Exhibit 70

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NORTH CAROLINA
SOUTHERN DIVISION
No. 7:23-CV-897

IN RE:	)
CAMP LEJEUNE WATER LITIGATION	)
	)
THIS DOCUMENT RELATES TO:	)
ALL CASES	)

RULE 26 REPORT OF STEPHEN H. CULP, M.D., Ph.D.

The following report is provided pursuant to the Federal Rule of Civil Procedure 26. I hold all opinions stated herein to a reasonable degree of scientific and medical certainty. My qualifications are summarized below and detailed in my *curriculum vitae*, attached as **Exhibit A**, which includes a list of all publications I have authored in the last 10 years. My fee schedule is attached as **Exhibit B** and the materials I considered in forming the opinions provided in this report are identified herein and in **Exhibit C** (to follow). I have not provided expert opinion testimony in deposition or at trial in the last four years.

I. QUALIFICATIONS

I, Stephen Culp, am a physician and surgeon licensed to practice medicine in the Commonwealth of Virginia and devote at least eighty (80) percent of my professional time to active clinical practice and instruction at the University of Virginia (UVa) School of Medicine. My license in Virginia or any other state has not been revoked or suspended at any time.

I am board-certified in Urology by the American Board of Urology (2013, renewed 2023). I completed medical (MD) and graduate school (PhD) at Virginia Commonwealth University in Richmond, Virginia in 2002. I underwent residency training in Urology at the University of Washington in Seattle, WA (2008). During this time, I obtained a Master of Science in Epidemiology (2006). I completed a Society of Urologic Oncology approved fellowship at the University of Texas M.D. Anderson Cancer Center in 2011. I have been practicing urology and urologic oncology at UVa since August 2011. I am currently Full Professor with Tenure in the Department of Urology at UVa.

I have received several honors and awards throughout my education, training, and career. I was selected for the AUA Foundation Research Scholar Program, a mentored research training award, in 2008; received the Thelma R. Swortzel Collaborative Research Award in 2012, which provides support for innovative research collaborations in cancer and other areas; and was elected to membership in the Urological Research Society.

As a practicing urologic oncologist, I manage patients and operate on all types of genitourinary cancer, including kidney, bladder, and prostate cancers. I specialize in open radical nephrectomy (including renal vein/inferior vena caval thrombus) and complex partial nephrectomy, radical cystectomy with urinary diversion, open prostatectomy, retroperitoneal lymph node dissection, and penectomy with inguinal lymph node dissection for penile cancer. In

addition, I specialize in the endoscopic management of urothelial carcinoma including transurethral resection of bladder tumors and ureteroscopy with holmium laser of ureteral tumors.

In my clinical practice, I employ the filtering method of differential diagnosis to identify the underlying cause of an injury or symptom. This approach involves systematically considering potential causes of a condition and utilizing available clinical information to assess and rule out possible etiologies. This methodology is a cornerstone of my daily clinical practice and has been integral to the care and treatment of thousands of patients—including civilians, veterans, and service members—throughout my career. For my patients with bladder cancer, I consider (or "rule in") all etiologies and conditions that may be causative, then systematically eliminate (or "rule out") potential causes based on the patient's medical history, lifestyle, and history of occupational and environmental exposures, in addition to my physical examination, testing, and review of the available data.

I have been actively and am presently involved in teaching residents and medical students. In addition, I have authored multiple manuscripts on population-based epidemiologic studies. I have participated and served as principal investigator on multiple institutional studies including those dealing with bladder cancer.

II. MANDATE

I was asked to review the published epidemiological literature and other relevant publications to determine whether there is a causal relationship between bladder cancer and exposure to PCE, TCE, benzene and the contaminated water at Camp Lejeune from approximately 1953 to 1987. The standard of proof for my review is determined by the Camp Lejeune Justice Act of 2022, which states:

> (c) BURDENS AND STANDARD OF PROOF.-
>
> > (1) IN GENERAL-The burden of proof shall be on the party filing the action to show one or more relationships between the water at Camp Lejeune and the harm.
> >
> > (2) STANDARDS.-To meet the burden of proof described in paragraph (1), a party shall produce evidence showing that the relationship between exposure to the water at Camp Lejeune and the harm is-
> >
> > > (A) sufficient to conclude that a causal relationship exists; or
> > >
> > > (B) sufficient to conclude that a causal relationship is at least as likely as not.

This legal standard is consistent with the "equipoise and above" classification of the evidence described in the scientific literature. Using this standard, my report will examine whether the published epidemiological literature on exposure to PCE, TCE, benzene, and the contaminated water at Camp Lejeune provides sufficient evidence to conclude that exposure to the same causes or is as likely as not a cause of bladder cancer.

III. METHODOLOGY

To determine whether the contaminated water at Camp Lejeune, including the individual contaminants of concern, are causally associated with bladder cancer, I reviewed and analyzed relevant epidemiological literature, studies, and materials, as I would in my research and clinical practice. To that end, I performed a literature search on PubMed (National Library of Medicine through the National Institute of Health) to identify literature relevant to the chemical exposures at issue in this case and the outcome of interest—*i.e.*, bladder cancer. I used the following search terms to identify potentially relevant literature:

- Bladder cancer
- Urothelial cancer
- Tetrachloroethylene (PCE)
- Trichloroethylene (TCE)
- Benzene
- Dry cleaning

I summarized all relevant studies, including a brief discussion of their strengths and weaknesses, below. My analysis of each study included an assessment of the quality of the study, the design of the study, and the study's power. I employed the same review as I would in my research and clinical practice.

To determine whether there is a causal relationship between bladder cancer and exposure to Camp Lejeune contaminated water and/or the contaminants of interest, I first reviewed the literature to determine whether an association exists. As described in more detail below, the literature demonstrates an association between bladder cancer and exposure to PCE, TCE, benzene and the contaminated water at Camp Lejeune.

Having confirmed an association between the exposure to PCE, TCE, benzene, and the contaminated water at Camp Lejeune and outcome of interest, I used the Bradford Hill factors to investigate whether a causal relationship exists. In 1965, English statistician Sir Austin Bradford Hill published and presented to the newly formed Section on Occupational Medicine a list of nine (9) factors that can support a causal relationship between an exposure and outcome:

1. **Strength of Association**: Though finding a small significant association does not exclude causation, the larger an association between exposure and effect supports a causal relationship.
2. **Consistency:** A causal relationship is strengthened by comparable findings through different studies with similar but separate cohorts. Reproducible results through separate studies support a cause and effect.
3. **Specificity:** A causal relationship is likely if data from a unique population at a specific site support a cause and effect when there exists no other possible explanation.
4. **Temporality**: To support a causal relationship, the effect needs to follow the exposure. Although a delay may exist between exposure and effect, the latter must follow the former.
5. **Dose-Response**: A causal relationship is strengthened if more exposure results in a higher incidence of the effect. Conversely, an inverse relationship may be observed (*e.g.*, higher exposure results in a lower incidence).

6. **Plausibility**: Data supporting a plausible relationship between exposure and effect strengthens a causal relationship. Initially limited by a lack of knowledge, new discoveries since 1965 have made this criterium stronger.
7. **Coherence**: A causal relationship is strengthened when laboratory findings correlate with epidemiological observations. As with plausibility, the influence of this criterium was initially limited but now is stronger due to a wealth of laboratory studies since 1965. It is important to note, however, that absence of laboratory data does not exclude an epidemiologic causal association.
8. **Experiment Evidence**: A causal relationship can be strengthened by any correlative experimental research.
9. **Analogy**: Occasionally, acknowledged outcomes in one realm can be applied to the exposure and outcome in the questioned causal relationship.

In addition to the above nine factors, some have also considered **Reversibility** as an important consideration. If an exposure is removed with subsequent decrease in effect, then this would further support a causal relationship.

As a clinical urological oncologist and epidemiologist, I routinely rely on data and observations from scientists in related fields to develop, design, and perform mechanistic studies, to model or measure toxic exposure levels, interpret results, and reach conclusions about the carcinogenicity of substances. Toxicology studies are particularly relevant to certain of the Bradford Hill factors. As such, my review of those factors relies on the general causation expert reports submitted by the bladder cancer toxicology experts which I have reviewed as referenced in my Bradford Hill analysis.

In its 2017 assessment of the Camp Lejeune water contamination, ATSDR applied the "at least as likely as not" standard (ATSDR, 2017). In doing so, it announced that it did not use confidence intervals to establish statistical significance, explaining that there are limitations of using statistical significance testing and that the failure to achieve statistical significance does not indicate lack of evidence for a causal association. ATSDR reiterated this decision in its 2018 assessment, stating:

> As in our previously published Camp Lejeune studies, we did not use statistical significance testing to interpret results (Rothman *et al.* 2008, 2010; Stang *et al.* 2010). We did not want to make a qualitative decision about the importance of a result in this study based on using an arbitrary cutoff for "significance" (*e.g.*, p <0.05 or a 95% CI that does not include the null value) (Rothman *et al.* 2008). This is because a result that fails to achieve statistical significance can still provide potentially useful information, and a result that achieves statistical significance can lack scientific and public health significance (Porta 2014). Therefore, we agree with the recommendation on page 163 in Modern Epidemiology, 3rd edition that states "…Because statistical hypothesis testing promotes so much misinterpretation, we recommend avoiding its use in epidemiological presentations and research reports" (Rothman *et al.* 2008). Instead, we interpreted the results from this study based on the magnitude of the OR and consistency with results from other published studies (Hill 1965).

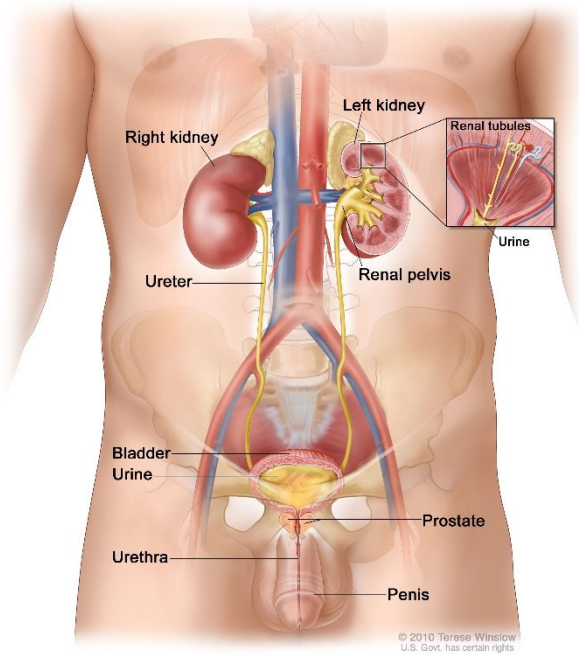
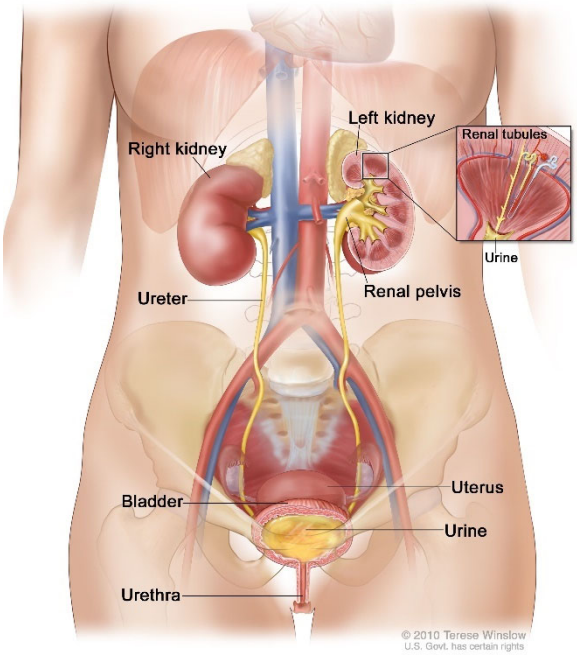
Given that the same standard governs my analysis here, in addition to other considerations regarding the relevant literature, I agree with ATSDR's approach and employ the same in my review.

The opinions set forth here are all based on my education, training, and clinical experience, and they are offered to a reasonable degree of medical and scientific certainty. In the event any new, relevant studies or information are published, obtained, or presented following the submission of this report, I reserve the right to review any such data and revise or supplement my report and opinions accordingly.

IV. THE URINARY SYSTEM & BLADDER CANCER

A. URINARY SYSTEM

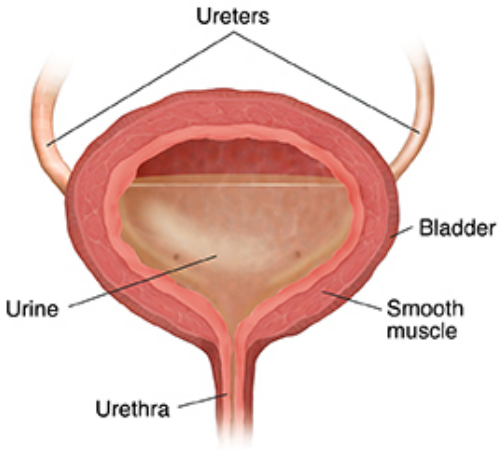
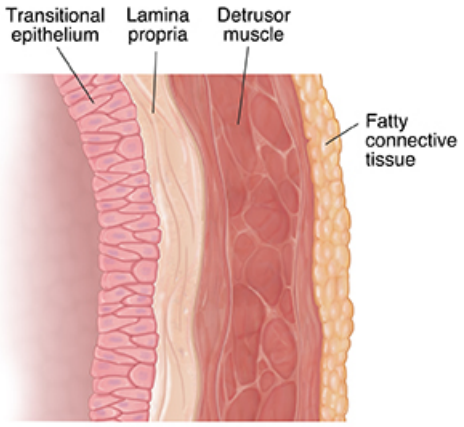
The organs that constitute the urinary system are the kidneys and ureters (upper urinary system) and the bladder and urethra (lower urinary system). Generally, the urinary system serves to filter blood and create urine to help eliminate waste. The kidneys remove waste products and drugs from the body and help balance the body's fluids. They do this by removing waste and extra fluid from the blood in the form of urine. Urine leaves the kidneys through narrow tubes called ureters which carry it to the bladder. This is accomplished by the muscles in the ureter walls tightening and relaxing to move the urine downward to the bladder. The bladder, a hollow muscular organ, stores the urine until it leaves the body through the urethra.

Male Urinary System	Female Urinary System
	

Images from *https://www.cancer.gov/publications/dictionaries/cancer-terms/def/bladder*

The bladder consists of the urothelium (the inner lining that prevents urine from leaking into the body), the lamina propria (the thin layer of connective tissue that surrounds the urothelium), and the muscularis propria (the three layers of smooth muscle that constitute the thick

outer layer). A healthy adult bladder is capable of holding about two cups of urine for up to five hours.

Anatomy of the Bladder	
Bladder	**Bladder Wall Tissue**
	
Images from *https://www.saintlukeskc.org/health-library/anatomy-bladder*	

B. BLADDER CANCER

1. Types

There are several types of bladder cancer, and the type of cancer is determined based on the type of cell in the bladder where the cancer originates. They include:

- Urothelial Carcinoma: Constituting the vast majority of bladder cancers in the U.S., this cancer forms in the cells that line the inside of the bladder (the urothelial cells).
- Squamous Cell Carcinoma: Though rare in the U.S., this type of cancer occurs due to chronic irritation of the bladder, such as that arising due to an infection.
- Adenocarcinoma: This type of cancer is also uncommon and occurs in the glandular cells of the bladder. It typically is associated with the urachus, a vestigial remnant located at the bladder dome.

2. Incidence

Only approximately two percent of people will get bladder cancer in their lifetime. The lifetime risk of developing bladder cancer is 1 in 28 (men) and 1 in 89 (women). There are currently estimated to be approximately 83,190 new cases of bladder cancer in 2024 (63,070 in men and 20,120 in women).

3. Diagnosis

This is a cancer predominantly occurring in older people (average age 73 years), with 90% of those diagnosed being over age 55 and 80% over age 65 (Saginala *et al.*, 2020). Symptoms of bladder cancer may include blood in the urine (hematuria), frequent urination (frequency), painful urination, and/or back pain. Bladder cancer may be diagnosed by performing a cystoscopy where

a scope is inserted through the patient's urethra to take a look at the inside of the bladder, transurethral resection of bladder tumor to biopsy a sample of the tissue, urine cytology, and/or imaging, including CT urogram or retrograde pyelogram.

Bladder cancer is staged from 0-IV. Stage 0 represents the least aggressive, most non-invasive of bladder cancer diagnoses while Stage IV constitutes aggressive, metastatic cancer. Clinical staging uses results of a physical examination, biopsies using cystoscopy or transurethral resection of bladder tumor (TURBT), and imaging, including CT scans, MRI scans, and x-rays. When a cystectomy is performed, pathological staging may also be done.

The below table describes the pathologic stages using the T, N, M categories. The T category references how far into the bladder wall the cancer has grown. The cancer is deemed more advanced the further it has grown into the deeper layers of the bladder. The N category indicates the cancer has spread to the regional lymph nodes (*i.e.* near the bladder and along the common iliac artery). The M category is for cancer metastasis to different (or distant) parts of the body.

Stage	Stage grouping	Stage description
0a	**Ta N0 M0**	The cancer is a non-invasive papillary carcinoma (Ta). It has grown toward the hollow center of the bladder but has not grown deeper into the connective tissue or muscle of the bladder wall[.] It has not spread to nearby lymph nodes (N0) or distant parts of the body (M0).
0is	**Tis N0 M0**	The cancer is a flat, non-invasive carcinoma (Tis), also known as carcinoma in situ (CIS). The cancer is growing in the inner lining layer of the bladder only. It has not grown inward toward the hollow part of the bladder, nor has it invaded deeper into the connective tissue or muscle of the bladder wall. It has not spread to nearby lymph nodes (N0) or distant parts of the body (M0).
I	**T1 N0 M0**	The cancer has grown into the layer of connective tissue under the lining layer of the bladder, but it has not reached the layer of muscle in the bladder wall (T1). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
II	**T2a or T2b N0 M0**	The cancer has grown into the inner (T2a) or outer (T2b) muscle layer of the bladder wall, but it has not passed completely through the muscle to reach the layer of fatty tissue that surrounds the bladder. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IIIA	**T3a, T3b, or T4a N0 M0**	The cancer has grown through the muscle layer of the bladder and into the layer of fatty tissue that surrounds the bladder (T3a or T3b). It might have spread into the prostate, seminal vesicles, uterus, or vagina, but it's not growing into the pelvic or abdominal wall (T4a). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
	OR	
	T1-4a N1 M0	The cancer has at least grown into the layer of connective tissue under the lining of the bladder wall (and may have grown farther), but it's not growing into the pelvic or abdominal wall (T1-T4a), AND the cancer has spread to 1 nearby lymph node in the true pelvis (N1). It has not spread to distant parts of the body (M0).
IIIB	**T1-T4a N2 or N3 M0**	The cancer has at least grown into the layer of connective tissue under the lining of the bladder wall (and may have grown farther), but it's not growing into the pelvic or abdominal wall (T1-T4a), AND the cancer has spread to 2 or more lymph nodes in the true pelvis (N2) or to lymph nodes along the common iliac arteries (N3). It has not spread to distant parts of the body (M0).
IVA	**T4b Any N M0**	The cancer has grown through the bladder wall into the pelvic or abdominal wall (T4b). It might or might not have spread to nearby lymph nodes (Any N). It has not spread to distant parts of the body (M0).
	OR	
	Any T Any N M1a	The cancer might or might not have grown through the wall of the bladder and into nearby organs (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to distant lymph nodes (M1a).
IVB	**Any T Any N M1b**	The cancer might or might not have grown through the wall of the bladder and into nearby organs (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to 1 or more distant organs, such as the bones, liver, or lungs (M1b).
Table from *https://www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/staging.html*		

Bladder cancer is also sometimes referred to, from the least to most extensive, as in situ, localized, regional, or distant. In situ bladder cancer constitutes half the number of diagnoses and involves cancer that was only found in the urothelium which is the inner lining of the bladder. Localized bladder cancer is confined to the bladder. Approximately one-third of bladder cancers are diagnosed at this stage. Both regional and distant stages indicate that the cancer has spread beyond the bladder; regional if in regional lymph nodes and distant if it has metastasized.

Bladder cancer is also graded as either low-grade or high-grade based on how the cells look microscopically. Cells that look more normal are expected to grow and spread more slowly. These cells are classified as low-grade. Abnormal cells are deemed high-grade and are more aggressive, requiring more aggressive treatment.

4. Treatment

Treatment options are based on type of cancer, stage and grade of cancer, and a patient's overall health. Depending on these factors, surgery to remove the cancer, chemotherapy in the bladder, chemotherapy for the entire body, radiation therapy, immunotherapy, and/or targeted therapy may be indicated.

i. Surgical Intervention

Surgery options include TURBT, partial cystectomy, and radical cystectomy with urinary diversion (ileal or continent diversion). These procedures are described in more detail below:

- TURBT, or transurethral resection of bladder tumor, involves surgical removal of the tumor through the urethra using a resectoscope and is used to both diagnose and treat bladder cancer. In patients with muscle-invasive disease (MIBC) unable to undergo radical cystectomy, maximal resection of the primary tumor is done with TURBT.
- Partial cystectomy is the partial surgical removal of the bladder. This is generally reserved for urachal adenocarcinomas of the bladder dome or tumors within a diverticulum or outpouching of the bladder wall (diverticulectomy).
- Radical cystectomy is removal of the whole bladder. This also includes a lymph node dissection of bilateral pelvic lymph nodes. In men, the prostate is also removed. In females, the uterus, ovaries, fallopian tubes, and anterior wall of the vagina may also be removed (anterior exenteration).
- Urinary diversion is needed once the bladder is removed. This is typically done using small intestine (ileum). The most common and straightforward is an ileal conduit which is an incontinent diversion draining urine out of a stoma in the lower abdominal wall. Typically, 15 centimeters of small intestine is removed. Both kidneys are connected to the ileal conduit either through a side to end (Bricker) or end to end (Wallace) anastomosis.
- Continent urinary diversions include ileal neobladder and Indiana Pouch. Ileal neobladder reconstruction involves taking 60 centimeters of small intestines, detubularizing them and constructing a spherical structure that is then connected to the native urethra. An Indiana Pouch involves taking the same amount of small bowel, creating a spherical structure but instead of connecting it to the native urethra, a catheterizable stoma is created and placed in the abdominal wall. Regardless of which continent urinary diversion is done, both are

more complex than an ileal conduit and entail higher risks of complications and metabolic abnormalities.

ii. Chemotherapy, Radiation Therapy, and Immunotherapy Options

Chemotherapy can be intravenous or intravesical (within the bladder). Radiation therapy for bladder cancer typically involves external beam radiation therapy (EBRT) and, for curative intent, usually done at the same time as systemic chemotherapy. Like chemotherapy, immunotherapy can also be given intravenously or within the bladder.

iii. Treatment by Stage

Stage 0 cancer treatment typically involves transurethral resection with fulguration followed by chemotherapy (*e.g.* Gemcitabine, Mitomycin C) within the bladder or Bacillus Calmette-Guerin BCG therapy (a type of immunotherapy). In general BCG therapy is reserved for high grade tumors or carcinoma in situ (CIS). Regular cystoscopies may be done following this treatment to ensure there is no evidence of recurrence or of new tumors. Chemotherapy can be instilled in the bladder at the same time as TURBT but BCG is only done once the bladder has healed to prevent systemic absorption. BCG is typically given at an induction schedule (once a week for six weeks) followed by maintenance (once a week for three weeks) every six months for three years.

Stage I bladder cancer is commonly treated with TURBT followed by chemotherapy or BCG therapy in the bladder. Again, this would be followed by regular office cystoscopy. If the cancer is deemed high-risk (either through higher grade, stage, or recurrence), radical cystectomy may be recommended.

Stage II and III cancer treatment includes TURBT and EUA (exam under anesthesia) to diagnose the pathologic stage. This is followed by either a radical cystectomy or chemotherapy/radiation for bladder preservation or in non-surgical candidates. Post-operatively, chemotherapy and immunotherapy may also be used. Chemotherapy administered prior to surgery, termed neo-adjuvant therapy, is done to treat any micro-metastatic disease outside the bladder that may not be visible on staging imaging.

Treatment for Stage IV cancer typically begins with immunotherapy, chemotherapy, and/or chemoradiation as surgery is unlikely to completely remove the cancer. After this treatment, the cancer is rechecked with cystoscopy, TURBT, or imaging and is followed by additional treatment as necessary, including cystectomy if possible and indicated. Treatment options for this stage are usually aimed at prolonging life and symptom reduction as opposed to curative goals.

5. Outcomes

The prognosis for a bladder cancer patient varies significantly depending on the stage at diagnosis. The five-year survival rate is less than 10% for distant (stage IV) bladder cancer, and approximately 40% for regional (stage III) bladder cancer. However, the five-year survival rate for in situ (stage I) and localized (stage II) bladder cancers—which constitute over 80% of cancer diagnoses—are significantly higher: approximately 95% and 70%, respectively.

When bladder cancer is diagnosed at an early stage, it is highly treatable. In 2019, bladder cancer deaths constituted just 2.9% of all cancer deaths, "which is lower than the incidence as a proportion of all cancers (4.6%), reflecting above-average survival for the disease (relative to other neoplasms)" (Saginala *et al.* 2020). This is important because many studies discussed later in this report analyzed the association between exposure to certain chemicals and bladder mortality, which would not capture incidence of bladder cancer cases where death did not result.

6. Latency

Bladder cancer typically develops decades after risk exposure. For example, some researchers have observed a latency period of up to 40 years between carcinogen exposure and cancer diagnosis (Miyakawa *et al.*, 2001). The latency period for bladder cancer rarely falls below 20 years (Mazeman, 1972). There is no upper limit on bladder cancer's latency period.

V. CAMP LEJEUNE WATER CONTAMINATION

In the 1970s and early 1980s, groundwater contamination was discovered at various locations within Marine Corps Base Camp Lejeune. The groundwater contamination led to the distribution of contaminated drinking water in the areas serviced by three of the eight on-base water treatment plants (WTPs)—Hadnot Point WTP, Tarawa Terrace WTP, and Holcomb Boulevard WTP—from 1953 to 1987 (ATSDR 2017; Maslia Expert Report).

Base operations and waste handling procedures caused water from the Hadnot Point WTP—which served the Hadnot Point area and, until June 1972, the Holcomb Boulevard area—to be contaminated by tetrachloroethylene (also known as perchloroethylene or "PCE"), trichloroethylene ("TCE"), vinyl chloride and petroleum products including benzene. The Hadnot Point WTP began taking the most contaminated wells offline in November 1984 and had completely stopped using contaminated wells by February 1985.

The Holcomb Boulevard WTP, which was brought online in June 1972, distributed largely uncontaminated water. However, contaminated water from the Hadnot Point WTP was distributed in the Holcomb Boulevard WTP service area when the new plant was offline for brief periods in June 1978, April 1981 and January-February 1985.

An offsite dry cleaner caused contamination of Tarawa Terrace WTP's groundwater wells with PCE and its degradation products, including vinyl chloride. The two most contaminated wells at Tarawa Terrace were shut in February 1985 and the Tarawa Terrace WTP was completely closed in March 1987.

VI. OPINIONS

A. PCE EXPOSURE IS A CAUSE OF BLADDER CANCER IN HUMANS.

PCE is a chlorinated solvent that was widely used as a drycleaning agent as well as for degreasing activities. ATSDR Hadnot Point Chapter A; ATSDR Tarawa Terrace Chapter A. PCE was a significant contaminant at the Tarawa Terrace WTP due to the presence of a drycleaning business across the street from the Tarawa Terrace housing area, but ATSDR also determined a meaningful amount of PCE contaminated the water supply at the Hadnot Point WTP. PCE has

been found to be probably carcinogenic to humans by IARC (Group 2a) and likely carcinogenic in humans by all routes of exposure by the EPA. IARC 2014; EPA 2011.

I performed a detailed review of the following studies investigating the link between PCE exposure and bladder cancer:

1. Meta-Analysis

a. Vlaanderen, Jelle *et al.* "Tetrachloroethylene exposure and bladder cancer risk: a meta-analysis of dry-cleaning-worker studies." Environmental health perspectives vol. 122,7 (2014): 661-6

This meta-analysis reviewed epidemiological studies that assessed occupational exposure to PCE or in workers in the dry-cleaning industry. The authors performed random-effects meta-analyses to assess exposure to tetrachloroethylene and bladder cancer including being specifically exposed to PCE and a dry cleaner employee. Using 3 studies (463 exposed bladder cancer cases), they found the meta-relative risk (mRR) among those exposed to PCE was 1.08 (95% CI 0.82, 1.42). However, in 7 studies (139 exposed bladder cancer cases) examining cases employed as a dry cleaner, the mRR was 1.47 (95% CI 1.16, 1.85). When examining 4 case-control studies which adjusted for smoking, the mRR was 1.50 (95% CI 0.80, 2.84). The authors concluded that these analyses indicated an increased bladder cancer risk in dry cleaners with some support for a causal relationship. The authors acknowledged that though dry cleaners were likely exposed to multiple chemicals, PCE was the primary solvent employed and thereby would in theory be most contributing. Finally, the authors hypothesized that the lack of an effect in "PCE-exposed workers" was likely due to inaccurate exposure determination.

2. Cohort Studies

i. Laundry, Dry Cleaning, and Dye House Workers' International Union Cohort, Missouri (1979)

a. Blair, A *et al.* "Causes of death among laundry and dry cleaning workers." American journal of public health vol. 69,5 (1979): 508-11

This study aimed to assess the frequency of specific causes of death of dry-cleaning workers compared with the general population to determine mortality risk using dry cleaners as a proxy for exposure to PCE and other solvents. The authors reviewed the death certificates of 330 laundry and drycleaning union workers from Kansas City and St. Louis, 279 of whom worked exclusively in dry cleaning shops while union members. 56 of the study subjects were 44 years of age or younger at the time of death and 191 were between the ages of 44 and 64. While the study did find excess deaths in the dry-cleaning workers group, bladder cancer did not contribute to that result. However, the authors cautioned that "[t]he small number of deaths, possible biases in the set of decedents obtained, and the general limitations of the [proportionate mortality ratio] methodology necessitate cautious interpretation of the study results."

b. Blair, A *et al.* "Cancer and other causes of death among a cohort of dry cleaners." British journal of industrial medicine vol. 47,3 (1990): 162-8

In this follow up to Blair 1979, Blair *et al.* reviewed records for 5,365 St. Louis workers holding union membership in Local 161, a union with members working exclusively in dry cleaning shops, for one year or more. The closing date of the study was January 1, 1979. The standardized mortality ratio (SMR) for bladder cancer was 1.7; 95% CI (0.7, 3.3). Information on potential confounders smoking and alcohol was not available in this study. The authors also suspected the healthy worker effect contributed to results due to the less than expected number of deaths from all causes. Additionally, data on which to base exposure estimates was limited, so the authors used a developed index of exposure based on published literature rather than actual measurements. The authors explained, "Relative risks for any particular chemical are likely to be diluted by inclusion of unexposed subjects to that chemical in the exposed categories which would tend to reduce estimates of relative risk and to mute exposure response relations."

c. Blair, Aaron *et al.* "Extended mortality follow-up of a cohort of dry cleaners." Annals of epidemiology vol. 13,1 (2003): 50-6

This was an extension of the mortality follow-up of the previous Blair cohort, Blair 1990, to further assess the association between organic solvents and cancers, including PCE and bladder cancer. This study extended the follow up from January 1, 1979, to December 31, 1993, and added four individuals for whom previously missing demographic information was obtained during the follow up. Bladder cancer deaths were elevated among white men and women, but not to a statistically significant degree. When the analysis was focused on deaths of those exposed after 1960, when PCE became the primary solvent used in dry cleaning in the U.S., the standard mortality ratio was 2.9 compared with 1.1 for those who entered the union prior to 1960. The number of events (*e.g.*, deaths) was based on limited data (3 deaths) and, again, was leading to a concern that this could influence an association with bladder cancer not being statistically significant. This study was limited in its ability to control for confounders like smoking and alcohol use and in its lack of detailed job histories for workers. Further, as with the other two studies by Blair *et al.*, only mortality was analyzed, not disease incidence leading to potential misclassification bias of bladder cancer-related death. Finally, data for this study came from only one union worker group raising the question of selection bias.

d. Callahan, Catherine L *et al.* "Extended Mortality Follow-up of a Cohort of Dry Cleaners." *Epidemiology (Cambridge, Mass.)* vol. 30,2 (2019): 285-290

Callahan *et al.* extended the mortality follow-up of 5,369 St. Louis dry cleaning union workers. Twenty-two years of follow-up through 2014 were added. With a 20-year lag, the authors found an exposure-response relationship between tetrachloroethylene and bladder cancer (HR=4.2; 95% CI 0.7, 24.5 for medium exposure and HR=9.1; 95% CI 1.1, 76.7 for high exposure).

ii. NIOSH Mortality Cohort of Dry-Cleaning Workers from Four Labor Unions, California, Illinois, Michigan and New York (1987)

a. Brown, D P, and S D Kaplan. "Retrospective cohort mortality study of dry cleaner workers using perchloroethylene." Journal of occupational medicine: official publication of the Industrial Medical Association vol. 29,6 (1987): 535-41

This cohort study was conducted of 1,690 dry-cleaning workers exposed to PCE for at least one year prior to 1960 and no known previous occupational exposure. Mortality was investigated through 1982. A sub-cohort was also designed to account for those workers who were knowingly only exposed to PCE (PCE-only sub-cohort), which had 615 subjects, as opposed to those who worked in shops where PCE exposure was confirmed but also shops where the solvents were unknown (PCE-plus sub-cohort). In those shops, the undetermined solvent usage could have been PCE or another solvent, potentially a petroleum solvent. Death certificates were used to determine decedents' causes of death. The standardized mortality ratio for bladder cancer was statistically significantly increased at 2.96; 95% CI (1.28, 5.86). This increased risk occurred after 20 or more years of latency which is consistent with occupational exposure. However, when the PCE-only sub-cohort was reviewed, there was no excess risk in bladder cancer mortality. This does not preclude PCE as the cause, but it does potentially attenuate the results. Data on smoking was not available, but the authors found it an unlikely confounder.

b. Ruder, A M *et al.* "Cancer mortality in female and male dry-cleaning workers." Journal of occupational medicine. : official publication of the Industrial Medical Association vol. 36,8 (1994): 867-74

This update to Brown 1987 provides data from the later of January 1, 1940, or after a year of employment at a PCE dry cleaner shop through the end of 1990 for 1,701 dry-cleaning workers. Workers in the PCE-plus cohort had a statistically significant standardized mortality ratio of 3.52; 95% CI (1.61, 6.68), though there were no deaths from bladder cancer in the PCE-only sub-cohort. Because PCE cannot be ruled out as the "other solvent," in the PCE-plus bladder cases, it could be the reason for the excess mortality in those. Both sub-cohorts had about 6 years of exposure to PCE, and the PCE-plus sub-cohort had an average of 5 more years of exposure to additional solvent(s). Though smoking was not adjusted for, the authors explained it is unlikely to be a confounder, as lung cancer mortality would be expected to be much higher than the SMR of 0.91 in this study if it were a factor.

c. Ruder, A M *et al.* "Mortality in dry-cleaning workers: an update." American journal of industrial medicine vol. 39,2 (2001): 121-32

A second update to Brown 1987, this study provided data for 1,703 workers through December 31, 1996, and showed a statistically significant increased standardized mortality ratio for bladder cancer of 2.22 (95% CI 1.06, 4.08). For those exposed for more than five years and with more than twenty years since their first exposure, there was a statistically significant SMR of

4.31; 95% CI (1.85, 8.76). However, these workers were all in the PCE-plus group. The authors noted that they could not quantify exposure due to insufficient information on job titles of the workers or personal exposure information. They were also unable to control for potential confounding from smoking, alcohol, and diet. As provided above, the original cohort authors did not deem smoking to be a likely confounder.

d. Calvert, Geoffrey M *et al.* "Mortality and end-stage renal disease incidence among dry cleaning workers." Occupational and environmental medicine vol. 68,10 (2011): 709-16

This study supplemented the original Brown 1987 cohort with additional mortality follow up data, with vital status updates through December 31, 2004, for 1,704 workers. This study found a statistically significant increase in overall cancer deaths. For bladder cancer specifically, mortality was statistically significantly higher for those who worked in one or more dry-cleaning shops that used PCE and one or more dry-cleaning shops where the primary solvent could not be identified but could have been PCE or some other solvent (SMR=2.59; 95% CI 1.24, 4.76). The study also showed the risk for bladder cancer was highest among those who were exposed for 5 or more years in PCE-using shops with 20 or more years latency since first employment in a PCE-using shop (SMR=4.08; 95% CI 2.13, 7.12). Because many work histories were unavailable after 1982, duration of exposure could be underestimated for some workers. Additionally, without job titles and personal exposure measurements, underestimates of exposure duration and lack of data on exposure intensity may have biased the findings toward the null (non-differential misclassification). This study was unable to control for potential confounding from smoking or alcohol, but smoking was not deemed likely to confound as described by authors of the original cohort.

iii. Bladder Cancer Cluster, Illinois (1990)

a. Mallin, K. Investigation of a bladder cancer cluster in northwestern Illinois. Am J Epidemiol. 1990 Jul;132(1 Suppl):S96-106

Based on cancer maps (1950 to 1979) showing higher than expected bladder cancer mortality (both females and males) in a number of northwestern Illinois counties, this bladder cancer incidence study was initiated in the 8 counties within this area. The authors found that only two zip codes within this region showed significantly elevated bladder cancer incidence. On further analyses, it was found that one town within one of these zip codes demonstrated significantly increased standardized incidence ratios in both females (SIR=2.6; 95% CI 1.2, 4.7) and males (SIR=1.7; 95% CI 1.1, 2.6). Interestingly, it was found that 1 of 4 public drinking water wells within this town had been closed in 1972 because of contamination. Testing of two wells located within 0.5 mile of a landfill demonstrated traces of multiple solvents, most notably tetrachloroethylene and trichloroethylene.

iv. Lockheed Martin aircraft manufacturing workers, California (1999)

a. Boice, J D Jr *et al.* "Mortality among aircraft manufacturing workers." Occupational and environmental medicine vol. 56,9 (1999): 581-97

Boice *et al.* conducted a retrospective cohort study of mortality among workers employed for at least one year at Lockheed Martin aircraft manufacturing facilities between 1960 and 1996, when follow up was complete. The cohort included 77,965 workers (45,323 factory, 32,642 non-factory) and SMRs adjusted for age, sex, race, and calendar year were calculated for workers exposed to chromate, TCE, PCE, and mixed solvents. The authors attempted to estimate workers' routine, intermittent, or no likely exposure and duration of exposure to each chemical. This study did not find an increased risk of death from bladder cancer in workers at the aircraft manufacturing facility from exposure to PCE or other solvents used to dissolve grease and oil (SMR= 0.70; 95% CI 0.09, 2.53). Though this is a large study that had an extensive follow up period (nearly 50 years for the earliest-exposed employees), limitations of the study include that the actual level of exposure to any substance (*e.g.* ppm) was not known and the authors relied on cause of death information in death certificates. Also, an adjustment for smoking by individual cohort members could not be made from the limited data. Funding for the study was provided by Lockheed Martin Corporation. Finally, controls were from the town/area but did not work at the plant.

b. Lipworth, Loren *et al.* "Cancer mortality among aircraft manufacturing workers: an extended follow-up." Journal of occupational and environmental medicine vol. 53,9 (2011): 992-1007

This study extends follow-up of the Lockheed Martin cohort to 2008. Investigators removed 22 duplicate data entries from the original cohort and identified 254 more deaths that occurred before 1997 but were not included in the Boice *et al.* study. This study evaluated the association between occupational exposure to solvents, including PCE, and cancer mortality among 77,943 aircraft workers. PCE-exposed employees did not experience an increased risk of bladder cancer mortality (SMR=0.84; 95% CI 0.49-1.35). This is a large cohort study that followed subjects for a substantial period; however, as with Boice *et al.*, it is limited by investigators' inability to quantify exposure levels for the specific compounds of interest and the lack of information about certain confounders. This study was also funded by Lockheed Martin Corporation.

v. Microelectronics and Business Machine Facility Workers, New York (2014)

a. Silver, S. *et al.* Retrospective Cohort Study of a Microelectronics and Business Machine Facility. American Journal of Industrial Medicine. 2014

Silver *et al.* assessed the association between workers at a microelectronics and business machine facility and certain health outcomes, including those associated with PCE exposure and bladder cancer. The study determined cancer mortality and incidence ratios for a cohort of 34,494

persons who worked for 91 days or more at the facility between 1969 and 2001. The cohort was followed until December 31, 2009. This study did not show an increased risk of bladder cancer with exposure to PCE (hazard ratio of 0.89 at 5 modified exposure years; 95% CI (0.37, 2.13)). However, the authors stated that the cohort showed a strong healthy worker effect. Limitations include a relatively young cohort and reliance on incomplete/contradictory information in work history databases, which were used to estimate exposures.

vi. Dry-Cleaners and Laundry Workers, Sweden (2011)

a. Selden, A. *et al.* Cancer morbidity in Swedish dry-cleaners and laundry workers: historically prospective cohort study. International Archives of Occupational and Environmental Health. 2011.

This historic prospective cohort study examined exposure to PCE and risk of bladder cancer in Swedish laundry and dry-cleaning workers from 1985 to 2006 (N = 10,389). The authors found significantly increased rates of lung cancer (standard cancer incidence ratio (SIR)= 1.45; 95% CI 1.03, 1.98) and non-Hodgkin's lymphoma (SIR=2.05; 95% CI 1.30, 3.07). Although no significant increased risk of bladder cancer was noted, the authors stated that risk assessment was limited by the absence of data (individual and collective) of PCE exposure from studied dry-cleaning and laundry businesses.

3. Case-Control Studies

a. Aschengrau, A *et al.* "Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts." Archives of environmental health vol. 48,5 (1993): 284-92

This case-control study examined the relationship between PCE in drinking water and bladder cancer following the discovery that pipes installed throughout Massachusetts in the late 1960s were leaching PCE into the drinking water from the inner vinyl lining. Concentrations in the affected lines in one town that had a large proportion of the pipes ranged from 1,600-7,750 micrograms/liter at the lower end and 1.5-80 at what were deemed medium and high use sites. Residents had been drinking the contaminated water for up to ten years by the time remediation efforts began. For the study, cases were selected from permanent residents of those diagnosed with bladder cancer, kidney cancer, and leukemia between 1983-1986 and controls were selected from demographically similar permanent residents of the same towns. Following the selection and exclusion criteria applied by the authors, there were 61 bladder cancer cases and 852 controls.

The participants' "relative exposure to PCE in drinking water was estimated using an algorithm developed by Webler and Brown." Using this algorithm, a relative delivered dose was calculated and defined as the "estimated mass of PCE in milligrams that entered a given house as a solute in drinking water over a specified time period." Exposure was classified as "ever" vs. "never" or unexposed, low, and high relative delivered doses, with low being up to the 90th percentile among exposed and high being above that. The authors used multiple logistic regression to control for potential confounding variables.

Because of the low number of bladder cancer cases, the authors were not able to take latency into account. The crude relative risk of bladder cancer increased among those exposed to high relative delivered doses (RDDs) at a statistically significant level, with an odds ratio of 6.04; 95% CI (1.32, 21.84). When adjusted for confounders, the relative risk for high RDDs was 4.03; 95% CI (0.65, 25.10). The crude relative risk of "ever" exposure was 1.55; 95% CI (0.74, 3.01) and adjusted relative risk was 1.39; 95% CI (0.67, 2.91).

As the authors noted, many estimates of association did not reach traditional statistical significance, but the size of case groups was small. The authors noted that the risk estimates found are likely biased downward because of nondifferential errors in exposure estimation. They also discuss the possibility of confounding and bias affecting the results, which they find to be unlikely. Confounding was controlled for in the multivariate analysis. Also, the procedures in place and manner of obtaining the cancer cases minimized the possibility of bias.

b. Pesch, B *et al.* "Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter Urothelial and Renal Cancer." International journal of epidemiology vol. 29,2 (2000)

This population-based study, with 1,035 urothelial cancer cases and 4,298 controls, focused on whether occupational exposure to certain chemicals, including chlorinated solvents, was associated with increased risk of urothelial cancer. The authors refer to urothelial cancer as originating in the mucosa of the lower urinary tract, and in most cases affecting the urinary bladder. Males assessed according to the job-task exposure matrix who were exposed to substantial PCE had a statistically significant increased odds ratio (OR=1.8; 95% CI 1.1, 3.1) of urothelial cancer after adjusting for smoking, study center, and age. The authors noted that due to their study being population-based, they could not exclude selection bias from a lower response rate of controls. Also, the statistical power was reduced due to low prevalence of participants working very long in some of the job tasks or occupations.

c. Lynge, Elsebeth *et al.* "Cancer in persons working in dry cleaning in the Nordic countries." Environmental health perspectives vol. 114,2 (2006): 213-9. doi:10.1289/ehp.8425

This study of dry-cleaning workers in four Nordic countries found a statistically significant increased risk (RR= 1.44; 95% CI 1.07, 1.93) for bladder cancer among such workers. Cases and controls were drawn from a pool of 46,768 laundry and dry-cleaning workers from Denmark, Finland, Norway, or Sweden. There were 351 bladder cases included in the analysis and 1,482 controls. Individuals evaluated for inclusion as cases included those with esophageal, gastric cardia, pancreatic, cervix uteri, bladder, kidney, or primary liver cancer. The authors selected three to six times the number of cases for controls depending on type of cancer (6 times for esophageal, 3 times for all others). Dry cleaning was used as a surrogate for PCE as that was the most commonly used chemical in dry cleaning at the relevant time, so cases and controls were categorized as exposed (explicitly described dry cleaners or other workers in small dry-cleaning shops); other workers in dry cleaning shops in all other size shops; unexposed laundry workers and others not working in dry cleaning; and unclassifiable persons. Exposed and unexposed were

further classified by length of employment in the shop in which they worked in 1970. The authors used length of employment as a proxy for relative, cumulated dose. However, there was much variation in exposure level among shops.

The increased risk that was found for bladder cancer was not associated with any length of employment. The authors noted several limitations of the study for which they attempted to account, including that though they were not able to divide individuals by exposure level, duration of employment was a suitable proxy given the "fairly stable exposure level throughout the study period." They also only had data on smoking for two of the four countries, but when adjusted in those two countries for smoking, the estimated risk only changed slightly.

d. Christensen, Krista Yorita *et al.* "Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal." Journal of occupational and environmental medicine vol. 55,2 (2013): 198-208

This case-control study evaluated the association between occupational exposures to solvents and cancer in men, including an assessment of the association between PCE and bladder cancer. The risk of bladder cancer was adjusted for smoking, coffee intake, and aromatic amine exposure. The study found that neither substantial exposure nor any exposure to PCE resulted in an excess risk of bladder cancer when compared to population and cancer controls.

Though the study did not find an increased association with PCE and bladder cancer, the authors noted that many of the associations examined were based on small numbers. The authors acknowledged a low study power – a large number of cases would be needed when looking at two chemical families, six chlorinated solvents and 11 sites of cancer. For PCE exposure, there were 62 bladder cancer cases and controls (4 cases, 6 population controls, and 52 cancer controls). Typically, the optimal number of controls per case should be 4:1 in a case-control study. However, this study had 533 population controls for 3,730 cases. The authors also found it important to note that due to the study design, the average exposure concentration was likely much lower "than in that of cohort studies focused on particular high-exposure industries." They also note that while there may have been error in the retrospective exposure assessment, it likely would have been nondifferential between cases and controls. The authors felt they controlled well for smoking.

e. Hadkhale, Kishor *et al.* "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries." International journal of cancer vol. 140,8 (2017): 1736-1746

This study, based on the Nordic Occupational Cancer (NOCCA) project cohort database and involving 113,343 cases and 566,715 controls, aimed to assess the relationship between exposure to certain solvents, including PCE, and bladder cancer risk. Exposure was quantitatively estimated based on the link between occupational codes and NOCCA-JEM which was developed from the Finnish job exposure matrix. A statistically significant increased risk of bladder cancer was found with medium exposure to PCE (HR=1.12; 95% CI 1.02-1.23). Exposures were defined by low, medium, or high, with low below the 50th percentile, medium between the 50th and 90th, and high above the 90th percentile. The authors noted that "trichloroethylene [TCE] and

perchloroethylene [PCE] are the subcategories of chlorinated solvents. Hence, it is difficult to disentangle their individual effects." But they also note that "[t]he study provides evidence of an association between occupational exposure to trichloroethylene, perchloroethylene, aliphatic and aromatic hydrocarbon solvents, benzene and toluene and bladder cancer risk." This study did not have direct information about smoking for those in the cohort, but the authors explained that if "the risk of lung cancer in a given occupation is elevated and there are no other work-related exposures than smoking, then the risk of bladder cancer should also be elevated due to smoking, but not as much as for lung cancer (because the RR due to smoking is lower for bladder cancer than for lung cancer). The RRs for bladder cancer clearly differ from this pattern."

f. Sciannameo, Veronica *et al.* "New insights on occupational exposure and bladder cancer risk: a pooled analysis of two Italian case-control studies." International archives of occupational and environmental health vol. 92,3 (2019): 347-359

In this study, the authors pooled data from two case-control studies on bladder cancer in males, ultimately analyzing 893 cases and 978 controls, to assess the association between occupations and occupational carcinogens and bladder cancer risks and whether they were influenced by the grade of the cancer. Occupational exposures were determined by detailed questionnaires completed by patients regarding their work history, lifestyle, and smoking history. A latency period of 10 years was used. Never/ever exposure was considered as well as cumulative exposure classified as no exposure, low exposure, and high exposure. Analysis by tumor grading was also performed. Odds ratios were adjusted for age, smoking status, and intensity of smoking. The study included 20 cases and 28 controls with ever exposure to PCE and 536 and 950 cases and controls respectively with never exposure for low-grade bladder cancer.

With "ever" exposure, there was an odds ratio of 1.43; 95% CI (0.76, 2.71) for low-grade cancer. With low exposure, there was an odds ratio of 1.93; 95% CI (0.82-4.5) for the same. High exposure did not show an increased risk (OR=0.97; 95% CI 0.36, 2.64). The authors noted that their "results were less strong than those observed in the previous studies, possibly because the increase in risk awareness and the implementation of control measures have reduced considerably the level of exposure to solvents in the last decades."

One noted limitation of this study is that since it was a hospital case-control, it is hard to know how much controls reflected the population that generated the cases. The authors attempted to test for this and did not find it likely that the associations observed resulted from a higher socioeconomic status of the controls. Another limitation of the study noted by the authors is their "use of a [job exposure matrix] to assign occupational exposure to the study population, which implies higher non-differential misclassification of the exposure than more detailed information at the individual level, with the consequence of a risk attenuation." But this also lessened the potential for recall bias. The authors also explained that the calculation of the cumulative dose of exposure through intensity weighted by probability may have led to misclassification and an underestimation of the cumulative exposure for some subjects which could explain why some associations were stronger in subjects with low versus high exposure.

g. Xie, Shuai *et al.* "Occupational exposure to organic solvents and risk of bladder cancer." Journal of exposure science & environmental epidemiology vol. 34,3 (2024): 546-553

This population-based case control study looked at exposure to solvents, including benzene, for 1,182 cases and 1,408 controls using a job-exposure matrix. The study did not find an increased risk associated with ever exposure of PCE and bladder cancer. However, only 6 cases and 19 controls were included as it related to that measure. As a result, the authors stated they were "unable to assess bladder cancer risk for exposure to PCE because they only identified 6 PCE-exposed cases."

4. Bradford Hill Analysis

A clear association between PCE exposure and bladder cancer is evident based on the epidemiological literature. Therefore, I conducted a Bradford Hill analysis to determine whether a causal relationship between PCE exposure and bladder cancer exists.

i. Strength of association

A significant association between PCE and bladder cancer found in multiple studies:

- Brown and Kaplan, "Retrospective cohort mortality study of dry cleaner workers using perchloroethylene". Standardized mortality ratio for bladder cancer statistically significant at 2.96. Increased risk occurred after 20 years of latency which is consistent with occupational exposure.
- Ruder *et al.,* "Cancer mortality in female and male dry-cleaning workers". Male workers in the PCE-plus cohort had a statistically significant increase in mortality (SMR 3.52).
- Ruder *et al.,* "Mortality in dry-cleaning workers: An update". This second update to Brown 1987 found a statistically increased SMR of 2.22 for bladder cancer in the PCE-plus group. In addition, those exposed more than 5 years and with a latency period of 20 years, SMR was 4.31.
- Calvert *et al.*, "Mortality and end-stage renal disease incidence among dry cleaning workers". Additional mortality follow-up to Brown 1987 – found increased mortality for bladder cancer in those who worked in one or more dry-cleaning shops using PCE and those shops where primary solvent could not be identified but likely was PCE (SMR=2.59; 95% CI 1.24, 4.76).
- Lynge *et al.,* "Cancer in persons working in dry cleaning in the Nordic countries". Study found a statistically increased risk for bladder cancer among dry cleaner workers (RR=1.44; 95% CI 1.07, 1.93).
- Aschengrau *et al.,* "Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts". Case-control study that found the crude relative risk of bladder cancer increased among those persons exposed to high relative delivered doses (OR=6.04; 95% CI 1.32, 21.84). When adjusted, significance disappeared but numbers were low thereby not negating an association.
- Pesch *et al.*, "Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter

Urothelial and Renal Cancer". This population-based study found that males exposed to substantial PCE had a significant increased risk of urothelial cancer (RR=1.8) after adjusting for smoking, study center, and age.

- Hadkhale *et al.*, "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries". A significant increased risk of bladder cancer noted in workers who had medium (50^{th} to 90^{th} percentile) exposure to PCE.
- Vlaanderen *et al.*, "Tetrachoroethylene exposure and bladder cancer risk: a meta-analysis of dry-cleaning-worker studies". This meta-analysis found that in 7 studies examining cases employed as a dry cleaner, the risk of bladder cancer was significantly increased (mRR=1.47; 95% CI 1.16, 1.85).
- Mallin *et al.,* "Investigation of a bladder cancer cluster in northwestern Illinois". This study found significantly increased standardized incidence rations in both females (SIR=2.6; 95% CI 1.2, 4.7) and males (SIR=1.7; 95% CI 1.1, 2.6) in an area of two contaminated public drinking wells, which contained both PCE and TCE.

ii. Consistency

A significant association between PCE and bladder cancer was observed among multiple studies with unique cohorts.

iii. Specificity

Bladder cancer has many potential causes. Notably, Bradford Hill cautions against "over-emphasiz[ing] the importance of" this factor. While specificity may support a finding of causal association, a lack of specificity does not negate it.

iv. Temporality

In studies finding a significant association between PCE and bladder cancer, all cases were exposed to PCE prior to development of bladder cancer.

v. Dose-Response

Significant trend noted in study by Callahan *et al.* "Extended Mortality Follow-up of Cohort of Dry Cleaners": HR=9.1; 95% CI 1.1, 76.7 for high vs. no exposure (P_{trend}=0.08) and Calvert *et al.,* "Mortality and end-stage renal disease incidence among dry cleaner workers" - Risk of bladder cancer highest in those exposed > 5 years with 20 or more years latency (SMR=4.08; 95% CI 2.13, 7.12).

vi. Biological Plausibility

Based on my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

vii. Coherence

Based on my review of the epidemiology literature discussed herein and my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

viii. Experimental evidence

Human experimental evidence is unavailable due to ethical considerations and animal experimental evidence is limited as it relates to this chemical exposure and bladder cancer.

ix. Analogy

Exposure to a known carcinogen (*e.g.*, smoking) increases the risk of certain cancers (*e.g.*, lung cancer). It would therefore reason that exposure to PCE (a known potential carcinogen and the major solvent used in dry cleaning during the questioned time period) would lead to increased risk of developing and dying from bladder cancer.

Based on the review of the Bradford Hill factors above, I am satisfied to a reasonable degree of scientific certainty that a causal relationship between PCE exposure and bladder cancer exists and that PCE can be a cause for bladder cancer.

B. TCE EXPOSURE IS A CAUSE OF BLADDER CANCER IN HUMANS.

TCE is a chlorinated solvent that was widely used for degreasing activities but also saw use as a drycleaning agent. ATSDR Hadnot Point Chapter A. TCE was a significant contaminant at the Hadnot Point WTP due to the amount of industrial activities that occurred on base; however, ATSDR also determined a meaningful amount of TCE contaminated the water supply at the Tarawa Terrace WTP. TCE has been determined to be carcinogenic to humans by IARC and carcinogenic in humans by all routes of exposure by the EPA (IARC 2014; EPA 2011). Below is my detailed review of the studies analyzing the association between TCE exposure and bladder cancer:

1. Meta-analyses

a. Morgan, R W *et al.* "Mortality of aerospace workers exposed to trichloroethylene." Epidemiology (Cambridge, Mass.) vol. 9,4 (1998): 424-31

Morgan *et al.* (1998) includes a cohort study of 20,508 aerospace workers, approximately 23% of whom were occupationally exposed to TCE, and a meta-analysis of this and three other cohort studies (specifically, Anttila *et al.*, 1995, Axelson *et al.*, 1994, and Spirtas *et al.*, 1991, which are addressed elsewhere in this epidemiology review). The meta-analysis showed an excess risk of bladder cancer mortality (meta-SMR=1.15; 95% CI 0.78, 1.62) for persons occupationally exposed to bladder cancer. This meta-analysis is limited by small numbers of bladder cancer deaths even when totals are aggregated across all four studies included therein.

b. Hansen, Johnni *et al.* "Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies." Journal of the National Cancer Institute vol. 105,12 (2013): 869-77

These investigators used three Nordic cohort studies of persons occupationally exposed to TCE (specifically, Danish, Finnish, and Swedish cohorts, discussed individually below) to create a pooled cohort of 5,553 persons. This analysis revealed a moderately elevated risk of bladder cancer incidence (SIR=1.17; 95% CI 0.75, 1.26) relative to the general population.

2. Cohort Studies

i. Hill Air Force Base, Utah (1991)

a. Spirtas, R *et al.* "Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results." British journal of industrial medicine vol. 48,8 (1991): 515-30

Spirtas *et al.* performed a retrospective cohort study of 14,457 civilian employees who worked at an aircraft maintenance facility at Hill Air Force Base, Utah for one (1) year or more between January 1952 and December 1956 to determine whether occupational exposure to TCE results in an excess risk of mortality. This study followed subjects until December 31, 1982. While the authors did not find a statistically significant association between exposure to TCE and any cause of death, data showed increasing cumulative exposure to TCE results in a "significant upward trend" of SMRs. The study lacked adequate power to detect a bladder cancer SMR for white female workers; however, white men occupationally exposed to TCE had a slightly elevated risk of bladder cancer mortality (SMR=1.37; 95% CI 0.65, 2.51). This study follows a relatively large cohort of individuals, including a substantial female subcohort, occupationally exposed to TCE and other organic solvents. The cohort's work environment involved exposures to numerous organic solvents, such that exposure to other solvents could not be controlled for while investigating the link between bladder cancer and TCE exposure. Additional limitations include the use of multiple comparisons and a lack of information about potential confounders.

b. Blair, A *et al.* "Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up." Occupational and environmental medicine vol. 55,3 (1998): 161-71

Blair *et al.* extended the Spirtas *et al.* follow up from the end of 1982 to the end of 1990 and evaluated cancer incidence in addition to cancer mortality. Incidence studies more accurately reflect the relationship between exposure and outcome for bladder cancer and other malignancies with comparatively high survival rates.

Rate ratios (95% CI) for bladder cancer deaths among men with no exposure and by cumulative exposure to TCE in unit-years			
No exposure	***< 5 unit-years***	***5-25 unit-years***	***>25 unit-years***
0.7 (0.2, 2.8)	1.8 (0.5, 6.2)	2.1 (0.2, 5.1)	1.0 (0.2, 5.1)
Rate ratios (95% CI) for bladder cancer incidence among men with no exposure and by cumulative exposure to TCE in unit-years			
No exposure	***< 5 unit-years***	***5-25 unit-years***	***>25 unit-years***
1.3 (0.5, 3.5)	1.7 (0.6, 4.4)	1.7 (0.6, 4.9)	1.4 (0.5, 4.1)

The female subcohort had only one bladder cancer death and two bladder cancer diagnoses, leaving the study underpowered to detect an association between occupational TCE exposure and risk of bladder cancer in women. The strengths and weaknesses of this study are largely reflected in the Spirtas *et al.*, 1991 summary, above.

c. Radican, Larry *et al.* "Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow- up." Journal of occupational and environmental medicine vol. 50,11 (2008): 1306-19.

Radican *et al.* extended the follow-up of the Hill Air Force Base civilian employee cohort an additional 10 years to the end of 2000. TCE exposure did not result in excess bladder cancer mortality in this follow-up study (HR=0.80; 95% CI 0.41,1.58). Cancer incidence was not evaluated. The strengths and weaknesses of this study are largely reflected in the Spirtas *et al.*, 1991 summary, above.

ii. TCE Exposed Workers, Sweden (1994)

a. Axelson, O *et al.* "Updated and expanded Swedish cohort study on trichloroethylene and cancer risk." Journal of occupational medicine: official publication of the Industrial Medical Association vol. 36,5 (1994): 556-62

This cohort study of 1,670 Swedish persons occupationally exposed to TCE whose urine was monitored for TCE metabolites. Investigators found that TCE exposure did not result in a significant increase in bladder cancer morbidity, SIR=1.02 SIR; 95% CI 0.44, 2.00. Risk of bladder cancer mortality was not calculated. Strengths of this study include the use of biomarkers to accurately quantify exposure, and weaknesses include the relatively small cohort size that may lack the power to detect an effect.

iii. TCE Exposed Workers, Finland (1995)

a. Anttila, A *et al.* "Cancer incidence among Finnish workers exposed to halogenated hydrocarbons." Journal of occupational and environmental medicine vol. 37,7 (1995): 797-806

Anttila *et al.* conducted a cohort study of cancer incidence in 3,974 Finnish employees who were biologically monitored for exposure to halogenated hydrocarbons, including TCE (3,089 individuals), from 1965 to 1983. The cohort was followed from January 1, 1967 or first U-TCA measurement until the earlier of December 31, 1992, emigration, or death. Cancer incidence in the TCE-exposed cohort compared to the local Finnish population. When stratified by years since first biomarker of TCE exposure, those followed for 20+ years showed an increased risk of bladder cancer (SIR=1.51; 95% CI 0.18-5.44) though the full cohort did not (SIR=0.82; 95% CI 0.27, 1.90). Study strengths include the use of biologic measurements to identify and quantify solvent exposure

iv. Hughes Aircraft manufacturing employees, Arizona (1998)

a. Morgan, R W *et al.* "Mortality of aerospace workers exposed to trichloroethylene." Epidemiology (Cambridge, Mass.) vol. 9,4 (1998): 424-31

Morgan *et al.* (1998) includes a cohort study of 20,508 workers at the Hughes Aircraft manufacturing site who were employed for at least six months from January 1, 1950 to December 31, 1985. The cohort was divided into four TCE exposure categories: none, low, medium, and high. Approximately 23% of the cohort was occupationally exposed to TCE, and most of those individuals had more than one category of exposure. Each individual's cumulative exposure and peak exposure (*i.e.*, the job with the highest exposure rating) were determined. Overall, the TCE-exposed subcohort had an excess risk of bladder cancer, SMR=1.36; 95% CI 0.59, 2.68. While the low TCE exposure group had no excess bladder cancer mortality, SMR=0.51; 95% CI 0.01, 2.83, the high TCE exposure group did have excess bladder cancer mortality risk, SMR=1.79; 95% CI 0.72, 3.69. Internal cohort analysis for peak and cumulative TCE exposure was performed. Those with medium and high peak exposures demonstrated excess risk as compared to those with low or no peak PCE exposure (RR=1.41; 95% CI 0.52, 3.81). Those with high cumulative exposure demonstrated excess bladder cancer risk (RR=2.71; 95% CI 1.10, 6.65). Only one person with low cumulative TCE exposure died of bladder cancer (RR=0.69; 95% CI 0.09, 5.36). The authors noted a "pronounced" healthy worker effect in this cohort and identified the following limitations: limited follow-up time, small numbers of cancer mortality in the exposed and unexposed cohorts, lack of data on individual exposure and confounders and no direct measure of individual solvent exposure.

v. Fernald Feed Materials Production Center employees, Ohio (1999)

a. Ritz, B. "Cancer mortality among workers exposed to chemicals during uranium processing." Journal of occupational and environmental medicine vol. 41,7 (1999): 556-66

Ritz *et al.* published this cohort study of 3,814 white male workers in uranium metal product fabrication with known or suspected occupational TCE exposure for at least three months between 1951 and 1972. Follow-up began on the later of January 1, 1951 or the date of hire and ended on the earlier of December 31, 1989 or date of death. Exposures were estimated by plant experts (*i.e.*, industrial hygienists, an engineer, and a plant foreman. Within the cohort, 2,792 persons had "light" TCE exposure, 179 persons had "moderate" TCE exposure, and none had "heavy" TCE exposure. About half of the "light" TCE exposure subcohort was also exposed to cutting fluids, which are believed to be carcinogenic. The authors found an excess risk of bladder and kidney cancer for those with "light" TCE exposure for two to 10 years, RR=1.94; 95% CI 0.59, 6.44, while those with more than 10 years of light TCE exposure did not show an excess risk of bladder and kidney cancers, RR=0.76; 95% CI 0.14, 4.00. Risk ratios for bladder and kidney cancers for those in the "moderate" exposure group could not be calculated because there was only one bladder and kidney cancer death in that subcohort. The authors adjusted for smoking and found it to be an unlikely explanation for the relationship between chemical exposure and disease outcome. They also noted that the healthy worker effect could cause a bias toward the null for internal comparisons of cancer mortality.

vi. Lockheed Martin aircraft manufacturing workers, California (1999)

a. Boice, J D Jr *et al.* "Mortality among aircraft manufacturing workers." Occupational and environmental medicine vol. 56,9 (1999): 581-97

This retrospective cohort study, more fully described in the PCE section (above), also investigated mortality risk for persons occupationally exposed to TCE. Approximately 7% of the cohort were exposed to TCE intermittently and approximately 5% were routinely exposed. Those routinely exposed to TCE did not experience an excess of bladder cancer mortality (SMR=0.55; 95% CI 0.18, 1.28). Standardized mortality ratios for those with intermittent TCE exposure was not calculated and bladder cancer incidence in the cohort was not investigated. Strengths and weaknesses of this study are reflected in the complete summary, above.

b. Lipworth, Loren *et al.* "Cancer mortality among aircraft manufacturing workers: an extended follow-up." Journal of occupational and environmental medicine vol. 53,9 (2011): 992-1007

This extended follow-up on the Boice *et al.*, 1999 retrospective cohort study, more fully described in the PCE section (above), found that employees routinely and intermittently exposed to TCE did not have an excess risk of bladder cancer mortality (SMR=1.03; 95% CI 0.72, 1.43). Strengths and weaknesses of this study are reflected in the complete summary, above.

vii. TCE Exposed Workers, Denmark (2001)

a. Hansen, J *et al.* "Cancer incidence among Danish workers exposed to trichloroethylene." Journal of occupational and environmental medicine vol. 43,2 (2001): 133-9

Hansen *et al.* studied cancer incidence in a cohort of 803 Danish workers using individual urinary measurements of TCE metabolites taken between 1947 and 1989 from exposed persons at 275 different companies and individual air measurements of TCE taken from 81 companies starting in 1974. The cohort was followed for cancer incidence from April 1, 1968 or date of first employment through December 31, 1996 or date of immigration/death. TCE-exposed males experienced a slight excess risk of bladder cancer (SIR=1.10; 95% CI 0.5, 2.0); no SIR was available for TCE-exposed females. Strengths of this study include a direct measurement of individual TCE exposure and the use of cancer diagnosis instead of cancer mortality; however, this is a relatively small cohort that may lack the power to detect an effect of TCE exposure.

viii. Blue Collar Workers, Denmark (2003)

a. Raaschou-Nielsen, Ole *et al.* "Cancer risk among workers at Danish companies using trichloroethylene: a cohort study." American journal of epidemiology vol. 158,12 (2003): 1182-92

In this study, Raaschou-Nielsen *et al.* evaluated cancer incidence in a cohort of 40,049 blue collar workers employed three months or longer at 347 Danish companies with documented TCE use between 1968 and 1997. Follow-up began on the later of April 1, 1968 or date of employment at TCE-using company; it ended on the later of death, emigration, disappearance or December 31, 1997. Men who were occupationally exposed to TCE did not show an excess bladder cancer incidence; however, women occupationally exposed to TCE did have excess bladder cancer risk, SIR=1.6; 95% CI 0.93, 2.57. The investigators did not have TCE exposure measurements for the cohort and they estimated some in the "blue collar" cohort would have experienced little or no TCE exposure, possibly resulting in nondifferential misclassification likely biasing SIRs toward the null. Investigators were unable to exclude confounding by exposure to other chemicals.

ix. Rocketdyne workers, California (2005)

a. Zhao, Yingxu *et al.* "Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers." American journal of industrial medicine vol. 48,4 (2005): 249-58

Zhao *et al.* conducted a retrospective cohort mortality study of 55,000 workers employed at a California aerospace company, and performed a cancer incidence analysis for a sub-cohort of 5,049 workers who were alive and had not yet been diagnosed with a primary cancer as of January 1, 1988. Follow-up began on the earlier of January 1, 1950 or start of employment and ended at death or on December 31, 2001. Employees in the low exposure group did not have an excess risk of bladder cancer mortality or incidence. However, the medium and high exposure groups had an excess risk of bladder cancer mortality, RR=1.27; 95% CI (0.43, 3.73), and RR=1.15; 95% CI

(0.29, 4.51), respectively, and an excess risk of bladder cancer incidence, RR=1.54; 95% CI (0.81, 2.92) and RR=1.98; 95% CI (0.93, 4.22), respectively. Effect estimates for bladder cancer incidence did not change when exposures were lagged, they increased with adjustment for occupational exposure to other chemicals, and they showed a monotonic exposure-response trend. Possible biases include exposure misclassification likely to be non-differential with respect to cancer outcome, and potential confounding by unmeasured risk factors. However, based on the weak association between smoking and occupational TCE exposure among a subcohort whose smoking history was known, authors believe smoking did not appreciably confound the exposure effects. Limitations include the lack of cancer incidence data before January 1, 1988. The authors noted that "[a] comparison of mortality and incidence data suggests that the occurrence[] of… bladder cancer…[was] considerably under-reported on death certificates."

b. Boice, John D Jr *et al.* "Mortality among Rocketdyne workers who tested rocket engines, 1948-1999." Journal of occupational and environmental medicine vol. 48,10 (2006): 1070-92

Boice *et al.* conducted a retrospective cohort mortality study of 8,372 employees at a rocket engine testing facility in southern California. The cohort includes all persons employed for at least six months starting on or after January 1, 1948 and was followed until death, age 95, or December 31, 1999. Test stand mechanics with exposure to TCE had an excess risk of bladder cancer mortality, SMR=1.66; 95% CI 0.54-3.87. The authors noted that the risk of TCE exposure was mitigated by using the compound episodically and outdoors, resulting in exposure that is less intense than would be possible in an indoor environment. Limitations include a relatively small number of exposed workers, exposure estimates inferred from work history information, and incomplete information about smoking history. This study was sponsored by The Boeing Corporation, which owned and operated the Rocketdyne facility when the study was conducted and results were published.

x. Microelectronics & Business Machine Facility Workers, New York (2014)

a. Silver, Sharon R *et al.* "Retrospective cohort study of a microelectronics and business machine facility." American journal of industrial medicine vol. 57,4 (2014): 412-24

This cohort, discussed more fully in the PCE section (above), also assessed the association between TCE and bladder cancer among workers at a microelectronics and business machine facility. Investigators found a 0.04 hazard ratio (95% CI; 0.00, 5.71) at 5 modified exposure years for TCE exposed workers. Limitations of the study are provided in the study summary above.

xi. Train Repair and Maintenance Workers, Norway (2016)

a. Buhagen, Morten *et al.* "Association Between Kidney Cancer and Occupational Exposure to Trichloroethylene." Journal of occupational and environmental medicine vol. 58,9 (2016): 957-9

Buhagen *et al.* conducted a retrospective cohort incidence study investigating the causal link between occupational TCE exposure and cancer, with a primary focus on kidney cancer. The cohort consists of 997 male employees who worked in train repair and maintenance at the Norwegian State Railroad Company for at least one year from 1954 forward. Follow-up ended on December 31, 2010, date of cancer diagnosis, or date of death. While the study focused on kidney cancer, the authors provided Standardized Incidence Ratios for cancer overall and for individual cancer sites, including bladder cancer, which showed no excess risk, SIR=0.7; 95% CI 0.4, 1.3. Strengths of the study include a long follow-up period, while weaknesses include a lack of information about smoking within the cohort.

3. Case-Control Studies

a. Greenland, S *et al.* "A case-control study of cancer mortality at a transformer-assembly facility." International archives of occupational and environmental health vol. 66,1 (1994): 49-54

This case control study examined site-specific cancer mortality for active or retired white male employees of a General Electric manufacturing plant. The 512 cancer cases were comprised of men employed at the facility between 1947 and 1985, who died between 1969 and 1984 at age 21 through 90. The 1202-person control group was comprised of non-cancer deaths from the same underlying cohort. An industrial hygienist conducted interviews with 18 knowledgeable employees to estimate exposures based on the employee's job title, department, and building. Employees occupationally exposed to TCE did not have an excess risk of bladder cancer mortality in this study (OR=0.85; 95% CI 0.32, 2.23). Limitations of this study include uncontrolled confounding, selection bias, and misclassification bias.

b. Christensen, Krista Yorita *et al.* "Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal." Journal of occupational and environmental medicine vol. 55,2 (2013): 198-208

This is a case-control study of 3,730 cancer cases and 533 population controls investigating occupational exposures and cancer outcomes in Quebec, Canada that included a population control series and a number of cancer case series. Study subjects were white males aged 35 to 70 who lived in Montreal. Authors found that neither substantial exposure nor any exposure to TCE resulted in an excess risk of cancer when compared to population and cancer controls. A more complete discussion of study strengths and weakness are provided in the summary above.

c. Hadkhale, Kishor *et al.* "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries." International journal of cancer vol. 140,8 (2017): 1736-1746

This case control study, described in more detail in the PCE discussion above, includes 113,343 cases of bladder cancer diagnosed in Nordic countries between 1961 and 2005 and 566,715 country-, sex-, and birth year-matched population controls. Highly TCE-exposed subjects (>129.5 ppm unit-years) experienced excess risk of bladder cancer, HR=1.23; 95% CI 1.12, 1.40. This study also shows a monotonic trend based on TCE exposure level, with low and moderate exposure groups (<32.8 ppm unit-years and 32.8-129.5 ppm unit-years, respectively) experiencing slightly elevated bladder cancer risk, HR=1.07; 95% CI 1.02, 1.12 and HR=1.07; 95% CI 1.00, 1.13, respectively. Additional details about this study, including a discussion of its strengths and weaknesses, are provided above.

d. Sciannameo, Veronica *et al.* "New insights on occupational exposure and bladder cancer risk: a pooled analysis of two Italian case-control studies." International archives of occupational and environmental health vol. 92,3 (2019): 347-359

Sciannameo *et al.*, more fully described in the PCE discussion above, pooled data from two Italian case control studies of bladder cancer and occupational carcinogen exposure, with 893 cases and 978 controls. TCE-exposed subjects experienced an excess risk of bladder cancer, OR=1.18; 95% CI 0.96, 1.46. Highly exposed persons had a slight excess risk, OR=1.08; 95% CI 0.83, 1.41, while those with low TCE exposure had greater risk, OR=1.33; 95% CI 1.02, 1.73. Additional details about this study, including a discussion of its strengths and weaknesses, are provided above.

4. Structured Questionnaire Study

i. Reset (formatting note – LNS to hide this text)

a. Reed, Oliver *et al.* "Occupational bladder cancer: A cross section survey of previous employments, tasks and exposures matched to cancer phenotypes." PloS one vol. 15,10 e0239338. 21 Oct. 2020

The authors conducted a structured questionnaire study to evaluate likelihood exposure in bladder cancer cases. Subjects self-completed a questionnaire regarding employment, exposures, tasks, smoking, family and lifestyle history. A total of 454 cases were included. In addition to increased risk to other exposures and occupations, a significant association was seen with solvents such as trichloroethylene. In fact, higher grade cancer was more common than low grade cancer in this cohort (43.2% vs. 38.4% and 18.4% for grade III vs. II vs. I cancer, respectively; $p<0.001$).

5. Bradford Hill Analysis

A clear association between TCE exposure and bladder cancer is evident based on the epidemiological literature. Therefore, I conducted a Bradford Hill analysis to determine whether a causal relationship between TCE exposure and bladder cancer exists.

i. Strength of association

A significant association between TCE and bladder cancer found in multiple studies –

- Morgan *et al.*, "Mortality of aerospace workers exposed to trichloroethylene". This study found a significant increased risk of bladder cancer in the high cumulative exposure sub-cohort (SMR=2.71; 95% CI 1.10, 6.65).
- Hadkhale *et al.*, "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries". This case-control study found that highly TCE-exposed ((>129.5 ppm unit-years) subjects experience increased risk of bladder cancer (HR=1.23; 95% CI 1.12, 1.40).
- Sciannameo *et al.,* "New insights on occupational exposure and bladder cancer risk: a pooled analysis of two Italian case-control studies". This study showed a non-statistical overall increased risk of bladder cancer but there was a significant association noted in those subjects with low exposure levels (OR=1.33; 95% CI 1.02, 1.73).
- Mallin *et al.,* "Investigation of a bladder cancer cluster in northwestern Illinois". This study found significantly increased standardized incidence rations in both females (SIR=2.6; 95% CI 1.2, 4.7) and males (SIR=1.7; 95% CI 1.1, 2.6) in an area of two contaminated public drinking wells, which contained both PCE and TCE.

ii. Consistency

Multiple studies with unique cohorts found an increased but not significant risk of bladder cancer in those exposed to TCE. This was true of the studies that did show a significant association.

iii. Specificity

Bladder cancer has many potential causes. Notably, Bradford Hill cautions against "over-emphasiz[ing] the importance of" this factor. While specificity may support a finding of causal association, a lack of specificity does not negate it.

iv. Temporality

In studies finding a significant association between TCE and bladder cancer, all cases were exposed to TCE prior to development of bladder cancer.

v. Dose-response

Hadkhale *et al.*, "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries". In addition to finding an increased risk of bladder cancer in the highly TCE-exposed cohort, this case-control study also found a dose response. Moderate and high exposure groups (32.8-129.5 ppm unit-years and >129.5 ppm unit-years, respectively) experienced elevated bladder cancer risk, HR=1.07; 95% CI (1.02, 1.12) and HR=1.23; 95% CI (1.12, 1.40), respectively, relative to unexposed subjects.

vi. Biological Plausibility

Based on my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

vii. Coherence

Based on my review of the relevant epidemiological literature discussed herein and my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

viii. Experimental evidence

Human experimental evidence is unavailable due to ethical considerations and animal experimental evidence is limited as it relates to this chemical exposure and bladder cancer.

ix. Analogy

Exposure to a known carcinogen (*e.g.*, smoking) increases the risk of certain cancers (*e.g.*, lung cancer). It would therefore reason that exposure to TCE (a known potential carcinogen and solvent used in dry cleaning during the questioned time period) would lead to increased risk of developing and dying from bladder cancer.

Based on the review of the Bradford Hill factors above, I am satisfied to a reasonable degree of scientific certainty that a causal relationship between TCE exposure and bladder cancer exists and that TCE can be a cause for bladder cancer.

C. BENZENE IS A CAUSE OF BLADDER CANCER IN HUMANS.

Benzene is a volatile organic compound that is present in petroleum products that leaked from underground storage tanks located within the Hadnot Point WTP. ATSDR Hadnot Point Chapter A. Benzene has been determined to be carcinogenic to humans by IARC (Group 1) and carcinogenic in humans by all routes of exposure by the EPA. IARC 2018; EPA 2002. The following studies evaluated the association of benzene exposure with bladder cancer. Below is my detailed review of the studies that evaluated benzene exposure and bladder cancer:

1. Meta-Analysis

a. Seyyedsalehi, Monireh Sadat *et al.* "Occupational benzene exposure and risk of kidney and bladder cancers: a systematic review and meta-analysis." *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP)* 20 Aug. 2024

This study was a meta-analysis assessing the association of benzene exposure and the risk of urinary tract (kidney and bladder) cancer. The study included 41 case-control and cohort studies listed in the International Agency for Research on Cancer (IARC) Monographs for exposure to benzene. A random-effects model was used to address study heterogeneity. The authors found a significant association between occupational benzene exposure and kidney/unspecified urinary tract carcinoma (RR=1.20; 95% CI 1.03, 1.39). In addition, a positive association was noted between benzene exposure and bladder cancer (RR=1.07; 95% CI 0.97, 1.18). Exposure level analysis demonstrated a significant trend for bladder cancer (p=0.01), and the authors concluded that a dose-effect association existed between benzene and bladder cancer.

2. Cohort Studies

i. Drake Superfund Site, Pennsylvania (1984)

a. Budnick, L D *et al.* "Cancer and birth defects near the Drake Superfund site, Pennsylvania." Archives of environmental health vol. 39,6 (1984): 409-13.

The study analyzed site-specific cancer mortality rates for Clinton County, PA, a county known to be contaminated with beta-naphthylamine, benzidene, and benzene. The authors found a significant increased number of deaths from bladder cancer in the 1970s in white males in the county.

ii. Dow Chemical, Michigan (1986)

a. Bond, G G *et al.* "An update of mortality among chemical workers exposed to benzene." British journal of industrial medicine vol. 43,10 (1986): 685-91

Bond *et al.* investigated mortality for 956 Dow Chemical workers exposed to benzene who worked for at least one month between the dates of 1938 and 1970 at particular jobs in three production areas. Follow up was through 1982. For the total cohort, bladder cancer mortality was not elevated (SMR=0.66; 95% CI 0.02, 3.71). The authors noted the potential for the healthy worker effect here as total mortality was significantly below that of the general population.

b. Bloemen, L J *et al.* "Lymphohaematopoietic cancer risk among chemical workers exposed to benzene." Occupational and environmental medicine vol. 61,3 (2004): 270-4

This update to Bond 1986 assessed mortality for 2,266 workers and extended the follow up to December 31, 1996. Mortality from bladder cancer was not elevated (SMR=0.39; 95% CI 0.08, 1.14). This was based on 3 deaths. The authors indicated that the "scarcity of deaths from some key causes . . . limited inferences they may draw from the results."

c. Collins, James J *et al.* "Lymphatic and hematopoietic cancers among benzene-exposed workers." Journal of occupational and environmental medicine vol. 57,2 (2015): 159-63

The third update of this cohort, Collins *et al.* updated the follow-up to December 31, 2009. At over 30 years latency, bladder cancer mortality was 1.04; 95% CI (0.52, 1.86). Several limitations to the study are discussed, including the reliance on death certificates due to the potential for misclassification, and that many cancers are treatable and survivable. Though the authors specifically referenced cancers of the hematopoietic and lymphatic system and myelodysplastic syndrome, these limitations would apply similarly to bladder cancer.

iii. Chemical Manufacturers Association, United States (1987)

a. Wong, O. "An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results." British journal of industrial medicine vol. 44,6 (1987): 365-81 ("Wong 1987a")

This cohort of 7,767 male chemical workers looked at workers who were at their job for at least six months who were exposed intermittently or continuously to benzene and those workers from the same plants who were never exposed to benzene to compare mortality rates and causes. Intermittent exposure indicated casual exposure where the worker was not assigned to a discrete area where benzene exposure occurred but periodically worked in such areas. Continuous exposure included jobs where a worker was assigned a discrete area where benzene exposure occurred at least three days a week. The standardized mortality ratio for bladder cancer mortality for all cohort members was 0.816; 95% CI (0.263, 1.903). For those exposed continuously, the SMR was 1.05; 95% CI (0.216, 3.069). Smoking as a confounder could not be adjusted for in this study due to unavailability of that data.

b. Wong, O. "An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses." British journal of industrial medicine vol. 44,6 (1987): 382-95 ("Wong 1987b")

This study, Part II of the original Wong cohort (Wong 1987a), provided data and dose-response analyses for latency, duration of exposure, cumulative exposure, and peak exposure for the chemical workers exposed to benzene. There was a not statistically significant increased risk of bladder cancer mortality for those exposed to benzene continuously for more than 15 years

(SMR=3.34); intermittently and continuously with a latency since first exposure of 20 years (SMR=1.515); and continuously exposed with a latency of 20 years since first exposure (SMR 1.639). The study did not take into account frequency of peak exposure due to limitations of that data. The author noted some limitations of the study included loss to follow up, small amount of coding error, and historical exposure levels for the early part of the study were limited for some of the plants.

iv. Nordic Service Station Workers, Denmark, Norway, Sweden, and Finland (1997)

a. Lynge, E *et al.* "Risk of cancer and exposure to gasoline vapors." American journal of epidemiology vol. 145,5 (1997): 449-58

In this study, a cohort of 19,000 service station workers from Denmark, Norway, Sweden, and Finland was analyzed for cancer incidence. The standardized incidence ratio for bladder cancer for men in the total cohort was 1.1; 95% CI (0.9, 1.3) and for women was 0.5; 95% CI (0.0, 1.9). The authors noted some limitations of the study include that individual data was not available on length of employment and level of benzene exposure.

v. UK Service Station Workers, England and Wales (2005)

a. Sorahan, T *et al.* "Cancer risks in a historical UK cohort of benzene exposed workers." Occupational and environmental medicine vol. 62,4 (2005): 231-6

This cohort study that assessed cancer mortality risk for 5,514 benzene-exposed workers did not find an increased risk of bladder cancer death, SMR=1.00; 95% CI (0.66, 1.46). For incidence, the study found SRR=1.04; 95% CI (0.81, 1.31) in those exposed. However, estimates of exposure were unavailable for the earlier years of exposure and what was obtained was the levels at the time of data collection. This data was also not provided in a standardized manner (*i.e.*, some factories measured peak exposure and some average ambient levels).

vi. CCDCP-NCI, China (2015)

a. Linet, Martha S *et al.* "A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers." International journal of cancer vol. 137,9 (2015): 2184-97

This retrospective cohort study analyzed all-cause mortality, including bladder cancer, of 73,789 benzene-exposed workers compared with 34,504 unexposed workers in 12 cities in China. The relative risk of bladder cancer mortality was 0.9; 95% CI (0.4, 2.2). This was a large cohort. However, there was a lack of individual exposure estimates. Additionally, most workers were under 60 years old at the end of the study follow up.

vii. Coal-Oil-Fired Thermal Plant, Italy (2017)

a. Collarile, Paolo *et al.* "Residence in Proximity of a Coal-Oil-Fired Thermal Power Plant and Risk of Lung and Bladder Cancer in North-Eastern Italy. A Population-Based Study: 1995-2009." International journal of environmental research and public health vol. 14,8 860. 31 Jul. 2017

This study evaluated the risk of bladder cancer in people residing near a coal-oil-fired thermal power plant by assessing the incidence according to tertiles of exposure to benzene and other chemicals. No increased risk was found for men or women under age 75. However, the study found that for women 75 or older, the risk of bladder cancer was significantly increased in those with high exposure to benzene with an incidence rate ratio (IRR) of 1.94; 95% CI (1.01, 3.74). The authors did not have information on cigarette smoking, which they acknowledge as a limitation of the study. The authors attempted to minimize smoking as a confounder but could not completely rule it out. There was also no information on the daily time participants spent in each risk area with the different levels of exposure and the presence of other industries near the study areas could have affected the results.

viii. Norwegian Offshore Petroleum Workers, Norway (2023)

a. Shala, Nita K *et al.* "Exposure to benzene and other hydrocarbons and risk of bladder cancer among male offshore petroleum workers." British journal of cancer vol. 129,5 (2023): 838-851

This was a prospective case cohort of male offshore petroleum workers evaluating the possible association between occupational petroleum-related hydrocarbon exposures and bladder cancer. The authors used job-exposure matrices developed by a group of industrial hygienists refined into semi-quantitative estimates to try to further define the contrasts in intensity of benzene exposure. Those considered to have been exposed to benzene long term had a statistically significant hazard ratio of 1.89; 95% CI (1.14, 3.13) compared to unexposed which was adjusted for smoking. The authors noted "the lack of information on work history during follow-up (1999–2017)… could have led to exposure misclassification and distortion of potential exposure response associations….In the present study of solid tumours, as opposed to lymphohematopoietic cancers, we would expect to see a clearer dose-response when the most recent exposures were disregarded, allowing for disease latency. When risk analyses were restricted to bladder cancer as the first primary cancer, and a 20-year lag was applied, the evidence was indeed stronger for a dose-related effect from cumulative benzene exposure."

A. Case-Control Studies

a. Greenland, S *et al.* "A case-control study of cancer mortality at a transformer-assembly facility." International archives of occupational and environmental health vol. 66,1 (1994): 49-54

This study is more fully described in the TCE section (above). As it relates to the association between benzene exposure and bladder cancer mortality, the odds ratio was 1.02; 95% CI (0.29, 3.51). Limitations of this study are also discussed above.

b. Gérin, M *et al.* "Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal." American journal of industrial medicine vol. 34,2 (1998): 144-56

This population-based case-control study analyzed the potential association between occupational exposure to various chemicals including benzene and different cancers. Chemists reviewed completed questionnaires to determine what potential exposures the study participants had. 3,370 cases and 533 controls were interviewed. Of those determined to have exposure to benzene (characterized as low, medium, or high exposure), only those with medium exposure showed any increased risk of bladder cancer (OR=1.2; 95% CI 0.7, 2.0). The authors did note that there was a limited number of highly exposed participants and the possibility of the risk of exposure misclassification which would bias the odds ratios towards the null.

c. Hadkhale, Kishor *et al.* "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries." International journal of cancer vol. 140,8 (2017): 1736-1746

This case control study is described in more detail in the PCE section (above). A statistically significant increased risk of bladder cancer was found with high exposure to benzene versus no exposure (HR=1.16; 95% CI 1.04, 1.31). The authors stated that "[t]he study provides evidence of an association between occupational exposure to . . . benzene . . . and bladder cancer risk."

d. Sciannameo, Veronica *et al.* "New insights on occupational exposure and bladder cancer risk: a pooled analysis of two Italian case-control studies." International archives of occupational and environmental health vol. 92,3 (2019): 347-359

Sciannameo *et al.* is more fully described in the PCE section (above). With low exposure to benzene, the odds ratio was 1.08; 95% CI (0.77, 1.52). Exposure to benzene with ever versus never exposure had an odds ratio of 0.99; 95% CI (0.77, 1.29) and with high exposure, an odds ratio of 0.94; 95% CI (0.67, 1.32).

e. Xie, Shuai *et al.* "Occupational exposure to organic solvents and risk of bladder cancer." Journal of exposure science & environmental epidemiology vol. 34,3 (2024): 546-553. doi:10.1038/s41370-024-00651-4

This population-based case control study, also discussed in the PCE section (above), evaluated exposure to benzene and bladder cancer incidence. After adjusting for smoking and other possible confounders, the study found a statistically significant increased risk of 1.63; 95% CI (1.14, 2.32) associated with "ever" exposure of benzene and bladder cancer. The authors noted that though recall bias of the study participants was possible, it would be unlikely that participants were aware of the association between solvent exposure and bladder cancer which lessens the potential impact.

3. Bradford Hill Analysis

A clear association between benzene exposure and bladder cancer is evident based on the epidemiological literature. Therefore, I conducted a Bradford Hill analysis to determine whether a causal relationship between benzene exposure and bladder cancer exists.

i. Strength of association

A significant association between benzene and bladder cancer found in multiple studies –

- Collarile *et al.*, "Residence in Proximity of a Coal-Oil-Fired Thermal Power Plant and Risk of Lung and Bladder Cancer in Northeastern Italy. A Population-based study: 1995-2009". This study found that risk of bladder cancer increased in women 75 years or older (RR=1.94).
- Shala *et al.*, "Exposure to benzene and other hydrocarbons and risk of bladder cancer among male offshore petroleum workers". This prospective case cohort study showed a significant increased risk of bladder cancer in male workers exposed to benzene long term compared to unexposed workers (RR=1.89).
- Hadkhale *et al.*, "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries". This study found a significantly increased risk of bladder cancer in those with high exposure to benzene versus no exposure.
- Xie *et al.*, "Occupational exposure to organic solvents and risk of bladder cancer". This population-based case control study showed a statistically increased risk of bladder cancer in those "ever" exposed to benzene (RR=1.63).

ii. Consistency

Studies finding significant associations between exposure to benzene and risk of bladder cancer were based on separate and unique cohorts. This was also true of studies that found an increased point estimate in risk but was otherwise not significant.

iii. Specificity

Bladder cancer has many potential causes. Notably, Bradford Hill cautions against "over-emphasiz[ing] the importance of" this factor. While specificity may support a finding of causal association, a lack of specificity does not negate it.

iv. Temporality

In studies finding a significant association between benzene and bladder cancer, all cases were exposed to benzene prior to development of bladder cancer.

v. Dose-response

Collarile *et al.*, "Residence in Proximity of a Coal-Oil-Fired Thermal Power Plant and Risk of Lung and Bladder Cancer in Northeastern Italy. A Population-based study: 1995-2009". The risk of bladder cancer was highest during the time period where benzene exposure was highest. Hadkhale *et al.*, "Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries". This case-control study found a dose-response for benzene exposure. Medium and high exposure groups had an increased HR of 1.05; 95% CI (1.00, 1.15) and 1.16; 95% CI (1.04, 1.31), respectively, versus no exposure.

vi. Biological Plausibility

Based on my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

vii. Coherence

Based on my review of the epidemiology literature discussed herein and my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

viii. Experimental evidence

Human experimental evidence is unavailable due to ethical considerations and animal experimental evidence is limited as it relates to this chemical exposure and bladder cancer.

ix. Analogy

Exposure to a known carcinogen (*e.g.*, smoking) increases the risk of certain cancers (*e.g.*, lung cancer). It would therefore reason that exposure to benzene (a known potential carcinogen and found in Camp Lejeune water during the questioned time period) would lead to increased risk of developing and dying from bladder cancer.

Based on the review of the Bradford Hill factors above, I am satisfied to a reasonable degree of scientific certainty that a causal relationship between benzene exposure and bladder cancer exists and that benzene can be a cause for bladder cancer.

D. PEOPLE WHO WORKED AND/OR LIVED AT MCB CAMP LEJEUNE BETWEEN 1953 AND 1987 WERE EXPOSED TO CONTAMINATED WATER THAT IS A CAUSE OF BLADDER CANCER.

1. Cohort Studies

a. Bove, Frank J *et al.* "Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study." Environmental health: a global access science source vol. 13,1 10. 19 Feb. 2014 ("Bove *et al.* 2014a")

Bove *et al.* conducted a retrospective cohort mortality study of Navy and Marine Corps personnel who began military service between April 1975 and December 1985 and were stationed at Camp Lejeune or Camp Pendleton during that period. There were 154,932 Navy and Marine personnel in the Camp Lejeune cohort and 154,969 in the Camp Pendleton cohort. Follow up began on the latter of January 1, 1979 or start of active duty service and ended on date of death or December 31, 2008. At the end of the follow-up period, most cohort members were under age 55. The Camp Lejeune cohort did not have an excess risk for bladder cancer mortality, SMR=0.84; 95% CI 0.42, 1.51, relative to the Camp Pendleton reference group, SMR=1.03; 95% CI 0.56, 1.72.

An internal cohort analysis was also performed to evaluate exposure-response relationships based on cumulative contaminant exposure (no, low, medium and high exposure).

Hazard Ratios for Bladder Cancer Mortality Stratified by Cumulative Exposure to Total Volatile Organic Compounds*		
Low Exposure	***Medium Exposure***	***High Exposure***
HR=0.63; 95% CI 0.06, 6.93	HR=3.33; 95% CI 0.64, 17.37	HR=1.20; 95% CI 0.17, 8.61
**Total Volatile Organic Compounds ("TVOC"): PCE, TCE, benzene, vinyl chloride, and trans- 1,2-dichloroethylene*		

The study's strengths include its large cohort size and minimal rate of loss to follow-up. Limitations include highly variable durations of exposure (length of residence at Camp Lejeune ranged from 3 to 102 months, with an average residence of 19 months) with many people that had short periods of exposure that likely reduced the magnitude of the effects. The authors also noted that exposure misclassification was a "serious limitation" of the study that is likely to bias hazard ratios between Camp Lejeune and Camp Pendleton toward the null. The study was also limited by lack of information about other risk factors (including smoking), small numbers for each specific cause of death due to the healthy veteran effect, and the relatively young age of both cohorts (*i.e.*, most under 55 years old) at the end of follow-up.

There are multiple important points to highlight in this study. First, given the significant latency period for bladder cancer and considering that 90% of bladder cancer diagnoses are in people over age 55, it is not probable that an effect would be found when 97.3% of the cohort is under age 55. Furthermore, this study examined mortality, not incidence. Besides the potential misclassification of cause of death, the cancer-specific mortality with bladder cancer is

approximately 20 percent. Because of this, increased incidence of bladder cancer as a result of exposure at Camp Lejeune may not translate to increased mortality, especially in the short term.

b. Bove, F.J., Ruckart, P.Z., Maslia, M. *et al.* Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. Environ Health 13, 68 (2014) ("Bove *et al.* 2014b")

In 2014, Bove *et al.* also conducted a retrospective mortality study of full-time civilian employees at Camp Lejeune and Camp Pendleton. The cohorts consisted of 4,647 workers and 4,690 workers, respectively, whose on-base employment began between April 1973 and December 1985. The cohorts were followed from the latter of January 1, 1979 or start of employment through date of death or December 31, 2008. The majority of civilian employees were under age 65 at the end of the follow-up period. The Camp Lejeune cohort did not show an elevated risk of bladder cancer, SMR=0.53; 95% CI 0.06, 1.92, relative to the reference group, SMR=0.69; 95% CI 0.19, 1.77. The cohorts examined in this study are significantly smaller than those from Bove *et al.* 2014a, but the studies' strengths and limitations are otherwise similar.

c. ATSDR, Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune, April 2018 ("ATSDR 2018")

In 2018, ATSDR conducted a retrospective cohort morbidity study of 10,655 Camp Lejeune Marines, 2,335 Camp Pendleton Marines, 786 Camp Lejeune civilian employees, and 473 Camp Pendleton civilian employees. Water distribution system models and ground water contamination fate and transport models were used to determine individual contaminant exposure. Civilian employees at Camp Lejeune did not have excess bladder cancer risk relative to Camp Pendleton civilian employees, OR=0.8; 95% CI 0.4, 1.8; however, Marines from Camp Lejeune have excess risk of bladder cancer morbidity when compared against Camp Pendleton Marines, OR=1.64; 95% CI 1.02, 2.64. Authors confirmed reported diagnoses in about half of the Marines and 60% of the civilian cohorts. Small numbers of cases, particularly in the civilian studies, resulted in wide confidence intervals. Additional limitations include potential exposure misclassification and limited information about historical workplaces within Camp Lejeune.

d. Bove, Frank J *et al.* "Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC base Camp Lejeune: a cohort study." Environmental health: a global access science source vol. 23,1 61. 3 Jul. 2024. ("Bove *et al.* 2024a")

Bove *et al.* 2024a is a cohort mortality study of Marines and Navy personnel who were stationed at Camp Lejeune or Camp Pendleton after entering active-duty service between 1975 and 1985. The Camp Lejeune cohort had 154,821 people and the Camp Pendleton cohort had 163,484 people. The investigators separately performed a cohort mortality study of civilians employed full time at Camp Lejeune (7,332 workers) or Camp Pendleton (6,677 workers) between October 1972 and December 1985. Follow-up for both groups ran from the later of January 1, 1979

or the start of employment or active duty service at either base and ended on December 31, 2018 or date of death. Camp Lejeune's Marine/Navy personnel cohort did not have an excess risk of bladder cancer mortality, SMR=0.97; 95% CI 0.74, 1.24; however, the bladder cancer mortality risk ratio for Camp Lejeune vs. Camp Pendleton was 1.02; 95% CI 0.72, 1.45. Civilian employees at Camp Lejeune did not have an excess risk of bladder cancer mortality, SMR=0.85; 95% CI 0.50, 1.34, and had a lower risk ratio than civilian workers at Camp Pendleton, RR=0.65 RR; 95% CI 0.34, 1.24. Strengths of this study include the large cohort size for the Marine/Navy personnel cohorts, long follow-up period with a small percentage lost to follow-up, comparison of demographically and socio-economically similar military bases, and analysis of the civilian cohorts with a majority of workers over age 65 at the end of follow-up. Weaknesses include the use of base location as a proxy for contaminated water exposure and the lack of data on other risk factors.

e. Bove, Frank J *et al.* "Cancer Incidence among Marines and Navy Personnel and Civilian Workers Exposed to Industrial Solvents in Drinking Water at US Marine Corps Base Camp Lejeune: A Cohort Study." Environmental health perspectives vol. 132,10 (2024): 107008. ("Bove *et al.* 2024b")

Bove *et al.* also performed a cohort cancer incidence study in 2024, evaluating cancer incidence in Marines/Navy personnel who entered active-duty service and were stationed at Camp Lejeune (N = 154,821) or Camp Pendleton (N = 163,484) between 1975 and 1985. The authors separately evaluated cancer incidence among civilian full-time employees at Camp Lejeune (N = 6,494) or Camp Pendleton (N = 5,797) between October 1972 and December 1985. Follow-up for all sub-cohorts began on January 1, 1996 and ended on December 31, 2017. Adjusted hazard ratios (aHRs) comparing cancer incidence risk at Camp Lejeune vs. Camp Pendleton were calculated using proportional hazards regression to adjust for sex, race, education, and rank – age was the time variable. The precision of aHRs was using the 95% confidence interval ratio (CIR).

Marines/Navy Personnel		
	Unadjusted HR (95% CI)	**Adjusted HR (95%CI) CIR**
Urinary bladder (malignant & *in situ*)	1.06 (0.93, 1.20)	1.09 (0.95, 1.24) 1.3
Papillary transitional cell carcinoma	1.04 (0.89, 1.21)	1.08 (0.93, 1.26) 1.4
Non-papillary transitional cell carcinoma	1.11 (0.85, 1.44)	1.11 (0.85, 1.46) 1.7
Urothelial	1.06 (0.93, 1.21)	1.09 (0.95, 1.25) 1.3
Civilian Employees		
	Unadjusted HR (95% CI)	**Adjusted HR (95%CI) CIR**
Urinary bladder (malignant & *in situ*)	1.02 (0.75, 1.37)	1.10 (0.81, 1.50) 1.9
Papillary transitional cell carcinoma	0.96 (0.67, 1.37)	1.07 (0.74, 1.56) 2.1
Non-papillary transitional cell carcinoma	1.28 (0.70, 2.34)	1.30 (0.70, 2.40) 3.4
Urothelial	1.04 (0.76, 1.41)	1.13 (0.82, 1.55) 1.9

Among Marines/Naval Personnel, authors noted a monotonic trend for bladder cancer risk by duration at Camp Lejeune.

Cancer outcomes for Marines/Naval Personnel at Camp Lejeune vs. Camp Pendleton stratified by duration at Camp Lejeune			
	Low Duration **aHR (95% CI)**	***Medium Duration*** **aHR (95% CI)**	***High Duration*** **aHR (95% CI)**
Urinary bladder (malignant & *in situ*)	1.02 (0.87, 1.20)	1.18 (0.95, 1.46)	1.20 (0.94, 1.52)
Papillary transitional cell carcinoma	0.99 (0.82, 1.19)	1.25 (0.98, 1.59)	1.19 (0.89, 1.58)
Non-papillary transitional cell carcinoma	1.13 (0.82, 1.56)	1.05 (0.67, 1.65)	1.11 (0.67, 1.82)
Urothelial	1.02 (0.87, 1.20)	1.20 (0.97, 1.48)	1.17 (0.91, 1.50)

It is important to note that sub-stratifying bladder cancer incidence based on histology decreases the power to detect an association. Nevertheless, the point estimates for *overall* incidence of bladder cancer were above 1.0 in both Camp Lejeune cohorts (*i.e.*, Marines/Navy personnel and civilian employees).

2. Bradford Hill Analysis

Epidemiological studies support an association between bladder cancer risk and exposure to PCE, TCE, and/or benzene. I performed a Bradford Hill Analysis supporting a causal relationship between each of these chemicals and bladder cancer. Based on the fact that chemical exposure at Camp Lejeune included all these chemicals, I conducted a Bradford Hill analysis to determine whether a causal relationship between chemical exposure at Camp Lejeune and bladder cancer exists.

i. Strength of association

In the Bove *et al.*2024b study, although not statistically significant, all point estimates for bladder cancer found in both Marine/Navy personnel and civilian employees were greater than 1.0: 1.06 (unadjusted) and 1.09 (adjusted) in Marines/Naval personnel and 1.02 (unadjusted) and 1.10 (adjusted) in civilians.

In the 2018 ATSDR report comparing the same cohorts (Camp Lejeune vs. Camp Pendleton Marines), the odds ratio (OR) for bladder cancer in Camp Lejeune was significantly higher (OR 1.64; 95% CI 1.02, 2.64). This would be interpreted as in those personnel who developed bladder cancer, the odds of exposure to Camp Lejeune chemicals leading to disease was 64 percent. In addition, high exposure (>90th percentile) to PCE in Camp Lejeune vs. Camp Pendleton Marines resulted in an OR of 2.07 (95% CI 1.12, 3.82).

ii. Consistency

The studies by Bove *et al.* as well as the ATSDR 2018 report examining Camp Lejeune vs. Camp Pendleton personnel were consistent in their findings, not only in cases diagnosed with bladder cancer but other cancers/diseases as well.

iii. Specificity

Bladder cancer has many potential causes. Notably, Bradford Hill cautions against "over-emphasiz[ing] the importance of" this factor. While specificity may support a finding of causal association, a lack of specificity does not negate it.

iv. Temporality

The studies by Bove *et al.* specifically examined incidence of and mortality from bladder cancer AFTER exposure at Camp Lejeune.

v. Dose-response

In the 2018 ATSDR report, high exposure (>90th percentile) to PCE in Camp Lejeune vs. Camp Pendleton Marines resulted in an OR of 2.07 (95% CI 1.12, 3.82).

In the Bove *et al.* study, duration of time at Camp Lejeune (low vs. medium vs. high) as a surrogate for dose exposure, there was a longitudinal increase in point estimates for bladder cancer (1.02 vs. 1.18 vs. 1.20, respectively) supporting a dose-response relationship.

vi. Biological Plausibility

Based on my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

vii. Coherence

Based on my review of the epidemiology literature discussed herein and my review of the general causation toxicology reports, I find that this Bradford Hill factor is satisfied.

viii. Experimental evidence

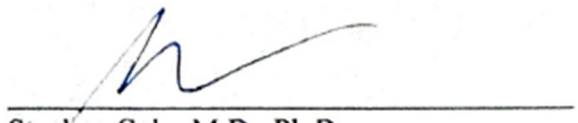
Human experimental evidence is unavailable due to ethical considerations and animal experimental evidence is limited as it relates to this chemical exposure and bladder cancer.

ix. Analogy

Exposure to a known carcinogen (*e.g.*, smoking) increases the risk of certain cancers (*e.g.*, lung cancer). Cigarette smoke contains several known chemicals known to be carcinogenic to humans. This would correlate with contaminated water at Camp Lejeune – *i.e.*, this contaminated water contained PCE, TCE, and benzene, each of which is a known human carcinogen. Regardless of whether the risk of one chemical outweighing the risk of another, the totality of these chemicals in the Camp Lejeune water can be concluded as a cause for bladder cancer development in this population.

Based on the above Bradford Hill Factors, there is sufficient evidence in my opinion that there is a causal relationship between exposure to chemicals at Camp Lejeune and the development of bladder cancer.

Dated: December 9, 2024



Stephen Culp, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Stephen Hembree Culp

I. PERSONAL DATA

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434-243-5874·(fax)
434-924-2224 (Urology Clinic)

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Place of Birth: Greenwood, South Carolina

Dr. Culp UVA Health Video

II. EDUCATION

2006	MS (Epidemiology)	University of Washington School of Public Health Seattle, Washington
2002	MD	Medical College of Virginia of Virginia Commonwealth University Richmond, Virginia
2002	PhD (Pathology)	Medical College of Virginia of Virginia Commonwealth University Richmond, Virginia
1994	BS (Biology)	Emory University. Atlanta, Georgia
1994	BA (Religion)	Emory University Atlanta, Georgia

III. POST-GRADUATE EDUCATION

07/08 – 06/11 Fellow, Urologic Oncology

	University of Texas M.D. Anderson Cancer Center Houston, TX
07/07 - 06/08	Chief Resident, Department of Urology University of Washington School of Medicine Seattle, WA
08/05 - 06/06	Clinical Research Fellow, Department of Epidemiology University of Washington School of Public Health Seattle, WA
01/04 - 06/07	Resident, Department of Urology University of Washington School of Medicine Seattle, WA
07/03 - 12/03	Resident, Department of Surgery University of Washington School of Medicine Seattle, WA
06/02 - 06/03	Intern, Department of Surgery University of Washington School of Medicine Seattle, WA

IV. ACADEMIC APPOINTMENTS

07/24 to present	Professor with Tenure, Department of Urology, University of Virginia, Charlottesville, VA
07/21 to 06/24	Associate Professor with Tenure, Department of Urology, University of Virginia, Charlottesville, VA
07/17 – 06/21	Associate Professor, Department of Urology, University of Virginia, Charlottesville, VA
08/11 – 06/17	Assistant Professor, Department of Urology, University of Virginia, Charlottesville, VA
07/07 – 06/08	Clinical Specialist, Department of Urology, University of Texas M.D. Anderson Cancer Center, Houston, TX

V. CERTIFICATION AND LICENSURE

A. Certification

American Board of Urology 02/2013 #17289 (renewed 2023)

B. Licensure

Virginia 2011-present Permanent 0101249368 (expires 10/31/26)

Texas	2008-2012	Permanent	M9232 (expired)
Washington	2002-2008	Temporary	ML20007178 (expired)

VI. HONORS AND AWARDS

2017	Fellow - Leadership in Academic Matters; University of Virginia (Spring 2017 cohort)
2016	Fellow - American College of Surgeons
2015	Elected to membership in the Urological Research Society
2012	Thelma R. Swortzel Collaborative Research Award – University of Virginia SOM
2009	Selected to participate in the AACR Molecular Biology in Clinical Oncology Workshop; Aspen, Colorado
2008	AUA Foundation Research Scholar (Two year scholarship)
2008	Resident Achievement Award, In-service Examination, Department of Urology, University of Washington School of Medicine
2006	Warren H. Chapman Resident Research Award, Department of Urology, University of Washington School of Medicine
2006	Ansel-Mason Research Scholar, Department of Urology, University of Washington School of Medicine
2006	Gerald P. Murphy Scholar, American Urological Association
2005	NCI Training Grant Recipient, University of Washington School of Public Health
2005	International Volunteers in Urology Traveling Resident Scholar (Cameroon)
1998	Travel Award, Society for Basic Urologic Research
1997	Alpha Omega Alpha, Medical College of Virginia
1997	Award for highest grade in MII microbiology and gastrointestinal courses
1997	Sydney Barham Scholarship, Medical College of Virginia
1996	Summer Research Fellowship, Medical College of Virginia Department of Pathology
1993	Phi Beta Kappa, Emory University

1993 Phi Sigma Honor Society (Biology), Emory University

1993 Theta Alpha Kappa Honor Society (Religious Studies/Theology), Emory University

VII. PROFESSIONAL AFFILIATIONS (INCLUDING OFFICES HELD)

2016 International Bladder Cancer Network
2015 Urological Research Society
2013 Sociétié Internationale d'Urologie
2011 Virginia Urological Society
2011 Mid-Atlantic Section American Urological Association
2009 American Association for Cancer Research
2008 Society for Basic Urologic Research
2008 American Society of Clinical Oncology
2008 Society of Urologic Oncology
2004 American Urological Association
2002 American College of Surgeons

*All active memberships

VIII. RESEARCH ACTIVITIES

A. Areas of Research Interest

CLINICAL

1. **RENAL CELL CARCINOMA**

- Cytoreductive nephrectomy
  - Indications and predictors of its use with targeted and immunotherapy
  - Predictors of survival
- Papillary renal cell carcinoma
  - Incidence and diagnosis
  - Predictors of survival
- Surgical management of renal vein/inferior vena cava thrombus
- Management of localized renal masses – Active surveillance vs. ablation vs. partial nephrectomy vs. radical nephrectomy

2. **BLADDER CANCER**

- Predictors of high vs. low risk muscle-invasive disease and need for neoadjuvant chemotherapy prior to radical cystectomy.
- The role of TMT in treated of patients with muscle-invasive bladder cancer.

3. **PROSTATE CANCER**

- Role of treatment of the primary tumor in metastatic disease
- PET imaging in prostate cancer
- SpaceOAR placement for patients undergoing external beam radiation treatment.

4. **UPPER TRACT UROTHELIAL CARCINOMA**

- Expression patterns of immune regulators in upper tract urothelial carcinoma
- Lynch Syndrome and upper tract urothelial carcinoma

5. PENILE CANCER

- InPACT Trial – The role of surgery alone vs. surgery following neoadjuvant chemoradiation in locally advanced penile cancer.
- Multi-modal management (e.g., Plastic Surgery) of Extramammary Paget disease of the scrotum
- Use of PREVENA™ for wound management in patients undergoing inguinal lymph node dissection

BASIC SCIENCE/TRANSLATIONAL

1. PATIENT DERIVED XENOGRAFT (PDX) PROGRAMS

A. **Renal Cell Carcinoma**

- Established in Fall 2011
- Over 250 patients enrolled.
- Serum and urine acquired both pre- and post-operatively (for future biomarker studies)
- Tumor tissue acquired at time of nephrectomy.
- Over a dozen *in vivo* models and >20 *in vitro* models established representing clear cell, papillary (types 1 and 2), and chromophobe RCC.
- Models can be used to efficiently examine why certain tumors respond to therapy while other do not and, most importantly, why tumors become resistant to currently approved systemic therapy.

B. **Prostate Cancer**

- Established in 2013

- Serum and urine acquired both pre- and post-operatively (for future biomarker studies)
- Tumor tissue acquired at time of prostatectomy (either primary or lymph node)

C. **Penile Cancer**

- Established in 2012
- Serum and urine acquired both pre- and post-operatively (for future biomarker studies) as well as swabs pre-operatively (Buccal and tumor) to assess HPV status.
- Tumor tissue acquired at time of penectomy (either primary or inguinal/pelvic lymph node)
- Three models established.

2. PROSTATE CANCER BIOMARKER AND RISK ASSESSMENT

A. **HULLK**

- Collaboration with Dr. Dan Gioeli
- Detection of HULLK (non-coding RNA) in urine from prostate cancer patients
- Correlation with tumor stage and grade (high vs. low risk disease)

B. **Nuclear Structure in prostate cancer and correlation with disease**

- Analysis of nuclear structure from histology in radical prostatectomy specimens
- Correlation of nuclear structure with disease aggressiveness (high vs. low risk)
- Ability to identify nuclear patterns on prostate biopsy (Future)

B. Current Projects

Clinical/Translational Trials at UVA

ACTIVE

1. Detection of HULLK in Prostate Cancer and its use in Risk Stratification
   IRB # 21797
   Role: Principal Investigator

2. International Penile Advanced Cancer Trial (International Rare Cancers Initiative Study)
   IRB # 21648
   Role: Principal Investigator (local site)

3. Risk Classification of Prostate Cancer Based on Nuclear Structure from Histopathology Images
   HSR # 220064
   Role: Co-Investigator

4. A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN*(rAd-IFN/Syn3) Administered Intravesically to Patient with High Grade, BCG unresponsive Bladder Cancer (NMIBC)
   IRB # 19217
   Role: Sub-investigator

5. A Pilot Study to Assess the Combination of High-Dose Conformal Radiation Therapy (HDCRT) and Pembrolizumab in Modulating Local and Systemic T-cell Responses in Advanced Malignancies
   IRB # 18488
   Role: Sub-Investigator

6. Partners in Discovery for Total Cancer Care at UVA
   IRB # 18445
   Role: Sub-Investigator

7. Partial Nephrectomy and Small Renal Mass Database
   IRB # 15260
   Role: Sub-investigator

8. Identification of Biomarkers in Diseased Human Tissues
   IRB # 13310
   Role: Sub-Investigator

CLOSED

1. A Phase I/II Open Label, Multi-Center, Non-Randomized Study of [F-18]SMS-5368 Positron Emission Tomography (PET) in Prostate Cancer Patients
   HSR # 210451
   Role: Principal Investigator (local site)

2. Uretero-intestinal Anastomosis Identification with India Ink
   IRB # 21312
   Role: Sub-Investigator

3. A Study to Evaluate Inter-Observer Variability and Cancer Detection rates with Cystoscopy Performed by Physicians and Physician Extenders
   IRB # 17573
   Role: Sub-Investigator

4. A pilot study to assess the combination of stereotactic body radiation therapy and CDX-1127 in modulating local and systemic T-cell responses against prostate cancer.
   IRB # 17456
   Role: Sub-Investigator

5. Circulating Tumor Cells in Genitourinary Cancers
   IRB # 18405

Role: Principal Investigator

6. An International Phase 3 Randomized Trial of Autologous Dendritic Cell Immunotherapy (AGS-003) Plus Standard Treatment of Advanced Renal Cell Carcinoma (ADAPT)
   IRB # 17031
   Role: Sub-Investigator

7. Exploratory Research in Prostate Cancer
   IRB # 16847
   Role: Principal Investigator

8. Exploratory Research in Penile Cancer
   IRB # 16021
   Role: Principal Investigator

9. Exploratory Research in Renal Cell Carcinoma
   IRB # 15908
   Role: Principal Investigator

10. Population-Based Analysis of Disease Progression and Patient Survival with Robotic versus open resection in Urothelial Carcinoma
    IRB # 19209
    Role: Principal Investigator

11. An Exploratory, Phase 0, Open Label, Single-Center, Non-Randomized Study of [F-18]SMS-5368 Positron Emission Tomography (PET) in Normal and Prostate Cancer Subjects
    IRB # 20966
    Role: Principal Investigator

12. Identifying Patients with Improved Outcomes with Multimodal Therapy versus Radical Cystectomy: A Population-based analysis.
    IRB # 19960
    Role: Principal Investigator

13. The effect of pre-treatment biopsy for non-neoplastic renal disease vs no biopsy on estimated glomerular filtration rate in patients with small renal mass: a single-center, single-blinded, randomized, parallel group clinical trial."
    IRB # 19081
    Role: Sub-Investigator

14. An Open Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non Muscle-Invasive Carcinoma in Situ (CIS) and /or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG)
    IRB # 18573
    Role: Sub-Investigator

15. The Prognostic Significance of a New Pathologic Sub-classification of Papillary Renal Carcinoma.
    IRB # 12618
    Role: Co-Investigator

16. Evaluation of Survival in Patients with Metastatic Prostate Cancer Undergoing Treatment of the Primary Tumor
    IRB # 16946
    Role: Principal Investigator

17. Protocol Number rAd-IFN-CS-002 A Phase II, Randomized, Open Label, Parallel Arm Study to Evaluate the Safety and Efficacy of rAd-IFN/Syn3 Following Intravesical Administration in Subjects with High Grade, BCG Refractory or Relapsed Non-Muscle Invasive Bladder Cancer (NMIBC)
    IRB # 16757
    Role: Sub-Investigator

18. Hypofranctionated Post-Prostatectomy Radiotherapy For Prostate Cancer to Reduce Toxicity and Improve Patient Convenience: A Phase I/II Trial
    IRB # 16604
    Role: Sub-Investigator

19. Exploratory Research in Renal Cell Carcinoma
    IRB # 15908
    Role: Principal Investigator

C. Research Collaboration/Team Science

CURRENT

1. Daniel Gioeli, Ph.D. (Microbiology, Immunology, and Cancer Biology)

- Prostate cancer

    - Detection of HULLK in urine as a biomarker for prostate cancer and its use in risk stratification
    - Assessment of nuclear morphology to predict prostate cancer aggressiveness (in collaboration with Gustavo Rohde, Ph.D. as well)

2. Tracey Krupski, M.D., M.P.H. (Urology)

- Bladder cancer

- Assessing differences in disease recurrence and patient survival in robotic vs. open radical cystectomy for muscle-invasive bladder cancer
- Optimizing the use of tele-cystoscopy in diagnosis and surveillance of bladder cancer.
- Fluorescent angiography
- Development of ORCAS – Optimizing Radical Cystectomy Assessment and Surgery

- Kidney cancer

  - Racial and gender variation in patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma.

3. Timothy Showalter, M.D. (Radiation Oncology)

- Bladder cancer

  - Defining populations that may benefit from trimodal therapy of bladder cancer (debulking, radiation, and chemotherapy) rather than radical cystectomy.

PAST

1. Helen Cathro, M.B.Ch.B., M.P.H. (Pathology)

- Papillary renal cell carcinoma

  - Better define subtypes of papillary RCC and incidence/prognosis based on subtype.

- Penile cancer

  - Histologic and Immunohistochemical Assessment of Penile Carcinomas in a North American Population

- Upper tract urothelial carcinoma

  - Expression patterns of immune regulators in upper tract urothelial carcinoma
  - Lynch Syndrome and upper tract urothelial carcinoma

- Other

  - The association of Quilty effect with clinically significant acute T-cell and antibody-mediated rejection

3. Kiel Neumann, Ph.D. (Radiology and Medical Imaging)

- Prostate cancer

- The use of PET (Positron Emission Tomography) in prostate cancer and identification of novel F-18 tracers

4. Kimberly Kelly, Ph.D. (Biomedical Engineering)

- PET-imaging in resistance to targeted therapy in RCC in human PDX models.
  - Examined PET-imaging using probes to VCAM to identify *de novo* or acquired resistance to targeted therapy in tumors prior to clinical progression.

- Evaluation of Hornerin on progression and resistance to targeted therapy in RCC.
  - Examine the effects of Hornerin (a S100 fused-type protein highly expressed in RCC) on progression and targeted therapy resistance in RCC.

5. **John Bushweller, Ph.D. (Chemistry) and Daniel Gioeli, Ph.D. (Microbiology, Immunology, and Cancer Biology)**

- Characterization of effects of CBFB/RUNX inhibitors on renal cell carcinoma
  - In vitro and in vivo effects of inhibiting the CBFB/RUNX pathway in papillary RCC PDX tumor models.

6. John Herr, Ph.D. (Cell Biology and Biomedical Engineering)

- SAS1B in renal cell carcinoma
  - Use of monoclonal antibodies to SAS1B to develop cytotoxic therapy in papillary RCC PDX tumor models.

7. Song Hu, Ph.D. (Biomedical Engineering)

- Photoacoustic microscopy and the mouse ear RCC xenograft model
  - Delineate changes in tumor microvasculature with tumor growth and targeted therapy.
  - Examine vascular anatomy and hemodynamic function (hemoglobin concentration and oxygenation and blood flow) and oxygen metabolism.

8. Hui Li, Ph.D. (Pathology)

- Identifying and characterizing chimeric RNAs as potential biomarkers in men with prostate cancer

9. Shayn Pierce-Cottler, Ph.D. (Biomedical Engineering)

- Development of mechanism to visualize in vivo tumor vessel formation and changes.

- Dorsal skinfold window chamber

IX. TEACHING ACTIVITIES

A. Clinical Teaching (in ward, clinic, OR)

- Resident Clinic – Urology (2014 to 2022) 15-20 days (8 hours) per year.
- Attending rounds – Urology ward (2011 to present) 6 weeks per year.
- Main OR – Urology (2011 to present) 8 times per month.
- GUOR – Urology (2011 to present) 4 times per month.

X. TEACHING ACTIVITIES OTHER THAN CLASSROOM OR CLINICAL, INCLUDING TEACHING OF UNDERGRADUATE (PRE-BACCALAUREATE), GRADUATE, POSTDOCTORAL STUDENTS AND CONTINUING EDUCATION MEDICAL STUDENTS.

A. Conferences, Grand Rounds, Journal Clubs, etc.

Resident Education (Urology, University of Virginia)

1. Didactic talks (one hour each)

- August 2011 Testicular cancer
- September 2011 Hereditary Renal Cell Carcinoma
- October 2011 Low-grade Transitional Cell Carcinoma of Bladder
- April 2012 Adverse features of Renal Cell Carcinoma
- September 2012 Penile Cancer: Diagnosis and Management
- April 2013 Prostate Specific Antigen and Prostate Cancer
- May 2013 Working with SEER
- September 2013 Renal Cell Carcinoma – Workup and Management
- June 2014 Testicular Cancer – Biology and Clinical Management
- April 2015 Advanced Renal Cell Carcinoma
- November 2024 Penile and Urethral Cancer

2. Monthly Journal Club (Urology)

3. Culp Teaching Rounds (Jan 2019 to March 2020)

   Dedicated 1-hour weekly teaching rounds to rotating medical students and Urology residents (those who are available). Unfortunately, discontinued with onset of COVID.

4. Weekly resident educational conference

*Beginning in Summer 2014, resident teaching conference format changed to resident led participation. I am involved in proctoring conferences dealing with urologic oncology as well as review for in-service exam. Since 2014, proctor and assist in approximately 5 conferences per year.

5. Department of Urology Grand Rounds (Sept 2020 to present) – Organizer

   Responsible for UVA Urology monthly grand rounds in inviting speakers from both within and outside UVA, organizing the meeting, and overseeing CME accreditation.

Didactic Presentations during Post-graduate Training

- Culp SH, "Prostate Cancer Chemoprevention: 5-α reductase inhibitors ARE appropriate agents to consider". Department of Urology, UT M.D. Anderson Cancer Center, January 2011.
- Culp SH, "Penile Cancer: Epidemiology and Risk Factors". Department of Urology, UT M.D. Anderson Cancer Center; November 2009.
- Culp SH, "Testicular Cancer: Epidemiology, Risk Factors, and Staging". Department of Urology, UT M.D. Anderson Cancer Center; September 2009.
- Culp SH, "Robotic Prostatectomy: Is it better?" Department of Urology, UT M.D. Anderson Cancer Center; March 2009.
- Culp SH, "Finasteride and Prostate Cancer". Department of Urology, UT M.D. Anderson Cancer Center; January 2009.
- Culp SH, "Renal Cell Carcinoma: Adverse Features". Department of Urology, UT M.D. Anderson Cancer Center; October 2008.
- Culp SH, "Bent but not Broken: Peyronie's Disease and Its Management". Department of Urology, University of Washington; March 2007.
- Culp SH, "Hereditary Renal Cell Carcinoma". Department of Urology, University of Washington; March 2006.
- Culp SH, "Renal Trauma: Diagnosis and Management". Multidisciplinary Trauma Conference, Harborview Medical Center, Seattle, WA; June 2005.
- Culp SH, "Testosterone and Prostate Cancer". Department of Urology, University of Washington; March 2005.

XI. OTHER PROFESSIONAL ACTIVITIES (BOARDS, EDITORSHIPS, ETC.)

Editorial Board

- Annals of Surgical Oncology (08/2015 to 07/2021)
- Guest Editor – Frontiers in Oncology (2019) - *Optimizing Local Therapy for High-Risk Prostate Cancer: Evidence and Emerging Options*
- Review Editor – Editorial Board of Genitourinary Oncology (specialty section of Frontiers in Oncology) (10/22 to present)

Ad Hoc Reviewer

- Journal of Urology
- Annals of Surgical Oncology
- British Journal of Urology
- European Urology
- CANCER
- Urologic Oncology: Seminars and Original Investigation
- Urology
- World Journal of Urology

XII. CLINICAL ACTIVITIES

1. **Medical Director** November 2017 to June 2024.

    a. Department of Urology – Fontaine 500
    b. Department of Pelvic Medicine – Fontaine 500

Clinical Productivity Summary

Clinical Activity (WRVU's)

Fiscal Year 2020: 2,291
Fiscal Year 2021: 3,033
Fiscal Year 2022: 2,877
Fiscal Year 2023: 3,182
(3 Sessions a week, 11-14 patients per session, includes clinic procedures, Consults)

Operative Activity: Main OR (WRVU's)

Fiscal Year 2020: 1,414
Fiscal Year 2021: 1,922
Fiscal Year 2022: 1,766
Fiscal Year 2023: 1,639
(Open Major Cases)

Operative Activity: Endoscopic or GUOR (WRVU's)

Fiscal Year 2020: 577
Fiscal Year 2021: 556
Fiscal Year 2022: 373
Fiscal Year 2023: 609
(Minor, endoscopic procedures, or same day surgeries)

	FY20	FY21	FY22	FY23
Actual Work RVUs (At Proposed 65% Clinical Effort)	4,282	5,511	5,016	5,430
50th Percentile Benchmark (At 65% Clinical Effort)	5,606	5,899	6,229	5,538

XIII. SCHOOL, UNIVERSITY, UVA HOSPITALS, DEPARTMENTS, NATIONAL, AND STATE COMMITTEES & COUNCILS

A. School of Medicine

2015 to 2021 — SOM Bylaws Committee
Chair – 2020 to 2021

2014 to 2019 — Academic Standards and Achievement Committee
Vice-Chair – 2014 to 2019

2021 to present — Lead – SOM Faculty Senate. Co-organizer of SOM General Faculty Meetings

B. University

2017 to present — University Faculty Senate Member (4 year term)

- 2017-18 — Collaboration, Communication, & Engagement Committee (University Faculty Senate)
- 2018-19 — Faculty Recruitment, Retention, Retirement, and Welfare Committee (Faculty Senate)
- 2019 to present — Faculty Grievance Committee (Faculty Senate)

C. UVA Hospitals

November 2017 to June 2024 – Medical Director

- Department of Urology – Fontaine 500
- Department of Pelvic Medicine – Fontaine 500

D. Department

2014 to 2024	Program Evaluation Committee, Department of Urology
2020 to present	Organizer for Monthly Department of Urology Grand Rounds
2021 to present	Program Director, Urologic Oncology Fellowship

E. National

2016 to present	North American Surgical Oversight Committee for InPACT (international penile cancer) Trial

F. International

2020 – 2022	Organizer and host for the annual meeting of the Urological Research Society (Charlottesville, Virginia) held October 2022.

G. Study Section Review Panels

Congressionally Directed Medical Research Programs (CDMRP) – Department of Defense

1. Peer Reviewed Cancer Research Program (PRCRP) Kidney Cancer – November 2016 – Reston, Virginia
2. PRCRP Kidney Cancer – February 2018 – Reston, Virginia
3. PRCRP Kidney Cancer – December 2018 (Co-Chair) – Baltimore, Maryland
4. PRCRP Bladder Cancer – November 2019 – Reston, Virginia
5. PRCRP Bladder Cancer – October 2020 – Virtual
6. PRCRP Kidney Cancer – November 2020 - Virtual
7. PRCRP Kidney Cancer – September 2021 (Chairperson) – Virtual
8. PRCRP Bladder Cancer – May 2022 (Chairperson) – Virtual
9. PRCRP Kidney Cancer – December 2022 – Virtual
10. PRCRP Prostate Cancer – October 2023 (Chairperson) – Virtual
11. PRCRP Kidney Cancer – December 2023 (Chairperson) - Virtual
12. PRCRP Kidney Cancer – November 2024 (Chairperson) - Online

XIV. FINANCIAL RESOURCES (GRANTS AND CONTRACTS)

A. Federal

i. Awarded

Title: **Optimizing Treatment Decision Making for Patients with Localized Renal Masses** (Lobo/Culp MPIs)

Major Goals: The primary goal of our study is to identify specific management plans that can be individualized for a patient with a localized renal mass (LRM). We will create an internet-based database shared between three different major academic hospitals. We will collect information about the health of the patient, how good their kidney function is, and the details of the LRM. We will develop a set of rules for management of a LRM using a Markov decision process model and real-world patient information. We will then use this model to identify treatment decisions that are in line with patient-driven goals, including what is best for their quality of life, and approaches that minimize health care cost. Our work will enable patients and their doctors to participate in a shared decision making process. We will create a web-based tool and assess the feasibility of community urologists helping with gathering patient information and collaboration to optimize patient management (i.e., community versus academic setting).

Status of Support: Awarded
Project Number: 1R01CA284057
Name of PD/PI: Lobo, Jennifer; Culp, Stephen H.
Source of Support: NIH/NCI
Primary Place of Performance: University of Virginia
Project/Proposal Start and End Date: 7/1/2023 – 6/30/2027.
Total Award Amount (including Indirect Costs): $1,639,122

Person Months (Calendar/Academic/Summer) per budget period – 1.2 calendar

Title: **Therapeutic drug targeting using ex vivo cultures from prostate cancer patients**

1R01CA282472-01A1 PI: Bushweller

Major goals: The development of resistance to current therapeutic approaches for the treatment of prostate cancer is common, leading to poorer patient outcomes, so there is a clear need for new therapeutic approaches. The transcription factor ERG is a driver in approximately half of prostate cancers. Transcription factors, proteins which bind to DNA and regulate gene expression, have traditionally been viewed as very challenging targets for drug development. The Bushweller lab has developed a small molecule inhibitor of ERG binding to DNA that is potent and specific, making it a strong candidate for use in prostate cancer. The grant will support further optimization of the inhibitor, evaluation of its functional effects on gene expression, and in vivo testing in mice to establish its potential clinical utility

Status of Support: Awarded
Project Number: 1R01CA282472-01A1
Name of PD/PI: Bushwell, John; Gioeli Daniel. Collaborator – Culp Stephen
Source of Support: NIH/NCI
Primary Place of Performance: University of Virginia
Project/Proposal Start and End Date: 7/1/2024 – 6/30/2029.
Total Award Amount (including Indirect Costs): $3,300,00

Person Months (Calendar/Academic/Summer) per budget period – 0.3 calendar

B. Industry

i. Completed

Title: **A Phase I/II Open Label, Multi-Center, Non-Randomized Study of [F-18]SMS-5368 Positron Emission Tomography (PET) in Prostate Cancer Patients**

Major Goals: The major goals of this project are to evaluate the ability of [F-18]SMS-5368 PET/CT to identify sites of disease in patients with biochemical recurrence of prostate cancer and to evaluate the accuracy of [F-18]SMS-5368 PET/CT to detect extra-prostatic disease in patients with Unfavorable Intermediate (UI) and High Risk (HR) Prostate Cancer. Further, in all patients, to assess the safety of [F-18]SMS-5368.

Project Number: HSR210451
Name of PD/PI: Culp, Stephen H.
Source of Support: SIEMENS PETNET
Primary Place of Performance: University of Virginia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 3/15/2022 – 7/15/2023.
Total Award Amount (including Indirect Costs): $509,074
Person Months – 0.96 calendar

Title: **An Exploratory, Phase 0, Open Label, Single-Center, Non-Randomized Study of [F-18]SMS-5368 Positron Emission Tomography (PET) in Normal and Prostate Cancer Subjects**

Major Goals: The major goals of this project were to evaluate the ability of [F-18]SMS-5368 PET/CT to identify sites of disease in patients with biopsy-proven prostate cancer (n=6) and compare with normal subjects (n=4). In addition, the safety and dose assessment of the tracer molecule was assessed.

Project Number: IRB-HSR # 20966
Name of PD/PI: Culp, Stephen H.
Source of Support: SIEMENS PETNET
Primary Place of Performance: University of Virginia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/5/2018 – 12/20/2019.
Total Award Amount (including Indirect Costs): $169,689
Person Months – 0.5 calendar

C. Other

1. Training grants

- July 2008 to June 2010 - Ruth L. Kirschstein National Research Service Award (Grant 5 T32 CA079449-09)
- June 2005 to June 2006 - Ruth L. Kirschstein National Research Service Award (Grant 5 T32 CA09168)

2. Institutional awards

- University of Virginia School of Medicine Transformative, Collaborative Science Pilot Grant
  Small Molecule Inhibitors of the ERG/RUNX Signaling Axis for Prostate Cancer
  Feb 2015 to July 2016
  $50,000
  Role: Co-investigator with Drs. John Bushweller, Daniel Gioeli, and Michael Weber.

- University of Virginia Research and Development Award
  The Dynamics of Pro-Survival Signaling and Microvascular Adaptation with Targeted Treatment of Renal Cell Carcinoma
  August 2014 to July 2015
  $25,000
  Role: Co-Principal Investigator with Dr. Song Hu (Department of Biomedical Engineering)

- University of Virginia Cancer Center Pilot Project
  The Urokinase-type Plasminogen Activator System and its Role in Progression and Therapy Resistance in Renal Cell Carcinoma and Pancreatic Adenocarcinoma
  June 2013 to May 2014
  $50,000
  Role: Co-Principal Investigator with Drs. Todd Bauer and Tom Parsons

- University of Virginia Cancer Center Pilot and Developmental Grant
  The Role of RalA and Hypoxia Signaling in Targeted mTOR Inhibition in Renal Cell Carcinoma Therapy
  April 2012 to March 2013
  $25,000
  Role: Co-Principal Investigator with Dr. Michael Harding

- Thelma R. Swortzel Collaborative Research Award (2012)
  TNF and NFkB Signaling in Targeted Therapy Resistance in Renal Cell Carcinoma
  August 2012 to February 2014
  $50,000
  Role: Co-Principal Investigator with Dr. Shayn Peirce-Cottler (Department of Biomedical Engineering).

XV. PAPERS PUBLISHED OR IN PRESS

A. Peer Reviewed

1. Yeaman C, Ignozzi G, Kazeem A, Isharwal S, Krupski TL, **Culp SH**. Impact of SPY Fluorescence Angiography on Incidence of Ureteroenteric Stricture after Urinary Diversion. J *Urol*. 2024 Dec;212(6):844-850. PMID: 39162209.
   Dr. Culp provided guidance of idea, clinical participation, and manuscript review.

2. Kazeem AO, Hasken W, Sims T, **Culp SH**, Krupski SH, Lobo JM. Patient Satisfaction with a Novel Tele-Cystoscopy Model: Expanding Access to Bladder Cancer Surveillance for Rural Patients. *Telemed Rep*. 2024 Aug 5;5(1):229-236. PMID: 39143957.
   Dr. Culp provided guidance of idea and manuscript review

3. Qui J, Ballantyne C, Lange M, Kennady E, Yeaman C, **Culp S**, Schenkman N, Lobo J*. Comparison of Microwave Ablation and Partial Nephrectomy for T1a Small Renal Masses. *Urologic Oncology: Seminars and Original Investigations*. 2023. Aug 17; PMID: 37598044.
   Cited 0 times. Rank 19 of 108 Urology journals.
   Dr. Culp provided guidance of idea, clinical participation, and manuscript review.

4. Hasken W, Sun F, Mithqal A, **Culp S**, Isharwal S*. Primary Neuroendocrine Prostate Cancer with Penile Metastasis. *Radiol Imaging Cancer* 2023. May;5(3). PMID 37144976. PMCID: PMC10240242.
   Cited 0 times. Rank 86 of 325 Radiology journals.
   Dr. Culp provided guidance of idea and manuscript review.

5. Tuong MN, Prillaman GE*, **Culp SH**, Nelson M, Krupski TL, Isharwal S. India Ink Tattooing of Ureteroenteric Anastomoses. *Tomography* 9(2), 449-458. PMID 36960996. PMCID: PMC10037650.
   Cited 0 times. Rank 87 of 321 Radiology journals.
   Dr. Culp provided guidance of idea, surgical participation, review of data, and manuscript review.

6. Yeaman CT*, Winkelman A, Maciolek K, Tuong M, Nelson P, Morris C, **Culp S**, Isharwal S, Krupski TL. Impact of Radiation on the Incidence and Management of Ureteroenteric Strictures: A Contemporary Single Center Analysis. *BMC Urol* 2021 Aug 4;21(1):101. PMID: 34348684. PMCID: PMC8336081.
   Cited 2 times. Rank 42 of 108 Urology journals.
   Dr. Culp provided guidance of idea, review of data, and manuscript review.

7. Lobo JM*, Erdogan SA, Berg BP, Kang H, Clements MB, **Culp SH**, Krupski TL. Provider Scheduling to Maximize Patient Access. *Urology Practice* 2020/9;7(5):335-341.
   Cited 1 time. Rank 72 of 108 Urology journals.
   Dr. Culp provided guidance of idea, review of data, and manuscript review.

8. Zaorsky NG, Spratt DE, Kishan AU, **Culp SH**, Showalter TN*. Editorial: Optimizing Local Therapy for High-Risk Prostate Cancer: Evidence and Emerging Options. *Frontiers Oncology* 2020 Aug 27;10:1616. PMID: 32984028. PMCID: PMC7481351
   Cited 1 time. Rank 80 of 369 Urology journals.
   Dr. Culp contributed to guidance of idea, review of data, and manuscript review.

9. Clements MB*, Abdall B, **Culp SH**, Costabile RA, Krupski TL. Prostate Cancer Characteristics in US Preventive Services Task Force Grade D Era: A Single-Center Study and Meta-Analysis. *Urol Int.* 2020;104(9-10):692-698. PMID: 32759606.
   Cited 2 times. Rank 46 of 108 Urology journals.
   Dr. Culp provided guidance of idea, review of studies, and manuscript review.

10. Lobo JM*, Horton B, Jones RA, Tyson T, Hill-Collins P, Sims T, Rueb JJ, Corey T, Rheuban K, Battle P, Beller H, Schenkman NS, **Culp SH**, Krupski TL. Blinded Comparison of Clarity, Proficiency and Diagnostic Capability of Tele-Cystoscopy Compared to Traditional Cystoscopy, a Pilot Study. *J Urol*. 2020. April 24. PMID: 32330408.
    Cited 7 times, Rank 3 of 108 Urology journals.
    Dr. Culp provided data acquisition, participation in video sessions, manuscript review, and supervision.

11. McIntosh AG, Umbreit EC, Holland L, Gu, C, Tannir NM, Matin, SF, Karam JA, **Culp SH^,** Wood CG*^. Optimizing patient selection for cytoreductive nephrectomy based on outcomes in the contemporary era of systemic therapy. Cancer 2020 Sep 1:126(17):3950-60. PMID: 32515845.
    ^Co-senior authors.
    Cited 37 times. Rank 29 of 369 Oncology journals.
    Dr. Culp provided data analysis, manuscript preparation and review, and supervision.

12. Ju JY, Mills AM, Mahadevan MS, Fan J, **Culp SH**, Thomas MH, Cathro HP*. Universal Lynch Syndrome Screening Should be Performed in All Upper Tract Urothelial Carcinomas. Am J Surg Pathol. 2018 Nov; 42(11):1549-1555. PMID: 30148743.
    Cited 56 times. Rank 8 of 204 Pathology journals.
    Dr. Culp provided data analyses, clinical input, and editing of manuscript.

13. Clements MB, Krupski, TL, **Culp, SH***. Robotic-Assisted Surgery for Upper Tract Urothelial Carcinoma: A Comparative Survival Analysis. *Ann Surg Oncol*. 2018 June 14. PMID: 29948423.
    Cited 28 times, Rank 50 of 492 Surgery journals.

14. **Culp SH***. Prostatic Artery Chemoembolization - A Viable Management Option for Men Diagnosed with Prostate Cancer?. Invited commentary - *J of Vasc Interv Radiol*. 2018 Mar: 29(3):306. PMID: 29455873.
    Cited 6 times. Rank 73 of 321 Radiology journals
    Invited commentary.

15. Song J*, Wang F, Yang, X, Ning B, Harp MG, **Culp SH**, Hu S, Huang P, Nie L, Chen J, Chen X. Gold Nanoparticle Coated Carbon Nanotube Ring with Enhanced Raman Scattering and Photothermal Conversion Property for Theranostic Applications. *J Am Chem Soc*. 2016 Jun 8:138(22):7005-15. PMID: 27193381.
    Cited 199 times, Rank 12 of 949 Chemistry journals.
    Dr. Culp performed *in vivo* experiments of mouse tumor ear injections and analysis.

16. **Culp SH***. Cytoreductive Nephrectomy and its Role in the Present-day period of Targeted Therapy. *Therapeutic Advances in Urology*. 1-11. 2015. Invited review.
    Cited 22 times, Rank 30 of 108 Urology journals.

17. **Culp SH*** and Pettaway CA. Penile Cancer: New Insights into the "Way Forward" for this Rare Disease. *J Urol*. 2015 Feb;193(2):394-5. PMID: 25447102. Invited editorial.
    Cited 1 time, Rank 3 of 108 Urology journals.

18. Jensen D, Patel MS, **Culp SH***. Penetrating Scrotal Trauma: A Case Report and Brief Management with Literature Review. *J Trauma Treat* 2014, 3:205.
    Cited 0 times, Rank n/a

19. Patel MS, Jensen D, **Culp SH***. Traumatic Penile Amputation: A Case Report and Acute Management. *J Trauma Treat* 2014, 3:210.
    Cited 4 times, Rank n/a

20. **Culp SH*.** Reconciling the Use of Cytoreductive Nephrectomy in the Targeted Therapy Era. *Eur Urol.* 2014 Jul 4. PMID: 25001889. Invited editorial.
    Cited 1 times, Rank 1 of 108 Urology journals.

21. **Culp SH***, Schellhammer PF, Williams MB. Might Patients Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor ? A SEER-Based Study. *Eur Urol.* 2014 Jun;65(6):1058-66. PMID: 24290503.
    Cited 459 times, Rank 1 of 108 Urology journals.

22. **Culp SH***, Karam JA, Wood CG. Population-Based Analysis of Factors Associated with Survival in Patients Undergoing Cytoreductive Nephrectomy in the Targeted Therapy Era. *Urologic Oncology: Seminars and Original Investigations.* 2014 Apr 4. PMID: 24709415
    Cited 40 times, Rank 19 of 108 Urology journals.

23. Mentrikoski MJ, Stelow EB, **Culp SH**, Frierson HF, Cathro HP*. Histologic and Immunohistochemical Assessment of Penile Carcinomas in a North American Population. *American Journal of Surgical Pathology*. 2014 Oct;38(10):1340-8. PMID: 25210933
    Cited 32 times, Rank 8 of 204 Pathology journals.
    Dr. Culp provided data analyses and editing of manuscript.

24. **Culp SH**, Dickstein RJ, Grossman HB, Pretzsch SM, Siefker-Radtke A, Millikan RE, Navai N, Wszolek MF, Kamat AM, Dinney CPN*. Refining Patient Selection for Neoadjuvant Chemotherapy Prior to Radical Cystectomy. *J Urol.* 2014 Jan;191(1):40-7. PMID: 23911605.
    Cited 184 times, Rank 3 of 108 Urology journals.

25. Burris MB, Cathro HP, Kowalik CG, Jensen D, **Culp SH**, Steers WD, Krupski TL*. Lower Urinary Tract Symptom Improvement after Retropubic Prostatectomy Correlates with Degree of Prostatic Inflammation. *Urology*. 2013 Nov 15. PMID: 24246320.
    Cited 9 times, Rank 38 of 108 Urology journals.
    Dr. Culp provided data analyses and editing of manuscript.

26. Margulis V*, Shariat SF, Rapoport Y, Rink M, Sjoberg D, Tannir NM, Abel EJ, **Culp SH**, Tamboli P, Wood CG. Development of Accurate Models for Individualized Prediction of Survival After Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma. *Eur Urol.* 2012 Nov 23. PMID: 23273681.
    Cited 75 times, Rank 1 of 108 Urology journals.
    Dr. Culp was instrumental with data collection and initial analysis.

27. Pirani Y*, Talner LB, **Culp SH**. Delayed Diagnosis of Ureteral Injury After Gunshot Wound to Abdomen. *Curr Probl Diagn Radiol.* 2012 Jul;41(4):138-9. PMID: 22607930.

Cited 4 times, Rank 193 of 321 Radiology journals.
Dr. Culp provided feedback regarding urological care.

28. Abel EJ, Carrasco A, **Culp SH**, Matin SF, Tamboli P, Tannir NM, Wood CG*. Limitations of Preoperative Biopsy in Patients with Metastatic Renal Cell Carcinoma: Comparison to Surgical Pathology in 405 Cases. *BJU Int.* 2012 Apr 13. PMID: 22503066.
Cited 75 times, Rank 6 of 108 Urology journals.
Dr. Culp provided data analyses and editing of manuscript.

29. Abel EJ^, **Culp SH**^, Tannir NM, Tamboli P, Matin SF, Wood CG*. Early Primary Tumor Size Reduction is an Independent Predictor of Improved Overall Survival in Metastatic Renal Cell Carcinoma Patients Treated with Sunitinib. *Eur Urol* 2011 Jul 14. PMID 21784574. ^Co-first authors.
Cited 82 times, Rank 1 of 108 Urology journals.

30. Chapin BF, Delacroix SE Jr, **Culp SH**, Gonzalez GM, Tannir NM, Jonasch E, Tamboli P, Wood CG*. Safety of Presurgical Targeted Therapy in the Setting of Metastatic Renal Cell Carcinoma. *Eur Urol* 2011 May 25. PMID: 21621907.
Cited 103 times, Rank 1 of 108 Urology journals.
Dr. Culp provided data collection, data analyses, and editing of manuscript.

31. Richey SL^, **Culp SH**^, Jonasch E, Matin SF, Wood CG, Tannir NM*. Reply to Benefit of cytoreductive nephrectomy in metastatic RCC: do we learn from retrospective studies and small prospective studies? *Ann Oncol* 2011 May;22(5):1243. PMID: 21521725. ^Co-first authors.
Cited 0 times, Rank 7 of 369 Oncology journals.

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32. Cost NG, Delacroix SE Jr, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, Karam JA, **Culp SH**, Abel EJ, Brugarolas J, Raj GV, Sagalowsky AI, Wood CG, Margulis V*. The Impact of Targeted Molecular Therapies on the Level of Renal Cell Carcinoma Vena Caval Tumor Thrombus. *Eur Urol.* 2011 Jun;59(6):912-8. PMID: 21367518.
Cited 218 times, Rank 1 of 108 Urology journals.
Dr. Culp provided data collection and editing of manuscript.

33. Karam JA, Zhang XY, Tamboli P, Margulis V, Wang H, Abel EJ, **Culp SH**, Wood CG*. Development and Characterization of Clinically Relevant Tumor Models from Patients with Renal Cell Carcinoma. *Eur Urol.* 2011 Apr:59(4):619-28. PMID: 21167632.
Cited 59 times, Rank 1 of 108 Urology journals.
Dr. Culp provided data collection including participation of establishment of models and editing of manuscript.

34. Abel, EJ^, **Culp SH**^, Tannir NM, Matin S, Jonasch E, Wood CG*. Primary Tumor Response to Targeted Therapy in Patients with Metastatic Renal Cell Carcinoma. *Eur Urol.* 2011 Jan;59(1):10-5. PMID: 20952123. ^Co-first authors.
Cited 128 times, Rank 1 of 108 Urology journals.

35. Richey SL^, **Culp SH**^, Jonasch E, Corn PG, Pagliaro L, Patel KK, Matin S, Wood CG, Tannir NM*. Outcome of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted

Therapy Without Cytoreductive Nephrectomy. *Ann Oncol*. 2011 May;22(5):1048-53. PMID: 21115604. ^Co-first authors.
Cited 66 times, Rank 7 of 369 Oncology journals.

36. Abel EJ, **Culp SH**, Matin S, Tamboli P, Wallace MJ, Jonasch E, Tannir NM, Wood CG*. Percutaneous Biopsy of Primary Tumor in Metastatic Renal Cell Carcinoma to Predict High Risk Pathologic Features: Comparison with Nephrectomy Assessment. *J. Urol*, 2010 Nov; 184(5): 1877-81. PMID: 20850148.
Cited 85 times, Rank 3 of 108 Urology journals.
Dr. Culp provided data collection and all analyses and editing of manuscript.

37. **Culp SH**, Tannir NM, Abel EJ, Margulis V, Jonasch E, Tamboli P, Matin S, Wood CG*. Can We Better Select Patients with Metastatic Renal Cell Carcinoma for Cytoreductive Nephrectomy? *CANCER*, 2010 Jul 15:116(14):3378-88. PMID: 20564061.
Cited 220 times, Rank 29 of 369 Oncology journals.

38. Abel EJ, **Culp SH**, Meissner M, Matin S, Tamboli P, Wood CG*. Identification of Risk for Disease Progression After Surgery for Localized Renal Cell Carcinoma. *BJU Int.* 2010 Nov;106(9):1277-83. PMID: 20394619.
Cited 26 times, Rank 6 of 108 Urology journals.
Dr. Culp provided data collection and all analyses and editing of manuscript.

39. **Culp SH*** and Porter MP**.** The Effect of Obesity and Lower Serum Prostate-specific Antigen Levels on Prostate-Cancer Screening Results in American Men. *BJU Int*. 2009 Nov; 104(10):1457-61. PMID: 19522868
Cited 60 times, Rank 6 of 108 Urology journals.

40. **Culp SH** and Wood CG*. Words of Wisdom Article – Re: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomized, placebo-controlled phase III trial. *Eur Urol.* 2009 Jun;55(6):1484-5. PMID: 19650216
Cited 3 times, Rank 1 of 108 Urology journals.

41. **Culp SH** and Wood CG*. Should patients undergoing surgery for renal cell carcinoma have a lymph node dissection? *Nat Clin Pract Urol*. 2009 Mar;6(3):126-7. PMID: 19204738
Cited 4 times, Rank 7 of 76 Urology and Nephrology journals.

42. Sim HG, Telesca D, **Culp SH**, Ellis WJ, Lange PH, True LD, Lin DW*. Tertiary Gleason Pattern 5 in Gleason 7 Prostate Cancer Predicts Pathologic Stage and Biochemical Recurrence. *J Urol.* 2008 May;179(5):1775-9. PMID: 18343432
Cited 95 times, Rank 3 of 108 Urology journals.
Dr. Culp provided data collection and analyses and editing of manuscript.

43. Plymate SR*, Tennant MK, **Culp SH**, Woodke L, Marcelli M, Colman I, Nelson PS, Carroll JM, Roberts CT Jr, Ware JL. Androgen Receptor (AR) Expression in AR-Negative Prostate Cancer Cells Results in Differential Effects of DHT and IGF-I on Proliferation and AR Activity Between Localized and Metastatic Tumors. *Prostate* 2004, 61(3):276-90. PMID: 15368471
Cited 55 times, Rank 12 of 108 Urology journals.

Dr. Culp was instrumental in establishing the prostate cancer cell lines outlined in manuscript as well as editing of the manuscript.

44. Astbury C, Jackson-Cook CK, **Culp SH**, Paisley TE, Ware JL*. Suppression of Tumorigenicity in the Human Prostate Cancer Cell Line M12 via Microcell-Mediated Restoration of Chromosome 19. *Genes, Chromosomes, and Cancer* 2001, 31(2):143-55. PMID: 11319802
Cited 27 times, Rank 70 of 347 Genetics Heredity journals.
Dr. Culp performed all *in vivo* work for the project as well as editing the manuscript.

A. Books and/or Chapters

1. Santen RJ, Duska LR, and **Culp SH**: Hormone Responsive Cancers, in Strauss JF and Barbieri RL (eds): Yen and Jaffe's Reproductive Endocrinology (ed VII), Elsevier, 2013

2. **Culp SH** and Wood CG: Locally Advanced Renal Cell Carcinoma, in Campbell SC and Rini BI (eds): Renal Cell Carcinoma: Clinical Management, Springer, 2013, pp 197-218

B. Short Communications

1. "Caring Beyond Cancer" – Radio show with Joe Thomas. Prostate Cancer Awareness Month – September 4, 2024.

2. WINA Live Well radio interview – Prostate Cancer Awareness Month. September 24, 2024.

3. "Metastatic Prostate Cancer: Have we got it all wrong?"; INNOVATION – Volume 5, 2015 p 23-24.

4. "Rethinking Prostate Cancer Treatment"; Vim and Vigor – Winter 2014, p.4

5. **Culp SH***: *Neoadjuvant Systemic Therapy in Locally Advanced Renal Cell Carcinoma: Pro and Con* – Con Argument. Kidney Cancer Journal. Volume 11, Number 3. 2013, 87-89.

6. "Prostate Playbook"; Vim and Vigor – Summer 2013 p.37

7. Mia Swartz and **Stephen Culp**, "A More Global View": IVU Traveling Resident Scholars in Cameroon. Medscape Urology, 6(2) 2005.

C. Abstracts

1. Hatcher PA, **Culp SH**, von Gall CC, Osborne DR, Fu Yitong, Smith WB, Moolupuri A, Whitaker DL. *A Phase 1, Open-Label, Multi-Center, Non-Randomized Study of [F-18]SMS-5368 Positron Emission Tomography in Prostate Cancer Patients with Biochemical Recurrence and Negative Conventional Imaging.* Presented at Annual Meeting of AUA May 2024

2. Dreyfus L, Fainberg J, Das A, Maciolek K, Berg RWV, Allen G, Borza T, Wells S, **Culp S**, Abel EJ, McClure T. *Multi-institutional Report of Patient Characteristics and Oncologic Outcomes Following Microwave Ablation of Biopsy-proven Renal Cell Carcinoma.* J Vasc and Int Radiol 33 (6), S26. 2022.

3. Young L, Laja O, **Culp S**, Cathro H. *Quilty Effect is Associated with Clinically Significant Acute T-cell Mediated Rejection, but Not with Antibody-Mediated Rejection.* Laboratory Investigation 102 (Suppl 1), 233-234. 2022. Presented at USCAP.

4. Gupta A, **Culp S**, Gaughan E, Mills A, Cathro H. *Loss of MHC Class 1 Expression is Associated with Shorter Progression-Free Survival in Patients with Advanced Urothelial Carcinoma Treated with Immune Checkpoint Inhibitors.* Laboratory Investigation 101 (SUPPL 1), 506-561. 2021. Presented at USCAP.

5. Dreyfus LD, Das A, Maciolek K, Allen G, Borza T, Wells SA, **Culp SH**, Abel EJ, McClure TD. *Recurrence Patterns Following Microwave Ablation of T1A Renal Masses: A Multicenter Analysis.* Presented at 2021 Annual Meeting of AUA. J Urol 206 (Supplement 3), e128-e128. 2021.

6. Maciolek K*, Yeaman C, Das A, Dreyfus L, Curci N, McClure T, Davenport M, Caoili E, Allen G, Wells SA, Borza T, Abel EJ, **Culp SH**. *Multi-Institutional Analysis of Risk Factors for Complications Following Thermal Ablation for Small Renal Masses.* Presented at 2021 Annual Meeting of AUA. J Urol 206 (Supplement 3), e281-e282. 2021.

7. Yeaman C*, Winkelman A, Maciolek K, Nelson P, Morris C, **Culp S**, Isharwal S, Krupski T. *Impact of Radiation on the Incidence and Management of Ureteroenteric Strictures: A Contemporary Single Center Analysis*. J Urol 2021/9;206(Supplement 3), 588. Presented at 2021 Annual Meeting of the AUA.

8. Cathro H, Ju J, Davick, Gru AA, **Culp S**. *PD-L1 and IDO Expression in Upper Tract Urothelial Carcinoma*. Laboratory Investigation 2019/3/1;99. Presented at USCAP.

9. McIntosh AG*, Umbreit EC, Gu, C, Matin, SF, Karam JA, Wood CG, Holland L, **Culp SH**. *Clinical factors that predict outcomes for patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma in the modern era of systemic therapeutics*. Presented at the 20th annual meeting of the SUO (Dec 2019).

10. McIntosh A, Wood CG, Karam JA, Matin S, Tannir N, Jonasch E, **Culp SH*.** *Clinical factors that predict outcome for patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma in the modern era of systemic therapeutics.* Presented at the 2019 Annual Meeting of the Urological Research Society, Bern Switzerland (October 2019).

11. Grauer R*, Lobo J, Erdoganb A, Bergc B, Kang H, Clements MB, **Culp SH**, Krupski TL. *Provider Scheduling to Maximize Patient Access.* Presented at the 2019 annual meeting of the AUA (May 2019).

12. Clements MB*, Krupski TL, **Culp SH**. *Risk of Intra-abdominal Recurrence of Urothelial Carcinoma Following Extripative Surgery Based on Disease Stage and Operative Approach: A Population-Based Study*. Presented at 19th Annual Meeting of the SUO (Nov 2018).

13. Clements MB*, Krupski TL, **Culp SH**. *Population-Based Analysis of Upper Tract Urothelial Carcinoma Outcomes Based on Type of Definitive Surgery.* Presented at the 75th Annual Meeting of the Mid-Atlantic Section of the American Urological Association. March 2018.

14. Ju J*, Mills A, **Culp S**, Cathro H. *Universal Lynch Screening Should Be Performed in Upper Tract Urothelial Carcinomas.* Presented at the 2018 Annual Meeting of the United States and Canadian Academy of Pathology.

15. Zillioux JM*, Schenkman NS, Cathro HP, **Culp SH**. *Cytoreductive Prostatectomy: Early Experience at a Single Institution.* Presented at the 65th Annual Kimbrough Meeting, Society of Government Service Urologists (January 2018).

16. Clements M*, Abdalla B, **Culp S**, Krupski T, Costabile R. *A Meta-Analysis of Prostate Cancer Characterstics in the U.S. Preventive Services Task Force Grade D Era.* Presented at the 18th annual meeting of the Society of Urologic Oncology (November 2017) and annual meeting of AUA (May 2018).

17. Clements M*, Showalter T, **Culp S**. *Identifying Patients who may benefit from Trimodal Therapy versus Extirpative Surgery in Bladder Cancer*. Presented at the 18th annual meeting of the Society of Urologic Oncology (November 2017).

18. **Culp SH***, Niece K, Seaman M, Krupski TL. *Feasibility Study of Using Circulating Tumor Cells to Risk-Stratify Patients Diagnosed with Bladder Cancer.* Presented at the 14th annual meeting of the International Bladder Cancer Network, Bochum Germany (October 2016).

19. Mills JT*, Krupski TL, **Culp SH**. *Trends and Predictors of Cytoreductive Nephrectomy with Targeted Therapy Introduction*. Accepted for the 2016 annual meeting of the Mid-Atlantic AUA (October 2016).

20. **Culp SH***. *Contemporary Assessment of Papillary Renal Cell Carcinoma in the United States.* Presented at the 2015 annual meeting of the Urological Research Society, Jerusalem, Israel (September 2015).

21. Mentrikoski M, **Culp S**, Cathro HP, Frierson HF, Stelow EB. *Intraepithelial Neoplasia and HPV Status in Penile Intraepithelial Lesions.* Laboratory Investigation 93, 234A-234A. 2013.

22. Mentrikoski MJ, **Culp S**, Stelow EB, Frierson HF, Cathro HP. *Histopathologic and Immunohistochemical Assessment of Penile Carcinomas.* Laboratory Investigations 93, 234A-234A. 2013.

23. Mo YD, **Culp SH**, Diolombi ML, Cathro HP. *Oncocytic Papillary Renal Cell Carcinomas Should be Classified Separately from Type 1 and Type 2 Tumors*. Laboratory Investigation 93, 235A-235A. 2013. Presented at GU ASCO.

24. Burris MB*, Steele MC, **Culp SH**. *Sarcoma of the Cord: A Population-Based Analysis of Incidence and Survival.* Presented at the 2013 annual meeting of the Mid-Atlantic AUA.

25. Steele MC*, Burris MB, **Culp SH**. *Primary Melanoma of the Urethra. A Population-Based Study of Incidence and Survival.* Presented at the 2013 annual meeting of the Mid-Atlantic AUA.

26. **Culp SH***, Mo YD, Diolombi M, Cathro HP. *Classification of Oncocytic Papillary Renal Cell Carcinoma*. Presented at the 2013 GU ASCO Symposium. February 2013. J Clin Oncol 31 (6_suppl), 467-467. 2013.

27. **Culp SH***, Dickstein R, Pretzsch S, Navai N, Wszolek M, Siefker-Radtke, Kamat A, Dinney C. *Refining Patient Selection for Neoadjuvant Chemotherapy Prior to Radical Cystectomy*. Presented at the 2012 annual meeting of the AUA. J Urol 187 (4S), e770-e770. 2012.

28. Kenney P*, Chapin B, **Culp SH**, Richey S, Nogueras-Gonzalez G, Tamboli P, Tannir N, Wood CG. *Does Cytoreductive Nephrectomy Improve Survival in Non-Clear Cell Renal Cell Carcinoma?* Presented at the 2011 annual meeting of the SUO and 2012 annual meeting of the AUA.

29. Dickstein R*, McCoy J, **Culp SH**, Pagliaro L, Pettaway C. *Pre-operative Chemotherapy for Regionally Advanced Squamous Carcinoma of the Penis: The M.D. Anderson Cancer Center Experience.* Presented at the 2012 annual meeting of the AUA. J Urol 187 (4S), e274-e274. 2012.

30. Burris MB*, Cathro HP, **Culp SH**, Steers W, Krupski TL. *Lower Urinary Tract Symptoms Improved in Prostatectomy Patients with Severe Prostatic Inflammation.* Presented at the 2012 annual meeting of the AUA. J Urol 187 (4S), e659-e659. 2012.

31. **Culp SH***, Zhang XY, Maity T, Wood CG. *Association of P95HER2 with Targeted Therapy Resistance in Type 2 Papillary Renal Cell Carcinoma.* Presented at the 2011 annual meeting of the AUA. J Urol 185 (4S), e100-e100. 2011.

32. Svatek R*, **Culp SH**, Munsell M, Pettaway C. *Comparative Prognostic ability of TNM Nodal staging systems and Lymph Node Density For Penile Squamous Carcinoma.* Presented at the 2011 annual meeting of the AUA. J Urol 185 (4S), e336-e337. 2011.

33. Delacroix SE*, Chapin BF, Cost N, Karam JA, **Culp SH**, Abel EJ, Gonzalez G, Margulis V, Wood CG. *Can Contemporary Targeted Therapies Provide Clinically Meaningful Changes in Renal Cell Carcinoma Venous Tumor Thrombi?* J Clin Oncol 29 (7_suppl), 390-390. 2011. Presented at 2011 Meeting of GU ASCO.

34. Richey SL, **Culp SH**, Jonasch E, Corn PG, Pagliaro LC, Tamboli P, Patel K, Matin SF, Tannir NM. *Long-term Survival of Patients with Metastatic Renal Cell Carcinoma (mRCC) Treated with Targeted Therapy (TT) without Cytoreductive Nephrectomy (CN).* J Clin Oncol 29 (7_suppl), 346-346. 2011.

35. Cost NG*, Delacroix SE, Sleeper JP, Smith P, Youssef RF, Chapin BF, Karam JA, **Culp SH**, Abel EJ, Brugarolas J, Raj GV, Sagalowsky AI, Wood CG, Margulis V. *The Impact of Targeted Molecular Therapies on the Level of Renal Cell Carcinoma (RCC) Venous Tumor Thrombus*.

Presented at the 2011 annual meeting of the AUA. J Urol 185 (4S), e710-e711. J Clin Oncol 29 (15_suppl), e15002-e15002. 2011.

36. Chapin BF*, Delacroix SE, **Culp SH**, Nogueras Gonzalez GM, Wood CG. *Post-operative Complications from Cytoreductive Nephrectomy after Neo-adjuvant Targeted Therapy for Metastatic Renal Cell Carcinoma.* Presented at the 2011 annual meeting of the AUA. J Urol 185 (4S), e709-e709. J Clin Oncol 29 (7_suppl), 300-300. 2011.

37. Chapin BF*, Delacroix SE, **Culp SH**, Nogueras-Gonzalez GM, Tannir N, Jonasch E, Tamboli P, Wood CG. *Timing of Cytoreductive Nephrectomy Does Not Influence Survival in Metastatic Renal Cell Carcinoma.* Presented at the 2011 annual meeting of the AUA. J Urol 185 (4S), e705-e705. 2011.

38. **Culp SH***, Abel EJ, Tannir N, Matin S, Tamboli P, Wood CG. *Early Primary Tumor Response in Patients with Metastatic RCC Undergoing Treatment with Sunitinib is an Independent Predictor of Overall Survival*. Presented at winter meeting of SUO, 2011 GU ASCO Symposium and 2011 annual meeting of the AUA. J Urol 185 (4S), e799-e800. J Clin Oncol 29 (7_suppl), 329-329. 2011.

39. Karam JA*, Zhang XY, Tamboli P, Margulis V, Wang H, Abel EJ, **Culp SH,** Wood CG. *Development and Characterization of Tumor Models from Patients with Renal Cell Carcinoma*. Presented at 2010 winter meeting of SUO and 2011 annual meeting of the AUA. J Urol 185 (4S), e161-e161. 2011.

40. Wilson C*, Durkal V, **Culp SH**, Grossman HB, Kamat A, Dinney C, Shah JB. *Bladder Tumor Location at TURBT Predicts Likelihood of Lymph Node Metastases at Cystectomy*. Presented at 2010 winter meeting of SUO and 2011 annual meeting of AUA. J Urol 185 (4S), e741-e742. 2011.

41. **Culp SH***, Zhang XY, Maity T, Wood CG. *Action of Targeted Therapy on Papillary Renal Cell Carcinoma Tumor Models*. Presented at 2010 annual meeting of the AUA. J Urol 183 (4), e33-e34.

42. Delacroix S*, **Culp SH,** Chen JJ, Tamboli P, Matin S, Wood CG. *Retroperitoneal Lymph Node Metastasis in M0 Renal Cell Carcinoma*. Presented at 2010 annual meeting of the AUA. J Urol 183 (4S), e698-e698. 2010.

43. Richey SL*, **Culp SH**, Patel KK, Wood CG, Corn P, Jonasch E, Tannir NM. *Outcome of Patients With Metastatic Renal Cell Carcinoma Treated with Targeted Therapy Without Cytoreductive Nephrectomy*. Presented at 2010 GU ASCO Symposium. J Clin Oncol 28 (15_suppl), 4613-4613.

44. Abel EJ*, Tannir NM, **Culp SH**, Matin S, Jonasch E, Wood CG. *Does Targeted Therapy Result in Reliable and Meaningful Primary Tumor Downstaging in Patients with Metastatic Renal Cell Carcinoma?* Presented at 2010 GU ASCO Symposium and 2010 annual meeting of the AUA. J Urol 183 (4S), e641-e642.

45. **Culp SH***, Choi S, Tamboli P, Matin S, Wood CG. *Predictors of Perinephric Desmoplastic Reaction in Patients Undergoing Partial Nephrectomy*. Presented at 2009 SUO winter meeting.

46. Delacroix S*, **Culp SH**, Choi S, Tamboli P, Matin S, Wood CG. *Predictive Factors for Kidney-related Complications in Partial Nephrectomy Patients.* Presented at 2009 SUO winter meeting.

47. Abel EJ*, Carrasco A, **Culp SH**, Matin S, Tamboli P, Tannir N, Wood CG. *Biopsy of Metastatic Sites in Renal Cell Carcinoma: Comparison of Pathologic Findings with Nephrectomy Specimens in 240 Cases.* Presented at 2009 SUO winter meeting.

48. **Culp SH***, Abel EJ, Margulis V, Bill KL, Swanson DA, Tamboli P, Wood CG. *Supra-Diaphragmatic Lymph Node Involvement is an Independent Predictor of Mortality in Patients with Conventional Renal Cell Carcinoma Undergoing Cytoreductive Nephrectomy.* Presented at 2009 annual meetings of GU ASCO Symposium and AUA. J Urol 181 (4S), 496-497.

49. **Culp SH***, Abel EJ, Margulis V, Bill KL, Tamboli P, Jonasch E, Matin S, Swanson DA, Tannir NM, Wood CG. *Identifying Patients with Metastatic Renal Cell Carcinoma Who Will Not Benefit from Cytoreductive Nephrectomy.* Presented at 2009 AUA annual meeting.

50. Abel EJ*, **Culp SH**, Stamatakis L, Bill KL, Tamboli P, Margulis V, Swanson DA, Wood CG. *Percutaneous Primary Tumor Biopsy is Unreliable to Predict High Risk Pathologic Features in Patients with Metastatic Renal Cell Carcinoma*. Presented at 2009 AUA annual meeting.

51. Abel EJ*, **Culp SH**, Meissner M, Stamatakis L, Margulis V, Tamboli P, Matin S, Swanson DA, Wood CG. *Risk Factors for Disease Progression in Patients with Localized (pT1, pT2) Renal Cell Carcinoma (RCC) Following Surgical Therapy.* Presented at 2009 AUA annual meeting. J Urol 181 (4S), 357-357.

52. **Culp SH***, Abel EJ, Stamatakis L, Meissner M, Bill KL, Margulis V, Wood CG. *Progression of Renal Cell Carcinoma Based on Gender and Ethnicity after Resection of Localized Disease.* Presented at 2008 SUO fall meeting.

53. Martin FM*, Robinson TL, **Culp SH**, Kamat AM. *Cytokine Response to Intravesical Bladder Cancer Therapy.* Presented at 2008 SUO winter meeting.

54. **Culp SH***, Porter MP, Lin DW, True LD, Weiss NS. *Incidence and Survival of Rare Histologic Subtypes of Prostate Cancer Over a 30-Year Period.* Presented at 2008 AUA annual meeting. J Urol 179 (4S), 205-206.

55. Sim HG*, Telesca D, **Culp SH**, Lange PH, Ellis WJ, True LD, Lin DW. *Cancer to Total Prostate Volume Ratio Influences Pathological Parameters and Biochemical Recurrence in Localized Prostate Cancer Treated by Radical Prostatectomy.* Presented at 2007 AUA annual meeting. J Urol 177 (4S), 340-340. 2007.

56. Sim HG*, Telesca D, **Culp SH**, Ellis WJ, Lange PH, True LD, Lin DW, *Tertiary Gleason Pattern 5 in Gleason 7 Prostate Cancer Predicts Pathologic Parameters and Biochemical Recurrence.* Presented at 2007 AUA annual meeting. J Urol 177 (4S), 157-158. 2007.

57. **Culp SH***, Lin DW, Li CI, De Roos AJ, Porter MP. *Variation in Mortality by Ethinicity among Patients with Renal Cancer in the United States.* Accepted for Presentation at the 2006 meeting of the Western Section of the AUA, October 2006. Presented at 2006 SUO winter meeting.

58. **Culp SH***, Lin DW, Li CI, De Roos AJ, Porter MP. *Racial and Gender Based Variation in Survival among Patients with Renal Cancer in the United States.* Presented at University of Washington Department of Urology Annual Research Day, June 2006.

59. **Culp SH***, Porter MP, Lin DW, True LD, Weiss NS. *Rare Prostate Cancer Histology: A Population Study of Incidence and Patient Survival.* Presented at University of Washington Department of Urology Annual Research Day, June 2006.

60. **Culp SH*** and Porter MP. *The Relationship between Serum PSA and Body Mass Index in American Men.* Presented at University of Washington Department of Urology Annual Research Day, June 2006, and accepted for presentation at 2006 meeting of the Western Section of AUA.

61. **Culp SH***, Marcelli M, Plymate SR, Ware JL. *Androgen Receptor Re-Expression Alters Prostate Cancer Tumorigenicity and In Vitro Behavior.* Presented at 2000 annual meeting of American Association for Cancer Research and 15th Annual MD/PhD Conference, Aspen CO July 2000.

62. **Culp SH***, Plymate SR, Ware JL. *Peptide Growth Factors Modulate Apoptotic Sensitivity in Prostate Cancer Progression.* Presented at 1998 SBUR annual meeting.

63. **Culp SH***, Plymate SR, Belfield H, Ware JL. *Apoptotic Resistance and Increased Aggressiveness of Human Prostate Cancer Cells.* Presented at 1999 annual meeting of American Association for Cancer Research.

*Abstract Presented

XVII. INVITED LECTURES AND SYMPOSIUM

1. Invited Speaker – 2024 UVA Interdisciplinary Urologic Oncology Update: A Case Board Update. November 14, 2024. Charlottesville, Virginia.

2. Invited Speaker – Optimizing Management of Localized Renal Masses, UVA Department of Nephrology – Renal Grand Rounds. March 26, 2024. Charlottesville, Virginia.

3. Co-Chair – Penile Cancer Session. Society of Urologic Oncology Annual Meeting. November 30, 2023. Washington DC.

4. Invited Speaker – 2023 UVA Interdisciplinary Urologic Oncology Update: A Case Board Update. November 16, 2023. Charlottesville, Virginia.

5. Impact of SPY Fluorescence Angiography on Incidence of Uretero-enteric Stricture after Urinary Diversion: Early Experience and Analysis. Presented at the Urological Research Society Annual Meeting. Heidelberg, Germany, October 7, 2023.

6. Cancer of the External Male Genitalia – Surgical Management and Tidbits. UVA Department of Urology Grand Rounds. May 4, 2022.

7. Nuts and Bolts of Managing PSA Referrals. AUA Fundamentals in Urology. June 12, 2021.

8. The Changing Paradigm of Treatment for Advanced Prostate Cancer – Where do we go from here?; Department of Urology, Columbia University, New York, New York. February 8, 2016.

9. Establishment and Clinical Usefulness of Renal Cell Carcinoma Patient-Derived Xenograft Models; Research Roundtables – Patient-derived tumors and pre-clinical models of disease, UVA Programs in Cancer Cell Signaling and Molecular Genetics and Epigenetics. December 14, 2015.

10. The Changing Paradigm of Treatment for Advanced Prostate Cancer – Where do we go from here?; UVA Pathology Grand Rounds. November 3, 2015.

11. To see the forest before the trees: The value of population-based studies in examining treatment of the primary tumor in metastatic prostate cancer; 2015 PCF Coffey-Holden Prostate Cancer Academy Meeting. San Diego, California. June 2015.

12. Neoadjuvant Chemotherapy in T2 TCCA Bladder CA; Virginia Urological Society 27th Annual Meeting. Staunton, Virginia. April 17, 2015.

13. Dissecting Mechanisms of Targeted Therapy Resistance in Renal Cell Carcinoma using Patient-derived Xenograft Models; UVA Hematology and Oncology Grand Rounds, November 12, 2014.

14. Cytoreductive Nephrectomy; 13th Annual Kidney Cancer Symposium, Chicago, Illinois, October 2014.

15. Dissecting Targeted Therapy Resistance in Renal Cell Carcinoma using Patient-derived Xenograft Models; University of Washington Paul H. Lange, MD, FACS and Robert L. Vessella, PhD Festschrift. March 14, 2014.

16. Moderator for Moderated Poster Session: Mid-Atlantic Section of AUA 2013 Annual Meeting. White Sulfur Springs, WV. October 24, 2013

17. Cytoreductive Surgery in Urology: Advancing Science while Improving Patient Care; UVA Cancer Center Seminar Series. October 4, 2013.

18. Cytoreductive Surgery in Urology: A Benefit for Both the Patient and Researcher and Management of Locally Advanced Renal Cell Carcinoma; Visiting Professor – University of California Davis. August 13, 2013.

19. Moderator for Panel Discussion: Testosterone Replacement in CaP Patient; Virginia Urological Society 2013 Annual Meeting. Fairfax, VA. March 15, 2013.

20. Co-leader of "Genitourinary Carcinogenesis" – Lunch roundtable discussion session, University of Virginia School of Medicine Research Retreat. February 9, 2013.

21. Renal Cell Carcinoma: from bedside to bench and back again; Dean's New Faculty Seminar Series. University of Virginia School of Medicine. January 23, 2013.

22. Cytoreductive Nephrectomy and its Current Role in Metastatic Renal Cell Carcinoma; 11th Annual Kidney Cancer Symposium, Chicago, Illinois, October 2012.

23. Renal Cell Carcinoma: From bedside to bench and back again; Department of Pathology Grand Rounds, University of Virginia. April 17, 2012.

24. The Role of Surgery in Metastatic Renal Cell Carcinoma; V Curso Interdisciplinario de Oncologia Tumores Urologicos, Oviedo, Spain, May 14, 2007.

25. Is There a Role for Cytoreductive Nephrectomy in the Era of Targeted Therapy?;V Curso Interdisciplinario de Oncologia Tumores Urologicos, Oviedo, Spain, May 14, 2007.

26. Management of Malignant Ureteral Obstruction; Department of Medicine Grand Rounds, University of Washington; November 2007.

XVIII. COMMUNITY

- 2015 to 2016 Mentor for UVA-Sponsored Charlottesville High School Symposium, Charlottesville, VA

- Bill Steers 4-Miler Committee

EXHIBIT B

Fee Schedule

CULP, STEPHEN H. – MD, MS, PHD

Associate Professor with Tenure, Department of Urology, University of Virginia, Charlottesville, VA. Masters of Science in Epidemiology, PhD in Pathology. American Society of Clinical Oncology, Americal Urological Association, Society of Urologic Oncology, American College of Surgeons, International Bladder Cancer Network.

Baseline billable rate …….$600.00 per hour

Travel time……....……$600.00 per hour

> ***Travel Policy:*** The client agrees to compensation for minimum commitment equivalent to a half day of the doctor's time when the client schedules the physician to travel more than 60 miles from home or office, for a meeting.

Deposition (Minimum 4 hours) and Trial (Minimum 8 hours) ……..$720.00 per hour

Cancellation/Rescheduling Policy (meeting, deposition, or testimony):

- Within 1 week of travel to a deposition or trial appearance, the client agrees to minimum commitment equivalent to a full day of the doctor's time when the client cancels or reschedules physician's time……$4,800 per calendar day
- The client assumes responsibility for travel fees, penalties, or supplemental costs resulting from change in travel plans.

Laboratory and Equipment Fees ……Advance quote prepared as needed

<u>Physician's Support Staff</u>:

Associate Scientist…..…….……..…..$185 to $255 per hour

Staff MD/PhD Epidemiologist…….……..…$235 to $375 per hour

Nurse Practitioner (advance practice) …….……..……..$205 to $295 per hour