Case Nos. 25-1383 (L), 25-1796

IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

MARY ELLOUISE BOND, et al.,

Plaintiffs-Appellants,

v.

MERCK & CO., INC. and MERCK SHARP & DOHME LLC,

Defendants-Appellees.

JORDAN AGUILAR, et al.,

Plaintiffs-Appellants,

v.

MERCK & CO., INC. and MERCK SHARP & DOHME LLC,

Defendants-Appellees.

On Appeal from the United States District Court
for the Western District of North Carolina

BRIEF OF APPELLEES MERCK & CO., INC. AND MERCK SHARP & DOHME LLC

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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

DISCLOSURE STATEMENT

- In civil, agency, bankruptcy, and mandamus cases, a disclosure statement must be filed by **all** parties, with the following exceptions: (1) the United States is not required to file a disclosure statement; (2) an indigent party is not required to file a disclosure statement; and (3) a state or local government is not required to file a disclosure statement in pro se cases. (All parties to the action in the district court are considered parties to a mandamus case.)
- In criminal and post-conviction cases, a corporate defendant must file a disclosure statement.
- In criminal cases, the United States must file a disclosure statement if there was an organizational victim of the alleged criminal activity. (See question 7.)
- Any corporate amicus curiae must file a disclosure statement.
- Counsel has a continuing duty to update the disclosure statement.

No. 25-1383 Caption: Mary Bond, et al. v. Merck & Co., Inc., et. al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Merck & Co., Inc.
(name of party/amicus)

who is appellee, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ David C. Wright III Date: 04/23/2025

Counsel for: Merck & Co., Inc. and Merck Sharp & Dohme LLC

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Merck Sharp & Dohme LLC
(name of party/amicus)

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INTRODUCTION

Merck's vaccine Gardasil, which has been administered over 500 million times since the FDA approved it in 2006, protects against cervical cancer and other severe conditions caused by the human papillomavirus. Plaintiffs claim they developed ailments called POTS and POI from the vaccine.[1] As in *Knight v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 984 F.3d 329, 337 (4th Cir. 2021), the "central issue on appeal is whether [plaintiffs' failure-to-warn] claim[s] [are] preempted" by federal regulations. That legal question depends on whether Merck had "newly acquired information" providing "evidence of a causal association" between Gardasil and the conditions Plaintiffs allege. *Id.* at 338. The District Court, after carefully examining the evidence, properly concluded that no such "newly acquired information," and no such "causal association," had been established between Gardasil and POTS or POI. JA19745, JA19750. Its conclusion comports with an overwhelming scientific consensus, reflected by Plaintiffs' own concession that "***no*** study has ***ever*** shown a statistically significant increase in POTS or POI

[1] "POTS" refers to Postural Orthostatic Tachycardia Syndrome, and "POI" refers to Primary Ovarian Insufficiency. Both are discussed further below. Stmt. IV.B, *infra*.

in [persons] who have taken Gardasil versus those who have not." JA19744–19745, Summ. J. Op. (emphasis in original).

As the District Court explained, Plaintiffs' claims are based on two conditions "commonly found in the same young women typically vaccinated with Gardasil." JA19737. The first, POTS, is a syndrome marked by increased heart rate when moving to a standing position. JA19729–19730, Summ. J. Op. The second, POI, is a condition in which a woman's menstruation stops before age 40. JA19745, Summ. J. Op.

Though Plaintiffs claim Gardasil caused them to develop POTS and POI, federal health authorities have long rejected Plaintiffs' theories. The Department of Health and Human Services ("HHS"), which is the FDA and CDC's parent agency, has emphasized that "there is no known association between HPV vaccination and the development of POTS."[2] HHS has also stressed that "the only reliable epidemiological evidence . . . demonstrates no causal association between the HPV vaccination and POI."[3] A library of rigorous studies confirms what HHS, the FDA, and the CDC have said for years: "[T]here is no medical or scientific evidence

[2] JA03611, HHS Br., *Wagner v. Sec'y of Health & Hum. Servs.*

[3] JA03624, HHS Br., *Brayboy v. Sec'y of Health & Hum. Servs.*

that the HPV vaccine causes POTS and safety monitoring has not shown any other problems." 82 Fed. Reg. 6294, 6298 (Jan. 19, 2017).

Plaintiffs nevertheless have contended that Merck should have added a POTS warning to Gardasil's labeling in 2011, and a POI warning in 2013. Under federal regulations, Merck could only have added those warnings if it had "newly acquired information" that provided "reasonable evidence of a causal association" between Gardasil and a risk. *Knight*, 984 F.3d at 341.

Merck had no such "newly acquired information." To support their argument that Merck should have added a POTS warning in 2011, Plaintiffs cited only "one published case of POTS and less than 20 unverified reports of POTS." JA19736, Summ. J. Op. To support their argument that Merck should have added a POI warning in 2013, Plaintiffs offered "[l]ess than a handful of POI case reports" and other "unverified . . . reports" about individual patients, as well as "uncertain disproportionality 'signals,'" which are computer data-mining readouts that Plaintiffs concede do not show a causal connection. JA19750, Summ. J. Op. As the District Court observed, requiring new warnings based on

Plaintiffs' meager evidence "would effectively make the regulatory standard meaningless." JA19737.

Plaintiffs aim to sidestep the regulatory standard set out in *Knight* by pointing to a separate preemption test. As the District Court explained, "there are ***two ways*** a vaccine manufacturer may prevail on a preemption defense." JA19725 (emphasis added). Here, Merck prevailed under the first: the "newly acquired information" test applied in *Knight*. The second, subsequent test preempts claims if a manufacturer ***can*** propose a warning change under *Knight*, but "clear evidence" nevertheless indicates that the "FDA would have rejected the . . . change" even if the manufacturer had made it. *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 812 (7th Cir. 2018). According to Plaintiffs, Merck can ***only*** prevail if it satisfies the second, "clear evidence" test. That is not the law. Moreover, even though Merck would also prevail on the "clear evidence" test—because overwhelming evidence shows federal authorities ***would have*** rejected Plaintiffs' proposed warnings—the District Court did not even reach that test because Plaintiffs lose under *Knight*. JA19718–19719 n.2.

Plaintiffs' other attempts to engage with the District Court's reasoning also fall flat. Plaintiffs cite many medical articles, but none supplies the newly acquired information needed to add their proposed warnings. And many have no relevance whatsoever—such as articles discussing lupus and rheumatoid arthritis. Plaintiffs also suggest they were forced to "come forth with an expert" to "defeat preemption," which is incorrect. Apt. Br. 6. The District Court sought ***factual evidence*** of the kind that would persuade scientists—*i.e.*, "experts qualified by scientific training and experience"—not ***testimony*** from ***litigation*** experts. JA19728.

Plaintiffs challenge two other orders that are legally correct but largely irrelevant. Plaintiffs first contest the District Court's limitations on their regulatory expert, Dr. Amato. The District Court correctly precluded him from offering legal conclusions about preemption, which "is a ***question of law***" for the Court to decide. *Knight*, 984 F.3d at 337 (emphasis added). The Court also precluded Dr. Amato, a non-physician, from re-diagnosing patients—a correct ruling that is irrelevant to deciding this appeal.

Further, the District Court properly rejected several other claims under Rule 12. Only one issue remains relevant: whether Plaintiffs' "direct warning" claims that Merck should have warned patients or parents, rather than physicians, are barred by the National Childhood Vaccine Injury Act ("Vaccine Act") and state-law learned intermediary doctrine. Every federal court that has interpreted the Act has held it eliminates such claims. The learned intermediary doctrine does the same.

In sum, Plaintiffs' unsupported theories clash with decades of medical research and agency statements that confirm the safety of a life-saving vaccine. As the District Court observed, the "regulatory test" governing vaccines "is undoubtedly difficult to apply in many circumstances," but "[n]ot so here." JA19718. This Court should affirm.[4]

STATEMENT OF ISSUES

1. Federal regulations prohibit manufacturers from changing vaccines' labeling without FDA approval, subject to a narrow exception

[4] The appeal of sixteen bellwether plaintiffs in the MDL, *Bond*, has now been consolidated with an appeal of plaintiffs in *Aguilar*, who agree they "will be bound by any ruling in *Bond*" and "the appeals are identical." *Aguilar* ECF 25 at 4.

where the manufacturer had "newly acquired information" demonstrating "reasonable evidence of a causal association" between the vaccine and a risk. Did the District Court err in holding that federal law preempted Plaintiffs' failure-to-warn claims where no such information showed that a risk of POTS or POI resulted from Gardasil vaccination?

2. Experts who lack medical training are not qualified to offer medical opinions, and experts cannot opine on whether a claim is preempted when that is the legal question the court is deciding. Did the District Court abuse its discretion by excluding the medical-causation opinions and legal conclusions offered by Plaintiffs' non-physician regulatory expert?

3. The Vaccine Act bars claims that a vaccine manufacturer failed to give direct warnings to patients or that vaccines were defectively designed. Did the District Court err in granting judgment for Merck on Plaintiffs' "direct warning" claims and attacks on Gardasil's design?

STATEMENT OF THE CASE

I. Gardasil Is an FDA-Approved Vaccine with a Decades-Long Global Safety Record and Proven Efficacy Against Cancer.

A. Gardasil Protects Against Cancers Caused by HPV and Has Been Administered Over 500 Million Times Worldwide.

Gardasil is an FDA-approved vaccine that protects against types of human papillomavirus ("HPV") that cause cancer. JA19720, Summ. J. Op.; *see also* JA03302, Gardasil Approval Letter; JA03312, Gardasil 9 Approval Letter. HPV, a viral infection, affects millions of Americans. The CDC estimates that "85% of people will get an HPV infection in their lifetime," and nearly 42 million people in the United States are currently infected with HPV. JA03680, CDC, Clinical Overview of HPV; JA02414, CDC, HPV & Cancer Prevention.

HPV is responsible for more than 600,000 global cancer cases every year, and over 36,000 cancer cases in the United States alone. JA19720, Summ. J. Op. (citing JA03691, CDC, Reasons to Get Vaccinated, and JA03694, WHO Statistics). HPV causes most cases of cervical cancer and can also cause anal, oropharyngeal, vulvar, vaginal, and penile cancers, as well as genital warts. JA03644, Gardasil 9 Label; JA02416, CDC, Basic Information about HPV and Cancer. Even with screenings, "HPV

causes 11,000 cases of cervical cancer each year in the U.S.," and the CDC estimates nearly 200,000 cervical precancer cases annually. JA02286, P.J.O.P. Op. (citing JA03700, CDC, Cancers Caused by HPV). Each year, approximately 4,000 women in the U.S. die of cervical cancer. JA03700, CDC, Cancers Caused by HPV.

Since Gardasil's approval nearly 20 years ago, over ***135 million doses*** of the vaccine have been administered in the United Sates, with ***over 500 million doses*** administered worldwide. JA19720–19721, Summ. J. Op. (citing JA03721, WHO, Weekly Epidemiology Record; JA03692, CDC, Reasons to Get Vaccinated). With few exceptions inapplicable here, the CDC recommends HPV vaccination "for both girls and boys through age 26 years." JA19720, Summ. J. Op. (citing JA03732, CDC, HPV Vaccination Recommendations). HPV infections and cervical precancers have "dropped" significantly following the approval and use of HPV vaccines like Gardasil. JA19720, Summ. J. Op. (citing JA03738, CDC, HPV Vaccination).

The development of Gardasil built on decades of research. In 1983, German virologist Harald zur Hausen discovered the link between HPV and cervical cancer, for which he later won the Nobel Prize in Medicine.

JA05627, Feigal Report. Merck began developing Gardasil years after this discovery, and after over a decade of development, the FDA approved Gardasil for use in the United States in 2006. JA06455, Feigal Report. In 2014, the FDA approved a new version of the vaccine, Gardasil 9, which adds protection for additional cancer-causing HPV types.[5] JA19720, Summ. J. Op.; JA03312, Gardasil 9 Approval Letter.

B. Gardasil's Safety Is Backed by the FDA, the CDC, and a Worldwide Medical and Scientific Consensus.

Since Gardasil was first approved, the FDA, the CDC, the World Health Organization ("WHO"), and other world regulators like the European Medicines Agency ("EMA") have repeatedly affirmed Gardasil's safety. To this day, the CDC confirms "HPV vaccines are safe" and "the body of scientific evidence overwhelmingly supports their safety." JA03743, CDC, HPV Vaccine Safety. And governmental bodies have confirmed that Gardasil does not cause POTS or POI:

- The CDC confirmed as recently as March 2025 that "[o]ngoing safety monitoring has not detected any safety concerns related to POTS following HPV vaccination," and that "CDC and FDA have not found any proof that HPV vaccines cause reproductive problems in women, including POI." CDC, HPV Vaccine Safety, *available at*

[5] Gardasil 9 is now the only version distributed in the United States. JA19720, Summ. J. Op. (citing JA03671, NCI, HPV Vaccines).

https://www.cdc.gov/vaccine-safety/vaccines/hpv.html (last updated Mar. 6, 2025).

- The WHO stated in 2017, and again in 2022, that HPV vaccination does not increase the risk of POTS or infertility. JA02444, WHO, Safety of HPV Vaccines 2017; JA03723, WHO, HPV Position Paper 2022.
- In 2015, the EMA "confirmed that the evidence does not support a causal link" between HPV vaccination and POTS. JA04083, EMA 2015.

These statements are buttressed by large-scale studies. JA19744, Summ. J. Op. As Plaintiffs concede, no study comparing vaccinated to unvaccinated persons has ***ever*** found an association between Gardasil and POTS or POI. JA19744–19745, Summ. J. Op.

II. Gardasil Met Rigorous Regulatory Requirements to Gain and Maintain FDA Approval.

A. A Robust Regulatory Framework Governs the Approval and Labeling of Vaccines like Gardasil.

Gardasil is part of the "highly regulated world of vaccines," including the FDA's rigorous approval process and strict post-approval reporting and labeling requirements. JA19720 n.3, Summ. J. Op. Vaccines like Gardasil are governed by both the Food, Drug and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHSA"). *E.g.*, JA03124, Amato Report. Under those statutes, vaccine manufacturers cannot

introduce a new vaccine in the United States without FDA approval. *See Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 226 (2011); 42 U.S.C. § 262(a)(1). To obtain FDA approval for Gardasil, Merck submitted comprehensive information about the vaccine's safety and efficacy through multiple phases of testing lasting over a decade. JA05628–05638, Feigal Report. The FDA also reviewed and approved the protocols for Gardasil's clinical trials, and reviewed the safety data from those trials before approving Gardasil. JA05634, Feigal Report. Even after the vaccine was approved in 2006, Merck has continued to assess Gardasil's safety. JA05640–05641, Feigal Report.

Under the FDCA and PHSA, the FDA extensively regulates vaccine labeling. "[T]he manufacturer [must] submit an application" for a vaccine's approval with data demonstrating its safety, as well as proposed "labels" with warnings that accompany the vaccine. 21 C.F.R. § 601.2(a). If the FDA grants approval, the "vaccine's license spells out the . . . warnings that must" appear in the label. *Bruesewitz*, 562 U.S. at 237. Federal regulations generally bar Merck from changing that label, with only a limited exception where narrow categories of "newly acquired information" arise. *Id.* (citing 21 C.F.R. § 601.12); JA19727, Summ. J. Op.

The FDA, the CDC, Merck, and regulators around the world have continued to monitor Gardasil's safety throughout the nearly two decades since its first approval:

- Merck has complied with the FDA's reporting requirements by sending monthly or quarterly compilations of adverse events. JA05643, Feigal Report. Merck has also continued to conduct its own safety testing. JA05640–05641, Feigal Report.
- The FDA and CDC independently monitor Gardasil's safety. They jointly maintain the Vaccine Adverse Event Reporting System ("VAERS"), a passive surveillance system that they routinely analyze for any safety concerns with Gardasil or other vaccines. JA19734, Summ. J. Op. (citing JA04122, CDC, About VAERS).
- The FDA also monitors Gardasil's safety through its Pediatric Advisory Committee ("PAC"), which conducts its own safety reviews and analyses. *E.g.*, JA04702–04705, Dec. 7, 2010 FDA PAC Meeting Tr.

Through Gardasil's nearly two decades of continuous FDA approval, the FDA has never required a warning for POTS or POI. JA08538, Fisher Dep., 339:19–341:4; JA04741–05592 (Gardasil labels from 2006 to 2024).

B. Gardasil Is Also Subject to the Vaccine Act, Which Mandates a Pre-Suit Administrative Process for Plaintiffs and Provides Manufacturers Litigation Protections.

Gardasil is also subject to the Vaccine Act, which Congress enacted to avert a "crisis" in the vaccine market. 42 U.S.C. § 300aa-10 *et seq.*;

Bruesewitz, 562 U.S. at 248 (Breyer, J., concurring). When the Act was passed in 1986, Congress found vaccines to be a "spectacularly effective public health initiative[]" that "prevented thousands of . . . deaths each year." *Blackmon v. Am. Home Prods. Corp.*, 267 F. Supp. 2d 667, 671 (S.D. Tex. 2002). But surging lawsuits had caused vaccine manufacturers to withdraw from the U.S. market until only ***one*** manufacturer of a key childhood vaccine remained. JA02826 (citing *Bruesewitz*, 562 U.S. at 227).

"Congress enacted the [Vaccine Act]" to "stabilize the vaccine market" through two major changes: (1) a mandatory administrative compensation program and (2) extensive protections for vaccine manufacturers in civil litigation. *Bruesewitz*, 562 U.S. at 228.

1. The Vaccine Act created a "no-fault compensation program" administered by special masters in the United States Court of Federal Claims, commonly called "Vaccine Court." JA02786, P.J.O.P. Op. The Act "requires claimants to seek relief through [Vaccine Court] before filing suit for more than $1,000" in a state or federal court. *Bruesewitz*, 562 U.S. at 229; *Watts v. Maryland CVS Pharmacy*, 142 F.4th 233, 234 (4th Cir. 2025). In Vaccine Court, "the Secretary of Health and Human Services,"

not the vaccine manufacturer, is "the respondent." *Bruesewitz*, 562 U.S. at 228.

Claimants need not "show that the administered vaccine was defective[]" to receive Vaccine Court compensation. *Id.* Payments come "out of a fund created by an excise tax" manufacturers pay "on each vaccine dose." *Id.* at 229.

2. The "*quid pro quo*" for this "no-fault compensation program" is "the provision of ***significant tort-liability protections*** for vaccine manufacturers" outside the Program. *Id.* at 228, 229 (emphasis added). The Vaccine Act bars ***all*** "design-defect claims" and dictates that a vaccine's design "is not open to question" in litigation. *Id.* at 232, 243; 42 U.S.C. § 300aa-22(b)(1). The Act also "bars liability claims against vaccine manufacturers for failing to provide 'direct warnings' to Plaintiffs," "their parents," or the general public. 42 U.S.C. § 300aa-22(c).

III. Federal Health Authorities Have Rejected the Theories Plaintiffs Present in This Litigation.

Because they were required to bring claims in Vaccine Court before filing civil suits, many of the Plaintiffs have already presented HHS with their theories that Gardasil caused POTS and POI, along with the same

arguments they present in this case.[6] Several of Plaintiffs' Vaccine Court cases included reports from persons who are also experts in this litigation. JA03578, Merck Summ. J. Mem. (collecting authorities).

As Congress directed, HHS formally responded to Plaintiffs' petitions. 42 U.S.C. § 300aa-12(b)(1). HHS roundly rejected Plaintiffs' theories with statements including the following:

- "[T]here is ***no known association between HPV vaccination and the development of POTS***, and [plaintiffs' expert's] report falls short" in arguing otherwise. JA03611, HHS Br., *Wagner v. Sec'y of Health & Hum. Servs.* (emphasis added).
- "There is currently no biologically plausible mechanism for causality by which the HPV vaccine can cause POTS." JA03759, HHS Br., *Hilton v. Sec'y of Health & Hum. Servs.*
- "[T]he only reliable epidemiological evidence that exists on this issue demonstrates ***no causal association between the HPV vaccination and POI***." JA03624, HHS Br., *Brayboy v. Sec'y of Health & Hum. Servs.* (emphasis added).

Agreeing with HHS, the Vaccine Court emphasized that its "extensive familiarity with the causal theory" and the facts in Gardasil

[6] *See, e.g.*, *Bond v. Sec'y of Health & Hum. Servs.*, No. 16-1615V, 2022 WL 17819496 (Fed. Cl. Nov. 14, 2022) (dismissed for insufficient proof); *Brayboy v. Sec'y of Health & Hum. Servs.*, No. 15-183V, 2022 WL 1316235 (Fed. Cl. Apr. 18, 2022) (dismissed for insufficient proof).

cases led it to reject such claims. *Humphries v. Sec'y of Health & Hum. Servs.*, No. 17-288V, 2021 WL 1733512, at *3 (Fed. Cl. Apr. 9, 2021).

That federal health authorities oppose Plaintiffs' Vaccine Court petitions is unsurprising: Plaintiffs recycle theories those authorities have rejected for years. For example, Plaintiffs claim Gardasil's aluminum adjuvant is "toxic" and "can result in very serious harm." *E.g.*, JA00596, Flores Compl. That same false claim has been pressed by anti-vaccine activists contending that aluminum in a range of vaccines causes autism and other conditions, and the FDA and CDC have rejected it.[7] The same is true for Plaintiffs' other attacks, such as on polysorbate 80 and yeast. JA03782; JA03796.

IV. The District Court Rejected Plaintiffs' Claims Because They Lacked Legal and Factual Support.

In 2022, the Judicial Panel on Multidistrict Litigation centralized actions relating to Merck's Gardasil vaccine in a multidistrict litigation ("MDL"). The MDL has grown to include over 200 plaintiffs who allege a

[7] *See* JA03763; JA03767; *Rogero v. Sec'y of Health & Hum. Servs.*, No. 11-770V, 2017 WL 4277580, at *1, 6, 26, 65 (Fed. Cl. Sept. 1, 2017) (rejecting petition claiming "polysorbate 80" and "aluminum adjuvant" in vaccines caused autism).

wide variety of injuries, including alopecia, irritable bowel syndrome, and epilepsy. JA19778–19782.

A. The District Court Dismissed Plaintiffs' Design-Defect and "Direct Warning" Claims Under the Vaccine Act.

After the MDL was formed, Merck moved for partial judgment on the pleadings. The District Court held that the Vaccine Act bars Plaintiffs' design-defect claims. JA02791. The court dismissed Plaintiffs' "direct warning" claims—that Merck failed to directly warn vaccinated individuals and their parents—under the Vaccine Act and state-law learned intermediary doctrine. JA02794. The court also held that Plaintiffs' fraud claims were inadequately pleaded. JA02799.

B. Plaintiffs Selected POTS and POI as Bellwether Injuries for the MDL.

Proceeding only on claims that Merck failed to warn Plaintiffs' physicians, the parties in the MDL selected two injuries for initial bellwether consideration: POTS and POI. JA02253. POTS is a circulatory condition characterized by an abnormally increased heart rate when moving from sitting or lying down to a standing position. JA2306, Cleveland Clinic, POTS. Although POTS is associated with many non-specific symptoms like headaches, dizziness, and fatigue, a POTS

diagnosis rests on specific medical criteria. JA02309–02312, Cleveland Clinic, POTS. POTS occurs most commonly in women, and most cases develop during adolescence. JA19537, Miglis Dep., 64:2–4; JA18711, Brinth 2015. The background incidence rate of POTS in the general population has been estimated to be between 0.2–1%. JA19537, Miglis Dep., 64:10–14.

POI is a reproductive condition characterized by the cessation of menstruation before age 40. JA03527, CDC, HPV Vaccine Safety. POI is diagnosed based on a combination of sustained irregular menstrual cycles and abnormal ovarian hormone levels. JA04551, Wodi 2023. Like POTS, POI has a background incidence rate in the general population, estimated to be 1% in women under forty, 0.1% in women under thirty, and 0.01% in women under twenty. JA04551, Wodi 2023.

Following the selection of POTS and POI, the District Court created an "Initial Bellwether Pool" of sixteen plaintiffs who received Gardasil doses between 2012 and 2021. JA02733. The Court set a schedule to "prioritize . . . dispositive motions on general causation and implied preemption" for those plaintiffs. JA02252.

C. Plaintiffs Claimed Merck Should Have Warned of POTS in January 2011 and of POI in November 2013.

In discovery, Plaintiffs exclusively claimed that Merck should have added a warning for POTS to Gardasil's label by 2011, and a warning for POI by 2013. Plaintiffs initially refused to respond to Merck's discovery requests seeking the content and dates of the POTS and POI warnings they alleged Merck should have given. JA03822–03824, Pls' Resp. to Merck's First Set of Interrogatories. But Plaintiffs agreed they would provide that information in their experts' reports. JA03840, May 22, 2024 Letter of Tracy Turner.

Plaintiffs' regulatory expert, Dr. Stephen Amato, opined that Gardasil's label should have warned of POTS "by January 2011" and of POI "by November 2013." JA03991–03992, Amato Report. As Plaintiffs conceded, no other expert opined on what warning Merck should have provided or when. JA19743 n.29, Summ. J. Op.

D. The District Court Excluded Plaintiffs' Regulatory Expert in Part and Held Plaintiffs' POTS and POI Claims Preempted.

Merck moved to exclude Dr. Amato's testimony. JA03080. Quoting FDA regulations, Dr. Amato opined that "reasonable evidence of a causal association" existed to add POTS and POI warnings to Gardasil's

labeling. JA03862, JA03972. Dr. Amato, who holds no medical degree, based his opinions on his re-diagnoses of patients who were the subjects of adverse event reports: he claimed they had POTS or POI, even when the patients had no such diagnoses. JA03911–03916, JA03965–03969, Amato Report. Merck argued that Dr. Amato's opinions constituted medical diagnoses that he was not qualified to provide, and the District Court agreed. JA19377. The District Court additionally excluded Dr. Amato's opinion that Merck had authority to add POTS and POI warnings to Gardasil's label, because that legal conclusion is reserved for the court. JA19377.

Merck also moved for summary judgment on the claims of the sixteen bellwether plaintiffs who alleged either POTS or POI. JA03568. Merck argued that FDA regulations would not have permitted a POTS or POI warning in Gardasil's labeling at any time, let alone by the dates alleged by Plaintiffs. JA03575.

The District Court agreed and granted summary judgment as to the bellwether plaintiffs. JA19717. By agreement, the District Court's summary judgment order applies to 107 additional MDL plaintiffs who,

like the bellwether plaintiffs, allege Gardasil caused them to develop POTS or POI. JA19772.

SUMMARY OF ARGUMENT

Merck could not have added the warnings Plaintiffs demand to Gardasil's labeling while complying with stringent federal regulations governing vaccines. The District Court correctly granted summary judgment, and this Court should affirm, because Plaintiffs' claims are preempted.

1. Under federal regulations and *Knight*, Plaintiffs' claims are preempted unless Merck could have used a narrow regulatory tool—the "Changes Being Effected" regulation—to add Plaintiffs' desired warning unilaterally. *Knight*, 984 F.3d at 332. To do so, Merck must have had "newly acquired information" "not previously submitted to the" FDA that showed "reasonable evidence of a causal association" between Gardasil and the claimed injuries—here, POTS and POI. 21 C.F.R. §§ 601.12(f)(2), (6); 201.57(c)(6)(i).

The District Court correctly held Merck had no such information about POTS or POI by the 2011 and 2013 dates when Plaintiffs claimed Merck should have warned. Only "***one*** published, verified case of POTS

and ***four*** published case reports of POI," plus a handful of unverified individual adverse event reports, existed by those dates. JA19718 (emphasis in original). And the District Court further held that Merck could not have added POTS or POI warnings at ***any*** date given the lack of evidence that Gardasil causes those conditions. JA19745, JA19748–19750. Plaintiffs' meager evidence is dwarfed by robust demonstrations of Gardasil's safety, including rigorous, large-scale studies; statements from federal authorities rejecting Plaintiffs' claims; and Plaintiffs' own admission that no study has ***ever*** shown a statistically significant increase in POTS or POI in those who have taken Gardasil versus those who have not.

Merck could also demonstrate preemption on a second, alternative basis—by showing, through "clear evidence," that federal authorities would have rejected a label change. The District Court did not reach this argument, JA19718–19719 n.2, and this Court need not reach it. But overwhelming evidence shows that Merck would prevail on this basis. Federal officials have rejected Plaintiffs' theories for years while approving Gardasil labeling without POTS or POI warnings.

2. Plaintiffs fail to show that the District Court abused its discretion by limiting Dr. Amato's testimony in two respects. First, the court correctly rejected Dr. Amato's legal conclusions about preemption. Other courts have done the same, chiefly because experts must help the trier of fact, not answer questions of ***law*** for a ***judge***. *See, e.g.*, *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 57 F.4th 327, 340 (1st Cir. 2023). The court also correctly precluded Dr. Amato, a non-physician, from re-diagnosing patients by applying his own diagnostic criteria to their paper records—an approach this Court has agreed is improper. *In re Lipitor*, 892 F.3d 624, 632–38 (4th Cir. 2018).

3. The District Court properly rejected a number of Plaintiffs' claims in deciding Merck's Rule 12 motion. This Court, however, need reach only one issue: whether Plaintiffs' "direct warning" claims, asserting that Merck should have warned patients or their parents rather than physicians, are barred by the Vaccine Act and the state-law learned intermediary doctrine. That is not a close call. Every federal court interpreting the Act has held it "eliminat[es] liability for not providing direct warnings to a claimant." *Holmes v. Merck & Co., Inc.*,

697 F.3d 1080, 1083 (9th Cir. 2012). The learned intermediary doctrine does the same.

The District Court also correctly held that the Vaccine Act preempts Plaintiffs' attacks on Gardasil's design using design-defect claims masquerading as failure-to-warn claims. *Bruesewitz*, 562 U.S. at 232. Even if those claims allege a failure to warn, as Plaintiffs now contend, they are ***separately*** preempted under *Knight* for several reasons. In particular, Gardasil's ingredients and clinical trials were not "newly acquired information," and thus could not have been used as the basis for new warnings.

STANDARDS OF REVIEW

Preemption is a legal question entirely "for a judge to decide, not a jury." *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 303 (2019). This Court reviews *de novo* a district court's legal conclusions about preemption. *Knight*, 984 F.3d at 337. As Plaintiffs acknowledge, this Court reviews any findings of fact underlying those legal conclusions for clear error. Apt. Br. 8 (citing *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 118 F.4th 322, 344 (3d Cir. 2024)).

This Court reviews "a district court's ruling on expert testimony for abuse of discretion." *United States v. Chikvashvili*, 859 F.3d 285, 292 (4th Cir. 2017). And this Court reviews *de novo* the District Court's granting of Merck's motion for partial judgment on the pleadings. *Drager v. PLIVA USA, Inc.*, 741 F.3d 470, 474 (4th Cir. 2014).

ARGUMENT

I. Plaintiffs' Claims Are Preempted Because Federal Law Barred Merck from Unilaterally Adding the Warnings Plaintiffs Demand.

Plaintiffs' claims are preempted for two independent reasons. ***First***, Plaintiffs' claims are preempted unless Merck could have used a narrow federal regulatory exception—called the "Changes Being Effected" or CBE regulation—to add a warning unilaterally. *Knight*, 984 F.3d at 332. Merck could not have done so. ***Second***, federal authorities "made clear through agency action . . . that [they] would not have allowed the [labeling] change" Plaintiffs demand. *Zofran*, 57 F.4th at 342. This Court need not reach this second argument because Plaintiffs lose at the first step. JA19718–19719 n.2, Summ. J. Op.

A. Failure-to-Warn Claims Are Preempted Unless a Vaccine Manufacturer Could Have Unilaterally Altered the FDA-Approved Label Using the CBE Regulation.

Vaccines like Gardasil are subjected to an "onerous and lengthy" approval process and regulatory framework. *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013) (process for prescription drugs); *see Bruesewitz*, 562 U.S. at 226 ("vaccines have been subject to the same . . . process as prescription drugs"). "[T]he manufacturer [must] submit an application" for a vaccine's approval with data demonstrating its safety, as well as proposed "labels" with warnings and information that accompany the vaccine. 21 C.F.R. § 601.2(a). If the FDA grants approval, the "vaccine's license spells out the . . . warnings that must" appear in the label. *Bruesewitz*, 562 U.S. at 237.

After approval, changes to the vaccine's warning label are tightly circumscribed. "Manufacturers ordinarily must obtain the Food and Drug Administration's . . . approval before modifying" the warnings that accompany a vaccine through submission to the FDA of a "Prior Approval

Supplement."[8] *Id.* (emphasis added) (citing 21 C.F.R. § 601.12); *Albrecht*, 587 U.S. at 326 (Alito, J., concurring).

Under a limited exception, the CBE regulation, a manufacturer can ship a special labeling amendment marked with the text "Special Labeling Supplement—Changes Being Effected" while the FDA reviews the proposed new label and decides whether to accept or reject it. 21 C.F.R. § 601.12(f)(2)(ii); *see also Knight*, 984 F.3d at 337–38. The CBE regulation "permits pharmaceutical companies to unilaterally modify their physician labels only to 'add or strengthen a . . . warning' based upon 'newly acquired information' about '[reasonable] evidence of a

[8] The parties agree that the labeling rules governing prescription drugs mirror those for vaccines. Apt. Br. 5; *Herlth v. Merck & Co.*, No. 3:21-CV-438, 2022 WL 788669, at *3 n.24 (D. Conn. Mar. 15, 2022). Notably, the CBE regulations for vaccines and drugs apply the same relevant standards. *Compare* 21 C.F.R. §§ 314.70(c)(6)(iii) *and* 601.12(f)(2)(ii).

Vaccines are considered "biologics" or "biological products." 42 U.S.C. § 262(i). As explained in 21 C.F.R. § 201.57 (first paragraph) and 21 C.F.R. § 201.56(b)(1), and based on Gardasil's 2006 approval date and Gardasil 9's 2013 BLA submission and 2014 approval date, Section 201.57 governs Gardasil's labeling. JA03302, Gardasil Approval Letter; *see also* 81 Fed. Reg. 88245-01 (Dec. 7, 2016) (submission and approval dates of Gardasil 9). As noted in 21 C.F.R. § 201.57(c)(6)(i), labeling ***changes*** for biologics such as Gardasil are governed by 21 C.F.R. §§ 601.12 and 201.57(c)(6)(i).

causal association' between the drug and a risk of harm." *Knight*, 984 F.3d at 332.

Given these regulations, "a tort action" about "FDA-approved warnings" "can . . . proceed," and avoids preemption, "only when the defendant had the unilateral ability to change that labeling" through the CBE procedure. *Id.* at 337–38.[9] "[W]hen a party cannot satisfy its state duties without the [FDA's] special permission and assistance," those state duties "are pre-empted." *PLIVA, Inc. v. Mensing,* 564 U.S. 604, 623–24 (2011). The question for preemption "is whether the private party could independently do under federal law what state law requires." *Id.* at 620. Because vaccine manufacturers can only add new warnings without FDA approval using the CBE process, a "claim is preempted" if requirements of that process cannot be satisfied. *Knight*, 984 F.3d at 337.

1. Supreme Court and Fourth Circuit Precedent Provide Two Separate, Independent Paths to Preemption.

As the District Court explained, "there are two ways a vaccine manufacturer may prevail on a preemption defense." JA19725. A claim

[9] *See also Dolin*, 901 F.3d at 812; *In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 41–42 (1st Cir. 2015).

against a manufacturer is preempted "if ***(1)*** it did not have the authority to make changes to the label" unilaterally under the CBE regulation, "***or (2)*** it establishes," by "clear evidence," "that the FDA would not have approved the changes to the label that the plaintiffs contend should have been made" even if a manufacturer could have unilaterally changed the label. JA19725, Summ. J. Op. (emphasis added). Multiple courts of appeals have laid out the same test. *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) (claims preempted if there is not "a labeling deficiency that [Defendants] could have corrected using the CBE regulation" or, alternatively, if "there is clear evidence that the FDA would not have approved a change to the [prescription drug's] label" (cleaned up)); *Zofran*, 57 F.4th at 342 (similar); *Dolin*, 901 F.3d at 812 (similar).

That stands to reason: manufacturers can attempt to add a warning unilaterally only using the CBE regulation. *See* Arg. I.A, *supra*. But even if a manufacturer could do so, "the FDA can [later] reject CBE submissions," and a claim is also preempted if "there was clear evidence the FDA would have rejected the proposed change." *Dolin*, 901 F.3d at 812 (emphasis omitted).

Plaintiffs disagree with this authority, instead proposing their own preemption standard that combines the two tests. *E.g.*, Apt. Br. 11–12. That proposal misapprehends the controlling precedent. Under that precedent, "clear evidence" is an ***independent*** means of demonstrating preemption. JA19724–19725 & n.7, Summ. J. Op. It is not, as Plaintiffs characterize it, the standard by which Merck must prove it had no newly acquired information. Apt. Br. 12–13, 18. Nor is it a second "element" that Merck must satisfy to preempt claims for which no newly acquired information exists. *See id.*

Plaintiffs particularly misconstrue *Albrecht* as mandating only a single "clear evidence" test. *See id.* at 5, 12–13, 15, 18. *Albrecht* explained that, before even reaching the "clear evidence" test, "manufacturers ***cannot propose a change that is not based on reasonable evidence***"—that is, without satisfying the CBE regulation. *Albrecht*, 587 U.S. at 315 (emphasis added). But critically, this first step was uncontested in *Albrecht*. The defendant "***conceded*** that the FDA's ***CBE regulation would have permitted [it] to try to change the label*** to add [the desired] warning." *Id.* at 308–09 (emphasis added). For this reason, *Albrecht* only considered the second step, explaining that "clear

evidence" is that which shows the FDA was "fully informed" of justifications for a new warning, and "the FDA" "communicate[d] its disapproval of a warning." *Id.* at 303, 315–16.

2. Plaintiffs Mischaracterize *Knight*, *Wyeth*, and Preemption Principles.

Plaintiffs misapprehend not only the two independent preemption tests, but other key principles and decisions governing preemption.

a. Plaintiffs Fail to Show that This Panel Should Overturn or Ignore *Knight*.

First, Plaintiffs argue that *Knight* was wrongly decided, and claim this panel is "not bound to follow" it, because *Knight* "did not consider *Albrecht*'s two-element preemption test or the presumption against preemption." Apt. Br. 15–16. That argument is mistaken for multiple reasons, including that *Knight* expressly cited *Albrecht* and did not ignore it. 984 F.3d at 337.

Nor do *Albrecht* and *Knight* conflict, as the cases concerned different preemption tests. *Knight* dealt with "newly acquired information," the first means of demonstrating preemption. *Albrecht*, in

contrast, concerned the second, "clear evidence" test.[10] *See Knight*, 984 F.3d at 338; Arg. I.A, *supra*. And regardless of whether Plaintiffs' criticisms of *Knight* are correct—though they are not—Plaintiffs cannot simply ask this panel to ignore that decision. *See Taylor v. Grubbs*, 930 F.3d 611, 619 (4th Cir. 2019).

Plaintiffs also fail to distinguish *Knight*. *Knight* "determine[s] [the] goalposts of 'newly acquired information,'" the same CBE standard that applies here. 984 F.3d at 332, 338. Plaintiffs overlook this point. They instead contend that *Knight* does not apply because the alleged "newly acquired information" analyzed in *Knight* was "preliminary." Apt. Br. 15. In reality, *Knight* is instructive for that reason. *Knight* held claims preempted where preliminary information "might" have justified a warning, but the company ultimately "came to a different conclusion" that "the scientific and regulatory community accepted." 984 F.3d at 339. Here, Merck, federal agencies, and the broader scientific community have ***never*** accepted the risks Plaintiffs allege—not even as a "preliminary"

[10] Plaintiffs' reference to the presumption against preemption is also irrelevant. *See* Arg. I.A.2.c, *infra*.

matter. *Infra* Arg. I.B. Thus, the "information" at issue here is even ***less*** compelling than the "preliminary" evidence that *Knight* rejected.

b. *Wyeth* Does Not Support Plaintiffs' Position.

Plaintiffs also suggest that *Knight* departs from *Wyeth v. Levine*. *See, e.g.*, Apt. Br. 16–19, 31–34. Plaintiffs are again mistaken. In *Wyeth*, the Supreme Court did not consider the first preemption test—concerning the CBE regulation—because that argument was unpreserved. 555 U.S. 555, 569 (2009). Further, the Court's dicta in *Wyeth* that the CBE regulation had been satisfied in no way applies here. This is because, in *Wyeth*, the FDA and Wyeth had both recognized the relevant risk. *Id.* at 558–60. Wyeth had already "worked with the [FDA] to change [its medicine's] label" to warn of it—the question was whether Wyeth should have "added a ***stronger*** warning." *Id.* at 569–70 (emphasis added). Wyeth had also "withdrawn" another drug posing the same risk. *See id.* at 569 n.4. None of that is true here.[11]

[11] Plaintiffs also argue, citing *Wyeth*, that the District Court's dicta about the FDA interpreting the FDCA as establishing "a floor and a ceiling" requires reversal. Apt. Br. 18. That footnote in the decision below was not essential to the legal analysis, which correctly applied Fourth Circuit law. *Knight*, 984 F.3d at 337–38, 341 (recognizing that "unnecessary warnings might flood labels and distract from real risks").

c. The Controlling Framework Accounts for the "Presumption Against Preemption."

Plaintiffs also argue that the controlling preemption framework is unfaithful to a generalized "presumption against preemption," a background principle long incorporated into preemption jurisprudence.[12] *Knight* accounted for that presumption. It explained that, "[i]n this context, federal preemption occurs when it is impossible for a private party to comply with both state and federal requirements," and relied on cases like *Wyeth* and *Albrecht* that further elaborated on the presumption. *Knight*, 984 F.3d at 337–38 (cleaned up); *Albrecht*, 587 U.S. at 311 (discussing *Wyeth*'s reasoning that preemption requires "clear and manifest purpose of Congress"). And after doing so, *Knight* and *Albrecht* offered two granular tests for preemption in the prescription-drug context: the "CBE regulation" test and the "clear evidence" test, which other courts have endorsed. Arg. I.A.1, *supra*. Those tests, not the abstract principle they incorporate, govern this case.

[12] *See, e.g.*, *Reid v. People of State of Colorado*, 187 U.S. 137, 148 (1902) ("the principle has been often reaffirmed" that preemption requires "direct and positive" "conflict" between state and federal rules "so that the two acts could not be reconciled").

Nor can Plaintiffs explain how this general presumption changes the overwhelming evidence showing preemption here. *See* Arg. I.B, *infra*. Plaintiffs refer to *Fosamax*, which that court described as "a close case," and in which it employed the presumption to interpret an allegedly "ambiguous" statement from the FDA.[13] *Fosamax*, 118 F.4th at 353–54. Nothing is "close" about this case, nor does it turn on any such individual statement.

d. Plaintiffs' Arguments Regarding the Burden to Show Preemption Are Both Incorrect and Irrelevant.

Plaintiffs further misstate the law when they suggest Merck has the burden to prove a negative—the ***nonexistence*** of information satisfying the CBE regulation. *E.g.*, Apt. Br. 13–14. Leading cases have instead held it is the plaintiff's burden to show the ***existence*** of newly acquired information, and *Knight* supports that approach. *E.g.*, *Celexa*, 779 F.3d at 41; *Gibbons*, 919 F.3d at 708;[14] *Knight*, 984 F.3d at 338

[13] *Fosamax* is also off-point for other reasons. *See* n.48, *infra*.

[14] Plaintiffs argue that *Gibbons* and *Celexa* are "inapposite" for factual reasons that do not make a difference. Apt. Br. 13, 18 n.8. Plaintiffs note *Gibbons* occurred at the motion-to-dismiss stage, but the Second Circuit

(rejecting plaintiffs' "claim [that] Boehringer's post-approval study" provided newly acquired information).

Plaintiffs fixate on a single phrase from *Wyeth* stating that Wyeth "misapprehend[ed]" "its burden in establishing a pre-emption defense." 555 U.S. at 569. The Supreme Court, however, did not elaborate on this language, and it did not hold that the defendant must show the lack of newly acquired information. *Id.* at 569.

Further, who bears the burden is irrelevant here: the evidence of preemption is overwhelming, as Merck demonstrates. Arg. I.B–C, *infra*.

B. Plaintiffs' Claims Are Preempted Because Merck Could Not Have Used the CBE Regulation to Add Warnings about POTS or POI.

Plaintiffs' claims are preempted because Merck could not have used the CBE regulation to provide the POTS and POI warnings they advance. 21 C.F.R. §§ 201.57(c)(6)(i); 601.12(f)(2). That is for three overarching and independent reasons, each dictated by the CBE regulation.

- Plaintiffs lack evidence showing Merck received "newly acquired information" demonstrating "reasonable evidence of a causal

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still required Plaintiffs to identify newly acquired information. 919 F.3d at 708. And Plaintiffs claim *Celexa* is irrelevant because it concerned efficacy, not safety, but that decision applied the same "newly acquired information" test applicable here. 779 F.3d at 41–42.

association" between Gardasil and POTS or POI, and voluminous evidence demonstrates ***no*** such information has ever existed. *Id.*

- Plaintiffs also lack evidence that anything "reveal[ed] risks of a different type or greater severity or frequency" pertinent to their desired warnings "than previously included in submissions to [the] FDA," a separate requirement of the CBE regulation. *See* 21 C.F.R. § 601.12(f)(2), (6).
- The FDA's repeated approval of Gardasil labeling omitting the warnings Plaintiffs now demand "undermines" any argument that newly acquired information existed. *Knight*, 984 F.3d at 339.

The District Court correctly held that Merck could not have used the CBE regulation to change Gardasil's labeling by the specific dates Plaintiffs and their expert claimed Merck should have warned: ***January 2011*** for POTS, and ***November 2013*** for POI. JA19740–19741.

Though Plaintiffs proposed only those warning dates throughout discovery, they now make a last-ditch attempt to abandon them, which this Court should reject. *See* Arg. I.B.1.b.ii, *infra*. But even if Plaintiffs can change their theory on appeal, the District Court ***also*** correctly determined that Merck could not have added new warnings about POTS or POI satisfying the CBE regulation ***at any time***.

1. Plaintiffs Fail to Show "Newly Acquired Information" Demonstrating "Reasonable Evidence of a Causal Association" between Gardasil and POTS.

To satisfy the CBE regulation, Plaintiffs must first present

evidence showing that (1) Merck received "newly acquired information," and (2) the new information demonstrated "a causal association" between Gardasil and POTS. 21 C.F.R. §§ 201.57(c)(6)(i); 601.12(f)(2); *Knight*, 984 F.3d at 338–41; *Herlth*, 2022 WL 788669, at *4. Because preemption bars state law from second-guessing the FDA's approval of a label, states may impose liability only if "new information not considered by the FDA" that satisfies the CBE regulation develops ***after*** the FDA approves a product's initial label. *See Celexa*, 779 F.3d at 41.[15] And that "new[] . . . information" must provide "reasonable evidence of a causal association" of a "clinically significant" "hazard" or "adverse reaction" linked to a vaccine. 21 C.F.R. §§ 201.57(c)(6)(i); 601.12(f)(2), (6); *Knight*, 984 F.3d at 338–41.

The District Court rightly concluded "Merck could not lawfully add a POTS warning to the Gardasil label in January 2011," or at any time, given these requirements. JA19737. That is clear for several reasons.

***First*,** federal regulatory authorities have repeatedly confirmed the non-existence of evidence linking Gardasil to POTS.

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[15] *See also, e.g.*, *Goodell v. Bayer Healthcare Pharm. Inc.*, No. 18-CV-10694, 2019 WL 4771136, at *4 (D. Mass. Sept. 30, 2019); *Mahnke v. Bayer Corp.*, No. 2:19-cv-07271, 2019 WL 8621437, at *5 (C.D. Cal. Dec. 10, 2019) (same).

Second, the only "evidence" Plaintiffs contend could justify a POTS warning by January 2011 is one article describing a single patient and a handful of individual adverse event reports. The District Court rightly held it an "understatement" that such evidence is insufficient to invoke the CBE regulation. JA19736.

Third, the District Court correctly rejected the jumble of "evidence" Plaintiffs presented in the years following 2011 as justifying a POTS warning at any time. JA19740–19745.

a. Statements by the FDA, CDC, and HHS Confirm the District Court's Conclusion that There is No Reasonable Evidence of a Causal Association Between Gardasil and POTS.

As summarized below, federal health authorities have rejected Plaintiffs' claim of an association between POTS and Gardasil for years. The District Court correctly observed that "there is substantial evidence that the FDA does not agree with Plaintiffs' allegations that there is a causal association between taking Gardasil and becoming sick with POTS." JA19718 n.2.

POTS: Examples of Federal Agency Safety Statements and Research with Federal Officials as Coauthors		
DATE	**AGENCY**	**STATEMENT**
2021	**CDC**	"Ongoing safety monitoring has not detected any safety concerns related to POTS following HPV vaccination." JA03744, CDC, HPV Vaccine Safety.
2019	**FDA, CDC**	A peer-reviewed paper coauthored by CDC and FDA officials, and cited in CDC publications, states that a review of VAERS "did not detect any unusual or unexpected reporting patterns" for POTS. JA04020–04021, Shimabukuro 2019.
First released 2009, current as of 2018	**FDA**	"FDA and the U.S. Centers for Disease Control and Prevention (CDC) take all concerns about vaccine safety seriously. . . . [N]one of the adverse events . . . were reported at rates . . . greater than expected in a population of this age and gender…." JA04028–04029, FDA, Gardasil Vaccine Safety.

First released 2011, current as of 2018	**FDA**	"FDA also continually reviews all reports of the Vaccine Adverse Event Reporting System after vaccination with Gardasil, and there is no evidence of unusual clinical patterns or high reporting rates of adverse events, including autoimmune diseases." JA04033, FDA Information on Gardasil.
2017	**HHS** (Parent Agency of FDA/CDC)	"CDC and FDA continue to evaluate [HPV] vaccines to ensure their safety. To date, there is no medical or scientific evidence that the HPV vaccine causes POTS and safety monitoring has not shown any other problems." 82 Fed. Reg. 6294, 6298.
2017	**FDA, CDC**	A peer-reviewed paper coauthored by CDC and FDA officials and cited by the CDC in public safety communications states that a review of VAERS "did not detect any unusual or unexpected reporting patterns that would suggest a safety problem" with respect to POTS. JA04036, Arana 2017. The paper considers all previously published case reports and case series regarding HPV vaccination and POTS, and the comprehensive assessment conducted by the EMA, which examined data from Merck's clinical trials, pharmacovigilance database, analyses of case reports worldwide, and available literature.

These statements accord with a mountain of peer-reviewed literature, including massive, high-quality studies finding no association between Gardasil and POTS.[16] Regulatory authorities around the world agree.[17]

b. The Only Evidence Plaintiffs Presented Before 2011—the Date Plaintiffs and Their Expert Claim Merck Should Have Warned—Failed to Satisfy the CBE Regulation.

None of the evidence dated prior to January 2011 that Plaintiffs presented would have given Merck the unilateral authority to add POTS to the Gardasil label. Because Plaintiffs and their expert argued that Merck should have warned of POTS in 2011, not at a later time, that means their claims are preempted.

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[16] *See, e.g.*, JA04047, Hviid 2020 ("[W]e observed no association between quadrivalent human papillomavirus vaccination and . . . postural orthostatic tachycardia syndrome"); JA04060–04067, Thomsen 2020 (using three study designs, including comparison of 314,017 vaccinated girls to 314,017 unvaccinated girls, "HPV vaccination among girls was not associated with subsequent increased risk of pain, malaise, fatigue, tachycardia, hypotension, or syncope").

[17] *See, e.g.*, JA04083, EMA, "HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS" (November 20, 2015); JA04088, Australian National Centre for Immunisation Research and Surveillance, HPV vaccines – Frequently Asked Questions (July 2024).

i. Plaintiffs Lack Evidence that Merck Could Have Warned of POTS in 2011.

The evidence concerning an alleged causal association between Gardasil and POTS after Gardasil was approved and before January 2011 is meager: (1) one published case report of a single patient who developed POTS following HPV vaccination; and (2) a handful of unverified adverse event reports of POTS. Apt. Br. 34–35, 43, 46 n.33. The remaining evidence Plaintiffs present is not specific to POTS, and is entirely irrelevant. Review of this evidence shows a lack of "newly acquired information" demonstrating "reasonable evidence of a causal association" between Gardasil and POTS by January 2011. 21 C.F.R. §§ 201.57(c)(6)(i); 601.12(f)(2), (6).

First*,** Plaintiffs identify a single publication before 2011 regarding Gardasil and POTS: a 2010 letter to an editor about ***one patient who developed POTS two weeks following her first dose of HPV vaccine. *See* Apt. Br. 43 (citing JA03433, Blitshteyn 2010). This publication, Blitshteyn (2010), purported to be "the first case report describing POTS after vaccination with Gardasil," and stated the cause of the patient's illness remained elusive and called for more research. JA03434. Although this publication reports that the patient developed POTS after receiving

Gardasil, the District Court cited ample precedent to conclude that "temporal association alone does not equate to 'causal association,' particularly in this context where tens of millions of young women and men received the vaccine."[18] Indeed, "[w]hen mass vaccination is introduced in a population, individuals will experience adverse events in close temporal relation to the vaccine purely by chance." JA04050, Hviid 2020. This observation clearly holds for HPV vaccines, which have been administered ***over 500 million*** times.[19] JA03721, WHO, Weekly Epidemiology Record.

Second, Plaintiffs offer a handful of reports of POTS following HPV vaccination, which cannot warrant a warning, particularly in light of the millions of HPV vaccine doses administered. Plaintiffs fail to explain how the ***fewer than twenty*** individual reports they cite in Merck's adverse event database before January 2011 establish any "causal association"

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[18] JA19733 (citing, *inter alia*, *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1323 (Fed. Cir. 2010); *In re Lipitor*, 227 F. Supp. 3d 452, 479 (D.S.C. 2017), *aff'd*, 892 F.3d 624 (4th Cir. 2018)); *see also Herlth*, 2022 WL 788669, at *4 (rejecting argument that "case reports from individual patients," including Blitshteyn 2010, constituted "reasonable evidence of a causal association" under the CBE regulation).

[19] Even by 2009, before the publication of Blitshteyn 2010, Gardasil had been administered "more than 23 million" times. JA09247, Slade 2009.

between Gardasil and POTS. *See* Apt. Br. 46 n.33. Plaintiffs offer no analysis of these adverse event reports, which include multiple reports from single patients and reports from patients never diagnosed with POTS.[20] "[A]dverse event reports, without any analysis indicating causality, cannot constitute 'newly acquired information.'" *Gayle v. Pfizer Inc.*, 452 F. Supp. 3d 78, 88 (S.D.N.Y. 2020), *aff'd*, 847 F. App'x 79 (2d Cir. 2021) (6,000 "adverse reports" did not "demonstrate 'reasonable evidence of a causal association'"); *see Knight*, 984 F.3d at 340–41 ("hypotheses, differing viewpoints and even preliminary conclusions" are not "newly acquired information"). That is especially true where, as here, Plaintiffs' own experts estimate a background rate of POTS as high as ***one percent*** in the population being vaccinated, and concede that POTS "is expected in every country around the world" even without Gardasil.[21]

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[20] Cited in Apt. Br. 46 n.33, *see, e.g.*, JA06835 (Plaintiffs describe as "2009 POTS case," but exhibit includes no POTS diagnosis); JA13854–13855, JA06793, JA20627–20629, JA11602 (all describing same patient, 0906USA02194, and identifying case as obtained "on request by the Company ***from the FDA***" (emphasis added)); JA06726–06727, JA06758–06759, JA12132 (all describing same patient, 707USA00729).

[21] *See* JA19536–19537, Miglis Dep. at 63:16–64:24; JA19730 n.15, Summ. J. Op. Plaintiffs are wrong to analogize this case to *Wyeth*, where

Zofran, 57 F.4th at 338 (no causal association established where "studies concluded that incidences . . . were within the background range").

The same reasoning applies to the additional "VAERS-reported Gardasil POTS cases" by 2011 to which Plaintiffs point. Apt. Br. 53. First, these reports are not "newly acquired information" because the FDA already knew about them. *See* 21 C.F.R. § 601.12(f)(2)(i) ("newly acquired information" is "information not previously submitted to the" FDA). As the District Court described, the "FDA and CDC jointly operate" VAERS, "which is a passive surveillance system" for "vaccines licensed in the United States." JA19734; *see also* JA04110, CDC, About VAERS. Further, the FDA and CDC have stated that VAERS reports do not "tell us whether a vaccine caused a medical issue."[22]

Plaintiffs also declare that pre-2011 VAERS reports presented a "stunning signal," but that is wrong. Apt. Br. 53. The documents

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individuals suffered rare, severe gangrene and amputations shortly after administration of a particular drug. *See* Apt. Br. 17; Arg. I.A.2.b, *supra*. Further, even at lower POTS background rate estimates now urged by Plaintiffs, *see* Apt. Br. 56–57 & n.41, "it would still be expected that there would be tens and later hundreds of thousands of cases among the tens and hundreds of millions of doses of Gardasil administered." JA19735 n.19, Summ. J. Op.

[22] JA04113, FDA, VAERS.

Plaintiffs cite show no "signal" of any kind by 2011. To the contrary, Plaintiffs rely on a litigation report claiming only ***eight*** POTS cases before 2011, and these cases, drawn from the FDA and CDC's own VAERS database, involved some patients not even diagnosed with POTS. *Id.* (citing JA20066–20067, Tomljenovic Rpt., Part IV 31–32 (reflecting "NA" for purported POTS signal before 2011)).

Third, the only other pre-2011 evidence Plaintiffs cite is irrelevant. Plaintiffs devote an entire section of their brief to information Merck allegedly had regarding "autoimmune disorders," Apt. Br. 38, but as the District Court found, "Plaintiffs regularly and erroneously conflate discussions and references to broad 'autoimmune' illness generally with POTS specifically." JA19739. Plaintiffs cite articles referring broadly to "autonomic and autoimmune disorders"—a massive category of conditions including ***lupus*** and ***rheumatoid arthritis***—that say

nothing about POTS. Apt. Br. 38–39, 42–43 & n.30.[23] These articles fail to satisfy the CBE regulation.[24]

Thus, Plaintiffs' only evidence that a POTS warning was warranted by January 2011 consists of "***one published case*** of POTS and ***less than 20 unverified reports*** of POTS." JA19736, Summ. J. Op. (emphasis added). As the District Court rightly found, permitting a warning on this basis "would effectively make the regulatory standard meaningless." JA19737.

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[23] JA09247–09248, Slade 2009 (referring to reports of autoimmune conditions such as "lupus," "rheumatoid arthritis," and "Sjögren syndrome" and concluding that "[t]he postlicensure safety profile presented here is broadly consistent with safety data from prelicensure trials"); JA06589, Harper 2009 (opinion article discussing Slade 2009, presenting no data, and not mentioning POTS); JA06580, Couette 2009 (discussing "[m]acrophagic myofasciitis (MMF)" and mentioning neither Gardasil nor POTS); JA14399, Shoenfeld 2011 (mentioning neither Gardasil nor POTS, and discussing whether vaccine adjuvants generally may be related to condition called "ASIA"); JA14025, Caulfield 2007, and JA06593, Harper 2010 (not mentioning POTS); JA13992, Cohen and Shoenfeld 1996 (not mentioning Gardasil or POTS).

[24] *See Herlth*, 2022 WL 788669, at *4 n.27 (rejecting Kanduc and Israeli articles); JA14047, Kanduc 2009 (theoretical discussion of proteins that mentions neither POTS nor Gardasil); JA06570, Israeli 2009 (no mention of POTS; claiming vaccine adjuvants could "potential[ly]" be associated with "abscesses" and "myofasciitis").

ii. Plaintiffs Should be Held to Their Position that Merck Should Have Warned of POTS in 2011, Not at Some Later Date.

That Merck could not have given a warning by January 2011 should doom Plaintiffs' POTS claims because Plaintiffs, and their experts, committed to a theory requiring a warning by that date. Merck served interrogatories seeking the text, dates, and bases of warnings Plaintiffs claim Merck should have given. JA03822–03824. Plaintiffs responded that they would answer only through their expert reports.[25] Just one of Plaintiffs' experts, Dr. Amato, offered an opinion on these points. He claims that "[b]y ***January 2011***, the Gardasil label should have encompassed [his proposed warning for POTS]." JA02991.

Plaintiffs repeatedly represented to the District Court that newly acquired information existed by January 2011, thus waiving any contrary argument.[26] *See United States v. Turner Constr. Co.*, 946 F.3d

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[25] JA03823–03824 (stating that experts "will be disclosed at the appropriate time" to provide text and date of proposed warning).

[26] *See, e.g.*, JA06529 (opposition to summary judgment stating "Merck could have warned about autoimmune disorders, such as POTS, in 2011, and about irregular menstruation, including POI, in 2013"); JA19743 n.29, Summ. J. Op. ("At oral argument, Plaintiffs conceded that Dr. Amato is their only expert opining on warning dates.").

201, 210 (4th Cir. 2019). Plaintiffs likely chose this date to avoid the flood of later publications confirming Gardasil's safety, and to preserve the claims of plaintiffs vaccinated on early dates.

Now Plaintiffs claim that they should not be held to the January 2011 date. They argue for the first time that Dr. Amato's use of the word "by" 2011 means that the District Court should have considered evidence ***after*** 2011. Apt. Br. 28–29. This is the opposite of their position below, where they argued Merck "could have warned" about POTS "in 2011" and about POI "in 2013."[27] It is also not what "by" means, which is "***not later than***." *Zitzow v. Diederich*, 337 N.W.2d 799, 802 (N.D. 1983) (emphasis added).

The District Court rightly held Plaintiffs to the January 2011 date, even as Plaintiffs tried to retreat from it at the hearing on Merck's motion for summary judgment. As that Court summarized: "Perhaps recognizing the dearth of evidence in support of adding a POTS warning in January 2011, ***at oral argument*** and in a supplemental brief filed after oral argument, Bellwether Plaintiffs asked the Court ***for the first time*** to consider finding that Merck had sufficient information to unilaterally

[27] JA06529, Summ. J. Opp'n.

add a POTS warning at some time after January 2011." JA19740 (emphases added).[28]

This Court should likewise hold Plaintiffs to the January 2011 date identified by Dr. Amato. That means their claims are clearly preempted.

c. Even if Plaintiffs Can Now Demand Merck Should Have Warned Post-2011, the District Court Correctly Concluded that Plaintiffs Failed to Present Evidence Satisfying the CBE Regulation at *Any Time*.

Even if this Court allows Plaintiffs to present a theory of the case demanding a post-2011 POTS warning, the District Court also correctly held that Merck could not have unilaterally warned of POTS at any time "***after*** January 2011"—an alternative holding Plaintiffs ***do not even mention***. JA19745 (emphasis added).

In reaching this conclusion, the District Court analyzed the evidence for adding a POTS warning after 2011, including by 2015—the only "specific alternate date" Plaintiffs identified—and "generally considered the time period after 2015" as well. JA19741–19744, Summ. J. Op. The District Court properly concluded that Merck never—at any

[28] Plaintiffs have never proposed a date other than November 2013 to add a POI warning. *See* JA19741 n.28, Summ. J. Op.

point—had information that "would have permitted it to unilaterally add a warning to the Gardasil label after January 2011." JA19745, Summ. J. Op.

That is not surprising. First, Plaintiffs fail to demonstrate that any evidence upon which they rely was "not previously submitted to the" FDA. 21 C.F.R. § 601.12(f)(6). Evidence previously submitted is not "by definition . . . 'newly acquired information.'" JA19731, Summ. J. Op.; *see also Celexa*, 779 F.3d at 41 (CBE regulation concerns "new information not considered by the FDA"). Plaintiffs concede that nearly all such evidence has long been in the FDA's possession. For example, Plaintiffs' sole regulatory expert, Dr. Amato, testified that the FDA had reviewed ***all*** clinical trial cases, postmarketing reports, and literature that he identified as supposedly justifying a POTS warning. JA06080–06081, Amato Dep., 365:19–366:7. He also admitted that Merck submitted to the FDA Gardasil's clinical trial protocols, final clinical study reports, and updated data submitted with supplemental applications. JA05958–05960, Amato Dep., 243:9–245:10. Merck also repeatedly provided

comprehensive safety updates to the FDA and other authorities.[29] As the District Court correctly held, all this information given to the FDA "fails as 'newly acquired information' under the regulatory definition." JA19732.

Plaintiffs' remaining evidence is either irrelevant or cannot show any "reasonable evidence of a causal association." *Knight*, 984 F.3d at 341.

1. Plaintiffs' incorrect critiques of Gardasil's clinical trials and ingredients, which the FDA explicitly approved ***before*** the vaccine's initial approval, are preempted. Apt. Br. 63–65. This information not only had been given to and approved by the FDA, *see supra* Stmt. II.A, but also would not have permitted a "***unilateral***" label change under the CBE regulation. *Knight*, 984 F.3d at 338 (emphasis added). Before Gardasil's approval, Merck had no unilateral authority to make ***any*** final decision regarding Gardasil, whether about its ingredients, trials, or

[29] *See, e.g.*, JA19628–19629, Conroy Dep. 348:6–349:1 (Merck witness "unaware of any reports that were not submitted" to FDA); JA14795, JA15001 (2006 FDA review of Gardasil clinical trials); JA06842–08253, JA11334–11593, JA11977–13839 (periodic safety updates sent to FDA); JA04035, Arana 2017 (publication with FDA/CDC coauthors citing articles emphasized by Plaintiffs and reviewing data from EMA); JA04551, Wodi 2023 (similar).

labeling: the FDA had to sign off before Gardasil was approved and shipped to physicians and patients. "[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance," "those state duties" are preempted. *Mensing*, 564 U.S. at 623–24. In addition, as elaborated below, *infra* at Arg. III.B, critiques of clinical trial procedures and ingredients are attacks on the vaccine's design, which the Vaccine Act bars.

2. Plaintiffs focus extensively on individual case reports, case series, or adverse event reports, which, as explained, do not constitute reasonable evidence of a causal association.[30] *Supra* Arg. I.B.1.b.i; Apt. Br. 39–43, 46–47 & n.33; *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S.

[30] *See, e.g.*, JA14170–14177, Hineno 2021 (case series of 87 patients with various symptoms, not POTS diagnoses, and noting "the frequency of . . . POTS . . . is very low, suggesting no causal association"); JA14078, Kinoshita 2014 (case report claiming four patients developed POTS); JA14095, Kinoshita 2015 (reply of authors from 2014 article referring to same four patients and admitting "no direct evidence showing a causative relationship"); JA14145, Hendrickson 2015 (letter to the editor with case report of one patient "rais[ing] a potential hypothesis"); JA09237, Schofield 2018 (case report of one patient); JA09132, Blitshteyn 2017 (case report of one patient who used different HPV vaccine); JA14159, Ozawa 2017 (case series discussing undefined subset of patients and acknowledging "a causal link has not been established").

27, 44 (2011) ("an adverse event, standing alone, does not mean that the drug caused that event").

3. Plaintiffs rely on alleged "safety signals" from "Merck's internal analysis" of adverse events. Apt. Br. 35–37. But Plaintiffs concede that such "signals," which may be detected by analyzing disproportionate adverse events reported after vaccine administration and expressed in what is called an "EB05 score," ***"do[] not prove reasonable evidence of a causal association."*** JA19738–19739, Summ. J. Op. (quoting Plaintiffs' counsel at oral argument) (emphasis added). A computer program, not a human, aggregates case reports and generates the "EB05 score." JA19702, Lehman Dep. 78:6–24. The FDA has long explained that "signal detection" with "[d]ata mining ***is not a tool for establishing causal attributions***."[31] And FDA officials have

[31] *Wells v. SmithKline Beecham Corp.*, No. A-06-CA-126-LY, 2009 WL 564303, at *12 (W.D. Tex. Feb. 18, 2009), *aff'd*, 601 F.3d 375 (5th Cir. 2010) (quoting FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005), available at https://www.fda.gov/media/71546/download (emphasis added)). Plaintiffs' criticism of the *Wells* case, Apt. Br. 24, is misplaced. The District Court simply cited that decision for its reference to the FDA's guidance on "data mining." JA19739. That same FDA guidance cautions

further spoken to "[d]isproportionality analys[e]s," emphasizing that they "might warrant further evaluation, such as clinical review of reports, but do[] not definitively demonstrate a . . . causal association, or a safety problem." JA03363, Shimabukuro 2015.

Moreover, as the District Court recognized, FDA and CDC officials have performed numerous disproportionality analyses of VAERS data at different times, always reaching the same conclusion: no safety concern exists for POTS (or POI). JA03559, Shimabukuro 2019; JA04035, Arana 2017; JA04579, Arana 2018; JA04551, Wodi 2023 (regarding POI); JA19744, Summ. J. Op. (noting same articles). And as the District Court acknowledged, "Plaintiffs have not disputed that Merck analyzed rather than ignored any relevant EB05 scores." JA19739 n.25.

4. The District Court rightly rejected Plaintiffs' after-the-fact ***re-*** analyses of adverse event data and articles in Plaintiffs' expert reports that, Plaintiffs contend, show "safety signals" that Merck "***would have***

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that "it is not unusual for a product to have several product-event combinations with [disproportionality] scores above a specified threshold," and that disproportionality analyses are "not a required part of signal identification or evaluation." FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005), at 8–9, available at https://www.fda.gov/media/71546/download.

found" "***if*** Merck had properly analyzed VAERS data." Apt. Br. 34–35 (citing expert reports submitted in this litigation) (emphasis added); *id.* at 52–55; *see* JA19743–19744, Summ. J. Op. First, as discussed, Plaintiffs concede that such "signals," even if Merck possessed them at the relevant time, are not reasonable evidence of a causal association. JA19738–19739, Summ. J. Op. Further, the "signals" or other conclusions identified in Plaintiffs' expert reports were gleaned by their experts long after Plaintiffs contend Merck should have amended Gardasil's warning label. Apt. Br. 34–35. These analyses cannot constitute "newly acquired information." *R.S.B. v. Merck & Co.*, No. 20-C-1402, 2021 WL 6128161, at *4 (E.D. Wis. Dec. 28, 2021) ("analysis conducted by an expert in preparation for litigation with the benefit of hindsight" is not "newly acquired information"); *Zofran*, 57 F.4th at 340 (similar).[32] This Court did not accept a similar argument in *Knight*, where the plaintiffs argued that their claims were not preempted because their expert "testified . . .

[32] *See also Gayle*, 452 F. Supp. 3d at 88 (defendant's "alleged failure" to "analyze[] adverse event reports" did not "amount[] to 'newly acquired evidence," and plaintiff cannot sidestep preemption "by merely alleging that a manufacturer ***should have created*** the 'newly acquired information'" (emphasis added)); *Bueno v. Merck & Co.*, 746 F. Supp. 3d 853, 877–78 (S.D. Cal. 2024) (collecting authorities).

that [certain] post-approval analyses . . . would have supported the CBE label changes sought by the Plaintiffs."[33] The Court's comprehensive opinion nowhere mentioned the testimony. *See generally Knight*, 984 F.3d 329.

The District Court did not, as Plaintiffs assert, require (and then disregard) litigation-based expert testimony. Apt. Br. 27–28, 52–53. Rather, the Court referred to longstanding FDA rulemaking to clarify the meaning of "reasonable evidence of a causal association." As several courts have recognized, "[t]he FDA has consistently defined reasonable evidence of a causal association as 'when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug.'" *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1272 (W.D. Okla. 2011) (quoting 44 Fed. Reg. 37434, 374634 (June 26, 1979)). "Experts" in this context refers to scientists, not litigation experts, and Plaintiffs identify nothing showing otherwise.

[33] Apt. Br. of Appellees, ECF 33 at 30, *Knight*, No. 19-1636 (4th Cir. Nov. 21, 2019).

5. Finally, Plaintiffs cite a host of irrelevant materials. *See* Apt. Br. 38–46. This includes:

- **Publications that are not relevant to POTS *or* POI**. These include articles discussing unrelated conditions such as ***lupus***. JA14061, Soldevilla 2012, and JA14064, Gatto 2013 (discussing lupus); JA14179, Garg 2018 (discussing lupus). Plaintiffs also cite articles discussing a proposed non-POTS condition called "ASIA," which FDA and CDC authors have described as "an ill-defined constellation of general symptoms and disparate illnesses [that] is ***not a medically recognized diagnosis***." JA04020, Shimabukuro 2019 (emphasis added).[34]

- **Publications that *explicitly disclaim* any finding of a causal association between HPV vaccination and Plaintiffs' alleged injuries.**[35] Plaintiffs rely on several articles written by Dr. Brinth, who has "made very clear" that her several case series on POTS following HPV vaccination are "working on the lowest steps of the ladder," and that her "findings should not be seen as proof of anything." JA18708–18709, Brinth 2015. Another frequent author, Dr. Blitshteyn, wrote in 2019 that based on "the existing evidence to date," including her own research, "***a causal relationship has***

[34] *See* JA14122, Anaya 2015; JA14147, Palmieri 2017; JA04196, Tomljenovic 2014; JA14262, Gherardi 2019; JA14034, Tervaert 2023 (focusing on ASIA and additional conditions other than POTS). Plaintiffs cite other articles that say nothing about POTS. *See, e.g.*, JA14210, Bizjak 2016; JA14011, Joura 2015; JA14239, Geier 2015; JA14097, Nishioka 2014; JA14316, Chandler 2018.

[35] *See, e.g.*, JA14134–14137, Brinth 2015 (study "do[es] not establish whether or not the Q-HPV vaccine is a cause of the symptoms"); JA14131, Brinth 2015 ("[o]ur findings do not confirm or dismiss a causal link"); JA04164, Chandler 2017 ("causal association . . . remains uncertain"); JA14327, Zi 2022 ("causal relationships between HPV vaccines and specific AEs cannot be established by current studies").

not been supported" between HPV vaccines and autonomic disorders like POTS. JA04107, Blitshteyn 2019 (emphasis added).

- **Articles that present "hypotheses, differing viewpoints and even preliminary conclusions" about the HPV vaccine, which are "not reliable evidence of new risks."**[36] *Knight*, 984 F.3d at 340 (quotations omitted).

- **Literature reviews that simply summarize preexisting data and add no new data or analysis.** *See, e.g.*, JA04003, Blitshteyn 2018; JA14226–14237, Tomljenovic 2013 (reviewing existing literature, providing no new evidence, stating "health authorities worldwide do not regard [POTS] as causally related to the vaccine," and noting that "[s]ystematic, prospective, controlled trials are needed to establish or reject causal relationships").[37]

- **One article that Plaintiffs emphasize, Jorgensen 2020, which does not support their claims.** JA04267 (Jorgensen 2020). The article makes no conclusions about Gardasil in particular—it combines data regarding Gardasil and ***a separate vaccine***, with ***over two thirds of the data coming from the other vaccine***. *See* JA04267–04289. When analyzing only Gardasil, the authors report ***no statistically significant*** increase in risk of adverse events "definitely associated with POTS" (*i.e.*, non-POTS adverse events that the authors determined were consistent with POTS) and ***no statistically significant*** increase

[36] *See, e.g.*, JA04196, Tomljenovic 2014 (single case report concluding more study needed to show causation); JA14072–14076, Blitshteyn 2014 (discussing six patients; concluding "[f]urther studies are necessary"); JA04239–04241, Martinez-Lavin 2015 (45 self-reported patient questionnaires with no "direct medical examination of affected individuals"); JA04243, Li 2014 (study not mentioning vaccines at all).

[37] *See also* JA14257–14259, Dahan 2016 (editorial reviewing existing VAERS data available to FDA, comparing data for Gardasil to data for chicken pox vaccine given to different patient population, and suggesting there "might be a [POTS] risk"); JA04259, Tomljenovic 2015 (reviewing "literature" and "clinical trials").

in risk of new medical conditions "definitely associated" with POTS. *See* JA04501, JA04506. The authors conclude by stating that "the ***analyses do not prove that the HPV vaccines cause POTS***." JA04286. Further, HHS is aware of this article from petitioners in Vaccine Court whose experts cited it. *See, e.g.*, JA04544.

In sum, safety studies and regulatory authorities confirm that Gardasil does not cause POTS, and Plaintiffs' materials do not satisfy the CBE regulation at any time.

2. Plaintiffs Also Fail to Satisfy the CBE Regulation's Requirements of "Newly Acquired Information" Demonstrating a "Causal Association" Between Gardasil and POI.

As with POTS, Merck also "did not have sufficient 'newly acquired information' to unilaterally add a POI warning to the Gardasil label in November 2013," the date Plaintiffs claim Merck should have warned, or at any date thereafter.[38] JA19750, Summ. J. Op.

First, medical literature and health authorities confirm no such

[38] In their brief, Plaintiffs contend that they request "a more generic warning for irregular menstruation." Apt. Br. 47. But the MDL focused on the specific bellwether injury of POI for years. *See* JA02252–02253 (3d Pretrial Order, limiting bellwether selection, "[a]s agreed by the Parties," to plaintiffs alleging POTS and "Primary Ovarian Failure ('POF')/Primary Ovarian Insufficiency ('POI')."). POI is very different from the broad, nonspecific condition of "irregular menstruation," which may include persons with conditions such as pregnancy or menopause that do not reflect any injury. Nor does Plaintiffs' evidence support a warning for "irregular menstruation" under the CBE regulation.

information exists:

POI: Examples of Federal Agency Safety Statements and Research with Federal Officials as Coauthors		
DATE	**AGENCY**	**STATEMENT**
2023	**CDC, FDA**	A peer-reviewed paper coauthored by CDC and FDA officials states that a review of VAERS reports "do[es] not suggest a safety concern" for POI following HPV vaccination, regardless of reports temporally associated with vaccination. JA04551, Wodi 2023.
First released 2021, current as of 2024	**CDC, FDA**	"CDC and FDA have not found any proof that HPV vaccines cause reproductive problems in women, including POI." JA03742, CDC, HPV Vaccine Safety.
First released 2009, current as of 2018	**FDA**	"FDA and the U.S. Centers for Disease Control and Prevention (CDC) take all concerns about vaccine safety seriously, and have been closely monitoring the safety of Gardasil. . . . However, none of the adverse events in the safety review . . . were reported at rates (number of adverse events/number of doses distributed) greater than expected in a population of this age and gender and with other known contributing factors to these adverse events." JA04028–04029, FDA, Gardasil Vaccine Safety.

2018	**CDC, FDA**	A peer-reviewed paper coauthored by CDC and FDA officials and cited by the CDC in public safety communications states that an evaluation of VAERS reports of POI following HPV vaccination "did not reveal any concerning patterns that would suggest a causal association with" quadrivalent Gardasil. JA04584, Arana 2018.

These statements echo conclusions of other large, peer-reviewed studies.[39]

Second, the relevant scientific literature "does not support a finding that Merck had reasonable evidence of a causal association by November 2013 (or later)." JA19748, Summ. J. Op. Before November 2013, Plaintiffs identify articles discussing ***only four patients*** who developed POI after HPV vaccination. *See* Apt. Br. 47–52. Two of these articles, Little 2012 and Colafrancesco 2013, are case reports discussing four patients. These articles offer only hypotheses, not any conclusion as to causality. JA14481, Little 2012; JA14492, Colafrancesco 2013. The third article, Little 2013 (JA14485), discusses the same patient as Little 2012 and only suggests that more studies should be performed.[40] Plaintiffs also cite a small number of adverse event reports or emails

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[39] *See, e.g.*, JA04588, Hviid 2021 (cohort study of 996,300 Danish-born females finding "no association between 4HPV vaccination and primary ovarian insufficiency"); JA04603, Naleway 2018 (study with CDC coauthor, cited on CDC website, that "did not find a statistically significant elevated risk of POI after HPV . . . vaccination in this population-based retrospective cohort study").

[40] Plaintiffs claim Little 2013 noted VAERS data reflecting "amenorrhea," which is not POI. Apt. Br. 47. "Amenorrhea" refers to "the absence of menstruation" and has a range of causes, such as pregnancy or menopause. JA19353, Mayo Clinic, Amenorrhea.

discussing those reports before November 2013. Apt. Br. 52 n.35. Just as with POTS, Plaintiffs fail to address the background rate for POI or the ***millions*** of patients administered HPV vaccines, and Plaintiffs include reports from patients Plaintiffs do not even claim were diagnosed with POI.[41] *See* Arg. I.B.1.b.i, *supra*.

Plaintiffs should be held to their 2013 POI warning date, which was "the lone date suggested by Plaintiffs' expert." JA19741 n.28, Summ. J. Op.; *see* Arg. I.B.1.b.ii, *supra*. But Plaintiffs' arguments fare no better for any date ***after 2013***. For the post-2013 period, Plaintiffs rely on the same categories of irrelevant evidence that Merck already explained cannot show "newly acquired information" as to POTS. *See* Arg. I.B.1, *supra*. In particular, Plaintiffs' remaining articles include case reports, case series, or disproportionality analyses that cannot show causation,[42] and others

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[41] *See* Apt. Br. 52 n.35 (referring to "amenorrhea," which is different from POI). Plaintiffs also make claims of a "safety signal," but refer only to Merck's disproportionality analyses, which cannot establish causation or satisfy the CBE regulation, *see* Arg. I.B.1.c, *supra*.

[42] *See* Apt. Br. 47–51 (citing JA14503, Little 2014, discussing three cases of POI; JA04640, Gong 2020 (adverse event study concluding "causal relationship needs further investigation" and conducting disproportionality analysis—a tool that cannot establish causation); JA14545, Tatang 2022 (search of VAERS data concluding that "further investigations are warranted")); *see Wells*, 2009 WL 564303, at *12.

that recycle previously published case reports.[43] Plaintiffs also cite articles not discussing POI,[44] as well as irrelevant publications by non-scientific advocacy groups.[45] Further, Plaintiffs cannot meet their burden to identify newly acquired information by citing materials that are not part of the voluminous record below, and which post-date Plaintiffs' vaccinations.[46] Nor can Plaintiffs meet their burden of showing "newly acquired information" for POTS or POI by referring to broader, ill-defined

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[43] Little 2012 (JA14482), Colafrancesco 2013 (JA14493), and Little 2014 (JA14503), which discuss six total patients, comprise, to this day, the "only six such case reports in the published literature." JA19747 n.38, Summ. J. Op. Other publications Plaintiffs cite recycle these six cases. *E.g.*, JA14558, Gruber 2015 (republishing table of 6 case reports); JA14565, Jankowska 2017 (referring to cases in Colafrancesco 2013; presenting no new information); JA14516, Little 2017 (similar).

[44] JA14162, Ozawa 2017 (discussing nonspecific "menstrual abnormality," not POI); JA14247, Geier 2017 (discussing nonspecific "ovarian damage," not POI).

[45] JA14541, Field 2016 (article by American College of Pediatricians providing no new information, stating that "[a]dverse events that occur after vaccines are frequently not caused by the vaccine and there has not been a noticeable rise in POF cases in the last 9 years since HPV4 vaccine has been widely used," and noting that the article's concerns had all been shared with FDA); *see* Southern Poverty Law Center, American College of Pediatricians, *available at* https://www.splcenter.org/fighting-hate/extremist-files/group/american-college-pediatricians ("The American College of Pediatricians (ACPeds) is a fringe . . . group that masquerades as the premier U.S. association of pediatricians").

[46] For example, Plaintiffs cite Wastila (2025), published after the last Gardasil dose administered to any plaintiff here.

conditions like "irregular menstruation" that were not bellwether injuries and are distinct from and far more common than POI. *See* n.38, *supra*.

3. Plaintiffs Lack Evidence Satisfying the CBE Regulation's Independent Requirement that Merck Learned of Risks Previously Unknown to the FDA.

Plaintiffs also lack evidence of new risks unknown by the FDA—an independent reason their claims are preempted. Merck can only change Gardasil's warnings under the CBE regulation "to reflect ***newly*** acquired information" that "reveal[s] ***risks of a different type or greater severity or frequency*** than previously included ***in submissions to FDA***." 21 C.F.R. § 601.12(f)(2)(i), (6) (emphasis added); *Knight*, 984 F.3d at 338. Plaintiffs produced no such evidence.

First, Plaintiffs' expert admitted he has no evidence that even the individual case reports he relied on were not submitted to the FDA. *See, e.g.*, JA06013, JA06019, JA06023, Amato Dep. 298:17–25, 304:2–10, 308:2–11. That is unsurprising since federal health officials, including the FDA and CDC, "closely monitor" "vaccines . . . using various surveillance systems." JA04661, FDA, Vaccine Development – 101. They have also repeatedly studied and published confirming Gardasil's safety.

See supra Arg. I.B.1.c.

Second, no information about HPV vaccination and POTS or POI has "reveal[ed] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 601.12(f)(6). As "Plaintiffs conceded," "***no*** study has ***ever*** shown a statistically significant increase in POTS or POI in [persons] who have taken Gardasil versus those who have not." JA19744–19745, Summ. J. Op. (emphasis in original).

4. The FDA's Repeated Approvals of Gardasil Labeling Confirm the Lack of Evidence Satisfying the CBE Regulation.

The FDA approved dozens of Gardasil labels from 2006 to 2024 "without any POTS or POI warnings." JA19718 n.2, Summ. J. Op. As the District Court put it, this shows "the FDA would not have approved the proposed warnings." JA19718 n.2. When "the FDA has continued to approve labels" without the warning plaintiffs request—particularly "after reviewing" the evidence and arguments the plaintiffs highlight—it "undermines" the argument that newly acquired information existed. *Knight*, 984 F.3d at 339. That is particularly true given that "Congress has imposed on the FDA a duty to initiate a label change if the [agency]

becomes aware of new information, including any new safety information[,] that the [agency] determines should be included in the labeling of the drug." *Albrecht*, 587 U.S. at 324 (Alito, J., concurring) (quotation marks and ellipsis omitted) (quoting 21 U.S.C. § 355(o)(4)(A)).

Here, HHS, the FDA, and the CDC were ***specifically aware*** of what Plaintiffs allege in this case, including through Vaccine Court where Plaintiffs made these precise arguments. *See, e.g.*, Stmt. III, *supra*. Not only did the FDA ***not*** require Merck to add Plaintiffs' warnings, but it ***repeatedly approved*** labeling for Gardasil without the warnings. *See* JA04741–05501 (Gardasil labels from 2006 to 2024). Where, as here, "the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Albrecht*, 587 U.S. at 324 (Alito, J., concurring); *Knight*, 984 F.3d at 339; 21 U.S.C. § 355(o)(4)(A).

C. The "Clear Evidence" Prong Is an Independent Basis for Preemption the District Court Did Not Reach in Its Order.

Plaintiffs' claims fail for another reason: Clear evidence shows that the FDA would have rejected any labeling change, even if Merck could

have made one under the CBE regulation. The District Court did not reach this argument, and this Court need not do so either.[47] JA19718–19719 n.2.

Nevertheless, overwhelming evidence, presented more fully below (JA03593–03598, JA19339–19341, Merck Summ. J. Briefing) and summarized here, shows that the FDA would have vetoed a labeling change to warn of POTS or POI, providing yet another reason Plaintiffs' claims are preempted. Even if Merck could have used the CBE regulation to add Plaintiffs' desired warnings—which is not so—"the FDA can [later] reject CBE submissions." *Dolin*, 901 F.3d at 812. As explained, Arg. I.A.1, *supra*, a claim is thus preempted if there is "***clear evidence*** that the FDA would not have approved a change to the prescription drug's label." *Gibbons*, 919 F.3d at 708 (cleaned up) (emphasis added). Plaintiffs incorrectly claim Merck cannot show preemption at this second step because the FDA "never rejected warnings." *See* Apt. Br. 30–31. In reality, the analysis only requires clear evidence that the FDA ***would***

[47] If this Court concludes the District Court should have reached this step, the Court may "remand to the district court" for it to "determine whether the evidence" justifies preemption on this alternative ground. *See, e.g.*, *Billioni v. Bryant*, 759 F. App'x 144, 151 (4th Cir. 2019).

have rejected the change, which is plainly true here.[48] *Zofran*, 57 F.4th at 341–42.

1. Federal Authorities Have Taken Specific Actions Showing "Disapproval" of Plaintiffs' Proposed Warnings after Studying Their Theories.

As already explained, *see* Arg. I.B, *supra*, the FDA, the CDC, and HHS have studied and rejected the causal link Plaintiffs suggest to POTS and POI in official safety statements, which clearly "communicate[d] [their] disapproval of a warning." *See Albrecht*, 587 U.S. at 316. The FDA has also heard, and debunked, key contentions presented by Plaintiffs in this case, such as that Gardasil's ingredients including polysorbate 80, aluminum, and DNA fragments pose risks. *See, e.g.*, JA04680–04681, Sep. 9, 2009 VRBPAC Transcript; JA03776–03779, CDC, Adjuvants and

[48] The Third Circuit in *Fosamax* similarly said the defendant must show "the FDA ***would have rejected***" a change. 118 F.4th at 357. Further undermining Plaintiffs' analogy to *Fosamax* is that there, unlike here, the FDA ultimately adopted a warning related to the claimed injuries. 118 F.4th at 336–37. This same distinction renders irrelevant the other cases Plaintiffs cite. *See Blackburn v. Shire U.S., Inc.*, No. 20-12258, 2022 WL 16729466, at *2 (11th Cir. Nov. 7, 2022) (FDA requested "renal failure" in label); *In re Actos (Pioglitazone) Prods. Liab. Litig.*, No. 12-CV-00064, 2014 WL 60298, at *2 (W.D. La. Jan. 7, 2014) (FDA later approved addition of bladder cancer to label); *Hayes v. SmithKline Beecham Corp.*, No. 07-CV-0682, 2009 WL 4912178, at *3 (N.D. Okla. Dec. 14, 2009) (FDA requested the manufacturer add "new data and recommendations to the *Warnings* section").

Vaccines; JA04033, FDA Information on Gardasil; JA04699–04700; JA04704, Dec. 7, 2010 FDA PAC Meeting Tr. The FDA's parent organization, HHS, vigorously opposed Plaintiffs' claims in Vaccine Court after fulfilling its statutory duty to inform the public and invite input about Plaintiffs' causation theories.[49] *See* Stmt. III, *supra*. At the same time, the FDA ***also*** approved dozens of Gardasil labels ***without*** POTS or POI warnings. *See* Arg. I.B.4, *supra*.

Plaintiffs claim HHS's views are irrelevant and only the FDA's position matters. Apt. Br. 32. But HHS is the FDA's parent agency, and Congress delegated labeling responsibilities to HHS in the first instance and directed HHS to establish a "National Vaccine Program" with broad responsibilities. 21 U.S.C. §§ 393(a); 355(b)(1)(A), (d); 321(d); 42 U.S.C. § 300aa-1, 2.

Plaintiffs also claim that HHS submissions in Vaccine Court and responses in the Federal Register to comments about Gardasil do not count. Apt. Br. 32–33. But the Supreme Court held "notice-and-comment rulemaking" (like HHS's statements in the Federal Register) is precisely

[49] *See, e.g.*, 82 Fed. Reg. 18654-55 (April 20, 2017); 80 Fed. Reg. 14391-92 (Mar. 19, 2015).

the type of action that can preempt claims. *Albrecht*, 587 U.S. at 315–16. And the Vaccine Act requires the Secretary to be "named as the respondent" in Vaccine Court, and for HHS to inform its own views regarding claimants' causation theories, so statements there can clearly be imputed to the agency. 42 U.S.C. § 300aa-12(b)(1).[50]

2. The FDA Refused to Allow Even a Reference to POTS in a Section of Gardasil Labeling Discussing Clinical Trials.

In 2015, the FDA rejected a labeling change Merck submitted under the CBE regulation to add a ***mere reference*** to POTS in a section of Gardasil's label discussing clinical trials. In 2015, Merck submitted a labeling change to the FDA for Gardasil, adding information about a case of POTS diagnosed in a clinical trial participant over three years after the patient's last vaccination. *See* JA04711, JA04719. The FDA

[50] Plaintiffs also misinterpret two provisions of the Vaccine Act. ***First***, Plaintiffs claim HHS's statement in the Federal Register is "the Vaccine Injury Table" and therefore cannot be considered here. Apt. Br. 33. That is incorrect. HHS made the statement when ***amending*** the Table, but the statement is not the Table itself, which appears at 42 C.F.R. § 100.3. ***Second***, Plaintiffs claim that Vaccine Court "[o]rders are also inadmissible," Apt. Br. 32, but the Act only bars admission of Vaccine Court "finding[s] of fact or conclusion[s] of law" at trial. 42 U.S.C. § 300aa-23(e) (section titled "Trial"). Merck's citation of HHS Vaccine Court ***briefing*** within a pre-trial ***motion*** is neither.

recommended Merck withdraw the amendment, explaining that the POTS case was "unlikely to be vaccine-related based on the clinical information available for [the FDA's] review to date," including an "***absence of data to support a causal association or link between HPV vaccines and POTS in the post-licensure safety monitoring***" in the "substantial timeframe since" Gardasil's original approval. JA04737 (emphasis added).

That confirms the FDA would have rejected a POTS warning. The "warning" Plaintiffs seek in the "warnings and precautions" labeling section (JA03991, Amato Report) could be added only upon "***reasonable evidence*** of a causal association." 21 C.F.R. § 201.57(c)(6) (emphasis added). But Merck attempted to add a reference to a POTS case to the "Adverse Reactions" section, which requires only "***some basis to believe*** there is a causal relationship." *See* 21 C.F.R. § 201.57(c)(7) (emphasis added). That the FDA rejected this addition, even to a section with a lower evidentiary standard, reaffirms the FDA would have rejected Plaintiffs' proposed POTS ***warning***.

II. The District Court Did Not Abuse Its Discretion in Excluding Limited Opinions Offered by Plaintiffs' Regulatory Expert.

Plaintiffs demanded to present a regulatory expert "specifically" for one purpose: "to address the ***legal*** questions" about ***preemption***—not to assist any jury's fact-finding. JA19374, Amato Op. (emphasis added). Plaintiffs offered Dr. Amato, a molecular biologist with an M.B.A. and no medical degree, as that expert. He sought to opine about when and how Merck should have warned about a causal association between Gardasil and POTS or POI. JA03231, JA03243, JA03261–03262.

The District Court appropriately precluded Dr. Amato from opining on the legal issue of preemption. *See, e.g.*, *Zofran*, 57 F.4th at 340. And although this Court need not even reach the second ruling—which is irrelevant to Merck's preemption victory—the Court also correctly precluded Dr. Amato, a non-physician, from re-diagnosing patients he had never met by applying his own criteria to adverse event reports. As explained, these supposed adverse event reports do not show causality, and thus do not change the preemption analysis. *See* Arg. I.B, *supra*.

A. The Court Properly Excluded Dr. Amato's Legal Conclusions about Preemption.

The District Court correctly precluded Dr. Amato's legal opinion that "Merck met the governing regulatory test" necessary to add warnings, which went "to the heart of what the Court must decide" on preemption. JA19373–19375. Expert testimony must "help the ***trier of fact***." Fed. R. Evid. 702(a) (emphasis added). Preemption, however, "is a ***question of law***." *Knight*, 984 F.3d at 337 (emphasis added). "Each courtroom comes equipped with a 'legal expert,' called a judge, and it is his or her province alone" to decide legal questions. *See Burkhart v. Washington Metro. Area Transit Auth.*, 112 F.3d 1207, 1213 (D.C. Cir. 1997). That is particularly true of preemption, which is for "a judge to decide, not a jury."[51] *Albrecht*, 587 U.S. at 303.

Other courts have likewise rejected expert testimony on whether FDA labeling requirements have been satisfied, explaining that "[e]xpert testimony on questions of law is rarely admissible because such testimony cannot properly assist the trier of fact." *Zofran*, 57 F.4th at 340

[51] Plaintiffs cite off-point cases related to whether regulatory experts "are useful in assisting the trier of fact," not to a ***court*** deciding the ***legal question*** of preemption. Apt. Br. 74–75 & n.54.

(cleaned up). And this Court did not mention a similar argument in *Knight*, even though plaintiffs contended that their claims were not preempted because their expert "testified . . . that [certain] post-approval analyses . . . would have supported the CBE label changes." *Supra* n.33. Consistent with these principles, the District Court properly excluded Dr. Amato's opinion on the main question of law before it. *Supra* Arg. I; *United States v. McIver*, 470 F.3d 550, 562 (4th Cir. 2006) ("opinion testimony that . . . draws a legal conclusion by applying law to the facts is generally inadmissible").

Plaintiffs' cited authorities do not undermine that ruling. *See* Apt. Br. 73–76. In particular, *Barile* and *Offill* allowed experts to testify about the factual landscape without applying those facts to the law.[52] Like in *Barile* and *Offill*, the Court allowed Dr. Amato to outline the factual landscape by "providing factual information to the Court" and "describing the details and timing of the warnings that Plaintiffs contend should

[52] *See United States v. Barile*, 286 F.3d 749, 761 (4th Cir. 2002) (expert could explain how 501(k) submissions were reasonable but could not draw the ultimate legal conclusion that the submissions contained materially misleading statements); *United States v. Offill*, 666 F.3d 168, 175 (4th Cir. 2011) (expert could explain federal securities registration requirements and the operation of Texas code provisions without offering an ultimate legal conclusion).

have been included." JA19374–19375. Dr. Amato was simply not allowed to draw the ultimate legal conclusion about preemption.

B. The District Court Did Not Abuse Its Discretion in Excluding a Non-Physician's Medical Opinions and Re-Diagnoses of Patients.

The District Court also correctly precluded Dr. Amato from opining that particular individuals referred to in adverse event reports, but never diagnosed with POTS or POI, actually ***did*** have those conditions. JA19375–19377. Dr. Amato is not a medical doctor; he has never diagnosed or treated anyone. JA05805–05807, Amato Dep., 90:4–92:11 Courts regularly stop non-physician experts from "implicitly provid[ing] [their] own causation opinion" by testifying to "causal association." *See, e.g.*, *Jones v. Novartis Pharms. Corp.*, 235 F. Supp. 3d 1244, 1257–58 (N.D. Ala. 2017), *aff'd*, 720 F. App'x 1006 (11th Cir. 2018).

Plaintiffs' claim that Dr. Amato did not re-diagnose patients is incorrect, and his effort to do so fails on grounds almost identical to an expert excluded in *Lipitor*, 892 F.3d at 632–38. Dr. Amato attributed symptoms of syncope and dysautonomia to POTS, and attributed symptoms of "irregular" "menstruation" to POI—all in real patients ***not diagnosed with POTS or POI***. JA09001–09003, JA09055, JA09057–

09058. Dr. Amato admitted that his work relied on symptoms he "just learned" "through reading," not "in medical school." JA05990–05993, JA06031, Amato Dep., 275:23–278:2, 316:7–23. This Court rejected a near-identical gambit in *Lipitor*, affirming exclusion of an expert, Dr. Jewell, who was "not a medical doctor" but sought to "second-guess . . . clinicians" as to which patients had diabetes and "replace the definition of diabetes used by the [clinicians] with one of his own." 892 F.3d at 636–38.

Plaintiffs cite *Lemons* and *Hill*, but those cases ***also*** prevented experts from opining on ***patient-level*** medical causation. Apt. Br. 77–78; *Lemons v. Novartis Pharms. Corp.*, 849 F. Supp. 2d 608, 615 (W.D.N.C., 2012); *Hill v. Novartis Pharms. Corp.*, No. 1:06-CV-00939, 2012 WL 5451809, at *2 (E.D. Cal. Nov. 7, 2012). And *Lemons* and *Hill* considered a witness who, unlike Dr. Amato, ***is*** a medical doctor.

III. The District Court Correctly Resolved Merck's Motion for Judgment on the Pleadings.

The District Court properly decided Merck's motion for partial judgment on the pleadings. Merck initially filed the motion as to two MDL plaintiffs, Bergin and America, whose claims were governed by North Carolina and New York law. JA02278, P.J.O.P. Mem.; Apt. Br. 79

n.57. After ruling, the District Court allowed all MDL plaintiffs to present "good cause" to "avoid the application" of the order to their cases; none claimed that different state law would have yielded a different result. JA02784.

All the District Court's rulings were correct. This Court, however, need reach only one issue: whether Plaintiffs' "direct warning" claims that Merck should have warned patients or their parents rather than physicians were properly dismissed. Every federal court to have interpreted the Vaccine Act has held it bars "direct warning" claims, and the learned intermediary doctrine does the same. JA02792–02793, P.J.O.P. Op.

Plaintiffs do not challenge the dismissal of their manufacturing-defect claims, and they say they do not bring any design-defect claims. Apt. Br. 79–81. The District Court properly dismissed the remaining claims based on Gardasil's ingredients and clinical trials as thinly veiled design-defect claims preempted by the Vaccine Act. Although Plaintiffs now contend those claims are based on a failure-to-***warn*** theory, they are ***separately preempted*** under *Knight* if that is true. For example, Gardasil's ***FDA-approved*** ingredients, and clinical trials conducted

pursuant to ***FDA-approved*** plans, cannot "reveal risks of a different type or greater severity or frequency than" those included in previous "***submissions to FDA***" and are therefore not "newly acquired information" allowing a new warning. 21 C.F.R. § 601.12(f)(2)(i), (6) (emphasis added). *Supra* Arg. I.

A. The Vaccine Act and the Learned Intermediary Doctrine Bar Plaintiffs' "Direct Warning" Claims.

1. The Vaccine Act Bars Claims for Failure to Warn Patients or Parents Directly.

Under the Vaccine Act, a plaintiff may pursue claims for failing to warn medical providers but ***not*** for failing to warn plaintiffs, their parents, or the public. *See* 42 U.S.C. § 300aa-22(c). This rule stems directly from the Act's text, which provides that "***[n]o vaccine manufacturer shall be liable*** in a civil action for damages arising from a vaccine-related injury . . . solely due to the manufacturer's ***failure to provide direct warnings*** to the injured party (or the injured party's legal representative)." *Id.* (emphasis added).

Every federal court interpreting the Act has held that it "eliminat[es] liability for not providing direct warnings to a claimant." *Holmes*, 697 F.3d at 1083; *see also, e.g.*, *Blackmon v. Am. Home Prods.*

Corp., 328 F. Supp. 2d 659, 666 (S.D. Tex. 2004) (similar).[53] That reading fits not just the Act's text, but also its purposes. Section 22(c) of the Act "codif[ies] the learned-intermediary doctrine," which eliminates the duty to warn patients directly. *See Abbot by Abbot v. Am. Cyanamid Co.*, 844 F.2d 1108, 1117 (4th Cir. 1988) (Wilkins, J., concurring). And the rule suits the Act's broader goals of providing "significant tort-liability protections." *Bruesewitz*, 562 U.S. at 229.

Plaintiffs argue that because they claim Merck failed to warn ***both*** them or their parents ***and*** their physicians, the Vaccine Act's bar on "direct warning" claims does not apply. Apt. Br. 81–82. Focusing on Section 22(c)'s use of the word "solely," Plaintiffs contend that they are "not 'solely'" relying upon statements to patients and parents, but also tacking on alleged misstatements to "doctors." Apt. Br. 82.

That is incorrect. As the District Court observed, "[p]ermitting a claim for failing to warn plaintiffs or their parents that is expressly

[53] Plaintiffs claim *Holmes* and *Colbath* support a contrary view, which is wrong. *Holmes* is quoted above, and *Colbath* allowed failure-to-warn claims only after clarifying that "Defendants ***do not have a duty*** to warn Plaintiff, his mother, or the public in general." *See Colbath v. Merck & Co., Inc.*, No. 3:21-CV-120, 2022 WL 935195, at *4 (S.D. Cal. Mar. 29, 2022) (emphasis added).

barred by the statute simply because they have similarly alleged that the vaccine manufacturer failed to adequately warn someone else—a critical exception found nowhere in the statute—would as a practical matter ***nullify the prohibition***." JA02793–02794 (emphasis added). Nor does the statute's text require that result. As the District Court explained, "the word 'solely' was included [in the Act] just to emphasize that despite the prohibition on 'direct warning' claims, a Plaintiff would still be able to assert a claim for failure to warn the medical providers." JA02794. "Simply put, the statute 'solely' (i.e. 'only') bars direct warning claims."[54] JA02794, P.J.O.P. Op.

2. The State-Law Learned Intermediary Doctrine Independently Bars the Claims.

State law also bars Plaintiffs' "direct warning" claims. JA02793, P.J.O.P. Op. Plaintiffs do not dispute that New York and North Carolina law govern, JA02459, JA02461, P.J.O.P. Opp'n, and both states recognize the learned intermediary doctrine, which holds that a drug

[54] Plaintiffs also misleadingly cite Section 23(d)(2) of the Vaccine Act to claim exceptions to the "direct warnings" bar that do not exist. Apt. Br. 83. Section 23(d)(2) contains a different tort-liability protection, namely that a "manufacturer shall not be held liable for punitive damages" except under certain conditions. 42 U.S.C. § 300aa-23(d)(2).

manufacturer's duty to warn is fulfilled by warning the prescribing physician, not the patient directly. JA02793 n.17, P.J.O.P. Op. (citing *Martin v. Hacker*, 83 N.Y.2d 1, 8–9, 628 N.E.2d 1308 (1993); N.C. Gen. Stat. § 99B-5(c)). Plaintiffs offer no authority to the contrary in these two states or any others.

3. Marketing Does Not Eliminate the Act's Protections or the Learned Intermediary Doctrine.

As a last resort, Plaintiffs argue that Merck lost these protections in the Vaccine Act and state law by marketing Gardasil publicly. Apt. Br. 82–83. Plaintiffs cite nothing in the Act's text, nor cases interpreting the learned intermediary doctrine, to support this argument, and district courts considering Gardasil claims have rejected it. *See, e.g.*, *Flores v. Merck & Co.*, No. 321CV00166MMDCLB, 2022 WL 798374, at *4 n.5 (D. Nev. Mar. 16, 2022). Plaintiffs instead cite cases unrelated to vaccines, many of which also involve a specific legal duty to speak affirmatively, which Plaintiffs do not allege here. *See* Apt. Br. 82–83.

B. Plaintiffs' Fraud Claims Are Also "Direct Warning" Claims, and Were Inadequately Pleaded.

The District Court also correctly dismissed "direct warning" fraud claims based on vaguely alleged statements to patients and parents.

Plaintiffs do not even challenge the dismissal of their other category of fraud claims—concerning unnamed members of "the medical community"—which they conceded below were inadequately pleaded. JA02797–02798, P.J.O.P. Op.

First, for reasons already noted, the District Court correctly dismissed Plaintiffs' fraud claims "alleg[ing] a fraudulent failure to adequately warn Plaintiffs, their parents and the public"—namely, that "the Vaccine Act's prohibition on 'direct warning' claims" bars them. JA02798; *see* Arg. III.A, *supra*.

Second, even if Plaintiffs' fraud claims were not barred by the Vaccine Act (though they are), they fail to satisfy Rule 9(b), which "requires a party to, at a minimum, describe the time, place, and contents of the false representations." *Bakery & Confectionary Union & Indus. Int'l Pension Fund v. Just Born II, Inc.*, 888 F.3d 696, 705 (4th Cir. 2018) (cleaned up). For example, Plaintiffs America and Bergin declare Merck's advertising "ubiquitous," but provide no specific fraudulent statements beyond that Gardasil was "safe" and "effective." JA02692, JA02693, America Compl.; JA02587, JA02590, Bergin Compl. "Merely stating there were 'themes' of safety and reliability over a period of years" does

not satisfy Rule 9(b). *Belville v. Ford Motor Co.*, 13 F. Supp. 3d 528, 544 (S.D.W. Va. 2014).

C. The District Court Correctly Held Plaintiffs' Thinly Veiled Design-Defect Claims Preempted.

The District Court also correctly dismissed Plaintiffs' design-defect claims—specifically, claims concerning Gardasil's ingredients, development, and overall safety—as preempted by the Vaccine Act. JA02789–02792. Plaintiffs claim they do not bring design-defect claims, and for good reason: "design-defect claims" against FDA-approved vaccines subject to the Vaccine Act are "pre-empted." *Bruesewitz*, 562 U.S. at 232; 42 U.S.C. § 300aa-22(b)(1).

Nevertheless, the District Court concluded that "Plaintiffs have asserted a number of preempted 'design defect' claims within their 'negligence' and 'manufacturing defect' causes of action." JA02790. Those claims expressly challenge "the safety of ***the ingredients***." *See* JA02841, Mar. 11, 2024 P.J.O.P. Hearing Tr. (emphasis added). Plaintiffs likewise attack intended and known constituents of Gardasil, such as "yeast," "sodium borate," "polysorbate 80," and its aluminum adjuvant—all of

which appear in FDA-approved labeling.[55] JA02790, P.J.O.P. Op. As the District Court observed, "Plaintiffs are simply complaining about how Gardasil is designed." JA02790.

The District Court also dismissed Plaintiffs' claims targeted to the ***totality*** of the vaccine's design, including its overall safety and efficacy, which Plaintiffs do not challenge here. JA02791–02792. And the District Court explained that an allegation of "inadequate testing" via clinical trials to ***reach*** the final design is barred.[56] JA02791. That stands to reason: allowing attacks on vaccine development and pre-approval clinical trials would evade *Bruesewitz*'s holding that manufacturers cannot be "held liable for failure to use a different design." 562 U.S. at 232, 238; JA02791.

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[55] Plaintiffs similarly attack "HPV LI-DNA fragments[]" in Gardasil as "potentially hazardous." *E.g.*, JA02636, America Compl. But the FDA long ago debunked Plaintiffs' claim that this constituent is unexpected or "hazardous." *See* JA02790, P.J.O.P. Op.

[56] As the Court further explained, alleged inadequate testing is not an "independent wrong," but rather something that "allegedly leads to a failure to include the best/safest ingredients." JA02791. Plaintiffs fail to rebut that sound reasoning, and the cases they cite, many of which concern safety testing on ***machines*** or medical ***devices***, rather than ingredients of ***vaccines***, are inapposite. Apt. Br. 80–81.

Plaintiffs argue that allegations targeting ingredients and clinical trials do not attack Gardasil's design, and instead relate to failure-to-warn theories. Apt. Br. 79. That is simply an attempt to escape the Act's rule that a vaccine's "design itself is ***not open to question***." *Bruesewitz*, 562 U.S. at 232, 237–38 (emphasis added). Further, despite attempting to recast their ***design*** claims as ***warning*** claims, Plaintiffs do not—and cannot—explain how these warning claims pass *Knight*'s preemption test. Arg. I, *supra*.

Plaintiffs also misread a footnote in *Bruesewitz* to suggest "negligence, failure to warn and fraud" claims are not preempted. Apt. Br. 79 (citing *Bruesewitz*, 562 U.S. at 229 n.25). That is mistaken. The footnote described ***showings*** a plaintiff must make to ***rebut the Act's separate presumptions*** that vaccines are "accompanied by proper directions and warnings" and that vaccine manufacturers "shall not be held liable for punitive damages." *See* 42 U.S.C. §§ 300aa-22(b)(2), 23(d)(2). Neither *Bruesewitz* nor the Act say negligence or fraud ***claims*** avoid preemption.

Multiple federal courts have rejected other Gardasil plaintiffs' similar efforts to camouflage preempted claims. *Stratton v. Merck & Co.*,

No. CV 2:21-02211, 2021 WL 5416705, at *2 (D.S.C. Nov. 17, 2021); *Colbath*, 2022 WL 935195, at *5; *Flores*, 2022 WL 798374, at *3. The District Court correctly followed suit.

D. Plaintiffs Fail to Show that the District Court Improperly Granted Partial Judgment on the Pleadings.

Plaintiffs offer a one-sentence argument that the District Court should not have granted judgment "as to something less than an entire claim." Apt. Br. 79. That is irrelevant: this Court "can affirm on any basis fairly supported by the record," so this procedural point is immaterial. *Eisenberg v. Wachovia Bank, N.A.*, 301 F.3d 220, 222 (4th Cir. 2002).

Further, Plaintiffs are incorrect. The District Court resolved "claims," not parts of them, and explained that Plaintiffs took pains to "assert[] a number of preempted 'design defect' ***claims*** within their 'negligence' and 'manufacturing defect' causes of action." JA02790. (emphasis added). Courts often "look beyond [the party's] characterization" of a claim and focus on "the conduct on which the claim is based" and its "gravamen." *Sheppard v. United States*, 537 F. Supp. 2d 785, 787–88 (D. Md. 2008).

Plaintiffs' argument also conflicts with *Independence News, Inc. v. City of Charlotte,* where this Court affirmed an order granting ***partial*** judgment on the pleadings, which adjudicated ***one theory of liability*** within a count. 568 F.3d 148, 153 (4th Cir. 2009). There, the plaintiffs pleaded a single count alleging a variety of First Amendment violations,[57] the defendants received judgment as to a particular as-applied theory, and this Court affirmed the "partial" ruling.[58] *Id.* at 157; *see also, e.g.*, *Pantastico v. Dep't of Ed.*, 406 F. Supp. 3d 865, 880 (D. Haw. 2019). Plaintiffs' authorities, by contrast, concern dismissal of elements or parts of a single claim, not any ***complete theory of liability***, and not an attempt to smuggle one type of claim into the case using another. *See BBL, Inc. v. City of Angola*, 809 F.3d 317, 323, 325 (7th Cir. 2015).

CONCLUSION

Merck requests that the Court affirm the decisions below.

[57] Am. Compl., ECF 35 at 12–14, No. 3:02-cv-00014 (Nov. 6, 2003).

[58] Apt. Br. in Supp. of Mot. for Partial Judgment on the Pleadings, ECF 41 at 9–11, No. 3:02-cv-00014 (Apr. 8, 2004); Order, ECF 45 at 3, No. 3:02-cv-00014 (June 3, 2004).

REQUEST FOR ORAL ARGUMENT

Merck defers to the Court's judgment on whether oral argument would aid the decision-making process.

This 27th day of August, 2025.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation set forth by this Court's Order (Doc. No. 37) because this brief contains 17,895 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface, using Microsoft Word 2016, in 14-point Century Schoolbook type.

This 27th day of August, 2025.

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