Exhibit 441

Report of Walter Stadler, M.D., FACP

Tukes v. United States, 7:23-cv-01553 (E.D.N.C.)

Walter Stadler

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Walter Stadler, M.D., FACP

April 8, 2025

Contents

I. Expert Background and Qualifications

I am a genitourinary oncologist focused on care and treatment of patients with kidney, bladder, prostate, and testicular cancer. Full details of my academic and clinical qualification are detailed in my CV. Briefly, I received my MD from the Yale University School of Medicine in 1988, followed by an internship/residency at the University of Chicago affiliate Michael Reese Hospital and then a fellowship in Hematology/Oncology at the University of Chicago that I completed in 1994. I have been a faculty member at the University of Chicago for most of my career but have recently taken a position as Chief Clinical Officer for City of Hope, Chicago where I will continue my clinical role as genitourinary oncologist as well as my academic role conducting and leading genitourinary cancer clinical trials. I will also take on administrative responsibilities for clinical operations. I have held a number of additional administrative roles including Section Chief for Hematology/Oncology,Deputy Director for the University of Chicago Comprehensive Cancer Center and Associate Dean for Clinical Science Research, Clinical Trials.

I have conducted research on novel treatments and management of patients with genitourinary cancer and have authored over 250 peer-reviewed original manuscripts and over 120 reviews, chapters, and commentaries in this field (see CV, Attachment A). I have specifically contributed to the development of gemcitabine in bladder cancer, vascular endothelial growth factor receptor (VEGFR) inhibitors in renal cancer, and hormonal therapies in prostate cancer. I routinely give presentations at national and international meetings regarding these malignancies.

From a clinical perspective, I continue to consult and manage patients with these diseases for approximately 30% of my time generating greater than the 65th percentile in prorated relative value units (RVU's) for my specialty (i.e. corrected for a full-time clinician, my clinical activity is equal to or greater than 65% of American oncologists). I have been recognized as a clinical expert through Castle Connolly Top Doctors every year since 2007.

I have testified as an expert witness at trial or deposition in the past four years only in support of Sandoz and other generic companies in their effort to invalidate Sanofi cabazitaxel patents (*Sanofi-Aventis U.S. LLC v. Sandoz Inc.*, Civ. No. 20-804-RGA, D. Del.). My hourly rate for my work here is $750/hr.

II. Basis of Opinions

My opinions are based on my extensive experience, standard guidelines from the National Comprehensive Cancer Network (NCCN), as well as generally accepted medical literature. For much of the latter, and unless referenced otherwise, I used information summarized in available textbooks including UpToDate, which is the most widely referenced source for practicing clinicians and for which I have acted as an Editor, and Holland-Frei Cancer Medicine, 10th edition, one of the major textbooks of oncology for which I also contributed a chapter. Other specific literature references are in the detailed report below and listed under References.

I have reviewed case and medical records provided by counsel including medical provider notes, and the depositions of plaintiff, her husband, Dr. McCarthy, Dr. Jayaram, Dr. Jones, Dr. Thomas, and genetic counselor Ms. Garbarini. I have also reviewed and rely upon the United States's general causation reports (Goodman Report; Shields Report, Lipscomb report), the United States's exposure report (LaKind Report), and the United States's risk assessment report (Bailey Report). I have also reviewed and rely

upon the United States's expert reports by Dr. Gail Vance and Dr. Duncan Johnstone. Finally, I have reviewed the expert depositions of Drs. Bove and Savitz.

A complete list of the facts and data I considered are listed in Attachment B, which will be provided separately.

I reserve the right to supplement the opinions offered here as appropriate, including if new information is made available to me.

III. Summary of Opinion

It is my opinion that Ms. Tukes's renal cancer is most likely genetic in origin and unlikely related to any Camp Lejeune exposures. It is furthermore my opinion that Ms. Tukes is most likely cured of her renal cancer, which is highly unlikely to metastasize or recur.

IV. Clinical Background

A. Oncogenesis

Generally, cancer is a disease that arises from a series of genetic errors, also known as mutations, within normal tissue. Most normal tissue typically regenerates through division and replication of normal cells. While this almost always occurs faithfully, amongst the billions of base pairs making up the DNA of a human cell and the trillions of cells in the human body, errors do occur. While the vast majority of these genetic mutations are corrected or eliminated, occasionally a cell with such mutations persists and can then go on to develop additional genetic mutations, which leads to ongoing replication and division without appropriate controls. Additional mutations and alterations can then give the cells the ability to move (or metastasize) to other areas of the body. Notably, there are a number of biological processes, including the immune system, that can eliminate these mutated cells. The complex interplay between accumulation of mutations and failure to eliminate mutated cells is scientifically known as oncogenesis and in patients is the disease known as cancer (see for example (Hanahan and Weinberg)).

It follows that anything that increases the frequency of mutations or inhibits the corrective mechanisms increases the risk for cancer. The single most common factor is age. Errors in cell replication are rare and generally must accumulate to cause cancer in a patient and this simply takes time. Additionally, error correction mechanisms and the immune system become less robust as we grow older.

Exposure to certain environmental toxins known as carcinogens, the most relevant being exposure to tobacco smoke, can also increase the risk of cancer. Toxin exposure can increase the rate of genetic mutations and thus the risk of developing a cancer. Importantly, it is both the amount of toxin exposure (typically known as "dose") and the duration of exposure that determines both the odds of developing cancer causing mutations and the development of cancer (Hofseth, Weston, and Harris). The science of toxin exposure and subsequent risk of developing cancer is generally conducted by epidemiologists and toxicologists.

While toxin exposure can increase the risk of cancer, it is important to specify that this simply increases the odds of developing this disease; not all exposed individuals will develop cancer and most individuals with cancer will not have a known exposure history (see Goodman report for further details).

Some patients are born with, or inherit, certain genetic abnormalities that make them more likely to develop a cancer. These genetic abnormalities, known as germ-line mutations, are typically tumor suppressor genes whose deletion is mechanistically related to oncogenesis. More importantly, these inherited predisposition syndromes make it much more likely that a mutated cell can accumulate the additional necessary mutations to become a clinical cancer. For example, patients that inherit a mutation of the Von-Hippel-Lindau (VHL) gene have up to a 45% risk of developing renal cancer in their lifetime (Binderup et al. 2022) as opposed to a 1.4% – 2.3% risk in the general American population (Siegel, Giaquinto, and Jemal 2024). Of note these predisposition syndromes are typically organ specific insomuch as patients with these inborn errors are more susceptible to some, but not necessarily all cancers. For example, patients born with a mutation in the VHL gene are at a higher risk of developing renal cancer, hemangioblastomas, pheochromocytomas, and pancreatic neuroendocrine tumors, but not other cancers such as upper tract urothelial cancer. Patients with such predisposition syndromes often develop multiple cancers in the same organ, with a classic example once again being the multiple independent clear cell renal cancers in patients with germ-line VHL mutations.

Finally, there are multiple families with specific cancers in multiple family members, without any common environmental exposure, but in whom a germline mutation has not been discovered. Therefore, there are almost certainly undiscovered and undescribed genetic predisposition mutations or syndromes and discovery of new cancer predisposing genes is an active area of scientific research (see for example (Roberts et al. 2016).

Chronic infection or inflammation has also been consistently linked to a number of different cancers. The scientific explanation for this is a bit more obscure, but two explanations have been offered (Zhao et al. 2021). First, the immune system produces a number of molecules designed to kill invading organisms and these substances can damage or mutate normal cells as well. As with toxin exposure the duration of the inflammation is critical. Second, the presence of chronic inflammation within a tissue or organ paradoxically leads to an immunosuppressive microenvironment, or in other words an environment in which the immune system is unable to function normally. This is critical because there is increasing evidence that the immune system is largely responsible for eliminating mutated cells that are destined to form a cancer. Thus, in a chronically inflamed tissue not only is the aforementioned rate and risk of developing cancer-causing mutations increased, the body's ability to eliminate such cells is compromised.

The above discussion emphasizes that development of cancer in any one individual is a random event that can occur in anyone. Certain clinical conditions or exposures can increase the odds of this random event (i.e. "cancer") occurring, but no one individual is absolutely protected or predestined to develop a cancer. Additionally, the increased odds for developing a cancer from any one condition can be low, modest or very high. Importantly, the difference between increased odds and absolute risk must be recognized. For example, if the odds of developing a specific cancer are 1/1000, even a doubling of risk means that the odds now are 2/1000 (see also Goodman report). Further, the studies determining these risks generally apply to a population and do not necessarily reflect the increased risk in an individual patient, and more importantly do not necessarily reflect whether that factor (like a toxic exposure) is causative in that specific patient.

Finally, given these issues it must be recognized that the exact etiology, or even the most likely etiology, of any specific cancer in any one individual can be difficult or impossible to ascertain. As a result, the cause for the vast majority of cancers is idiopathic (i.e. unknown).

B. Kidney (Renal) Cancer

Kidney cancer is generally described as a single entity in broad epidemiologic studies (e.g. (Siegel, Giaquinto, and Jemal 2024)); however, it is critical to note that this broad description represents a variety of distinct malignancies composed of multiple histologic subtypes arising from the kidney. The diagnosis of a cancer is typically based on the appearance of the tissue (from a biopsy or surgical specimen) under the microscope as assessed by an expert pathologist. Different cancers have different appearances, but these differences may be quite subtle. More recently, specialized staining and molecular analyses has clarified that cancers that were once thought to be a single entity, or disease, are really composed of multiple separate and distinct cancers, each with its own causative factors, prognosis, and treatment.

The most common cancers arising in the kidney are upper tract urothelial cancer (UTUC) and renal carcinoma (also known as renal cell cancer). The latter is further subdivided into over 20 distinct histologies (Gansler et al. 2018; Moch et al. 2022). The most common renal carcinoma subtype, comprising approximately 70% of all renal cancers, is clear cell (or conventional) renal carcinoma (Gansler et al. 2018). The next most common is papillary renal cancer comprising 10-15% of renal cancers, which traditionally was subdivided into "Type I" and "Type II", but more recent studies demonstrate that this subclassification masks an even greater number of molecular defined cancers (Moch et al. 2022). More rare renal cancer subtypes typically comprising <5% of cases include chromophobe, collecting duct, and medullary renal cancers. Some subtypes, such as clear cell papillary, have only recently been recognized and described.

There are approximately 82,000 new cases of renal cancer in the United States annually, occurring typically in the sixth to eighth decade of life with a median age of 65 (NCI 2024). Based on this SEER data, the incidence of renal cancer in men <50 is 5.5/100,000/year and 90.4/100,000/year in men 65 and older. It is approximately two times more common in men than in women. Overall, the lifetime risk for developing kidney cancer in men is about 1 in 43 (2.3%) and for women is about 1 in 73 (1.4%) (Siegel, Giaquinto, and Jemal 2024). The incidence of renal cancer has been increasing. The etiology for this increased incidence rate is unknown but may be partially explained by increased detection of small asymptomatic cancers.

Established etiologic factors for renal cancer that I have considered are (1) obesity; (2) smoking; (3) hypertension; (4) chronic kidney disease; (5) diabetes; (6) occupational exposures to cadmium, asbestos, petroleum byproducts, and trichloroethylene; and (7) heavy use of over the counter analgesics [See also (Scelo and Larose 2018) and Goodman report]. Other recognized risk factors that I have considered based on the above description of oncogenesis are (8) genetic predisposition syndromes; and (9) chronic infection and inflammation.

1) Obesity. The relative risk of developing renal cancer for obese individuals is reported as 1.97 (CI: 1.56 – 2.50), with risk increasing with body mass index (BMI) (Adams et al. 2008). Other

studies report relative risks from 1.2 to 3.0. High BMI has been estimated to be responsible for 29% of all incident renal cancers (Safiri et al. 2020).

2) Smoking is an established risk factor, for which the relative risk in current smokers and former smokers are 1.36 (CI: 1.19-1.56), and 1.16 (CI: 1.08-1.25), respectively (Cumberbatch et al. 2016; Tsivian et al. 2011).

3) Hypertension is an established risk factor with a relative risk of 1.67 (CI: 1.46-1.90) (Hidayat et al. 2017)

4) Chronic kidney disease is a risk factor, especially in patients with end-stage kidney disease and those that develop cystic disease as a complication of long term dialysis (El-Zaatari and Truong 2022; Truong et al. 1995). Some studies suggest that less severe chronic kidney disease may also be associated with a slight increased risk of renal cancer with a relative risk of 1.81 (CI: 1.51 – 2.17) for patients with grade 3b renal dysfunction (see below for definitions) (Lowrance et al. 2014).

5) Diabetes is associated with development of renal cancer but has been difficult to disentangle from typically concomitant obesity and hypertension. Nevertheless, some studies do suggest an independent contribution with a relative risk of 1.12 (CI: 0.99 – 1.27) to 1.29 (CI: 1.05 – 1.58) (Larsson and Wolk 2011).

6) Occupational exposures to cadmium, asbestos, petroleum byproducts, and trichloroethylene has been associated with renal cancer. Studies of occupational exposure oftentimes do not distinguish between specific chemical exposures making it more difficult to assign causation (Mandel et al. 1995). The specific chemical most strongly associated with renal cancer is trichloroethylene used as a metal cleanser and degreaser, which confers a relative risk of 1-2, but only in occupational settings with high cumulative exposures [See Goodman report for further details].

7) Heavy use of over the counter analgesics have also been associated with development of renal cancer, but the associations have been inconsistent across different studies implicating or not implicating acetaminophen for example (Cho et al. 2011; Karami et al. 2016). Additionally, statistically significant associations have generally been reported with more than 10 years of regular (more than 7 tablets weekly) use (Cho et al. 2011). Phenacetin, the agent with the strongest epidemiological data (Antoni et al. 2014), is specifically associated with upper tract urothelial cancer (UTUC) and has generally not been available in the United States.

8) Genetic predisposition syndromes for renal cancer have been identified, but most of these are rare with Von-Hippel-Lindau disease (VHL), occurring in approximately 1/27,000 – 1/43,000 live births, being most common and the one associated with clear cell renal cancer (Binderup et al. 2022). As noted above, patients with genetic predisposition syndromes often develop multiple independent cancers in the kidney, which is extremely rare in renal cancers not due to a genetic predisposition syndrome.

9) Chronic infection and inflammation is considered a common etiologic factor in many cancers. Inflammatory conditions associated with renal cancer include chronic hepatitis C, with a relative risk of 1.77 (CI: 1.05 – 2.98) (Gordon et al. 2010), and a history of kidney stones, which are often associated with infection, with a relative risk of 1.41 (CI: 1.11 – 1.80) for renal cancer only in men and a relative risk of 2.14 (CI: 1.35 – 3.40) for urothelial cancer across both sexes (Cheungpasitporn et al. 2015).

Despite multiple potential etiologies, the major factors are obesity for which the population attributable risk in North America is approximately 29% and smoking for which the attributable risk is approximately 18% (in other words the fraction of renal cancer patients for whom obesity and smoking is a contributing risk factor for their renal cancer), with the population attributable risk for all other factors, including environmental toxin exposure, being negligible (Safiri et al. 2020). Notably many patients have multiple risk factors such as smoking, obesity, diabetes, and hypertension, since these factors tend to occur together, making assignation of causation for any one factor impossible in such cases. Finally, and as discussed above for cancer in general, risk factors increase the odds of developing a cancer, but it is not possible to distinguish the causative roles, if any, of specific risk factors in an individual patient. As such, the cause or etiology for most patient's specific cancer is unknown ("idiopathic" in medical parlance).

Historically, the most common presenting symptoms for renal cancer are gross hematuria i.e. visible blood in the urine, an abdominal mass noted by the patient or their physician, pain, and weight loss. The latter three are typically the result of locally advanced or metastatic disease and an increasing number of renal cancers are diagnosed incidentally during imaging for an unrelated cause (i.e. detection of a renal mass on a radiologic procedure performed for other indications). This in turn likely explains at least some of the increased population incidence of renal cancer noted above.

Notably, there is a long list of possible causes for gross hematuria, including kidney stones, glomerulonephritis (a specific class of non-malignant kidney diseases), infection, and exercise induced hematuria such that the majority of individuals with hematuria do not have a urinary tract malignancy.

Treatment of localized renal cancer typically involves radical nephrectomy or partial nephrectomy in which only the cancer is removed sparing normal kidney tissue. A radical nephrectomy involves complete removal of the kidney and occasionally the adjacent adrenal gland and some lymph nodes. An issue with complete removal of the kidney is that there is some decrement in renal function, which can have its own health impacts, especially in patients with pre-existing renal disease (see below). As such, partial nephrectomy in which only the cancerous tumor is removed, sparing normal renal tissue, has been increasingly utilized. The choice of radical versus partial nephrectomy is generally based on the size and location of the cancer within the kidney, as well as baseline renal function and experience of the surgeon.

Traditionally, partial or radical nephrectomy have been performed utilizing large abdominal incisions with techniques termed as "open." While this approach is still required for technically more complex resections, the vast majority of nephrectomies are currently performed using a typically robotic, laparoscopic approach. The lack of a large incision makes surgical recovery more rapid and decreases the risk of some complications such as abdominal wall hernias (Zhou and Carlson 2018). Occasionally, ablative techniques using radiofrequency, ultrasound, or freezing are also utilized, especially in patients

in whom surgery is considered too risky. The exact technical approach to treatment of the primary renal cancer is based on surgical experience, body habitus (the shape and size of a person's body) and tumor location and in general has limited to no impact on long term cancer outcome.

Following nephrectomy or partial nephrectomy, additional adjuvant systemic therapy to prevent recurrence (including chemotherapy and immunotherapy) has not been utilized; although, some more recent studies suggest that there may be some value to adjuvant immunotherapy (Choueiri et al. 2024). Recommended standard follow up and monitoring of renal cancer following nephrectomy or partial nephrectomy is CT scans of the chest, abdomen and pelvis every 6 months for 3 years followed by annual scans up to 5 - 6 years post-surgery. Although renal cancer can occasionally recur beyond 5 and even beyond 10 years, routine scanning beyond 5 or 6 years is generally not recommended.

Prognosis and survival of localized renal cancer is highly dependent on stage and renal cancer subtype. Staging is based on both extent and size of the tumor within the kidney, presence of spread to lymph nodes, and presence of metastatic disease (TNM system).

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
T1	N0	M0	I
T1	N1	M0	III
T2	N0	M0	II
T2	N1	M0	III
T3	NX, N0	M0	III
T3	N1	M0	III
T4	Any N	M0	IV
Any T	Any N	M1	IV

Adapted from the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

The five-year cancer-specific survival rates for patients with clear cell renal cancer stage I, II, and III disease are >90%, 75%, and 60-70% respectively. Specific factors associated with recurrence and worse survival include renal pelvis and vena cava involvement and lymph node positivity, which are incorporated into the staging system. Clear cell renal cancers are also graded according to the Fuhrman/ISUP system, which is based on the appearance of the cancer under the microscope. High grade disease is also associated with a higher risk of recurrence. Risk of recurrence beyond 10 years for clear cell renal cancers is 6%, with the major risk factor being lymph node positivity, for which there is a 6-fold higher risk of such a late recurrence (Miyao et al. 2011). Recurrence 20 years after nephrectomy are reported but are rare.

Prognosis and outcome of renal cancers that are not clear-cell are generally similar to clear cell renal cancer, but can be markedly different for specific subtypes. For example, medullary renal cancers are extremely aggressive with the majority of patients developing metastases and dying from their disease within 2 years (Ezekian et al. 2017), whereas chromophobe renal cancers metastasize only very rarely (Volpe et al. 2012). Data for rare subtypes, and especially for subtypes that have only been described more recently, is often incomplete and typically not included in descriptions of general renal cancer outcomes based on TNM staging.

A major potential long-term complication of nephrectomy is decreased renal function. Renal dysfunction, or chronic kidney disease (CKD), is generally graded by the estimated glomerular filtration rate (GFR), which is based on serum creatinine levels:

- G1 = ≥ 90 ml/min/1.73 m^2 (normal)
- G2 = 60-89 ml/min/1.73 m^2 (mildly decreased)
- G3a = 45-59 ml/min/1.73 m^2 (mildy to moderately decreased)
- G3b = 30-44 ml/min/1.73 m^2 (moderately to severely decreased)
- G4 = 15-29 ml/min/1.73 m^2 (severely decreased)
- G5 = <15 ml/min/1.73 m^2 (kidney failure)

The implications and outcomes for patients with CKD include hypertension, fluid retention, electrolyte imbalances and in the worst case scenario need for dialysis. Overall, and depending on the patient's age, the relative risk for all-cause mortality among patients with isolated G3a CKD is 1.2 (CI: 1.0 – 1.5) – 1.9 (CI: 1.4 – 2.5), with a specific relative risk of cardiovascular mortality of 1.3 (CI: 0.6 – 3.2) – 1.4 (CI: 1.2 – 1.8), and risk of developing the need for dialysis of 3.1 (CI: 1.1 – 8.3) – 3.4 (CI: 1.6 – 7.2), which for the former reflects an increased risk from 48/10,000 to 65/10,000 and the latter reflects an increased risk from 5.7/10,000 to approximately 18.6/10,000 (Levey et al. 2011).

Notwithstanding the aforementioned, the most common causes for CKD are hypertension, diabetes, hypercholesterolemia and smoking. Chronic non-steroidal anti-inflammatory drug use, with medications such as ibuprofen, may also increase the risk of chronic renal disease. However, in patients with modest renal dysfunction, it is only high dose use, on the order of 3.5 or more 200mg ibuprofen pills daily (i.e. 700 mg or more), that is significantly associated worsening renal function (Gooch et al. 2007).

V. Overview of Plaintiff Case

Plaintiff Jacqueline Tukes was born on [redacted] and was married to Willie Lee Tukes on 4/21/84. Mr. Tukes enrolled in the military from 10/31/80 through 9/30/2011 and Ms. Tukes resided at Camp LeJeune while her husband was stationed there between 12/19/85 and 1/8/87. She may have also resided at or spent time on-base at Camp Lejeune for intermittent periods from 6/1985 to 12/19/1985 (see LaKind report). Ms. Tukes first presented with her renal cancer problem on 6/11/10 when a CT demonstrated an incidental 1.3 cm right renal mass. On 8/20/10 she underwent a right partial nephrectomy at UNC Chapel hill with pathology demonstrating a T1 clear cell, Fuhrman grade 2 renal cancer. A Pulmonary evaluation on 4/6/11 for small pulmonary nodules opined that these were benign and not related to her cancer, and there has not been any concern for metastatic disease since.

As part of routine monitoring, a left renal cyst was noted in 12/15 and in 3/16 was noted to be slightly larger. Due to lack of enhancement on the CT scans, this was considered to be benign. An additional right renal cyst, also thought to be benign was noted on 6/29/16, and was redemonstrated on 1/25/17 on an abdominal MRI. Further routine monitoring and imaging on 3/21/18 demonstrated a right complex renal cyst and a left renal mass. On 4/26/18 she underwent a left partial nephrectomy with pathologic analysis at University of North Carolina demonstrating 3 separate clear cell papillary tumors, a histologic renal cancer subtype that was first recognized around this time (see further discussion on this subtype below).

The unusual pathology, multiple tumors, and a family history of renal cancer in Ms. Tukes mother and a cousin prompted a Genetic Counselor evaluation on 8/8/18. This confirmed a strong family history of rhabdomyolysis and germline testing by InVitae revealed a variant of unknown significance (VUS) in the gene SMARCA4, which was reclassified as likely benign in 4/20 and a VUS in the gene PMS2, which was also classified as likely benign 9/22. Ms. Tukes declined to participate in investigational whole exome sequencing.

Based on development of additional masses on imaging Ms. Tukes underwent a left partial nephrectomy on 3/14/19 demonstrating a clear cell renal cancer as per interpretation by a general community based pathologist. With development of additional renal masses, she underwent a right laparoscopic nephrectomy on 5/23/22. Pathologic analysis revealed multifocal cancers ranging from 0.4-1.3 cm in all

poles with clear cell papillary histology. Official staging was recorded as pT1aNx, grade 3. Chronic tubulointerstitial nephritis and multiple additional cysts were also noted.

Due to persistent additional masses and loss of renal mass, on 1/5/23 Ms. Tukes underwent surgery for creation of an arterial-venous fistula in anticipation of the future need for dialysis. On 6/12/23 she underwent left nephrectomy with pathologic analysis by a community based general pathologist demonstrating 2 papillary and 1 cystic renal cancer.

In 1/24 she was deemed to be an appropriate candidate for renal transplantation and at a very low risk for metastases. She received a renal transplant in 4/24.

VI. Opinion

In order to assess likely and unlikely causes for any one individual's cancer I assess whether any of the known causes apply to the individual, whether that individual's cancer presentation is typical for known causes, and to what degree other potential causes need to be considered in this context. Additionally, I consider the complex multi-step and somewhat random nature of oncogenesis discussed above, as well as the increased risk attributable to and the clinical significance of any known potential causative factor. For example, a known factor, such as smoking, is likelier to be a cause if that factor is persistent and long standing. Conversely, a known factor might still be unlikely to be a cause if exposure is brief and clinically minimal.

Given the medical history and aforementioned discussion regarding renal cancer etiology, it is my opinion that Ms. Tukes renal cancer was unlikely due to Camp LeJeune drinking water and more likely related to an underlying genetic predisposition syndrome. This is based evaluation of the aforementioned etiologic factors for renal cancer.

1) Obesity. Per the provided medical records Ms. Tukes is not obese.

2) Smoking. Ms. Tukes does not have a smoking history.

3) Hypertension. There is no evidence for hypertension prior to Ms. Tukes renal cancer diagnosis.

4) Acquired cystic disease of the kidney. Ms. Tukes did not have end stage kidney disease or known cystic disease of the kidney at the time of diagnosis and only developed end stage renal disease as a consequence of her renal cancer therapy (nephrectomies).

5) Occupational exposure to cadmium, asbestos, and petroleum byproducts. These etiologic factors have not been demonstrated to be relevant outside of occupational settings in which prolonged and high exposure levels have been documented. Ms. Tukes has no history of such occupational exposure. See also Goodman and Lipscomb reports regarding trichloroethylene exposure as risk factor and LaKind and Bailey reports regarding plaintiff exposure and risk estimates.

6) Heavy use of non-steroidal anti-inflammatory drugs, acetaminophen and phenacetin. Ms. Tukes does not have any history of using any analgesic of more than 7 pills weekly for 10 or more years, which is the defined heavy use most consistently associated with renal cancer (Cho et al., 2011). Additionally, the most well documented cancer associated with these agents is upper tract urothelial cancer and not clear cell renal cancer.

7) Genetic predisposition syndromes. Although Ms. Tukes underwent formal genetic counseling and testing and no defined genetic abnormality was found, the family history of renal cancer in her mother and a cousin and the multiple independent tumors strongly suggest the presence of an unrecognized genetic predisposition syndrome. (See also Vance report). One of the most comprehensive analyses of clear cell papillary renal cancer from Memorial Sloan Kettering Cancer Center (MSKCC), an international center of excellence for renal cancer, demonstrated that this disease was more common in African-American women and commonly presented as multi-focal independent tumors (Weng et al. 2021). The analysis also described patients with both multiple clear cell papillary cancers as well as multiple clear cell papillary and conventional clear cell cancers.

8) Chronic infection and inflammation. There is no evidence for any pre-diagnostic chronic kidney infection or inflammation in Ms. Tukes's case.

Importantly, the above case series from MSKCC as well as other case series (e.g (Steward et al. 2021)) suggest that the risk of metastases, especially when all the resected tumors are T1 as in Ms. Tukes's case, is extremely low. This has been corroborated by Ms. Tukes' current providers who deemed her appropriate for a renal transplant, which she has already received. Ms. Tukes transplanted kidneys do not carry the same genetic information as her native kidneys, and thus with both of her native kidneys removed further primary renal cancers cannot develop.

As such, Tukes' renal cancer is unlikely to be related to Camp Lejeune exposures and most likely due to an undiagnosed genetic predisposition syndrome. Furthermore, her risk of developing future recurrent cancer is extremely low.

VII. Responses to Plaintiff's Experts

A. General Responses

It is my opinion that plaintiff's experts make some fundamental errors in their causation assessment. For example, plaintiff's experts refer to the Bradford-Hill criteria assessing whether an association between exposure and subsequent health event (in this case renal cancer) is likely to be causative. For example, Dr. Mallon considered Bradford Hill criteria to "contextualize [his] findings, and to help with [his] analysis using a differential diagnosis." (Mallon report at 4). These criteria, however, focus on potential causation within a ***population*** and do not necessarily apply to causation in an ***individual***. This becomes especially important when the relative risk associated with such an exposure is small and less than 2, which is acknowledged by plaintiff experts even under a worst-case scenario. In other words, within even an exposed population most of the patients with a specific cancer would have gotten that cancer even in the absence of exposure. To thus attribute any single individual's cancer to such an exposure, even if there are no other obvious known causative conditions, is not accurate.

Secondly, and relatedly, plaintiff experts ignore the implications of the multi-step and random events for oncogenesis in general and renal cancer specifically. For example, Dr. Mallon opines that "[g]iven there are no other significant potential risk factors for Ms. Tukes [sic] development of kidney cancer, other than a very slightly elevated risk due to her hypertension and weight, it is clear Ms. Tukes' exposure to the toxins at Camp Lejeune was a substantial contributing factor and cause of her kidney cancer." (Mallon report at 18). As I have noted and plaintiff experts acknowledge, multiple genetic and other

events must occur for a clinical cancer to develop and there is a certain randomness to each event and oncogenesis in general (a phenomenon known as "stochastic"). For example, Dr. Allen explains that "many people with these risk factors will never develop cancer, while others with no known risk factors will." (Allen report at 11-12). As such, clinicians like myself consider most cancers in any specific individual to be idiopathic, which is not even considered by plaintiff experts. It would be very unusual, however, for an idiopathic cancer to develop in both kidneys and with multiple tumors in each. Ms. Tukes's bilateral, multifocal cancer is far more consistent with a genetic cause than a toxic exposure or other explanation. Plaintiff's experts not only fail to convincingly "rule out" idiopathic cause; they ignore it altogether.

Additionally, plaintiff experts over-emphasize the role any toxin exposure in Camp LeJeune water may have played, despite incomplete information on true exposure, differences in opinion from exposure experts regarding level of exposure, and very small levels of increased risk, all the while minimizing the role other risk factors such as low-level smoking or mild obesity may play. For example, Dr. Josephson acknowledges Ms. Tukes "did have some risk factors for the development of kidney cancer," such as her obesity and hypertension. (Josephson report at 16). Dr. Mallon similarly discounts Ms. Tukes's obesity and hypertension as only "a very slightly elevated risk." (Mallon report at 18). As I explain above, Ms. Tukes's obesity and hypertension are not likely a "cause" because the degree of obesity and hypertension at the time of diagnosis was minimal. Similarly, even if Ms. Tukes's exposure to Camp Lejeune water increased her risk of kidney cancer, I would not assign causality to those exposures because the vast majority of studies suggest that high levels of sustained exposure to such toxins in occupational settings is necessary, which is not the case for Ms. Tukes. I have chosen to consistently eliminate ***all*** low risk level risk factors with limited clinical exposure as causative and have concluded that the etiology of Ms. Tukes's renal cancer is most likely genetic and less likely idiopathic.

B. Specific Responses

I agree with plaintiff expert Dr. Josephson's opinion that Ms. Tukes "was diagnosed at a young age and ultimately developed numerous renal tumors," and that the development of her cancers were "inconsistent with sporadic disease related to hypertension or obesity." (Josephson report at 16). Similarly, Dr. Cooper describes Ms. Tukes's bilateral and multifocal tumors as "a very unique presentation." (Cooper report at 14). But this presentation ***is*** consistent with a hereditary renal cancer, which as I discuss above typically results in multiple primary tumors. (See also Vance report).

Plaintiff's experts also correctly observe that Ms. Tukes's race and gender may be relevant. Dr. Mallon describes "a slightly increased risk of kidney cancer due to her ethnicity." (Mallon report at 18). Dr. Cooper similarly recognizes "a slight increased risk for RCC" related to Ms. Tukes's race. (Cooper report at 13). Ms. Tukes's race may be particularly relevant here given her histology and presentation insomuch as prior studies have suggested that there is a predilection for this syndrome of multiple papillary clear-cell tumors in African-Americans. Such a predilection is more consistent with an unrecognized genetic predisposition than with a toxic exposure as a cause.

I acknowledge that aspects of Ms. Tukes's family history lack confirmation, that testing did not reveal a pathogenic mutation in the few dozen genes tested, and that the previously described variants of unknown significance have since been classified as likely benign (see also Vance report). But I disagree that it is "very highly unlikely that her kidney cancer was hereditary." (Mallon report at 18). As explained

above, Ms. Tukes's presentation is consistent with a hereditary renal cancer, of which the genetic testing is only one component (see Vance report). Further, as Dr. Allen acknowledges, Ms. Tukes's genetic testing results "do not constitute a definitive test for the selected condition(s) in all individuals" and is only "one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan but is not a diagnosis itself." (Allen report at 19).

VIII. References

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