APPENDIX A

FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

STEPHEN WENDELL; LISA WENDELL, for themselves and as successors-in-interest to Maxx Wendell, deceased, *Plaintiffs-Appellants*, v. GLAXOSMITHKLINE LLC; TEVA PHARMACEUTICALS USA, INC., *Defendants-Appellees*.	No. 14-16321 D.C. No. 4:09-cv-04124-CW OPINION

Appeal from the United States District Court
for the Northern District of California
Claudia Wilken, District Judge, Presiding

Argued and Submitted September 16, 2016
San Francisco, California

Filed June 2, 2017

Before: Ronald M. Gould and
Marsha S. Berzon, Circuit Judges, and
William K. Sessions III,[*] District Judge.

[*] The Honorable William K. Sessions III, United States District Judge for the District of Vermont, sitting by designation.

OPINION

GOULD, Circuit Judge:

Maxx Wendell[1] tragically died at the age of 21 of Hepatosplenic T-cell lymphoma (HSTCL), an exceedingly rare and aggressive form of cancer. For many years before his development of HSTCL, Maxx was treated with a combination of drugs for inflammatory bowel disease. After his death, his parents, Stephen and Lisa Wendell (Plaintiffs), sued the manufacturers and distributors of these drugs, asserting claims under California law for negligence and strict liability. Plaintiffs alleged that the drugs caused Maxx to develop HSTCL and that the manufacturers and distributors did not give adequate warnings about the risks associated with the drugs.

The district court granted summary judgment to Teva Pharmaceuticals USA, Inc. (Teva), concluding that the Plaintiffs did not present admissible expert testimony of causation and did not show that Maxx's prescribing physician relied on the warning labels. For the same reasons, the district court dismissed as moot Plaintiffs' motion for leave to file a motion for reconsideration of the district court's prior order granting summary judgment to GlaxoSmithKline LLC (GSK). We reverse and remand.

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[1] We refer to Maxx Wendell by his first name to avoid confusion.

I

In 1998, at the age of twelve, Maxx was diagnosed with a form of inflammatory bowel disease (IBD) called ulcerative colitis. IBD is an autoimmune disease characterized by chronic inflammation. Maxx began treatment with Dr. Edward Rich, a pediatric gastroenterologist at Kaiser Permanente in San Francisco. Relevant here, in June 1999, Dr. Rich prescribed mercaptopurine (6-MP), an immunosuppressant, and one of a class of drugs known as thiopurines. At the time, 6-MP was manufactured by GSK and marketed as Purinethol. Although it has been widely used off-label since 1980 to treat IBD,[2] Purinethol has never received approval for this use.

In July 2002, Dr. Rich prescribed an additional drug, the tumor necrosis factor alfa antagonist (anti-TNF) drug infliximab, marketed as Remicade. Anti-TNF drugs are approved to treat various autoimmune disorders, such as Crohn's disease and rheumatoid arthritis.

Maxx received his last dose of Remicade in March 2006, after which his IBD went into remission. Two months later, the Food and Drug Administration approved a new label for the drug. The label included a warning reporting postmarketing cases of HSTCL in young male patients with Crohn's disease treated with both Remicade and a thiopurine such as

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[2] Off-label use of a drug is legal, and is "generally based on published scientific reports purporting to show a beneficial effect of the drug in such indications or patient populations."

6-MP or azathioprine. Centocor, the maker of Remicade, also issued a "Dear Health Care Provider" letter alerting prescribers to the labeling change and giving more details on the cases of HSTCL. When Maxx's symptoms returned, Dr. Rich prescribed another anti-TNF drug, Humira, which Maxx took until June 2007. At the time Dr. Rich prescribed Humira, its label did not warn of the risk of HSTCL.

Maxx remained continuously on 6-MP from June 1999 until about March or April 2007. GSK stopped marketing Purinethol on July 1, 2003, and transferred ownership rights for the drug to Teva. Maxx continued on Teva's Purinethol until July 2004, when Dr. Rich switched him to a generic 6-MP. According to Maxx's mother, Maxx decided to stop taking 6-MP in 2007 after reading in *Men's Health* that young men on a combination of Remicade and other immunosupressive medication had developed HSTCL.

In July 2007, Maxx checked into the emergency room with fevers, fatigue, and malaise. Several days later he was diagnosed with HSTCL—a non-Hodgkin's lymphoma that is exceedingly rare and aggressive. It has "low responses to chemotherapy, frequent relapses after contemporary treatments and the inability of the majority of the patients to undergo bone marrow transplantation." Most patients die within the first year of diagnosis; only a very small fraction achieve long-term survival. Maxx died from HSTCL on December 6, 2007, at the age of 21.

In July 2009, Plaintiffs, Maxx's parents, sued multiple drug companies in Superior Court in California. The case was removed to federal court in September 2009. Plaintiffs filed the operative fourth amended complaint in April 2011. Several defendants, including GSK and Teva, then moved for summary judgment. The district court granted the motion, but subsequently withdrew its summary judgment order in light of Plaintiffs' need for further discovery. In July 2012, after reviewing new evidence, the district court denied the motion for summary judgment as to Teva and two other drug companies, Par Pharmaceutical, Inc. and Abbott Laboratories. The court granted summary judgment to GSK because it determined that Plaintiffs had not presented sufficient evidence that a reasonable jury could find GSK had a duty to warn of the risk of HSTCL before July 1, 2003, when GSK stopped distributing Purinethol. A year later, the district court granted summary judgment to Par Pharmaceuticals.

In January 2014, the remaining defendants—including Teva—filed another motion for summary judgment. Plaintiffs settled their claims against the remaining defendants, except for Teva, before the district court ruled on the motion for summary judgment.

On June 30, 2014, the district court granted Teva's motion for summary judgment because the testimony of Plaintiffs' causation experts, Dr. Andrei Shustov and Dr. Dennis Weisenburger, was not reliable and therefore not admissible under Federal Rule of Evidence 702, and because Plaintiffs did not present

evidence that Maxx's prescribing physician relied on Teva's warning labels. It also denied Plaintiffs' motion for leave to file a motion for reconsideration of the Court's July 2012 order granting summary judgment to GSK. Plaintiffs filed a timely notice of appeal, challenging the district court's grant of summary judgment to Teva and its denial of their motion for leave to file a motion for reconsideration.

II

We review the district court's ruling on the admissibility of expert testimony for an abuse of discretion. *Messiah v. Novartis Pharm. Corp.*, 747 F.3d 1193, 1196 (9th Cir. 2014). However, we "review *de novo* the 'construction or interpretation of . . . the Federal Rules of Evidence, including whether particular evidence falls within the scope of a given rule.'" *Id.* (alteration in original) (quoting *United States v. Durham*, 464 F.3d 976, 981 (9th Cir. 2006)). We also review *de novo* the district court's grant of summary judgment. *Id.* at 1199.

III

The issues presented in this appeal arise under the Federal Rules of Evidence and California substantive law. *See Motus v. Pfizer Inc. (Roerig Div.)*, 358 F.3d 659, 660 (9th Cir. 2004) (explaining that in diversity actions the court applies state substantive law and the federal rules of procedure). We begin with the rules of evidence.

A

Federal Rule of Evidence 702 governs expert testimony. It provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
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> (c) the testimony is the product of reliable principles and methods; and
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> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702.

Pursuant to the Federal Rules of Evidence, the district court judge must ensure that all admitted expert testimony is both relevant and reliable. *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589 (1993). Defendants do not contest that the opinions of Dr. Weisenburger and Dr. Shustov are relevant; the only question, therefore, is whether they are reliable.

Scientific evidence is reliable "if the principles and methodology used by an expert are grounded in the methods of science." *Clausen v. M/V New Carissa*,

339 F.3d 1049, 1056 (9th Cir. 2003). The focus of the district court's analysis "must be solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509 U.S. at 595. As we explained in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the court's "task . . . is to analyze not what the experts say, but what basis they have for saying it." 43 F.3d 1311, 1316 (9th Cir. 1995) (hereinafter *Daubert II*).

To assist courts with this task, the Supreme Court has listed several non-exclusive factors that judges can consider when determining whether to admit expert testimony under Rule 702. *See Daubert*, 509 U.S. at 593-95. These include: "whether the theory or technique employed by the expert is generally accepted in the scientific community; whether it's been subjected to peer review and publication; whether it can be and has been tested; and whether the known or potential rate of error is acceptable." *Daubert II*, 43 F.3d at 1316. We also consider whether experts are testifying "about matters growing naturally" out of their own independent research, or if "they have developed their opinions expressly for purposes of testifying." *Id.* at 1317. These factors are illustrative, and they are not all applicable in each case. *Id.* The inquiry is "flexible," *Daubert*, 509 U.S. at 594, and "Rule 702 should be applied with a 'liberal thrust' favoring admission," *Messick*, 747 F.3d at 1196 (quoting *Daubert*, 509 U.S. at 588).

The district court concluded that the expert testimony of Dr. Shustov and Dr. Weisenburger did not meet the *Daubert* standard of reliability. The

district court first focused on the fact that the experts developed their opinions specifically for litigation, and had never conducted independent research on the relationship between 6-MP and anti-TNF drugs and the development of HSTCL. The court also noted that both doctors conceded that although their opinions were based on a reasonable degree of medical certainty, they "would not satisfy the standards required for publication in peer-reviewed medical journals." It concluded that the lack of independent research combined with the doctors' reluctance to publish, "casts doubt [on] the reliability of their methodologies under Rule 702."

Second, the district court determined that the lack of animal or epidemiological studies showing a causal link between HSTCL and the combination of 6MP and anti-TNF drugs also undermined the experts' methodology. The court concluded that although it might be difficult to conduct such studies, given the rarity of HSTCL, that type of causal evidence was "especially important here in light of the fact that more than seventy percent of observed HSTCL cases are idiopathic."[3] "[W]ithout some reliable evidence of a positive link between the drugs at issue and the disease," the district court concluded that the experts "cannot reasonably eliminate other potential causes of Maxx's HSTCL."

Finally, the district court found that the studies Drs. Weisenburger and Shustov cited did not "purport[] to show that the specific combination of

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[3] A disease that is idiopathic, or de novo, is one that does not have a known cause.

drugs prescribed to Maxx actually causes HSTCL." Although these studies contained statistics about the incidence of HSTCL in different patient populations, the court found that the experts did not show "that all of the observed differences in these incidence rates are statistically significant or that they account for plausible alternative causes of HSTCL, such as IBD itself." Further, the doctors did not present scientific evidence to support their opinion that IBD is not a risk factor for HSTCL.

Although we think it a close question, we conclude that the district court erred by excluding the experts' testimony. The district court looked too narrowly at each individual consideration, without taking into account the broader picture of the experts' overall methodology. It improperly ignored the experts' experience, reliance on a variety of literature and studies, and review of Maxx's medical records and history, as well as the fundamental importance of differential diagnosis by experienced doctors treating troubled patients. The district court also overemphasized the facts that (1) the experts did not develop their opinions based on independent research and (2) the experts did not cite epidemiological studies. We hold that all together, these mistakes warrant reversal. *Cf. Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1228-30 (9th Cir. 1998) (concluding that the expert's reliance on studies that showed a connection between collagen and autoimmune disorders combined with the expert's observations of the patient and review of her medical history was a sufficiently reliable methodology even though the cause-effect

relationship between the collagen and the disease was not conclusively established).

To begin, the experts were highly qualified doctors. Dr. Shustov is a licensed, board-certified physician and an Associate Professor of Medicine at the University of Washington Medical Center. He specializes in the diagnosis and treatment of lymphomas, with a clinical research focus on T-cell leukemia and lymphomas. He has treated "hundreds of patients with T-cell lymphomas," and "thousands of patients with lymphomas," including seven patients with HSTCL. Two of those patients were treated with the combination of drugs at issue here. Given the rarity of HSTCL, Dr. Shustov estimated that he has seen more cases of the disease than 99% of oncologists in the country. Dr. Weisenburger is an expert hematopathologist—a physician trained in the study and diagnosis of diseases of the bone marrow and the immune system—with more than 30 years of experience diagnosing non-Hodgkin lymphoma. He is the professor and Chair of the Department of Pathology at City of Hope Medical Center. Although he has not written specifically on HSTCL, he has written hundreds of papers on the subject of non-Hodgkin's lymphoma, including some on the potential causes of non-Hodgkin's lymphoma.

The doctors employed sound methodologies to reach their conclusions. Dr. Shustov based his opinions "on medical records as well as [his] education, training and experience, knowledge of the pertinent medical literature and [his] knowledge of the epidemiology, diagnosis and natural history of HSTCL." He explained: "I reviewed the literature, I

pulled the facts out of the literature." He found that the literature shows there is an increased risk of HSTCL in patients taking 6-MP over the general population. After reviewing the literature, he "compiled the numbers about frequency of diseases, about frequency of inflammatory bowel disease and [he] looked at the biological causation of lymphoma pertaining to this case."

Dr. Shustov stated that he performs differential diagnosis in attempting to diagnose every patient, and that he has applied the same technique to determine the cause of a disease. When performing a differential diagnosis, he first assumes the pertinence of all potential causes, then rules out the ones as to which there is no plausible evidence of causation, and then determines the most likely cause among those that cannot be excluded. We have recognized that this method of conducting a differential diagnosis is scientifically sound. *See Clausen*, 339 F.3d at 1057-58. For cases of HSTCL in patients that have taken 6-MP, like Maxx, Dr. Shustov recognized:

> that 6-MP is a well-known mutagen and carcinogen and puts every person who takes it at risk. And given the frequency of hepatosplenic lymphoma in [the] general population as . . . [compared to] those who take 6-MP, it makes it plausible or biologically plausible that that's [an] etiologic factor. You construct your differential diagnosis . . . [of] what might have caused lymphoma. You come up with the strongest probability that patient was taking carcinogen and developed lymphoma and you start thinking

> again what can cause his lymphoma, you can't identify anything else in the patient's history or his medical records.

Regarding Maxx specifically, Dr. Shustov stated that there was a one in six million chance that Maxx would have developed HSTCL without being exposed to 6-MP. In light of those odds, Dr. Shustov stated that "based on [his] experience in T-cell lymphomas, knowledge of the literature and being involved in T-cell lymphoma research in the past ten years" he determined "that it's much more likely that exposure to mutagen and immunosuppressants caused the lymphoma." Dr. Shustov did not need to eliminate all potential causes; "[i]t is enough that a [proposed cause] be a substantial causative factor." *Messiah*, 747 F.3d at 1199.

Dr. Weisenburger described his methodology for reaching his opinions as follows:

> I reviewed the medical records. I reviewed the pathology slides and confirmed the diagnosis. I reviewed all of the pathology records. I reviewed the literature on the disease, hepatosplenic lymphoma. And I reviewed all the literature I could find on causes of hepatopathic T-cell lymphoma, including literature on inflammatory bowel disease and treatments for inflammatory bowel disease. And then I used the Bradford Hill

> methodology to come to the conclusion that I did.[4,5]

Regarding Maxx specifically, Dr. Weisenburger based his opinion on "a summary of the medical records of [Maxx] as well as copies of the pathology reports, and the original slides of the diagnostic bone marrow," which he evaluated with over 30 years of experience diagnosing non-Hodgkin lymphoma. He stated that he considered that Maxx's HSTCL might have been idiopathic, and that although he was not entirely able to rule that possibility out, "[w]hen you have a patient with obvious and known risk factors, you tend to assume that those risk factors were the cause." He did not base that assumption on pure conjecture. As he discussed throughout his deposition testimony and in his expert report, the literature shows that patients exposed to 6-MP and anti-TNF drugs are at an increased risk for HSTCL. Dr. Weisenburger also weighed other risk factors, including Maxx's sex and age, and determined that those were "weak risk factors; whereas, the disease he had, particularly in the setting of the drugs he received would be considered very strong risk factors."

The proposed testimony was sufficiently reliable that the Plaintiffs' experts should have been allowed to testify under *Daubert*. The district court improperly required more. The Supreme Court in

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[4] The Bradford Hill methodology refers to a set of criteria that are well accepted in the medical field for making causal judgments.

[5] Dr. Weisenburger also identified at least one paper that showed there was no risk of lymphoma in IBD patients.

Daubert aimed at screening out unreliable or bogus expert testimony. Nothing in *Daubert*, or its progeny, properly understood, suggests that the most experienced and credentialed doctors in a given field should be barred from testifying based on a differential diagnosis.

First, the district court was wrong to put so much weight on the fact that the experts' opinions were not developed independently of litigation and had not been published. While independent research into the topic at issue is helpful to establish reliability, its absence does not mean the experts' methods were unreliable. Where "the proffered expert testimony is not based on independent research," the experts can instead present "other objective, verifiable evidence that the testimony is based on 'scientifically valid principles.'" *Daubert II*, 43 F.3d at 1317-18. To be sure, "[o]ne means of showing [that the testimony is based on scientifically valid principles] is by proof that the research and analysis supporting the proffered conclusions have been subjected to normal scientific scrutiny through peer review and publication." *Id.* at 1318. However, expert testimony may still be reliable and admissible without peer review and publication. *See Clausen*, 339 F.3d at 1056. That is especially true when dealing with rare diseases that do not impel published studies. *See Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 24 (1st Cir. 2011) (recognizing that the "rarity" of a particular form of leukemia was one reason that it would be "very difficult to perform an epidemiological study of the causes of [the disease] that would yield statistically significant results.").

The district court also wrongly conflated the standards for publication in a peer-reviewed journal with the standards for admitting expert testimony in a courtroom. Dr. Weisenburger stated on cross-examination that to publish his opinion he would use a "more rigorous" standard than the one he used to come up with his expert opinion. Dr. Shustov stated that he would not be comfortable publishing his opinion because he did not have any new data, and any meta-analysis or review of the literature could only be published upon invitation. The district court viewed these statements regarding the experts' willingness to publish as evidence that their *methods* were not up to snuff. But this analysis misses that while an expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999), the standards for courtroom testimony do not necessarily parallel those of the professional publications, *see Ambrosini v. Labarraque*, 101 F.3d 129, 138 (D.C. Cir. 1996) ("[T]he fact 'that science would require more evidence before conclusively considering the causation question resolved is irrelevant [to the admissibility of expert testimony].'") (quoting *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1536 (D.C. Cir. 1984)). For example, Dr. Shustov explained that, "[o]pinions are not publishable. Data is publishable. What I'm reporting here is my opinion." Although unwillingness to publish weighs against admissibility, it alone is not determinative. *See Daubert II*, 43 F.3d at 1318 n.9 ("That plaintiffs' experts have been unable or unwilling to publish

their work undermines plaintiffs' claim that the findings these experts proffer are 'ground[ed] in the methods and procedures of science' and 'derived by the scientific method.'" (alteration in original) (quoting *Daubert*, 509 U.S. at 590)). We have previously held expert opinions to be reliable that were not subject to peer review through publication. *See Clausen*, 339 F.3d at 1056, 1061.

The district court also wrongfully required that the experts' opinions rely on animal or epidemiological studies. Neither are necessary for an expert's testimony to be found reliable and admissible. *See Kennedy*, 161 F.3d at 1229. We have long recognized that it may not always be possible to conduct certain types of studies. *See, e.g., Daubert II*, 43 F.3d at 1318 n.9 ("There may well be good reasons why a scientific study has not been published. For example, it may be too recent or of insufficiently broad interest."). HSTCL is an exceedingly rare cancer, with only 100 to 200 cases reported since it was first recognized. It is not surprising that the scientific community has not invested substantial time or resources into investigating the causes of such a rare disease.

Although they did not rely on animal or epidemiological studies, the experts here did rely on other published studies and articles. The district court only addressed a few of these, quickly dismissing them because they are case reports and do not control or account for alternative causes of HSTCL. Although case studies alone generally do not prove causation, they "may support other proof of causation." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d

1194, 1199 (11th Cir. 2002). Here, the experts relied not just on these studies—which not only examined reported cases but also used statistical analysis to come up with risk rates—but also on their own wealth of experience and additional literature.[6]

We also note that "[n]ot knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even when we don't know precisely *how* the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage *somehow*." *Daubert II*, 43 F.3d at 1314 (emphasis in original). That there is no study that definitively states HSTCL is caused by the ingestion of 6-MP and anti-TNF drugs does not prevent the admission of Plaintiffs' experts' testimony. *See Kennedy*, 161 F.3d at 1230.

Finally, the district court erred when it excluded Plaintiffs' experts' opinion testimony because of the high rate of idiopathic HSTCL and the alleged inability of the experts to rule out an idiopathic origin or IBD itself. We do not require experts to eliminate all other possible causes of a condition for the expert's testimony to be reliable. *Messick*, 747 F.3d at 1199. It is enough that the proposed cause "be a substantial causative factor." *Id.* This is true in patients with multiple risk factors, and

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[6] Teva argues that its own experts highlight the dearth of scientific evidence to support Plaintiffs' claims and undermine any assertion that Drs. Shustov and Weisenburger employed sound scientific methodology. The district court did not consider this evidence, and we decline to do so in the first instance.

analogously, in cases where there is a high rate of idiopathy. *See id.* (holding that the district court abused its discretion when it excluded expert testimony as unreliable because the expert could not determine which of multiple risk factors caused plaintiff's disease). Moreover, when an expert establishes causation based on a differential diagnosis, the expert may rely on his or her extensive clinical experience as a basis for ruling out a potential cause of the disease. *See id.* at 1198. The district court abused its discretion by excluding Dr. Shustov's and Dr. Weisenburger's testimony because they could not completely rule out the possibility that Maxx's HSTCL was idiopathic.

Perhaps in some cases there will be a plethora of peer reviewed evidence that specifically shows causation. However, such literature is not required in each and every case. "The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed." *Clausen*, 339 F.3d at 1060 (quoting *Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1209 (8th Cir. 2000)). In the case of a rare disease like HSTCL, the Supreme Court's mandate that in determining the admissibility of expert testimony, the focus "must be solely on principles and methodology, not on the conclusions that they generate," is especially important. *Daubert*, 509 U.S. at 595.

Where, as here, the experts' opinions are not the "junk science" Rule 702 was meant to exclude, *see*

Estate of Barabin v. AstenJohnson, Inc., 740 F.3d 457, 463 (9th Cir. 2014), the interests of justice favor leaving difficult issues in the hands of the jury and relying on the safeguards of the adversary system—"[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof"—to "attack[] shaky but admissible evidence," *Daubert*, 509 U.S. at 596. Because we conclude that the district court erred in excluding the testimony of Dr. Shustov and Dr. Weisenburger, we reverse the district court's grant of summary judgment. *See Messick*, 747 F.3d at 1199. As explained in *Messick*, "[m]edicine partakes of art as well as science." *Id.* at 1198. Where, as here, two doctors who stand at or near the top of their field and have extensive clinical experience with the rare disease or class of disease at issue, are prepared to give expert opinions supporting causation, we conclude that *Daubert* poses no bar based on their principles and methodology. That defendants may be able to offer other equally qualified medical opinion opposing causation also does not support the idea that *Daubert* should bar the admission of the testimony of the doctors offered as experts by Plaintiffs. Instead, the testimony of Dr. Weisenburger and of Dr. Shustov should have been admitted as expert testimony under Federal Rules of Evidence 702. The defendants' expert testimony could have been offered in opposition. Then, the jury, as the trier of fact, would be empowered to decide, based on the law given in proper jury instructions and the facts as determined by the jury.

B

The district court granted summary judgment to Teva on the duty to warn claim for two reasons. First, the district court held that the lack of admissible causation evidence precluded Plaintiffs from prevailing on their duty to warn claims. Second, Plaintiffs did not produce "any evidence to suggest that Dr. Rich actually relied on Teva's warning labels before prescribing Purinethol to Maxx." For the reasons discussed above, we reverse on the district court's first ground. For the reasons discussed below, we reverse on the district court's second ground.

Under California law, drug manufacturers have a duty to warn physicians of risks that are known or scientifically knowable at the time of the drug's distribution. *See Carlin v. Superior Court*, 920 P.2d 1347, 1349-54 (Cal. 1996). "A plaintiff asserting causes of action based on a failure to warn must prove not only that no warning was provided or the warning was inadequate, but also that the inadequacy or absence of the warning caused the plaintiff's injury." *Motus v. Pfizer Inc.*, 196 F. Supp. 2d 984, 991 (C.D. Cal. 2001), aff'd, 358 F.3d 659. "[A] product defect claim based on insufficient warnings cannot survive summary judgment if stronger warnings would not have altered the conduct of the prescribing physician." *Motus*, 358 F.3d at 661.

In this case, viewing the evidence in the light most favorable to Plaintiffs, there is a genuine dispute of material fact as to whether Dr. Rich's conduct would

have changed with warnings from Teva and GSK. Summary judgment was improper.

Although Dr. Rich testified that it is not his "regular practice to look at drug labeling," when he does read them it is "one of the things that is part of [his] decision-making process." He also testified that "a black box warning means there is a significant side effect that I need to be aware of."[7] Indeed, this type of warning did influence Dr. Rich's prescribing decisions for Maxx. Centocor began circulating warnings—both a black box warning and a Dear Health Care Provider letter—about HSTCL for Remicade in May 2006, just a few months after Maxx stopped taking Remicade. When Maxx's IBD relapsed in November 2006, Dr. Rich prescribed Humira—which did not have a warning about HSTCL—in place of Remicade. Dr. Rich testified that he prescribed Humira because he believed it had a better safety profile, noting that at that point there were no reports of HSTCL developing in patients who took Humira. This change in prescribing practices which can, at least in part, reasonably be attributed to the lack of a warning for Humira creates a question of material fact as to whether the presence of a warning on Teva's Purinethol would have changed Dr. Rich's prescribing practices as to Maxx.

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[7] A black box warning is a warning that is placed in a box in a drug's labeling information. According to Plaintiffs' pharmacovigilance expert, a black box warning may only be used with FDA authorization, and it is "the strongest possible warning that can be given short of restricting distribution of a drug or completely withdrawing it from the market."

There is also evidence that Dr. Rich changed his prescribing practices generally after he learned of incidents of HSTCL in patients taking both 6-MP and anti-TNF agents. As the information came out, his prescribing practices evolved. He now no longer prescribes combination therapy but uses only monotherapy. Viewing the facts in the light most favorable to the Plaintiffs, there are questions of material fact as to whether warnings would have changed Dr. Rich's prescribing practice. *See Stanley v. Novartis Pharm. Corp.*, 11 F. Supp. 3d 987, 1003 (C.D. Cal. 2014) ("[C]hanges to treatment and prescription procedures create[d] a triable question of fact on specific causation."). We reverse the district court's grant of summary judgment in favor of Teva.[8]

C

Teva urges us to affirm the district court on four alternative grounds.[9] Although we may affirm on

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[8] GSK asserts that Plaintiffs' warning expert's testimony shows that Purinethol's label should have been changed in 2006, approximately three years after GSK stopped distributing the drug. It argues that there can be no causal connection between the alleged failure to warn and the harm. The district court did not address this argument, and we decline to do so. *See Greater L.A. Council on Deafness, Inc. v. Zolin*, 812 F.2d 1103, 1107 & n.5 (9th Cir. 1987), *superceded by statute on other grounds*.

[9] Briefly, Teva argues that we should affirm on each of the following four bases: (1) it had no duty to warn about the alleged risk of HSTCL arising from an off-label use of Purinethol; (2) it had no duty to warn about alleged risks from use of a competitor's product; (3) Plaintiffs cannot maintain a failure to warn claim because Dr. Rich had already received the

any ground raised below and supported by the record, *see Proctor v. Vishay Intertechnology Inc.*, 584 F.3d 1208, 1226 (9th Cir. 2009), the issues that Teva raises would require extensive fact finding, and are matters on which the district court did not rule. It would be inappropriate for us to reach these issues, and we decline to do so. *See Greater L.A. Council on Deafness, Inc. v. Zolin*, 812 F.2d 1103, 1107 & n.5 (9th Cir. 1987), *superceded by statute on other grounds*. They may be raised with the district court on remand.

D

Finally, Plaintiffs challenge the district court's order denying Plaintiffs' motion for leave to file a motion for reconsideration of the district court's July 2012 order granting summary judgment to GSK. GSK asserts that, as Plaintiffs' opening brief does not challenge the district court's underlying grant of summary judgment to GSK, Plaintiffs abandoned their argument that the district court erroneously granted summary judgment to GSK.

GSK's argument is unpersuasive. As to GSK, Plaintiffs are challenging *only* the district court's denial of its motion for leave to file a motion for reconsideration. A challenge to a denial of a motion for leave to file a motion for reconsideration brings up just the denial of that motion, not the underlying merits. *Cf. Molloy v. Wilson*, 878 F.2d 313, 315 (9th

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information; and (4) because Plaintiffs cannot prove that Maxx developed HSTCL after May 2006, they cannot prove that an alleged failure to warn by Teva was the proximate cause of Maxx's injuries.

Cir. 1989) ("An appeal from a denial of a Rule 60(b) motion brings up only the denial of the motion for review, not the merits of the underlying judgment."). Plaintiffs did raise this argument in their opening Brief, asserting that because the district court's rulings regarding the admissibility of expert testimony and causation were erroneous, "the ruling on Plaintiffs' motion likewise should be vacated so that it can be decided on its merits on remand."

We agree with Plaintiffs. The district court denied their motion "as moot" because "Plaintiffs cannot prevail on their claims against [GSK] for the same reasons they cannot prevail on their claims against Teva": lack of admissible causation evidence, and lack of evidence showing Dr. Rich's reliance on warnings. Because we reverse the district court on those issues, we also reverse the district court's denial of Plaintiffs' motion for reconsideration.

REVERSED AND REMANDED.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

STEPHEN WENDELL, et al., Plaintiffs, v. JOHNSON & JOHNSON, et al., Defendants. /	No. C 09-4124 CW ORDER GRANTING MOTION FOR SUMMARY JUDGMENT; DENYING MOTION FOR LEAVE TO FILE MOTION FOR RECONSIDERATION (Docket Nos. 257, 319, 355)

Plaintiffs Stephen and Lisa Wendell brought this action as successors-in-interest to their deceased son, Maxx Wendell. They asserted claims for negligence and strict liability against Defendants Johnson & Johnson, Centocor, Inc., Abbott Laboratories, Teva Pharmaceuticals USA, GlaxoSmithKline, and Par Pharmaceutical, Inc.[1] In January 2014, Defendants Johnson & Johnson, Centocor, Abbott Labs, and Teva moved jointly for summary judgment on all claims against them; however, shortly after the Court took this motion under submission, Plaintiffs

[1] Plaintiffs also initially brought suit against Gate Pharmaceuticals. However, because Gate is merely a division of Teva, rather than a separate entity, the Court construes the claims against Gate as claims against Teva.

reached a settlement in principle of their claims against Johnson & Johnson, Centocor, and Abbott Labs. The parties finalized their settlement agreements in June 2014. As a result, Teva is now the only Defendant remaining in this action and the only party still seeking summary judgment. Plaintiffs oppose Teva's motion for summary judgment. After considering the parties' submissions and oral argument, the Court grants the motion.

BACKGROUND

The following facts are undisputed except where otherwise noted.

Maxx Wendell was diagnosed with inflammatory bowel disease (IBD) in 1998 when he was twelve years old. Soon afterward, he began receiving treatment from Dr. Edward Rich, a pediatric gastroenterologist, at Kaiser Permanente in San Francisco, California.

In June 1999, Dr. Rich prescribed a six-mercaptopurine (6MP) drug to treat Maxx's IBD. The drug was manufactured by GlaxoSmithKline, then known as SmithKline Beecham, and marketed under the brand name Purinethol.

Three years later, in July 2002, while Maxx was still taking Purinethol, Dr. Rich prescribed him an anti-tumor necrosis factor (anti-TNF) drug called Remicade, which was manufactured, marketed, and distributed by Centocor.

In July 2003, GlaxoSmithKline sold its distribution rights for Purinethol to Teva and ceased distributing the drug. Maxx continued to take the Teva-distributed Purinethol until July 2004 when he switched to a generic 6MP drug distributed by Par Pharmaceutical, Inc. Maxx continued to take the generic 6MP drug until April 2007.

In May 2006, after Maxx's IBD symptoms had subsided, Dr. Rich directed Maxx to stop taking Remicade. In November 2006, however, after Maxx's symptoms returned, Dr. Rich prescribed him another anti-TNF drug called Humira. Maxx continued to take Humira, which is manufactured, marketed, and distributed by Abbott Labs, until June 2007.

One month later, in July 2007, Maxx was diagnosed with a rare, incurable, and aggressive form of cancer known as hepatosplenic T-cell lymphoma (HSTCL). He passed away in December 2007 at the age of twenty-one.

Plaintiffs initiated the present lawsuit in July 2009 and filed their fourth amended complaint (4AC) in April 2011. Docket No. 165, 4AC. In their 4AC, they alleged that Maxx had developed HSTCL as a result of taking the combination of drugs that he was prescribed between 2002 and 2007—specifically, the combination of 6MP and anti-TNF drugs. Plaintiffs further alleged that the manufacturers and distributors of those drugs failed to issue adequate warnings about the risks associated with taking 6MP drugs in combination with anti-TNF drugs. They asserted claims under California law for negligence and strict liability against Johnson & Johnson,

Centocor, Abbott Labs, GlaxoSmithKline, Par, and Teva. 4AC ¶¶ 62–101.

In 2011, Defendants Abbott Labs, GlaxoSmithKline, Teva, and Par moved for summary judgment. The Court granted the motion in December 2011, finding that Plaintiffs had failed to produce sufficient evidence to support an inference that different warning labels would have changed Dr. Rich's decision to prescribe the specific combination of drugs at issue in this case. The Court based its decision, in part, on the undisputed evidence "that Dr. Rich was already aware of the risk of lymphomas associated with 6– MP, but still chose to prescribe the drug" to Maxx in combination with an anti-TNF drug. Docket No. 204, Dec. 2011 Summary Judgment Order, at 15.

Plaintiffs subsequently moved for reconsideration of the December 2011 ruling after they discovered new evidence suggesting that Dr. Rich may not have known about the risks associated with these drugs before prescribing them. Based on this new evidence, the Court granted Plaintiffs' motion for reconsideration and withdrew its December 2011 summary judgment order. In July 2012, after reviewing Plaintiffs' new evidence, the Court denied Teva's, Par's, and Abbott Labs' motions for summary judgment. The Court granted summary judgment to GlaxoSmithKline, however, because it found that Plaintiffs had presented "insufficient evidence for a reasonable jury to find that, before July 1, 2003 when [GlaxoSmithKline] discontinued distribution of Purinethol, it had a duty to warn of the risk of hepatosplenic T-cell lymphoma." Docket No. 232,

July 2012 Summary Judgment Order, at 27. One year later, the Court granted Par's unopposed motion for summary judgment. Docket No. 293, May 2013 Summary Judgment Order, at 1.

In January 2014, the four remaining Defendants—Johnson & Johnson, Centocor, Abbott Labs, and Teva—filed the instant motion for summary judgment. As noted above, Plaintiffs subsequently settled their claims against all of these Defendants other than Teva.

LEGAL STANDARD

Summary judgment is properly granted when no genuine and disputed issues of material fact remain, and when, viewing the evidence most favorably to the non-moving party, the movant is clearly entitled to prevail as a matter of law. Fed.R.Civ.P. 56; *Celotex Corp. v. Catrett*, 477 U.S. 317, 322–23 (1986); *Eisenberg v. Ins. Co. of N. Am.*, 815 F.2d 1285, 1288–89 (9th Cir.1987).

The moving party bears the burden of showing that there is no material factual dispute. Therefore, the court must regard as true the opposing party's evidence, if supported by affidavits or other evidentiary material. *Celotex*, 477 U.S. at 324; *Eisenberg*, 815 F.2d at 1289. The court must draw all reasonable inferences in favor of the party against whom summary judgment is sought. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986); *Intel Corp. v. Hartford Accident & Indem. Co.*, 952 F.2d 1551, 1558 (9th Cir.1991).

Material facts which would preclude entry of summary judgment are those which, under applicable substantive law, may affect the outcome of the case. The substantive law will identify which facts are material. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). Where the moving party does not bear the burden of proof on an issue at trial, the moving party may discharge its burden of production by either of two methods:

> The moving party may produce evidence negating an essential element of the nonmoving party's case, or, after suitable discovery, the moving party may show that the nonmoving party does not have enough evidence of an essential element of its claim or defense to carry its ultimate burden of persuasion at trial.

Nissan Fire & Marine Ins. Co., Ltd., v. Fritz Cos., Inc., 210 F.3d 1099, 1106 (9th Cir.2000).

If the moving party discharges its burden by showing an absence of evidence to support an essential element of a claim or defense, it is not required to produce evidence showing the absence of a material fact on such issues, or to support its motion with evidence negating the non-moving party's claim. *Id.*; *see also Lujan v. Nat'l Wildlife Fed'n*, 497 U.S. 871, 885 (1990); *Bhan v. NME Hosps., Inc.*, 929 F.2d 1404, 1409 (9th Cir.1991). If the moving party shows an absence of evidence to support the nonmoving party's case, the burden then shifts to the non-moving party to produce "specific evidence, through affidavits or admissible discovery material, to show that the dispute exists." *Bhan*, 929 F.2d at 1409.

If the moving party discharges its burden by negating an essential element of the non-moving party's claim or defense, it must produce affirmative evidence of such negation. *Nissan*, 210 F.3d at 1105. If the moving party produces such evidence, the burden then shifts to the non-moving party to produce specific evidence to show that a dispute of material fact exists. *Id.*

If the moving party does not meet its initial burden of production by either method, the non-moving party is under no obligation to offer any evidence in support of its opposition. *Id.* This is true even though the non-moving party bears the ultimate burden of persuasion at trial. *Id.* at 1107.

DISCUSSION

As previously noted, Plaintiffs assert claims against Teva for negligence and strict liability. Teva contends that these claims must fail because Plaintiffs have failed to present sufficient evidence to support an inference that Purinethol, either alone or in combination with anti-TNF drugs, caused Maxx to develop HSTCL. Teva further contends that Plaintiffs lack sufficient evidence to support an inference that it had a duty to warn about the risks associated with taking Purinethol. Each of these arguments is addressed separately below.

A. Causation

"An essential element in claims for product strict liability and negligence is causation." *Cox v. Depuy Motech, Inc.*, 2000 WL 1160486, at *5 (S.D.Cal.).

Thus, a plaintiff claiming that he or she was personally injured by a pharmaceutical product must "establish that the substance at issue was capable of causing the injury alleged (general causation), and that the substance caused, or was a substantial factor in causing, the specific plaintiff's injury (specific causation)." *Avila v. Willits Envtl. Remediation Trust*, 633 F.3d 828, 836 (9th Cir.2011). Under California law, " 'causation must be proven within a reasonable medical probability based upon competent expert testimony.'" *Id.* (citing *Jones v. Ortho Pharmaceutical Corp.*, 163 Cal.App.3d 396, 402 (1985)).

Here, Plaintiffs rely on the opinions of two experts to show causation: Drs. Dennis Weisenburger and Andrei Shustov.[2] Drs. Weisenburger and Shustov are both medical doctors who opined in their expert reports that the combination of 6MP drugs and anti-TNF drugs prescribed to Maxx increased his likelihood of developing HSTCL and, ultimately, caused his death. Because these opinions are not based on sufficiently reliable scientific data, they are not admissible under Federal Rule of Evidence 702 and do not support an inference of causation.

Rule 702 permits an expert to offer opinion testimony on a subject if

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[2] Because Plaintiffs' third expert, Dr. David Ross, has not offered any opinions on causation, the Court does not discuss the admissibility of his opinions here. *See* Docket No. 337, Pls.' Opp. 24 ("Plaintiffs are not, however, offering Dr. Ross as a medical causation expert, but as an expert on the FDA's regulatory requirements.").

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed.R.Evid. 702. In short, expert opinion testimony is only admissible if the opinion the expert seeks to offer is both relevant and reliable. *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579, 589 (1993) (*Daubert I*); *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 141 (1999). Although Teva does not dispute that the opinions of Drs. Weisenburger and Shustov are relevant here, it contends that they are not reliable.

To evaluate the reliability of expert opinion testimony, a court must consider the factors set out in *Daubert I*, which include "whether the theory or technique in question can be (and has been) tested, whether it has been subjected to peer review and publication, its known or potential error rate and the existence and maintenance of standards controlling its operation, and whether it has attracted widespread acceptance within a relevant scientific community." 509 U.S. at 593–94. The "test of reliability is 'flexible,' and *Daubert's* list of specific

factors neither necessarily nor exclusively applies to all experts or in every case." *Kumho Tire*, 526 U.S. at 141 (citations omitted). The focus, in other words, "must be solely on principles and methodology, not on the conclusions that they generate." *Daubert I*, 509 U.S. at 595.

The opinions of Drs. Weisenburger and Shustov do not meet this standard. First, neither doctor has ever conducted any independent research or published any studies on the specific relationship between 6MP and anti-TNF drugs and the development of HSTCL. Although both conclusorily stated during their depositions that their opinions on this subject were based on a reasonable degree of medical certainty, they also conceded that their opinions would not satisfy the standards required for publication in peer-reviewed medical journals. For instance, when Dr. Weisenburger was asked whether his opinions in this case would be publishable in a medical article, he replied that the standard for publication would "probably be more rigorous" than the standard he applied in forming his opinions. *See* Docket No. 320, Defs.' Ex. 4, Weisenburger Depo. 118:22–119:4. Similarly, Dr. Shustov testified that he would not be comfortable publishing his opinions in this case regarding the alleged causal link between 6MP and anti-TNF drugs and HSTCL. Defs.' Ex. 6, Shustov Depo. 74:4–75:9. The fact that both of Plaintiffs' causation experts are reluctant to publish their opinions—and appear to have developed their opinions specifically for the purposes of this litigation—casts doubt the reliability of their methodologies under Rule 702. *See Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th

Cir.1995) (*Daubert II*) ("One very significant fact to be considered [under Rule 702] is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying.").

So, too, does their failure to identify any animal studies or epidemiological studies showing a causal link between HSTCL and the combination of 6MP and anti-TNF drugs prescribed to Maxx. Plaintiffs admit that they have not identified any such studies, arguing instead that such studies are impossible to conduct because HSTCL is an "exceedingly rare" disease. See Docket No. 349, March 13, 2014 Hrg. Tr. 16:18–:22 ("If it were possible to do the kind of epidemiological study that the Defendants insist is required here, that would have been done a long time ago. Nobody has done it."). The difficulty of conducting these studies, however, does not relieve Plaintiffs of their obligation to present evidence of causation. Indeed, the need for such evidence is especially important here in light of the fact that more than seventy percent of observed HSTCL cases are idiopathic, meaning that they have no known cause. Weisenburger Depo. 174:4–:15; Shustov Depo. 106:5–:24. Given this high rate of idiopathic cases, Plaintiffs cannot reasonably eliminate other potential causes of Maxx's HSTCL without some reliable evidence of a positive link between the drugs at issue and the disease. *Daubert II*, 43 F.3d at 1319 (finding expert testimony inadmissible under Rule 702 where expert offered "no tested or testable

theory to explain how, from [ ] limited information, he was able to eliminate all other potential causes").

This is precisely why courts often exclude expert medical testimony under Rule 702 when the expert fails to cite any specific epidemiological studies suggesting that a given drug caused a disease with a high rate of idiopathic cases. In *Lopez v. Wyeth–Ayerst Labs.*, for instance, this Court excluded the testimony of a medical expert under Rule 702 because his testimony was not based on reliable epidemiological evidence and failed to "eliminate all other potential causes" of the plaintiff's condition. 1996 WL 784566, at *3 (N.D.Cal.), *aff'd*, 139 F.3d 905 (9th Cir.1998). The Court found that the expert's failure to rule out other possible causes of the plaintiff's Guillain–Barre Syndrome (GBS) was "particularly troubling in light of [the expert]'s statement that 30 to 40% of the GBS cases have idiopathic or unknown causes." *Id.* The Court also specifically noted that the defendant's expert had presented "uncontroverted testimony that there has been no epidemiological study showing increased incidence of GBS in persons receiving a non-swine flu vaccine," like the one that the plaintiff alleged had caused him to develop GBS. *Id.* Plaintiffs have not distinguished the present case from *Lopez* nor from any of the other cases where courts have excluded expert medical evidence under Rule 702 for failing to eliminate potential alternative causes of the plaintiff's harm.[3] *See, e.g., Henricksen v.*

[3] Plaintiffs failed to discuss *Lopez* in their briefs and, when asked to distinguish the case at the hearing, noted simply that

ConocoPhillips Co., 605 F.Supp.2d 1142, 1163 (E.D.Wash.2009) ("[B]ecause [the expert]'s methodology employed fails to adequately account for the possibility that [plaintiff]'s AML was idiopathic, the court finds that his conclusion that prolonged exposure to benzene in gasoline was the cause of his AML is unreliable and therefore inadmissible."); *Soldo v. Sandoz Pharm. Corp.*, 244 F.Supp.2d 434, 567 (W.D.Pa.2003) (excluding expert testimony under Rule 702 because it did not "reliably rule out reasonable alternative causes of [the plaintiff's condition] or idiopathic causes").

Although Plaintiffs cite a handful of studies and case reports discussing possible causes of HSTCL, none of these purports to show that the specific combination of drugs prescribed to Maxx actually causes HSTCL. Rather, the studies—only some of which are actually cited in Plaintiffs' expert reports[4]—contain statistics about the incidence of HSTCL among different patient populations, including patients with IBD. Plaintiffs contend that these statistics, viewed as a whole, show that patients exposed to a combination of 6MP and anti-TNF drugs are more likely to develop HSTCL than other patients. However, Plaintiffs have not shown that all of the observed differences in these incidence rates are statistically significant or that they account for plausible alternative causes of HSTCL, such as

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Lopez was decided "a long time ago." March 13, 2014 Hrg. Tr. 35:3–:13. This is not a relevant distinction.

[4] Neither Dr. Weisenberger nor Dr. Shustov appears to have cited the 2010 letter-to-the-editor written by David Kotlyar et al. or the 2013 article written by Prakkal Deepak et al.

IBD itself. Indeed, Dr. Shustov himself acknowledged during his deposition that the studies he reviewed failed to control for IBD as a possible risk factor. Shustov Depo. 25:19–26:12. Although he and Dr. Weisenberger both stated that they do not believe IBD is a risk factor for HSTCL, they have not presented any scientific evidence to support that opinion. *See Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir.1999) (" '[W]here a defendant points to a plausible alternative cause and the doctor offers no explanation for why he or she has concluded that was not the sole cause, that doctor's methodology is unreliable.'" (quoting *In re Paoli Railroad Yard PCB Litig.*, 35 F.3d 717, 759 n.27 (3d Cir.1994))); *Casey v. Ohio Med. Products*, 877 F.Supp. 1380, 1385 (N.D.Cal.1995) (explaining that "case reports are not reliable scientific evidence of causation, because they simply describe[ ] reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group" and "do not isolate and exclude potentially alternative causes").

In sum, the opinions of Drs. Weisenburger and Shustov do not provide sufficiently reliable evidence of causation and must be excluded under Rule 702. Plaintiffs have not presented any other admissible evidence sufficient to support an inference of "a reasonable causal connection" between the combination of Purinethol and anti-TNF drugs and the development of Maxx's HSTCL. *Jones*, 163 Cal.App.3d at 399, 402 (recognizing that causation "must be proven within a reasonable medical probability based upon competent expert testimony" and that "[m]ere possibility alone is insufficient to

establish a prima facie case"); *see also Avila*, 633 F.3d at 836 (quoting same). Accordingly, Teva is entitled to summary judgment on all of Plaintiffs' remaining claims against it for negligence and strict liability.

B. Duty to Warn

Plaintiffs' failure to produce any admissible evidence of causation is sufficient to preclude them from prevailing on any of their claims under a failure-to-warn theory. *See Finn v. G.D. Searle & Co.*, 35 Cal.3d 691, 701 (1984) ("The strength of the causal link thus is relevant both to the issue of whether a warning should be given at all, and, if one is required, what form it should take."). But Teva is also entitled to summary judgment on Plaintiffs' claims under this theory for another, independent reason: specifically, because they have not adduced any evidence to suggest that Dr. Rich actually relied on Teva's warning labels before prescribing Purinethol to Maxx.

Dr. Rich testified during his deposition that he cannot recall reading the Purinethol label in making his decision to prescribe the drug and that it is "not [his] regular practice to look at drug labeling." Defs.' Ex. 1, Rich Depo. 192:6–:7; id. 283:13–:15 ("I don't remember specifically reading the label for Purinethol 6–MP or generic [sic] at any particular time."). Plaintiffs have not identified any evidence to contradict this testimony or otherwise suggest that Dr. Rich actually relied on the Purinethol warning label. Accordingly, they cannot prevail on their negligence claim under a failure-to-warn theory.

Conte v. Wyeth, Inc., 168 Cal.App. 4th 89, 112 (2008) ("There can be no proximate cause where, as in this case, the prescribing physician did not read or rely upon the allegedly inadequate warnings promulgated by a defendant about a product."); *Motus v. Pfizer Inc.*, 358 F.3d 659, 661 (9th Cir.2004) ("Because the doctor testified that he did not read the warning label that accompanied Zoloft or rely on information provided by Pfizer's detail men before prescribing the drug to [plaintiff], the adequacy of Pfizer's warnings is irrelevant to the disposition of this case."). To the extent that Plaintiffs have asserted a claim against Teva for negligent misrepresentation, that claim fails for the same reason. *Apollo Capital Fund, LLC v. Roth Capital Partners, LLC*, 158 Cal.App. 4th 226, 243 (2007) (recognizing that one of the "elements of negligent misrepresentation" is "justifiable reliance on the misrepresentation").[5] Teva is therefore entitled to summary judgment on all of Plaintiffs' claims based on a failure-to-warn theory.

CONCLUSION

For the reasons set forth above, Teva's motion for summary judgment (Docket No. 319) is GRANTED. Plaintiffs' request to strike the supplemental declarations of Teva's experts, Drs. Robert Valuck and Andrew Place, is DENIED as moot as the Court did not rely on either of these supplemental declarations in reaching its decision.

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[5] Plaintiffs conceded at the hearing that they cannot prevail on their strict liability claims against Teva under a failure-to-warn theory. March 13, 2014 Hrg. Tr. 50:24–:25 (Plaintiffs' Counsel: "What I agree is we can't hold Teva liable under strict liab[ility].").

In addition, Plaintiffs' motion for leave to file supplemental material (Docket No. 355) is DENIED. Plaintiffs have failed to establish that the March 2014 statements and documents issued by Health Canada and Teva Canada, neither of which is a party in this action, are admissible. Furthermore, even if the statements and documents were admissible, they would not alter the outcome of this case. A warning notice issued by a foreign government under an unidentified regulatory standard is not sufficient to support an inference of causation here, particularly when the warning notice only pertains to Purinethol, rather than the full combination of drugs at issue in this case.

Finally, Plaintiffs' motion for leave to file a motion for reconsideration of the Court's July 2012 order granting summary judgment to GlaxoSmithKline (Docket No. 257) is DENIED as moot. Plaintiffs cannot prevail on their claims against GlaxoSmithKline for the same reasons they cannot prevail on their claims against Teva: once again, they have not presented sufficient evidence to support an inference of (1) a causal link between the combination of 6MP and anti-TNF drugs and HSTCL; nor (2) actual reliance by Dr. Rich on the warning label for Purinethol. Maxx's untimely death was tragic but, without this evidence, Teva cannot be held liable as its cause.

The clerk shall close the file and the parties shall bear their own costs.

IT IS SO ORDERED.

Dated: 6/30/2014

[Claudia Wilken]
CLAUDIA WILKEN
United States District Judge

APPENDIX C

UNITED STATES COURT OF APPEALS

FOR THE NINTH CIRCUIT

STEPHEN WENDELL; LISA WENDELL, for themselves and as successors-in-interest to Maxx Wendell, deceased, Plaintiffs-Appellants, v. GLAXOSMITHKLINE LLC; TEVA PHARMACEUTICALS USA, INC., Defendants-Appellees.	No. 14-16321 D.C. No. 4:09-cv-04124-CW Northern District of California, Oakland ORDER

Filed July 21, 2017

Before: GOULD and BERZON, Circuit Judges, and SESSIONS,[15] District Judge.

Judges Gould and Berzon voted to deny the petitions for rehearing en banc, and Judge Sessions so recommended.

The full court has been advised of the petitions for rehearing en banc and no judge of the court has

[15] The Honorable William K. Sessions III, United States District Judge for the District of Vermont, sitting by designation.

requested a vote on whether to rehear the matter en banc. Fed. R. App. P. 35.

The petitions for rehearing en banc are DENIED.

APPENDIX D

[Seattle Cancer Care Alliance]
Fred Hutchinson Cancer Research Center
University of Washington Academic Medical Center
Children's Hospital & Regional Medical Center

REPORT OF ANDREI SHUSTOV, M.D.
Wendell v. Johnson & Johnson, et al

QUALIFICATIONS AND MATERIALS REVIEWED

I am a US- licensed physician, boarded In Internal Medicine, Hematology and Medical oncology. I am an Associate Professor of Medicine at the University of Washington Medical Center specializing in diagnosis, and treatment of lymphomas and lymphoid leukemias (cancers of the lymph nodes and Immune system), The focus of my clinical research is T-cell leukemia and lymphomas. A copy of my CV is attached.

I have reviewed Maxx Wendell's medical records relating to his treatment for ulcerative colitis as well as his treatment for hepatosplenic T-cell lymphoma (HSTCL) diagnosed in July, 2007. In reaching my opinions In this matter, I relied upon these medical records as well as my education, training and experience, knowledge of the pertinent medical literature: and my knowledge of the epidemiology, diagnosis and natural history of HSTCL. I personally have treated 7 cases of HSTCL—an exceedingly rare non-Hodgkin's lymphoma - over the course of my career.

I hold all of the opinions expressed in this report to a reasonable degree of medical probability.

BACKGROUND

Maxx Wendell was born on August 20,1986 in California. In or about September of 1998 at the age of 12, he was diagnosed with inflammatory bowel disease (JBD), specifically ulcerative colitis (UC) and began treatment with Edward Rich, M.D., a pediatric gastroenterologist at Kaiser Permanente in San Francisco. Dr. Rich initially treated Maxx with a course of mercaptopurine (6-MP) and prednisone, a steroid. The use of mercaptopurine in the treatment of inflammatory bowel diseases has a long history dating back to the 1980's at least although it is only approved for the treatment of a type of leukemia. In OT about May, 2002, Dr. Rich recommended adding Remicade—a tumor necrosis factor (TNF) antagonist-to the regimen with a course of steroid weaning and in July, 2002, Maxx received his first dose of Remicade. Dr. Rich continued him on 6-MP while attempting to reduce the steroids. According to the pharmacy records, Maxx received 19 infusions of Remicade between July 10, 2002 and March 7, 2006.

In or about November, 2005, after about 3.2 years of successful treatment, Dr. Rich began to consider whether Maxx might be taken off Remicade. He decided to give Maxx one more dose after which he would do a colonoscopy to see if there was any lingering disease activity. Maxx received his last dose of Remicade in March, 2006 and he underwent a colonoscopy In May, 2006 which showed no signs of

disease. Remicade was discontinued but he was continued on 6-MP. Around this time the Remicade label was amended to add a boxed warning about cases of hepatosplenic T-cell lymphoma uncovered in young, predominantly male patients who were taking a combination of Remicade and mercaptopurine for treatment of inflammatory bowel disease.

In November of 2006 he was restarted on another TNF-antagonist, this time Humira, following a flare up of his disease, from the pharmacy records it appears that his prescription for Humira was renewed times, the last being on June 15, 2006. His last prescription for mercaptopurine was in March, 2006. According to Maxx's mother, Lisa, Maxx stopped taking mercaptopurine in April, 2006 after he read an article or saw an advertisement In Men's health magazine relating to the Remicade boxed warning- She testified that even though he hadn't been taking Remicade for some time, he was nevertheless concerned that because he had taken that combination he might be at risk for developing HSTCL According to Lisa Wendell, she spoke with Dr. Rich in March or April, 2007 about going off of the drugs and a decision was made to stop the 6-MP at that point.

On July 6, 2006, Maxx presented to the Emergency Department at Kaiser Permanente in San Rafael with complaints of the onset of fevers of 102 to 103 degrees over the prior ten days as well as progressive fatigue and malaise. It was noted that these symptoms followed the extraction of his wisdom teeth approximately one week before that. Initial

testing revealed thrombocytopenia and he was also noted to be significantly hypotensive (systolic pressure 70) presumed secondary to volume depletion. Current medications were noted as

> Asacol 400 mg, 6 tablets [at bedtime].
>
> Humira 40 mg subcutaneously every other week; last dose was on 6/30. The patient has been taking this medication since 10/2006. Previously, he was on Remicade which he took for about three years.
>
> Mecaptopurine 75 mg daily. Patient discontinued this medication about 6 weeks ago. He had been on this medication regularly for about 5-6 years.
>
> Vicodin has been discontinued Advil and Tylenol [as needed).

His blood work was noted to be abnormal; including abnormal liver function tests and the Impression was a febrile illness with abnormal CBC and liver dysfunction, thought possibly due to acute mononucleosis or cytomegalovirus and perhaps related to immunosuppressive therapy with Humira. The plan was to admit for observation to monitor hydration and oral intake and to type and cross-match his blood for possible transfusion due to anemia.

He was seen in consultation by infectious diseases 3nd hematology/oncology. Dr. Lakes of hematology/oncology who saw him on 7/7 noted

> [A] 20 year old man admitted yesterday because of lingering febrile illness, dehydration, and hematologic abnormalities. Patient had wisdom teeth removed on 6/21. His throat healed quickly but he then developed fevers (max 102) and weakness. Minimal rigors. He would feel particularly weak in the morning but he was able to continue to work as an aide at Gold's Gym.

Dr. Lakes also note a past medical history of

> Longstanding ulcerative colitis. On Remicade until 9 months ago when switched to every 2 weeks subcutaneous Humira. On 6 MP for years, but he stopped it 6 months ago out of concern for long term complications of immunosuppression. Colitis is controlled.

The assessment was

> Anemia and neutropenia probably due to Humira suppression with superimposed infection (viral, toxo, etc). Parvo virus, which causes aplastic anemia (low retics) is unlikely. I doubt this is a primary bone marrow disorder such as leukemia, lymphoma or MDS. Elevated LFT's due to infection. Gilbert syndrome

Based upon the assessment, however, Dr. Lakes wanted a bone marrow biopsy with cytogenetics which was performed on July 9. In the interim he underwent a CT of the pelvis and abdomen which revealed an enlarged spleen and moderate hepatomegaly (enlarged liver). Ascites (fluid) was also identified surrounding the gallbladder.

The bone marrow biopsy demonstrated scattered large atypical lymphoid cells in the sinusoids . . . [which] by immunohistochemical analysis . . . [are] positive for CD3 with a subset faintly positive for CD7 and negative for all other stains. A concurrent flow cytometry analysis reported an abnormal T cell population [which] comprises approximately 80% of lymphocytes and 40% of total events. It was noted that

> These cells express TCR Gamma/delta as well as CD56 and show an immunophenotype typical of that seen in hepatosplenic T cell lymphoma. Antibodies to the 24 most common Alpha/beta T cell receptor antigen show positivity for one (Vb20).

By flow cytometry, the cells were positive for CD3, CDS, CD56 and CD2 but negative for all other stains including all but one alpha/beta T cell receptor antigens.

Cytogenetic analysis demonstrated a normal 46 XY karotype.

The pathologist noted discussing the case with Dr. Lakes on July 10 where Dr. Lakes related that this patient Is on tumor necrosis factor inhibitor for ulcerative colitis and has been on other drugs for this condition as well. The bone marrow core biopsy was then sent out to Kaiser in San Francisco for additional immunohistochemical analysis which was nearly identical to the analysis done at San Rafael noting that overall, the findings support marrow

involvement by T-cell lymphoma, most consistent with hepatosplenic T-cell lymphoma.

Following the diagnosis, Dr. Lake consulted a number of other oncologists searching for treatment protocols for this rare form of lymphoma and ultimately settled on hyperCVAD because of its dose intensiveness compared to the alternative PEGS as initial therapy. The plan was to admit the patient on July 19 for a chemotherapy regimen consisting Cytoxan 2 doses per day on days 1-3; Adriamycin on day 4, Vincristine on day 4 and Dexamethasone days 1-4. Vincristine and Dexamethasone were then to be repeated on day 11. This was described as Part A. Additionally, as Part B of the cycle the patient would be readmitted several weeks later for a 24 hour infusion of methotrexate on day 1 and Ara-C twice daily infusions on days 2 and 3 followed by 8 doses of Leucovirin every 6 hours following the methotrexate infusion.

On July 19 he was admitted for the first round of hyperCVAD. In his admitting history and physical Dr. Lakes noted

> The patient has had ulcerative colitis since he was 13. He was initially managed with steroids but then switched to Remicade approximately 5 years ago. This was discontinued in early 2006, but within 9 months his symptoms returned. He was then switched to Humira which he self-administered as directed. He was also on 6-MP for a number of years, but the patient, himself, wanted that discontinued, because he was aware there was a risk of lymphoma associated with

> this immunosuppressive treatment. Ironically, the very lymphoma that has been reported as a complication of such therapy is now what he has.

Mr. Wendell was hospitalized from July 19 to July 23 and thereafter presented to the Emergency Department at Kaiser on July 25 with a chief complaint of fever. He was prescribed an antibiotic and was then seen by Dr. Lakes on July 30 still complaining of fevers at night. Dr. Lakes' impression was that it was a staph infection of unknown origin and he continued his antibiotics. He was next seen on August 2 still complaining of fevers at night but otherwise seemed somewhat improved. Of note was the fact that there was a marked fall In his LDH from 8000 to 800 which Dr. Lakes observed hopefully represents less hemolysis and also less tumor burden. The plan was to admit him for "Part B" therapy on 8/8 followed by round 2 of "Part A" therapy on 8/29. In the interim Dr. Lakes planned to have him evaluated for an allogeneic bone marrow transplant at Stanford.

On August 8 he was admitted for Part B therapy at which time Dr. Lakes noted his profound thrombocytopenia which he believed was on an immune basis since his platelet count rose sharply following the initial round of hyperCVAD only to fall again. He was discharged on August 11 and thereafter seen by Dr. Lakes on August 16 who again noted his dropping blood counts as well as elevated liver enzymes. He continued neupogen and instructed him to return in one week.

He was next seen on August 21 continuing to demonstrate thrombocytopenia despite a platelet infusion the day before. Dr. Lakes noted that it was most likely due to his hemolytic anemia and not from residual effects from chemotherapy.

Thereafter, he was seen at Stanford on August 27 by Judith Shizuru for evaluation for allotransplant. Dr. Shizuru noted that unfortunately HLA testing ruled out his sister as a potential donor. She nevertheless believed that allogeneic transplantation, with preparative myeloablative regimen offered the best chance for long term disease survival. She noted, however, that the best chance for success was with minimal residual disease present before starting the transplant. The plan was to wait for restaging results following the second cycle of hyperCVAD to see whether there was evidence of chemotherapy responsive disease.

Additionally, the bone marrow biopsy samples From July were submitted for review at Stanford. The reviewing pathologist noted that:

> We agree with the originating institution=s diagnosis of a gamma/delta T-cell lymphoma, but no other findings indicate the primary site. In this age group, the most common primary site for a gamma/delta T-cell lymphoma is from the liver or the spleen, which represents the entity of hepatosplenic T-cell lymphoma. Hepatosplenic T-cell lymphomas have been associated with isochromosome 7q and repeating the cytogenetic studies may be helpful in further supporting this diagnosis. Cases of hepatosplenic T-cell

> lymphoma have been reported in the literature in association with antibody to tumor necrosis factor-alpha. Clinicopathological correlation is required. In addition, given the background of erythroid precursors and megakaryocytes show dysplastic features, but given the normal cytogenetic karotype, this finding is of uncertain significance.

On September 1, he underwent the second round of Part A hyperCVAD and underwent Part B therapy on September 17. On October 2 he underwent another bone marrow biopsy which was interpreted as demonstrating recurrent/residual hepatosplenic T-cell lymphoma. This biopsy was positive for CD3, CD4 and CD7. The concurrent flow cytometry reported a population of gamma/delta T cells [which] account for approximately 25 to 30% of lymphocytes and less than 0.5% of the total events and was positive for CD3, CD8(moderately bright), CD16 & 56, CD2, CD7 and TCR gamma/delta. The final pathologic diagnosis was residual hepatosplenic T-cell lymphoma . . . consistent with history of chemotherapy.

Significantly, on the same day as the biopsy, Dr. Lakes noted that Mr. Wendell reported that he had been told that a matched unrelated donor for transplant had been identified.

Mr. Wendell was then evaluated again by Dr. Shizuru on October 8 who noted that he has achieved some response as measured by the involvement in his bone marrow. Given the lead time necessary to prepare for transplantation and Its

relationship to the next scheduled round of Part A therapy, Dr. Shizuru recommended that Mr. Wendell undergo the next cycle and that the transplant target would be in approximately 4 to 5 weeks.

On October 15 Mr. Wendell underwent the third cycle of HyperCVAD after which things appeal to have begun to unravel. On October 25 he was admitted to the hospital for pneumonia, fever and pancytopenia and was treated with a course of IV antibiotics. He was discharged on October 27. On October 29 he was again seen at Stanford for preparation for allotransplant. Because he was febrile, however, the transplant was delayed one week.

He was then readmitted to Kaiser on November 5 following an Emergency Department presentation for weakness, dehydration and elevated LDH. A bone marrow biopsy done that day also demonstrated recurrent disease which was most profound in his marrow. Flow cytometry demonstrated 30-35% residual T-cell lymphoma.

Given the recurrence, Dr. Hjortsvang (who had taken over from Dr. Lakes) initiated second line PEGS therapy as planned. He noted having a discussion with Dr. Shizuru and that there were contrasting schools of thought about whether to forge ahead with transplant or attempt disease reduction with chemotherapy in order to increase the odds of successful transplantation, Following a discussion with the family it was decided to initiate another round of chemotherapy.

He underwent 4 days of chemotherapy between 11/9 and 11/12 and was discharged to home on 11/13. He was readmitted, however, on 11/15 because of a significantly low platelet count which was deemed to be due to a combination of his autoimmune process and his recent chemotherapy. He was discharged on November 23 and in the discharge summary it was noted that

> Mr. Wendell underwent a prolonged hospitalization, secondary to his pancytopenia and deconditioning. The patient was treated as a neutropenic fever due to his recent chemotherapy. The patient was seen by the Infectious Disease Service due to an increased right lower lobe infiltrate, and started on broad spectrum antibiotics. Over the next several days the patient slowly improved with blood product support and IV antibiotics. He was quite deconditioned and received Physical Therapy evaluation and treatment. The patient was deemed stable for discharge an the 23rd of November, to follow-up with his oncologist Dr. Hjortsvang. A platelet count was 6,000, white count was 25,000, and this was thought to be due to Neupogen. Hemoglobin and hematocrit remained stable. The patient had no signs or symptoms of acute blood loss.

Following discharge, he was then seen by Dr. Hjortsvang on November 26 who noted that

> Mr. Wendell is status post two full cycles of Hyper-CVAO both A and B treatments and has finished the third A cycle of his Hyper CVAD.

> He has had one cycle of PEGS chemotherapy. He has had issues with anemia and thrombocytopenia. He requires steroids to ensure his platelet count does not decrease below 5k.

The plan was to do a bone marrow biopsy on 11/28 but it is not clear that one was in fact done. Indeed, he apparently traveled to New York in early December to Columbia Presbyterian Hospital for evaluation for treatment with Pralatrexate. Because his platelets were so low (5,000) he was not eligible for the treatment and the plan was to increase his platelets to over 300,000 after which he would undergo splenectomy before receiving Pralatrexate. He was seen in consultation with Andrew Gumbs, M.D. a surgeon concerning splenectomy. Dr. Gumbs noted that

> Mr. Wendell is a 21-year old male with a long history of Ulcerative Colitis that was treated with the unfortunate combination of Remicade and 6-Mercaptopurine. It is now known that this combination can lead to the development of a primary splenic lymphoma, in this case gamma-delta T-cell lymphoma, also known as hepatosplenic T-cell lymphoma. Mr. Wendell tragically related that he was reading the Men=s Health Journal when he found an article explaining the risk of developing hepatosplenic T-cell lymphoma when patients are treated with both Remicade and/or Azathioprine/6 Mercaptopurine. Because of this he asked his gastroenterology to stop this therapy. At that time his Ulcerative Colitis was in complete

> remission, however, 8 months later (May 2007) he developed chronic fevers and was diagnosed with gamma-delta T-cell lymphoma. Since then he has failed multiple different chemotherapy regimens. Over the last three weeks his condition rapidly deteriorated after treatment with PEGS where his course was complicated by pneumonia and the exacerbation of thrombocytopenia.

Dr. Gumbs noted that his blood work was markedly abnormal including extreme thrombocytopenia and that Mr. Wendell appeared as an emaciated man who looks considerably older than his stated age . . . [who] has been clearly ravaged by this disease process. The plan was to pulse dose steroids and gamma interferon with an infusion of platelets at initiation followed by transection of the splenic artery with rapid infusion of 6-packs of platelets to replenish his stores. Unfortunately, Mr. Wendell died early in the morning of the day after his admission before any treatment could be attempted. Of note is the fact that the slides from the initial bone marrow biopsy from July were reviewed at Columbia and the diagnosis of gamma/delta T-cell lymphoma was once again confirmed.

DISCUSSION

Hepatosplenic T-cell lymphoma (HSTCL) - is an exceedingly rare subtype of T-cell lymphoma, comprising no more than 1% of diagnoses. Relative frequency of HSTCL among all non-Hodgkin lymphomas is less than 0.1%. The clinical course of

HSTCL is that of an aggressive cancer with low responses to chemotherapy, frequent relapses after contemporary treatments and the inability of the majority of the patients to undergo bone marrow transplantation. The majority of the patients succumb to their disease within the first year after the diagnosis and long term survival is achieved by only a small fraction of those affected by this lymphoma.

There have been approximately 200 cases of HSTCL reported worldwide since it was first recognized as a distinct disease entity in 1994. A significant proportion of the earliest cases reported were solid organ transplant recipients taking Immunosuppressive agents like azathioprine to prevent rejection. More recently, a remarkable cluster of cases has emerged among young, predominantly male patients with a history of IBD treated with the combination of purine analogues (i.e. 6-MP 3nd azathioprine) and TNF alpha inhibitors (i.e., infliximab, adalimumab). Kotlyar, et al[1] described 36 cases of HSTCL among this cohort seemingly arising with the increasing use of the combination of TNF antagonists with purines for the treatment of inflammatory bowel diseases. Of the 31 patients in this cluster whose gender could be determined, only 3 were female. The known age range was 12 to 58 years with a median age of 23. Significantly, all 36 of the patients were treated with

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[1] Kotlyar DS, *et al* "A Systematic Review of Factors That Contribute to Hepatosplenic T-Cell Lymphoma in Patients With Inflammatory Bowel Disease," *Clinical Gastroenterology and Hepatology* 2011; 9:36-41

a thiopurine— either mercaptopurine or azathioprine--and 20 (55,5%) also received a TNF antagonist either infliximab or adalimumab (in four case, one of whom was Maxx Wendell, the patient was exposed to adalimumab subsequent to infliximab and in one case the patient received infliximab, adalimumab and natzlizumab). Among the combination users the median time of onset of the disease from the initiation of thiopurine therapy was 5.5 years. For those on monotherapy, the median time from initiation of therapy to disease onset was 6 years. This difference was not statistically significant (likely due to the very small sample size). It is thought that this drug combination might cause both DNA damage (purine analogue), leading to the development of malignant or cancerous clones and immunosuppression (TNF-alpha inhibitors), that allows for a reduced immunologic surveillance for cancer.[2] While the evidence is highly suggestive that the use of thiopurines alone for the treatment of inflammatory bowel diseases in young male patients might be sufficient to cause or contribute to the development of HSTCL in these patients (all of the

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[2] The persistence of immunosuppression in reducing immunologic surveillance following withdrawal is not known. The duration of immunosuppressive therapy may have a cumulative effect which persists after the drug is discontinued. In Maxx Wendell's case there was a six month gap in treatment with TNF antagonists between March, 2006 (discontinuation of Remicade) and November, 2006 (initiation of Humira). It is unknown whether his 3.5 year history of treatment with Remicade had lingering immunosuppressive effects-particularly since he continued on mercaptopurine which also has immunosuppressive effects-predisposing him to the development of HSTCL when he re-initiated combination therapy with another TNF antagonist.

patients had exposure to a thiopurine while only slightly more than half were exposed to a TNF antagonist), it is likely that the combination of thiopurines and TNF antagonists further increases the risk of HSTCL over that of thiopurines alone.

Given the absolute rarity of this disease generally, a cluster of 36 cases arising in young, predominantly male patients treated for IBD with thiopurines and TNF antagonists stands as almost a signature of the disease. While the precise mechanism by which these drugs used in the setting of IBD in young patients give rise to HSTCL is not known, it is clear that the use of these drugs, either individually (in the case of the thiopurines) or in combination, either causes or contributes to the development of HSTCL in certain patients. This high an incidence of an exceedingly rare cancer in this distinct cohort is compelling evidence of causation.

Maxx Wendell was one of those patients. He was a young male with ulcerative colitis (a form of inflammatory bowel disease) with a history of 5+ years of treatment with a thiopurine in combination with the TNF antagonists Remicade and Humira who developed an exceedingly rare cancer almost uniquely associated with this treatment regimen in this cohort. To a reasonable degree of medical probability, the combination use of a thiopurine with TNF antagonists for the treatment of his inflammatory bowel disease caused, or substantially contributed, to the development of HSTCL to which he succumbed four months after diagnosis despite multiple aggressive therapies.

I hold all of these opinions to a reasonable degree of medical probability.

[Andrew R Shustov]

Andrei R. Shustov, M,D.
Associate Professor of Medicine
University of Washington Medical Center

Attending Physician
Hematologic Malignancies Program
Seattle Cancer Care Alliance &
Fred Hutchinson Cancer Research Center

Seattle, WA 98109

Tel. (206) 2SS-6739
Fax (206) 288-S473

APPENDIX E

[Letterhead]

August 20, 2013

Via: [email]

Kevin Haverty, Esq.
Williams, Cuker, Berezofsky
210 Lake Drive East, Suite 101
Cherry Hill, N.J. 08022

RE: Maxx H. Wendell

Dear Mr. Haverty:

I am an expert hematopathologist with over 30 years of experience in the diagnosis of non-Hodgkin lymphoma (NHL), and with a special interest in T-cell NHL. My qualifications are detailed in my curriculum vitae. At your request, I have reviewed a summary of the medical records of Mr. Wendell as well as copies of the pathology reports, and the original slides of the diagnostic bone marrow (IBC07-6413, 7/9/2007). Based on these materials, I will render my opinion on the diagnosis and cause of Mr. Wendell's illness.

In September of 1998, at age 12 years, Mr. Wendell was diagnosed with inflammatory bowel disease (IBD), specifically ulcerative colitis (UC). He was treated initially with a course of 6-mercaptopurine (6-MP) and steroids. In July of 2002, he was also started on Remicade and the steroids were tapered. He received 19 infusions of Remicade between July of 2002 and March of 2006 while continuing on the 6-

MP. In May of 2006, a colonoscopy showed no sign of UC and the Remicade was discontinued. However, in November of 2006, the UC recurred and he was started on subcutaneous Humira every other week, receiving the last dose on June 30, 2007, he had stopped taking the 6-MP in April, 2007.

On July 6, 2007, at age 20 years, he presented to the emergency room with fevers of 102-103 degrees for the prior 10 days, as well as progressive fatigue and malaise. He was noted to be hypotensive and laboratory tests revealed anemia (Hgb 10.6 g/dl) and thrombocytopenia (31,000/ul), and abnormal liver function. A CT scan of the abdomen revealed an enlarged spleen and liver. A bone marrow exam on July 9 revealed a diagnosis hepatosplenic gamma/delta T-cell lymphoma, with positive flow cytometry but normal cytogenetic studies. On July 19, he was started on hyperCVAD chemotherapy but remained symptomatic and thrombocytopenic. He was referred to Stanford University on August 27 for evaluation for possible allogeneic bone marrow transplantation. However, he was continued on hyperCVAD and received two more cycles, but disease persisted in the bone marrow and his condition worsened. He was given another chemotherapy (PEGS) in November but developed pancytopenia. In December, he was evaluated for Pralatrexate chemotherapy and splenectomy at Columbia Presbyterian Hospital in New York City, but he appeared emaciated at the time of evaluation and died shortly after admission, before any treatment could be given.

Based on my review of the diagnostic bone marrow slides (IHC07-6413) from July 9, 2007, I concur with the original diagnosis of hepatosplenic gamma/delta T-cell lymphoma (HSTCL). The lymphoma cells exhibited the characteristic sinusoidal infiltrate and the phenotype by immunostaining and flow cytometry was confirmatory (1). In addition, this diagnosis was also confirmed by pathologists at Stanford University and Columbia University. The clinical presentation and aggressive course of Mr. Wendell's disease are also typical of HSTCL.

It is well known that patients with IBD who are treated with thiopurines (6-MP) and anti-tumor necrosis factor (anti-TNF) agents (Remicade, Humira) have an increased risk (3-5 fold) of developing a lymphoproliferative disorder such as HSTCL (2, 3). This disease typically occurs in young men (<35 years) who have been treated for prolonged periods with thiopurines alone or in combination with anti-TNF agents. Therefore, it is my opinion with reasonable medical certainty that the combination of anti-TNF agents and 6-MP used in the treatment of Mr. Wendell caused or substantially contributed to the development of HSTCL.

Sincerely,

[Dennis D. Weisenburger, M.D.]

Dennis D. Weisenburger, M.D.
Professor and Chairman
Department of Pathology

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