Exhibit 428

Consultation to The Department of Justice

Re: Frank Mousser
DOB: ██████ 1963

Dear Attorneys and Staff of the United States Department of Justice,

I have reviewed primary and summary documents for Mr. Frank Mousser regarding his chronic kidney disease. I have been asked to provide my opinions on his condition, including his kidney function, life expectancy, and need for future care. He is seeking judgement against the US Government for his kidney disease.

This opinion includes 5 sections:

1) My qualifications, on which this opinion is based.
2) An explanation of kidney function, chronic kidney disease, dialysis, and kidney transplantation.
3) A description of Mr. Mousser's clinical history.
4) My overall conclusions on kidney function for Mr. Mousser, following his nephroureterectomy, including his life expectancy and need for renal replacement therapy and future care.
5) Responses to the report of Dr. Matthew Cooper.

1. My qualifications to serve as an expert witness.

I have been a practicing nephrologist for nearly 20 years. I am currently the Clinical Director of Nephrology and Associate Professor in the Department of Medicine at the University of Kansas. In this position, I am responsible for the care of patients with kidney disease at the University of Kansas Hospital, including oversight of hospitalized patients, evaluation of outpatients with kidney disease, with a goal of delaying or preventing progression, or patients with rare electrolyte disorders, care of patients on dialysis, quality improvement initiatives regarding these patients, and involvement with the teaching of nephrology to students and resident physicians.

My professional affiliations include the American Society of Nephrology, the National Kidney Foundation, the American College of Physicians, and the Renal Physicians Association. I have authored over 25 journal articles, a book chapter, edited the Nephrology syllabus for the University of Pittsburgh Medical School, and served as a peer reviewer for professional journals and for annual meetings of the American Society of Nephrology and the American College of Physicians. My education included Harvard College with a degree in History and Science, a combined MD and PhD degree from the University of Washington, Medicine Residency at Northwestern University, Nephrology Fellowship training at the University of Michigan, and then faculty appointments at the University of Michigan, the University of Pennsylvania, Temple University, the University of Pittsburgh, and the University of Buffalo.

I have received awards for Teaching and Clinical Service from the University of Pennsylvania, four from Temple University, and two from the University of Pittsburgh. My clinical area of expertise is glomerular disease, but I have never placed limits on who I will see in clinic. I have cared for patients with kidney stones, electrolyte disorders, chronic kidney disease caused by common or rare disorders, patients receiving hemodialysis in clinic, dialysis patients receiving home therapy, and recipients of kidney transplants. In summary, based on my training and professional experience, I feel qualified to discuss kidney disease across a wide spectrum.

I am charging $850/hour for my work on this matter. I have not testified at trial or by deposition in the previous four years. I reserve the right to supplement my opinions in light of new information.

2. **General Introduction of kidney function, chronic kidney disease, dialysis, and kidney transplantation.**

2a. What do kidneys really do?

We have two kidneys, each about the size of a clenched fist. Our kidneys are shaped- not surprisingly- like kidney beans. Both kidneys are located in the upper retroperitoneum, which roughly means- as shown in the picture below, in your mid-back, behind the stomach and intestines, on either side of the aorta and inferior vena cava, which are the largest blood vessels in the body.
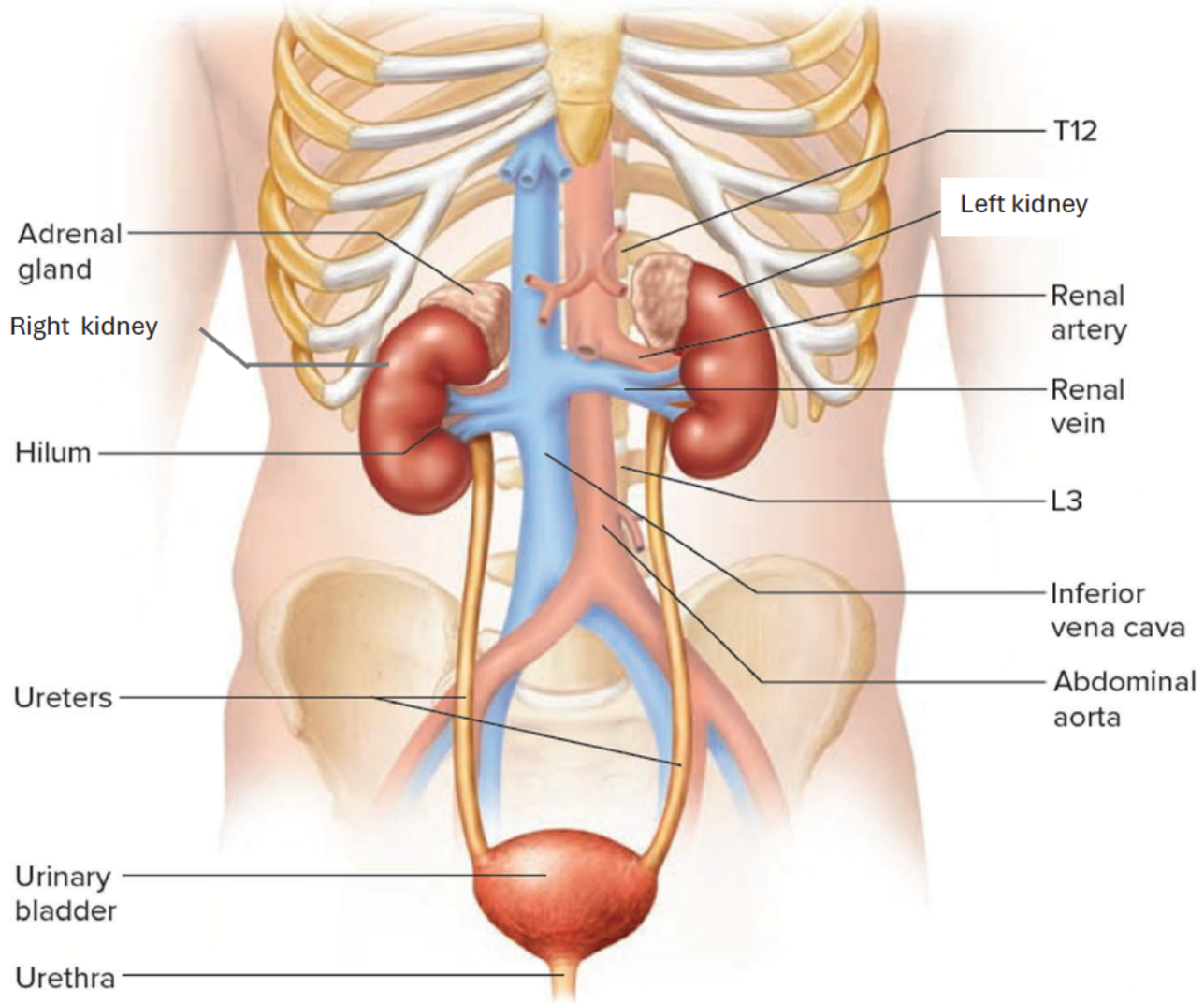
Each kidney filters your blood, every minute of every day, to accomplish two basic tasks: to keep your blood and all the cells of your body in a stable balance of salts and water, and to remove toxins and waste products from your body (in cooperation with the liver). To maintain chemical balance, your kidneys sense what is happening in your body and respond accordingly, to keep the concentration of multiple salts and acid-base level within your blood stable. For example, if you are walking on a hot day and losing water and sodium, your brain and kidneys sense these losses, and the kidneys respond by holding onto as much

water and sodium as possible. If your blood is too high or too low in potassium, calcium, magnesium, phosphorous, or alkali, your kidneys will sense these changes and respond accordingly to bring you abnormal level back into balance. If you drink a half-gallon of water that you do not really "need," your brain and kidneys sense that your blood is becoming dilute, and your kidneys will dump all the excess water quickly as dilute urine. If you eat salted jerky, your kidneys will dump the excess sodium, sulfates, and phosphates in urine. In the end, no matter what is coming into your body through eating and drinking, or being removed from your body through sweating, diarrhea, vomiting, bleeding, and more, the kidneys sense and respond to changes in blood chemistry to keep our bodies in balance.

To understand the second task of toxin removal, it may come as a surprise that most of the toxins and waste products removed by your kidneys every day come from your own metabolism. When cells make energy, build proteins, synthesize new DNA, and carry out all cellular metabolic functions, the biological chemistry involved in these processes creates waste products that must be removed. A single-cell organism excretes these waste products into the environment around them, whereas people excrete metabolic waste products from cells into the blood. Once in the blood, most metabolic waste products and other toxins are removed from our bodies by the kidney, liver or by the cooperative action of both organs. Once the waste products are small-sized and electrically charged, they are easily filtered by kidneys and excreted in urine.

Separate from their work maintaining balance of water and electrolytes, and removing waste products from your body, your kidneys also regulate other organs in your body. First, if you become anemic and your body needs to make more red blood cells, this is sensed by special cells in the kidney that release the hormone erythropoietin, which in turn tells your bone marrow to make new red blood cells. When your anemia resolves, the kidneys turn down release of erythropoietin to avoid making your blood too thick. Second, your kidneys regulate your skeleton, including the main components of bones, which are calcium and phosphate. To accomplish this, the kidney makes the enzyme that converts the storage form of vitamin D into the biologically active form (1,25 dihydroxy vitamin D), which increases reabsorption of calcium from urine, increases absorption of dietary calcium and phosphorous from intestines, and increases the activity of osteoclasts, which "chew holes" in bone to release more calcium and phosphorous. The kidneys also sense and regulate the amount of calcium and phosphorous we reabsorb from urinary filtrate directly, without vitamin D. Third, your kidneys are considered part of your immune system because they synthesize molecules that are part of our response to infection, inflammation, and trauma, including colony stimulating factor, interleukin1, and tumor necrosis factor. Lastly, the kidneys convert certain amino acids into glucose, which is critical because our brain cells only use glucose for energy. Many people think the liver is the only organ that creates glucose for our brains, but the kidney can produce up to 50% of glucose production.

In summary, when kidneys are healthy, they work 24-hours per day, 7 days a week to regulate and stabilize the water and electrolyte concentrations in our blood, to remove metabolic waste products and toxins from our blood, to instruct other organs what to do, including our bone marrow, skeleton, intestines, and inflammatory system, and to produce glucose for our brain cells.
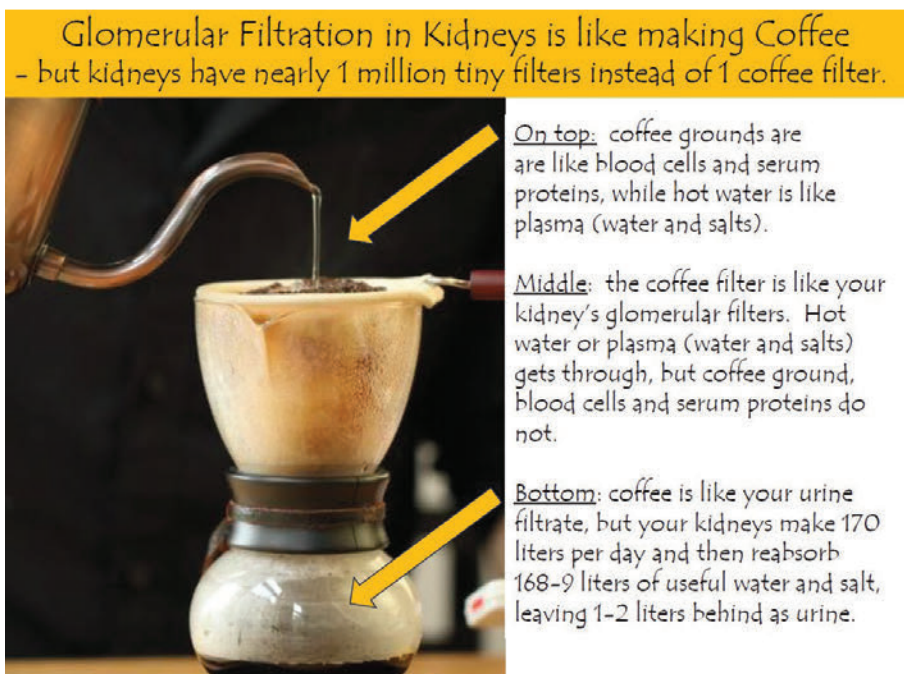
2b. What is Chronic Kidney Disease?
Chronic kidney disease (CKD) arises when kidneys lose function due to disease, aging, or other circumstances. Patients who are referred by their primary doctors for chronic kidney disease often protest that they are still making plenty of urine, but we can make a normal amount of urine with only 1-2 % of

normal kidney function, as is true for some patients on dialysis. Understanding what we mean by kidney function helps appreciate the stages of chronic kidney disease.

Kidneys make urine in two basic steps. In the first step, the heart pumps a large amount of blood to kidneys through the renal arteries, which branch out into many thousands of smaller blood vessels, eventually branching into nearly 1 million capillaries called glomeruli, which filter the blood. The amount of blood that is filtered by our kidneys is huge, about 172 liters, or 45 gallons of urinary filtrate each day. This raw urine filtrate is then processed through renal tubules, which reabsorb everything from the filtrate that is useful, and excrete a few more toxins through secretion. The vast majority of salt water in the filtrate is useful and is reabsorbed by tubules. At the end of these long tubules, everything that has not been reabsorbed becomes our urine, which includes excess water and salts, unwanted metabolic waste products, and other toxins.

This first step, when the kidneys filter blood in glomeruli to create a large volume of filtrate is what we mean by "kidney function," and it is also called the glomerular filtration rate, or GFR. To understand glomerular filtration, imagine a drip-coffee maker as shown in the figure below, with coffee grounds and hot water on top, a coffee filter in the middle, and a filtrate of coffee on the bottom. Our kidneys filter blood within glomeruli similar to a coffee maker. Our blood has plasma, akin to hot water, that will be pushed across the filter under pressure, and our blood has serum proteins and blood cells, akin to coffee grounds, that should not cross the filter.

Glomerular Filtration in Kidneys is like making Coffee - but kidneys have nearly 1 million tiny filters instead of 1 coffee filter.

On top: coffee grounds are are like blood cells and serum proteins, while hot water is like plasma (water and salts).

Middle: the coffee filter is like your kidney's glomerular filters. Hot water or plasma (water and salts) gets through, but coffee ground, blood cells and serum proteins do not.

Bottom: coffee is like your urine filtrate, but your kidneys make 170 liters per day and then reabsorb 168-9 liters of useful water and salt, leaving 1-2 liters behind as urine.

The glomerular filter is composed of special proteins in a matrix and lets water and small molecules through but keeps large proteins and large cells within the blood. Kidney function refers to the rate at which all glomeruli in both kidneys filter blood, and collectively, if our glomeruli make about 172 liters of filtrate per day, then our normal glomerular filtration rate (GFR), or normal kidney function, is 120 milliliters per minute.

2c. Kidney Function and the Stages of Chronic Kidney Disease:
Chronic kidney disease (CKD) is divided into stages of severity based, primarily, on kidney function, and secondarily on the amount of albumin in urine. To appreciate how kidney function is related to the stages of

CKD, consider the drip coffee maker for comparison. If a coffee machine normally makes 1 cup per minute, but a damaged coffee machine makes only ½ cup per minute, then the machine is working at only 50% function and is moderately "diseased." A coffee machine that makes only ¼ cup per minute is working at only 25% function and is severely "diseased."

We divide chronic kidney disease into stages of severity according to kidney function as follows (remembering that a normal glomerular filtration rate, or GFR, is 120 mL per minute):

- Stage 1 CKD (or stage G1): GFR 90-120 mL/min (75-100% of normal kidney function).
- Stage 2 CKD (or G2): GFR of 60-89 mL/min (50%- 75% kidney function).
- Stage 3 CKD (or G3): GFR of 30-59 mL/min (25%-50% kidney function).
- Stage 3 is subdivided into Stage 3a (G3a): GFR 45-59 mL/min.
     And Stage 3b (G3b): GFR 30-44 mL/min.
- Stage 4 CKD (or G4): GFR 15-29 mL/min (12.5% to 25% kidney function).
- Stage 5 CKD (or G5): GFR less than 15 mL/min (less than 12.5% kidney function).
- End Stage Kidney Disease (ESRD): patients who start dialysis or receive a kidney transplant.

GFR can be measured directly, but this is difficult, invasive, and rarely done in clinical practice. More often, we "estimate" GFR based on the level of creatinine in blood (eGFR). Creatinine is produced by active, healthy muscle cells release creatine into blood, where it is converted to creatinine and then removed from blood by the kidneys, primarily by glomerular filtration. If the level of creatinine in blood is rising, then kidney function is falling (with rare exceptions). There are additional considerations, because muscle mass can increase with exercise or decrease with malnutrition or illness, and the kidneys also remove creatinine from blood by tubular secretion, which can contribute 10-30% of total creatinine clearance, and this tubular secretion is separate from kidney function based on glomerular filtration. Nevertheless, as long as the level of creatinine in your blood is stable (an important requirement that we call "the steady state") then by measuring your blood creatinine level, we can estimate your kidney function / glomerular filtration rate (GFR) fairly accurately. These estimates of kidney function are not valid if we know only a single value of creatinine, as discussed below.

The second component to determining CKD stage is the amount of protein in the urine, or specifically the amount of albumin in urine. Albumin is the most common protein in blood. Even with a normal, healthy glomerular filter, a small albumin of albumin leaks across the glomerular filter from blood into the urine filtrate, and our kidneys reabsorb the majority of albumin that gets through, but a tiny amount of albumin is always left behind in normal urine (about 15-30 milligrams per day). If we see higher amounts of albumin in urine, the primary reason is excessive leakage across a diseased glomerular filter. Using drip coffee as an analogy again, if we poke holes in a coffee filter with a pencil, then coffee grounds will leak into our cup of coffee, and the more coffee grounds we find in our coffee, the worse the damage must have been to the coffee filter. Similarly, if we see excessive albumin in urine, then kidney disease must be creating microscopic "holes" in the glomerular filter. To account for the process of urine concentration, which occurs in the kidney after blood is filtered, we measure the ratio of albumin to creatinine in urine (ACR). A normal ACR is less than 15 to 30 mg of albumin per gram creatinine in the urine and is classified as "A1." A moderately elevated urine ACR of 30 to 300 mg/gram is classified as "A2," and a high urine ACR of more than 300mg/gram is "A3." Extremely high urine ACR of 3000mg/gram and more is termed "nephrotic range," and is a subset of severe kidney disease. Combining kidney function/GFR with urine albumin leakage, there are 15 stages of chronic kidney disease: CKD stage G1-G5 based on the GFR, each of which

is divided by urine ACR into A1-A3. This combined CKD stage is important because it predicts, at a population level, three important outcomes:

1. The likelihood a patient with CKD will progress to end-stage kidney disease.
2. The likelihood a patient with CKD will have a major adverse cardiac event, such as heart attack or new heart failure, which are closely associated with kidney disease severity.
3. The likelihood a patient with CKD will die from any cause, which increases with kidney disease severity.

The figure below, for example, is a "heat map" showing the Relative Risk of progression to End Stage Kidney Disease.[1] Green boxes indicate no statistical difference in risk compared to people with normal kidney function, yellow boxes indicate moderate risk, orange indicates high risk, and red alerts to a very high risk. The precise relative risk varies a bit from study to study. To provide one example, in the 2013 publication of the CKD consortium, patients with CKD stage G3aA1 with low urine protein (yellow box) had a relative risk of ESKD of 5.2, meaning that ESKD is expected 5.2 times as frequently as people with similar medical problems who have normal kidney function. Patients in the same study with equivalent kidney function but high urine protein (CKD stage G3aA3, red box on the same row), had a relative risk of 147, meaning that ESKD is expected 147 times more frequently as people with similar medical problems and normal kidney function.[2]

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories Description and range		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73m²) Description and range	G1	Normal or high	≥90		
	G2	Mildly decreased	60-89		
	G3a	Mildly to moderately decreased	45-59		
	G3b	Moderately to severely decreased	30-44		
	G4	Severely decreased	15-29		
	G5	Kidney failure	<15		

Figure 9 | Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International.* Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

Recent research has helped to create a clinical tool, the Kidney Failure Risk Equation (KFRE) that can estimate the absolute risk for that a patient with CKD will progress to End Stage Kidney Disease, based on

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[1] KDIGO Guideline for Chronic Kidney Disease. Kidney International Supplements (2013) 3, 1; doi:10.1038/kisup.2012.73

[2] Matsushita K, et. al., "Cohort Profile: The Chronic Kidney Disease Prognosis Consortium," International Journal of Epidemiology 2013;42:1660–1668. doi:10.1093/ije/dys173.

stable measurements of serum creatinine and urine ACR.[3] The KFRE is most accurate for a population of people, and most accurate for common causes of kidney disease, but with the understanding that the tool is only an estimate, it has helped with clinical decision making. For example, a 65-year-old man with CKD stage 3a, eGFR 50 cc/min and a normal urine ACR of 20 mg/g has only a 0.25% chance of progressing to End Stage in 2 years, and only 0.79% of progressing to End Stage in 5 years. In comparison, a 50-year-old woman with diabetes and eGFR 29 cc/min and urine ACR 350 mg/g has a 28.02% chance of being on dialysis in 5 years.

2d. Important details on how we correctly determine the Stage of Chronic Kidney Disease.

The diagnosis of CKD requires a person to have a persistently elevated creatinine, or excessive albumin in the urine, or both, for at least 3 months. A single, elevated level of creatinine is never sufficient to diagnose chronic kidney disease, because a person may have acute kidney injury, which most often heals (just like a cut with a kitchen knife can heal). Acute kidney injury is different than chronic kidney disease with respect to causes, the chance for full recovery of kidney function, and the associated risks of illness and death. In fact, serum creatinine must be stable for at least several days in order to use the creatinine-based equations that estimate kidney function.

To illustrate this, pretend that I have normal kidney function, with serum creatinine of 1 mg/dL, and I am on an operating table. If someone clamps off both of my kidneys, my kidney function at that point becomes zero. Five minutes later, a blood test will show my serum creatinine is barely above 1mg/dL, and IF this level were stable, the estimating equations would say that I have normal kidney function. However, at the time of this blood test, my actual kidney function is zero, so the equation is grossly overestimating my kidney function. Twelve hours later, my creatinine would be 1.5 and the equation might estimate a kidney function of 60%. Twenty-four hours later, my creatinine would be 2.0 and the equation might estimate kidney function of 40%, but still these are incorrect overestimates of actual kidney function (which is 0%), and the estimating equations should not be used, because the serum creatinine is still rising from one day to the next. To reverse this thought process, if the creatinine rose to 10 and then clamps were removed, my kidney function would start to heal and recover. If the creatinine fell from 10 to 8 mg/dL in one day, we might estimate that I have a GFR of 7 cc/min or about 6% normal kidney function, but this would be true only if my creatinine stays at 8. If the creatinine keeps improving each day, then my actual kidney function is much better than 6% (and we cannot use the estimating equations until the healing is complete and my creatinine is stable again).

Even if serum creatinine is stable, it is not a perfect test of kidney function. First, some medications including trimethoprim, cimetidine, and cyclin-dependent kinase inhibitors such as palbociclib can raise serum creatinine by blocking tubular secretion without changing actual kidney function/glomerular filtration, leading to a falsely low estimate of GFR and a false impression of kidney disease. Second, people with high or low extremes of muscle mass or muscle metabolism will generate atypically high amounts of creatinine in the blood, leading to an erroneous impression that they have kidney disease. Conversely, a patient who has lost muscle mass from Lou Gehrig's disease or a similar condition might have moderately severe kidney disease, but their serum creatinine could be normal, resulting in false reassurance about their kidney function. Kidney function can be measured without using creatinine by measuring the rate of clearance from blood of inulin, iothalamate, or iohexol, but these tests are difficult, may require
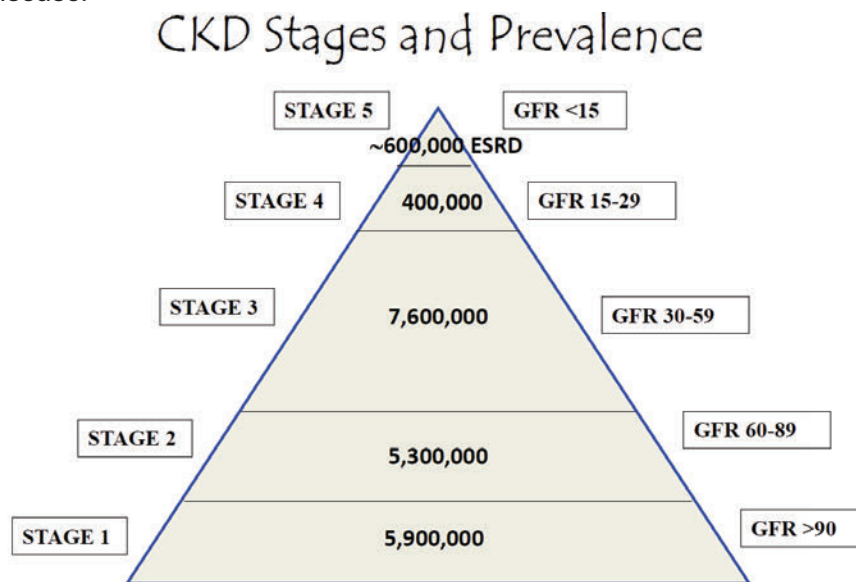
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[3] Tangri N, et al, "A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure." *JAMA*. *2011;305(15):1553-1559*. doi:10.1001/jama.2011.451.

radionuclides, and are usually reserved for clinical research only. In recent years, blood testing of cystatin-C has become a favored alternative to creatinine for estimating kidney function. The level of cystatin-C in blood is much less dependent on muscle mass and has fewer interactions with medications. Cystatin-C can be falsely high in patients with inflammation, so it is not a perfect test, but it is a convenient and increasingly available alternative to serum creatinine for estimating the presence and severity of CKD.

2e: The Prevalence of Chronic Kidney Disease.

It is quite common to have a modest elevation in creatinine with age over 40-45, as will be discussed in additional later, and the result is that mild-moderate CKD is quite common in the general population. From recent statistics, 14% of adults in the USA (1 in 7) have CKD, mostly at mild-moderate stages.[4] Because mild-moderate CKD has no symptoms, up to 90% of adults with CKD are _not_ aware they have kidney disease, and even with severe CKD (stages 4-5), 30% of adults are not aware they have kidney disease due to lack of symptoms.

The prevalence of each stage of CKD in the USA can be illustrated with a Pyramid diagram, as shown below. The base of the pyramid is widest for CKD stage 1 to illustrate the largest number of affected patients, and at each stage of increasing severity, the pyramid narrows, to illustrate that fewer people are affected (the prevalence is lower). Severe CKD (stages 4-5) is less prevalent/common than milder stages for two reasons: first, some forms of kidney disease tend to progress very slowly and do not reach higher stage before someone reaches the end of life; second, patients with CKD stages 4 & 5 have high cardiovascular risks and may pass away from stroke or heart attack before reaching End Stage Kidney Disease.
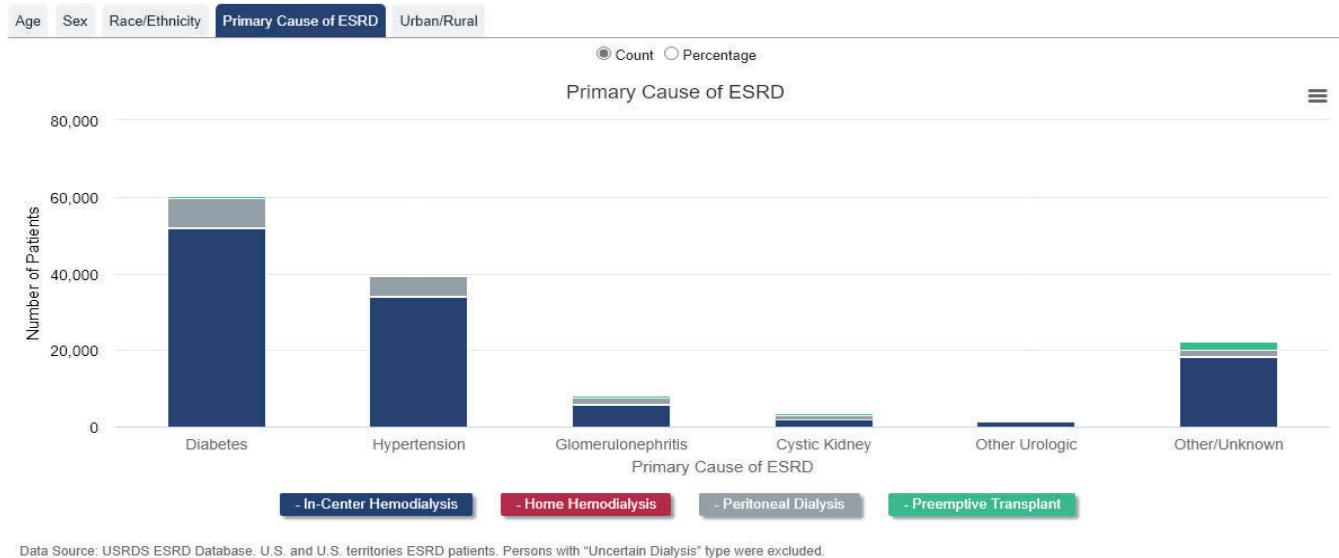
CKD Stages and Prevalence

STAGE 5	~600,000 ESRD	GFR <15
STAGE 4	400,000	GFR 15-29
STAGE 3	7,600,000	GFR 30-59
STAGE 2	5,300,000	GFR 60-89
STAGE 1	5,900,000	GFR >90

2f. What are the Causes of Chronic Kidney Disease?

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[4] "Chronic Kidney Disease in the United States, 2023" https://www.cdc.gov/kidney-disease/media/pdfs/CKD-Factsheet-H.pdf

In this section, we will distinguish <u>causes</u> of kidney disease from <u>risk factors</u> that are associated with developing kidney disease but may not be the direct cause. The most common cause of chronic kidney disease (CKD) is diabetes. Among patients with diabetes, up to 40% have at least moderate kidney disease, CKD stage G3 or higher. To look at this from the other end, for 50% of people in the USA every year who reach End Stage Kidney Disease (ESKD, or ESRD) the cause was diabetes. Other common causes of CKD include genetic disease such as polycystic kidney disease, vascular disease, congestive heart failure, glomerular diseases (many of which are rare), various urologic conditions, certain types of cancer, severe kidney injury from critical illness without recovery, and the deleterious effects of prescription or non-prescription medications. For some patients the cause of kidney disease is certain, with proof obtained by kidney biopsy or genetic testing. For other patients, the cause of CKD is not proven and is based on an educated guess. Among patients who start dialysis every year, the 5 most common causes of ESKD according to the United States Renal Data Systems annual report are listed in the figure below: diabetes, hypertension, glomerulonephritis, cystic kidney diseases, other Urologic disorders, and "other/unknown."[5]

Figure 1.9 Modality at incidence of ESRD by patient characteristics, 2021

Data Source: USRDS ESRD Database. U.S. and U.S. territories ESRD patients. Persons with "Uncertain Dialysis" type were excluded.

We should recognize that "cause" of kidney disease in this chart comes from checking a box on a form 2728 submitted to the government in the first month someone begins dialysis, and this cause is often not "proven" by high quality testing. For example, the USRDS report lists "hypertension" as the #2 cause of ESKD but this is controversial. Rather than hypertension causing CKD, increasing evidence suggests it is the other way around, with unidentified causes of CKD resulting in hypertension.[6,7] Similarly, risk factors for CKD such as age, obesity, and our diet (whether we eat fresh food versus food with preservatives) do not have an established cause-and-effect with kidney disease, but any activity good for overall health is likely good, on average, for long term kidney function. The figure below combines diseases that we know <u>cause</u>

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[5] USRDS 2023 annual report. Annual Data Report | USRDS (nih.gov). Among 113,309 incident dialysis patients in 2021, diabetes was believed to be "the cause" in 60,101 patients.
[6] Shantha M et al, "Renal function during antihypertensive treatment," The Lancet Vol 345: 749-51. 1995. DOI:10.1016/S0140-6736(95)90638-X.
[7] Freedman BI and Sedor JR, "Hypertension-associated kidney disease: perhaps no more," J Am Soc Nephrol Vol 19:2047-41. 2008. doi: 10.1681/ASN.2008060621.

CKD (such as polycystic kidney disease and diabetes) with conditions that are not the cause *per se* but which are correlated with kidney disease.[8]

Box 2 | **Risk factors for chronic kidney disease onset**

- Monogenic kidney disease (for example, autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry disease, Alport syndrome and complementopathies such as atypical haemolytic-uraemic syndrome)
- Congenital abnormalities (for example, congenital anomalies of the kidney and the urinary tract and vesico-ureteric reflux)
- Type 1 or type 2* diabetes mellitus
- Poorly controlled arterial hypertension
- Obesity*
- Prolonged exposure to nephrotoxins* (for example, chemotherapy for cancer treatment, proton pump inhibitors, NSAIDs, antimicrobial agents, contaminated herbs and plant-based food, agricultural chemicals, heavy metals and irradiation)
- Climate (excessive heat exposure and dehydration)
- Infections and chronic inflammation* (for example, HIV, hepatitis virus, malaria, bacterial infections and autoimmune diseases)
- Malignancy* (for example, multiple myeloma)
- Episodes of acute kidney injury*
- Low nephron endowment at birth (due to low birthweight or fetal dysmaturity)
- Obstructive uropathy

*Denotes risk factors that also influence chronic kidney disease progression, which also include arterial hypertension, proteinuria, obstructive uropathy, smoking, hyperhomocysteinaemia and hyperuricaemia.

Most people loose kidney function with age, which can either contribute to CKD severity or provide reassurance, depending on the circumstances. Aging can contribute to CKD severity if someone already has CKD by middle age (for example, from diabetes, heavy cigarette smoking or other causes). At that point, even if they become health conscious, CKD can continue to worsen over time due to aging. On the other hand, aging can provide reassurance for adults over 70 who are labeled as having CKD but are otherwise very healthy. In one study of active adults without diabetes, heart disease, or hypertension, serum creatinine was high enough for a diagnosis of CKD stage 3 in about 50% of adults >70 years, and at the rate these people were losing kidney function with aging, the worst 5-10% might need dialysis by age 105-110 years old.[9] In other words, to a large degree, "CKD of aging" is a natural process of life, and if no other causes of CKD are found on evaluation, then the risk of reaching End Stage Kidney Disease during one's lifetime is not increased, leading to suggestions by leading kidney doctors that these patients do not really have a kidney "disease," and should be dismissed from requiring kidney clinic visits.[10],[11]

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[8] Romagnani P, et al; "Chronic Kidney Disease," *Nat Rev Dis Primers* **3**, 17088 (2017). doi.org/10.1038/nrdp.2017.88.

[9] Wetzels JFM et al, "Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study," Kidney Int, 2007. 72(5):632-7. doi: 10.1038/sj.ki.5002374.

[10] Liu P, et al "Accounting for Age in the Definition of Chronic Kidney Disease," JAMA Intern Med. 2021. Vol 181(10):1359–1366. doi: 10.1001/jamainternmed.2021.4813.

[11] Oliva-Damaso N et al, "Risk-based versus GFR threshold criteria for nephrology referral in chronic kidney disease," Clin Kidney J. 2022. Vol 15(11):1996-2005. doi: 10.1093/ckj/sfac104.

2g. What are the treatments for Chronic Kidney Disease?

The best treatment for CKD depends on the cause. Some forms of progressive kidney disease can be reversed or at least markedly improved if accurately diagnosed, especially if these reversible causes are identified early, before fibrosis occurs. Examples of the benefits of early diagnosis and treatment include tolvaptan for Polycystic Kidney disease, enzyme therapy for Fabry's disease, immunosuppression for ANCA vasculitis, chemotherapy for Myeloma kidney, or discontinuation of medications that cause allergic interstitial nephritis.

Additional treatments are applicable to most kidney diseases. These treatments do not directly block the cause of a kidney disease, but they slow progression of most kidney diseases. First, inhibition of the renin-angiotensin-aldosterone axis with either angiotensin converting enzyme inhibitors or aldosterone receptor blockers (Ace-I or ARB) slows the rate of progression to ESRD in patients with CKD and proteinuria, whether the cause is diabetes or other glomerular diseases.[12] Related medications that block aldosterone activity at the mineralocorticoid receptor are also helpful for reducing proteinuria in CKD, as well as controlling resistant hypertension in patients with kidney disease.[13]

Two recent classes of medications intended to treat diabetes have additional benefit for slowing progression of chronic kidney disease. Sodium/glucose co-transporter inhibitors, collectively referred to as "flozins," inhibit reabsorption of glucose in the proximal tubule and mildly improve glucose control. When added to Ace-I or ARB therapy, these SGLT-2 inhibitors decrease the rate of kidney disease progression, especially in patients with proteinuria due to diabetic or non-diabetic CKD.[14] Similarly, GLP-1 agonists such as semaglutide and liraglutide, which improve glucose control by reducing appetite, stimulating insulin release and reducing glucagon release, have the added benefits of reducing the rate of progression of chronic kidney disease, and of reducing the risk of heart diseases in patients with CKD.[15]

Lastly, there are treatments that are widely beneficial for most causes of CKD. First, for most causes of CKD, treatment of hypertension is recommended, with a goal blood pressure 130/80 or less, and possibly under 120 in high-risk patients. Whether hypertension is the cause or the effect of kidney disease is controversial, as described above in section 2f, but regardless of cause or effect, good control of hypertension significantly reduces a patient's risk of stroke, and probably reduces the risk of heart attack. In CKD patients with high urine protein (>300 mg/gm spot ratio), good control of hypertension also slows the rate of progression towards End Stage Kidney Disease.[16] A second treatment for most causes of CKD is

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[12] Heerspink H.J.L. et al, "Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis," 2015. J Am Soc Nephrol, 26(8): 2055-64. doi: 10.1681/ASN.2014070688.

[13] Bomback A.S. et al, "Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review," 2008, Am J Kidney Dis. 51(2):199-211. doi: 10.1053/j.ajkd.2007.10.040.

[14] Reyes-Farias, C.I. et al, "The effect of sodium-glucose cotransporter 2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes mellitus on cardiovascular and renal outcomes: A systematic review and meta-analysis" 2023, PLoS One, Vol 18(11):e0295059. doi: 10.1371/journal.pone.0295059.

[15] Chen, J-Y. et al, "Kidney and Cardiovascular Outcomes Among Patients With CKD Receiving GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis of Randomized Trials," Am J Kidney Dis, 2025. doi:10.1053/j.ajkd.2024.11.013.

[16] Lewis, C.E. et al, "Final Report of a Trial of Intensive versus Standard Blood-Pressure Control," N Engl J Med 2021;384:1921-30. DOI: 10.1056/NEJMoa1901281.

the use of HMG-CoA reductase inhibitors, or "statins," which block cholesterol biosynthesis to slow atherosclerosis and reduce the rate of heart attack. CKD patients have particularly high rates of cardiovascular disease, for several reasons, and "statins" are effective in reducing these risks. "Statins" are particularly important for patients with CKD caused by atherosclerosis of the renal arteries, which is also called chronic ischemic nephropathy.[17]

2h. What are the long-term complications of Chronic Kidney Disease?

The two long-term complications of kidney disease are an increased risk of major adverse cardiovascular events (including stroke, heart attack, and sudden cardiac death) and progression to ESRD (including dialysis, kidney transplantation, and conservative care).

Major adverse cardiovascular events increase with higher stages of kidney disease. As illustrated in the heat map of cardiovascular mortality below,[18] the red box with the number "4.3" indicates that a patient with CKD stage G3a, A3, has a relative risk 4.3 times greater than someone without kidney disease but with similar age, smoking, diabetes, and family history. In contrast, for CKD stage 2 with minimal proteinuria, the relative risk of death due to heart disease is not significantly increased, as illustrated by the green numbers "1.0" and "1.1."

Cardiovascular Mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

In patients with advanced age and multiple cardiovascular risk factors, the most likely complication of CKD stage 4/5 is death by heart attack, but the complication that concerns patients the most is the question of dialysis. Patients who progress to ESRD actually have 3 options: dialysis, kidney transplantation, and conservative care, and the "best" choice depends on the patient's risks and goals.

If patients chose dialysis, the main benefit is to sustain life, especially as a bridge to kidney transplantation. The best time to start dialysis, once a patient reaches stage 5, remains an active area of research. The most straightforward reasons for starting dialysis are:

[17] Hicks, C.W. et al, "Atherosclerotic Renovascular Disease: A KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference," Am J Kid Dis, 2022, Vol 79(2): 289-301. DOI: 10.1053/j.ajkd.2021.06.025.

[18] Matsushita K, et. al., "Cohort Profile: The Chronic Kidney Disease Prognosis Consortium," International Journal of Epidemiology 2013;42:1660–1668. doi:10.1093/ije/dys173.

- Recurrent hyperkalemia that is resistant to diuretics and dietary counselling and is severe enough to risk cardiac arrythmia.
- Volume overload that is resistant to diuretics and dietary counselling and is severe enough to cause shortness of breath or hospitalization for hypertension.
- "Uremia," which is the term for the symptoms caused by CKD, which are improved by dialysis.

As mentioned above in section 2e, up to 30% of patients with CKD stage 4/5 were never aware they had kidney disease and had no symptoms. Uremic symptoms sometimes start when GFR falls below 15 cc/min, but more often, there are no symptoms until the GFR is lower than 10 cc/min, and rare patients continue to feel fine even when GFR is 5 cc/min or less (about 4% of total kidney function). Uremic symptoms are caused by several molecules that we do not routinely measure, which rise in tandem with BUN and creatinine. These unmeasured molecules, such as indoxyl sulfate & p-cresyl sulfate, interfere with nerve conduction and irritate brain areas related to eating, smelling, and taste, resulting in symptoms of decreased appetite, a foul or metallic taste in the mouth, intolerance of meat/umami flavors, and nausea. Uremia also interferes with circadian sleep cycles, and eventually leads to decreased activity of our entire brain, resulting in symptoms of progressive sleepiness. Uremia can also predispose to seizures, and can result in inflammation of the pericardium, which is the fibrous sac that surrounds the heart. In patients with CKD 5 who have no symptoms, stable potassium and stable volume, there is no evidence that starting dialysis is helpful, and as GFR continues to fall, the KDIGO (Kidney Disease Improving Global Outcomes) expert suggestion is to "consider" starting dialysis when eGFR reaches 6-8 cc/min/1.73m2.

If a patient choses dialysis, there are three basic modalities available: in-center hemodialysis, home hemodialysis, and home peritoneal dialysis. Each of these three options can substitute as an artificial kidney to clean the blood and remove fluid, and the final choice of modality depends on patient preference. In some countries, such as Hong Kong and Australia, home peritoneal dialysis and home hemodialysis are quite popular. For historical reasons, in-center hemodialysis is the most common dialysis modality in the USA. Patients receiving in-center hemodialysis receive 3 dialysis sessions per week, each about 3.5-4 hours long, and this short amount of time replaces what their kidneys used to do 24 hours per day, 7 days per week. As such, the 3.5-4 hour dialysis treatments require rapid removal of fluid and toxins. Patients may gain 4-10 pounds of fluid between dialysis sessions and need to have all this fluid removed during a single treatment, along with all excess salts, by-products of metabolism, and toxins. Removing 10 pounds of fluid during dialysis means that, as fluid is removed from the vascular space, the fluid must be refilled from other parts of the body, or else a patient's blood pressure will drop precipitously. Shifts of fluid and salt during dialysis can lead to muscle cramping (which can be painful), headaches, changes in heart rhythm, or changes in blood pressure that result in fainting or rarely, in cardiac arrest. Afterwards, most dialysis patients in surveys report severe fatigue lasting from 2-10 hours.[19] Many patients on chronic dialysis continue to work, support their families, and have fulfilling lives, but dialysis treatments are not easy.

Hemodialysis requires ultrapure water. Contamination problems of dialysis water include bacteria, which can result in infection, chloramines, which can result in hemolytic anemia, aluminum, which can result in arthritis or dementia, and more. Ultrapure water and concentrated dialysate are mixed and then adjusted for each patient, to account for varied needs of sodium, potassium, and acid removal. Overall, the risk of infection is lowest among patients who use a native arteriovenous fistula, increases in patients with

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[19] Rayner HC et al, "Recovery time, quality of life, and mortality in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS)." Am J Kidney Dis. 2014. 64(1):86-94. doi: 10.1053/j.ajkd.2014.01.014.

a synthetic graft, and is highest among patients using a tunneled dialysis catheter, because the artificial material provides a haven for bacteria to hide from the immune system. Infections sometimes result in sepsis, and may spread to other parts of the body, causing endocarditis, septic thrombophlebitis, septic arthritis, or an abscess. Next to cardiovascular disease, infectious complications are the major risk of morbidity and mortality among dialysis patients. In combination, if we combine the increased risks of infection with the increased risk of cardiovascular disease among dialysis patients, the risk of death is significantly higher than the general population and is similar to patients with Duke's Stage C colon cancer. A recent study from Ontario, Canada found that the risk of death among dialysis patients is a bit worse than patients with breast or colon cancer (including all stages of cancer).[20]

With the pros and cons of dialysis in mind, it will be easy to appreciate why kidney transplantation is the preferred treatment for patients with End Stage Kidney Disease. Transplantation offers improved 5 and 10-year rates of survival to dialysis, and better quality of life compared to dialysis. The figure below is based on risk of mortality, over 8 years, of patients with ESRD who received a kidney transplant, compared with matched patients with ESRD who were still on dialysis, awaiting transplant.[21] It shows an increased risk of death from the transplant surgery itself, at day 0, and by 106 days following transplant surgery, the risks and benefits for mortality are even. Thereafter, we see a clear mortality benefit for transplantation (about 1/3rd the risk of death for patients after kidney transplantation compared to matched patients on hemodialysis). Transplant also dramatically improves quality of life, including energy level, dietary options, strength, sleep, and even the ability to become pregnant.
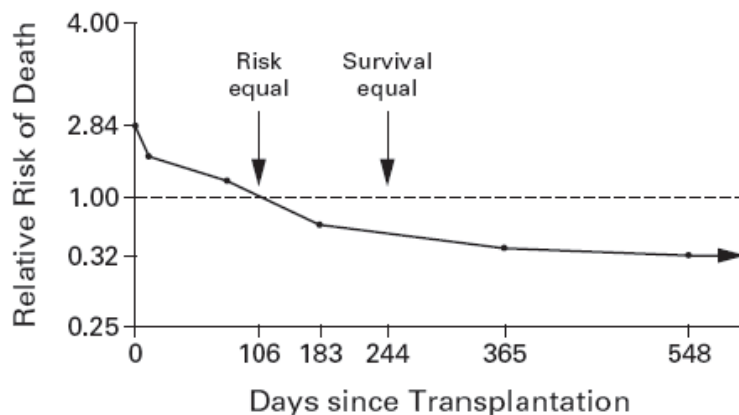

Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

Transplantation, in addition to its many benefits, caries certain risks and requires careful clinical monitoring of potential complications. The major risk following kidney transplantation is organ rejection. Careful matching of patients with recipient organs has helped to reduce incompatibility and rejection rates, as have advances in immunosuppression medications that promote "tolerance" of transplanted organs. Nevertheless, acute and chronic rejection remain a major concern, especially within the 1st year after

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[20] Naylor, K.L. et al, "Mortality in Incident Maintenance Dialysis Patients Versus Incident Solid Organ Cancer Patients: A Population-Based Cohort," Am J Kidney Dis. 2019. 73(6):765-776. doi: 10.1053/j.ajkd.2018.12.011.

[21] Wolfe, R.A. et al, "Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant." N Engl J Med. 1999. 341(23):1725-30. doi: 10.1056/NEJM199912023412303.

transplant, and can lead to loss of transplant (necessitating immediate return to dialysis), or severe illness (necessitating hospital care).

The chance that a kidney transplant successfully works, which is known as "graft survival," is shown below, along with the range expressed as a 95% confidence interval. A transplant from a living donor (family or friend) has the highest chance of long-term success, with 97.5% working at 1 year, and 85.6% working at 5 years. Cadaveric donors, from patients who die of other causes and wish to donate their organs, have a lower but still appreciable success of 93.2% at 1 year, and 74.4% at 5 years.

Organ Procurement and Transplantation Network
Kidney Kaplan-Meier Graft Survival Rates For Transplants Performed : 2008 - 2015

> **Information!** Based on OPTN data as of January 26, 2025.

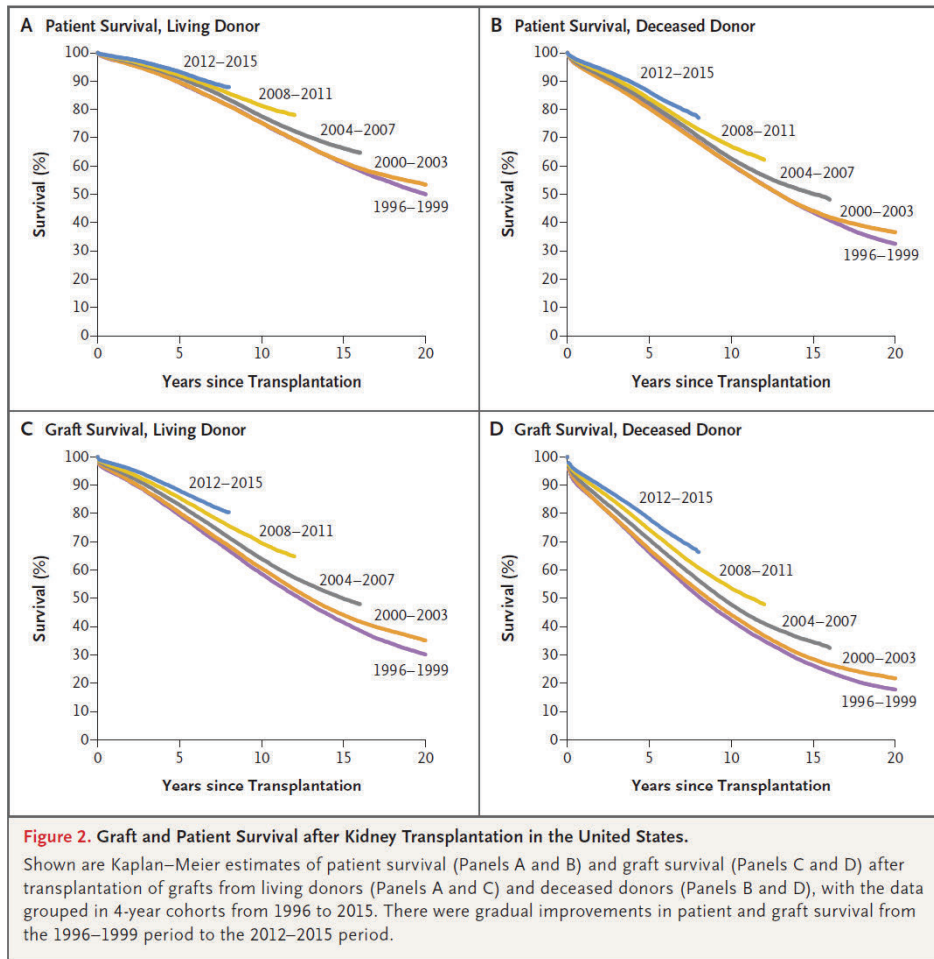Change Report (Optional):   Create a New Report

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Kidney ∨ Graft ∨ Go

| Region	Donor Type	Years Post Transplant	Number Functioning / Alive	Survival Rate	95% Confidence Interval
U.S.	Cadaveric	1 Year	42400	93.2	(93.0, 93.4)
U.S.	Living	1 Year	21739	97.5	(97.3, 97.7)
U.S.	Cadaveric	3 Year	35582	85.1	(84.7, 85.4)
U.S.	Living	3 Year	20743	92.5	(92.2, 92.9)
U.S.	Cadaveric	5 Year	28854	74.4	(74.0, 74.8)
U.S.	Living	5 Year	18925	85.6	(85.2, 86.1)

Data subject to change based on future data submission or correction.This report shows OPTN data for Kidney Kaplan-Meier Graft Survival Rates For Transplants Performed : 2008 - 2015 through January 26, 2025. OPTN Data

Due to advances in organ matching, surgical techniques, and medical therapies, recently transplanted kidneys are expected to last longer than in the past, and transplanted patients are expected to survive longer. As shown in the figure below, when all transplant patients since 1996 are grouped into 4-year intervals according to date of their surgery, the progressive improvement in kidney transplant function and patient survival is evident.[22] The most recent data are from 2012-2015, because it is too soon to have long-term data on 2016-2019, much less for 2020-2023.

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[22] Hariharan S, et al, "Long term survival after Kidney Transplantation," New Eng J Med. 2021. 385(8):729-743. doi: 10.1056/NEJMra2014530.

Figure 2. Graft and Patient Survival after Kidney Transplantation in the United States.
Shown are Kaplan–Meier estimates of patient survival (Panels A and B) and graft survival (Panels C and D) after transplantation of grafts from living donors (Panels A and C) and deceased donors (Panels B and D), with the data grouped in 4-year cohorts from 1996 to 2015. There were gradual improvements in patient and graft survival from the 1996–1999 period to the 2012–2015 period.

A large majority of kidney transplants are from cadaveric donors, and the quality of the donor kidney makes a significant difference on long term transplant outcomes. The Kidney Donor Prediction Index provides a scoring system for the quality of a cadaveric kidney. The lower the KDPI, the better the quality of the organ, and lower KDPI score correlates with longer transplant function for patients, as shown below. However, the benefit of having the highest quality kidney is counterbalanced by how long it might take on the transplant waitlist to receive such a kidney. For patients on dialysis, a lower quality kidney (higher KDPI) that comes quickly is often preferable to remaining on the waitlist, hoping for a high-quality kidney. Prolonged time on the waitlist caries a lower quality of life while on dialysis, and a higher risk of adverse cardiovascular and infectious outcomes, including death.
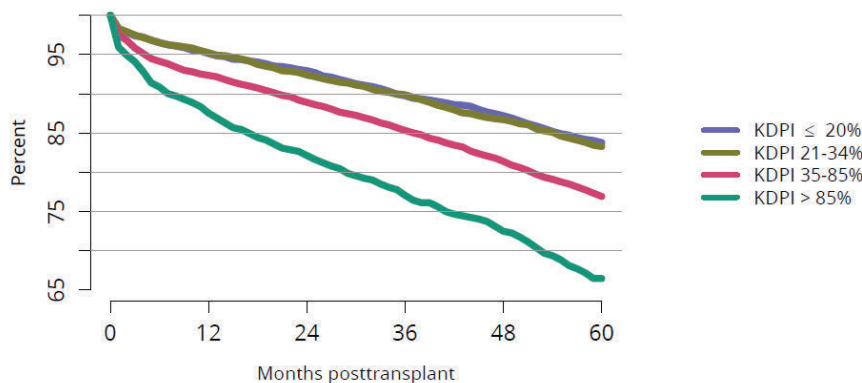
After a successful surgery, a kidney transplant patient requires clinical monitoring. There is no universal standard for management of patients after kidney transplantation, and each medical center has small differences in medication management and required testing. A comprehensive general reference is the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Patients.[23] The general aims of post-transplantation clinical monitoring are as follows:

1. Blood tests to monitor transplant kidney function for purposes of detecting and treating any episodes of rejection as soon as possible
2. Blood tests to ensure transplant immune suppressing medications remain at the goal level (high enough to minimize the risk of rejection, but not so high as to cause side effects or toxicity. For example, high levels of the calcineurin inhibitors cyclosporine or tacrolimus can cause acute kidney injury, chronic kidney disease, predispose to new onset diabetes, tremor, and hypertension.
3. Clinical monitoring and blood tests for signs of infection. Transplant medications, by virtue of suppressing the immune system enough to prevent rejection, also predispose to infections. This includes infections that arise only in the immunosuppressed, such as Pneumocystis or BK virus, and increased chance of infections seen in the general population. Because the levels of immune suppression are highest shortly after transplant can are gradually tapered over 1 year, the most likely infectious in transplant patients change if within 1 month of transplantation, if within 6-12 months, or if 1 year after transplantation, as shown in the figure below.[24]

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[23] Kidney Disease: Improving Global Outcomes. Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(Suppl 3):S1–S157.

[24] Fishman, J.A. "Infection in Solid-Organ Transplant Recipients." N Engl J Med. 2007 357:2601-2614. DOI: 10.1056/NEJMra064928
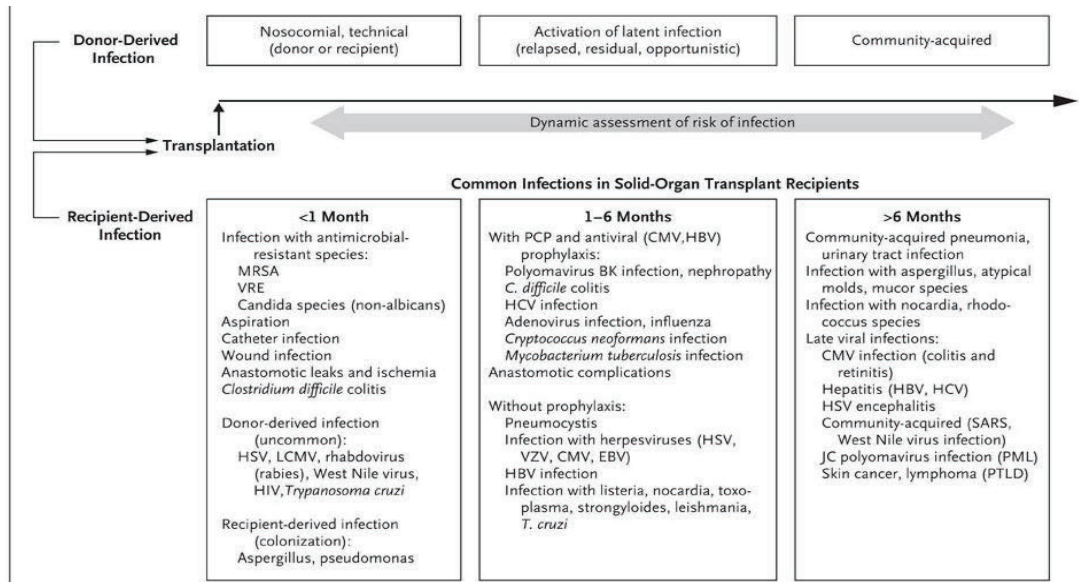
4. Clinical monitoring and treatment for cardiovascular disease after kidney transplantation, which includes appropriate treatment for hypertension, dyslipidemia, and any new onset diabetes.
5. Clinical monitoring for cancer after kidney transplantation, particularly skin cancer. Many recent advances in cancer treatment help augment the body's immune system to attack anything foreign, with the aim of attacking cancer cells. The converse of this is that transplant patients, by virtue of immune suppressing medications, have a decreased ability to fight off cancer. The risk of cancer after kidney transplantation in the USA, expressed as a Standardized Incidence Ratio, is more than twice that of the general population, and is especially high for skin cancer in sun-affected areas, and for non-Hodgkin's lymphoma.[25] In some cases, the treatment for cancer includes reducing immune suppressing medications, especially for post-transplant lymphoproliferative disorder, but reducing medications also increases the risk of transplant rejection.

A succinct table that summarizes most of the scheduled monitoring for the care of a patient following kidney transplantation is shown below, from a summary of the 2009 KDOQI guidelines for transplant care.[26] A more comprehensive table is shown below that, which includes suggestions for the frequency of clinical visits, blood testing, monitoring for cardiovascular disease, and monitoring for cancer.[27]

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[25] Chapman, J.R. et al, "Cancer in the transplant recipient," Cold Spring Harb Perspect Med. 2013 3(7):a015677. doi: 10.1101/cshperspect.a015677.

[26] KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Kidney Dis*. 2010;56:189-218.

[27] Hariharan, S. "Recommendations for Outpatient Monitoring of Kidney Transplant Recipients." 2006. AJKD 47(4) S22-S36.

SCREENING and GRAFT MONITORING

- Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment that may improve outcomes.
- Suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. [R 8.4 (2C)]

ROUTINE SCREENING AFTER KIDNEY TRANSPLANTATION

Screening Test	Screening Intervals by Time After Transplantation					
	1 week	1 month	2-3 months	4-6 months	7-12 months	>12 months
Creatinine[a]	Daily	2-3 per week	Weekly	Every 2 weeks	Monthly	Every 2-3 months
Urine protein[b]	Once		Every 3 months			Annually
Complete blood count[c]	Daily	2-3 per week	Weekly	Monthly		Annually
Diabetes[d]	Weekly		Every 3 months			Annually
Lipid profile[e]	–	–	Once	–	–	Annually
Tobacco use[f]	Prior to discharge		–	–	–	Annually
BKV NAT[g]	Monthly		Every 3 months			–
EBV NAT (seronegative)[h]	Once	Monthly		Every 3 months		–
Blood pressure, pulse, height, body weight	Each clinical visit					

BKV, BK polyoma virus; EBV, Epstein-Barr virus; NAT, nucleic acid testing.
[a]Serum creatinine. Suggest estimating GFR whenever serum creatinine is measured [R 8.3.1 (2D)] using one of several formulas validated for adults (2C), or the Schwartz formula for children and adolescents (2C).
[b]Urine total protein and/or urine albumin.
[c]Complete blood count, including white blood count, hemoglobin and platelet counts.

[d]Screen for diabetes with fasting blood glucose, glucose tolerance test, or HbA_{1c} level.
[e]Lipid profile includes fasting cholesterol, LDL-C, HDL-C, and triglycerides.
[f]Screen for tobacco use.
[g]Screen for BKV using plasma NAT.
[h]Screen for EBV using plasma NAT in patients with no antibody to EBV at transplant.

Table 1. Recommended Schedule for Posttransplantation Monitoring of Adult Kidney Transplant Recipients[1]

	0-1 Month	1-3 Months	4-6 Months	7-12 Months	13-24 Months	>25 Months
Physical examination/history	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/6 mo	1 time/6 mo
Blood pressure	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/6 mo	1 time/6 mo
Weight and body mass index	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/6 mo	1 time/6 mo
Drug-related side effects	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/6 mo	1 time/6 mo
Adherence	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/6 mo	1 time/6 mo
Graft function						
Renal function (SCr, blood urea nitrogen)	3 times/wk	1 time/wk	Every other wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Urinalysis	Within first 2 wk, then every 3-6 mo for 1 y, then every 6-12 mo					
Urine spot (protein-creatinine ratio)	Within first 2 wk, then every 3-6 mo for 1 y, then every 6-12 mo					
CrCl/GFR	3 times/wk	1 time/wk	Every other wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Renal histology*	At 1 mo	At 3 mo	At 6 mo	At 12 mo		
Hematologic						
Complete blood count	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Platelets	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Hemoglobin/hematocrit	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Anti-HLA antibodies*	At 1 mo	At 3 mo	At 6 mo	At 12 mo	At 24 mo	Annually
Metabolic/other						
Lipids	Every 6 mo for 1 y, then at least annually					
Blood glucose (fasting)	1 time/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Hemoglobin A$_{1c}$	Annually after the first transplantation y					
Uric acid	Every 6 mo for 2 y, then 1 time/y					
Calcium and phosphorous	1 time/wk	1 time/mo	1 time/3 mo	1 time/3 mo	Annually	Annually
Parathyroid hormone†	At 1 mo		At 6 mo	At 12 mo	Annually	Annually
Liver function	1 time/mo 1, followed by 1 time/3 mo during the first y and then every 6 mo					
Therapeutic drug levels‡	3 times/wk	1 time/wk	1 time/2 wk	1 time/mo	1 time/1-3 mo	1 time/1-3 mo
Virology						
CMV§ (blood, by PCR)		Every 3 mo for the first y				
EBV§ (blood, by PCR)		Every 3 mo for the first y				
BK virus‖ (blood and urine, by PCR)	At 1 mo	At 3 mo	At 6 mo	At 12 mo	At 24 mo	
Hepatitis B and C	No specific recommendation; however, patients with hepatitis B and C infection may need periodic liver function evaluation and selected individuals may need viral load monitoring					
Bone densitometry	At the time of transplantation, 6 mo, and then annually, if previous results abnormal				Every other y	

(Continued)

Table 1 (Cont'd). Recommended Schedule for Posttransplantation Monitoring of Adult Kidney Transplant Recipients[1]

	0-1 Month	1-3 Months	4-6 Months	7-12 Months	13-24 Months	>25 Months
Malignancy						
Skin examination				Annually		
Papanicolaou smear				Annually		
Mammography				Annually		
Prostate-specific antigen				Annually		

NOTE. In addition to the published article cited,[1] some recommendations in this table are based on the clinical experience of Sundararm Hariharan, MD (written communication, November 2005).

Abbreviations: CrCl, creatinine clearance; SCr, serum creatinine; GFR, glomerular filtration rate; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction.

*Not routinely recommended; may be performed, depending on immunologic risk and potential for intervention.

†Additional tests to be performed when patients experience hypercalcemia.

‡Primarily cyclosporine, tacrolimus, and sirolimus. The utility of obtaining mycophenolic acid levels is under investigation.

§For seronegative recipients of a seropositive donor kidney only.

‖BKV screening is recommended if transplant center has a high rate of BK virus infection.

Adapted from Kasiske BL, Vasquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol 2000;11:S1-S86.

The last option for patients who progress to End Stage Kidney Disease is conservative care. Dialysis and transplantation are sometimes not attractive options for patients who are too frail for surgery, or too frail for outpatient dialysis, or for personal reasons would prefer to let nature takes its course. These

patients are treated with medications to preserve the quality of life, and the quantity of good life, as they see fit.[28]

      In summary, ESRD is a life-changing event. Early diagnosis and treatment of chronic kidney disease is always the preference, to prolong kidney function and delay the onset of ESRD. As a kidney doctor, delaying the need for dialysis as long as possible is always a primary aim. Unfortunately, because kidney disease often lacks symptoms, some people have already progressed to advanced stage CKD at the time of diagnosis. Regardless of cause, when ESRD becomes inevitable, physicians and patients work together to plan for dialysis at home or in-center, line up for kidney transplantation, or opt for conservative care.

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[28] Bansal A.D. et al, "Ten Tips Nephrologists Wish the Palliative Care Team Knew About Caring for Patients with Kidney Disease," J Palliat Med. 2018 A21(4):546-551. doi: 10.1089/jpm.2018.0087.

3. Relevant Clinical History for Mr. Frank Mousser.

Chronologically, Mr. Mousser's genitourinary issues begin in 1983, shortly after he arrived at Camp Lejeune, when he experienced gross hematuria, visible blood in the urine. His evaluation at that time was reassuring, including a negative intravenous pyelogram and a cystoscopy consistent with cystitis. Mr. Mousser experienced gross hematuria again in 2013, 2017, and July 2020. Mr. Mousser has testified to a smoking history while in the Marines, which is a major risk factor for urothelial carcinoma. He underwent repeat evaluation for hematuria. He also underwent evaluation for proteinuria at this time and was started empirically on lisinopril followed by empagliflozin. However, his evaluation was negative for serologic causes of glomerular disease and, in retrospect, his elevated urine protein may have been an epiphenomenon of cancer, because his CT Urogram in August 2020 revealed a 3.7 cm right kidney mass, suspicious for cancer. On ureteroscopy, cytology of cells was consistent with urothelial carcinoma. In October 2020 he had a robotic right nephroureterectomy, followed by gemcitabine washing of the bladder and residual tumor bed. Pathology of the resected kidney confirmed high grade, non-invasive, papillary renal carcinoma, with negative margins and negative lymph nodes.

Following his surgery, in 2021, his creatinine was 1.5-1.6, with an eGFR in the upper 40 cc/min. In early 2022 his creatinine rose to 1.9 but creatinine improved one month later (This peak creatinine of 1.9 cannot be used to calculate a CKD stage, as described in section 2d of the "General Introduction to Kidney Disease" since it was an acute change in creatinine, which improved 1 month later.) From records at the Audie Murphy Veterans Memorial Hospital, his kidney function remained stable over the next several years including serum creatinine 1.5 mg/dL on Jan 12, 2024, then slightly improved to creatinine 1.4 mg/dL (eGFR 57) on Nov 8, 2024, and then creatinine 1.3 mg/dL (eGFR 63) on Jan 6, 2025. To complete the staging of his kidney disease, his urine albumin/creatinine ratio was checked 4 times in 2024 (Jan 12, May 15, July 15 and Nov 8, 2024), and on each occasion was either less than 30 mg/g or the albumin was so low that a ratio could not be calculated. It seems the proteinuria that was found prior to his cancer had fully resolved (with the caveat that he was being treated with medication that reduce proteinuria). With respect to staging of his kidney disease, he had CKD stage G3a, A1 throughout 2024, and based on the most recent data from Jan 2025, his only value of creatinine would be slightly improved to CKD Stage G2, A1. For a review of the stages of CKD, please see section 2c and 2d, above, in the "General Introduction to Kidney Disease".

A complete medical problem list for Mr. Mousser includes the following, according to his Jan 6, 2025 Urology follow up note, combined with his Anesthesia pre-operative evaluation note:
- High grade urothelial carcinoma, for which he underwent a robotic nephroureterectomy in Oct 2020, non-invasive on pathology, with negative margins and negative lymph nodes, including gemcitabine irrigation of the tumor bed.
- History of cigarette smoking
- Coronary artery disease, for which he underwent percutaneous coronary intervention x 4, as well as Coronary artery bypass graft surgery (4 vessel) about 7 years ago
- Diabetes mellitus
- Peripheral artery disease
- Hypertension
- Obesity with BMI > 30
- Obstructive sleep apnea
- Chronic back pain for which he underwent surgery
- Anxiety

- Depression

4. Conclusions on the clinical course of Mr. Mousser's CKD, including future expectations following his nephroureterectomy, and the need for future care.

a) Plaintiff is seeking judgement against the USA on the basis that contaminated water from Camp Lejeune caused upper tract urothelial carcinoma (UTUC), which resulted in nephroureterectomy, which Plaintiff claims will result in additional, significant, adverse health outcomes described below. With regard to the cause of urothelial cancer, I defer to experts in that area.

b) With regard to concerns of the future risk of progressive kidney disease following nephroureterectomy, Mr. Mousser actually has a good prognosis. I am uncertain why Mr. Mousser chose to stop work following his nephroureterectomy in 2020, but the cause of his decreased functional capacity for work and life activity is not related to having a single, remaining left kidney.

To begin with, the immediate effects of removing one kidney should be an increase in creatinine and a decrease in kidney function by half, using estimated GFR (though, as described below, hypertrophy will begin to make up this decrease). Normal kidney function is 100-120 cc/min, and after nephroureterectomy in October 2020, Mr. Mousser had a creatinine of 1.6, and then for most of the next year in 2021, his eGFR as in the upper 40s to lower 50s, very close to expectations. Over the next several years, his creatinine increased at times, and then improved back to baseline. The highest creatinine of 1.9 was ascribed to low blood pressure and use of lisinopril, and after his doctors decreased his dose of lisinopril, the creatinine improved back to baseline within one month. This short-term increase in creatinine, also called acute kidney injury, is different from CKD, and for Mr. Mousser, the reasons that a decrease in lisinopril might lower creatinine are entirely expected. Low blood pressure decreases blood flow to the kidneys and thereby decreases kidney function, and if anti-hypertensive medications such as lisinopril reduce blood pressure a bit too much, then we expect to see a small rise in creatinine, which will improve back to baseline kidney function if blood pressure mediations are reduced, and blood pressure rises back to normal. In addition, lisinopril is particularly effective at decreasing intra-glomerular filtration pressure, which reduces the glomerular filtration rate (and raises creatinine). This confers a long-term benefit for certain types of kidney disease, but it is known and expected that, in the short term, lisinopril may increase serum creatinine by up to 30%. In combination, when a patient is on lisinopril AND has low blood pressure, creatinine increases for two reasons—low systemic blood pressure AND low intra-glomerular pressure. In this scenario, when the dose of lisinopril is reduced and blood pressure rises back to normal, both of these processes reverse, allowing kidney function to rapidly improve.

The fact that creatinine can change acutely, up and down, also illustrates that the highest creatinine experienced by a patient should not be used in deciding the stage of CKD. While not always obvious at the time if a creatinine value is acute or chronic disease, if creatinine significantly improves later, then the peak creatinine was not CKD. As described in section 2, "General Introduction to Kidney Disease", in order to diagnose CKD, the creatinine must be elevated for at least 90 days, and to accurately stage CKD, the creatinine should be stable.

In the months and years after nephroureterectomy, creatinine can moderately improve, which is a well described phenomenon, due to hypertrophy and hyperfiltration of the remaining

kidney.[29] Quite literally, the remaining, single kidney starts to work a bit harder. Over 20-40 years, this can be deleterious, but over shorter time frames, less than 20 years, the result is that a single kidney can adapt and provide better than 50% kidney function, which is what seems to have occurred with Mr. Mousser. His most recent creatinine in 2024-25 is moderately better than most values in 2021, with a similarly improved eGFR , such that his kidney disease this past year is Stage 2 or 3a (Stage G2A1, or Stage G3aA1, depending on whether the eGFR that day is slightly worse or slightly better than 60 cc/min).   Based on these blood and urine tests, his 5-year-risk of ending up on dialysis is 0.1% to 0.35%, per the Kidney Failure Risk Equation (as described in section 2, the General Introduction to Kidney Disease). In my practice, I would reassure patients who have a prognosis as good as this and offer them the opportunity to "graduate" from Kidney Clinic follow-up, meaning that they no longer need to be followed for this condition.

In addition, it should be noted that there are no symptoms from kidney disease at Stage G2A1 or Stage G3aA1, and this degree of kidney disease is not dissimilar from healthy adults of a similar age who experience age-related, mild decline in kidney function, as described at the end of section 2f, above, in the "General Introduction to Kidney Disease."

c) Regarding his life expectancy, Mr. Mousser's kidney function is unlikely to have any adverse effect on mortality. Instead, the major medical issues expected to effect his mortality are his prior history of smoking, diabetes, obesity, vascular disease, hypertension, and particularly his coronary artery disease including percutaneous interventions and open-heart surgery (which cannot have been caused by nephroureterectomy because his open-heart surgery pre-dates his nephroureterectomy).

Section 5) Responses to the report of Dr. Matthew Cooper.

Dr. Cooper opines: "Based on Mr. Mousser's decline in GFR following unilateral nephrectomy with episodic elevations in Cr as well as the expected hyperfiltration of his remaining kidney, Mr. Mousser will to a reasonable degree of medical certainty require renal replacement therapy in 3-5 years while in his early 60s." I disagree that Mr. Mousser will require renal replacement therapy in 3-5 years because, as explained in Section 4 above, the immediate effect of nephrectomy is a reduction in kidney function to 50% of normal, but that 50% is expected to remain stable for many years, and not to drop to 5 % within 5 years as Dr. Cooper contends. Using all the lab values from the Audie Murphy Memorial VA in 2024-2025, Mr. Mousser has stablized or modestly IMPROVED kidney function 4-5 years after his nephrectomy. One of Mr. Mousser's VA nephrologists recently recognized this, finding that "kidney function remains stable as reflected by the serum creatinine [his] baseline of 1.4." (Dr. Adams-Krick, 00667_Mousser_VHA_01624-01626). Further, using the Kidney Failure Risk Equation, as performed in Section 4 above, the chance that Mr. Mouser will require dialysis within the next 5 years is significantly less than 1%.

Dr. Cooper mischaracterizes the trends in Mr. Mousser's creatinine levels. Although he does not identify the specific "episodic elevations" that support his opinion, Mr. Mousser's creatinine levels are expected to oscillate up and down with changes in blood pressure, particularly while on the medications he takes, but the overall trend of kidney function is most consistent with a stable, CKD Stage G3aA1

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[29] Chapman, D. et al, "Residual renal function after partial or radical nephrectomy for renal cell carcinoma," Can Urol Assoc J. 2010. Vol 4:337-343. doi: 10.5489/cuaj.909.

diagnosis, as calculated in Section 4. In fact, Dr. Smith, another plaintiff's expert, also recognizes that Mr. Mousser's CKD is Stage 3a.

I disagree with Dr. Cooper that Mr. Mousser will be at "increased risk" of hypertension due to his nephroureterectomy because for Mr. Mousser, hypertension is one of his known medical problems, and one that pre-dated his nephroureterectomy. Similarly, while CKD can increase the risk of cardiovascular disease, as described in section 2, "General Introduction," Mr. Mousser already has rather severe cardiovascular disease, which also pre-dated his nephroureterectomy and included open heart bypass surgery about 7 years ago.

Lastly, I disagree with plaintiff that the nephroureterectomy, leading to a single, remaining kidney, requires that Mr. Mousser must stop working and dramatically alter his daily activities of living. Patients born with a single kidney, or patients with ESRD who receive a kidney transplant have- like Mr. Mousser- a single, functioning kidney, and the vast majority live a satisfying and productive life.

Conclusions:

Plaintiff is seeking judgement against the USA on the basis that contaminated water from Camp Lejune caused urothelial carcinoma, which required right nephroureterectomy, resulting in CKD, which plaintiff contends has prevented him from productive work and satisfying life, and will result in high likelihood to need dialysis within 5 years. Based on the records made available to me and my training and experience as a nephrologist, I would characterize his kidney disfunction as mild, and his prognosis for kidney disease as excellent. Mr. Mousser's VA urologist, Dr. Andrew Rockwood, and nephrologist, Dr. Daniel Flood, agree with this conclusion. Further, I find it very unlikely that Mr. Mousser will need dialysis in the future, much less a kidney transplant. Any negative impacts to his quality of life from being left with a single kidney are negligeable, and negative impacts from having a single kidney on his life expectancy are both speculative and are outweighed by the effects of his pre-existing hypertension and cardiovascular disease. It is more likely than not that he will not require medical treatment by virtue of having a single, functioning kidney, and were he a patient in my clinical practice, I would offer him the opportunity to "graduate" from kidney clinic.

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