

NOT FOR PUBLICATION WITHOUT THE
APPROVAL OF THE APPELLATE DIVISION

SUPERIOR COURT OF NEW JERSEY
APPELLATE DIVISION
DOCKET NO. A-3789-07T3

VIRGINIA PALAZZOLO,
Administrator Ad Prosequendum
of the Estate of Christopher
Tremain, VIRGINIA PALAZZOLO,
individually, and JAMES
PALAZZOLO,

Plaintiffs-Appellants,

and

ELENOR WRIGHT, AMANDA
CALLAIS by her Guardian Ad Litem,
LORI CALLAIS, and LORI CALLAIS
and ALVIN CALLAIS, individually,
and JESSICA BOERS, ARIE BOERS,
and JANE BOERS,

Plaintiffs,

v.

HOFFMAN LA ROCHE, INC., and
ROCHE LABORATORIES, a member of
the Roche Group,

Defendants-Respondents.

Argued December 14, 2009 - Decided February 3, 2010

Before Judges Rodríguez, Reisner and Chambers.

On appeal from the Superior Court of New Jersey,
Law Division, Essex County, L-5498-99.

Michael J. Ryan argued the cause for appellants (Dell'Italia, Affinito & Santola, attorneys; David P. Affinito, on the brief).

Colleen M. Hennessey (Peabody & Arnold, L.L.P.) of the Massachusetts bar, admitted pro hac vice, argued the cause for respondents (Gibbons P.C. and Ms. Hennessey attorneys; Ms. Hennessey and Matthew J. Griffin, of counsel and on the brief; Michelle M. Bufano, on the brief).

PER CURIAM

Plaintiffs, Virginia Palazzolo, individually and as administrator ad prosequendum of her son's estate, and James Palazzolo, appeal from a trial court order dated January 16, 2008, precluding their general causation expert from testifying, and from a March 11, 2008 order dismissing their complaint on summary judgment. We affirm in part and remand this matter to the trial court.

I

Much of the relevant evidence will be discussed later in this opinion. However, in summary, plaintiffs filed a product liability and consumer fraud complaint against defendants Hoffman La Roche, Inc. and Roche Laboratories, claiming that Accutane, a drug used to treat acne, caused their family member Christopher Tremaine, to develop depression which led to his suicide. They contended that at the time of Christopher's death in 1997, Accutane should have carried a warning label concerning

the possibility that the drug could cause depression and suicide.

As one element of their product liability cause of action, plaintiffs needed to establish "general causation," by showing that Accutane can cause depression and suicide.¹ See Kemp v. State, 174 N.J. 412, 417 (2002); Coffman v. Keene Corp., 133 N.J. 581, 594 (1993). On that issue, plaintiffs retained Dr. James Bremner, an expert in psychiatry and nuclear medicine. Bremner had already done some research on the connection between Accutane (isotretinoin) and depression. Plaintiffs paid Bremner to undertake a further study. There is no dispute that the study was commissioned specifically for use in this litigation.

In the study at issue, Bremner and a team of other scientists used positron emission tomography (PET) technology to compare changes in brain metabolism between two groups of subjects being treated for acne. One group was receiving antibiotic treatment and the other group was being treated with Accutane. In brief, before and after they underwent the acne treatment, the subjects were injected with a radioactive glucose, and their brains were scanned with a PET machine. The PET machine took images of "slices" of designated portions of

¹ Accutane is a chemical known as isotretinoin or 13-cis-retinoic acid; it belongs to a family of drugs known as retinoids, a Vitamin A derivative.

the brain, and allowed scientists to measure brain metabolism by detecting the glucose, which is used in brain activity.

According to Bremner, the PET study demonstrated that the subjects treated with Accutane showed decreased metabolism in the orbital frontal cortex, a portion of the brain associated with depression. He published a peer-reviewed article about the study in a scientific journal, describing his methodology and his conclusions. J. Douglas Bremner, M.D., et. al., Functional Brain Imaging Alterations in Acne Patients Treated With Isotretinoin, 162 Am. J. Psychiatry 983 (May 2005). Based on the PET study as well as other scientific evidence, Bremner issued an expert report opining that Accutane can cause depression and suicide.

Defendant challenged the admissibility of Bremner's expert report, and the trial judge determined to hold a pre-trial hearing under N.J.R.E. 104. Prior to holding the Rule 104 hearing, the judge made clear to counsel that one of the primary purposes of the hearing was to allow Bremner to explain to the court what he believed the PET scan established. In particular, the judge questioned how the PET scan study, which all parties agreed did not diagnose depression, nonetheless allowed Bremner to reach the conclusion that Accutane caused depression. The

judge expressed the need to have Bremner explain his methodology and his conclusions, and the relationship between the two.

During the lengthy Rule 104 hearing, which spanned several months, Bremner was repeatedly confronted with problems in the PET study, including missing data, inaccurate data, and deviations from the methodology he claimed to have followed. As a result, in the middle of the Rule 104 hearing, the court permitted Bremner to re-work his study data and issue a supplemental expert report and allowed defendant to re-depose him. When the hearing resumed, Bremner admitted that certain underlying data, known as "Bmax numbers" which had been used to make critical calculations in the study, was not retrievable from its computerized format, and some of the data concerning individual study subjects was still inaccurate.

In a lengthy oral opinion placed on the record on November 8, 2007, the trial judge explained her conclusion that Dr. Bremner would not be permitted to testify as an expert witness on general causation. Key to her decision was her conclusion that the PET study was the linchpin of Dr. Bremner's expert opinion that Accutane "is capable of causing depression." The PET study was specifically designed to show that "Accutane has an effect on the brain" and specifically on the orbital frontal cortex. Because the judge determined that Dr. Bremner's opinion

would stand or fall on the PET study, her opinion focused entirely on that study.

After reviewing in great detail the contradictions in Dr. Bremner's testimony about how he undertook the PET study, what data he relied on, and the lack of documentation to support his conclusions, she concluded that

Dr. Bremner did not follow his own methodology and has failed to persuade this Court that his conclusion in the case that Accutane causes depression was reached after following his own methodology and/or following any methodology that the Court could view as a scientific methodology. . . . it's not the uniqueness of the conclusion but rather, the lack of methodology in reaching it that has led the Court to . . . this ruling.

II

Our review of the trial court's summary judgment decision is de novo, using the same standard employed by the trial judge. See Atl. Mut. Ins. Co. v. Hillside Bottling Co., 387 N.J. Super. 224, 230 (App. Div.), certif. denied, 189 N.J. 104 (2006); Brill v. Guardian Life Ins. Co. of Am., 142 N.J. 520, 540 (1995). However, we review the trial judge's decision to exclude expert testimony for abuse of discretion. Hisenaj v. Kuehner, 194 N.J. 6, 12 (2008).

We begin our review by considering the law as it relates to the admissibility of expert testimony in a case of this type.

[I]n toxic-tort litigation, a scientific theory of causation that has not yet reached general acceptance may be found to be sufficiently reliable if it is based on a sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field. The evidence of such scientific knowledge must be proffered by an expert who is sufficiently qualified by education, knowledge, training, and experience in the specific field of science. The expert must possess a demonstrated professional capability to assess the scientific significance of the underlying data and information, to apply the scientific methodology, and to explain the bases for the opinion reached.

[Rubanick v. Witco Chemical Corp., 125 N.J. 421, 449 (1991).]

"Rubanick changed the focus of the inquiry from the scientific community's acceptance of the substance of the [expert's] opinion to its acceptance of the methodology and reasoning underlying it." Clark v. Safety-Kleen Corp., 179 N.J. 318, 337 (2004). In Rubanick, the Court focused on the expert's use of a sound methodology, rather than on the conclusions the expert reached using that methodology:

In determining if the scientific methodology is sound and well-founded, courts should consider whether others in the field use similar methodologies. "What is necessary is that the expert arrived at his causation theory by relying upon methods that other experts in his field would reasonably rely upon in forming their own, possibly different opinions, about what caused the patient's disease."

[Rubanick, supra, 125 N.J. at 449-450
(citation omitted).]

However, the Court also cautioned that the trial judge is not to second-guess the scientific community in deciding if the expert's methodology was sound, but rather should limit its determination to whether the methodology is accepted by others in the scientific community:

We do not believe that in determining the soundness of the methodology the trial court should directly and independently determine as a matter of law that a controversial and complex scientific methodology is sound. The critical determination is whether comparable experts accept the soundness of the methodology, including the reasonableness of relying on this type of underlying data and information. Great difficulties can arise when judges, assuming the role of scientist, attempt to assess the validity of a complex scientific methodology. Nevertheless, the trial court here "independently reviewed" each of the thirteen studies on which Dr. Balis relied, and decided that they "do not say what plaintiff's expert concludes." In engaging in such an analysis, the court substituted its own assessment of the studies for that of an acknowledged expert. . . . "[T]he interpretation of the data . . . is the function of the qualified expert [C]ourts should be loath to determine whether the particular expert has properly relied upon data which experts in the field generally rely on." Thus, the inquiry is not the reliability of the expert's ultimate opinion nor is it whether the expert thought his or her own reliance on the underlying data was reasonable, nor whether the court thinks that the expert's reliance was reasonable. The proper inquiry is whether

comparable "experts in the field [would] actually rely" on that information.

[Id. at 451-52 (1991) (citations omitted; emphasis added).]

The trial court must, however, evaluate the expert's reasoning to determine whether it is based on the methodology and the evidence obtained by using that methodology, or whether the expert is expressing a net opinion:

In resolving these issues, the trial court should not substitute its judgment for that of the relevant scientific community. The court's function is to distinguish scientifically sound reasoning from that of the self-validating expert, who uses scientific terminology to present unsubstantiated personal beliefs.

[Landrigan v. Celotex Corp., 127 N.J. 404, 414 (1992).]

"Rule 104 hearings are intended to determine admissibility, not credibility." Hisenaj, supra, 194 N.J. at 24. Therefore, attacks that only go to the weight a jury might give an expert's opinion are beside the point, as long as the expert used a methodology recognized in the scientific community and can explain the data produced using that methodology and the conclusions drawn from the data. "Expert testimony should not be excluded merely because it fails to account for some condition or fact that the opposing party considers relevant." State v. Dreher, 302 N.J. Super. 408, 464 (App. Div.), certif.

denied, 152 N.J. 10 (1997), cert. denied, 524 U.S. 943, 118 S. Ct. 2353, 141 L. Ed. 2d 723 (1998).

However, if placed in issue, the trial court must necessarily determine whether the expert in fact followed his chosen methodology and obtained the claimed data. That is different from deciding the credibility of the expert's conclusions drawn from the data. Instead, it is part of the court's obligation to determine whether the expert's study results were "'soundly and reliably generated' and . . . 'of a type reasonably relied on by comparable experts in the particular field.'" Landrigan, supra, 127 N.J. at 419-20 (citation omitted).

III

Having reviewed the record, we substantially agree with the trial judge's well-reasoned November 8, 2007 opinion on the PET study and we affirm her decision barring Dr. Bremner from testifying about it at the trial. The trial judge concluded that Bremner did not actually use the methodology he claimed to have used. Although his PET scan article was peer-reviewed, he admitted that he did not in fact follow the steps described in the article.

Significantly, contrary to representations made in the article, he did not get before-and-after Skindex questionnaires

from many of the subjects.² Those questionnaires were designed to elicit the extent to which the subjects might be worried about their acne. This was relevant because some scientists were of the view that worrying, as well as depression, could affect activity in the orbital frontal cortex.

Bremner also could not document much of the data on which his published results were based. Further, he admitted that some of the statistical analysis was inaccurate. For example, in the October 2, 2006 hearing session, Bremner admitted that, for each study participant, comparing the activity in the orbital frontal cortex with the activity in the whole brain revealed no difference between the subjects who took Accutane and those who took antibiotics.

Retreating from the results claimed in his 2005 article, he testified at the hearing that the "absolute metabolic rates" for the two groups was significantly different, and contended that was the key finding of the PET study. However, Bremner claimed that he could not produce the source data for that analysis because the "Bmax" numbers used to calculate those metabolic rates was on an optical computer drive that could not be opened.

² As described in Bremner's 2005 article, Functional Brain Imaging, supra, at 984, "[t]he Skindex is a 16-item self-report questionnaire with questions about emotional, functional, and symptomatic aspects of acne that has been validated for use in acne patient populations."

Further, while he admitted that some of the Bmax numbers he used in his calculations were inaccurate, he could not check the accuracy of the remaining numbers because the original data could not be retrieved.

An expert's scientific peers cannot fairly judge the expert's written work, including whether it is worthy of publication, if his article does not accurately represent either the underlying data or what the author did to produce his results. We agree with the trial judge that, in essence, Bremner's study was not "'soundly and reliably generated.'" Landrigan, supra, 127 N.J. at 419.

Further, we find no error in the judge's August 24, 2006 oral opinion precluding Bremner from providing supplemental reports or information after the Rule 104 hearing record closed. The judge allowed Bremner multiple opportunities to correct errors in his study before the record closed. "The orderly conduct of litigation demands that expert opinions reach closure." Miller v. Pfizer, Inc., 356 F.3d 1326, 1334 (10th Cir.), cert. denied, 543 U.S. 917, 125 S. Ct. 40, 160 L. Ed. 2d 201 (2004).

In summary, we find no abuse of discretion in the trial judge's decision to exclude the PET scan study. See Hisenaj, supra, 194 N.J. at 12.

Plaintiffs, however, contend that even without the PET study, Dr. Bremner can still offer an opinion that Accutane can affect the brain and produce depression. In that connection, plaintiffs argue that the trial judge did not address the remaining bases for Dr. Bremner's opinions. We agree, and therefore remand this matter to the trial court for reconsideration of the decision precluding Dr. Bremner from testifying.

A. Dr. Bremner's expert report

Dr. Bremner's 2005 expert report indicated that in determining "causality in connection with a particular side effect with a particular drug," he "used generally accepted scientific methods" which included consideration of six factors: (1) literature review; (2) temporal association; (3) de-challenge/re-challenge; (4) dose response; (5) mechanism of action; and (6) class effect. The PET study only related to factor 5, mechanism of action.

In discussing factor 1, literature review, Dr. Bremner first focused on rebutting studies reporting that Accutane either had no impact on psychological symptoms or improved them. However, under "case reports," he next discussed a wide variety of anecdotal reports and small studies indicating that patients

who took isotretinoin developed depression and in some cases attempted suicide.

In considering factor 2, temporal relationship, Dr. Bremner addressed "the spontaneous adverse events of depression and suicide reported to the FDA by the manufacturer." While he admitted that causality could not be inferred solely from this data, he opined that the data must be considered as a factor in the analysis. In addressing factor 3, dechallenge/rechallenge, Dr. Bremner cited to several FDA reports of "strong evidence" that psychiatric side effects have been observed to go away when a patient stops taking Accutane and return when the patient starts taking it again. Discussing factor 4, dose response, Bremner noted studies showing that "the greater the dosage of Accutane the greater the number of side effects."

The next section of Bremner's report was a lengthy discussion of factor 5, mechanism of action. The PET study was one piece of evidence among many that Bremner addressed in his analysis of this factor. Bremner first addressed evidence that isotretinoin affects areas of the brain that may be "implicated in depression." He also explained why he focused his study on the prefrontal cortex area of the brain, citing multiple studies that used PET technology to measure brain functions. After discussing prior PET studies, he concluded that "there are

multiple studies showing a relationship between changes in brain function, most notably prefrontal cortex and hippocampus, and the development of depression."

Bremner next addressed briefly a 1997 study he undertook, using PET scans to measure brain function during experimentally induced depressive relapse. He concluded that those findings were "consistent with dysfunction of prefrontal cortex in depression."³ He then discussed the PET study which became the subject of the trial judge's opinion. As Bremner stated in his report, the purpose of that study was to determine "whether it is biologically possible for Accutane to produce changes in the brain, which would be consistent with depression." He opined that his study "found evidence that Accutane does produce changes in the metabolism in areas of the brain implicated in depression and suicidality."

³ In his testimony at the Rule 104 hearing, Bremner explained the 1997 study in much greater detail. Based on this study, he concluded that "decreased orbital frontal function was associated with depression." In his testimony, he also discussed a second study which he also concluded showed "greater decreases in orbital frontal function" in patients with chemically-induced depression. This in turn explained why the 2005 PET study focused on the orbital frontal cortex. The defense agreed that there were "articles in the scientific literature which have found a decrease in the orbital frontal cortex in depressed patients" but did not agree that "there is a consensus in the scientific community" on that point.

Finally, Bremner's expert report addressed factor 6, class effect, which he described as: "an examination as to whether or not this particular effect is seen in other drugs with similar chemical structure or pharmacokinetics as the drug at issue." In this section, Bremner discussed the chemical similarity between isotretinoin and Vitamin A, a chemical which "is associated with mental changes" when taken in excessive doses. However, this conclusion was based on anecdotal reports rather than large studies.

He concluded that "[b]ased on an analysis of all the above factors, I am of the opinion that there is a positive relationship in connection with each factor mentioned above, which supports my opinion and conclusion based upon a reasonable degree of medical probability that Accutane does cause depression and suicide in some individuals." The report was supported by a seven-page single-spaced bibliography of the scientific literature Bremner reviewed in reaching his conclusions.

Apart from the discussion of the PET study, the report substantially tracked an article Bremner published in 2003, before he undertook the study. J. Douglas Bremner, M.D., Does Isotretinoin Cause Depression and Suicide?, 37 Psychopharmacology Bulletin 64 (Winter 2003). In that article,

he recommended that doctors prescribing isotretinoin should counsel their patients about the possibility of developing depression and periodically assess the patients for possible symptoms of depression.

Finally, Bremner's 2005 article, reporting on the results of the PET study, did not claim that the study was definitive. Rather, the article admitted that "a randomized, placebo-controlled study would provide more definitive results than the current study." The article also modestly concluded:

To our knowledge, this is the first study of the effects of isotretinoin on human brain functioning. The findings suggest that isotretinoin may affect brain functioning, providing a possible biological mechanism by which isotretinoin treatment could lead to depression in a minority of vulnerable acne patients. Future studies using randomized designs to evaluate the effects of isotretinoin on brain functioning are warranted.

B. Dr. Bremner's hearing testimony

Bremner's explanation as to why he undertook the study is enlightening. At the hearing, he explained that there were already studies showing that Accutane patients developed depression at a statistically higher rate than found in the general population. However, those studies were not clinical trials, and Bremner was aware of claims that Accutane could not cause depression "because there was no biological mechanism" by

which it could produce such a result. Hence, he set out to show that there was a possible "biological pathway."

However, he was very clear in his testimony that the PET study was not intended to diagnose depression or, in isolation, to prove that Accutane causes depression. When the judge asked Bremner, on the first day of the Rule 104 hearing, to explain how he got from his PET study results to his conclusion that Accutane causes depression, he gave a very long and specific explanation detailing all of the other available scientific evidence that supported his conclusion. That evidence included animal studies published after he began planning his own study in 2001, and a study report presented by Dr. Ferguson in 2004, before Bremner issued his 2005 expert report.

In fact, later in the hearing, the court specifically asked Bremner about the narrowness of the conclusion he reached from the PET study:

Q: Would I be able to say that your conclusion from this study is that Accutane has a pathway to the brain which is a part of the brain that affects mood?

A: Yes.

Q: That's the beginning and end of the conclusions you reached from the study?

A: Yes

Bremner also specifically explained that he was relying on the six factors discussed in his report, and that "the study is a subpart of . . . one of the six [factors,] . . . biological plausibility." He further specified that his PET study was "one part of the group of studies that are in the category of biological plausibility." Finally, at the end of the hearing day, the judge asked Dr. Bremner directly: "Excluding your PET scan study, can you determine to a reasonable cause of medical probability that Accutane causes depression?" He answered "Yes."

Moreover, on cross-examination during the next hearing day on May 31, 2006, Dr. Bremner testified that at the time he published the 2003 article, even before undertaking the PET study, he was "of the opinion that Accutane caused depression and suicide." After hearing that testimony as well as cross-examination about the basis for Bremner's opinion in 2003, the judge indicated to counsel her view at that juncture that a jury would have to decide whether his testimony on that point was credible; in other words, a jury would have to decide the credibility of Dr. Bremner's opinions reached without the PET study. Nonetheless, in later rendering her decision excluding Dr. Bremner from testifying as an expert, the trial court only addressed the PET study and did not address any of the other bases for Bremner's opinion that Accutane causes depression.

We therefore remand this case to the trial judge to consider whether Dr. Bremner should be permitted to testify as an expert on general causation, without reference to the PET study. We leave to the judge's discretion whether to permit or require any further proceedings prior to issuing a decision on remand. We do not retain jurisdiction.

Affirmed in part, remanded in part.

I hereby certify that the foregoing
is a true copy of the original on
file in my office.



CLERK OF THE APPELLATE DIVISION