Admitting and Excluding General Causation Expert Testimony: The Eleventh Circuit Construct

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Abstract

Success in mass toxic tort and product liability cases often turns on the plaintiffs' ability to present reliable expert evidence of general causation that can survive Daubert *scrutiny and create a triable issue for a jury. The Eleventh Circuit Court of Appeals has provided litigants with clear guidance on these issues. A litigant's ability to follow that guidance can make the difference between winning and losing a major case.*

Introduction

Often multi-plaintiff (or mass) toxic tort and product liability cases turn on the question of causation. Plaintiffs frequently can prove that they have injuries or illnesses and that they used a defendant's product or were exposed to a chemical compound sold by a defendant—or at the very least, they can present enough evidence on these elements to survive summary judgment. Where plaintiffs face a more difficult hurdle is in trying to prove that the defendant's product or chemical compound can cause the injury or illness the plaintiffs suffered (general causation), and, further, that the product or compound in fact caused each plaintiff's injury or illness (specific causation).[1]

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[1] *See* Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1334 n.4 (11th Cir. 2010); *accord* Howell v. Centric Grp., LLC, 508 F. App'x 834, 836 (10th Cir. 2013) (order denying motion for reconsideration) (noting that "courts throughout the country routinely require plaintiffs to show both general and specific causation"); Johnson v. Arkema, Inc., 685 F.3d 452, 468-69 (5th Cir. 2012) (per curiam) (citing Knight v. Kirby Inland Marine, Inc., 482 F.3d 347, 351 (5th Cir. 2007)) (noting that courts can only evaluate specific causation after finding general causation); Junk v. Terminix Int'l Co., 628 F.3d 439, 450 (8th Cir. 2010) (citing Ranes v. Adams Labs., Inc., 778 N.W.2d 677, 688 (Iowa 2010)) ("To prevail in a toxic tort case such as this, the plaintiff must show both general and specific causation."); *In re* Meridia Prods. Liab. Litig., 328 F. Supp. 2d 791, 798 (N.D. Ohio 2004), *aff'd sub nom*. Meridia Prods. Liab. Litig. v. Abbott Labs., 447 F.3d 861, 869 (6th Cir. 2006) (same); *In re* Hanford Nuclear Reservation Litig.,

In such actions, plaintiffs' likelihood of success is commonly driven by the admissibility of their experts' general causation testimony under Rule 702 of the Federal Rules of Evidence and *Daubert v. Merrell Dow Pharmaceuticals*.[2] If that testimony is not admissible under *Daubert*, the action is dismissed; if it is admissible, a defendant often feels irresistible pressure to settle the action rather than risk a battle of experts at trial that, if the defendant loses, can cost exponentially more than the settlement cost of the action.[3]

Given the significant role played by *Daubert* challenges to general causation expert testimony in resolving mass toxic tort and product liability cases, guiding precedent in many United States courts of appeals on such challenges is either sparse or, worse, inconsistent.[4] The decisions

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292 F.3d 1124, 1133 (9th Cir. 2002) ("Causation in toxic tort cases is typically discussed in terms of generic and specific causation."); Raynor v. Merrell Pharms. Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997) ("testimony on specific causation had legitimacy only as follow-up to admissible evidence that the drug in question *could* in general cause birth defects"); Rutigliano v. Valley Bus. Forms, 929 F. Supp. 779, 783 (D.N.J. 1996), *aff'd sub nom.* Valley Bus. Forms v. Graphic Fine Color, Inc., 118 F.3d 1577 (3d Cir. 1997) (granting summary judgment for the defendant as the plaintiff failed to prove general and specific causation). *See generally* RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL & EMOTIONAL HARM § 28 cmt. c (2010) ("The concepts of general causation and specific causation are widely accepted among courts confronting causation issues with toxic agents.").

[2] 509 U.S. 579 (1993). References hereinafter to "*Daubert*" are shorthand for both Rule 702 and the Supreme Court's *Daubert* decision and its progeny. Rule 702 was amended in 2000 to codify the principles of *Daubert* and its then-existing progeny. *See* FED. R. EVID. 702 advisory committee's note. Rule 702 permits an expert to testify to opinions if, among other things, the expert's (1) "knowledge will help the trier of fact to understand the evidence or to determine a fact in issue," (2) "testimony is based on sufficient facts or data," (3) "testimony is the product of reliable principles and methods," and (4) "appli[cation of] principles and methods to the facts of the case" is reliable. FED. R. EVID. 702; *see also* Hendrix v. Evenflo Co., 609 F.3d 1183, 1194 (11th Cir. 2010) (construing *Daubert*).

[3] In all but the rarest of circumstances, a plaintiff cannot prove—or even create a triable issue of fact as to—general causation without expert testimony. *See Hendrix*, 609 F.3d at 1203 (affirming summary judgment in favor of defendant after exclusion of experts); *see also Kilpatrick*, 613 F.3d at 1334 n.4 (general and specific causation expert testimony required in products liability cases).

[4] *See* Berry v. City of Detroit, 25 F.3d 1342, 1352-54 (6th Cir. 1996) (excluding nonscientific expert testimony because it failed to meet the four *Daubert* factors), *cert. denied*, 115 S. Ct. 902 (1995); Marcel v. Placid Oil Co., 11 F.3d 563, 567-68 (5th Cir. 1994) (excluding testimony of economist because conclusions not based on sufficient data made the testimony unreliable); Habecker v. Clark Equip. Co., 36 F.3d 278, 289-90 (3d Cir. 1994) (finding testimony of accident simulation expert inadmissible after assessing expert's methodology under *Daubert*), *cert. denied*, 115 S. Ct. 1313 (1995).

of the Eleventh Circuit Court of Appeals, however, are noteworthy exceptions to this. They have established a clear framework for how a district court is to determine if expert testimony on general causation is admissible under *Daubert*.[5] This Article discusses the framework with which every litigator handling a toxic tort or product liability case in the Eleventh Circuit—whether representing plaintiffs or defendants—should be familiar.[6]

I. The Eleventh Circuit's General Framework

Before delving into whether an expert's general causation opinions are based on sound and reliable methodologies as required under *Daubert*, the threshold issues are whether a district court even needs to subject those opinions to close *Daubert* scrutiny and how tailored do those opinions need to be to the facts of a given case. The Eleventh Circuit has addressed and resolved each of these issues.

In *McClain v. Metabolife International, Inc.*,[7] the Eleventh Circuit explained that toxic tort and product liability cases fall within two categories: (1) "those in which the medical community generally recognizes the toxicity of the [substance] at issue," and (2) "those [] in which the medical community does not."[8] District courts "need not" conduct an extensive *Daubert* general causation analysis for cases in the first category, whereas they must for cases in the second category.[9] Thus,

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[5] *Compare* McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1237-38 (11th Cir.), *reh'g denied*, 159 F. App'x 183 (11th Cir. 2005), *with In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 741 (3d Cir. 1994), *cert. denied*, 115 S. Ct. 1253 (1995).

[6] In fact, given that the Florida legislature has recently passed a bill to replace the *Frye* standard historically used by Florida courts with the *Daubert* standard, Eleventh Circuit *Daubert* precedent is likely to be of great influence in Florida courts, especially in the early years before the Florida courts develop their own body of *Daubert* interpretations and applications. *See* H.B. 7015, 23d Legis., First Reg. Sess. (Fla. 2013) (amending FLA. STAT. § 90.702 (1976)); *see also* Frye v. United States, 293 F. 1013 (D.C. Cir. 1923); *Daubert*, 509 U.S. 579.

[7] 401 F.3d 1233 (11th Cir.), *reh'g denied*, 159 F. App'x 183 (11th Cir. 2005).

[8] *McClain*, 401 F.3d at 1239.

[9] *Id.* at 1239.

while *McClain permits* a district court to bypass "an extensive *Daubert* analysis" in some circumstances, it never *compels* such circumvention.[10]

Furthermore, the *McClain* court was clear that its first category is very limited: It applies only in the narrow circumstance "where the reliability of the expert's methods is properly taken for granted."[11] *McClain* provided the following examples of agents and illnesses that fall within the first category: asbestosis and mesothelioma; cigarette smoke and lung cancer; and silica and silicosis.[12] All of these causal connections gained widespread acceptance from decades of research and rigorous data analysis.[13]

The Eleventh Circuit, in *McClain* and its progeny, also addressed the need for an expert opinion on general causation to be tied closely to the product or chemical compound at issue in a lawsuit.[14] It is not enough for an expert to opine that (1) similar products, related chemicals, or drugs within the same class can cause the injury or illness suffered by a plaintiff, or (2) a defendant's product or chemical compound can cause illnesses or injuries analogous to the injury or illness of the plaintiff.[15] Rather, admissible general causation expert testimony must address whether the agent in question (be it a product or a chemical compound) can cause the specific injury in question.[16] This is required because

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[10] *Id.*; *see also* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152-53 (1999) ("The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability . . . as it enjoys when it decides *whether or not* that expert's relevant testimony is reliable.").

[11] *McClain*, 401 F.3d at 1239 n.5 (quoting *Kumho*, 526 U.S. at 152).

[12] *Id.* at 1239.

[13] The *McClain* court was clear that its two-category paradigm "is not an effort to resurrect the test first announced in *Frye*." *McClain*, 401 F.3d at 1239 n.5 (referencing *Frye*, 293 F. at 1014). Accordingly, the touchstone for admissibility remains whether an expert's opinion is based on scientifically reliable methodologies and fits the facts of the case at hand. If this is not true, then the expert's opinions are inadmissible even if consistent with what the medical community might generally recognize. *See Daubert*, 509 U.S. at 592-93.

[14] *See McClain*, 401 F.3d at 1239.

[15] *Id.*

[16] *Id.* ("[I]n this case, Plaintiffs' experts must offer reliable opinions about Metabolife's general toxicity for the harm Plaintiffs allege."); *id*. at 1237 ("Plaintiffs must prove the toxicity of [Metabolife's] ephedrine/caffeine combination and that it had a toxic effect on them . . . ."); Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1334 n.4 (11th Cir.

"[e]ven minor deviations in chemical structure can radically change a particular substance's properties and propensities," so extrapolating from one product to another, or from one type of injury to another, is not easily done.[17]

II. Evaluation of General Causation Methodologies

Just as Eleventh Circuit precedent creates a clear structure for a district court to assess general causation expert opinions, it also provides clear guidance to district courts on how to evaluate the methodologies that an expert has employed to form an opinion on general causation. More specifically, the Eleventh Circuit has addressed the reliability of various methodologies experts use to formulate general causation opinions and explained why some of the methodologies are simply insufficient to warrant an admissible opinion on general causation.[18] In so doing, the Eleventh Circuit has not created a strict checklist of required methodologies. Instead, it has developed—consistent with standard practice by scientists researching causation outside the courtroom—a structured hierarchy of methodologies based on their probative value in demonstrating causation.[19] Although experts are not required to employ the most

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2010) ("Kilpatrick must offer proof . . . that the device in question can cause harm of the type Kilpatrick alleges . . . ."); *see also* Goldstein v. Centocor, Inc., 310 F. App'x 331, 332-33 (11th Cir. 2009) (per curiam) (involving the issue of whether Remicade caused pulmonary fibrosis); Kilpatrick v. Breg, Inc., No. 08-10052-CIV, 2009 WL 2058384, at *4 (S.D. Fla. June 25, 2009) ("[T]he key issue is . . . whether that [chemical] compound as delivered via a particular medical device inserted in a particular location . . . could and did cause injury."), *aff'd*, 613 F.3d 1329 (11th Cir. 2010); Guinn v. AstraZeneca Pharms. LP, 598 F. Supp. 2d 1239, 1242 (M.D. Fla. 2009) (order granting defendant's motion for summary judgment) ("Guinn must show both that Seroquel can generally cause diabetes and that Seroquel was a specific cause of her diabetes."), *aff'd*, 602 F.3d 1245 (11th Cir. 2010) (per curiam).

[17] *McClain*, 401 F.3d at 1246 (alteration in original) (quoting Rider v. Sandoz Pharms. Corp., 295 F.3d 1194, 1201 (11th Cir. 2002)); *see also* Wells v. SmithKline Beecham Corp., 601 F.3d 375, 380 (5th Cir. 2010); Knight v. Kirby Inland Marine Inc., 482 F.3d 347, 350-53 (5th Cir. 2007).

[18] *See infra* notes 21-55 and accompanying text.

[19] *See Rider*, 295 F.3d at 1202-03 (rejecting the argument that the district court "requir[ed] a checklist of types of evidence to prove causation," but rather "was highlighting the plaintiffs' failure to present evidence in any of several categories that

probative methodologies, the Eleventh Circuit has repeatedly held that an expert's general causation testimony that neglects these critical methodologies is subject to heightened examination and can rarely, if ever, survive *Daubert* scrutiny.[20]

A. Most Probative Methodologies

The most probative method for proving that a product causes a specific injury or illness to humans is controlled human experimentation (such as randomized clinical trials).[21] For obvious reason, however, that method is rarely available (and appropriately so) in situations where a product is alleged to cause significant injury or a serious illness. Fortunately, other methodologies exist that have been established as reliable for demonstrating general causation without the need for direct human testing. These methodologies share a common trait of being based on data (not subjective judgment) that can be tested and the results either replicated or refuted.

1. Dose-Response Relationship

"The dose-response relationship is '[a] 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.'"[22] It 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."[23] Consequently, in the Eleventh Circuit, the

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would have been persuasive"); *see also* Hendrix v. Evenflo Co., 609 F.3d 1183, 1196-97 (11th Cir. 2010).

[20] *See, e.g.*, *Kilpatrick*, 613 F.3d at 1336-38; *Hendrix*, 609 F.3d at 1196-99; *McClain*, 401 F.3d at 1240; *Rider*, 295 F.3d at 1198, 1202.

[21] *See, e.g.*, *Rider*, 295 F.3d at 1201-02; *Kilpatrick*, 613 F.3d at 1338.

[22] *McClain*, 401 F.3d at 1241-42 (alteration in original) (quoting Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 390 (2d ed., 2000)).

[23] *Id*. at 1242 (quoting David L. Eaton, *Scientific Judgment and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL. 5, 11, 15 (2003)). This factor is so significant, in part, because the reality is that most substances—even water—can cause adverse effects in high enough quantities, but also can have positive

"expert who avoids or neglects this [dose-response] principle . . . casts suspicion on the reliability of his methodology" and the admissibility of his opinions.[24]

2. Analytic Epidemiological Studies

Analytic epidemiological studies (such as case-control studies, cohort studies, and cross-sectional studies) have designs and controls that allow an expert to determine whether an agent and a disease occur together more frequently than can plausibly be explained by chance.[25] The Eleventh Circuit has described analytic epidemiologic studies as "the best evidence of causation in toxic tort actions."[26] Although "[t]he absence of such evidence is not fatal," the absence "makes [the expert's] task to show general causation more difficult."[27] Indeed, when expert testimony is not buttressed by analytic epidemiological studies, the Eleventh Circuit has held the "nature of the other evidence (case reports, animal studies, *in vitro* studies) becomes that much more important, and the court's consideration of such evidence and the methodologies used *must be that much more searching*."[28]

3. Background Risk and Additional Risk

The background risk of a disease identifies the chance of someone acquiring a disease without exposure to the agent in dispute.[29] It is the

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effects in lower quantities. This is the basis behind perhaps the most quoted adage in toxicology, originally attributed to Paracelsus: "[T]he dose differentiates a poison from a remedy." *E.g.*, David L. Eaton, *Scientific Judgment and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL'Y 5, 11 (2003).

[24] *McClain*, 401 F.3d at 1241-42; *see also Kilpatrick*, 613 F.3d at 1339 (same).

[25] *See* Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 549, 555-63, 566 (3d ed., 2011), *available at* http://www.au.af.mil/au/awc/awcgate/fjc/manual_sci_evidence.pdf. Generally speaking, analytic epidemiology studies are analyses of health and disease data that attempt to control for chance, bias, and confounding factors to determine, with some degree of statistical reliability, the patterns, causes and effects of health and disease conditions in defined populations.

[26] *Rider*, 295 F.3d at 1198.

[27] *Kilpatrick*, 613 F.3d at 1336-37 (citation omitted).

[28] *Id.* at 1337 n.9 (emphasis added).

[29] *See McClain*, 401 F.3d at 1243.

baseline against which an expert measures whether someone exposed to the agent has any greater risk of acquiring the disease than individuals without exposure (what is called the "additional risk").[30] The Eleventh Circuit has emphasized that an expert opining on general causation must have a reliable means of determining both the background risk and the additional risk. When an expert "offer[s] no evidence of additional risk," the Eleventh Circuit has directed that a district court "*must assume that it does not exist*."[31] Such an assumption essentially forecloses general causation expert testimony that does not account for "background risk" and "additional risk."

4. Physiological Process

Another critical element of an expert opinion on general causation is the ability of an expert to identify a credible physiological process (such as the biological mechanism) by which the product or chemical compound being challenged can cause the illness or injury suffered by the plaintiffs. This is one of "[t]he underlying predicates of any cause-and-effect medical testimony."[32] Absent such identification, it is difficult for an expert to opine that an association between an agent and a disease, even a statistically significant association, is actually evidence of causation.[33]

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[30] *See id.* Scientists often refer to this as the "relative risk" or the "odds ratio," depending on the type of study being conducted. This "additional risk" is assessed at the level of a relevant population, whereas the toxicology-related dose-response relationship described earlier is assessed at the level of an individual. *See* Green et al., *supra* note 25, at 566-67.

[31] *Id.* (emphasis added). The Eleventh Circuit has not had to address whether the additional risk/relative risk assessment has to account for confounding factors (other conditions or events that may explain why a subpopulation exposed to an agent acquired a disease), but it is standard epidemiological practice to account (and adjust) for confounding factors.

[32] *Id.* at 1253 (quoting Black v. Food Lion, Inc., 171 F.3d 308, 314 (5th Cir. 1999)).

[33] *Kilpatrick*, 613 F.3d at 1338 (alteration in original) ("[S]howing [an] *association* is far removed from proving *causation*." (quoting Allison v. McGhan Med. Corp., 184 F.3d 1300, 1315 n.16 (11th Cir. 1999))).

B. Least Probative Methodologies

Eleventh Circuit case law addressing the most reliable methodologies for an expert to employ to determine general causation is of great assistance to both litigants and experts attempting to prove or disprove causation. Equally valuable is the Eleventh Circuit precedent explaining those methodologies that are least reliable—the ones that may bolster general causation opinions directly supported by other, stronger evidence, but that are too weak themselves to justify an admissible opinion on general causation.

1. In Vitro/Test Tube Studies

How a chemical compound reacts in a test tube is often quite different from how it reacts in, and impacts, the complex biological system that is the human body.[34] Consistent with this, the Eleventh Circuit has recognized that test tube studies alone are unreliable to establish causation and of limited evidentiary value.[35] That limited value is diminished even further when an expert is unable to explain how test tube results can be extrapolated to the human body and why such extrapolation is scientifically reliable.

2. Animal Studies

Animal studies have the same basic limitation as in vitro studies: How a chemical compound affects an animal is not necessarily the same as, and quite often is materially different than, how the compound affects

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[34] *See, e.g.*, *id.* at 1340-42.

[35] *See, e.g.*, *id.* at 1340-44; *In re* Accutane Prods. Liab., 511 F. Supp. 2d 1288, 1294-95 (M.D. Fla. 2007) (order granting motion to exclude general causation testimony) ("'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.' That is, studies such as these necessarily remove the cells from the dynamic metabolic context in which the human body actually processes chemical compounds."); *see also* Allen v. Pa. Eng'g Corp., 102 F.3d 194, 198 (5th Cir. 1996) (stating cell biology tests are "the beginning, not the end of the scientific inquiry and prove[] nothing about causation without other scientific evidence").

humans.[36] Moreover, such studies commonly use high dosages of compounds to expedite reactions in animals, which further complicates extrapolating from animal studies to humans exposed to lower levels of the compounds.[37] Courts therefore regard animal studies alone as an unreliable means of showing general causation as to humans, though they may provide support for the interpretation of human epidemiological or clinical data.[38]

3. Case Reports (and Medical Textbooks Based on Case Reports)

A case report is an article discussing the unique symptoms, diagnosis, and treatment of an individual patient or a small group of patients.[39] It does not reflect a controlled clinical trial or a large, statistically significant sample of patients.[40] Case reports frequently hypothesize associations between agents and injuries or illnesses, but those hypotheses, in turn, are frequently invalidated by subsequent analytic epidemiological studies.[41] Case reports also lack scientific controls (such as a control

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[36] *Kilpatrick*, 613 F.3d at 1338-39 (citations omitted); *see also* Johnson v. Arkema, Inc., 685 F.3d 452, 463 (5th Cir. 2012) (per curiam) ("We have previously recognized the very limited usefulness of animal studies when confronted with questions of toxicity.") (citation omitted) (internal quotation marks omitted).

[37] *Arkema*, 685 F.3d at 463-64 (citing Gulf S. Insulation v. U.S. Consumer Prod. Safety Comm'n, 701 F.2d 1137, 1146 (5th Cir. 1983)).

[38] *See, e.g.*, Rider v. Sandoz Pharms. Corp., 295 F.3d 1194, 1202 (11th Cir. 2002); *Allison*, 184 F.3d at 1313-14; *Allen*, 102 F.3d at 197; Wade-Greaux *ex rel.* Greaux v. Whitehall Labs., Inc., 874 F. Supp. 1441, 1445 (D.V.I.), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1223, 1241 (E.D.N.Y. 1985), *aff'd sub nom.*, *In re* "Agent Orange" Prod. Liab. Litig. MDL No. 381, 818 F.2d 187 (2d Cir. 1987); Blum *ex rel.* Blum v. Merrell Dow Pharms., Inc., 705 A.2d 1314, 1323 (Pa. Super. Ct. 1997), *abrogated by* Trach v. Fellin, 817 A.2d 1102 (Pa. Super. Ct. 2003).

[39] *See, e.g.*, Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, *in* FED. JUDICIAL CTR, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 439, 474 (2d ed. 2000).

[40] *Id.*

[41] *See, e.g.*, Ralph R. Cook, *Epidemiology for Toxicologists*, *in* PRINCIPLES AND METHODS OF TOXICOLOGY 549, 559 (Hayes ed., 5th ed. 2008) ("Although the theories derived from case studies are not always wrong, history teaches that they are seldom right."); *see also* McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1253 (11th Cir.),

group and protections against selection bias).[42] Accordingly, the Eleventh Circuit has repeatedly held that case reports are simply anecdotal medical evidence that cannot establish causation.[43] The same result holds true for medical textbooks that opine on a causal connection or association between an agent and an injury or illness when the support they cite for such a conclusion are case reports.[44] Textbooks that simply rely on case reports have no more authority than the underlying case reports.[45]

4. FDA Adverse Event Reports

Adverse Event Reports (AERs) are similar to case reports—they address the unique symptoms, diagnosis, and treatment of an individual

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reh'g denied, 159 F. App'x 183 (11th Cir. 2005) (quoting Black v. Food Lion, Inc., 171 F.3d 308, 314 (5th Cir. 1999)).

[42] Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1411 (D. Or. 1996) ("[C]ase reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls. . . . Therefore, these cannot be the basis of an opinion based on scientific knowledge under *Daubert*.").

[43] *See, e.g.*, Hendrix v. Evenflo Co., 609 F.3d 1183, 1197 (11th Cir. 2010) (finding case reports are "insufficient to show general causation"); *McClain*, 401 F.3d at 1254 ("[C]ase reports raise questions; they do not answer them."); *Allison*, 184 F.3d at 1316 (stating "case studies pale in comparison" to epidemiological studies); s*ee also Rider*, 295 F.3d at 1199 (finding case reports cannot rule out idiosyncratic or confounding factors); *In re* Accutane Prods. Liab., 511 F. Supp. 2d 1288, 1298 (M.D. Fla. 2007) (finding case reports cannot rule out coincidence).

[44] *See In re* Welding Fume Prods. Liab. Litig., No. 1:03-CV-17000, 2005 WL 1868046, at *35 (N.D. Ohio Aug. 8, 2005) (citing *In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003)) (stating that medical textbooks are "non-epidemiological lines of evidence of general causation"); Richardson v. Richardson-Merrell, Inc., 857 F.2d 823, 830 (D.C. Cir. 1988) (stating that non-epidimological evidence "[is] not capable of proving causation"), *cert. denied*, 493 U.S. 882 (1989).

[45] Glastetter v. Novartis Pharms. Corp., 252 F.3d 986, 990 (8th Cir. 2001) (per curiam) (noting medical texts did not "present persuasive scientific evidence that Parlodel causes vasoconstriction" because "[s]ome of the texts were largely grounded upon case reports and other anecdotal information"); Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1370 (N.D. Ga. 2001) (order granting motion to exclude expert testimony) ("The statements in the treatises are clearly based on case reports and, therefore, provide no more support than the case reports themselves." (citation omitted)), *aff'd sub nom.* Rider v. Sandoz Pharms. Corp., 295 F.3d 1194 (11th Cir. 2002).

patient that used an FDA-approved product.[46] Based on AERs, the FDA may issue a Notice and Recommended Action or warning letter to prompt a manufacturer to make changes to its product or issue additional warnings.[47]

The Eleventh Circuit has recognized that AERs, even when they lead to FDA action, are "one of the least reliable sources" to support opinions on general causation.[48] This is in part because AERs are a product of a voluntary reporting system that lacks significant controls and "are subject to a variety of reporting biases" and the underlying "data may be affected by . . . reporting stimulated by publicity or litigation."[49] Consequently, even the FDA cautions that AERs are only evidence of a safety "signal" indicating "the need for further investigation, which may or may not lead to the conclusion that the product caused the event."[50] Moreover, the FDA uses a lower threshold to decide when it should take action versus the threshold courts have set for demonstrating causation.[51] Thus, AERs may prompt FDA action (such as issuing a Notice) even though they demonstrate nothing more than a possible association between a product and an adverse effect.[52]

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[46] *See* 21 U.S.C. § 360i(b)(1), (5)-(6) (2006).

[47] FDA, REGULATORY PROCEDURES MANUAL §§ 4-1-1, 4-1-3, 4-2-1, 10-2-3 (2012).

[48] *McClain*, 401 F.3d at 1250.

[49] FDA, GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 9 (2005) [hereinafter FDA, *Guidance for Industry*], *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf.

[50] *Id*. at 4; *see also id*. at 7 ("Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.").

[51] *Rider*, 295 F.3d at 1201 (noting the FDA employs an analysis that "involves a much lower standard than that which is demanded by a court of law").

[52] *Id.* (noting the FDA applies a different risk-utility analysis than that employed by a court, and the FDA's actions are not scientific proof of causation). The same applies to regulatory action by other agencies, which often impose protective or prophylactic limits based on evidence of potential risks or associations as opposed to proof of actual causation. *See* Johnson v. Arkema, Inc., 685 F.3d 452, 464 (5th Cir. 2012) (per curiam).

5. Differential Diagnosis and Differential Etiology

The differential diagnosis (or differential etiology) technique is essentially a process-of-elimination approach. A physician or investigator starts by considering all explanations for a person's injury or illness and then eliminates them one-by-one based on tests, examination of the person or a review of his medical history until the physician or investigator is left (or hopes to be left) with only one possible explanation.[53] This last explanation is then assumed to be the cause of the injury or illness.[54]

As this simple description of the technique reflects, advance knowledge by the physician or investigator of the potential causes for an injury or illness is critical to its effectiveness. The Eleventh Circuit has accordingly held that application of the differential diagnosis or etiology technique cannot itself demonstrate general causation: "[A] fundamental assumption underlying [differential diagnosis] is that the final, suspected 'cause' . . . must actually be capable of causing the injury."[55] Hence, an expert's "purported use of the differential [diagnosis] method 'will not overcome a fundamental failure to lay the scientific groundwork' for the theory that [an agent] can, in general, cause [a disease]."[56] Stated differently, a differential diagnosis is inadmissible if there is no independent, reliable evidence to "rule in"—as a matter of general causation—that the agent can cause the medical condition in the first place, even if a physician or investigator can "rule out" alternative explanations for a medical condition other than the agent in question.[57]

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[53] *See* Hendrix v. Evenflo Co., 609 F.3d 1183, 1194 n.5, 1195 (11th Cir. 2010).

[54] *See id.* at 1195.

[55] *McClain*, 401 F.3d at 1253 (alteration in original) (citing Clausen v. M/V New Carissa, 339 F.3d 1049, 1057-58 (9th Cir. 2003)).

[56] *Hendrix*, 609 F.3d at 1195 (quoting *McClain*, 401 F.3d at 1252).

[57] *See id.* at 1197-98; Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1342 (11th Cir. 2010) (stating differential diagnosis "assumes the existence of general causation"); *McClain*, 401 F.3d at 1253 ("A valid differential diagnosis, however, only satisfies a *Daubert* analysis if the expert can show the general toxicity of the drug by reliable methods."). Other circuits are in accord. *See, e.g.*, *Arkema*, 685 F.3d at 468 (finding "an expert may not rely on a differential diagnosis to circumvent the requirement of general causation" (citation omitted)); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002) (stating "experts would need to present reliable evidence that the drug can cause strokes" for differential diagnosis to be admissible); Glastetter v. Novartis Pharms. Corp., 252 F.3d 986, 989 (8th Cir. 2001) (per curiam) (affirming

6. Combining Evidence from Unreliable Methodologies

A final "methodology" sometimes presented by experts to support their opinions is what has been described (or misdescribed) as a "weight of the evidence" approach, whereby the expert supports her opinion by application of a variety of methodologies, none of which individually is reliable, but all of which in combination are (the expert claims) reliable. The Eleventh Circuit has effectively rejected this method: where each piece of evidence upon which an expert relies to form her opinion has been found to be scientifically unreliable, the Eleventh Circuit has held the expert's opinion is properly excluded.[58] This is consistent with the standard application of the scientific method.[59] That method allows such untestable, judgment-driven assessments to be used either as preliminary assessments of possible causation (i.e., to identify "signals" meriting further investigation)[60] or to evaluate the best conclusion to draw from

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exclusion of a differential diagnosis because experts could not first "rule in" the agent as a possible cause using an independent, scientifically reliable methodology); Raynor v. Merrell Pharms. Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997) (stating a differential diagnosis "had legitimacy only as a follow-up to admissible evidence that the drug in question *could* in general cause birth defects").

[58] *See, e.g.*, *Kilpatrick*, 613 F.3d at 1337-41; *Hendrix*, 609 F.3d at 1202-03; *McClain*, 401 F.3d at 1255; *Rider*, 295 F.3d at 1202.

[59] *Rider*, 295 F.3d at 1197.

[60] An example of this is the Naranjo Scale, used to evaluate case reports and AERs involving adverse drug reactions. It consists of ten questions, which examine factors such as "previous *conclusive* reports" of adverse reactions, the timing of an adverse reaction, whether the adverse reaction improved when use of a drug was discontinued (called "dechallenged"), whether it reappeared when the drug was readministered (called "rechallenged"), dosage levels, and the exclusion of alternative causes. C.A. Naranjo et al., *A Method for Estimating the Probability of Adverse Drug Reactions*, 30 CLINICAL PHARMACOL. THER. 239, 240 (1981). Points are assigned or subtracted based on responses to the questions, with 13 being the highest possible score. *Id.* Scientists do not use the Naranjo Scale to make conclusions about general causation. Rather, it is used to assess the strength of a case report as a potential "safety signal." FDA, *Guidance for Industry*, *supra* note 49, at 4-7; Ronald H.B. Meyboom et al., *Causal or Casual? The Role of Causality Assessment in Pharmacovigilance*, 17 DRUG SAFETY 374, 376-79 (1997). Thus, although the Naranjo Scale yields "provisional" assessments that are used to guide further research, conclusions about causation can be determined only "through further analytical, or if possible, experimental studies." Ronald H.B. Meyboom et al., *Causal or Casual? The Role of Causality Assessment in Pharmacovigilance*, 17 DRUG SAFETY 374, 376, 382 (1997); *see* FDA, *Guidance for Industry*, *supra* note 49, at 7; *see also* Rhodes v. Bayer Healthcare Pharms., Inc., No.

testable, analytic data (such as epidemiological studies) that can support more than one conclusion on causation.[61] The scientific method, however, does not recognize such patchwork, malleable, "weight of the evidence" reasoning as an independent basis to determine that causation exists.[62] Hence, an expert cannot aggregate "individual categories of evidence deemed unreliable by [a] court . . . to form a reliable theory" of general causation, since to do so "would be to abandon 'the level of intellectual rigor' of the expert in the field."[63]

10-1695, 2013 WL 1289050, at *6 (W.D. La. Mar. 26, 2013) ("[T]he Naranjo algorithm/methodology appears, in actuality, to be a classification system, not a method used to determine actual causal relationships assessments." (citation omitted)).

[61] An example of this is a Bradford-Hill analysis. Scientists use a Bradford-Hill analysis to assess causation *only after a statistically significant association has first been established*, normally through analytic epidemiological studies. *See* Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROC. ROYAL SOC'Y MED. 295 (1965). Thus, Bradford-Hill applies only when an association has been established as "perfectly clear cut and beyond what we could care to attribute to the play of chance." *Id.* at 295; *see also* Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) ("Bradford Hill criteria is a method for determining whether the results of an epidemiological study can be said to demonstrate causation and not a method for testing an unproven hypothesis."); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 569 (W.D. Pa. 2003) (finding the Bradford-Hill analysis was unwarranted because there were no analytic epidemiological studies demonstrating a statistically significant association); Green et al., *supra* note 25, at 599 n.141 (applying Bradford-Hill factors without an analytic epidemiological study "does not reflect accepted epidemiologic methodology"). Two federal appellate cases have been cited as permitting experts to use the Bradford-Hill factors to opine on causation, but that is an overstatement of the cases. *See* Milward v. Acuity Specialty Prods. Grp., Inc., 639 F.3d 11, 23-24 (1st Cir. 2011); *In re* Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124, 1128-30, 1134-35 (2d Cir. 1995). In both cases the experts at issue applied the Bradford-Hill factors to the evaluation of analytic epidemiological evidence as well as evidence of a dose-response relationship, an additional risk beyond the background risk of a disease (described as "relative risk," "standardized mortality ratio," or "odds ratio" in the cases) and a plausible biological mechanism. *See id.*

[62] *See* Sheldon Krimsky, *The Weight of Scientific Evidence in Policy and Law*, 95 AM. J. PUB. HEALTH S129-130 (2005).

[63] Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1216 n.21 (10th Cir.) (citing Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999)), *cert. denied*, 537 U.S. 1088 (2002); Glastetter v. Novartis Pharms. Corp., 252 F.3d 986, 992 (8th Cir. 2001) (per curiam) ("[W]e do not believe that the aggregate of this [unreliable] evidence presents a stronger scientific basis for Glastetter's supposition that Parlodel can cause ICHs."); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 577 (W.D. Pa. 2003) (stating "plaintiff's experts 'cannot lump together lots of hollow evidence' and reach a reliable conclusion").

Conclusion

Litigants' success in mass tort actions is most often determined by whether plaintiffs can present sufficiently reliable expert evidence of general causation to survive *Daubert*[64] scrutiny and create a triable issue for a jury. By developing an extensive and consistent body of case law on this issue, the Eleventh Circuit has provided litigants with great guidance that, in turn, leads to reasonable predictability as to the admissibility of general causation expert testimony. Every mass tort litigator needs to be knowledgeable about this guidance or else risks either losing a winnable case or wasting substantial time, effort, and money on an unwinnable case.

Epilogue

The most vocal criticism of the Eleventh Circuit's general causation *Daubert* jurisprudence is that it makes it difficult, if not impossible, for plaintiffs to prevail when they are relying on emerging science, even if leading scholars endorse the new scientific theory and it has not been refuted (or at least not yet) by empirical evidence. But "[t]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it."[65]

Jurors of varying education levels receiving evidence at the speed of trial are ill-equipped to make judgments about cutting-edge science, but instead are "more likely . . . to be awestruck by [an] expert's mystique."[66] This is especially true given the unique flexibility afforded experts testifying at trial—"no other kind of witness is free to opine about a complicated matter without any firsthand knowledge of the facts in the case, and based upon otherwise inadmissible hearsay."[67] All of this means that the "importance of *Daubert*'s gatekeeping requirement cannot be overstated."[68] Personal injury statutes of limitations, moreover,

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[64] Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993).

[65] *Rider*, 295 F.3d at 1197 (quoting Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996)).

[66] Allison v. McGhan Med. Corp., 184 F.3d 1300, 1310 (11th Cir. 1999).

[67] United States v. Frazier, 387 F.3d 1244, 1260 (11th Cir. 2004) (en banc).

[68] *Id*.

generally afford plaintiffs time to allow empirical evidence to be collected, digested and published, and in the interim regulatory agencies are empowered to take preemptive or prophylactic action based on a lesser standard than actual causation. Finally, of course, there are numerous examples of "cutting-edge" scientific findings that were proven erroneous with the passage of time.[69] For all of these reasons, the Eleventh Circuit's approach, which both counsels caution and fosters clarity and predictability, strikes the proper balance among science, law, and the demands of our legal system.

[69] Well-known examples include erroneous preliminary conclusions that silicone breast implants cause systemic disease, coffee consumption causes pancreatic cancer, and Bendectin causes birth defects. *See Allison*, 184 F.3d at 1315; *Daubert*, 43 F.3d at 1320-22; John B. Wong et al., *Reference Guide on Medical Testimony*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 687, 723-24 (3d ed., 2011) (citing Brian MacMahon et al., *Coffee and Cancer of the Pancreas*, 304 NEW ENG. J. MED. 630-33 (1981)), *available at* http://www.au.af.mil/au/awc/awcgate/fjc/manual_sci_evidence.pdf.