# "Indispensable" Methods for Admitting General Causation Experts in the Eleventh Circuit

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*This article analyzes the standards for admitting general causation expert testimony in the Eleventh Circuit pursuant to the governing* Daubert *jurisprudence, including the court's most recent* Daubert *decision in* Chapman v. Procter & Gamble Distributing, L.L.C. *After Part I's introduction, Part II explains the importance of the court's "gatekeeping" function in determining the types of expert testimony that are admissible and permitted before a jury. Part III reviews the* Chapman *decision and details the various methodologies the Eleventh Circuit has found scientifically reliable and unreliable in analyzing expert testimony, including the methodologies the court has recently deemed "indispensable" for general causation testimony. Given that expert testimony is a prerequisite for survival in products liability cases, this article aims to provide both plaintiffs and defendants a roadmap to better prepare their experts and to analyze the strengths and weaknesses of their cases.*



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## I. Introduction

Cases involving medical causation often turn on the plaintiff's ability to offer admissible expert testimony. In fact, in products liability cases proceeding in the Eleventh Circuit, plaintiffs are *required* to have admissible expert testimony establishing both general causation—that the agent in question is capable of causing the type of harm alleged—and specific causation—that the agent did in fact cause the plaintiff's injury.[1] Given this requirement, plaintiffs in products liability cases routinely spend thousands (if not hundreds of thousands) of dollars searching for and engaging the leading scientists in the field in order to meet this burden. Defendants similarly undertake this same practice in search of expert testimony to rebut causation. Regardless of the experts' qualifications, however, if they do not adhere to the reliability standards espoused under Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[2] they will never be permitted onto the witness stand to convince a jury of their opinions. And without any expert testimony to offer the jury, a plaintiff's case will necessarily be dismissed.[3] Thus, products liability cases are often won or lost at the *Daubert* stage, making the court's *Daubert* order the centerpiece of the litigation.

Pursuant to the basic tenets of *Daubert*, an expert must employ a scientifically reliable methodology in reaching its opinion.[4] The Eleventh Circuit has had numerous opportunities to interpret and apply *Daubert*'s reliability requirements in the context of general causation testimony. Notably, the Eleventh Circuit initially adopted a much more lenient interpretation of *Daubert*, but was twice overturned by the Supreme Court in post-*Daubert* decisions.[5] Since those reversals, the Eleventh Circuit has embraced an increasingly rigorous approach to the

1. *See, e.g.*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296, 1316 (11th Cir. 2014) ("To prove [that the agent at issue] caused [the plaintiff's injury], the [plaintiffs] were *required* to have *Daubert*-qualified, general and specific-causation-expert testimony that would be admissible at trial to avoid summary judgment."), *cert. denied*, 135 S. Ct. 2312 (2015); Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1334 n.4 (11th Cir. 2010) ("In order to prevail on his products liability claims, Kilpatrick must offer proof of both general causation . . . and proof of specific causation. . . . To meet this burden requires the use of expert testimony."); McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1237 (11th Cir. 2005) (similar).

2. For a discussion of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), see *infra* text accompanying notes 15–19.

3. *See supra* note 1 and accompanying text.

4. *Daubert*, 509 U.S. at 592–93.

5. *See* Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999), *overruling* Carmichael v.

examination of experts, particularly with respect to causation testimony.[6] The Eleventh Circuit now closely examines the bases for an expert's general causation testimony, deeming certain types of methodologies scientifically reliable for establishing general causation and certain other types of methodologies inherently unreliable.[7] Yet, prior to the decision in *Chapman v. Procter & Gamble Distributing, L.L.C.*,[8] the Eleventh Circuit had never clarified which methodologies, if any, were actually necessary in order for an expert to reliably opine on general causation. The decision in *Chapman* expounds upon Eleventh Circuit *Daubert* jurisprudence, labeling three methodologies "indispensable" to general causation: epidemiological studies, dose-response relationship, and background risk of disease.[9] Presumably all three methodologies are not required, but it appears as though an expert must rely on at least one of these methodologies to survive *Daubert*.[10]

In light of the recent decision in *Chapman*, this article details the methodologies deemed "indispensable" by the Eleventh Circuit, as well as those deemed unreliable as a basis for inferring general causation. These principles bear on all aspects of expert discovery, including retaining experts, developing and disclosing expert opinions, and preparing and responding to *Daubert* motions. In fact, they are so significant to the outcome of litigation that they should also inform any assessment of a case's outlook and viability. Thus, practitioners facing products liability cases should pay close attention to the recent developments in Eleventh Circuit *Daubert* jurisprudence in developing and pursuing their litigation strategy.

## II. THE COURT'S "GATEKEEPING" ROLE UNDER *DAUBERT*

In *Daubert*, the Supreme Court charged trial courts with the respon-

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Samyang Tire, Inc., 131 F.3d 1433 (11th Cir. 1997); Gen. Elec. Co. v. Joiner, 522 U.S. 136 (1997), *overruling* 78 F.3d 524 (11th Cir. 1997).

6. *See* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1320–21 (11th Cir. 1999) (upholding a Georgia court's decision to bar testimony "because [the expert's] degree of certainty would not be sufficient to establish probable cause and would thus be irrelevant," and saying that "the court did not abuse its discretion by excluding . . . testimony which was based on mere possibility of causation").

7. Many of these methodologies are well described in the *Reference Manual on Scientific Evidence*, "the leading reference source for federal judges for difficult issues involving scientific testimony." *See* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at ix (3d ed. 2011) [hereinafter REFERENCE MANUAL]; *see also infra* Part III.

8. 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

9. *See Chapman*, 766 F.3d at 1308.

10. *See id.* ("Given the deposition admissions of [plaintiffs' experts] regarding their lack of knowledge of dose-response, epidemiological evidence, and background risk of disease . . . we conclude that the testimonies of these proffered experts could not establish general causation . . . .").

sibility of acting as gatekeepers over expert testimony.[11] Rule 702 of the Federal Rules of Evidence, which governs the admission of expert testimony, was amended in response to *Daubert* and requires that courts exercise this gatekeeping function by ensuring that experts not only are qualified to testify, but also that their testimony (a) assists the trier of fact, (b) is "based on sufficient facts and data," (c) is the "product of reliable principles and methods," and (d) "reliably applie[s] the principles and methods to the facts of the case."[12] The Eleventh Circuit has further articulated that *Daubert*'s gatekeeping function requires "'the trial court to conduct an exacting analysis' of the *foundations* of expert opinions to ensure they meet the standards for admissibility under Rule 702."[13] As the Eleventh Circuit noted in *Frazier*, the "importance of *Daubert*'s gatekeeping requirement cannot be overstated" because "no other kind of witness is free to opine about a complicated matter without firsthand knowledge of the facts in the case, and based upon otherwise inadmissible hearsay."[14]

The Supreme Court has provided much guidance as to what it means for expert testimony to be reliable. For example, in *Daubert*, the Supreme Court held that "[t]he subject of an expert's testimony must be 'scientific . . . knowledge.'"[15] This "implies a grounding in the methods and procedures of science . . . [and] connotes more than subjective belief or unsupported speculation."[16] Thus, "in 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."[17] To determine whether a specific methodology will produce reliable "scientific knowledge," the Supreme Court suggested a list of relevant factors to consider:

> (1) whether the expert's theory can be and has been tested; (2) whether the theory [or technique] has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally

11. *See* Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 589 (1993). While the Court in *Daubert* held that the trial judge must ensure that "any and all *scientific* testimony . . . is not only relevant, but reliable," the Court in *Kumho Tire* clarified that this gatekeeping function applies to *all* expert testimony, not just scientific testimony. *See* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 147 (1999) (emphasis added) (citing *Daubert*, 509 U.S. at 589); *see also infra* note 28.

12. FED. R. EVID. 702.

13. United States v. Frazier, 387 F.3d 1244, 1260 (11th Cir. 2004) (en banc) (quoting McCorvey v. Baxter Healthcare Corp., 298 F.3d 1253, 1257 (11th Cir. 2002)).

14. *Frazier*, 387 F.3d at 1260.

15. *Daubert*, 509 U.S. at 589–90 (alteration in original) (quoting FED. R. EVID. 702).

16. *Id.* at 590.

17. *Id.*; *see also* McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1237–38 (11th Cir. 2005) (stating that the proponent of the testimony must establish that it is "derive[d] from the scientific method; good grounds and appropriate validation must support it").

> accepted in the scientific community.[18]

However, this is not to be construed as "a definitive checklist or test" because many different factors could bear on the inquiry depending on the context.[19]

In expounding upon these basic principles, the Supreme Court in *Daubert* cautioned that courts must focus "solely on principles and methodology, not on the conclusions that they generate."[20] Thus, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof" should be used to attack expert evidence that is "shaky but admissible."[21] Nevertheless, as the Supreme Court observed more recently in *General Electric Co. v. Joiner*:

> [C]onclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data. But 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.[22]

Notably, the Supreme Court in *Joiner* reversed the decision of the Eleventh Circuit, which had overturned the district court's exclusion of a plaintiff's general causation experts.[23] In doing so, the Supreme Court rejected the Eleventh Circuit's reasoning that *Daubert* was intended to "make it easier to present legitimate conflicting views of experts for the jury's consideration."[24] The Supreme Court also made it clear that the Eleventh Circuit was wrong in holding that the district court impermissibly "drew different conclusions from the research than did each of the experts."[25] The Supreme Court reasoned that it was "within the District Court's discretion to conclude that the studies upon which the experts relied were not sufficient . . . to support [the experts' causation] conclu-

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18. Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1335 (11th Cir. 2010) (quoting *Daubert*, 509 U.S. at 593–94).

19. *Daubert*, 509 U.S. at 593.

20. *Id.* at 595.

21. *See id.* at 596; *see also* Quiet Tech. DC-8, Inc. v. Hurel-Dubois U.K. Ltd., 326 F.3d 1333, 1341 (11th Cir. 2003) ("[I]t is not the role of the district court to make ultimate conclusions as to the persuasiveness of the proffered evidence. . . . '[A] district court's gatekeeper role under *Daubert* is not intended to supplant the adversary system or the role of the jury.'") (quoting Maiz v. Virani, 253 F.3d 641, 666 (11th Cir. 2001)).

22. Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997).

23. The Supreme Court held that the Eleventh Circuit failed to properly apply the abuse of discretion standard in overturning the district court's decision and that the district court did not abuse its discretion when it excluded the proffered expert testimony. *Id.* at 143, 146–47.

24. Joiner v. Gen. Elec. Co., 78 F.3d 524, 530 (11th Cir. 1996), *rev'd*, 522 U.S. 136 (1997).

25. *See Joiner*, 522 U.S. at 141.

sions."[26] In other words, an expert cannot simply present a study with some bearing on the issue and summarily opine that it supports his or her opinion; rather, an expert must affirmatively demonstrate how a particular study reliably demonstrates the proffered conclusion. As the Eleventh Circuit recently put it, the court cannot "simply . . . 'tak[e] the expert's word for it.'"[27] This marked the beginning of a new era of far more rigorous assessment of expert testimony under Eleventh Circuit *Daubert* jurisprudence, particularly with respect to medical causation testimony.[28]

## III. The Eleventh Circuit's Interpretation of the "Gatekeeping" Role with Respect to General Causation Testimony

The Eleventh Circuit has made clear that, in the context of general causation testimony, it is especially important that the court not "simply take the expert's word for it."[29] That is because, as the Eleventh Circuit emphasized, "the courtroom is not the place for scientific guesswork, even of the inspired sort."[30] Thus, according to the Eleventh Circuit's current interpretation of the gatekeeping role: "[w]hile meticulous *Daubert* inquiries may bring judges under criticism for donning white coats and making determinations that are outside their field of expertise, the Supreme Court has obviously deemed this less objectionable than dumping a barrage of questionable scientific evidence on a jury."[31]

Pursuant to this interpretation, the Eleventh Circuit has delineated that the district court is to closely examine the bases for an expert's general causation opinion so as to ensure that the expert employs the

26. *Id.* at 146–47.

27. *See* Cooper v. Marten Transport, Ltd., 539 F. App'x 963, 966 (11th Cir. 2013) (quoting Hendrix *ex rel*. G.P. v. Evenflo Co., 608 F.3d 1183, 1201 (11th Cir. 2010)) (second alteration in original).

28. Following the decision in *Joiner*, the Supreme Court again overturned an Eleventh Circuit decision interpreting *Daubert*. *See* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 146 (1999), *overruling* Carmichael v. Samyang Tire, Inc., 131 F.3d 1433 (11th Cir. 1997). In *Kumho Tire*, the Supreme Court ruled that the Eleventh Circuit erred when it held that *Daubert* only applied to testimony that relies on the application of scientific principles, rather than on skill or experience-based observation. *Kumho Tire*, 526 U.S. at 146. On the heels of *Joiner* and *Kumho Tire*, the Eleventh Circuit immediately began embracing a more rigorous review of expert testimony, beginning with the decision in *Allison v. McGhan Medical Corp.*, 184 F.3d 1300 (11th Cir. 1999). In fact, in *Allison*, the Eleventh Circuit specifically noted that it had been "twice overruled on *Daubert* decisions" by the Supreme Court, making clear that a stricter admissibility standard should be applied. *Id.* at 1312.

29. *See supra* note 27 and accompanying text.

30. McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1247 (11th Cir. 2005) (quoting Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996)) (internal quotation marks omitted).

31. *Allison*, 184 F.3d at 1310.

types of methodologies deemed reliable for establishing causation.[32] The most frequently cited Eleventh Circuit *Daubert* case on this issue is *McClain v. Metabolife International, Inc. McClain* was a products liability case that, like many products liability cases, dealt with a toxic tort claim—"[a] civil wrong arising from exposure to a toxic substance, such as asbestos, radiation, or hazardous waste."[33] In assessing the plaintiffs' experts' general causation opinions, *McClain* laid out a variety of methodologies that experts may and may not rely upon to establish causation.[34] In subsequent cases, the Eleventh Circuit further expounded on the types of methodologies that an expert may and may not rely on in other toxic tort cases—most recently in *Chapman*.[35]

The Eleventh Circuit has indicated that the principles articulated in *McClain* and other toxic tort cases properly apply to *any* type of products liability case in which a medical injury is alleged to have arisen from the use of a defective product.[36] To illustrate, in *Hendrix*, the plaintiff attempted to distinguish his case from *McClain*—and thereby avoid application of *McClain*'s rigorous *Daubert* inquiry—because his case dealt with an "ordinary trauma" allegedly arising from the use of a defective product, as opposed to a toxic tort.[37] The Eleventh Circuit rejected that distinction, reasoning that because "the court was required to analyze expert medical opinions regarding the cause of an injury . . . the relevant inquiry was similar."[38] Thus, the court concluded, "the principles articulated in *McClain* with regard to admitting expert medical testimony on the cause of an injury may properly guide our reliability inquiry on the causation issue."[39] As such, while the majority of the Eleventh Circuit jurisprudence regarding the admissibility of general causation testimony has been decided in the context of toxic torts claims, the principles discussed herein apply equally to any products liability case in which the plaintiff offers expert medical opinions regarding the general cause of an injury.

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32. *See McClain*, 401 F.3d at 1237–38.

33. *See* Hendrix v. Evenflo Co., 609 F.3d 1183, 1196 n.6 (11th Cir. 2010) (quoting BLACK'S LAW DICTIONARY (8th ed. 2004)) (internal quotation marks omitted).

34. *See generally McClain*, 401 F.3d at 1237–55; *see also infra* Part III.C–D.

35. *See, e.g.*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296, 1308 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015); Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1336–37 (11th Cir. 2010); Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1199, 1200–01 (11th Cir. 2002); *Allison*, 184 F.3d at 1316.

36. *Hendrix*, 609 F.3d at 1196 n.6.

37. *Id.*

38. *Id.*

39. *Id.*

### A. *Two Categories of General Causation*

The Eleventh Circuit has held that products liability cases dealing with medical injuries fall into two categories (the "*McClain* categories"): (1) those in which the medical community generally recognizes that a certain chemical or product can cause the injury alleged, and (2) those in which the medical community does not.[40] The first category is one in which "the cause and effect or resulting diagnosis has been proved and accepted by the medical community."[41] Should an expert's testimony fall under the first category, the Eleventh Circuit has held that the district court "need not undertake an extensive *Daubert* analysis."[42] Although this likely does not foreclose a *Daubert* analysis altogether, courts are instructed to direct their focus to specific, rather than general, causation.[43] Notably, this is not the same as the "general acceptance" standard that was rejected in *Daubert* as only very limited types of cases have met this category. Indeed, in *McClain*, the Eleventh Circuit provided examples of the types of limited cases where general causation has been "generally recognized": asbestos and mesothelioma, cigarette smoke and lung cancer, and silica and silicosis, for example.[44] Moreover, even if a case falls under the first category, the court must always conduct a *Daubert* analysis as to specific causation.

The majority of cases, however, fall into the second category. In these cases, the court is first required to assess general causation, i.e., "whether the drug or chemical *can* cause the harm plaintiff alleges."[45] As discussed herein, the Eleventh Circuit has identified certain methodologies on which an expert may and may not rely in testifying to general causation.[46] It was never clear, however, which, if any, of these methodologies was *necessary* to establishing causation in products liability cases. The Eleventh Circuit's decision in *Chapman* has now provided guidance on that ambiguity in the *Daubert* jurisprudence.

### B. *The Eleventh Circuit's Ruling in* Chapman

In *Chapman*, the plaintiff alleged that her heavy use of Fixodent

40. *See* McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1239 (11th Cir. 2005); *see also Hendrix*, 609 F.3d at 1196.

41. Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296, 1303 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

42. *Id.* at 1239.

43. *Id.*

44. *McClain*, 401 F.3d. at 1239. The other examples provided by *McClain* were that "too much alcohol causes cirrhosis of the liver, and that the ingestion of sufficient amounts of arsenic causes death." *Id.* at 1239 n.5.

45. *Id.*

46. *See supra* notes 34–35 and accompanying text.

denture adhesive over an eight-year period caused her to develop a rare myelopathy (a disease of the spinal cord) that resulted in neurological symptoms.[47] The case was prompted by the publication of a 2008 case report hypothesizing that the zinc in denture cream products may lead to copper deficiency, which in turn may lead to neurological injury.[48] Thereafter, the plaintiff, along with various others across the country, filed suit against Procter & Gamble Company and other makers of zinc-containing denture cream products.[49]

On appeal, the plaintiff argued that her case should have been analyzed under *McClain* category one "because there is a general consensus in the medical community that ingestion of zinc causes [copper deficiency myelopathy]."[50] But the plaintiff only pointed to evidence recognizing an association between excess zinc and a copper deficiency.[51] She "fail[ed] to show that the zinc compound in Fixodent [was] in *McClain* category one of medically accepted, cause-and-effect toxins."[52] Although the plaintiff alleged that Fixodent was toxic because it contained zinc, she could not reconcile this with the fact that—unlike those exposed to cigarette smoke or asbestos—zinc is an essential nutrient in the body, and millions of consumers had used Fixodent for decades without complaint.[53] As a result, the court found that Fixodent was properly analyzed under *McClain* category two.[54]

The plaintiff offered four general causation experts in support of her general causation theory.[55] Yet, none employed any of the methodologies the Eleventh Circuit had previously deemed reliable for purposes of establishing general causation.[56] In particular, no expert demonstrated

47. *Chapman*, 766 F.3d at 1300.

48. *Id.* (citing S.P. Nations et al., *Denture Cream: An Unusual Source of Excess Zinc, Leading to Hypocupremia and Neurologic Disease*, 71 NEUROLOGY 639 (2008)).

49. *Id.* at 1300–01. The plaintiff's causation allegations bear mentioning because they illustrate the complex scientific theory plaintiff's experts were required to reliably support. She alleged that her use of Fixodent necessarily caused her to swallow the product. By doing so, her body absorbed the zinc contained in Fixodent, which led to increased zinc levels and decreased copper levels in her body. The suppressed copper levels led to a copper deficiency, and this prolonged copper deficiency caused her myelopathy. *See In re* Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d 1345, 1357 (S.D. Fla. 2011), *aff'd*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

50. *Chapman*, 766 F.3d at 1304.

51. *See id.*

52. *Id.*

53. *Id.*

54. *Id.*

55. *See id.* at 1306, 1313.

56. *Id.* at 1306–07 ("The judge reviewed reliable methodologies, including dose-response relationship, epidemiological evidence, background risk of the disease, physiological processes involved, and clinical studies. The judge determined the Chapmans' experts did not satisfy any of these recognized methodologies.") (internal citation omitted).

the dose-response relationship—i.e., how much Fixodent was necessary to cause a copper deficiency or myelopathy.[57] No expert identified the background risk of the disease—i.e., the number of unexposed people that develop myelopathy.[58] Nor did any expert present epidemiological evidence demonstrating that Fixodent users were at a greater risk than non-denture cream wearers of developing a myelopathy.[59] Instead, the plaintiff's experts relied on methodologies that the Eleventh Circuit had—on several previous occasions—found insufficient to establish causation, including anecdotal case reports and animal studies.[60]

Upon recounting these issues, the Eleventh Circuit held:

> Given the deposition admissions of [plaintiffs' experts] regarding their lack of knowledge of dose-response, epidemiological evidence, and background risk of disease, methodologies this circuit has recognized as *indispensable* to proving the effect of an ingested substance, we conclude that the testimonies of these proffered experts could not establish general causation of myelopathy by Fixodent.[61]

By using the term "indispensable," the Eleventh Circuit clarified that at least one of these methodologies is necessary to pass *Daubert* muster in a products liability case.[62] Indeed, the Court went on to articulate that "[b]ecause these experts have failed to demonstrate the primary methods for proving [general causation], their secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation."[63] Accordingly, the district court's *Daubert* ruling excluding the testimony of the plaintiff's general causation experts was affirmed.[64]

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57. *Id.* at 1307.

58. *Id.*

59. *Id.*

60. *Id.* at 1308; *see also infra* Part III.D.5. In addition, as recounted by the district court, the plaintiff's experts also relied upon adverse event reports, FDA findings, and a temporal relationship. *See In re* Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d 1345, 1360–65 (S.D. Fla. 2011), *aff'd*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

61. *Chapman*, 766 F.3d at 1308 (emphasis added).

62. *See id.* The word "indispensable" is defined as something that is "absolutely necessary," "essential," or "not subject to being set aside or neglected." WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY 614 (9th ed. 1983).

63. *Chapman*, 766 F.3d at 1308.

64. *Id.* The effect of the lack of scientifically reliable evidence was well described by the district court:

> Plaintiffs have put forth a superficially appealing hypothesis that prolonged use of very large amounts of Fixodent may cause copper-deficiency. Plaintiffs' experts have based their conclusions on a modest amount of animal studies, mechanistic processes, epidemiological studies, and case studies indicating elemental zinc in an unknown dose amount may cause a copper deficiency, which, if allowed to persist for an unknown time, may cause nervous system problems in some individuals. From this information, they induce that the zinc contained in the polymer in

## C. *The "Indispensable" Methods for Establishing General Causation*

As noted in the previous Section, the court in *Chapman* stated that the Eleventh Circuit has recognized that at least one of three methodologies were "indispensable" for establishing general causation: epidemiological evidence, dose-response relationship, and background risk of disease.[65] These methodologies are not simply preferred by the court, but are relied upon in the scientific community and are based upon toxicological and epidemiologic principles. In obtaining and preparing expert causation opinions—and, conversely, in challenging an expert's causation opinions—it is critical for practitioners to understand exactly what these methodologies entail and the way in which the Eleventh Circuit has considered them in assessing causation under *Daubert*.

### 1. Epidemiological Evidence

The Eleventh Circuit has held that epidemiological evidence is "generally considered to be the best evidence of causation in toxic tort actions" and is therefore a scientifically reliable method for establishing general causation.[66] As the *Reference Manual* explains, epidemiological evidence concerns itself with "the question of general causation"—for example, studies may have designs and controls that allow an expert to determine whether a particular environmental exposure or agent is causally associated to the risk of developing a particular disease.[67] There are several types of epidemiological studies that can be performed, with varying degrees of strength.[68] The strongest is a randomized trial, in which subjects are randomly assigned to either a group exposed to the agent of interest or a group not exposed to the agent.[69] "After a period of

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> Fixodent can be absorbed in significant enough quantities to form the first link in the causal chain—the unknown dose of zinc.
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> This theory is not ridiculous, but neither is it necessarily true; it is ripe for testing. In short, taking everything together, there is enough data in the scientific literature to *hypothesize* causation, but not to *infer* it. Hypotheses are verified by testing, not by submitting them to lay juries for a vote. It may very well be that Fixodent in extremely large doses over many years can cause copper deficiency and neurological problems, but the methodology Plaintiffs' experts have used in reaching that conclusion will not reliably produce correct determinations of causation. In a toxic torts case, more reliable evidence is required.

*In re Denture Cream*, 795 F. Supp. 2d at 1367.

65. *See supra* notes 61–62 and accompanying text.

66. Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1198 (11th Cir. 2002) ("It is well-settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff's case."); *see also* Hendrix v. Evenflo Co., 609 F.3d 1183, 1197–98 (11th Cir. 2010).

67. *See* Reference Manual, *supra* note 7, at 552.

68. *See id.* at 555–65.

69. *See id.* at 555.

time, the study participants in both groups [are] evaluated for the development of a disease."[70] While this is considered the "gold standard" for determining causal relationships, these studies are rarely performed because it is often unethical to randomly assign subjects to either receive or not receive a potentially harmful exposure.[71] Thus, most studies that investigate risk factors for a disease are "observational" studies, such as cohort studies[72] and case-control studies.[73] Rather than actively exposing subjects to a particular agent, these types of studies "'observe' a group of individuals who have been exposed to an agent of interest . . . and compare [their rate of disease] with another group of individuals who have not been exposed."[74]

If an epidemiological study finds that there is an association between exposure and disease, the strength of that association is reported as either statistically significant or statistically insignificant.[75] A study that is statistically significant has results that are unlikely to be the result of random error.[76] Thus, the Eleventh Circuit has found that when epidemiological studies do not yield "statistically significant results," they do not supply an adequate foundation for a causation opinion.[77] For instance, in *Rider*, none of the four epidemiological studies presented by the plaintiffs contained statistically significant results linking Parlodel—the agent of interest—to stroke—the disease at issue.[78] In the absence of statistically significant epidemiological studies, the *Rider* court demanded alternative proof of medical causation.[79] Similarly, in *Allison*, the court rejected certain epidemiological studies on which the

70. *Id.*

71. *See id.*

72. A cohort study identifies two different groups of people ("cohorts"), one group exposed to the risk of interest and the other group not exposed. Both groups are then followed over time to see who develops the disease, and the frequency of the disease is compared between the exposed cohort and the unexposed cohort. Cohort studies are used to study diseases that are relatively common because enough patients with the disease will be observed over time in order to judge which group (exposed or unexposed) has the highest incidence of disease. *See id.* at 557–59.

73. In contrast to a cohort study, a case-control study finds all of the persons with a disease in a defined population ("cases") and then selects a sample of persons who do not have the disease ("controls") as a comparison group. The investigator then compares the proportion of cases that have been exposed to the risk factor with the proportion of controls that have been exposed to that factor in order to determine whether there is an increased rate of exposure in the group with the disease versus the group without the disease. The case-control study is the preferred study design for extremely rare or uncommon diseases because it does not require long-term investigations or large groups of participants in order to draw conclusions. *See id.* at 559–60.

74. *Id.* at 555–56.

75. *See id.* at 555–57, 575–83.

76. *See id.* at 575.

77. Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1198 (11th Cir. 2002); *see also* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1315 (11th Cir. 1999).

78. *Rider*, 295 F.3d at 1198.

79. *Id.* at 1202.

expert relied because one "found no statistical correlation" and the other had "a finding so significantly close to 1.0 that . . . the study was not worth serious consideration for proving causation."[80]

The Eleventh Circuit has also held that in order to be admissible, an expert must explain "how the findings of [epidemiological] studies may be reliably connected to the facts of the particular case."[81] Thus, even if statistically significant epidemiological studies exist, if they do not address the same or comparable agents and diseases as those at issue, they are unlikely to provide a reliable basis for an expert's opinion. The Eleventh Circuit in *Allison* rejected an expert's reliance on certain epidemiological studies on these grounds, noting that one such study was "irrelevant because it specifically scrutinized muscular rheumatism, not [the disease at issue]," and the other "found correlations between implants and increased risk of joint pain, a complaint which [the plaintiff] did not have."[82]

Similarly, in *McClain*, the court rejected a study that showed a fifteen-fold increase in the risk of hemorrhagic strokes in patients who took phenylpropanolamine as a diet supplement because, among other reasons, the chemical agent at issue was ephedrine—not phenylpropanolamine—and the disease at issue was ischemic stroke—not hemorrhagic stroke.[83] Because the authors drew no conclusions about ephedrine or ischemic stroke, and nowhere reported that these were analogous to the agent and disease that had been studied, the court found that the "study offer[ed] no support for [the expert's] opinions."[84] Indeed, the *McClain* court made clear that an expert does not utilize a reliable methodology if he or she makes "unauthorized conclusions from limited data—conclusions the *authors* of the study d[id] not make."[85] An expert's drawing of unauthorized conclusions shows a "lack of scientific rigor," a relevant factor under *Daubert*, because the intellectual rigor employed should be "conservative and [ ] not leap to specific conclusions."[86] The *McClain* court also articulated an additional methodological shortcoming with the expert's approach. The *McClain* expert

80. *Allison*, 184 F.3d at 1315. In *Allison*, the latter study found a "relative risk of only 1.24." *Id.* "The threshold for concluding that an agent more likely than not caused a disease is 2.0. A relative risk of 1.0 means that the agent has no causative effect on incidence." *Id.* at 1315 n.16.

81. Hendrix v. Evenflo Co., 609 F.3d 1183, 1196–97 (11th Cir. 2010).

82. *Allison*, 184 F.3d at 1315.

83. McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1246 (11th Cir. 2005).

84. *Id.*

85. *Id.* at 1248 (emphasis added); *see also* Gen. Elec. Co. v. Joiner, 522 U.S. 136, 145 ("Given that [the authors] were unwilling to say that PCB [polychlorinated biphenyls] exposure had caused cancer among the workers they examined, their study did not support the experts' conclusion that Joiner's exposure to PCBs caused his cancer.").

86. *McClain*, 401 F.3d at 1248.

simply assumed that the chemical analogy—between ephedrine and phenylpropanolamine—was valid, without offering any scientific evidence to support that assumption.[87] However, "[s]uch presumptions do not make for reliable opinions in toxic tort cases" because "even minor deviations in chemical structure can radically change a particular substance's properties and propensities."[88]

Practitioners, therefore, should be aware that while epidemiological studies remain "the best evidence of causation in toxic tort cases," it is clear that the Eleventh Circuit demands statistically significant epidemiological studies dealing with the same or comparable agents and diseases on which an expert has issued a causal opinion.[89]

### 2. The Dose-Response Relationship

Another reliable method for establishing causation is through evidence of the dose-response relationship, which is the "relationship in which a change in amount, intensity, or duration of exposure to an agent is associated with a change—either an increase or decrease—in risk of disease."[90] In other words, an expert should be able to opine as to how much of an agent is too much. Because all substances—even water—are potentially toxic at a large enough dose, the Eleventh Circuit has held that the dose-response relationship is the "hallmark of basic toxicology" and "the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect."[91] Thus, an "expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology."[92]

This method was discussed at length in *McClain*. There the Eleventh Circuit found that an expert's testimony was suspect and ultimately unreliable because the expert could not determine the dose of Metabolife (the product at issue) required to injure the plaintiff, or anyone else.[93] The court observed that "[o]ften low dose exposures—even for many years—will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage.'"[94] The

87. *See id.* at 1246.

88. *Id.* (quoting Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1201 (11th Cir. 2002)) (internal quotation marks omitted); *see also infra* Part III.D.6.

89. *See Rider*, 295 F.3d at 1198.

90. *McClain*, 401 F.3d at 1241–42 (citation omitted); *see also* Reference Manual, *supra* note 7, at 622.

91. *McClain*, 401 F.3d at 1242 (citation omitted).

92. *Id.*; *see also* Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1339 (11th Cir. 2010).

93. *McClain*, 401 F.3d at 1242–43.

94. *Id.* at 1242 (internal citations and quotation marks omitted); *see also In re* Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d 1345, 1352 (S.D. Fla. 2011) ("Common sense suggests that one would expect consuming three-fifths of a pound of denture cream per week for eight years

court further stated that even for "chronic" exposure cases, there will always be some threshold, "such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual."[95] The expert in *McClain*, in contrast, testified that *any* amount of Metabolife was dangerous, contradicting basic toxicological principles and casting doubt on his own testimony.[96]

Based on these principles, it is clear that even if an expert cannot opine on the precise dose-response relationship, he or she should not blindly ignore it in forming a causal conclusion. Certainly, the more support an expert has for a dose-response relationship, the more likely his or her testimony will be admitted. Of course, as with epidemiological evidence, any dose-response relationship evidence on which an expert attempts to rely must be relevant and comparable to the causal relationship at issue.[97]

### 3. Background Risk of the Disease

The third methodology that the Eleventh Circuit found reliable for establishing general causation is evidence of the background risk of the disease.[98] As the court stated in *McClain*, "[a] reliable methodology should take into account the background risk."[99] "The background risk is not the risk posed by the chemical or drug at issue in the case."[100] Instead, "[i]t is the risk a plaintiff and other members of the general public have of suffering the disease or injury that [the] plaintiff alleges *without* exposure to the drug or chemical in question."[101] Background risk will look at all causes of a disease, "whether known or unknown, excluding the drug or chemical in question."[102] For example, in *In re Denture Cream*, the district court described the background risk as the

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would have some type of negative consequence. 'Thus, the question for causation purposes is: At what levels of exposure do what kinds of harm occur?' ") (quoting Cavallo v. Star Enter., 892 F. Supp. 756, 769 n.27 (E.D. Va. 1995)), *aff'd*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

95. *McClain*, 401 F.3d at 1242 (internal citations and quotation marks omitted).

96. *Id.* at 1243.

97. For instance, as discussed in Part III.D.5 *infra*, if an expert attempts to rely on animal studies to prove a dose-response relationship, the expert must be able to provide a convincing explanation for why the results of the animal studies can be extrapolated to humans.

98. *See McClain*, 401 F.3d at 1243.

99. *Id.*

100. *Id.*

101. *Id.*; *see also* Reference Manual, *supra* note 7, at 620 (defining background risk of disease as the "[r]ate of disease in a population that has no known exposures to an alleged risk factor for the disease").

102. *McClain*, 401 F.3d at 1243 (further explaining that background risk is "the risk that everyone faces of suffering the same malady that a plaintiff claims without having exposure to the same toxin").

incidence of myelopathy (the disease at issue) in the general population in the United States.[103]

The court in *McClain* explained the usefulness of background risk methodology for purposes of establishing causation:

> [I]t would help to know how much additional risk for heart attack or ischemic stroke Metabolife consumers have over the risks the general population faces. If ephedrine or an ephedrine/caffeine combination do not increase the incidence of heart attack and ischemic stroke in persons who ingest it, as opposed to all those who do not and still have heart attacks and strokes, that fact would reduce the likelihood that Metabolife harmed Plaintiffs. Likewise, if Plaintiffs could show that taking Metabolife increases the risk of heart attack and ischemic stroke beyond the usual incidence of these common diseases, that would support their methodology in this case.[104]

The district court in *In re Denture Cream* also expounded on the relevance and importance of this type of evidence: "[b]ecause epidemiology aims to identify 'agents that are associated with an increased risk of disease,' one must know the background prevalence of a disease before one can determine if exposure to an agent has increased the risk of that disease."[105] Indeed, without this information, it is difficult to determine whether any incidence of the disease in individuals exposed to an agent at issue is anything more than coincidence.[106]

The expert in *McClain* offered no evidence of background risk.[107] Thus, the court held that it "must assume" no additional risk of the disease exists in the population exposed to the drug beyond the usual incidence of the disease.[108] Similarly, in *Kilpatrick*, the court found that the reliability of the expert's causal conclusions were in doubt because the expert failed to take into account the background risks for the disease, including the potential for idiopathic incidents of the disease.[109]

Based on these holdings, it seems as though evidence of the back-

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103. *In re* Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d 1345, 1355 (S.D. Fla. 2011), *aff'd*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015). The *Reference Manual* provides the example that "the background risk for all birth defects is 3–5% of live births." REFERENCE MANUAL, *supra* note 7, at 620.

104. *McClain*, 401 F.3d at 1244.

105. *In re Denture Cream*, 795 F. Supp. 2d at 1355 (quoting REFERENCE MANUAL, *supra* note 7, at 552).

106. As the court in *In re Denture Cream* noted, because the plaintiffs' experts did not know the background of the disease, "it is possible (and depending on the incidence of myelopathies, likely) that some denture-cream users have an idiopathic myelopathy [unknown cause of the disease] simply due to the background distribution of that disease. Without a baseline, any incidence may be coincidence." *Id.* at 1356.

107. *McClain*, 401 F.3d at 1244.

108. *Id.*

109. Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1342 (11th Cir. 2010).

ground risk of a disease at issue—while not required for an admissible causation opinion—is certainly a critical component of any general causation opinion.

### D. *Scientifically Unreliable Methodologies for Establishing General Causation*

Beyond addressing the types of methodologies that an expert can use to form a reliable causation opinion, the Eleventh Circuit has also identified certain types of evidence that it considers insufficient for proving general causation.[110] It is critical to be aware of the ways in which the Eleventh Circuit has approached these types of evidence, given the frequency with which they arise in the context of general causation opinions. Notably, the Eleventh Circuit has not said that these types of evidence have *no value* for proving causation; when used in combination with other reliable methodologies, they can certainly provide useful *supplemental* evidence. The problem arises when an expert attempts to rely on one of these types of evidence alone or in combination with other types of unreliable evidence.[111]

#### 1. Case Reports and Adverse Event Reports

A case report or case series is a description of medical observations for either a single patient (a case report) or a small number of subjects (a case series). The Eleventh Circuit has held time and time again that general causation may not be inferred based solely on case reports or case series because they "are merely accounts of medical events [that] reflect only reported data, not scientific methodology."[112] In other words, they are anecdotal, lack controls, and do not provide information from which to conduct meaningful statistical analyses.[113] In fact, as the court in *Rider* pointed out, "[s]ome 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."[114] As such, "'case reports and case series are universally regarded as an insufficient scien-

110. *See, e.g.*, Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1203 (11th Cir. 2002) (affirming the district court's decision that the plaintiffs' scientific proof of causation is legally unreliable and therefore inadmissible).

111. *See id.*

112. *Id.* at 1199. *See also, e.g.*, Hendrix v. Evenflo Co., 609 F.3d 1183, 1197 (11th Cir. 2010) (case reports by themselves are "insufficient to show general causation"); *McClain*, 401 F. 3d at 1254 ("case reports raise questions; they do not answer them").

113. *See McClain*, 401 F.3d at 1253 ("[Case] reports are anecdotal, meaning that they are based on descriptions of unmatched individual cases rather than on controlled studies.") (internal quotation marks omitted); *see also Kilpatrick*, 613 F.3d at 1339 (expert himself acknowledging that the case report "cannot establish medical causation").

114. *Rider*, 295 F.3d at 1199.

tific basis for a conclusion regarding causation' . . . . [T]hey [simply] do not supply scientific knowledge upon which an opinion can be based under *Daubert.*"[115]

Following this precedent, the Eleventh Circuit has routinely excluded expert testimony that relies on case reports while being devoid of any of the methodologies the courts have deemed reliable.[116] For instance, in *McClain*, the court rejected an expert's reliance on case reports by pointing out that "if [the expert] had taken his findings and opinions about [the] Plaintiffs and submitted them to a medical journal for publication, they would simply be case reports—anecdotal information, nothing more."[117] Thus, reliance on anecdotal evidence will not overcome the failure of experts to offer scientifically reliable data that proves causation while satisfying *Daubert.*[118] Similarly, in both *Kilpatrick* and *Rider*, the Eleventh Circuit rejected the experts' reliance on case reports, finding that they were "insufficient to create a reliable methodology which passes *Daubert* muster."[119]

Like case reports, adverse event reports and other anecdotal consumer complaints also do not provide a sufficient basis for a causation opinion, on their own. These types of reports are considered "one of the least reliable sources to justify opinions about both general and individual causation" because they supply what amounts to "[u]ncontrolled anecdotal information."[120] Adverse event reports simply entail "consumers call[ing] in to describe medical problems that they *think* they are experiencing from taking a product" but without any medical controls or scientific assessment.[121] Thus, although adverse event reports are often the first signal that a product may contain an issue, they are not to be relied upon in court without additional scientifically reliable evidence.

### 2. Clinical Experience and Differential Diagnosis

A differential diagnosis is a method whereby a physician identifies the cause of a plaintiff's condition through the elimination of potential alternative causes.[122] Specifically, it is "a medical process of elimination

115. Allison v. McGhan Med. Corp., 184 F.3d 1300, 1316 (11th Cir. 1999) (quoting Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1411 (D. Or. 1996)); *see also supra* note 112.

116. For a discussion of the methodologies that the Eleventh Circuit has deemed reliable, see *supra* Part III.C.

117. *McClain*, 401 F.3d at 1254 (causation testimony based on case reports, animal studies, FDA recommendations, and a differential diagnosis excluded as unreliable).

118. *Id.*

119. *See* Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1341 (11th Cir. 2010); Hendrix v. Evenflo Co., 609 F.3d 1183, 1197, 1201 (11th Cir. 2010); *see also Rider*, 295 F.3d at 1199.

120. *McClain*, 401 F.3d at 1250.

121. *Id.*

122. *Hendrix*, 609 F.3d at 1195.

whereby the possible causes of a condition are considered and ruled out one-by-one, leaving only one cause remaining."[123] While differential diagnosis is a scientifically accepted methodology for opining on specific causation so long as it is reliably applied,[124] the Eleventh Circuit has declared on several occasions that it cannot be used as the basis for a reliable opinion on general causation.[125] For example, in *McClain*, a differential diagnosis could not "overcome the [plaintiffs' experts'] fundamental failure of laying a scientific groundwork for the general toxicity of the drug and that it [could] cause the harm a plaintiff suffered."[126] Thus, a physician cannot attempt to establish *general* causation by opining that she examined a patient and determined the agent at issue to have caused the patient's disease. That physician must also rely upon one of the reliable methodologies previously discussed demonstrating that the agent is indeed capable of causing the disease.

In *Hendrix*, the court explained the rationale for why a differential diagnosis by itself—without underlying evidence of general causation—is insufficient to reach a general causation opinion. As the court observed, "[a] reliable differential [diagnosis] is performed in two steps."[127] The first step involves compiling a "comprehensive list of hypotheses that might explain the set of salient clinical findings under consideration. . . . The issue at this point in the process is which of the competing causes are *generally* capable of causing the patient's symptoms."[128] Unlike the first step, which centers on general causation, the second step involves specific causation and looks to "eliminate all causes but one."[129]

In conducting a differential diagnosis, an expert assumes that all the potential causes that he or she considers are actually capable of causing the harm alleged.[130] However, an expert can easily "rule in" certain

123. *Id.*

124. Indeed, an expert's application of the differential diagnosis method does not, by itself, render a specific causation opinion reliable. Rather, "the reliability of the method must be judged by considering the reasonableness of applying the differential etiology approach to the facts of this case and the validity of the experts' particular method of analyzing the data and drawing conclusions therefrom." *Id.*

125. *See, e.g.*, Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1342–43 (11th Cir. 2010); *McClain*, 401 F.3d at 1253.

126. *McClain*, 401 F.3d at 1252; *see also* Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296, 1309 (11th Cir. 2014) (same), *cert. denied*, 135 S. Ct. 2312 (2015); *Hendrix*, 609 F.3d at 1195 (similar).

127. *Hendrix*, 609 F.3d at 1195; *see also Chapman*, 766 F.3d at 1308–09 (describing the same process in three steps).

128. *Hendrix*, 609 F.3d at 1195 (alteration in original) (quoting *McClain*, 401 F.3d at 1253) (internal quotation marks omitted).

129. *Id.* However, an analysis of specific causation is beyond the scope of this article.

130. *Id.* (quoting *McClain*, 401 F.3d at 1253) ("'[A] fundamental assumption underlying [the

causes in the first step of their differential diagnosis without scientifically reliable evidence supporting that causal relationship.[131] Thus, in the first step of the analysis, the district court "must ensure that . . . each possible cause the expert 'rules in'" is actually capable of causing the injury at issue.[132]

Because the expert in *Hendrix* could not "'rule in' his theory of . . . causation" through scientifically reliable evidence, he could not establish the reliability of his opinion simply by claiming that he performed a differential diagnosis on the plaintiff.[133] The court in *McClain* held the same; it stated that because the plaintiffs' experts had not presented reliable evidence of general causation, and because a "valid differential diagnosis . . . only satisfies a *Daubert* analysis if the expert can show the general toxicity of the drug by reliable methods," the experts could not establish the reliability of their opinions by simply claiming they had performed a differential diagnosis.[134]

Along these same lines, the Eleventh Circuit has held that clinical experience alone (whether it is accompanied by a differential diagnosis or not) is an insufficient basis for a general causation opinion.[135] As the court in *Wilson v. Taser International, Inc.* analogized, "[a] medical degree does not authorize [an expert] to testify when he does not base his methods on valid science."[136] In other words, although a doctor's clinical experience "serves him well every day in the clinical practice of medicine . . . his clinical impression is not the sort of scientific methodology that *Daubert* demands."[137] The *Siharath* court aptly articulated the reasoning behind this principle:

> [D]octors every day seek to determine causes of injury and illness and make patients healthier. In their eternal quest for "the answer," however, doctors sometimes believe that they have found a cause when they have not necessarily done so. Doctors in their day-to-day practices stumble upon coincidental occurrences and random events and often follow human nature, which is to confuse association and

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first step of the differential diagnosis] is that the final suspected 'cause' . . . must actually be capable of causing the injury.'").

131. *See In re* Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d 1345, 1365 (S.D. Fla. 2011) ("Without a reliable basis to infer Fixodent causes copper-deficiency myelopathy, a differential diagnosis reaching that conclusion is, in effect, a detailed, unpublished case report."), *aff'd*, Chapman v. Procter & Gamble Distrib., L.L.C., 766 F.3d 1296 (11th Cir. 2014), *cert. denied*, 135 S. Ct. 2312 (2015).

132. *Hendrix*, 609 F.3d at 1195.

133. *Id.* at 1202.

134. *McClain*, 401 F.3d at 1253.

135. *See, e.g.*, *Hendrix*, 609 F.3d at 1197 ("clinical experience, used alone and not merely to bolster other evidence, [is] insufficient to show general causation").

136. 303 F. App'x 708, 714 (11th Cir. 2008).

137. Siharath v. Sandoz Pharm. Corp., 131 F. Supp. 2d 1347, 1372 (N.D. Ga. 2001).

> causation. They are programmed by human nature and the rigors and necessities of their clinical practices to conclude that temporal association equals causation, or at least that it provides an adequate proxy in the chaotic and sometimes inconclusive world of medicine. This shortcut aids doctors in their clinical practices because their most important objective day-to-day is to help their patients and "first, do no harm," as their Hippocratic oath requires. Consequently, "they make a leap of faith. And then in retrospect they build a bridge constructed of other anecdotal evidence, in some cases totally unrelated about heart attacks in older men and things like that and animal data, a bridge to help lead others across the chasm."[138]

### 3. Temporal Relationship

A temporal relationship exists when a person is exposed to a substance and thereafter experiences injury.[139] The temporal relationship is often the starting point for investigating the cause of an injury in clinical practice. Despite the fact that experts often rely on the existence of a temporal relationship in support of their causation opinions, the Eleventh Circuit has held that such a relationship is not sufficient to prove causation.[140] The court in *McClain* stated that "[d]rawing such a [causation] conclusion from temporal relationships leads to the blunder of the *post hoc ergo propter hoc* fallacy."[141] This fallacy, literally translated as "after this, because of this," "assumes causality from temporal sequence."[142] As the *McClain* court pointed out, it is inappropriate to "make[ ] an assumption based on the false inference that a temporal relationship proves a causal relationship"[143]—merely because one event precedes another does not make the first event the cause of the second. The requirement of adequate scientific literature (such as epidemiologic research) "ensures that decision makers will not be misled by the *post hoc ergo propter hoc* fallacy."[144] Moreover, "[i]t is also subject to the problem of assuming what the witness is trying to prove."[145] Thus, standing alone, the existence of a temporal relationship "is entitled to little weight in determining causation."[146]

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138. *Id.* (citation omitted).

139. *See* Reference Manual, *supra* note 7, at 601 ("A temporal, or chronological, relationship must exist for causation to exist. If an exposure causes disease, the exposure must occur before the disease develops. If the exposure occurs after the disease develops, it cannot have caused the disease. . . . Without exposure before the disease, causation cannot exist.").

140. *See, e.g.*, McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1243 (11th Cir. 2005).

141. *Id.*

142. *Id.* (quoting Black's Law Dictionary 1186 (7th ed. 1999)).

143. *Id.*

144. *Id.* (citation omitted).

145. *Id.* at 1254.

146. *Id.* (quoting Moore v. Ashland Chem., Inc., 151 F.3d 269, 278 (5th Cir. 1998)) (internal

The Eleventh Circuit reiterated this principle in *Hendrix*, noting that a temporal relationship is one of the "methods that, when used alone, [is] unable to provide scientifically valid proof of general causation."[147] Indeed, "a mere temporal relationship between an event and a patient's disease or symptoms does not allow an expert to place that event on a list of possible causes of the disease or symptoms."[148]

### 4. Government Findings Based on a Risk-Benefit Analysis

Experts will often attempt to rely on the findings of government agencies, such as the Food and Drug Administration ("FDA") with respect to a particular drug. For instance, in *Rider*, the plaintiffs' expert presented evidence that the FDA issued a statement withdrawing approval of the drug's indication for the prevention of lactation.[149] But, in that instance, the FDA statement—like many government-issued findings—"did not purport to have drawn a conclusion about causation. Instead, the statement merely state[d] that possible risks outweigh the limited benefits of the drug."[150] As the *Rider* court explained, "[t]his risk-utility analysis involves a much lower standard than that which is demanded by a court of law."[151] Indeed, "[a] regulatory agency such as the FDA may choose to err on the side of caution."[152] In contrast, however, courts are required by *Daubert* to ensure that an expert's opinion "has sufficient scientific basis to be considered reliable."[153] Thus, the court held that "[t]he district court did not abuse its discretion in concluding that the FDA [statement did] not, in this case, provide scientific proof of causation."[154]

The Eleventh Circuit also addressed this issue in *McClain*, expounding on the distinction between the type of risk assessment a government agency follows for establishing public health guidelines and the type of analysis an expert must employ with respect to causation in a toxic tort case.[155] Citing the *Reference Manual*, the court explained:

> [P]roof of risk and proof of causation entail somewhat different ques-

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quotation marks omitted); *see also* Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1343 (11th Cir. 2010) (quoting *McClain*, 401 F.3d at 1243) (internal quotation marks omitted) (rejecting expert's causation testimony because it was "rooted in a temporal relationship," which "does not establish a *causal* relationship").

147. Hendrix v. Evenflo Co., 609 F.3d 1183, 1197 (11th Cir. 2010).

148. *Id.*

149. Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1201 (11th Cir. 2002).

150. *Id.*

151. *Id.*

152. *Id.*

153. *Id.*

154. *Id.*

155. McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1249 (11th Cir. 2005).

> tions because risk assessment frequently calls for a cost-benefit analysis. The agency assessing risk may decide to bar a substance or product if the potential benefits are outweighed by the possibility of risks that are largely unquantifiable because of presently unknown contingencies. Consequently, risk assessors may pay heed to any evidence that points to a need for caution, rather than assess the likelihood that a causal relationship in a specific case is more likely than not.[156]

As a result of the factors that often guide government agencies in establishing rules for public health, the *McClain* court held that although it "is not rejecting public health rules from consideration in a *Daubert* analysis," the court must assess "both what the agency intended by setting the guidelines and how the expert uses the guidelines to support his opinions."[157] Where the evidence is focused on a risk-benefit analysis of the drug rather than a causation analysis—as it most often is—governmental proposals or findings cannot provide a reliable basis for a causation opinion in a court of law.[158]

### 5. Unsupported Extrapolations from Animal and In Vitro Studies

In seeking to determine causal relationships in humans, investigators often employ toxicology models based on animal studies. These types of studies usually involve exposing laboratory animals to chemical or physical agents, monitoring the outcomes, and comparing the outcomes with those for an unexposed control group.[159] Animal studies offer a number of advantages. For instance, researchers can conduct true experiments and control all aspects of the animals' lives, including by carefully controlling and measuring exposure.[160] Critically, because of the ethical limitations involved in exposing humans to known doses of chemical agents, studies performed on animals may be the only ethically feasible way in which to obtain scientific information about the dose at which an agent may cause disease (i.e., the dose-response relationship). These studies, however, also have significant disadvantages. Most importantly, the "results must be extrapolated to another species—human beings—and differences in absorption, metabolism, and other factors may result in interspecies variation in responses."[161]

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156. *Id.* (citing Margaret A. Berger, *The Supreme Court's Trilogy on the Admissibility of Expert Testimony*, *in* Fed. Judicial Ctr., Reference Manual on Scientific Evidence 33 (2d ed. 2000)).

157. *Id.*

158. *See id.*

159. Reference Manual, *supra* note 7, at 639.

160. *Id.* at 563.

161. *Id.*

Because of this critical inadequacy, the Eleventh Circuit has—on several occasions—found that animal studies could not provide a sufficient basis for an expert's causation opinion, even when they are used to provide support for the dose-response relationship. For instance, in *Kilpatrick*, the plaintiff's expert attempted to rely on a study performed on rabbits that supported a dose-response relationship between the agent and the disease.[162] The court rejected the study as a reliable basis for the expert's causal opinion because the authors of the study acknowledged that "'no data exists regarding the human-equivalent dosing of [the agent at issue]'"[163] and because the expert "could not explain the possible differences in dose-response relationship between humans and rabbits."[164] The court further observed that the authors at most suggested a connection between the agent and the disease in rabbits, which "does not equate to a conclusion of direct causation . . . between the [agent] and [the disease] in humans."[165]

In addressing the limitations of animal studies, the Eleventh Circuit has explained that such studies are often insufficient because "a large analytical leap must be made between the facts and the opinion."[166] Thus, experts frequently employ "improper extrapolation" when they rely on animal studies.[167] Indeed, even in *Quiet Technology*, a case in which the Eleventh Circuit upheld an expert's (non-medical) causation testimony, the court noted that:

> [A]nimal studies may be methodologically acceptable to show that chemical X increases the risk of cancer in animals, but they may not be methodologically acceptable to show that chemical X increases the risk of cancer in humans. . . . Thus, even if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge for *purposes of the case*.[168]

While the Eleventh Circuit has routinely rejected experts' reliance on animal studies, it has not held that such studies are *per se* unreliable

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162. Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1338–39 (11th Cir. 2010).

163. *Id.* (quoting Andres Gomoll et al., *Chrondrolysis After Continuous Intra-Articular Bupivacaine Infusion: An Experimental Model Investigating Chondrotoxicity in the Rabbit Shoulder*, 22 ARTHROSCOPY 813, 813–19 (2006)).

164. *Id.* at 1339.

165. *Id.* at 1338.

166. McDowell v. Brown, 392 F.3d 1283, 1299 (11th Cir. 2004).

167. *Id.* at 1298; *see also* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1312 (11th Cir. 1999).

168. Quiet Tech. DC-8, Inc. v. Hurel-Dubois U.K. Ltd., 326 F.3d 1333, 1348 (11th Cir. 2003) (alteration in original) (quoting *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994)) (holding that the study on which the expert relied was scientifically valid for purposes of that case because "in the terms employed by the Third Circuit, Quiet essentially placed into dispute the effect of chemical X on animals").

evidence of causation. Instead, animal studies could potentially be reliable so long as "there [are] good grounds to extrapolate from animals to humans."[169] But it is unclear what constitutes "good grounds" under Eleventh Circuit jurisprudence. For instance, in *Allison*, the court rejected several animal studies on which an expert relied, despite the fact that some of the studies were peer reviewed and/or published in a medical journal and despite the fact that the expert "did indeed explain the linkage between the [animal] studies and [the plaintiff's] disease."[170] The court reasoned that publication and peer review "do[ ] not alone establish the necessary link required under *Daubert*."[171] Rather, an expert is required to explain the correlation of the results of the animal studies to symptoms in a human patient, and the district court "was within its discretion to simply find [the expert's explanation] inadequate."[172] Similarly, in *Rider*, the court upheld the district court's rejection of the animal studies because the plaintiffs offered "insufficient evidence [to show] that the effect of [the agent] would be the same on humans as it [wa]s on animals."[173]

Like animal studies, "[t]oxicologists also use in vitro studies, in which human or animal tissue or cells are grown in laboratories and are exposed to certain substances."[174] As described by the Eleventh Circuit in *Kilpatrick*, "[i]n vitro refers to procedures performed in a controlled environment, such as a test tube or petri dish."[175] The problem with this approach is also extrapolation—whether one can generalize the findings from the artificial setting of tissues in laboratories to whole human beings.[176] Thus, as the court held in *Kilpatrick*, the in vitro study on which the expert relied suffered from the same deficiencies as the animal study on which the expert relied: the authors of the study "could not state how their test results would transfer when conducted on a live

169. *Paoli*, 35 F.3d at 743; *see also* Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1202 (11th Cir. 2002) ("[I]t is necessary for plaintiffs to offer some rationale for the suggestion that the vascular structures of humans and animals are sufficiently similar in this context to conclude that [the agent's] effects on animals may be extrapolated to humans."). Indeed, as the *Reference Manual* explains, "[a]nimal studies often provide useful information about pathological mechanisms." REFERENCE MANUAL, *supra* note 7, at 563. And evidence of the pathological (i.e., physiological) mechanism—if properly described and extrapolated to the human body—may enable an expert to survive *Daubert*. *See* Hendrix v. Evenflo Co., 609 F.3d 1183, 1197 (11th Cir. 2010).

170. *Allison*, 184 F.3d at 1313–14.

171. *Id.* at 1314.

172. *Id.*

173. *Rider*, 295 F.3d at 1201.

174. REFERENCE MANUAL, *supra* note 7, at 564.

175. Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1340 n.16 (11th Cir. 2010); *see also* REFERENCE MANUAL, *supra* note 7, at 623 ("In vitro" means "[w]ithin an artificial environment, such as a test tube (e.g., the cultivation of tissue in vitro).").

176. *Kilpatrick*, 613 F.3d at 1340–41.

human subject."[177] As such, the expert's testimony was deemed unreliable under *Daubert*.

In sum, animal and in vitro studies are not *per se* unreliable under Eleventh Circuit case law. However, an expert must have a carefully reasoned explanation for why a study's results can be extrapolated from the animal (or the petri dish) to the human body in the context of what is being studied. Absent such an explanation, these types of evidence cannot provide a sufficient basis for a causation opinion. Notably, no Eleventh Circuit decision has yet accepted an expert's justification in support of extrapolation for either animal or in vitro studies.

### 6. Unsupported Extrapolations from Analogous Agents or Diseases

Experts routinely attempt to rely on existing evidence regarding analogous chemical agents and diseases in opining on a causal relationship between the particular agent and disease at issue.[178] However, the Eleventh Circuit has noted that this type of evidence is wholly insufficient without specific scientific support to validate the analogy. For instance, in *Rider*, the plaintiffs' experts opined that Parlodel—one of many drugs in the class of drugs known as ergot alkaloids—caused vasoconstriction in light of evidence that other ergot alkaloids caused vasoconstriction.[179] The court rejected that analysis, however, because "[e]rgot alkaloids encompass a broad class of drugs with great chemical diversity, and '[e]ven minor deviations in chemical structure can radically change a particular substance's properties and propensities.'"[180] Because the plaintiffs' experts "failed to come forward with a theory as to why the mechanism that causes some ergot alkaloids to act as vasoconstrictors would more probably than not be the same mechanism by which [Parlodel] acts to cause vasoconstriction[, t]he district court did not abuse its discretion" in finding the evidence insufficient to prove general causation.[181] Similarly, in *McClain*, the plaintiffs' experts attempted to rely on a drug analogy—namely, evidence regarding phenylpropanalomine—to show the toxicity of Metabolife (the drug at issue).[182] But, as in *Rider*, the expert provided no evidence to validate the analogy, which the court called "'[s]ubjective speculation . . . mas-

177. *Id.*; *see also supra* notes 162–65 and accompanying text.

178. *See supra* Part III.C.1.

179. Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1200–01 (11th Cir. 2002).

180. *Id.* (quoting Glastetter v. Novartis Pharm. Corp., 252 F.3d 986, 990 (8th Cir. 2001)); *see also supra* note 88 and accompanying text.

181. *Rider*, 295 F.3d at 1200–01.

182. McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1244–45 (11th Cir. 2005).

querade[ing] as scientific knowledge.'"[183] The court emphasized that allowing one to "presume[ ] the same effect by drugs in the same class until proven otherwise . . . do[es] not make for reliable opinions in toxic tort cases."[184]

In both *Rider* and *McClain*, the Eleventh Circuit also rejected the experts' reliance on evidence regarding analogous diseases. Specifically, in *Rider*, the plaintiffs' experts relied on evidence that Parlodel caused ischemic stroke to opine that Parlodel causes hemorrhagic stroke (the disease at issue).[185] The court found this "the most untenable link in the causal chain," because, although the two conditions share a name, they "involve a wholly different biological mechanism."[186] Thus, the court concluded that evidence regarding ischemic stroke did not apply to situations involving hemorrhagic stroke and could not be used as a reliable basis for the experts' causal opinion.[187] Likewise, in *McClain*, the plaintiffs' experts attempted to rely on evidence regarding hemorrhagic stroke to opine on a causal relationship involving ischemic stroke and heart attack.[188] But, reiterating the sentiments in *Rider*, the court rejected this analogy because it was "'a leap of faith' supported by little more than the fact that both conditions are commonly called strokes."[189]

In light of these Eleventh Circuit holdings, it is clear that experts must be cautious of relying on analogies regarding other chemicals or diseases. As with animal studies and in vitro studies, such analogies are not *per se* unreliable. They are highly suspect, however, and should only be used when there is a clear scientific basis to support the comparison.

## IV. Conclusion

Since the Supreme Court's decision in *Joiner*, the Eleventh Circuit has adopted a particularly rigorous review of expert testimony, especially testimony pertaining to causation in products liability cases. As one author aptly observed: "having been rebuffed by the Supreme Court in its prior significant *Daubert* decisions, [the Eleventh Circuit] has now embraced [a] rigorous examination" of proffered expert testimony.[190] Indeed, it has been said that "the Eleventh Circuit, at least in civil cases, applies *Daubert* with a vengeance."[191] And the *Chapman* decision has

183. *Id.* at 1245 (quoting *Glastetter*, 252 F.3d at 989).
184. *Id.* at 1246.
185. *Rider*, 295 F.3d at 1202.
186. *Id.*
187. *Id.*
188. *McClain*, 401 F.3d at 1246.
189. *Id.* (quoting *Rider*, 295 F.3d at 1202).
190. Marc T. Treadwell, *Evidence*, 51 Mercer L. Rev. 1165, 1181 (2000).
191. Marc T. Treadwell, *Evidence*, 57 Mercer L. Rev. 1083, 1105 (2006).

only affirmed the Eleventh Circuit's commitment to the strict application of *Daubert*, clarifying precisely the types of methodologies that are sufficiently reliable for establishing general causation. Because the outcome of a products liability case often turns on whether a plaintiff can present reliable general causation testimony, it is critical that practitioners are aware of this Eleventh Circuit jurisprudence and its recent developments.

Practitioners on both sides of the aisle should carefully examine the types of evidence that are required by Eleventh Circuit precedent—and those that are inherently insufficient—before retaining and preparing experts. In addition, because products liability cases are often taken on a contingency fee basis, plaintiffs' attorneys would be wise to evaluate to what extent the requisite types of evidence exist before agreeing to undertake representation of a case requiring general causation testimony. Conversely, defense attorneys can evaluate the likelihood of their success—and the resulting interests in settlement—at the outset based on the reasonably predictable guidance provided by Eleventh Circuit jurisprudence. Either way, the principles and tenets of Eleventh Circuit *Daubert* law on general causation should guide all aspects of litigation preparation and strategy, and certainly should not be ignored until the preparation of *Daubert* motions.