Rationale for Kidney Cancer Medical Monitoring Protocol
June 4, 2013

The reasons the Medical Panel does not recommend universal medical screening of adults for kidney cancer are that the annual incidence of kidney cancer is very low; there is no accepted medical screening test to detect asymptomatic kidney cancer; and the utility of the test to detect microscopic hematuria is limited because a positive test has a low prevalence (i.e., blood detected in the urine) in the general population, a positive test is a poor predictor in detecting kidney cancer, and the test has a high false positive rate because microscopic hematuria has many causes that are much more common than kidney cancer. The Medical Panel does recommend that Class Members with symptoms and signs suggestive of kidney cancer be medically evaluated. Medical care providers should ask Class Members about these symptoms and signs and do diagnostic testing as clinically indicated. Although universal screening for microscopic hematuria is not recommended, the Medical Panel recommends that medical screening for adults 50 years and older include assessment of microscopic hematuria using a urine dipstick because this test is low cost and minimal risk, and it targets older adults who have the highest incidence of kidney cancer.

Incidence of kidney cancer. The annual incidence of developing kidney cancer is low at all ages, but especially among adults less than 50 years of age. Renal cell cancer occurs mostly in the 6^{th} and 7^{th} decades of life. In a study conducted by the C-8 Science Panel based on 10 years of cancer registry data, the age at diagnosis ranged from 16 to 102 years (incident cancer cases less than 15 years of age were not included in the study, but would likely be due to genetic or congenital causes). The median age at diagnosis was 66 years and the 25^{th} percentile was 57 years, so most of the kidney cancer cases developed among people older than 50 years.

The number of new kidney cancer cases that are likely to develop each year among the Class Members is likely to be small. The same Science Panel study examined the association between PFOA exposure and kidney cancer risk. The investigators divided the population of persons living in the PFOA contaminated water districts into high, medium, and low exposure categories with people from uncontaminated water districts in Ohio and West Virginia serving as an unexposed category. About 10% of the population within the “high” exposure group were considered to have the highest PFOA exposure and were assigned to a “very high” exposure category. They compared the relative risks of developing kidney cancer by comparing the number of cases across the contaminated and uncontaminated water districts.

One analysis was based on the six contaminated water districts and nearby uncontaminated water districts in Ohio and West Virginia. The investigators reported that over 10 years, there were 94 new cases of kidney cancer in the six contaminated water districts, which is an average of less than 10 new cases per year. The risk of developing kidney cancer was significantly elevated in the Tuppers Plain water district [AOR (adjusted odds ratio)=2.0 (95% CI: 1.3, 3.1), *n=10*]; not significantly elevated in Little Hocking [AOR=1.7 (95% CI: 0.9, 3.3), *n=23*] and Belpre [AOR=1.4 (95% CI: 0.8, 2.3), *n=17*], and the same as in unexposed water districts in the Lubeck [*n=9*] and Mason [*n=35*] water districts. No cases were reported in the Pomroy.

Another analysis was based on estimated PFOA serum concentrations that were modeled using linked environmental, exposure, and pharmacokinetic models. This analysis required geocoding addresses reported in the cancer registries, so it was limited to Ohio where this information was provided by the cancer registries. The investigators reported in the published study:

> "Kidney cancer was positively associated with very high and high exposure categories [2.0, (95% CI: 1.0, 3.9) *n* = 9 and 2.0 (95% CI: 1.3, 3.2) *n* = 22, respectively], whereas AORs (adjusted odds ratios) [which is a measure of relative risk] for medium and low exposure categories were close to the null compared with the unexposed."

Thus, the study reported that the total number of newly diagnosed cases of kidney cancer in the very high and high exposure groups of Ohio combined over a 10 year period was 31, or about 3 per year, of which approximately one-half (because of the relative risk of 2.0 in these groups) may be associated with the PFOA exposure. Therefore, the number of new cases of kidney cancer that is likely to develop each year among the Class Members is small.

The findings of the study also suggest that the risk of kidney cancer associated with PFOA exposure may be limited mostly to the sub-groups of people who had the highest exposure to PFOA. Although the Medical Panel did not distinguish among Class Members based on PFOA exposure in defining the recommended Medical Monitoring protocol, this information may be taken into consideration by Class Members who could decide whether to be screened for kidney cancer based on which water district they lived in or their past PFOA serum levels.

Medical Screening for Kidney Cancer. Even with some increase in kidney cancer risk among Class Members, the Medical Panel did not recommend universal medical screening for kidney cancer because there is no accepted medical screening test for kidney cancer. Section 12.3.2(c) of the Settlement Agreement stipulates that a recommendation for periodic monitoring can only be made if a screening test exists, which does not exist for kidney cancer.

Although there is not an accepted screening test for kidney cancer among asymptomatic adults, the Medical Panel determined that it may be possible to provide some Medical Monitoring of the Class Members. As explained in the Medical Panel report, renal-cell cancer typically does not have early warning signs. Common symptoms at the time of presentation of patients with kidney cancer are visible blood in the urine (hematuria) (in 59% of cases), abdominal pain (41%), and a palpable abdominal or flank mass (45%). Other findings are anemia (21%) and fever (7%). As reported in the Medical Panel report, a study in Japan found in a cross-sectional screening of the general population, the probability of kidney cancer was 0.005 when symptoms and signs were present compared to 0.00046 when symptoms were absent. The risk of kidney cancer was very low in both groups, but was more than ten-fold higher in the presence of symptoms, so the Medical Panel concluded that asking about symptoms and signs of kidney cancer is a useful way to screen. It is a low cost and minimal risk procedure for medical care providers to ask about these symptoms and signs. Furthermore, the notification to Class Members could encourage Class Members to make appointments with their personal physician for evaluation if they have these symptoms or signs.

Although it is not accepted standard of care to test the urine for microscopic hematuria among asymptomatic adults, some medical experts consider microscopic hematuria to be a useful clue to earlier stage kidney cancer. There are several reasons that testing urine for microscopic hematuria is not an accepted universal screening test for kidney cancer. First, it is not common to find microscopic hematuria in asymptomatic adults. Again in the study from Japan mentioned in the Medical Panel report, only 1667 individuals out of 45,905 in the cross-sectional survey had microscopic hematuria. Second, even after a positive screening test for microscopic hematuria, the probability of kidney cancer is very low; the large majority of apparently healthy people with microscopic hematuria do not have kidney cancer. In the study in Japan, none of the 1667 persons with microscopic hematuria had kidney cancer. The Medical Panel report cited another study that found in a retrospective study of 500 men referred for urologic

evaluation because of asymptomatic hematuria, only 2 had renal neoplasm. In data reported on the Family Practice notebook.com website, renal tumor is the cause of 0.5% or 5 per 1,000 of identified asymptomatic microscopic hematuria in the general population. Third, microscopic hematuria in an asymptomatic adult has a high false positive rate for kidney cancer because there are many causes of microscopic hematuria that are much more common than kidney cancer, especially among adults less than 50 years of age. Examples of conditions include genitourinary infection, nephrolithiasis (kidney stones), prostatic disease in males, menstrual bleeding (that contaminates the urine sample) in females, and a condition called "benign essential hematuria" for which the cause of the small amount of blood in the urine is not identified. These other conditions account for 99.5% of the causes of asymptomatic microscopic hematuria.

On the other hand, the risk of developing kidney cancer increases with age. According to SEER incidence data, the most reliable cancer statistics for the United States, from 2006-2010 the median age at diagnosis for cancer of the kidney and renal pelvis was 64 years of age. Approximately 1.2% were diagnosed under age 20; 1.7% between 20 and 34; 6.0% between 35 and 44; 16.4% between 45 and 54; 25.9% between 55 and 64; 25.0% between 65 and 74; 17.8% between 75 and 84; and 5.8% 85+ years of age. The age-adjusted incidence rate was 15.3 new cases per 100,000 men and women per year.

According to SEER mortality data, the age-specific death rate for kidney cancer is 8.2 per 100,000 for people less than 65 compared to 64.8 for those 65 and older. The annual mortality rate for people 40-44 years is 8.4 per 100,000, increasing to 21.6 per 100,000 for people 50-54 years. Therefore, the data indicate that the age-related increase in kidney cancer mortality increases notably beginning in the late 40s to 50s. It is also about this age that some of the other false-positive causes of microscopic hematuria become somewhat less likely. Finally, as noted in the Medical Panel report, the initial screening test for microscopic hematuria is doing a urine dipstick for blood, which is low cost with no risk to the patient.

Therefore, the Medical Panel determined that an appropriate balance between the low performance of the microscopic hematuria screening test, but improved performance with a person's age due to the increasing age-specific incidence would justify that the microscopic hematuria screening test be recommended for older adults only (which is the current Medical Panel recommendation), while all adults should be screened for the presence of the symptoms and signs that are suggestive of kidney cancer. The Medical Panel with input from medical experts determined that age 50 years was a reasonable age to recommend for the microscopic hematuria screening test.

Because the statement of the Medical Monitoring protocol for kidney cancer may not have been clear that all adults should be asked about suggestive symptoms and signs with the screening for microscopic hematuria beginning at age 50 years, the recommendations will be re-stated to be more explicit:

- For all adult Class Members, the personal physician should ask about gross hematuria, abdominal or flank pain, unexplained weight loss, and sustained fever or fever of unknown origin; and may do an abdominal examination. Based on physician's judgment, for positive responses, do urine test for microscopic hematuria. Do follow-up diagnostic testing (e.g., abdominal CT) as clinically indicated.

- For adult Class Members 50 years of age and older, in addition to above screening, do careful abdominal examination for masses and dipstick urine test for microscopic

hematuria. If dipstick test is +1 or greater, then order urine examination for hematuria and CBC to assess anemia. Do follow-up diagnostic testing as clinically indicated, which could include abdominal imaging studies, such as ultrasound, CT scan, and MRI.

The rationale for a selective screening policy is well-accepted: screening for cancers that are very uncommon in an age group using tests that are positive for many conditions other than the cancer is generally ill-advised. At present, no professional organization recommends routine screening for kidney cancer in any age group, so the Medical Panel's recommendation to screen older adult class members goes somewhat beyond what is considered the standard of practice. Extending the medical screening test for hematuria to age groups in which kidney cancer is very uncommon even in Class Members would go too far beyond generally accepted medical practice in the judgment of the Medical Panel.