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*Ruggiero v. Warner-Lambert Co.*, a decision involving the diabetes drug Rezulin, brought the Second Circuit into line with other circuits on the issue of when experts may use differential diagnosis as the basis for an opinion that a product can cause a particular type of injury, say attorneys David Klingsberg and Bert L. Slonim. In this article, the authors review the current state of the law.



In attempting to prove general causation in a toxic tort or defective product case, “merely having a physician or other expert testify to a differential diagnosis will not satisfy the *Daubert* reliability requirement,” the authors say. But “a challenge to expert causation testimony will not succeed merely by urging that differential diagnosis is inherently an unreliable scientific methodology,” the authors caution.

## Physicians’ Differential Diagnosis as Causation Proof: Recent Case Law Holds the Line in Requiring *Daubert* Reliability

By DAVID KLINGSBERG AND BERT L. SLONIM

David Klingsberg is Special Counsel to Kaye Scholer LLP, and Visiting Lecturer at Rutgers University School of Law. Bert L. Slonim is Counsel to Kaye Scholer. Both lawyers specialize in product liability litigation and much of their practice involves litigating the admissibility of expert scientific opinion evidence. They represented the pharmaceutical manufacturer in the *Ruggiero* case discussed in this article.

Klingsberg can be reached at [dklingsberg@kayescholer.com](mailto:dklingsberg@kayescholer.com). Slonim’s email is [bslonim@kayescholer.com](mailto:bslonim@kayescholer.com).

In the 12 years since *Daubert v. Merrell Dow Pharm.*, 509 U.S. 579 (1993), a number of decisions have elaborated the standards for deciding in advance of trial whether proposed expert testimony is inadmissible because of unreliability or irrelevance. A recurring issue has been whether to allow expert opinion testimony on medical causation by a physician who engages in differential diagnosis—that is, arriving at the cause of injury by elimination of other potential causes.

Medical causation is often a pivotal issue in pharmaceutical products and toxic tort cases. The fact finder must first decide the issue of general causation, “whether a substance is capable of causing a particular injury or condition in the general population.”<sup>1</sup> If that

<sup>1</sup> *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224 (D. Colo. 1998). See also Federal Judicial Center, *Reference*

question is answered in the affirmative, the next issue is specific causation, “whether a substance caused a particular individual’s injury.”<sup>2</sup>

In a recent decision, *Ruggiero v. Warner-Lambert Co.*, 424 F.3d 249 (2d Cir. 2005), the Second Circuit significantly limited a decade-old precedent, *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038 (2d Cir. 1995), and brought that Circuit into harmony with a number of other circuits in holding that experts may not opine that a product can cause a particular type of injury based on differential diagnosis unless there is an independent predicate that satisfies the *Daubert* standards for including that potential cause in the analysis. In this article, we review the current state of the law on this important issue.

## Second Circuit: Limits on Differential Diagnosis

In *Ruggiero*, the Second Circuit affirmed the exclusion of the testimony of plaintiff’s medical expert that a diabetes drug, Rezulin, was capable of causing or exacerbating the cirrhosis of the liver from which the plaintiff’s decedent died. The court of appeals held that *Daubert* was not satisfied by the expert’s reliance on review of the medical records and a differential diagnosis.

In *Daubert*, the U.S. Supreme Court charged federal courts with a “gatekeeping” role of assessing proposed scientific evidence to determine scientific reliability—“whether the reasoning or methodology underlying the testimony is scientifically valid.” 509 U.S. 579 at 592-93. The general causation issue in *Daubert* was whether “Bendectin can cause birth defects,” and in particular whether it was “a substance capable of causing malformations in fetuses.” *Id.* at 582-83. In that case, the expert physicians relied on animal studies, pharmacological studies, and published epidemiological (human statistical) studies. Nevertheless, because the studies were not sufficiently reliable, the proposed expert causation evidence was held inadmissible.

Proponents of expert opinion testimony have sometimes attempted to bypass the need for reliable data and studies by offering a physician’s opinion based on examination of the patient or medical records and a purported differential diagnosis. A “differential diagnosis is a ‘patient-specific process of elimination that medical practitioners use to identify the ‘most likely’ cause of a set of signs and symptoms from a list of possible causes.’” *Ruggiero*, 424 F.3d at 254.<sup>3</sup> In *Ruggiero*, district court Judge Kaplan reasoned that “the final, suspected ‘cause’ remaining after this process of elimination must actually be capable of causing the injury.” *Id.* The Second Circuit agreed and held that in addition to

*Manual on Scientific Evidence* 444 (2d ed. 2000) (“General causation is established by demonstrating, often through a review of scientific and medical literature, that exposure to a substance can cause a particular disease (e.g., that smoking cigarettes can cause lung cancer). Specific, or individual, causation, however, is established by demonstrating that a given exposure is the cause of an individual’s disease (e.g., that a specific plaintiff’s lung cancer was caused by his smoking).”).

<sup>2</sup> *Id.*

<sup>3</sup> The *Reference Manual on Scientific Evidence* explains that “‘most physicians use the term [‘differential diagnosis’] to describe the process of determining which of several diseases is causing a patient’s symptoms,” while “courts sometimes characterize causal reasoning as ‘differential etiology.’” *Id.* Federal Judicial Center, *Reference Manual on Scientific Evidence* 443-44 (2d ed. 2000).

ruling out other potential causes, the expert must “‘rule in’ the suspected cause.” *Id.* The latter exercise requires the use of scientifically valid methodology that provides reliable support for an opinion under the *Daubert* standards.

## Flawed Methodology: Weight or Admissibility?

In *Ruggiero*, the Second Circuit also clarified the scope of its earlier opinion in *McCullock*, which stated that faults in a medical expert’s use of differential etiology as a methodology, or lack of textual authority for his opinion, “go to the weight, not the admissibility, of his testimony.” 61 F.3d at 1044. Plaintiff in *Ruggiero* relied on that statement, which the Second Circuit explicitly found “unpersuasive.”

The court of appeals examined *McCullock* in light of the Supreme Court’s subsequent opinion in *General Electric Co. v. Joiner*, 522 U.S. 136, 141 (1997), which affirmed exclusion of physicians’ opinions that PCB exposure can cause small cell lung cancer. While the Supreme Court in *Joiner* did not comment specifically on differential diagnosis, the Eleventh Circuit (in the opinion that gave rise to the *Joiner* appeal) highlighted the fact that the two physicians whose opinion testimony was excluded, had “utilized traditional medical assessment techniques” and eliminated other potential causes of *Joiner*’s lung cancer, which is the essence of differential diagnosis.<sup>4</sup> The Supreme Court affirmed the exclusion of this expert testimony because of the absence of reliable animal and epidemiologic studies.

In limiting *McCullock*, the Second Circuit also pointed to its post-*Joiner* decision in *Amorgianos v. Nat’l R.R. Passenger Corp.*, 303 F.3d 256, 270 (2d Cir. 2002). *Amorgianos*, like *Joiner*, did not explicitly address differential diagnosis; however, a careful review of the facts reveals that the physician there based her causation opinion on the timing of the onset of symptoms and elimination of other known causes, which is the essence of differential diagnosis. Applying the principles of *Joiner*, the Second Circuit affirmed the exclusion of the physician’s opinion because of the analytic gap between the studies on which she relied and her conclusion that paint fumes could cause the neurologic injuries about which plaintiff complained.

Considering *McCullock* in light of the subsequent *Joiner* and *Amorgianos* decisions, the Second Circuit in *Ruggiero* held that it would be reading *McCullock* too broadly to conclude that it approved differential diagnosis, without more, as a reliable basis for a general causation opinion. In that circumstance, as held by *Joiner*, trial courts may conclude that there is simply too great an analytic gap between the data and opinion offered. Accordingly, in *Ruggiero*, where plaintiff’s medical expert had no data to support general causation, the Circuit Court affirmed the district court’s decision excluding the proposed testimony.<sup>5</sup>

## The Second Circuit Joins Five Others

The *Ruggiero* opinion brings the Second Circuit squarely into harmony with the Fourth, Fifth, Eighth, Tenth and Eleventh Circuits’ decisions on differential diagnosis.

<sup>4</sup> 78 F.3d 524, 531 (11th Cir. 1996).

<sup>5</sup> The Court of Appeals left open the possibility that there may be some instances where a differential diagnosis is sufficient to support a general as well as a specific causation opinion.

The most recent circuit court case preceding *Ruggiero* is *McClain v. Metabolife Int'l Inc.*, 401 F.3d 1233, 1253 (11th Cir. 2005), where the Eleventh Circuit excluded expert opinion that an herbal appetite suppressant containing ephedrine caused heart attacks, strokes and other injuries. Plaintiffs' expert based his causation opinion on a differential diagnosis: he "took medical histories from the plaintiffs, examined them, and did some tests [and then] concluded that he could rule out all the usual causes for plaintiffs' injuries." *Id.* at 1252-253. The Court held that "[a] valid differential diagnosis . . . only satisfies a *Daubert* analysis if the expert can show the general toxicity of the drug by reliable methods." *Id.* at 1253. The expert could not offer "a reliable explanation of the physiological process by which Metabolife causes heart attacks and ischemic strokes, i.e., establish general causation. . . . In the absence of such a foundation for a differential diagnosis analysis, a differential diagnosis generally may not serve as a reliable basis for an expert opinion on causation in a toxic tort case." *Id.*

The Eighth Circuit in *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001), affirmed a lower court decision excluding a proposed expert physician's testimony based on differential diagnosis about the cause of plaintiff's stroke where "its major premise"—that defendant's prescription medication Parlodel caused vasoconstriction—"remains unproven." *Id.* The court of appeals agreed with the district court that "[t]he data and methods of plaintiff's experts are not scientifically valid bases for the conclusion that Parlodel can cause [a stroke] in a human." *Id.* Because the experts had no reliable general causation predicate, they "lacked a proper basis for 'ruling in' Parlodel as a cause of [stroke] in the first place." *Id.*

The Fifth Circuit in *Black v. Food Lion Inc.*, 171 F.3d 308 (5th Cir. 1999), rejected proposed medical causation testimony where the expert physician failed to rule in the proposed cause. In that case, the physician followed the protocol of "(a) taking a medical history . . . (b) ruling out prior or subsequent 'causes' of fibromyalgia, (c) performing or reviewing physical tests . . . , and (d) deducing that the . . . fall was the only possible remaining cause of fibromyalgia that appeared nine months later." *Id.* at 313. The Court held that "[t]his is not an exercise in scientific logic but in the fallacy of *post-hoc propter-hoc* reasoning, which is as unacceptable in science as in law." *Id.*

In the Fourth Circuit, a district court held that differential diagnosis was not usable in a toxic tort case to prove general causation because "a fundamental assumption underlying this method is that the final, suspected 'cause' remaining after this process of elimination must actually be capable of causing the injury." The appeals court affirmed this holding. *Cavallo v. Star Enter.*, 892 F. Supp. 756, 771 (E.D. Va. 1995), *aff'd on this ground, rev'd on other grounds*, 100 F.3d 1150 (4th Cir. 1996).

The Ninth and Third Circuits have recognized that differential diagnoses must be "reliable" but have not had occasion to exclude testimony as the other Circuits discussed above have done. In its most recent decision on differential etiology the Ninth Circuit allowed an expert to "rule in" an oil spill as a cause of oyster mortality based upon a variety of objective, verifiable evidence

including tests and government reports. *Clausen v. M/V Clarissa*, 339 F.3d 1049, 1057-58 (9th Cir. 2003).<sup>6</sup>

The Third Circuit's latest opinion, which is six years old, seems to be more lenient with the kind of scientific studies found sufficient to support the general causation predicate of a differential diagnosis. *Heller v. Shaw Industries Inc.* 167 F.3d 146 (3d Cir 1999). Even there, however, the Third Circuit ruled that "reliable methods for making a diagnosis cannot sanitize an otherwise untrustworthy conclusion" and that it would "not necessarily be error to exclude [the physician's] causation conclusion as unreliable if he relied on no scientific studies." *Id.* at 156. The Supreme Court in *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999) held that *Daubert* applies to all types of expert testimony. Accordingly, insofar as decisions such as *Heller* relaxed the *Daubert* standard because a physician was offering the causation opinion, they are suspect in light of *Kumho*.<sup>7</sup>

## Recent District Court Decisions

In *In re Ephedra Products Liability*, 2005 WL 2260204 (S.D.N.Y. Sep. 18, 2005), a district court in New York granted and denied in part a motion to exclude expert testimony that ephedra products can cause heart attacks, strokes and other injuries. The court found that the experts cite "a considerable amount of medical literature" to support their causation opinions, including FDA findings resulting in a ban of the product, although there were no epidemiologic studies with statistically significant results linking ephedra to the alleged injuries.

There is nothing remarkable about the court's view that such epidemiologic studies are not always required to satisfy *Daubert*.<sup>8</sup> However, as an illustration of that principle, even though differential diagnosis was apparently not an issue in the case, the *Ephedra* opinion in a *dictum* stated that "'differential etiology' properly performed by a qualified physician is sufficiently reliable to render admissible a physician's opinion on causation" under the Second Circuit's opinion in *McCulloch*. 2005 WL 2260204 at \*4.

Notably, the *Ephedra* opinion did not address the question that was the subject of the Second Circuit's holding in *Ruggiero* as to the necessary general causation predicate for a valid differential diagnosis. The district court apparently was unaware of the *Ruggiero* opinion, which was filed three days earlier and is not cited or discussed in its decision. Thus, the *Ephedra* opinion quoted *McCulloch*'s statement that disputes about differential etiology go to weight rather than ad-

<sup>6</sup> In *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1228 (9th Cir. 1998), the Ninth Circuit found that "peer reviewed publications and clinical studies" provided a predicate for a differential diagnosis that collagen can cause lupus.

<sup>7</sup> See Federal Judicial Center, *Reference Manual on Scientific Evidence* 443 (2d ed. 2000).

<sup>8</sup> E.g., *Benedi v. McNeil P.P.C., Inc.*, 66 F.3d 1378, 1384 (4th Cir. 1995) ("Under the *Daubert* standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound."); *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."); *In re Berg Litigation*, 293 F.3d 1127, 1130 (9th Cir. 2002) ("Nor is epidemiological evidence the sole method of establishing causation.").

missibility even though, as discussed above, in *Ruggiero* the Second Circuit sharply rejected that argument.

Although some of the statements in the *Ephedra* opinion are inconsistent with *Ruggiero*, in the end none of the differential diagnosis *dicta* impacted the court's rulings on the proposed general causation expert testimony. The testimony was held to be admissible, subject to certain limitations, because it was supported by several studies and literature, not because the experts used differential etiology.

Prior to *Ruggiero*, two district courts in the Second Circuit suggested in *dicta* that, under *McCulloch*, differential diagnosis could be used to establish general causation. Thus, in *Perkins v. Origin Medsystems Inc.*,<sup>9</sup> a district court in the Second Circuit stated that differential diagnosis alone "is a reliable basis to prove general causation in this circuit." Similarly, in *Plourde v. Gladstone*,<sup>10</sup> a district court stated, "according to the Second Circuit, if a qualified expert performs a reliable differential diagnosis, the plaintiff need not satisfy the general causation requirement." Notably, in *Perkins* there were *Daubert* factors apart from differential diagnosis that supported general causation,<sup>11</sup> and in *Plourde* the key issue was the extent of exposure to a toxic substance, rather than general causation.<sup>12</sup> Most importantly, as *Ruggiero* makes clear, the quoted *dicta* is no longer an accurate statement of Second Circuit law.<sup>13</sup>

Other recent district court decisions have excluded differential diagnosis opinions when the expert lacked independent reliable evidence of general causation. *E.g.*, *Golden v. Ch2M Hill Hanford Group, Inc.*, 2005 WL 1868794 at \*1-2 (E.D. Wash., Jul. 29, 2005) (while "a reliable differential diagnosis may provide the proper foundation for a causation opinion . . . differential diagnosis assumes that general causation has been proven for the list of possible causes it eliminates, which has not occurred here"); *In re Welding Fume Products Liability Litigation*, 2005 WL 1868046 at \*32 (N.D. Ohio, Aug. 8, 2005), ("the expert must 'rule in' the suspected cause as well as 'rule out' other possible causes. And, of course, expert opinion on this issue of 'general causation' must be derived from a scientifically valid methodology.").

<sup>9</sup> 299 F. Supp. 2d 45, 57 (D. Conn. 2004).

<sup>10</sup> 190 F. Supp. 2d 708, 722 (D. Vt. 2002).

<sup>11</sup> In *Perkins*, the proposed expert was the plaintiff's original treating physician, who had arrived at her diagnosis as part of her treatment—a fact the court said "dramatically limit[s] concerns" about the reliability of her opinion/diagnosis. *Perkins*, 299 F. Supp. 2d at 55. The expert had previously brought her concerns regarding the use of the device at issue directly to the defendant/manufacture and to the Food and Drug Administration, and had "presented her opinions at medical seminars to other physicians." *Id.* at 58. *Id.* Further, the expert based her opinion on a retrospective study and report, albeit not yet completed, to examine the frequency with which patients developed pain from such devices. *See id.* at \*51.

<sup>12</sup> The court held that "[w]here direct evidence of the precise level of toxic exposure is limited, courts have looked favorably on causation that is primarily based on differential diagnosis." *Plourde v. Gladstone*, 190 F. Supp. 2d 708, 722 (D. Vt. 2002).

<sup>13</sup> In *Green v. McAllister Bros. Inc.*, 2005 U.S. Dist. LEXIS 4816 (S.D.N.Y. Mar. 24, 2005) at \*35 n.14, decided a few months before the Second Circuit's opinion in *Ruggiero*, the Court observed that "Judges in this Circuit disagree as to whether a plaintiff . . . may establish general causation through differential diagnosis." *Ruggiero* ended this disagreement.

These recent decisions are in accord with earlier district court decisions. *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1413 (D. Or. 1996) (differential diagnosis does not "speak to the issue of general causation . . . . [It] assumes that general causation has been proven for the list of possible causes"); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 516 (W.D. Pa. 2003) ("differential diagnosis is not a reliable methodology for determining general causation"); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1230 (D. Colo. 1998) (differential diagnosis not reliable as to general causation; "expert opinion on . . . issue of 'general causation' must be derived from a scientifically valid methodology.").

## Conclusion

In attempting to prove general causation in a case alleging injury from toxic substances or allegedly defective products, merely having a physician or other expert testify to a differential diagnosis will not satisfy the *Daubert* reliability requirement. By the same token, a challenge to expert causation testimony will not succeed merely by urging that differential diagnosis is inherently an unreliable scientific methodology.<sup>14</sup>

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The key focus is whether in the differential diagnosis analysis the final cause that has not been "ruled out" can be "ruled in" based on independent scientific proof that meets the *Daubert* criteria. While none of these criteria is dispositive, the courts consistently look to whether there has been testing (such as controlled clinical studies, epidemiological studies, toxicological studies, and the like), and whether such testing has been published in peer-reviewed literature. Moreover, the studies must be of the particular substance and of the specific disease or injury at issue,<sup>15</sup> and there must not be analytic gaps in the evidence linking the study results to the causation opinions sought to be offered in

<sup>14</sup> *See, e.g., Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262-63 (4th Cir. 1999) ("Differential diagnosis, or differential etiology, is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated. . . . Thus, we hold that a reliable differential diagnosis provides a valid foundation for an expert opinion.") (citing numerous cases).

<sup>15</sup> *See Joiner*, 522 U.S. at 144 (animal studies finding mice contracted one type of lung cancer did not prove that PCBs could cause small cell lung cancer); *Wills v. Amerada Hess Corp.*, 379 F.3d 32, 39 (2d Cir. 2004) (rejecting studies linking benzene to one type of cancer (leukemia) to prove it is capable of causing squamous cell carcinoma); *Amorgianos*, 303 F.3d at 270 (studies showing paint solvents can cause symmetrical motor dysfunction insufficient to establish general causation as to claimed asymmetrical motor dysfunction).

the case.<sup>16</sup> Unsupported extrapolations or proposed opinions that go beyond the results found by the researchers who conducted the studies will render the testimony inadmissible.<sup>17</sup>

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<sup>16</sup> *Id.*

<sup>17</sup> In *Amorgianos*, the Second Circuit held that “it is critical that an expert’s analysis be reliable at every step. . . . ‘[A]ny

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step that renders the analysis unreliable under the Daubert factors renders the expert’s testimony inadmissible.’ ” 303 F.3d at 267 (quoting *In re Paoli R.R. Yard PCB Lit.*, 35 F.3d 717, 745 (3d Cir. 1994); emphasis in original); see also *In re Rezulin Products Liability Litig.*, 369 F. Supp. 2d 398, 424 (S.D.N.Y. 2005) (holding inadmissible “extrapolation from the existing literature that never has been tested, peer-reviewed, published, or widely accepted.”).