NOT TO BE PUBLISHED IN THE OFFICIAL REPORTS

IN THE COURT OF APPEAL OF THE STATE OF CALIFORNIA

SECOND APPELLATE DISTRICT

DIVISION THREE

NANCY COOPER, Individually and as Successor, etc.,

Plaintiffs and Appellants,

v.

TAKEDA PHARMACEUTICALS AMERICA, INC., et al.,

Defendants and Respondents.

B250163

(Los Angeles County Super. Ct. No. CGC-12-518535)

APPEAL from a judgment of the Superior Court of Los Angeles County, Kenneth R. Freeman, Judge. Reversed and remanded with directions.

Esner Chang & Boyer, Stuart B. Esner; The Miller Firm, Michael J. Miller and Jeffrey A. Travers for Plaintiffs and Appellants.

Sidley Austin and Catherine Valerio Barrad for Defendants and Respondents.

INTRODUCTION

The defendants are Takeda Pharmaceuticals America, Inc., Takeda Pharmaceuticals U.S.A., Inc. (formerly Takeda Pharmaceuticals North America, Inc.), and Takeda Pharmaceutical Company Limited, referred to collectively as "Takeda."[1] In coordinated litigation, numerous plaintiffs have sued Takeda, manufacturers of the prescription drug Actos® (the trade name for pioglitazone HCl tablets), which is used to treat type 2 diabetes mellitus. Jack Cooper and Nancy Cooper are plaintiffs in one of the coordinated cases and alleged that Jack Cooper developed bladder cancer from ingesting the drug.[2]

The matter was tried to a jury in early 2013. The jury found Takeda liable on causes of action for strict liability failure to warn, negligent failure to warn, and loss of consortium. Specifically, the jury found that Takeda failed to adequately warn Jack Cooper's treating physician of the risk of bladder cancer, and that this failure to warn was a substantial factor in causing his harm. The jury awarded damages to Jack Cooper of $5 million, and to Nancy Cooper in the amount of $1.5 million for loss of consortium.

Before, during, and after trial, Takeda challenged the admissibility of causation testimony by the Coopers' expert urologic oncologist. At trial, the trial court permitted the expert to testify that, based on his performance of a differential diagnosis, he believed Actos® was a substantial factor in causing Jack Cooper's bladder cancer. However, the court later ordered the expert's testimony stricken, concluding that the testimony was speculative and lacking in foundation, and granted Takeda's motion for judgment

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1 Plaintiffs did not challenge on appeal the judgment in favor of defendant Takeda California, Inc. (formerly Takeda San Diego, Inc.).

2 The trial court granted a preference trial in October 2012, due to the poor state of Jack Cooper's health. This court also granted plaintiffs' motion for calendar preference. Regrettably, Jack Cooper died in July 2014, and we have granted the motion to substitute Nancy Cooper, as successor-in-interest, in place of appellant and decedent Jack Cooper.

notwithstanding the verdict. The trial court also granted Takeda's alternative motion for new trial on the grounds that without the testimony of plaintiffs' expert, Dr. Smith, the evidence was insufficient to support the verdict, and that the trial court should not have instructed the jury regarding concurrent causation.

In this appeal by the Coopers, we conclude that the trial court erred in striking the expert's testimony. By requiring that the expert rule out all other possible causes for Jack Cooper's bladder cancer, even where there was no substantial evidence that other such causes might be relevant, the court exceeded the proper boundaries of its gatekeeping function in determining the admissibility of the complex scientific testimony. We also conclude that the evidence supported giving a jury instruction on multiple causation. Accordingly, we reverse the judgment notwithstanding the verdict and the order granting a new trial, as well as the subsequent judgment entered in favor of Takeda, and remand the matter to the trial court with directions to enter a new judgment based on the jury's verdict.

PROCEDURAL AND FACTUAL BACKGROUND

Takeda, a pharmaceutical company headquartered in Japan, manufactures pioglitazone, a prescription drug used to treat type 2 diabetes, marketed in the United States since 1999 under the brand name Actos®. In 2006, plaintiff Jack Cooper was prescribed Actos® to treat his type 2 diabetes. He took Actos® continuously until he was diagnosed with bladder cancer in November 2011.

Jack and Nancy Cooper filed the present lawsuit against Takeda, alleging that Actos® caused Jack Cooper's bladder cancer, and that Takeda failed to adequately warn of this risk. Cooper and his wife (hereafter referred to collectively and in the singular as Cooper) asserted claims for negligent failure to warn and strict liability failure to warn, negligent misrepresentation, fraudulent concealment, and loss of consortium, and also sought punitive damages.

Because the issues on appeal revolve around the causation testimony by Cooper's expert witness, Dr. Norm Smith, we primarily focus our summary of the evidence on that testimony, supplemented by the testimony of one other expert.

I. Cooper's Expert Evidence

A. *Dr. Alfred Neugut*

Dr. Alfred I. Neugut, an epidemiologist and oncologist, testified that to a reasonable degree of medical certainty, "Actos . . . contribute[s] to or cause[s] the development of bladder cancer." His opinion was based primarily on his review of 15 epidemiological studies (the same studies relied on by Dr. Norm Smith, the expert whose testimony is in issue in this appeal). Regarding those studies, Dr. Neugut stated that any single study can be criticized in isolation. But when, as here, most studies consistently reach a similar result, an epidemiologist can be confident that the consistent result is correct. Regarding Actos®, most of the studies gave a positive result (meaning Actos® contributed to bladder cancer), and most of the studies with negative results "leaned in the positive direction."

Dr. Neugut explained that studies use a "hazard ratio," which compares the number of cases in which a disease actually occurs to the number of cases in which it was expected to occur. Thus, if the disease occurred in 30 cases when it was expected to occur in only 10, the hazard ratio would be three (30 actual cases divided by 10 expected cases). As relevant to studying whether a particular drug causes a particular disease, a hazard ratio of three suggests that in the population studied a person who ingested the drug would be three times as likely to develop the disease than people who did not ingest the drug.

Among the studies involving Actos®, the "Mamtani Study," published in 2012 in one of the best peer-reviewed journals, produced a hazard ratio of 6.97 for people exposed to the drug for five years or more. According to Dr. Neugut, a risk ratio of seven (the ratio of the Mamtani Study rounded off) is "uncommonly high."

B. Dr. Norm Smith

1. *Qualifications*

Dr. Smith is a urologic oncologist (a surgeon who specializes in cancers of the urinary tract), and is the codirector of the urologic oncology section at the University of Chicago. He is certified by the American Board of Urology, and was selected to participate in the American Urology Association Leadership Program, designed to train surgeons to be leaders in that organization. Dr. Smith treats patients, 80 percent of his practice being devoted to treating patients with bladder cancer, and he also teaches medical students. He is cochair of a working group within the Bladder Cancer Advocacy Network that awards research grants in the field of bladder cancer. He has served as a reviewer to determine the merit of other scientists' research studies and their suitability for publication for such publications as the Journal of the American Medical Association, Cancer, the Journal of Urology, the European Urology Journal, Urologic Oncology Seminars and Investigations, the British Journal of Urology International, and the American Journal of Pathology. He serves as an editor for the online journal, Advances in Urology. He was the lead author of an article published in the peer-reviewed journal, Urologic Oncology Seminars and Investigations, called "Bladder Cancer Risk from Occupational and Environmental Exposures," (Urol Oncol. 2012 Mar-Apr; 30(2): 199-211)[3] and has published over 56 articles in the peer-reviewed literature dealing with causes and origins of bladder cancer. He also conducts his own clinical research trials.

2. *Dr. Smith's General Causation Testimony*

As of mid-2011 when Dr. Smith finished cowriting the Kiriluk paper on bladder cancer risk from occupational and environment exposures, there was limited data available regarding the association between Actos® use and bladder cancer, and therefore that subject only covered one paragraph in the Kiriluk paper. By the time of his second deposition in this case, Dr. Smith had reviewed 15 epidemiological and clinical studies

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3 The paper Dr. Smith co-authored was referred to at trial as the Kiriluk paper.

showing an increased risk of bladder cancer among patients taking Actos® for diabetes. Among the studies Dr. Smith had reviewed were confidential materials provided by Takeda regarding the association between Actos® and bladder cancer. Dr. Smith stated that since completing his paper in July 2011, a large volume of data had been revealed that in his opinion constituted "very powerful data" regarding the risk of bladder cancer associated with Actos®. Dr. Smith testified it was his opinion that, to a reasonable degree of medical certainty, Actos® causes bladder cancer. His opinion was based on his review of the 15 epidemiological studies which, particularly when taken as a whole, indicate that Actos® use is associated with a significantly increased risk of bladder cancer. Many of the studies he reviewed found that this biological effect was greatest among long-term users and those with a larger cumulative dose. Asked if the studies on which he relied took into account diabetes and older white male subjects, Dr. Smith answered in the affirmative, saying that many of the studies that found a relationship between Actos® and bladder cancer had "adjusted for sex, race, smoking, hemoglobin[] A1C, et cetera, yes."[4]

For example, among the eight Takeda-funded studies, the Second Interim Kaiser Cohort from 2007 found, after adjusting for age and sex, a statistically significant association between the incidence of bladder cancer and increasing levels of exposure to Actos® (among patients who started Actos® 18 to 36 months prior, those who had 12 to 24 months of use, and those with between 7,000 mg and 18,000 mg of cumulative dose) as compared with patients that never used Actos®. Adjusting for smoking, diabetes duration, and baseline glycosylated hemoglobin concentration (HbA1c, a measure of the severity of diabetes) diminished the risk estimates although the patterns remained the same. The Takeda meta-analysis, which combined the results of numerous previous studies with both positive and negative findings, found a hazard ratio of 2.642, i.e., a

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[4] Dr. Smith testified that hemoglobin A1C is a measure of the severity of diabetes; some of the studies he reviewed adjusted for that factor.

statistically significant increased risk for bladder cancer among subjects treated with Actos®. The Second Interim Nested Case Control study found use of Actos® was associated with a 2.5 times increased risk of bladder cancer, which Dr. Smith described as "very alarming." That number increased slightly to 2.6 after adjusting for race, smoking history, high risk occupations, urinary tract infections, and HbA1c concentration.

Among the seven independent, peer-reviewed studies Dr. Smith reviewed, the Piccinni study found the hazard ratio for Actos® use to be 4.3. The Neumann study (published in 2012), a study performed in France involving 1.4 million people, though criticized for its methodology, also found that Actos® exposure was significantly associated with an increased risk of bladder cancer. Dr. Smith opined that study was significant, aside from its methodological shortcomings, because of the very large sample size. The Colmers meta-analysis also showed a significant increased risk of bladder cancer with Actos®, as did the Bosetti article, which is a meta-analysis involving 17 studies, both positive and negative.

Takeda acknowledged to the FDA in an e-mail sent in May 2012 that the potential development of bladder cancer is now an identified risk of Actos®.[5]

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[5] We granted Cooper's request to take judicial notice of the fact that in April 2014, the Office of Environmental Health Hazard Assessment added pioglitazone to the list of chemicals known to the State of California to cause cancer for the purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

3. *Dr. Smith's Specific Causation Testimony*

a. *Differential Diagnosis in General* [6]

Dr. Smith testified that the way bladder cancer presents in a patient's body does not indicate what caused it. He said that the relevant factors in creating a differential diagnosis for bladder cancer fall into two broad categories: smoking history and exposure history. Smith stated that smoking is the "most important risk factor in the development of bladder cancer" and that time since the patient stopped smoking is critical in assessing the risk because of the long latency period ("several decades") between tobacco exposure and emergence of cancer. He testified that other important factors are "exposure history," such as "past medical treatments like radiation exposures" and "environmental exposures," age, gender, race, diabetic condition, past medical history, surgeries, medication history (including dose and duration of Actos®), allergies, and family history.

Dr. Smith was later asked to explain to the jury "what differential diagnosis means," and responded in a manner that describes differential diagnosis as a means of considering a patient's physical symptoms and determining from those symptoms the disease most likely to be the cause of those symptoms, rather than considering a patient's known disease and determining the most likely cause or causes of the disease. He said, "Differential diagnosis is a concept that, when you see a patient for whatever problem it might be, one of the common ones in urology is blood in the urine. You say to yourself what are all the possible causes of blood in the urine, and it generates this long list. Then you go through a process of eliminating them one by one to the best of your ability to say well, this is my best guess as to what the problem is. And then you proceed with testing and/or diagnostics to figure out exactly the cause to the best of your ability." Cooper's

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[6] "Differential diagnosis" is defined as "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings." (http://www.medilexicon.com/medicaldictionary.php?t=24388, citing Stedman's Medical Dictionary (2006).)

counsel continued, "And in the real world practice of bladder cancer surgery in the last year, have you put Actos on your differential diagnosis as a cause of bladder cancer?" Dr. Smith replied, "Yes," impliedly acknowledging that the differential diagnosis method is also used to determine the likely cause of a disease.

Dr. Smith stated that the differential diagnosis he performed regarding Cooper was dissimilar from one he would conduct with a patient he was treating in that with his own patient he would review all outside medical records and could also talk to the patient. He said he often does not have a detailed discussion with every patient about cause because the treatment is the same regardless of the cause. He discusses with the patient those "modifiable factors" that the patient can change to improve their outcome, such as cessation of smoking. Dr. Smith stated that he did not speak to or examine Cooper at any time.

b. *Dr. Smith's Differential Diagnosis Regarding the Cause of Cooper's Bladder Cancer*

Dr. Smith said he based his specific causation opinion on his own paper regarding potential exposure-related causes of bladder cancer; on a particular table from an epidemiology study relating to Actos®; and a combination of all the published literature, the Takeda studies, his experience taking care of bladder cancer patients, and his experience in having written on exposures and risks for bladder cancer.

Dr. Smith also reviewed about 1,000 pages of Cooper's medical records. He noted that Cooper had taken over 50,000 milligrams of Actos® over the course of slightly more than five years. Dr. Smith had also reviewed Cooper's deposition and had reviewed 15 epidemiological and clinical studies examining the relationship between bladder cancer and ingestion of Actos®.

Cooper was described in the medical records as being in generally good health, with no history of kidney stones. There were incongruent references in the records to diabetes, borderline diabetes, and type II diabetes. Cooper had "transitional cell" bladder cancer, also referred to as "urothelial" cancer. It was a high grade cancer, meaning that it was biologically aggressive and spread rapidly. Dr. Smith's best estimate was that the

cancer was present for about six months before Cooper was diagnosed in November 2011.

The medical records indicated that Cooper had no family history of bladder cancer, and that he was a retired construction supervisor and "has had no occupational exposure." Cooper did not use alcohol. He was described both as a former smoker and as a "never smoker," with benign essential hypertension, type 2 diabetes mellitus, and chronic kidney disease, stage 3. He had a history of basal cell carcinoma of the face. Cooper was White, and his date of birth was August 28, 1933.

Regarding Cooper's history of smoking, Dr. Smith testified that there were discrepancies in the medical records. Some records stated he never smoked, and elsewhere it was reported that he quit smoking in 1992 or 1994. A form completed by Cooper in December 2011, after he was diagnosed with bladder cancer, indicated he had a 40-year history, ending in 1994, of smoking one pack per week. Whenever the records stated he smoked, however, it was described as less than one pack per week, or about three to four cigarettes per day.[7]

In performing the differential diagnosis, Dr. Smith considered as factors to rule *in* Cooper's race, his sex, his smoking history (including secondhand smoke), and his occupation as a construction supervisor. Cooper had been a construction supervisor for 15 years, and had been retired for over 13 years thereafter. Dr. Smith reviewed the records prepared by Dr. Xavier, Cooper's medical oncologist, and the records from all of his doctors. Dr. Xavier reported that there was no history of any occupational cause of Cooper's bladder cancer. Dr. Smith stated that there is "a very long list of occupations" associated with the development of bladder cancer and cited some examples. Despite there being "a long, long list," however, he stated that "none of those, to my opinion and review, fit Mr. Cooper." He "evaluated all the potential occupations on this list and felt

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[7] Cooper testified at trial, as did his family members, that he stopped smoking cigarettes and a pipe in 1974, because he promised his daughter he would do so if she won a national skating competition, which she did that year.

that it [occupational exposure] did not substantially apply to Mr. Cooper." During the section 402 hearing, Dr. Smith stated he was not aware of any literature that would indicate a retired Pacific Phone supervisor would have a risk of developing bladder cancer of even half of the risk posed by his Actos® exposure.

Based on Cooper's medical records, Dr. Smith ruled out radiation exposure, chemotherapy, infections, immunosuppression, the pain medication phenacetin, aristolochia fungi, arsenic exposure, HPV virus, chlorinated or fluoridated water, and vitamin D deficiency. Dr. Smith noted that Cooper had two bouts of skin cancer, in 2002 and 2009, apparently due to prolonged sun exposure. From that fact he concluded that there was no likelihood of a vitamin D deficiency, a known cause of bladder cancer. He acknowledged that direct contact with gasoline or diesel, which contain polycyclic aromatic hydrocarbons (PAH), can cause skin cancer, and are also known to be bladder cancer carcinogens. He considered Cooper's skin cancer to be sun related rather than caused by direct contact with gasoline or diesel fuel. He stated that he did not rule in occupational exposure to PAH and then investigate further in order to rule it out. There was no mention made in the medical record that Cooper worked around diesel and gasoline engines during the 40 years he worked at construction sites which could have exposed him to polycyclic aromatic hydrocarbons.

Asked if the fact Cooper had diabetes was a risk factor for bladder cancer, Dr. Smith stated there were some papers indicating a slight risk associated with diabetes, while other studies found no elevated risk. The former studies found a relative risk in only the 1.2 range, i.e., a low range.[8]

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[8] Another of Cooper's experts, Dr. Neugut, testified that he had not seen any persuasive evidence that diabetes itself causes bladder cancer, and that in virtually every study regarding Actos®, all study subjects were diabetic (or the study controlled for diabetes) to avoid the concern that it was diabetes that was the underlying cause of the bladder cancer.

Dr. Smith stated that there was no discussion in his Kiriluk paper about whether diabetes is a risk factor for bladder cancer because "we considered it and didn't put it in because we didn't think that it warranted it." He and his colleagues determined that although there was some conflicting data on diabetes as a cause of bladder cancer, there was not enough data to comment on it in their paper.

Dr. Smith acknowledged that Dr. Brunsting (Cooper's primary care physician), told Cooper in May 2004, two years before prescribing Actos® to Cooper, that he was borderline diabetic. Dr. Smith stated that kidney disease is a known complication of diabetes and could be an indication of worsening diabetes, but could also be caused by hypertension. Eight months before being diagnosed with bladder cancer, Cooper's doctor stated in a medical record that Cooper had a history of chronic kidney disease, stage 3. Dr. Smith's opinion was that there was no relevant difference in determining whether Cooper's kidney disease was caused by worsening diabetes or hypertension. He agreed it would be relevant if one accepted the proposition that the severity of diabetes may itself be a cause of bladder cancer, but of course Dr. Smith's opinion was to the contrary.

Importantly, Dr. Smith stated that all of the epidemiological studies he reviewed had adjusted for age, sex, and race. Asked more specifically if the studies on which he relied took into account diabetes and older, white, male subjects, Dr. Smith answered in the affirmative. He said that the studies that found a relationship between Actos® and bladder cancer had "adjusted for sex, race, smoking, hemoglobin[] A1C, et cetera, yes." Dr. Smith also acknowledged the hypothesis that renal insufficiency and albuminuria directly contribute to the incidence of bladder cancer, but he disagreed with that theory. He also said there was no data to support the association between exposure to electromagnetic power lines and bladder cancer.[9]

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[9] Defendants' expert, Dr. Schoenberg, mentioned the hypotheses that electromagnetic fields such as Cooper might have encountered in being a telephone lineman, and diabetes, might be associated with development of bladder cancer. He described the literature on these specific issues as being "hypothesis generating, but by no means offering proof." He opined he would apply the same description to the papers

Dr. Smith summarized that he concluded that occupational exposure "went into the rule out category and [he] was really left with trying to evaluate smoking versus Actos as the most substantial risk factors."

Several studies involving the causation of bladder cancer by Actos® that Dr. Smith had reviewed accounted for the effect of smoking in their analysis. Dr. Smith stated that, compared to the issue under study, i.e., Actos®, smoking proved to be not as important a factor as Actos® in causing bladder cancer. The studies indicated that use of Actos® for more than five years resulted in a 600 percent increased risk of getting bladder cancer. Dr. Smith was asked if anything about Cooper's history of being a former smoker "remotely comes close to having that degree of association." He answered that in general looking at all of the exposures evaluated, the only factor that would approach a similar hazard ratio would be a person's being a current, heavy smoker. He noted that Cooper was not a current smoker, and was never a heavy smoker.

The Takeda meta-analysis indicated that being on Actos® for more than 24 months resulted in a hazard ratio of 4.4 and having been exposed to a cumulative dose greater than 28 milligrams resulted in a hazard ratio of 4.6. Considering that Cooper was taking Actos® for about 62 months and his cumulative dose was 55,000 milligrams, Dr. Smith stated, "my concern would be that these numbers would be higher in his specific case." Asked, "So whatever his risk may be for being Caucasian, for smoking, or even if he was in a high risk occupation, or even if he had a severe A1C, that's been accounted for when we talk about this increased risk?" Dr. Smith replied in the affirmative with regard to the Takeda meta-analysis.

Dr. Smith testified that the risk of bladder cancer associated with being a smoker decreased by 40 percent the first four years after cessation of smoking. Recent studies indicated that if one smoked any amount but quit by the age of 40, one avoided practically all risk of smoking-related death. If a person quit smoking at a later age, he or

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hypothesizing that Actos® causes bladder cancer, that is, generating a hypothesis but not constituting proof.

she reverted to the risk that would be seen in a person who smoked less than 10 cigarettes per week. Those studies, published in the New England Journal of Medicine by Jha and Thun, examined deaths from all causes. In accordance with those studies, if Cooper had stopped smoking in the 1970's, he still had a 20 percent increased risk of death from smoking-related causes. If someone smoked until they were 55 to 64 years of age, the hazard ratio would be 1.7, i.e., a 70 percent increased risk of death from smoking-related causes over somebody who never smoked.

Dr. Smith said that in reaching his differential diagnosis, he considered Cooper's history of smoking, environmental exposures, and occupational exposures. He noted that it was sometimes hard to define a single agent to which a patient might have been exposed. "But if you look once again at all of that, you don't really get hazard ratios out of the ones whereas in the Mamtani article, that seems to fit Mr. Cooper very well with his . . . 50-plus thousand milligrams cumulative dose greater than five years that has a hazard ratio of almost seven. So I think in his case when you try to weigh that all in, that's really what is formative of the opinion that Actos caused bladder cancer for Mr. Cooper." Cooper's counsel asked Dr. Smith, "Let's go with half as risky as Actos. Actos, Mamtani, five years, 700 percent increased risk—odds ratio of 7. Is there anything in Mr. Cooper's history that's even half as risky scientifically? Former smoking?" Dr. Smith answered, "the relative risks of that go down to the ones, and this new article would suggest maybe even lower than that if you quit at age 40." He testified, "[I]f you looked at people that quit smoking, all comers, the odds ratios are usually in the 1's, and they approach that of nonsmokers when one has quit for many, many years and was a light smoker like Mr. Cooper."

Dr. Smith definitively stated: "[A]fter review of all the potentials, differential diagnosis, ruling in, ruling out, carefully evaluating the occupational, environmental, and smoking, that it's my opinion that the most substantial causative factor for Mr. Cooper was his length of Actos and cumulative dose of Actos."

II. The Jury Verdict

The jury returned a 9-3 verdict for Cooper on the strict liability failure to warn claim and a 10-2 verdict for Cooper on the negligent failure to warn and loss of consortium claims. Specifically, the jury found that Takeda failed to adequately warn Cooper's treating physician of the risk of bladder cancer, and that this failure to warn was a substantial factor in causing Cooper's harm. Similarly, the jury found that Takeda negligently failed to adequately warn Cooper's treating physician of the risk of bladder cancer, and that this failure to warn was a substantial factor in causing Cooper's harm. The jury returned a verdict for Takeda on the claims for negligent misrepresentation (12-0), intentional concealment (11-1), and punitive damages (12-0). The jury awarded Cooper $5 million in compensatory damages and $1.5 million in damages for loss of consortium.

III. Post Verdict Rulings

The procedural history contesting the admissibility of Dr. Smith's testimony that Actos® was a substantial factor in causing Cooper's bladder cancer is lengthy and complicated. By various procedural mechanisms -- motion in limine, motion to strike, motion for nonsuit, motion for directed verdict, and finally motion for judgment notwithstanding the verdict (JNOV) -- Takeda sought to exclude Dr. Smith's testimony or have it stricken. In large part, the procedural particulars are not material to this appeal. To the extent they are, we summarize them.

Throughout the proceedings, the trial court expressed the same concern about Dr. Smith's testimony: that without a competent differential diagnosis based on Cooper's history and medical condition that accounted for all potential causes, and ruled out each potential cause except Actos®, Dr. Smith's specific causation opinion was unreliable. Nonetheless, the court permitted Dr. Smith to testify, making clear that his testimony could later be stricken.

After the verdict, the court, which had deferred ruling on Takeda's motion in limine, motion to strike, and motion for nonsuit, ruled on those motions. In a lengthy ruling (which we examine in more detail below, in the Discussion section of this

opinion), the court concluded that Dr. Smith's differential diagnosis was speculative and unreliable. Therefore, the court struck the testimony on causation, and purported to grant Takeda's motion for nonsuit. Later, the court vacated the order granting nonsuit, and considered instead Takeda's motions for JNOV and for new trial.

Takeda's JNOV motion argued, as here relevant, that Cooper's two failure to warn claims and the loss of consortium claim failed because there was no evidence that Actos®, as opposed to some other factor or factors, caused Cooper's bladder cancer. The court adopted the reasoning of its prior ruling striking Dr. Smith's testimony, and concluded: (1) without Dr. Smith's testimony, evidence of causation was lacking, and (2) even if the testimony were not stricken, it did not constitute substantial evidence of causation. Therefore, the court granted JNOV.

Takeda had also moved in the alternative for a new trial, pursuant to Code of Civil Procedure section 657, subdivisions (1), (6) and (7), on Cooper's claims for failure to warn and loss of consortium. The trial court granted the motion on two independent grounds. First, it concluded the evidence was insufficient to support the jury's verdict on the three claims because "there is no evidence of specific causation in this case" for the reasons in the court's order striking Dr. Smith's testimony, and therefore plaintiffs "could not have met their burden of showing that any failure to warn was a substantial factor in causing harm" to Cooper.

Second, the trial court concluded that it was error to give a multiple causation instruction. The court held that the instruction was not supported by substantial evidence, since neither side introduced evidence of multiple causation. The court further held that (1) "the CACI 431 instruction was prejudicial and probably affected the jury verdict, given the lack of evidence of concurrent causation" because "[w]ithout the instruction, the jury would not have been in a position to consider multiple concurrent causes"; and (2) it was not supported by substantial evidence at trial. The court entered judgment for Takeda on all causes of action on July 18, 2013. This timely appeal followed.

DISCUSSION

I. JNOV

Cooper contends that the trial court erred in granting Takeda's JNOV motion. For the reasons explained below, we agree.[10]

A. The Standard of Review

"Typically, if a defendant believes that the plaintiff has not presented substantial evidence to establish a cause of action, the defendant may move for a nonsuit if the case has not yet been submitted to the jury, a directed verdict if the case is about to be submitted, or a judgment notwithstanding the verdict (jnov) following an unfavorable jury verdict.

"While made at different times, the three motions are analytically the same and governed by the same rules. (See *Beavers v. Allstate Ins. Co.* (1990) 225 Cal.App.3d 310, 327 ['. . . different aspects of the same judicial function and have long been held to be governed by the same rules'].) The function of these motions is to prevent the moving defendant from the necessity of undergoing any further exposure to legal liability when there is insufficient evidence for an adverse verdict. (E.g., *Reynolds v. Willson* (1958) 51 Cal.2d 94, 99.) Put another way, the purpose of motions for nonsuit, directed verdicts and jnovs is to allow a party to prevail as a matter of law where the relevant evidence is *already in*.

"And naturally, given the constitutional right to jury trial and a policy of judicial economy against willy-nilly disregarding juries' hard work (even, in the case of a motion

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10 As we have explained, after the verdict, the trial court initially struck Dr. Smith's testimony and purported to grant Takeda's motion for nonsuit. Thereafter, it vacated the grant of nonsuit, and granted JNOV in favor of Takeda. Cooper argues that the trial court erred procedurally by granting JNOV while also finding inadmissible Dr. Smith's testimony regarding specific causation, where the trial court had failed to rule on the motion to strike that testimony before the jury rendered its verdict. Because we find the court's substantive error in granting JNOV dispositive, it is unnecessary to discuss the alleged procedural error.

for nonsuit, the work of the jury in listening to the case up to that point), the basic rules regarding these motions are predictably strict. Conflicts in the evidence are resolved *against* the moving defendant and in favor of the plaintiff; all reasonable inferences to be drawn from the evidence are drawn against the moving defendant and in favor of the plaintiff. (See, e.g., *Nally v. Grace Community Church* (1988) 47 Cal.3d 278, 291 [for nonsuit, ' " 'every legitimate inference which may be drawn from the evidence' " ' should be drawn in plaintiff's favor, and the evidence should be evaluated ' "in the light most favorable to the plaintiff" ']; *CC-California Plaza Associates v. Paller & Goldstein* (1996) 51 Cal.App.4th 1042, 1050-1051 [' "A nonsuit or a directed verdict may be granted 'only when, disregarding conflicting evidence and giving to plaintiff's evidence all the value to which it is legally entitled, herein indulging in every legitimate inference which may be drawn from that evidence, the result is a determination that there is no evidence of sufficient substantiality to support a verdict in favor of the plaintiff if such a verdict were given.' " ' (italics omitted)]; *Hansen v. Sunnyside Products, Inc.* (1997) 55 Cal.App.4th 1497, 1510 [for judgments notwithstanding the verdict, ' " ' "[i]f there is any substantial evidence, or reasonable inferences to be drawn therefrom, in support of the verdict, the motion should be denied" ' " ']."] (*Fountain Valley Chateau Blanc Homeowner's Assn. v. Department of Veterans Affairs* (1998) 67 Cal.App.4th 743, 750-751.)

An order granting JNOV is reviewed de novo. A reviewing court determines whether substantial evidence supports the verdict, considering the evidence in the light most favorable to the party obtaining the verdict. (*Tognazzini v. San Luis Coastal Unified School Dist.* (2001) 86 Cal.App.4th 1053, 1057-1058.)

B. The Trial Court's Ruling

In granting Takeda's JNOV motion, the court adopted its reasoning from the prior order striking Dr. Smith's testimony. Thus, it is necessary to examine the ruling striking the testimony in some detail.

The court examined the foundation for Dr. Smith's testimony from his deposition, section 402 hearing, trial testimony, and applicable admitted exhibits and concluded that,

although Dr. Smith identified many possible causes of bladder cancer, he did not "sufficiently consider [them] and then rule them out *as to Mr. Cooper specifically*." The trial court therefore excluded from evidence Dr. Smith's specific causation opinion, stating, "[I]t is evident to the Court that the manner in which Dr. Smith conducted his differential diagnosis is based on speculation, is not reliable, not done with the intellectual rigor expected of an expert, and is therefore inadmissible under prevailing California law."

The court acknowledged that Dr. Smith testified that he performed a differential diagnosis and ruled out "smoking, environmental exposures, occupational exposure." But the court concluded that Dr. Smith did not have a foundation for ruling out these potential causes of Cooper's bladder cancer. For instance, as to environmental and occupational exposures, the court stated that Dr. Smith, at his deposition, when asked what Cooper did for a living, testified that he could not recall. When asked whether he knew if Cooper had any exposures at his workplace that had any sort of association with bladder cancer, Dr. Smith testified that it was " 'a difficult question to answer because . . . we don't understand all the exposures.' Absent a foundational basis for ruling in, and then ruling out, these occupational and environmental exposures (potential exposures which Dr. Smith identifies as belonging to a 'huge list'), Dr. Smith could not reliably perform a differential diagnosis to arrive at his specific causation opinion. [Fn.]" The court noted that "the fact that Dr. Smith did not examine or interview Mr. Cooper does not, by itself, render his specific causation inadmissible. However, Dr. Smith *was* required to otherwise establish a reliable foundation for his differential diagnosis, which he did not do as to Mr. Cooper. Dr. Smith's testimony that Dr. Xavier mentioned 'no history of occupational exposures', and his reliance on that mere statement, is not sufficient, from a foundational standpoint, to rule in, and rule out, such potential exposures to reach a differential diagnosis as to the specific cause of Mr. Cooper's bladder cancer." Dr. Smith could not testify whether Cooper was exposed to secondhand smoke at work, whether he may have had any exposures at his work associated with bladder cancer, and "whether he may have had exposure to anything during his Army

service." Rather, Dr. Smith merely reviewed Cooper's medical record and did not take a history from Cooper. The court said, "[R]uling in, and ruling out, potential causes of Mr. Cooper's bladder cancer is critical for purposes of establishing a foundation as to Dr. Smith's specific causation opinion by way of a differential diagnosis."

As to Cooper's history of smoking, the court stated that "without knowing the date Mr. Cooper ceased smoking, Dr. Smith could not (and did not) properly rule out smoking as a potential cause of Mr. Cooper's bladder cancer in conducting his differential diagnosis" given Dr. Smith's testimony that smoking is a significant risk factor and the time since cessation of smoking is important in assessing smoking as a risk factor. The court continued, "An expert physician, evaluating a patient's medical records, would thoroughly study them, noting anything of significance, and follow up on every detail necessary to come up with an accurate diagnosis. Since the date Mr. Cooper stopped smoking and his level of tobacco consumption is a critical fact in the diagnosis, an expert would do all he or she could to resolve any ambiguities. Pursuant to *Sargon*,[11] Dr. Smith was required to 'employ[] in the courtroom *the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.*' *Sargon*, *supra*, 55 Cal.4th at 772 (emphasis added)." The court said, "Yet, Dr. Smith, not having noticed the multiple medical record entries indicating smoking cessation in the 1992-4 timeframe or Mr. Cooper's history of moderate emphysema, steadfastly continued to use as [a] basis for his opinion the statement of Mr. Cooper's attorney that Mr. Cooper stopped smoking in the 1970s."

The court further stated that Dr. Smith did not consider Cooper's history of chronic kidney disease or his various episodes of skin cancer. There was no evidence that Dr. Smith reviewed these records in reaching his differential diagnosis. The court indicated that, "These records in particular are important because if diabetes is a risk

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11 *Sargon Enterprises, Inc. v. University of Southern California* (2012) 55 Cal.4th 747 (*Sargon*).

factor for bladder cancer, they are a measure of the seriousness of Mr. Cooper's diabetes."

The court also found that Dr. Smith had changed his position as to whether age, race and gender were risk factors without citing any basis for eliminating these factors, and ruled out diabetes as a risk factor without providing support for doing so. The court noted that "the very epidemiological studies upon which Dr. Smith relies for his Actos causation opinion treat the level of the underlying diabetes as a cause of bladder cancer."

The court then examined the epidemiological studies upon which Dr. Smith relied and pointed out specific problems and "flaws" in each of them, questioning whether epidemiological studies can generally be used as a basis for a differential diagnosis. The court concluded that the studies did not serve as reasonable bases for Dr. Smith's specific causation opinion, and "do not 'actually support' Dr. Smith's reasoning." Furthermore, the court rejected Cooper's assertion that Dr. Smith's general causation opinion rendered his specific causation opinion reliable, stating, "There is nothing in Dr. Smith's deposition transcript, nor anything stated at the §402 hearing or during his trial testimony, which demonstrates that Dr. Smith could disregard the identified risk factors as they specifically relate to Mr. Cooper. Again, a differential diagnosis is a *patient-specific* process. It is evident to the Court that Dr. Smith did *no* patient-specific analysis that satisfies the admissibility standards under Evidence Code §§ 801 and 802. [¶] Moreover, instead of his differential diagnosis being patient specific, based upon a review [of] the patient's medical history, clinical tests, biological and physiological markers, and physical examination of the patient, Dr. Smith rendered a diagnosis based upon speculation, conjecture and leaps of logic. His sole remaining risk factor is not patient-specific, but is instead based upon statistical studies. Dr. Smith's diagnosis would virtually apply to any male, non-smoker who took Actos for more than five years, since he has no physiological or biological markers to distinguish Mr. Cooper's bladder cancer from the myriad of bladder cancer patients he treats with no known causes." The court emphasized that it was not ruling on the weight of Dr. Smith's opinion, but only its admissibility.

C. The Trial Court Erred

As we explain, in finding Dr. Smith's testimony inadmissible, the trial court's reasoning is inconsistent with California law on the acceptable bounds of expert testimony regarding causation, as well as on the trial court's gate keeping function of excluding unreliable expert testimony.

1. *Standards for Admission of Expert Testimony*

"Trial judges have a substantial gatekeeping responsibility when it comes to expert testimony. (*Sargon*, [*supra*,] 55 Cal.4th 747 at p. 769.) In particular, courts are to ensure that opinions are not speculative, based on unconventional matters or grounded in unsupported reasoning. (*Id.*, at pp. 771-772.) We review a court's execution of these gatekeeping duties for an abuse of discretion. ([*City of San Diego v.*] *Sobke* [(1998)] 65 Cal.App.4th [379] at p. 396.)" (*People ex rel. Dept. of Transportation v. Dry Canyon Enterprises, LLC* (2012) 211 Cal.App.4th 486, 493.)

Based on the provisions of Evidence Code sections 801 and 802[12], "the trial court act[s] as a gatekeeper to exclude expert opinion testimony that is (1) based on matter of a type on which an expert may not reasonably rely, (2) based on reasons unsupported by

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12 Evidence Code section 801 provides that, "If a witness is testifying as an expert, his testimony in the form of an opinion is limited to such an opinion as is: [¶] (a) Related to a subject that is sufficiently beyond common experience that the opinion of an expert would assist the trier of fact; and [¶] (b) Based on matter (including his special knowledge, skill, experience, training, and education) perceived by or personally known to the witness or made known to him at or before the hearing, whether or not admissible, that is of a type that reasonably may be relied upon by an expert in forming an opinion upon the subject to which his testimony relates, unless an expert is precluded by law from using such matter as a basis for his opinion."

Evidence Code section 802 states: "A witness testifying in the form of an opinion may state on direct examination the reasons for his opinion and the matter (including, in the case of an expert, his special knowledge, skill, experience, training, and education) upon which it is based, unless he is precluded by law from using such reasons or matter as a basis for his opinion. The court in its discretion may require that a witness before testifying in the form of an opinion be first examined concerning the matter upon which his opinion is based."

the material on which the expert relies, or (3) speculative." (*Sargon Enterprises, Inc. v. University of Southern California* (2013) 215 Cal.App.4th 1495, 1504-1505 (*Sargon II*).) " '[E]ven when the witness qualifies as an expert, he or she does not possess a carte blanche to express any opinion within the area of expertise. [Citation.] For example, an expert's opinion based on assumptions of fact without evidentiary support . . . or on speculative or conjectural factors . . . has no evidentiary value . . . and may be excluded from evidence. [Citations.]' (*Jennings v. Palomar Pomerado Health Systems, Inc.* (2003) 114 Cal.App.4th 1108, 1117; see also *Bushling v. Fremont Medical Center* (2004) 117 Cal.App.4th 493, 510 ['expert opinion may not be based on assumptions of fact that are without evidentiary support or based on factors that are speculative or conjectural . . . '].) 'Therefore, an expert's opinion that something could be true if certain assumed facts are true, without any foundation for concluding those assumed facts exist in the case before the jury, does not provide assistance to the jury because the jury is charged with determining what occurred in the case before it, not hypothetical possibilities.' (*Jennings v. Palomar Pomerado Health Systems, Inc., supra,* 114 Cal.App.4th at p. 1117.)" (*Dee v. PCS Property Management, Inc.* (2009) 174 Cal.App.4th 390, 404.)

Here, the trial court considered Dr. Smith's testimony regarding specific causation to be speculative, unreliable, and "not done with the intellectual rigor expected of an expert, and [] therefore inadmissible under prevailing California law."

2. *The Court's Misapplication of the Substantial Factor Test*

In part, the court found Dr. Smith's testimony unreliable and inadmissible because Dr. Smith did not adequately consider and definitively rule out potential causes of Cooper's bladder cancer other than Actos® . The court's reasoning misapprehended the substantial factor test of causation.

"The law is well settled that in a personal injury action causation must be proven within a reasonable medical probability based upon competent expert testimony. Mere possibility alone is insufficient to establish a prima facie case. [Citations.] That there is a distinction between a reasonable medical 'probability' and a medical 'possibility' needs little discussion. There can be many possible 'causes,' indeed, an infinite number of

circumstances which can produce an injury or disease. A possible cause only becomes 'probable' when, in the absence of other reasonable causal explanations, it becomes more likely than not that the injury was a result of its action. This is the outer limit of inference upon which an issue may be submitted to the jury. [Citation.]" (*Jones v. Ortho Pharmaceutical Corp.* (1985) 163 Cal.App.3d 396, 402-403.)

"With cancer the question of causation is especially troublesome. . . . Under the present state of scientific knowledge . . . it is frequently difficult to determine the nature and cause of a particular cancerous growth. . . . [¶] The fact that a determination of causation is difficult to establish cannot, however, provide a plaintiff with an excuse to dispense with the introduction of some reasonably reliable evidence proving this essential element of his case. Although juries are normally permitted to decide issues of causation without guidance from experts, 'the unknown and mysterious etiology of cancer' is beyond the experience of laymen and can only be explained through expert testimony. [Citation.] Such testimony, however, can enable a plaintiff's action to go to the jury only if it establishes a reasonably probable causal connection between an act and a present injury." (*Jones v. Ortho Pharmaceutical Corp., supra*, 163 Cal.App.3d at p. 403.)

"[P]roffering an expert opinion that there is some theoretical possibility the negligent act *could have been* a cause-in-fact of a particular injury is insufficient to establish causation. (*Saelzler v. Advanced Group 400* (2001) 25 Cal.4th 763, 775-776 [expert testimony positing a ' "mere possibility of such causation is not enough; and when the matter remains one of pure speculation or conjecture, or the probabilities are at best evenly balanced, *it becomes the duty of the court to direct a verdict for the defendant*" ']; accord, *Leslie G. v. Perry & Associates* (1996) 43 Cal.App.4th 472, 487.) Instead, the plaintiff must offer an expert opinion that contains a reasoned explanation illuminating why the facts have convinced the expert, and therefore should convince the jury, that it is *more probable than not* the negligent act was a cause-in-fact of the plaintiff's injury." (*Jennings v. Palomar Pomerado Health Systems, Inc., supra*, 114 Cal.App.4th at p. 1118.)

In the instant case, the trial court's reasoning concerning the flaws in Dr. Smith's differential diagnosis held Cooper's expert to a more rigid standard than is required to prove causation in civil cases. Under the applicable substantial factor test, it is not necessary for a plaintiff to establish the negligence of the defendant as the proximate cause of injury with absolute certainty *so as to exclude every other possible cause of a plaintiff's illness*, even if the expert's opinion was reached by performance of a differential diagnosis. The jury here was required to determine whether there was any substantial evidence that other known risk factors for bladder cancer acted on plaintiff and provided an alternative explanation for his disease. But only if the existence of an alternative explanation, supported by substantial evidence and not mere speculation, as a matter of law *defeated* the explanation proffered by Cooper (i.e., Actos®) would JNOV be appropriate.

The decision in *Sarti v. Salt Creek Ltd.* (2008) 167 Cal.App.4th 1187 (*Sarti*) is instructive. In *Sarti*, a restaurant patron sued the restaurant for breach of warranty after developing food poisoning shortly after eating at the restaurant. The jury entered a verdict in favor of the plaintiff, but the trial court granted JNOV in favor of the restaurant. On the plaintiff's appeal, the appellate court reinstated the verdict in the plaintiff's favor.

The evidence at trial showed that plaintiff ate raw tuna at the restaurant, then developed a serious illness due to the ingestion of a particular bacteria found in raw chicken but not in raw tuna. However, the evidence also demonstrated that the restaurant's specific practices could have led to cross-contamination of raw food consumed by the plaintiff. Plaintiff's expert testified that anything that might have touched something that touched raw chicken would be cross-contaminated. The restaurant's dishwasher did not adequately sterilize dishes, the waiter frequently used an unsterilized rag to wipe various surfaces, and raw chicken juice may have leaked onto some of the vegetables stored beneath it. The appellate court concluded that a reasonable jury could infer that a rag used to wipe down a raw chicken board was used to wipe down

a vegetable or tuna board, or that raw chicken juice could have dripped onto food later consumed raw.

Important for our purposes here, the court in *Sarti* noted that "[t]here was plenty of substantial evidence on which the jury could have found the restaurant *not* liable." (*Sarti, supra*, 167 Cal.App.4th at p. 1191.) Plaintiff's friend who ate the same food did not get sick, the restaurant took other careful measures to separate its raw tuna from its raw chicken, and plaintiff herself "worked as a supermarket checker the day she became ill, and could, at least in theory, have picked up campylobacter from a leaking bag of raw chicken she might have scanned." (*Id.* at pp. 1191-1192.) The trial court commented that although such evidence was presented, it would have voted with the jury in finding the restaurant liable. However, the court felt constrained to enter JNOV based on its reading of the case of *Minder v. Cielito Lindo Restaurant* (1977) 67 Cal.App.3d 1003 (*Minder*) as setting forth a black-letter rule of law that food poisoning cases have heightened causation requirements. The trial court read *Minder* as establishing " 'that the concept of inferences, which are otherwise permitted in civil cases, apparently play little or no role in food poisoning cases. And remember, an inference is not evidence itself, an inference is the result of reasoning based upon collateral evidence.' " (*Sarti, supra*, at p. 1192.)

As observed by the *Sarti* court, however, "The *Minder* court never expressly said that it thought that defendants in food poisoning cases deserved a break from ordinary rules of tort causation, but that thought permeated the court's analysis, and it was certainly picked up by the trial judge in our own case, who described *Minder* as enunciating a 'heightened' standard of causation. [¶] We cannot agree, however, with the strong implication in the *Minder* analysis that food poisoning cases are somehow unique in tort law."[13] (*Sarti, supra*, 167 Cal.App.4th at pp. 1201-1202.) The *Sarti* court

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13 The *Sarti* court closely analyzed the *Minder* case, and concluded that the real issue precluding a finding of liability was that there simply was not enough of a specific link demonstrated between the particular kind of food poisoning involved and any particular

concluded that "[t]o the degree that the *Minder* opinion does indeed suggest a no-inference rule (or, at least, a presumption against inferences different from other tort cases), it contradicted established precedent in existence at the time." (*Id.* at p. 1203.) For example, the court held in *Dougherty v. Lee* (1946) 74 Cal.App.2d 132 (*Dougherty*), that " ' "It is not necessary *in the trial of civil cases* that the circumstances shall establish the negligence of the defendant as the proximate cause of injury with such absolute certainty *as to exclude every other conclusion. It is sufficient if there is substantial evidence upon which to reasonably support the judgment.* (*Ley v. Bishopp* [(1928)] 88 Cal.App. 313, 316.)" ' (*Dougherty, supra*, 74 Cal.App.2d at p. 136, italics added [quoting from *Barham v. Widing* (1930) 210 Cal. 206, 215.])" (*Sarti, supra*, at pp. 1203-1204.)

In addition, the *Sarti* court observed that the *Minder* opinion strongly suggested the existence of a requirement that the plaintiff rule out all other causes of the illness. The restaurant argued "for an 'all alternatives must be ruled out' approach" as being required by California law. (*Sarti, supra*, 167 Cal.App.4th at p. 1205.) The *Sarti* court, relying on *Mitchell v. Gonzales* (1991) 54 Cal.3d 1041, flatly rejected the assertion that exclusion of alternatives with absolute certainty is required. (*Sarti , supra*, at p. 1205.) Suffice it to say that we agree with the *Sarti* court that *Mitchell*, in endorsing a jury instruction telling the jury to determine " 'whether the defendant's conduct was a *substantial factor* in bringing about the injury' " (*Mitchell* at p. 1049, italics added), "plainly demonstrated that California law on causation is 'substantial factor.' And, as the prior *Dougherty* opinion expressly stated, a plaintiff need not ' "exclude every other conclusion" ' than the defendant's negligence. (*Dougherty, supra*, 74 Cal.App.2d at p. 136.)" (*Sarti, supra*, at p. 1210.)

Thus, because California has rejected the notion that a plaintiff must definitively "exclude all 'possibilities' " (*Sarti, supra*, 167 Cal.App.4th at p. 1210) other than the

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unsanitary condition at the restaurant. The testimony from the plaintiffs' treating physician came close but did not actually connect the offending pathogen to the unsanitary conditions found at the restaurant. (*Sarti, supra*, 167 Cal.App.4th at p. 1195.)

defendant's conduct or product as the cause of plaintiff's harm, clearly an expert, in reaching a specific causation opinion, need not exclude all other possibilities before he or she can express an opinion that defendant's conduct or product caused the plaintiff's harm.

As recognized by the *Sarti* court, something more than bare conceivability or plausibility of other causes must be required before another cause of injury, as a matter of law, must be chosen as the cause in fact over the defendant's conductor, by extension, before an expert's opinion is held inadmissible as being speculative or lacking in foundation. "For example, in a food poisoning case, how could the plaintiff disprove that she *didn't* pick up some nasty bacteria (here, campylobacter) because she touched a doorknob that had been previously touched by someone who had been handling raw chicken or who had changed a diaper, and hadn't washed his or her hands? Well, yes, one might reason, it is conceivable that that might have happened. It is ludicrous, though, to suggest that such bare conceivability must, *as a matter of law,* defeat a food poisoning claim. [¶] The relevant question is this one: Was there any *substantial evidence* that someone who had just handled raw chicken (or changed a diaper or whatever) and who hadn't washed his or her hands, touched something that the plaintiff soon touched, and then the plaintiff, say, ate a hamburger or a sandwich without washing her hands, after which she became sick within a time frame consistent with the illness that she, indeed, contracted?" (*Sarti, supra*, 167 Cal.App.4th at pp. 1210-1211.) The court found that the restaurant had "cited no substantial evidence *requiring a finding* that Sarti picked up the campylobacter from handling a leaky package of chicken while working at a checkstand, or handling a cat, or somehow being exposed to a baby in the house, or eating in the lunchroom with the employees from the meat department," and thus the court was "spared the tough problem of whether the existence of an alternative 'explanation' supported by substantial evidence competing with the finding the jury actually chose might somehow defeat, as a matter of law, the jury's finding of food poisoning from the restaurant meal." (*Id.* at p. 1211.) The court continued, "One must remember, it is the winning party after a jury trial, not the losing party, who gets the benefit of reasonable

inferences from the evidence. Under classic rules of appellate review, we are required to accept the inference, if reasonable, that Salt Creek got sloppy with its wipe-down rags over the inference that Sarti ran a leaky bag of chicken through a checkout scanner and then didn't wash her hands before touching some food she ate." (*Ibid.*)

Just as food poisoning cases are not unique in California tort law, cases in which expert physicians perform a differential diagnosis to "rule in" and "rule out" other possible causes of a disease are not unique; the substantial factor rule of causation still applies in such cases. Thus, Dr. Smith was not required to rule out all other possible causes of bladder cancer before his testimony could be deemed admissible. The trial court's ruling to the contrary contravened California law.

The trial court rejected Dr. Smith's opinion because, in the court's view, he did not have sufficient foundation to rule in and rule out other causes of Cooper's cancer. Specifically, the court faulted Dr. Smith for not conducting further investigation into other possible causes, saying that although Dr. Smith identified many possible causes of bladder cancer, he did not "sufficiently consider [them] and then rule them out *as to Mr. Cooper specifically*." The court said, "Differential diagnosis is 'the *patient-specific process* of elimination that medical practitioners use to identify the "most likely" cause of a set of signs and symptoms from a list of possible causes' and is 'undoubtedly important to the question of specific causation.' See Matthew Bender, *Drug Product Liability*, §5.01(b)(2012) (emphasis added). [¶] 'Differential diagnosis is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated. *It is typically performed after taking physical examinations and medical histories, and reviewing clinical tests.*' *Id.* (Emphasis added.) [¶] . . . [¶] Importantly, '[m]ost courts require that a reliable differential diagnosis at least *consider* other factors that could have been the sole cause of the plaintiff's injury. Nevertheless, the expert need not rule out every conceivable cause for his or her differential-diagnosis-based opinion to be admissible.' *Id.*" The trial court nonetheless concluded that, "instead of his differential diagnosis being patient specific, based upon a review [of] the patient's medical history, clinical tests, biological and physiological

markers, and physical examination of the patient, Dr. Smith rendered a diagnosis based upon speculation, conjecture and leaps of logic. His sole remaining risk factor is not patient-specific, but is instead based upon statistical studies. Dr. Smith's diagnosis would virtually apply to any male, non-smoker who took Actos for more than five years, since he has no physiological or biological markers to distinguish Mr. Cooper's bladder cancer from the myriad of bladder cancer patients he treats with no known causes."

The court found that Dr. Smith did not have a foundation for ruling out occupational and environmental exposures because at trial Dr. Smith did not recall Cooper's profession, and acknowledged it was difficult to know if Cooper had any exposures at his workplace that had any sort of association with bladder cancer, " 'because . . . we don't understand all the exposures.' " The trial court found Dr. Smith's reliance on Cooper's treating physician's statement that Cooper had " 'no history of occupational exposures' " was "not sufficient, from a foundational standpoint, to rule in, and rule out, such potential exposures to reach a differential diagnosis as to the specific cause of Mr. Cooper's bladder cancer." The trial court said that Dr. Smith could not testify whether Cooper was exposed to secondhand smoke at work, whether he may have had any exposures at his work associated with bladder cancer, and whether he may have had exposure to anything during his Army service. The court said, "[R]uling in, and ruling out, potential causes of Mr. Cooper's bladder cancer is critical for purposes of establishing a foundation as to Dr. Smith's specific causation opinion by way of a differential diagnosis."

As to Cooper's history of smoking, the court stated that "without knowing the date Mr. Cooper ceased smoking, Dr. Smith could not (and did not) properly rule out smoking as a potential cause of Mr. Cooper's bladder cancer in conducting his differential diagnosis" given Dr. Smith's testimony that smoking is a significant risk factor and the time since cessation of smoking is important in assessing smoking as a risk factor. However, Dr. Smith did not rule out smoking as a potential cause of Cooper's bladder cancer. He plainly admitted that smoking "could be a cause of his bladder cancer."

Dr. Smith testified further that regardless of when Cooper stopped smoking, Actos® ingestion was, in his opinion, still more likely to have been the *most* substantial factor in causing Cooper's bladder cancer than his smoking history. Based on a study examining all smoking-related deaths by duration and age of cessation of smoking, Dr. Smith agreed that if someone quit smoking at 35 to 44 years of age, he or she would have a 20 percent increased risk of dying of cancer compared to someone who never smoked. If a person smoked until they were 55 to 64 years of age, he or she would have a 70 percent increased risk of dying of cancer compared to someone who never smoked. Another source Dr. Smith reviewed, the Brennan paper, indicated that if Cooper smoked for 20 years, until 1974, he had a 100 percent increased risk of developing bladder cancer. If he smoked for 40 years, until 1994, he had perhaps a 300 percent increased risk for bladder cancer. If he stopped in 1994, 17 years would have passed before he was diagnosed with bladder cancer. He would not have reached the risk level of a nonsmoker, but he was always a light smoker and his risk declined the longer it had been since he stopped smoking. Dr. Smith opined, "even in the time frame of 17 years, the risk of . . . smoking-related cancers and diseases goes down significantly in that time frame." He concluded: "[A]fter review of all the potentials, differential diagnosis, ruling in, ruling out, carefully evaluating the occupational, environmental, and smoking, that it's my opinion that the most substantial causative factor for Mr. Cooper was his length of Actos and cumulative dose of Actos."

In essence, Dr. Smith was presented with two hypotheticals, one in which Cooper stopped smoking in 1974, and one in which he stopped smoking around 1994, and testified regarding both. Asked, "Doctor, you will agree, would you not, sir, that Mr. Cooper's history of smoking, whether it be 20 years or 40 years, certainly could be a cause of his bladder cancer?" He replied in the affirmative, and said that it was one of the things he ruled in. This testimony was entirely adequate to illuminate the subject for the jury, without further investigation or clarification by Dr. Smith of the discrepancy in the medical records. "Expert testimony has its own rules given its issues of reliability because the expert is not testifying to percipient facts, but instead relies on a multitude of

materials, including hearsay, in forming his or her opinion. Further, the expert is not bound by actual facts in rendering an opinion, but may opine on hypothetical situations . . . ." (*Sargon II, supra,* 215 Cal.App.4th at p. 1505.) It is the jury's role and function to determine whether the hypothetical fact pattern is supported by the evidence, and whether to credit the expert's opinion. (*People v. Vang* (2011) 52 Cal.4th 1038, 1050.) The jury here could decide based on the testimony when they believed Cooper stopped smoking, and evaluate the persuasiveness of Dr. Smith's testimony on that basis.

In evaluating Cooper's medical records that were provided to him, Dr. Smith was not required to "follow up on every detail necessary to formulate an accurate diagnosis," and "do all he . . . could to resolve any ambiguities," before he could offer an opinion on causation. Dr. Smith was not required to affirmatively negate every other possible cause by engaging in further investigation and evaluation of Cooper and his medical history, in order for his causation opinion to meet the threshold of reliability required for admissibility. In our view, the trial court's condemnation of Dr. Smith's review of Cooper's medical records did not point out any critical information that Dr. Smith overlooked. Rather, the trial court appeared to be speculating that some unknown exposure could be lurking in the unexamined records. But as we have said, Dr. Smith was not required to search for evidence that even Takeda's counsel failed to find and present to the jury. Takeda also did not point out any relevant evidence regarding other causes that Dr. Smith overlooked, whether in Cooper's medical records or in the deposition testimony of other witnesses. Nor was Dr. Smith obliged to "perform physical examinations" or do clinical testing to investigate the matter further. The court cited those things as typically being involved in the performance of a differential diagnosis, by definition, not accounting for the fact that differential diagnoses most frequently occur in a clinical setting and are aimed at identifying the disease from which a patient suffers in order to provide treatment (rather than identifying the cause of a disease for forensic purposes). There is no indication here that any physical examination or clinical tests would have shed any further light on the cause of Cooper's bladder cancer. The court's implicit criticism of Dr. Smith in that regard was therefore inapt.

The court indicated that Dr. Smith did not consider Cooper's history of chronic kidney disease or his various episodes of skin cancer, which was important because if diabetes is a risk factor for bladder cancer, those things are measures of the seriousness of Cooper's diabetes. However, Dr. Smith opined, based on research he did when co-authoring the Kiriluk paper and the fact that many of the epidemiological studies controlled for the presence and severity of the test subjects' diabetes, that he did not consider diabetes to be a risk factor for bladder cancer. Therefore, his relative disregard of information on those topics was warranted. Similarly, the court was critical of Dr. Smith's apparently overlooking a radiographic report for Cooper indicating a finding on x-ray of moderate emphysema, which could indicate a severe extent of lung damage from smoking. However, Dr. Smith testified that, although he was not an emphysema expert, he could authoritatively state that a radiographic finding was not the same thing as a clinical diagnosis. Indeed, Dr. Smith pointed out that the same radiologist who made the observation of moderate emphysema on the x-ray interpreted a CT scan performed on Cooper after the x-ray as finding "No visible pulmonary or pleural disease."

Dr. Smith did *consider* other possible causes of bladder cancer suggested by Cooper's medical records. Dr. Smith ruled out radiation exposure, chemotherapy, infections, immunosuppression, the pain medication phenacetin, aristolochia fungi, arsenic exposure, HPV virus, chlorinated or fluoridated water, and vitamin D deficiency. He noted that vitamin D deficiency was unlikely because Cooper had two bouts of skin cancer, probably due to sun exposure, so he inferred Cooper was not vitamin D deficient. Dr. Smith acknowledged that direct contact with gasoline or diesel, which contain polycyclic aromatic hydrocarbons (PAH), can cause skin cancer, and are also known to be bladder cancer carcinogens. As already noted, he considered Mr. Cooper's skin cancer to be sun related rather than caused by direct contact with gasoline or diesel fuel,[14]

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[14] Indeed, one or both of the episodes of skin cancer occurred on his face, not a location where he was likely to have had prolonged skin contact with diesel or gasoline.

and there was nothing in the medical record indicating that Cooper worked around diesel and gasoline engines during the 40 years he worked at construction sites which could have exposed him to polycyclic aromatic hydrocarbons. Takeda introduced no substantial evidence to indicate that he had; it only raised the speculation that he might have.

That is the critical point: Takeda cannot point to any substantial evidence to indicate that another cause of bladder cancer, other than Actos®, was ignored by Dr. Smith, such that his opinion was unreliable.[15] In order to accept Dr. Smith's opinion as being sufficiently intellectually rigorous, and before finding admissible his opinion on specific causation, the trial court would have had Dr. Smith investigate beyond the medical records and evidence made available to him by Cooper—and Takeda—in search of substantial evidence that other causes of bladder cancer operated on Cooper. That is not the standard of admissibility for expert opinion on medical causation. Bare conceivability that other causes of bladder cancer *might* have affected Cooper, raised by Dr. Smith's acknowledgement that there are so many possible causes and so much still unknown about the causation of bladder cancer, in the absence of any substantial evidence to support the notion that Cooper was in fact affected by those causes, was not a proper basis for the court to exclude Dr. Smith's testimony. California has rejected the notion that an expert must "exclude all 'possibilities' " in reaching a specific causation opinion. (*Sarti*, *supra*, 167 Cal.App.4th at p. 1210.) Bare conceivability of another possible cause does not defeat a claim; the relevant question is whether there is "substantial evidence" of an alternative explanation for the disease. (*Id.* at pp. 1210-1211.)

In purporting to assess the admissibility of Dr. Smith's testimony and disavowing that it was ruling on the weight of Dr. Smith's opinion, the trial court altogether excluded

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15 As stated above, Dr. Smith acknowledged that smoking presented a significant risk to Cooper of developing bladder cancer, but opined that on balance Actos® played a more substantial role in Cooper's development of the disease.

Dr. Smith's testimony essentially because he failed to demonstrate that Actos® was the exclusive factor in causing Cooper's bladder cancer. The trial court held Dr. Smith to a standard by which he was required to present for consideration every possible alternative cause of Cooper's cancer, demonstrate that he had personally conducted a comprehensive investigation into the evidence supporting and refuting each other cause as a possible causative factor in Cooper's cancer, and testify that based on that evidence he concluded that Actos® was the exclusive factor in causing Cooper's bladder cancer. California law certainly does not require that rigorous standard as a *threshold* test for the *admissibility* of an expert's opinion regarding causation. To be admissible, an expert physician's testimony, even in the context of the physician's performance of a differential diagnosis, need not *rule out* the applicability of all other possible causes of disease where there is no substantial evidence that other known risk factors for bladder cancer acted on Cooper and provided an alternative explanation for his disease. Perhaps Cooper inhaled too much secondhand smoke from coworkers over 15 years ago, was exposed to PAH's by having direct skin contact with diesel fuel, or was exposed to other myriad possible causes of bladder cancer, but it was entirely speculative for Takeda to assert that other known risk factors *could have* played a role where it presented no *substantial evidence* to support such notions.

Dr. Smith freely acknowledged that smoking also played an important role in the development of bladder cancer, and that older white men were at higher risk of developing the disease. But the jury was free to give weight to Dr. Smith's testimony that, to a reasonable degree of medical probability, Actos® was the most substantial factor in causing Cooper's bladder cancer, based in part on the fact that the studies upon which he relied in forming that opinion controlled for smoking and demographic factors.[16] To paraphrase *Sarti*, because after a jury trial the winning party gets the benefit

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16 The trial court criticized Dr. Smith for changing his testimony from the time of his first deposition when he said that age, race, and sex are risk factors, to saying at trial that these factors are simply the demographic of people who tend to get bladder cancer,

of reasonable inferences from the evidence (*Sarti, supra*, 167 Cal.App.4th at p. 1211), and because we have concluded that the trial court erred in excluding plaintiff's expert testimony regarding specific causation, we are required to accept the inference, if reasonable, that Actos® was a substantial factor in causing Cooper's bladder cancer, if the foundation for that causation is reliable.

Of course here, the trial court condemned Dr. Smith's reliance on many of the studies he cited in support of his opinions. We therefore turn next to examining whether the trial court erred in concluding that the materials cited by Dr. Smith were not a reliable basis upon which to form the opinion that Actos® causes bladder cancer, and caused it in Cooper's case.

3. *The Epidemiological Studies*

In finding Dr. Smith's testimony unreliable, the court examined the epidemiological studies upon which Dr. Smith relied and pointed out specific problems and "flaws" in each of them, questioning whether epidemiological studies can generally be used as a basis for a differential diagnosis. The court concluded that the studies did not serve as reasonable bases for Dr. Smith's specific causation opinion, and "do not 'actually support' Dr. Smith's reasoning." In doing so the trial court was substituting its opinion for the opinion of Dr. Smith and the opinions of the authors of the studies. This is not the proper function of the trial court.

Specifically, the trial court noted that the authors of the KPNC nested case control study cautioned against use of the data in the study for making risk assessment. The trial court categorically found unreliable the studies upon which Dr. Smith relied based on the study's "secondary endpoint" data because Dr. Smith admitted that secondary endpoint data must be viewed with caution. The court pointed out that Dr. Smith had reviewed the

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without citing any basis for eliminating these factors. However, we find adequate Dr. Smith's explanation that describing these things as risk factors or demographics is a matter of semantics. Importantly, however, Dr. Smith stated that all of the epidemiological studies upon which he relied had adjusted for age, sex, and race. Thus, the trial court's criticism that he eliminated those factors without any basis is factually incorrect.

PROactive study, the Lewis paper in 2011, and the Piccinni paper, prior to his retention as an expert in this case, and at that time found the data in those studies was insufficient for him to reach the opinion that Actos® can cause bladder cancer. The trial court also discounted the reliability of two studies upon which Dr. Smith relied that found a statistically significant association between Actos® and bladder cancer in the primary endpoint data, the Azoulay and Neumann studies. The court dismissed the results of the Neumann study because its authors changed methodology after beginning the study, and the positive association in the study came only after the authors excluded 250,000 of the original patients; in the study as originally conceived, no significant association was found. In addition, the court found the study to be seriously flawed because the primary endpoint studied the association between "ever and never users" of Actos®. The authors themselves also noted several key limitations in their study, including that it " 'lack[ed] data on tobacco use, know[n] to be the third main risk factor for bladder cancer after age and male sex" and that it did not " 'report data on the duration of diabetes.' "

The court also concluded that the Azoulay study "suffers from fundamental flaws" in that the Azoulay authors admitted the research database they used lacked data on other occupational exposures, race, and family history of bladder cancer. The Azoulay study also did not control for smoking based on the number of years the subject smoked, when they smoked, or how much they smoked. In short, the court concluded that "neither the Neumann study nor the Azoulay study (which, again, were the only two studies relied on by Dr. Smith whose primary endpoints were statistically significant) serve as 'reasonable [bases]' for Dr. Smith's specific causation opinion. *Sargon*, *supra*, 55 Cal.4th at 772."

To the extent the trial court found inadmissible Dr. Smith's opinions based on its conclusion that the epidemiological studies on which Dr. Smith relied lacked scientific validity, the court abused its discretion. In briefing filed in the trial, Cooper set forth detailed information refuting the criticisms of the epidemiological studies leveled by Takeda and later by the trial court. This material demonstrates that the trial court's rejection of these studies was too simplistic, because it did not take into account the varied scientific principles involved in determining the validity of the studies.

As an example, Cooper pointed out that Takeda's experts said of the protocol for the KPNC study, which they authored, that "Although the primary analysis will examine 'ever exposure' to Actos, we will conduct additional analyses that account, one at a time, for these two aspects of exposure [ever exposure and dose response]. We hypothesize that a true biological effect would be greatest among long-term users and expect to see a greater effect in patients who began the medications longest ago." In other words, the study was designed to look first at "ever exposure" to Actos® as the primary endpoint and then at length of exposure ("dose response") as the secondary endpoint. The study authors anticipated that the secondary endpoint would be essential to help determine if Actos® functions as a cancer initiator, in which case brief exposures might be crucial, or if Actos® functions as a promoter, such that the amount of exposure might be more important.

As to the Neumann study, Dr. Smith testified that the study was significant, aside from its methodological shortcomings, because of the very large sample size involved. In addition, the study's author explained that the study was altered after its initiation so the maximum age of participants was 79 because "[t]he misclassification of bladder cancer cases in this age group is such that it did not appear feasible to draw any valid conclusions, which is why we decided to limit our analysis to results obtained in patients aged 40 to 79 years." The author also pointed out countervailing factors mitigating the absence of covariates such as history of diabetes and smoking (i.e., diabetes duration was in fact estimated by other means, and the study result viewed in relation to smoking suggested a possible underestimation of the risk of bladder cancer related to exposure to Actos®).

Regarding the Azoulay study, published in the British Medical Journal, the authors acknowledged the database they used lacked information on risk factors for bladder cancer such as arsenic, occupational exposures, race/ethnicity, and family history of bladder cancer. They continued, "However, it is unlikely that these variables were differentially distributed between ever users of pioglitazone and ever users of other oral hypoglycaemic agents. Thus *we do not believe that the absence of these variables*

affected the internal validity of the study, although residual confounding may still be present." (Italics added.) The database did contain information on several important confounders, such as body mass index, excessive alcohol use, and smoking. In addition, the study had the distinct strength of relying on a large cohort of patients with type 2 diabetes, followed for up to 22 years, enabling the identification of a large number of bladder cancer cases with varying durations of diabetes. The database also contained prerecorded information on prescriptions, thus eliminating the possibility of recall bias.

From the foregoing discussion we mean to illustrate and emphasize that the validity of these studies, and both their strengths and their weaknesses, are subject to considerable scientific interpretation and debate. The trial court abused its discretion by essentially stepping in and resolving the debate over the validity of the studies. In particular, the trial court's piecemeal rejection of individual studies was inappropriate and ignored the testimony by Drs. Neugut and Smith that the results of the individual studies considered as a whole, including in the meta-analyses, was what really persuaded them that Actos® causes bladder cancer. All studies have limitations and flaws, and it is entirely valid to interpret each study's results by taking into account these limitations and flaws. However, it is essential that the results of other studies conducted by other scientists on the same subject, that aim to correct for the limitations and flaws in prior studies, be taken into account, and the body of studies be considered as a whole.[17] As Dr. Neugut testified, any one study can be criticized, but if most studies consistently reach a similar answer, that gives confidence to an epidemiologist that the answer is correct.

As recognized by the trial court here, "courts must also be cautious in excluding expert testimony. The trial court's gatekeeping role does not involve choosing between competing expert opinions. The high court warned that the gatekeeper's focus 'must be

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17 For example, the Colmers meta-analysis showed a significant increased risk of bladder cancer with Actos®, as did the Bosetti article, which was a meta-analysis involving 17 studies that had both positive and negative findings.

solely on principles and methodology, not on the conclusions that they generate.' (*Daubert v. Merrell Dow Pharmaceuticals, Inc.* [(1993)] 509 U.S. [579,] 595.) The advisory committee on the 2000 amendments to Federal Rules of Evidence, rule 702 (28 U.S.C.), which codified the rule established in *Daubert*, noted that the trial court's task is not to choose the most reliable of the offered opinions and exclude the others: '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. The amendment is broad enough to permit testimony that is the product of competing principles or methods in the same field of expertise.' (Advisory Com. Notes to Fed. Rules Evid., rule 702, 28 U.S.C.)

"The trial court's preliminary determination whether the expert opinion is founded on sound logic is not a decision on its persuasiveness. The court must not weigh an opinion's probative value or substitute its own opinion for the expert's opinion. Rather, the court must simply determine whether the matter relied on can provide a reasonable basis for the opinion or whether that opinion is based on a leap of logic or conjecture. The court does not resolve scientific controversies. Rather, it conducts a 'circumscribed inquiry' to 'determine whether, as a matter of logic, the studies and other information cited by experts adequately support the conclusion that the expert's general theory or technique is valid.' [Citation.] *The goal of trial court gatekeeping is simply to exclude 'clearly invalid and unreliable' expert opinion.* [Citation.] In short, the gatekeeper's role 'is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.' [Citation.]" (*Sargon, supra*, 55 Ca1.4th at p. 772; italics added.)

Indeed, the court purported to be following the dictates of *Sargon*. It stated in its order: "As part of the Court's duties under Evidence Code §802, as set forth in *Sargon*, the Court 'may inquire into . . . not only the type of material on which an expert relies, but also whether that material *actually supports the expert's reasoning*. "A court may conclude that there is simply too great an analytical gap between the data and the opinion

proffered." ' *Sargon*, 55 Cal.4th at 771[-772] (citing *General Electric Co. v. Joiner* (1997) 522 U.S. 136, 146) (emphasis added)."

We find that the trial court erred in excluding Dr. Smith's opinion testimony regarding specific causation as being clearly speculative, unreliable, lacking in intellectual rigor, and based only on studies that did not actually support his reasoning. Dr. Smith is one of the foremost experts in the world on bladder cancer, and provided helpful and appropriate expert testimony to assist the jury in deciding the complicated issue of whether Cooper's cancer was caused by Actos®.

The expert testimony rejected by the Supreme Court in *Sargon* provides a distinct and illustrative contrast to the testimony wrongfully deemed inadmissible in the case before us. In *Sargon*, the manufacturer of a novel dental implant brought an action for breach of contract against a university with which it contracted to perform clinical testing of the device. In support of the manufacturer's claim for lost profits, an expert testified that the small manufacturer, that had annual net profits of $101,000, would have become a worldwide leader in the dental implant industry and would have earned profits ranging from $200 million to $1 billion if the university had not breached its contract. The trial court excluded that expert's opinion as speculative and unreliable, and the Supreme Court affirmed that ruling. The expert's market share approach to computing lost profits was based upon a comparison of Sargon to six large, multinational dental implant companies that were the dominant market leaders in the industry. (*Sargon*, *supra*, 55 Cal.4th at p. 756.) Unlike the comparator companies, Sargon had no meaningful marketing or research and development organization, and no parent company to assist it. The expert testified that the product was so innovative and superior that within 10 years Sargon would have become the market leader. (*Id.* at p. 757.) He acknowledged that he had no expertise in the dental implant field or in determining how innovative Sargon's device was, and that the damages calculation depended on the innovativeness of the product, as well as his assumption that the market share of each of the six comparator companies reflected its degree of innovativeness. The trial court deemed inadmissible the expert's testimony, finding " '[t]o the extent that this ranking of "innovativeness," . . . rests on the

fact that some [dental implant companies] have larger market shares, it rests on nothing more than a tautology. As there is no evidentiary basis that equates the degree of innovativeness with the degree of difference in market share, the question posed to the jury—to rank innovativeness and assign a market share, the *sine qua non* of [the expert's] opinion—has no rational basis.' " (*Id.* at pp. 763-764.) The expert testified that if there had been no breach of contract, Sargon would have gone from a three-person operation to sharing industry leadership with a multi-million dollar international corporation, and would have done so in part by investing in research and development that would have produced new products. (*Id.* at pp. 765-766.) The trial court found this to be " 'absolutely devoid of any factual basis about an industry where he has no expertise.' " (*Id.* at p. 766.)

After the Court of Appeal reversed the trial court's ruling, the Supreme Court granted review and found that the trial court had not erred in excluding the expert's testimony. The high court concluded, "An accountant might be able to determine with reasonable precision what Sargon's profits would have been *if* it had achieved a market share comparable to one of the 'Big Six.' The problem here, however, is that the expert's testimony provided no logical basis to infer that Sargon *would* have achieved that market share. The lack of sound methodology in the expert's testimony for determining what the future would have brought supported the trial court's ruling." (*Sargon*, *supra*, 55 Cal.4th at p. 781.)

The Court observed, "The trial court's preliminary determination whether the expert opinion is founded on sound logic is not a decision on its persuasiveness. The court must not weigh an opinion's probative value or substitute its own opinion for the expert's opinion. Rather, the court must simply determine whether the matter relied on can provide a reasonable basis for the opinion or whether that opinion is based on a leap of logic or conjecture. The court does not resolve scientific controversies. Rather, it conducts a 'circumscribed inquiry' to 'determine whether, as a matter of logic, the studies and other information cited by experts adequately support the conclusion that the expert's general theory or technique is valid.' [Citation.] The goal of trial court gatekeeping is

simply to exclude 'clearly invalid and unreliable' expert opinion. [Citation.]" (*Sargon*, *supra*, 55 Cal.4th at p. 772.)

The nature and reliability of Dr. Smith's testimony in this case bears no resemblance to the expert testimony in *Sargon*. In *Sargon*, the expert had no reasonable basis for his opinion on lost profits, and reached his conclusions only by speculating and making readily discernible leaps of logic. The same cannot be said about Dr. Smith's testimony. Although the trial court denied doing so, it did in fact weigh the probative value of Dr. Smith's opinion, and the studies upon which he relied, and substituted its own opinion for Dr. Smith's. The court did engage in settling a scientific controversy when it looked piecemeal at a large body of epidemiological studies before finding the expert's opinion based on those studies wholly lacking in foundation, when it engaged in an analysis of whether studies reporting secondary endpoints were inherently unreliable, and when it disregarded other studies because it found the methodology, which was fully explained to the scientific community in peer-reviewed journals, to be misleading. "The courts' evidentiary gatekeeping function is . . . not a warrant for judicial intervention in genuine scientific debates over substantive principles." (*People v. Superior Court (Vidal)* (2007) 40 Cal.4th 999, 1014.) The flaws in the study methodologies were explored in detail through cross-examination and with the defense expert witnesses, and constituted evidence that went to the weight and not the admissibility of Dr. Smith's opinion testimony based on those studies. Those were matters for the jury to decide. Fortunately the trial court allowed the jury to weigh those criticisms and explanations, and permitted the jury to render a verdict which we may now restore.

Even if the court had not found that Dr. Smith could not reasonably rely on the epidemiological studies and that his opinion was unsupported by the materials, the trial court questioned what other basis Dr. Smith had for his differential diagnosis, other than ruling in Actos® based on the studies. The court noted that the studies showing an increased risk of bladder cancer in people taking Actos®, "appeare[d] to be the one thing that is ruled in," but the court wanted an explanation of what, "in addition to the study, does he have to show that Mr. Cooper got bladder cancer because of that? Because

Dr. Smith says that he has a lot of patients in this age group who have bladder cancer, and he can find no cause. So the question is what, in addition to these studies, is Dr. Smith basing his differential diagnosis on."

The epidemiological studies relied on by Dr. Smith indicated exposure to Actos® resulted in hazard ratios for developing bladder cancer ranging from 2.54 to 6.97.[18] By demonstrating a relative risk greater than 2.0 that a product causes a disease, epidemiological studies thereby become admissible to prove that the product at issue was more likely than not responsible for causing a particular person's disease. "When statistical analyses or probabilistic results of epidemiological studies are offered to prove *specific* causation . . . under California law those analyses must show a relative risk greater than 2.0 to be 'useful' to the jury. [*Daubert v. Merrell Dow Pharmaceuticals Inc.* (9th Cir. 1995) 43 F.3d 1311, cert. den. 516 U.S. 869 [116 S.Ct. 189, 133 L.Ed.2d 126] *Daubert II*, at p. 1320. This is so, because a relative risk greater than 2.0 is needed to extrapolate from generic population-based studies to conclusions about what caused a specific person's disease. When the relative risk is 2.0, the alleged cause is responsible for an equal number of cases of the disease as all other background causes present in the control group. Thus, a relative risk of 2.0 implies a 50% probability that the agent at issue was responsible for a particular individual's disease. *This means that a relative risk that is greater than 2.0 permits the conclusion that the agent was more likely than not responsible for a particular individual's disease.* [Reference Manual on Scientific Evidence (Federal Judicial Center 2d ed. 2000) ("Ref. Manual"),] *Ref. Manual* at 384, n. 140 (citing *Daubert II*)." (*In re Silicone Gel Breast Impl. Prod. Liab. Lit.* (C.D.Cal. 2004) 318 F.Supp.2d 879, 893; italics added.) Thus, having considered and ruled out

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18 For example, the second Interim Nested Case Analysis of the Kaiser Permanente study demonstrated that long-term users of Actos® had a relative risk for bladder cancer of 4.6. Takeda's own meta-analysis of its clinical trials showed a statistically significant hazard ratio of 2.642. In Azoulay, the authors found a statistically significant hazard ratio of 2.54 for patients exposed to more than 28,000 mg of Actos®.

other background causes of bladder cancer based on his medical records, Dr. Smith could conclude based on the studies that it was more likely than not that Cooper's exposure to Actos® caused his bladder cancer. In other words, because the studies, to varying degrees, adjusted for race, age, sex, and smoking, as well as other known causes of bladder cancer, Dr. Smith could rely upon those studies to make his differential diagnosis ruling in Actos®—as well as smoking—and concluding that Actos® was the most probable cause of Cooper's disease.

4. *Materials Reviewed After First Deposition*

We briefly note that the trial court also ruled that Dr. Smith could not rely for his opinion at trial on the Mamtani study or Cooper's deposition testimony, because he had not reviewed those documents before his deposition. We conclude that this was error.

Evidence Code section 801, subdivision (b) states an expert may base his or her opinion on any reliable information "perceived by or personally known to the [expert] witness or made known to him [or her] at or before the hearing." The cases cited by the court indeed held that an expert cannot state at trial undisclosed opinions. (See *Kennemur v. State of California* (1982) 133 Cal.App.3d 907, 919; *Bonds v. Roy* (1999) 20 Cal.4th 140, 141, 148.) However, those cases are entirely distinguishable from the one before us. In *Kennemur*, the court merely held that an expert must disclose the *general substance* of his or her opinions through a designation or a deposition. In *Bonds,* the court excluded an expert's testimony where the proffered opinion was one the expert had expressly disavowed at his deposition, also citing the rule that a party must disclose "the general substance of an expert's expected testimony." (*Bonds*, *supra*, at p. 148.)

Here, Dr. Smith's expert designation, served on December 7, 2012, stated "Dr. Smith will explain that Mr. Cooper's distant history of smoking is far less likely than Actos® to have contributed to his bladder cancer. Mr. Cooper smoked fewer than three cigarettes per day before quitting in 1974." He further stated he had performed a differential diagnosis, and "ha[d] given careful consideration to, and *ruled out* other confounding factors in causing Jack Cooper's bladder cancer." Dr. Smith was deposed on December 7, 2012, and then again on February 12, 2013. At the second deposition, he

stated that he had by then also reviewed the Mamtani article, and Takeda's counsel thoroughly examined Dr. Smith regarding the Mamtani study. Dr. Smith had also read Cooper's deposition transcript prior to his second deposition. In any event, Takeda never pointed to any relevant information in the deposition which was not contained in the medical records. We conclude that Dr. Smith was entitled to rely on both documents for his opinion at trial. He had previously disclosed the general substance of his opinion, he did not disavow that opinion at any time, and in any event, Takeda had the opportunity to examine his opinion on those matters before trial.

II. The Motion for New Trial Based on Instructional Error

A. *Factual Background and Jury Instructions on Causation*

In addition to granting JNOV, the trial court also granted Takeda's motion for new trial, on two independent grounds. First, it concluded the evidence was insufficient to support the jury's verdict because "there is no evidence of specific causation in this case," the court having struck Dr. Smith's testimony in that regard, and therefore plaintiffs "could not have met their burden of showing that any failure to warn was a substantial factor in causing harm" to Cooper. In view of the foregoing discussion, we of course conclude that the court erred in granting the motion for new trial on this basis. The evidence was clearly sufficient to support the jury's finding that Actos® was a substantial factor in causing Cooper's bladder cancer.

Second, the trial court concluded that it was error to have given what it had termed in the jury instructions a "multiple causation" instruction. The court granted the motion for new trial on the basis that the instruction should not have been given because it was not supported by substantial evidence, since neither side introduced evidence of multiple causation. The court further held that "the CACI 431 instruction was prejudicial and probably affected the jury verdict, given the lack of evidence of concurrent causation" because "[w]ithout the instruction, the jury would not have been in a position to consider multiple concurrent causes." This ruling was premised on the court's perception that there was no evidence offered that Actos® combined with some other cause resulting in

Cooper's development of cancer, and that Dr. Smith had specifically ruled out smoking as a factor in causing Cooper's bladder cancer.

The court had also instructed the jury based on a version of CACI 430, entitled "Causation: Substantial Factor," as follows: "You have heard me mention the requirement that conduct be a substantial factor in causing harm. A substantial factor in causing harm is a factor that a reasonable person would consider to have contributed to the harm. It must be more than a remote or trivial factor. It does not have to be the only cause of the harm. [¶] Conduct is not a substantial factor in causing harm if the same harm would have occurred without that conduct."

At Cooper's request and over Takeda's repeated objections, the court also gave the "multiple causation instruction" (a version of CACI 431). As given, that instruction stated that: "A person's negligence may combine with another factor to cause harm. If you find that Takeda's negligence was a substantial factor in causing Mr. Cooper's harm, then Takeda is responsible for the harm. Takeda cannot avoid responsibility just because some other person, condition, or event was also a substantial factor in causing Mr. Cooper's harm."

Takeda contends on appeal, as it did in the trial court in discussing jury instructions and in its motion for new trial, that the instruction on multiple causation should not have been given because neither Cooper nor Takeda presented evidence that some other factor *combined with Actos®* to cause Cooper's bladder cancer.

B. *Discussion*

Based on our review of the record, we find that there was substantial evidence to support the giving of the challenged instruction, and therefore the trial court committed error in granting the motion for new trial on the ground that it should not have been given and resulted in prejudice to Takeda.

Dr. Smith did not rule out smoking as a potential cause of Cooper's bladder cancer. He said in conducting his differential diagnosis, after ruling out other exposures, he "was really left with trying to evaluate smoking versus Actos as the most substantial risk factors." Dr. Smith stated that, compared to Actos®, smoking proved to be *not as*

important a factor as Actos® in causing bladder cancer. He candidly admitted that smoking "could be a cause of his bladder cancer." When asked, "Doctor, you will agree, would you not, sir, that Mr. Cooper's history of smoking, whether it be 20 years or 40 years, certainly could be a cause of his bladder cancer?" He unambiguously replied in the affirmative, and said that it was one of the things he ruled in.

Dr. Smith testified that regardless of when Cooper stopped smoking, Actos® ingestion was, in his opinion, more likely to have been the *most* substantial factor in causing Cooper's bladder cancer than his smoking history. He concluded: "[A]fter review of all the potentials, differential diagnosis, ruling in, ruling out, carefully evaluating the occupational, environmental, and smoking, that it's my opinion that *the most substantial causative factor* for Mr. Cooper was his length of Actos and cumulative dose of Actos." (Italics added.)

From this testimony, it is evident that Cooper did not argue that he developed bladder cancer only because he was exposed to Actos®. He allowed for the possibility that his smoking history played a role as well. He sought, however, to convince the jury that the effect of Actos® was more pronounced, that it played a significantly more prominent role in his development of bladder cancer than did smoking. As such, we conclude the jury was properly instructed.

DISPOSITION

The trial court's order granting Takeda's judgment notwithstanding the verdict and in the alternative its motion for new trial, filed June 27, 2013, and the trial court's order granting judgment in favor of Takeda, filed July 18, 2013, are reversed. The trial court is ordered to enter judgment for Cooper in accordance with the jury verdict of April 26, 2013, without further proceedings. Plaintiff Cooper is to recover his costs on appeal.

NOT TO BE PUBLISHED IN THE OFFICIAL REPORTS

ALDRICH, J.

We concur:

EDMON, P. J.

KITCHING, J.