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Just What the Doctor Ordered: The Admissibility of Differential Diagnosis in Pharmaceutical Product Litigation

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Just What the Doctor Ordered: The Admissibility of Differential Diagnosis in Pharmaceutical Product Litigation

I.	INTRODUCTION	1227
II.	BACKGROUND	1233
	A. <i>The Causation Element: General Versus Specific</i> ..	1233
	B. <i>The Daubert Standard</i>	1236
	C. <i>Applying the Daubert Standard to Differential Diagnosis Evidence</i>	1238
III.	DIFFERENTIAL DIAGNOSIS OF ADVERSE DRUG REACTIONS	1239
	A. <i>Differential Diagnosis in General</i>	1239
	B. <i>Adverse Drug Reactions</i>	1240
	C. <i>Approaches to the Diagnosis of ADRs</i>	1243
	1. Clinical Judgment (Global Introspection) and Qualitative Algorithms	1244
	2. Quantitative Algorithms	1248
	3. The Bayesian Approach.....	1251
IV.	IMPLICATIONS	1252
	A. <i>The "Ruling In" Requirement: Reliability</i>	1253
	B. <i>The "Ruling In" Requirement: Sufficiency</i>	1257
	C. <i>Why Does the Distinction Matter?</i>	1260
V.	CONCLUSION.....	1263

I. INTRODUCTION

In the decade since *Daubert v. Merrell Dow Pharmaceuticals Inc.*, federal judges have exercised their role as gatekeepers of expert witness testimony to evaluate many different categories of scientific evidence.¹ They have not done so without controversy, however. Because the element of causation in pharmaceutical product litigation

¹509 U.S. 579 (1993).

is frequently dispositive,² the application of *Daubert* to scientific evidence of causation has been particularly contentious. Plaintiffs in such cases must prove both general causation—that the product is capable of causing an injury of the type from which the plaintiff suffers—and specific causation—that the product was the actual cause of the plaintiff's injury.³ *Daubert* itself involved the admissibility of evidence of general causation in a pharmaceutical product liability action.⁴ Of particular interest here is *Daubert's* application to a common type of specific causation evidence known as differential diagnosis evidence. "Differential diagnosis" refers to the process by which a clinical physician, for purposes of treatment, identifies the condition affecting his patient and/or its cause.⁵ The admissibility of differential diagnosis evidence is crucial to a plaintiff's pharmaceutical product liability case, as testimony from a clinical physician that the drug product is the most likely cause of the plaintiff's condition is frequently the plaintiff's only means of proving specific causation.⁶

Application of the *Daubert* standard to differential diagnosis testimony has engendered particular disagreement and confusion in the federal courts over the past several years. The recent series of cases surrounding Sandoz Pharmaceuticals Corporation's ("Sandoz") lactation-suppressing drug Parlodel aptly illustrates the uncertainty surrounding the admissibility of differential diagnosis evidence. After reports of a possible association between Parlodel and strokes, Sandoz withdrew the drug from the market as a lactation suppressant in 1994 at the request of the Food and Drug Administration.⁷ In the ensuing litigation, plaintiffs claimed that their ingestion of Parlodel caused them to suffer strokes.⁸ Courts have disagreed, however, on the reliability of the differential diagnosis evidence offered by these

2. See Michael B. Kent, *Daubert, Doctors and Differential Diagnosis: Treating Medical Causation Testimony as Evidence*, 66 DEF. COUNS. J. 525, 525 (1999).

3. See *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188, 1200 (6th Cir. 1988).

4. 509 U.S. at 582-85.

5. "Differential diagnosis," as I use the term in this Note, is more properly referred to as "differential etiology." The term "differential diagnosis" actually refers to the process by which physicians diagnose a patient's condition, rather than the cause of that condition. See, e.g., FAIGMAN ET AL., *MODERN SCIENTIFIC EVIDENCE: THE LAW AND SCIENCE OF EXPERT TESTIMONY* § 20-1.1 (2d ed. 2002). "Differential etiology," on the other hand, refers to the process of causal assessment. See *id.* This Note uses the term "differential diagnosis" to refer to the process of elucidating the cause of the plaintiff's injury, rather than "differential etiology," because courts typically refer to the process of causal determination as "differential diagnosis."

6. See *infra* notes 35-38 and accompanying text.

7. See, e.g., *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1197-98 (10th Cir. 2002).

8. See, e.g., *id.* at 1198-99 (discussing the Parlodel controversy in the courts).

plaintiffs as part of their effort to prove causation.⁹ For example, on September 12, 2001, a federal district court judge in Illinois granted Sandoz's motion to exclude the expert opinions of two physicians prepared to testify based on a differential diagnosis that Parlodel caused the plaintiff to suffer a stroke several days after ingesting the drug.¹⁰ Nine days later, a federal magistrate in Alabama denied a similar motion brought by the same defendant regarding the same experts, the same drug, and the same type of injury in a suit brought by a different plaintiff.¹¹ Purportedly applying the same admissibility standard—namely, Rule 702 of the Federal Rules of Evidence¹² (“Rule 702” or “the Rule”)—the federal court in Alabama found the proffered differential diagnosis testimony reliable and therefore admissible, while the federal court in Illinois had found it unreliable and therefore inadmissible.¹³ In addition to excluding this crucial expert testimony on causation, the Illinois court granted the defendant leave to file a motion for summary judgment.¹⁴ The Alabama case, on the other hand, proceeded to trial.¹⁵

As these two cases demonstrate, the admissibility of clinical medical evidence of causation has a tremendous impact on the course of product liability litigation and is therefore a determination that should be undertaken carefully. Too much judicial control over scientific evidence of causation may prematurely end potentially meritorious litigation with a summary judgment motion in the defendant's favor. Such an outcome fails to compensate a potentially deserving plaintiff for her injury and allows the perpetrator of potentially tortious activity to escape liability.

On the other hand, too little control over scientific evidence of causation risks jury verdicts that are inconsistent with the weight of the scientific evidence. For example, the series of cases involving Bendectin, a drug prescribed to prevent nausea during pregnancy,

9. See, e.g., Mark Hansen, *When Expert Testimony Fails the Test: District Courts Disagree on What Defines Causation Evidence in Drug Disability Cases*, 88 A.B.A. J. 22, 22 (2002).

10. *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1046, 1048 1053 (S.D. Ill. 2001).

11. See *Brasher v. Sandoz Pharm. Corp.*, 160 F. Supp. 2d 1291, 1299 (N.D. Ala. 2001).

12. FED. R. EVID. 702:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

13. *Brasher*, 160 F. Supp. 2d at 1299; *Caraker*, 172 F. Supp. 2d at 1053.

14. *Caraker*, 172 F. Supp. 2d at 1053.

15. See *Brasher*, 160 F. Supp. 2d at 1299 (denying defendant's motion for summary judgment).

resulted in repeated verdicts for plaintiffs, despite the fact that the scientific evidence ultimately disproved any causal association between Bendectin and birth defects.¹⁶ Several phenomena characteristic of mass tort litigation may contribute to this undesirable result. First, commentators have observed that jurors may “commingle” the elements of tort cases, substituting strong evidence of one element for weak evidence of another.¹⁷ For example, when the plaintiff has clearly suffered an egregious injury but no causal association has been established, jurors may trade proof of causation for proof of injury.¹⁸ Second, large plaintiffs’ verdicts early in the mass tort litigation, mass media coverage, and public outrage may fuel the success of individual claims despite the inadequacy of the evidence.¹⁹ Particularly in pharmaceutical product liability litigation—where the defendant’s manufacture of a single product may result in mass tort litigation involving thousands of plaintiffs—a series of large plaintiffs’ verdicts based on unreliable or insufficient evidence of causation may precipitate the bankruptcy of a pharmaceutical company whose product in fact caused no injury.

The disparate outcomes of the two illustrative Parlodel cases—cases involving the same pharmaceutical product, the same alleged injury, the same type of evidence, and the same expert witnesses—raise a question as to the whether federal trial courts across the country properly apply the expert witness admissibility rules to differential diagnosis testimony. This inquiry involves several interrelated questions. Is there an identifiable cause of the variation in outcomes of similar cases? Should we care about the observed variation or is that variation a permissible result of the exercise of judicial discretion authorized by Rule 702 that should be applauded rather than scrutinized? If we should care, how should federal trial courts approach the admissibility of differential diagnosis testimony so that they exercise neither too much nor too little control over the scientific evidence that is presented to the jury? Although the highly fact-specific and amorphous nature of a trial court’s expert witness

16. See Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 STAN. L. REV. 1, 3 (1993); see *id.* (discussing the Bendectin litigation and the disparity between the scientific data and the evidence presented at trial); see also Rebecca S. Dresser et al., *Breast Implants Revisited: Beyond Science on Trial*, 1997 WIS. L. REV. 705, 709-15 (discussing the breast implant litigation and the ultimate disproof of any causal association between silicone gel breast implants and immune system disorders).

17. Sanders, *supra* note 16, at 52-54 (describing commingling in the Bendectin cases).

18. *Id.*

19. See David E. Bernstein, *The Breast Implant Fiasco*, 87 CAL. L. REV. 457, 484 (1999) (reviewing MARCI ANGELL, *SCIENCE ON TRIAL: THE CLASH OF MEDICAL EVIDENCE AND THE LAW IN THE BREAST IMPLANT CASE* (1996)).

admissibility determination renders these questions difficult to answer, the ever-increasing importance of pharmaceutical product liability litigation in this country necessitates their consideration.

This inquiry must begin with Rule 702 of the Federal Rules of Evidence, the federal admissibility standard for expert witness testimony. Rule 702 incorporates the test articulated by the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*²⁰ The *Daubert* Court established a gatekeeping role for the judge that requires him to evaluate the proffered testimony for relevance and reliability.²¹ In *General Electric Co. v. Joiner* and *Kumho Tire Co. v. Carmichael*, the Court more fully described the judge's role as gatekeeper: the judge should evaluate the expert's reasoning, specifically the gap between the data presented and the conclusions drawn,²² to ensure that the expert has applied in his analysis the same level of intellectual rigor characteristic of those who practice in his field.²³

The Supreme Court's explication of the Rule 702 standard in *Joiner* and *Kumho Tire* is particularly relevant to a trial court's evaluation of the reliability of differential diagnosis testimony. The *Kumho Tire* standard, when applied to differential diagnosis evidence, dictates that courts evaluate the reliability of that evidence based on its consistency with the methodologies employed by clinical physicians in their everyday practice of medicine. Indeed, as explained in more detail below, in pharmaceutical product litigation, courts should look specifically to the methods by which clinical physicians diagnose adverse drug reactions ("ADRs").²⁴

This Note begins in Part II with a description of the plaintiff's burden of proving causation in a typical pharmaceutical product liability litigation and the general nature and importance of differential diagnosis testimony. Part II then explains Federal Rule of Evidence 702 and the Supreme Court cases which together provide the context for analyzing the admissibility of expert testimony. Part II concludes by briefly applying the concept of differential diagnosis testimony to this general framework while also pointing out the need

20. 509 U.S. 579 (1993).

21. See *id.* at 587-95 (describing the judge's gatekeeping role); discussion *infra* Part II.B (same).

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

23. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147-52 (1999) (holding that *Daubert* also applies to testimony based on "technical" or "other specialized knowledge").

24. The World Health Organization defines an adverse drug reaction as any response to a drug that is "noxious and unintended" and occurs at prescription-level doses. Fred E. Karch & Louis Lasagna, *Adverse Drug Reactions: A Critical Review*, 234 JAMA 1236, 1236 (1975).

to examine how physicians conduct differential diagnoses when treating patients. Part III describes the approach of clinical physicians in conducting differential diagnoses of adverse drug reactions, including a discussion of the importance of focusing specifically on the differential diagnosis of ADRs as opposed to differential diagnosis methodologies in general.

Finally, Part IV applies the clinical methodology of ADR differential diagnosis to suggest a resolution to an important issue that currently divides federal courts—namely, when a differential diagnosis expert testifies as to causation, whether he must demonstrate that he has properly “ruled in” the drug in question as a possible cause of the plaintiff’s injury before “ruling out” alternative causes and concluding that the defendant’s product is the most likely cause of the plaintiff’s injury.²⁵ This Note concludes that courts should not categorically exclude a differential diagnosis opinion because the expert does not provide evidence that he has “ruled in” the drug as a possible cause of the plaintiff’s injury, as some courts do. However, absent such evidence—provided by the differential diagnosis expert or by other evidence offered by the plaintiff—that the drug is a possible cause of the plaintiff’s injury, the court should consider the evidence a question of sufficiency, and, if appropriate, grant summary judgment in the defendant’s favor on that ground.²⁶

25. See FAIGMAN ET AL., *supra* note 5, § 20-1.4.2 (identifying the “ruling in” requirement as a current point of contention).

26. Note that several commentators have recently attempted to address the variation in federal court approaches to the admissibility of differential diagnosis evidence of causation. See, e.g., Henry Berry, *Logical Analysis: A Method of Examination of Expert Medical Opinion Through the Basic Logic of Medical Reasoning*, 34 TORT & INS. L.J. 949 (1999); Harvey Brown, *Eight Gates for Expert Witnesses*, 36 HOUS. L. REV. 743 (1999); Jean Macchiaroli Eggen, *Clinical Medical Evidence of Causation in Toxic Tort Cases: Into the Crucible of Daubert*, 38 HOUS. L. REV. 369 (2001); Kent, *supra* note 2; Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241 (1999); Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, LAW & CONTEMP. PROBS., Autumn 2001, at 107; Gary Slohoda, *Differential Diagnosis or Distortion?*, 35 U.S.F. L. REV. 301 (2001); Note, *Navigating Uncertainty: Gatekeeping in the Absence of Hard Science*, 113 HARV. L. REV. 1467 (2000). Although these commentators provide valuable insight into the problem of differential diagnosis testimony, none specifically addresses the “ruling in” requirement, as *Kumho Tire* requires, in the context of a searching analysis of the clinical methodology of the differential diagnosis of adverse drug reactions.

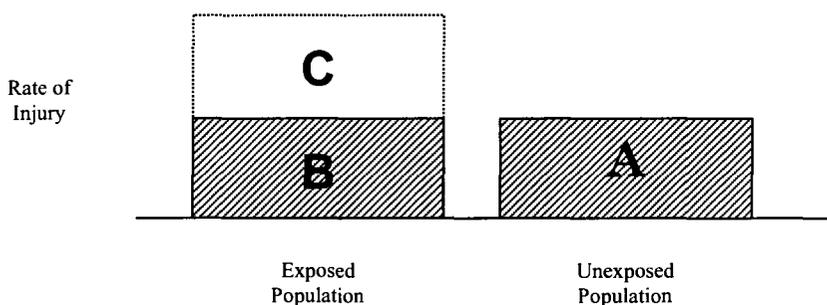
II. BACKGROUND

A. *The Causation Element: General Versus Specific*

As in any tort cause of action, the plaintiff in a product liability action must prove causation. To recover in negligence, the plaintiff must prove by a preponderance of the evidence that the defendant breached a duty that caused the plaintiff's injury. To recover in strict liability, a typical claim brought in litigation involving pharmaceutical product liability, the plaintiff must prove, inter alia, the existence of an injury caused by a product sold by the defendant.²⁷ To carry her burden on causation in a pharmaceutical product liability action, the plaintiff must prove both general causation—that the defendant's product is capable of causing an injury of the type from which the plaintiff suffers—and specific causation—that the defendant's product is the cause in fact of this particular plaintiff's injury.²⁸

Figure 1 illustrates the difference between general and specific causation:

Figure 1. Risks in Exposed and Unexposed Populations²⁹



27. RESTATEMENT (SECOND) OF TORTS § 402A(1) (1965).

28. See *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188, 1200 (6th Cir. 1988); see also FAIGMAN ET AL., *supra* note 5, § 20-1.2; Daniel A. Farher, *Toxic Causation*, 71 MINN. L. REV. 1219, 1227-28 (1987).

29. This figure is based on Michael D. Green et al., *Reference Manual on Scientific Evidence*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 352 (2d ed. 2000).

Most pharmaceutical products cause nonunique injuries.³⁰ Rather, in the general population of individuals not exposed to a particular pharmaceutical product, the injury that is associated with the drug nonetheless occurs at some frequency (Figure 1, Region A). Thus, a background rate of injury that is entirely unrelated to drug exposure exists in the exposed population (Region B). Evidence of general causation demonstrates whether and to what extent the product is capable of increasing the rate of injury above the background rate—i.e., whether Region C exists at all and, if so, to what extent. Once it is determined that Region C exists—in other words, that the drug is capable of causing the plaintiff's injury—then evidence of specific causation is intended to prove whether the plaintiff is part of the population that would have suffered an injury regardless of drug exposure (Region B) or instead, part of the population that would not have suffered her injury but for drug exposure (Region C). If the plaintiff demonstrates both that Region C exists (general causation) and that her injury falls within it (specific causation), then she has met her burden as to the causation element of her product liability action.

The best and most common type of evidence of general causation is the epidemiological study. Epidemiology is the study of the incidence of disease in human populations.³¹ Epidemiological studies are designed specifically to demonstrate whether exposure to a particular agent increases the incidence of disease in an exposed versus an unexposed human population.³² The result of an epidemiological study is a calculation of the "relative risk" of acquiring the disease. The relative risk is a figure that represents the risk of acquiring the disease from exposure to the drug compared to the background rate of injury. For example, a relative risk of 1.0 indicates that the agent in question does not increase the likelihood of acquiring the disease—that the individual is just as likely to contract the disease without exposure. Proof of a relative risk any greater than 1.0 is proof that the agent is capable of causing the disease in question, and a relative risk of 2.0 indicates that exposure doubles an

30. Sanders & Machal-Fulks, *supra* note 26, at 110 (noting that asbestosis—a unique injury caused by exposure to asbestos—is an exception). This nonuniqueness means that adverse drug reactions "ADRs" are difficult to recognize and to diagnose because of their similarity to other disorders. See also Michel Auriche & Elizabeth Loupi, *Does Proof of Causality Ever Exist in Pharmacovigilance?*, 9 DRUG SAFETY 230, 230 (1993); Nelson S. Irey, *When Is a Disease Drug Induced?*, in *PATHOLOGY OF DRUG-INDUCED AND TOXIC DISEASES* 1, 2 (Robert H. Riddell ed., 1982).

31. See, e.g., *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224 (D. Colo. 1998).

32. See, e.g., *Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1158 (E.D. La. 1997).

individual's risk of acquiring the disease.³³ A properly conducted epidemiological study is considered relevant and reliable evidence of general causation and is therefore admissible under the federal standards established in *Daubert*.³⁴ Other evidence of general causation, albeit less conclusive than epidemiological studies, includes case reports and toxicological studies of the drug in question or of other drugs in the same class.

Proving specific causation can be more difficult, because the relevant evidence is often scarce.³⁵ Epidemiological evidence, although extremely important as to the issue of general causation, has only limited utility in proving specific causation.³⁶ Accordingly, even if the plaintiff produces reliable epidemiological evidence proving a relative risk greater than 1.0, she must produce additional evidence of specific causation. Differential diagnosis assumes its key role in making this showing of specific causation. Testimony by a clinical physician that he has considered all aspects of the specific plaintiff's injury, including other possible causes of that injury, and concluded that the defendant's product is the most likely cause of the injury—that is, that the plaintiff most likely falls in Region C, as opposed to Region B—is valuable evidence of specific causation.³⁷ As such, the admissibility of

33. *E.g.*, *DeLuca v. Merrell Dow Pharm., Inc.*, 911 F.2d 941, 958-59 (3d Cir. 1990).

34. *See Pick*, 958 F. Supp. at 1158 (holding that “[e]pidemiological studies are reported in peer-reviewed journals and the methodology is widely accepted as scientifically valid”); *infra* Part II.B for a discussion of the *Daubert* framework.

35. *Sanders & Machal-Fulks*, *supra* note 26, at 111.

36. Courts may, under certain circumstances, allow epidemiological studies *alone* to satisfy the plaintiff's burden to prove specific causation, but only if the relative risk is at least 2.0. *See, e.g.*, *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1321 (9th Cir. 1995) (holding that, as a matter of relevance, the relative risk must be greater than 2.0); *DeLuca*, 911 F.2d at 958-59. To explain the justification for the 2.0 requirement, refer to Figure 1. When the relative risk equals 2.0—i.e., when drug exposure exactly doubles the risk of contracting the disease—the exposed population contains twice as many injured persons. As such, for any person randomly selected from the exposed population, there is a fifty percent chance that drug exposure caused her injury. In other words, there is a fifty percent chance that the plaintiff falls into Region C (causation) and a fifty percent chance that the plaintiff falls into Region B (no causation). With all being equal, because the usual standard of proof for tort causes of action is “more likely than not,” a relative risk of *any greater* than 2.0 will raise the likelihood of causation above fifty percent, thereby satisfying the “more likely than not” standard. Usually, however, all else is not equal. If, for example, epidemiological studies show that the relative risk is just over 2.0 but the defendant introduces evidence demonstrating that the plaintiff has some other risk factor that is a generally accepted alternative cause of her condition, a relative risk just over 2.0 is probably insufficient for a jury finding on causation. Thus, epidemiological evidence has a limited ability to carry the plaintiff's burden on specific causation.

37. Note the difference between evidence of specific causation and evidence of general causation—as a general matter, evidence of general causation is any evidence derived from a study of the *drug*, and evidence of specific causation is any evidence derived from a study of the *patient*.

differential diagnosis testimony often is critical to the success of the plaintiff's claim.³⁸

The following section provides the basic legal framework—Rule 702 and the Supreme Court cases interpreting that Rule—for evaluating the admissibility of expert testimony in federal trial courts.

B. The Daubert Standard

Rule 702 provides the standard according to which federal courts evaluate the admissibility of all expert witness testimony:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.³⁹

The Advisory Committee amended Rule 702 to incorporate the admissibility standard enunciated by the U.S. Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*⁴⁰ The Court's decision in *Daubert* gave trial judges a "gatekeeping" role, requiring them to exclude testimony that is unreliable or irrelevant.⁴¹ As gatekeeper, the trial judge must engage in "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts at issue."⁴²

Several years later, in *General Electric Co. v. Joiner*,⁴³ the Supreme Court reaffirmed *Daubert* and further explained the judge's role as gatekeeper:

[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

38. Sanders & Machal-Fulks, *supra* note 26, at 111.

39. FED. R. EVID. 702.

40. See FED. R. EVID. 702 advisory committee's note.

41. *Daubert*, 509 U.S. at 579.

42. *Id.* at 592-93. Until the Supreme Court decided *Daubert* in 1993, the federal standard for admissibility of expert testimony was that established by the United States Court of Appeals for the District of Columbia Circuit in the 1923 case of *Frye v. United States*. 293 F. 1013, 1014 (D.C. Cir. 1923). The *Frye* court established a test that has become known as the "general acceptance test," and it required that the scientific principle at issue have achieved a level of general acceptance in the relevant scientific community before an expert could testify as to that matter in court. *Id.* The *Frye* general acceptance test remained undisturbed by the Federal Rules of Evidence until the Supreme Court reconsidered the question in 1993 in an effort to clarify confusion that had arisen among the lower federal courts as to whether Rule 702 superseded the *Frye* general acceptance test. See *Daubert*, 509 U.S. at 587.

43. 522 U.S. 136 (1997).

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.⁴⁴

In *Joiner*, the plaintiff alleged that exposure to polychlorinated biphenyls ("PCBs") caused, at least in part, his small-cell lung cancer.⁴⁵ The plaintiff offered expert witnesses to testify that animal and epidemiological studies support a causal association between PCB exposure and lung cancer.⁴⁶ The Supreme Court affirmed the district court's exclusion of the expert testimony because the experts had failed to explain their extrapolation from the studies to the conclusion that PCBs contributed to the plaintiff's lung cancer.⁴⁷

As the *Joiner* Court stated, the federal admissibility standard allows experts to arrive at conclusions through extrapolation from existing data, as long as the gap between the data and their conclusions is not "too great."⁴⁸ Several years later, in *Kumho Tire Co. v. Carmichael*,⁴⁹ the Supreme Court explained the standard according to which a court should evaluate the expert witness's analytical leap:

[*Daubert's* gatekeeping requirement] is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.⁵⁰

The Court held that a trial court's admissibility determination should specifically take account of "the nature of the issue, the expert's particular expertise, and the subject of his testimony."⁵¹ In applying the standard it articulated, the Court considered the tests used by other experts in the relevant industry, concluded that these other experts did not use the test that the plaintiff's expert witness used in formulating his opinion (indeed, that the witness himself may not have used that test in the course of his employment), and consequently affirmed the district court's exclusion of the evidence.⁵²

Together, the *Daubert*, *Joiner*, and *Kumho Tire* opinions provide the federal standard for admissibility of expert witness testimony ("the *Daubert* standard"). The *Daubert* standard permits federal courts to admit a broader range of expert testimony than the standard it replaced but gives the court a very active role in screening

44. *Id.* at 146.

45. *Id.* at 139-40.

46. *Id.* at 143-46.

47. *See id.* at 144-45.

48. *See id.* at 146.

49. 526 U.S. 137 (1999).

50. *Id.* at 152.

51. *Id.* at 150.

52. *See id.* at 157-58.

that evidence for relevance and reliability.⁵³ To cabin the liberalization of admissibility standards that the *Daubert* Court announced, however, the Court clarified that even if the trial judge admits the evidence and the evidence later turns out to be insufficient to allow a reasonable juror to find for the plaintiff as to that issue, the court remains free to grant a motion for a directed verdict or summary judgment.⁵⁴ The Court stated that “[t]hese conventional devices, rather than wholesale exclusion under an uncompromising ‘general acceptance’ test, are the appropriate safeguards where the basis of scientific testimony meets the standards of Rule 702.”⁵⁵

C. Applying the Daubert Standard to Differential Diagnosis Evidence

As a general matter, the admissibility of differential diagnosis evidence of causation is not seriously disputed.⁵⁶ As the Court of Appeals for the Eighth Circuit stated in *Turner v. Iowa Fire Equipment Co.*, “differential diagnosis is a tested methodology, has been subjected to peer review/publication, does not frequently lead to incorrect results, and is generally accepted in the medical community.”⁵⁷ Indeed, most federal courts of appeals have held that a reliable differential diagnosis is admissible evidence of causation.⁵⁸ Although some commentators have suggested that certain courts categorically exclude differential diagnosis testimony as proof of causation because it is not scientific,⁵⁹ the cases cited for this proposition consistently evince a willingness by courts to entertain such testimony, provided the opinion is supported by sound scientific methodology.⁶⁰ Disparate admissibility results therefore stem not from

53. See *Joiner*, 522 U.S. at 142.

54. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

55. *Id.*

56. FAIGMAN ET AL., *supra* note 5, § 20-1.4.1.

57. 229 F.3d 1202, 1208 (8th Cir. 2000) (summarizing prevailing court of appeals opinions).

58. See, e.g., *id.*; *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262-63 (4th Cir. 1999); *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 154-55 (3d Cir. 1999); *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1228-30 (9th Cir. 1998); *Baker v. Dalkon Shield Claimants Trust*, 156 F.3d 248, 252-53 (1st Cir. 1998); *Zuchowicz v. United States*, 140 F.3d 381, 385-87 (2d Cir. 1998); *Ambrosini v. Labarraque*, 101 F.3d 129, 140-41 (D.C. Cir. 1996); *Glaser v. Thompson Med. Co.*, 32 F.3d 969, 978 (6th Cir. 1994).

59. See, e.g., *Ned I. Miltenberg & Anthony Z. Roisman*, 32 ENVTL. L. REP. 10980, 10981 (2002) (concluding that some courts view differential diagnosis testimony as an “illegitimate nonscientific tool”) (citing *Black v. Food Lion, Inc.*, 171 F.3d 308, 313-14 (5th Cir. 1999); *Allen v. Pa. Eng’g Corp.*, 102 F.3d 194, 195-96 (5th Cir. 1996); *Sorensen v. Shaklee Corp.*, 31 F.3d 638, 649 (8th Cir. 1994)).

60. In *Allen*, for example, the court excluded the differential diagnosis evidence because the evidence was either unreliable or insufficient to support the expert’s opinion of a causal association. See 102 F.3d at 197-99. And in *Black*, the court excluded the evidence because the

an unwillingness to consider differential diagnosis evidence, but rather from different understandings of what constitutes sound scientific methodology.

In the context of a pharmaceutical product liability action, *Kumho Tire* requires the judge to ensure that the witness's differential diagnosis opinion is conducted with the same intellectual rigor that characterizes the practice of a clinical physician in his everyday diagnosis of adverse drug reactions.⁶¹ If he has met that standard, the opinion should not be excluded as unreliable under the *Daubert* standard. Before a judge can begin to determine whether an expert has met that standard, however, he must have some idea of how clinical physicians diagnose adverse drug reactions. The following part details the methodology by which clinical physicians conduct differential diagnoses of adverse drug reactions.

III. DIFFERENTIAL DIAGNOSIS OF ADVERSE DRUG REACTIONS

A. Differential Diagnosis in General

Dr. Richard C. Cabot remarked that differential diagnosis is “a very dangerous topic—dangerous to the reputation of physicians for wisdom.”⁶² Cabot explained that it is very difficult to establish a set of rules that reliably identify the condition from which the patient suffers and excludes similar conditions. He remarked that physicians are hesitant to “commit their thoughts to paper” and “suspicious of any attempt to tabulate their methods of reasoning.”⁶³ The clinical physician's reluctance to memorialize in writing his diagnostic practices explains some of the difficulty inherent in the following attempt to describe accurately the methodology by which clinical physicians conduct differential diagnoses of adverse drug reactions. Despite this difficulty, the *Daubert* framework requires courts to have some understanding of the methodologies by which physicians conduct differential diagnoses of adverse drug reactions.

As discussed above, differential diagnosis—also referred to as “clinical medical evidence of causation”—is a process employed by clinical physicians in everyday practice to determine the disease or

physician's only basis for the conclusion was his ruling out all other possible causes. See 171 F.3d at 313-14.

61. See *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

62. A. MCGEHEE HARVEY & JAMES BORDLEY, III, *DIFFERENTIAL DIAGNOSIS: THE INTERPRETATION OF CLINICAL EVIDENCE* 2 (2d ed. 1970) (quoting Dr. Cabot).

63. *Id.* (quoting Dr. Cabot).

other condition from which a patient suffers. The crucial element of a differential diagnosis is "selecting from a number of possibilities the disease or diseases which come nearest to explaining the clinical and laboratory findings in the case in question."⁶⁴ In conducting this differential diagnosis, physicians, after first detecting an abnormality, try to match that abnormality with known diseases, develop an interim diagnosis, and then make a final diagnosis.⁶⁵ For example, a patient complaining of shortness of breath, a persistent cough, and chest pain may suffer from, *inter alia*, lung cancer or bronchitis. The process of determining which of these two conditions is affecting the patient is the process of differential diagnosis.

The term "differential diagnosis," however, is also used to refer to the process by which the physician, once he identifies the patient's condition, for example lung cancer, determines the cause of that lung cancer. As with differential diagnosis of a disease, clinicians attempting to determine the cause of the disease make a list of potential causal agents and, through a process of elimination, identify the agent that remains on the list as the most likely cause of the disease. For example, the physician attempting to identify the cause of his patient's lung cancer may include both tobacco and asbestos exposure on a list of possible causative agents. The process of identifying the causal agent is properly termed "differential etiology."⁶⁶

B. Adverse Drug Reactions

The following explanation of the differential diagnosis methodology focuses exclusively on the differential diagnosis of adverse drug reactions, rather than on the process by which physicians conduct differential diagnoses in general. The reason for such specificity is the particular complexity of the diagnosis of adverse drug reactions.

As alluded to above, the standard differential diagnosis is one that identifies the most likely disease from a list of possible diseases. When a clinician conducts such a differential diagnosis, he creates his list of potential diseases from medical textbooks, medical treatises, and his own experience as a diagnostician.⁶⁷ These sources help him identify diseases commonly known to manifest themselves in the types of symptoms that his patient has experienced. In other words, in many

64. *Id.* at 3.

65. JENNIFER J. JAMISON, DIFFERENTIAL DIAGNOSIS FOR PRIMARY PRACTICE 3-4 (1999).

66. *See supra* note 5.

67. *See HARVEY & BORDLEY, supra* note 62, at 3.

differential diagnoses, the association between the causal agent and the disease is well established. The diagnosis of adverse drug reactions is substantially more complex, however, precisely because the association between the causal agent (the drug) and the disease is not well established.

Many new drugs are approved by the Food and Drug Administration ("FDA") and enter the market every year.⁶⁸ Despite the voluminous safety studies the FDA requires for each drug presented for approval,⁶⁹ millions of adverse drug reactions⁷⁰ occur every year, resulting in over 100,000 fatalities annually.⁷¹ The majority of these ADRs are not recognized before the drug is approved.⁷² The number of patients exposed to the drug in premarketing clinical trials is simply too small to reveal some of the more uncommon side effects.⁷³ Variables such as age, gender, drug interactions, genetic makeup, and preexisting diseases affect the ability of a particular drug to produce a particular adverse reaction.⁷⁴ In fact, it is possible that a particular adverse drug reaction suffered by one patient will not occur in any other patient.⁷⁵ Thus, new and unexpected adverse drug reactions consistently arise as a result of the many new drugs entering the market every year.⁷⁶ Further, when the Food, Drug, and Cosmetic Act is amended to tighten regulations for drugs and medical devices, existing drugs and devices may be "grandfathered"—that is, they may be exempt from certain safety and

68. See J.D. Kleinke & Scott Gottlieb, *Is the FDA Approving Drugs Too Fast?*, 317 BRIT. MED. J. 899, 899 (1998) (stating that the FDA had recently been approving, on average, forty new drugs per year); see generally FOOD & DRUG ADMIN., CDER NEW AND GENERIC DRUG APPROVALS: 1998-2002 (listing recent FDA drug approvals), at <http://www.fda.gov/cder/approval/index.htm> (last visited Apr. 9, 2003).

69. See generally FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, NEW DRUG APPLICATION (NDA) PROCESS (providing an overview of the new drug application process), at <http://www.fda.gov/cder/regulatory/applications/NDA.htm> (last visited Apr. 9, 2003).

70. The World Health Organization defines an adverse drug reaction "as any response to a drug that is noxious and unintended" which occurs at prescription-level doses. Karch & Lasagna, *supra* note 24, at 1236.

71. Funmilayo O. Ajayi et al., *Adverse Drug Reactions: A Review of Relevant Factors*, 40 J. CLINICAL PHARMACOLOGY 1093, 1093 (2000); Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies*, 279 JAMA 1200, 1203 tbl.4 (1998).

72. Ajayi et al., *supra* note 71, at 1094.

73. *Id.*

74. See *id.*

75. Auriche & Loupi, *supra* note 30, at 231.

76. See *id.*

efficacy studies required for the approval of new drugs and devices.⁷⁷ The grandfathering of existing drugs may also contribute to the high incidence of adverse events in marketed drugs.

Because premarketing studies are incapable of determining all adverse effects that might surface as the drug is prescribed to many patients, the FDA also requires substantial postmarketing surveillance for the drugs it approves.⁷⁸ If and when that postmarketing surveillance data suggest that the harmful effects of the drug outweigh its benefits, the product may be withdrawn from the market, either by the FDA or by the manufacturer.⁷⁹

Withdrawal from the market, however, does not establish a causal association between the drug and the patient's injury. Rather, the FDA or the manufacturer may withdraw a product from the market based on only a suspicion of its having deleterious side effects.⁸⁰ Even absent concrete evidence of a causal association, however, clinical physicians must attempt to identify the cause of the condition. In other words, they must determine whether the condition is actually an adverse drug reaction. This causal assessment helps the physician determine how to treat the patient's symptoms, whether to cease drug treatment (in cases in which the drug has not been withdrawn) and how to interrupt the progression of the disease.⁸¹ Yet the information on which the physician bases this causal assessment may be scant—perhaps the warning section of the drug label, a few case reports of other patients who have suffered adverse reactions while taking the drug, and some experience with drugs in a similar class.

All of this suggests that when a physician diagnoses an adverse drug reaction in his everyday practice of medicine, general

77. For example, when silicone gel breast implants were brought within the scope of the FDCA in 1976, they were grandfathered, even though their safety had never been confirmed through systematic studies. See ANGELL, *supra* note 19, at 21, 51.

78. Ajayi et al., *supra* note 71, at 1097 (noting the importance of postmarketing surveillance). Ajayi and her co-authors estimate that two to three years of postmarketing surveillance are required to obtain a good understanding of the range of adverse drug reactions for a new drug. *Id.* at 1100.

79. See *id.* A recent well-known example involved the weight-loss drugs Redux and Pondimin, withdrawn from the market on September 15, 1997 because of a possible association with heart valve abnormalities. U.S. DEPT OF HEALTH & HUMAN SERVS., PUB. NO. P97-32, FDA ANNOUNCES WITHDRAWAL OF FENFLURAMINE AND DEXFENFLURAMINE (Sept. 15, 1997), available at <http://www.fda.gov/bbs/topics/NEWS/NEW00591.html>. See generally FOOD & DRUG ADMIN., RECALLS/WITHDRAWALS (listing drugs recalled or withdrawn from the market), at <http://www.fda.gov/cber/recalls.htm> (last modified Dec. 16, 2002).

80. See, e.g., U.S. DEPT OF HEALTH & HUMAN SERVS., *supra* note 79 (requesting that the drug company voluntarily withdraw the drugs based on nothing more than a series of case reports suggesting an association between the drugs and valvular abnormalities).

81. See Irey, *supra* note 30, at 1.

causation—i.e., whether the drug is capable of causing the patient's condition—may not be established for relatively new drugs. Accordingly, the physician cannot rely on a well-established body of data collected in his textbooks, treatises, and prior experience to develop his list. So what is he to do? He presumes, at least initially, "that the drug is a possible factor in the adverse event until, after weighing all the available evidence, a diagnosis is established."⁸² In other words, with respect to the diagnosis of adverse drug reactions, physicians do not "presume the innocence of the drug until proven guilty beyond all reasonable doubt."⁸³ Thus, the physician's approach to the differential diagnosis of adverse drug reactions is markedly different from his approach to the diagnosis of diseases with well-classified lists of possible causes. The significance of this difference will be discussed below in Part IV.⁸⁴ For now it is sufficient to note the difference as the reason that the following discussion focuses specifically on the differential diagnosis of adverse drug reactions, rather than on the process of differential diagnosis in general.

C. Approaches to the Diagnosis of ADRs

As Danan and Benichou point out, "assessing the causal role of a drug in the occurrence of an adverse medical event remains one of the most controversial issues."⁸⁵ This controversy has led to the development of varying approaches to the differential diagnosis of adverse drug reactions. These approaches fall into three general categories: clinical judgment, quantitative algorithms, and the Bayesian approach.⁸⁶ Within each category there is tremendous variety. The remainder of this section explains each methodology using some paradigmatic examples as illustrations of each approach.⁸⁷

82. M.D.B. Stephens, *The Diagnosis of Adverse Medical Events Associated with Drug Treatment*, 1 ADVERSE DRUG REACTION AC. POISON. REV. 1, 2 (1987).

83. *Id.* at 1 (internal quotations omitted).

84. See discussion *infra* Part IV.

85. Gaby Danan & Christian Benichou, *Causality Assessment of Adverse Reactions to Drugs—I. A Novel Method Based on the Conclusions of International Consensus Meetings: Application to Drug-Induced Liver Injuries*, 46 J. CLINICAL EPIDEMIOLOGY 1323, 1323 (1993). For example, M.D.B. Stephens points out that between 1972 and 1986 alone, eighteen new methods for assessing adverse drug event reports were proposed. Stephens, *supra* note 82, at 4.

86. See Krista L. Lancôt & Claudio A. Naranjo, *Pharmacoepidemiology and Drug Utilization: Comparison of the Bayesian Approach and a Simple Algorithm for Assessment of Adverse Drug Events*, 58 CLINICAL PHARMACOLOGY & THERAPEUTICS 692, 692 (1995); C.A. Naranjo et al., *A Method for Estimating the Probability of Adverse Drug Reactions*, 30 CLINICAL PHARMACOLOGY & THERAPEUTICS 239, 239 (1981).

87. Note that there are at least three different groups of physicians who diagnose adverse drug events: clinical physicians—i.e., those who treat patients; physicians working on behalf of

1. Clinical Judgment (Global Introspection) and Qualitative Algorithms

The clinical judgment approach, also known as "global introspection,"⁸⁸ is the most traditional and common methodology for the differential diagnosis of adverse drug reactions.⁸⁹ This methodology is based on a variety of data that the doctor subjectively factors into an assessment of the cause of a patient's condition.⁹⁰ One physician describes the method of global introspection as follows:

The assessor attempts to consider each factor that could possibly affect the causal link between one or more administered drugs and a subsequently observed adverse event. He or she makes a mental list of these factors, weighs them according to some sense of their relative importance, mixes the complicated brew in a fashion somewhat reminiscent of the witches in *Macbeth*, and then spews forth a decision about the probability of drug causation.⁹¹

In general, this assessment is largely a matter of "inner conviction" as to whether or not the sum of these factors amounts to causation.⁹² Indeed, according to one expert, "it is all a matter of opinion."⁹³ Studies confirm the disparity among physicians' causality assessments of the same cases.⁹⁴ For example, a 1976 study compared the independently developed opinions of three clinical pharmacologists as to whether or not sixty patients had suffered an adverse drug reaction.⁹⁵ The three clinical pharmacologists agreed on only thirty of the sixty cases.⁹⁶ Of the remaining thirty cases, nineteen involved major disagreement—for example, when one pharmacologist found a definite ADR and the other definitely concluded that no ADR had occurred.⁹⁷

administrative agencies; and physicians in the pharmaceutical industry. Stephens, *supra* note 82, at 5. These groups diagnose adverse drug reactions for different reasons—ranging from treatment of patients to monitoring drug safety—and the precise method varies slightly according to the purpose. *See id.*

88. *See, e.g.*, Michael S. Kramer, *Assessing Causality of Adverse Drug Reactions: Global Introspection and Its Limitations*, 20 DRUG INFO. J. 433, 433 (1986).

89. Lanctôt & Naranjo, *supra* note 86, at 692.

90. Michael S. Kramer, *Assessing Causality of Adverse Drug Reactions: Global Introspection and Its Limitations*, 20 DRUG INFO. J. 433, 433 (1986).

91. *Id.*

92. Auriche & Loupi, *supra* note 30, at 231.

93. Stephens, *supra* note 82, at 2.

94. *See, e.g.*, Auriche & Loupi, *supra* note 30, at 231.

95. Fred E. Karch et al., *Commentary: Adverse Drug Reactions—A Matter of Opinion*, 19 CLINICAL PHARMACOLOGY & THERAPEUTICS 489, 489 (1976).

96. *Id.* at 491.

97. *Id.*

The highly subjective and imprecise nature of the clinical judgment approach⁹⁸ led to efforts to develop operational definitions for the diagnosis of adverse drug reactions.⁹⁹ These operational definitions, or qualitative algorithms, produce greater consistency among diagnosticians than the clinical judgment approach itself, which involves little in the way of articulable criteria or standards. The operational definitions, however, are intended to approximate the general calculus performed by physicians in the course of a differential diagnosis based on clinical judgment. The first operational definition of ADR diagnosis was developed by Nelson Irey.¹⁰⁰

According to Irey, at the first step of any method of ADR diagnosis, the physician must determine whether a particular drug is an eligible cause of the symptoms the patient experiences.¹⁰¹ Although there is no single standard according to which all physicians will consider an adverse drug reaction an "eligible" cause, the threshold for inclusion of the drug as a potential factor generally is quite low. For example, Irey suggests that a drug is an eligible cause of the adverse event when the clinician confirms by the drug label that the drug ordered is the drug the patient received ("identification"), that the patient took the drug as ordered ("administration"), that ADR onset followed drug administration ("temporal eligibility"), and that the interval between initial exposure to the drug and onset of the adverse reaction is reasonable for that particular drug ("latent period").¹⁰² Essentially, as Stephens has suggested, when a patient experiences any symptoms after administration of a drug, the physician should presume the involvement of that drug in causing those symptoms until he definitively establishes a proper diagnosis.¹⁰³

After an adverse drug reaction is deemed eligible, the physician attempts to confirm or to deny a possible causal association.¹⁰⁴ Six other factors help the physician to confirm the causal association: exclusion, de-challenge, re-challenge, singularity of the drug, pattern, and drug identification (both quantitative and qualitative).¹⁰⁵ "Exclusion" refers to the process by which other possible drug causes

98. See *id.* at 492.

99. See, e.g., Karch & Lasagna, *supra* note 24, at 1237.

100. Stephens, *supra* note 82, at 5.

101. See Nelson S. Irey, *Tissue Reactions to Drugs*, 82 AM. J. PATHOLOGY 617, 622 (1976).

102. *Id.* at 622-24. The latent period is a unique characteristic of each drug and may also vary from patient to patient. Irey, *supra* note 30, at 4.

103. Stephens, *supra* note 82, at 2.

104. See, e.g., Irey, *supra* note 30, at 3.

105. *Id.*

are eliminated.¹⁰⁶ “De-challenge” is the process by which the patient is taken off the suspected drug for the purpose of observing whether the adverse drug event ceases and is reversible.¹⁰⁷ Following de-challenge, “re-challenge” is the process of reexposure to the drug to determine if the adverse drug reaction resumes.¹⁰⁸ When a physician evaluates the “singularity of the drug,” he considers whether the patient was exposed to only one drug when the adverse event occurred, as well as whether any other disease or condition from which the patient suffers could have caused the adverse event.¹⁰⁹ “Pattern” refers to either precedent in the literature¹¹⁰ or previous clinical experience with the drug or other drugs in its class indicating an association between the drug and the adverse event in question.¹¹¹ “Drug quantitation” is the process of determining the level of the drug in the body fluids and is most helpful in overdose cases.¹¹² Finally, “drug qualification” refers to an analysis of the body fluids for the mere presence of a drug.¹¹³

Clearly, much subjectivity enters the physician’s analysis of each of these factors. Similarly, determining how each of these individual factors fits with the others to produce a final causal determination involves a great deal of subjectivity. The next step of Irey’s operational model is therefore to apply each of these factors to a set of causality criteria.¹¹⁴ Each of Irey’s five degrees of causality—causative, probable, possible, coincidental, or negative—defines the quantum of evidence required for a causality assessment to that particular degree of certainty.¹¹⁵

According to Irey’s model, a finding of “causative” requires drug eligibility,¹¹⁶ singularity of the drug, a known drug response pattern consistent with the observed event, and elimination of any preexisting

106. *Id.* at 5. Exclusion is often represented as a time-flow chart, employing time relationships to eliminate other drug causes. *Id.* at 6.

107. *Id.* at 6.

108. *Id.* Of course, doctors are often reluctant to conduct a re-challenge experiment when the adverse drug event is serious and the drug is most likely responsible. *Id.*

109. *Id.* at 7. Irey notes that when all other nondrug causes can be ruled out and there is a well-established association between the condition and the drug, the diagnosis is relatively straightforward. *See id.*

110. Examples include case reports, epidemiological studies, and toxicological studies.

111. Irey, *supra* note 30, at 7.

112. *Id.* at 8; Irey, *supra* note 101, at 632. In cases of death, toxicologic screening may help to eliminate other possible drugs, for example, drugs that were present at levels insufficient to be lethal. Irey, *supra* note 30, at 8-9.

113. Irey, *supra* note 30, at 9.

114. *See* Irey, *supra* note 101, at 636-44.

115. *See id.*

116. *See supra* notes 101-102 and accompanying text.

diseases as an explanation of the event.¹¹⁷ A finding that the drug was a “probable” cause of the adverse event requires that all of the same criteria except singularity of the drug be met, but at least one of the other six factors must be satisfied in its stead.¹¹⁸

Irey considers the drug a “possible” cause of the adverse event in one of three situations.¹¹⁹ First, all of the criteria for “probable” have been established, but other potential drug causes cannot be ruled out.¹²⁰ Second, most of the criteria for a “probable” diagnosis are met, but data are unavailable to establish all the relevant criteria.¹²¹ Finally, all of the criteria for a “probable” diagnosis have been established, but the literature has not yet described the pattern of this drug.¹²² According to Irey, “[w]hen such a case may constitute a new, emergent entity, it is put in the ‘possible’ category, awaiting further confirmatory experience or a more extensive search of the literature.”¹²³ The “coincidental” category includes those cases in which the patient was exposed to the drug, but either the drug is ineligible or there is a viable alternate cause for the event.¹²⁴ Finally, Irey characterizes the causal association as “negative” when laboratory studies exclude the drug as a possible cause.¹²⁵

Various other models defining degrees of causality have been offered since the development of Irey’s operational model.¹²⁶ These attempts at categorization vary dramatically, however. In particular, Lanctôt and Naranjo suggest that these unquantified approaches produce high rates of disagreement among diagnosticians in particular cases, stating that “one expert’s ‘probable’ could be equivalent to another expert’s ‘possible.’”¹²⁷ Thus, even with the operational

117. Irey, *supra* note 101, at 637-38. Irey has suggested that the “causative” category is so rarely satisfied that it is usually reserved for those cases involving overdose, where the evidence is primarily a report of a lethal drug level in body fluids and/or tissues. Irey, *Drug Induced*, *supra* note 30, at 12.

118. Irey, *supra* note 101, at 638-39.

119. *Id.* at 639-40.

120. *Id.* at 639.

121. *Id.*

122. *Id.* at 640.

123. Irey, *supra* note 30, at 14.

124. Irey, *supra* note 101, at 640-41.

125. *Id.* at 641-42.

126. See, e.g., Karch & Lasagna, *supra* note 24, at 1237 (describing the operational definitions first offered by the Registry of Tissue Reactions to Drugs).

127. Lanctôt & Naranjo, *supra* note 86, at 692-93. Indeed, where Irey requires the adverse event to follow a known response pattern of the drug for categorization as “probable,” but not “possible,” see *supra* note 118 and accompanying text, Karch and Lasagna require a known response pattern for either category. Karch & Lasagna, *supra* note 24, at 1237. Where “possible” differs from “probable” in their categorization is that a “possible” causal association cannot rule out alternative causes. *Id.*

definitions, physicians' causality assessments are not consistently replicable. This reproducibility problem with the clinical judgment approach and other qualitative models led to the development of quantitative methods for diagnosing adverse drug reactions.

2. Quantitative Algorithms

Quantitative algorithms are a second method of assessing adverse drug reactions.¹²⁸ These algorithms were not developed to change the substance of the causal assessment. Instead, they were designed to quantify the relative importance of the factors in a way that would reflect what clinicians had been doing subjectively but would produce more consistent results.¹²⁹

An algorithm is a series of questions relating to the various factors that a doctor considers in his analysis of a potential adverse drug event.¹³⁰ Associated with each question is a weight that varies according to the answer given and the relative importance of that particular factor in the overall causality assessment.¹³¹ Many different algorithms have been developed to assess adverse drug reactions.¹³²

To illustrate the function of an algorithm, this section describes the twenty-three question algorithm developed by Venulet.¹³³ The first step of the Venulet algorithm is to answer the following twenty-three questions:

128. Lanctôt & Naranjo, *supra* note 86, at 692-93.

129. *See id.* at 693.

130. *See, e.g., id.*

131. *See, e.g., id.*

132. For example, the Adverse Drug Reaction Probability Scale ("APS") is a simple algorithm consisting of a ten-question questionnaire, taking account of the following factors: pattern of response (which refers to previous conclusive reports on the reaction), temporal sequence, de-challenge, re-challenge, alternative causes, placebo response, drug levels in body fluids or tissues, dose-response relationship, experiences of previous patients with the drug, and confirmation by objective evidence. Naranjo et al., *supra* note 86, at 240. The FDA has also developed a simple algorithm for causality assessment based on case reports. *See* Judith K. Jones, *Determining Causation from Case Reports*, in PHARMACOEPIDEMOLOGY 275, 282 (Brian L. Strom ed., 1989); *see also* Danan & Benichou, *supra* note 85, at 1325-27 (describing a new algorithm for causality assessment); Michael S. Kramer et al., *An Algorithm for the Operational Assessment of Adverse Drug Reactions*, 242 JAMA 623, 624-29 (1979).

133. J. Venulet et al., *Updating of a Method for Causality Assessment of Adverse Drug Reactions*, 24 INT'L. J. CLINICAL PHARMACOLOGY, THERAPY & TOXICOLOGY 559, 560 (1986).

Figure 2. Twenty-Three Question Venulet Algorithm¹³⁴

	Encircle One			
	Known	Yes	No	Unk
All questions refer to the Suspected Drug or in case of Interactions to both Drugs				
I. History of present adverse reaction				
1. Dose or duration of treatment exceeded? (as per "Basis Text")		Yes	No	Unk.
2. Drug given prior to event? (as per dates)		Yes	No	Unk.
3. Concomitant or preceding drug therapy?		Yes	No	Unk.
4. Reaction at site of application?		Yes	No	Unk.
5. ADR immediately follows the drug? (within approx. 1 hour)		Yes	No	Unk.
6. Dechallenge positive? (if ADR reversible) (without treatment with treatment = Y).	Known	Yes	No	Unk.
7. Rechallenge positive?		Yes	No	Unk.
8. Were concomitant drugs stopped at the same time? (only if 3 = Y)		Yes	No	Unk.
II. Patient's past adverse reaction history				
9. Same ADR to this drug before?		Yes	No	Unk.
10. Other ADR to this drug before?		Yes	No	Unk.
11. Similar symptoms in the past? (not related to drug treatment)		Yes	No	Unk.
12. Similar ADR with other drugs in the past?		Yes	No	Unk.
III. Monitor's experience				
13. Drug/ADR interval compatible with event? (Typical = K; Compatible = Y; Incompatible = N)	Known	Yes	No	Unk.
14. Adverse event of rare spontaneous occurrence? (Y or N only)		Yes	No	Unk.
15. Similar events known to occur with the disease treated or with concomitant disease(s)?		Yes	No	Unk.
16. ADR occurrence facilitated by the disease treated by concomitant diseases?		Yes	No	Unk.
17. Contributory role of non-drug therapies?		Yes	No	Unk.
18. Other contributory factors (habits, environment, etc.)?		Yes	No	Unk.
19. ADR known with the suspected drug? (K, Y or N only) (known = K; suspected = Y)	Known	Yes	No	Unk.
20. ADR explainable by the biological properties of the drug? (only if 19 = N)		Yes	No	Unk.
21. ADR known with pharmacologically-related drugs? (only if 19 = N)		Yes	No	Unk.
22. ADR known with concomitant or preceding drug therapy? (only if 3 = Y; if well known = K)	Known	Yes	No	Unk.
23. Drug interaction as a possible cause of ADR (only if 3 = Y)		Yes	No	Unk.

134. Reproduced from Venulet's article. *Id.*

As this figure demonstrates, most questions are answered as yes, no, or unknown. An answer of known is used only when an answer other than yes, no, or unknown is called for (as explained in the parentheticals following that particular question).

Many of these questions can be grouped in classes that correspond to the factors clinicians utilize in the qualitative approaches to ADR diagnosis. Questions 2, 5, and 13 refer to temporal association and latent period. Questions 3, 8, 11, 12, 15, 16, 17, 18, and 22 refer to alternative causes or contributory factors such as diseases, other drugs, or environmental factors. Question 19 is the question that most specifically addresses the issue of general causation—i.e., whether or not the drug is capable of causing the adverse event—and accounts for the same type of information that Irey's approach referred to as the drug's response pattern.¹³⁵ With respect to question 19, Venulet suggests that a drug falls into the suspected category—the “yes” answer—if the adverse event has been reported in association with the drug only several times.¹³⁶ The reaction is considered “known” only when the causal relationship has been proven or when the occurrence of the adverse reaction with the drug is generally accepted.¹³⁷ Questions 20 and 21—generally only important if the answer to Question 19 is “no”¹³⁸—refer to whether the physician can explain the adverse event based upon the properties of the suspected drug or a pharmacologically related drug. Question 6 involves the patient's response to de-challenge, and Question 7 involves her response to re-challenge.

After the diagnostician answers each of these questions, each answer is assigned a weight ranking commensurate with its probative value.¹³⁹ For example, according to Venulet, the most probative of the twenty-three categories of evidence—a positive re-challenge—is worth +30 points, while a negative re-challenge is worth -25.¹⁴⁰ A known response pattern is worth +10, a suspected response pattern is worth +5, and an unknown response pattern is worth -5.¹⁴¹ When all of the

135. See discussion *supra* Part III.C.1.

136. Venulet et al., *supra* note 133, at 562.

137. *Id.*

138. *Id.*

139. See generally *id.* at 564-65 (charts assigning weight to each category). Note also that there is another level of categorization that has been omitted from this discussion for the purpose of simplicity. This category involves classifying the reaction as dose-related or unrelated, whether the reaction occurs only on drug withdrawal, whether the reaction is a result of addiction to the drug, etc. See *id.* at 563. By and large, the assignment of weight to each answer is the same regardless of this categorization. See *id.* at 564-65.

140. See *id.* at 564.

141. See *id.*

answers have been assigned a weight value, the values are totaled and compared to a causality level.¹⁴² Seventy points results in a “definite” causal association, 40 to 65 is “probable,” 5 to 35 is “possible,” -15 to 0 is “unlikely,” and less than -30 is “unrelated.”¹⁴³

Only two of the twenty-three questions can result in answers that are dispositive of the causal assessment. If the answer to either Question 2—whether the drug was given prior to the event (temporal proximity)—or Question 13—whether the drug/ADR interval is compatible with the event (appropriate latency period—is no, then that answer requires a conclusion of not related.¹⁴⁴ No other answer, including an unknown response pattern, is dispositive of the diagnosis.¹⁴⁵

3. The Bayesian Approach

A third method of differential diagnosis of adverse drug reactions is the Bayesian approach.¹⁴⁶ The Bayesian approach is the most recently developed methodology for assessing adverse drug reactions. The underlying premise is a statement of probability known as the Bayes Theorem.¹⁴⁷ The Bayesian approach compares the probability of an adverse event occurring after drug exposure to the probability of the event occurring without drug exposure.¹⁴⁸

The calculation involves evaluating the patient’s history, the temporal proximity between exposure to the drug and the onset of symptoms, results of de-challenge and re-challenge experiments, the epidemiology of the suspected drug, and any other relevant factors.¹⁴⁹ These factors are separated into two groups—prior odds, a measure which accounts for information known about the particular adverse event (e.g., epidemiological studies), and likelihood ratios, a measure which accounts for information about the patient’s case (e.g., time of

142. *See id.* at 566.

143. *Id.*

144. *Id.* at 564-65. This process is consistent with Irey’s operational model, according to which a drug is not considered an “eligible” cause absent temporal proximity and a reasonable latency period. *See* discussion *supra* Part III.C.1.

145. Note, however, that not all algorithms consider a lack of temporal proximity and an unreasonable latency period as dispositive of the outcome. *See, e.g.,* Naranjo et al., *supra* note 86, at 240 tbl.1 (describing an algorithm according to which an adverse event appearing before drug administration results in a subtraction of one point from the total score, rather than a conclusive finding that the drug and the adverse event are unrelated).

146. *See* Lanctôt & Naranjo, *supra* note 86, at 692.

147. Judith K. Jones, *A Bayesian Approach to Causality Assessment*, 23 PSYCHOPHARMACOLOGY BULL. 395, 396 (1987).

148. Jones, *supra* note 132, at 283.

149. *Id.*

onset).¹⁵⁰ The product of the prior odds and the likelihood ratio is the posterior odds,¹⁵¹ expressed in terms of a posterior probability, a figure that ranges from 0% (not drug related) to 100% (definitely drug related).¹⁵² The Bayesian methodology is more complicated in its execution, but this simplified description suffices for this discussion.¹⁵³

IV. IMPLICATIONS

The foregoing discussion of the methodology by which clinical physicians conduct differential diagnoses of adverse drug reactions demonstrates the absence of a single method according to which physicians assess the causal association between a drug and an adverse reaction. Nonetheless, there are several implications of this discussion that are relevant to a court's consideration of the reliability of an expert witness's differential diagnosis opinion. To examine these implications, it is useful to consider a representative case.

In *Glastetter v. Novartis Pharmaceuticals Corp.*, the United States District Court for the Eastern District of Missouri held that the testimony from the plaintiff's expert witness on causation was not sufficiently reliable and therefore was inadmissible.¹⁵⁴ Plaintiff Tina Glastetter was prescribed the drug Parlodel, manufactured by the defendant Novartis Pharmaceuticals Corporation, for the prevention of postpartum lactation.¹⁵⁵ After thirteen days of Parlodel treatment, she suffered symptoms and was diagnosed with an intracerebral hemorrhage that resulted in a stroke.¹⁵⁶

The plaintiff sought to prove by expert testimony that bromocriptine mesylate, the active ingredient in Parlodel, caused her intracerebral hemorrhage.¹⁵⁷ Both experts relied on differential diagnosis methodology to form their opinion that Parlodel caused the plaintiff's stroke.¹⁵⁸ At the pretrial *Daubert* hearing, the two experts testified that they considered case reports, animal studies, epidemiological studies, characteristics of drugs in the same family as Parlodel, the plaintiff's medical records, evidence of temporal

150. Naranjo et al., *Advances in the Diagnosis of Adverse Drug Reactions*, 32 J. CLINICAL PHARMACOLOGY 897, 901 (1992).

151. *Id.*

152. Lanctôt & Naranjo, *Comparison*, *supra* note 86, at 693.

153. For further discussion of the Bayesian methodology, see generally Jones, *supra* note 147.

154. 107 F. Supp. 2d 1015, 1016 (E.D. Mo. 2000), *aff'd*, 252 F.3d 986 (8th Cir. 2001).

155. *Id.* at 1017.

156. *Id.*

157. *Id.*

158. *Id.* at 1019.

proximity, and possible alternative causes such as other diseases, conditions, or external factors.¹⁵⁹

In evaluating the opinion of one of the plaintiff's experts, the court explicitly stated that because the physician's differential diagnoses opinion was not based on scientific studies, it was "in the final analysis, reposed in the realm of 'may cause' or 'possibly could cause.'"¹⁶⁰ Further, with respect to both experts, the *Glastetter* court concluded that both opinions were unreliable because the experts did not come forward with evidence "ruling in" Parlodel as a possible cause of intracerebral hemorrhage.¹⁶¹ By "ruling in" the drug as a possible cause, the court was referring to the issue of general causation—i.e., whether the drug is capable of causing the alleged injury.¹⁶² The court suggested that a differential diagnosis opinion on causation is unreliable whenever that expert has not also formed an opinion, based on scientific studies, on general causation.¹⁶³

This requirement—that a differential diagnosis expert demonstrate how he has "ruled in" the drug at issue as a potential cause—has been adopted in several other recent cases.¹⁶⁴ The purported reason for this requirement is to ensure that the causal agent that remains on the list after everything else has been ruled out is actually capable of producing the adverse event.¹⁶⁵ With this discussion in mind, the following two sections consider the permissibility and utility of a "ruling in" requirement.

A. The "Ruling In" Requirement: Reliability

The Court in *Kumho Tire v. Carmichael* prescribed that courts hold expert witness analyses to "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."¹⁶⁶ As such, in considering whether a differential diagnosis expert should be held to an absolute "ruling in" requirement when offering testimony on specific causation, the court must compare the witness's analytic

159. See generally *id.* at 1019-31 (describing the experts' differential diagnosis methodology).

160. *Id.* at 1025.

161. *Id.* at 1028.

162. See *id.*

163. See *id.*

164. See, e.g., *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1209 (10th Cir. 2002); *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1371 (N.D. Ga. 2001), *aff'd*, *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1230 (D. Colo. 1998); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1412-13 (D. Or. 1996); *Cavallo v. Star Enter.*, 892 F. Supp. 756, 771 (E.D. Va. 1995).

165. See, e.g., *Siharath*, 131 F. Supp. 2d at 1362-63 (quoting *Hall*, 947 F. Supp. at 1413).

166. 526 U.S. 137, 152 (1999); see also discussion *supra* Part II.B.3.

process to the process employed by clinical physicians in their everyday practice of medicine.¹⁶⁷ That comparative analysis leads to the following inescapable conclusion: Clinical physicians, with respect to the differential diagnosis of adverse drug reactions, neither assume general causation nor require evidence of general causation before they consider a drug a possible cause of an adverse event.¹⁶⁸ Accordingly, courts should not require a differential diagnosis expert to present evidence of general causation as a condition of admissibility under *Daubert*.

Regardless of the methodology used, a properly conducted differential diagnosis is multifactored.¹⁶⁹ The factors involved in any ADR diagnosis are essentially the same. They are as follows: temporal association; response pattern of the drug;¹⁷⁰ de-challenge; re-challenge; and exclusion of other possible drugs, toxins, conditions, and diseases as alternative causes.¹⁷¹ Where the three approaches diverge is in the methodology by which each determines the degree of certainty of the diagnosis—specifically, a judgment made by a clinical physician after taking account all of the factors, a methodological evaluation pursuant to some quantitative algorithm, or a calculation based on a Bayesian equation.¹⁷²

Although the approaches are multifactored, several of those factors may be dispositive. Both Irey and Venulet suggest that if the adverse event occurred before the drug was taken (temporal proximity), or if the period between exposure and the adverse event is inconsistent with a known latency period for that adverse drug event, the conclusion must be that the adverse event is unrelated to drug exposure.¹⁷³ Otherwise, however, once temporal proximity and latent period confirm the drug's eligibility, there is no consensus as to any

167. See 526 U.S. at 157 (considering the type of tests used by other tire experts in its evaluation under *Daubert* of the witness's conclusion that a tire defect caused the tire to blow out).

168. See discussion *supra* Parts III.B-C. But see, e.g., *Hall*, 947 F. Supp. at 1413 (“[D]ifferential diagnosis assumes that general causation has been proven for the list of possible causes it eliminates.”). Such an assumption may be appropriate for the differential diagnosis of a *disease*, but for the reasons stated above regarding the specific problems associated with the differential diagnosis of adverse drug reactions, and as the foregoing discussion demonstrates, this assumption does not hold true for the differential diagnosis of ADRs. See discussion *supra* Part III.B.

169. See generally discussion *supra* Part III.C (describing the primary approaches to ADR differential diagnosis).

170. Examples include epidemiological studies, case reports, and toxicological studies.

171. See discussion *supra* Part III.C.

172. See *id.*

173. See *id.*

single dispositive factor in the diagnosis of adverse drug reactions.¹⁷⁴ The importance of each factor depends on which of the three approaches is taken, the particular operational model, algorithm, or equation that is used, and the physician who applies it.¹⁷⁵

One of the nondispositive factors in a clinician's differential diagnosis is the response pattern of the drug.¹⁷⁶ Not only is an unknown response pattern not dispositive of the physician's causality assessment, but other factors in the assessment may be much stronger evidence of specific causation than whether or not the drug has a known response pattern.¹⁷⁷ For example, where Venulet gives evidence of positive re-challenge thirty points of the forty points necessary for a finding of probable causation, he gives evidence of a known response pattern only ten points.¹⁷⁸ Thus, a physician can reliably base an ADR diagnosis on several of these other factors without any evidence of general causation. For example, if a new drug is introduced in the market, a number of serious adverse events are immediately reported, the drug is withdrawn, and no subsequent controlled epidemiological studies are performed because of the withdrawal, the physician has little or no basis for a conclusion as to general causation. Yet that physician still may reliably base a positive ADR diagnosis on positive results on de-challenge, positive results on re-challenge, temporal evidence, a consistent latent period, and exclusion of all other possible causes. Thus, despite the lack of evidence of general causation, according to the diagnostic constructs examined above, the physician may have more than sufficient evidence upon which to reliably base a conclusion that the drug caused his patient's injury.

Evidence of the drug's response pattern is tantamount to evidence of general causation—that is, evidence that “rules in” the drug as a possible cause—because, as explained above, evidence of a response pattern includes either precedent in the literature or previous clinical experience with the drug or other drugs in its class.¹⁷⁹ Accordingly, if an unknown drug response pattern is not necessarily dispositive of the clinician's diagnostic assessment (and since evidence

174. *See id.*

175. *See id.*

176. *See supra* note 111 and accompanying text; *see also* discussion *supra* Part III.C.2 (listing the factors in the Venulet algorithm, one of which is the known response pattern of the drug). Note that some ADR differential diagnosis methods do not consider whether the association between the drug and the adverse event has been previously recognized. *See, e.g., Jones, supra* note 147, at 395.

177. *See* discussion *supra* Part III.C.2.

178. *See* Venulet et al., *supra* note 133, at 564.

179. *E.g., Irely, supra* note 30, at 7.

of a drug's response pattern is roughly equivalent to the general causation and to the "ruling in" requirement), then *Kumho Tire* provides that the absence of evidence "ruling in" the drug as a possible cause should not be dispositive of a court's *Daubert* analysis. Whether the suspected agent is actually capable of causing the patient's disease is simply not one that the differential diagnosis process is designed specifically to answer.¹⁸⁰

Courts that improperly condition the admissibility of differential diagnosis testimony on evidence that the expert has "ruled in" the drug as a possible cause appear to do so for one of two reasons. First, some courts fail to recognize the importance of *Kumho Tire* to the consideration of this "ruling in" requirement. For example, in *Siharath v. Sandoz Pharmaceuticals Corp.*, the district court excluded the plaintiff's expert's differential diagnosis testimony under the reliability prong of *Daubert* while admitting that "[t]he Court also does not question that the methodology Dr. Kulig discussed at the *Daubert* hearing serves him well every day in the clinical practice of medicine."¹⁸¹ The *Siharath* court further suggests that even the best clinical methodology available does not satisfy the requirement of *Daubert*.¹⁸² This approach is flatly inconsistent with the *Kumho Tire* Court's explication of the *Daubert* reliability prong, which defines reliability according to the consistency of the expert's analytical process with that of other experts in his field. Second, other courts misunderstand the clinical practice of differential diagnosis. For example, the Court of Appeals for the Eighth Circuit, affirming *Glastetter*, defined differential diagnosis as the process by which "a physician . . . 'rul[es] in' all scientifically plausible causes of the plaintiff's injury . . . [and] then 'rules out' the least possible causes of injury until the most likely cause remains."¹⁸³ As illustrated by the foregoing discussion of the clinical process of differential diagnosis, this conception of differential diagnosis, at least with respect to the

180. Differential diagnosis experts, recognizing the difference between general and specific causation, do not represent that their diagnoses are intended to prove general causation, and they explicitly state in some cases that differential diagnoses are not designed for that purpose. See, e.g., *Glastetter v. Novartis Pharm. Corp.*, 107 F. Supp. 2d 1015, 1028 (E.D. Mo. 2000), *aff'd*, 252 F.3d 986 (8th Cir. 2001). For example, the court in *Siharath v. Sandoz Pharm. Corp.*, after stating that the "ruling in" question is one of general causation, notes that general causation is a question of epidemiology or toxicology, not clinical medicine. 131 F. Supp. 2d 1347, 1362-63 (N.D. Ga. 2001), *aff'd*, *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002). Accordingly, an expert called to testify as to specific causation based on a differential diagnosis cannot be expected to provide evidence of general causation.

181. *Siharath*, 131 F. Supp. 2d at 1372.

182. See *id.*

183. *Glastetter*, 252 F.3d at 989; see also *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1209-10 (10th Cir. 2002).

differential diagnosis of adverse drug reactions, is incorrect.¹⁸⁴ Either way, courts such as those deciding *Siharath* and *Glastetter* are effectively converting an otherwise relatively minor factor in a clinician's causality assessment into the dispositive requirement of the court's *Daubert* determination.

Some courts also hold experts to an inappropriately high standard with respect to other factors in the multifaceted differential diagnosis analysis. For example, some courts have expressly stated that a differential diagnosis expert *must* rule out other potential causes before he can offer his opinion that the defendant's product caused the plaintiff's injury.¹⁸⁵ However, just as evidence of a known response pattern is only one of a series of nondispositive factors in the physician's diagnostic consideration, so too is exclusion of diseases, conditions, or other external factors as alternative causes.¹⁸⁶ Only if the expert "utterly fails to consider alternative causes or fails to offer an explanation for why the proffered alternative cause was not the sole cause," should the testimony be excluded as unreliable under *Daubert*.¹⁸⁷

The message here is simple: When a court evaluates the reliability of clinical medical evidence of causation, the expert's inability to offer evidence that any single causal criterion supports his opinion—namely, evidence of general causation—should not render an expert opinion unreliable under the *Daubert* standard.

B. The "Ruling In" Requirement: Sufficiency

Although a differential diagnosis opinion that is not based at least in part on evidence of general causation may be reliable and admissible under *Daubert*, that opinion may be insufficient to allow reasonable jurors to conclude that the drug caused the patient's injury. It is important to note at the outset of this discussion that the question of sufficiency is a question of substantive law, and, under *Erie Railroad Co. v. Tompkins*,¹⁸⁸ is determined by the law of the

184. Note that the stated definition would be correct if by "ruling in all scientifically plausible causes of the plaintiff's injury," these courts acknowledged that clinicians presumptively "rule in" an eligible drug as a possible cause. See *supra* notes 82-83 and accompanying text. Instead, courts equate the "ruling in" requirement with evidence of general causation.

185. See *Glastetter*, 107 F. Supp. 2d at 1027; *Siharath*, 131 F. Supp. 2d at 1362-63; *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1413 (D. Or. 1996).

186. See discussion *supra* Part III.C.

187. *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001) (citing *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265-66 (4th Cir. 1999)).

188. 304 U.S. 64 (1938).

forum state when a federal court sits in diversity jurisdiction. As such, exactly how far a particular differential diagnosis goes toward meeting the plaintiff's burden is a matter of state law,¹⁸⁹ and state law varies considerably with respect to the quantum of evidence required to support a finding of causation.¹⁹⁰

That said, the general rule across jurisdictions is that satisfaction of the causation element requires evidence of both general and specific causation.¹⁹¹ The plaintiff must first prove that, as a general matter, the drug is capable of causing the observed adverse event and then must prove through evidence specific to the plaintiff that the drug is the most likely cause of the plaintiff's observed adverse event.¹⁹² A reliable differential diagnosis provides the latter type of evidence, but it does not necessarily provide the former. Many times, however, the plaintiff offers a differential diagnosis expert without any other expert witnesses, such as an epidemiological expert, to provide evidence of general causation. Thus, even if a jury were to conclude after hearing all of the evidence that the plaintiff's differential diagnosis expert has offered credible evidence of specific causation, the jury still cannot return a verdict for the plaintiff because the plaintiff has offered no evidence of general causation.

Courts should not resolve this problem, however, by excluding the differential diagnosis as unreliable. The evidence is not unreliable; it is merely insufficient to allow reasonable jurors to conclude that the defendant's product caused the plaintiff's injury.¹⁹³ Because substantive law requires the plaintiff to prove general causation, evidence capable of establishing only specific causation is always insufficient to carry the plaintiff's entire burden on causation. Although reliable, a differential diagnosis that stands by itself as to the causation element and that lacks evidence of general causation does not go very far in satisfying the legal element of causation. Simply put, a differential diagnosis that does not "rule in" the drug as a possible cause—because of the legal requirement of general causation—cannot help a jury issue a verdict for the plaintiff as much

189. See, e.g., *Raynor v. Merrell Pharm. Inc.*, 104 F.3d 1371, 1376 (D.C. Cir. 1997).

190. See generally Robin Kundis Craig, *When Daubert Gets Erie: Medical Certainty and Medical Expert Testimony in Federal Court*, 77 DENVER U. L. REV. 69, 71-77 (1999) (describing varying state law standards granting expert evidence of medical causation).

191. See *supra* note 28 and accompanying text.

192. See *supra* note 28 and accompanying text.

193. Some courts also suggest that differential diagnosis evidence, when not supplemented by evidence of general causation, is excludable under *Daubert* because it is irrelevant. See *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1229-39 (D. Colo. 1998); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1413 (D. Colo. 1996); see also *Ambrosini v. Labarraque*, 101 F.3d 129, 145 (6th Cir. 1994) (Henderson, J., dissenting).

as it can help a physician diagnose a patient with an ADR. A reliable differential diagnosis may simply be insufficient in light of the substantive law's general causation requirement. As such, the judge may grant the defendant's summary judgment motion. Accordingly, differential diagnosis opinions that do not provide evidence of general causation, while not necessarily unreliable under *Daubert*, may still be excluded if those opinions constitute the sum total of the plaintiff's causation evidence.

Conversely, a reliable ADR differential diagnosis, standing alone, may under some circumstances (and depending on the applicable substantive law) constitute reliable, relevant, and sufficient evidence of causation. The process of ADR differential diagnosis, contrary to its characterization by some courts,¹⁹⁴ is not as simple as eliminating from a list of possible causes the least likely candidates until one cause remains.¹⁹⁵ It requires consideration of a host of other factors, including some that are specific to the patient (providing evidence of specific causation) and some that concern only the drug or adverse event in question (providing evidence of general causation).¹⁹⁶ Thus, although some ADR differential diagnoses may serve only as reliable evidence of specific causation, some may provide reliable evidence of both specific and general causation. Whether any given differential diagnosis does one or both depends on the type of data available to and incorporated by the physician in making his causality assessment. For example, a differential diagnosis based upon a very strong and reliable showing of temporal proximity, de-challenge, re-challenge, and exclusion of alternative causes, but lacking evidence of a known response pattern or biologic plausibility, could be reliable and admissible evidence of specific causation. That testimony, however, does nothing in terms of proving general causation. On the other hand, differential diagnosis testimony based upon all of the evidence of specific causation, as well as evidence from which the drug can be "ruled in" as a possible cause (e.g., a known response pattern, case studies, epidemiological studies, animal studies, toxicological studies, etc.), may provide not only solid evidence of specific causation but also evidence of general causation. If, after dissecting the expert's differential diagnosis opinion, the court concludes that the expert has provided sufficient evidence "ruling in" the drug as a possible cause, an ADR differential diagnosis alone may provide relevant and

194. See *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001).

195. See generally discussion *supra* Part III.C (laying out the differential diagnosis approaches).

196. See, e.g., *supra* Part III.C.2 fig.2 and accompanying text.

sufficient evidence as to the plaintiff's entire causation burden. In this vein, several courts have explicitly distinguished questions of admissibility from questions of sufficiency in the evaluation of differential diagnosis evidence of causation.¹⁹⁷

C. Why Does the Distinction Matter?

This Note suggests that the exclusion of clinical medical evidence of causation based on the expert's inability to "rule in" the drug as a possible cause should be evaluated in terms of sufficiency. This suggested approach derives from the application of the federal standard for admissibility of expert testimony—most importantly, from *Kumho Tire*—to the differential diagnosis methodology. In many cases, however, the sufficiency approach to the "ruling in" requirement ultimately leads to the same result as the approach taken by courts that require a differential diagnosis expert to "rule in" the drug as a matter of reliability. Specifically, if the expert has not "ruled in" the drug as part of his diagnostic analysis, the result may be summary judgment for the defendant either way. So, why is the distinction between these two approaches even relevant?

First, the suggested approach appropriately recognizes that differential diagnosis evidence may be reliable even without evidence of general causation and, consequently, would be admissible if the plaintiff offers additional testimony on general causation. The trend emerging in recent case law threatens to permanently entrench "ruling in" as a black-letter requirement of all differential diagnosis experts.¹⁹⁸ This requirement may result in the overexclusion of clinical medical evidence of causation when the clinical physician, while experienced in diagnosing and treating patients, is not qualified to

197. In *McCullock v. H.B. Fuller Co.*, the Court of Appeals for the Second Circuit affirmed the admission of testimony from an expert witness who had conducted a differential diagnosis and concluded that plaintiff's polyps were caused by glue fumes inhaled at her workplace. 61 F.3d 1038, 1043 (2d Cir. 1995). No medical literature supported the expert's opinion. *Id.* Citing *Daubert*, the court stated that all of the potential faults in his use of differential diagnosis go to the weight to be accorded his testimony, not to its admissibility. *Id.* at 1043-44. Similarly, the Court of Appeals for the District of Columbia Circuit, when evaluating the expert's opinion that the drug Depo-Provera caused the plaintiff's birth defects, stated that "[t]he fact that several possible causes might remain 'uneliminated' only goes to the accuracy of the conclusion, not the soundness of the methodology." *Ambrosini*, 101 F.3d at 140 (citing *Mendes-Silva v. United States*, 980 F.2d 1483, 1487 (D.C. Cir. 1993)); see also *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001) (holding that the adequacy of the expert's consideration of other possible causes is a question of weight); *Globetti v. Sandoz Pharm. Corp.*, 111 F. Supp. 2d 1174, 1179 (N.D. Ala. 2000) (same).

198. See, e.g., *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1209 (10th Cir. 2002) (holding that differential diagnosis experts must "rule in" the drug as a possible cause and failing to distinguish variations in differential diagnosis opinions); *Glastetter*, 252 F.3d at 989 (same).

testify to general causation. Upon such improper exclusion, a court may grant summary judgment for the defendant based on the absence of specific causation evidence even though the plaintiff has presented one expert who can reliably testify as to general causation and one expert who can reliably testify as to specific causation. Thus, to preserve the value of differential diagnosis testimony in proving specific causation, it is crucial to distinguish between issues that are matters of reliability under *Daubert* and issues that are better conceived of as questions of weight.

Second, this approach more appropriately accounts for the incredible variety in differential diagnoses and better reflects the numerous complex considerations that enter a physician's ADR differential diagnosis. A black-letter rule that the differential diagnostician must in all cases prove general causation is based on an oversimplified conception of the process by which physicians diagnose an adverse drug reaction and is inconsistent with the Court's prescription in *Kumho Tire* that an expert analysis should be evaluated according to "the intellectual rigor that characterizes the practice of an expert in the relevant field."¹⁹⁹

Third, appropriately treating the "ruling in" requirement as what it is—that is, a question of sufficiency—rather than as an admissibility question, allows the court to account for the variety that exists in state substantive law with respect to the general causation issue.²⁰⁰ If, as this Note suggests, the utility of a differential diagnosis that has not "ruled in" the drug in question as a possible cause is indeed a question of weight rather than of admissibility, then the court must consider applicable state substantive law as part of its summary judgment consideration.²⁰¹ If the court's inquiry stops at admissibility, however, there is no room for the court to consider the applicable state law because federal procedural law dictates the results. However, if the court's inquiry moves beyond admissibility to sufficiency, the court can and should consider the evidence offered by the witness in the context of the applicable state substantive law. As an illustration of this point, suppose that state law differs with respect to whether the plaintiff can prove general causation without epidemiological evidence. State A may allow proof of general causation if other causal evidence—for example, de-challenge data, re-challenge data, exclusion of other causes, toxicological studies, case reports, or

199. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

200. See *supra* notes 188-190 and accompanying text.

201. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 257 (1986) (holding that when a federal court determines whether to grant summary judgment, it must consider the particular burden of proof prescribed by the substantive law to be applied).

animal studies—is strong. State B, on the other hand, may require epidemiological proof. Federal admissibility rules cannot account for this difference—that is, if the testimony is reliable under *Daubert* in a federal court sitting in State A, then (in theory), that testimony should be reliable under *Daubert* in a federal court sitting in State B. As a matter of sufficiency, however, a differential diagnosis opinion lacking epidemiological support may be sufficient to carry the plaintiff's burden in State A but would be insufficient to carry that burden in State B. So, to the extent that state substantive law of general causation varies, appropriately categorizing the “ruling in” requirement as a question of weight respects that variation.²⁰²

Finally, as a more general matter, the suggested approach respects the language and intent of the Supreme Court's decision in *Daubert*. The Court explicitly recognized that the Federal Rules of Evidence, provide for admissibility of a broader range of expert testimony than had been admissible under the pre-*Daubert* admissibility test.²⁰³ In *Daubert* itself, the Court stated that the judge's role as gatekeeper does not supplant the traditional tools that ensure that faulty testimony does not unduly influence the jury's conclusions.²⁰⁴ These tools include cross-examination of expert witnesses and the use of summary judgment and directed verdicts.²⁰⁵ According to the express language of *Daubert*, then, courts should avoid using *Daubert*'s reliability prong in lieu of the more traditional tools. Imposing a “ruling in” requirement as a precondition to reliability, as opposed to evaluating the evidence for relevance or sufficiency, is contrary to *Daubert*'s prescription.

In sum, a distinction between admissibility and sufficiency with respect to courts' treatment of the “ruling in” issue is more than mere formalism. Evaluating the differential diagnosis expert's evidence of general causation as a question of weight respects the applicable legal framework under the *Federal Rules of Evidence*, follows the medical framework of ADR differential diagnoses, allows the court to account for the variation in state substantive law of

202. This discussion, in light of the above description of the ADR differential diagnosis methodology, suggests an interesting question: Should courts categorically require distinct evidence of general causation (e.g., epidemiological studies) when clinical physicians may justifiably conclude (albeit under rare circumstances) that a drug is the probable cause of the adverse event without such evidence? The answer to this question cannot be found in *Kumho Tire*, as it is a question of substantive law as opposed to evidence law, but perhaps substantive law on causation could also better reflect the physician's diagnostic processes. That question is beyond the scope of this Note.

203. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 142 (1997).

204. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 595 (1993).

205. *Id.* at 595-96.

causation, and maintains the value of differential diagnosis evidence for the purpose of proving specific causation.

V. CONCLUSION

The admissibility of expert testimony to prove causation is one of the most difficult issues facing trial courts in pharmaceutical product liability litigation. The admissibility of differential diagnosis testimony to prove causation in pharmaceutical products liability cases is particularly difficult because of the absence of a uniform methodology for its practice among physicians. It is therefore important to develop a consistent admissibility standard with respect to this frequently utilized type of expert witness testimony.

One relevant issue that currently divides the federal courts is whether a differential diagnosis opinion, as a prerequisite to admissibility, must “rule in” the drug as a possible cause of the adverse event. The Court in *Kumho Tire* instructed the trial court to evaluate expert testimony according to the standards of a practitioner in the relevant field. Clinicians conduct differential diagnoses according to a multifactorial approach by which no one factor, with few exceptions, is dispositive. Thus, whether an expert has specifically “ruled in” the drug as a possible cause—i.e., provided evidence of general causation—should not be a black-letter requirement of reliability. Instead, even in the absence of any general causation evidence, reliable evidence of specific causation ought to be considered a question of sufficiency under the applicable state substantive law of causation.

Adopting such an approach will help to ensure that cases involving the same product, the same defendant, the same expert witnesses, and the same alleged injury receive substantially similar treatment with respect to determinations of the admissibility of clinical medical evidence of causation. Although Rule 702 and *Daubert* give trial courts significant discretion in making their admissibility determinations, that discretion should not remain entirely unbounded.

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