UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	))))	**MDL No. 16-2740** **SECTION: "H" (5)**
This document relates to: Elizabeth Kahn, 16-17039	))	

ORDER AND REASONS

Before the Court is Defendants' Motion to Exclude Expert Testimony of Dr. David Madigan (Doc. 11003). The Court held oral argument on the Motion on October 6, 2020. For the following reasons, the Motion is **GRANTED IN PART** and **DENIED IN PART**.

BACKGROUND

Plaintiffs in this multidistrict litigation ("MDL") are suing several pharmaceutical companies that manufactured and/or distributed a chemotherapy drug, Taxotere or docetaxel,[1] that Plaintiffs were administered for the treatment of breast cancer or other forms of cancer. Among these companies are Defendants sanofi-aventis U.S. LLC and Sanofi U.S. Services Inc. (collectively, "Sanofi" or "Defendants"). Plaintiffs allege that the drug caused permanent alopecia—in other words, permanent hair loss. Plaintiffs bring claims of failure to warn, negligent misrepresentation, fraudulent misrepresentation, and more. The first bellwether trial was held in September 2019, and the second trial is set for 2021.[2]

In the instant Motion, Sanofi moves to exclude the testimony of Dr. David Madigan. Dr. Madigan is an expert biostatistician that Plaintiff

[1] Docetaxel is the generic version of Taxotere.
[2] The second trial was continued due to the COVID-19 pandemic.

Elizabeth Kahn, the second bellwether plaintiff, plans to call as a witness at trial. Plaintiff Kahn opposes Sanofi's Motion.

LEGAL STANDARD

The admissibility of expert testimony is governed by Federal Rule of Evidence 702, which provides as follows:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> > (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> > (b) the testimony is based on sufficient facts or data;
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> > (c) the testimony is the product of reliable principles and methods; and
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> > (d) the expert has reliably applied the principles and methods to the facts of the case.[3]

The current version of Rule 702 reflects the Supreme Court's decisions in *Daubert v. Merrell Dow Pharms., Inc.*[4] and *Kumho Tire Co. v. Carmichael*.[5] The threshold inquiry in determining whether an individual may offer expert testimony under Rule 702 is whether the individual has the requisite qualifications.[6] After defining the permissible scope of the expert's testimony, a court next assesses whether the opinions are reliable and relevant.[7] As the

[3] FED. R. EVID. 702.
[4] 509 U.S. 579 (1993).
[5] 526 U.S. 137 (1999).
[6] Wagoner v. Exxon Mobil Corp., 813 F. Supp. 2d 771, 799 (E.D. La. 2011). *See also* Wilson v. Woods, 163 F.3d 935, 937 (5th Cir. 1999) ("A district court should refuse to allow an expert witness to testify if it finds that the witness is not qualified to testify in a particular field or on a given subject.").
[7] *See* United States v. Valencia, 600 F.3d 389, 424 (5th Cir. 2010). *See also* Wellogix, Inc. v. Accenture, L.L.P., 716 F.3d 867, 881–82 (5th Cir. 2013).

"gatekeeper" of expert testimony, the trial court enjoys broad discretion in determining admissibility.[8]

First, to assess reliability, a court considers whether the reasoning or methodology underlying the expert's testimony is valid.[9] The party offering the testimony bears the burden of establishing its reliability by a preponderance of the evidence.[10] Courts should exclude testimony based merely on subjective belief or unsupported speculation.[11] Courts must, however, give proper deference to the traditional adversary system and the role of the jury within that system.[12] "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence."[13] After assessing reliability, a court evaluates relevance.[14] In doing so, a court must determine whether the expert's reasoning or methodology "fits" the facts of the case and will thereby assist the trier of fact in understanding the evidence.[15]

Federal Rule of Evidence 703 further provides that an expert may offer opinions based on otherwise inadmissible facts or data but only if (1) they are of the kind reasonably relied upon by experts in the particular field; and (2) the testimony's probative value substantially outweighs its prejudicial effect.[16]

LAW AND ANALYSIS

Sanofi raises three challenges to Dr. Madigan's testimony. Sanofi argues (1) that Dr. Madigan offers a medical causation opinion that falls outside the

[8] *Wellogix*, 716 F.3d at 881.
[9] *See Daubert*, 509 U.S. at 592–93.
[10] *See* Moore v. Ashland Chem. Inc., 151 F.3d 269, 276 (5th Cir. 1998).
[11] *See Daubert*, 509 U.S. at 590.
[12] *See id.* at 596.
[13] *Id.*
[14] Burst v. Shell Oil Co., 120 F. Supp. 3d 547, 551 (E.D. La. June 9, 2015).
[15] *Id.*
[16] FED. R. EVID. 703.

scope of his expertise; (2) that Dr. Madigan conducted unreliable analyses; and (3) that in searching certain databases, Dr. Madigan used a methodology that does not comport with FDA guidance.

I. Dr. Madigan's Causation Opinion

Sanofi first argues that Dr. Madigan offers an opinion that goes beyond the scope of his expertise. Sanofi notes that in the first bellwether trial, the *Earnest* trial, Dr. Madigan focused his opinion on statistics. Now, according to Sanofi, Dr. Madigan opines on medical causation in addition to statistics. In response, Plaintiff disputes that Dr. Madigan has expanded his opinion to address medical causation, and Plaintiff concedes that Dr. Madigan has not conducted a Bradford Hill analysis to support any such opinion.

After reviewing Dr. Madigan's reports, the Court sees that Dr. Madigan has in fact revised his opinion from the first bellwether trial. In that trial, Dr. Madigan identified "adequate statistical evidence supporting a causal association between Taxotere (docetaxel) and permanent/irreversible alopecia."[17] In his report for Plaintiff Kahn, Dr. Madigan concludes that "there is adequate statistical evidence that docetaxel causes irreversible alopecia."[18] As revised, this opinion improperly encroaches on the second prong of the general causation inquiry—a prong that Dr. Madigan has not analyzed.

As this Court has explained, to prevail in a pharmaceutical products liability case, a plaintiff must establish both general and specific causation through reliable expert testimony.[19] "General causation is whether a substance is capable of causing a particular injury or condition in the general population, while specific causation is whether a substance caused a particular

[17] Doc. 6144-1 at 21.
[18] Doc. 11462-4 at 26.
[19] *See* Burst v. Shell Oil Co., No. 14-109, 2015 WL 3755953, at *3 (E.D. La. June 16, 2015); In re Abilify (Aripiprazole) Prods. Liab. Litig., 299 F. Supp. 3d 1291, 1306 (N.D. Fla. 2018).

individual's injury."[20] To assess whether general causation exists between an agent and a disease, the case law recognizes a two-prong test.[21] First, there must be evidence showing a "statistically significant association" between the agent and the disease.[22] Second, once an association is found, researchers assess whether a true causal relationship underlies the association.[23] Typically, an expert applies the Bradford Hill criteria to evaluate this second prong.[24] The Bradford Hill criteria are: (1) temporal relationship; (2) strength of the association; (3) dose-response relationship; (4) replication of findings; (5) biological plausibility; (6) consideration of alternative explanations; (7) cessation of exposure; (8) specificity of the association; and (9) consistency with other knowledge.[25]

Plaintiff concedes that Dr. Madigan has not conducted a Bradford Hill analysis. Dr. Madigan, then, has not assessed whether a true causal relationship underlies the statistical association he has identified. For this reason, Dr. Madigan cannot tell the jury that there is evidence "that docetaxel causes irreversible alopecia," as he states in his report. Instead, he must take care to state only that the evidence shows an association between the two.[26]

Plaintiff points to deposition testimony from the *Earnest* trial and avers that the Court has previously permitted Dr. Madigan to state that Taxotere

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[20] Knight v. Kirby Inland Marine Inc., 482 F.3d 347, 351 (5th Cir.2007).
[21] *See Burst*, 2015 WL 3755953, at *5 (E.D. La. June 16, 2015); *Wagoner*, 813 F. Supp. 2d at 803–04.
[22] *See Wagoner*, 813 F. Supp. at 803–04; *Burst*, 2015 WL 3755953, at *5.
[23] *See Wagoner*, 813 F. Supp. at 803–04; *Burst*, 2015 WL 3755953, at *5.
[24] *See Wagoner*, 813 F. Supp. at 803–04; *Burst*, 2015 WL 3755953, at *5. The Bradford Hill criteria derive from a 1965 lecture by a British epidemiologist and statistician, Sir Austin Bradford Hill. In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II), 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018). In the lecture, he identified nine criteria that can aid researchers in deciding whether a reported association in an epidemiological study is causal. *Id.*
[25] *Burst*, 2015 WL 3755953, at *5.
[26] *See Abilify*, 299 F. Supp. 3d at 1361 (finding Dr. Madigan's "admitted lack of expertise" in relevant medical fields precluded an opinion on general causation).

causes irreversible alopecia. The Court finds this argument unpersuasive. Sanofi did not challenge this testimony in the *Earnest* trial, and the Court, therefore, did not consider whether Dr. Madigan's testimony was encroaching on the second prong of the general causation analysis.[27] The Court, then, did not issue a ruling on its admissibility as Plaintiff suggests. Because Plaintiff has failed to prove the admissibility of the testimony at issue, Dr. Madigan will be precluded from testifying that Taxotere causes permanent alopecia.

II. Dr. Madigan's Analyses

a. TAX 316 Analysis

For the *Earnest* trial, Dr. Madigan analyzed the results of a certain clinical trial known as TAX 316. As this Court has explained, as part of the TAX 316 trial, 744 patients were given a Taxotere regimen; this regimen included Taxotere, Adriamycin, and Cyclophosphamide.[28] Researchers called this the "TAC" arm of the study. The other arm of the study was a control/comparator arm—the "FAC" arm. In this arm, patients received a chemotherapy agent called Fluorouracil instead of Taxotere.

According to Sanofi, "Dr. Madigan has previously conceded that the results of TAX 316 were not statistically significant when calculated according to the 'standard conventional' measurement using a p-value of 0.05."[29] Specifically, Dr. Madigan testified that when looking at "a ten-year meeting follow-up," the difference in the rates of permanent alopecia between the two arms was not statistically significant at a p-value of 0.05.[30] Sanofi avers that in his report for Plaintiff Kahn's trial, however, Dr. Madigan conducted a new

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[27] *See* In re Welding Fume Prods. Liab. Litig., No. 1:03-cv-17000, 2010 WL 7699456, at *69 (N.D. Ohio June 4, 2010) (allowing video to be played in first two bellwether trials where there was no objection but sustaining objection in later bellwether trial).
[28] For more background on TAX 316, see Doc. 11332.
[29] Doc. 11003-1 at 5.
[30] Doc. 11003-5 at 5.

analysis of the TAX 316 data, and this time he found that the results were statistically significant.[31] Calling it a litigation-driven analysis, Sanofi argues that this new analysis is inadmissible. In response, Plaintiff does not dispute that Dr. Madigan conducted a new analysis. Instead, Plaintiff argues that he had good reason for analyzing the data differently.

After reviewing Dr. Madigan's reports, the Court finds that Sanofi is mischaracterizing Dr. Madigan's opinions. Sanofi is correct that in his *Earnest* report, Dr. Madigan analyzed the TAX 316 results, as well as the TAX 301 results, using a "p-value" of 0.05, which he said was "standard" and "conventional."[32] Notably, though, in his *Kahn* report, Dr. Madigan included the very same analysis.[33] Below is the chart that is featured in both reports.[34]

TAX 316				
Not resolved within:	TAC (*n*=744)	FAC (*n*=736)	Rate Ratio	p-value
22 weeks	178	141	1.25	0.026
6 months	112	82	1.35	0.026
12 months	53	27	1.94	0.003
24 months	36	19	1.87	0.022
60 months	31	16	1.92	0.029
120 months	29	16	1.79	0.053
TAX 301				
Not resolved within:	TAC (*n*=744)	FAC (*n*=736)	Rate Ratio	p-value
22 weeks	11	2	5.39	0.013
6 months	9	1	8.81	0.012
12 months	4	1	3.92	0.186
24 months	3	1	2.94	0.327
60 months	3	1	2.94	0.327
120 months	3	1	2.94	0.327

[31] *See* Doc. 11003-1 at 5–6.
[32] *See* Doc. 11003-5.
[33] Doc. 11003-3 at 26.
[34] *Id.*; Doc. 6144-1 at 20–21.

In both reports, too, Dr. Madigan offers this conclusion based on his charts: "A random effects meta-analysis combining the data from the two studies at completion yields a rate ratio of 1.85 with a corresponding 95% confidence interval (1.04 , 3.31) and a p-value of 0.04."[35]

Despite what Sanofi suggests, Dr. Madigan's *Kahn* report does not contradict his *Earnest* report. Dr. Madigan has not abandoned his *Earnest* analysis in favor of a new, manipulated analysis in *Kahn*. What Sanofi challenges is just one additional paragraph that Dr. Madigan has included in his *Kahn* report. In Paragraph 67, Dr. Madigan stated as follows:

> I am aware of a Sanofi document suggesting much shorter TAX 316 follow-up times for alopecia than those provided in the actual TAX 316 [clinical] trial SAS data. Even if those follow-up times were correct, which they are not, alopecia with a duration of two years or more occurred in five TAC patients but did not occur in any [FAC] patients, a statistically significant imbalance, P=0.03.[36]

This is the opinion that is based on a "mid-p approach."[37]

Sanofi suggests that Dr. Madigan included this new opinion because Plaintiff realized that using a mid-p approach would produce statistical significance. However, as Dr. Madigan implied in the above paragraph, he included this new opinion to address a certain interpretation of the TAX 316 data that Sanofi has adopted. As this Court has explained in prior rulings, Dr. Michael Kopreski is a Sanofi witness who evaluated the TAX 316 data and concluded that the numbers reported to the FDA do not accurately show how many patients suffered persistent or permanent alopecia.[38] According to Dr. Kopreski, it is not correct to state that 29 of the 744 TAC patients experienced

[35] Doc. 11003-3 at 27; Doc. 6144-1 at 21.
[36] Doc. 11003-3 at 27. *See* Doc. 11086-1 at 6 (acknowledging typo in report).
[37] *See* Doc. 11086-1 at 5–6.
[38] *See* Doc. 11332.

persistent or permanent alopecia at 120 months.[39] He found that only 6 of these patients had persistent or permanent alopecia at 120 months.[40]

In *Kahn*, Dr. Madigan added Paragraph 67 to his report to address Sanofi's version of the TAX 316 numbers. Dr. Madigan's goal was to note that under Sanofi's version of the numbers, there would be statistical significance.[41] Specifically, per Dr. Madigan, there would be statistical significance between the five TAC patients who had hair loss at 24 months after treatment and the zero FAC patients who had hair loss at 24 months after treatment.[42]

In this calculation, Dr. Madigan was dealing with smaller numbers than he was in *Earnest*, and Dr. Madigan testified that when small numbers are involved, the mid-p value is a widely accepted, standard practice of adjustment.[43] Dr. Madigan, then, used a sound methodology to support Paragraph 67 of his report, and the Court will permit him to testify about it. On cross-examination, Sanofi can show the jury that Dr. Madigan used a mid-p approach instead of a p-value of 0.05, and Sanofi can show the jury that other calculations based on Sanofi's numbers would not be statistically significant.

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[39] Dr. Kopreski found that although certain patients were documented as having "ongoing alopecia," some of these patients withdrew from the study. For example, Patient No. 15808 finished her Taxotere treatments in September 1998, was recorded as having ongoing alopecia in December 1998 when she was diagnosed with a breast cancer relapse, and then she was no longer followed in the TAX 316 study. *Id.* at 6. Thus, while she was included in the 29 patients who had "ongoing alopecia," Sanofi had no records showing that her alopecia continued beyond three months.

[40] *See id.*

[41] *See* Doc. 11003-3 at 27.

[42] According to Sanofi, these are the updated numbers.

Duration	TAC (n=744)	FAC (n=736)
6 months	7	4
12 months	5	3
18 months	5	1
24 months	5	0

See Doc. 11003-1 at 7.

[43] Doc. 11086-1 at 3.

b. Analysis of Reports in Sanofi's Database

Sanofi next takes issue with Dr. Madigan's analysis of alopecia reports in Sanofi's pharmacovigilance database. Sanofi criticizes Dr. Madigan's use of broad search terms in searching the database, and Sanofi further argues that Dr. Madigan has identified a purported "incidence rate" that it is inaccurate and misleading. In response, Plaintiff argues that Sanofi can cross-examine Dr. Madigan on the limitations of his work, and Plaintiff argues that Sanofi mischaracterizes Dr. Madigan's calculation as an incidence rate.

The Court agrees with Plaintiff. Sanofi acknowledges that there is no reliable way to calculate an incidence rate of Taxotere and permanent hair loss. As Sanofi explains, an "incidence rate" is defined as "[t]he number of people in a specified population falling ill from a particular disease during a given period."[44] To calculate such a rate for Taxotere, Dr. Madigan would need to know how many patients have ever taken Taxotere. This number would serve as the denominator in his calculation, and the nominator would be the number of these patients who suffered permanent hair loss. Sanofi has admitted, however, that without knowing how many patients have ever taken Taxotere, Sanofi cannot calculate a true incidence rate.

Dr. Madigan, therefore, has not attempted to calculate an incidence rate. Instead, he conducts a different calculation that a jury will easily understand. His calculation only shows that a high percentage of the total reports of alopecia that Sanofi received from 1999 to 2015 involved permanent or irreversible alopecia. As his nominator, he uses the number of Taxotere patients who suffered permanent alopecia and reported it. As his denominator, he uses the number of reports of alopecia that Sanofi has received. As Sanofi notes, there are undoubtedly many other patients who suffered alopecia but

[44] Doc. 11003-1 at 8–9.

did not report it to Sanofi. Dr. Madigan's work, therefore, has limitations, and he acknowledges this. In his report, he writes as follows, making clear the scope of his testimony and precluding any reference to an incidence rate:

> I note that it is not possible to directly calculate the rate at which irreversible alopecia occurs in the population (either per person or per person-time) from spontaneously reported events such as those in Sanofi's database. The FDA's 2005 Guidance for Industry on "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" states:
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> > "In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate."
>
> Spontaneously reported events do permit calculation of reporting rates (as utilized in my FAERS analysis above) but the FDA goes on to state:
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> > "Reporting rates can by no means by considered incidence rates, for either absolute or comparative purposes."[45]

Consistent with this, Dr. Madigan may refer only to the reporting rate that he calculated based on the spontaneously reported events that were available. On cross-examination, Sanofi can emphasize for the jury that Dr. Madigan's work has limitations and does not reflect an incidence rate.

Lastly, insofar as Sanofi criticizes Dr. Madigan's broad search terms, this Court has previously rejected this argument.[46] For the same reasons, and

[45] Doc. 11003-3 at 22–23.

[46] Doc. 8094 at 8–9. ("The Court finds that Dr. Madigan's methodology passes muster. In his report, Dr. Madigan makes clear that the statistical analysis he conducted is accepted in the industry. It is used by drug companies and the FDA. The limitations Sanofi identifies

for the additional reasons provided in Section III of this opinion, the Court rejects Sanofi's argument here.

c. Dr. Madigan's Meta-Analysis

Sanofi challenges Dr. Madigan's meta-analysis of four observational studies. Sanofi quotes a publication in which Dr. Madigan wrote as follows:

> Many different potential biases and sources of variability can undermine the validity of epidemiologic analysis of observational databases. Even when holding data source constant, heterogeneity can persist, presumably because of observed and unobserved patient characteristics that vary across databases.
>
> [. . .]
>
> [I]dentifying specific elements that explain variability across observational data can prove challenging. Certainly, deriving a composite estimate in the face of significant heterogeneity should be discouraged. Moreover, observing large heterogeneity should raise questions about the ability of observational data to address the clinical question at all.[47]

In response, Plaintiff avers that Dr. Madigan acknowledges the limitations of his meta-analysis. Plaintiff further argues that despite a "relatively high heterogeneity," the evidence should not be dismissed.

Plaintiff has failed to convince the Court that Dr. Madigan's meta-analysis is reliable and admissible. The Court finds it significant that Dr. Madigan himself has written that "[i]n the face of high heterogeneity, simply pooling data or performing a meta-analysis will generally not provide

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are not weaknesses in Dr. Madigan's methodology; they are limitations beyond his control that he deliberately worked around. Accordingly, Sanofi's concerns relate to the weight of Dr. Madigan's testimony, not its admissibility, and on cross-examination, Defendants can highlight these limitations for the jury.").

[47] Doc. 11003-18 at 4–6.

satisfactory outputs."[48] As Sanofi notes, an "expert must employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."[49] Therefore, since Dr. Madigan discourages relying on observational data in the face of significant heterogeneity, the Court will not permit him to do so for the sake of this MDL. Indeed, Plaintiff has not presented the Court with any law to support a different ruling.

III. Dr. Madigan's Database Searches

Lastly, Sanofi raises an additional argument regarding Dr. Madigan's searches of Sanofi's pharmacovigilance database and the FDA database of adverse event reports. Sanofi acknowledges that Dr. Madigan's methodology has not changed since the *Earnest* trial, but Sanofi argues that new guidance from the FDA advises against what Dr. Madigan has done. Specifically, according to Sanofi, the FDA recommends that after locating case reports in a database, a researcher should then individually assess each case report to ensure that it does in fact relate to the adverse event at issue. In response, Plaintiff argues that if Dr. Madigan were required to assess the case reports returned in his searches, he would also want to assess the case reports that were not returned in his searches. However, this would be an impossible task.

The Court agrees with Plaintiff and finds that Dr. Madigan's methodology passes muster for the same reasons it did in *Earnest*.[50] Sanofi's citation to the FDA's draft guidance does not change its reliability. As Plaintiff notes, Sanofi confuses signal identification with signal evaluation. Sanofi quotes from Section 7 of the FDA draft guidance, which is titled "Signal Evaluation and Documentation."[51] However, Dr. Madigan, being a statistician,

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[48] *Id.* at 6.
[49] Wells v. SmithKline Beecham Corp., 601 F.3d 375, 378 (5th Cir. 2010) (quoting *Kumho Tire*, 526 U.S. at 152).
[50] *See supra* text accompanying note 46.
[51] Doc. 11003-1 at 18; Doc. 11003-25 at 30.

focused on signal identification, which would be governed by Section 6 of the FDA document, which is titled "Safety Signal Identification."[52] Despite Sanofi's contentions, the Court finds that Dr. Madigan was not required to conduct a signal evaluation for his opinion to be reliable. According to the FDA document, such an evaluation would involve an epidemiologic assessment,[53] and this would fall outside Dr. Madigan's realm of expertise.

Additionally, if Dr. Madigan were required to assess each case report he located to check for error, he would similarly want to check all the reports that were not returned. Given that he is searching expansive databases, this would be impossible. The Court, therefore, finds that Dr. Madigan's methodology is sufficiently reliable, and on cross-examination, Sanofi may emphasize for the jury that Dr. Madigan's work has limitations.

CONCLUSION

For the foregoing reasons, Defendants' Motion to Exclude Expert Testimony of Dr. David Madigan (Doc. 11003) is **GRANTED IN PART** and **DENIED IN PART**. Dr. Madigan's testimony will be limited as described in this opinion.

New Orleans, Louisiana, this 29th day of January, 2020.

JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE

[52] *Id.* at 24.
[53] *Id.* at 33 ("Epidemiologic assessments are often an integral part of the signal evaluation process.").