SUPERIOR COURT OF NEW JERSEY
APPELLATE DIVISION
DOCKET NO. A-4952-16T1

IN RE: ACCUTANE LITIGATION

Argued January 7, 2020 – Decided January 17, 2020

Before Judges Fisher, Accurso and Rose.

On appeal from the Superior Court of New Jersey, Law Division, Atlantic County, Case No. 271 (MCL).

Bruce Daniel Greenberg argued the cause for appellants (Seeger Weiss LLP, attorneys; David Robert Buchanan, on the brief); (Mary Jane Bass (Beggs & Lane) of the Florida bar, admitted pro hac vice, on the brief); (Lite DePalma Greenberg, LLC, attorneys; Bruce Daniel Greenberg, on the brief); (Weitz & Luxenberg, PC, attorneys; Peter Samberg, on the brief); (Eisbrouch Marsh, LLC, attorneys; David Lloyd Eisbrouch, on the brief); (Cohen Placitella & Roth, PC, attorneys; Jillian Audrey Smith Roman, on the brief); (Cohn Lifland Pearlman Herrmann & Knopf, LLP, attorneys; Leonard Zee Kaufman, on the brief); (D'Arcy Johnson Day, attorneys; Andrew James D'Arcy, on the brief); (Folkman Law Offices, PC, attorneys; Paul C. Jensen, on the brief); (Hutton & Hutton Law Firm, LLC, attorneys; Blake A. Shuart, on the brief); (Lopez McHugh, LLP, attorneys; Michael Scott Katz, on the brief); (Meyerson & O'Neill, attorneys; Jack A. Meyerson, on the brief); (Mintz & Geftic, attorneys;

Bryan H. Mintz, on the brief); (Nagel Rice, LLP, attorneys; Andrew L. O'Connor, on the brief); (Marc J. Bern & Partners LLP, attorneys; Diane M. Coffey, on the brief); (Oshman & Mirisola, LLP, attorneys; Ted Oshman, on the brief); (Parker Waichman LLP, attorneys; Jerrold S. Parker, on the brief); (Perskie & Fendt, PC, attorneys; Robert Fendt, on the brief); (Rheingold, Valet, Rheingold, McCartney & Giuffra, LLP, attorneys; Morris Dweck, on the brief); (Sugarman Law LLC, attorneys; Barry Sugarman, on the brief); (The D'Onofrio Firm LLC, attorneys; Lou D'Onofrio, on the brief); (The Ferrara Law Firm LLC, attorneys; Michael A. Ferrara, Jr., on the brief); (The Lanier Law Firm, PLLC, attorneys; Richard D. Meadow, on the brief); (The Miller Firm, LLC, attorneys; Tayjes Matthew Shah, on the brief); (The Orlando Firm, PC, attorneys; Roger W. Orlando, on the brief); (Wilentz Goldman & Spitzer, PC, attorneys; Gregory Shaffer, on the brief); (Williams Cuker Berezofsky, LLC, attorneys; Esther Berezofsky, on the brief); (Jacob Fuchsberg Law Firm, attorneys; Christopher Michael Nyberg, on the brief); (Locks Law Firm, attorneys; Michael Andrew Galpern, on the brief); and (Lieff Cabraser Heimann & Bernstein, LLP, attorneys; Adam Herbert Weintraub, on the brief).

Paul W. Schmidt (Covington & Burling LLP) of the District of Columbia bar, admitted pro hac vice, argued the cause for respondents Hoffmann-La Roche Inc. and Roche Laboratories Inc. (Gibbons, PC, Dughi Hewit & Domalewski, PC, and Paul W. Schmidt, attorneys; Natalie H. Mantell, Kim Marie Catullo, Russell L. Hewit, Paul W. Schmidt, Michael X. Imbroscio (Covington & Burling LLP) of the District of Columbia bar, admitted pro hac vice, and Colleen M. Hennessey (Peabody & Arnold) of the Massachusetts bar, admitted pro hac vice, on the brief).

PER CURIAM

This multicounty litigation consists of thousands of cases filed by plaintiffs who alleged they developed inflammatory bowel disease, either in the form of ulcerative colitis or Crohn's disease as a result of their use of Accutane (isotretinoin). In 2015, the trial judge granted a defense motion to exclude two plaintiffs' experts – Dr. Arthur Kornbluth, a gastroenterologist, and Dr. David Madigan, a statistician – from testifying that Accutane, a prescription acne drug manufactured by defendants Hoffman-La Roche Inc., and Roche Laboratories, Inc., can cause Crohn's disease. We reversed that determination, In re Accutane Litigation, 451 N.J. Super. 153 (App. Div. 2017), but the Supreme Court reversed our judgment and upheld the trial judge's exclusion of the expert testimony of Drs. Kornbluth and Madigan, In re Accutane Litigation, 234 N.J. 340, 348 (2018).

In early 2017, the trial judge conducted a ten-day Kemp[1] hearing and, for the reasons expressed in a thorough written opinion, granted a defense motion to bar the expert testimony of Dr. David Sachar, a gastroenterologist, and Dr. April Zambelli-Weiner, an epidemiologist, about whether Accutane caused

[1] Kemp ex rel. Wright v. State, 174 N.J. 412 (2002).

plaintiffs' ulcerative colitis. A later order identified the 3231 claims that were dismissed as a result of that determination.

Plaintiffs filed a timely appeal, which we stayed while awaiting the Supreme Court's decision concerning Drs. Kornbluth and Madigan's opinions. Once the Court rendered its decision, we requested supplemental briefs as to whether the Daubert[2] factors of expert admissibility adopted by the Court ought to be applied here, and if so, whether the existing record was sufficient or a remand was required. In their supplemental briefs, the parties agreed that the Daubert factors applied and a remand was not required.

After close examination of the record in light of the guidelines and factors adopted in the Supreme Court's recent Accutane decision, we conclude that although Drs. Sachar and Zambelli-Weiner appear to be qualified, the judge did not abuse his discretion in excluding their testimony because the opinions of these experts incorporated the same methodological defects identified by the Court, including the disregarding of eight of the nine epidemiological studies in favor of animal studies and case reports. And, even though the data in the epidemiological studies is slightly more supportive of an association between Accutane and ulcerative colitis, there is not enough evidence of a difference

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

between these subtypes of irritable bowel disease (IBD) to warrant excluding the causation experts' testimony on Crohn's disease while allowing similar expert causation testimony as to ulcerative colitis.

No one disputes that the cause or causes of ulcerative colitis and Crohn's disease remain for now unknown, but the diseases share the same core symptoms, and the biological mechanism for both diseases is essentially the same. So, despite the differences between the matter at hand and the rulings regarding Drs. Kornbluth and Madigan, we conclude that the trial judge did not exceed his discretion in excluding Dr. Sachar's and Dr. Zambelli-Weiner's causation testimony.

I

We start by agreeing with the parties that the Supreme Court's recent Accutane decision is applicable even though it was decided after the trial judge's ruling here. In civil cases, judicial decisions are "presumed to apply retroactively." In re Contest of Nov. 8, 2011 Gen. Election of Office of N.J. Gen. Assembly, 210 N.J. 29, 68 (2012) (quoting Fischer v. Canario, 143 N.J. 235, 243 (1996)). To avoid that presumption, a party must show the decision established a new principle "either by overruling clear past precedent on which litigants may have relied . . . or by deciding an issue of first impression whose

resolution was not clearly foreshadowed." Coons v. Am. Honda Motor Co., Inc., 96 N.J. 419, 427 (1984) (quoting Chevron Oil Co. v. Hudson, 404 U.S. 97, 106 (1971)).

The Supreme Court's Accutane decision, which came down while this appeal was pending, did not alter N.J.R.E. 702 or 703, nor would its holding "produce substantial inequitable results if applied retroactively." Coons, 96 N.J. at 427 (quoting Chevron Oil Co., 404 U.S. at 107). Instead, in reaching its decision, the Supreme Court "perceive[d] little distinction between Daubert's principles regarding expert testimony and our own, and believe[d] that its factors for assessing the reliability of expert testimony will aid our trial courts in their role as the gatekeeper of scientific expert testimony in civil cases." Accutane Litigation, 234 N.J. at 347-48. The Court merely "reconcile[d] our standard under N.J.R.E. 702, and relatedly N.J.R.E. 703, with the federal Daubert standard to incorporate its factors for civil cases." Id. at 348. And so, we will apply the Court's recent holding to the issues presented in this appeal.

An expert's opinion on causation in prescription drug cases may be admitted when "based on a sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field." Id. at 349-50 (quoting Rubanick v. Witco Chem. Corp., 125

N.J. 421, 449 (1991)). In cases "involving novel theories of causation," a court must review the "data and studies relied on by experts proffering an opinion in order to 'determine whether the expert's opinion is derived from a sound and well-founded methodology that is supported by some expert consensus in the appropriate field.'" Id. at 350 (quoting Landrigan v. Celotex Corp., 127 N.J. 404, 417 (1992)). A court must also assess "the soundness of the proffered methodology and the qualifications of the expert." Rubanick, 125 N.J. at 454. The focus must be "solely on principles and methodology, not on the conclusions that they generate." Kemp, 174 N.J. at 426 (quoting Daubert, 509 U.S. at 594-95).

Given the adversarial setting and full record before it, the Court took the opportunity to "clarify and reinforce the proper role for the trial court as the gatekeeper of expert witness testimony," Accutane Litigation, 234 N.J. at 388, and explained that when it adopted the more relaxed approach for causation expert testimony in toxic tort and medical cause-effect expert testimony, it envisioned

> the trial court's function as that of a gatekeeper – deciding what is reliable enough to be admitted and what is to be excluded. Those are not credibility determinations that are the province of the jury, but rather legal determinations about the reliability of the expert's methodology.

[Ibid.]

In performing that function, "the trial court is responsible for advancing the truth-seeking function of our system of justice, while still allowing for new or developing opinions on medical causation that may not yet have gained general acceptance." Id. at 389. In essence, the trial court "is the spigot that allows novel expert testimony in areas of evolving medical causation science, provided the proponent of the expert can demonstrate that the expert adheres to scientific norms in distinct ways that we have identified." Ibid.

This gatekeeping role "requires care." Ibid. The Court emphasized that the trial court "must ensure compliance with the requirement of 'some expert consensus that the methodology and the underlying data are generally followed by experts in the field,'" ibid. (quoting Rubanick, 125 N.J. at 450), "distinguish scientifically sound reasoning from that of the self-validating expert," Landrigan, 127 N.J. at 414, and disallow "unsubstantiated personal beliefs," Kemp, 174 N.J. at 427. "Properly exercised, the gatekeeping function prevents the jury's exposure to unsound science through the compelling voice of an expert." Accutane Litigation, 234 N.J. at 389.

The Court emphasized that it expects trial courts "to assess both the methodology used by the expert to arrive at an opinion and the underlying data

used in the formation of the opinion" to "ensure that the expert is adhering to norms accepted by fellow members of the pertinent scientific community." Id. at 396-97. In short, "[m]ethodology, in all its parts, is the focus of the reliability assessment, not outcome." Ibid. "It is not for a trial court to bless new 'inspired' science theory; the goal is to permit the jury to hear reliable science to support the expert opinion." Id. at 397; cf. Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996) (observing that "the courtroom is not the place for scientific guesswork, even of the inspired sort").

The Court therefore concluded that New Jersey law and Daubert were "aligned in their general approach to a methodology-based test for reliability. Both ask whether an expert's reasoning or methodology underlying the testimony is scientifically valid." Accutane Litigation, 234 N.J. at 397 (citing Daubert, 509 U.S. at 594-95 and Rubanick, 125 N.J. at 449). "[B]oth standards look to whether that reasoning or methodology properly can be applied to facts in issue." Ibid. The Court, thus, "[d]istilled" the Daubert factors into the following "general factors":

> 1) Whether the scientific theory can be, or at any time has been, tested;
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> 2) Whether the scientific theory has been subjected to peer review and publication, noting that publication is one form of peer review but is not a "sine qua non";

> 3) Whether there is any known or potential rate of error and whether there exist any standards for maintaining or controlling the technique's operation; and
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> 4) Whether there does exist a general acceptance in the scientific community about the scientific theory.
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> [Id. at 398.]

These factors, according to the Court, "dovetail with the overall goals of our evidential standard and . . . provide a helpful – but not necessary or definitive – guide for our courts to consider when performing their gatekeeper role concerning the admission of expert testimony." Id. at 398-99. The factors, the Court held, should be incorporated for use by our courts, with no obligation to apply the federal case law or the case law of any other state that adopted the factors. Id. at 399; see Dreier, Karg, Keefe & Katz, Current N.J. Products Liability & Toxic Torts Law § 9:4-2(b) (2019) (recognizing that application of the Daubert factors may serve to strengthen the court's role as a gatekeeper).

The Court concluded that its "view of proper gatekeeping in a methodology-based approach to reliability for expert scientific testimony requires the proponent to demonstrate that the expert applies . . . scientifically recognized methodology in the way that others in the field practice the methodology." Accutane Litigation, 234 N.J. at 399-400. When a proponent fails to demonstrate "the soundness of a methodology, both in terms of its

approach to reasoning and to its use of data, from the perspective of others within the relevant scientific community, the gatekeeper should exclude the proposed expert testimony on the basis that it is unreliable." Id. at 400.

II

The trial judge conducted a Kemp hearing over the course of ten days, during which he heard the testimony of plaintiffs' experts: Drs. Sachar and Zambelli-Weiner. Defendants also provided the testimony of experts: Dr. Steven Goodman, an epidemiologist and biostatistician, and Dr. Maria Oliva-Hemker, a gastroenterologist. At the hearing's conclusion, the trial judge entered an order that precluded the expert testimony of plaintiffs' experts. In his written decision, the judge examined the expert testimony and scientific studies, set forth the relevant legal standard for the admission of expert testimony, and found that plaintiffs' experts' testimony failed to meet that standard.

In ascertaining whether the expert testimony was based on a "sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field," Rubanick, 125 N.J. at 449, the judge correctly considered "whether other scientists in the field use similar methodologies in forming their opinions and also should consider other factors that are normally relied upon by medical professionals." He

explained that the "appropriate inquiry is not whether the [c]ourt thinks that the expert's reliance on the underlying data was reasonable, but rather whether comparable experts in the field would actually rely on that information." He identified "[t]he trial court's role" as essentially requiring a determination "whether the expert's opinion is derived from a sound and well-founded methodology" and is supported by "some expert consensus."

Applying that standard, the judge found unsound the experts' methodology. He found that Dr. Zambelli-Weiner appeared to have had "very limited exposure" to issues related to pharmaco-epidemiology, and frequently disregarded "the fundamentals of the scientific method, particularly, the medical-evidence hierarchy." For example, the judge found that Dr. Zambelli-Weiner's inclusion of the widely-criticized Sivaraman[3] non-peer-reviewed

[3] This was a case-control questionnaire study comprising 509 subjects summarized in a published abstract. Susil Sivaraman et al., Risk of Inflammatory Bowel Disease from Isotretinoin: A Case-Control Study, Am. J. Gastroenterol. (Oct. 2014). The authors found that antibiotic exposure prior to IBD diagnosis was associated with a risk for ulcerative colitis but not Crohn's disease. After adjusting for antibiotic exposure, the risk for IBD following isotretinoin exposure lost statistical significance; the authors concluded the "[r]isk of IBD from isotretinoin is modulated by antibiotic exposure."

abstract in her meta-analysis and the exclusion of the Rashtak[4] study bespoke "litigation-driven science." The judge also found that the expert's reliance on case reports (including those contained in the scientific literature) of anecdotal information and her characterization of that evidence as "quite compelling" demonstrated a "disregard for the hierarchy of scientific evidence" because case reports "are at the very bottom of the medical-evidence hierarchy." Her reliance on challenge/dechallenge/rechallenge reports in case reports as evidence of a causal relationship also ignored "the evidence-based medical hierarchy" and was inconsistent with the nature of the disease, which waxes and wanes.

[4] In this retrospective, single-center cohort study, the authors reviewed the electronic medical records of Mayo Clinic patients who sought treatment for severe acne. Shadi Rashtak et al., Isotretinoin Exposure and Risk of Inflammatory Bowel Disease, 150 JAMA Dermatol. 1322 (Dec. 2014). They selected 1078 patients; 576 were exposed to isotretinoin and 502 never received isotretinoin or received it after their diagnosis of IBD. The authors found that IBD developed less frequently in the isotretinoin-exposed group versus the non-exposed group. The authors reported the event counts for ulcerative colitis and Crohn's disease, noting that, "[i]nterestingly, a subsequent diagnosis of IBD was found in only 5 of 576 exposed patients (1 with Crohn disease and 4 with ulcerative colitis) compared with 13 of 502 nonexposed patients (3 with Crohn disease and 10 with ulcerative colitis)." The authors observed that even though "these results may be due to chance given the small number of IBD cases, the anti-inflammatory and immune-modulating effects of isotretinoin may be worth exploring." They wrote, "clinicians should not unnecessarily avoid prescribing this effective acne therapy for largely unfounded or meager associations with IBD."

The judge next found that her testimony regarding the rate ratio (RR) and odds ratio (OR) results from the epidemiological studies was inconsistent with the standards set forth in the Federal Judicial Center and National Research Council's Reference Manual on Scientific Evidence (Nat'l Acad. Press 3d ed. 2011) at 602, 612 (Reference Manual), about the degree of strength necessary to reflect a true causal relationship.[5] He found that Dr. Zambelli-Weiner failed to follow the scientific methodology in placing "unswerving reliance" on only one study, the Crockett study,[6] which had never been replicated. In conducting

[5] The commonly used method for measuring association is relative risk or rate ratio (RR) in cohort studies, and odds ratio (OR) in case-control studies. Reference Manual at 568-69. This is also referred to as the "point estimate." Accutane Litigation, 234 N.J. at 360 n.17 (citing Reference Manual at 292). RR is the ratio of the incidence rate of disease in exposed individuals to the incidence rate in unexposed individuals. Reference Manual at 566. OR is the ratio of the odds that one with the disease was exposed to the odds that one without the disease was exposed. Id. at 568. For most purposes, the RR from a cohort study is "quite similar" to the OR from a case-control study. Id. at 625.

[6] The Crockett study – Seth D. Crockett et al., Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study, 105 Am. J. Gastroenterol. 1986 (Sept. 2010) – is the only study that found a statistically significant association between isotrentinoin and ulcerative colitis. It is a case-control study using a large insurance claims database from the United States comprised of 8189 cases of IBD (4428 ulcerative colitis, 3664 Crohn's disease and 97 IBD unspecified). The study population included men and women of all ages. Sixty of the subjects were exposed to isotretinoin (24 cases and 36 controls). The controls were matched by age, gender, geographic region, health plan, and enrollment. The authors of the Crockett study concluded that ulcerative colitis

her meta-analysis, Dr. Zambelli-Weiner improperly excluded – according to the trial judge – the results of the Rashtak study without more information about the participants and failed to submit her study for peer review.

The judge found that Dr. Sachar's methodology was unsound because he "frequently disregard[ed] the fundamentals of the scientific method," that he

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was "strongly associated with previous isotretinoin exposure," but there was "no apparent association" between isotretinoin and Crohn's disease. Increasing the dose of isotretinoin was associated with an elevated risk of ulcerative colitis; the risk of ulcerative colitis was highest in those exposed to the drug for more than two months. The authors concluded that:

> [t]his case-control study demonstrates a possible causal association between isotretinoin use and UC [ulcerative colitis], but not CD [Crohn's disease]. Temporality, effect specificity, and increasing effects for both intensity and duration of therapy provide further evidence of causation. As this is the first epidemiological study to describe a positive association between isotretinoin and UC, these results should be confirmed by additional studies in other populations. Although the absolute risk of developing IBD after taking isotrentinoin is likely quite small, clinicians prescribing isotretinoin as well as prospective patients should be aware of this possible association.
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> [(Emphasis added).]

In a 2010 published interview, one of the authors of the Crockett study explained that the conflicting results of the Crockett studies with another study indicated that "causality cannot be firmly established."

significantly deviated from the accepted scientific methodology in elevating case reports and animal studies above epidemiological studies. The judge also found Dr. Sachar's "cavalier use of disparaging language toward the peer-reviewed treatises of other scientists [was] indicative of the 'hired gun' mentality." Notably, in the judge's view, Dr. Sachar characterized the Alhusayen study[7] as "insane" during his testimony but then relied on it in his written report. He similarly exhibited, according to the judge, a "lack of

[7] Raed O. Alhusayen et al., Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study, 133 J. Invest. Dermatol. 907 (Oct. 2012). During the twelve-year study period comprised of approximately 1.7 million subjects between age twelve to twenty-nine, the authors identified 46,922 subjects treated with isotretinoin, 184,824 subjects treated with topical acne medication, and 1,526,946 untreated subjects. As adjusted for potential confounders including age, gender, socioeconomic status, medical care and prescription drug use, the authors of the Alhusayen study found no statistically significant association between isotretinoin use and IBD, or the subtypes, ulcerative colitis and Crohn's disease. The authors said they had conducted separate analyses of Crohn's disease and ulcerative colitis because the diseases had different pathogeneses and concluded that "[o]ur primary analyses found no association between isotretinoin and IBD." In a prespecified secondary analysis, the authors of the Alhusayen study found that, as adjusted, isotretinoin use was associated with IBD among individuals twelve to nineteen years old, but that topical acne medication was also associated with IBD among individuals in that same age group. They concluded that this result suggested a "possible association between IBD and acne itself," and recommended additional research "to explore this possibility."

'restraint' in his role as an advocate," by testifying that he "guess[ed]," without having done a calculation, that the Etminan study[8] was underpowered.

Further, Dr. Sachar had not published a peer-reviewed article or proposed "a hypothesis on the purported causal association between isotretinoin and IBD, nor do any of the peer-reviewed articles cited by him propose such a hypothesis." Absent a hypothesis pulling together lines of evidence, the judge found Dr. Sachar's opinions lacked theoretical coherency:

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[8] This is a 2012 case-control study using a large United States health claims database. Mahyar Etminan, Isotretinoin and Risk of Inflammatory Bowel Disease: A Case-Control Study (2012). The author selected 20,237 cases of IBD – 11,426 with ulcerative colitis, 8868 with Crohn's disease – and 60,136 controls, and the controls were matched by age and entry to the cohort. The study found a statistically significant negative association between Accutane and IBD, no association between previous tetracycline use and IBD, and did not separately analyze ulcerative colitis and Crohn's disease. The author concluded that the "results of this study are consistent with a protective effect of isotretinoin use and IBD," although they acknowledged that it was "possible that the study is subject to confounding bias." The Etminan 2013 study is a nested case-control study comprised of 45,500 subjects, using the same insurance database as the Crockett study. Mahyar Etminan et al., Isotretinoin and Risk for Inflammatory Bowel Disease, 149 JAMA Dermatol. 216 (Feb. 2013). The authors formed a cohort of women age eighteen to forty-six, who had received prescriptions for oral contraceptives over an eight-year period. They identified 2159 IBD cases (1056 ulcerative colitis and 1103 Crohn's disease) and matched them with 43,180 controls. The authors found no statistically significant association between isotretinoin and ulcerative colitis or Crohn's disease. The authors stated that their study differed from the Crockett study in that they nested their cohort in a population of women, all of whom had been prescribed oral contraceptives, thereby reducing the risk of confounding bias.

> It seems likely that one of the reasons Dr. Sachar has declined to subject his opinion on isotretinoin to the greater scientific community is that he knows that in the peer-review process he would have to be "rigorously honest" (Reference Manual, page 50). In the courtroom he can point to, and highlight, various threads of marginal proofs such as animal studies (including zebrafish larva) and case reports, and cite them as "compelling evidence." Yet Dr. Sachar knows that in the peer-review process his editors will scrutinize the plausibility of the opinions on which he stands quite alone in the scientific community, and force him to defend his contentions or risk rejection of his article.

That said, the judge recognized that Dr. Sachar's failure to write a peer-reviewed article supporting his causation opinion "is not in and of itself, disqualifying to an expert in a Kemp [h]earing." But that failure did "bespeak[] an expert who expresses a different set of opinions in the courtroom than he is willing to express to his colleagues." The judge also concluded, in quoting Reference Manual at 786, that "'[i]f something is not published in a peer-reviewed journal, it scarcely counts.'" "The scientific community has little regard for opinions confined to the courtroom." The judge found that Dr. Sachar had

> more than ample time to organize his thoughts and present them for scrutiny by the scientific community. He refuses to provide both his colleagues and this [c]ourt with a clear articulation of why and how isotretinoin can cause [ulcerative colitis]. Absent the whys and wherefores of his opinion on the purported

> causal relationship between isotretinoin and IBD, Dr. Sachar's opinion is little more than conjecture, and a net opinion.

Thus, the judge found that Dr. Sachar's and Dr. Zambelli-Weiner's testimony "suffer[ed] from multiple deficiencies, the most salient of which is their selectivity of the evidence relied upon in disregard of the medical-evidence hierarchy." Although Dr. Sachar was considerably more qualified than Dr. Zambelli-Weiner, the judge found both utilized a methodology "slanted away from objective science and in the direction of advocacy." Notably, while some of the epidemiological studies showed a positive association between Accutane and ulcerative colitis, the experts were unable to point to any consistent showing across the studies. The judge concluded that the opinions expressed by the experts were "motivated by preconceived conclusions, and that they have failed to demonstrate 'that the data or information used were soundly and reliably generated and are of a type reasonably relied upon by comparable experts'" (quoting Rubanick, 125 N.J. at 477).

With these views, and aided by expert testimony offered by the defense, the judge barred plaintiffs' experts from testifying – a determination that led to the dismissal of these 3231 claims.

III

As the Supreme Court emphasized in its recent opinion, appellate courts must apply an abuse of discretion standard when viewing such determinations. Accutane Litigation, 234 N.J. at 391; see also Townsend v. Pierre, 221 N.J. 36, 52 (2015); Hisenaj v. Kuehner, 194 N.J. 6, 12 (2008). For the same essential reasons that led the Court to reinstate the trial judge's exclusion of the expert testimony of Drs. Kornbluth and Madigan, we affirm the judge's similar disposition here.

The Court upheld the trial judge's exclusion of Drs. Kornbluth and Madigan's expert testimony, finding their "methodology was unsound" essentially because they did not "interpret the relevant data and apply it to the facts of this case as would other experts in the field." Accutane Litigation, 234 N.J. at 346. There, 2076 plaintiffs claimed they developed Crohn's disease from using Accutane. Id. at 346, 371. All published epidemiological studies concluded there was no causal relationship between Accutane and IBD and between Accutane and Crohn's disease. Id. at 346.[9] None of the studies found

[9] Medical societies, including the American Academy of Dermatology, filed an amicus brief in support of defendants' position stating that "[i]n the past decade, numerous epidemiological studies have established that isotretinoin use does not increase the risk of IBD."

a statistically significant adjusted association between the drug and Crohn's disease. Only one small study found a statistically significant unadjusted positive association, two found a positive association, and four found a statistically insignificant negative association, one of which found a statistically significant association for a protective effect.

Like the record before us, the testimony at the Kemp hearing that concerned Drs. Kornbluth and Madigan "focused intently" on the epidemiological studies. Id. at 352. Those experts substantially relied on only the unadjusted results of the Sivaraman study, a very small study presented in poster form at a medical conference. Id. at 392-94. They disputed the conclusions of the other larger studies, calling them flawed and lacking in value. Ibid. Having rejected the evidence and conclusions of those epidemiological studies, Dr. Kornbluth relied on the same facts and other forms of data at issue here, including animal studies, case reports, causality assessments, internal Roche documents, and his own biological mechanism hypotheses to support his conclusion. Id. at 358.

In addressing the epidemiological studies, the Supreme Court discussed in detail the general principles and methodology used in conducting such studies, as set forth in the Reference Manual. Id. at 352-55. The Court stated

that when using epidemiological studies in legal matters, three basic questions arise in assessing a study's methodological soundness:

> 1. Do the results of an epidemiologic study or studies reveal an association between an agent and disease?
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> 2. Could this association have resulted from limitations of the study (bias, confounding, or sampling error), and, if so, from which?
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> 3. Based on the analysis of limitations in Item 2, above, and on other evidence, how plausible is a causal interpretation of the association?
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> [Id. at 354 (quoting Reference Manual at 554).]

In affirming the trial court's ruling regarding Drs. Kornbluth and Madigan, the Court identified several methodological defects that are similarly applicable here.

First, the Court found that Drs. Kornbluth and Madigan both "employed a methodology whereby they disregarded eight of nine epidemiological studies and relied on case reports and animal studies to support their opinion." Id. at 392. Case reports are clearly "at the bottom of the evidence hierarchy," and courts from other states have been "skeptical of their value in proving causation . . . ." Id. at 392-93 (quoting Reference Manual at 724). Notably, the Court found that "initial animal studies may have suggested a possible causal connection between Accutane and Crohn's disease, but since that time a uniform

body of epidemiological evidence has dispelled any such theory." Id. at 393. The Court explained that it did "not mean to suggest that animal studies and case reports can never be relied upon for forming an opinion on causation," but the Court found "ample support for the trial court's determination that it was not proper to do so here in light of the uniform body of epidemiological evidence." Ibid. Similarly, Dr. Sachar relied extensively on non-epidemiological evidence, including animal studies, individual case reports that contained challenge/dechallenge/rechallenge events, causality assessments, internal Roche documents, biological plausibility hypotheses, and clinical studies, despite the almost uniform body of epidemiological evidence that has found no association between Accutane and ulcerative colitis. In doing so, he failed to apply the methodology followed by other experts in the field. Accutane Litigation, 234 N.J. at 393-96; Rubanick, 125 N.J. at 450-52.

For example, in this case, Dr. Sachar testified that he uses the scientific hierarchy of evidence "to the extent" that he does not reject it but does not "rely on it blindly." He explained that although an epidemiological study is generally considered a higher level of evidence, a "case report with . . . good challenge/rechallenge evidence is better than a lousy epidemiological study." The Reference Manual at 723-24, however, provides that "[w]hen ordered from

strongest to weakest, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational studies, physiological studies, and unsystematic clinical observations." Accutane Litigation, 234 N.J. at 355. "Evidence at the bottom of the hierarchy may sometimes be 'the first signals of adverse events or associations that are later confirmed with larger or controlled epidemiological studies.'" Ibid. (quoting Reference Manual at 724). As in the Court's recent Accutane decision, Dr. Sachar did not follow the accepted scientific methodology in elevating these lower forms of evidence.

Second, the Supreme Court observed that Drs. Kornbluth and Madigan had applied a selective form of reasoning in relying on only one small study, even as they disagreed with the author's ultimate conclusion. Id. at 393-94. In this way, according to the Court, "plaintiffs' experts dismissed published studies examining thousands of subjects as underpowered and biased in favor of relying on portions of a single unpublished study that examined 509 total subjects." Id. at 394. Similarly, Dr. Sachar extensively relied on a portion of the Crockett study, which found a strong statistically significant association between Accutane and ulcerative colitis, even though he strongly disagreed with the authors' conclusion on the absence of any link between Accutane and Crohn's

disease. The Crockett study is a smaller study than others and the study's authors concluded there was only a "possible causal association" between Accutane and ulcerative colitis, results that "should be confirmed." Importantly, those findings were published nearly ten years ago and have never been replicated. In fact, the Etminan study, which used the same database as the Crockett study (using a cohort of women prescribed oral contraceptives), found no statistically significant association between Accutane and ulcerative colitis.

In exclusively relying on one study that has never been replicated, Dr. Sachar failed to follow accepted scientific methodology. See Cadarian v. Merrell Dow Pharm., Inc., 745 F. Supp. 409, 412 (E.D. Mich. 1989) (expert could not rely on a study where the authors "concluded that the results could not be interpreted without independent confirmatory evidence"). In this regard, the Reference Manual notes:

> Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists.
>
> The need to replicate research findings permeates most fields of science. In epidemiology, research findings often are replicated in different populations. Consistency in these findings is an important factor in making a judgment about causation. Different studies that examine the same exposure-disease relationship

> generally should yield similar results. Although inconsistent results do not necessarily rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality.
>
> [Reference Manual at 604 (footnotes omitted).]

And Dr. Sachar dismissed the other published studies examining thousands of subjects as underpowered or otherwise flawed, another position that requires skepticism about his methodology. Accutane Litigation, 234 N.J. at 394.[10] Instead, Dr. Sachar was willing to rely on single case reports and small animal studies. Moreover, the two published meta-analyses, and defendants' expert's unpublished analysis, which were performed to increase the power of the studies, found no statistically significant association between Accutane and ulcerative colitis. In her meta-analysis, Dr. Zambelli-Weiner found a statistically significant association, but her analysis did not conform to the scientific methodology because she did not include all relevant studies.

Third, the Supreme Court found that the trustworthiness of the methodology employed by Drs. Kornbluth and Madigan was undermined by

[10] Dr. Sachar, unlike Dr. Kornbluth (regarding Crohn's disease), did not find that the studies were flawed for failing to account for ulcerative colitis's "prodrome," i.e., the period between the onset of a disease's symptoms and the actual diagnosis. Accutane Litigation, 234 N.J. at 358.

internal inconsistencies, including their refusal to examine the Rashtak and Fenerty[11] studies because those studies did not report on Crohn's disease, while relying on case reports not specific to Crohn's disease and studies performed on animals incapable of developing IBD. Id. at 394-95. Dr. Sachar similarly refused to consider those same studies, even though he relied on animal studies, causality assessments, internal Roche documents, and published scientific literature that was not specific to ulcerative colitis. None of the animals in the studies relied on by Dr. Sachar can develop IBD, or the subtypes ulcerative colitis and Crohn's disease. Id. at 395.

[11] We briefly described the Rashtak study earlier. See n.4, above. The authors of the Fenerty case-control study, using a Medicaid dataset, identified 176,889 acne patients who had no prior IBD diagnosis. Sarah Fenerty et al., Impact of Acne Treatment on Inflammatory Bowel Disease, 68 J. Am. Acad. Dermatol. 6751 (Apr. 2013). They followed these patients for four years, during which 324 patients were diagnosed with Crohn's disease and 194 patients were diagnosed with ulcerative colitis. They found that there was no association between the use of isotretinoin and IBD, and that oral antibiotic use was associated with a decreased risk of the disease. The authors set forth that this association was comparable for both ulcerative colitis and Crohn's disease, but they did not separately report the confidence interval findings for the subgroups. They concluded "[t]here is an inverse association between oral antibiotics and the development of IBD in acne patients with a dose-response relationship. Clinicians and prospective patients should be cognizant of the lack of a causal relationship between isotretinoin for acne and the development of IBD."

Fourth, Dr. Sachar, like Dr. Kornbluth, organized his testimony to support a personal view that a causal association existed between Accutane and ulcerative colitis through use of the Hill guidelines,[12] including the temporal relationship, dose-response relationship, biological plausibility, and cessation of exposure. Id. at 395-96. But, as the Court recognized, "those guidelines are invoked only after an association between an agent and a particular disease has been determined to be present; their pointed purpose is to determine whether a detected association reflects true causality, it is not to create an association that has not already been detected through appropriate studies." Id. at 396 (citing Reference Manual at 598-99). The criteria were only meant to be applied after "an association has been found between exposure to a particular agent and development of a specific disease." Id. at 354. In its recent decision, the Supreme Court observed that "not one of the epidemiological studies found any statistically significant association between Accutane and Crohn's disease." Id. at 396.

The epidemiological studies also do not support an association between exposure to Accutane and ulcerative colitis. When considering the admissibility

[12] Austin Bradford Hill, The Environment and Disease: Association or Causation?, 58 Proc. of the Royal Soc'y of Med. 295 (1965).

of the testimony of Drs. Kornbluth and Madigan, the Supreme Court observed that not one of the studies found a statistically significant association between Accutane and Crohn's disease (only one study found an unadjusted statistically significant association between Accutane and Crohn's disease, three found a positive association, and four found a negative association). Id. at 396. All of the studies, except Crockett, found no statistically significant association between Accutane and ulcerative colitis. And all of the studies – except Crockett, which has not been replicated – concluded there is no association between Accutane and IBD or the subtype ulcerative colitis. Like the circumstances in the Supreme Court's recent decision, Dr. Sachar improperly used the Hill guidelines to create an association that had not been detected by the studies.

In short, there is little to distinguish between the Court's disposition of the trial judge's ruling as to Drs. Kornbluth and Madigan, and the disposition under review here. The epidemiological data is only slightly more favorable in the case of ulcerative colitis, but it does not support a finding that there is an association, much less a causal association, between Accutane and ulcerative colitis. Significantly, the data has become even less favorable since the prior judge's March 2014 decision, where she considered six epidemiological studies,

and one meta-analysis. Since then, two more epidemiological studies and another meta-analysis pushed the estimate even further away from an association between Accutane and ulcerative colitis. Despite that data, Dr. Sachar continued to rely on the same lines of evidence that the Court found problematic in its recent decision. In adhering to the trial judge's gatekeeping role as described in Accutane, Dr. Sachar's testimony on ulcerative colitis was similarly unreliable.

There is also no evidence that the subtypes of IBD are so different as to warrant exclusion of the expert testimony of Drs. Kornbluth and Madigan and the admission of the expert testimony of Drs. Sachar and Zambelli-Weiner here. It is undisputed that the cause of IBD, including the subtypes ulcerative colitis and Crohn's disease, is unknown, thereby complicating proof of the causative link. It is also undisputed that the diseases share the same core symptoms and some of the same risk factors, and in fact, patients are often misdiagnosed. Significantly, Dr. Sachar admitted that the biological mechanism for both ulcerative colitis and Crohn's disease is essentially the same. He also admitted that he did not have enough information to conclude that Accutane operates in opposite directions as a risk factor for ulcerative colitis and Crohn's disease.

* * *

In the final analysis, we find little to distinguish between the record here concerning the proffered expert testimony of Drs. Sachar and Zambelli-Weiner, and the record that led the Supreme Court to reinstate the trial judge's exclusion of the expert testimony of Drs. Kornbluth and Madigan. The trial judge did not abuse his discretion in barring the expert testimony in question. Instead, he engaged in the very same type of gatekeeping which the Supreme Court approved in its prior decision.

Affirmed.