UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:	:	
	:	17-MD-2767 (PAE)
MIRENA IUS LEVONORGESTREL-RELATED PRODUCTS LIABILITY LITIGATION (NO. II)	:	17-MC-2767 (PAE)
	:	OPINION & ORDER
This Document Relates to All Actions	:	

PAUL A. ENGELMAYER, District Judge:

This multi-district litigation involves products liability claims regarding a contraceptive product: the Mirena intrauterine device developed, manufactured, and distributed by defendants Bayer HealthCare Pharmaceuticals, Inc., Bayer Pharma AG, and Bayer Oy (together, "Bayer"). The Mirena IUD functions by releasing a synthetic steroid hormone known as levonorgestrel ("LNG"). Plaintiffs claim that the hormonal component of Mirena caused them to suffer from a disease known as idiopathic intracranial hypertension ("IIH"), also known as pseudotumor cerebri ("PTC"). IIH is an uncommon disease marked by increased cerebrospinal fluid ("CSF") pressure in the skull. If untreated, IIH can cause headaches and vision problems, including, in extreme cases, blindness.

Currently before the Court are motions by each side, pursuant to *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), to exclude the other's expert testimony with respect to the issue of general causation—that is, whether Mirena's release of its hormonal component, LNG, is capable of causing IIH. In overseeing this MDL, this Court, heeding the guidance of the United States Judicial Panel on Multi-District Litigation ("JPML"), prioritized discovery and *Daubert* motions and briefing with respect to this issue.

Plaintiffs have put forward seven expert witnesses on general causation. Each opines that use of Mirena can cause IIH. These are: two obstetrician-gynecologists ("OB/GYNs"), an

ophthalmologist, a neuroscientist, a pediatric neurologist, an epidemiologist, and a pharmacologist-toxicologist. In response, Bayer has put forward 12 expert witnesses. Each opines that the available scientific evidence does not reliably permit the conclusion that using Mirena can cause IIH. These are: three epidemiologists, a pharmaco-kineticist, five neuro-ophthalmologists, and three OB/GYNs.

Each of these 19 expert witnesses submitted an expert report, was deposed, and was the subject of separate *Daubert* briefing. On April 10–11, 2018, the Court held a *Daubert* hearing and heard argument as to the admissibility of each expert's testimony as to general causation.

For the reasons that follow, the Court grants Bayer's motions under *Daubert* to preclude the testimony of plaintiffs' general causation experts. In light of the possible implications of this ruling for this litigation, the Court denies as potentially moot plaintiffs' motions to preclude the testimony of Bayer's general causation experts. This ruling is without prejudice to plaintiffs' right to renew their motions to preclude Bayer's general causation experts should the litigation proceed past summary judgment.

I. Procedural Background

A. Brief History of This Litigation

1. The JPML's Centralization of Mirena IIH Cases Before This Court

On April 6, 2017, the JPML centralized in this District pretrial proceedings in the 113 cases then pending across 17 districts nationwide in which plaintiffs had alleged IIH injuries caused by the hormonal component of the Mirena IUD. Most of the Mirena/IIH cases were at a relatively early stage of discovery or at the pleading stage, although fact and expert discovery had closed in the 10 longest pending actions. *See generally* Dkt. 1, at 2–3 (JPML transfer order).

The JPML had previously, in July 2014, denied a motion to centralize the Mirena/IIH actions, at a time when nine such actions, spanning six districts, were pending. Explaining its

2017 decision to centralize the pending cases, the JPML emphasized several factors that made centralized proceedings more efficient. Two are relevant here.

First, the JPML noted the heightened difficulty coordinating discovery and other pretrial proceedings given the increased number and dispersal of pending actions and of participating law firms. *Id.* at 2. "The record," the JPML stated, "demonstrates that centralization is necessary to facilitate the efficient conduct of common discovery." *Id.* at 3.

Second, the JPML noted, general causation had emerged as an important issue common to all proceedings. "[T]he records in the many actions filed since [2014] demonstrate that discovery and pretrial motions concerning the issue of general causation have been, or will be, at the center of all actions—that is, whether the hormonal component in Mirena is capable of causing intracranial hypertension." Dkt. 1, at 3; *see also id.* at 4 ("Issues concerning general causation [and] the background science . . . will be common to all actions.").[1]

2. Organization of This MDL

In overseeing this action, this Court has given priority to the matters that led the JPML to centralize the Mirena/IIH actions.

Specifically, on June 21, 2017, after appointing plaintiffs' leadership team and reviewing written submissions and eliciting input at an initial conference as to the proper sequencing of proceedings, *see generally* Dkt. 51 (transcript of June 13, 2017 hearing), the Court issued an

[1] Although the JPML had earlier expressed concern that plaintiff-specific causation issues might predominate, the JPML, in its 2017 centralization order, concluded that these issues were not an obstacle to centralization. "Once discovery and other pretrial proceedings related to the common issues have been completed," the JMPL explained, "the transferee judge may suggest Section 1407 remand of actions to their transferor courts for more individual discovery and trial, if necessary." *Id.* at 3. That a handful of actions were in "an advanced procedural posture" also did not disfavor transfer, the JPML reasoned, because the transferee judge "possesses broad discretion to formulate a pretrial program that accounts for any significant differences among the actions and ensures that duplicative activity is minimized or eliminated." *Id.*

order stating that priority would be given to: (1) "the process of providing common fact discovery to plaintiff from Bayer," and (2) "resolving whether plaintiffs have admissible evidence sufficient to establish general causation" by Mirena of IIH. Dkt. 40, at 1 (June 21, 2017). The Court has done so as follows.

Outgoing discovery from Bayer: On July 27, 2017, after receiving submissions delineating the 14 discovery disputes identified by the parties and inquiring about them at a hearing, the Court resolved these disputes in a series of bench rulings. *See generally* Dkt. 51, at 10–59 (transcript of July 27, 2017 hearing). The Court ordered that Bayer broadly produce written discovery on all common issues, including electronic records from more than 50 Bayer custodians, and including broad production from Bayer's adverse-events database. Both as to custodians and as to search parameters, the common discovery ordered from Bayer extended well beyond the parameters theretofore utilized in the individual cases comprising the MDL. It also substantially exceeded the discovery that Bayer had produced in an immediately prior MDL also relating to the Mirena IUD. *See* MDL No. 2434 (the "Perforation MDL"). In that case, overseen by the Hon. Cathy Seibel of this District, the plaintiffs had alleged different injuries: that the hormone-release feature of Mirena had caused the IUD to migrate within the uterus after its insertion, leading to uterine perforation and related migration injuries.

General causation: The Court directed that the issue of general causation be litigated in the MDL as a threshold issue. To facilitate that issue's prompt resolution, the Court ordered that all fact discovery relating to general causation—including all document and deposition discovery—be completed by December 8, 2017.[2] Dkt. 62. Alerted by counsel that each side

[2] In contrast, as to common discovery on other topics (*e.g.*, Mirena's labeling), the Court ordered that written discovery be produced by January 31, 2018. *See* Dkt. 62, at 2. The Court directed

expected to make *Daubert* challenges to the admissibility of each other's experts on general causation,[3] the Court set deadlines spanning late December 2017 through late March 2018 for the submission of all expert reports on general causation, depositions of general causation experts, and reciprocal *Daubert* briefing. The Court set for the week of April 9, 2018 a "Science Day" tutorial for the Court on the background scientific issues in the case, followed by a *Daubert* hearing as to expert testimony on general causation. *Id.*

In prioritizing general causation, the Court was informed by, in addition to the guidance of the JPML, the representations of counsel in this case that the issue of general causation would be common and identical to all potential Mirena/IIH plaintiffs so as make it an appropriate issue for this transferee court to resolve at the threshold. *See, e.g.*, Dkt. 51, at 29. The Court was also informed by the experience of the Perforation MDL. There, Judge Seibel held that plaintiffs' proposed expert testimony as to the general causation proposition at issue—that the Mirena IUD's release of the hormone LNG was capable of causing the Mirena IUD to migrate after insertion and cause uterine perforation—was not reliable under *Daubert*. *See In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 427–461 (S.D.N.Y. 2016) ("*Mirena Perforation / Daubert*"). Based on that ruling, Judge Seibel thereafter granted summary judgment for Bayer on all claims, holding that, without any admissible expert testimony, the remaining evidence was

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that any depositions on these other topics would be scheduled, if necessary, after the Court's resolution of the *Daubert* motions with respect to general causation experts. *Id.*

[3] In several Oklahoma cases consolidated into the MDL, a transferor court had resolved a pretrial *Daubert* challenge by Bayer to the plaintiff's expert on the issue of general causation, and denied this challenge in a brief summary order. These cases had not reached trial; Bayer had noted its intent to appeal the adverse *Daubert* ruling; and that ruling had effectively been overtaken by the unexpected death of plaintiffs' proposed general causation witness, Dr. John Maggio. Counsel in the MDL agreed that these cases would be governed by this Court's resolution of the *Daubert* issue. *See, e.g.*, Dkt. 51, at 27–28.

insufficient to establish general causation. *See In re Mirena IUD Products Liability Litigation*, 202 F. Supp. 3d 304, 310–28 (S.D.N.Y. 2016) ("*Mirena Perforation / SJ*", *aff'd*, 713 Fed. Appx. 11 (2d Cir. 2017). The possibility of a similar outcome here, this Court determined, counseled deferring other time- and cost-intensive phases of this litigation pending resolution of the anticipated *Daubert* motions.

For that reason, the Court deferred almost all plaintiff-side discovery until after the anticipated *Daubert* motions were resolved. The MDL currently encompasses more than 850 plaintiffs, a result of the fact that, since creation of this MDL, nearly 750 plaintiffs have filed new lawsuits that have been received into it. The Court required only that each existing or new plaintiff file a detailed fact sheet (*e.g.*, as to her Mirena usage, medical history, and symptoms). *See* Dkt. 62; *see also* Dkt. 78 (August 30, 2017) (order approving plaintiff fact sheet). The requirement of filing such fact sheets was intended to enable the litigation to move forward expeditiously in the event that admissible evidence sufficient to establish general causation were to be found, including by expediting selection of plaintiffs for individualized discovery in anticipation of bellwether trials.

B. The Expert Witnesses at Issue

The seven expert witnesses whom plaintiffs propose to call as to general causation are: (1) Dr. Lemuel A. Moyé, an epidemiologist; (2) Dr. Laura M. Plunkett, a pharmacologist and toxicologist; (3) Dr. James M. Wheeler, an OB/GYN; (4) Dr. Frederick W. Fraunfelder, an ophthalmologist; (5) Dr. Philip Darney, an OB/GYN; (6) Dr. Conrad E. Johanson, a neuroscientist; and (7) Dr. Vincent Salpietro, a pediatric neurologist.

The 12 expert witnesses whom Bayer would call are: (1) Dr. Robert Langer, an epidemiologist; (2) Dr. Kurt T. Barnhardt, an epidemiologist; (3) Dr. Todd A. Lee, an epidemiologist; (4) Dr. William Jusko, a pharmaco-kineticist; (5)–(9) Drs. Nancy J. Newman,

Gregory Van Stavern, Joseph F. Rizzo, Dean M. Cestari, and Marc J. Dinkin, each a neuro-opthalmologist; and (10)–(12) Drs. Vanessa Dalton, Geri D. Hewitt, and Dana R. Gossett, each an OB/GYN.

Each expert has authored a report, was deposed, and was the subject of individualized *Daubert* briefing and oral argument.[4]

II. Factual Background

This section sets out background relevant to all *Daubert* motions. It addresses: (1) the Mirena product; (2) Mirena's hormonal component, the progestin LNG; (3) the disease IIH and its history and characteristics; and (4) the state of scientific research, prior to the instant *Daubert* proceedings, regarding both the causes of IIH in general and, more specifically, as to whether contraceptives (including Mirena) that use LNG as a hormonal component can cause IIH.[5]

A. Mirena

Mirena is a commonly used type of long-acting reversible contraceptive ("LARC"). There are several different types. Some LARCs are copper intrauterine devices ("IUDs").[6] Others are subdermal, hormone-releasing implants. Others, of which Mirena is by far the most

[4] For each expert, the Court cites here to the expert's report using the format "[Expert Name] Rpt."; to the expert's deposition using the format "[Expert Name] Dep."; and to the parties' briefs as to that expert using the format "[Pl. or Bayer] [Expert Name] [Br. or Opp. Br.]." The parties each submitted an omnibus brief in support of their motions to preclude, which were each followed by an opposition brief and a reply. The Court cites to these using the format "[Pl. or Bayer] Omnibus [Br., Opp., or Rep. Br.]." Citations to "[] Tr. []" are to argument before the Court on the date indicated. Deposition testimony of fact witnesses is cited using the same convention, with testimony given pursuant to Fed. R. Civ. P. 30(b)(6) identified as such.

[5] To the extent that the ensuing background discussion cites to facts contained in reports by experts who are subject to *Daubert* motions, the Court does so solely as to background factual propositions that the Court understands not to be meaningfully disputed.

[6] Some scholarly literature and expert reports cited here alternatively refer to IUDs as IUSs (intra-uterine systems). For consistency, the Court uses the term IUD.

predominant, are hormone-releasing IUDs. Of these types of LARCs, hormone-releasing implants are generally considered the most effective at preventing conception, followed by hormone-releasing IUDs, followed by copper IUDs. Statistically, all LARCs are far more effective in preventing conception than traditional contraceptive methods such as the Pill or the male condom.

Mirena is made of a T-shaped polyethylene frame with a silicon-based steroid reservoir around the vertical stem. It is inserted into the uterus vaginally. *See* Mirena Prescribing Information and Label § 11.1 (Dkt. 135-6) ("Mirena Label"). In the uterus, Mirena releases the synthetic steroid hormone LNG, a progestin, at an initial rate of 20 µg LNG/day, decreasing over its five-year life-span. *See* Mirena Label §§ 2, 11, 12.3.

The FDA approved Mirena on December 6, 2000, following studies for safety and efficacy in two large clinical trials in Finland and Sweden. It is currently approved in the United States for up to five years of use. *See id.* §§ 14.1–14.2. As of May 2017, an estimated 45.5 million Mirenas had been inserted worldwide amounting to close to 142 million woman-years of use since its introduction. *See* Bayer Response to Questions from German Federal Institute for Drugs and Medical Devices ("BfArM") (Oct. 2017) (Dkt. 167-71) ("Bayer BfArM Response"), at 44–45.

In contrast to combined oral contraceptives, which contain both progestin and estrogen and whose effectiveness among obese women has been questioned, Mirena is believed to be effective regardless of the user's weight. Also commending its use among obese women, studies indicate that Mirena does not increase the risk of weight loss and blood clots and does not expose the user to potential risks associated with estrogen-containing contraceptives. *See, e.g.*, Alison Edelman & Bliss Kaneshiro, *Contraception counseling for obese women*, UptoDate.com (Jan.

25, 2017) at 2 (Dkt. 167-26) ("Edelman & Kaneshiro") (terming efficacy of oral contraceptives "suboptimal" for obese women; reasons hypothesized include "that the inherent effectiveness of oral contraceptives may be diminished in obese women because obesity increases metabolic rate, increases clearance of hepatically metabolized drugs, increases circulating blood volume, and increases absorption of contraceptive steroids by adipose tissue"); *id.* ("[T]he pharmacokinetics of steroid hormones appear to be altered in obese oral contraceptives users compared with normal weight users."); Mary L. Marnach, et al., *Current issues in contraception*, 88 Mayo Clin Proc. 295, 297 (2013) (Dkt. 167-43) ("Progestogen-only and non-hormonal contraceptives are preferred methods of contraception for women who are obese."); *see generally* Centers for Disease Control and Prevention, *US medical eligibility criteria for contraceptive use, 2016*, Morbidity and Mortality Weekly Report (July 29, 2016) (Dkt. 167-77); Darney Dep. at 99–100.

As a result, Mirena is widely believed to be preferentially, *i.e.*, disproportionately, prescribed to overweight and obese women. One recent study found that 63% of Mirena users were overweight or obese, compared to 48% of the general population of reproductive-age women. *See* Bayer Omnibus Br. at 3 (collecting studies); *see also* Edelman & Kaneshiro, *supra*, at 3 (terming such IUDs "the best contraceptive option for obese women who have no contraindications to use of this method" and stating that [LNG] implants "appear to be highly effective in overweight and obese women"); *id.* at 6 (recommending such IUDs for this population); Cestari Rpt. at 14 ("According to evidence-based guidelines, Mirena is a preferred contraceptive for obese women."); Wheeler Rpt. at 12 ("[O]ral contraceptives are less effective in obese women."); Wheeler Dep. at 90 ("[H]ormonal IUDs are preferentially prescribed to obese women.").

B. Levonorgestrel

LNG, the hormone Mirena releases, is a synthetic progestin compound derived from testosterone. It has "been used as an active ingredient in contraceptives since the 1980's." Plunkett Rpt. at 9.

LNG mimics the effects of the naturally occurring sex hormone progesterone, which is involved in pregnancy and menstruation. LNG is widely used in gynecology, including in hormonal replacement therapy. Its primary use is in numerous contraceptives. These include (1) LNG-releasing intrauterine devices such as Mirena; (2) LNG-releasing subdermal implants such as Norplant, which from 1991 to 2002 was marketed in the United States, and Jadelle, which is currently marketed in Europe; (3) in the single-dose hormone contraceptive known as Plan B; and (4) as the progestin component of numerous combined oral contraceptives (which usually include both LNG and an estrogen compound). *Id*. at 8–9.

The exact mechanism by which LNG prevents pregnancy is unknown. *See* Mirena Label § 12.1 ("The local mechanism by which continuously released LNG enhances contraceptive effectiveness of Mirena has not been conclusively demonstrated."). However, it is generally understood that LNG, and Mirena by extension, inhibits contraception by bringing about various systemic effects, including blocking ovulation, thickening cervical mucous (decreasing sperm penetration), and altering the endometrium, the lining of the uterus (impairing the implantation of fertilized eggs). *See id.* ("Studies of Mirena and similar LNG IU[D] prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium."); *see also* Plunkett Rpt. at 9–10.

The Court notes here two chemical characteristics of LNG relevant to the pending motions. These characteristics are germane to the analyses of the plaintiff experts, who theorize scientific mechanism(s) by which Mirena can cause IIH.

First, as noted, LNG is a progestin. It is not an androgen, a male sex hormone like testosterone. However, progestins can have androgenic effects. LNG, for example, is known to have a low but substantial affinity to bond with androgen receptors and to cause systemic androgenic side effects, such as acne. *See* Philip D. Darney, *The Androgenicity of Progestins*, 98 Am. J. Med. (1995) at 1A-105S (Dkt. 199-8); Christina Björklun, *Expert report on the toxico-pharmacological documentation to the application for drug marketing approval of Mirena* (2003), at 8 (Dkt. 199-9) ("Björklun") ("LNG is not a pure progesterone agonist. It has a low, but substantial affinity to the androgen receptor and the mineralocorticoid receptor, and to some transport proteins."); Hofmann 30(b)(6) Dep. at 167–68. Androgen receptors are found in the choroid plexus ("CP"), the area of the brain that produces cerebrospinal fluid ("CSF"). As discussed below, IIH arises from the excessive buildup of CSF.

Second, LNG is known to bond with mineralocorticoid receptors ("MRs"). *See* Björklun, *supra*, at 8. It is a point of dispute in this litigation whether LNG is an MR agonist (meaning it binds to a receptor and activates it) or antagonist (meaning it binds to a receptor and blocks it). MRs are also found in the choroid plexus. *See* Brian E. McGeeney & Deborah I. Friedman, *Pseudotumor Cerebri Pathophysiology*, 54 Headache 445, 452 (2014) (Dkt. 196-14) ("McGeeney & Friedman").

C. Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension, or IIH, "is the clinical syndrome of raised intracranial pressure, in the absence of space-occupying lesions or vascular lesions, without enlargement of the cerebral ventricles, for which no causative factor can be identified." Alex K.

Ball & Carl E. Clarke, *Idiopathic intracranial hypertension*, 5 Lancet Neurology 433, 433 (2006) (Dkt. 167-17) ("Ball & Clark"); *see also* McGeeney & Friedman, *supra*, at 445. IIH is alternatively referred to in the scientific literature as "pseudotumor cerebri syndrome" ("PTC" or "PTCS"). *See, e.g.*, Deborah Friedman, et al., *Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children*, 81 Neurology 1159 (2013); Fraunfelder Rpt. at 7.

By whichever name, these terms connote a syndrome marked by heightened intracranial pressure that derives not from a tumor or other lesion but from the excessive buildup of cerebral spinal fluid, or CSF. Because the parties have most often used the term IIH in this litigation, and because the term "idiopathic" usefully captures the heretofore scientifically indeterminate causes of the applications of the syndrome at issue here, the Court will use the term IIH in this decision, save when directly quoting sources that use other terms.[7]

Although the immediate cause of IIH is the excessive buildup of CSF, IIH's pathogenesis—the biological mechanism that brings it about—is poorly understood. *See* McGeeney & Friedman, *supra*, at 445 ("[C]erebrospinal fluid dynamics and homeostatis in PTCS are complex and incompletely understood."); Ball & Clark, *supra*, at 435 ("The pathophysiology underlying the raised intracranial pressure is unclear."); Cestari Rpt. at 9 (canvassing alternative theories and noting that "[t]he mechanism by which excess weight and weight gain increase the risk for IIH is [also] poorly understood"); *see also* Bayer Omnibus Br. at 2 n.1 (quoting scholarly literature sources cited by plaintiffs' experts to the effect, *inter alia*,

[7] Some literature uses a third term, "intracranial hypertension" ("IH"), interchangeably with IIH and PTC and PTCS, although this term is often used to encompass *all* instances of increased CSF or intracranial pressure, including those caused by lesions such as tumors. Some literature uses a fourth term, "benign intercranial hypertension" ("BI"). This early term for IIH fell out of favor after it became clear that severe cases of IIH carry extremely serious consequences. *See* Cestari Rpt. at 8 ("IIH is no longer considered benign."); Fraunfelder Rpt. at 7; Moyé Rpt. at 25–26.

that IIH's pathogenesis "is currently unknown," that its "pathogenesis remains a mystery," that its "underlying pathogenesis is uncertain," and that "IIH is a disorder of unclear pathophysiology") (citations omitted).

Some scientists have theorized that IIH is caused by an increase in the production of CSF. *See* Johanson Rpt. at 8–9. Others have theorized that IIH is caused by impaired CSF absorption; this latter theory appears to have a greater number of proponents. *See* Vincenzo Salpietro, et al., *Recent insights on pediatric pseudotumor cerebri syndrome pathophysiology: From the "Unifying neuroendocrine perspective" to the "Integrated bioenergetic-hormonal mechanism*," 13 J. Pediatric Neurology 11, 12 (2015) (Dkt. 167-57) (noting that "the paraphysiology of [PTCS] is still poorly understood," but describing "hampered outflow of CSF into the venous system" as "a more generally accepted hypothesis" of the cause of IIH); McGeeney & Friedman, *supra*, at 447 (reviewing competing theories, and noting that "[m]ost of the focus in PTCS has been on resistance to CSF absorption"); Ball & Clark, *supra*, at 435 (observing that the "more popular hypothesis is that [IIH] is a syndrome of reduced CSF absorption").

Symptoms of IIH vary dramatically. The most common is a headache, which occurs in almost all (92–94% of) cases. Many patients (64–87%) also experience a whooshing sound in their ears called pulsatile tinnitus. Other symptoms include papilledema, photophobia, phonophobia, nausea, transient visual obscurations, binocular diplopia, and blurred vision. Papilledema, the swelling of the optic nerves due to intracranial pressure, is sometimes called the hallmark symptom of IIH. However, a patient can still be diagnosed with IIH without this symptom, and these symptoms can result from other causes. A papilledema is detected with an ophthalmoscopic or funduscopic examination. Most patients show a degree of visual loss. And, in extreme cases, if untreated, papilledema can cause serious vision loss and even blindness. *See*

Ball & Clark, *supra*, at 433, 436–438; Vincent Giuseffi, et al., *Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): A case-control study*, 41 Neurology 239, 239–41 (1991) (Dkt. 167-33) ("Giuseffi"); Cestari Rpt. at 4–7; Darney Rpt. at 21; Fraunfelder Rpt. at 4; Moyé Rpt. at 26; Plunkett Rpt. at 24; Salpietro Rpt. at 12–13.

Ultimately, IIH is a diagnosis of exclusion. While doctors use two largely overlapping sets of diagnostic criteria—the "modified Dandy criteria" and the "Friedman criteria"—in their diagnoses, IIH is ultimately diagnosed by excluding alternative causes of these symptoms. Fraunfelder Rpt. at 4. Papilledema, for example, can also be caused by brain tumors, meningitis, or intracranial thrombosis, *id.*, and headaches can arise from numerous causes. To exclude alternative causes of IIH, doctors use a combination of neural imaging, neurologic examination, and a spinal tap or lumbar puncture, which directly measures CSF pressure. *See* Bayer BfArM Resp. at 9–11; Cestari Rpt. at 2–3; Fraunfelder Rpt. at 4; Moyé Rpt. at 25–27.

IIH is an extremely rare disease. It occurs with a frequency of about one case per year out of a population of 100,000. *See, e.g.*, Giuseffi, *supra*, at 239; Ball & Clark, *supra*, at 433 (canvassing studies reporting incidences of IIH of between 0.03 per 100,000 and 2.2 per 100,000); Cestari Rpt. at 3 (0.9 cases per 100,000 population); Fraunfelder Rpt. at 5. As reviewed *infra*, IIH differentially affects certain demographic groups. Relevant here, IIH occurs by far most commonly—and its incidence is far greater—among women of child-bearing age, and in particular among overweight and obese such women.

IIH is treated in a variety of ways. It is typically recommended that overweight patients with IIH lose weight; medications are often prescribed to assist weight loss. Doctors also often prescribe acetazolamide, a diuretic, to prevent CSF production. Lumbar punctures, which are used to diagnose IIH, can also be used to drain excess CSF. Optic nerve sheath fenestration—the

"cutting into the sheath, or covering, of the optic nerve"—"may [also] be used to decrease pressure on the optic disc, thereby preserving vision." Fraunfelder Rpt. at 7. Finally, shunts can be placed in the brain or lumbar spine to drain excess CSF into the abdominal cavity. *See* Ball & Clark, *supra*, at 439–40; Cestari Rpt. at 7–8; Moyé Rpt at 28.

D. Incidence of, and Risk Factors for IIH

Symptoms consistent with intracranial hypertension were first observed centuries ago by Eskimos, who came to associate these symptoms with excess ingestion of polar bear liver. John Chen & Michael Wall, *Epidemiology and risk factors for idiopathic intracranial hypertension*, 54 Int'l Ophthalmology Clinics 1, 6 (2014) (Dkt. 196-10) ("Chen & Wall").[8] More recently, however, the cause or causes of the elevated CSF pressure in the skull that marks IIH have proven elusive to scientists. Their inquiries have been complicated by factors including the rarity of the condition and, as discussed *infra*, the practical inability to study causation using randomized, prospective trials involving control groups.

Scientists have, however, identified a number of risk factors associated with IIH. These include: (1) being a woman of child-bearing age; (2) being overweight, obese, or having experienced recent weight gain; (3) using certain drugs, such as vitamin A and retinoids; and (4) experiencing endocrine disturbances caused by diseases such as Addison's Disease and steroid withdrawal. *See generally* Ball & Clark, *supra*, at 434–35; Chen & Wall, *supra*, at 5–6; Giuseffi, *supra*, at 239–40; McGeeney & Friedman, *supra*, at 450–53; *see also* Fraunfelder Rpt. at 5; Moyé Rpt. at 27–28; Salpietro Rpt. at 12–13.

[8] Intracranial hypertension "has been known for centuries by the Eskimo (Inuit) who hunt polar bears for fur and meat but avoid eating the liver for fear of the headaches and blurred vision that result from its ingestion. Polar bears have high hepatic vitamin A levels because they are at the top of the Arctic food chain, and therefore ingestion of the liver was likely inducing intracranial hypertension." *Id.*

The first two risk factors are particularly common, as IIH "predominantly affects obese women of childbearing age." Cestari Rpt. at 2; *see also* Fraunfelder Rpt. at 5.

More than 90% of patients afflicted with IIH are women, *see* Chen & Wall, *supra*, at 5. And the incidence of IIH among women of child-bearing age is approximately 3.3 to 3.5 cases per 100,000, more than three times that of the population as a whole. *Id.* at 1; Cestari Rpt. at 3.

IIH's incidence among obese women, meanwhile, has been calculated as close to 20 times that of women of normal weight; and its incidence among overweight women has been calculated as some 6.5 times that of women of normal weight. Calculations on this point vary among the scientific literature, but in general, researchers describe IIH's incidence among obese women as between approximately 15 and 22 cases per 100,000 population, and as particularly affecting women who have recently gained weight. This literature also describes IIH's incidence as rising over time in the United States as the nation's population has become more obese. *See, e.g.*, Anthony B. Daniels, et al., *Profiles of obesity, weight gain and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri)*, 143 Am. J. Ophthalmology 635, 637 & n.1 (2007) (Dkt. 167-22) (noting that IIH "tends to occur in young women of childbearing age"; "the strongest evidence for association exists for obesity and weight gain"); *see also* Giuseffi, *supra*, at 239; Ball & Clark, *supra*, at 433, 440 (reporting 15 to 19 IIH cases per 100,000 women who are 20% or more above their normal body weight; IIH's "association with female sex and obesity is striking"); McGeeney & Friedman, *supra*, at 445 (reporting 11.9 IIH cases per 100,000 obese women; "studies have confirmed that the vast majority of patients with IIH are obese women of child-bearing age"); Chen & Wall, *supra*, at 2 (reporting 19 IIH cases per 100,000 obese women); *see also* Bayer BfArM response, *supra* (reporting more than 20 IIH cases per 100,000 obese women); Cestari Rpt. at 3 (reporting 19.3 IIH cases per 100,000 obese women);

Fraunfelder Rpt. at 5 (reporting 11.9 to 21.4 IIH cases per 100,000 population); Moyé Rpt. at 27 (reporting 22 IIH cases per 100,000 obese women).

As addressed later, the heightened incidence of IIH among overweight and obese women of reproductive age complicates the study of the relationship between Mirena and IIH. That is because Mirena, by definition, is prescribed only to women of reproductive age, and because Mirena is widely understood to be disproportionately prescribed to overweight or obese women.

E. Studies and Data, Outside of this Litigation, Bearing on Whether Use of Mirena Causes IIH

The Court next reviews the state of research, outside of the instant litigation, as to the question whether use of Mirena is a cause of IIH.

In brief, although plaintiffs' experts in this litigation have now so opined, outside of this litigation, no medical organization, regulatory agency, article in peer-reviewed scientific literature, or other research has found that use of Mirena is a cause of IIH.

However, writings in several categories exist that bear on this question. First, two published epidemiological studies have addressed the possibility of a causal connection between use of Mirena and IIH. One was principally authored by Dr. Mahyar Etminan; the other, by Reuben M. Valenzuela.

In addition, epidemiological studies have been conducted as to certain other contraceptive products containing LNG. None have found that the use of these products causes IIH.

Finally, published case reports involving patients with IIH symptoms, where the patient had used Mirena or another LNG-based contraceptive, have raised the question of a connection between the use of these products and IIH.

The above-summarized pre-litigation writings figure prominently in the reports of the experts in this case and in the parties' *Daubert* briefing. In particular, to varying degrees,

plaintiffs' seven experts draw on these materials to support their claim that using Mirena can cause IIH. Various of these experts also draw upon case reports made to Bayer of "adverse events." The subset of Bayer's "adverse events" database relating to Mirena and IIH was made available in discovery during this MDL.

Because these materials are foundational sources for the experts who are the subjects of the instant *Daubert* motions, the Court—before considering any individual expert—reviews the preexisting scholarship and data. The Court first discusses conceptually the categories of studies and other evidence upon which experts may draw in exploring whether a drug can cause a given disease. The Court then reviews the publications that exist, outside of this litigation, regarding Mirena and IIH. Lastly, the Court reviews the publications regarding other (*i.e.*, non-Mirena) LNG-based contraceptive products and IIH.

1. Categories of Studies Generally

In general, three broad categories of human studies can be used to explore a possible causal connection between a drug and a disease or the efficacy of particular modes of treatment of a disease: randomized control trials, epidemiological studies, and studies analyzing anecdotal evidence (*i.e.*, case reports).

Randomized control trials: A randomized control study is widely considered the gold standard of human studies. Such a study consists of a "true clinical experiment in which an intervention is compared with a standard treatment, no treatment, or a placebo, with allocation to treatment by chance." Leon Speroff & Philip D. Darney, *A Clinical Guide for Contraception* 429 (5th ed. 2011) (Dkt. 167-62) ("Speroff & Darney"). Such experiments are often used to test possible treatments for a disease. The hallmarks of a classic clinical trial include a contemporary control group, the allocation of participants so as to assure that participant characteristics are distributed evenly across the treatment and placebo groups, and blinded as to both participants

and investigators. These features enable researchers, *inter alia*, to control for known and unknown confounding factors. However, in the context of testing the capacity of a drug to cause a disease, randomized control studies are often unattainable in practice. Constraints presented by norms of medical ethics may preclude certain tests. And, in the context of rare ailments, such a study might have to be impracticably large to yield statistically significant results, particularly where confounding factors are present. *See, e.g.*, Moyé Rpt. at 12, 15–16.

Epidemiological studies: Epidemiology is the study and analysis of the distribution and determinants of health and disease conditions in defined populations. The two most common types of epidemiological studies are cohort observational studies and case-controlled observational studies.

Cohort studies involve sorting subjects into separate groups based on their exposure (or lack of exposure) to the drug in question. Such studies may be prospective or retrospective. In prospective cohort studies, patients are followed over time to see which persons develop the disease; in retrospective studies, patients are interviewed to determine whether they have been diagnosed with the disease and, if so, under what circumstances. *See* Speroff & Darney, *supra*, at 429–30. A case-control study, in contrast, involves sorting patients into separate groups based on their having been diagnosed with having (or not having) the disease in question, and comparing these groups. *Id.* at 430.

Relative to randomized control tests, however, both types of epidemiological studies, when used to test a thesis of general causation, present inherent challenges controlling for potential confounding factors. Addressing such factors calls for intelligent study design and/or rigorous statistical analysis of results. *See id.* at 431.

Anecdotal evidence/case reports: Anecdotal evidence in cases involving claims that a drug caused a disease usually takes the form of "case reports." A case report is a report of an individual incident or episode, generally keyed to a specific user of a drug, "that serves to bring attention to a possible problem or condition." *Id.* at 430.

Individual manufacturers of drugs, such as Bayer, maintain their own adverse events databases. Another database—relevant here because one of the two epidemiological studies of Mirena and IIH, that by Dr. Etminan, drew upon it—is maintained by the Food and Drug Administration (FDA): the FDA Adverse Event Reporting System ("FAERS"). It contains approximately 5 million adverse event reports, medication error reports, and product quality complaints resulting in adverse events that were submitted to the FDA. The database is designed, *inter alia*, to support the FDA's post-marketing safety surveillance program for FDA-approved biologic products. Reports are submitted to FAERS by healthcare professionals, consumers, and manufacturers. Reports from healthcare professionals (*e.g.*, physicians, pharmacists, and nurses) and consumers (*e.g.*, patients, family members, and lawyers) are voluntary. If a manufacturer receives a report from a healthcare professional or consumer, however, regulations require it to send the report to the FDA.

Consistent with the case law reviewed *infra*, scholars, including plaintiffs' experts in this litigation, agree that while case reports often have utility in generating hypotheses about the possible relationship between a drug and a medical condition, such anecdotal accounts—except in extremely rare circumstances—cannot, without more, demonstrate the causation by a drug of such a condition.[9] *See, e.g.*, Darney Dep. at 206 ("[C]ase reports cannot establish causation.");

[9] Plaintiffs' expert Dr. Moyé offers an example of the rare circumstance in which anecdotal reports were a central factor in demonstrating the cause of a disease: the famous outbreak of "Legionnaires Disease" in 1976 at a Philadelphia hotel hosting an American Legion convention.

id. at 144 (noting that the "principal use" of case reports is "to generate a hypothesis for epidemiologic . . . investigation"); Moyé Rpt. at 21 ("[I]t is the rare case report that demonstrates causality in and of itself"; case reports are "essential to the causation process" because they "demonstrate what is possible"); Moyé Dep. at 131 ("[C]ase reports are not even sufficient to show association because there is no comparison group."); Plunkett Dep. at 184 (noting case reports "show[] associations, not general cause"); Wheeler Dep. at 206 ("[A]dverse event data cannot be used to establish causation" and "the proper use of adverse event report data is . . . hypothesis generating . . . ."); *cf.* Fraunfelder Rpt. at 8 (observing that case reports may serve as "signals," defined as "reported information on a possible causal relationship between an adverse event and a drug").

Animal studies: Animal studies can sometimes be used to test a causal connection between a drug and a disease. Advantages of animal studies include the fact that, because fewer ethical constraints apply to such studies, these can be "conducted as true experiments." Michael D. Green, et al., *Reference Guide on Epidemiology*, *in* Reference Manual on Scientific Evidence 549, 563 (Fed. Jud. Ctr., 3d ed. 2000). But animal studies have several disadvantages. One is that it may be difficult to extrapolate from such studies to the context of humans. Another "difficulty with inferring human causation from animal studies is that the high doses customarily used in animal studies require consideration of the dose–response relationship and whether a threshold no-effect dose exists." *Id*. at 345–46. Animal studies are of limited relevance in this case, in that no such study has assessed whether LNG (however administered) causes IIH. The

See Moyé Rpt. at 22 (noting that case reports were key to "the demonstration that the acute, debilitating pneumonia inflicting a collection of veterans [at the convention] was due to a heretofore unknown bacterium, Legionella pneumophilia," found at the hotel; "[c]ase report methodology accomplished the identification of the cause and cure of this disease").

animal studies cited by the parties (involving other hormones) instead relate to discrete steps in longer biological chains of causation posited by individual experts who opine as to possible mechanisms by which Mirena might cause IIH.

2. Studies and Case Reports Regarding Mirena

a. Randomized Control Trials

There have not been randomized control trials addressing whether Mirena can cause IIH. The parties appear to agree that such a trial would not realistically be attainable, as a result of medical ethics and/or prohibitive cost. The latter is because IIH's rarity would likely make it prohibitive to design a statistically significant study. *See, e.g.*, Moyé Rpt. at 16.

b. Epidemiological Studies

Outside of this litigation, two epidemiological studies have been published addressing the relationship between Mirena and IIH: the Etminan and Valenzuela studies. Because these two studies figure centrally in the *Daubert* litigation, the Court reviews each in detail. As to the Etminan study, the Court further reviews the unusual series of events that culminated in lead author Etminan's repudiation of a significant portion of his study.

(i) The Etminan study

2015—Etminan's initial study: Etminan's study was published in 2015 in the Journal of Therapeutic Advances in Drug Safety. *See* Mahyar Etminan, et al., *Risk of intracranial hypertension with intrauterine levonorgestrel*, 6 Therapeutic Advances in Drug Safety 110 (2015) (Dkt. 167-27) ("Etminan" or the "Etminan study"). At the time that he published the study, Dr. Etminan was serving as a retained expert for plaintiffs in the pre-MDL Mirena/IIH litigation. The Etminan study did not disclose this relationship. The study declared in its "conflict of interest statement" that the authors did not have any conflict of interest to declare. *Id.* at 113.

The Etminan study contained two analyses designed to supplement one another. The outcomes of the analyses pointed in opposite directions. The first was a "disproportionality analysis" (DPA) of adverse event reports in the FDA's FAERS database. *Id.* The DPA analysis found that the "reporting odds ratio" as to IIH, and as to search terms associated with IIH, was higher for Mirena than for a comparison group consisting of users of all other drugs in the FAERS database, which captured some 5 million reported adverse events. *Id.* at 112.[10] Etminan opined that this finding was statistically significant. *Id.* at 112.

The second analysis consisted of a retrospective cohort study. It compared the risk of intracranial hypertension between, on the one hand, LNG-releasing IUDs, and, on the other hand, two combination oral contraceptives that did not contain LNG: ethinyl estradiol (EE) and norethindrone and EE-norgestimate. *Id.* at 111. The study drew upon a large health claims database, IMS LifeLink, which contained more than 102 healthcare plans. This comparison was undertaken, Etminan stated, because "[o]ral and intramuscular contraceptives including progestins have been linked to [intracranial hypertension]." *Id.* at 112. This second analysis did not find any difference in the risk of IIH between users of EE-norgestimate and Mirena. *Id.* It found, in fact, a lower risk of IIH for users of EE-norethindrone relative to users of Mirena, although it concluded that that result was not statistically significant. *Id.*

Etminan's study, which described itself as "the first large epidemiologic study that has examined the risk of [IIH] with Mirena," *id.* at 112, did not definitively conclude that Mirena causes IIH. And, the study noted, the authors "did not have information on all risk factors for

[10] Etminan's 2015 study did not make explicit what the comparison group of approximately 5 million adverse events in the FAERS database comprised. His later affidavit, submitted after the 2015 study came under attack, explained that the comparison group had consisted of adverse events associated with all other drugs in the database, not merely, for example, contraceptive products or a subset of contraceptive products. *See* Dkt. 167-29 ("Etminan Affidavit").

[IIH]." *Id.* at 113. However, the authors urged that "the risk of [IIH] with Mirena must be clearly conveyed to young women who are planning to use them." They further opined that "the small risk of [IIH] may outweigh the risk of unintended pregnancies." *Id.* at 113.

2016—Dr. Friedman's critique: In 2016, the Etminan study came under attack. Dr. Deborah Friedman, the author of various studies relating to IIH, published, in the same journal as the Etminan study, a letter critiquing on multiple grounds the Etminan study's methodology. Centrally, she noted that Etminan's disproportionality analysis—the part of his study that had pointed to an increased IIH risk for Mirena uses—had failed to adjust for age and gender, thus comparing Mirena patients (reproductive-age females) to populations like older men who almost never get IIH. Friedman termed the Etminan study's conclusions "erroneous and misleading." *See* Deborah Friedman, *Risk of intracranial hypertension with intrauterine levonorgestrel*, 7 Therapeutic Advances in Drug Safety 23, 23 (2016) (Dkt. 213-7) ("Friedman Letter").

As to Etminan's DPA analysis, Friedman wrote, the search terms that Etminan had used to isolate IIH-related symptoms within the FAERS database had been overbroad and had included terms not demonstrably related to that condition. *Id*. As to Etminan's second analysis—the cohort study comparing Mirena to two oral contraceptives in the IMS LifeLink database—Friedman wrote, Etminan's data set and methodology were problematic in multiple respects.[11] Etminan's cohort study was also faulty, Friedman wrote, because it did not include a

[11] First, Friedman wrote, the study contained a mismatch between claims data—which covered "women aged 15 to 45 years who were newly prescribed any of the three aforementioned hormonal contraceptives between 2009 and 2013"—and medical events, which covered events up to 2012. *Id.* ("Prescriptions written after 2012 are obviously irrelevant to events that occurred before a patient ever took the medications being studied."). Second, the study did not assure that the medical events had developed between 2009 and 2012; the claims database also encompassed "existing, chronic and unrelated conditions . . . ." *Id.* Third, the study did not ascertain how long women had used the contraceptives between 2009 and 2012; it included, for example, instances where the Mirena IUD "may have been discontinued after a brief period of

control group of women who were not using the hormonal contraceptives at issue, or any such contraceptives at all. *Id.* at 24. The study, she stated, had not found a statistically significant difference in the development of IIH between users of the two oral contraceptives and Mirena. Further, it had failed to assess whether the rate among users of Mirena "is higher than would be expected in their population sample in general." *Id.* She noted that no published evidence had shown a causal relationship between IIH and hormonal contraception. *Id.*[12]

2016—Dr. Etminan's letter response: In 2016, Dr. Etminan published a brief (1.5 page) letter response to Friedman's letter. That letter, Dr. Etminan acknowledged, had raised "some questions." *See* Mahyar Etminan, *Risk of intracranial hypertension with intrauterine levonorgestrel: reply*, 7 Therapeutic Advances in Drug Safety (2016) (Dkt. 167-28) ("Etminan Letter").[13]

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time or before the disorder causing intracranial hypertension developed." *Id.* Fourth, the study did not consider when the Mirena IUD had been inserted: "A Mirena device inserted at the end of the study period cannot be considered with equivalency to a device implanted earlier in the study time frame," and "[t]here are likely many women included in the database who were using either the oral contraceptives or Mirena and were not captured because medication was prescribed before 2009, yet the patients remained on the treatment of interest." *Id.* Fifth, the search terms used for this analysis "were even more egregious than in the first methodology," in that they included various conditions unrelated to hormonal contraceptives and to IIH. *Id.*

[12] Friedman also faulted the study's authors for not disclosing the "major and relevant conflict of interest" of lead author Dr. Etminan—his retention "as a medical expert for a lawsuit against Bayer by the plaintiff's attorney who is suing the company for alleged cases of [IIH] related to Mirena use." *Id.* Friedman's letter disclosed that she had been retained by Bayer as an expert witness, and that, for that reason, she had earlier declined an invitation by the journal to review the Etminan manuscript for publication. *Id.*

[13] Dr. Etminan's letter disclosed for the first time, "potential conflicts of interest"—that he is "currently an expert on the Mirena/Intracranial hypertension litigation." *Id.* at 1–2. Although Dr. Etminan later revealed it, his letter did not state which party (plaintiffs) had retained him as an expert in that litigation. *Id.*

As to his DPA analysis, Dr. Etminan's 2016 letter stated that, even limiting the search terms used within the FAERS database to exclude conditions such as "cerebral edema" not associated with IIH, there were still a disproportionate number of adverse events associated IH for "women with Mirena." *Id.* at 1. As to his cohort study, Dr. Etminan clarified and/or defended his methodology.[14] Finally, Dr. Etminan disputed "that there are no epidemiological studies linking hormonal contraceptives to intracranial hypertension." He noted two studies (from 1990 and 1993) that he acknowledged "lacked statistical power," and a 2015 case-control study (a study by Rai, *et al.*, that previewed the Valenzuela study addressed *infra*) that, Etminan stated, had found a statistically significant increase in IIH among women with intrauterine LNG use compared to nonusers, but which, Dr. Etminan acknowledged, did "not seem to have adjusted for body mass index (BMI), a major confounder for this question." *Id.*

2016—Dr. Etminan's affidavit repudiating his findings: Later in 2016, Dr. Etminan changed course. He repudiated much of his study's analysis. On December 17, 2016, after being served with a notice of a deposition in a lawsuit against Bayer that is now part of this MDL, Dr. Etminan furnished to counsel for Bayer a sworn affidavit retracting many of his study's findings. *See* Dkt. 167-29 ("Etminan Affidavit").

Addressing his study's disproportionality analysis, Dr. Etminan clarified that the study had calculated "reporting odds ratios" (RORs) for Mirena "versus all other products in the FAERS database"; "the comparator group," he now acknowledged, "had not been limited to oral

[14] Dr. Etminan wrote that "[a]ll events in [the cohort] study were ascertained after the dispensation date for a Mirena prescription." *Id.* at 1. In response to Dr. Friedman's critique that the Etminan study had not compared the incidence of IIH among Mirena users with nonusers of hormonal contraceptives, Dr. Etminan disclaimed interest in that comparison: "[W]e did not have information on other covariates . . . . [T]he objective of the study was not to compare the risk of PTC with nonusers of hormonal contraceptive, but only to compare the risk of intracranial hypertension or papilledema with two oral progestin-based contraceptives." *Id.*

contraceptive pills or any other specific product." *Id.* ¶¶ 3-4. Further compromising the results, Dr. Etminan admitted, the analyst whom he had used to extract data from that database

> did not limit the groups compared in the FAERS DPA to reproductive age females. Because the background incidence of intracranial hypertension is higher in reproductive age females than in other demographic groups, failing to limit the comparator group to reproductive age females can artificially inflate the ROR for Mirena, as almost all Mirena users are reproductive age females. Therefore, a proper analysis would be limited to women of reproductive age.
> .

Id. ¶ 6. And, Dr. Etminan stated, the study's DPA analysis might separately be flawed in that:

> I do not know if my analyst used unique cases, or instead used unique reports, for the FAERS DPA. Because the same individual case can have multiple unique reports filed in the FAERS database, using unique reports can result in individual cases being counted more than once in the analysis. The proper analysis should use unique cases, not unique reports.

Id. ¶ 7. In sum, Dr. Etminan stated, as to his study's DPA analysis:

> I have no basis to say that the results of the FAERS DPA would have been statistically significant, or that the point estimate would have been greater than 2.0, had the control group been properly limited to reproductive age females and had the analysis properly used unique cases rather than unique reports. *Indeed, re-running DPA analysis of the FAERS data using OpenVigil 2.1 software and properly limiting it to unique cases and women of reproductive age results in no elevated ROR for Mirena, suggesting that intracranial hypertension and Mirena use are "likely not related."*

Id. ¶ 8 (emphasis added).

As for his retrospective cohort study, Dr. Etminan's affidavit noted that it had not found any statistically significant difference in risk between Mirena and either of the combination oral contraceptive comparators. *Id*. ¶ 9. Dr. Etminan further explained, "For neither the FAERS DPA nor the retrospective cohort analysis did I have weight data (BMI or recent weight gain) that would have allowed me to control for weight as a potential confounding variable as the FAERS data do not generally provide BMI information for each case." *Id.* ¶ 10.

Dr. Etminan summed up the implications of his revelations as follows.

> Based on the above, as the lead author of this article, I acknowledge that *neither of the analyses in the article provide evidence that Mirena use increases the risk for intracranial hypertension*. Therefore, there is no basis to say, based on these analyses, that the risk of intracranial hypertension with Mirena use outweighs the risk of unplanned pregnancies.

Id. ¶ 11 (emphasis added).[15]

2017—Dr. Etminan's letter repudiating his findings: In April 2017, Dr. Etminan submitted another letter to the editor. *See* Mahyar Etminan, *Revised disproportionality analysis of Mirena and benign intracranial hypertension*, 8 Therapeutic Advances in Drug Safety 299, 299–300 (2017) (Dkt. 167-30) ("Etminan Second Letter"). The letter largely reprised the points Dr. Etminan had made in his affidavit. It acknowledged that both of his 2015 analyses had failed to "control[] for reproductive age[,] which has a strong correlation with [IIH]." *Id.* at 1. In this 2017 letter, Dr. Etminan added: "[A]n unstratified analysis by reproductive age can artificially overestimate the risk of [IIH] with Mirena." *Id.* at 1 (illustrating the point with data). And he further conceded, "Based on the age-restricted analysis a signal is *not* detected with Mirena with respect to [IIH] when child bearing age is accounted for." *Id.* (emphasis added).

(ii) The Valenzuela study

The Valenzuela study was published in 2017. *See* Reuben M. Valenzuela, et al., *An estimation of the risk of pseudotumor cerebri among users of the levonorgestrel intrauterine device*, 41 Neuro-Ophthalmology 192 (2017) (Dkt. 167-64) ("Valenzuela" or the "Valenzuela

[15] Elaborating on the conflict of interest he had by then acknowledged, Dr. Etminan admitted in his affidavit that at the time that he had "conducted these analyses and submitted them for publication, [he] was being paid by lawyers suing Bayer in cases alleging that Mirena caused users to develop idiopathic intracranial hypertension (IIH)," but that he had not disclosed that relationship. *Id*. at ¶ 12. Dr. Etminan's affidavit stated that while he had given sworn expert testimony in that litigation, he had since withdrawn as an expert in those cases. *Id.* ¶¶ 12, 17.

study"). A retrospective case-control study, it addressed the risk of IIH among certain patients in Utah and Denmark.[16]

In particular, the study examined whether IIH patients in these populations were using LNG-releasing IUDs (principally Mirena),[17] whether the use of such IUDs was associated with an increased risk of IIH, and whether IIH patients who used such IUDs had signs or symptoms different from those observed in IIH patients who did not use such IUDs. *Id.* at 1–2. Towards this end, the study compared the incidence of IIH among reproductive age women who used LNG-releasing IUDs with the incidence of IIH among reproductive age women who were not using LNG-releasing IUDs. *Id.* at 2.

The Valenzuela study found a statistically significant correlation between a patient's use of an LNG-releasing IUD and the patient's having IIH. However, the authors emphasized that they had not found causation of IIH by use of an IUD, but merely a correlation between the two:

> Our investigation does *not* indicate that an LNG-IU[D] [such as Mirena] can cause PTC, and the number of women with an LNG-IU[D] was too small to determine if an LNG-IU[D] is an *independent* risk factor for PTC. Although use of an LNG-IU[D] seems [to] be associated with an increased risk of PTC, it is possible that this observation occurred because use of an LNG-IU[D] is also associated with other established risk factors that are known to be associated with PTC (e.g., obesity and recent weight gain). This analysis was also limited by the lack of temporal data to

[16] The Utah component of the study drew upon databases at the University of Utah, one of which (the "PTC database") included all patients who had received a PTC diagnoses, the other of which (the "Electronic Billing database") included all women who had been billed for insertion of LNG-based IUDs. *Id.* at 2. The Denmark component of the study drew upon patient files at Rigshospitalet Hospital and in the IIH database of its Ophthalmology Department. *Id.*

[17] In addition to Mirena, which had been approved in 2000, the Valenzuela study considered an LNG-IUD that had been approved for use in Europe in 2012 under the trade name Jaydess, an LNG-IUD that had been approved for use in the United States in 2013 under the trade name Skyla, and an LNG-IUD that had been approved for use in the United States in 2015, under the name Liletta. *Id.* at 1. Jaydess and Skyla are manufactured by Bayer affiliates; Liletta is manufactured by Allergan plc.

> confirm that exposure to LNG-IU[D] occurred prior to PTC symptom onset or diagnosis.

Id. at 4 (emphasis in original).

The Valenzuela study noted two possible explanations for the correlation between IIH and use of LNG-based IUDs. *Id.* at 5. One is that LNG causes increased intracranial pressure, through an as-yet undetermined biological mechanism. *Id.* at 5.[18] The other

> is that LNG does not cause increased intracranial hypertension, but that the PTC is more likely to occur in the same population of women who are more likely to have an LNG-IU[D] recommended to them by their physician. LNG-IU[D] is often, although not exclusively, recommended for women who may have difficulty with other forms of contraception. For instance, women with obesity, headache, and/or polycystic ovarian syndrome are more likely to be intolerant to oral contraceptives. For this group of women, LNG-IU[D] may be better tolerated as a form of contraception. This same group of women, with obesity, headache, and polycystic ovarian syndrome, are also more likely to develop PTC. When interpreting the findings presented here, it is also important to consider that the risk analysis does not account for potential confounders.

Id. (footnotes omitted).

The Valenzuela study further noted that future research "may or may not be able to distinguish between these two possibilities." *Id.* As to possible future areas of research, the study noted that there are currently "no reliable animal models of PTC," and that a prospective trial of LNG-IUDs in a population of women at risk for PTC "would likely be too costly and would not settle the question of whether an LNG actually causes [IIH]." *Id.* The authors added that "[l]imitations of our study include the retrospective nature of the investigation and the

[18] As to possible such mechanisms, the study stated: "It has been hypothesized that LNG could cause increased intracranial pressure through a number of mechanisms, including Vitamin A metabolism or venous microthrombi, mechanisms that have both been previously proposed as causes of PTC. It is unclear why LNG would cause this syndrome but other progestins used for birth control would not. It is also unclear why exogenous LNG would cause this syndrome but endogenous progestins (such as those associated with pregnancy) would not cause this syndrome." *Id.* at 4–5 (noting possibility that if LNG does cause IIH, it is "through another, as yet unknown mechanism").

relatively small number of PTC subjects with an LNG-IU[D] at the time of diagnosis." *Id.* The authors emphasized that "[o]ur findings are preliminary, and caution should be exercised in applying this information to clinical practice." *Id.*

The Valenzuela study concluded: "We do not recommend the removal of LNG-IU[D]s from women with PTC, as the benefit of effective contraception for these women likely outweighs the risk. Likewise, if a woman with PTC or at risk for PTC needs contraception, an LNG-IU[D] should still be considered as an effective form of contraception." *Id.* at 6.[19]

c. Case and Adverse Event Reports

Outside of this litigation, two published case reports have addressed IIH in the context of usage of LNG-based IUDs.

One 2010 report from a doctor discussed the case of a 45-year-old woman and noted a possible connection between an LNG-based IUD and IIH. *See* H. Martinez, et al., *Atypical pseudotumour cerebri*, 34 Neuro-Ophthalmology 255 (2010) (abstract); *but see* Cestari Rpt. at 14 (questioning whether this woman, who did not have headaches or papilledema, met the Dandy

[19] In litigating the *Daubert* motions, Bayer identified what it argues is a methodological problem with the Valenzuela results as to its finding of a correlation between use of an LNG IUD and IIH. Bayer noted that, as to each of the populations it studied, the Valenzuela study had used different methods to determine the number of Mirena users in its case (IIH) and control (non-IIH) groups. Among the Utah population, for example, the researchers interviewed all IIH patients to determine whether they had a Mirena implanted when their symptoms began, and did so regardless of when or where the Mirena had been implanted. In contrast, as to the Utah control group, the researchers included only patients who had their Mirenas inserted at the University of Utah during the study period, thereby excluding persons who had Mirenas inserted before the study began or whose Mirena devices were inserted outside the University of Utah system. Bayer argues that this asymmetric methodology—and a similar asymmetry affecting the Denmark study—may produce an undercounting of Mirena usage in the control group, thereby inflating the apparent correlation between Mirena usage and IIH. This, Bayer argues, is relevant to the reliability of the proposed testimony of those plaintiffs' experts who rely on the Valenzuela study. *See* Bayer Omnibus Br. at 17 n.9. The Court amplifies on this debate in discussing the *Daubert* challenge to Dr. Moyé, the first of plaintiffs' experts who so rely.

criteria for IIH and noting that the case report did not state whether the woman was overweight or had had recent weight gain or whether her IUD use predated the IIH symptoms).

A second case report, published in 2017, described an overweight woman who had developed IIH approximately two years after starting use of Mirena. It noted that the woman, soon before developing symptoms, had been prescribed a medicine, minocycline, that is associated with IIH, and that the IIH symptoms had abated shortly after the minocycline use (although not the woman's Mirena use) had ceased. *See* F.J. Ros Forteza, et al., *Minocycline-induced intracranial hypertension in a patient with a levonorgestrel intrauterine device*, Neurologia (2017) (letter to the editor) (in Spanish).

As to adverse event reports, Bayer has periodically conducted "signal analyses" regarding Mirena and IIH, utilizing the adverse events reports in its pharmacovigilance database.

The most recent, and therefore the most comprehensive, was in October 2017 during discovery in this case. Bayer summarized the findings of this analysis in a submission to a German regulator, BfArM. Bayer identified a total of 315 reported cases involving symptoms indicative of possible IIH symptoms among users of Mirena, and an additional four cases indicative of possible IIH symptoms involving Bayer's more recent Skyla IUD product, which is also LNG-based. *See* Bayer BfArM Response at 44–45. Of those patients for whom weight data is available, Bayer reported, most were obese or overweight. *See* Cestari Rpt. at 20. More than 60% of the 315 reported cases were in the form of lawsuits filed after December 2013. *See* Bayer BfArM Response at 17, 45–46. As developed later, various of plaintiffs' experts draw upon case reports within this set in support of their conclusions. *See, e.g.*, Darney Rpt. at 24; Fraunfelder Rpt. at 17–24; Moyé Rpt. at 34–37; Plunkett Rpt. at 28, 34; Salpietro Rpt. at 30; Wheeler Rpt. at 39.

3. Studies of Other LNG-Based Contraceptive Devices

The Court next summarizes the existing studies and data bearing on the relationship between other LNG-based contraceptives and IIH.

a. Combined Oral Contraceptives

Between 1984 and 1993, five epidemiological studies into IIH were conducted that considered, among other issues, whether there was a link between combined oral contraceptives (those containing both estrogen and progestin) and IIH.[20] LNG-containing oral contraceptives result in a substantially higher rate of LNG circulating in the user's blood stream than does Mirena. *See* Plunkett Rpt. at 22 and Plunkett Dep. at 94 (noting that LNG-containing oral contraceptives have LNG levels between 3,000-6,000 pg/ml, some 20-30 times more than in Mirena).

All five studies failed to find a causal link.[21] Two of plaintiffs' experts, Drs. Fraunfelder and Darney, in fact, have acknowledged that science has largely *disproven* a link between IIH

[20] The studies were addressed to oral contraceptives generally as opposed to testing specific products. However, during the period covered by most of these studies, oral contraceptives containing the progestin LNG were among the most common oral contraceptives on the market. *See* B. Burt Gerstman, et al., *Trends in the content and use of oral contraceptives in the United States,1964–88*, 81 Am J. Public Health 90, 93 fig. 4 (1991) (Dkt. 167-31).

[21] *See* Kathleen B. Digre, et al., *Pseudotumor cerebri and pregnancy*, 34 Neurology 721, 727 (1984) (Dkt. 167-23) (study examined charts of all women of reproductive age at Iowa hospital who were admitted between 1966 and diagnosed with IIH; "[w]e found no significant difference between oral contraceptive use in patients with PTC and controls"); F. Jane Durcan, et al., *The incidence of pseudotumor cerebri: Population studies in Iowa and Louisiana*, 45 Arch Neurology 875–77 (1988) (Dkt. 167-25) (study examined Iowa and Nebraska patients in 1984-1985 who were treated for IIH; study inquired about use of birth control pills and found that "[t]here is no significant difference between our population of patients with PTC taking birth control pills and the general female population taking the pill"); Belinda Ireland, et al., *The search for causes of idiopathic intracranial hypertension: A preliminary case-control study*, 47 Arch Neurology 315, 316 (1990) (Dkt. 167-37) (study focused on patients in 1980–1990; study found that "[q]uery of characteristics of prior oral contraceptive use revealed no significant differences in the following categories: ever using oral contraceptives, age when use began, type of oral contraceptives used, length of time used, and usage immediately prior to IIH diagnosis or

and combined oral contraceptives containing LNG. *See* Fraunfelder Dep. at 16 (agreeing that "an association between oral contraceptives and IIH has been largely disproven"); Darney Dep. at 43 ("My opinion is that [oral contraceptives] do not [cause IIH]."). Bayer's experts similarly assess the state of such research. *See, e.g.*, Cestari Rpt. at 11 ("This lack of an association has been consistently confirmed . . . .")

b. Norplant

Norplant, a contraceptive product manufactured by American Home Products and its subsidiary, Wyeth-Ayerst Laboratories, was approved by the FDA in 1990 and introduced in 1991. Norplant released LNG from an implant placed in the woman's arm. Norplant marketing was discontinued in the United States in 2002 and globally in 2008, although a different implant that releases LNG, Jadelle, is currently marketed by Bayer outside the United States. Norplant contained substantially more LNG than Mirena and produced substantially higher total blood concentrations of LNG. *Compare* 1997 Norplant Label, Dkt. 167-69, at 00055905 (216 mg) *with* Mirena Label at § 11.1 (52 mg); *compare* 1997 Norplant Label, at 00055898 (327 ± 119 pg/mL after one year) *with* Mirena Label at § 12.3 (180 ± 66 pg/mL after one year).

As various plaintiffs' experts observe, *see, e.g.*, Darney Rpt. at 22; Fraunfelder Rpt. at 16; Plunkett Rpt. at 34, Salpietro Rpt. at 28–29, during the period Norplant was in use, several case studies noted an association or possible association between Norplant and IIH. *See* John B.

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the corresponding reference time"); Giuseffi, *supra*, at 239 (study involved patients referred to Tulane University medical school neuro-opthalmology clinic between 1982–1988 who were diagnosed with IIH; "we found no association between IIH and . . . oral contraceptive [use]"); Kurupath Radhakrishnan, et al., *Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study*, 116 J Neurology Sci. 18, 24 (1993) (Dkt. 167-51) (study of patients in Libya between 1982 and 1989 found "[n]o significant association . . . between IIH patients and . . . oral contraceptive use . . . "); *see also* Ball & Clark, *supra*, at 440 ("No consistent correlations have been found between visual outcome and . . . oral contraceptive use, steroid treatment, CSF opening pressure, duration or type of symptoms, and chronicity of papilledema.").

Alder, et al., *Levonorgestrel implants and intracranial hypertension*, 332 New England J. Med. 1720, 1720–21 (1995) (Dkt. 167-16) ("Alder") (letter to editor, reporting the development of IIH in two women following the insertion of Norplant and identifying 56 additional possible cases of IIH; author, however, notes existence of confounding factors and adds, "[LNG] may have contributed to the onset of [IIH], or it may have had nothing to do with it"); A.J. Sunku, et al., *Benign intracranial hypertension associated with levonorgestrel implants*, 34 Annals Neurology 299, 299 (1993) (Dkt. 167-63) ("Sunku") (poster presentation, reporting two women who developed IIH while using Norplant; author concludes that further study is needed to determine whether relationship between Norplant and IIH is "etiological or coincidental"); *see generally* Diane E. Wysowski & Lanh Green, *Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System*, 85 Obstet Gynecology 538, 540 (1995) (Dkt. 167-67) ("Wysowski & Green").

Another study drawn from the FDA's adverse events database described 39 reports of women with symptoms associated with IIH that developed during Norplant use between February 2001 and December 2003. *See* Wysowski & Green, *supra*, at 540. Of the 39 women, the study noted, all for whom weight data was available were obese (16 women) or overweight (2 women). The study noted that the duration of time between the insert of the Norplant and the onset of IIH symptoms had ranged from one to 17 months; that four patients had continued using Norplant yet the symptoms resolved; that 16 patients had the Norplant removed and the symptoms resolved; and that six had the Norplant removed but their IIH symptoms continued. *Id.* The authors found the assembled data inconclusive. They stated, "[I]t is not possible to determine whether Norplant, obesity or weight gain, or both factors are related to the occurrence of [IIH] . . . . Epidemiologic research (case-control or cohort studies) would be required to

determine if a causal association between Norplant and . . . [PTC] exists." *Id.* at 541. No such studies of Norplant, however, were ever conducted. *See* Valenzuela, *supra*, at 4 ("[T]hese previous [Norplant] reports did not imply a causative role in the pathogenesis of PTC.").

Notwithstanding the absence of epidemiological studies, as a result of early adverse event reports of IIH, Norplant's manufacturer in 1993 voluntarily placed the following language on Norplant's label:

> There have been reports of idiopathic intracranial hypertension in NORPLANT SYSTEM users. . . . Patients with these symptoms, particularly obese patients or those with recent weight gain, should be screened for papilledema and, if present, the patient should be referred to a neurologist fur further diagnoses and care. NORPLANT SYSTEM should be removed from patients experiencing this disorder.

1997 Norplant Label (Dkt. 167-69) at 00055901. A similar warning as to IIH has been—and remains—included on the label of Bayer's Jadelle product, an LNG-based implant that is not currently marketed in the United States. *See* Fraunfelder Rpt. at 15; Plunkett Rpt. at 9 n.7.

c. Other Contraceptive Devices Containing LNG

Finally, apart from the contraceptives reviewed above—Mirena, combined oral contraceptives, and Norplant and Jadelle—other contraceptive devices have had LNG as their hormonal component. Those referenced in the expert reports include: (1) Kyleena and Skyla, both of which are IUDs manufactured by Bayer (Skyla, approved in 2013, has an average release rate of 6 µg LNG/day for up to three years, while Kyleena, approved in 2016, has an average *in vivo* release rate of 9 µg LNG/day for up to 5 years); and (2) Allergan's Liletta, an IUD releasing 19.5 µg LNG/day for up to three years. Darney Rpt. at 7; Plunkett Rpt. at 9 n.8, 23–24; Wheeler Rpt. at 2. The parties have not drawn to the Court's attention studies or case reports bearing on a possible connection between these products and IIH.

III. Bayer's Challenges to Plaintiffs' Expert Witnesses

The state of research outside of this litigation as to the general causation proposition here—that using the Mirena IUD can cause a woman to develop IIH—presents a challenge for an expert witness here who would so testify.

As the above review reflects, to date, no prospective experiments have been undertaken that sought to address that question. Two epidemiological studies have examined that question but neither has found such causation. One such study, Etminan, has been retracted to the extent that it—based on its DPA analysis of reports in the FAERS database—had initially found an increased IIH risk among Mirena users. And the surviving half of the Etminan study (which compared Mirena with oral contraceptives) did not find any such increased risk. The other epidemiological study (Valenzuela) found a correlation between Mirena use and IIH. But it found only that. In language that warned against conflating correlation with causation, the Valenzuela study emphasized that its finding of such a correlation "does not indicate" that an LNG-based IUD such as Mirena is an "independent risk factor" for IIH. Rather, as Valenzuela recognized, alternative explanations for the correlation between Mirena and IIH are apparent—notably, the confounding factors of overweightness and obesity among reproductive-age women. As to the other contraceptive products using LNG, five studies of combined oral contraceptives have affirmatively found that these products, which contain notably higher amounts of LNG than Mirena, do not cause IIH. And no study has established a causal link between IIH and Norplant, which also contained substantially more LNG than Mirena.

In the face of this assembled historical record, with no medical organization or regulator or peer-reviewed scientific literature having found that Mirena or any contraceptive product using LNG is a cause of IIH, an expert witness who would so opine as to Mirena necessarily would break new ground in this litigation.

Each of plaintiffs' seven expert witnesses reach this conclusion in their reports. None has done so through an experiment, laboratory work, or a new epidemiological study of his or her own. Four of plaintiffs' expert witnesses (Drs. Moyé, Plunkett, Wheeler, and Fraunfelder) arrive at this result largely by drawing upon existing sources. These include the Valenzuela study plus, depending on the witness, some or all of the following: the repudiated portion of the Etminan study; case reports regarding Mirena; case reports regarding Norplant and other subdural implants; and Norplant's warning label. These experts also draw upon a newly available source of data: the case reports regarding Mirena first added in Bayer's 2017 signal investigation, which was made available to plaintiffs in discovery. To varying degrees, each of these four experts also articulates a theory as to a biological mechanism by which Mirena might cause IIH.

Plaintiffs' remaining three expert witnesses (Drs. Darney, Johanson, and Salpietro) are predominantly "mechanism" experts. Their reports each develop a thesis as to how, biologically, use of Mirena may cause IIH.

Bayer, for its part, argues that plaintiffs' experts' proposed testimony is unreliable, measured against the requirements for admission of expert testimony. As to the four experts who rely largely on existing studies and data, Bayer contends, *inter alia*, that the alchemy is elusive by which a witness can reliably find such causation where the studies that comprise the expert's central source material have not so found. As to the three "mechanism" experts, Bayer contends that their untested theories are based on conjecture, and often on mishandling the scholarship on which they postulate causal mechanisms. Overall, Bayer contends that, rather than reflecting rigorous application to scientific methodologies, the conclusions of each of the seven witnesses amounts to a non-scientific *ipse dixit*.

The Court's analysis proceeds as follows.

The Court first reviews the legal standards governing receipt of expert testimony as set out in *Daubert* and ensuing decisions.

The Court then summarizes each witness' proposed testimony and assesses it against these standards. The Court first considers the four witnesses who reach the conclusion that Mirena is a cause of IIH based largely on existing studies and data. These witnesses describe the multi-factor methodologies they use in assessing this evidence as, alternatively, a "Bradford Hill" and/or a "totality of the circumstances" methodology.

The Court then considers the remaining three witnesses, whose reports, as noted, largely articulate theories about biological mechanisms by which Mirena might cause IIH.

A. Applicable Legal Standards

Trial courts serve as "gatekeep[ers]," responsible for "ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." *Daubert*, 509 U.S. at 597; *see also Wills v. Amerada Hess Corp.*, 379 F.3d 32, 48 (2d Cir. 2004). Pursuant to Federal Rule of Evidence 702, the party seeking to admit expert testimony must show by a preponderance of the evidence that: (i) the expert is qualified, (ii) the testimony is based on sufficient data, (iii) the testimony is the product of reliable methods reliably applied, and (iii) the testimony is relevant and will assist the jury.

In *Daubert*, the Supreme Court set out a list of non-exclusive factors that courts should consider in determining whether an expert's methodology is reliable. These are: (1) whether the expert's technique or theory can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether there is a high error rate for the expert's technique, and whether there are "standards controlling the technique's operation"; and (4) whether the expert's technique or theory is generally accepted by the relevant scientific community. *Daubert*, 509 U.S. at 592–94; *accord Nimely v. City of New York*, 414 F.3d 381, 396 (2d Cir. 2005). Courts

also consider whether the proffered expert opinions were developed for the purposes of litigation. *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 420 (S.D.N.Y. 2005) ("*In re Rezulin II*").

A proffered opinion may fail all four *Daubert* reliability factors and still be admitted. Before admitting proposed testimony in those circumstances, however, a court must "carefully scrutinize," pause, and take a "hard look" at the expert's methodology. *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 430, 449; *In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.*, 593 F. Supp. 2d 549, 564 (S.D.N.Y. 2008). "The flexible *Daubert* inquiry gives the district court the discretion needed to ensure that the courtroom door remains closed to junk science while admitting reliable expert testimony that will assist the trier of fact." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002).

Experts can fail to meet Rule 702 and *Daubert*'s standards for various reasons, relating to the expert's qualifications and/or methodology:

Qualifications: The witness simply may not be qualified to address the area in question. *See* Fed. R. Evid. 702 (providing that in order to testify as an expert under Rule 702, a witness must be "qualified as an expert by knowledge, skill, experience, training, or education."). "To determine whether a witness qualifies as an expert, courts compare the area in which the witness has superior knowledge, education, experience, or skill with the subject matter of the proffered testimony." *United States v. Tin Yat Chin*, 371 F.3d 31, 40 (2d Cir. 2004).

In determining whether the witness has the relevant experience, courts consider factors including the degree to which that experience was developed for the litigation. *See, e.g.*, *Mancuso v. Consol. Edison Co. of N.Y.*, 967 F. Supp. 1437, 1443 (S.D.N.Y. 1997) ("We cannot help but conclude that [the plaintiffs' expert] was not in fact an expert . . . when he was hired by

plaintiffs, but that he subsequently attempted, with dubious success, to qualify himself as such by a selective review of the relevant literature."); *Prohaska v. Sofamor, S.N.C.*, 138 F. Supp. 2d 422, 437 (W.D.N.Y. 2001) (criticizing "litigation-driven expertise" where expert "relied upon the plaintiff's attorney to provide him with the relevant scientific literature"). Although extensive experience can make up for an absence in specialized training,[22] if the witness does not possess superior knowledge, education, experience, or skill in the relevant area, the Court must exclude his or her testimony. *See, e.g.*, *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 439 (excluding witness with experience in engineering and biomaterials but without experience in hormonal contraception).

Methodology: A witness may also be excluded if his or her proposed methodology is not sufficiently rigorous. *See Nimely*, 414 F.3d at 396 ("[R]eliability within the meaning of Rule 702 requires a sufficiently rigorous analytical connection between that methodology and the expert's conclusions."). The following are among the principles that guide a court's assessment of reliability.

"To warrant admissibility, . . . it is critical that an expert's analysis be reliable at every step." *Amorgianos*, 303 F.3d at 267. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). "A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered" to permit admission. *Id.*

[22] *See McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1043 (2d Cir. 1995) (admitting testimony of a doctor who had practiced for decades in relevant area even though he was not a specialist in environmental medicine).

Courts have found analytical gaps to be too great, for example, when a critical step in a prospective expert's reasoning is based on a highly dubious analogy. *See, e.g.*, *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 439 ("Such a subjective comparison of muscle of a pig heart to a female uterus creates simply too great an analytical gap between the data and the opinion proffered to pass muster under Rule 702 and *Daubert*." (quotation marks omitted)); *Shatkin v. McDonnell Douglas Corp.*, 727 F.2d 202, 208 (2d Cir. 1984) (rejecting expert methodology based on an "apples and oranges" comparison).

An expert is, further, expected to "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). "Expert testimony should be excluded if it is speculative or conjectural," *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir. 1996), or where the proffered opinion is "based on data, a methodology, or studies that are simply inadequate to support the conclusions reached," *Amorgianos*, 303 F.3d at 266.

"[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study." *In re Accutane Prods. Liab.*, No. 8:04-MD-2523-T-30TBM, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009), *aff'd*, 378 F. App'x 929 (11th Cir. 2010); *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 452 (same).[23]

Opinions that assume a conclusion and "reverse-engineer[] a theory" to fit that conclusion are, similarly, inadmissible. *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 430; *In re Gen. Motors LLC Ignition Switch Litig.*, No. 14-CV-5810, 2017 WL 6729295, at *8 (S.D.N.Y. Dec. 28, 2017); *see also Faulkner v. Arista Records LLC*, 46 F. Supp. 3d 365, 381

[23] There is, however, no requirement that an expert cite published studies that "unequivocally support his or her conclusions." *Amorgianos*, 303 F.3d at 266; *see also Zuchowicz v. United States*, 140 F.3d 381, 386–87 (2d Cir. 1998); *McCullock*, 61 F.3d at 1043–44.

(S.D.N.Y. 2014) ("[M]ethodology . . . aimed at achieving one result . . . is unreliable, and . . . must be excluded."); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 796–800 (3d Cir. 2017) ("*In re Zoloft*") (affirming exclusion of "conclusion-driven" analysis).

Finally, "an expert may not 'pick and choose' from the scientific landscape and present the Court with what he believes the final picture looks like." *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) ("*In re Rezulin I*"). Where an expert ignores evidence that is highly relevant to his conclusion, contrary to his own stated methodology, exclusion of the expert's testimony is warranted. *See id.*

B. Dr. Lemuel Moyé

Dr. Moyé is a trained medical doctor with a Ph.D. in Community Sciences Biostatistics. He bases his opinion that Mirena is a cause of IIH on what he describes as an application of the Bradford Hill criteria.

1. Qualifications

Dr. Moyé works as a tenured professor of biostatistics within the Department of Biostatistics and Data Sciences at the University of Texas School of Public Health in Houston, Texas. He became a licensed physician in Texas in 1984 and worked as a general practitioner for eight years. *See* Moyé Rpt. at 2. Dr. Moyé does not, however, hold himself out as an expert in pharmacokinetics or pharmacodynamics, specialties associated with expertise in developing biological mechanisms for diseases. Moyé Dep. at 85–86.

Dr. Moyé has extensive experience in conducting large clinical trials and analyzing their results statistically. He has been a Principal Investigator in a large cardiovascular study, a Coordinating Center Principal Investigator in a study regarding the treatment of strokes, and is currently the Coordinating Center Principal Investigator for the Cardiovascular Cell Therapy

Research Network. He has published numerous peer-reviewed articles about the studies he has conducted, as well as several books on the use of statistics in medicine. *See* Moyé Rpt. at 2–3.

Dr. Moyé has also been hired as an expert witness on numerous occasions. In the last four years, he has been deposed as an expert witness 14 times. Before this litigation, he did not have any experience related to Mirena, and he had limited exposure to IIH. Moyé Dep. at 85. Outside of this litigation, he has never conducted research on LNG. *Id.* at 85–88.

2. The Bradford Hill Criteria

The Bradford Hill criteria derive from a 1965 lecture by a British epidemiologist and statistician, Sir Austin Bradford Hill. *See* David E. Bernstein, *The Admissibility of Scientific Evidence After Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 15 Cardozo L. Rev. 2139, 2167 (1994) ("In a celebrated lecture in 1965, Sir Austin Bradford Hill proposed nine criteria to aid scientists in deciding whether a reported association in an epidemiological study is causal."). "The Bradford Hill criteria are metrics that epidemiologists use to distinguish a causal connection from a mere association." *In re Zoloft*, 858 F.3d at 795. These criteria "start with an association demonstrated by epidemiology and then apply" eight or nine criteria to determine whether that association is causal. *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1234 (D. Colo. 1998).

The nine Bradford Hill criteria are as follows.

> **Statistical Association [alternatively referred to as "Strength of Association"].** There must be some degree of statistical association between a cause and its effect. A strong association (large in magnitude) is more likely to represent causation than a weak association (small in magnitude).
>
> **Temporality.** A cause must precede its effect. Strength in temporality, such as when a cause immediately precedes its effect, supports an inference of causation.

> **Biological Plausibility** . . . A cause and effect relationship between exposure and disease should be biologically plausible . . . with other information about the disease or harm.
>
> **Coherence.** A cause and effect relationship between exposure and disease should be . . . consistent with other information about the disease or harm.[24]
>
> **Dose-Response Effect.** Causation is more likely if greater amounts of the putative cause are associated with corresponding increases in the occurrence of disease or harm.
>
> **Consistency.** When similar findings are generated by several epidemiological studies involving various investigators, causation tends to be supported.
>
> **Analogy.** Substantiation of relationships similar to the putative causal relationship increases the likelihood of causation.
>
> **Experimental Evidence.** Causation is more likely if removing the exposure in a population results in a decrease in the occurrence of disease or harm.
>
> **Specificity.** When there is but a single putative cause for the disease or harm, causation is supported.

Thompson, *supra*, at 268; *see also In re Zoloft*, 858 F.3d at 795; Moyé Rpt. at 16–20.

3. Proposed Testimony

Dr. Moyé principally relies on the following materials in applying the Bradford Hill criteria: (1) the Valenzuela study, (2) 36 case reports, drawn from among the 315 adverse event reports as to Mirena and IIH noted in Bayer's 2017 signal investigation, and Bayer's summary of that investigation in its BfArM submission; (3) a single published article involving Norplant, and (4) a review of literature based upon which Dr. Moyé develops a theory as to a "biologic[ally] plausib[le]" mechanism. Moyé Rpt. at 39; *see id*. at 29–43. He applies the nine Bradford Hill criteria, or factors, to that evidence as follows:

[24] Some writings list biological plausibility and coherence as part of a single factor. *See, e.g.*, Melissa Moore Thompson, *Causal Inference in Epidemiology: Implications for Toxic Tort Litigation*, 71 N.C. L. Rev. 247, 268 (1992). The Court here treats them as distinct.

Strength of association: Dr. Moyé bases his finding of a "positive" strength of association, Moyé Rpt. at 34, on the Valenzuela cohort study. *See id.* at 29–34. As noted, that study reviewed populations in Utah and Denmark. Dr. Moyé concludes that that, as to both populations, the Valenzuela data revealed an association between Mirena and IIH. The relative risk ratio (a measure of the likelihood of IIH occurring in patients using Mirena compared to those not using Mirena) for both populations was, he states, statistically significant. *See id.* at 31 (relative risk ratio for LNG-IUD group in Utah population was 7.69); *id.* at 32 (relative risk ratio for LNG-IUD group in Denmark population was 3.90). Dr. Moyé concedes that those ratios, being derived from Valenzuela, did not control for the confounding factors of age or weight. He terms that shortcoming "regrettable." *Id.* at 31. Nevertheless, Dr. Moyé concludes, because the relative risk ratios (particularly as to Utah) were substantial, "it would be unreasonable to assume that the large odds ratios observed in the Utah cohort would be completely adumbrated by adjustment for obesity and age." *Id*. at 31–32. The association between Mirena and IIH, he states, was "not likely to be overshadowed by any adjustment for confounders." *Id.* at 32.

In discussing this factor, Dr. Moyé also responds to Bayer's argument that the Valenzuela study, independent of its not having controlled for confounding factors, was compromised by selection-bias flaws in its choice of populations.[25] Bayer has argued that the Valenzuela study ascertained Mirena usage differently between its IIH (case) groups and its non-IIH (control) groups, causing the study to undercount Mirena use in the control groups and to make Mirena

[25] Selection bias occurs when different groups in a study (*i.e.*, case vs. control) have systematic characteristics that distinguish them from the population intending to be studied such that the results of the study are skewed by those characteristics. Misclassification bias occurs when a study participant is incorrectly placed with the wrong category or group.

use appear comparatively more common among IIH patients. Bayer Omnibus Br. at 16–17.[26] In his response as to the Utah population, Dr. Moyé does not address whether it was inappropriate for Valenzuela to include certain types of patients in the case but not the control group. Instead, he states that "there is no perfect process by which one can ascertain exposure status." Moyé Rpt. at 31.[27] In his response as to the Denmark population, Dr. Moyé does not address whether (as Bayer has claimed) it had been wrong not to consider the amount of time between the start of

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[26] In particular, Bayer has contended as to the Utah group that:

> [I]n the Utah group, the authors used telephone interviews to determine whether patients with IIH (cases) had used Mirena when their symptoms began, regardless of where (University of Utah versus elsewhere) or when (during the study period versus prior to 2008) their IUD was inserted. But for the control group they relied on billing records documenting only those patients whose Mirena was inserted at the University of Utah during the study period, thereby missing patients who received Mirena at sources like Planned Parenthood, community OB/GYN practices, or out-of-state, or who had their IUD inserted before 2008 but were still using it.

Bayer Omnibus Br. at 17 n.9. And, Bayer has noted as to the Denmark group that:

> [I]n the Denmark arm of the study, the authors counted women with IIH (cases) as Mirena 'users' if their medical records indicated that they had a Mirena in place at the time their IIH occurred, regardless of whether their Mirena was placed that year or some earlier year. Among women without IIH (controls), the authors estimated Mirena "use" by dividing the number of Mirenas sold in Denmark in a single calendar year (2014) by the female reproductive-age population in the entire country. As Mirena is used on average for more than one year, this differentially miscategorized women in the controls as non-users, resulting in much higher Mirena rates in the case group than in the control group.

Id.

[27] Dr. Moyé notes a possible selection bias pointing the opposite way: Insofar as Valenzuela's selection criteria required the IIH patients to have been on a contraceptive for at least three months before they developed IIH, the study, he states, might have excluded patients who "were exposed to LNG-IU[D], developed [IIH] shortly thereafter, but cannot recall their contraception history prior to LNG-I[D]S." *Id.* This, Dr. Moyé states, might lead to an *underestimation* of the IIH cases.

the patient's Mirena usage and the patient's manifestation of IIH symptoms. Instead, he responds to Bayer's separate argument that the correct proportion of women using Mirena in Denmark at the time is 10%, and not the 3.5% used by Valenzuela. Dr. Moyé questions the study on which Bayer's 10% calculation was based.[28] *Id.* at 33. Dr. Moyé ultimately concedes that, lacking the underlying data the studies used, "it is impossible to determine the relationship between the two and reconcile the apparent contradiction between the two papers . . . ." *Id.*[29] In the end, Dr. Moyé states, "selection and misclassification biases would need to be overwhelming to reverse" his finding of an association between Mirena and IIH in the two populations. *Id.* at 34. He observes that "the consistency of the finding from two different populations is striking, even after taking into account that the results are provided by the same investigators." *Id.*

Temporality: Dr. Moyé finds the temporality factor met, based on case reports in Bayer's 2017 adverse events database. *See* Moyé Rpt. at 34–37. "Temporality requires that exposure occur before the disease," Dr. Moyé notes, and "[c]ases in the Bayer database demonstrate the occurrence of [IIH] after the insertion of the Mirena device." *Id*. at 34. Dr. Moyé identifies 13 cases in that database that he states showed that Mirena had likely caused the patient's IIH symptoms. *Id.* at 34–36. Each, he contends, reflected "a reasonable time relationship between Mirena exposure" and the patient's IIH; "it is unlikely," he states, "that the [IIH] would be attributed to other factors." *Id*. at 37. Dr. Moyé draws these 13 examples from the

[28] *See* Lindh et al., *Contraceptive use in the Nordic countries*, 96 Acta Obstetricia et Gynecologica Scandinavica 19 (2017).

[29] Dr. Moyé does address Bayer's proposed "corrected" version of Valenzuela, which substituted, in lieu of the Valenzuela controls, Bayer's own calculation based on data from two other studies. Disputing the usefulness of such data, Dr. Moyé notes that it had been collected for the purpose of a state-by-state study of Zika preparedness, not to enable a study involving whether contraceptive use is linked to IIH. Moyé Rpt. at 30.

approximately 36 case reports that he reviewed from the Bayer database. Moyé Dep. at 231. It is unclear how the 36 cases were selected. Dr. Moyé appears to have reviewed them either in the order they were provided to him by counsel and/or by reviewing a chart of all case reports and deciding (based on criteria that are unclear) which to examine. Dr. Moyé did not review all of Bayer's adverse event reports regarding IIH. *Id.* at 229, 231.

Biological gradient: Dr. Moyé finds that "there is a biological gradient"—*i.e.*, that IIH occurs more frequently in Mirena users whose LNG levels are highest. *See* Moyé Rpt. at 39; *id.* at 37–39. He bases this finding on three sources: (1) the Valenzuela study, (2) Bayer's 2015 signal investigation, and (3) Bayer's 2017 BfArM response.[30] He explains that a "biologic gradient involves the presence or absence of a relationship between the exposure to the potential hazard and the occurrence of the disease." *Id.* at 37. Dr. Moyé finds such a dose-response effect because (1) in the Valenzuela study, the average duration of exposure prior to symptom onset was 22 months; (2) in Bayer's 2015 signal investigation and its 2017 response to BfArM, respectively, 77.8% and 62.9% of the cases of IIH (with time-to-onset information) occurred within the first two years of patients' Mirena exposure; and (3) during the first two years of usage, LNG levels are the highest and most variable. *Id.* at 39. However, Dr. Moyé concedes that he did not have the full underlying data for the time-to-onset discussed in the Valenzuela paper nor the median time to onset. *Id.* He therefore infers, based on the fact that the mean

[30] Dr. Moyé also cites the Mirena label, and Bayer's studies of ovarian cysts as they relate to Mirena and other hormone-releasing contraceptive devices, as supporting that the appropriate way to analyze the biological gradient for IIH and Mirena is to look at the patient's short-term exposure to LNG, as opposed to her cumulative exposure to LNG due to long-term Mirena use. *Id*. at 38–39. However, on the record before the Court, those materials do not indicate, with respect to short-term exposure to LNG, a dose-response relationship with respect to IIH. The Mirena label is silent as to that point. And while Bayer's study of ovarian cysts is not in evidence, its analysis presumably addressed ovarian cysts, not IIH.

exposure was less than two years, that the majority of IIH cases addressed there had occurred within the first two years of the patient's Mirena use. *Id.*

Biological plausibility: Dr. Moyé proposes a biological mechanism as to how LNG might plausibly cause IIH. He embraces an "androgen" theory: He posits that LNG mimics "the action of the mineralocorticoid aldosterone, thereby increasing sodium ion and water flow into the central spinal fluid, and subsequently increasing CSF pressure." Moyé Rpt. at 40. Dr. Moyé does not develop this theory. Instead, he recites nine propositions for which he stated there are biomedical sources. These, he states, when viewed in combination, support such a causal mechanism for Mirena. *Id.* Dr. Moyé includes a blanket citation to 40 academic articles. *Id.* at 40–41.

Coherence: Dr. Moyé finds this factor met, because the biological mechanism he endorses "relies on known science . . . and is therefore in concordance with modern molecular biology." *Id.* at 41.

Consistency: Dr. Moyé finds this factor met, because the Valenzuela study had involved two different populations and had used different protocols to select patients (health data in Utah; census data in Denmark). *Id.*

Specificity: Dr. Moyé concedes that IIH has multiple causes. But, he states, alternative causes to Mirena "can either be excluded, statistically adjusted out of consideration, or accounted for in a multi-factorial causation model." *Id.* He does not state that this exercise has ever been performed anywhere.

Experimental evidence: In finding this factor met, *id.* at 41–42, Dr. Moyé relies on five case reports drawn from the 2017 Bayer database. He terms these "representative" examples of a "challenge-dechallenge"—that is, a situation in which a patient developed IIH while using

Mirena, and then, after the Mirena had been removed, "either recovered or improved." *Id.* at 41. Dr. Moyé's examples, however, are not representative of the cases in Bayer's adverse events database, as described in Bayer's BfArM report. That report states that, of the 68 patients whose Mirena had been removed and for whom further information was available, 31 (or 46%) "did not recover," 23 (or 34%) had "improved," and 14 (or 20%) had "recovered." Bayer BfArM Response at 49. For an additional 128 patients, "no information on the further course of the disease was provided. *Id.* In contrast, of Dr. Moyé's five case reports, four patients (80%) had recovered, one (20%) had "improved," and none "did not recover." *See* Moyé Rpt. at 41–42. Pressed in his deposition on his claim that his five-case sample was "representative," Dr. Moyé stated that he had viewed his sample as representative not of the Bayer database, but of the subset of patients where the "phenomenon of dechallenge was observed"—that is, where the IIH symptoms had disappeared after a Mirena was removed. Moyé Dep. at 241.

Analogy: In finding this factor met, Moyé Rpt. at 42–43, Dr. Moyé analogizes to one published study of Norplant, by Wysowski and Green. He opines that it supported that Mirena causes IIH. However, as noted earlier, that study is not an epidemiological study. It discusses a collection of adverse event reports involving Norplant. Wysowski and Green concluded that, based on the evidence before them, it was "not possible" to determine whether "a causal association exists" between Norplant and IIH. Wysowski and Green, *supra*, at 541.

4. Analysis Under *Daubert*

Either explicitly or implicitly, Dr. Moyé finds that each of the nine Bradford Hill factors is met here. On that basis, he opines that use of the Mirena IUD is a cause of IIH.

Of the four plaintiffs' experts who reached this conclusion by applying the Bradford Hill or on a similar totality-of-the-circumstances approach, Dr. Moyé's assessment of the constituent

factors is, in the Court's assessment, the most thorough and substantial. However, on inspection, his analysis is flawed by serious methodological deficiencies. These include an unweighted and unmoored application of the nine Bradford Hill factors, a failure to consider known contrary evidence, a contravention of principles which Dr. Moyé has acknowledged should guide an epidemiologist's inquiry, a selective use of case report data, a lack of qualification to opine on biological mechanisms by which Mirena might cause IIH, and the citation of the Valenzuela study for propositions that it did not find. Under *Daubert* principles, these flaws, reviewed below, make Dr. Moyé's proposed testimony unreliable and inadmissible.

To begin, as appears undisputed, Dr. Moyé's opinion does not satisfy any of the four reliability factors identified in *Daubert*. He has not tested his theory. He has not subjected it to peer review or had it published. He has not identified an error rate for his application of the nine Bradford Hill factors. And vetting of a multi-factor inquiry to yield a numeric error rate appears realistically impossible, as there are no "standards controlling the technique's operation." *Daubert*, 509 U.S. at 594. Finally, the theory he advances in this litigation has not been "generally accepted by the relevant scientific community." *Id*. at 584. Quite the contrary: Outside of this litigation, there is a complete absence of scholarship opining that Mirena, or for that matter any LNG-based contraceptive, is a cause of IIH.

The Court therefore must take a "hard look" at Dr. Moyé's methodology. *See Mirena Perforation / Daubert*, 169 F. Supp. 3d at 430, 449.

Such scrutiny is particularly warranted given Dr. Moyé's choice of methodology. As courts have recognized, it is imperative that experts who apply multi-criteria methodologies such as Bradford Hill or the "weight of the evidence" rigorously explain how they have weighted the criteria. Otherwise, such methodologies are virtually standardless and their applications to a

particular problem can prove unacceptably manipulable. Rather than advancing the search for truth, these flexible methodologies may serve as vehicles to support a desired conclusion.

As the Third Circuit has put the point: "To ensure that the Bradford Hill/weight of the evidence criteria is truly a methodology, rather than a mere conclusion-oriented selection process . . . there must be a scientific method of weighting that is used and explained." *In re Zoloft*, 858 F.3d at 796 (quotation marks omitted); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607 (D.N.J. 2002) (same), *aff'd*, 68 F. App'x 356 (3d Cir. 2003). And as the First Circuit has required, while the expert's bottom-line conclusion need not be independently supported by each of the nine Bradford Hill factors,[31] in analyzing the factors, separately and together, the expert must employ "the 'same level of intellectual rigor' that he employs in his academic work." *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 26 (1st Cir. 2011) (quoting *Kumho Tire*, 526 U.S. at 152).

Accordingly, where experts have claimed to apply Bradford Hill, courts have insisted on a clear explication of the weighting assigned to the different criteria. They have also demanded that the expert's application of the individual criteria be performed with proper rigor. "[T]he specific techniques by which the weight of the evidence/Bradford Hill methodology is conducted must themselves be reliable according to the principles articulated in *Daubert*." *In re Zoloft*, 858 F.3d at 796; *see id.* ("An expert can theoretically assign the most weight to only a few factors, or draw conclusions about one factor based on a particular combination of evidence. The specific way an expert conducts such an analysis must be reliable; 'all of the relevant evidence must be

[31] *See* Austin B. Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295, 299 (1965) ("None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*.").

gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science.'" (quoting *Magistrini*, 180 F. Supp. 2d at 602)). Insistence upon such rigor guards against the pitfall of which Judge Seibel warned in excluding expert testimony in the earlier Mirena litigation: "reverse-engineering a theory to fit the desired outcome." *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 430; *see also Faulkner*, 46 F. Supp. 3d at 381.

Measured against these standards, Dr. Moyé's report falls short.

At the most general level, his report does not explain the weight that he attaches to any of the Bradford Hill criteria or address the relationship among them. Instead, he finds that *all* nine criteria support a finding that Mirena causes IIH. Indeed, he nowhere concedes that any criterion even is only weakly supportive of a finding of causation. By leaving obscure the weight that he attaches to each of the nine Bradford Hill factors and the relationship among them, Dr. Moyé's approach effectively disables a finder of fact from critically evaluating his work.

To illustrate the point: A finder of fact might, for example, take issue with Dr. Moyé's assessment of the first factor—the gating factor of strength of association. Dr. Moyé finds a "strong association" based principally on the Utah component of the Valenzuela study. Moyé Rpt. at 31. Dr. Moyé's fellow expert, Dr. Wheeler, however, reaches a different conclusion—he concludes that, based on the Valenzuela and Etminan studies, "there is no association demonstrated." Wheeler Dep. 200. And the Valenzuela study on which Dr. Moyé bases his strength-of-association finding stopped well short of finding a strong association. The authors pointedly cautioned that "[a]lthough use of an LNG-IU[D] seems [to] be associated with an increased risk of PTC, it is possible that this observation occurred because use of an LNG-IU[D] is also associated with other risk factors that are known to be associated with PTC (e.g., obesity

and recent weight gain)." Valenzuela, at 4; *see also id.* at 5 ("[I]t is also important to consider that the risk analysis does not account for potential confounders."). A finder of fact might therefore come to a conclusion other than that of Dr. Moyé as to strength of association, perhaps finding, for example, in between Drs. Moyé and Wheeler, that there is a statistical association, but only a weak one, between Mirena and IIH. Such a finder would then have to consider whether the other Bradford Hill factors, if now viewed in the context of only a weak statistical association, support a finding of causation. Dr. Moyé's failure to weigh or explain the relationship among the factors in his analysis, however, would disable such an inquiry.

Alternatively, a finder of fact might take issue with Dr. Moyé's conclusions that other Bradford Hill factors support Mirena's causation of IIH. A finder might so conclude based on concerns about proper methodology (including along the lines discussed below). Or a finder might substantively disagree with Dr. Moyé as to particular factors. Such a finder would then need to assess whether to find general causation in the absence of certain factors. Dr. Moyé's failure to weight factors or explain the relationship among them would preclude this assessment, too. Does Dr. Moyé's conclusion of causation still stand if the Bradford Hill factor of analogy is not found to favor that result? Or the factor of specificity? Or the factor of consistency? Or all of the above—or yet other factors? Dr. Moyé's unscientific "black box" approach to Bradford Hill review almost entirely prevents the finder of fact, or other experts seeking to validate or check his work, from conducting a meaningful and informed review.

As to his assessment of individual Bradford Hill factors, Dr. Moyé's mode of analysis, too, departs repeatedly from reliable methodology. Four examples, among others, illustrate the point.

As to the Bradford Hill factor of analogy, this factor requires "substantiation of relationships similar to the putative causal relationship . . . ." Thompson, *supra*, at 268. Dr. Moyé elsewhere has acknowledged this requirement.[32] In this case, Dr. Moyé finds that this factor supports concluding that Mirena causes IIH based on an analogy he makes to Norplant. But this analogy is founded on an unestablished hypothesis about Norplant. As noted, a cause-and-effect relationship between Norplant and IIH has never been substantiated. No epidemiological study of the relationship, if any, between Norplant and IIH has ever been conducted. Dr. Moyé bases his conclusion that Norplant causes IIH, and hence can be the basis for an analogy, solely on case reports discussing Norplant as reviewed in the study by Wysowski and Green. But these Norplant case reports, as Dr. Moyé admitted in his deposition, were all subject to confounding factors such as obesity and weight gain. Moyé Dep. at 270–72. And the Wysowski and Green study, on which Dr. Moyé relies, clearly stated that this evidence falls well short of establishing a causal relationship between Norplant and IIH. *See* Wysowski and Green, *supra*, at 541; *see also* Reference Manual on Scientific Evidence at 218 (Dkt. 167-86) ("Anecdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group."); *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1254 (11th Cir. 2005) ("[C]ase reports raise questions; they do not answer them."). In his deposition, Dr. Moyé admitted that he is unable to opine that Norplant causes IIH, and that it is an open question whether Norplant does so. Moyé Dep. at 56. Dr. Moyé's analytic approach as to the analogy factor, based as it is on "the *ipse dixit* of the expert," *Gen. Elec. Co.*, 522 U.S. at 146—on an

[32] *See* Lemuel A. Moyé, *Multiple Analyses in Clinical Trials: Fundamentals for Investigators* 389 (2006). ("Analogy: This would include a similarity to some other *known* cause-effect association." (emphasis added)).

inaccurate account of the scholarship as to whether the analog product, Norplant, causes IIH—is therefore foundationally unsound.

As to the Bradford Hill factor of specificity, this factor inquires into the number of causes of a disease. As Dr. Moyé explained: "The greater the number of causes of a disease (*i.e.*, the more multifactorial the risk factors causing the disease), the more nonspecific the disease is, and the more difficult it is to demonstrate a new causal agent is involved in the production of the disease." Moyé Rpt. at 19. In finding the specificity factor satisfied, Dr. Moyé devoted two sentences to his discussion. In the first, he admits that "[IIH] has multiple causes." *Id*. at 41. In the second, he states that the alternative causes (*i.e.*, all but Mirena) "can either be excluded, statistically adjusted out of consideration, or accounted for in a multi-factorial causation model." *Id.* Dr. Moyé's reliance on this conclusory statement as a basis for finding the specificity factor met, too, departs from rigorous methodology. Dr. Moyé does not cite any study in which any such statistical adjustment has actually been performed so as to isolate Mirena as a cause of IIH, as distinct from other factors. His conceptual point about the potential to exclude alternative causes is, at best, theoretical. And the one epidemiological study on which Dr. Moyé relies in his Bradford Hill analysis, Valenzuela, did not undertake any such statistical adjustment. On the contrary, it pointedly *disclaimed* any finding that Mirena causes IIH, on account of confounding risk factors prevalent among the dominant population of Mirena users. *See* Valenzuela at 5 ("When interpreting the findings presented here, it is also important to consider that the risk analysis does not account for potential confounders.").

As to the Bradford Hill factor of consistency, it tends to require "similar findings . . . generated by several epidemiological studies involving various investigators." *See* Thompson, *supra*, at 268; *see also* Reference Manual on Scientific Evidence at 604 ("It is important that a

study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists."). Dr. Moyé opines that the Valenzuela study "satisfies the consistency metric," because Valenzuela considered two separate populations. Moyé Rpt. at 41. These studies, however, were conducted by the same investigators.[33] More problematic as a matter of methodology, neither cohort study in Valenzuela found what was "important"—"a causal relationship." Reference Manual on Scientific Evidence at 604. Even accepting Valenzuela as containing "similar findings" from multiple epidemiological studies, Dr. Moyé's finding that the consistency metric was satisfied ignores the very limited point that the studies addressed and on which they were therefore consistent. The studies were consistent only as to the fact of a correlation—subject, as Valenzuela repeatedly pointed out, to potential confounders—between Mirena and IIH. They explicitly disclaimed a finding of causality.

Finally, as to the Bradford Hill factor of biologic plausibility, Dr. Moyé bases his finding that this factor was satisfied on his conclusion that a mineralocorticoid (MR) theory by which Mirena causes IIH is plausible. He posits that LNG mimics "the action of the mineralocorticoid aldosterone, thereby increasing sodium ion and water flow into the cerebral spinal fluid, and subsequently increasing CSF pressure." Moyé Rpt. at 40; *see* Moyé Dep. 249 ("Q: As I understand what you have written in your report you rely on the MR theory; is that correct?" A: Correct. Q: Not the androgen receptor theory? A: [T]hat is correct."). But, as Bayer rightly argues, Dr. Moyé—a medical doctor who doubles as a professor of biostatistics—is not qualified

[33] This shortcoming would not independently require exclusion of an otherwise methodologically sound Bradford Hill analysis at trial. *See* Reference Manual on Scientific Evidence at 604 (citing *Smith v. Wyeth-Ayerst Labs. Co.*, 278 F. Supp. 2d 684, 710 n.55 (W.D.N.C. 2003), for the point that replication is difficult to establish when there is only one study that has been performed at the time of trial, and that this may satisfy the "legal standard").

to opine about a biological mechanism by which Mirena might cause IIH. Dr. Moyé is not educated in the relevant disciplines: pharmacokinetics and pharmacodynamics. Moyé Dep. 85–86 ("Q: Do you hold yourself out as a pharmacokinetics expert? A: No. Q: Do you hold yourself out as a pharmacodynamics expert? A: No."). He is not trained in gynecology, either. And plaintiffs have not come forward with evidence that Dr. Moyé has acquired sufficient practical experience in these areas to make up for his lack of relevant education or training. Before this litigation, Dr. Moyé had not conducted research on LNG generally or on its hormonal impact on MR receptors. *Id.* at 85, 262. Dr. Moyé, instead, provides a blanket citation to 40 academic articles, none of which address Mirena, to support his finding of biological plausibility based on an MR mechanism.

Simply stated, by any measure, Dr. Moyé is unqualified to give an expert opinion as to a biological mechanism of causation of IIH. His lack of qualifications to so opine makes unreliable not only Dr. Moyé's assessment as to biological plausibility—that the MR mechanism is a biologically plausible one. It also compromises his assessment of the companion Bradford Hill factor of coherence, because Dr. Moyé finds that factor met explicitly based on his assessment that the mechanism he had endorsed is a coherent one. *See* Moyé Rpt. at 41 ("The mechanism of 1) increased egress of Na+ ion and water flow into the CSF from the choroid plexus producing CSF, and 2) decreased flow []either by decreased activity of carbonic anhydrase, or reversal of the effect of steroid hormones that mimic aldosterone in the MR can reduce the symptoms of [IIH] does not contradict known science.")

Common to Dr. Moyé's misapplications of the above Bradford Hill factors is this: Each of Dr. Moyé's departures from settled and rigorous methodology favors the same outcome. Each enables him to find that the Bradford Hill factor at issue supports concluding that Mirena is a

cause of IIH. At bottom, as the Supreme Court instructed in *Daubert*, expert testimony "must be supported by appropriate validation—*i.e.*, good grounds, based on what is known." *Daubert*, 509 U.S. at 590 (internal quotation marks omitted). Dr. Moyé's unidirectional misapplication of a series of Bradford Hill criteria is concerning—it is a red flag. Rather than suggesting a scholar's considered neutral engagement with the general causation question at hand, it suggests motivated, result-driven, reasoning. *See Faulkner*, 46 F. Supp. 3d at 381 ("[M]ethodology . . . aimed at achieving one result . . . is unreliable.").

Yet other methodological lapses also preclude, as unreliable under *Daubert*, Dr. Moyé's proposed testimony.

For one, Dr. Moyé ignores scientific standards that he has conceded govern inquiries into general causation. In his deposition, Dr. Moyé agreed, for example, with certain widely accepted principles of medical research. One is that case reports do no more than raise the question of a causal connection between a drug and a disease; they cannot establish causation. Moyé Dep. at 272. A related principle that he acknowledged is that, to prove general causation, observational studies, such as a case control study or a cohort study, generally are required. *See id.* at 125 (agreeing that a single observational study "[r]arely, if ever . . . persuasively demonstrate[s] a cause-effect relationship"); *id.* (agreeing that "it is important that an observational study be replicated in different populations and by different investigators before a causal relationship is accepted").

Dr. Moyé's report is unfaithful to these precepts. Dr. Moyé finds causation of IIH by Mirena in the absence of any of the sorts of studies that he concedes generally are required. As to studies, he relies solely on the Valenzuela study, a retrospective epidemiological study which stopped well short of finding causation, recognizing that it had not controlled for major

confounding variables such as obesity and weight gain that are prevalent both among IIH patients and the population of Mirena users. In his deposition, Dr. Moyé admitted Valenzuela's limitations. *See, e.g.*, Moyé Dep. at 215 ("Q: Would you conclude causation with just the results of Valenzuela standing alone? A: No, sir, I would not."); *id.* at 216 ("I think an appropriate statement would be to say that it's possible that LNG-IU[D] causes PTC, but this study doesn't show it."). And Dr. Moyé also appears to rely on case reports for more than merely raising a question about whether a causal relationship between Mirena and IIH existed. In his report, Dr. Moyé uses case reports (and a study aggregating such reports) almost exclusively to establish three of the nine Bradford Hill factors: experimental evidence, temporality, and analogy. *See Amorgianos*, 303 F.3d at 269 (affirming exclusion of proffered expert who "fail[ed] to apply his stated methodology reliably to the facts of the case") (internal quotation marks omitted); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 561 (W.D. Pa. 2003) (excluding experts "[b]ecause consistency is a hallmark of the scientific method [and] plaintiff's experts must be required to satisfy their own standards of reliability"); *cf. Kumho Tire Co.*, 526 U.S. at 152 (expert is expected to "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field").

Dr. Moyé also chooses not to consider evidence that undercuts his opinion—potentially very materially. This is a separate methodological failing. It is most strikingly apparent in Dr. Moyé's consideration of the analogy factor. Dr. Moyé elects to analogize to Norplant. As to Norplant, he draws on isolated case reports canvassed in a study (Wysowski and Green) that disclaimed a finding of causation. He also analogizes to case reports in which, he states, a relationship was indicated between IIH and "elevated testosterone levels." Moyé at 42–43. As

to this factor, he thus is willing to range outside the area of LNG-containing intra-uterine devices, considering case reports as to other products and other hormones.

In so doing, however, Dr. Moyé, tellingly, does not consider an analogy between Mirena and other LNG-containing contraceptive drugs: combined oral contraceptives containing LNG. Consideration of those products stood to seriously undermine Dr. Moyé's conclusion. As noted, five epidemiological studies have uniformly *failed* to demonstrate a link between such oral contraceptives and IIH, even though LNG-containing oral contraceptives generally contain far higher doses of LNG than Mirena, and IIH. Whatever the scientific distinctions that might have been made between oral and intra-uterine delivery systems for LNG, these studies demanded Dr. Moyé's consideration. Yet Dr. Moyé does not review them. Moyé Dep. at 51–52.

Dr. Moyé's decision to brush aside these epidemiological studies, while analogizing to a different medical device and a different hormone based exclusively on case reports, departs from reliable, rigorous methodology. "[A]n expert may not pick and choose from the scientific landscape." *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d at 563 (internal quotation marks omitted); *see also MTX Commc'ns Corp. v. LDDS/WorldCom, Inc.*, 132 F. Supp. 2d 289, 293 (S.D.N.Y. 2001) (excluding expert who omitted "major variables" from his analysis); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) ("*In re Bextra*") ("[R]ejecting or ignoring" unfavorable evidence "is not 'good science.'").[34]

[34] A separate issue with regard to disregarding contrary evidence is presented by Dr. Moyé's treatment of the Etminan study. Like other plaintiffs' experts, Dr. Moyé does not consider Etminan's retrospective cohort study—the portion of Etminan's work as to Mirena and IIH that has not been repudiated. As noted, that study did not find any statistically significant difference in IIH risk between Mirena and combined oral contraceptives. Bayer argues that Dr. Moyé's failure to consider this study was a separate lapse.

Finally, Dr. Moyé's sampling of case reports—which played a central role in his report at various points—is performed in a manner not bespeaking scientific rigor or neutrality. Rather than selecting case reports through random sampling or by a representative cross section, Dr. Moyé appears to draw the case reports that he considers from those presented to him by counsel or from a spreadsheet whose design is elusive. This skewed methodology has obvious potential to yield a skewed sample and result. Relatedly, Dr. Moyé's five chosen "dechallenge" cases are unrepresentative of the much larger sample covered by the BfArM report; and the examples he chooses tended to favor his bottom-line causation conclusion.[35]

Dr. Moyé's failure to apply neutral selection methodology as among such anecdotal evidence is unscientific. Viewed in combination with the other deficiencies noted, this failing, too, supports excluding his testimony. *See U.S. Info. Sys., Inc. v. Int'l Bhd. of Elec. Workers Local Union No. 3, AFL-CIO*, 313 F. Supp. 2d 213, 235 (S.D.N.Y. 2004) (excluding expert who relied on biased sample of data); *Rowe Entm't, Inc. v. William Morris Agency, Inc.*, No. 98 Civ. 8272 (RPP), 2003 WL 22124991, at *3 (S.D.N.Y. Sept. 15, 2003) (same); *but see Auto. Ins. Co. of Hartford, Conn. v. Electrolux Home Prods., Inc.*, No. 10-CV-0011 CS, 2012 WL 6629238, at

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The Court agrees with Bayer that a complete analysis by Dr. Moyé ought to have at least considered this scholarship, particularly insofar as Etminan is just one of two epidemiological studies (the other being Valenzuela) of Mirena and IIH, and insofar as the Etminan's study's conclusion in the retrospective cohort study was contrary to the interests of the litigation party that had retained Dr. Etminan. However, given Dr. Etminan's unusual and dramatic repudiation of the other half of his study, the Court regards Dr. Moye's decision not to consider *any* part of the Etminan study as more understandable and defensible than his other methodological failings. The Court's rulings excluding Dr. Moyé and plaintiffs' other proposed general causation experts do not depend on these experts' failure to consider the Etminan retrospective cohort study.

[35] Although collections of adverse event reports are often inherently skewed—they reflect the particular experiences and reporting impulses of the doctors, lawyers, and others who choose to make reports—it is reasonable to expect a scholar presented with a collection of such reports to use neutral principles in selecting among them. Cherrypicking among them risks compounding the skew.

*2 (S.D.N.Y. Dec. 20, 2012) ("Potential sample bias is a subject for cross-examination, and goes to the weight, not the admissibility, of the expert testimony.")

In conclusion, Dr. Moyé's proposed testimony is compromised by a range of serious methodological flaws. It fails to meet the standard for reliability required by *Daubert*. The Court must exclude it.

B. Dr. Laura Plunkett

1. Qualifications

Dr. Plunkett is a pharmacologist and toxicologist with more than 20 years' experience in those fields. She received her B.S. in 1980 from the University of Georgia and a Ph.D. in pharmacology in 1984 from the University of Georgia, College of Pharmacy. Plunkett Rpt. at 1. She has worked as a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences (approximately two years), an Assistant Professor of Pharmacology and Toxicology at the University of Arkansas for Medical Sciences (almost three years), and a consultant for ENVIRON Corporation (almost eight years). *Id.* at 1–2. Dr. Plunkett has also served as a consultant for Integrative Biostrategies and at Plunkett & Associates. *Id.* Her professional career has consisted predominantly of working as a paid consultant, including substantial service as a compensated expert. *See* Plunkett Dep. at 351 (expert work made up about 55% of her income in 2016). In the last five years she has testified approximately 65 times. *See* Plunkett Rpt. at App'x C.

Dr. Plunkett has experience "examining the risks associated with exposure to hormones and the risks associated with altered hormonal status in women." *Id.* at 2. However, she is not a medical doctor. She has neither published on IIH nor spoken about the disease to doctors who treat it. Plunkett Dep. at 111–12.

2. Proposed Testimony

Dr. Plunkett's proposed testimony can be divided into two parts: (1) a discussion of the pharmacokinetics of LNG-releasing contraceptives, and (2) an application of the Bradford Hill methodology, which she alternatively describes as a "weight of the evidence" analysis, with the conclusion that Mirena causes IIH.

a. The Pharmacokinetics of LNG

Dr. Plunkett's discussion of the pharmacokinetics of LNG informs her application of the Bradford Hill methodology. Because Bayer either concedes or does not substantially contest most of this discussion, the Court highlights only Dr. Plunkett's major points.

First, Dr. Plunkett discusses the difference between "free" LNG and total LNG. She asserts that free LNG levels should be used to access a patient's exposure and response to the hormone. The vast majority of LNG in the blood stream is not "free" floating. Instead, she states, upwards of 98% of LNG is bound to plasma proteins (specifically albumin and a carrier protein called steroid hormone binding globulin). However, she states, LNG's effects are not generally created by such bound LNG. Rather, they are created by "free" LNG activating nuclear hormone receptors. Thus: "It is the free or unbound LNG levels that correlate best with the biological responses observed in humans, not the total level of LNG in blood." Plunkett Rpt. at 7.

Dr. Plunkett also states that, although free LNG levels for Mirena are lower than the levels associated with other LNG-releasing contraceptive devices (such as Norplant), the LNG levels in the blood of patients using such devices overlap with the levels observed in Mirena patients. This overlap, Dr. Plunkett asserts, justifies analogizing Mirena to Norplant and other LNG-containing contraceptive devices. *Id.*

Dr. Plunkett notes that LNG is a progestin, which mimics the effects of progesterone. She observes that, relative to other progestins, LNG is androgenic, meaning that it can bind with androgen receptors. However, Dr. Plunkett notes, discerning a mechanism to explain the pharmacological and toxicological effects of progestins like LNG is extremely complicated. *Id.* at 10–12.

b. Application of Bradford Hill

Dr. Plunkett applies the Bradford Hill factors, as follows.

Strength of association: Dr. Plunkett frames her discussion of this threshold factor by quoting Sir Bradford Hill himself, to the effect that a scholar "must not be too ready to dismiss a cause and effect hypothesis merely on the grounds that the observed association appears to be slight," *id.* at 26 (citation omitted), and that "[n]o formal tests of significance can answer" whether there is a "cause and effect relationship," *id.* Dr. Plunkett then opines that three studies in the scientific literature "show[] that exposure to LNG from LNG intrauterine drug products has been associated with an increased risk of intracranial hypertension." *Id.* at 27. These were: (1) Etminan, (2) Valenzuela, and (3) Rai et al., *The Relationship Between the Levonorgestrel-Releasing Intrauterine System and Idiopathic Intracranial Hypertension*, ARVO (2015) ("Rai poster board presentation"). Beyond citing these studies, Dr. Plunkett does not discuss any of them in more than a sentence. As to the Etminan study, Dr. Plunkett acknowledges that, after Etminan's 2017 letter to the editor that factored in age-adjusted results, the results of his retrospective cohort study "were no longer statistically significant." *Id.* Nevertheless, she writes of the three studies:

> These human studies are an important piece of the weight-of-the-evidence for LNG exposure with Mirena and PTC, as they have shown a statistically significant risk of PTC when women are exposed to LNG drug products, including intrauterine devices such as Mirena. I used these human studies as part of my weight-of-the-evidence assessment.

Id. Dr. Plunkett's report does not mention or contend with the fact that the Valenzuela study had explicitly disclaimed a finding of a causal connection between IIH and Mirena. Nor does Dr. Plunkett's report note that the Rai poster presentation was a preview of the Valenzuela data presented prior to its 2017 publication and thus was substantively the same study as Valenzuela. In her deposition, Dr. Plunkett conceded those facts. Plunkett Dep. at 136–37, 165–66.

Temporality: In finding this factor satisfied, Dr. Plunkett states that she relies on three studies which, she stated, had "addressed" temporality (by Valenzuela, Rai, and Alder) and on three case reports drawn from the Bayer database. Plunkett Rpt. at 28. Beyond identifying these materials, however, Dr. Plunkett does not address their contents. The Valenzuela authors, for instance, specifically noted in their publication that they lacked temporal data. *See* Valenzuela, *supra*, at 4 ("The analysis was also limited by the lack of temporal data to confirm that exposure to LNG-IU[D] occurred prior to PTC symptom onset or diagnosis."). And Rai, as noted, was a precursor to Valenzuela and based on the same data. The third publication she cites, by Alder, was a letter to the editor that discussed two cases of IIH which arose in Norplant users after the Norplant's implantation. The Alder authors disclaimed any causal findings: "[Norplant] may have contributed to the onset of [IIH], or it may have had nothing to do with it." Alder, *supra*, at 1721. Dr. Plunkett's report does not note this disclaimer. As to the three case reports Dr. Plunkett cites, two involved Mirena and one involved Skyla.[36] While the Court assumes *arguendo* that the patients described in these reports developed IIH symptoms after they began use of the LNG-based contraceptive product, Dr. Plunkett's report does not so state. *Id.* at 28.

[36] Skyla is marketed in Europe as Jaydess. Dr. Plunkett incorrectly states that Jaydess and Jadelle are the same product. Plunkett Rpt. at 30. Jadelle is a sub-dermal contractive implant, similar to Norplant, which is placed in the arm. Skyla is an intrauterine device.

Biological gradient: Dr. Plunkett quotes Sir Bradford Hill in framing her discussion of this factor, in recognizing the "difficulty [of] secur[ing] some satisfactory" data to permit assessment of a dose-response effect. *Id.* In finding a possible such effect with respect to Mirena and IIH, Dr. Plunkett states that she relies on three sources: (1) a 1992 article (V. Brache, et al., *Free Levonorgestrel Index and Its Relationship with Luteal Activity During Long-Term Use of Norplant Implants*, 8 Soc'y for the Adv. of Contraception 319 (1992) ("Branche"); (2) Bayer's 2015 signal investigation; and (3) the Mirena 2017 signal assessment. The Branche article, according to Dr. Plunkett, had shown that in the first two years of LNG exposure, free LNG levels are higher than they otherwise would be. Plunkett Rpt. at 29. Dr. Plunkett finds that probative of a biological gradient, because approximately 75–80% of the IIH adverse events in Bayer's 2015 signal investigation had been reported during the first two years of Mirena use. *Id.* at 29. As for Bayer's 2017 signal assessment, Dr. Plunkett notes, it had compared the reporting frequency for IIH in Mirena and Skyla, which releases substantially less LNG than Mirena. The reporting frequency of IIH for each product was the same, which might seem to suggest, Dr. Plunkett acknowledges, the lack of a biological gradient. *Id.* at 30. However, Dr. Plunkett rejects that conclusion. She notes that there is "variability in LNG pharmacokinetics with both products, which would affect the levels of LNG in the blood achieved from patient to patient, and confound any attempt to identify a dose-response for LNG exposure and [IIH] in humans." *Id.* She also ventures that adverse events as to these drugs may have been significantly under-reported, a phenomenon particularly likely as to "drugs that may have been on the market for many years." *Id*. She ultimately concludes that "the available dose-response data provide support for the cause and effect assessment in terms of showing that increased levels of LNG in blood are more likely to be associated with adverse effects generally." *Id.* at 31. However, she

acknowledges, "[u]nfortunately, no dose or blood level threshold that is associated with an increased risk of [IIH] has been identified to date." *Id.*

Biological plausibility: Dr. Plunkett embraces the "androgen theory" of how LNG might cause IIH.[37] She does not, however, articulate a proposed mechanism to support that theory, as had Dr. Moyé. Instead, she cites literature that she contends found a link between IIH and androgens. *See id.* at 31–32; Plunkett Dep. at 311–16. Although acknowledging that LNG is a progestin, not an androgen, she terms it an "androgenic progestin." Plunkett Rpt. at 32.

Coherence: Dr. Plunkett does not cite any sources as to this factor, which she addresses in a short paragraph. Instead, she refers to her discussion of the biological plausibility that Mirena causes IIH, in that IIH "has been linked with androgenic activity." *Id.* at 33. She also cites "human epidemiological data" as to Mirena and IIH, apparently although not explicitly referring to the Valenzuela and Etminan studies. "[T]he data reported" in those studies, she states, "are consistent with what is known about the etiology of [IIH]." *Id.*

Consistency: Dr. Plunkett describes the consistency factor as turning on "whether the association being investigated has been seen repeatedly by different people, in different circumstances, and/or at different times." *Id.* at 27. She concludes that this factor is met, citing, although not further discussing, (1) the Valenzuela and Etminan studies, (2) several Norplant studies reviewed earlier (Wysowski & Green, *supra*; Sunku, *supra*; Alder et al., *supra*; and R.A. Tang, et al., *Pseudotumor Cerebri Associated with the Norplant Contraceptive Device*, Investigative Ophthalmology & Visual Science 36 (1995), and (3) an analogy to case reports of IIH experienced by patients using Norplant. *Id.* In her deposition, Dr. Plunkett acknowledged

[37] As articulated by Dr. Moyé, the "androgen theory," described above, posits that LNG causes an increased sodium ion and water flow into the central spinal fluid, thereby increasing CSF pressure.

that such case reports could not alone demonstrate causation. Plunkett Dep. 181–82 ("Absolutely. You need more than the case studies.").

Specificity: Dr. Plunkett states that this factor considers "whether the association is limited to specific types of activities or injuries." *Id.* at 27. Dr. Plunkett does not explicitly find this factor met, stating more obliquely that "considering specificity of the relationship has been part of my overall assessment." *Id.* at 28. She acknowledges that the scientific literature addressing the relationship between Mirena and IIH described "confounding factors . . . such as obesity [and] female gender." *Id.* at 27–28.

Experimental evidence: Dr. Plunkett casts this factor as "relat[ing] to the ability to collect data in order to analyze the cause and effect relationship." *Id.* at 33. In finding it met, Dr. Plunkett relies on publications above regarding Norplant, and on Bayer's 2015 signal assessment data, the latter of which, she stated, contained examples of "dechallenge." She concedes, however, that animal or cell experiments are the evidence typically used in experiments used to find causation, and that none have been conducted regarding LNG and IIH. Plunkett Rpt. at 35.

Analogy: Dr. Plunkett analogizes Mirena to Norplant. She relies on the publications cited above regarding Norplant. As noted, however, these were not epidemiological studies—they instead discussed case reports—and none found causation by Norplant of IIH. Dr. Plunkett also cites several studies which discuss IIH's etiology and list LNG as associated with IIH. None, however, had found that LNG is causally linked to IIH. *See id.* at 34–35.

3. Analysis Under *Daubert*

Bayer argues that Dr. Plunkett's methodology in applying Bradford Hill is unreliable. Bayer is correct. The application of Bradford Hill in Dr. Plunkett's report has a number of

methodological flaws. Some are common with those noted in connection with Dr. Moyé. Dr. Plunkett's report is also validly called out for independent lapses, as reflected in the Court's assessment, below, of her applications of certain Bradford Hill factors.

To begin, in common with Dr. Moyé, Dr. Plunkett's report does not meet any of the four *Daubert* reliability factors. She has not tested her theory. She has not subjected it to peer review or had it published. She has not identified an error rate for her technique, and, as with Dr. Moyé's application of the Bradford Hill methodology, there are no standards controlling its operation. Finally, Dr. Plunkett's theory that Mirena is a cause of IIH, far from achieving general acceptance, has not been accepted by any part of the scientific community outside of this litigation. A "hard look" is therefore warranted as to her analysis, too. Compounding these problems, Dr. Plunkett, in common with Dr. Moyé, does not explain the weights she places on the various Bradford Hill factors. Instead, she reviews each in isolation, and opines or (where unable or willing expressly to so state) implies that each has been satisfied. And Dr. Plunkett's handling of individual factors is subject to grave methodological deficiencies. For all these reasons her application of Bradford Hill does not survive *Daubert* scrutiny.

The Court begins with Dr. Plunkett's reliance on the discredited portion of the Etminan study. That study is a centerpiece of her application of the first Bradford Hill factor. That factor requires a statistical, or strong, association between the cause under review and its asserted effect. [38] This factor is a necessary, or gating, factor for any Bradford Hill analysis to proceed, such that, if such a statistical association is not found, there is no charter to undertake a Bradford Hill analysis at all. *See* Federal Judicial Center, Reference Manual on Scientific Evidence, 599

[38] Dr. Plunkett also cited the Etminan study in finding satisfied the Bradford Hill factor of consistency.

n.141 (3d. ed. 2011) ("In a number of cases, experts attempted to use these guidelines to support the existence of causation in the absence of any epidemiologic studies finding an association. . . . There may be some logic to that effort, but it does not reflect accepted epidemiologic methodology."); Restatement (Third) Torts § 28 cmt. (c)(3) ("Even when epidemiologic studies find an association between a substance and a disease, further analysis is necessary before a causal conclusion can be drawn. . . . [I]f an association is found, epidemiologists use a number of factors (commonly known as the 'Hill guidelines') for evaluating whether that association is causal or spurious."); *see also In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 640 (4th Cir. 2018) ("*In re Lipitor*") (noting that the Reference Manual on Scientific Evidence and case law require a demonstrated epidemiological association).[39]

As reviewed earlier, Dr. Etminan retracted as unsound the disproportionality analysis in his study. He did so expressly in his 2016 affidavit and again functionally in his 2017 letter to the editor. As he explained in those writings, once the control group in the FAERS database was limited to reproductive age females, no elevated reporting odds ratio was observed for Mirena (statistically significant or otherwise). This, Dr. Etminan stated, "suggest[ed] that intracranial hypertension and Mirena use are 'likely *not* related.'" Etminan Affidavit ¶ 8 (emphasis added).

Notwithstanding these serial retractions, Dr. Plunkett relies on the Etminan study as a whole, including its DPA analysis, as a basis for her finding of a significant statistical association

[39] The Court does not hold here that a statistically significant association is required to justify the application of Bradford Hill. However, the Fourth Circuit has found that it was not an abuse of discretion for a judge to so require. *Id.* at 642.

between Mirena usage and IIH.[40] Her report acknowledges Dr. Etminan's letter to the editor stating that the data he reviewed in fact was not statistically significant as to a relationship between Mirena and IIH. Plunkett Rpt. at 27. Her report, however, then proceeds as if Dr. Etminan's repudiation had not occurred. Pressed at her deposition to justify relying on Dr. Etminan's discarded findings, Plunkett vaguely stated that the Etminan study's earlier analysis could be considered as "part" of a "weight of the evidence" analysis and that it was "supportive of [her] overall opinions." *See* Plunkett Dep. 146–52; *id*. at 152. ("Q: So now having seen the Etminan affidavit, you're still relying on Etminan 2015 as support for your causation opinion, correct? A: I am relying on that paper as part of the weight of the evidence. Certainly it by itself is not sufficient to prove causation." (objection omitted)); *id.* at 148 ("Q: Dr. Etminan states, 'Based on the above, as a lead author of this article, I acknowledge that neither of the analyses in the article provide evidence that Mirena use increases the risk for [IIH].' Do you disagree with that statement? A: Well, that's his opinion, so I can't agree with—disagree with his opinion. I do believe that there is data within this that is informative to weight of the evidence." (objection omitted)); *id* at 443 ("It is part of my overall weight of the evidence."); *id*. at 445 ("I think it is supportive of my overall opinions."). But, beyond stating that Dr. Etminan's initial findings could be considered as part of an overall mix, she did not explain on the merits why the repudiated findings warranted rehabilitation.[41] In the Court's assessment, Dr. Plunkett's

[40] Dr. Plunkett testified in her deposition that the separate, retrospective cohort study aspect of Etminan's work supports her conclusion. *See* Plunkett Dep. at 140–41. As reviewed above, however, that aspect of Etminan's study, on its face, does not support a finding of a correlation between Mirena and IIH.

[41] Defending Dr. Plunkett and the other plaintiffs' experts who continue to rely on Dr. Etminan's DPA analysis, plaintiffs argue that a scholar's affidavit repudiating a former study is not the sort of source material on which experts commonly rely. While that is surely empirically true, that is because repudiations—whatever the format—are themselves rare. In any event, Dr. Etminan

embrace of these author-repudiated findings is presumptively unsound methodology. *See* Moyé Dep. at 283–84 ("Q: Now, as a matter of epidemiology, would it be appropriate to rely on any part of a paper that was functionally retracted? A: I don't believe so."). It is reasonable to expect of an expert who relies upon a study repudiated by its own author to justify coherently this improbable approach.

Dr. Plunkett did not do so. Defending this component of her analysis in her deposition, Dr. Plunkett embraced anew the results of Etminan's study. She testified that the 1.85 reporting odds ratio used in Dr. Etminan's 2015 disproportionality analysis survived and remained "a reliable piece of evidence to be used within the weight of the evidence for causation." *See* Plunkett Dep. at 138–39. That premise is wrong. In his 2016 affidavit, Dr. Etminan explicitly repudiated the 1.85 reporting odds ratio. He implicitly did so again in his 2017 letter to the editor. There, he made clear that once the subject's reproductive age was taken into account, the reporting odds ratio would change.[42] Dr. Plunkett's uncritical and unwarranted reliance on the Etminan 2015 study in the face of the ultimate red flag—the study author's serial repudiations of

functionally expressed the same views, retracting this aspect of his analysis, in his 2017 letter to the editor of the same publication, Therapeutic Advances in Drug Safety, in which his original study had been published. There is no claim that a scholar's follow-on letter in the same forum as his original study is anomalous for a reviewing expert to consider.

[42] To the extent that Dr. Etminan's 2017 letter corrected data from his original study, it did so as to the proportional reporting ratio. Following that analysis, the association between Mirena and IIH disappeared. In describing (although proceeding not to heed) Dr. Etminan's 2017 letter, Dr. Plunkett states merely that the letter had indicated that the results from this aspect of the Etminan study were no longer statistically significant. In fact, the corrected results show more than that: Following Dr. Etminan's corrected analysis, the proportional odds ratio for Mirena was 0.90, meaning that there was a greater proportion of IIH cases reported among the *control group* than among the group using Mirena. In other words, on Dr. Etminan's corrected analysis, no signal—not even a statistically insignificant one—was detected at all.

it—is not consistent with rigorous dispassionate thinking. It suggests the sort of "conclusion-driven" analysis, *In re* Zoloft, 858 F.3d at 798, that *Daubert* does not permit.

A similar methodological lack of rigor is reflected in Dr. Plunkett's application of Bradford Hill's analogy factor. In finding that the analogy factor supported finding that Mirena causes IIH, Dr. Plunkett, like Dr. Moyé, centrally analogizes Mirena to Norplant. Plunkett Rpt. at 34–35. But, as Dr. Plunkett conceded in her deposition, she has not concluded that Norplant causes IIH. *See* Plunkett Dep. at 33–34. Nor, as noted earlier, has any existing scholarship reached that conclusion, as various of plaintiffs' other experts conceded. *See, e.g.*, Darney Dep. at 138. Dr. Plunkett's treatment of the analogy factor, like Dr. Moyé's, is therefore unsound, insofar as the premise of its analogy is an assumed, not an established, fact. For both of these experts, there is too great an analytic gap between the available data and the conclusion they draw.

Dr. Plunkett's approach as to the Bradford Hill factor that assesses experimental evidence is also problematic. Like Dr. Moyé, Dr. Plunkett does not, and given the non-existence of any experiment testing whether Mirena tended to cause IIH, could not point to any such experiment.

To find the experimental evidence factor satisfied, Dr. Plunkett instead, like Dr. Moyé, turns to examples of purported "dechallenges." Dr. Plunkett does not, however, cite, let alone analyze, any concrete such example. Instead, she cites without comment Bayer's 2015 signal assessment and publications addressing Norplant. Even on Dr. Plunkett's own terms, however, these sources were flawed as a basis for that conclusion, because the "dechallenge" examples addressed therein either explicitly were, or potentially were, subject to confounding factors. Bayer's 2015 signal assessment, for example, states that "[n]o unambiguous case of positive dechallenge could be identified." Bayer BfArM Resp. at 49. The writings that Dr. Plunkett cites

regarding Norplant are much the same. Sunku's poster presentation recounted two anecdotal examples of dechallenge; in each, the patient was treated with diuretics, supplying an obvious alternative to the removal of the Norplant as an explanation for the resolution of the patient's IIH symptoms. *See* Sunku, et al., *supra*. And Wysowski's study is silent about whether the Norplant removal of the patients that he described coincided with other treatment. *See* Wysowski & Green, *supra*, at 540. In any event, all the patients addressed by Wysowski for whom weight data was available were overweight, and most were obese. *Id.*

Like Dr. Moyé's, Dr. Plunkett's report also departs at points from standards that she acknowledges govern her work. This is exemplified by her discussion of the Bradford Hill factor of temporality. As background, Dr. Plunkett is not a medical doctor. She is not qualified to diagnose IIH or to apply a differential diagnosis to determine what caused a patient's IIH. And in her deposition, she therefore acknowledged that she cannot offer an opinion on why a patient's IIH resolved. Plunkett Dep. at 111, 124, 127–29, 131–35. Rather, she acknowledged that, when considering case reports, she was limited to considering "what is described by the doctor." *Id.* at 126. Dr. Plunkett, however, does not thus confine the analysis in her report. Drawing on Bayer's adverse events database in the course of discussing the Bradford Hill factor of temporality, her report cites three case reports. *See* Dkt, 167-73 ("Case Report A"); *id.* Ex. 74 ("Case Report B"); *id.* Ex. 75 ("Case Report C"). Yet in each, the patient's physician specifically reported that it was *unlikely* that the patient's apparent "IIH" had been caused by the Mirena (or Skyla). *See* Case Report A at MIR_JSEU_01057385 ("Reporter's comment: The event is unlikely related to study medication."); Case Report B at MIR_PIEU_157046 ("original reporter's clinical assessment" was of "no relationship" between the patient's IIH and Mirena); Case Report C at MIR_INDNDA_00473903 ("The investigator considered the event as not

related to study drug and as not related to study conduct."). In fact, in Case Report A, the physician did not even specifically diagnose IIH. *See* Case Report A at MIR_JSEU_01057384–85. And in Case Report B, the physician stated that the diagnosis was "very unsure." *See* Case Report B at MIR_PIEU_157046. Dr. Plunkett, however, exceeds the boundaries of this source material. In finding the temporality factor met, she goes beyond what the percipient physicians had concluded, notwithstanding her own lack of medical training. This, too, is unsound methodology.

Dr. Plunkett also fails to consider evidence that did not support her opinion. In her discussion of Bradford Hill's biological gradient (dose-response effect) factor, for example, Dr. Plunkett does not consider any data regarding combined oral contraceptives that contain LNG. These contraceptives have total LNG serum levels that are some 20–30 times higher than Mirena. To be sure, Dr. Plunkett asserts in her report and stated in her deposition that the more relevant measure of LNG exposure is the patient's free LNG level, not total LNG serum levels. But Dr. Plunkett does not take the next logical step: to explore the free LNG levels of combined oral contraceptives, which would have permitted her to make a useful comparison between Mirena and these contraceptives, which, as noted, have been found in five epidemiological studies not to cause IIH. *See* Plunkett Dep. 22, 28, 30, 95–96. She instead writes off these products as irrelevant. Dr. Plunkett's decision to liken Mirena to Norplant (as to which no epidemiological studies regarding IIH exist) while ignoring the entire category of LNG-based combined oral contraceptives (which have been studied extensively) is suggestive, too, of an

outcome-driven approach, not a search for truth. *See in re Rezulin*, 309 F. Supp. 2d at 563 ("[A]n expert may not pick and choose from the scientific landscape . . . .").[43]

Dr. Plunkett's handling of the Valenzuela study is similarly problematic. Her report cites that study (and its preview in Rai) as support for finding no fewer than three of the nine Bradford Hill criteria: strength of association, Plunkett Rpt. at 27; consistency, *id.*; and temporality, *id.* at 28. But the report's citations of that study contain no discussion or analysis of that study. Instead, Dr. Plunkett effectively treats the study, *ipse dixit*, as affirmatively establishing those criteria. But her report nowhere acknowledges the vital limitation emphasized by the Valenzuela authors: that the study had not controlled for important confounding factors (obesity and recent weight gain) and therefore could not be read as finding causality. Nor did Dr. Plunkett otherwise contend with the fact of these alternative explanations for the IIH symptoms of the patients covered in the Valenzuela study. *See* Plunkett Dep. at 372–75 (admitting she did not know the background rate of IIH among obese women or their relative risk); *cf. In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1353 (N.D. Fla. 2018) ("Dr. Glenmullen also

[43] Plaintiffs' defenses of Dr. Plunkett's treatment of LNG-based oral contraceptives fall short. They note that "Norplant is more similar to Mirena than combined oral contraceptives." Pl.'s Plunkett Opp. Br. at 10. Plaintiffs are correct that, all else equal, that factor might justify giving "more weight to Norplant than combined oral contraceptives." *Id.* But it does not justify giving wholesale inattention to the category of combined oral contraceptives, particularly given that, in contrast to Norplant, such contraceptives have been the subject of epidemiological studies into causation (or not) of IIH. Also wide of the mark is plaintiffs' suggestion that combined oral contraceptives are categorically irrelevant. *Id*. at 10 n.10. To support this proposition, they cite a report of a different expert in this case, Dr. Johanson, who theorized that the effect of the estrogen component in combined oral contraceptives is to balance out—to offset—the effects of LNG. Whatever the merits of that assertion, Dr. Plunkett did not so justify her decision not to consider IIH-related studies of LNG-based combined oral contraceptives. She testified only that the estrogen component made a comparison to combined oral contraceptives a "little bit more complex." Plunkett Dep. at 95.

considered alternative explanations for the association between Abilify, impulsive gambling, and other impulse control disorders.").

This lapse bespeaks a larger methodological deficiency characterizing Dr. Plunkett's proposed testimony. For an expert's testimony to be reliable, she "must demonstrate that [she] has adequately accounted for obvious alternative explanations." *U.S. Info. Sys., Inc.*, 313 F. Supp. 2d at 238; *see also* Reference Manual on Scientific Evidence ("[R]esearchers first look for alternative explanations for the association, such as bias or confounding factors. . . . Once this process is completed, researchers consider how guidelines for inferring causation from an association apply to the available evidence."); *In re Lipitor*, 174 F. Supp. 3d at 916 (same). Although his report proved methodologically deficient on other grounds, Dr. Moyé at least attempts to engage with Valenzuela's caveat about confounding factors, opining that because of the large reporting ratio observed in Valenzuela's Utah population, the correlation between Mirena and IIH was not likely to be confounded. Dr. Plunkett's report makes no such effort. Nor does it advance any scientific argument for why the IIH of the patients in Valenzuela could not equally plausibly be attributed to the non-Mirena factors of obesity and recent weight gain.

Finally, Dr. Plunkett's embrace of the "androgen theory" of the biological mechanism by which Mirena might cause IIH suffers from severe analytical gaps. As addressed *infra* in connection with Dr. Darney's and Dr. Johanson's proposed testimony, it is not tenable for an expert simply to assume that LNG, a progestin, causes IIH by the same mechanism as androgens (*e.g.*, testosterone). *See Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1157 (D. Mont. 1999) ("Testimony extending general conclusions about similar drugs does not meet Daubert's requirement of reliability."); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 681 (M.D.N.C. 2003) ("Dr. Kulig's assertion that because bromocriptine is an ergot alkaloid and *may*

behave like other ergot alkaloids and cause vasoconstriction simply does not support the proposition that Parlodel causes stroke in postpartum women."); *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 433 ("To conclude that Mirena would cause the same effect as Depo-Provera because they both contain progestin . . . is to impermissibly draw grossly 'overreaching conclusions,' which are connected solely to the data by [the witness's] say-so." (internal citation omitted)). Yet Dr. Plunkett did so here.

For all the above reasons, Dr. Plunkett's proposed testimony is beset by methodological deficiencies. It falls far short of satisfying *Daubert*'s standard of reliability. Her testimony, too, must be excluded.

C. Dr. James Wheeler

1. Qualifications

Dr. Wheeler is an OB/GYN who works in private practice. He is a graduate of Harvard College and Baylor College of Medicine, where he received his medical degree and concentrated in reproductive medicine. Wheeler Rpt. at 3–4. He completed a residency in obstetrics and gynecology at Baylor, and a post-residency subspecialty in reproductive endocrinology and infertility at Yale University School of Medicine. *Id.* at 4. While at Yale he was a member of Yale's Robert Wood Johnson Clinical Scholars Program, which teaches clinical epidemiology[44]; he also earned a masters in public health (M.P.H.) from the Yale University School of Public Health, majoring in Biostatistics with a minor in Maternal/Child Health. *Id.* at 5. He worked as a faculty member at Baylor between 1988 and 1994. He also earned a J.D. from the University

[44] Dr. Wheeler explains: "Clinical epidemiology is distinguished from 'classical epidemiology' because it is, first, practiced by clinicians actually treating patients, and secondly, although interested in cause-effect relationships causing disease, it is from a distinctly clinical approach rather than the statistical mining of huge cross-sectional data sets available from government and insurance entities." Wheeler Rpt. at 5.

of Houston Law Center, where he concentrated in health law, and earned a Legal Nurse Consulting diploma in 2016. *Id*. at 6.

Since 1994, Dr. Wheeler has been in private practice. *Id.* at 4–5. He has provided contraceptive counseling and advice, including as it relates to IUDs, to thousands of patients. *Id.* He has personally placed or supervised the placement of many IUDs, including Mirenas. *Id.* at 5. However, Dr. Wheeler has not conducted research on Mirena or LNG outside of this litigation. Nor has Dr. Wheeler ever diagnosed a case of IIH. Wheeler Dep. at 39–40, 63, 329–30. Dr. Wheeler frequently serves as an expert in litigation. During the last five years, he estimates, he has spent between 15 and 20 percent of his professional time on legal matters. *Id.* at 46.

2. Proposed Testimony

Dr. Wheeler's testimony that Mirena causes IIH, like that of Drs. Moyé and Plunkett, is primarily based on an application of the Bradford Hill factors. *See* Wheeler Rpt. at 31, 34–39.[45] As the source material for his Bradford Hill analysis, Dr. Wheeler relies mostly on (1) a dataset of 115 case reports drawn from Bayer's 2015 signal investigation in which patients were diagnosed with IIH after having had a Mirena inserted, and (2) the Valenzuela study (and its Rai precursor). Dr. Wheeler also cites Norplant case reports. He also notes the fact that the labelling

[45] Dr. Wheeler's report also states that he reached this result using two other methodologies: "differential diagnosis" and "risk-benefit analysis." However, as to differential diagnosis, the Court, on its review, is unable to isolate where in Dr. Wheeler's report such a methodology, as distinct from basic deductive reasoning, is applied. In any event, "differential diagnosis does not speak to the issue of general causation." *In re Rezulin*, No. 00-Civ.-2843 (LAK), 2004 WL 2884327, at *4 (S.D.N.Y. Dec. 10, 2004) (internal quotation marks omitted). This term is instead used to refer to a process of elimination used with respect to a single patient, *i.e.*, a specific causation analysis. *Id.* As to risk/benefit methodology, Dr. Wheeler conceded in his deposition that, contrary to the implication of his report, risk-benefit methodology "cannot be used to determine whether a medicine causes an adverse event in the first place." Wheeler Dep. at 118.

on both Norplant and Jadelle warns of a possible, although by no means established, connection between LNG and IIH.

He applies the Bradford Hill factors as follows.

Strength of association: In finding this factor "sufficiently demonstrated," Dr. Wheeler notes that within Bayer's 2015 dataset, there were "115 cases of [IIH] in women with a Mirena in situ." Wheeler Rpt. at 35. Although he acknowledges "the potential for selection bias and accrual bias operating due to the manner in which these cases were collected," he states that "this is nonetheless a significant number of cases collected." *Id.* Dr. Wheeler also cites the Rai/Valenzuela study as "medical literature reporting on possible association of [IHH] with intrauterine use of LNG." *Id.*

During his deposition, however, Dr. Wheeler reversed course. He conceded that the Rai/Valenzuela study does not demonstrate an association between Mirena and IIH:

> Q: And the—so as you sit here today, you would agree there is no epidemiological evidence establishing even an association between Mirena and [IIH], true?
>
> A: Based on these papers and what we've reviewed, there's no demonstration of an association. The question is raised, but there is no association demonstrated.

Wheeler Dep. 200 (objection omitted).

Consistency of association: Dr. Wheeler opines that this factor is met because of a "sufficient degree of heterogeneity" in his dataset of 115 cases that he drew from Bayer's 2015 signal investigation, because "the association of [IIH] and LNG was sufficiently consistent with other LNG-containing devices to be included in the Product Information brochure of LNG implants Norplant and Jadelle," and because "the Rai/Valenzuela group found a statistically significant increased risk of [IIH] in a large case-control observational study of two different groups." Wheeler Rpt. at 35.

Specificity: Dr. Wheeler opines that this factor is met based on the 115 cases he draws from Bayer's data set, the Rai/Valenzuela study, and the Norplant and Jadelle labels. Although Dr. Wheeler's report elsewhere notes that IIH has associated risk factors, *id*. at 44, his analysis of specificity does not address these factors, *id.* at 36.

Temporality: Because almost every case in the data set that Dr. Wheeler extracts from Bayer's 2015 signal investigation arose after a Mirena had been inserted, Dr. Wheeler finds that the "[a]nalysis of Temporality favors a causal relationship." *Id.*

Biological gradient: Dr. Wheeler notes that within Bayer's 2015 signal investigation, one case had been included involving Bayer's lower-dose LNG, Skyla. While Dr. Wheeler states that he does not know why only one Skyla case was included in that data set, he postulates that, "if it is the only known case, or one of only a few," in which IIH was associated with Skyla, given the larger number of IIH cases associated with Mirena, "a dose-response between LNG and [IIH] may be proposed." *Id.* at 36–37. Dr. Wheeler also notes that women with an embedded Mirena have higher systemic levels of LNG and that at least two patients in Bayer's 2015 dataset had an embedded Mirena. "This," he states, "also lends support to a biologic gradient." *Id.*

Biological plausibility: Addressing this factor, Dr. Wheeler embraces the androgen theory of IIH causation. It is "more likely than not," he states, that IIH is "caused by sex hormones including androgens." *Id.* at 37. He does not articulate a mechanism by which this occurs.

Coherence: Dr. Wheeler states that "based on the medical literature analysis" and the IIH warning that appears on "other LNG-containing devices," "I conclude Coherence is satisfied in proposing a causal relationship between LNG-IU[D] and [IIH]." *Id*. at 38.

Experimental evidence: Dr. Wheeler acknowledges that, in epidemiology, "'experiment' usually means a randomized clinical trial." *Id*. at 38. But, he states, a "randomized placebo-controlled trial involving contraceptive choices" is likely "not practical, and potentially not ethical due to the differential likely effects on pregnancy rates and complications within a placebo-controlled group, of a comparison otherwise-treated group." *Id.* at 38. Dr. Wheeler states that, in lieu of experiments, he would look to "'challenge-dechallenge-rechallenge'" evidence. *Id.* He states that the 11 "dechallenge" cases he had noted in Bayer's dataset, of which nine patients "recovered" from their symptoms and signs of IIH, "may also inform this criterion." *Id*. at 25, 38. Dr. Wheeler admits, however, that "the sample to which this applies is relatively small," *id*. at 38, and that he had been "unable to discover any dechallenged, then rechallenged, patients" within the dataset. *Id.* at 25.

Analogy: Dr. Wheeler states that "[IIH] is associated with other hyperandrogenic symptoms including Polycystic Ovary Syndrome" and that "[t]his clinical observation satisfies Analogy to a reasonable degree." *Id*. at 38.

3. Analysis Under *Daubert*

For the reasons reviewed below, methodologically, Dr. Wheeler's application of Bradford Hill is flawed in multiple respects. Some flaws echo those noted about the Bradford Hill analyses conducted by Drs. Moyé and Plunkett. Other flaws are specific to Dr. Wheeler's analysis.

Specific to Dr. Wheeler, his use of Bradford Hill is fatally compromised, at the threshold, by a concession he made at his deposition. He testified that there is no statistical association between Mirena and IIH. As explained earlier, the Bradford Hill criteria are, at bottom, a methodology for evaluating whether a demonstrated epidemiological association is, or is not, causal. It follows that, absent such an association, there is no basis to apply the Bradford Hill

criteria. *See* Federal Judicial Center, Reference Manual on Scientific Evidence 599, n.141 (3d. ed. 2011) ("In a number of cases, experts attempted to use these guidelines to support the existence of causation in the absence of any epidemiologic studies finding an association. . . . There may be some logic to that effort, but it does not reflect accepted epidemiologic methodology."); *see also Soldo*, 244 F. Supp. 2d at 569 ("The Bradford-Hill criteria start with an association demonstrated by epidemiology and then apply such criteria as the temporal sequence of events, the strength of the association, the consistency of the observed association, the dose-response relationship, and the biologic plausibility of the observed association."); *Dunn*, 275 F. Supp. 2d at 679 ("The first step in the causation analysis pursuant to Bradford Hill is an epidemiological study that has identified an association between two variables."); *cf. In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 187 (S.D.N.Y. 2009) ("[W]here there is a positive association between the exposure and the disease," "epidemiologists often apply a set of considerations described by Sir Austin Bradford Hill in a famous 1965 lecture").[46]

Here, in contrast to Drs. Moyé and Plunkett, Dr. Wheeler admitted in his deposition that the one study in which an epidemiological relationship between LNG and IIH was demonstrated and not later withdrawn—the Valenzuela study—does not provide evidence of association, given the presence of obvious confounding factors as noted by the study's authors. *See* Wheeler Dep. at 200 ("[T]here's no demonstration of an association. The question is raised, but there is no association demonstrated."). Although these proposed experts disagree amongst themselves on whether the Valenzuela study supplies evidence of an association between Mirena and IIH—and although Dr. Wheeler is perhaps to be commended for his candor under oath in disavowing any

[46] As Bayer notes, in his seminal 1965 publication, Sir Bradford Hill indicated that his criteria were to be applied only if a clear-cut case of association has been established. *See* Sir Austin Bradford Hill, 58 Proceedings of the Royal Society of Medicine 295 (1965).

such association—once Dr. Wheeler conceded the lack of a statistical association, there was no longer a logical charter for him to undertake a Bradford Hill inquiry at all. *See* Federal Judicial Center, Reference Manual on Scientific Evidence 599, n.141 (3d ed. 2011).

The only other evidence which Dr. Wheeler's report cites in finding Bradford Hill's first factor ("strength of association") satisfied are the 115 adverse event reports that he drew from Bayer's 2015 signal assessment. *See* Wheeler Rpt. at 39 ("Additional evidence that Mirena causes or substantially contributes to [IIH] is derived from the collection of 115 cases of women with [IIH] who have a Mirena in place."); *id.* at 35 ("This is a sizable series of [IIH] patients, especially with any knowledge as to their contraceptive practices."). But these case reports—on which Dr. Wheeler relies in his report to satisfy fully five of the nine Bradford Hill factors, *see id*. at 34–39—are inadequate as a basis upon which to find Bradford Hill's vital first factor, an association demonstrated by epidemiology. As virtually all experts in this case (including Dr. Wheeler) acknowledge, adverse event data primarily serves instead a more limited function—as a tool to generate hypotheses.[47]

And the set of case reports on which Dr. Wheeler relies, without more, certainly do not reveal the required association. An association exists when the rate of a reported condition is greater among the group taking a drug than among the portion of the population not taking that drug. The adverse event reports which Dr. Wheeler cites, however, by definition cannot reveal any such association, because they are silent as to the comparison group: They do not reveal the reporting rate of IIH among the portion of the population not taking Mirena. They do not

[47] *See, e.g.*, Wheeler Dep. at 206 ("Q: So adverse event report data cannot be used to establish causation, true? A: Not to prove it, not to absolutely prove it, not to establish it, that's correct. Q: And the proper use of adverse event report data is as a hypothesis generating for guiding future study? A: Yes, and to generate better answers to a[n] interesting question.").

provide a basis on which Dr. Wheeler can opine as to whether there is an elevated rate at which Mirena patients experience IIH relative to persons without a Mirena inserted—*i.e.*, whether there is an association between Mirena and IIH. Dr. Wheeler has not undertaken this inquiry. *See* Wheeler Dep. at 221 ("Q: So you can't tell us whether there is an elevated reporting rate of intracranial hypertension with Mirena users compared to any other group of patients, true? A: True."); *see also id.* at 220–23.

The 115 adverse event reports, which Dr. Wheeler draws from a spreadsheet given to him, in fact supply an unusually good illustration of why the case law, including in the earlier round of Mirena litigation before Judge Seibel, has hesitated to base findings of causation or even an epidemiological association on adverse event data alone. *See, e.g.*, *Mirena Perforation / SJ*, 202 F. Supp. 3d at 304 ("Case reports are not reliable evidence of causation."); *see also McClain*, 401 F.3d at 1250 (noting that "reports reflect complaints called in by product consumers without any medical controls or scientific assessment"); *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1298 (M.D. Fla. 2007) ("[Adverse event] reports are unreliable as proof of causation because, in general, the events were not observed in such a way as to rule out coincidence or other potential causes."); *Cloud v. Pfizer, Inc.*, 198 F. Supp. 2d 1118, 1138 (D. Ariz. 2001) ("[I]ndividual case reports and retrospective medical articles summarizing individual case reports are not an adequate basis from which a jury could conclude that Zoloft causes suicide."). The adverse event reports made to Bayer reporting an IIH diagnosis were not necessarily filed by a medical professional, as Dr. Wheeler acknowledges. Instead, they were filed by "someone (clinician, lawyer, nurse, medical student, relative, or consumer themselves)." Wheeler Rpt. at 21. Of the 115 adverse event reports that Dr. Wheeler cites, 32 were generated by the filing of a lawsuit against Bayer, a fact of which Dr. Wheeler was unaware at the time of

his report.[48] (These 32 appear to have been plaintiffs in the IIH lawsuits later consolidated in this MDL. Today, with more than 850 plaintiffs having joined this litigation since the formation of the MDL and the Court's appointment of lead and liaison counsel for plaintiffs, commensurately more adverse event reports presumably have been recorded by Bayer.) The filing of such lawsuits—and Bayer's required, ministerial act of logging such lawsuits as adverse event reports—is not evidence of causation or association.

Further, even assuming that all 115 case reports on which Dr. Wheeler relied could be credited as true to the extent they reported that the subject both had used Mirena and had experienced IIH symptoms, the observation that the number 115 is "sizable," Wheeler Rpt. at 35, falls short of supporting an epidemiological association between these two facts. More than this absolute number would be needed for this correlation to have such meaning. Such information would include how the 115 reports (as among the broader universe of Mirena users) compared with the incidence of such symptoms in the population generally. It would also include whether the subject cases were subject to confounding factors (*e.g.*, obesity, recent weight gain) that could supply obvious alternative explanations for the IIH symptoms. In his deposition, Dr. Wheeler acknowledged that Mirena is preferentially prescribed to the precise population with the highest reporting of IIH—obese women of reproductive age.[49]

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[48] Wheeler Dep. at 217 ("Q: Do you know that some portion of the 115 cases are actually comprised of lawsuits filed in the litigation in which you've been designated as an expert? A: I did not know that fact."); *id.* at 219 ("Q: And so including lawsuit-generated adverse event reports would be one of the stimulated reportings that would confound any analysis of adverse event data[?] A: Yes. Q: You would agree to that? A:—it would.").

[49] *See* Wheeler Dep. at 233 (Q: You would expect compared to other forms of prescription contraceptives, obese women are preferentially prescribed Mirena? A: Yes, you would see Mirena over—overrepresented in that group.")

Unsurprisingly, then, at his deposition, Dr. Wheeler retracted his report's claim of a statistical association between Mirena and IIH. That claim had been based on two data points—the Valenzuela study and the 115 adverse event reports—neither of which could sustain finding such an association. However, with such an association disclaimed, the vital precondition for embarking on a Bradford Hill analysis was eliminated. This alone warrants exclusion of Dr. Wheeler's testimony under *Daubert*.

Independent of his inability to find this gating criterion, Dr. Wheeler's proposed expert testimony report, like that of Dr. Moyé and Dr. Plunkett, does not satisfy any of *Daubert*'s four core reliability factors: It is untested; it has not been subject to peer review; there is neither an error rate nor are there standards controlling its operation; and his conclusion lacks any acceptance, let alone general acceptance, in the scientific community outside of this litigation.[50] This requires the Court to carefully scrutinize his methodology, too. Dr. Wheeler's ensuing analysis does not withstand this scrutiny. Rather, as with the two prior experts, Dr. Wheeler's application of the Bradford Hill factors to find that Mirena causes IIH is subject to a series of methodological flaws that independently preclude its admission.

These include:

Lack of weighting or discussion of relationship of factors: Like Drs. Moyé and Plunkett, Dr. Wheeler applies the Bradford Hill factors without revealing the weight he attaches to individual factors or addressing the relationship among them. *See* Wheeler Rpt. at 35–39. As discussed in connection with Dr. Moyé, this malleable and vague approach is in tension with first

[50] Dr. Wheeler acknowledged in his deposition that he was unaware of a single medical article, abstract, or poster presentation where the authors concluded that Mirena causes IIH, Wheeler Dep. at 96, that he was unaware of any person "in the world" other than plaintiffs' experts in this case who has concluded that Mirena causes IIH, *id*. at 99–100, and that there is no consensus of opinion that Mirena causes IIH, *id*. at 281.

principles under *Daubert*, because it makes it all too easy for an expert to manipulate the Bradford Hill factors to support a desired conclusion of causation, and far too hard for an ensuing expert to replicate and rigorously test the expert's analytic approach. *See In re Zoloft*, 858 F.3d at 796 ("To ensure that the Bradford Hill/weight of the evidence criteria is truly a methodology, rather than a mere conclusion-oriented selection process . . . there must be a scientific method of weighting that is used and explained." (internal quotation marks omitted)).

Generalized assessments of individual factors: In serially reviewing the factors, Dr. Wheeler's report generally pronounces each satisfied. With two exceptions, he does not indicate that the factor was anything more than minimally satisfied. *See, e.g.*, Wheeler Rpt. at 35 (strength of association factor "is sufficiently demonstrated"); *id.* at 36 (specificity factor "is sufficiently demonstrated"); *id.* (temporality factor "is satisfied"); *id*. at 37 ("[T]here is sufficient information that Biologic Gradient is demonstrated . . . ."); *id.* at 38 ("Coherence is satisfied . . . ."); *id.* at 38 ("[T]here is sufficient evidence of an Experimental type" as to experimental evidence factor); *id.* ("I conclude Analogy is sufficient to support a causal relationship between LNG-IU[D] and [IIH]."); *but see id.* at 35–36 (consistency of association is "particularly well established"); *id.* at 37 ("Analysis of Biologic Plausibility definitely favors a causal relationship.").[51] Such a "check-box-approach" to the application of a nine-factor test, too, obscures the expert's weighting of the various factors. For a scholar seeking to replicate and test the expert's work, and to validate or disprove his ultimate conclusion, this minimalist approach inhibits, if it does not preclude altogether, meaningful validation.

[51] Dr. Wheeler elsewhere in his report acknowledges that two factors (the experimental evidence factor and the biologic gradient factor) are "less strong" than the other seven. There, he terms the experimental evidence factor "impossible to satisfy for practical reasons." Wheeler Rpt. at 46.

Factors conceded to lack evidentiary support: Like Dr. Moyé, Dr. Wheeler finds that all Bradford Hill factors support a finding of causation, even though, as his deposition testimony revealed, some demonstrably cannot, or cannot non-speculatively, be so viewed. Three examples are illustrative.

As to the first factor, strength of association, as noted, Dr. Wheeler, in his deposition, took back his conclusion that this fact had been "sufficiently demonstrated." Wheeler Dep. at 264–65; Wheeler Rpt. at 35.

As to the third factor, specificity, Dr. Wheeler's report finds it, too, met, on the basis of the adverse event reports found in 2015 Bayer signal investigation, whose limitations as a basis for positing causation or even epidemiological association are addressed above. Dr. Wheeler's discussion of that factor does not address the alternative demonstrated and/or theorized causes and risk factors for IIH. This is so even though elsewhere in his report Dr. Wheeler acknowledges the confounding factors (*e.g.*, obesity) that outside this litigation have prevented all scholars (including the Valenzuela study authors) from isolating Mirena as a cause of IIH. *See, e.g., id.* at 21–24. In his deposition, Dr. Wheeler agreed that the Valenzuela study merely "raises the question of an increased risk of IIH with Mirena, but does not establish an association." Wheeler Dep. at 190; *see Dunn*, 275 F. Supp. 2d at 681 ("Opinions merely expressing 'possibilities' do not suffice to support the admissibility of expert testimony.").

And, as to the eighth factor, experimental evidence, Dr. Wheeler's statements are internally contradictory. His report acknowledges the lack of any such actual experimental evidence, explaining that practical considerations made this factor "impossible to satisfy." *Id.* at 46. Yet in his tally of the nine factors, Dr. Wheeler, rather than treating this factor as null,

ultimately opines that it, too, was supported by "sufficient evidence," in the form of a "relatively small" sample of "dechallenge" cases reported by clinicians. *Id.* at 38.

Unsubstantiated assumptions about Norplant and the Norplant/Jadelle labeling: As to two of its foundational factual propositions, both involving Norplant, Dr. Wheeler's report departs from sound methodology by assuming facts that have nowhere been established.

First, on the apparent premise that LNG-based implant Norplant has been found to cause IIH, Dr. Wheeler, in finding various Bradford Hill factors met, repeatedly analogizes Mirena to Norplant. *See, e.g.*, Wheeler Rpt. at 35 (consistency of association); *id.* at 36 (specificity); *id.* at 37 (coherence). However, as reviewed above, no epidemiological study has so found as to Norplant, Jadelle, or any other LNG-based contraceptive. The data that exists as to these different (and higher-LNG) products is limited to case reports that have not been controlled for potential confounders. To the extent that Dr. Wheeler's anticipated testimony is built on an analogy to products that he only assumes to be associated with or causal of IIH, it, like the reports of Drs. Moyé and Plunkett, starts from an unsound premise.

Second, and relatedly, on the premise that the Jadelle and Norplant labels bespeak a predicate finding of causation of IIH, Dr. Wheeler repeatedly cites these labels as fortifying his claim of Mirena's causation of that condition and as supporting finding certain Bradford Hill factors. *See, e.g.*, Wheeler Rpt. at 35 ("[T]he association of [IIH] and LNG was sufficiently consistent with other LNG-containing devices to be included in the Product Information brochure of LNG implants Norplant and Jadelle."); *id.* at 36 ("[T]he Product Information regarding [IIH] risk with Norplant and Jadelle adds to the finding of sufficient specificity to

strengthen a causal relationship between LNG-IU[D] and [IIH].").[52] However, on their faces, these labels, which for Norplant dated to 1993, establish nothing of the kind. They state only that: "There have been reports of Idiopathic Intracranial Hypertension in NORPLANT SYSTEM users." *See, e.g.*, 1997 Norplant Label at 00055901; Fraunfelder Rpt. at 15 (noting similar Jadelle label); Plunkett Rpt. at 9 n.7 (same). This statement reveals only the existence of historical case reports. In his deposition, Dr. Wheeler conceded that he has no idea about the origin of the information about IIH in the Norplant warning label. Wheeler Dep. 163, 266. Absent a factual basis to assume that the manufacturer's decision to include the Norplant or Jadelle labels reflected evidence bearing on causation—as opposed to a prudent means of guarding against legal risk by a manufacturer alerted to case reports—Dr. Wheeler has no basis to rely on these labels as supporting his finding of causation. This pillar of his Bradford Hill analysis, too, is based on unacceptable speculation.

Speculative androgen theory: In finding the factor of biological plausibility met, Dr. Wheeler opines that it is "more likely than not" that IIH is caused by sex hormones including androgens and that it is biologically plausible "that LNG from Mirena could cause [IIH] as an androgenic side effect." Wheeler Rpt. at 37–38 ("Analysis of Biologic Plausibility definitely favors a causal relationship."). Bayer counters that Dr. Wheeler's conclusion to this effect is unduly speculative. Although aspects of Bayer's critique conflate issues of factual persuasiveness reserved for the trier of fact with issues of admissibility under *Daubert*, the Court is persuaded that Dr. Wheeler's theory is sufficiently grounded in conjecture and guesswork to

[52] Dr. Wheeler separately volunteers that Bayer had been unreasonable in not including on Mirena a warning similar to that which had appeared on Norplant and Jadelle. *See id.* at 41 ("A reasonable and prudent healthcare provider would expect a similar warning in any LNG-containing implantable device."); *id.* at 41–43. That opinion is not a subject of the instant *Daubert* litigation.

make his testimony on this point unreliable as a matter of law. In his deposition, Dr. Wheeler was not able to identify any peer-reviewed publication establishing his androgen theory, nor any presentation to this effect at a scientific conference supportive of this theory. Wheeler Dep. at 132. He testified that it was "too early" for any support to be published. *Id.* at 143 ("[T]oo early. Hasn't been done."). And while there is scientific evidence that LNG has androgenic effects, LNG itself is a progestin, not an androgen. All of the articles on which Dr. Wheeler relies, however, involve androgens. None involve progestins, let alone LNG. *See* Wheeler Dep. at 140, 147 (sources cited do not involve progestins, LNG, or Mirena); *id.* at 142 (LNG a progestin, not an androgen).

Under these circumstances, Dr. Wheeler's theory as to the Bradford Hill factor of biologic plausibility relies on too many unsupported leaps. To permit Dr. Wheeler to testify to his theory of causation would invite the jury to guess as to the validity of a novel and untested theory based essentially on his say-so. "[T]he courtroom is not the place for scientific guesswork, even of the most inspired sort. Law lags behind science; it does not lead it." *Golod v. La Roche*, 964 F. Supp. 841, 861 (S.D.N.Y. 1997) (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 36 (7th Cir. 1996)); *Mirena Perforation / Daubert*, 169 F. Supp. 3d at 450 ("[I]t is not that experts 'are insincere in their opinions or that their opinions may not some day be validated through scientific research and experiment; it is simply that the law cannot wait for such a confirmation.'") (internal citation omitted).

For all the above reasons, Dr. Wheeler's proposed testimony fails to meet the standard for reliability set out in *Daubert*. As to various components of his reasoning, there is "too great an analytical gap between the data and the opinion proffered" to permit the testimony to be found reliable. *See Gen. Elec. Co.*, 522 U.S. at 146 (1997) ("[N]othing in either *Daubert* or the Federal

Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytic gap between the data and the opinion proffered."). His testimony, therefore, must be excluded.

D. Dr. Frederick Fraunfelder

1. Qualifications

Dr. Fraunfelder is a 1990 graduate of Baylor University, where he received a Bachelor of Arts in Economics, and a 1994 graduate of Oregon Health Sciences University in Portland, where he received a degree as a medical doctor. Dr. Fraunfelder then completed a residency in ophthalmology and several fellowships. He was certified by the American Board of Opthalmology in June 2002 and was recertified in January 2013.

Dr. Fraunfelder has worked in clinical practice and as a professor. He served in Portland, Oregon, as an Assistant Professor at the Casey Eye Institute, then an Associate Professor, and then a Director. Dr. Fraunfelder then moved to Missouri, where he chaired the Mason Eye Institute. He has done work on drug safety monitoring, written books on ocular therapy, and been a reviewer for several medical journals. *See* Fraunfelder Rpt. at 2–3.

He does not, however, have independent expertise in IIH. *See* Fraunfelder Dep. at 129–30 ("I'm not an expert in IIH or the mechanism of IIH."); *id.* at 104 (when asked about textbook criteria for diagnosing IIH, responding, "I need you to refresh me on those").[53]

2. Prior Writings Regarding LNG and IIH

[53] Dr. Fraunfelder testified in a deposition in the pre-MDL phase of this litigation that he considers himself "the world's expert on spontaneous reports on pharmacovigilance in ophthalmology." 4/12/16 Fraunfelder Dep. at 34. He also claims to have "experience in drugs . . . [that] would eclipse most human beings or doctors[]." *Id.* at 107.

Dr. Fraunfelder is the only one of plaintiffs' experts who, before this litigation, had written publicly about the relationship between LNG and IIH. He is also the only plaintiffs' expert who had authored an expert report on that subject prior to the formation of this MDL.

In a 2015 book he co-authored, *Drug-Induced Ocular Side Effects*, Dr. Fraunfelder stated that he believed there was a possible, rather than a probable, causal association between LNG and IIH. Fraunfelder Rpt. at 23 (citations omitted). His expert report in this case explained what he had meant in that book by the terms "possible" and "probable": "Causation of an event is assessed as *possible* where there is a temporal relationship, but the association could also be explained by concurrent disease or other drugs or chemicals, and information on drug withdrawal (dechallenge) may be lacking or unclear." *Id.* "An event is listed as *probable/likely* where there is a temporal relationship unlikely to be attributed to concurrent disease or drugs, and the event follows a clinically reasonable response on withdrawal (positive dechallenge)." *Id.* Dr. Fraunfelder largely based the assessment in his 2015 book of a "possible" causal relationship between LNG and IIH on a database of case reports[54] that he and a colleague had reviewed, on a publication discussing cases in that database in which the patient had used Norplant, and on a publication discussing two other cases of IIH. *See id.* at 15. Dr. Fraunfelder's 2015 book did not take into account either the Etminan or the Valenzuela studies, which had not yet been published.

On January 21, 2016, Dr. Fraunfelder filed an expert report on behalf of plaintiffs in a case that later became part of this MDL. *See* Dkt. 167-79 ("Fraunfelder 2016 Rpt."). Dr. Fraunfelder spent about 10 hours on that 12-page report. Fraunfelder Dep. 79. Opining there that Mirena is a cause of IIH, Dr. Fraunfelder's 2016 report relied on the Etminan study. It termed Etminan's two analyses—a disproportionality analysis of adverse event reports in the

[54] This database was the National Registry of Drug-Induced Ocular Side Effects.

FDA's database, and a cohort study—"two important pieces of literature." *See* Fraunfelder 2016 Rpt. at 11. Dr. Fraunfelder's 2016 report contained four paragraphs of analysis. Two covered published medical literature:

> Medical literature has demonstrated an increasing concern regarding the growing number of [case] reports. In 2010, a case report described a patient who developed PTC while on Mirena, although with a somewhat atypical presentation. In 2015, two important pieces of literature were also published. Etminan et al. generated an ROR for Mirena at 1.78, and also attempted to evaluate the impact of confounders to yield statistically significant results with Bayesian analysis. Etminan et al. also performed a cohort analysis and found that risk of PTC was similar to norgestimate, while norethindrone had a lower risk associated with the use. These findings could suggest a possible class effect.
>
> In addition to these useful findings, Rai et al. published an abstract with Association for Research in Vision and Ophthalmology ("ARVO"), indicating that they had obtained extremely significant results in a cohort study comparing PTC patients to non-PTC patients. Their symptoms were similar, and the authors ensured that only cases where PTC developed while the patient was using Mirena were counted. They were not significantly different from the non-users in terms of known confounders BMI, age, or recent weight gain. Exposure to LNG-IU[D] was 7.7 times more likely among PTC patients than the non-PTC cohort.

Fraunfelder 2016 Rpt. at 13–14.

3. Proposed Testimony

Dr. Fraunfelder's 28-page report in the current litigation expands upon his earlier report. In connection with the current report, he testified, he did an additional "probably . . . less than ten hours" work. Fraunfelder Dep. at 80.

His report opines that based on his "systematic analysis" of various items of evidence and his "education, experience, and training in drug safety monitoring and drug-induced ocular side effects," "it is more likely than not that Mirena causes or substantially contributes to causing PTC," Fraunfelder Rpt. at 1, and that this is so "to a reasonable degree of medical probability." *Id.* at 27.

As to the report's methodology, Dr. Fraunfelder disclaimed having performed a Bradford Hill analysis. Fraunfelder Dep. at 23. Asked in his deposition what methodology he had used, he responded that he had considered multiple pieces of evidence. *Id.* at 598–99 ("I looked at individual case reports. I looked at spontaneous reports. I looked at the available literature. I looked at the epidemiological papers. I looked at the plausible biological mechanism for sex hormones causing pseudotumor cerebri."). Although Dr. Fraunfelder did not label it as such, his approach appears best styled as a weight-of-the-evidence approach.

The evidence which Dr. Fraunfelder cites in his report in support of his conclusion that Mirena likely causes IIH consists of the following: (1) his assessment of IIH's "biological mechanism," (2) the Valenzuela study, (3) the Etminan study, (4) a discussion of Norplant, and (5) a discussion of case reports.

Mechanism: Dr. Fraunfelder's report does not set out in any detail the mechanism by which Mirena ostensibly causes IIH. Instead, in a page and a half, he articulates two broader propositions from which, he suggests, this conclusion follows. First, he states, it is likely that IIH's "underlying mechanism relate[s] to sex hormones." Fraunfelder Rpt. at 6. In support, Dr. Fraunfelder notes that IIH is common among obese women of childbearing age, has been observed in men with testosterone deficiency, and has been reported in transgender individuals undergoing testosterone therapy. *Id.* at 6. Second, he states, steroid hormones are associated with IIH. *Id.* at 6–7. In support, Dr. Fraunfelder notes that the medicines and medical conditions with which high rates of PTC are associated mostly consist of "steroid hormones, steroid hormone derivatives, or states of endocrine dysfunction," although the mechanism by which this occurs "is also unknown." *Id.* at 6. He states that "[s]teroid hormone activity in the region of the

brain where CSF is produced (the Choroid Plexus) may be one important modulator of CSF production." *Id.* at 7.[55]

At his deposition, however, Dr. Fraunfelder repudiated his opinion as to a mechanism by which Mirena ostensibly causes IIH. He attested: "I think . . . the mechanism is unknown. I'm not being put forward as an expert on the mechanism of [IIH and Mirena]." Fraunfelder Dep. at 384. He stated that although he believes there is "a plausible biological mechanism," "[t]hat's not something that I'm going to be an expert on." *Id.* at 571. Consistent with his distancing himself from the mechanism opinion that his report articulated, Dr. Fraunfelder, during his deposition, disclaimed knowledge of biological facts potentially germane to this inquiry. These included whether there is data suggesting that LNG can cross the blood-brain barrier, whether there are mineral corticoid receptors in the brain, and whether, if there were such receptors, Mirena could act on them. *See, e.g.*, *id.* at 578–83; *see also id.* at 571, 573 (admitting lack of knowledge about hormone levels, stating, "I don't know women's hormones levels," "I do not want to opine on the hormone levels of childbearing women," and "[y]ou know I'm an ophthalmologist, right?"); *id.* at 515 ("I told you a couple times all throughout the day that I'm not [a] pharmacokinetics expert.").

The Valenzuela study: Dr. Fraunfelder recounts the Valenzuela study's methodology and the populations that that study considered (in Utah and Denmark). Fraunfelder Rpt. at 11–12. He concludes: "Valenzuela et al. suggest that women with an LNG-IU[D] have an increased risk of developing PTC, despite identifying possible limitations to their methods and analyses." *Id.* at

[55] Dr. Fraunfelder's report cites two studies for this proposition: one discussing a possible mechanism involving ion and water transport in the corticoid plexus resulting in CSF secretion, and another discussing a novel, anti-mineralocortioid and anti-androgen, progestogen apparently used to treat some IIH patients (specifically children who have a condition where excess aldosterone is secreted). *Id.* at 7 & n.5–6.

12. Dr. Fraunfelder notes that, as the Valenzuela study itself recognized, "patients with an LNG-IU[D] device may not be aware that their device contains a drug, and are less likely to report the LNG-IU[D] device during their intakes with medical practitioners when presenting for symptoms such as headache and vision disturbances, even when specifically questioned about 'current medications.'" *Id.* at 12. He notes that the Valenzuela study authors gave two alternative explanations for their results: "1) that LNG causes increased intracranial pressure, through an already-postulated or yet unknown mechanism; or 2) that PTC is more likely to occur in the same population of women who are more likely to have an LNG-IU[D]." *Id.* Dr. Fraunfelder discounts the second explanation—that the correlation between Mirena and IIH resulted from confounding factors: "[E]ven considering the possibility of confounding by other risk factors, a causative or contributory role for LNG cannot be excluded from a differential diagnosis, even accounting for the possibility of confounders." *Id.*

The Etminan study: Dr. Fraunfelder's report extensively discusses the Etminan study. Fraunfelder Rpt. at 12–15. He recounts the study and Dr. Etminan's ensuing exchange with Dr. Friedman. In so doing, Dr. Fraunfelder notes a methodological flaw in the Etminan study. *See id*. at 13 ("[T]his methodology assumed a binominal distribution, and the relationship between BMI and Mirena may be more complex."). In the main, however, Dr. Fraunfelder's report focuses on undermining the methodology that Dr. Etminan used in 2017 when retracting his disproportionality (DPA) analysis. *Id.* at 14–15. In particular, Dr. Fraunfelder challenges the manner in which Dr. Etminan conducted his age-adjusted analysis, stating that Dr. Etminan had failed to explain why his corrected analysis had excluded wholesale "cases without reported age data." *Id.* at 14. He writes: "Although it is possible that some of those cases involve women over 40, it is inappropriate to assume that all of those cases involve women over 40." *Id.* Dr.

Fraunfelder adds that while it was "unfortunate that many of the adverse event reports" in the FAERS database "did not include age information," it had been "unreasonable" to assume that such cases involved women over 40. *Id.*

Norplant: Dr. Fraunfelder also cites information relating to Norplant as supporting that Mirena likely causes IIH. *Id.* at 15–17. He notes that Norplant, marketed in the United States between 1991 and 2000, had been "plagued by allegations of harmful side effects." *Id.* at 15. He notes that, in 1993, Norplant's label had been changed "to include warnings about reports" of IIH; that the 1993 Sunku and 1995 Alder studies had described cases of IIH observed among Norplant users; and that the 2015 book that Dr. Fraunfelder co-authored had listed IIH "as a possible side effect of Norplant/LNG . . . ." *Id.* Dr. Fraunfelder acknowledges, however, that while "epidemiological research was needed in order to investigate the potential increased risk of PTC with use of the Norplant," none had been undertaken. *Id.* at 16 ("[N]o large epidemiological study was ever undertaken by Bayer, its predecessor companies, or any other pharmaceutical company to compare the incidence rate of PTC while using Norplant with the incidence rate among non-users or users of other hormonal contraceptives."). He notes that the updated label on Jadelle—Norplant's successor, marketed exclusively outside the United States—"continues to warn of [IIH], including the direction to remove Jadelle if diagnosed." *Id.*

Case reports: Dr. Fraunfelder's report draws upon case reports from several sources. First, he reviews reports relating to three patients from among the subjects included in Mirena's clinical trials for safety: (1) a 2001 case involving a 23-year-old woman of normal body weight who was diagnosed with diplopia and chronic papilledema but never, it appears, IIH; (2) a case dating to 2008 of a 37-year-old obese woman who was diagnosed with IIH; and (3) a case dating to 2009 of a 17-year-old woman of normal body weight (or possibly slightly overweight) who

had first been diagnosed with IIH in 2009, had a Mirena inserted in 2012, and thereafter experienced IIH symptoms. *Id.* at 17–19. Dr. Fraunfelder's report also lists a number of cases drawn from Bayer's signal assessments that he describes as examples of dechallenges—where IIH symptoms abated after the removal of a Mirena. He identifies four cases of "unambiguous dechallenge"; eight of "positive dechallenge" (where some recovery by the patient was noted); three where the "patient was recovering while receiving treatment"; and five where, among conflicting data, some was suggestive of dechallenge. *Id.* at 21–23. At his deposition, Dr. Fraunfelder admitted, however, that the cases he cited, including those he called "unambiguous dechallenge," were subject to possible confounding variables. *See* Fraunfelder Dep. at 428–52.

Finally, Dr. Fraunfelder's report notes that over the past several decades, medical literature has increasingly noted an association between LNG and IIH and raised the question whether LNG causes IIH. "In practice," he notes, "physicians often look to the medical literature when identifying potential causes of disease in patients." *Id.* at 27.

4. Analysis Under *Daubert*

Dr. Fraunfelder's proposed testimony amounts to a blend of disparate items that he contends together show that Mirena causes IIH. Unlike Drs. Moyé, Plunkett, and Wheeler, Dr. Fraunfelder does not purport to use the flexible Bradford Hill methodology to guide his analysis. Instead, his approach consists of listing factors that he argues support this conclusion. Beyond its non-replicable mode of analysis, Dr. Fraunfelder's handling of individual items has hallmarks of unreliability—some shared with other proposed expert witnesses, others unique to Dr. Fraunfelder. His proposed testimony falls short of *Daubert*'s standards.

At the outset, like the testimony of the three preceding witnesses, Dr. Fraunfelder's proposed testimony fails to meet any of the *Daubert* reliability factors. His opinion that Mirena

causes IIH has not been tested; it has not been subjected to peer review; it has no known error rate and there are no standards controlling its operation; and it has not been generally accepted by the scientific community. His analysis, developed in the course of litigation, therefore merits a "hard look."

Dr. Fraunfelder's handling of virtually every one of the individual items on which he relies is, however, methodologically suspect.

The Court considers, first, Dr. Fraunfelder's handling of the repudiated Etminan study. In his report, Dr. Fraunfelder—tracking his 2016 report—placed substantial weight on Etminan's disproportionality analysis, effectively brushing aside, or at best scarcely weighting, its author's 2017 repudiation of it. Clinging to a study finding that has been explicitly renounced by its own author is methodologically dubious, to say the least. It suggests a commitment to advocacy over scientific rigor. *See In re Bextra & Celebrex Mktg. Sales Practices & Prods. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) ("[R]ejecting or ignoring" unfavorable evidence "is not 'good science'").

Beyond this shortcoming, Dr. Fraunfelder, in seeking to rehabilitate the Etminan study's DPA analysis, overlooks the flaw in that study that ultimately led Dr. Etminan himself to correct his methodology and repudiate its initial finding. As noted above, Dr. Fraunfelder objects to Dr. Etminan's decision in the course of correcting that study in 2017 to exclude patients within the LNG-IUD group as to whom age data was lacking. Dr. Fraunfelder notes that, inasmuch as most women using a Mirena IUD are presumably of reproductive age, excluding Mirena patients for whom age data was lacking may have not been strictly necessary.

That critique is coherent. But in training his critique on this narrow point, Dr. Fraunfelder misses the bigger picture: The reason why a corrective was necessary lest the

Etminan DPA analysis be methodologically unsound. As diagnosed by Dr. Friedman and belatedly admitted by Dr. Etminan, there was a gaping design flaw in the Etminan study's DPA analysis: It did not exclude women of non-reproductive age from the control group. The FAERS database includes data related to all kinds of drugs, most of which (unlike Mirena) are not earmarked for reproductive-age women, the group all but uniquely at risk for IIH. By failing to limit his control group to reproductive age women (and by using an experimental group that was *de facto* limited to reproductive age women), Etminan's DPA study was subject to a severe sample bias. This compromised its results. Dr. Etminan's 2017 correctives attempted to redress that defect. *See* Etminan Affidavit ¶ 6 ("[A] proper analysis would be limited to women of reproductive age."). The result of these correctives was to eliminate the statistical basis for inferring Mirena's causation of IIH. The corrected data showed "no elevated [risk] for Mirena, suggesting that intracranial hypertension and Mirena use are 'likely not related.'" *Id.* ¶ 8; *see also id.* ¶ 11 ("[N]either of the analyses in the article provide evidence that Mirena use increases the risk for intracranial hypertension.").

Dr. Fraunfelder's expert report does not grapple with this methodological deficiency at the heart of the DPA analysis on which he relies—despite the fact that by the date of his report (December 23, 2017), he had access not only to Dr. Friedman's critique of Etminan's DPA study but also to Dr. Etminan's letter and affidavit repudiating the study's methodology and outcome. And, when confronted at his deposition with the Etminan study's design flaw, Dr. Fraunfelder reaffirmed his reliance on the DPA study as supporting his finding that Mirena use likely causes IIH. To be sure, Dr. Fraunfelder eventually admitted that the Etminan study had less value than he had initially assigned it. But Dr. Fraunfelder continued to make the repudiated study a basis for his opinion. *See* Fraunfelder Dep. at 268 (stating that he relies on Etminan to "a very small

amount"); *id.* at 318 ("I think that his first paper has some validity."); *id.* at 331 ("I put his paper low on the evidence scale as far as the data I used to form my opinion."). As another plaintiffs' expert has recognized, reliance on analysis that has been repudiated by its author is bad science. *See* Moyé Dep. at 137–38, 283–84 (agreeing, in response to questions from both plaintiffs' and defense counsel, that Etminan had functionally retracted his DPA analysis and that it would be inappropriate as a matter of epidemiology to rely on a paper that had been functionally retracted).

Dr. Fraunfelder's continued embrace of Etminan's repudiated DPA analysis is, further, methodologically suspect in that Dr. Fraunfelder attaches little to no weight to the other half of Etminan's study: the retrospective cohort portion of its analysis, which has never been retracted. And the retrospective cohort study did *not* find a statistically significant difference between the risk for IIH among individuals using Mirena and those using two types of oral contraceptives, EE-norethindrone and EE-norgestimate. Dr. Fraunfelder's selectivity—in which he embraces the spoiled half of Etminan's 2015 study while disregarding the unspoiled half—strongly suggests outcome bias, if not a predetermined outcome. Without a good explanation for this counter-intuitive approach, the Court finds it unreliable and inconsistent with rigorous scientific inquiry. *See In re Rezulin*, 369 F. Supp. 2d at 425 (excluding experts who "selectively chose [their] support from the scientific landscape").

This lapse was not anomalous. Dr. Fraunfelder's report elsewhere chooses not to engage with consequential evidence contrary to his outcome. Like plaintiffs' first three experts—who referenced Norplant in applying the Bradford Hill analogy factor—Dr. Fraunfelder's report likens Mirena to Norplant. Dr. Fraunfelder uses these analogies to support both his claim that Mirena, ostensibly like Norplant, causes IIH, and his conclusion—subsidiary to his mechanism opinion—that IIH is related to sex hormones. *See* Fraunfelder Rpt. at 5–6. Yet, like Drs. Moyé,

Plunkett, and Wheeler, Dr. Fraunfelder does not consider another analogy that was in plain sight: to combined oral contraceptives. Dr. Fraunfelder's report acknowledges that an association between oral contraceptives and IIH has been "largely disproven." *Id*. at 27. Such contraceptives, too, involve synthetic sex hormones. But Dr. Fraunfelder does not consider what the studies exonerating IIH-heavy oral contraceptives might signify as to whether Mirena causes IIH. Dr. Fraunfelder's decision not to grapple with these studies is all the more dubious given his reliance on lesser evidence (case reports) related to Norplant and mortally compromised evidence (the initial Etminan DPA study) as to Mirena.

In the same vein, in his consideration of the Valenzuela study, Dr. Fraunfelder fails to consider the alternative, and benign, explanations that that study identified for the correlation it found between Mirena and IIH. *See In re Rezulin*, 369 F. Supp. 2d at 425 ("A factor that courts have considered in *Daubert* analyses is whether an expert has accounted adequately for obvious alternative explanations."); *U.S. Info. Sys., Inc.*, 313 F. Supp. 2d at 238 ("An expert must demonstrate that he has adequately accounted for obvious alternative explanations in order for his testimony to be reliable."); *In re: Gen. Motors LLC Ignition Switch Litig.*, No. 14-MD-2543 (JMF), 2015 WL 9480448, at *2 n.1 (S.D.N.Y. Dec. 29, 2015) (explaining that an expert must address "obvious alternative causes") (emphasis omitted)). The Valenzuela study, by its own account, did not control for the widely accepted IIH risk factors of obesity and recent weight gain; for that reason, the study disclaimed any finding that Mirena caused IIH.

Dr. Fraunfelder's report, however, pays only lip service to Valenzuela's caveat about confounders. It nowhere reveals that the Valenzuela study had not controlled for obesity or recent weight gain, as Dr. Fraunfelder later acknowledged at his deposition. *See* Fraunfelder Dep. at 171–72. Instead, his report treats the correlation Valenzuela found—and the fact that

Valenzuela did not rule out Mirena as an IIH cause—as if such were affirmative evidence of causation. It concludes: "[E]ven considering the possibility of confounding by other risk factors, a causative or contributory role for LNG cannot be excluded from a differential diagnosis, even accounting for the possibility of confounders." Fraunfelder Rep. at 12. Despite deploying the Valenzuela study as positive evidence supporting his causation conclusion, Dr. Fraunfelder does not attempt independently to examine the data underlying that study. He does not, for example, attempt to perform a corrected analysis of Valenzuela to try to account for obesity or recent weight gain. And Dr. Fraunfelder's casual treatment of isolated patient case studies does not, and by the nature of case studies could not, close this methodological hole.[56]

Dr. Fraunfelder, finally, makes his mechanism opinion an important component of his expert report. But at his deposition, he repeatedly distanced himself from it—indeed, he repudiated any mechanism opinion as beyond his expertise. The removal of that pillar alone is fatal to Dr. Fraunfelder's weight of the evidence analysis. In any event, had Dr. Fraunfelder not repudiated his mechanism opinion, the Court would have found—as was inescapable—that he is not qualified to offer it. Dr. Fraunfelder admits that he is "not a pharmacokinetics expert." Fraunfelder Dep. at 515; *see also id.* at 571 ("You know I'm an ophthalmologist, right?"). Plaintiffs have not mustered any evidence of practical experience on his part—or prior publications of pharmacokinetics studies—that could make up for a lack of training in

[56] Of the three clinical trial case studies that Dr. Fraunfelder discusses, although two involved patients who were not obese, only one was actually diagnosed with IIH; she had developed that IIH before the Mirena was inserted. And Dr. Fraunfelder's handling of examples of dechallenge leaves much to be desired. He does not address whether these examples involved obese patients or patients who had experienced recent weight gain, the very confounders that Valenzuela had stated prevented finding causation of IIH by Mirena. Here, too, Dr. Fraunfelder's analysis is limited by his failure to contend with "obvious alternative explanations" for the observed correlation between Mirena and IIH. *See In re Rezulin*, 369 F. Supp. 2d at 425.

pharmacokinetics. He is unqualified to offer a mechanism opinion. *See* Fed. R. Evid. 702 (providing that expert witness must be "qualified as an expert by knowledge, skill, experience, training, or education").

For all these reasons, Dr. Fraunfelder's proposed testimony does not meet the standards for reliability articulated in *Daubert.* It, too, must be excluded.[57]

E. Dr. Philip Darney

1. Qualifications

Dr. Darney is an obstretrician/gynecologist. He attended the University of California at Berkeley for his undergraduate studies, the University of California at San Francisco for his medical doctor degree, and the London School of Hygiene and Tropical Medicine for his master of science. Darney Rpt. at 1. He is board certified in preventative medicine and obstetrics and gynecology. *Id.* He has trained in epidemiology at the Center for Disease Control in Atlanta, and obstetrics and gynecology, including reproductive endocrinology, at Brigham and Women's Hospital in Boston. *Id.* He has served on faculties at Harvard University, the Oregon Health and Science University, and the University of California at San Francisco. *Id.* He has chaired the Medical Advisory Boards of the Planned Parenthood Federation of America and the International Planned Parenthood Federation. *Id.* He has collaborated with pharmaceutical companies about

[57] While Bayer's arguments for excluding Dr. Fraunfelder's testimony are generally on target, one was wide of the mark. Bayer faults Dr. Fraunfelder for suggesting in his 2015 textbook that it was only "possible" that LNG causes IIH, while opining now that LNG's causation was "probable." Dr. Fraunfelder's heightened level of confidence in his conclusion is not inherently impeaching. In theory, new information (*e.g.*, the Valenzuela and Etminan studies or the adverse event reports produced in discovery) could have led him to view the issue of general causation differently. For the reasons reviewed, Dr. Fraunfelder's handling of these materials is methodologically unsound and cannot support this general causation conclusion. But it does not follow that Dr. Fraunfelder was precluded from revising his outlook if presented with new information.

contraceptive research and development, and served as an editor or reviewer for such esteemed publications as the *Journal of the American Medical Association* and the *New England Journal of Medicine*. *Id.* He has been once before and is currently a Principal Investigator on a study funded by Bayer and Berlex, a company Bayer has since acquired. *Id.* at 4. Dr. Darney is a Distinguished Professor Emeritus in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco, and is the Founding Director of the Bixby Center for Global Reproductive Health, a "clinical and epidemiological research organization" at the University of California, San Francisco. *Id.* at 1.

2. Proposed Testimony

Dr. Darney's opinion, unlike those of the four earlier discussed experts, predominantly concerns a mechanism by which IIH is caused. He embraces the "androgen theory" by which Mirena purportedly causes IIH—specifically, that androgens may cause IIH and, that, because LNG, while a progestin, has androgenic effects, LNG in turn may cause IIH.

Before this litigation, Dr. Darney had not published on or addressed any relationship between Mirena and IIH. He has recommended—and continues to recommend—Mirena to his patients, though he states he no longer recommends it to "those who are androgen sensitive." Darney Dep. at 100.

Dr. Darney has published on Mirena generally, and has addressed its side effects (some of which are considered androgenic in nature, like a reduction in acne).

In a 2002 article, for example, Dr. Darney endorsed Mirena: Mirena, he wrote, "is the most effective form of reversible contraception currently available, even more effective than female sterilization." Eleanor A. Drey & Philip D. Darney, *Recent Developments in Hormonal Contraception*, 3 Reviews in Endocrine & Metabolic Disorders 257, 261 (2002) (Dkt. 167-24).

In that same publication, Dr. Darney stated that "[Mirena] causes few hormonal adverse effects," *id.*, although he did identify a 2002 clinical monograph in which a colleague suggested, in a different publication, that women using the LNG-based implant Jadelle should have it removed if they experience papilledema. *See* Darney Rpt. at 22; Irving Sivin, et al., *Jadelle Levonorgestrel Rod Implants: A Summary of Scientific Data and Lessons Learned from Programmatic Experience*, Population Council (2002), http://www.respondproject.org/pages/files/4_result_areas/Result_1_Global_Learning/LA_PM_CoP/june2009-launch/Jadelle-Levonorgestrel-Rod-Implants.pdf.

In a 2011 book, Dr. Darney addressed the issue of androgenic effects of LNG-based IUDs: "Sufficient progestin reaches the systemic circulation from the levonorgestrel-containing IU[D] so that androgenic side effects, such as acne and hirsutism, can occur. However, in one study no change could be detected in the circulating levels of sex hormone binding globulin ["SHBG"] and, therefore, marked clinical effects are unlikely." Leon Speroff & Philip D. Darney, *A Clinical Guide for Contraception* 239, 253 (2011 5th ed.) (Dkt. 167-62). In the same article, Dr. Darney stated that "there is little reason to suspect a cause-and-effect relationship" between Norplant and IIH. *Id.* at 195.

In this litigation, Dr. Darney articulates new conclusions. He opines, for the first time, that an LNG-based product may have the capacity to cause IIH. The central thesis of his expert report is that "[i]n susceptible individuals, relatively high unbound LNG concentrations can cause, or be a substantial contributing factor in causing intracranial hypertension/pseudotumor

cerebri (IH/PTC)." For this purpose, Dr. Darney defines "susceptible individuals" narrowly.[58] Darney Rpt. at 5; Darney Dep. at 296.

This opinion, Dr. Darney states, derives from linking four distinct propositions:

1. Levonorgestrel (LNG) is a potent androgenic progestin (gestagen, progestogen).

2. Intrauterine delivery, compared to other routes, e.g., oral, subdermal and transdermal, results in wide intra- and inter-individual serum concentrations of LNG.

3. Individual women vary greatly in their physiologic reactions to LNG, regardless of the route of administration.

4. In susceptible individuals, relatively high unbound LNG concentrations can cause, or be a substantial contributing factor in causing, intracranial hypertension/pseudotumor cerebri (IIH/PTC).

Darney Rpt. at 5.

The Court recaps Dr. Darney's proposed testimony as to each of these propositions. The instant *Daubert* litigation focuses on the fourth of these propositions.

LNG is a potent androgenic progestin: In support of this first proposition, Dr. Darney describes certain properties of LNG. It is a synthetic progestin that is derived from testosterone. And, like other synthetic progestins derived from testosterone, it has had removed from its chemical structure the element carbon 19, present in testosterone, "in order to change the major hormonal effect from androgenic to progestogenic [while] retain[ing] varying degrees of androgenic activity." *Id.* at 11.

[58] Dr. Darney opines that Mirena can cause IIH under a narrow set of circumstances—involving susceptible individuals with relatively high levels of unbound LNG concentrations. At his deposition, Dr. Darney clarified that he defines "susceptible individuals" extremely narrowly: women who previously have had PCOS (defined *infra* at 115), IIH, or other problems with androgenic side effects. *See* Darney Dep. at 296. In light of these limitations, Dr. Darney's testimony as to Mirena's capacity to cause IIH appears narrower than the general causation propositions that plaintiffs' other experts articulate.

Dr. Darney further states that three factors affect the androgenicity of a sex steroid: its ability to bind to the relevant receptors, its effects on SHBG, and the degree to which it binds to SHBG. *Id.* at 13.

As to the first factor, LNG, he states, "is the most potent and androgenic of the progestins used in contraceptives." *Id.* at 11. Dr. Darney notes that—as is undisputed—LNG can and does bond to androgen receptors. *Id.* at 13. Dr. Darney acknowledges that LNG's affinity for such receptors is still only 22% of that of the androgen standard, dihydrotestosterone ("DHT"). *See id.* at 11. LNG's androgen-to-progestin receptor bonding ratio ("A/P ratio"), used to judge a progestin's likelihood of causing androgenic effects, is 11. That is substantially lower than of the next most androgenic progestin (which has a 28 A/P ratio), but substantially higher than that of the androgenic progrestin DHT (which has only a 0.02 A/P ratio). *See id.* at 12.

As to the second factor, Dr. Darney states, "LNG is known to decrease SHBG over time." *Id.* at 13. Oral administration of LNG alone results in an approximately 50% decrease in SHBG; "a mean decline of about 30% [in SHBG] was seen up to 6 months after insertion of Mirena in 10 healthy young women." *Id.* This result is important, he states, because "a decrease in SHBG means that a higher proportion of circulating androgens are 'free' and available for binding to androgen receptors resulting in androgenic side effects." *Id.*

As to the third factor, involving the degree to which LNG binds with SHBG, Dr. Darney states that LNG does so "with high specificity" and "affinity." *Id.* But, he acknowledges, LNG's affinity to SHBG is only 50% of that of endogenous DHT, and 13% that of (presumably non-endogenous) DHT. *Id.* Dr. Darney asserts that, when LNG binds to SHBG, it prevents endogenous androgens from doing the same, leaving them "free" to activate androgen receptors

and cause IIH. *Id.* Studies involving Norplant, Dr. Darney states, have "found resultant increase in circulating androgens." *Id.*

As a result of these factors, Dr. Darney opines, "androgenic side effects of LNG can be expected even at low doses." *Id.* Dr. Darney states that concerns about the androgenic effects of LNG have led Bayer to work to develop new synthetic progestins and to release new products, such as Skyla and Kyleena with lower rates of expected LNG release. *See id.* at 14–15.

Intra-uterine delivery results in wide variations in serum concentration of LNG: In support of his second proposition, that intrauterine delivery "results in wide intra- and inter-individual serum concentrations of LNG," *id.* at 15, Dr. Darney focuses on the "profound effects" of LNG on the structure of the endometrium, the layer of epithelial cells in the uterus. "These changes include: the appearance of prominent, dilated surface vessels, and cytoplasmic contraction, increased electron density, and plasmolemmal vesicles of the capillaries. Endometrial veins are also increased and dilated . . . ." *Id.* Because LNG can affect the endometrium, Dr. Darney states, it "provides a much less stable network for drug absorption than subdermal (for implant contraception) or intestinal (for oral contraception) vasculature networks that are not primarily modulated by sex hormones." *Id.* at 16. "Hence, systemic LNG concentrations from intrauterine delivery systems like Mirena are much less predictable and stable than those from subdermal or oral administration." *Id.* Comparative studies, Dr. Darney states, show that LNG concentrations vary more when IUDs are used than with other forms of LNG-based contraception. *Id.* at 16–17. And, the same individual may experience substantial variability with an LNG-based IUD. A Japanese study demonstrated, anecdotally, that some women had higher LNG levels after six months than after one month despite the anticipated decline in the release of LNG. *Id.* at 17.

Wide range of physiological reactions to LNG: In support of his third proposition, that women vary in their physiological reactions to LNG, Dr. Darney makes several points.

First, he asserts, it is important to consider concentrations of circulating SHBG and the resultant levels of free LNG when assessing LNG's effects (including its androgenic ones). That is because "only the free or unbound hormone is available for receptor binding and cellular expression." *Id*. at 18. The more circulating SHBG there is to which LNG can bind, the less free LNG there is. And because "LNG is *so* highly bound to SHBG," he states, "small changes in binding . . . may have important implications." *Id.* at 18 (emphasis added); *see id.* ("A decrease in the relative distribution of bound LNG from 98% to 96% would result in a doubling of the unbound fraction from 2% to 4% and, hence, greatly increase the probability of untoward hyperandrogenic effects."). Second, two factors have been shown to result in a decrease in circulating SHBG levels: (1) the "relatively high initial release rate of LNG from Mirena" (which results in an approximate 30% decrease in SHBG levels)[59] and (2) obesity (which results in a decrease in baseline SHBG levels up to 50%). *Id*. at 18–19. Third, some women may be more sensitive to sex hormones than others. As to that point, he cites a study involving hirsutism ("condition of unwanted, male-pattern hair growth in women"[60]), his clinical observations of acne and hair loss among women using LNG-based contraceptives of all types, and studies

[59] Dr. Darney also cites two studies for the proposition that LNG inhibits the effects of SHBG: a 1998 study that demonstrated that the free levonorgestrel index increased with the administration of LNG, and a 2016 study that "observed that the fraction of LNG unbound, or free percentage, was inverse to SHBG levels." Darney Rpt. at 19. The second study also demonstrated that "[s]erum SHBG levels were significantly lower in obese compared to normal BMI women," and "[c]ompared to normal BMI women, the increase in [the] fraction [of free LNG] found was approximately 35% in obese women." *Id*. at 19–20.

[60] *Hirsutism*, Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/hirsutism/symptoms-causes/syc-20354935.

comparing LNG-containing IUDs that showed smaller such adverse effects among users of lower-dose IUDs. *Id.* at 20.

In susceptible individuals, high unbound LNG may contribute to IIH: Dr. Darney's fourth and most consequential proposition, that LNG can cause or substantially contribute to IIH in susceptible persons under certain circumstances, is based on twin premises: that androgens cause IIH; and that LNG, as a progestin with androgenic side effects or qualities, similarly does so.

In support of this proposition, Dr. Darney relies on an article by Charles J. Glueck, et al., *Idiopathic intracranial hypertension, polycystic-ovary syndrome, and thrombophilia*, 145 J. Lab. Clin. Med. 72 (2005) (Dkt. 167-34) ("Glueck"). Darney Rpt. at 21. Glueck had reviewed case studies of 65 women diagnosed with IIH. Thirty-seven, all obese, had polycystic-ovary syndrome ("PCOS"), a condition diagnosed when a patient experiences two of three symptoms: (1) irregular periods, (2) excess androgen, and (3) polycystic ovaries, which become "enlarged and contain follicles that surround the eggs" causing abnormal ovary function.[61] *Id.* Glueck's study, Dr. Darney opines, "provides a biologically plausible explanation of the association of PCOS with PTC through thrombophilia and hypofibrinolysis," conditions which some of the 37 had, as LNG can cause "androgenic side effects like acne and hirsutism, which are also the most common findings in PCOS women." *Id.* at 21–22.

At his deposition, however, while noting that PCOS patients develop IIH at a higher rate than patients without PCOS, Dr. Darney acknowledged that the Glueck study had not concluded

[61] *Polycystic ovary syndrome (PCOS)*, Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/syc-20353439; *see also* Glueck, *supra*, at 74 (listing the following criteria as those from which PCOS is diagnosed, provided two of the three are met "oligovulation/anovulation, clinical or biochemical hyperandrogenism [*i.e.*, excess androgens] or both; confirmed polycystic ovaries").

that the high levels of androgens in PCOS patients cause IIH. *See* Darney Dep. at 247. To the contrary, that study hypothesized that a different hormone, estrogen, might cause IIH, or that PCOS-driven morbid obesity might be responsible. *See* Glueck, *supra*, at 76 ("The increased prevalence of PCOS in women with IIH may reflect PCOS-driven morbid obesity, which in turn facilitates the development of IIH." (internal citations omitted)); *id.* ("[P]aradoxically high levels of endogenous estrogens, common in PCOS and in severe obesity . . . may play a role in the development of IIH . . . ."); *id.* at 72 ("We speculated that PCOS, associated with obesity and extreme obesity in adolescence and young adulthood, is a treatable promoter of IIH."). When confronted with these aspects of the Glueck study, Dr. Darney retreated from his earlier characterization of that study. He asserted that a link between androgens and IIH "may[ ]be the understanding of the author," Darney Dep. at 249, and stated that the study had an "implication for something [the link between androgens and IIH] that's not yet well understood." *Id*. at 251.

In the final two pages of his report, Dr. Darney cites a series of other writings. He cites a "2013 study," Ainat Klein, et al., *Hyperandrogenism is associated with earlier age of onset of idiopathic intracranial hypertension in women*, 38 Current Eye Research 972 (2013) (Dkt. 167-40). Dr. Darney cites this study for the proposition that circulating androgens "were clearly linked to an early age of onset of IIH." Darney Rpt. at 22. He cites Connar Westgate, et al., *Evaluating the role of testosterone in cerebrospinal fluid secretion*, 50 Endocrine Abstracts P325 (2017) (Dkt. 167-66), for the proposition that "women with increased secretion of CSF also have high androgen levels." Darney Rpt. at 22; *see also* Darney Dep. at 256–58 (discussing Westgate). In fact, as Dr. Darney acknowledged in his deposition, the Westgate abstract did not so establish, or even test the relationship between androgen levels and CSF. It instead recounted an *in vitro* study of the effect of testosterone on rats' choroid plexus cells—the choroid plexus

being the area of the brain that produces CSF. From that, Westgate "speculate[d] that testosterone may have a pathogenic role in IIH though modulation of CSF formation and increasing [intercranial pressure]." Darney Dep. at 258

Dr. Darney, finally, cites sources which some or all of the earlier experts addressed: the Valenzuela study, the notation on the Norplant and Jadelle labels to the effect that there had been reports of IIH among users of these products, Bayer's BfArM response, and certain case studies (as to Mirena, the Martinez and Ros Forteza case studies; and as to Norplant, the Wysowski and Green case study). *Id.* at 23–24. In describing Valenzuela as "f[inding] a significantly greater risk among women who used or were using Mirena," Dr. Darney, like Dr. Fraunfelder, does not acknowledge that the Valenzuela study had not controlled for obesity or recent weight gain, or that it had disclaimed any finding of causation of IIH by Mirena. *Id.* at 2. In his deposition, however, Dr. Darney acknowledged these points, Darney Dep. 184, and that a study "would have to control for [body mass index], female gender, and age, in order to conclude that Mirena is associated with IIH," *id.* at 165.

3. Analysis Under *Daubert*

Dr. Darney is the first of plaintiffs' experts who does not base his opinion largely on an assessment of study and case report data bearing on the relationship (if any) between Mirena and IIH. Instead, Dr. Darney articulates a mechanism theory: In an opinion articulated for the first time in his report in this litigation, he opines that "relatively high unbound LNG concentrations can cause" IIH in "susceptible women" through "androgenic side effects." Darney Rpt. at 5, 21–24; Darney Dep. at 295–96 (defining "susceptible women" as women with a history of androgenic side effects, such as acne). This theory, however, does not withstand *Daubert* review.

As a threshold consideration, Dr. Darney's theory that Mirena causes IIH through androgenic side effects does not satisfy any of the four *Daubert* reliability factors. First, he has not tested it in a direct experiment, an epidemiological study, or a clinical trial. And Dr. Darney does not claim that such testing would be impossible.[62] Second, Dr. Darney's androgen-based theory, in the absence of such testing, does not have a known error rate. *See Mirena Perforation / Daubert*, 169 F. Supp. 3d at 448 (noting that expert's "theory of second perforation has not been tested, and therefore has no known error rate"). Third, Dr. Darney has not published his opinion in the peer-reviewed literature or anywhere outside of his expert report. On the contrary, Dr. Darney's prior writings minimizing Mirena's side effects, and his longstanding practice of prescribing Mirena, are in tension with his new opinion. *See* Darney Dep. at 235 (testifying he has not "written these opinions . . . anywhere other than [his] expert report"); *id.* at 202 (testifying that none of his publications mention a concern about Mirena being associated with IIH); *id.* at 94–95 (testifying that resources offered to patients and providers through his research organization do not mention IIH). Fourth, as Dr. Darney acknowledged, it is "not generally accepted" either that Mirena causes IIH, *see id*. at 201; *id*. at 203 (agreeing there is "no consensus" regarding causation), or that androgens play a role in causing IIH, *see id*. at 240–41 (admitting that he cannot say that his theory that androgens play a role in IIH is generally accepted).[63] Dr. Darney testified that he is unaware of any published article that concludes that IIH is caused by the androgenic effects of any hormone, much less that at issue here, LNG. *Id*. at

[62] Dr. Darney's fellow androgen-theory proponent, Dr. Johanson, testified that such testing would take just a week. Johanson Dep. at 15, 17.

[63] Dr. Darney was unaware of any published article that concludes that IIH is caused by the androgenic effects of any hormone, much less LNG. *Id*. at 239, 240; *see also id*. at 194 (unaware of any published literature concluding that Mirena can cause IIH); *id*. at 200 (unaware of any scientific or medical organization that has concluded that Mirena can cause IIH).

239, 240; *see also id*. at 194 (stating that he is unaware of any published literature concluding that Mirena can cause IIH); *id*. at 200 (stating that he is unaware of any scientific or medical organization that has concluded that Mirena can cause IIH); that, at most, there is "curiosity" and "concern" about an association between Mirena and IIH, *id*. at 200; and that "the prospect that androgens play a role in [IIH] is still a hypothesis today." *Id.* at 243–44.

Under these circumstances, the Court—like Judge Seibel in considering the theory that Mirena causes uterine perforation, also largely based on mechanism opinions articulated for the first time in the litigation—must "pause and take a hard look before allowing a jury to consider" Dr. Darney's new opinion. *See Mirena Perforation / Daubert*, 169 F. Supp. 3d at 430.

Here, that opinion turns on two premises, each captured within the fourth and final step of his syllogism: (1) that androgens can cause IIH; and (2) that by extension, LNG, a progestin, can cause IIH. A "hard look" at Dr. Darney's analysis as to each premise is necessary, because, to warrant admissibility, "it is critical that an expert's analysis be reliable at every step," and "any step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Amorgianos*, 303 F.3d at 267.

Bayer argues that Dr. Darney's analysis is deficient as to each premise. While Bayer's critiques are valid, before addressing them, the Court discerns a broader overarching lapse of methodology affecting Dr. Darney's mechanism opinion: Dr. Darney's expert report scarcely addresses IIH. His limited discussion of the disease, Darney Rpt. at 21–23, at no point engages with the threshold issue of what IIH is and how this condition comes about. In venturing a mechanism theory as to Mirena's purported causation of IIH, Dr. Darney does not explain the most fundamental proposition about IIH: that it is caused by the build-up of CSF in the brain resulting in an increase in intracranial pressure. And he does not acknowledge, let alone address,

the unresolved debate about whether IIH is caused by CSF's over-production or under-absorption or both, despite the fact that that the debate over this unsettled question is identified by the sources he cites. *Compare* Westgate, *supra*, at P325 ("The etiology [of IIH] is poorly understood but involves imbalance of cerebrospinal fluid (CSF) secretion and absorption. . . . We hypothesise that obesity and androgen excess may be pathogenic in IIH through dysregulation of CSF secretion."); *with* Glueck, *supra*, at 72 ("Our hypothesis: IIH results in part from inadequate drainage of cerebrospinal fluid (CSF) resulting from thrombotic obstruction to CSF resorption-outflow . . . .").

In theorizing based on a syllogistic construct why a "potent androgenic progestin" might cause IIH in "susceptible individuals" who have "relatively high unbound LNG concentrations," Darney Rpt. at 5, Dr. Darney gives scant attention to the actual pharmacokinetic process that must underlie the causal sequence that he postulates. He does not identify the androgen receptors in the human body with which LNG supposedly bonds to trigger the biological pathway that, on his theory, causes the over-production and/or the under-absorption of CSF.[64] He does not explain, once such bonding to an androgen receptor has occurred, the ensuing process that ostensibly triggers this overproduction and/or underabsorption.

Dr. Darney's silences on these points—about the mechanics of IIH, and about the basic operation of the "mechanism" and "pathway" that he posits link Mirena to this rare disease—are non-trivial lacunas. For a litigation expert who advances a novel conceptual theory as to the cause and the mechanism of a disease, they are failures of methodology. Presented with Dr.

[64] As discussed *infra*, Dr. Johanson opines that the relevant androgen receptors are those in the choroid plexus.

Darney's general causation syllogism and no more, a jury would be left, unhelpfully, with Dr. Darney's bare assumption that some such biological pathway must exist.

It is true that, where more than a correlation between a product and a disease has been shown, it may be appropriate for an expert as to general causation to opine that a biological pathway exists but is not well understood. *Cf. Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1314 (9th Cir. 1995) ("Causation can be proved even when we don't know precisely *how* the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage *somehow*."). But this is a far cry from such a case. As reviewed above—and as the Valenzuela study on which plaintiffs heavily rely states as an explicit caveat—scholarship has *not* shown more than a correlation, subject to identifiable confounders, between Mirena and IIH. In these circumstances, it is not enough for a mechanism expert to assume *arguendo* a biological pathway between a posited cause and effect.

Independent of Dr. Darney's failure to engage with the biology of IIH, Bayer, as noted, faults his report for the speculative "leaps" it makes in support of his two central premises: that androgens can cause IIH, and that LNG, a progestin with androgen receptor affinity, can cause IIH. The Court holds with Bayer on both points: For the reasons that follow, as to each premise, Dr. Darney's conclusion lacks a reliable foundation.

First, as to the premise that androgens cause IIH, Dr. Darney does not cite any article that so concludes. Instead he cites, or refers to without explicitly citing, several articles that speculate or hypothesize about the role of androgens in IIH. These include the Glueck, Klein, and Westgate studies discussed earlier.

The Glueck and Klein studies identified some possible characteristics of patients already diagnosed with IIH. These studies did not attempt to, nor did they find, any definitive causal link

between those characteristics and IIH. And the design of both studies—case series of patients who were diagnosed with IIH, with no control group—would not permit this conclusion.

Notably, neither the Glueck nor the Klein study concluded (or even speculated) that androgens specifically cause IIH. The authors of the Glueck study hypothesized that the number of patients with PCOS, a condition often characterized by excess androgen, might indicate a relationship between IIH and obesity or estrogen. At no point did they state that androgens were in fact related to IIH. At his deposition, Dr. Darney conceded that the Glueck study only "suggests an implication" of a causal relationship between androgens and IIH. Darney Dep. at 251.

The Klein study also did not conclude that androgens cause IIH. It found that "circulating androgens . . . originating in either the ovaries or the adrenal cortex, were clearly linked to an early age of onset of IIH." Klein, *supra*, at 975. Based on this finding, the Klein study notes that one might "speculate . . . that in women susceptible to the evolution of IIH, increased circulating androgens might function as a precipitating factor allowing earlier expression of the disease." *Id*. (emphasis added). However, the Klein study does not purport to establish such a causal role. *See In re Accutane Prods. Liab.*, 2009 WL 2496444, at *2 ("[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study."); *In re Mirena Perforation / Daubert*, 169 F. Supp. 3d at 452 (same).

Dr. Darney also overstates the findings of the Westgate study. Dr. Darney states that Westgate "observ[ed] that women with increased secretion of CSF also have high androgen levels." Darney Rpt. at 22. But the Westgate study did not so observe. It did not study women specifically, let alone receive or evaluate data on women's (or men's) androgen levels. Westgate

studied rats, not women—specifically, choroid plexus cells in rats. At the conclusion of his abstract, Westgate merely "*hypothesise[d]* that obesity and androgen excess *may be* pathogenic in IIH through dysregulation of CSF secretion and hence [IIH]." Westgate, *supra*, at P325 (emphasis added).

Apart from assigning undue weight to propositions that the studies upon which he relies present as mere hypotheses, Dr. Darney fails to explain how the inferences from these studies, or others, separately or concatenated, support that IIH is caused by androgens. The most apposite of the three above studies is Westgate. It at least speculated about a relationship between androgens and IIH. It performed an *in vitro* experiment to test that proposition: an immortalized choroid plexus cell line (*i.e.*, a cell line, not in a live rat) was incubated with testosterone, a potent androgen,[65] and an increase in a measure related to CSF secretion was observed, *see* Westgate, *supra*, at P325. But the study did not (and by nature could not) go further to test whether IIH symptoms would ensue. *See id.* The Westgate study also did not test the effects of other androgens, to assess whether other androgens might behave similarly to testosterone.[66] The gaps between this study and the proposition for which Dr. Darney uses it (that androgens cause IIH) are too great, particularly insofar as this proposition is a cornerstone of his overall opinion. *See Joiner*, 522 U.S. at 144 (affirming that conclusion that exposure to PCBs had contributed to plaintiffs' cancer could not be extrapolated from study of living infant mice which

[65] *See* Punith Kempegowda, et al., *Women with idiopathic intracranial hypertension have a distinct andro-metabolic signature compared to polycystic ovarian syndrome and simple obesity*, Endocrine Abstracts (2016) (Dkt. 135-11) (poster presentation).

[66] One poster presentation cited by Dr. Darney, which describes a case series study, speculated that IIH is characterized by increased testosterone but not androstenedione, another potent androgen. *See* Kempegowda, *supra*.

had been given massive doses of PCBs). And other studies cited by Dr. Darney, such as Glueck and Klein, speculate about propositions at best collateral to the proposition that androgens can cause IIH.[67] While a court may not replace the jury as factfinder, "conclusions and methodology are not entirely distinct from one another." *Joiner*, 522 U.S. at 144. And where "studies . . . are simply inadequate to support the conclusions reached," a court must exclude the expert's opinion. *Amorgianos*, 303 F.3d at 266; *see also id.* at 267 ("[A]n expert's analysis [must] be reliable at every step."). Such is the case here.

As to Dr. Darney's second premise, that progestin LNG is akin to androgens in ways that make it a cause of IIH, it, too, rests on speculation. Dr. Darney theorizes that LNG, because it has stronger androgenic potential than other progestins, can also cause IIH. But Dr. Darney has not identified any article that has tested whether (much less found that) LNG can cause IIH through an androgenic pathway. Darney Dep. at 255–56. The sources he cites for his androgen hypothesis do not involve LNG. They discuss testosterone or other androgens. *See id*. And Dr. Darney testified that he is unaware of any article that tested whether LNG has a role in causing IIH through an androgenic pathway. *Id.* Dr. Darney's attempt to catapult from testosterone and other androgens to LNG does not reliably follow, because LNG is far from a clear analog to those androgens. In potentially significant respects, as Dr. Darney concedes, the progestin LNG is different from androgens and from the entire category of hormones. LNG only has 22% of the

[67] For example, Dr. Darney also references case reports of transgender male patients who developed IIH. Those postulate, but tentatively, that testosterone might be related to IIH. *See, e.g.*, Mowl, et al., *Secondary pseudotumor cerebri in a patient undergoing sexual reassignment therapy*, 5 Clinical & Experimental Optometry 449, 452 (2009) ("The exact cause and a complete understanding of idiopathic intracranial hypertension elude us. . . . If his symptoms recur with the rechallenge of increased testosterone, providing stable weight, it may point more directly to testosterone playing a causative role."). Dr. Darney does not explain why those cases are not distinguishable on the ground that they involved massive doses of the highly potent androgen testosterone.

bonding affinity relative to the standard androgen; and its bonding affinity to SHBG is 50% of that of endogenous DHT, and 13% that of (presumably non-endogenous) DHT. *See* Darney Rpt. at 11. Dr. Darney does not consider the implications of these divergences for his analysis.[68]

"Even minor deviations in molecular structure can radically change a particular substance's properties and propensities." *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002). And courts regularly exclude expert opinions built on analogies to different chemical compounds than the one at issue. *See, e.g.*, *Glastetter*, 252 F.3d at 990 (excluding opinion that "hypothesized that bromocriptine may behave like its chemical cousins" because the "generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value"); *McClain* 401 F.3d at 1246 (excluding opinion where expert "failed to show that the PPA analogy is valid or that the differences in chemical structure between PPA and ephedrine make no difference"); *Konrick v. Exxon Mobil Corp.*, No. 14-CV-524, 2016 WL 439361, at *7 (E.D. La. Feb. 4, 2016) (excluding opinion that "relies heavily on studies that focus on 'solvents' or 'organic solvents' as a class, instead of the specific substances that allegedly caused plaintiff's stillbirth"); *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 893 (E.D. Ark. 2010) (excluding expert testimony that analogized to two different kinds of estrogen based on a class effect, noting that "where an expert summarily attributes effects of one substance to another similarly classified substance, federal courts have consistently concluded that such methodology is not reliable."). Here, Dr. Darney has formulated a theory—a proposed analogy—that may or may not merit

[68] Relatedly, Dr. Darney does not opine on whether there is some threshold dose or level of free androgens at which they become unsafe and likely to cause IIH. Nor does he assess what the comparable levels of LNG would be. Dr. Darney admitted that the set of dose-response data provided to him by plaintiffs' counsel did not show that higher free LNG corresponds to more androgenic side effects. *See* Darney Dep. at 289.

further close scientific review. But, for purposes of admissibility under Rule 702 and *Daubert*, his leap extends too far given the existing scholarship. Even assuming the validity of his first premise that androgens cause IIH, he has not adduced a sound basis on which to claim to have demonstrated that LNG behaves sufficiently like such androgens to also cause this condition.

As noted, in support of his ultimate opinion, Dr. Darney cites, briefly, the Valenzuela study and various Norplant case studies. These materials do not close the gaps in his mechanism theory. They do not speak, at all, to whether androgens cause IIH or whether LNG behaves like other androgens in ways relevant to the causation of IIH. And, for the reasons reviewed above, viewed as epidemiological source material, those studies have severe limitations as a basis for concluding the general causation by Mirena of IIH.

Relatedly, Dr. Darney briefly suggests that there is a dose-response relationship between LNG and IIH, *see* Darney Rpt. at 14, but he ignores contrary data about contraceptives that use LNG in much higher doses (*i.e.*, combined oral contraceptives) which Dr. Darney acknowledges do not cause IIH. *See* Darney Dep. at 43, 233; *see also In re Rezulin*, 369 F. Supp. 2d at 425 ("A factor that courts have considered in *Daubert* analyses is whether an expert has accounted adequately for obvious alternative explanations."); *U.S. Info. Sys., Inc.*, 313 F. Supp. 2d at 238 ("An expert must demonstrate that he has adequately accounted for obvious alternative explanations in order for his testimony to be reliable."); *In re: Gen. Motors LLC Ignition Switch Litig.*, 2015 WL 9480448, at *2 n.1 (noting that an expert must address "obvious alternative causes") (emphasis omitted)).

In the end, while Dr. Darney's credentials are sterling, the methodology underlying his opinion in this case is not. He relies on supposition and attempts to link disconnected studies by others. And he uses some of his source material for more than it can fairly support. The result is

a hypothesis that may or may not bear up when and if it is ultimately tested, not a reliable expert opinion admissible under the governing standards. The Court therefore must exclude his testimony.[69]

F. Dr. Conrad Johanson

1. Qualifications

Dr. Johanson is a physiologist and neuroscientist. He completed his undergraduate studies at Eastern Nazarene College, and received his Ph.D in physiology from Kansas University Medical School in 1970. Johanson Rpt. at 4. He has been a professor at the University of Utah in Salt Lake City and is currently a professor of clinical neuroscience/neurosurgery at Brown University Medical School, where he has worked for the last 30 years. *Id.* His academic research has been focused on brain fluid dynamics, choroid plexus-CSF physiology and pharmacology, and intracranial hypertension and hydrocephalus. *Id.* He has "conducted investigations in cerebral ischemia, hyperthermia, Alzheimer's disease, and arterial hypertensive effects on CNS barrier systems and CSF." *Id.* He has presented lectures on IIH "at the meetings of the Intracranial Hypertension Research Foundation." *Id.* at 5. He was a founding member of the journal *Cerebrospinal Fluid Research* (now known as *Fluids and Barriers of the CNS*). *Id.* He has served as a consultant for the National Aeronautics and Space

[69] As with Dr. Fraunfelder, the Court rejects Bayer's separate accusation that Dr. Darney's change of view was disingenuous. Dr. Darney's previous publications regarding Mirena and LNG date to 2002 and 2011, before some literature relevant to his analysis was published. *See, e.g.*, Valenzuela, *supra*; Alison Edelman, et al., *Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing*, 94 Contraception 52, 52–57 (2016). And Bayer, for whom Dr. Darney has done work, concedes through its experts that Dr. Darney is "highly respected in the field around contraception and family planning," Hewitt Dep. at 24–25, and "has no particular bias against any particular product or method . . . including Mirena," Gossett Dep. at 193. While the Court finds that Dr. Darney's conclusion in this case is methodologically inadequate, the Court does not find his analysis disingenuous.

Agency and has been awarded the Pudenz Prize for research in the fields of CSF physiology and hydrocephalus. *Id.* at 4.

2. Proposed Testimony

Dr. Johanson's report is substantially more technical than any of the reports reviewed previously. For the sake of accessibility to the lay reader, the Court's summary is pitched at a high level.

Dr. Johanson's report begins by discussing the formation, travel, and reabsorption of CSF, and normal versus elevated levels of CSF pressure. *Id*. at 6–9. His discussion of IIH in this respect is brief. Relevant here, Dr. Johanson suggests that IIH is caused by the "hypersecretion of CSF"; for this proposition, he cites, in the commentary he appends to a graphic illustrating the CDF circulatory system, the following article: P. Gideon, et al., *Assessment of CSF dynamics and venous flow in the superior sagittal sinus by MRI in idiopathic intracranial hypertension: a preliminary study*, 36 Neuroradiology 350, 353 (1994) (Dkt. 167-32) ("Gideon"). Johanson Rpt. at 9. The Gideon article, however, expressly does not endorse this proposition. *See* Gideon, *supra*, at 353 ("Our results do not support the suggestion that hypersecretion is an important factor in the majority of patients with IIH."). And, as noted, while the issue is unresolved, the bulk of scholarship appears to adopt the alternative hypothesis: that the root cause of excess CSF in IIH patients is impaired absorption of CSF. *See* Vincenzo Salpietro, et al., *Recent insights on pediatric pseudotumor cerebri syndrome pathophysiology: From the "Unifying Neuroendocrine Perspective" to the "Integrated Bioenergetic-Hormonal Mechanism*," 13 J. Pediatric Neurology 11, 12 (2015) (Salpietro) (observing that the more generally accepted hypothesis for the cause of CSF production is "hampered outflow of CSF into

the venous system"). Dr. Johanson acknowledged this in his deposition. *See* Johanson Dep. at 84 (agreeing that hampered CSF outflow is the more generally accepted hypothesis).

Dr. Johanson's report then discusses the choroid plexus's role in generating CSF. He cites clinical studies that, he states, have demonstrated that the choroid plexus is the source of CSF production. Among these studies are ones that demonstrate that surgically cauterizing and removing choroid plexus cells reduce CSF pressure; and that patients with abnormal choroid plexuses over-secrete CSF. Johanson Rpt. at 10. Dr. Johanson states that, in addition to this clinical evidence, "[p]harmacologic experimentation reinforces the concept of a high-capacity fluid production at the blood-CSF interface." *Id.* Therefore, he states, "it is now widely accepted by neuroscientific and neurosurgical communities that [the choroid plexus] is the focal point of fluid production within the [central nervous system]."[70] *Id.*

Dr. Johanson then discusses how, in his view, sodium channel and pump activity drive CSF formation in the choroid plexus. At its most basic level, the process is as follows: sodium is diffused into the epithelial cells of the choroid plexus through sodium channels (Step 1), where it is then expelled from the cells into the CSF through a sodium pump (Step 2). This creates a sodium imbalance between the choroid plexus epithelial cells and the CSF. To correct this imbalance, water flows through aquaporin channels, causing the formation of CSF (Step 3). Johanson Rpt. at 14–15. This process is summarized in the chart below, copied from Dr. Johanson's report.

[70] Dr. Johanson also addresses other regions of the brain—the arachnoid membrane, brain interstitial fluid compartment, and cerebral venous system—that have the potential to affect CSF flow and pressure. But, Dr. Johanson concludes, the choroid plexus is the primary source of CSF, whose overproduction, he states, causes IIH. Johanson Rpt. at 11–12.

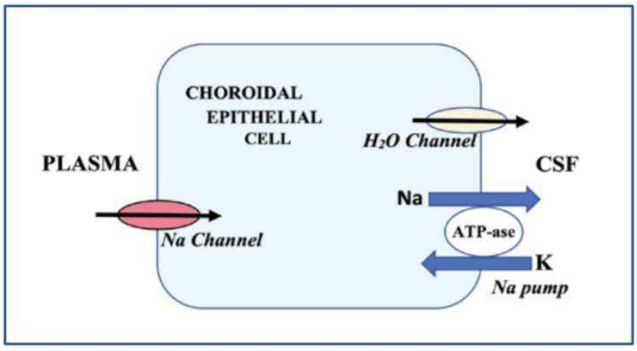

Fig. 8: Sodium transport and distribution in CSF formation: First, Na diffuses down gradient (left) into choroid cell by ENaC. Next, Na is actively extruded by Na pump on CSF-facing membrane. Then, water moves down osmotic gradient, via aquaporin 1, into CSF. Hormones modulate various aspects of the CSF secretory process.

Id. at 15.

Dr. Johanson then sets out his view of the role of sex hormones and their receptors in this process. He posits that, when the androgens testosterone and dihydrotestosterone bind to androgen receptors in the choroid plexus, they trigger the sodium mediated mechanism by which CSF is generated. As he sets out, the building blocks of this hypothesis are (1) the fact that "androgen receptors (AR) have been characterized in CP of female and male mice," (2) an analogy to studies of the effect of testosterone on the kidneys of rats, (3) two case reports of the development of IIH in transgender men who were taking high doses of testosterone, and (4) studies involving the effect of testosterone on sodium channels, pumps and aquaporins—the only one involving the choroid plexus being the Westgate study.[71] *See* Johanson Rpt. at 18, 20, 22. However, as Dr. Johanson admitted at his deposition, he is not aware of any peer-reviewed study that has concluded that androgens cause IIH. *See* Johanson Dep. at 113. And, as noted in connection with the discussion of Dr. Darney, the Westgate study did no more than hypothesize about the role of testosterone in CSF formation. *See* Westgate, *supra*, at P325

[71] According to Dr. Johanson, the choroid plexus is a "renal-type organ" that "shares many common features . . . [with the] kidney." *Id.* at 13. Thus, "one can compare physiology of kidney . . . for insight on [choroid plexus] transport phenomena and fluid turnover." *Id.*

("[H]ypothesis[ing] that obesity and androgen excess may be pathogenic in IIH through dysregulation of CSF secretion and hence [IIH].").

Dr. Johanson also opines that two other hormones, estrogen and progesterone, affect CSF production. He suggests that estrogen imbalance with progesterone increases CSF production. *See id.* at 18–19, 21–22. Progesterone, on the other hand, he states, likely inhibits CSF production. In particular, Dr. Johanson suggests that progesterone reduces the transport of sodium into the choroid plexus epithelial cells (Step 1) by "reducing channel opening time" and "lowering channel expression." *Id.* at 21. It also inhibits sodium pumps generally (Step 2), and down regulates the aquaporins in multiple tissues and, by analogy, in the choroid plexus too (Step 3).[72] *See id.*

Finally, Dr. Johanson pivots to consider LNG. He proposes the following mechanisms as to how LNG causes CSF production and thus IIH. First, he posits, LNG directly travels to the central nervous system and choroid plexus and bonds to the androgen and MR. This causes CSF production for the reasons described above as to the androgen mechanism and for the reasons described in Dr. Salpietro's report with respect to the MR mechanism. *See id.* at 25. Second, he posits, LNG "impacts metabolism and upsets endocrine balance" by increasing androgen, estrogen, and insulin in the blood while decreasing progesterone. *Id.* In support, Dr. Johanson cites (1) studies suggesting that an early age onset of IIH in women might be associated with testosterone, (2) a study of women with IIH that noted elevated testosterone among some of them, (3) a study that demonstrated lower progesterone in patients using Mirena, and (4) a study

[72] Dr. Johanson distinguishes LNG from progesterone by citing to Dr. Salpietro's report for the proposition that LNG, unlike progesterone, does not antagonize MR receptors, and thus inhibits CSF production. *See id.*

that demonstrated stable estrogen levels but an increase in the ratio of estrogen to progesterone among Mirena users three months after Mirena was implanted.[73] *See id.* at 26.

In addition to these hormone-related factors, Dr. Johanson also suggests that LNG induces the secretion of insulin which "can drive androgen production in the ovaries." *Id.* at 27. However, as Dr. Johanson later acknowledges, the evidence is mixed in suggesting that LNG increases insulin levels. He also suggests that hormone and insulin-related weight gain (a so-called "secondary mechanism") might support his finding that LNG causes IIH because obese patients and those with recent weight gain are more likely to develop IIH.[74] *Id.* at 28.

Finally, Dr. Johanson points to "epidemiological evidence" of LNG's ostensible ability to cause IIH, citing what appears to be a single case of a "dechallenge." He did not, however, review either the Valenzuela or Etminan studies or consider any clinical data showing that Mirena users, given the preferential prescribing practices of that contraceptives, are at an increased risk for IIH. *See* Johanson Rpt. at 38–50 (list of authorities does not include Valenzuela or Etminan); Johanson Dep. at 135. At his deposition, Dr. Johanson admitted that no study, in animals or humans, had tested LNG and found that it dysregulated sodium transport in the choroid plexus or increased CSF production. *See id.* at 119, 173.

3. Analysis Under *Daubert*

As with the previous experts, Dr. Johanson's opinion—that the LNG in Mirena causes the hypersecretion of CSF and thus IIH, based on a mechanism consisting of a series of theorized steps—fails to satisfy any of the *Daubert* reliability factors.

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[73] He also, at a later point in his opinion, notes that LNG reduces serum SHBG, raising the "bioavailable (free) androgens in susceptible individuals . . . [and] further exacerbat[ing] the sex hormone imbalance." *Id.* at 30.

[74] He also suggests androgen-related inflammation may play a role in IIH. *See id.* at 29.

Dr. Johanson first developed this theory in the course of this litigation. In his deposition, he admitted that he had never communicated this theory outside of this litigation and that, before being hired by plaintiffs, he had never even considered whether LNG could cause IIH. Johanson Dep. at 109. Nor has this theory been tested: As to the mechanism he proposes by which LNG would have this effect, Dr. Johanson acknowledges that he has not tested the effects of LNG on choroid plexus ion transporters, even though he stated that it would take only one week to do so. *Id.* at 14–15. Dr. Johanson is unaware of anyone else who has tested this theory. *Id*. at 119. He also has not published the theories he articulates in his expert report anywhere, including in a peer-reviewed journal. He is unaware of anyone else who has done so. *Id.* at 63; *see also id.* at 109–10, 173–74. And he admits that his theory is no more than a "plausible working model":

> You can extract data from a lot of literature, a lot of pieces of the puzzle, and I think I very cleverly build it together to make a plausible working model. It's not established, but it's heading in the right direction, my opinion.

Id. at 215.

Under these circumstances, the "cleverly buil[t] together . . . plausible working model" that is Dr. Johanson's mechanism opinion is arguably, by his own account, "speculative" and "conjectural," so as, without more, to require exclusion. *Boucher*, 73 F.3d at 21. At a minimum, because it fails the *Daubert* reliability factors, this opinion, like those of the experts addressed earlier, requires the following "hard look."

The mechanism that Dr. Johanson theorizes, while complex, can be reduced to the following series of premises and steps: (1) IIH is caused by an overproduction of CSF; (2) the choroid plexus produces CSF through a sodium mechanism; (3) the sodium mechanism that produces CSF is triggered by androgens binding to androgen receptors in the choroid plexus; and (4) LNG binds to those same androgen receptors, triggering the same mechanism. In connection

with these propositions, Dr. Johanson adds his views about how certain other hormones (estrogen and progesterone) activate or inhibit that same sodium mechanism, and how LNG affects those hormones. Dr. Johanson also articulates a secondary, indirect mechanism of causation, under which Mirena causes a patient to gain weight, which in turn causes IIH.

As the Second Circuit has held, "it is critical" that the analysis of an expert "be reliable at every step." *Amorgianos*, 303 F.3d at 267. Otherwise, the expert's opinion must be excluded. *See In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994) ("[A]ny step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible.") That proposition guides the Court's analysis of Dr. Johanson's opinion, comprised as it is of a sequence of postulates. Bayer disputes as unreliable and conjectural steps one, three, and four of Dr. Johanson's proposed biological mechanism, as well as some of his secondary premises. The Court considers these in turn.

In support of his theory's first step—that IIH is caused by an overproduction of CSF—Dr. Johanson cites the Gideon study. However, as noted, the authors of that study do not so state. Their study explains that "CSF production may contribute to the development of [IIH]" in some individuals, but the study's results "*do not support* the suggestion that hypersecretion is an important factor in the majority of patients with IIH." Gideon, *supra*, at 353 (emphasis added).

When confronted with this aspect of the Gideon study at his deposition, Dr. Johanson backtracked. No longer relying on the conclusion of the study, he argued that three outlier data points in that study "kind of stood out" so as to favor his conclusion. *Id.* at 168. He blamed the Gideon study's authors for "misjudgment." *Id*. But, as noted earlier in connection with similar handling of others' studies by others of plaintiffs' experts, "exceed[ing] the limitations the authors themselves" placed on their studies is not good science. *See Mirena Perforation /*

Daubert, 169 F. Supp. 3d at 431 (quoting *In re Accutane Prods. Liab.*, 2009 WL 2496444, at *2); *see also Anderson v. Bristol Myers Squibb Co.*, No. CIV.A. H-95-0003, 1998 WL 35178199, at *11–12 (S.D. Tex. Apr. 20, 1998) (excluding expert testimony where expert drew a "causation conclusion that the authors of the study never even reached in their published work"). Ignoring contrary evidence in an effort to preserve one's opinions is, similarly, a flag of unreliability. *See In re Rezulin*, 309 F. Supp. 2d at 563.

Significant too, the premise that IIH results from the overproduction—rather than the under-absorption—of CSF, which Dr. Johanson endorses in this litigation, is one that he has not previously embraced, despite addressing this subject in a prior writing. Specifically, an article Dr. Johanson co-authored recognized that CSF overproduction is the less favored hypothesis in the academy. The article did not indicate that any of the authors embraced that hypothesis. *See* Salpietro, *supra*, at 12. The article instead stated, as Dr. Johanson synopsized in his deposition, that the molecular physiology basis for elevated CSF pressure in IIH is unknown and that "the patho-physiology of PTCS [IIH] is still poorly understood." Johanson Dep. at 76–78, 82–83. To be sure, Dr. Johanson's earlier article falls short of making his present report a reversal of position for purposes of litigation. But it does bear on the reliability of the view he has adopted in this litigation, particularly insofar as Dr. Johanson's new view does not derive from new or original research. And, as noted, this hypothesis is disputed in the literature, the majority of which has hypothesized an under-absorption theory. Dr. Johanson's report does not seriously engage with this contrary theory, including the writings that he cites in his earlier co-authored article, which question that CSF overproduction is the more probable explanation for IIH. *See In re Rezulin*, 309 F. Supp. 2d at 563.

As to the first step in Dr. Johanson's analysis, the Court—and a jury—would be left only with the non-supportive Gideon study and Dr. Johanson's *ipse dixit* assertion that an increase in CSF production is the likely cause of IIH. That is too great an analytic leap. His opinion on this critical first step lacks a sufficient evidentiary basis to permit it, under *Daubert*, to reach a jury. *See R.F.M.A.S., Inc. v. So*, 748 F. Supp. 2d 244, 248 (S.D.N.Y. 2010) ("Expert testimony that is merely subjective belief or unsupported speculation should be excluded." (quotations omitted)).

The next disputed step in Dr. Johanson's mechanism theory is his statement that the sodium mechanism that produces CSF is triggered by androgens binding to androgen receptors in the choroid plexus. By far the most apposite writing cited by Dr. Johanson for this point is the Westgate study. But, as discussed in connection with Dr. Darney's report, that was an *in vitro* study involving the choroid plexus cells in rats and involving testosterone. Bayer validly argues that extrapolating from a study involving testosterone and rats to the context of non-androgen LNG (a progestin) and humans is too great a leap. The Court agrees. In any event, even if such extrapolation were otherwise a viable basis for permitting such a theory to reach a jury, the Westgate study speculated, but stopped short of concluding, that testosterone may play a role in the production of CSF so as to cause IIH. *See* Westgate, *supra*, at P325 ("[*H*]*ypothesis[ing]* that obesity and androgen excess *may be* pathogenic in IIH through dysregulation of CSF secretion and hence [IIH]." (emphasis added)); *see also* Johanson Dep. 188–89.

Dr. Johanson also cited in support of his litigation theory's second step (1) two case reports involving transgender patients who had taken massive doses of testosterone, and (2) *in vitro* studies involving sodium transport in other organs, such as the kidneys. The authors of the transgender case reports, however, emphasize that the relationship between testosterone and IIH

is speculative.[75] And the authors of the *in vitro* (rat-based) studies involving other organs do not appear even to speculate about the choroid plexus or about IIH at all.[76] The gaps between these studies and case reports and the proposition for which Dr. Johanson proposes to use them are too great to support such trial testimony. *See Joiner*, 522 U.S. at 144 (affirming holding that factfinder could not extrapolate conclusion that exposure to PCBs had contributed to plaintiffs' cancer from study of living infant mice who had been given massive doses of PCBs); *see also Amorgianos*, 303 F.3d at 266 (where "studies . . . are simply inadequate to support the conclusions reached," court should exclude expert's opinion).

Step four in Dr. Johanson's mechanism theory posits that LNG binds to androgen receptors in the choroid plexus, causing sodium ion transport. But this theory, too, does not rest on a base of data that is nearly solid enough to reach a factfinder. As Dr. Johanson admitted at his deposition, he is unaware of any study suggesting that LNG dysregulates sodium transport in

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[75] *See, e.g.*, Kapil G. Kapoor, *Regarding secondary intracranial hypertension from testosterone therapy in a transgender patient*, 30 Seminars in Ophthalmology 241, 241 (2015) (Dkt. 167-38) ("While testosterone levels may play a role in these cases, it seems there is insufficient evidence to draw these conclusions definitely, and we must be cautious in drawing these conclusions."); Soo Park, et al., *Secondary intracranial hypertension from testosterone therapy in a transgender patient*, 29(3) Seminars in Ophthalmology 156, 157 (2015) (Dkt. 167-48) ("The exact mechanism of how raised testosterone causes intracranial hypertension is not known."); Catherine Hornby, et al., *What do transgender patients teach us about idiopathic intracranial hypertension?*, 41(6) Neuro-Ophthalmology 326, 326 (2017) (Dkt. 167-36) (suggesting that "[i]t is interesting to speculate that IIH, akin to PCOS, could be driven by androgen excess"). In his deposition, Dr. Johanson acknowledged that the Kapoor, Park, and Hornby studies, as quoted above, had stopped short of the step-three conclusion for which he cites them. *See* Johanson Dep. at 197–98 (Park), 205 (Kapoor), 210–11 (Hornby).

[76] *See, e.g.*, Bei Liu & Daniel Ely, *Testosterone increases: Sodium reabsorption, blood pressure, and renal pathology in female spontaneously hypertensive rats on a high sodium diet*, 2011 Advances in Pharmacological Sciences 817835; Su Yi Loh, et al., *Effects of gonadectomy and testosterone treatment on aquaporin expression in the kidney of normotensive and hypertensive rats*, 242 Experimental Biology & Med. 1376 (2017); Naguib Salleh, et al., *Testosterone induces increase in aquaporin (AQP)-1, 5, and 7 expressions in the uteri of ovariectomized rats*, 248 J. of Membrane Biology 1097 (2015).

the choroid plexus *or* that LNG results in an increase in CSF production or pressure. Johanson Dep. 173 ("Q: [C]an you identify any study that [] found that LNG dysregulates sodium transport in the choroid plexus? A: No. I cannot."); *see also id.* at 119. He also testified that he is unaware of any articles that discuss LNG and its androgenic activity in relation to IIH. *Id.* at 214–15. Relative to Dr. Darney, Dr. Johanson devotes little attention to discussing the androgenic potential of LNG. But, as noted in the discussion of Dr. Darney's similar postulate, LNG's androgenic potential is substantially less than that of testosterone. Even assuming *arguendo* that testosterone could cause the sodium transport posited by Dr. Johanson, it does not non-speculatively follow that LNG has a similar androgenic effect—especially to the degree necessary to cause IIH.

More generally, despite the central role that the androgen sodium mechanism plays in his mechanism theory, Dr. Johanson cites little evidence in support of this vital step. He relies mostly on citations to Dr. Salpietro's report in this litigation and on the same case reports and case studies the Court has discussed elsewhere in this decision. In some circumstances, experts can permissibly rely on the opinions of other experts. *See, e.g.*, *In re Accutane Prods. Liab. Litig.*, 2007 WL 4404176, at *1 (allowing expert on specific causation to rely on opinion of general causation expert "if doctors in his profession normally rely upon the opinions of other experts"). Here, however, for the reasons reviewed in connection with his report, Dr. Salpietro's report itself falls short of *Daubert*'s standards. And, as noted elsewhere, except in the rarest of circumstances, isolated case reports cannot alone prove propositions as to causation. As to his fourth step, too, then, there is too great a gap between the slim evidence cited by Dr. Johanson and the proposition for which he cites it: that LNG binds to androgen receptors in the choroid plexus, causing sodium ion transport.

There are thus infirmities precluding a finding of reliability as to three of the four steps on which Dr. Johanson's theory of Mirena's causation of IIH is based. Beyond that, to the extent that he sought to buttress his conclusion as to this point with clinical data, Dr. Johanson's use of evidence was impermissibly selective. To the extent he dipped into existing scholarship with respect to the relationship between Mirena and IIH, Dr. Johanson did so by citing case reports. In so doing, he elected not to consider the most important scholarship bearing on that point. He did not consider the Valenzuela study (or any part of the Etminan study, including its uncompromised part) at all. *See* Johanson Dep. at 38 ("Q: Did you review any of the clinical studies on Mirena and IIH? A: I did not. I have not, no."); *id.* at 85–86 ("Q: Did you review the literature showing whether patients who used Mirena have an increased rate of IIH as compared to controls? . . . A: No."); *see also id.* at 135–36. To be sure, Dr. Johanson's opinion is ultimately about a theorized mechanism of causation. He was not obliged to have considered these epidemiological studies in formulating his opinion. But, having deployed clinical evidence in the form of case reports in support of his ultimate conclusion, it is fair to examine whether he looked holistically, or only selectively, at this body of evidence. His cherry-picking approach is at odds with principles of sound science.

Finally, as noted, Dr. Johanson articulates a secondary, indirect theory of causation. He asserts that LNG has potential to cause obesity, hypertension, and hormonal imbalance. From these effects, he asserts, it may indirectly cause IIH. But this conclusion is flawed by the same sorts of data holes and analytical gaps as his discussion of the several steps addressed above. As to obesity, for example, Dr. Johanson opines that "weight gain . . . can occur with Mirena usage." Johanson Rpt. at 27–28. But the articles he cites for that proposition articles do not support it. He cites Natália Dal'Ava, et al., *Body weight and composition in users of levonorgestrel-*

releasing intrauterine system, 86 Contraception 350 (2012) (Dkt. 167-21), for the proposition that users of LNG-containing IUDs gained an average of seven pounds per year, and that those taking another progestin, depot-medroxyprogesterone, gained 15 pounds. Johanson Rpt. at 28. But Dal'Ava compared LNG-containing IUDs to copper (non-LNG) IUDs. Dal'Ava found "no significant difference in body weight change between the two groups of users at 12 months." Dal'Ava, *supra*, at 350. Dr. Johanson also cites Waleska Modesto, et al., *Weight variation in users of depot-medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine system and a copper intrauterine device for up to ten years of use*, 20 Eur. J. of Contraception & Reproductive Health Care 57, 60 (2015), for the proposition that LNG-containing IUDs can lead to weight gain. Johanson Rpt. at 28. But that study also found no significant difference between the weight gain in those using LNG-containing IUDs and copper-containing IUDs. It noted that there was "no plausible reason why the presence of a [copper-containing]-IUD *in utero* would influence weight." Modesto, *supra*, at 61. In other words, Modesto, *supra*, ultimately did *not* find that LNG-containing IUDs cause weight gain. And in his deposition, Dr. Johanson admitted he would need to do further research into the issue and that he could not offer a clinical opinion that Mirena users gain significantly more weight than other persons. Johanson Dep. at 317–18. He agreed that a clinician would be better suited to assess the indirect mechanism he posited, in which Mirena causes weight gain, which in turn causes IIH. *See id.* at 321–26.

Dr. Johanson's opinion must be sound at every critical step to be admissible. Instead, it is unsound methodologically at nearly each step. The Court must exclude it.

G. Dr. Vincenzo Salpietro

Dr. Salpietro, plaintiffs' final expert, offers an alternative mechanism explanation with respect to IIH to those of Drs. Darney and Johanson, plaintiffs' other mechanism experts.

1. Qualifications

Dr. Salpietro is a pediatrician and pediatric neurosurgeon. Salpietro Rpt. at 2. He received his medical training at the University of Messina and the University of Pavia in Italy, and at Imperial College London in the United Kingdom. Dr. Salpietro works in the field of molecular neuroscience. Dr. Salpietro has published extensively in peer-reviewed journals in recent years. In addition to his research, Dr. Salpietro teaches students at Imperial College London Medical School and the University College London Institute of Neurology. *Id*. at 3.

His research focuses on investigating "the molecular and metabolic alterations causing rare neurological disorders of yet poorly understood pathophysiology." *Id.* Dr. Salpietro is currently working to characterize the metabolic and genetic basis for a number of rare neurological disorders, including IIH. *Id.* However, as reviewed *infra*, before this litigation, his research into a mechanism for causation of IIH had never identified LNG as such a cause.

2. Proposed Testimony

Dr. Salpietro's opinion is fundamentally about a mechanism by which Mirena might cause IIH. His report embraces a mineralocorticoid theory of a causal link between LNG and IIH. He posits that, because mineral corticoids may cause IIH and because LNG can bind to mineralocorticoid receptors ("MR" or "MRs"), LNG in turn may cause IIH.

Dr. Salpietro's report begins by discussing the basics of LNG, and in particular explains that, as acknowledged by Bayer, LNG binds to MRs. *Id*. at 6–8. Dr. Salpietro also concludes that LNG exerts agonist (rather than antagonist) effects)\ because mineralocorticoid activation symptoms (increase in body weight or blood pressure) have been reported in case reports regarding LNG-IUD users. *Id.* at 9–10. Animal studies conducted by Bayer have, according to Dr. Salpietro, demonstrated that Mirena use results in weight gain. In Bayer's clinical studies of

Mirena, patients also reported some symptoms that are associated with mineralocortoid agonism, including edema, bloating, and weight gain. *Id.* at 10–12.

Dr. Salpietro then turns to discuss IIH. After reviewing its characteristics and symptoms, *id*. at 12–14, he notes that "[t]he pathophysiology of PTCS is incompletely understood," *id.* at 14, that studies have reached conflicting results whether the disease is caused by "increased CSF production or pressure at the choroid plexus level and/or reduced CSF outflow in the arachnoid membrane and the cerebral venous system," *id.* at 15, and that "[s]everal studies evidence a probable role for steroid hormones in PTCS," *id.* Prior literature, he notes, has identified various possible causal mechanisms for IIH. These include "impaired cerebral hemodynamics, including cerebral edema, increased cerebral blood volume, increased CSF production, and/or pressure along with decreased CSF reabsorption or venous flow." *Id*. at 15–16. He states, however, that cerebral edema has been excluded as a cause of IIH, and that there is limited evidentiary support for the remaining theories. *See id.* at 16 ("Another model . . . linked PTCS to excessive CSF production; however, measurement of the production CSF rate would require invasive procedures (*i.e.*, infusion or perfusion techniques) for the patients . . . and no evidence from previous research gave conclusive support for this model, except (probably) two ventricular infusion studies which documented elevated CSF secretion in a number of PTCS patients."); *id.* ("An additional, alternative, pathophysiological model links hampered CSF outflow into the arachnoid villi and the venous system to PTCS pathophysiology. The only possible evidence to support this theory came from a CSF infusion study which demonstrated reduced CSF drainage in PTCS.").

Dr. Salpietro then articulates his theory—namely, that many cases of IIH were related "to the primary event of raised CSF pressure," and that this increase in pressure is caused by

"derangements in transport of electrolytes like sodium (Na+) or potassium (K+)." *Id*. at 17. He states: "Activation of the choroid plexus MRs and their downstream pathways more likely than not stimulates the generation of Na+ (sodium) /K+ (potassium)-ATPase pumps, leading to greater movement of sodium ions at the choroid plexus epithelial cells (CPEC) apical membrane into the cerebral ventricles, thereby actively creating an osmotic gradient to drive secretion of CSF." *Id.* This mechanism has similarities to the model that Dr. Johanson proposes, although the driver of this mechanism posited by Dr. Salpietro is MR activation, not androgen receptor activation as posited by Dr. Johanson. Dr. Salpietro likens the mechanism he posits to mechanisms seen in the kidney. *Id*. at 18.

In support of the mechanism he endorses, Dr. Salpietro cites case reports and case series in which PTCS was observed in patients with excess aldosterone—a mineralocorticoid, which binds to MRs in the epithelial cells of the choroid plexus. *Id.* at 18. However, when questioned on this point at his deposition, Dr. Salpietro disclaimed reliance on case reports to prove his mechanism theory. *See* Salpietro Dep. at 137 ("Q: You cite a number of case reports in your report, correct? A: Yes. Q: Are you relying on those case reports to prove your mechanism theory? A: No."). Dr. Salpietro further acknowledged that, while he regards his mechanism model as "biologically plausible," it "is not proven." *Id*. at 350, 393.

In support of this mechanism theory, Dr. Salpietro cites studies that observe MR expression in animal choroid plexus, and other studies that observe the expression of an Na+-K+ -ATPase subunit in rat choroid plexus. Salpietro Rpt. at 19–21. He further notes that studies have shown "that children and adults with excess of aldosteronism can develop PTCS as a complication." *Id.* at 21. One study, he noted, has shown that IIH patients who did not respond to conventional treatment experienced an improvement of their symptoms when treated with an

"aldosterone receptor antagonist." *Id.* Dr. Salpietro's report, however, acknowledged that there are other possible risk factors for (or causes of) IIH, some of which are more widely accepted and understood than others. These actual or possible risk factors include obesity and weight gain, recombinant growth hormones, excess or low Vitamin A, retinoids, sulfa drugs, amiodarone, lithium, tetracyclines, and quinolones. *Id.* at 24–27.

As to an association between LNG and IIH, Dr. Salpietro cites studies that observe that some women taking oral contraceptives containing LNG have experienced symptoms associated with IIH. *Id.* at 28 (noting study in which four of 59 women using oral contraceptives were reported with IIH symptoms; also noting a 1968 study which described a "high proportion of neuro-opthalmic consequences" among 129 women taking oral contraceptives). None of those studies, however, have concluded that the oral contraceptives caused IIH. *See id.* Dr. Salpietro also cites the Norplant case studies discussed earlier (Sunku; Alder; and Wysowski and Green). *Id.* at 28–29. Dr. Salpietro also cites a case report in which a patient, after exposure to the powerful progestin Depo Provera, experienced IIH, *id.* at 29, and the Martinez case report, cited earlier, of a woman whose visual disturbances resolved after an LNG-released IUD had been removed and treatment with the diuretic acetazolamide had begun, *id*. Finally, Dr. Salpietro also cites the Valenzuela study, *id.*, and to Bayer's summary of individual case reports as submitted to German regulator BfArM. *Id.* at 29–30.

With respect to the mechanism he posits, Dr. Salpietro terms it "biologically plausible," and consistent with various known facts about IIH. *Id*. at 30.[77] He acknowledges that there are a

[77] He writes that "PTCS-related causal mechanisms are in a very large proportion related to underlying imbalances of steroid hormones, especially female sex hormones." *Id*. at 32. Dr. Salpietro notes that this conclusion is corroborated by observations that "(a) the very low incidence of PTCS in pre-pubertal children vs. adults; (b) the much higher incidence of PTCS in post-pubertal women vs. men; (c) the absence of a gender preference (women vs. men) before

limited number of studies in the field. *Id*. at 30. In support of the critical step in his mechanism that links LNG to MR activation in the choroid plexus and thus the sodium/potassium mediated increase in CSF, he cites two studies with respect to the effect of progesterone activity on MRs, and to an animal study involving rabbits that found that a combined administration of estrogen and progestin altered CSF dynamics in the choroid plexus. *Id.* But the conclusions of that study, as Dr. Salpietro noted, are cabined and qualified: "There *may* be several kinds of cellular mechanisms involved in the action of progesterone on the choroid plexus function. One mechanism *could* be an interaction with aldosterone in terms of competition between progesterone and aldosterone at cellular receptors." *Id.* at 31 (citing Lindvall-Axelsson & Owman, *Actions of sex steroids and corticosteroids on rabbit choroid plexus as shown by changes in transport capacity and rate of cerebrospinal fluid formation*, 12 Neurology Res. 181, 181–86 (1990)) (emphasis added). Finally, Dr. Salpietro cites to Dr. Johanson's report in this litigation for the proposition that LNG can cause or substantially contribute to IIH though an androgen-mediated mechanism. *Id*.

At the end of his report, Dr. Salpietro articulates an indirect mechanism by which LNG may cause IIH. He posits a relationship between IIH, LNG, and obesity, in which, because the levels of SHBG are lower in obese women, and because LNG is available to bind to hormonal receptors only when it is "free," the absence of SHBG available results in increased hormonal effects from LNG in obese women. *Id.* at 33–34. He also posits that use of LNG causes weight gain; and that, because weight gain is a risk factor for IIH, LNG is therefore a risk factor for IIH. *Id.* at 34–36.

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puberty; (d) the notably higher PTCS incidence in young obese women vs. normal weighted women; (e) the tendency to relative testosterone deficiency in those (rare) men affected with PTCS in their post-pubertal age." *Id.* at 32.

In his deposition—addressed further *infra*—Dr. Salpietro admitted that he was not an expert in epidemiology and that he cannot testify about either it or pharmacology. *See* Salpietro Dep. 424 – 25 ("I have included all this pharmacology and epidemiology . . . because I wanted to do a proper job . . . . But it's something that I did challenging myself and going in a different territory, so I cannot testify about that."); *id.* at 427 ("I cannot absolutely testify about pharmacology or epidemiology or gynecology. I mean, I would never—I would never do that."); *id.* at 137 ("It is not my expertise. I have been not trained like an epidemiologist. I have no experience of epidemiology."); *id.* at 163 ("[B]ecause I am not an epidemiolog[ist], I exchanged thoughts with [Plaintiff counsel], and she—she helped me to analyze, to interpret this data.").

3. Analysis Under *Daubert*

Unlike the preceding six experts, Dr. Salpietro has written prior to this litigation to propose a component of the theory that he now propounds. In 2012 and 2014, he proposed an MR-mediated mechanism for IIH, although Dr. Salpietro did not then connect it to LNG, let alone to Mirena. Dr. Salpietro did suggest a causal connection to IIH of aldosterone, a classic MR agonist, and progesterone. To be sure, as articulated in his 2012 and 2014 publications, Dr. Salpietro's theory as to such a mechanism for IIH was put in far more qualified and tepid terms than in his present report. *See generally* Vincenzo Salpietro, et al., *Idiopathic intracranial hypertension: a unifying neuroendocrine hypothesis through the adrenal-brain axis*, 33 Neuroendocrinology Lett. 569, 569, 572 (2012) (Dkt. 196-23) ("Salpietro 2012") (stating that he was "working toward" a "hypothesis" of IIH that involves MRs in the choroid plexus, that it is "conceivable" that progesterone "can lead to IIH through stimulation of the MR pathway that leads to active sodium secretion . . . at the apical membrane of the choroid plexus," but that "[t]hus far, however, there is not a credible and comprehensive hypothesis . . . of IIH despite the different mechanisms proposed"); *see also* Vincenzo Salpietro, et al., *Pediatric idiopathic*

intracranial hypertension and the underlying endocrine-metabolic dysfunction: a pilot study, 27 J. Pediatric Endocrinology & Metabolism 107 (2014) (Dkt. 196-26) ("Salpietro 2014"). And Dr. Salpietro's 2014 writing, which was focused on other IIH co-morbidities, made only a passing reference to progesterone, to which it referred only in a chart. *See* Salpietro 2014, at 112.

Bayer articulates several objections to Dr. Salpietro's expert conclusion that Mirena is a cause of IIH. At the outset, Bayer does not concede Dr. Salpietro's starting premise, to wit, that MR agonists can bind to MR receptors in the choroid plexus, triggering a biological chain reaction that can leads to an increase in CSF production. This theory, Bayer asserts, is purely a scholar's working hypothesis and has been admitted by Dr. Salpietro himself as unproven. Overwhelmingly, though, Bayer focuses its methodological challenge under *Daubert* on two "leaps" or "gaps" in Dr. Salpietro's proposed application of that thesis to Mirena: first, that progesterone and LNG are MR agonists, and, second, that IIH is caused by an increase in CSF production. Bayer argues that these necessary steps in Dr. Salpietro's ultimate opinion as to Mirena's causation of IIH are no more than speculative working theories and, indeed, that Dr. Salpietro has repeatedly admitted that these are conjectural and unproven.

For the reasons that follow, Bayer is correct. The two "gaps" (unsupported assumptions) that it identifies are central to Dr. Salpietro's theory. Each unsubstantiated leap of logic is too great and too consequential to make Dr. Salpietro's ultimate conclusion as to Mirena the product of reliable methodology. And Dr. Salpietro, in his deposition testimony, repeatedly—and at times, memorably—acknowledged that his is no more than a conjectural, unproven working hypothesis. *See, e.g.*, Salpietro Dep. at 409 ("[W]e are still in the prehistoric age in regard to the research of pseudotumor cerebri."); *id*. "[W]e don't know the genes involved, the pathways involved, and as a consequence we are not able to offer . . . etiologically targeted treatments but

just symptomatic reliefs."); *id*. at 89 ("There is no one in the world who knows the exact cause of pseudotumor cerebri.").

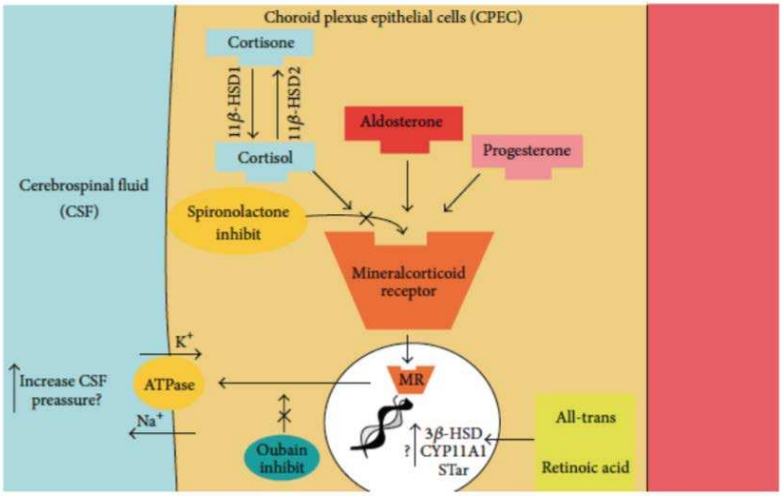
Before addressing the gaps in Dr. Salpietro's mechanism theory, the Court notes that, as related above, Dr. Salpietro has jettisoned the remaining opinions articulated in his report, *i.e.*, all but his mechanism opinion. These include his opinions as to pharmacology, epidemiology, case reports, and Dr. Conrad Johanson's androgen theory. In his deposition, Dr. Salpietro disclaimed reliance on these opinions. *See* Salpietro Dep. at 424 ("I would never testify about the pharmacology underlying Mirena or the—or the epidemiology or the gynecology side of this litigation."); *id.* at 274 ("There may be several mechanisms involved in the androgenicity of Mirena, but I am not in the position [to] offer you a proper opinion [about Dr. Johanson's androgen theory] because I should read much more about this."); *id.* at 423 ("I mean, the only thing I can really offer is my model. I mean, I cannot talk about anything else than my model because I'm not a pharmacologist; I am not an epidemiologist."); *see also id.* at 137, 163, 274, 423–25. And, following Dr. Salpietro's lead, plaintiffs in their opposition brief did not defend the aspects of his report that embrace these other opinions.

As to Dr. Salpietro's opinion as to a mechanism by which Mirena ostensibly causes IIH, the Court assumes, *arguendo*, that existing scholarship provides a reliable basis for the starting premise of that opinion: that MR agonists can bind to MR receptors in the choroid plexus, triggering a biological chain reaction that can lead to an increase in CSF production. Like Bayer, the Court focuses its analysis on the two ensuing steps in the reasoning Dr. Salpietro uses to connect that starting premise to his opinion here. The Court gives this analysis a "hard look,"

because—like the opinions of the preceding six experts—Dr. Salpietro's opinion does not meet any of the *Daubert* criteria for reliability.[78]

Whether progesterone and LNG are MR agonists: At the threshold, plaintiffs seek to deflect Bayer's critique as to this point by stating that Dr. Salpietro's model does not require LNG and progesterone to be MR agonists. That is flatly incorrect. By its own explicit terms, Dr. Salpietro's model is based on "*activation* of the choroid plexus MRs." Salpietro Rpt. at 17. He posits a biological pathway which can be triggered by the "*agonistic* activity of aldosterone on the epithelial cells of the choroid plexus," *id.* at 18 (emphasis added); *see also* Salpietro 2012 at 57 ("Aldosterone can stimulate MR; spironolactone can antagonize MR"), and which is inhibited by spironolactone, "a classic MR *antagonist*," Salpietro Rpt. at 18 (emphasis added). And Dr. Salpietro includes in his report the following chart, taken from his 2014 article, that sets forth his unified theory of IIH etiology and which, through its use of arrows, clearly demonstrates his view that the mechanism is triggered by MR *agonists*.

[78] Dr. Salpietro admits that he did not perform any tests to determine whether LNG acts as an MR agonist, Salpietro Dep. at 146, and that there is "no literature I am aware of which show[s] an agonistic effect of LNG," *id.* at 257. The one study he cites on this point indicates that LNG has an *antagonistic* effect or no effect on the MR. *See* Donita Africander, et al., *Molecular mechanisms of steroid receptor-mediated actions by synthetic progestins used in HRT and contraception*, 76 Steroids 636, 639 (2011) (Dkt. 167-15) (cited in Salpietro Rpt. at 5). Because Dr. Salpietro has never tested LNG, his methodology has no error rate. And, far from garnering acceptance within the scientific community, Dr. Salpietro's thesis that IIH is caused by overproduction rather than under-absorption of CSF is distinctly in the minority, and the other steps in the chain of reasoning leading to Dr. Salpietro's mechanism opinion (*e.g.*, that LNG is an MR agonist and that LNG causes certain side effects) are not scientifically accepted. Dr. Salpietro concedes that his opinion is "controversial." Salpietro Dep. at 55.



Along the same lines, Dr. Salpietro also cites Anny Souque, et al., *The mineralocorticoid activity of progesterone derivatives depends on the nature of the C18 substituent*, 136 Endocrinology 5651 (1995) (Dkt. 167-61), for the proposition that "progesterone has a low agonist mineralocorticoid (MC) activity." Salpietro Rpt. at 9. This is not a small point. Dr. Salpietro's model depends on this proposition. It does not logically cohere if progesterone and LNG are not MR agonists.

However, fatally from a *Daubert* perspective, the studies that his report cites and that he referenced at his deposition for this proposition do not support that progesterone and LNG are MR agonists. The first study, M. Quinkler & S. Diedrich, *Difference of in vivo and in vitro antimineralocorticoid potency of progesterone*, 28 Endocrine Res. 465 (2002) (Dkt. 167-50), appears to directly contradict itself. It reports both that the preexisting literature found that progesterone was "only a weak transactivation activity and is therefore a MR *antagonist*," *id.* at 466 (emphasis added), and that his study affirmed that literature's conclusions by demonstrating that progesterone "has a low *agonist* [mineralocorticoid]-activity," *id.* at 467. The study also states that "progesterone is a potent *anti-[mineralocorticoid]* in vivo," *id.* (emphasis added), suggesting again that progesterone's effects are *antagonistic*. At best, the study is equivocal. It

is sufficiently inconsistent as to neither support nor undercut the proposition on which Dr. Salpietro relies.

The Souque study paints a more internally consistent, while complex, picture. But in the end, this study does not help Dr. Salpietro's theory either. The study finds that progesterone and several of its derivatives "behave as antagonists." Souque, *supra*, at 5656. This, of course, is contrary to a core premise of Dr. Salpietro's report. (Plaintiffs' expert Dr. Johanson similarly disagrees with Dr. Salpietro, opining that progesterone is an MR antagonist. *See* Johanson Rpt. at 18; Johanson Dep. at 175.) That said, the Souque study does find that one progesterone derivative has "agonist properties." *Id.* But the proposition that one derivative of progesterone has agonist properties is an insufficient ground on which to find a reliable basis for Dr. Salpietro's thesis. The Souque study's findings emphasize the difficulty, even the futility, of inferring from the behavior of one hormone that of a similar hormone—it underscores that one cannot assume that because one hormone has a certain effect, a similar hormone will necessarily have the same effect. As another study puts the point: "[T]he relationship between affinity and biological activity or potency is not straightforward or predictable, and appears be cell and promoter-specific, as well as ligand-dependent." Africander, *supra*, at 641. Under *Daubert*, Dr. Salpietro's analysis must be "reliable at every step." *Amorgianos*, 303 F.3d at 267. But the studies he cites for the necessary proposition that progesterone is an MR agonist are "simply inadequate to support" that conclusion. *Id.* at 266. They do no more than make that proposition possibly true.[79]

[79] In his deposition, Dr. Salpietro testified that "I'm not saying that the colleagues and the researchers who wrote this is an antagonist are wrong. This is a controversial subject, and I don't think that anyone will be able to prove his opinion to the scientific standard." Salpietro Dep. at 205.

Conceivably, Dr. Salpietro's opinion on this aspect of his mechanism opinion could have been salvaged had he contended with this nuance. Conceivably, for example, he might have explained, if true, that the chemical structure of LNG is closely akin to that of the MR-agonist progesterone derivative addressed by the Souque study, while it is unlike that of derivatives that are not MR agonists. Dr. Salpietro did not, however, do so.

The only evidence, in fact, that Dr. Salpietro musters in support of his thesis that LNG is a MR agonist is his statement that LNG causes "MR agonism-related side effects." Salpietro Rpt. at 10. The side effects that Dr. Salpietro mentions in this regard include bloating or edema, weight gain, and increased blood pressure. *Id*. at 11. But this statement is problematic because these symptoms may have many causes, and because, with the possible exception of high blood pressure, the evidence that Dr. Salpietro cites does not bear out that LNG causes these symptoms.

Dr. Salpietro supports his opinion that LNG causes edema by citing to patient self-reports of edema and bloating as recounted in a clinical study by Bayer. Dr. Salpietro assumed that the doctors had "objectively assessed" the reports of edema. Salpietro Dep. at 336. In his deposition, he admitted that had the study merely documented patients' self-reports, that would influence his view of the study's value. *Id.* at 345 ("Q: On that study A46796, would it change your opinion if the edema you rely on was reported but then not objectively assessed? Would that impact your view of— A: Yes. Q: Because— A: If it was not a doctor. Q: Yes. A: If it was a self-report, yeah.") Yet that is what the study documented. Further, as Dr. Salpietro acknowledged, the self-reported edema and bloating was potentially attributable to confounding factors, such as kidney problems. *See id.* at 336.

Dr. Salpietro supports his opinion that LNG causes weight gain by citing to human and animal studies. At his deposition, however, Dr. Salpietro recognized that he had not read some of the studies he cites, and that others do not support his conclusions. A few examples illustrate the casual nature of Dr. Salpietro's inquiry, and the consequent unreliability of his methodology. Dr. Salpietro cites three animal studies that purportedly show LNG causes weight gain. He read only one of them. *See* Salpietro Dep. at 286–87. One of the two he did not read was written in Japanese. *See id.* at 312. Dr. Salpietro also relies on human studies by Dal'Ava and Napolitano. Those studies, however were focused on body composition, not weight. *See* Salpietro Rpt. 35–36; *see also* Salpietro Dep. 315, 327–28 (recognizing that Dal'Ava and Napolitano studies did not show a statistically significant increase in weight gain). Dr. Salpietro also cites a study by Silva-Filho involving self-reported weight gain by users of LNG-containing IUDs. However, Dr. Salpietro himself admitted that he did not "believe much in this because [it] is a self report." Salpietro Depo. at 332.

Finally, Dr. Salpietro supports his opinion that LNG increases blood pressure by citing to two studies. The first describes a single case report of increased blood pressure. *See* A.G. Vos, et al., *Hypertension and use of an intrauterine levonorgestrel-releasing device*, 70 Neth J. of Med. 431 (2012) (Dkt. 167-65). As the Court has noted repeatedly in this decision, case reports alone do not establish causation. *See also* Salpietro Dep. at 124 (single case report "very weak" evidence of connection between LNG and increased blood pressure). The second includes a single sentence stating that increases in blood pressure have been reported with Norplant, and citing to three additional studies. T. Rosenthal, et al., *Chapter 70: Oral contraceptives, hormone replacement therapy, and hypertension, in* Comprehensive Hypertension Clinical Approaches: Secondary Hypertension 865, 877 (2007). In any event, even assuming *arguendo* that such

studies did prove that Norplant causes increased blood pressure, it is too great a leap to assume, on this basis, that LNG is therefore an MR agonist that can trigger Dr. Salpietro's biological mechanism. *See Amorgianos*, 303 F.3d at 266.

Whether IIH is caused by CSF overproduction: In accusing Dr. Salpietro of a second "leap," Bayer faults his report and testimony for refusing to address whether IIH is caused by CSF overproduction, as opposed to by under-absorption of CSF. As Dr. Johanson recognized, this is indeed a "pivotal question" for an expert proposing to opine on whether Mirena causes IIH. Johanson Dep. at 15–16. The Court reads Dr. Salpietro's report differently from Bayer. In the Court's view, Dr. Salpietro's report, while not a model of clarity, is best read to take the position that IIH is caused by CSF overproduction. As Bayer notes, Dr. Salpietro's mechanism theory would otherwise make little sense.

Dr. Salpietro, however, does not cite any direct evidence that LNG causes an increase in CSF production. He articulates that proposition as an assumption, not as a finding based on data or scientific experimentation. Moreover, even if reliable evidence existed that LNG causes an increase in production of CSF, Dr. Salpietro would need to contend with the next logical step in his thesis, which is whether IIH is caused by increases in the production of CSF. As noted earlier, numerous studies suggest that IIH is actually caused by the under-absorption of CSF; Dr. Salpietro's contrary thesis that IIH is the product of overproduction of CSF is decidedly the minority theory. *See supra*, pp. 119–20, 134–35.

Plaintiffs do not contest that Dr. Salpietro's theories lack such support. They argue instead that Mirena's purported MR-related side effects, specifically edema and weight gain, themselves reliably establish that LNG increases production of fluids. For multiple reasons, this is far too threadbare and speculative a basis to support Dr. Salpietro's thesis. First, it is too far a

leap to posit that an increase in production of a type of fluid in one region of the body (e.g., the limbs) necessarily means that production of a different type of fluid (CSF) is similarly increased in another region (e.g., the brain). Second, as noted, the scientific evidence Dr. Salpietro cites in support of his conclusions that Mirena causes edema and weight gain does not solidly support these conclusions. Third, as noted, even if Dr. Salpietro had non-speculatively tied an increase in CSF production to use of Mirena, he does not establish that over-production of CSF, as opposed to its under-absorption, causes IIH.

In sum, Dr. Salpietro's untested mechanism hypothesis, which he admits is "not proven," Salpietro Dep. at 241, 350, is not reliable. It is beset by analytic and evidentiary gaps at multiple steps, which Dr. Salpietro proposes to fill with theories and assumptions, not data. Accepting Dr. Salpietro's never-vetted model would, unacceptably, require the jury to accept "the *ipse dixit* of the expert." *Gen. Elec. Co.*, 522 U.S. at 146. This *Daubert* does not permit.

IV. Plaintiffs' Challenges to Bayer's Expert Witnesses

As noted, plaintiffs have moved to exclude defendants' 12 expert witnesses. The reports of these witnesses are directed principally to the topic of general causation. In large measure, these reports take issue with the methodology of plaintiffs' experts.

In light of this ruling excluding the general-causation testimony of all plaintiffs' experts, the Court does not perceive at this time any reason to resolve plaintiffs' motions to exclude the testimony of Bayer's responsive general-causation experts. The Court expects that this litigation, tracking the Perforation MDL, will likely move next to a defense motion for summary judgment on the issue of general causation. The Court accordingly denies as potentially moot plaintiffs' *Daubert* motions aimed at Bayer's general-causation experts. This ruling is without prejudice:

In the event that this case survives such a motion, the Court will then seek counsel's views as to whether to take up *Daubert* motions with respect to Bayer's experts.

CONCLUSION

For the foregoing reasons, the Court grants Bayer's motion to exclude the testimony of plaintiffs' seven general-causation witnesses, and denies, as potentially moot, plaintiffs' motions to exclude Bayer's 12 general-causation witnesses. The Clerk of Court is respectfully directed to terminate the motions pending at Dkts. 134, 136, 138, 141, 143, 145, 147, 149, 151, 153, 155, 158, 160, 162, 165, 168, 170, 172, and 175.

An order as to next steps in this case will follow shortly.

SO ORDERED.

Paul A. Engelmayer

Paul A. Engelmayer
United States District Judge

Dated: October 24, 2018
New York, New York