United States Court of Appeals
FOR THE EIGHTH CIRCUIT

No. 11-1809

Pamela Kuhn, *

Appellant, *

v. *

Wyeth, Inc., formerly known as American Home Products; Wyeth Pharmaceuticals, Inc., formerly known as Wyeth-Ayerst Pharmaceuticals, Inc., *

Appellees. *

Arkansas Trial Lawyers Association, *

Amicus Curiae. *

Appeals from the United States District Court for the Western District of Arkansas.

No. 11-1815

Shirley Davidson, *

Appellant, *

v. *

Wyeth; Wyeth Pharmaceuticals, Inc., *

Appellees. *

Submitted: January 10, 2012
Filed: July 26, 2012

Before WOLLMAN, LOKEN and GRUENDER, Circuit Judges.

WOLLMAN, Circuit Judge.

Pamela Kuhn and Shirley Davidson were prescribed Prempro, a hormone therapy drug comprised of estrogen and progestin and manufactured by Wyeth.[1] Kuhn took Prempro for three years and twenty-eight days; Davidson took it for one year and nine months. Both women developed breast cancer and filed separate lawsuits against Wyeth in the Western District of Arkansas. The complaints alleged, among other things, that the use of Prempro increased the risk of breast cancer and that Wyeth failed to adequately warn of the drug's adverse effects. Both cases were transferred to the Multidistrict Litigation proceedings in the Eastern District of Arkansas, where Wyeth moved to preclude any expert testimony that Prempro use increases breast cancer risk when taken for three years or less.

On behalf of Kuhn and Davidson (collectively, Plaintiffs), Donald F. Austin, M.D., opined that short-term use of Prempro increases the risk of breast cancer. The magistrate judge to whom the evidentiary matter was referred concluded that Dr. Austin's opinion was not sufficiently reliable to meet the admissibility standard set forth in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and thus granted Wyeth's motion. Thereafter, the district court overruled Plaintiffs' objections

[1]This opinion uses the name "Wyeth" to refer to the named defendants, Wyeth, Inc.; Wyeth Pharmaceuticals, Inc.; and Wyeth.

to the Daubert order, granted Wyeth's motion for summary judgment, entered judgment dismissing the two cases, and denied Plaintiffs' post-trial motions.

Kuhn and Davidson appeal. They argue that the magistrate judge abused his discretion in granting Wyeth's motion to preclude expert testimony and that summary judgment based on the preclusion of expert testimony was inappropriate. Kuhn also argues that her case did not qualify as a short-term use case because she had taken Prempro for more than three years. We conclude that the magistrate judge abused his discretion in precluding Dr. Austin's expert testimony, and thus we reverse and remand for further proceedings.

I. Background

A. General Background

Prempro is a combination hormone therapy composed of conjugated equine estrogen and medroxyprogesterone acetate.[2] It is used to treat symptoms of menopause, including vasomotor symptoms and vaginal atrophy. See Physician's Desk Reference 3394 (65th ed. 2011).

[2]Medroxyprogesterone acetate is a progestin. Dorland's Illustrated Medical Dictionary 1137 (31st ed. 2007). Progestin, also called progestogen, is a progestational agent, meaning that it has effects similar to those of progesterone. Id. at 39, 1546. Progesterone is "the principal progestational hormone of the body . . . it prepares the uterus for the reception and development of the fertilized oocyte . . . and maintains an optimal intrauterine environment for sustaining pregnancy." Id. at 1546.

In the 1990s, the National Institutes of Health began studying the effects of hormone therapy drugs as part of its Women's Health Initiative (WHI).[3] More than 160,000 postmenopausal women between fifty and seventy-nine years of age enrolled in a set of clinical trials, including a randomized controlled trial of combined estrogen and progestin (the WHI study). The WHI study included 16,608 participants and assessed the risks and benefits of taking Prempro daily, compared to taking a placebo, in the prevention of certain chronic diseases. Id. at 3400-01. The study was brought to a premature conclusion, however, after the increased risk of breast cancer and certain cardiovascular events exceeded the study's specified benefits. Id. at 3401. As reported in the Journal of the American Medical Association, the WHI study found that the use of estrogen plus progestin increases the risk of breast cancer. Jacques E. Rossouw et al., *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women*, 288 JAMA 321 (2002).

Following the publication of the WHI study results, thousands of women filed lawsuits against Wyeth and other hormone therapy drug manufacturers, alleging that hormone therapy increased the risk of breast cancer and that the companies had failed to warn of that risk. In 2003, the federal lawsuits were consolidated in the Eastern District of Arkansas.

B. Procedural Posture of Kuhn's and Davidson's Lawsuits

In late October 2010, the district court selected Kuhn's and Davidson's cases to go to trial. Earlier that month, the district court had directed the parties to provide "a list of all 'short-term use' Plaintiffs who filed cases in either the Eastern District

[3]"The Women's Health Initiative (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women." Jacques E. Rossouw et al., *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women*, 288 JAMA 321, 321 (2002).

or Western District of Arkansas." Kuhn App. 49. The district court selected Davidson from the list of plaintiffs who had used Prempro for three years or less. The court also selected Kuhn, who had taken Prempro for slightly more than three years and thus was not listed as a "short-term use" plaintiff.

On October 29, 2010, Wyeth advised the court that a short-term use case was proceeding to trial in the District of Puerto Rico and that it planned to file a Daubert challenge to the general causation opinions of the plaintiff's experts. Because Wyeth would file similar challenges in both Puerto Rico and Arkansas, Wyeth suggested that the two courts hear together the Daubert challenge. The courts agreed, and a joint hearing was scheduled for November 29, 2010, in Puerto Rico.

Prior to the hearing, Wyeth filed its motion to preclude expert testimony.[4] Wyeth argued that there existed no reliable scientific basis for Plaintiffs' experts to conclude that taking Prempro for less than three years increases a woman's risk of developing breast cancer. Wyeth relied on the WHI study's report that women who took Prempro for three years or less had fewer incidents of breast cancer than those who took the placebo. It argued that the medical and scientific communities had accepted the WHI study as definitive and that the studies that Plaintiffs would rely upon were methodologically flawed. Moreover, Wyeth cited evidence that the experts Plaintiffs likely would call upon had admitted that Prempro does not increase the risk of breast cancer when taken daily for three years or less.

In opposition, Plaintiffs set forth their position that estrogen plus progestin (E+P) is a "growth promoting agent" that causes cancer-susceptible cells to become

[4]The motion to preclude was filed before case-specific discovery had been completed and before the parties had designated their experts. Accordingly, Wyeth did not challenge Plaintiffs' expert's opinions and methodologies, but rather tried to anticipate their position.

cancerous. Kuhn App. 168. According to Plaintiffs, the promotion effect can be seen in a matter of months. Hormone therapy plaintiffs typically have relied on the WHI study to show that use of Prempro causes an increased risk of breast cancer, but Kuhn and Davidson argued that the study was not powerful[5] enough to detect whether short-term use of Prempro caused an increased risk. Moreover, Plaintiffs argued that the WHI study failed to account for gap time[6] and that subsequent analysis of the study showed an increased risk of breast cancer after two years of Prempro use. Plaintiffs cited a number of observational studies that found an increased risk of breast cancer from E+P use of three years or less.

In its reply, Wyeth argued that Plaintiffs' evidence failed to establish a reliable basis for concluding that short-term use of Prempro increases the risk of breast cancer. Wyeth argued that Plaintiffs' criticisms of the WHI study's findings were misguided, particularly because hormone therapy litigation experts had relied so heavily on the study in the past and because the WHI study was a randomized control study, the "gold standard" of epidemiological studies. Wyeth accused Plaintiffs of "cherry picking" from the relevant observational studies, relying upon the ones that showed an increased risk of breast cancer rather than the great weight of the studies

---

[5]Statistical power is "the probability of rejecting the null hypothesis in a statistical test when a particular alternative hypothesis happens to be true." Merriam-Webster Collegiate Dictionary 973 (11th ed. 2003). In other words, it is the probability of observing false negatives. Power analysis can be used to calculate the likelihood of accurately measuring a risk that manifests itself at a given frequency in the general population based on the sample size used in a particular study. Such an analysis is distinguishable from determining which study among several is the most reliable for evaluating whether a correlative or even a causal relationship exists between two variables.

[6]Gap time is the time from menopause onset to treatment initiation. See Hr'g Tr. 48. Throughout this opinion, Hr'g Tr. refers to the transcript of the January 12, 2011, Daubert hearing.

that showed no increased risk. Moreover, Wyeth argued that the observational studies cited by Plaintiffs were inapplicable because they evaluated hormone therapy formulations other than Prempro and failed to reliably assess participants' duration of use. Wyeth also rebutted the promotion theory, noting that even experts for hormone therapy litigation plaintiffs regarded the theory as insufficient to establish causation.

C. Dr. Austin's Opinion

The day before the evidentiary hearing in Puerto Rico, Plaintiffs filed the declaration of Dr. Austin, who opined that "E+P can, and often does cause clinically detectable breast cancer in short-term durations including a matter of months." Kuhn App. 3905. Dr. Austin set forth in his declaration his standards for reviewing observational studies, including that he would not rely on "underpowered" studies, which he defined as studies that were not likely to identify an association or an effect, if one existed.[7] The declaration also listed the following studies as useful in determining whether a short-term risk existed: The Million Women Study, the French Teachers Study (Fournier), the Li (2000) study, and the Saxena (2010) study.

Dr. Austin also opined that the WHI study's estimate of short-term risk was "quite poor" due to shortcomings "that diminish the estimate of the effect of short-term exposure." Kuhn App. 3902. He explained that the WHI study participants

[7]Dr. Austin also opined that studies employing "ever used" as the measure of exposure were unreliable because they included both women who were taking E+P during the study and those who were not. He explained that because the risk for women who had ceased using E+P would have returned to a baseline risk, those cases were not suitable for assessing short-term risk. Dr. Austin also would not rely upon studies that analyzed conjointly the risk of E+P and E-only because "the causal effect of estrogen alone on the breast is considerably less than that of E+P." Kuhn App. 3900.

were more than ten years past the onset of menopause, meaning that they were much older than the women who typically start hormone therapy. Moreover, the study tended to exclude women who were experiencing moderate hot flashes. According to Dr. Austin, those women were more likely to be estrogen deficient and more likely to be susceptible to the carcinogenic effects of E+P. Dr. Austin also explained that the WHI study's analysis necessarily underestimates the relative risk because approximately forty percent of the participants dropped out of the study and about eleven percent of the placebo group began taking E+P.[8] The study's first report was thus flawed, Dr. Austin opined, because "women were counted as E+P users who actually were not and vice versa." Id. Dr. Austin also listed other shortcomings that led the WHI study to underestimate short-term risk, including that E+P makes breast cancer detection more difficult and that the study included hormone-negative tumors in its results.

D. Daubert Hearings and Order Excluding Dr. Austin's Expert Opinion

Given that Dr. Austin's declaration was filed on November 28, 2010, it was not fully considered at the November 29, 2010, hearing in Puerto Rico. Because no witnesses were called to testify, the hearing was limited to counsels' arguments.

Shortly after the hearing, the district court asked Plaintiffs and Wyeth to address the WHI study's finding that breast cancer incidents were lower among the participants taking Prempro than those who were taking the placebo during the first three years. Specifically, the court asked, "With respect to short term use, please give me a short, pointed, pithy brief explaining what evidence of your's meets the WHI findings on this point." Kuhn App. 3912. Plaintiffs reiterated the arguments they had made in opposition to Wyeth's motion to preclude, including that the WHI study was

[8]During the first three years of the study, twenty-three percent of the participants dropped out.

not powerful enough to detect a short-term risk, that it was not designed to do so, and that other studies established a short-term effect. After reviewing the parties' submissions, the district court ordered a second Daubert hearing and called for live testimony from the parties' experts.

On January 12, 2011, the magistrate judge held a lengthy Daubert hearing. Dr. Austin and Wyeth's expert, Kurt Barnhart, M.D., testified, fielding questions from the attorneys and the court. During the hearing, Dr. Austin conceded that the Li (2000) and Saxena (2010) studies should not have been included in his expert report. Dr. Austin thus based his opinion that short-term use of Prempro causes breast cancer on the Million Women Study, the Fournier study, and the American Cancer Society Study (Calle study).[9]

The magistrate judge issued an order the following week, granting Wyeth's motion to preclude expert testimony.[10] The order stated, "The issue before the Court is whether Dr. Austin, an epidemiologist and Plaintiffs' general causation expert, can testify reliably that short-term use of Prempro increases the risk of breast cancer." Order of January 19, 2011, at 1 (footnote omitted). The magistrate judge ultimately

---

[9]Although the Calle study was not cited in Dr. Austin's expert report, it was cited in Plaintiffs' opposition to Wyeth's motion to exclude, and Dr. Austin testified regarding the Calle study during the January 2011 Daubert hearing. When quoting material from the articles describing these studies, we will cite Kuhn's Exhibit Appendix, hereinafter Ex. App. Those articles include the following: Agnes Fournier et al., *Estrogen-Progestagen Menopausal Hormone Therapy and Breast Cancer: Does Delay From Menopause Onset to Treatment Initiation Influence Risks?*, J. Clinical Oncology (published online ahead of print on Sept. 14, 2009); Eugenia E. Calle et al., *Postmenopausal Hormone Use and Breast Cancer Associations Differ by Hormone Regimen and Histologic Subtype*, Cancer 936 (Mar. 1, 2009); *Breast cancer and hormone-replacement therapy in the Million Women Study*, 362 Lancet 419 (Aug. 9, 2003).

[10]Identical orders were filed in both Kuhn's and Davidson's cases.

excluded the expert evidence because it found that Dr. Austin failed to discredit the WHI study's results and failed to base his opinion on epidemiological studies that "reliably support[ed] his position." Id. at 21.[11] The district court denied Plaintiffs' objections to the order and their motion to reconsider and later granted Wyeth's motion for summary judgment.

II. Discussion

A. Expert Evidence

We review the decision to exclude expert evidence for an abuse of discretion. Gen. Elec. Co. v. Joiner, 522 U.S. 136, 143 (1997); Junk v. Terminix Int'l Co., 628 F.3d 439, 447 (8th Cir. 2010). The opinion of a qualified expert witness is admissible if (1) it is based on sufficient facts or data, (2) it is the product of reliable principles and methods, and (3) the expert has reliably applied the principles and methods to the facts of the case. Fed. R. Evid. 702. The expert's scientific, technical, or specialized knowledge must also "assist the trier of fact to understand the evidence or determine a fact in issue." Id. The district court is thus vested with a gatekeeping function, ensuring that "any and all scientific testimony or evidence admitted is not only relevant, but reliable." Daubert, 509 U.S. at 589. The function also serves "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." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 152 (1999).

"[T]he requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." Daubert, 509 U.S. at 590. The

[11]Wyeth did not challenge Dr. Austin's qualifications or the general practice of relying on epidemiological studies to support an expert opinion.

Supreme Court explained that evidentiary reliability means trustworthiness. Id. at 591 n.9. "Proposed testimony must be supported by appropriate validation—*i.e.*, 'good grounds,' based on what is known." Id. at 590. The standard for judging the evidentiary reliability of expert evidence is "lower than the merits standard of correctness." In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744 (3d Cir. 1994). Proponents of expert testimony need not demonstrate that the assessments of their experts are correct, and trial courts are not empowered "to determine which of several competing scientific theories has the best provenance." Milward v. Acuity Specialty Prods. Grp., 639 F.3d 11, 15 (1st Cir. 2011) (quoting Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co., 161 F.3d 77, 83 (1998)); see Fed. R. Evid. 702 advisory committee's note (discussing 2000 amendments) ("When a trial court, applying this amendment, rules that an expert's testimony is reliable, this does not necessarily mean that contradictory expert testimony is unreliable."). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596.

The Supreme Court identified in Daubert a number of factors that might assist the district court in determining the admissibility of expert evidence: (1) whether the theory or technique applied can be tested, (2) whether the theory or technique has been subject to peer review or publication, (3) the known or potential rate of error, and (4) whether it is accepted in the relevant discipline. Id. at 593-94. It instructed district courts to focus on "principles and methodology, not on the conclusions that they generate." Id. at 595. The Court later recognized that "conclusions and methodology are not entirely distinct from one another." Joiner, 522 U.S. at 146. Accordingly, a district court's focus on principles and methodology "need not completely pretermit judicial consideration of an expert's conclusions." Milward, 639 F.3d at 15 (quoting Ruiz-Troche, 161 F.3d at 81). Expert evidence may be excluded if the court determines "that there is simply too great an analytical gap between the data and the opinion proffered." Joiner, 522 U.S. at 146.

1. WHI Study

Plaintiffs involved in hormone therapy litigation have long relied on the WHI study to prove general causation: that is, that use of Prempro increases the risk of breast cancer. A 2003 article about the WHI study reported:

> For women with no menopausal hormone use before entering the study, invasive breast cancer rates were lower for the initial 2 years in the estrogen plus progestin group compared with placebo, and similar in the third year. In the fourth year and thereafter, invasive breast cancer rates were higher in the estrogen plus progestin group . . . .

Ex. App. 55.[12]

The magistrate judge found that Dr. Austin failed to meet his burden "to present reliable science to support his conclusion regarding the unreliability of the WHI." Order of Jan. 19, 2011, at 9. Plaintiffs, as the proponents of Dr. Austin's testimony, however, do not necessarily have a burden to disprove the WHI study's finding that short-term use of Prempro does not increase the risk of breast cancer. Instead, it is their burden to show that Dr. Austin arrived at his contrary opinion in a scientifically sound and methodological fashion. If they can meet that burden, the question becomes one for the jury to decide. See Bonner v. ISP Techs., Inc., 259 F.3d 924, 930 (8th Cir. 2001) ("[Q]uestions of conflicting evidence must be left for the jury's determination.").

As an initial matter, we note that the magistrate judge did not address Dr. Austin's testimony that women who took Prempro had "[l]ower recorded rates of

---

[12]Rowan T. Chlebowski et al., *Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women*, 289 JAMA 3243 (2003).

breast cancer in the first two years, not three years." Hr'g Tr. 152. Dr. Austin distinguished between annual incidents of breast cancer and cumulative incidents of breast cancer, acknowledging that a graph contained in a 2006 article showed that the placebo group had higher rates of breast cancer during the first three years of the trial. See Ex. App. 19.[13] Dr. Austin explained that the graph measured cumulative incidents, not annual incidents, and that it did not plot individual occurrences:

> Now, it is true that if you look at the number of cases occurring in a year, not cumulative starting from the beginning, but how many in year one, there were more placebo cases; year two, more placebo cases; year three, there were more Prempro cases. So by year three, the Prempro group had caught up and even had surpassed. But if you look at all three years, they were still behind because they hadn't made up for the deficits in year one and two.

Hr'g Tr. 154. The magistrate judge's opinion addresses only Dr. Austin's testimony that the cumulative incidents showed no increase in the breast cancer risk in the first three years. When asked at oral argument before this court whether the magistrate judge had made a mistake in interpreting the graph, Wyeth's counsel responded that he had not because the magistrate judge was interpreting Dr. Austin's testimony, not the underlying evidence, and because Dr. Austin previously had testified that the WHI study shows no increased risk when Prempro is taken for three years or less. Dr. Austin's hearing testimony, however, distinguished between the cumulative and annual incidents, and any conflict with his previous testimony, addressed more fully below, presents issues of credibility.

We conclude that the magistrate judge abused his discretion in deciding that Dr. Austin's criticisms of the WHI study were unfounded and inconsistent with his

---

[13] Garnet L. Anderson et al., *Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin*, Maturitas (2006).

reliance on the study in other hormone therapy cases. When asked by the court how the WHI could be the "gold standard" to show that E+P is a carcinogen but could not be relied upon to show that its short-term use does not increase the risk of breast cancer, Dr. Austin replied that the WHI study was an ideal study design—"the gold standard for what it was designed for"—but that it was designed to show what effect E+P had on heart disease. Hr'g Tr. 69. He explained that although the study monitored incidents of breast cancer, the women were not selected to test whether Prempro causes breast cancer. According to Dr. Austin, this resulted in a study population that was at a much lower risk because (1) the study discouraged the participation of women with moderate menopausal symptoms and (2) the participants had a longer gap time between menopause and beginning hormone therapy treatment than women who begin hormone therapy on their own volition. Dr. Austin went on to explain that, despite its shortcomings, the study showed that E+P causes breast cancer:

> Now, with all of these disadvantages, it still showed that after five years, the E plus P group had a statistically significantly higher risk, and so high that they had to stop the study. So with all those things against it, it still demonstrated cause, even the way they analyzed it, the fact they didn't use gap time, the fact that they picked women that are not really representative of the general population who use E plus P. In spite of all those things, they still found it was a cause and demonstrated it was a cause.

Id. at 69-70. In light of this testimony and its supporting evidence, Dr. Austin's reliance on the WHI study to prove general causation does not foreclose his opinion that the study did not accurately assess the risk of breast cancer associated with the short-term use of Prempro.

The magistrate judge also found that Dr. Austin previously had contradicted his opinion that the WHI study lacked power to detect an increased risk of breast

cancer from short-term use of Prempro. The court noted that "previously, Dr. Austin agreed that WHI, as a clinical trial, had the greatest power when assessing HRT [hormone therapy] and women's health." Order of Jan. 19, 2011, at 7. Dr. Austin now offers a more nuanced opinion than he has in the past, setting forth the foundation for his present concerns, for as he explained,

> Well, that's because there's two separate concepts. One is, is it a cause or not? And the other one is, what is the risk estimate? And observational studies have different strengths and weaknesses on those two points. They're not as good for demonstrating cause and effect, but they're much better at estimating the size of the risk. So different study designs are used to try to do different things, and in this [WHI], even though it wasn't designed to see what the effect on breast cancer was, it did, and the causal nature was demonstrated and it's irrefutable.

Hr'g Tr. 71-72.

Wyeth will certainly challenge Dr. Austin's credibility based on his previous testimony, including his agreement that the WHI study would be a "good study to look at in determining whether a certain duration of exposure to Prempro increases the risk of breast cancer." Id. at 145. But his previous reliance on and testimony regarding the WHI study does not render his opinion inadmissible, as it was not his burden to disprove the WHI's finding that short-term use of Prempro does not increase the risk of breast cancer.

Finally, in determining that Dr. Austin failed to support his criticisms of the WHI study, the magistrate judge found that Dr. Austin's opinions were "hastily formed in an attempt to overcome overwhelmingly reliable evidence to the contrary." Order of January 19, 2011, at 9. Dr. Austin testified that the short-term use issue was presented to him shortly before the Daubert hearing in Puerto Rico. He wrote the expert report in approximately five hours, with the assistance of Plaintiffs' counsel.

The magistrate judge's concerns about Dr. Austin's opinions, however, go to his credibility as a witness, not to the admissibility of his testimony as an expert. Wyeth argues that, like the expert testimony in In re TMI Litigation, 193 F.3d 613 (3d Cir. 1999), Dr. Austin's testimony should be excluded based on his reliance on Plaintiffs' counsel. In that case, however, the expert relied on medical history summaries prepared at the direction of plaintiffs' counsel, which the court found unreliable. Id. at 697-98. Here, Dr. Austin relied on epidemiological studies that, at most, were compiled for him by Plaintiffs' counsel. Unlike the medical history summaries, the supporting observational studies provide adequate foundation for Dr. Austin's testimony.

2. Supporting Observational Studies

Dr. Austin ultimately relied on three observational studies to support his opinion: the Calle study, the Million Women Study, and the Fournier study. The magistrate judge analyzed each study separately and concluded that the studies failed to reliably support Dr. Austin's position. On appeal, Kuhn and Davidson argue that the magistrate judge usurped the role of factfinder and that any problems with the studies go to the weight of the evidence, not to the studies' validity. Wyeth responds that the magistrate judge properly determined that the studies were insufficient to support Dr. Austin's opinion because there existed too great an analytical gap between the underlying studies and Dr. Austin's opinion, see Joiner, 522 U.S. at 146-47, and because in relying on the studies, he failed to employ the rigorous methods that he uses in other contexts, see Kumho Tire Co., 526 U.S. at 152.

a. Calle Study

Dr. Austin relied on the Calle study, a study of 67,754 American women that "examined prospectively the relation between postmenopausal hormone use and the risk of incident of breast cancer . . . ." Ex. App 32. When the participants enrolled

in 1992, they completed self-administered mailed questionnaires that collected information regarding demographic, medical, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent in 1997, 1999, 2001, and 2003 "to update exposure information and to ascertain newly diagnosed cancers." Id. According to the authors, "[i]nformation regarding postmenopausal hormone use was collected at the time of enrollment and on all follow-up questionnaires." Id. at 33. Women with unknown type or duration of hormone use were excluded from the analysis. The authors observed no increase in risk with use of E+P in the first two years of use. "However, we observed a significant increase in risk for both types of breast cancer at 2 to 3 years of use . . . and all years thereafter." Id. at 37.

The magistrate judge found the study unreliable because "there was no way to measure how it accounted for previous use [of hormone therapy]" and because it failed to meet Dr. Austin's criteria to characterize exposure "carefully and accurately." Order of Jan. 19, 2011, at 17. Plaintiffs argue that the magistrate judge erred in finding that the study failed to monitor exposure and duration of use. We agree. As set forth above, the study explains that women with unknown type or duration of hormone use were excluded from the analysis and that the authors gathered information regarding hormone therapy use at the time of enrollment and again in 1997, 1999, 2001, and 2003.[14] Consistent with the study, Dr. Austin testified that he believed that information regarding breast cancer occurrence and duration of hormone therapy use was collected in each follow-up questionnaire.

[14]The participants returned self-administered questionnaires to report their hormone use, and Dr. Austin testified that self-reporting lends itself to some error. We note that the WHI study assessed some breast cancer risk factors and initial reports of cancer outcomes by self-administered questionnaires. Ex. App. 53. Based on the reliance on the WHI study by all the parties in this case, we conclude that self-reporting alone does not render a study unreliable in this context.

b. Foreign Studies

Dr. Austin also relied on two foreign studies: the Million Women Study from England and the Fournier study from France. "The Million Women Study was set up to investigate the effects of specific types of [hormone therapy] on incident and fatal breast cancer." Ex. App. 165. As its name suggests, the study involved more than one million women between fifty and sixty-four years of age, including more than 20,000 participants who took medroxyprogesterone acetate combined with conjugated equine estrogen, the same formulation as Prempro. It found that combined estrogen and progestin therapy increased the risk of breast cancer and that "[r]esults varied little between specific oestrogens and progestagens or their doses; or between continuous and sequential regimens." Id. Specifically, the study reported:

> Other than the substantial difference between the effects of oestrogen-only and oestrogen-progestagen combinations, these results suggest no large variations between the effects of specific oestrogens (equine oestrogen and oestradiol) or between specific progestagens (medroxyprogesterone acetate, norgestrel, and norethisterone). They also suggest that results on the risk of breast cancer for the specific constituents used in the Women's Health Initiative trial do not differ materially from the results for other oestrogen-progestagen combinations.

Id. at 172. Upon joining the Million Women Study, the participants reported information regarding their hormone therapy use including their "ever use; current use; age at first and last use; total duration of use; and the name of the proprietary preparation used most recently and duration of its use." Id. at 165. The participants thus reported their duration of use when they enrolled, but the study did not measure their use after enrollment. Instead, it found that "[t]he breast cancers were diagnosed on average 1.2 years after recruitment" to the study. Id. at 167.

A table in the Million Women Study shows an elevated relative risk of breast cancer among women who reported using estrogen plus progestagen for less than one year. Because the study measured duration of use at enrollment rather than diagnosis, the precise duration of use by those women diagnosed with breast cancer was unknown. Dr. Austin suggested that by adding the average 1.2 years from enrollment to diagnosis to the less than one year of use, the study supported his short-term use opinion because it showed an elevated risk in less than 2.2 years. He testified that, "we have very large numbers here, and small amounts of misclassifications don't really make a lot of difference." Hr'g. Tr. 27.

Dr. Austin also relied upon the Fournier study, which investigated "whether the relation between estrogen-progestagen menopausal hormone therapy (EP-MHT) and breast cancer risk varies according to the delay between menopause onset and treatment initiation." Ex. App. 83. More than 50,000 postmenopausal French women participated in the study. The results suggested that "in recent users of some EP-MHT, the timing of treatment initiation modulates the risk of breast cancer: short durations (≤2 years) of use were associated with significant increases in risk—with the exception of MHT containing progesterone—when initiated in the 3-year period following menopause, but not when initiated later."[15] Id. at 86-87. In other words, as Dr. Austin explained, the study showed an increased risk of breast cancer in women taking hormone therapy for less than two years when the women began hormone therapy shortly after the onset of menopause.

French women typically use a different type of hormone therapy than American women. In the Fournier study's cohort, "the estrogenic component consisted almost exclusively of estradiol compounds, with progesterone and dydrogesterone as the

[15]The Fournier study observed that using progesterone may be safer than other progestagens, but that the finding "needs to be confirmed in other settings." Ex. App. 88.

most frequently associated progestagens." Id. at 87. Although relatively few participants took formulations comprised of conjugated estrogens combined with medroxyprogesterone acetate, like Prempro, more than one hundred participants using hormone therapy comprised of progestagens were diagnosed with breast cancer.

> With more than 100 participants diagnosed with breast cancer among those using EP-MHT (containing progestagens other than progesterone or dydrogesterone) for 2 years or less, we found significant doubling in risk when the MHT began within 3 years of menopause compared with MHT never use. For the other durations of use, estimates of the WHI and ours are consistent.
>
> Our results of breast cancer risks increased even with relatively short durations of some EP-MHT are consistent with epidemiological studies that found significant increases in risk for current or recent short-term (<5 years) use of EP-MHT, although some did not find significant increases.

Id. In an editorial commenting on the Fournier study, Leslie Bernstein, M.D., thus wrote, "[I]t will be important for other cohorts that focus on use of HT in United States populations to evaluate breast cancer risk associated use immediately after menopause." Id. at 28.[16]

Dr. Austin acknowledged that the Fournier study did not separate Prempro's formulation from other hormone therapy formulations. He testified that medroxyprogesterone acetate is combined only with conjugated estrogens and that its risk estimates are similar to those of other of synthetic progesterones that are combined with other estrogens. "Since we look at them separately and they're similar, I think no violence is done to the analysis by combining them." Hr'g Tr. 119.

---

[16]Leslie Bernstein, *Combined Hormone Therapy at Menopause and Breast Cancer: A Warning—Short-Term Use Increases Risk*, J. Clinical Oncology (published online ahead of print on Sept. 14, 2009).

On cross-examination, however, Dr. Austin was confronted with an expert report he authored in 2007, wherein he opined that estradiol and conjugated equine estrogen should be considered separately "to determine if they have statistically different long-term effects." Id. at 117. When asked if that same analysis should be done to determine the short-term effects, Dr. Austin responded, "It's the most ideal, yes. . . . Fournier did not do that." Id. Dr. Austin also acknowledged that the Fournier study provided no separate analysis of Prempro formulation at three years or less.

The magistrate judge concluded that the foreign studies did not reliably support Dr. Austin's opinion because most participants in the studies took hormone therapy formulations other than Prempro and because the studies did not analyze Prempro separately from other hormone therapy formulations after three years.[17] With respect to the Million Women Study, the magistrate judge determined that the study's failure to accurately assess years of use rendered the study unreliable. The court found Dr. Austin's suggestion to add the "average underestimate of 1.2 years" use irreconcilable with "his position that when looking at short-term use, one must be quite precise in the analysis." Order of Jan. 19, 2011, at 16.

Although the foreign studies have important limitations, they nonetheless provide support for Dr. Austin's opinion. As set forth above, the Million Women Study explained that there exists no material difference in risk among the combined estrogen and progestin hormone therapy formulations, including Prempro. With this finding, and its finding that less than one year's use of combined hormone therapy increases the risk of breast cancer, the Million Women Study provides support for Dr. Austin's opinion regarding short-term use. Likewise, the differences between

[17]The Million Women Study considered separately participants' use of Prempro for five years or less and found that the relative risk of breast cancer was 1.62. The magistrate judge found this analysis unhelpful because "the issue before the Court involves usages of around three years or fewer; the MWS did not separately assess Prempro for around three years or fewer." Order of Jan. 19, 2011, at 15.

Prempro and the French combined hormone therapy formulation do not render the study unreliable to support Dr. Austin's opinion.

Citing Glastetter v. Novartis Pharmaceuticals Corp., 252 F.3d 986 (8th Cir. 2001) (per curiam), Wyeth argues that Dr. Austin's testimony relating the European formulations to the American formulations constitutes an unsupported assumption. In Glastetter, the plaintiff's experts hypothesized that the chemical at issue, bromocriptine, "may behave like its chemical cousins," ergot alkaloids, which were known to cause a condition that was a known risk factor for the plaintiff's injury. Id. at 989-90. We concluded that the "generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value." Id. at 990. Here, Dr. Austin presented evidence that the Million Women Study considered estrogen plus progestin hormone therapy formulations separately and found little difference between the effects of the different formulations.[18] His testimony was thus not a "generic assumption," but rather was supported by the study's findings.

Along with the different formulations, we recognize that the Million Women Study's computation of duration of use is imprecise and that the "average underestimate of 1.2 years" is disputed. Like the formulation differences, the duration issues, however, do not create so great an analytical gap between the data and the opinion as to render the opinion inadmissible.

As set forth above, the magistrate judge relied on Dr. Austin's testimony in other cases and his earlier statements to find that the foreign studies did not reliably support his opinion. Specifically, the court found that the studies failed to meet Dr.

[18]We note that the magistrate judge did not address the study's finding that results varied little between specific estrogen plus progestin hormone therapy formulations.

Austin's criteria of (1) accurately characterizing exposure to the drug, (2) identifying the specific drug formulations, and (3) analyzing the Prempro formulation separately. At the hearing, Dr. Austin acknowledged that, ideally, a study would measure exposure precisely and analyze the Prempro formulation separately, but he did not concede that the studies on which he based his opinion were unreliable. Instead, he explained,

> [The foreign studies] give us information that other studies don't because of their large number, and the fact that, like in this one, where they were able to eliminate the gap time, they are imperfect in that they mix together drugs of similar types so that it loses its specificity. But it does gain in the fact that they have large numbers for the things that we're interested in with short-term use. So although there's no study that's perfect that I'm aware of for answering this specific question, the fact that these two studies are consistent in their findings is important.

Hr'g Tr. 51-52. Although the foreign studies are not perfect, they provide useful information that, along with the Calle study, provides an adequate foundation for Dr. Austin's opinion. His prior testimony may well call his credibility into question, but it does not prove that he failed to follow his own general practice or that he relied on unfounded assumptions in his analysis. Cf. Junk, 628 F.3d at 448 (holding that the expert's "failure to follow his own general practice and his reliance on unfounded assumptions in his comparative method created 'too great an analytical gap' between his opinion and the data on which it relied" (quoting Joiner, 522 U.S. at 146); Fireman's Fund Ins. Co. v. Canon U.S.A., Inc., 394 F.3d 1054, 1059 (8th Cir. 2005) (noting that the sudden reversal of opinion regarding the meaning of burn pattern evidence "seriously undermine[d] the reliability of the experts' opinions").

c. Supporting Observational Studies Sufficient to Support Dr. Austin's Opinion

Dr. Austin's testimony is admissible because the studies upon which he relied were sufficient to support his opinion that short-term use of Prempro increases the risk of breast cancer. Taken together, the Calle study and the foreign studies constitute appropriate validation of and good grounds for Dr. Austin's opinion. The studies' limitations may be presented to the jury, and Dr. Austin's reliance on the studies may be tested through the traditional means of cross examination and presentation of contrary evidence.[19]

3. Wyeth's "Cherry Picking" Allegation

Wyeth argues that Dr. Austin "cherry picked" the Calle study and the two foreign studies from a wealth of studies showing no increased risk of breast cancer from short-term Prempro use. Wyeth compares this case to Norris v. Baxter Healthcare Corp., 397 F.3d 878 (10th Cir. 2005), in which the defendant presented at least seventeen epidemiological studies in support of its contention that silicone breast implants do not cause disease. The plaintiffs in Norris offered no epidemiological studies to support their contrary position, instead relying upon differential diagnosis and case studies. The Norris court concluded that "[p]laintiff's experts' differential diagnoses and case studies are unreliable because they assume what science has largely shown does not exist-a causal connection between silicone

[19]In his expert report, Dr. Austin opined that E+P is "both a promoter and a growth stimulant, meaning its effect is both to cause new cancers to occur, and to cause [estrogen receptive] tumors to grow more quickly." Kuhn App. 3904. Accordingly, he opined that the effect of E+P on cell proliferation is "almost immediate." Id. Because we conclude that Dr. Austin's opinion is adequately supported by epidemiological studies, we do not address Plaintiffs' argument that "basic biology confirms the causal associations shown by several epidemiological studies." Kuhn Br. 70.

breast implants and disease." Id. at 886. Unlike those experts, Dr. Austin has presented reliable epidemiological evidence to support his opinion that short-term use of Prempro increases the risk of breast cancer. There may be several studies supporting Wyeth's contrary position, but it is not the province of the court to choose between the competing theories when both are supported by reliable scientific evidence.

B. Summary Judgment

The grant of summary judgment in favor of Wyeth was based on the preclusion of Dr. Austin's opinion. Because we hold Dr. Austin's opinion is admissible, we reverse the order granting summary judgment.

III. Conclusion

We reverse the orders granting Wyeth's motions to preclude expert testimony and for summary judgment. Because our reversal is based on the conclusion that Dr. Austin's opinion is admissible, we do not reach the merits of Kuhn's argument that the Daubert order did not apply to her because she had used Prempro for more than three years. The case is remanded for further proceedings.

LOKEN, Circuit Judge, dissenting.

Early in its lengthy analysis, the district court described the "methodology" of plaintiffs' expert, Dr. Donald Austin:

> according to Dr. Austin, his short-term use report was written in about five hours at the behest and assistance of Plaintiffs' counsel. Dr. Austin testified that he had never really thought about the short-term use issue before Plaintiffs' counsel presented it to him shortly before the recent *Daubert* challenge in Puerto Rico. He testified, "[i]t had never been

> raised as an issue to me, is there an important, a biologically important and clinically important risk within three years. It was just not an issue that I had thought about."

After thoroughly reviewing the bases for Dr. Austin's opinion in an analysis the court now finds statistically faulty in some respects, the district court concluded:

> Dr. Austin contends that short-term use of Prempro causes breast cancer, and cites five studies to support his conclusions. However, he conceded the following: two of the studies he admitted should not have been included in his report (Li (2000) and Saxena (2010)); two of the studies primarily involved drug combinations that were not Prempro (MWS [Million Women Study], French Teachers Study [Fournier]); and one of the studies did not reliably track duration of use, which is essential when making a short-term use causation finding (Calle (2009)). With no studies to reliably support his position, along with a failed effort to discredit WHI results, Dr. Austin's opinion on short-term use causation [is] not sufficiently reliable to be admissible under *Daubert*.

Like the district court in General Electric Co. v. Joiner, 522 U.S. 136 (1997), the district court excluded opinion testimony of plaintiffs' only expert. In my view, the district court's Daubert analysis is supported by the record and properly focused on the gate-keeping function mandated by the Supreme Court and by Rule 702. We review that ruling for abuse of discretion and must affirm unless it is "manifestly erroneous." Joiner, 522 U.S. at 142. We may not subject the ruling to "a more searching standard of review" because it was "'outcome determinative.'" Id. at 142-43. I conclude that, like our sister circuit the Supreme Court reversed in Joiner, the court has "appl[ied] an overly 'stringent' review to that ruling [and] failed to give the trial court the deference that is the hallmark of abuse of discretion review." Id. at 143. Accordingly, I respectfully dissent.
