentrations to reveal dose-dependent trends." *Id*. For all GBCAs tested, cell death increased with exposure dose and clinically relevant doses of agents with lower kinetic stability exhibited toxicity. *Id*. "Reduction of mitochondrial membrane potential and oxidative respiratory function also generally mirrored the agents' structural kinetic stabilities, with greater impairment at lower concentration for the less stable agents." *Id*. The authors concluded that GBCAs caused a toxic effect on mitochondrial respiratory function and cell viability, and the toxicity increases as agent concentration increases and as the kinetic stability decreases. *Id*.

The authors noted that the study was conducted in vitro, "which has its inherent limitations in directly applying results to human beings." *Id*. at 29.

> First, contrast agents in culture medium have easy access to cell membranes. Second, the medium itself is clearly different from the interstitium in human brain. Third, cells in culture inherently have a different environment to those in the brain and do not replicate the tissue and synaptic complexity in vivo.

Id. The authors also concluded, however, that "it is not unreasonable to project that neurons in the human brain would experience some degree of the toxicity observed in cultured human neurons." *Id*. at 30. The findings suggested that "a single contrast-enhanced MRI scan would not be expected to achieve this concentration of agent within the brain. However, with numerous repeated administrations, and evidence that the lower stability agents may accumulate and persist longer, our findings suggest that repeated administrations, particularly of the lower kinetic stability of GBCAs, could result in neural toxicity." *Id*. Still the authors also noted that clinical effects resulting from the cellular dysfunction are not clear. *Id*.

Defendants argue this study cannot be relevant because it was a test tube study where the cells were essentially bathed in GBCAs. 7/3/2019, LiveNote Hearing Tr. at 32. Further, the authors drew no connections to clinical effects and instead noted the limitations of applying the study to humans. *Id*.

Plaintiffs provide very little explanation regarding the significance of this study. They do not address the limitations identified by the authors. Nor do they explain why this study may reliably be extrapolated to humans with healthy kidneys considering the methods in which the cells were exposed to the GBCA – a test tube bath in GBCAs. And because the study does not actually identify GBCA-caused clinical adverse effects, it is unclear how it can support Dr. Wagner's general causation opinion. The authors noted that loss of neurons "was concerning" and could "accelerate cell death due to normal aging," or cause other problems in patients with neural disease. Doc. 209-1 at 30. The

actual implications of the study appear to be speculative and, at most, it seems to offer evidence researchers must consider to continue evaluating GBCAs and GBCA retention.

Plaintiffs' supplemental references do not change the Court's determination that Dr. Wagner's opinions are inadmissible.

VII. Rule 702(c) and (d) – Specific Discussion of Dr. Tversky's Opinions.

A. Opinions.

Dr. Tversky starts with the same foundational facts as Dr. Wagner. He states that gadolinium is toxic, GBCAs dechelate in the body, gadolinium is retained in the bodies of individuals with normal renal function, and it causes NSF, which is just a form of gadolinium-induced toxicity in humans that represents the severe end of a continuum of adverse effects caused by gadolinium. Doc. 154-9 at 1-8. He opines that impaired renal functioning is not a prerequisite for the development of NSF, nor does every gadolinium-induced injury manifest as NSF. *Id*. at 4, 14. He opines that NSF is caused by an increased retention of gadolinium, and it is probable that the tissue injury that occurs in NSF patients is similar to the injuries experienced by patients with normal kidney function because both injuries arise from exposure to gadolinium retained in the body in a dechelated state. *Id*. at 6.

Dr. Tversky states that medical case reports describe adverse events attributed to GBCAs in patients with normal renal function. Patients appear to suffer from symptoms that are milder than NSF, but in many cases are consistent with the early symptomatology seen in NSF patients. *Id*. at 8. He notes that by September 2018, the FDA accumulated several hundred adverse events reports tied to linear GBCAs in patients with normal renal function. *Id*. Symptoms varied, but tended to cluster around skin, muscle, bone, and the nervous system, as well as chronic pain. *Id*. Other symptoms included thickening and tightening of the skin, pain in the extremities, persistent headache, and mental fogginess. *Id*. It is unknown what conditions increase the risk for an individual to experience gadolinium toxicity. *Id*. at 10. The disease presentations are varied and seem unique to

individual patients. *Id*. at 15. Finally, Dr. Tversky applies the Bradford Hill criteria to evaluate the association between gadolinium retention and toxic effects in patients with normal renal function. *Id.* at 10-14.

B. Analysis.

1. Dr. Tversky's Assumptions.

Throughout his opinion, Dr. Tversky relies on NSF data. He concludes that because dechelated gadolinium is toxic, gadolinium is retained in the tissues and organs of individuals with normal kidney function, and the accumulation of gadolinium appears to be dose-dependent – meaning that more exposure to GBCAs equates to a higher risk of accumulation – then "gadolinium accumulation and toxicity among patients with renal insufficiency . . . share parallel mechanisms compared to those with normal renal function." Doc. 154-9 at 5. But he cites no evidence that retention in patients with normal renal function is equal in method or quantity to the accumulation in renally-impaired patients, and he merely assumes as probable that "tissue injury that occurs from GBCAs in renally impaired patients shares the same mechanisms of toxic injury with patients who have normal kidney function." *Id*. at 6. Confusingly, he also asserts twice that gadolinium tissue retention alone does not lead to disease, when his theory seems to be that gadolinium retention causes these adverse effects. *Id*. at 7-8. And he offers no citation for one of his most crucial assertions – that patients' symptoms matched early manifestations of NSF.

Dr. Tversky's vague language describing the disease process makes it near impossible to assess the reliability of his theory. *See id*. at 5 (describing parallel mechanisms of causing injury), 6 (stating that it is probable that there are shared mechanisms for causing toxic injury). It is unclear how Dr. Tversky can make the leap that gadolinium retention in patients with healthy kidneys is the same as accumulation in NSF patients and will cause the same type of symptoms, particularly when there are

unknown variables (as he acknowledges) that affect the progression of NSF. Doc. 154-9 at 7. And he provides no concrete information demonstrating how the injury occurs.

Essentially, Dr. Tversky presents a hypothesis that if gadolinium is not cleared from the body in one type of patient and causes disease, then gadolinium that is retained in another type of patient, possibly in a different manner, causes disease too. The disease caused by the latter situation is both similar to the former and different, and it is unknown how or why it is different or what causes the differences. This broad hypothesis, which Dr. Tversky does not show to be validated by reliable principles and methods, is not admissible under Rule 702(c). *See In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 450 (S.D.N.Y. 2016) ("By assuming, without any apparent basis, that secondary perforation is an undisputed phenomenon, and then positing a mechanism by which she believes it may occur, [the doctor] indulges in at most, scientifically-grounded speculation: an untested and potentially untestable hypothesis." (internal quotation marks and citation omitted)); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 684 (M.D. N.C. 2003) ("While hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination of whether liability exists. Ultimately, speculation is unreliable evidence and is inadmissible.").

2. Questionable Evidence.

Dr. Tversky relies on a number of studies to assert that gadolinium causes acute and chronic tissue damage in both humans and animals. *See* Doc. 154-9 at 6. But he offers only one-line conclusions summarizing the results of these studies with no explanation about why these studies can reliably be applied to the causation issue in this case or how they relate to his opinions. For example, without context, he states: "free gadolinium has been shown to damage lung tissue in rats" and "[g]adolinium causes destruction and death of fibroblast cells in rats that may lead to tissue fibrosis and scarring." *Id*. at 6. This is particularly concerning given that most of the results of the

studies seem irrelevant to the question at hand. For example, Dr. Tversky cites a study examining gadolinium chloride – which Plaintiffs never show to be relevant to any issue in this case – and another concerning NSF. *Id*. He cites two NSF studies to support the statement that gadolinium damages rat and human fibroblasts. *Id*. The Court cannot determine how reliably these studies can be used to support Dr. Tversky's conclusions regarding a gadolinium-illness continuum because he provides no analysis or support. Dr. Tversky may rely on other scientists' work, but he must explain why it supports his opinion and why it is reliable. *See Daubert II*, 43 F.3d at 1318.

Dr. Tversky also relies largely on case reports. But he mischaracterizes the number of reports that support his theories. He states that "[b]y September 2018, the FDA accumulated over 14,000 adverse events associated with linear GBCAs." Doc. 154-9 at 8. He states that "at least several hundred" of these individual case reports occurred in patients with normal renal function who developed chronic symptoms after having been exposed to a GBCA. *Id*. During his deposition, Dr. Tversky testified that he came up with these numbers in his own review of the FDA database. But surprisingly, he admitted that the 14,000 number included NSF cases, and he could not provide the number of non-NSF cases, a significant deficiency for his opinions in this non-NSF case. The best he could say is that "[i]t's somewhere between 132 and 14,000." Doc. 155-2 at 40. This kind of imprecision compounds the lack of reliability in case reports.[10]

Plaintiffs argue that Dr. Tversky properly relied on extensive literature to support his opinions, including animal, in vitro, in vivo, toxicological, mechanistic, and observational studies. Plaintiffs assert that the following studies considered by Dr.

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[10] The 2017 MIDAC report Dr. Tversky cites to support this statement identified 139 patients with normal renal function and adverse events in conjunction with gadolinium retention – 98 from the medical literature and 41 from FAERS. Doc. 154-43 at 40. The only other source he cites to support the number of identified adverse events is the FDA public dashboard, which is a link to the FDA's homepage and does not provide any specific information related to the FAERS reports. *Id*. And he cites the Semelka (2016) study instead of any of the FAERS reports when categorizing the symptoms found in the FAERS reports. *Id*.

Tversky support his opinions: (1) Agarwal (2014), which is a comprehensive review and meta-analysis of NSF; (2) Do (2014), a study analyzing a type of MRI contrast, tissue gadolinium, and fibrosis; (3) Gibby (2004), a study demonstrating GBCA retention in human bone; (4) Kanda (2014), a study demonstrating retention in the human brain; (5) Knoepp (2017), a study demonstrating the effect of GBCAs on human epithelial channels; and (6) Gathings (2015), a case study about gadolinium-associated plaques.

After reviewing these studies, the Court cannot conclude that they reliably move Dr. Tversky's opinion from hypothesis to conclusion. Agarwal and Do involved NSF and do not look at adverse health effects in patients with normal renal function. *See* Agarwal et al. (2014), Doc. 191-14 at 2 (finding an association between GBCAs and the development of NSF); Do et al. (2014), Doc. 191-7 (concluding that different types of GBCAs can cause NSF). Gibby and Kanda examined gadolinium retention, but they do not identify any injuries or adverse effects. Gibby et al. (2004), Doc. 191-8; Kanda et al. (2014), Doc. 191-9. Knoepp found that gadolinium ions released from linear GBCAs reduced the activity of human epithelial sodium channels, and that this effect was not observed with macrocyclic GBCAs. Knoepp et al. (2017), Doc. 191-10 at 9. But the authors noted that all remarks were speculative and required further investigation. *Id.* The authors also concluded that the low incidence of side effects should not affect the use of GBCAs in healthy individuals. *Id.* The final study, Gathings, is the plaque case study involving two patients who exhibited skin plaques with markers of NSF. *See* Gathings et al. (2015), Doc. 191-11. As noted above, this case study certainly could prompt a hypothesis that GBCAs can cause NSF-like symptoms, but it does not provide a reliable basis for Dr. Tversky's general causation opinion. Again, "case reports raise questions, they do not answer them." *McLain*, 401 F.3d at 1245.

Finally, Dr. Tversky fails to address the five human studies discussed above with respect to Dr. Wagner's opinions. These relevant studies suggest that there is no link between GBCAs and many of the symptoms amalgamated in GDD.

3. Bradford Hill Criteria.

"The Bradford Hill criteria are metrics that epidemiologists use to distinguish a causal connection from a mere association." *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 795 (3rd Cir. 2017). "These criteria 'start with an association demonstrated by epidemiology and then apply' eight or nine criteria to determine whether that association is causal." *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018) (quoting *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1234 (D. Colo. 1998)). The criteria can be summarized as follows:

> **Strength of Association**. There must be some degree of statistical association between a cause and its effect. A strong association (large in magnitude) is more likely to represent causation than a weak association (small in magnitude).
>
> **Temporality**. A cause must precede its effect. Strength in temporality, such as when a cause immediately precedes its effect, supports an inference of causation.
>
> **Biological Plausibility**. A cause and effect relationship between exposure and disease should be biologically plausible with other information about the disease or harm.
>
> **Coherence**. A cause and effect relationship between exposure and disease should be consistent with other information about the disease or harm.
>
> **Dose-Response Effect**. Causation is more likely if greater amounts of the putative cause are associated with corresponding increases in the occurrence of disease or harm.
>
> **Consistency**. When similar findings are generated by several epidemiological studies involving various investigators, causation tends to be supported.
>
> **Analogy**. Substantiation of relationships similar to the putative causal relationship increases the likelihood of causation.
>
> **Experimental Evidence**. Causation is more likely if removing the exposure in a population results in a decrease in the occurrence of disease or harm.

> **Specificity**. When there is but a single putative cause for the disease or harm, causation is supported.

See In re Mirena IUS, 341 F. Supp. 3d at 242-43; *see also Zoloft*, 858 F.3d at 795.

Dr. Tversky's Bradford Hill analysis is the centerpiece of his report. Doc. 154-9 at 10-14. He uses this analysis to conclude that GBCAs cause a range of symptoms in patients with normal renal function. *Id.* at 16. Although Bradford Hill is a well-recognized method for evaluating causation, the Court finds that Dr. Tversky has not applied it reliably as required by Rule 702(d). The Court will address the criteria in the order they appear in his expert report.

a. Strength of Association.

The Reference Manual provides this helpful guidance on the need for an association:

> the first question an epidemiologist addresses is whether an association exists between exposure to the agent and disease. An association between exposure to an agent and disease exists when they occur together more frequently than one would expect by chance. Although a causal relationship is one possible explanation for an observed association between an exposure and a disease, an association does not necessarily mean that there is a cause-effect relationship.

2011 WL 7724261 at *10 (footnote omitted).

The Reference Manual makes clear that the observed association is the trigger – the starting point – for the causation analysis. "*Once an association has been found* between exposure to an agent and development of a disease, researchers consider whether the association reflects a true cause-effect relationship." *Id.* at *28 (emphasis added). "We emphasize that [the Bradford Hill criteria] are employed *only after a study finds an association* to determine whether that association reflects a true causal relationship." *Id.* (emphasis added); *see also In re Mirena IUS*, 341 F. Supp. 3d at 242 ("There must be some degree of statistical association between a cause and its effect."); *Dunn* 275 F. Supp. 2d at 678-79 ("The greater weight of authority supports Sandoz' assertion that [use

of] the Bradford Hill criteria is a method for determining whether the results of an epidemiologic study can be said to demonstrate causation and not a method for testing an unproven hypothesis."); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 514 (W.D. Pa. 2003) ("The Bradford-Hill criteria 'were developed as a mean[s] of interpreting an *established association* based on a body of epidemiologic research for the purpose of trying to judge whether the observed association reflects a causal relation between an exposure and disease.'" (quoting report of court-appointed expert)).

As these authorities make clear, the association that starts the Bradford Hill analysis normally is established by an epidemiologic study. But in this case, Plaintiffs admit that "there are no epidemiologic studies in patients with normal renal function concerning the long-term effects of gadolinium." Doc. 192 at 9. And Dr. Tversky does not find such an association elsewhere – he identifies no study-established association between GBCAs and GDD.

Not to be deterred from reaching his causation conclusion, Dr. Tversky launches his Bradford Hill analysis on the basis of a different association – the association between GBCAs and NSF. Doc. 154-9 at 10. He begins: "The best-known and most studied population of patients that have suffered injury from gadolinium toxicity are those renally impaired patients diagnosed with NSF." *Id*. But the purpose of his Bradford Hill analysis is not to show a causal link between GBCAs and NSF. It is to show a causal link between GBCAs and GDD. Dr. Tversky starts his causation analysis with the wrong illness.

After discussing the association between GBCAs and NSF and citing studies that support such an association, Dr. Tversky says this about Plaintiffs' illnesses: "As to the effect of gadolinium retention in patients with normal renal function, there is no medical or scientific reason to expect any less toxic effect of retained gadolinium in human tissue from linear GBCAs." *Id*. Thus, rather than identifying an established association between GBCAs and GDD, he assumes an association. Rather than presenting evidence

of an association, he flips the burden of proof and states that there is no reason to expect it does not exist. As the authorities cited above emphasize, however, this is an incorrect application of the first Bradford Hill criterion. Dr. Tversky never attempts to explain why the first criterion can be applied to an association between GBCAs and NSF. And the lack of a study-established association between GBCAs and GDD appears to be a primary reason that regulatory and medical bodies around the world have been unwilling to find causation.

At the end of his discussion of the first Bradford Hill criterion, Dr. Tversky seems to concede that he cannot evaluate strength of association when no association has been shown to exist. He refers to strength of association as "effect size" (Doc. 154-9 at 10), explains his view that doctors may be confused into underdiagnosing GDD because the misnomer in NSF (nephrogenic) causes them to assume that the symptoms can appear only in patients with impaired kidneys, and then states: "For this and other reasons [that he never identifies] it is not possible to state precisely the size of the effect of gadolinium toxicity in renally sufficient patients." Doc. 154-9 at 10-11. In other words, it is not possible to state the strength of association between GBCAs and GDD in kidney-healthy patients like Plaintiffs. *Id.* And yet that is the very thing the first Bradford Hill factor requires an expert to address. *See In re Mirena IUS*, 341 F. Supp. 3d at 242 ("There must be some degree of statistical association between a cause and its effect. A strong association (large in magnitude) is more likely to represent causation than a weak association (small in magnitude).").

b. Consistency.

This factor considers whether similar findings have been generated by several studies involving various investigators. Is there a consistency among the various studies that have evaluated the link between the substance and the illness it is alleged to cause? Dr. Tversky does not start his analysis of this factor with a consistency among any studies about GBCAs and GDD. Instead, he again he looks at NSF: "This criterion has been

met, certainly in the context of NSF where the strongest signal of gadolinium toxicity was first recognized." *Id.* at 11.

Although he later appears to broaden his focus to gadolinium-caused symptoms generally, the only source he cites is the FAERS database. *Id.* He notes that 80% of symptoms reported in the database associated with GBCAs involved the skin, nervous system, or musculoskeletal system. *Id.* As noted above, however, the FAERs database consists of a collection of individual reports made to the FDA from a broad range of sources, many of them not scientific or even medical. It certainly does not meet the consistency criterion of Bradford Hill – it does not constitute a series of scientific studies completed under carefully controlled conditions. Even the FDA states that "FAERS data cannot be used to calculate the incidence of an adverse event[.]" Questions and Answers on FAERS, https://www.fda.gov/ drugs/surveillance/fda-adverse-event-reporting-system-faers (last visited July 8, 2019).

c. Specificity.

The Reference Manual provides this explanation of specificity:

> An association exhibits specificity if the exposure is associated only with a single disease or type of disease. The vast majority of agents do not cause a wide variety of effects. For example, asbestos causes mesothelioma and lung cancer and may cause one or two other cancers, but there is no evidence that it causes any other types of cancers. Thus, a study that finds that an agent is associated with many different diseases should be examined skeptically.

2011 WL 7724261 at *31 (footnotes omitted).

Dr. Tversky's discussion of specificity focuses on NSF. He notes that gadolinium is the primary cause of NSF, there have been no reliable reports of NSF without gadolinium exposure, and cases of NSF dropped when the use of GBCAs in renally-impaired patients dropped. Doc. 154-9 at 11-12. "This fact alone," he states, "is strong confirmation of a cause and effect relationship." *Id.* at 11. But again, the question in this case is not whether GBCAs cause NSF. And the only comment Tversky makes about

GDD and specificity is this: "the pattern of disease, history of exposure to linear GBCA and cluster of symptoms noted in NSF is very similar to that seen among patients with normal renal function." *Id.* Dr. Tversky does not explain how "very similar" is the equivalent of specificity.

Nor does he attempt to reconcile the fact that GBCAs are claimed in this case to cause a wide variety of symptoms in patients with healthy kidneys, with the fact that "[a]n association exhibits specificity if the exposure is associated only with a single disease or type of disease." Reference Manual, 2011 WL 7724261 at *31. To the contrary, Dr. Tversky acknowledges that "a universal set of symptoms associated with exposure to GBCAs has not yet been established among patients with normal renal function[.]" Doc. 154-9 at 12. And even if there was a study linking GBCAs to the wide range of symptoms claimed by Plaintiffs, it would be viewed with doubt: "a study that finds that an agent is associated with many different diseases should be examined skeptically." Reference Manual, 2011 WL 7724261 at *31.

d. Temporality.

This factor considers timing – when the disease appears in relation to exposure. Logically, "[i]f an exposure causes disease, the exposure must occur before the disease develops. Reference Manual, 2011 WL 7724261 at *29. Dr. Tversky again talks mostly about NSF, but states: "all credible reports of GBCA induced disease in patients with normal renal function must occur sometime after exposure." Doc. 154-9 at 12. He states that credible reports "must occur" after exposure, but he does not state whether they do. And he cites no studies or other authorities on the subject.

Temporality also considers whether symptoms arise close in time to exposure. "Strength in temporality, such as when a cause immediately precedes its effect, supports an inference of causation." *In re Mirena IUS*, 341 F. Supp. 3d at 242. On this point, Dr. Tversky notes that "[f]rom cases of NSF we learned that there can be a wide range of temporality in terms of the onset of symptoms after exposure to GBCAs." Doc. 154-9

at 12. Elsewhere in his report he notes that symptoms can occur days, months, or even years after exposure. *Id.* at 15. And he acknowledges that "we can expect a range in time from exposure to manifestation of disease." *Id.* at 12. He never explains how such wide-ranging timing supports the temporality criterion of causation.

e. Biological Gradient.

This factor is referred to in different sources as the "dose-response effect." It is premised on the notion that "[c]ausation is more likely if greater amounts of the putative cause are associated with corresponding increases in the occurrence of disease or harm." *In re Mirena IUS*, 341 F. Supp. 3d at 242. Without citing any specific study, Dr. Tversky asserts that gadolinium toxicity "has been shown to be dose dependent in both humans and animals." Doc. 154-9 at 12. He does not explain how this assertion squares with Dr. Wagner's opinion that "there does not appear to be a minimum threshold dose for appearance or occurrence of NSF." Doc. 154-10 at 16; *see also id.* at 17 ("[E]ven a miniscule amount of a GBCA is capable of triggering GBCA-induced systemic fibrosis.").

With respect to dose dependency in GDD, Dr. Tversky offers only this: "Selection bias is plausible, however given the lessons learned from renally impaired patients and animal models, in my opinion a true biological gradient does exist." Doc. 154-9 at 12. This is unvarnished *ipse dixit*. And he adds: "Individual susceptibility as well as other risk factors play a role in the extent of health effects experienced by any given patient." *Id.* He never identifies these "other risk factors," but this statement seems to be a concession that GDD symptoms are not dose dependent – that other factors influence their appearance and severity.

f. Plausibility.

This factor notes that "[a] cause and effect relationship between exposure and disease should be biologically plausible with other information about the disease or harm." *In re Mirena IUS*, 341 F. Supp. 3d at 242. As Dr. Tversky notes, this normally

requires "a plausible mechanism between cause and effect." Doc. 154-9 at 12. Dr. Tversky admits that the mechanisms for gadolinium toxicity "are not fully elucidated." *Id.* And in place of describing the mechanism that renders his causation opinion plausible, he again resorts to burden-shifting: "The experience of NSF established that de-chelated gadolinium is toxic and causes severe even lethal damage in humans. There is no evidence that renal function alters the fact or nature of that toxicity." *Id.* at 13. This, of course, presents no plausible mechanism by which GBCAs cause GDD. Dr. Tversky simply assumes plausibility in the absence of contrary evidence.

g. Coherence.

This factor notes that "[a] cause and effect relationship between exposure and disease should be consistent with other information about the disease or harm." *In re Mirena IUS*, 341 F. Supp. 3d at 242. After discussing the recognized cause of NSF, Dr. Tversky resorts to conclusions: "symptom[s] among individuals without renal impairment exposed to GBCAs overlap[] with those of patients with NSF," patients with healthy kidneys retain gadolinium, and "[t]he evidence shows that gadolinium exposure from linear GBCAs will lead to injury in some patients regardless of renal function." Doc. 154-9 at 13. He summarily compares GDD causation to NSF, but he does not address what this factor considers: whether GBCA causation of GDD is consistent with other information known about GDD. *In re Mirena IUS*, 341 F. Supp. 3d at 242.

h. Experiment.

This factor focuses on what has been learned from experimentation: "Causation is more likely if removing the exposure in a population results in a decrease in the occurrence of disease or harm." *Id.* Dr. Tversky does not identify any experimentation regarding GDD, but instead notes the evidence that GBCAs cause NSF. He then states: "As awareness increases, well-vetted case reports will be added to the FDA database and other directories so that more robust calculations can be made." Doc. 154-9 at 13. His

message seems to be: "we don't have experimentation data yet, but I am sure it is coming." Such speculation cannot be used to prove causation.[11]

i. Analogy.

This factor notes that "[s]ubstantiation of relationships similar to the putative causal relationship increases the likelihood of causation." *In re Mirena IUS*, 341 F. Supp. 3d at 242. The analogy Dr. Tversky points to, of course, is NSF. Doc. 154-9 at 13. And it does appear to be relevant.

j. Bradford Hill Summary.

In summary, with the exception of the last of nine factors – analogy – Dr. Tversky does not reliably apply any of the Bradford Hill criteria. His opinion therefore is not admissible under Rule 702(d).

4. General Acceptance in the Scientific Community.

As with Dr. Wagner's opinions, the methods Dr. Tversky uses for reaching his opinions are not shared by the many regulatory and medical organizations that have examined the same evidence. The Court therefore "may fairly suspect that [his] principles and methods have not been faithfully applied." Fed. R. Evid. 702 advisory committee's note to 2000 amendment; *see also Lust*, 89 F.3d at 598.

C. Conclusion.

Plaintiffs have not shown by a preponderance of the evidence that Dr. Tversky's opinions are based on reliable principles and methods that have been applied to the facts of this case reliably. His opinions therefore are not admissible under Rule 702(c) and (d).

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[11] With respect to experimentation, Plaintiffs assert repeatedly in their briefs that prospective, blind studies – giving GBCAs to some patients and not to others to see what differences are produced – are not ethical. *See, e.g.*, Doc. 185 at 17. But they never dispute that other kinds of valid epidemiological studies are possible. Dr. Tversky notes that "[e]xperimental evidence must be based upon animal models and retrospective cohort analysis in humans." Doc. 154-9 at 13. But he does not discuss the five human studies discussed above. And the authors of the Parillo (2016) study propose prospective studies with active surveillance of symptoms. Doc. 154-26 at 7.

VIII. Rule 702(c) and (d) – Specific Discussion of Dr. Whittaker's Opinions.

Dr. Whittaker, a Ph.D. toxicologist, adopts an approach similar to Drs. Wagner and Tversky. She notes that linear GBCAs are retained in the bodies of MRI patients with healthy kidneys. Doc. 154-11 at 17. She opines that GBCAs dechelate in the body. *Id.* at 18. And she asserts that gadolinium is highly reactive and toxic in its free, ionic form. *Id*. at 19. She opines that gadolinium and linear GBCAs have a proliferative effect on fibroblasts – the type of cell that is responsible for making and maintaining connective tissue. *Id*. at 20. An overabundance of fibroblasts can result in a condition known as fibrosis. *Id*. Dechelated or free gadolinium can also become a competitive inhibitor of important physiologic processes that depend on calcium. *Id*. And she reviews the science showing that GBCAs cause NSF. *Id.* at 22-23.

A. Description of GDD.

To define and describe GDD, Dr. Whittaker turns to other evidence. She cites three articles by Semelka, et al., for the proposition that GDD is a disease in subjects with normal or near normal renal function who develop persistent symptoms after receiving GBCAs. *Id*. at 23, 43-44.

The first article does not purport to show that GBCAs cause GDD. In fact, it is titled "*Presumed* Gadolinium Toxicity in Subjects With Normal Renal Function." Doc. 187-34 (emphasis added). The article is a five-page report on four individual cases of persons who developed various symptoms after receiving GBCA-enhanced MRIs. *Id.* This is the article's conclusion:

> In summary, we report 4 patients with normal renal function, who developed clinical symptoms arising shortly after receiving GBCA administration and who developed an apparent toxicity to it. This disease may share clinical manifestations with NSF but in less severe form. Importantly, it is unknown which GBCA agents may cause this collection of signs and symptoms. Well-designed clinical studies are warranted to investigate this presumed disease more fully[.]

Id. at 6. The article treats case reports appropriately – it uses them to raise questions, not answer them. *See McLain*, 401 F.3d at 1245. The article advances a hypothesis – "[t]his disease may share clinical manifestations with NSF" – and recommends that it be investigated through clinical studies.

The second Semelka article is not a scientific study. It is a four-page article based on an on-line survey of 42 people from two gadolinium toxicity support groups. Doc. 156-16 at 2-3. The survey was anonymous – meaning that the people responding did not even have to identify themselves – and asked a series of questions about their claimed conditions. *Id.* The authors acknowledged the limitations of their work:

> There are various limitations of our study. *Major problems* include that it is a survey and relies on knowledge and integrity of the respondents. Despite that a survey provides all the participants with a standardized stimulus, eliminating researcher's own biases, *it is recognized that self-report studies may have validity problems*. Although the study is subjective, in that we rely on patient descriptions, it should also be appreciated that there was a generally common pattern of symptomatology. A control group of subjects who received multiple administrations of GBCAs, but who do not have symptoms would be helpful.

Id. at 5 (emphasis added).

The third Semelka article does not purport to establish causation. The four-page article notes that some studies have confirmed that GBCAs can deposit in the brain and in bone, but states: "To our knowledge, neither the bone deposition first reported by Gibby et al. nor the brain deposition first reported by Kanda et al. have been associated with recognized disease." Semelka et al., Gadolinium in Humans: A Family of Disorders, https://www.ajronline.org/doi/pdf/10.2214/AJR.15. 15842 at 229-30 (last visited July 8, 2019) (footnotes omitted). The article recounts reports from patient advocacy groups of various symptoms that developed after receipt of GBCAs, and states: "Our *preliminary investigation* has convinced us that this phenomenon is a true disease process, which we propose naming 'gadolinium deposition disease.'" *Id.* at 230 (emphasis added).

Dr. Whittaker next cites a survey that reports various symptoms in 17 patients. Doc. 154-11 at 24. The survey was copyrighted by www.GadoliniumToxicity.com, the website for a gadolinium-related patient advocacy group and was written by two of the survey participants. *See* Gadolinium Toxicity: A Survey of the Chronic Effects of Retained Gadolinium from Contrast MRIs, https://gdtoxicity.files.wordpress.com/2014/09/gd-symptom-survey.pdf at 1, 10 (last visited July 9, 2019). The authors stated that "[t]he conclusions are based on a small sample and suggest[ed] that a larger study should be conducted," and that "[n]o attempt is made to determine what, if any, level of Gadolinium, is safe to remain in the body." *Id.* at 1.

Dr. Whittaker cites the similar Burke (2016) survey of 50 anonymous, self-reporting individuals who identified the top three adverse effects of GDD as bone and joint pain, head and neck pain, and skin problems. Docs. 154-11 at 24; 187-33 at 2. The survey authors acknowledged that, as an anonymous survey, the study has validation issues due to patients forgetting important details or exaggerating symptoms. Doc. 187-33 at 3. Another recognized limitation of this survey is selection bias, "as self-selected volunteers completed [the] survey" and the symptoms may have been self-reported by patients who did not have documented gadolinium retention. *Id.* The authors also stated that the "risk of severe adverse reaction to GBCA exposure is extremely small, hence it may be difficult to determine characteristics of individuals that predispose to this type of reaction," but it could be caused by an individual genetic abnormality. *Id.* (footnotes omitted).

The authors of the Burke article concluded:

> This survey represents a first description of patients with normal renal function who self-described toxicity related to GBCA administration. Despite its limitations, our opinion is that there most likely is toxicity associated with GBCA administration in patients with normal renal function. At the very least, this study highlights the need to further investigate the subject of patients with normal renal function who complain of severe long-lasting symptomatology following GBCA administration.

Id. Dr. Whittaker does not address the inherent limitations of this survey, nor those recognized by the authors.

Dr. Whittaker next turns to the FDA's FAERS database. She notes that a 2017 FDA analysis identified 139 adverse events related to GBCAs in healthy patients, 41 from FAERS and 98 from medical literature. *Id.* at 25. She asserts that the FDA analysis identified a clustering of symptoms around cutaneous, musculoskeletal, cognitive or neurological, and pain syndrome clinical categories. *Id*. at 25-26.

Dr. Whittaker does not note the limitations in this data. The FDA medical officer who presented this data at the 2017 MIDAC conference, Dr. David Croteau, stated that 7 of the 41 cases from the FAERS database reflected gadolinium retention with no adverse health events, only 5 of the 98 literature cases had documented gadolinium retention, and 92 of the literature cases "were from two online surveys posted to a private blog on a gadolinium toxicity support group website and a public gadolinium toxicity Facebook page." MIDAC Trans., Doc. 156-7 at 149-50. The data actually included a wide range of 39 symptoms, with a median of 7 symptoms per patient. *Id*. at 152. Dr. Croteau further explained: "Even though published in peer-reviewed journals, those two surveys could have been excluded from the review given the nature of the data provided, but it was felt important to include all the data published, given the overall paucity of data on the topic." *Id.* at 150. Dr. Croteau added this caveat: "It's also important to point out that the bulk of the medical literature cases, that is, 96 out of 98 cases, were authored by the same UNC Chapel Hill radiology group, leading to possible duplicate cases and an actual total number of medical literature cases lower than 98." *Id.*

Additionally, although Dr. Whittaker focuses on clustering around four categories of symptoms, Dr. Croteau stated that "[d]espite clustering around certain clinical categories, the marked heterogeneity of clinical adverse events reported makes interpretation of the data challenging. In addition, many factors may influence the interpretation of the data and may result in either an over- or underestimation of the

importance of the problem." MIDAC Trans., Doc. 156-7 at 158; *see also* Doc. 154-43 at 14 (MIDAC Briefing Document) ("[W]e observed some clustering around cutaneous, musculoskeletal, neurological/cognitive, and pain syndromes clinical categories. However, the clinical category "other" accounted for the highest number of adverse events, emphasizing the heterogeneity of the adverse events reported."). Dr. Croteau then discussed some of these factors, including "unverified self-reported information" and "alternative etiology" – meaning alternative causes – for the symptoms. *Id.* at 157-58. He concluded: "at this juncture, considering the totality of the data, including case reports, case series, and published online surveys identifying our review along with the data limitations outlined earlier, we are unable to determine a causal association between reported clinical adverse events and GBCA exposure." *Id.* at 161.

Dr. Whittaker notes that in 2017 and 2018, the FDA reportedly received another 623 claimed adverse events related to linear GBCAs. *Id.* at 26. These included 25 different categories of symptoms, and, she notes, large numbers of cutaneous, musculoskeletal, cognitive or neurological, and pain syndrome clinical categories. *Id.* But her citation for this data is simply to the FAERS Public Dashboard (*id.* at 46), suggesting that Dr. Whittaker must have counted these events herself. She says nothing about how she identified or counted these events, and nothing about the reliability of the data – clearly an important issue in light of the FDA's own recognition of the data's limitations in its MIDAC presentation noted above.

B. Toxicological Studies.

Dr. Whittaker next turns to toxicological investigations of adverse effects of GBCAs. She notes, but does not discuss, 16 toxicological investigations done in connection with the FDA's approval of six linear GBCAs. *Id.* at 28. The investigations presumably contributed to the FDA's decision to approve the GBCAs for public medical use. Dr. Whittaker then focuses her attention on studies related to three categories of potential harm: neurotoxicity, cutaneous toxicity, and nephrotoxicity.

1. Neurotoxicity.

Dr. Whittaker discusses three rodent studies: (1) a 1986 paper by Taber and Bryan that concluded there was a "potential danger" if GBCAs "were allowed direct access to the brain"; (2) a 1994 study where rats were injected with GBCAs following disruption of their blood-brain barrier, which "reported no gross neurological toxicity"; and (3) a 2018 study, discussed above, where the babies of mice injected with GBCAs displayed abnormal behavior and decreased muscle strength. *Id.* at 28-29. She also discusses the study in which dogs whose blood-brain barriers had been disrupted were injected with GBCAs. *Id.* at 28.

Apparently because two of the three rodent studies she discusses were less than conclusive – one reported only a "potential danger" and the other found no neurological toxicity – Dr. Whittaker states that "[t]here is disagreement among scientists regarding the utility of using rodents for evaluating the neurotoxicity of GBCAs." *Id.* at 29. She then cites a fourth rodent study by Lohrke et al. (2017), which asserted that rats were suitable test subjects but found no "histological [i.e, microscopic] changes in the brain of rodents administered GBCAs." *Id.* Dr. Whittaker dismisses this fourth study as lacking a "robust assessment of neurotoxicity," concludes that it "does not answer the question of whether exposure to any of the GBCAs resulted in neurological impairment," and alternatively notes that "it may also be the case that the rodent is not a good model to assess impaired neurological function following exposure to linear GBCAs." *Id.*

All of this leaves Dr. Whittaker's discussion of neurotoxicity rather muddled. Three of the four studies are inconclusive, two suggest that GBCAs do not cause neurotoxicity, and the fourth concerned only behavior and muscle strength in baby mice. The only other neurotoxicity study mentioned by Dr. Whittaker is the dog study, which she seeks to elevate with this speculation: "the primitive nature of the rat brain . . . may explain why adverse neurological effects were reported in a canine study." *Id.* But she never explains why the dogs in question were suitable test subjects for evaluating the

effects of GBCAs in humans with healthy kidneys, whether the doses given to the dogs were relevant to humans, and why disruption of the dogs' blood-brain barriers produced results that can be used to draw conclusions for humans with healthy kidneys. In sum, Dr. Whittaker's discussion of neurotoxicity studies provides no scientific basis for concluding that GBCAs cause GDD.

2. Cutaneous Toxicity.

Dr. Whittaker opines that "[s]kin lesions similar to those reported among patients with NSF have been reported in laboratory animals exposed to linear GBCAs, and animal studies also confirm that exposure to linear GBCAs is associated with organ-specific increases in fibrotic tissue." *Id.* at 30. She further asserts:

> For assessing cutaneous toxicity of linear GBCAs, rodent studies reliably mimic effects in the skin that appear to be associated with GBCA exposure. Available human case report data and studies in animal models and cell systems indicate that cutaneous toxicity is a risk factor for humans with normal renal function who are exposed to linear GBCAs.

Id. But she provides no citations for this statement, and no explanation of why rodent and humans skin are sufficiently similar to justify the comparison.

She then cites three rodent studies, Plunkett et al. (1992), Lohrke et al. (2017), and Do et al. (2014), to support her opinion that GBCAs can cause skin problems in humans with normal kidney function. Doc. 154-11 at 30. (The Lohrke study, by the way, is the one she criticized on the previous page as lacking a "robust assessment." *Id.* at 29.) But she never addresses dose or other distinguishing characteristics of these studies. As noted above, dose matters when extrapolating from animal studies. *See* Reference Manual, 2011 WL 7724262 at *8.

The Plunkett study injected rats with GBCA doses of 0.1, 2.0, and 5.0 mmol/kg three times per week for three weeks. Doc. 154-11 at 30. It found skin lesions only in rats that received the highest dose – 50 times higher than the lowest doses. *Id.* Rats in the Lohrke study were injected with 20 daily intravenous injections of GBCAs at a dose

of 2.5 mmol/kg. Four of ten in the linear GBCA group were later found to have skin lesions. Rats in the Do study had their kidneys removed and were injected with a daily GBCA dose of 2.5 mmol/kg over a period of four weeks. Some of the animals were later found to have greater epidermal thickness and fibronectin production. *Id.*; Do et al. (2014), Doc. 191-7.

Dr. Whittaker never explains why the high doses in these studies are comparable to doses humans might receive with MRI contrast agents. Nor does she explain why removal of the kidneys in the Do study produced results relevant to GBCA effects in humans with normal kidneys.

3. Nephrotoxicity.

Nephrotoxicity means toxicity to the kidneys. Dr. Whittaker discusses three studies, one on dogs and two on rats, that suggest GBCAs can result in nephrotoxicity. Doc. 154-11 at 31. But she never explains why the rats and dogs in these studies are appropriate subjects for demonstrating human effects, and she never addresses the relevancy of the doses used in the studies. What is more, she does not explain why nephrotoxicity is even relevant to this case. It is not one of the primary symptoms Dr. Whittaker identifies for GDD (cutaneous, musculoskeletal, neurological/cognitive, and pain syndromes (Doc. 154-11 at 25-26)), and although Ms. Fischer alleged kidney damage in her original complaint, she did not include kidney injury in her amended complaints or her deposition testimony. *See* Doc. 154-2 at 15; Fischer Docs. 1, 10, 60. Additionally, both Ms. Fischer and Ms. Davis allege gadolinium retention in the kidney as an injury, but neither refers to toxicity or injury of the kidney. Doc. 142 ¶ 4; Fischer Doc. 10 ¶ 3.

4. Toxicological Studies Summary.

Although Dr. Whittaker is a toxicologist, her discussion of toxicological studies suffers from many shortcomings. The studies she addresses under neurotoxicity are more unfavorable than favorable to her opinion, and she never explains why they reliably

support her opinions. She fails to show the relevancy of the studies she discusses under cutaneous toxicity. She provides no support for her assertion that rodent studies reliably mimic human skin response, she never addresses whether the high doses in these studies are comparable to doses humans might receive with MRI contrast agents, and she does not explain why removal of the kidneys from rodents in the Do study produced results relevant to this case. Her nephrotoxicity discussion likewise fails to address the relevancy of rodent and canine studies or the doses used in the studies, and she does not explain the relevancy of nephrotoxicity to any issue in this case. The Court cannot conclude by a preponderance of the evidence that her reliance on these various studies constitutes the use of reliable principles and methods as required by Rule 702(c).

C. Bradford Hill Criteria.

Dr. Whittaker engages in a brief discussion of the Bradford Hill criteria. This is her discussion in full:

> Case report data in humans with normal to near-normal renal function identify ***strength of association***, ***specificity***, and ***temporality*** among patients exposed to linear GBCAs followed by development of consistent symptoms. Secondly, data derived from studies in humans and test animals exposed to linear GBCAs establish a ***biological gradient***, with higher doses of linear GBCAs associated with longer residence times. This biological gradient is also seen among patients with compromised renal function who developed NSF following exposure to GBCAs, with patients exposed to linear GBCAs demonstrating higher incidences of NSF compared to those exposed to macrocyclic GBCAs. Third, injury from linear GBCAs is ***plausible*** and coherent based on data demonstrating that gadolinium is released from linear GBCAs, as well as data demonstrating that the gadolinium ion (Gd3+) is toxic. Fourth, ***experimental manipulation*** of GBCAs administered to patients demonstrate that adverse symptomology is lower among patients administered macrocyclic GBCAs compared to linear GBCAs. Finally, our understanding of the etiology of NSF disease among patients with impaired renal function who were exposed to linear GBCAs provides ***analogous*** information on the cause-effect relationship that help explains the symptomology reported among patients with adequate kidney function following exposure to linear GBCAs.

Doc. 154-11 at 32-33 (emphasis in original). This analysis, like Dr. Tversky's, is deeply flawed.

1. Strength of Association, Specificity, and Temporality.

For strength of association, Dr. Whittaker relies solely on case reports. *Id.* But as discussed above, case reports are among the weakest of scientific data and far from the epidemiological studies normally relied on to provide the starting point for a Bradford Hill analysis – an association. *See* Reference Manual, 2011 WL 7724263 at *22 (unsystematic clinical observations or case reports "are at the bottom of the evidence hierarchy"). Case reports have no control group to answer the fundamental question of an association: whether exposure to GBCAs and GDD "occur together more frequently than one would expect by chance." Reference Manual, 2011 WL 7724261 at *10. The way to determine whether an association even exists is to compare individuals exposed to a substance with individuals not exposed and see if disease occurs in the exposed group more frequently than would occur by mere chance, as seen in the unexposed group. As the Reference Manual explains: "Typically, [case] reports are not even sufficient to show association, because there is no comparison group." *Id.* at *4. Not only can case reports not establish an association, they certainly cannot indicate the strength of the association.[12]

The case reports also fail to establish specificity. As noted above with respect to specificity: "The vast majority of agents do not cause a wide variety of effects. . . . Thus, a study that finds that an agent is associated with many different diseases should be examined skeptically." Reference Manual, 2011 WL 7724261 at *31 (footnotes omitted).

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[12] Several courts have held that it is not proper methodology for an expert to apply the Bradford Hill factors without data from a controlled study that shows an association. *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 188 (S.D.N.Y. 2009); *In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 126-27 (D. Mass. 2009); *Dunn*, 275 F. Supp. 2d at 678 (finding that "pharmacological properties . . . , statistically insignificant epidemiological studies, clinical studies, case reports, and animal studies" are insufficient for establishing an association for Bradford Hill analysis).

Dr. Whittaker's own report notes that case reports in the FAERS database – upon which she relies – purport to associate GBCAs with 25 different categories of symptoms, including disorders of the nervous system, heart, ear, reproductive system, and even "infections and infestations." *See* Doc. 154-11 at 27, Figure 4. The case reports lack specificity.

And Dr. Whittaker does not explain how the case reports show temporality. She does not describe when symptoms appeared in case reports after exposure, and therefore makes no effort to show that temporality is satisfied.

2. Biological Gradient.

As noted above, this factor is also referred to as the "dose-response effect." It holds that "[c]ausation is more likely if greater amounts of the putative cause are associated with corresponding increases in the occurrence of disease or harm." *In re Mirena IUS*, 341 F. Supp. 3d at 242. Asked simply, does increased exposure result in increased disease? As Sir Bradford Hill stated in his seminal lecture: "For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarettes smokers have a higher death rate than non-smokers." Doc. 154-19 at 5.

Dr. Whittaker does not address whether increased exposure to GBCAs results in more or worse GDD. She states instead that "higher doses of linear GBCAs [are] associated with longer residence times." Doc. 154-11 at 32. But the key link in this criterion is not between dose and residence times, but between dose and the existence or seriousness of the illness. She also cites NSF evidence, noting that "patients exposed to linear GBCAs demonstrat[e] higher incidences of NSF compared to those exposed to macrocyclic GBCAs." *Id.* This is the same tack Dr. Tversky took, looking to NSF evidence to prove GDD causation. Dr. Whittaker, like Dr. Tversky, does not explain why this is an appropriate application of Bradford Hill.

3. Experimental Manipulation.

This factor focuses on what has been learned from experimentation: "Causation is more likely if removing the exposure in a population results in a decrease in the occurrence of disease or harm." *In re Mirena IUS*, 341 F. Supp. 3d at 242. Dr. Whittaker states that "experimental manipulation of GBCAs administered to patients demonstrate that adverse symptomology is lower among patients administered macrocyclic GBCAs compared to linear GBCAs." Doc. 154-11 at 32. Dr. Whittaker does not say what experiments she is referring to, but her report identifies several studies which have shown that linear GBCAs break down in the body more readily than macrocyclic GBCAs. *See, e.g.*, Doc. 154-11 at 23. She also cites case reports and an anonymous survey that have attributed adverse symptoms more often to linear than macrocyclic GBCAs. *Id.* at 20 (Burke et al. (2016)), 26 (FDA literature review). But this analysis again relies on types of data that cannot prove causation, and Dr. Whittaker does not explain why the least reliable class of data provides a reliable scientific basis for the Bradford Hill evaluation of causation.

4. Analogy.

On her last criterion, Dr. Whittaker identifies NSF as an analogous disease. *Id.* at 32-33. As with Dr. Tversky, this comparison is relevant.

5. Dr. Whittaker's Additional Explanation.

As part of her Bradford Hill discussion, Dr. Whittaker seems to acknowledge the lack of genuine science on GDD causation. She states:

> An enormous challenge associated with preparing an unbiased opinion is posed by the state of peer-reviewed publications as well as the state of the pre-clinical toxicology dataset. The majority of peer-reviewed publications on this topic are authored by individuals who work directly for, or have been compensated by, GBCA manufacturers. For some publications, this conflict of interest is apparent, as exampled by overly exuberant conclusions relating to the safety of GBCAs, e.g., "their accumulated safety record is extraordinarily positive" (e.g., Kanal and Tweedle 2015); however, for many peer-reviewed publications, the bias of

> authors is unclear. Disclosure of past or present affiliations in a publication's conflict of interest section merely discloses the affiliation but does not guarantee that the publication itself is free of bias or selective data reporting.

Doc. 154-11 at 33. This seems to be a lament that there is not enough evidence to prove that GBCAs cause GDD. Dr. Whittaker seeks to excuse the lack of evidence by asserting that it is due to bias, even in authors whose bias is "unclear."

She continues:

> An equal challenge associated with discerning the toxicity of linear GBCAs using toxicological data is posed by inherent limitations of studies performed on these compounds as part of the drug approval process. The majority of preclinical toxicity studies on linear GBCAs were not designed to evaluate endpoints associated with GDD such as: cutaneous toxicity (rash, erythema, skin lesions), musculoskeletal toxicity (e.g., arthralgia/joint pain, muscle weakness, bone pain, muscle spasms), or neurological/cognitive effects (e.g., paranesthesia/tingling, tremor, dizziness).

Id. Here, Dr. Whittaker seems to be explaining why there is not enough evidence to address GDD causation on the basis of toxicological data. But even if her concerns about the lack of usable data are warranted, they do not make her opinion admissible. The Bradford Hill criteria cannot be applied to unreliable data simply because reliable data do not exist. And neither is it the role of the Court to admit unreliable evidence because an expert is at the disadvantage of not having reliable data. Rule 702 requires opinions based on adequate facts and data and reliable principles and methods, applied reliably. Fed. R. Evid. 702(b)-(d). There is no exception for opinions that do not meet these standards.

6. Bradford Hill Conclusion.

With the exception of the last factor – analogy – Dr. Whittaker does not reliably apply the Bradford Hill criteria. Thus, even though the criteria represent a well-accepted method for evaluating causation, her application of the criteria is not admissible under Rule 702(d).

D. Other Concerns.

Defendants argue that Dr. Whittaker's opinions lack independent research. In the absence of independent research or peer review, an expert must explain the process by which she reaches her conclusions and identify the objective sources she relies on. *Daubert II*, 43 F.3d at 1318-19. The expert should also demonstrate that the "research and analysis supporting the proffered conclusions have been subjected to normal scientific scrutiny through peer review and publication." *Id.* at 1317-18. For all of the reasons discussed above, Dr. Whittaker has not shown that her opinion has been subjected to normal scientific scrutiny.

Defendants also argue that Dr. Whittaker's opinions should be excluded because they were prepared solely for the purpose of litigation. Doc. 156 at 16. Dr. Whittaker has never published her opinions or subjected them to peer review. Nor has she conducted any clinical studies, animal studies, or other studies on gadolinium. *See* Doc. 156-1 at 46-48. Indeed, Dr. Whittaker seems to have very little experience with gadolinium prior to writing her expert report. *Id.* As discussed above, in the absence of independent research or peer review, experts must explain the process by which they reach their conclusions and identify what objective sources they rely on. *Daubert II*, 43 F.3d at 1318-19. As explained above, Dr. Whittaker fails to cite reliable evidence to support her opinion.

Finally, like Drs. Wagner and Tversky, Dr. Whittaker never discusses important human epidemiological studies on this issue. Doc. 157 at 12. These include McDonald (2017), which compared 1,315 patients who received GBCAs to 2,946 patients with no history of GBCA exposure and found no association between GBCA use and cognitive decline, poor neuropsychological performance, or diminished motor performance. Doc. 153 at 19; *see also* Doc. 154-23.

E. Dr. Whittaker Conclusion.

Plaintiffs have failed to show by a preponderance of the evidence that Dr. Whittaker has used reliable principles and methods and has applied them to the facts of this case reliably. As a result, her opinions are not admissible in evidence under Rule 702(c) and (d).

IX. Two Cases Cited by Plaintiffs.

A. *Wendell.*

Plaintiffs cite the Ninth Circuit's decision in *Wendell v. GlaxoSmithKline, LLC*, 858 F.3d 1227 (9th Cir. 2017), throughout their briefing. In *Wendell*, the parents of a young man who developed Hepatosplenic T-cell lymphoma (HSTCL), a rare and aggressive form of cancer, sued the manufacturer of drugs their son had taken for other health issues. The district court found two of plaintiffs' doctors unreliable and excluded their testimony. *Id.* at 1232-33. The Ninth Circuit found it to be a "close case," but reversed, finding the district court failed to consider the "broader picture of the experts' overall methodology." *Id*. at 1233. The court of appeals found both doctors to be highly qualified and noted that one had conducted clinical research on T-cell leukemia and lymphomas and had experience treating "hundreds of patients with T-cell lymphomas, and thousands of patients with lymphomas, including seven patients with HSTCL." *Id*. at 1233 (internal quotations omitted). Because HSTCL is rare, the doctor had seen more cases than 99% of the oncologists in the country. *Id*. at 1234. The second doctor had extensive research and clinical experience with non-Hodgkin's lymphoma. *Id*.

One doctor conducted a literature search and found articles showing an increased risk of HSTCL in patients prescribed the drug the plaintiffs' son had taken, and, significantly, performed a differential diagnosis to determine the cause of the son's HSTCL. *Id*. The Ninth Circuit stated: "Nothing in *Daubert*, or its progeny, properly understood, suggests that the most experienced and credentialed doctors in a given field should be barred from testifying based on a differential diagnosis." *Id*. at 1235.

The other doctor "based his opinion on 'a summary of the medical records of [the son] as well as copies of the pathology reports, and the original slides of the diagnostic bone marrow,' which he evaluated with over 30 years of experience diagnosing non-Hodgkin lymphoma." *Id.* He "also weighed other risk factors, including [the son's] sex and age, and determined that those were 'weak risk factors; whereas, the disease he had, particularly in the setting of the drugs he received would be considered very strong risk factors.'" *Id.*

The court concluded that "the experts relied not just on these studies – which not only examined reported cases but also used statistical analysis to come up with risk rates – but also on their own wealth of experience and additional literature." *Id.* at 1236. The court found that "when an expert establishes causation based on a differential diagnosis, the expert may rely on his or her extensive clinical experience as a basis for ruling out a potential cause of the disease." *Id.* at 1237.

This case is different. The HSTCL at issue in *Wendell* was a recognized illness; the GDD in this case is a wide-ranging and imprecisely defined illness proposed in some medical literature. The experts in *Wendell* performed a differential diagnosis on the basis of facts specific to the plaintiffs' son; the experts in this case have not performed a differential diagnosis and have not examined Plaintiffs or their medical histories. Granted, this is because the current issue in this case is general causation, not specific causation, but this fact points up a distinction between this case and *Wendell*. *Wendell* addressed a different set of experts, with considerable relevant experience, addressing a known illness, and still found it to be a close case. The Ninth Circuit relied heavily on the doctors' experience, their differential diagnoses, and their case-specific analysis of the son's medical history. Similar facts are not present here. *Wendell* is distinguishable.

B. *In Re GBCAs*.

Plaintiffs cite the decision of Judge Polster in the NSF MDL holding that the plaintiffs' experts provided admissible opinions on general causation. *In re GBCAs*, 2010

WL 1796334. But there are significant differences between that case and this one. In the NSF MDL, the fact that GBCAs caused NSF was strongly supported by the timing of NSF's rise and decline. As Judge Polster explained: "NSF is a singular disease. NSF rapidly emerged, and just as rapidly declined, with the administration of GBCAs to persons with severe renal impairment." *Id.* at *6. That is, "the rapid emergence and decline of NSF associated with the rise and fall of [GBCAs'] use in renally impaired persons" strongly suggested that the GBCAs caused NSF. *Id.* Additionally, Plaintiff's theory that GBCAs caused NSF had "been subjected to publication and peer review" and had "been generally accepted in the relevant scientific and medical community." *Id.*; *see also id.* at *7. This case has no comparable increase and decrease of the illness linked to the increase and decrease of GBCA use, nor has Plaintiffs' causation theory been embraced by the scientific and medical communities. To the contrary, every regulatory and medical organization to consider the question has found insufficient evidence to conclude that GBCAs cause GDD. *In re GBCAs* is distinguishable.

X. Chemistry Opinion of Dr. Raymond.

Plaintiffs' counsel stated in their briefs and during the hearing that they will not ask Dr. Raymond, a chemist, to provide an opinion on general medical causation. Plaintiffs intend to have him teach the jury about the chemistry of gadolinium and GBCAs, and experts can appropriately be used to provide tutorials to the jury. *See* Fed. R. Evid. 702 advisory committee's note to 2000 amendment ("The amendment does not alter the venerable practice of using expert testimony to educate the factfinder on general principles."). Because the parties have not briefed the admissibility of the tutorial testimony contained in Dr. Raymond's report, the Court will not attempt to draw admissibility distinctions now. The Court will, however, hold Plaintiffs to their representation that he will not provide general medical causation opinions.

XI. Conclusion.

For the reasons stated above, the Court finds that (1) the opinions of Drs. Brent Wagner, Jody Tversky, and Margret Whittaker are inadmissible under Rule 702; and (2) Dr. Raymond's opinions will be limited to the chemistry of GBCAs and gadolinium.

IT IS ORDERED:

1. Defendants' omnibus motion to exclude the testimony of Plaintiffs' experts (Doc. 153) is **granted** with respect to Drs. Brent Wagner, Jody Tversky, and Margret Whittaker, and **denied** with respect to Dr. Kenneth Raymond. Dr. Raymond's opinions will be limited to the chemistry of GBCAs and gadolinium and will not include medical causation.
2. Defendants motion to exclude the expert testimony of Brent Wagner, M.D. (Doc. 157) is **granted**.
3. Plaintiffs' Motion for leave to file supplement references for Brent Wagner, M.D. (Doc. 209) is **granted**.
4. Within 14 days of this order, the parties shall provide the Court with a joint memorandum setting forth their views of what should happen next in these cases in light of the Court's ruling. The parties should include a discussion of what should happen with the *Drescher* case, CV 19-00096.

Dated this 2nd day of August, 2019.

David G. Campbell
Senior United States District Judge