C-8 Medical Panel Report

May 24, 2013

Background and Charge

In February 2005, the West Virginia Circuit Court approved a class action Settlement Agreement in a lawsuit about releases of a chemical known as C-8, or PFOA, from DuPont's Washington Works facility located in Wood County, West Virginia. The Settlement Agreement had several parts.

One part of the Settlement was the creation of a Science Panel to conduct research in the community in order to evaluate whether there is a probable link between PFOA exposure and any human disease. A "probable link" was defined in the Settlement Agreement to mean that given the available scientific evidence, it is more likely than not that class members are at increased risk of certain diseases because of their exposure to PFOA in drinking water.

Between December 2011 and October 2012, the Science Panel reported that PFOA was probably linked to the following diseases and conditions: pregnancy-induced hypertension and preeclampsia, testicular cancer, kidney cancer, ulcerative colitis, thyroid disease, and high cholesterol (hypercholesterolemia). The Science Panel concluded that there were not probable links for other cancers, other autoimmune diseases, diagnosed high blood pressure, or coronary artery disease.

Another part of the Settlement established a Medical Panel to develop a Medical Monitoring Protocol for the human diseases for which the Science Panel found a probable link. Medical Monitoring was defined in the Agreement as “diagnostic medical examinations, tests or procedures utilized to detect Human Disease,” so the definition encompasses both screening and diagnostic testing. The Agreement stated that the Medical Panel shall consider the following factors:

> (a) *Increased Risk* – that the Class Member has a significantly increased risk of contracting the particular diseases relative to the risk in the absence of exposure;
> (b) *Necessity of Diagnostic Testing* – that the Class Member should undergo specific periodic diagnostic testing that would not be required in the absence of exposure to C-8. The Settlement further specified that the desires of Class Members for reassurance that they did not have a probable link condition was a sufficient rationale for testing, and factors such as financial cost and the frequency of testing need not be given significant weight in assessing the need for testing; and
> (c) *Existence of Monitoring Procedures* – that testing procedures must exist that it is not necessary to show that detection and treatment in a pre-symptomatic state reduces the burden of the probable link condition.

The Agreement mandated that the Medical Panel develop a form by which the personal physician can certify that the reason for testing for a probable link condition was the Class

Member's exposure to PFOA and not because the testing was standard community practice for unexposed individuals. This form will provide the basis for the Administrator to determine whether the Class Member should be reimbursed for the medical monitoring.

Approach and Methods

The Medical Panel followed the Settlement Agreement provisions to develop the Medical Monitoring Protocol for the six probable link conditions. The Panel members reviewed the Agreement to understand the criteria and specifically the distinction between Medical Monitoring as defined in the Agreement and the general understanding of this concept in the fields of medicine and public health. This issue is relevant because the Panel members decided that the Medical Monitoring Protocol including diagnostic tests should, to the extent possible, be based on generally accepted evidence-based recommendations for medical screening and diagnostic testing for the probable link conditions.

Guidelines for medical screening and medical monitoring are developed by professional medical societies, international and national governmental agencies, and other expert bodies. These guidelines are based on the best judgment of medical experts based on a review of the peer-reviewed medical and scientific literature. The Medical Panel decided to give substantial weight to the consensus recommendations of these guidelines for the probable link outcomes in developing the Medical Monitoring protocol. However, the criteria for medical monitoring used generally in the fields of medicine and public health are different from those specified in the Agreement. Most medical monitoring guidelines take into consideration factors such as cost and potential benefits of conducting medical tests for the early detection and treatment of disease among asymptomatic individuals who may or may not be at high risk of the disease of interest. However, as previously noted, the Settlement Agreement specifies that cost does not necessarily need to be considered, nor does the medical testing have to be justified primarily by the demonstrated benefits of early detection and treatment for the disease conditions. Therefore, the Medical Panel took into consideration the consensus medical guidelines, especially regarding the most appropriate screening and diagnostic tests, but the Panel developed eligibility criteria for Class Members to participate in the Medical Monitoring protocol screening tests based on the criteria specified in the Settlement Agreement.

For each of the six probable link findings, the Medical Panel members reviewed the Science Panel findings for the probable link outcome and the medical literature on the description of the health outcome, its prevalence and epidemiology, and known risk factors. The Panel compiled the current medical screening recommendations for the outcome. Methods used by the Medical Panel to identify medical screening guidelines included use of an electronic search of the medical literature to identify existing recommendations of expert medical panels including the U.S. Preventive Services Task Force, medical specialty expert panels and international medical expert bodies. Generally the recommendations in these guidelines relied on evidence published in the peer-reviewed medical literature. As needed, the Medical Panel members read key published articles cited by the expert bodies and did additional searches of the peer-reviewed medical literature. The Medical Panel compiled a listing of the recommendations of expert

panels about screening for the probable link conditions. The recommendations of the expert panels regarding the standard of care for screening of the probable link conditions (i.e., defining who in the population should be screened) are relevant for assessing whether the screening tests would ordinarily be ordered by a personal physician in an unexposed general population.

The Medical Panel also reviewed clinical practice reference documents, published literature, and the expert panels' recommendations about how to evaluate a patient with an abnormal screening result for the six probable link findings. As needed, the Panel members obtained input from leading medical specialty experts concerning the most appropriate diagnostic testing procedures and standard of care for evaluating patients with abnormal screening test findings.

After developing recommendations for the medical screening tests and diagnostic testing procedures, the Medical Panel members consulted with recognized medical authorities for the specific disease conditions about the Panel's 's recommendations for the medical screening and diagnostic testing procedures. This peer-review process is a standard and expected component in developing guidelines such as the Medical Monitoring protocols. The medical authorities agreed with the recommendations developed by the Panel. In seeking these consultations, the Panel members did not share the draft protocols or discuss issues such as criteria for eligibility of Class Members to be screened, so the consulted medical authorities did not influence the Medical Panel about these issues.

Definitions and Issues

We list definitions of terms and describe issues the Medical Panel has had to address or will have to address in developing the Medical Monitoring protocol:

Target population: The target population is the Class Members with putative exposure to PFOA. The Medical Panel recommends that every member of the Class should have access to screening and diagnostic testing, regardless of whether they have a primary care physician or medical insurance. Access to medical care providers for screening and to obtain the screening and diagnostic tests should be determined only by the eligibility criteria specified in the Medical Monitoring Protocols.

The recommended medical screening tests for some of the probable link outcomes are not the same for every Class Member. The Protocols indicate that Class Members may be eligible for specific medical screening tests or diagnostic tests based on criteria such as the person's age or pregnancy status. These criteria were established based on medical and scientific evidence regarding the effectiveness of the proposed screening tests. The Medical Panel determined that it is not feasible at this time to recommend different medical screening protocols for different sub-groups of Class Members based on estimates of putative PFOA exposure. One reason is that the Settlement Agreement in Section 12.3.2(a) indicates that "no particular level of quantification is necessary" to conclude that there is increased risk among Class Members. The Panel concluded that medical screening should be offered to all Class Members regardless of individual or sub-group risk quantification unless it could be determined definitively that some

Class Members were at no excess risk. However, it is not feasible without doing individual exposure assessment to determine if individual or specific sub-groups of Class Members actually may have had no PFOA exposure and, thus, no excess risk. Another reason is that the research reported by the Science Panel was not always sufficient to assess directly the excess risk among the study populations. Except for some analyses for the cancer outcomes, most of the epidemiological studies did not include non-exposed comparison populations, so these studies only could evaluate the relative associations between the outcome rates and PFOA exposure in the Mid-Ohio Valley population. For the majority of studies that did not include non-exposed comparison populations, the absolute level of risk even in the lowest exposed PFOA groups within these study populations cannot be determined because the levels of PFOA exposure in the lowest groups were still higher than in the general US population. Therefore, the Medical Panel recommends that all eligible Class Members be offered the opportunity to participate in the appropriate Medical Monitoring Protocols for the probable link conditions.

Screening and Diagnostic Testing: The Settlement Agreement defines Medical Monitoring to be "diagnostic testing." The Medical Panel distinguishes three types of testing: screening (the initial test performed to detect a condition in a person with no clinical evidence of the target condition), diagnosis (a sequence of tests to establish a definite diagnosis following an abnormal screening test result), and monitoring (periodic testing done in patients who did not have the condition on the initial screening test). The Protocols will define the appropriate screening tests and diagnostic tests for each probable link condition. In addition, as noted above, the Protocols will indicate the current standard of community practice about screening for the conditions in a general population that is not exposed to PFOA. This information should facilitate adjudication of which screening tests were done solely because the person is a Class Member.

The Medical Panel will summarize what is considered appropriate diagnostic testing follow-up after a positive screening test. As noted above, this information is based on standard clinical references, expert guidelines, and professional consensus. Those with a true-positive test (i.e., a positive test in a person who actually has the target condition) will need to make a decision about further testing and possible treatment.

Monitoring: In the Medical Panel's protocols, this term refers to screening tests done after the first screening test. For most screening tests, the interval between negative tests is determined by professional consensus rather than good quality evidence. Because the evidence for which test to perform is much better than the evidence for the best interval to repeat screening, the Medical Panel decided to defer work on the follow-up "monitoring" protocol, in order to concentrate on establishing which initial screening tests are indicated and the protocols for diagnostic testing after a positive screening test.

When to Stop Screening: This question presents a difficult problem because we do not know the length of time between exposure to PFOA ceased and when the incidence of new cases might decline to a rate typical of an unexposed general population. This issue involves considerations of toxicokinetics and knowledge of disease mechanisms. Moreover, we don't know the disease induction (latency) period, which is the time between the PFOA exposure and the time that a

disease first becomes detectable, either by screening tests or because the patient develops symptoms, or the lag time before potentially reversible conditions appear in response to changes in PFOA exposure or body concentrations. One possible approach is to monitor for the target diseases in the Class Members to determine when the incidence falls to a level consistent with baseline exposure such as would occur in someone who was not in the exposed class. This follow-up monitoring could also include measurement of serum PFOA as a biological indicator of internal dose. The Medical Panel decided to defer addressing this issue (along with the "monitoring" issue) in order to concentrate on defining the protocol for initial screening and diagnostic testing.

Standard of Care: In preparing its report, the Panel reviewed many "standard of care" clinical practice guidelines to assess current practice recommendations for the six probable link findings. The term "Standard of Care" will be used throughout this document and refers to "diagnostic and treatment processes that a clinician would use for certain types of patients, diseases or circumstances—(which are) often evidence based" (Studdert, 2004).

Such standard of care approaches also include "the quality of care that would be expected of a reasonable practitioner in similar circumstances" (Studdert, 2004) and historically were determined based on the opinions of individual subject-matter experts. More recently, in the present climate of "evidence-based" medicine, practice guidelines developed by expert panels have become the *de facto* standard of care for many conditions. Practice guidelines, as defined by the Institute of Medicine (IOM) are "systematically developed statements to assist practitioner and patient about appropriate healthcare for specific clinical circumstances" (IOM, 1990).

In the past twenty years, there has been an avalanche of guidelines development spanning the spectrum from complex screening protocols for specific diseases or conditions, to standards for the content of a typical "well child" clinic visit, for example. These documents assisted the Medical Panel in assessing the "standard of care" for both the screening tests and the diagnostic testing protocols for the six probable link conditions.

Shared decision-making: Informed consent is a legal and moral necessity in medical practice. In the best processes of informed consent, the patient becomes informed about the health states that can occur after screening (and absent screening). These health states and the likelihood of their occurrence constitute the benefits and harms of screening. The patient becomes informed (perhaps by watching a video presentation or reading a pamphlet) and then discusses the decision with a health professional with the goal of making a decision that is consistent with the patient's values and preferences.

The Medical Panel recommends that Class Members should provide informed consent for screening for each of the probable link conditions, since the risk and benefits of screening, diagnosis, and treatment vary among the probable link conditions. The Panel plans to create educational materials that will help to inform the Class Members about the benefits and harms of screening. The Panel believes that Class Members who have a regular physician should talk about the screening decision with their physician. Class Members who do not have a regular

physician should discuss the screening decision with a health professional as part of the screening process.

Medical Monitoring Protocol Reports

This document contains reports on the recommended medical monitoring protocol for each of the probable link conditions. Information on the background, charge, and methods used to develop the protocols is described above and is not repeated in the individual reports.

The reports begin with a section on "Description and Epidemiology" of the health outcome. This section describes the prevalence or incidence of the target condition and identifies recognized risk factors in the general population with no PFOA exposure. This information may be used to estimate the "baseline" risk or the number of cases that may be expected to occur in a general population with no PFOA exposure. Information on the risk factors is relevant because many guidelines recommend targeted screening based on the presence of recognized risk factors.

The next section on "Probable Link Evaluation" reviews the main findings of the C8 Science Panel for the health outcome. These summaries focus on the Science Panel's estimates of the increase in risk across the PFOA exposure range within the study populations and, if available, estimates of the excess number of cases associated with the PFOA exposure. The purpose of these summaries is not to reevaluate the conclusions of the Science Panel, but it is to include in this Report a quantitative estimation of the increase in likelihood that a Class Member might develop the outcome condition (i.e., the difference in the rates of developing a health outcome among the Class Members across on the range of PFOA exposure or, for those studies that included a non-exposed comparison population, the rates compared to the rate of developing the health outcome in the non-exposed population). This type of information could be relevant to the individual Class Members and their physicians in deciding whether to do the screening tests recommended by the Medical Panel. For example, Class Members who lived in water districts that had higher putative exposure to PFOA associated with higher risk for developing a probable link outcome may be more inclined to request medical screening than persons who lived in areas with lower PFOA exposure, although Class Members in all of the areas would be eligible for the medical screening.

The third section of the reports on "Screening and Diagnostic Testing" describes the Medical Panel's recommended screening tests for the outcome conditions. It has a sub-section on "Screening" that identifies the Class Members who should be eligible for the screening test (e.g., pregnant women for screening of pregnancy-induced hypertension) and describes the screening tests to be ordered. Screening tests are the first step in evaluating people who may be at increased risk of having a health condition, but who do not currently have specific clinical symptoms or signs. Screening tests suitable for mass population screening are typically inexpensive and safe but are seldom conclusive evidence of the target condition.

The sub-section on "Follow up/Diagnostic Pathway" describes the diagnostic tests that should be considered by the medical providers to establish a diagnosis if the screened person has a

positive screening test. The reports describe the recognized "standard of care" approach to the diagnostic testing for each condition. Nevertheless, there can be some variation in the approach or specific sequence of testing among medical care providers. Ultimately, the decision about which specific diagnostic test will be order should be made by the medical care provider in partnership with the individual patient (Class Member).

The next sub-section on "Standard of Care for Screening" provides a summary of the guideline recommendations for screening in a general population that is not exposed to PFOA. This information will be relevant to the Medical Monitoring Program Administrator in assessing whether the screening tests ordinarily would be ordered by the Class Member's personal physician even if the Class Member had not been exposed to PFOA. This criterion is specified in Section 12.3.2(d) of the Settlement Agreement.

The last sub-section of Screening and Diagnostic Testing provides additional information that may be considered for "Shared Decision Making" by the Class Member and the Class Member's personal physician in deciding whether to undertake the screening tests. This shared decision-making needs to balance consideration of the likely excess risk of having or developing the health outcome with the burden and risks of the screening tests and possible diagnostic tests. While treatment is not within the scope of the Settlement Agreement, the decision to undertake the screening tests to establish a diagnosis would logically also include consideration of the potential benefits (cure of the target condition) and harms (e.g., side effects of treatment) of being diagnosed with the health condition.

The last section on "Conclusion and Recommendation" provides a summary of the Medical Panel's recommendations for screening and diagnostic testing.

Forms

The Settlement Agreement specifies in section 12.3.2(d) that the Medical Panel shall develop a form to be completed by the personal physician of any Class Member seeking reimbursement for any Medical Monitoring included in the protocol. This Report of the Medical Panel does not include a form, although the protocols do describe the information (about screening eligibility criteria among Class Members, symptoms and signs of the outcome conditions, and standard of care criteria for screening in a general non-exposed population) that should be collected by such a form.

The Medical Panel decided that it would be better to provide the reports at this time, rather than waiting until the form could be developed. In addition, the Medical Panel believes it would be efficient and effective for the Medical Panel members to interact with the Administrator of the Medical Monitoring Program to discuss the design and structure of the form (e.g., hard copy or electronic copy that could be accessed via the Internet), since the Administrator will be responsible for distributing, collecting, and processing the form. The Panel will seek to clarify with the Settling Parties the role of the Panel members in developing the form, such as whether the Panel members should specify the domains and content of the form items which could then

be developed by a contractor, or whether the Panel members should design the form and write the text for each item. The Panel does not have a specific position regarding these issues, but would like to discuss options with the Settling Parties before developing the form.

Data Collection in the Medical Monitoring Protocol

The Settlement Agreement does not address the issue of data collection as a component of the Medical Monitoring Protocol. The Medical Panel notes that it is considered standard practice for medical screening programs to collect data about medical findings, screening test results, and clinical outcomes for subsequent evaluation of the program implementation even if formal analysis of the aggregate data – such as for an epidemiological study – is not planned. The Medical Panel recommends that the Administrator of the Medical Monitoring Program be charged to develop a mechanism to gather relevant data on the implementation and findings of the Medical Monitoring Protocol. The Medical Panel would use this information to evaluate whether to change the Medical Monitoring Program, which is a charge to the Medical Panel in Section 12.3.3 of the Settlement Agreement.

References

Studdert, DM; Mello, MM; Brennan, TA. Medical Malpractice—Health Policy Report. New England Journal of Medicine; 350:283-292, 2004.

IOM Clinical Practice Guidelines: Directions for a New Program. Washington DC. National Academy Press. 1990.

Medical Monitoring Protocol for High Cholesterol (Hypercholesterolemia)

Description and Epidemiology

Cholesterol is a lipid the human body needs to function properly. The two most important types of cholesterol for clinical evaluation are low density lipoprotein cholesterol (LDL-C) which is considered to be “bad” cholesterol and high density lipoprotein cholesterol (HDL-C) which is considered to be “good” cholesterol. Total cholesterol (TC) is the amount of all cholesterols combined. People with high blood cholesterol do not have symptoms but they may have a higher risk of getting heart disease and stroke.

Abnormal cholesterol levels may be due to unhealthy lifestyle factors, including eating a diet that is high in fat, being overweight, heavy use of alcohol, and lack of exercise. Certain health conditions can lead to high cholesterol, including: diabetes, hypothyroidism, polycystic ovary syndrome, kidney disease, and pregnancy and other conditions that increase levels of female hormones. Medicines such as birth control pills, diuretics, beta-blockers, and antidepressants can raise cholesterol levels. Some genetic disorders lead to abnormal cholesterol levels, including: familial combined hyperlipidemia, familial dysbetalipoproteinemia and familial hypercholesterolemia. (from (A.D.A.M. Medical Encyclopedia 2012))

A national survey of the US population (NHANES) showed that 13% of adults aged 20 years and over had high total serum cholesterol ($\geq$240 mg/dL). (Carroll, Kit and Lacher 2012) This percentage did not include people who were already under treatment. Another study also based on the NHANES survey used different criteria by counting adults with TC above 200 mg/dL plus people who had been told by their doctors that they had high cholesterol, finding that almost 55% of the US adult population have high cholesterol. (Ford, et al. 2010) The Ford et al. study reported that 54% of the people who had been told they had high cholesterol were using cholesterol-lowering medications. Overall about one-third of adults with high cholesterol has the condition under control. In summary, national survey data show that having high cholesterol is common in the US adult population and more than half of adults who have high cholesterol take medications to lower their cholesterol levels.

The proportion of children and adolescents in the US population with high cholesterol is lower than in adults, but criteria to define high cholesterol are different and more varied than in adults. Many reports define high blood cholesterol in children as a TC above 200 mg/dL. Using this criterion, the NHANES survey found that during the early 1990s about 10% of adolescents had high blood cholesterol. (Hickman, et al. 1998) More recently, a study based on the NHANES survey for 1999-2006 used a different criterion of LDL-C above 130 mg/dL and reported that the proportion of adolescents with high LDL-C was 7.6%. (May, Kuklina and Yoon 2010) The Child and Adolescent Trial for Cardiovascular Health study reported that 13% of children 9-10 years of age had TC above 200 mg/dL. (Jolliffe and Janssen 2006) Despite variation among the reports, there is a general consensus that the prevalence of children and adolescents with high cholesterol is substantial and increasing because of the obesity epidemic.

Probable Link Evaluation for High Blood Cholesterol

According to the Probable Link report, the C8 Science Panel considered high cholesterol in adults to mean serum concentrations sufficiently high to result in a doctor prescribing medication, which was defined as TC above 240 mg/dL. The Science Panel conducted the probable link evaluation by taking into consideration published scientific research and by conducting population studies in the Mid-Ohio Valley. The Panel concluded that "there is positive evidence that serum PFOA is associated with serum cholesterol in several cross-sectional studies and a small number of longitudinal studies, although a few studies do not show any association." "In C8 Science Panel work in the Mid-Ohio Valley, both analyses of exposure level by water district, and longitudinal follow-up of cholesterol analyzed in relation to the degree of drop in PFOA serum levels, suggested that the association of PFOA and cholesterol is due to PFOA…" (Frisbee, et al. 2010) (Steeland, et al. 2009) "There was mixed evidence in the overall analysis of the C8 Science Panel's large community/work cohort study…" Nevertheless, the Science Panel concluded that despite some inconsistent evidence, there is a probable link between exposure to PFOA and diagnosed high blood cholesterol. The Panel concluded that there was not a probable link with changes in HDL-C or triglycerides.

As an estimate of the strength of association between PFOA exposure and cholesterol in adults, Steenland and colleagues reported on the levels of total serum cholesterol by levels of serum PFOA divided into decile categories. (Steeland, et al. 2009) After adjustment for other risk factors for high cholesterol, they found that total serum cholesterol increased about 11 mg/dL from the lowest to highest decile of serum PFOA levels. Most of the increase in TC occurred in the first five deciles of the categories with median serum PFOA concentrations ranging from approximately 10 ng/mL to 30 ng/mL. For comparison, the median serum PFOA concentration in the US general population was 4 ng/mL based on the NHANES survey. Steenland et al. also did an analysis looking at the proportion of people with high serum cholesterol ($\geq$240 mg/dL) in relation to quartiles of PFOA serum levels. Using a logistic regression analysis, they reported that the odds ratios of having high serum cholesterol by increasing quartiles of serum PFOA were 1.00 (in the reference category of lowest PFOA level), 1.21, 1.33, and 1.40. Each of the odds ratios in the higher quartiles were significantly different than the reference category and the test for trend was statistically significant ($p<0.0001$). These odds ratio mean, for example, that people in the highest quartile of serum PFOA ($\geq$67 ng/mL) were 1.4 times more likely to have high cholesterol than the people in the lowest quartile of serum PFOA (0-13.1 ng/mL).

Frisbee and colleagues examined the association between serum PFOA and serum cholesterol among children and adolescents in the C8 Health Project. (Frisbee, et al. 2010) They used a general linear model to adjust for covariates and found that the adjusted TC increased 4.6 mg/dL between the lowest and highest quintiles of serum PFOA. They also examined the association between serum PFOA and high cholesterol, defining high cholesterol as TC $\geq$170 mg/dL, using a logistic regression analysis to adjust for other risk factors. They reported that the odds ratio of high TC by quintiles of serum PFOA were 1.00 (the reference category of lowest PFOA level), 1.1, 1.2, 1.2, 1.2. Each of the odds ratios in the higher quintiles were significantly different than the reference category. The test for trend was statistically significant

for both sexes combined ($p<0.001$), although the exposure-response association appeared to be sub-linear with the largest increases in TC levels and the odds of high TC seen at the lowest range of PFOA concentrations and the exposure-response slope attenuated at higher serum PFOA concentrations. These odds ratios mean that children and adolescents in the top quintile of PFOA exposure were 1.2 times more likely to have high total cholesterol than those in the lowest quintile of PFOA exposure.

Screening and Diagnostic Testing

a) Screening

Screening for high cholesterol is done by obtaining a blood sample that is analyzed for concentrations of TC, LDL-C, and HDL-C. The blood test is called a serum cholesterol panel test, lipid profile test, or lipid panel test. The most commonly used test directly measures TC, HDL-C, and triglycerides, and uses these values to calculate the LDL-C level.

The concentrations of TC and HDL-C in the serum do not fluctuate much with meals, so a test to measure just TC and HDL-C can be drawn any time (called a random blood test). However, the concentration of LDL-C and triglycerides fluctuate with meals, so blood to be drawn for a lipid profile blood test should be drawn after the person fasts for at least 9 hours. The generally recommended screening test is to obtain a fasting blood sample to be analyzed for serum concentrations of TC, LDL-C, and HDL-C. For patients who do not want to or are not able to fast for at least 9 hours prior to the test, an alternative test is to obtain a random cholesterol blood test to measure total cholesterol and HDL. The generally recognized cut-points for TC and LDL by age in mg/dL are shown in the following table:

Age group - test	Acceptable	Borderline	High	Reference
Adults				
TC	<200	200-239	≥240	(Baron 2013) (US Preventive Services Task Force 2008)
LDL	<130	130-195	≥195	
Young adults 20-24				
TC	<190	190-224	≥225	(Expert Panel 2012)
LDL	<120	120-159	≥160	
Children <20 years				
TC	<170	170-199	≥200	(Kwiterovich 2008) (Daniels 2011)
LDL	<110	110-129	≥130	

Cholesterol levels can fluctuate somewhat over time in addition to changes with meals, so a single measurement may not reflect average cholesterol levels. Therefore, screening guidelines recommend that the fasting lipid profile test be done twice with an interval between 2 weeks and three months and that the reported values be averaged for interpretation of the findings. (Expert Panel 2012) On the other hand, the general practice of physicians is to obtain only one fasting

lipid profile test, but to repeat the test after at least two weeks if the first test indicated high or borderline high values for the TC or LDL.

b) Follow Up/Diagnostic Pathway

The diagnosis of high cholesterol is established by the fasting serum lipid profile test that is used for screening, so there is not a specific follow-up or diagnostic pathway test.

c) Standard of Care for Screening

People with high cholesterol do not have symptoms. The primary concern about having high cholesterol is that it is a risk factor coronary heart disease (CHD). Therefore, the primary objective for screening cholesterol in the general population is to assess whether individuals may have increased risk of developing CHD, so these people can consider whether to modify their behaviors or take medications to lower their cholesterol levels. Thus, general screening guidelines for cholesterol are not directly relevant to the Medical Monitoring protocol related to the putative PFOA exposure. Screening guidelines indicate when medical providers would obtain a cholesterol panel blood test in a non-PFOA exposed general population.

Several governmental agencies and professional organizations have developed guidelines for screening for cholesterol and lipid disorders. Guidelines for adults and for children and adolescents have been developed separately. The US Agency for Healthcare Research and Quality (AHRQ) maintains a National Guideline Clearinghouse of guidelines on health topics. As of March 2013, the AHRQ website listed 157 guidelines related to cholesterol screening and treatment (http://www.guidelines.gov/search/search.aspx?term=cholesterol).

Cholesterol screening in adults. The most generally accepted US guidelines for cholesterol screening in adults are the reports by the US Preventive Services Task Force (USPSTF) in 2008 (US Preventive Services Task Force 2008) and by the National Cholesterol Education Program (NCEP) of the National Institutes of Health which was updated in 2002, although a new update in being reviewed (National Cholesterol Education Program 2002). In summary, USPSFT guidelines recommend that a screening lipid profile blood test be done as follows:

- Males ≥35 years of age
- Males 20-35 years of age if they are at increased risk for CHD
- Females ≥ 45 years of age
- Females 20-45 years of age if they are increased risk for CHD

CHD risk factors to be considered include personal history of diabetes, previous CHD or non-coronary atherosclerosis, tobacco use, hypertension (high blood pressure), obesity, and a family history of CHD before 50 years of age in a male relative or 60 years of age in a female relative. The USPSFT guideline statement indicated that there was not sufficient evidence of benefit in screening for the younger males and females who are not at increased risk for CHD to make a recommendation for or against screening.

The American Academy of Family Practice generally recommends following the USPSFT guidelines. The Michigan Quality Improvement Consortium generally follows the USPSFT guidelines except that the age for males and females to consider starting cholesterol screening is 18 years old. The NCEP differs from the USPSFT guidelines by recommending that all males and females older than 20 years be screened with a fasting lipoprotein panel, although the NCEP guidelines gives greater emphasis to assessment of CHD risk in all adults as a component of the screening. In summary, the standard of care for cholesterol screening is to screen all males ≥35 years of age and all females ≥45 years of age regardless of CHD risk, and to screen younger adult males and females ≥20 years of age if there is increased CHD risk because of recognized CHD risk factors. Most of the guidelines state that there is no good evidence to make specific recommendations on the periodicity of testing, but generally recommend that screening should be repeated every 5 years if the tests are normal.

Cholesterol screening in children and adolescents. Guidelines for cholesterol screening in children and adolescents are not as consistent as the guidelines for adults. The most widely accepted guidelines for cholesterol screening in children are those by the National Cholesterol Education program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents which recommended in 1992 that targeted screening be performed based on a child's family history of CHD risk factors, premature CVD or dyslipidemias. (Daniels 2011) (Kwiterovich 2008) These guidelines have been followed by the American Heart Association, American Academy of Pediatrics, American Academy of Family Practice, and American Diabetes Association. The UPSTF concluded in 2007 that there was insufficient evidence to recommend for or against routine cholesterol blood test screening.

Some recent guidelines and medical experts argue that there should be universal screening for cholesterol and dyslipidemias in children. (Expert Panel 2012) (Gillman and Daniels 2012) Although the trend in the development of guidelines is to consider doing universal blood cholesterol screening in children and adolescents, the current standard of practice is still to do targeted screening only among children with personal or family histories for elevated CHD risk.

d) Shared decision-making: benefits and harms of screening and diagnostic testing

The blood test to screen for high cholesterol is a minimal risk standard venipuncture to draw a small specimen of blood. A major focus of the guidelines is on how medical care providers should interpret the test findings and whether they should consider interventions or treatment among children and adults with high cholesterol. The interventions include behavioral modifications including increasing exercise, losing weight if overweight, and eating foods that are lower in fat and cholesterol. There are health benefits, but no apparent risks from adopting these recommended behaviors. Medical care providers may consider prescribing medications such as statins to lower TC and LDL cholesterol for persons who continue to have elevated cholesterol after attempting the behavioral changes. Medical care providers are aware of the potential risks of these medications and can explain them to their patients who may wish to consider taking the medications.

Conclusion and Recommendations

Because Class Members are at elevated risk for having high cholesterol, the Medical Monitoring protocol should include cholesterol blood test screening for all Class Members ages 2 years and older unless they have already been screened during the prior five years, have already been diagnosed, or are under treatment for high blood cholesterol. The reason to initiate screening at age 2 years is because some guidelines (e.g., American Academy of Pediatrics) recommend risk-based targeted screening of children beginning at age 2 years. The reason an interval of five years is recommended is that 5 years is the screening interval recommended for the general non-exposed population and because the findings of the C8 Science Panel in a follow-up study of residents in the Mid-Ohio Valley found that during a 4 year follow-up period the TC did not change materially and that, among the study population, a decrease in serum PFOA was associated with a decrease in LDL-C and in TC (Fitz-Simon, et al. 2013). Therefore, it is reasonable to conclude that the effects of the past PFOA exposure on serum cholesterol are likely to be stable or decreasing, so cholesterol screening during the most recent five years should be sufficient to evaluate whether a person has high cholesterol.

The intent of this protocol is that all Class Members should be screened for high cholesterol unless they have already been screened or treated during the past five years. The published guidelines on cholesterol screening and treatment discussed above indicate the current standard of care for cholesterol screening. This information may be relevant to making an administrative determination about whether the cholesterol blood screening test would ordinarily be obtained by a medical provider and reimbursed by a person's medical insurance.

Summary of Recommended Protocol. Class Members ages 2 years and older should be screened for high cholesterol – including TC, LDL-C, and HDL-C - using a fasting serum lipid profile test if they have not been screened by this blood test during the past five years, have not been previously diagnosed by a medical provider to have hypercholesterolemia, or are not already taking medications to lower blood cholesterol levels. The preferred method is to obtain the fasting lipid profile blood test two times with an interval of 2 weeks to 3 months and average the findings for interpretation. However, it is standard medical practice and a reasonable option to obtain the blood test once, but repeat the test if the TC or LDL-C levels are in the high or borderline high range for the person's age. A non-fasting lipid profile test can be offered if the person is unable or unwilling to complete the fasting test. If a non-fasting test is done, the findings should be used to calculate the non-HDL-C (= TC – HDL-C). A fasting lipid profile test should be obtained if the non-HDL-C is $\geq$ 145 mg/dL and HDL-C < 40 mg/dL.

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Medical Monitoring Protocol for Thyroid Dysfunction

Description and Epidemiology

This protocol is about whether to and how to screen for subclinical thyroid dysfunction in members of the exposed class. Thyroid dysfunction can mean either hyperthyroidism or hypothyroidism, either of which can be overt or subclinical. Patients with overt thyroid dysfunction usually present with symptoms, whereas those with subclinical disease (meaning no symptoms) are detected during screening and therefore present with abnormalities of thyroid function tests but no symptoms. The evidence presented in this section is based on studies of apparently healthy individuals in the general population, which we will apply to the decision to screen members of the exposed class.

The usual definitions of subclinical and overt thyroid dysfunction are: (1)

	TSH level	**FT4 or FT3 levels***
Hypothyroidism, overt	>5	Below normal
Hypothyroidism, subclinical	>5	Normal
Hyperthyroidism, overt	Low or undetectable	Above normal
Hyperthyroidism, subclinical	Low or undetectable	Normal

* FT4 and FT3 refer to free thyroxine and free tri-iodothyronine, respectively. TSH refers to thyroid stimulating hormone, which controls the production of thyroid hormone by the thyroid gland.

The Whickham Study, a 20 year follow-up of a community sample of residents of a town, determined the annual incidence (frequency of new cases) of overt thyroid disease in people with normal thyroid function at baseline. The annual incidence of spontaneous overt hypothyroidism was 3-4/1000 women and 0.6/1000 men. The annual incidence of spontaneous overt hyperthyroidism was 0.8/1000 women and nil in men. (2)

Thyroid dysfunction is more common in women and older people, and hypothyroidism is 15- 20 times more common than hyperthyroidism. In the 2002 NHANES study of a representative sample of the U.S. population aged 12 years or greater, the prevalence of *subclinical* hyperthyroidism was 0.2% and the prevalence of subclinical hypothyroidism was 3.9%. The prevalence of subclinical thyroid disease was about 50% higher in women than in men. (3) The prevalence of hypothyroidism rose steadily with age. The Whickham Study, a cross-sectional community-based study in a town in the United Kingdom, found a similar prevalence of hypothyroidism. (4) In the Cardiovascular Health Study (5), a cohort study of 3233 community-dwelling U.S. adults 65 years and older, 82% (n = 2639) had normal thyroid function,15% (n = 496) had subclinical hypothyroidism, 1.6% (n = 51) had overt hypothyroidism. 1.5% (n = 47) had subclinical hyperthyroidism, and 0.1% (N=4) had overt hyperthyroidism.

The clinical consequences of subclinical thyroid dysfunction are 1) progression to overt thyroid dysfunction; and 2) cardiovascular disease. Subclinical thyroid dysfunction is a precursor of

overt disease. In the Whickham Study, 20 year follow-up showed that subclinical thyroid dysfunction progressed to overt thyroid dysfunction at a rate of 2-3% per year. (2) In the Cardiovascular Health Study, subclinical hyperthyroidism doubled the risk of incident atrial fibrillation over 12.5 years of follow-up. However, subclinical thyroid dysfunction did not increase the risk of incident coronary heart disease, cerebrovascular disease, cardiovascular death, or all-cause death. (5)

Probable Link Evaluation for Thyroid Dysfunction

On April 15, 2012, the Science Panel announced a probable link between exposure to PFOA exposure and thyroid dysfunction.

Past studies: The Science Panel first reviewed past epidemiological studies in humans: In the cross-sectional nationally representative NHANES study, PFOA serum levels correlated positively with self-reported thyroid disease (NHANES).. The NHANES study observation was considered weak evidence since the outcome measure was self-report of thyroid disease and the range of exposure was lower and much narrower than in the exposed class.

The Panel also reviewed three studies of occupational exposure, which involved higher exposure to PFOA. PFOA levels had no association with TSH, the most sensitive measure of mild thyroid dysfunction, and most thyroid hormone levels were within the normal range. The Panel reviewed two prior studies of Mid-Ohio Valley residents possibly exposed to PFOA. One showed no association of exposure with thyroid hormone levels in residents of a highly contaminated water district. Another study showed no association between PFOA exposure and TSH levels. In summary, past studies showed inconsistent correlations of PFOA exposure and thyroid dysfunction

Pursuant to the Settlement Agreement of the Leach-DuPont case, the Science Panel performed two cohort studies and one cross-sectional study of class members.

Incidence studies: The Science panel relied on cohort studies, in which new cases are measured in a defined population, for its conclusions about whether PFOA caused thyroid disease. In 2005/2006, 69,030 participants in the C8 Health Project had their PFOA serum levels measured, provided a medical history, and also had a panel of blood tests, including thyroid hormones, cholesterol, uric acid, etc.

Incidence Study 1: The Panel estimated PFOA exposure for a decade before the 2005/2006 study and measured the incidence of thyroid disease during the period 2008 to 2011. The Panel did a statistical test for trend to see if the risk of thyroid disease increased as PFOA exposure levels increased, which is one criterion for inferring that the exposure causes the disease.

PFOA exposure was unrelated to the incidence of new, verified hypothyroidism and hyperthyroidism in women but not men: for hypothyroidism in women, the relative risk (RR) of

hypothyroidism from the lowest to the highest exposure were 1.0, 1.3, 1.3, 1.3, 1.5. For hyperthyroidism the RRs were 1,0, 1.0, 1.3, 1.5, 1.4.. These results are statistically weak evidence for a trend.

> The Science Panel concluded: "Overall, there was some evidence of a relationship between the incidence of thyroid disease and estimated PFOA exposure, but results were inconsistent across sex, type of thyroid disease, inclusion or exclusion of experience before onset of elevated exposure"

Cross-sectional Study: A cross-sectional Science Panel study measured the relationship of serum PFOA levels in 2005/2006 to concurrent serum TSHand free thyroid hormone (T4). The Panel found small changes in TSH levels as PFOA levels varied over a wide range. In women, but not men, increasing PFOA levels were correlated with changes in T4. The Panel also examined the relationship between PFOA exposure and subclinical thyroid disease by excluding patients with self-reported thyroid disease from the analysis. The Panel found no association of PFOA levels and subclinical hypothyroidism and a lower risk of subclinical hyperthyroidism with increasing PFOA levels.

> The Science Panel concluded:: a weakly positive effect of PFOA levels and measured TSH suggests possibly subclinical hypothyroidism but this finding was not consistent with the absence of effect of PFOA exposure and subclinical thyroid disease. These two parts of the study appear to contradict one another.

Incidence study 2: The other incidence study was in children. To quote the Panel's report

> "The Science Panel study of childhood thyroid disease and function found that self-reported thyroid disease was positively associated with measured PFOA serum levels in the child (RR=1.44, 95% CI: 1.02 to 2.03) for an interquartile contrast of 13 to 68 ng/mL in serum PFOA measured in 2005-2006. Most of the cases were reported as hypothyroidism (n=39), and the association just for hypothyroidism was similar (RR=1.54, 95% CI: 1.00 to 2.37). The study also reported cross sectional analyses of thyroid hormones T4 and TSH in relation to measured PFOA in serum. The Panel found no association of PFOA levels and these thyroid test results.

The evidence in children is weak because thyroid disease was self-reported in the incidence study and not verified by measuring hormone levels.

The Science Panel's final evaluation: Study 1 showed "inconsistent suggestions for an association between PFOA and thyroid function or disease." Study 2 gave results that were inconsistent with Study 1, showing no effect or inverse relationships of PFOA and hormone levels. Study 3, in children, showed a positive effect on self-reported, non-validated thyroid disease. The Panel concluded:

> "After taking into account the available evidence in its totality, despite inconsistencies in the evidence, the Panel concluded that there was evidence of a probable link between C8 and thyroid disease."

In these studies, different analyses did not show a consistent relationship between PFOA exposure and thyroid disease. Taking all the evidence into account, the Science Panel decided that PFOA exposure was associated with thyroid disease.

Screening and Diagnostic Testing

a) Screening Tests for thyroid dysfunction

Clinical findings: One strategy for screening is to use the clinical history and examination to select patients for thyroid testing. This section explores that possibility. One study addressed the ability of symptoms of thyroid disease to predict the serum level of thyroid hormone in individuals who had no history of thyroid disease. (6) The study population in the second study was individuals with suspected thyroid disease. (7) In both, the authors systematically reviewed medical records to see what symptoms of thyroid disease were recorded and also the results of thyroid hormone tests (the gold standard). (6,7) Both of these studies were cross-sectional in design; the symptoms were used to predict a simultaneously obtained test of thyroid function, not to predict the future development of thyroid dysfunction. The list of 34 thyroid symptoms and physical findings follows:

Thyroid:

Goiter	Heat intolerance	Cold intolerance
Thyroid bruit	Sweating	Hair loss
Fine tremor	Lethargy	Dry skin
Weight loss	Weight gain	Constipation
Increased appetite	Hoarseness	Short stature
Lid lag	Family history	Delayed relaxation of deep tendon reflexes

Cardiovascular disease:

Recent MI, CHF, CHD	Arrhythmias, HR>90	Hypertension

The authors developed two simple prediction rules for classifying patients at high, average, and low risk of thyroid disease.

Number of findings	Patients (no.)	Patients with thyroid dysfunction (n, %)	Likelihood ratio	Risk of thyroid dysfunction
Study 1 (Drake, 6)				
At least 5	8	4 (50%)	6.75	High
2-4	59	5 (8.6%)	1.14	Average
0-1	68	1 (1.5%)	0.2	Low

Study 2 (White, 7)				
At least 5	23	18 (78%)	18.6	High
3-4	35	1 (2.9%)	0.70	Average
1-2	442	2 (0.45%)	0.11	Low

The likelihood ratio (right hand column) is a measure of discrimination. The pre-test odds of disease times the likelihood ratio equals the post-test odds of disease. The important message from both studies is that a few patients with 0, 1, or 2 symptoms had abnormal thyroid function tests. Having none or just a few symptoms lowered the odds of abnormal thyroid function tests but did not eliminate the possibility. This finding argues for doing a test of thyroid function on all members of the exposed class, rather than just those with 3 or more signs or symptoms of thyroid dysfunction.

Tests of thyroid hormone production: The TSH (thyroid stimulating hormone) test is universally accepted as the most sensitive test of thyroid function. It measures the blood level of thyrotropin, the hormone that controls the production of thyroid hormone by the thyroid gland. As the production of thyroid hormone increases, the level of TSH falls. As the production falls, the level of TSH rises, seemingly trying to stimulate a failing thyroid gland to produce more thyroid hormone. Interestingly, the evidence base for the accuracy of the TSH test is not strong. A 2010 systematic review of the studies of the sensitivity of the TSH test found that the studies had important shortcomings.(8) These concerns notwithstanding, the TSH test is certainly the standard of care for screening for thyroid dysfunction and as the first test to confirm clinical suspicions based on signs and symptoms.

b) Follow Up/Diagnostic Pathway

The follow-up protocol for an abnormal TSH level should take account of several facts:

- Abnormal TSH results in a screening program frequently revert to normal in follow-up. In screening studies, 50-75% of people with an elevated TSH level will revert to normal levels during follow-up.
- The benefits of treatment of subclinical hypothyroidism are still unclear despite 12 randomized trials (9). Two more trials are in progress.

The diagnostic and treatment pathway for adults and children with an abnormal serum TSH is as follows:

1. Obtain a free T4 test in order to document the severity of thyroid dysfunction (overt vs. subclinical).
    a. Rationale: Overt thyroid disease should be treated. The decision to treat subclinical disease requires a shared decision making process to weigh the benefits and harms.

2. Obtain a test for anti-thyroid antibodies. Autoimmune thyroiditis is a common cause of hypothyroidism. It probably accelerates the progression of subclinical hypothyroidism to

overt disease. Anti-thyroid antibodies would be an indication to monitor thyroid function more frequently in patients with subclinical disease.

3. If the patient's T4 is normal:
    a. A follow-up TSH test should be obtained in 2-4 weeks. The TSH level can be normal, decreased (suggesting hyperthyroidism), or increased (suggesting hypothyroidism).
        i. Many patients with an increased screening TSH level will have a normal result if the test is repeated. If still abnormal, the patient probably has subclinical hyperthyroidism or hypothyroidism rather than a false-positive TSH test.
            1. A shared decision making process is indicated for deciding about treating subclinical thyroid dysfunction.
            2. If the chosen course is to monitor the patient and not treat subclinical thyroid dysfunction, the patient's thyroid function should be monitored for progression to overt disease.
        ii. If the follow-up TSH test is normal, the initial result was probably a false-positive, and the patient should be placed in a routine monitoring category (to be described).

4. If the patient's free T4 is abnormal, the patient has overt thyroid dysfunction (hyper or hypo function) , which should be treated.

c) Standard of Care for Screening

A practice guideline is the most reliable indicator that a standard of care exists. Moreover, a practice guideline for screening is usually based on a review of the evidence for screening, so it is likely to be the most trustworthy standard of practice.

<u>A sample of current guidelines for screening in the general population</u>: (10,11,12,)

- USPSTF gives an I recommendation (cannot say yes or no; evidence for value of treating subclinical thyroid disease is lacking). This 2004 recommendation hasn't been updated.
- The American Thyroid Association recommends measuring thyroid function in all adults beginning at age 35 years and every 5 years thereafter, noting that more frequent screening may be appropriate in high-risk or symptomatic individuals.
- The Canadian Task Force on the Periodic Health Examination recommends maintaining a high index of clinical suspicion for nonspecific symptoms consistent with hypothyroidism when examining peri-menopausal and postmenopausal women.
- The American Academy of Family Physicians recommends against routine thyroid screening in asymptomatic patients younger than age 60.

These recommendations, which represent the best efforts of health professionals to create a standard for care, do not agree The recommendations vary from never screen to always

screen. Given the lack of a consensus, that the Medical Panel concludes that there is no universally accepted standard of care for screening for subclinical thyroid disease in the general adult population.

Standard of care guidelines for thyroid function screening do exist for newborn children and children with Down Syndrome.

Newborn screening for hypothyroidism: This screening test is mandated for all newborns throughout the United States. The programs are state-run and the state chooses which tests to perform. West Virginia does screen for congenital hypothyroidism.

Children with Down syndrome: The American Academy of Pediatric guideline on supervision of children with Down syndrome states (14):

> "Obtain thyroid-stimulating hormone (TSH) concentration if state newborn screening only measures free thyroxine (T4); congenital hypothyroidism can be missed if only the T4 concentration is obtained in the newborn screening. Many children with Down syndrome have mildly elevated TSH and normal free T4 levels. Management of children with abnormal thyrotropin or T4 concentrations should be discussed with a pediatric endocrinologist."

d) Shared Decision Making

The principal harm of testing (which requires only drawing a sample of blood) is the downstream consequences of an abnormal test result. Treating overt thyroid disease is universally accepted good practice. Treating subclinical hypothyroidism is controversial, and could lead to treatment that would not benefit and might even harm the patient. The consequences of treating subclinical hypothyroidism with replacement thyroid hormone were the subject of a Cochrane systematic review of 12 randomized controlled trials (involving 350 patients and 6-14 months of follow-up during treatment (9). The following facts should be made available to patients who are considering treatment for confirmed subclinical hypothyroidism.

Possible benefits of treating subclinical hypothyroidism:

- Perhaps the best evidence that the benefits are uncertain is the two current randomized trials of treatment. If there were a consensus, these trials would not be ethical and would not be taking place.
- Several cardiac ultrasound imaging studies have shown that the heart functions somewhat better with treatment. The clinical significance of these findings for a person's exercise capacity is unknown.
- Several studies have shown that treatment reduces serum cholesterol. No one knows whether this change has any long-term benefit, though one would expect that lowering serum cholesterol would lower the risk of heart attack and stroke. According to the best evidence treating with thyroid hormone does not alter the risk of these events. (9)
- Several good quality studies have shown that treatment does not improve quality of life or reduce symptoms. (9)

- 2-3% of patients with subclinical hypothyroidism progress to overt hypothyroidism each year. This progression can be monitored by periodic testing, but another approach would be to start treatment, which would make further testing unnecessary.

Harms of treatment. Several studies have compared the effects of treating subclinical hypothyroidism with thyroid hormone with treatment with a placebo. In these studies, the rate of adverse symptoms have been the same with thyroid hormone or with a placebo. Therefore, treatment with proper doses of thyroid hormone does not cause adverse effects, as one would expect when giving a pure chemical that is identical to the one that the body produces naturally.

Conclusion and Recommendations

Screening for thyroid dysfunction in adults: The prevalence of subclinical thyroid dysfunction in apparently healthy people is high relative to most asymptomatic diseases and the exposed class appears to be at twice the normal risk. In addition, the Settlement Agreement stated that accurately detecting disease in asymptomatic individuals was a sufficient rationale for recommending screening; showing that early detection led to better outcomes was not necessary, according to the Settlement Agreement. A TSH test is the standard of care for detecting thyroid dysfunction in apparently healthy adults, and there is ample evidence that symptoms and signs alone do not detect everyone with subclinical thyroid dysfunction. Unlike other commonly used thyroid tests, a serum TSH level detects both overt and subclinical hypothyroidism and hyperthyroidism.

> The Medical Panel recommends one-time screening of all adult of class members with a serum TSH level.

Pregnancy: The most serious potential adverse effect of subclinical thyroid disease is disordered neuropsychological development of the fetus in pregnant women with subclinical hypothyroidism (13). Pregnancy speeds up the degradation of thyroid hormone. A normal thyroid would simply produce more hormone to keep its concentration in the normal range. The thyroid in subclinical hypothyroidism may be unable to increase its output of thyroid hormone to keep up with the faster rate of degradation, placing the patient and the fetus at risk. Therefore, if the patient is pregnant and has subclinical hypothyroidism, thyroid hormone replacement should be started.

> The Medical Panel recommends that the screening program should make an especially determined effort to identify pregnant women or women trying to become pregnant and screen them for thyroid disease.

If a woman is planning to become pregnant and has an abnormal screening TSH, ask her to delay efforts to become pregnant for a month in order to obtain a follow-up TSH test. If it confirms subclinical hypothyroidism, start treatment. If the follow-up TSH test does not confirm subclinical disease, do not treat.

Children: Screening for thyroid dysfunction in children is not standard practice. Thyroid disease is very uncommon in children, in contrast to adults. The Science Panel study showed that the

risk of self-reported thyroid disease was higher in children with greater exposure to PFOA. However, this evidence that exposure to PFOA causes thyroid dysfunction in children is weak, partly because the Science Panel study did not verify parents' report that their child had thyroid disease and partly because the small number of cases means that any results are subject to statistical uncertainty. The Panel members concluded that the decision should be left to the child's physician, who could take into account parental concern about the unpleasantness of drawing blood from a child and wanting to know if the child has a rare condition.

> The Medical Panel recommends against routine screening for thyroid dysfunction in children but encourages physicians to talk with parents about whether to screen.

The Medical Panel also recommends that standard of care guidelines for thyroid dysfunction screening in newborn children and children with Down Syndrome be followed. (14)

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Medical Monitoring Protocol for Pregnancy-Induced Hypertension

Description and Epidemiology

The C8 Science Panel defined "pregnancy-induced hypertension" (PIH) as an elevation in blood pressure that begins after the 20th week of pregnancy and reaches levels considered to be significantly elevated. The Panel noted that "preeclampsia" is diagnosed when the elevation in blood pressure is accompanied by the presence of protein in the urine (proteinuria). Data used for the Panel studies on birth outcomes were based on birth certificate reports of "pregnancy-induced hypertension" or on self-reports of "preeclampsia" in questionnaires. Because it was not possible for the Panel to differentiate between PIH alone and preeclampsia, the Panel combined these outcomes using the term PIH (whether or not there was proteinuria).

In order to encourage consistency in terminology, the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy published guidelines that divided blood pressure disorders during pregnancy into four categories (NHBPEP 2000):

- Chronic hypertension (hypertension that developed prior to the pregnancy)
- Gestational hypertension (transient hypertension that develops during pregnancy)
- Preeclampsia (gestational hypertension with proteinuria)
- Preeclampsia superimposed on chronic hypertension

The NHBPEP classification is the most widely used terminology for pregnancy-related blood pressure disorders. (Leeman and Fontaine 2008) (Solomon and Seely 2011) (Vest and Cho 2012) (Sibai 2012) Medical authorities refer to these disorders collectively as "hypertensive disorders of pregnancy" (HDP). This report will consider PIH to encompass gestational hypertension and preeclampsia, but it does not include uncomplicated chronic hypertension.

The most widely accepted definition of hypertension is having a systolic blood pressure (BP) >140 mmHg or a diastolic BP >90 mmHg. Technically the diagnosis requires detection of the elevated blood pressure on at least two occasions at least 6 hours apart, but no more than 7 days apart. Systolic BP between 140 and 160 mmHg and diastolic BP between 90 and 110 mmHg are considered to be mild hypertension, while systolic BP > 160 mmHg or diastolic BP > 110 mmHg are considered to be severe hypertension. "Gestational hypertension" is defined as hypertension that develops after the 20th week of gestation. The increase in blood pressure most commonly occurs during the third trimester and resolves shortly after delivery, although less commonly hypertension can develop earlier during pregnancy and rarely after delivery.

The diagnosis of "preeclampsia" is made when a pregnant woman has hypertension and develops proteinuria. The criterion for proteinuria is considered to be greater than 300 mg protein in a 24-hour urine collection. About 10% of women who develop preeclampsia do not have proteinuria, although they develop symptoms and signs consistent with preeclampsia such as headaches, blurred vision, abdominal pain, thrombocytopenia, and elevated liver enzymes (AST and LDH). (Lindheimer, Taler and FG 2009) (Vest and Cho 2012) Therefore, medical providers should consider the possibility of preeclampsia if a woman develops these symptoms.

The primary medical concerns about preeclampsia are that the condition can progress from mild preeclampsia to severe preeclampsia and lead in 5-12% of women with preeclampsia to the "HELLP" Syndrome which is characterized by hemolysis, elevated liver enzymes, and low platelet count, or to "eclampsia" in which the woman develops seizures. (Leeman and Fontaine 2008) (Lindheimer, Taler and FG 2009) Therefore, clinical management of all pregnancies should include screening for blood pressure and proteinuria.

Epidemiology. Hypertensive disorders in pregnancy (HDP) occur in 5% to 10% of pregnancies with chronic hypertension preexisting in 1-5% of pregnancies and gestational hypertension developing in 6-7% of pregnancies. (Vest and Cho 2012) Preeclampsia occurs in 2-5% of all pregnancies and 10% of first pregnancies. About 50% of women diagnosed with gestational hypertension develop preeclampsia. (Leeman and Fontaine 2008) About 20-25% of women with chronic hypertension develop superimposed preeclampsia. (Vest and Cho 2012)

Risk factors for preeclampsia include first pregnancy, maternal age >40 years, preexisting hypertension, obesity, carrying multiple fetuses (multiparity), and having preeclampsia or gestational hypertension during a prior pregnancy. Other conditions associated with an increased incidence of preeclampsia include pre-pregnancy diabetes, kidney disease, systemic lupus and other autoimmune disorders, and other less common medical disorders. African American women appear to be at higher risk, but it is unclear whether this association is independent of body weight and blood pressure. Risk is also higher in women with first-degree relatives who had preeclampsia, but it is not clear whether this association is because of genetics or because the relatives share similar non-genetic risk factors. Cigarette smoking is associated with a lower risk of developing preeclampsia.

Probable Link Evaluation for Pregnancy-Induced Hypertension

The Science Panel probable link evaluation for PIH was based primarily on four studies of estimated PFOA exposure and PIH reported on birth certificates and two studies of estimated PFOA exposure and self-reported preeclampsia in the mid-Ohio Valley population. One study of PIH was based on ZIP code of residence for Ohio births that included some of the region served by the Little Hocking Water Association. (Nolan, et al. 2010) The study found no apparent association between residential water source and PIH. The other studies were conducted by the Science Panel. The findings were summarized in the Probable Link report and in three publications as of April 2013. (Stein, Savitz and Dougan 2009) (Savitz, Stein and Bartell, et al. 2012) (Savitz, Stein and Elston, et al. 2012)

One Science Panel study of PIH was based on birth certificate records (n=8,253) from 1990-2004 for five counties in Ohio and West Virginia. Historical serum PFOA concentrations at the time of pregnancy were estimated by linking a geographical and temporal model of PFOA exposure in the region and pharmacokinetic modeling of serum PFOA to pregnant women's place of residence reported on the birth certificate. There was no apparent association between estimated serum PFOA and PIH in the overall study population based on residential zipcode,

but there was a weak positive association in an analysis that restricted the analysis to 66% of the births with street-level geocoded addresses and complete data on covariates. The investigators interpreted that the stronger findings in the sub-analysis were because of using more accurate street addresses to estimate exposure and better control of confounding. The adjusted odds ratios for PIH by quintiles of estimated serum PFOA were 1.0 (reference) for the lower two quintiles combined compared to 1.2, 1.1, and 1.3 for the 3rd, 4th, and 5th quintiles, respectively, with none of the odds ratios being significantly increased. (Savitz, Stein and Elston, et al. 2012)

A related study was conducted using the same exposure modeling methods, but it was restricted to birth certificate records of women who participated in the C8 Health Project and reported having births from 1990-2004 (n=4,547). This study had complete residential histories reported by the participants, so the analysis could be based on improved estimates of the past PFOA exposure. The study found "sporadic positive associations but little overall support for an association with pregnancy-induced hypertension." (Savitz, Stein and Elston, et al. 2012)

The Probable Link Report provided a summary of another study of PIH that linked birth records for 2005-2010 to participants in the 2005-2006 C8 Health Project (n=1,584). A strength of this study was that the serum PFOA levels were estimated based on the women's measured serum PFOA in the health survey adjusted for decline in serum PFOA after removal of PFOA from the municipal water supplies. This study found a clear association between serum PFOA and birth certificate reported PIH. The adjusted odds ratios by increasing quintiles of serum PFOA were 2.2 (95% CI = 1.0- 5.1), 2.9 (95% CI = 1.3-6.4), 2.6 (95% CI = 1.2-5.9), and 2.8 (95% CI = 1.2-6.4) for the 2nd, 3rd, 4th, and 5th quintiles, respectively, compared to the lowest quintile.

The Science Panel also conducted two studies of self-reported preeclampsia among women who participated in the C8 Health Project survey. One study was based on live births in the five years prior to the survey (2000-2006) and restricted to women who had lived in the same water district from their pregnancy until they participated in the survey, so presumably past exposure to PFOA would have been consistent. This study found that serum PFOA was weakly associated with preeclampsia with an adjusted odds ratio of 1.3 (95% CI = 0.9-1.4) for women with serum PFOA greater than the median compared to those with serum PFOA below the median (Stein, Savitz and Dougan 2009)

Recently the Science Panel reported a related larger study of self-reported preeclampsia among the C8 Health survey participants for pregnancies from 1990-2006 (n=11,737). (Savitz, Stein and Bartell, et al. 2012) This study used modeling methods to estimate historical serum PFOA levels at the time of pregnancy that were similar to those used for the birth certificate studies of PIH. The study found that preeclampsia was weakly associated with PFOA exposure. The adjusted odd ratios by increasing quintiles of estimated PFOA were 1.2 (95% CI = (1.0-1.5), 1.1 (95% CI = 0.9-1.4), and 1.2 (1.0-1.6), for the 3rd, 4th, and 5th quintiles, respectively, compared to the lowest two quintiles combined. (Savitz, Stein and Bartell, et al. 2012)

Overall the findings of the Science Panel studies were suggestive of a weak association between estimates of serum PFOA exposure at time of pregnancy and pregnancy blood pressure outcomes. The findings indicated that the risks of PIH or preeclampsia were modestly increased in the range of 20-30% across the various studies when comparing the highest exposed to the least exposed women in the mid-Ohio Valley study populations.

Screening and Diagnostic Testing

a) Screening

Screening for hypertension by measuring blood pressure is done as a standard component of prenatal care. (Gregory, Niebyl and Johnson 2012) Although there is some variation in the recommended visit schedules, medical authorities recommend regular prenatal care visits beginning as soon as the pregnancy is recognized. (NICE 2008) (Akkerman, et al. 2010) Visits should be scheduled approximately as follows: initial visit when pregnancy is first recognized; visits every four weeks from weeks 5 through 26; visits every two weeks from weeks 26 to 38; and weekly visits after week 38. (Gregory, Niebyl and Johnson 2012)

The blood pressure should be measured at every prenatal care visit using the correct technique and a blood pressure cuff of the appropriate size. (Lindheimer, Taler and FG 2009) The woman should be in a sitting position and resting for five minutes prior to the measurement with the arm positioned so the cuff is at heart level. The recommended procedure is to measure the blood pressure twice during each visit with an interval of at least five minutes. However, the common practice is to measure blood pressure once, but to repeat the measurement if the pressure is borderline high or has increased since the previous visit. Non-severe hypertension should be confirmed with readings >6 hours apart, while severe hypertension should only be diagnosed with two readings >15 min apart.

Guidelines to screen for preeclampsia are less consistent about the protocol to be used. The typical clinical approach is for the urine to be tested for proteinuria using a urine dipstick at each prenatal visit. The urine dipstick test has high false-negative rate and false positive rate, so most authorities recommend that a protein-to-creatinine (or alternatively albumin-to-creatinine) ratio test on a spot urine sample be used instead of a dipstick test if the blood pressure becomes elevated or the woman reports experiencing symptoms that may be suggestive of preeclampsia, such as headache, blurred vision, or upper abdominal pain. (Morris, et al. 2012) A protein-to-creatinine ratio urine test should also be ordered if the urine dipstick is 1+ or more for protein. If the protein-to-creatinine spot urine test is $\geq$0.15 mg/mg, then a 24-hour urine collection test should be done. (Morris, et al. 2012) (Gangaram, Naicker and Moodley 2009)

Guidelines generally agree on risk factors for pregnant women to develop preeclampsia, but indicate that there currently are no specific recommended screening tests or risk scores that can be used to predict which women will develop preeclampsia. (ACOG Practice Bulletin 2002) (Lindheimer, Taler and FG 2009) (Magee, et al. 2008) (Sibai 2012) (Vest and Cho 2012) Screening tests to predict higher risk of developing preeclampsia is an area of active research.

Examples of potential screening tests include uterine artery Doppler and measurement of several biomarkers in blood tests. (Vest and Cho 2012) (Sibai 2012) (Di Lorenzo, et al. 2012) (Abdelaziz, et al. 2012) It is likely that some of these screening tests for preeclampsia will be recommended for prenatal care in the future, but none of the tests is recommended by standard guidelines at this time.

b) Follow Up/Diagnostic Pathway

If a pregnant woman has chronic hypertension, medical authorities recommend that initial testing should include quantitative assessment of proteinuria using the spot urine protein-to-creatinine ratio test or the 24-hour urine collection test, complete blood count (hemoglobin, WBC, platelets), serum creatinine, serum uric acid, and liver enzymes (ALT, AST, LDH, bilirubin) so baseline levels can be established for possible later diagnosis of preeclampsia and the "HELLP" Syndrome. (Vest and Cho 2012) (Lindheimer, Taler and FG 2009)

If a women develops mild gestational hypertension, ongoing monitoring for development of more severe preeclampsia should include:

- Measure blood pressure twice weekly
- Obtain laboratory tests weekly: CBC, platelet count, ALT, AST, LDH, uric acid, creatinine
- Assess for proteinuria: screen with dipstick or spot protein/creatinine ratio and obtain periodic 24-hour urine collection (Leeman and Fontaine 2008)

c) Standard of Care for Screening

Guidelines for prenatal care and monitoring for hypertension and preeclampsia have been issued by several organizations and are generally consistent regarding the scheduling of visits and monitoring for blood pressure and preeclampsia as described above. The following are some of the major guidelines for prenatal care and for diagnosis and management of hypertension and preeclampsia:

<u>Prenatal Care</u>:

- National Institute for Health and Clinical Excellence (NICE) – 2008 (NICE 2008)
- Institute for Clinical Systems Improvement (ICSI) – 2012 (Akkerman, et al. 2010)

<u>Hypertension and preeclampsia</u>:

- National High Blood Pressure Education Program. Working group report on high blood pressure in pregnancy - 2000 (NHBPEP 2000)
- American College of Obstetricians and Gynecologists – 2002 (ACOG Practice Bulletin 2002)
- Society of Obstetrics and Gynaecology of Canada – 2008 (Magee, et al. 2008)
- American Society of Hypertension: Hypertension in Pregnancy - 2009 (Lindheimer, Taler and FG 2009)

Guidelines and medical authorities generally recommend the same prenatal care protocols for high risk and low risk patients because risk factors individually or collectively (based on risk prediction modeling) do not sufficiently discriminate between high and low risk patients to allow providers to change the standard of care based on risk stratification. Most authorities recommend instead that providers increase their vigilance for patients with risk factors for preeclampsia. More intense monitoring may involve scheduling more frequent prenatal care visits and suggesting that patients could monitor their blood pressure at home during prenatal visits to allow closer tracking of changes in blood pressure. (Gaillard, et al. 21011)

d) Shared decision-making: potential benefits and harms of screening and diagnostic testing

Screening for the onset of gestational hypertension and preeclampsia is a standard component of prenatal care. The harms are minimal. The screening tests to measure blood pressure and test for protein in the urine are minimal risk procedures. Additional tests recommended to evaluate preeclampsia (serum creatinine, blood count, serum uric acid, and liver function tests) require taking samples of blood, which is also considered to be a minimal risk procedure. The benefits of early detection and treatment are substantial. The balance of harms and benefits strongly favor the benefits. Therefore, this screening should be available to all pregnant women.

Conclusion and Recommendations

Medical screening for the onset of gestational hypertension and preeclampsia is a standard component of prenatal care which should be made available to all Class Members who become pregnant. At each prenatal care visit, screening should include blood pressure measurement and assessment of symptoms that may be suggestive of preeclampsia. It is current standard of care to assess proteinuria during each visit using a urine dipstick for protein, despite the poor screening performance of the urine dipstick.

The general consensus is that currently no specific screening tests have sufficient predictive validity to allow medical providers to distinguish between women at higher or lower risk of developing gestational hypertension and preeclampsia. Therefore, the standard of care for women at high risk is not formally different from women at lower risk of developing these conditions. Nevertheless, because Class Members may be at increased risk of developing gestational hypertension and preeclampsia, medical care providers should increase their vigilance to detect the onset of these conditions by the following:

1. If providers use a urine dipstick for regular prenatal care visits, they should order a protein-to-creatinine ratio spot urine test if the dipstick is 1+ or higher for protein.
2. They should use the protein-to-creatinine ratio spot urine test or a timed urine collection test to monitor for proteinuria if the woman's blood pressure increases systolic BP > 30 mmHg or systolic BP >15 mmHg compared to the first prenatal care visit.

3. They can recommend that a pregnant woman who is concerned about developing gestational hypertension do home monitoring of blood pressure in between visits beginning at the 20th week of gestation; and
4. They should obtain appropriate laboratory tests to assess preeclampsia if the woman reports symptoms consistent with preeclampsia. These test include at a minimum a complete blood count, serum creatinine, serum uric acid, and serum liver enzymes.

Because development and evaluation of screening tests to predict the likelihood of developing preeclampsia is an active field of research, the C8 Medical Panel will continue to monitor this field and the major guideline organizations to evaluate whether recommendations on screening protocols and tests change in the future.

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Medical Monitoring Protocol for Ulcerative Colitis

Description and Epidemiology

Ulcerative Colitis (UC) is a type of inflammatory bowel disease (IBD) which involves recurring episodes of inflammation of bowel mucosa, almost always involving the rectum, but which can extend to include other parts of the colon. UC is characterized by recurring episodes of rectal bleeding, bloody diarrhea, passage of mucus and crampy abdominal pain, with intermittent bouts of constipation that can advance to severe courses of pain, excessive bleeding, fever and weight loss. Based on a large U.S. study of nine million health insurance claims, the prevalence of UC was found to be about 200 cases per 100,000 people in the population (Kappelman, 2007).

Epidemiology. While the pathogenesis of IBD is unclear, there are several risk factors that have been identified that increase the likelihood of disease development. Specifically for UC, there are age, gender, racial and ethnic differences in disease frequency observed. Two age peaks for the onset of UC are seen; the first between ages 15-40 years and a second peak occurring after age 50. While both genders are affected, there is a slight preponderance in men. Most interestingly, there are frank differences in UC frequency as a function of race and ethnicity with an excess observed in persons of Jewish descent and with lower rates in blacks and Hispanics. This suggests both genetic and environmental factors in play, with diet being a principal environmental trigger which has been studied. The current belief is that certain food antigens, possibly milk proteins and dietary fats, may trigger IBD through an auto-immune mechanism, though the specific triggers are unknown. Infections of the gastro-intestinal tract that upset the bowel bacteria balance have also been implicated, as have certain medications. (reviewed in Loftus, 2004 and summarized from Up to Date (a) and (b); retrieved 11/19/12).

Probable Link Evaluation for Ulcerative Colitis

The Science Panel's comprehensive assessment of potential health effects and probable link findings attributable to PFOA exposure included autoimmune diseases. These disorders relate to altered function of the body's immune system, such that the body "attacks" itself. This disordered immune function can result in typically chronic diseases that can occur in a number of different organs of the body. The Science Panel investigated the five most common of these diseases (rheumatoid arthritis, lupus, type 1 diabetes, Crohn's disease (a type of inflammatory bowel disease) and multiple sclerosis) to determine if a probably link existed between any of them and PFOA exposure.

From the Probable Link Evaluation of Autoimmune Disease-Page 6,**:** "The science panel investigated the incidence of inflammatory bowel disease (IBD) in the C8 exposed populations as one of five of the most commonly occurring auto-immune – mediated conditions in the mid-Ohio valley.

Inflammatory Bowel Disease (IBD). Inflammatory bowel disease showed a positive trend of increased risk with increasing cumulative exposure in our main analyses based on 245 cases, which was statistically significant. (The Science Panel notes that there were 747 participants reporting IBD, but only 245 could be validated from medical record review (p. 5 of report). Results by quartile of cumulative exposure were RRs of 1.00, 1.74 (95% CI: 14 to 2.65), 1.80 (1.18-2.73), and 2.20 (1.43-3.39), respectively. These RRs indicate that those in the top 25% of cumulative exposure to PFOA had a risk of inflammatory bowel disease twice that of the lowest 25%. A test of trend in these RRs were statistically significant (p=0.001). Prospective analyses based on 44 cases, however, showed no positive trend (RRs of 1.0, 0.69, 0.92, and 1.00, respectively).

Ulcerative Colitis (UC). Among the validated inflammatory bowel disease cases, we conducted separate analyses for ulcerative colitis (161 cases) and Crohn's disease (96 cases), based on the subject's self-report of the type of inflammatory bowel disease. The positive trend with PFOA exposure was found primarily for ulcerative colitis, for which there was a strong dose-response gradient. RRs by quartile of increasing exposure were 1.0, 1.89 (1.08-3.31), 2.58 (1.52-4.38), and 3.18 (1.84-5.51), p value test for trend <0.0001). The analogous RRs for Crohn's disease were 1.0, 1.36, 1.22, and 1.10 (p value for trend 0.39). Prospective analyses (from 2005-2006 onwards) were restricted to 30 cases for ulcerative colitis. These analyses also showed a positive although non-statistically significant trend by quartile of increasing exposure, with RRs of 1.0, 1.49, 1.84, 2.18 (p value for trend 0.28). There were too few cases of Crohn's disease (n=14) to do a prospective analysis".

Screening and Diagnostic Testing

a) Screening

Unlike many cancers, for example, ulcerative colitis is an entity which is not typically considered a candidate for screening during periodic health assessments. Rather, its insidious onset and presentation as an episode of bloody diarrhea with or without crampy abdominal pain (Kornbluth and Sachar, 2004) usually presents a different clinical challenge, that of clarifying which of the multiple possible causes of such symptoms is responsible for the patient's presentation. Therefore, there are no available studies assessing screening protocols and no current recommendations for screening per se.

Patients give a history of gradual onset of symptoms as above and the physical exam may be normal, although pallor, abdominal tenderness and a stool positive for blood upon chemical testing may be found on rectal exam.

b) Follow-up/Diagnostic Pathway

While there is no specific screening protocol for UC, there are recommendations on the clinical pathway to pursue to evaluate a patient who presents as above.

Careful history taking will assist to identify possible other causes (ie, recent antibiotic therapy, possibly suggesting clostridium difficile colitis, other recent infectious diarrheal causes, possibly from a recent foodborne illness, (salmonella, shigella, campylobacter, , E coli 0157) other infectious causes and certain medication use (i.e., NSAIDS, gold and retinoic acid). Other risk factors include family history and there are also ethnic risk factors, i.e. higher risk in Jewish populations.

In addition to the history, the diagnosis is made from the characteristic appearance on endoscopy. The most recent practice guidelines from the American College of Gastroenterology, now suggest biopsy as well as sigmoidoscopy or colonoscopy to make the diagnosis, together with a negative evaluation upon stool examination for infectious causes of the presenting symptoms (Kornbluth and Sachar, 2010).

A longer term complication for some UC patients, related to disease duration and extent of colon involvement (typical seen seven to eight years after onset of symptoms) is a small increased risk of colon cancer -- about a half of one percent/year increased risk compared to the general population.

c) Standard of Care for Screening

Screening for asymptomatic people is not recommended.

d) Risk Communication/ Shared Decision-Making

The decision to undergo endoscopy (sigmoidoscopy or colonoscopy) in the symptomatic patient should be made during a conversation between the patient and the clinician. The important points to discuss include the size of the UC excess risk in the C8 exposed population and the presence of any other risk factors in the patient's personal medical history. The Science Panel noted that 'for all five diseases (the autoimmune diseases they reviewed), the prevalence in the Mid-Ohio Valley conforms broadly with that expected from U.S. population statistics, although data on the expected prevalence of these diseases is imprecise.

They then estimated about a two-fold excess risk when comparing the highest exposed quarter of the C8 exposed population to the lowest exposed quarter.

Also, the presence of other known UC risk factors such as family history and ethnicity should be considered during the shared decision-making conversation. This is then balanced against the risk of a serious complication during colonoscopy, most commonly a bowel tear, estimated to be about (0.35%) - (Dominitz JA, 2003; Levin TR, 2006) or for sigmoidoscopy, estimated to be about half the above rate, reflecting that the colonoscopy examines a longer segment of bowel (Gatto, NM, 2003). The decision about choosing sigmoidoscopy versus colonscopy is also made based on the symptoms and the required sedation that colonoscopy, but not sigmoidoscopy typically requires (Up to Date (c), 2013.

Conclusion and Recommendations

A questionnaire to elicit symptoms of UC should be completed beginning at age 15 (the lower bound generally, of the age range of UC onset), asking about a history of chronic or bloody diarrhea, abdominal pain and weight loss. The questionnaire should also query about risk factors for UC such as ethnicity, food intolerance, and history of other causes of such symptoms including food poisoning or antibiotic use, temporally related to symptoms or recent foreign travel allowing possible parasite infection.

Sigmoidoscopy or colonoscopy and biopsy for symptomatic persons should be performed. The choice of type of endoscopy should be left to the clinician and be a function of the presenting clinical picture and sedation desirability. Stool testing for C. difficile and other pathogens should also be obtained in the symptomatic patient. The clinician may obtain other laboratory testing including a blood count, measures of inflammation (erythrocyte sedimentation rates (ESR) or C-reactive protein (Up to Date, (b)).

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Medical Monitoring Protocol for Testicular Cancer

Description and Epidemiology

While reported as the most common cancer in young men ages 15-35, testicular cancer (TC) is still quite uncommon nationally, comprising only about 1% of all cancers in men. Of the 8500 U.S cases reported in 2012, fully half occurred in this young age group. Importantly, the five year survival rate of U.S. men diagnosed and treated between 2001 – 2007 was 95%, hence, the prognosis for this cancer is excellent, even for advanced cases (Up to Date (a); retrieved 11/19/12).

Well recognized risk factors for this cancer are cryptorchidism (undescended testes), a family history of testicular cancer or cancer in the opposite testicle (Up to Date (a)).

Common presentations of TC include a mass present in the testicle or scrotum (with or without tenderness), testicular firmness and/or scrotal fullness.

Probable Link Evaluation for Testicular Cancer

From the Probable Link Evaluation Report for Cancer (p. 5):

"The most notable finding across all four types of analyses was that of an elevated risk for testicular cancer in higher exposure areas, although the findings were based on small numbers since testicular cancer is rare. The RR for testicular cancer in the highest exposure category in the Ohio analyses (6 highest exposed cases) was 3.0 (0.9-9.4) (individual–level approach), and 6.7 (2.3-19.7) (geographical area-level approach), compared to non-exposed subjects. Tests for trend of increased RR with increasing exposure gave low p-values, with p=0.08 using the individual–level and p=0.0003 using the geographical area-level approach. Comparing exposed water districts to non-exposed areas, the RR for testicular cancer in Little Hocking (most highly exposed water district, 8 cases) was 5.9 (2.2-15.7) (individual-level approach). The p-value for test for trend of increased RR with increasing exposure was p=0.002.

And from page 10 of the Probable Link Report:

"For **testicular cancer**, there is evidence of a positive trend in risk across exposure groups, in some analyses, with the highest exposure group in both the internal analyses of the cohort study and the geographical cancer study showing estimated relative risks ranging from 3 to over 6, comparing the highest to lowest exposure groups. On the other hand there was little or no evidence of increasing risk in analyses from the same cohort compared with the US population, and in the period after 2005, there were no new cases compared to about five expected). The high exposure group, where the higher risk was observed, comprises only six cases therefore there remains some uncertainty. The Science Panel notes that there is experimental evidence of testis cancer being increased in exposed animals. The Science Panel considers observed excesses to indicate a probable link between PFOA and testicular cancer."

Screening and Diagnostic Testing

a) Screening

There have been no randomized or "quasi–randomized" controlled trials on the efficacy of testicular self-exam (Lin et. al., 2010; Ilic and Misso, 2011), which is the only currently available prevention activity to screen for testicular cancer. Further, according to the U.S. Preventive Services Task Force (USPSTF, 2011), there is no evidence that self-exam or clinical palpation increases case finding or survivorship (2011).

Evidence of benefits associated with screening can be derived from a large symptomatic cohort studied by Carmignani et.al., 2003. Symptoms in this group included infertility, scrotal swelling, pain or trauma, varicocele or erectile dysfunction. Carmignani found that among these 1320 patients, 2% had focal lesions (27 lesions total) on ultrasound, of which 80% were benign, but importantly, only 2/3 of which were palpable on exam. They reported the positive predictive value to be 0.2 in this symptomatic population.

With only three studies in the peer reviewed literature available for review on this topic, the USPSTF therefore, determined that it is not appropriate to recommend routine screening for testicular cancer in an asymptomatic population (Corresponding to Recommendation D in USPSTF Evidence Hierarchy). This is also in keeping with the current recommendations of the American Academy of Family Physicians (AAFP, 2011) and the American Academy of Pediatrics (AAP, 2007).

The USPSTF however, has not addressed the benefits of screening in higher risk for testicular cancer populations. The same lack of evidence exists for the benefit of screening in such higher risk groups, such as persons with a family history of testicular cancer, or cryptorchidism, populations which may serve as proxies for a putative higher risk population such as those exposed to C8.

The USPSTF makes the argument that both physician performed and self- testicular exam is likely of minimal harm and so, in a higher risk population, such a recommendation could reasonably be made for primary screening. Systematic reviews however, found no studies providing a quantitative assessment of the harms of screening from testicular exam. Note, however, that the American Cancer Society still recommends including a testicular exam as part of a periodic-cancer-screening check-up, but does not recommend the teaching of the self-exam (ACS, 2011).

Therefore, given the recommendations against screening of asymptomatic persons generally and the advice against teaching testicular self-exam, the Panel recommends clinical testicular exam and questionnaire for the asymptomatic child or adult. Concerned adults may also perform monthly testicular exam after discussion with their care provider about what to look for. Because the pediatric community, while acknowledging the lack of evidence of benefit for testicular self-exam still considers it part of the well adolescent visit, encouraging testicular self-exams in older children or adolescents may be recommended (Marcell, 2011).

A targeted health history questionnaire should be completed on patients of all ages. Pertinent questionnaire elements include: family history of testicular cancer, history of cryptorchidism or previous testicular abnormality (scrotal pain, fullness, mass or stone, change in testicular size) and history of gynecomastia.

For the person with additional risk factors and or symptoms, with or without a testicular mass found on exam, ultrasound may be considered.

b) Follow-up/Diagnostic Pathway for a Testicular Mass

The typical follow up for a mass detected on testicular palpation is ultrasound (US), to characterize the mass. In this setting, ultrasound sensitivity is near 100% (Up to Date (b)) in differentiating intra-versus extra-testicular lesions, although the specificity of ultrasound, is only about 44% due to problems distinguishing benign from malignant US patterns (Coret, et. al., 1995). None the less, US would be the appropriate initial step to evaluate the testicular mass and would also be used to screen the contralateral side for abnormalities.

Magnetic Resource Imaging (MRI) may assist in interpreting an inconclusive ultrasound. Muglia, (2002) and colleagues assessed 622 men with scrotal abnormalities among whom 17 had an ultrasound result suspicious, but not conclusive for cancer. In this series, no lesion defined as benign by MRI was found to be malignant, yielding a negative predictive value of 100 percent. However, two benign inflammatory lesions were first thought to be malignant, yielding a positive predictive value of 70 percent. This summary illustrates the sufficient utility of ultrasound in the vast majority of cases and the benefit of MRI in the instance of unclear results (Up to Date (b)).

In the setting of a testicular mass confirmed on US imaging, a complete physical exam is indicated with emphasis on determining other abnormalities that may indicate metastatic disease such as abdominal masses or enlarged liver and lymph nodes (abdominal or supraclavicular). A high resolution computed tomography (CT) scan of the abdomen and pelvis and a chest x-ray are generally also performed (Bosl, 1998).

If ultrasound findings indicate the need for surgery to make the diagnosis, additional assessment elements prior to surgery would include:

1) Measure of tumor markers in serum including:

   a. Alpha feto-protein (AFP)
   b. Beta human chorionic gonadotropin (B-hCG)
   c. Lactate dehydrogenase (LDH)

A recent European Association of Urology review reports that 50% of tumors have an increase in one of these markers (EAU, 2011). Therefore, a negative result for these markers does not rule out the condition.

2) Inguinal exploration and orchiectomy are performed to allow histologic (cell type) assessment (Up to Date (b)). Testis-sparing intra-operative biopsy using the inguinal approach may be chosen depending on the age of the patient and appearance of the lesion (Giannarini, 2008).

c) Standard of Care for Screening

There is no standard screening recommendation for people who are not symptomatic. As described above, there is no evidence of benefit for either clinician performed, or patient self-exam, although these conclusions were reached for the asymptomatic population. However, at least in the pediatric population, the physician performed testicular and genitalia exam is considered part of the usual well child and adolescent exam (Up to Date, (c)).

d) Risk Communication/Shared Decision-Making

The decision of a class member to undergo a testicular exam and to initiate testicular self-exam should be made during a conversation between the patient and the clinician. The important points to discuss include the size of the TC excess risk in the C8 exposed population, which is estimated by the Science Panel as between 3 fold (individual PFOA level analysis) and 6 fold (geographical area water district level analysis) higher than the risk in comparison populations in non-exposed areas, though this finding was based on only a few total cancers observed (Vieira, 2013). The clinician should also discuss with the patient the presence of other known TC risk factors such as family history, cryptorchidism and a history of a previous testicular lesion or new onset of gynecomastia.

For the patient with one of these risk factors, an additional discussion about ultrasound of the testes should be considered. Recall that in one of the only large studies assessing the benefits of screening in symptomatic patients, 1/3 of lesions found on imaging were not palpated on exam as described above (Carmignani, 2003).

All of these issues should be raised with the patient and then balanced against the risk of harm from screening, which should be small given the ultrasound procedure. For both the ultrasound procedure and the testicular examinations, the possible harm anticipated would be that of a false positive result and the anxiety attendant to that with possible need for further, clarifying follow-up procedures. This harm is thought to be of low probability, though a systematic review examining potential harm from screening has only been performed for the testicular exam, with no studies providing a quantitative assessment of the harms of screening identified.

Conclusion and Recommendations

A questionnaire (history of cryptorchidism, previous testicular cancer or other testicular abnormality, gynecomastia or family history of testicular cancer) should be administered and testicular exam performed by a clinician for all beginning at age 15 through age 50.

For male class members younger than age 15, we note that the testicular exam should be performed as part of the exam of genitalia which is the pediatric standard of care in well child visits, as discussed above.

Testicular self-exam teaching at an age appropriate time and through adulthood should also be done.

While testicular cancer is rare after age 50, the clinician should have heightened vigilance in history taking if a class member > 50 years reports a testicular complaint.

Beyond the questionnaire and testicular exam, ultrasound is recommended for additional high risk persons—e.g. symptomatic or with other risk factors.

If ultrasound results suggest the need for surgery, additional imaging may be performed and tumor markers (alpha feto-protein, beta human chorionic gonadotropin and lactate dehydrogenase) should be obtained. The inguinal approach with intra-operative biopsy and / or orchiectomy is the recommended standard of practice.

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Medical Monitoring Protocol for Kidney Cancer

Description and Epidemiology

Cancer of the kidney most commonly arises from renal tubular cells. It accounts for 2% of cancer cases in the U.S. and will be the 6th most common cancer in men and the 8th most common in women in 2013. (1) It is commonest in North Americans and Scandinavians. Based on past trends, 65,150 cases of kidney cancer are expected to occur in 2013, and 13,680 people are expected to die from kidney cancer. These figures are remarkably close to the figures for bladder cancer (2). Cancer arising from renal tubular cells accounts for 85% of kidney cancer. Transitional cell cancer of the renal pelvis is the other common form of kidney cancer in adults

Renal-cell cancer typically does not have early warning signs. Common symptoms at the time of presentation of patients with kidney cancer are hematuria (in 59% of cases), abdominal pain (in 41%), and a palpable abdominal or flank mass (in 45%). (3) The classic triad comprised of all three symptoms is the presenting finding in 9%. Other findings at the time of the diagnosis are anemia (21%) and fever 7%. With the increasingly widespread use of abdominal CT or ultrasound scans, roughly half of cases are now discovered before symptoms occur. (4)

Renal cell cancer is an aggressive disease. Symptoms or physical signs due to metastases are the first sign of kidney cancer in 10% of cases, and 30-40% of patients have metastases at the time of diagnosis. Renal-cell cancer spreads most commonly to the lung (55%), lymph nodes (34%), liver (33%), bone (32%), adrenal gland (19%) and contralateral kidney (11%). The median length survival of patients with metastases is 13 months. (4,5)

The treatment of kidney cancer is surgical removal if distant metastases are not present. Renal cell cancer can invade the inferior vena cava and may grow within the lumen up to the right side of the heart. Patients with this form of direct extension can be cured by surgery. One-third of patients who undergo surgical resection for what appears to be localized disease will have a recurrence. Renal-cell cancer is resistant to chemotherapy and radiation therapy. Biological agents are more successful, particularly those that affect the immune response.

Epidemiology. Renal cell cancer occurs 1.6 times more often in men than in women, equally in whites and African-Americans, and mostly in the 6th and 7th decades of life. In one study, the age at diagnosis ranged from 16 to 102 years. The median age at diagnosis was 66 years. The 25th percentile was 57 years, and the 75the percentile was 75 years. A 40 year old man has a 1.5% chance of renal cell cancer in his remaining lifetime. (4) A first degree relative with renal cell cancer increases one's risk 4-fold. Risk factors include cigarette smoking, obesity (especially in women), hypertension, occupational exposure to petroleum products, asbestos, or heavy metals. Unopposed estrogen therapy raises the risk. (4) The incidence of renal cell cancer is rising (as are many cancers as people live longer), due in part to earlier detection as an incidental finding in an abdominal imaging test (ultrasound, CT, and MRI), and so is 5-year

survival, reflecting the increasing proportion that are detected in people without symptoms of kidney cancer.

Probable Link Evaluation for Cancer of the Kidney

On April 15, 2012, the Science Panel announced a probable link between exposure to PFOA exposure and testicular cancer and kidney cancer. The panel did not find a probable link to any other form of cancer.

Three prior epidemiological studies performed by investigators other than the Science Panel had inconsistent results.

The Science Panel studied two populations: a community-based population ("community sample") and one comprised of workers at the DuPont Washington Works plant ("worker sample"). The Panel combined the two samples for a study of past PFOA levels and the occurrence of disease (N=32,254).

The Science Panel conducted several studies of residents of the Mid-Ohio Valley. It also followed up the participants in an earlier study for an additional 6 years and did not detect any new cases of kidney cancer, which lowered the relative risk from 1.8 in the earlier study to 1.28 (95% confidence intervals 0.66 to 2.24). However, they observed a statistically significant trend toward increasing incidence with increasing estimated serum PFOA levels over time.

A second Science Panel study compared the incidence of kidney cancer in Ohio and West Virginia regions that were exposed to PFOA to the incidence in unexposed regions and found "some inconsistent trends of increased risk in kidney cancer."

A third Science Panel study examined the relationship between *measured* PFOA levels in 2005/2006 and the recent incidence of several cancers in a study population of 49,082 people. The Panel did not find a relationship between exposure to PFOA and the incidence of kidney cancer.

A fourth Science Panel study monitored cancer incidence through 2009 to 2011 in a population of 32,254 adults who had serum PFOA measurement in 2005/2006 (a cohort study design, a relatively strong study design). They did two analyses. In a "lagged" analysis, they included PFOA exposure only for the period ending 10 years before the diagnosis of cancer (on the assumption that later levels would be less likely to trigger a cancer that would grow large enough to be diagnosed in 2009-2011). The Panel found a statistically not significant trend of increasing incidence with increasing exposure with relative risks of 1.0, 1.0, 1.7, and 1.4for the lowest to the highest quartile of exposure . The Panel also did an "unlagged" analysis (counting PFOA exposure in years right up to before the diagnosis of kidney cancer). The relative risks for kidney cancer incidence were 1.0, 1.2, 1.4, and 1.6. The Panel also did analyses based on cases that occurred after 2005/2006 (a prospective cohort design, the most rigorous design).

These analyses did not show evidence for increasing kidney cancer incidence with increasing exposure.

However, the Science Panel based its conclusion on the entire set of studies as described above.

In April 2012, the Science Panel reported its conclusion that the incidence of kidney cancer was probably linked to PFOA exposure. Some of their analyses showed a relationship to PFOA exposure. Others did not. The kidney cancer risk in the most exposed group was about twice the incidence in the general population. The annual incidence of kidney cancer in white men is 21.2 per 100,000 people (or 2 cases per 10,000 men). (1) Twice this rate would be 4 cases per 10,000 per year in men.

Twelve months after its probable link report, in March 2013, the Science Panel and collaborators described their findings in a peer-reviewed journal. (6) In this article, the exposure to PFOA was the estimated serum PFOA levels over 10 years using models based on serum PFOA levels measured in 2005/2006. The individual-level exposure varied widely, from annual serum levels of 3 µg/L to 655 µg/L. Water district average exposures varied from 125 µg/L to 5 µg/L depending on proximity to the DuPont Washington Works plant. The cancer rates were obtained for 10 years prior to 2005/2006 from state cancer registries, which meant that the cases had been verified. The authors divided the population of 69,000 into a very high exposure group representing the 10% of the population with the highest exposure. They divided the remaining individuals into low, medium, and high exposure with people from uncontaminated water districts as the reference group. To quote the main result for kidney cancer:

> "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) for medium and low exposure categories were close to the null compared with the unexposed."

This analysis shows an increased risk of kidney cancer in class members exposed to high levels of PFOA.

Screening and Diagnostic Testing

a) Screening

Standards of care for screening for kidney cancer: Our task is to describe the standard of care for a probable link condition in the DuPont-Leach case. If one exists, we should recommend it. If one does not exist, the Medical Panel must nonetheless recommend screening practice for the exposed class.

Guidelines for screening are the most tangible evidence of a professional consensus about a standard of care. Three searches of the AHRQ Guideline Clearinghouse did not identify any guidelines for screening for kidney cancer in average-risk adults. A urologist-consultant confirmed that guidelines do not exist.

The Medical Panel concludes that a standard of care for screening for kidney cancer does not exist. The Medical Panel made a recommendation for the exposed class, as described in the next section.

Possible screening tests for kidney cancer

Given that there is no standard of practice for screening for kidney cancer in asymptomatic persons, the Medical Panel must form its own judgment about whether to recommend screening. We use the next two sections to evaluate two possibilities for screening: ask about symptoms of kidney cancer and do a screening urinalysis.

Evaluating symptoms of kidney cancer: The commonest finding in proven kidney cancer is visible blood in the urine (gross hematuria) (in a study done in 1956, gross hematuria was present in 59% of cases at the time of diagnosis. (3) Abdominal pain was present on 41% of patients (3). The standard of care for patients with a history of visible hematuria is to perform cystoscopy (examination of the bladder) and an imaging study of the abdomen (ultrasound, CT or MRI).

The yield of asking about symptoms and signs of renal cell cancer may be estimated from a Japanese study performed from 1982 to 1988. (7) 45,905 persons had abdominal ultrasound; 21,818 had the test as part of an annual employee health examination, and 24,087 had the test because of symptoms. Apparently, patients in both groups were queried about symptoms of kidney cancer (gross hematuria, flank pain, fever, unexplained weight loss, fever of unknown origin, and metastatic disease); unfortunately, the article does not say how these data were obtained. Of the 45,905 individuals, 2874 (6.2 %) had symptoms or signs of renal cell cancer, and 15 of them had kidney cancer (0.03% of those asked and 0.5% of those with symptoms). 41,364 people had no symptoms of bladder or kidney cancer; 19 had kidney cancer (0.046%, or roughly 1 in 2,177 individuals). The Japanese study shows that the probability of kidney cancer is 0.005 when signs and symptoms are present and 0.00046 when symptoms are absent. These data show that symptoms of urologic malignancy increase the probability of kidney cancer. However, since only 44% of patients with kidney cancer had symptoms of urologic malignancy, the absence of symptoms is not reassuring. The Medical Panel concludes that asking about symptoms and signs of kidney cancer is a useful way to screen.

Screening for microscopic hematuria: Gross hematuria, abdominal mass, and chronic abdominal pain occur relatively late in the progression of kidney cancer, which has led the urology community to look for signs that occur earlier in the disease Microscopic hematuria in asymptomatic people is a sign of kidney cancer. The value of microscopic hematuria in predicting neoplasm is unclear because the evidence is limited and unsatisfactory. In one

retrospective study of 500 men referred for urologic evaluation because of asymptomatic hematuria, 2 had renal neoplasm (8). All patients had excretory urography (intravenous pyelogram) and in some cases retrograde urography (the study was done in 1956). In the study from Japan (6), 1667 individuals out of 45,905 had asymptomatic microscopic hematuria (the authors did not state their definition of microscopic hematuria). None of these patients had kidney cancer. Microscopic hematuria was not a predictor of kidney cancer in this study; however, the expected incidence of kidney cancer in the 1667 asymptomatic individuals would have been about one case per year, so the study had little power to assess the frequency of asymptomatic hematuria as a presenting finding in kidney cancer.

According to medical experts, urologists consider microscopic hematuria to be a useful clue to earlier stage kidney cancer.

The best indicator of microscopic hematuria is the examination of the urine sediment under a microscope. This procedure is time-consuming and probably not suitable for mass screening. The alternative is a dipstick that tests for blood in the urine. A systematic review examined 14 studies of dipstick urinalysis as a predictor of microscopic hematuria as detected by microscopic examination of the urine sediment. (9) This study showed that the median likelihood ratio positive was 5.6, which means that the odds of microscopic hematuria increase by a multiple of 5.6 when the dipstick is positive. The median likelihood ratio negative was 0.24, which means that the odds of microscopic hematuria decrease by a multiple of 0.24 when the dipstick is negative. These test performance characteristics are good for a screening test for hematuria, in which the pre-test odds of microscopic hematuria are quite low.

Microscopic hematuria on two of the three urinalyses in the absence of evidence of kidney disease (proteinuria or an elevated serum creatinine concentration) should prompt referral to a urologist.

b) Follow Up/Diagnostic Pathway

Signs and symptoms of renal cancer: In contrast to screening guidelines, guidelines for evaluating patients with hematuria do exist. (10) In patients with symptoms or physical findings suggestive of kidney cancer, the recommended next step is abdominal imaging. CT scan detects 94% of renal masses that are at least 3 cm in diameter. (4) Since renal cell cancer is an uncommon cause of hematuria or abdominal pain, a negative CT scan is usually good reassurance, unless the patient has many findings suggesting kidney cancer (and therefore a relatively high pre-test probability of kidney cancer). Magnetic resonance imaging (MRI) detects a large proportion of cancers and would be the preferred test if the patient is allergic to intravenous contrast material or has renal failure. Referral to a urologist is indicated if a renal mass is present on imaging tests. These recommendations are based on expert consensus. Randomized trials are entirely lacking.

Guidelines for follow-up of microscopic hematuria: As noted above, an abnormal dipstick test for hematuria does not necessarily mean that the patient has hematuria. If a dipstick test is

positive for blood, the next step is to perform a microscopic examination of the urinary sediment after centrifugation of freshly voided urine. Microscopic hematuria is usually defined as 3 or more red blood cells per high powered field on one urine specimen. The American Urological Association has issued guidelines for evaluating patients with microscopic hematuria. (11)

c) Standards of Care for Screening

Practice guidelines: As discussed, there are no practice guidelines for screening for kidney cancer. All of the guidelines focus on confirming the diagnosis and initial treatment options in patients with gross hematuria and patients with microscopic hematuria. These guidelines are based on consensus of expert opinion, not on a strong body of evidence about the consequences of taking action.

d) Shared Decision Making About Screening and Follow-up

Benefits of screening: The patient will know that he or she has kidney cancer and can seek care for the condition. Since we lack accurate screening tests, a negative result does not necessarily provide reassurance that kidney cancer is not present, and patients should be counseled to be watchful for blood in the urine.

Harms of screening: The recommended screening test is to ask about hematuria (blood in the urine), examine the patient for an abdominal mass, and perform a dipstick test of the urine. If the patient states that he or she has had hematuria or has verified microscopic hematuria, the consensus of expert opinion is that the kidney should be imaged using renal ultrasound with intravenous urography, abdominal CT scan (preferred), or abdominal MRI (for patients with allergy to the intravenous contrast material that is given to highlight the presence of a tumor. An imaging test that uses an intravenous contrast agent may cause an allergic or toxic reaction, which occurs in 4.1% of patients receiving ionic contrast dye and 0.69% of those who receive non-ionic contrast dye. Moderate or severe reactions occurred in 1.8% of patients exposed to ionic contrast dye and 0.11% of patient exposed to non-ionic contrast dye. Treatment was required with 1.3% and 0.2% of reactions to ionic and non-ionic contrast dye respectively (12).

Conclusion and Recommendations

The Science Panel concluded that kidney cancer was probably linked to exposure to PFOA. The risk of kidney cancer in the top quartile of PFOA exposure was 2.0, which means that the annual incidence of kidney cancer in the most exposed individuals was at least 4 in 10,000 exposed individuals. Kidney cancer is among the top ten malignancies, but it is very uncommon at any one point in time. To our knowledge, no guidelines or standards of care exist that recommend screening for kidney cancer. Unlike many common malignancies, there is no inexpensive, accurate test suitable for mass screening for kidney cancer. The consensus of urologists is that an abdominal CT scan is a standard of care in patients with gross hematuria. The evaluation of microscopic hematuria is more complicated because many more diseases can cause microscopic hematuria.

Recommendation: The Medical Panel recommends that members of the exposed class aged 50 years or older receive the following:

1. Ask about a history of gross hematuria.
2. Do a physical examination of the abdomen to detect an abdominal mass.
3. Ask about a family history of kidney cancer.
4. Ask about chronic abdominal pain, recent involuntary weight loss, and unexplained fever for at least a week.
5. Do a dipstick urine test for blood.

Follow-up protocol: Class members with gross hematuria or an abdominal mass should receive an imaging test of the abdomen. If a class member has unexplained weight loss, chronic abdominal pain, or unexplained fever over at least one week, the follow-up is up to the examining physician's judgment. However, kidney cancer should certainly be among the diagnoses under consideration. Class members with a positive test for blood in the urine should have a microscopic examination of freshly voided urine to see if microscopic hematuria (3 more red blood cells per high powered field) is present.

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