Circuit Court for Baltimore City
Case No. 24C13000002

UNREPORTED

IN THE COURT OF SPECIAL APPEALS

OF MARYLAND

No. 2260

September Term, 2016

KAREN LARSON, as Guardian for KRAIG LARSON

v.

ABBOTT LABORATORIES, INC.

Meredith,
Nazarian,
Zarnoch, Robert A.
(Senior Judge, Specially Assigned),

JJ.

Opinion by Zarnoch, J.

Filed: July 19, 2018

This appeal arises out of product liability claims involving the prescription biologic, HUMIRA (adalimumab), which was manufactured by Abbott Laboratories, Inc. and is now manufactured by AbbVie, Inc. (collectively "Abbott"). Kraig Larson ("Mr. Larson") -- formerly a highly-educated space engineer -- suffered permanent brain injuries associated with his development of progressive multifocal leukoencephalopathy (PML) a few months after beginning treatment for his psoriasis with HUMIRA. Although Mr. Larson survived, he was left with permanent cognitive impairments, mobility issues, and the inability to care for his basic needs.

Mr. Larson was diagnosed as positive for human immunodeficiency virus ("HIV+") in 2004, but his immune status was considered "well-controlled" until November 2009. Appellant Karen Larson ("Ms. Larson"), Mr. Larson's sister and guardian, brought product liability claims against Abbott, alleging that Mr. Larson's development of PML was caused by Abbott's failure to include adequate warnings of the risks of prescribing it to HIV+ patients. The Circuit Court for Baltimore City (Fletcher-Hill, J.) granted summary judgment in favor of Abbott after finding that Ms. Larson could not prove that HUMIRA was a substantial factor in Mr. Larson's development of PML, and alternatively, that the warning Abbott included was adequate as a matter of law. Ms. Larson timely appealed and asks that we review the following list of issues:

> 1. Did the trial court err by assuming that *Frye-Reed* applied even though the causation opinions were not novel?
>
> 2. Did the trial court err by excluding the causation opinions of an expert the court described as having "superior training and experience in the field of infections disease, focused

> especially on HIV" and for whom "[t]he court has no reservations about . . . qualifications or with methodology of his theorizing?"[1]
>
> 3. Did the trial court err by prohibiting Johns Hopkins physicians from opining as to medical causation when they formed their causation opinions during their regular care and treatment of the patient and used ordinary processes?
>
> 4. Did the trial court err by prohibiting Plaintiff from proving causation by demonstrating that Plaintiff would not have been injured if the product contained an adequate label?
>
> 5. Did the trial court err by ruling that the product label was adequate as a matter of law given that the prescribing physician's knowledge is in dispute?
>
> 6. Did the trial court err in granting Defendant's motion to bar the testimony of Plaintiff's causation experts and granting summary judgment?

Paragraphs 1 through 3, however, are resolved by our review of the issues contained in paragraph 6 -- whether the circuit court erred in finding that Abbott was entitled to summary judgment based on the inadmissibility of Ms. Larson's expert causation witnesses. Without sufficient evidence that Mr. Larson's use of HUMIRA was a proximate cause of his development of PML, Ms. Larson could not prevail on any of her claims. Accordingly, if the circuit court's decision with respect to the inadmissibility of Ms. Larson's causation experts is correct, we need not answer the questions contained in

[1] We assume this statement refers to Ms. Larson's primary causation expert witness, Dr. Mark Jacobson.

paragraphs 4 and 5, related to whether Abbott's warnings were adequate as a matter of law, or whether the question of proximate causation was for the finder of fact.

BACKGROUND & PROCEDURAL HISTORY

History of Mr. Larson's Medical Treatment Prior to PML Diagnosis

In early 2009, Mr. Larson was a thirty-nine year old space engineer working at NASA's Goddard Space Flight Center. After he was diagnosed as HIV+ in 2004 until the spring of 2010, Mr. Larson's HIV condition and immune health was monitored by infectious disease specialist Dr. Ellen Yang, M.D. at Annapolis Infectious Disease Associates, LLP ("AIDA"). For the first five years after his diagnosis, his HIV condition remained "well-controlled," as indicated by blood tests monitoring his level of "T cells" or "CD4 count" and viral load.[2]

Mr. Larson also suffered from the inflammatory skin condition, plaque psoriasis, since 1995. Psoriasis is a genetic, immunological disorder in which "the cytokines that regulate function in the skin are abnormal," and typically manifests as red or scaly patches of skin. For several years, Mr. Larson treated his psoriasis with at-home remedies, but he eventually found his condition to be unmanageable and sought treatment with dermatologists. In 2007, he began seeing physician's assistant Julie Catlin, P.A. ("Ms. Catlin"). Mr. Larson tried prescription treatments for his psoriasis, such as topical corticosteroids, UVB therapy, and laser therapy, but he was not satisfied with his progress.

[2] We discuss the importance of CD4 count and viral load in further detail below.

At a routine infectious disease appointment in October 2009, Dr. Yang noted that Mr. Larson's plaque psoriasis had worsened since his last visit in March 2009. Dr. Yang informed him that his HIV appeared asymptomatic, but she had not yet received his lab results to evaluate his CD4 count and viral load.

In November 2009, after researching other psoriasis treatments, Mr. Larson asked Ms. Catlin about treatment with HUMIRA. Because Ms. Catlin did not have experience prescribing biologics to HIV+ patients, but believed it could be used in some circumstances, she agreed to look into a referral. On November 24, 2009, at a lunch meeting with two Abbott sales representatives at her office, Ms. Catlin asked the representatives to recommend a dermatologist that treated HIV+ patients with HUMIRA. The representatives recommended Monte S. Meltzer, M.D., who was the director of the dermatology clinic at Union Memorial Health Services, Inc. ("Union Memorial") and maintained a private practice -- Monte S. Meltzer, M.D., LLC.[3]

The representatives also arranged for Ms. Catlin to receive a Medical Information Letter ("Letter") from Abbott's medical department containing information about prescribing HUMIRA to HIV+ patients. The Letter, dated November 24, 2009, said, in pertinent part, the following:

> Our representative, Laura Rose, has informed us of your request. We are responding to your inquiry regarding

[3] Dr. Meltzer also served as a consultant for Abbott, which involved giving two or more presentations per year to other doctors on the safety and efficacy of HUMIRA, the content of which was "dictated by Abbott." None of his presentations, however, involved the safety or efficacy of treating HIV+ patients with HUMIRA.

> Humira® (adalimumab, Abbott) and use in patients with concomitant [HIV].
>
> Abbott has not specifically evaluated the safety or efficacy of adalimumab therapy in patients with comorbid [HIV] infection. The effect of adalimumab therapy, if any, on HIV is unknown. [. . .] [P]atients with a known history of HIV infection were excluded from participating in the adalimumab clinical trials . . . . [. . .]
>
> The possibility exists for tumor necrosis factor (TNF) blocking agents, including adalimumab, to affect host defenses against infections since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with adalimumab on the development and course of chronic infections is not fully understood.
>
> * * *
>
> Very limited data suggest that the use of TNF blockers in patients with well-controlled HIV infection, who are not severely immunocompromised, does not appear to exacerbate HIV viral load or adversely [a]ffect CD_4 cell counts.
>
> * * *
>
> MONITORING AND PATIENT MANAGEMENT
> Since the safety and efficacy of TNF blockers in patients with comorbid HIV infection has not been established, recommendations regarding specific monitoring parameters of HIV such as CD_4 cell count or viral load are not available. Such monitoring is at the discretion of the healthcare professional. Since the potential exists for TNF blocker therapy to reactivate HIV replication and induce opportunistic infections, suppression of HIV with antiretroviral therapy prior to initiation of TNF blockers and close monitoring of clinical and laboratory parameters by physicians knowledgeable in HIV management is recommended in the published literature.

(Endnotes omitted). The Letter also described a "retrospective, open-label case series," which examined the safety of the use of "TNF blocker therapy . . . in 8 HIV-1 infected patients with various rheumatic conditions." According to the letter, because "TNF blocker

therapy was generally well-tolerated and did not adversely [a]ffect HIV viral load or CD_4 cell count," the results of the case series suggested that,

> if a patient's HIV infection is controlled and they are not severely immunocompromised (CD_4 count of >200 mm^3 and HIV viral load of <60,000 copies/mm^3), TNF blocker therapy may be administered with a reasonable ratio of benefits to risks profile in patients refractory to standard therapy for rheumatic diseases.

Abbott's medical department did not send the letter to Dr. Meltzer.

On December 10, 2009, Ms. Catlin referred Mr. Larson to Dr. Meltzer based on the information she received from Abbott. Dr. Meltzer saw Mr. Larson on January 6, 2010 at his private practice and diagnosed him with moderate-to-severe plaque psoriasis. Mr. Larson told Dr. Meltzer that he was HIV+, the status of his HIV was "well-controlled," he was not on HAART, and he was being monitored by an infectious disease doctor. Dr. Meltzer reviewed Mr. Larson's medication list and observed that "he wasn't on [HAART] therapy and he wasn't on antibiotic prophylaxis for opportunistic infection." He did not ask for the name of Mr. Larson's infectious disease doctor, attempt to consult with Dr. Yang, or look into other information related to the state of Mr. Larson's HIV. He did, however, perform a tuberculosis skin test, as recommended by the prescribing information. Dr. Meltzer then prescribed HUMIRA.

Treatment of Psoriasis with HUMIRA

HUMIRA is a biologic-response modifying drug ("BRMD").[4] It is also an "immunosuppressant" that suppresses certain adverse immunological reactions. HUMIRA is classified as a "TNF inhibitor"[5] -- a specific class of biologics, which work by blocking or decreasing the body's production of tumor necrosis factor ("TNF"). TNF is a type of cytokine that mediates inflammation and regulates the response of other immune cells, but it also acts as an inflammatory stimulus. Blocking TNF can improve conditions such as Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and psoriasis. Psoriasis is a genetic disorder of the immune system in which the cytokines that regulate function in the skin are abnormal, and one of those cytokines is TNF. By blocking TNF and decreasing inflammation, therefore, HUMIRA can help to clear psoriasis plaques.

HUMIRA was first approved by the Food and Drug Administration (FDA) in 2002 for the treatment of rheumatoid arthritis.[6] On January 18, 2008, the FDA approved the use of HUMIRA for "adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate." From 2005 to early 2009, the healthcare marketing agency

[4] Our description of HUMIRA and associated terms is derived from Ms. Larson's First Amended Complaint, as well as the deposition transcripts of physicians involved with the case.

[5] This class of drugs is also referred to as "anti-TNF" or "TNF blocker" therapy.

[6] Facts regarding the FDA's approval and regulation of HUMIRA are taken from Ms. Larson's First Amended Complaint.

Harrison & Star ("H&S") marketed HUMIRA on behalf of Abbott.[7] Abbott began promoting HUMIRA to dermatologists for the treatment of psoriasis in 2008. Following Abbott's advertisement of HUMIRA in the *Post Meeting News* -- a publication distributed by the American Academy of Dermatology (AAD) to its members[8] -- the FDA issued a warning letter to Abbott stating, in part:

> The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with HUMIRA . . . misleadingly suggest[ing] that HUMIRA is safer than has been demonstrated.

Thereafter, Abbott terminated its relationship with H&S.

In 2010, when Dr. Meltzer prescribed HUMIRA to Mr. Larson, Abbott's prescribing information for HUMIRA included the following "Warnings and Precautions":

> Serious infections, sepsis, tuberculosis and cases of opportunistic infections, including fatalities, have been reported with the use [of] TNF blocking agents including HUMIRA. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis could predispose them to infections . . . . Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.
>
> Treatment with HUMIRA should not be initiated in patients with active infections including chronic or localized infections. Patients who develop a new infection while undergoing treatment with HUMIRA should be monitored closely . . . . Physicians should exercise caution when considering the use of HUMIRA in patients with a history of recurrent infection or underlying conditions which may predispose them to

[7] H&S was previously named as a defendant in this litigation.

[8] Dr. Meltzer was a member of AAD.

> infections . . . . The benefits and risks of HUMIRA treatment should be carefully considered before initiation of HUMIRA therapy.

Under "Immunosuppression," the package insert continued:

> The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses . . . . The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood . . . . The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Thereafter, the label provided a warning for the "risk of serious infection" and included specific precautions related to tuberculosis (TB):

> Tuberculosis, invasive fungal infections, and other opportunistic infections have been observed in patients receiving HUMIRA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with HUMIRA. [. . .]
>
> Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating HUMIRA and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

Despite including several pages of warnings for prescribing physicians, the label does not mention HIV specifically or recommend any particular screening or monitoring precautions specific to treating HIV+ patients with HUMIRA.

Monitoring & Treatment for HIV+ Patients

HIV is the virus that can lead to Acquired Immune Deficiency Syndrome (AIDS). The virus destroys what are commonly referred to as "CD4 cells," which are cells involved in preventing infections. A "CD4 count" -- the number of CD4 cells per one cubic milliliter of blood -- is an important indicator of a HIV+ individual's immune health status and one of several factors used by physicians to determine whether the patient's HIV is "well-controlled." An individual's "viral load" -- an important measure of an HIV+ individual's viral progression -- refers to the number of HIV particles (or "HIV RNA") per one cubic milliliter of blood. Generally, a decrease in CD4 count negatively correlates with an increase in viral load, because the decrease of CD4 cells renders the body's immune system less able to control HIV replication, and the increase in HIV particles, in turn, destroys more CD4 cells. In addition, a decreased CD4 count indicates that the body's existing immune system is less capable of fighting off other types of infections, such as "opportunistic infections." An individual is considered to have AIDS when his or her CD4 count drops below 200 or when he or she develops an opportunistic infection considered an "AIDS-defining illness," such as PML.

The current treatment to reduce HIV replication is HAART, which involves a combination of drugs that interfere with the natural progression of HIV by decreasing the chances of HIV replication, thereby giving the immune system, including CD4 levels, a chance to recover. The general guideline that applied in late 2009 and early 2010 provided that physicians should prescribe HAART when a patient's CD4 count drops below 350

cells per milliliter[9] or drops more than 120 points in a year, but many doctors encourage HIV+ patients to begin HAART as early as possible. Additionally, a patient's development of an AIDS-defining illness, including PML, requires initiating HAART. Because of the potential for an individual's HIV to develop an immunity to specific antiretroviral drugs if not taken consistently, patients who begin HAART must adhere closely to treatment regimens and continue taking HAART for the rest of their lives.

PML & JCV

PML is a rare disease caused by the "JC virus" ("JCV"),[10] which is present in the majority of adults in the United States.[11] Typically, JCV remains inactive, but it can be reactivated in severely immunocompromised individuals. When reactivated, JCV infects the central nervous system and enters the brain, resulting in PML. PML is a demyelination disease, meaning it affects the covering around the nerves, called myelin. It primarily affects the white matter of the brain, where impulses are transferred from one part of the brain to the other, leading to impaired coordination and cognitive abilities. Although PML is extremely rare, it is most commonly found among HIV+ patients with severely compromised immune systems. Prior to the widespread use of HAART, infectious disease

[9] Dr. Gary Simon, one of Dr. Yang's expert witnesses, explained that the general guidelines in 2009 recommended that "if it's under 350, you probably should start [HAART]. If it's under 200, you definitely start."

[10] "JC Virus" is the common abbreviation for the "John Cunningham" virus.

[11] This information was taken from Dr. Simon's testimony.

doctors treated more patients who were severely immunocompromised, and therefore, more likely to develop opportunistic infections like PML. Today, PML is extremely rare, despite the relative ubiquity of JCV.

Mr. Larson's HIV Progression & PML Diagnosis

Mr. Larson's typical schedule for seeing Dr. Yang and having his CD4 count and viral load tested was twice or more per year. Although he experienced considerable fluctuations, his CD4 count remained well above 350 prior to November 2009. Dr. Richard Berg[12] noted in his deposition that the only "uncommon" aspect of Mr. Larson's CD4 counts from October 2004 through March 2009 was that "there [was] wilder variation" than he typically saw in his experience. He added, "You can see, for instance, he went from 611 in 2006 in the summer to 454 and then to 797 in March of 2007 and then to 488. So the fluctuations were a little greater than one often will see but certainly one sees it and they are all pretty normal." In part because Mr. Larson's CD4 count remained consistently above 350 prior to October of 2009, Dr. Yang considered his HIV to be "well-controlled" and had not recommended that he begin HAART.

Mr. Larson saw Dr. Yang for routine monitoring of his HIV status on October 21, 2009. She did not receive his lab work, however, until November 3, 2009, which indicated that his CD4 count was 266 and his viral load was 138,500 copies. These numbers were in stark contrast to his prior lab work in March 2009, which indicated a CD4 count of 636 and viral load of 9,490 copies. In addition to the 370-point drop in his CD4 count, the

[12] Dr. Berg was originally one of Dr. Yang's expert witnesses.

November 3, 2009 results were the first indication that his viral load had surpassed 100,000 copies. Dr. Yang testified in her deposition that she attempted to talk to Mr. Larson via phone and left at least one voicemail requesting that Mr. Larson return to recheck his blood work, but Mr. Larson did not return her calls and it is not clear whether he received her message. According to Dr. Yang's expert witnesses' reviews of Dr. Yang's records and testimony, Mr. Larson had always been a compliant and dependable patient prior to November 2009.

Few facts are available regarding the interim period between January 15, 2010, when Mr. Larson received his first injection of HUMIRA, and April 13, 2010, when Mr. Larson returned to Dr. Meltzer's office for a follow-up evaluation. At that visit, Dr. Meltzer observed that Mr. Larson's psoriasis "had basically disappeared," but he was experiencing headaches and "extreme fatigue." He advised Mr. Larson to stop his HUMIRA injections and see his primary care and infectious disease physicians.

Mr. Larson saw his primary care physician, John D. Jackson, on April 15, 2010. Dr. Jackson noted that Mr. Larson, who was brought in by his sister, had "obvious left peripheral facial droop," which began two weeks prior, but that he was alert and oriented. Dr. Jackson suspected Bell's Palsy and, among other things, recommended that he follow up with Dr. Yang. Mr. Larson saw Dr. Yang on April 21, 2010, which was more than five months after his last visit with her. She noted that his CD4 count on March 31, 2010 was 198 and that his viral load was over 2.4 million. In addition to his facial droop, she observed that Mr. Larson appeared disheveled and confused about the dates. She also

learned, for the first time, that he had received HUMIRA from January until March. Dr. Yang suspected that Mr. Larson had a CNS lesion and sent him to the emergency room at Anne Arundel Medical Center (AAMC).

Mr. Larson continued to decline at AAMC, and his family requested that he be transferred to Johns Hopkins University Hospital (JHUH) due to his poor condition. He arrived at JHUH on May 2, 2010, where he was treated by neurologist Dr. Justin McArthur and infectious disease specialist Dr. Gregory Kirk. Both doctors had substantial experience treating HIV+ patients. Dr. Kirk suspected that HUMIRA may have led to his "loss of virologic control and markedly high plasma HIV RNA," although he was not yet aware that Mr. Larson had experienced his first CD4 drop to 266 prior to his first HUMIRA injection. Drs. McArthur, Kirk, and other members of their medical team diagnosed Mr. Larson with PML and successfully treated it by initiating HAART. Mr. Larson, however, continues to suffer from severe cognitive impairment and other permanent health conditions as a result of PML. He is unable to care for his daily needs or be left alone for long periods of time, and he now lives with his sister, Ms. Larson, who has become his caretaker.

Procedural History

Ms. Larson, as guardian for her brother, filed suit in January of 2013, reasserting her claims already filed in a previously dismissed suit against Dr. Meltzer, Dr. Yang, and their respective practices, and added new product liability claims against Abbott and

H&S.[13] On February 2, 2013, Abbott attempted to have the case heard in U.S. District Court, but after finding no merit in Abbott's arguments in favor of the court's subject matter jurisdiction, the District Court (Hollander, J.) remanded the case back to the circuit court on November 6, 2013. Thereafter, Ms. Larson filed her "First Amended Complaint" in the Circuit Court for Baltimore City, on January 6, 2014.[14] She alleged that Abbott's prescribing information was inadequate because it did not warn physicians that HUMIRA should not be prescribed to HIV+ patients without particular precautions, such as those included in Abbott's Letter to Ms. Catlin. Among others, one such precaution was the recommendation that the patient be on HAART before taking HUMIRA, and receive HUMIRA only if under close monitoring by a physician knowledgeable in treating HIV+ patients.

Based on these allegations, Ms. Larson asserted the following claims against Abbott: (1) Strict product liability -- failure to warn; (2) product liability -- negligent failure to warn; (3) product liability -- breach of implied warranties; (4) violations of Maryland's Consumer Protection Act; and (5) common law misrepresentation. Ms. Larson sought to support her argument that Mr. Larson's use of HUMIRA was a substantial contributing

[13] Ms. Larson originally filed suit against Dr. Meltzer in the circuit court alleging medical malpractice and negligence. She filed an amended complaint in July 2012, adding Union Memorial, Dr. Yang and AIDA. All of the parties, however, filed a joint stipulation of dismissal without prejudice in November 2012.

[14] Ms. Larson ultimately settled out of court with Drs. Meltzer and Yang on her medical malpractice claims on February 23, 2015, and Abbott was the only remaining defendant by the time the circuit court issued its final order.

factor in his development of PML with four "causation experts." Mr. Larson's primary causation expert was Dr. Jacobson, a highly-regarded infectious disease specialist with significant experience treating HIV+ patients. She also relied on the testimony of Dr. Justin C. McArthur, a neurologist with substantial experience treating HIV+ patients and one of Mr. Larson's treating physicians at JHUH. As the circuit court explained, "[Ms. Larson] also relie[d] secondarily on the opinions of Gary Simon, M.D. and Richard Berg, M.D., both infectious disease specialists retained for this action by Defendant Ellen Yang, M.D."[15]

Abbott ultimately filed three related motions: (1) Motion for Summary Judgment; (2) Motion to Exclude the Testimony of Causation Experts under Maryland Rule 5-702; and (3) Motion [to] Exclude the Testimony of Plaintiff's Warnings Experts under Maryland Rule 5-702. The circuit court held a hearing on the motions on January 20, 2015. The court entered a partial ruling on the motions on February 5, 2015, reserving its issuance of a more detailed memorandum opinion for a later date.

On December 21, 2016, the circuit court issued a final order. The court granted Abbott's motion to exclude the testimony of Ms. Larson's causation experts under Maryland Rule 5-702 and, accordingly, granted Abbott's motion for summary judgment. In a thorough, fifty-one page memorandum opinion, the circuit court reasoned that the testimony of Ms. Larson's causation experts' testimony was inadmissible, and therefore,

[15] Ms. Larson also proffered Uwe W. Maennl, M.D. and James O'Donnell, Pharm.D as expert witnesses who would testify regarding Abbott's duty to warn and the prescribing information included in HUMIRA's package insert.

that Ms. Larson could not prove an essential element of her claims against Abbott. Alternatively, the court ruled that Abbott was entitled to judgment because of its finding that Abbott's warning label was adequate as a matter of law. The court determined it was not necessary to rule on Abbott's motion to exclude Ms. Larson's warning experts. Ms. Larson now appeals the circuit court's order granting summary judgment.

DISCUSSION

I. Standard of Review When Summary Judgment is Based on the Absence of a Sufficient Basis for Expert Opinion.

We review the circuit court's decision to grant summary judgment *de novo*. *Piscatelli v. Van Smith*, 424 Md. 294, 305 (2012). The Court of Appeals explained in *Blackwell v. Wyeth* that appellate courts will not disturb a trial court's determination of the qualifications of experts unless it is "founded on an error of law or some serious mistake, or if the trial court clearly abused its discretion." 408 Md. 575, 618 (2009) (quoting *Radman v. Harold*, 279 Md. 167, 173 (1977)). However, if the court's decision to grant summary judgment was based on its finding "that [an] expert witness 'lacks a sufficient factual basis of admissible facts and the admissible evidence (if any) is insufficient independently to prove causation," we review the exclusion of expert testimony as part of the summary judgment decision. *See Roy v. Dackman*, 445 Md. 23, 39-40 (2015) (quoting *Hamilton v. Kirson*, 439 Md. 501, 521 n. 11 (2014)). Thus, we review "the legal decision to grant summary judgment in the absence of any admissible evidence of medical causation" *de novo*. *See id.* at 40.

Maryland Rule 2-501(f) provides that the circuit "court shall enter judgment in favor of . . . the moving party if the motion and response show that there is no genuine dispute as to any material fact and . . . the party in whose favor judgment is entered is entitled to judgment as a matter of law." The "dispute as to a material fact" must be "sufficient to provide an issue to be tried." *Roy*, 445 Md. at 39 (quoting *Charles Cnty. Comm'rs v. Johnson*, 393 Md. 248, 263 (2006)) (Internal quotation marks omitted). As the Court of Appeals explained in *Rite Aid Corp. v. Hagley*:

> The party opposing a motion for summary judgment must produce admissible evidence to show that a genuine dispute of material fact, i.e., one "the resolution of which will somehow affect the outcome of the case," *King v. Bankerd*, 303 Md. 98, 111, 492 A.2d 608, 614 (1985) does exist . . . . This requires more than "general allegations which do not show facts in detail and with precision."

374 Md. 665, 684 (2003) (quoting *Beatty v. Trailmaster Prods., Inc.*, 330 Md. 726, 738 (1993) (Citations omitted). Additionally, "[w]e review independently the record to determine whether the parties generated a dispute of material fact," viewing the facts in "the light most favorable to the non-moving party," and we "construe any reasonable inferences that may be drawn from the well-pled facts against the moving party." *Id.* (quoting *Tyler v. City of Coll. Park*, 415 Md. 475, 499 (2010)).

II. The Circuit Court Did Not Err in Granting Summary Judgment in Favor of Abbott.

The issues before this Court pertain primarily to Ms. Larson's "failure to warn" product liability claims, including counts of strict liability, negligence, and breach of implied warranties. Although minor differences exist, all three theories of recovery require

"a plaintiff [to] show 'three product litigation basics—defect, attribution of defect to seller, and a causal relationship between the defect and the injury.'" *Laing v. Volkswagen of Am., Inc.*, 180 Md. App. 136, 159 (2008) (quoting *Ford Motor Co. v. Gen. Accident Ins. Co.*, 365 Md. 321, 335 (2001) (Internal quotation marks omitted). As the Court of Appeals said, "Certainly, it is true that a strict liability claim based on failure to warn bears a strong resemblance to a claim of negligence. Concepts of duty, breach, causation, and damages are present in both." *Mazda Motor of Am., Inc. v. Rogowski*, 105 Md. App. 318, 325, *cert. denied*, 340 Md. 501 (1995). In *Gourdine v. Crews*, therefore, the Court observed, "We have recognized . . . that negligence concepts and those of strict liability have 'morphed together' . . . in failure to warn cases." 405 Md. 722, 743 (2008) (citing *ACandS, Inc. v. Asner*, 344 Md. 155, 168 (1996)).

As the Court in *Doe v. Pharmacia & Upjohn Co.* explained, "[t]he existence of a legal duty is a question of law, to be decided by the court." 388 Md. 407, 414 (2005) (Citations omitted). Further, regarding a manufacturer's breach of its duty, the Court of Appeals has said that, "[i]n a strict liability failure to warn case, the alleged defect is the failure of the seller to give an adequate warning." *Owens-Illinois, Inc. v. Zenobia*, 325 Md. 420, 438 n. 8 (1992) (citing *Ellsworth v. Sherne Lingerie, Inc.*, 303 Md. 581, 597 (1985)). The manufacturer's duty to warn must be established, therefore, before the question of whether the manufacturer's failure to warn was a proximate cause of the injury becomes relevant.

Additionally, "[o]ur analysis of whether a duty is owed to a plaintiff in a failure to warn case is the same whether recovery is sought under a negligence or a strict liability in tort theory." *Gourdine*, 177 Md. App. at 478 (Citation omitted). "In cases involving personal injury, 'the principal determinant of duty becomes foreseeability.'" *Pharmacia & Upjohn Co.*, 388 Md. at 416 (quoting *Jacques v. First Nat'l Bank*, 307 Md. 527, 535 (1986)) (Internal quotation marks omitted). Indeed, the manufacturer of pharmaceuticals has a duty "to give a reasonable warning, not the best possible one . . . ." *Nolan v. Dillon*, 261 Md. 516, 523 (1971) (citing *Levin v. Walter Kidde & Co.*, 251 Md. 560, 563 (1968)). Regarding the plaintiff's burden to establish the manufacturer's duty, the Court in *Owens-Illinois* noted,

> The seller . . . need not give any warning if the requisite state of the art or knowledge does not require it. Thus, where a product lacks a warning because of insufficient knowledge on the part of the manufacturer or in the scientific field involved, the product is not defective.

325 Md. at 438 n. 8. Even if the manufacturer's warning was defective or additional warnings would have prevented the plaintiff's injury, therefore, the injury sustained by the plaintiff must be reasonably foreseeable to establish the manufacturer's duty to warn. *See Gourdine*, 177 Md. App. at 479

In pharmaceutical failure to warn cases, the "learned intermediary" doctrine provides an exception to a manufacturer's duty to warn the consumer directly; instead, the

duty to warn runs to the prescribing physician.[16] *Id.* at 478 (quoting *Ames v. Apothecon, Inc.*, 431 F. Supp. 2d 566, 572 (D. Md. 2006)). Therefore, a pharmaceutical manufacturer has a duty to "warn physicians or other personnel authorized to prescribe drugs by state law of *risks known or reasonably foreseeable at the time the product was administered*." *See Doe v. Miles Labs., Inc., Cutter Labs. Div.*, 927 F.2d 187, 194 (4th Cir. 1991) (Emphasis added) (Citations omitted). In sum, therefore, a pharmaceutical manufacturer has a duty to adequately warn prescribing physicians of significant risks of the drug to patients, if those risks were reasonably foreseeable, given the knowledge within the medical field at the time the drug was prescribed. Evidence that an injury or risk was foreseeable when a drug was prescribed is, therefore, part of the plaintiff's burden to establish that the manufacturer had a duty to warn.

Generally, the "proximate causation element" in a failure to warn case against a pharmaceutical manufacturer is established by proof that the allegedly inadequate warning was a substantial contributing factor to the plaintiff's injury. *See, e.g.*, *Grinage v. Mylan*, 840 F. Supp. 2d 862, 868-69 (D. Md. 2011) (discussing requirements under Maryland law to sufficiently plead causation). In certain product liability cases, however, such as the case before us, the parties disagree over whether sufficient evidence exists to show that the product, itself, can cause the specific injury alleged and, therefore, whether the

[16] As Judge Fletcher-Hill observed, the Court of Appeals has not adopted the "learned intermediary" doctrine for pharmaceutical failure to warn cases in Maryland. Given our resolution on the circuit court's exclusion of expert testimony, we need not decide whether the doctrine applies to the proximate causation element of the failure to warn claim.

manufacturer had a duty to provide different or additional warning to prevent the injury. *See, e.g.*, *Blackwell*, 408 Md. at 579 (explaining the "seminal question" was whether the appellants could support their claim of "general causation"). What is often termed "general causation" is present "when a substance is capable of causing a given disease." *See* Restatement (Third) of Torts, § 28 cmt. c(3). General causation, therefore, relates to the element of duty -- i.e., whether the risk of the type of injury the plaintiff suffered was reasonably foreseeable, and therefore, whether the manufacturer had a duty to warn the prescribing physician in the first place.

In addition, the plaintiff must prove that the product was a substantial contributing factor to his or her specific injury. *See Owens-Corning Fiberglas Corp. v. Garrett*, 343 Md. 500, 526 (1996). This preliminary causation issue is often referred to as "specific causation" -- i.e. that exposure to or use of the manufacturer's drug was a substantial factor to the plaintiff's specific injury. *See Aventis Pasteur, Inc. v. Skevofilax*, 396 Md. 405, 412 (2007); *see also In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Prods. Liability Litig.*, ____ F.3d ____ (4th Cir. June 12, 2018) (Citations omitted) ("For specific causation, the plaintiff must demonstrate that the substance actually caused injury in her particular case.").

Evidence demonstrating general and specific causation, therefore, must exist independent of whether the manufacturer's allegedly defective warning label was a proximate cause of the injury. In other words, evidence of general and specific causation was necessary in this case to establish Abbott's duty to warn; it was not an "alternative

theory" of liability, as Ms. Larson posited before the circuit court and continues to argue on appeal. Evidence showing that a different label, containing additional precautions, would have changed the physician's course of conduct and prevented Mr. Larson's injury, therefore, cannot substitute for evidence of general and specific causation.

A. Clarification of Causation Issues Before the Circuit Court

Despite the necessity of general and specific causation evidence, Ms. Larson sought to "advance two possible and *alternative* theories of causation" (Emphasis added) in opposing Abbott's motion for summary judgment:

> First, Plaintiff will establish that an adequate warning would have resulted in Mr. Larson being placed on antiretroviral therapy prior to his use, if at all, of HUMIRA. If Mr. Larson had been timely placed on antiretroviral therapy, he would not have developed PML. *This causation theory does not rely on whether HUMIRA causes PML*.
>
> Second, and *in the alternative*, Plaintiff will establish that HUMIRA can cause PML -- general causation. [. . .]
>
> Third, Plaintiff will establish that Mr. Larson's HUMIRA use was a proximate cause of his developing PML -- specific causation. As with general causation, Plaintiff's experts rely on generally accepted scientific methodologies as well as the medical facts specific to [Mr. Larson] to establish specific causation.

The court attempted to clarify Ms. Larson's arguments by referring to her assertion that HUMIRA can and did cause PML in Mr. Larson's case (general and specific causation) as her "direct" theory of causation, and her contention that a different warning label would have prevented Mr. Larson's development of PML (typically considered the "proximate

causation element" in failure to warn claims) as her "indirect" theory of causation. The circuit court explained:

> Plaintiff places far greater emphasis on her first theory of causation -- that deficiencies in Abbott's warnings caused a delay in the initiation of HAART for Mr. Larson and that Mr. Larson would not have developed PML had HAART been started earlier. Plaintiff's second, alternative theory is that Mr. Larson's ingestion [or rather, injection] of HUMIRA in fact contributed in a legally substantial degree to his development of PML. Despite Plaintiff's emphasis on the first theory, the Court will discuss the second theory first because it, unlike the first theory, is more direct.

To address Ms. Larson's arguments on appeal, however, our analysis focuses on the causation issues involved in establishing whether Abbott owed a duty to warn in the first place -- i.e., issues of specific and general causation. The issue of whether Abbott's allegedly inadequate prescribing information was a proximate cause of Mr. Larson's injury relates to the "proximate causation element" of her failure to warn claims. As we explain below, without evidence of general and specific causation, Ms. Larson could not have established that Abbott had a duty to provide additional warnings that would have prevented the harm suffered by Mr. Larson.[17]

[17] In some product liability cases, circumstantial evidence may obviate the product's role in the injury by "eliminate[ing] other causes, such as product misuse or alteration." *Laing*, 180 Md. App. at 159 (quoting *Ford Motor Co.*, 365 Md. at 337) (Internal quotation marks omitted). "An example of when such an inference may reasonably be drawn is when a new vehicle malfunctions and results in an accident." *Id.* at 159-60 (Citations omitted); *see also, e.g.*, *Miles Labs.*, 927 F.2d at 189 (explaining that the plaintiff, who allegedly contracted AIDS from the defendant's blood product, "possesse[d] no high risk factors for AIDS" and that the product she received was distributed before the defendant began screening plasma donors for evidence of AIDS). This case differs, however, because the

Adding to the confusion surrounding Ms. Larson's "direct" versus "indirect" theories of liability, Abbott also inaccurately characterizes Ms. Larson's burden of causation. Judge Fletcher-Hill described one such instance when he noted that "[i]t is important to understand the nuances of [Ms. Larson's] more direct causation theory because Abbott engages in something of a straw-person argument." The court explained,

> Abbott posits [as Ms. Larson's theory of causation] something like the following causal chain: (1) HUMIRA causes a drop in the patient's CD4 count; (2) the drop in the patient's CD4 count activates the patient's HIV; and (3) the increased HIV causes the development of PML. Abbott then takes aim at the first link because it argues that none of the expert witnesses can support the basic proposition that HUMIRA causes a decrease in CD4 counts. [. . .] Plaintiff emphasizes a different causal path: "[T]he [Plaintiff's] experts' opinion[s] [are] not that HUMIRA directly causes CD4 counts to drop but rather that HUMIRA causes immunosuppression, which in turn allows opportunistic infections to attack."

(Emphasis omitted, format altered). Evidence that Mr. Larson's CD4 count had declined prior to treatment with HUMIRA, therefore, did not undercut Ms. Larson's argument that HUMIRA suppressed Mr. Larson's immune system in such a way that it accelerated his development of PML. Ms. Larson's experts testified that Mr. Larson's development of PML was unusual, given his likely CD4 count above 200 when he developed PML.[18] Thus,

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precautions that Ms. Larson argues should have been included might have prevented Mr. Larson's development of PML, whether or not his exposure to HUMIRA contributed at all.

[18] Dr. Jacobson, however, testified that in the many cases of PML he had treated throughout his career, he had never observed PML in a patient with a CD4 count of above 100.

Ms. Larson argued that the immunosuppressant effect of HUMIRA permitted the "unmasking" of JCV, despite the fact that Mr. Larson had a CD4 count that was above the normal range for HIV+ patients who develop PML.

On appeal, Abbott contends that Ms. Larson's expert witness testimony failed to establish "but-for" causation, because under that test, "the plaintiff must show that 'the injury would not have occurred absent the defendant's actions.'" (quoting *Pittway Corp. v. Collins*, 409 Md. 218, 244 (2009)). First, Abbott asserts that "Dr. Jacobson expressly said: 'I do *not* hold the opinion that if Mr. Larson had never taken HUMIRA that he would have never developed PML.'" (emphasis in original). Next, Abbott emphasizes that Dr. McArthur "conceded that '[b]ased on the statistics that [Abbott's counsel] already reviewed for people with HIV who are substantially [at] a heightened risk of PML, [Mr. Larson] may have gone on 'naturally' without HUMIRA to develop PML."

Abbott's references to the record, however, do not accurately reflect the context of the experts' statements. Indeed, the quote from Dr. Jacobson's testimony was his attempt to clarify Abbott's counsel's hypothetical before answering. Both physicians implied that they assumed Mr. Larson never initiated antiretroviral therapy in answering the hypothetical. Moreover, Abbott, in its reliance on these excerpts, mischaracterizes the question of "but-for" causation. The well-established rule that, generally, an actor is not liable for his or her "negligent actions if the harm suffered would have occurred regardless of the actor's negligence" does not apply unless "the injury would have occurred *at the same time* regardless of the actor's negligence." *Certain-Teed Prod. Corp. v. Goslee*

Roofing & Sheet Metal, Inc., 26 Md. App. 452, 469 (1975) (citing Restatement (Second) of Torts, § 432(1)) (Emphasis added). "It thus does not apply in cases . . . where the harm occurred sooner because of [the actor's] breach than it would have otherwise." *Id.* The more consequential inquiry, therefore, was whether Mr. Larson would have developed PML *at the same time* that he did develop PML, had he not started HUMIRA in January 2010, rather than whether he would have "gone on 'naturally'" to develop it.

The focus of our review, then, is on whether Ms. Larson's experts' testimony provided reliable evidence that Mr. Larson's use of HUMIRA was likely a substantial contributing factor to his "develop[ment] [of] PML and severe brain damage along with a temporary acceleration of his HIV status to AIDS." Although we are not convinced by Abbott's characterization of the various causation issues involved, Ms. Larson had the preliminary burden to put forth sufficient evidence that treatment with HUMIRA was a substantial factor in Mr. Larson's development of PML. Without such evidence, she could not show that Abbott owed a duty to warn Mr. Larson's treating dermatologist of the risk of prescribing HUMIRA to HIV+ patients without consulting the patient's infectious disease doctor or confirming that the patient was on HAART.

B. Admissibility Ms. Larson's Causation Expert Testimony

Rule 5-702 governs the trial court's decision whether to admit an expert's opinion. It states the following:

> Expert testimony may be admitted, in the form of an opinion or otherwise, if the court determines that the testimony will assist the trier of fact to understand the evidence or to determine a fact in issue. In making that determination, the

> court shall determine (1) whether the witness is qualified as an expert by knowledge, skill, experience, training, or education, (2) the appropriateness of the expert testimony on the particular subject, and (3) whether a sufficient factual basis exists to support the expert testimony.

Here, the parties' dispute relates to the third consideration -- "whether a sufficient factual basis exist[ed] to support" the testimony of Ms. Larson's expert witnesses. *See id.* The Court of Appeals has interpreted this standard to require "two subfactors: an adequate supply of data and a reliable methodology." *Rochkind v. Stevenson*, 454 Md. 277, 286 (2017) (citing *Roy*, 445 Md. at 42-43). In *Rochkind*, the Court explained:

> To constitute "more than mere speculation or conjecture," the expert's opinion must be based on facts sufficient to "indicate the use of reliable principles and methodology in support of the expert's conclusions." *Ford*, 433 Md. at 478, 71 A.3d 105 (citation and internal quotation marks omitted). To demonstrate a sufficient factual basis, an expert must establish that her testimony is supported by both subfactors.

Id.

For an expert's testimony to be reliable, he or she must have "a sound reasoning process for inducing [the] conclusion from the factual data" and "an adequate theory or rational explanation of how the factual data led to the expert's conclusion." *Id.* at 287 (quoting *Exxon Mobil Corp. v. Ford*, 433 Md. 426, 481 (2013)). This requirement helps to avoid "conjecture, speculation, or incompetent evidence." *Sugarman v. Liles*, 234 Md. App. 442, 466 (2017), *cert. granted*, 457 Md. 399 (2018) (quoting *Giant Food, Inc. v. Booker*, 152 Md. App. 166, 182–83, *cert. denied*, 378 Md. 614 (2003)). A trial court errs in denying summary judgment, therefore, "where proof of causation" must rely on expert

testimony, and the expert testimony "lack[s] a sufficient factual basis to support the expert's conclusions." *See id.* (citing *Giant Food, Inc.*, 152 Md. App. at 189-90).

Adopting the standard outlined in *Frye v. United States*, 293 F. 1013 (1923), the Court of Appeals held that "before a scientific opinion will be received as evidence, the basis of that opinion must be shown to be generally accepted as reliable within the expert's particular scientific field." *Reed v. State*, 283 Md. 374, 381 (1978). The Court explained that, in some cases, "the validity and reliability of a scientific technique may be so broadly and generally accepted in the scientific community that a trial court may take judicial notice of its reliability." *Id.* at 380. In others, however, the court must determine whether the techniques used are considered reliable within the scientific community.[19] *Id.*

Notably, "unlike the question . . . of the helpfulness of particular expert testimony to the trier of facts, . . . [t]he answer to the question about the reliability of a scientific technique or process does not vary according to the circumstances of each case." *Id.* at 381. In Maryland, the reliability of an expert's testimony is a question of law, which is based on the test articulated in *Frye*, 54 U.S. App. D.C. at 47 and adopted by *Reed*. *See id.* at 380. The *Frye-Reed* standard requires that "if a new scientific technique's validity is in controversy in the relevant scientific community, or if it is generally regarded as an

[19] This determination can be made by examining expert testimony, as well as by taking notice of "articles from reliable sources that appear in scientific journals, and other publications which bear on the degree of acceptance by recognized experts . . . ." *Id.* (Citations omitted).

experimental technique, then expert testimony based upon its validity cannot be admitted into evidence." *Id.*

The Court, in *Blackwell*, held that the *Frye-Reed* test applies, even where an expert used generally accepted methods for gathering data, but applied such data "to support a novel theory." 408 Md. at 596. There, the Court explained:

> *Frye* was deliberately intended to interpose a substantial obstacle to the unrestrained admission of evidence based upon new scientific principles because lay jurors tend to give considerable weight to "scientific" evidence when presented by "experts" with impressive credentials.

Id. at 586-87 (quoting *Reed*, 283 Md. at 386).

Turning to the exclusion of Ms. Larson's experts, the circuit court found that "[t]he risk that jurors will be led astray by opinions stated by eminent experts but unsupported by *sufficient* science is particularly relevant here." (Emphasis added). The court concluded the following:

> The Court finds that Dr. Jacobson's secondary or more direct causation theory lacks sufficient scientific foundation or reliability to be admissible. The problem is not with Dr. Jacobson's qualifications or with the methodology of his theorizing. The Court has no reservations about Dr. Jacobson's superior training and experience in the field of infectious diseases, focused especially on HIV. Nor does the Court take issue with Dr. Jacobson's scientific approach to the problem. He draws on the type of information and data routinely used by physicians and medical researchers to formulate his hypotheses. *The problem with his conclusions supporting his secondary causation theory is that they have not been sufficiently tested and proven to qualify as reliable forensic conclusions rather than scientific hypotheses*.

The circuit court noted Dr. Jacobson's primary contention regarding the causal association between TNF inhibitors and the development of PML:

> It is extremely likely that in addition to general HIV disease progression, *some additional functional immune deficit must be present* for PML to occur. Otherwise, since the JC virus is present in a majority of the population, PML would occur in a majority of patients with advanced HIV disease, which it does not.

In response, however, the trial court concluded that Dr. Jacobson's assertion was "just a return to the same basic premise -- something else must be at work to explain the relatively rare instance of PML even among cases of severe HIV disease." Dr. Jacobson did not, for instance, consider in his analysis other potentially contributing factors, except to say that the progression of Mr. Larson's HIV was likely not enough to make him susceptible to PML. *See Ross v. Housing Auth. of Baltimore Cty.*, 430 Md. 648, 660 (2013) (holding an expert's testimony did not have a sufficient factual basis where she conceded that, if any lead-based paint was detected on a property, she assumed the property was the source of exposure "until proven otherwise"). Even if Mr. Larson's recent HIV progression and declining CD4 levels were not enough to make him vulnerable to PML, Ms. Larson's expert could not provide a sufficient factual basis for his opinion that the missing link was most likely the use of HUMIRA and not something else.

Ms. Larson emphasizes the following portion of what she terms Dr. Jacobson's "direct causation opinion" as support for her specific causation argument:

> TNF-inhibitor drugs are immunosuppressive and were known to be associated with an increased risk of PML in 2009. PML is also a well-described opportunistic infection that can

> complicate advanced HIV disease. However, more than 90% of HIV-associated PML cases occur in patients who have a CD4 count lower than Mr. Larson's was at the time of his PML diagnosis, which makes HUMIRA a likely contributing factor to his developing PML.

To constitute a sufficient basis for his general causation opinion, Dr. Jacobson needed to provide support for his contention that "TNF-inhibitor drugs . . . were known to be associated with an increased risk of PML in 2009," beyond simply asserting that TNF inhibitors are immunosuppressants. Ms. Larson contends that Dr. Jacobson's support for this assertion was that HUMIRA includes a "top black box warning" which states that there is an "[i]ncreased risk of serious infections leading to hospitalization or death, including tuberculosis . . . and infections due to other opportunistic pathogens." Dr. Jacobson then concluded:

> Since there have been well-documented reports of PML occurring in patients who have received TNF inhibitors like, and including, HUMIRA, this black box warning is an acknowledgment by Abbott that HUMIRA is immune-supressive and that HUMIRA therapy carries the risk of causing catastrophic opportunistic infectious diseases like PML.

Dr. Jacobson, however, did not discuss the "well-documented reports of PML" or explain how these reports helped form the basis of his opinion.

Additionally, Ms. Larson asserts that Dr. Jacobson supported his opinion by citing "an Abbott's report wherein the manufacturer stated" that "seven reports of PML have been received coincident with adalimumab therapy." The Abbott report -- apparently written in 2012 in response to an inquiry by Dr. Meltzer -- explains that among the seven reports of

PML conincident with adalimumab therapy, only two cases were confirmed. The remaining six reports "lacked adequate evidence of substantial neurologic symptoms or diagnostic criteria to confirm a diagnosis of PML." Of the two confirmed cases, the first was a patient with Wegener's granulomatosis who "was treated with adalimumab and cyclophosphamide for approximately 4 years." The second report (the "only published post-marketing case of PML associated with the use of adalimumab") was published by Dr. McArthur and described Mr. Larson's PML diagnosis.[20]

Next, Ms. Larson asserts that Dr. Jacobson relied on "peer-reviewed studies, reviews of other biologicals, [and] FDA Adverse Event Reporting data"[21] in his Declaration.[22] He did not, however, explain how the existence of case reports demonstrated a causal association or assisted in drawing his conclusions. Dr. Jacobson cited one article in the Journal of the American Academy of Dermatologists as support, which he contended "document[ed] cases of PML associated with TNF inhibitor use." The article, however,

[20] According to his deposition testimony, when Dr. McArthur published the report, he believed that Mr. Larson's sharp decline in CD4 count occurred after initiating HUMIRA and did not know that Mr. Larson's CD4 count dropped to 266 in November 2009.

[21] Dr. Jacobson noted in his Declaration that "[o]ver 60 cases of PML have been reported to the FDA's prospective adverse event surveillance team." He also argued that the claim that "case reports of PML in patients receiving HUMIRA are not sufficient to 'establish a causal relationship' is refuted by data from the FDA Adverse Event Reporting system."

[22] Ms. Larson asserts that the circuit court did not adequately consider Dr. Jacobson's deposition testimony and focused exclusively on his "supplemental" Declaration. We combed through Dr. Jacobson's deposition for additional support for his causation opinion. His Declaration adequately summarized his primary contentions in his deposition testimony.

examined three adverse event reports of PML in patients who were treated with efalizumab (Raptiva®). Kothary, et al., *Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients*, 65 AM. ACAD. DERMATOL. 546, 547 (2011). Efalizumab was a biologic intended to treat psoriasis, but it used a different mechanism of action than TNF inhibitors like HUMIRA. For that reason, among others, the article did not provide a reliable basis for his assertion of an association between HUMIRA, which is a TNF inhibitor, and the development of PML.

To summarize his conclusions, Dr. Jacobson asserted the following:

> That [TNF inhibitors] are inherently immunosuppressive is obvious and well established scientifically, and not just a biologic hypothesis.
>
> * * *
>
> [A]s noted, the biologic plausibility of a causative link between the TNF inhibitor class BRMDs, which by definition are immune suppressive, and PML, an opportunistic infectious complication of immune suppression, is scientifically and reliably obvious.

We agree with the circuit court's response on this point, however: "This is sound scientific reasoning to suggest that an effect on T cell production of TNF *could be* a factor, but it falls short of showing with any degree of reliability that it *is* a factor, much less a substantial contributing cause" to Mr. Larson's development of PML. Although the lack of scientific support could be due, in part, to the rarity of PML in the first place, other types of biologics with different mechanisms of action, as Dr. Jacobson noted, *have been* causally linked to increased incidences of PML.

We also reviewed, in-depth, the depositions and declarations of Drs. McArthur, Berg, and Simon. All three physicians agree with many of Dr. Jacobson's assertions, including the following: HUMIRA is an immunosuppressant that blocks TNF; other types of biologics have been associated with PML; PML rarely occurs except in severely immunocompromised individuals; among HIV+ patients who develop PML, CD4 counts at PML diagnosis are typically below 100; Mr. Larson's CD4 count was likely between 266 and 198 and above 200 when he developed PML, therefore, his development of PML was unusual; initiation of HAART in November 2009 would likely have prevented Mr. Larson's development of PML, whether or not Mr. Larson received HUMIRA in January 2010, because HAART is the most effective way to prevent PML in all HIV+ patients. None of these assertions, however, provide a reliable basis for the conclusion that a causal association between TNF inhibitors and PML is established and was known in early 2010. Indeed, Dr. McArthur conceded that a scientifically reliable causal association between TNF inhibitors and PML has not been established.

Although Ms. Larson's experts believed that Mr. Larson's use of HUMIRA likely contributed to his immunological decline, none could provide a sufficient factual basis for that conclusion. For instance, none of the experts could explain why his use of HUMIRA could provide the only missing link between his CD4 count above 200 and the reactivation of JCV. Moreover, Dr. McArthur opined that Mr. Larson's "drop by almost 400 points in the space of 6 months, 7 months indicates that there's more going on than simply the natural progression of untreated HIV." The sharp drop, however, occurred in November 2009,

suggesting that the additional factor that Dr. McArthur referenced was already present, before Mr. Larson's first HUMIRA treatment.

Dr. Simon stated more unequivocally that he believed Mr. Larson's "CD4 count was falling independent of HUMIRA," "representing progression of his HIV disease."[23] He also confirmed that the risks posed by the mechanisms of action of each type of biologic are different, even within various types of TNF inhibitors. Dr. Simon discussed an article that he believed established "the theoretical possibility" that PML is associated with TNF inhibitors, but explained, "I mean, it doesn't necessarily establish causation, but it explains how it could happen and I believe that's how it could happen." Further, Dr. Simon candidly acknowledged regarding whether HUMIRA contributed to Mr. Larson's PML that "right now from the data that I have here, it's theoretical."

Similar to the other causation experts, Dr. Jacobson's opinion that HUMIRA was a substantial contributing factor in Mr. Larson's development of PML was derived, almost entirely, from the fact that HUMIRA is an immunosuppressant and, some other factor in addition to natural progression of untreated HIV must have been present to reactivate JCV in Mr. Larson. He did not, however, exclude other potential contributory factors as the elusive additional variable that could explain Mr. Larson's vulnerability to reactivation of JCV.

[23] In Dr. Jacobson's notes incorporated by reference in his Declaration, however, he asserted emphatically that "[s]uch a dramatic increase" in Mr. Larson's viral load in November 2009 "typically precedes an imminent marked acceleration of HIV disease progression."

Although we agree with the circuit court that Ms. Larson's expert witnesses possessed superior knowledge in their respective fields, they each acknowledged that the conclusions that can be drawn regarding the causal relationship of HUMIRA and PML are limited by the fact that PML is a rare disease and the mechanisms involved in its progression are not fully understood. We do not doubt what Ms. Larson's experts emphasized, repeatedly -- that the types of studies that Abbott insists are required to provide sufficient evidence of a causal relationship could not be conducted ethically with this population. Even Abbott, in its Medical Information Letter, acknowledged "the potential . . . for TNF blocker therapy to reactivate HIV replication and induce opportunistic infections." The experts' explanations of the biologic plausibility that use of TNF inhibitors can increase the vulnerability of HIV+ patients to reactivation of JCV, however, was not sufficient to establish either general or specific causation in this case.

The Court of Appeals, in adopting the standard in *Frye*, recognized that it "has been subjected to some criticism, primarily on the grounds that it is too conservative and unduly prevents or delays the admission of relevant scientific evidence." *Reed*, 283 Md. at 384, 391 A.2d 364, 369 (1978). Further, we agree with the following comments articulated by the circuit court:

> It may well be that additional research will confirm some or all of Dr. Jacobson's hypotheses. What is determinative in this case, however, is that *those causal theories have not been established now nor were they established in 2009 and early 2010, when the acts allegedly giving rise to liability occurred.*

We hold that Ms. Larson's experts' opinions were not grounded on an "adequate supply of data," *see Rochkind, supra*, 454 Md. at 286, and therefore, the circuit court properly excluded their testimony.

As Ms. Larson's experts noted, ethical considerations prevent researchers from conducting controlled studies of the effects of TNF inhibitors on HIV+ individuals who are not on HAART. Moreover, PML is a rare disease, and therefore, the amount of epidemiological data that could be useful is limited. Thus, even if grounded in science, only theoretical assertions could be drawn from the small amount of existing data. Because we conclude that Ms. Larson could not establish Abbott's duty to warn prescribing physicians of the risks she asserted, we need not decide if the question of whether Abbott's warning label was the proximate cause of Mr. Larson's PML was for the trier of fact.[24] Accordingly, there was no "dispute as to a material fact sufficient to provide an issue to be tried." *Roy, supra*, 445 Md. at 39. We, therefore, affirm the judgment of the circuit court.

[24] We note that Ms. Larson pointed to several portions of Dr. Meltzer's testimony that suggest he would have acted differently if precautions specific to HIV+ patients were included. For instance, Dr. Meltzer followed the label's recommendation and tested Mr. Larson for TB before prescribing HUMIRA. Dr. Meltzer did not appear to believe that precautions specific to HIV+ patients were necessary, however, other than asking each HIV+ patient whether his or her HIV was "well controlled." Instead, he insisted that the label did not recommend precautions such as considering whether to begin HAART or consulting with the patient's infectious disease physician. Evidence offered to rebut the presumption that Dr. Meltzer would have followed additional precautions would have been for the trier of fact to consider. *See, e.g.*, *U.S. Gypsum Co. v. Mayor & Cty. Council of Baltimore*, 336 Md. 145, 162 (1994) ("[E]vidence . . . to rebut the presumption was for the trier of fact to consider in determining whether receipt of a post-sale warning would have changed the City's behavior."). Ms. Larson, however, did not provide sufficient evidence of Abbott's duty to include the warnings that she asserted in the first place.

JUDGMENT OF THE CIRCUIT COURT FOR BALTIMORE CITY AFFIRMED. COSTS TO BE PAID BY APPELLANTS.