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September 21, 2011

Donald Kopp, Clerk
Circuit Clerk of Harrison County
301 West Main Street
Clarksburg, WV 26301

Re: Perrine, et al., v. E.I. DuPont De Nemours & Co., et al.
Civil Action No.: 04-C-296-2

Dear Mr. Kopp:

Please find enclosed an original certificate of service evidencing service of the attached "Submission of Guardian Ad Litem Regarding the Preliminary CT Rule and Preliminary Medical Monitoring Budget", as well as, attached referenced materials. Please file the same in the above-referenced court file.

Should you have any questions regarding this correspondence, do not hesitate to contact me at (304) 842-9401. Your attention to this matter is appreciated.

Sincerely,

Meredith H. McCarthy

Enclosures
cc: The Honorable Thomas A. Bedell
Edgar C. Gentle, III, Esq.
Virginia Buchannan, Esq.
Stephanie D. Thacker, Esq.
J. Farrest Taylor, Esq.

IN THE CIRCUIT COURT OF HARRISON COUNTY, WEST VIRGINIA

LENORA PERRINE, et al.,

Plaintiffs,

vs.

Case No. 04-C-296-2
(Honorable Thomas A. Bedell)

E.I. DU PONT DE NUMOURS AND COMPANY, a Delaware corporation doing business in West Virginia; et al.,

Defendants.

SUBMISSION OF GUARDIAN AD LITEM REGARDING THE PRELIMINARY CT RULE AND PRELIMINARY MEDICAL MONITORING BUDGET

Now comes Meredith H. McCarthy, Guardian Ad Litem for the minor children and incompetent adults in the above-referenced action, and in accordance with the Claims Administrator's Supplemental Report filed August 24, 2011, ordered by the Court on August 31, 2011, as well as, the Claims Administrator's Supplemental Submission of September 1, 2011, tenders her pleading with respect to the contested budgetary issues. As indicated by the Claims Administrator, the contested issues are as follows: (1) the preliminary CT Scan Utilization Guidelines and (2) the budget concerns, including bridge funding issues and the "inactive" claimant and "minor-no" claimant rules. With regard to the draft CT Scan Rule, this counsel argues that the examining physician alone should determine whether to recommend a CT Scan for a claimant without the restrictive symptom-based approach provided in the "medical necessity" factors of paragraph 7 of the Guidelines. Further, with regard to the budget concerns, this counsel argues that the Claims Administrator is in the best position to analyze the number-crunching aspect of the Medical Monitoring Program given his extensive experience with similar monitoring programs

throughout the country.[1] Finally, this counsel also advocates that the rules governing the "inactive" and "minor-no" claimant as proposed by the Claims Administrator be adopted by the Court in total.

ARGUMENT

I. THE EXAMINING PHYSICIAN ALONE SHOULD DETERMINE THE "MEDICAL NECESSITY" OF CT SCAN FOR MEDICAL MONITORING CLAIMANT WITHOUT GUIDANCE OF CLAIMS ADMINISTRATOR OR FINANCE COMMITTEE

It should be noted initially that the Perrine/DuPont class claimants are considered a high risk population based upon their proximity to the Spelter smelting facility and exposure to heavy metals therefrom, mainly arsenic, cadmium and lead.[2] Based upon guidance from the Environmental Protection Agency and professional periodicals, Dr. Charles L. Werntz found the toxic and carcinogenic effects of the heavy metal agents that came from the Spelter facility to be cumulative and additive. *See* Exhibit A. After more than six years of litigation, the parties negotiated a Memorandum of Understanding (MOU) on November 19, 2010, which was incorporated in the Final Order Approving Settlement entered January 4, 2011. The language of the MOU which addressed the Medical Monitoring Program and currently causes objections among the parties provides as

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[1] Edgar C. Gentle, III has administered large class action settlements for approximately twenty years. Specifically, since 1992 Mr. Gentle has served as Escrow Agent for the MDL 926 Court in the Baxter, Bristol and 3M Breast Implant Settlement which involved more than 1.1 billion dollars where he provides financial, business, accounting and tax support for all MDL 926 Qualified Settlement Funds. Since 2003, Mr. Gentle has been the Claims Administrator for the $300 million Monsanto PCB Settlement in Oliver and Tolbert v. Monsanto Co. Finally, Mr. Gentle has been the Claims Administrator for the above-referenced action pursuant to Court Order entered February 25, 2008, and was instrumental in the settlement of the case.

[2] *See* Anticipated Health Effects of the Contamination of Spelter, WV and Surrounding Communities with Arsenic, Cadmium and Lead, and Recommendations for Medical Monitoring, Charles L. Werntz, III D.O., MPH, March 30, 2007; Medical Surveillance Guidelines and Recommendation, James P. Kornberg, M.D., Sc.D. Nov. 11, 2005. This Court heard testimony regarding high incidence of lung and other cancers in Harrison County, WV. *See* Feb. 25, 2008 Final Order Regarding the Scope, Duration and Costs of the Medical Monitoring Plan at p 7.

follows:

> c. The program shall provide those examinations and tests set forth in the Court's Order of February 25, 2008 with the exception that no routine CT scans shall be performed as part of the medical monitoring program. The defendant does agree to provide CT scans that are diagnostically medically necessary as determined by a competent physician as relevant to possible exposure to the heavy metal contamination at issue in this litigation.

The Claims Administrator charged with the duty of implementing the Medical Monitoring Program drafted preliminary CT Scan Utilization Guidelines for the participating physicians. Paragraph 6 of the proposed CT Scan Guidelines allows that an examining physician will, in his discretion, decide "whether to recommend a CT Scan for the Claimant as being medically necessary and relevant to possible exposure to heavy metals. . . contamination. . . ." Paragraph 6 conforms to the parties MOU. Paragraph 7, however, addresses factors which satisfy medical necessity and includes as follows:

> (1) **Signs and Symptoms**, including but not limited to, paraneoplastic syndromes (production of hormone like symptoms from the tumor cells), unexplained weight loss, fever, fatigue, pain, persistent coughing or hoarseness, hemoptysis, unusual bleeding or discharge, dysphagia, persistent shortness of breath, thickening or lumps in the body, hyper pigmentation, jaundice, shoulder pain (Pancoast's Syndrome), pneumonia, persistent headaches, and/or other medical signs and symptoms which are widely accepted in the medical community as potential indicators of cancer.
>
> **AND/OR**
>
> (2) **Medical history** (including known diagnoses).

The primary problem with the preliminary CT Scan Guidelines proposed by the Claims Administrator is that it implements a "signs and symptom" based approach, limiting access to CT Scans to only symptomatic class members, and thereby effectively excluding that screening tool. It is well established that by the time lung cancer presents symptoms, it has progressed into advanced stages and metastasized to other parts of the body, thereby precluding the possibility of effective treatment, and drastically curtailing life expectancy of individuals found to have developed lung cancer. "More than 80 percent of patients with an abnormality on evaluation have metastatic disease. Patients presenting with anorexia, weight loss and fatigue have an especially poor prognosis." Lauren G. Collins, *et al.*, Lung Cancer: Diagnosis and Management, American Family Physician 75(1):56-63 at 60 (Jan. 1, 2007).

"Most persons with lung cancer present with symptomatic disease at advanced stage (stage III or IV) and at that point have little chance of curative treatment." Jett, J.R., Midthun, D.E., Screening for Lung Cancer: For Patients at Increased Risk for Lung Cancer, It Works, *Ann Intern Med.* 2011 Sep 5 [Epub ahead of print]. Five year survival with localized (early stage) disease is 50 percent, whereas is only 4 percent in those with distant (stage IV) disease. *Id.* More simply stated, "[t]he presence of symptoms at the time of diagnosis is associated with a high probability of advanced disease." Harvey I. Pass, David P. Carbone, David H. Johnson, Principles and Practice of Lung Cancer: The Office Reference Text of the IASLC at 671 (Lippincott Williams & Wilkins, 2009).

Given the reality that by the time lung cancer becomes symptomatic, it has often spread through the body and is in very advanced stages has led some in the medical community to advocate for a screening methodology proven to actually reduce mortality, so that this aggressive form of

cancer can be detected and treated in its earliest stages, before major damage has been done to the body and before metastasis occurs. "Screening for lung cancers in such patients [i.e., high risk populations like smokers] will find many cancers at an early stage when they are amenable to cure. Today, we have the knowledge and the technology that could change the outcome of lung cancer." Petty, T.L., The Early Diagnosis of Lung Cancer, *Dis Mon.* 2001 Jun; 47(6):204-64. The sole reason that screening has not been widely employed to combat lung cancer in the past was that data were lacking which provided that a particular screening tool in fact decreased mortality. *Id.* The newly published results of the National Lung Screening Trial (NLST), however, has now supplied the data that an annual screening program employing low-dose CT Scans to test *asymptomatic* high-risk individuals for lung cancer in fact drastically reduces the mortality of the disease. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening, *N. Engl. J. Med.* 2011; 365:395-409, Aug. 4, 2011.

The NLST trial enrolled 53,454 current or former heavy smokers to determine the efficacy of a screening protocol (defined as baseline testing of high-risk *asymptomatic* population for disease, with annual follow up scans thereafter, so as to catch the malady in the earliest and most treatable stages). The results confirm a dramatic reduction in mortality realized by screening *before* symptoms arise. Specifically, the participants who received low-dose helical CT Scans had a 20.3 percent reduction in lung cancer mortality than participants who received standard chest X-rays. An ancillary finding of the NLST showed that all-cause mortality (deaths due to any factor, including lung cancer) was 7 percent lower with low-dose helical CT than in those screened with chest X-ray.

It was noted a decade ago that low-dose CT scanning, utilized in an annual screening protocol of an *asymptomatic* high-risk population, could detect the disease in earlier stages while the cancer

was more amenable to treatment. "The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low radiation dose computed tomography in persons at high-risk for lung cancer." Henschke C.L., et al., Early Lung Cancer Action Project: A Summary of the Findings on Baseline Screening, *Oncologist* 6(2):147-52 (2001). This study concluded that "[b]aseline CT screening for lung cancer provides for detecting the disease and presumably more commonly curable stages in a cost-effective manner." *Id.;* See also, The International Early Lung Cancer Action Program Investigators, Survival of Patients with Stage I Lung Cancer Detected on Ct Screening, *N. Engl. J. Med.* 355(17);1763-71 Oct. 26, 2006.

The Claims Administrator contends that the following concerns remain: 1) exposure to CT Scan radiation must be justified and weighted against a benefit to the Claimant and 2) that his office is unaware of evidence that CT scanning of all Claimants would result in a decrease in cancer mortality rates. However, the weighing of the NLST proven mortality benefits of CT Scan screening protocol in high-risk populations (by locating cancers early- in more treatable stages) against the possible psychological trauma of receiving false positives, false negatives or an increase cancer risk caused by the scans themselves, should properly be left to the exposed claimant and his/her examining physician. Further, any low-dose CT Scan offered as a part of the Monitoring Program is not mandatory. Each claimant, in conjunction with advice from his/her treating physician, would decide whether to participate and how often to receive CT Scans.

The Claims Administrator also notes that none of the major cancer organizations have moved (in the month since the NLST study was published) to recommend annual CT Scan screening to combat lung cancer. However, on the ground medical providers are already adopting low-dose CT Scan screening to identify early-stage cancers in high-risk populations, given that this screening

has now been shown to reduce mortality by one-fifth.

> There are no official recommendations or guidelines for lung cancer screening, and the NLST authors say it's too early in the research to make such recommendations, but many hospitals have moved ahead with screening programs anyway, saying the potential to same lives is too great to wait any longer.

Courtney Hutchinson, CT Scans for Smokers Could Lower Lung Cancer Deaths by 20 percent, ABC News Medical Unit. As the results from the NLST are further analyzed, some organizations may update their recommendations and official stances on lung cancer screening for high-risk populations. Meanwhile, medical centers across the county currently have or plan to develop a lung screening protocol for high-risk patients. *See* Hospitals Offering Lung Cancer CT Scans, ABC News Medical Unit, June 29, 2011.

The most relevant submission of the Claim Administrator regarding the proposed CT Rule is the critique offered by Andrea H. McGuire, M.D., M.B.A. *See* Exhibit B. Dr. McGuire, in her professional capacity and as a neutral to these proceedings, was requested to evaluate the proposed guidelines. As Dr. McGuire correctly emphasized, the references relied upon by the Claims Administrator are inapplicable in that they describe scanning tools other than the low-dose chest CT scans at issue here and/or are outdated given the current research of the NLST. Dr. McGuire opines that all the Perinne/DuPont claimants should receive CT scans as diagnostically medically necessary because of the high risk associated with the possible exposure to heavy metal contamination at issue in this litigation. Dr. McGuire's opinion is consistent with the post-settlement opinion of Dr. Werentz. *See* Exhibit C.

For the record, medical monitoring is a theory of liability that allows for screening of *asymptomatic* individuals to check or screen for the presence of disease. Jerome R. Doak, *What is*

Medical Monitoring?, American Conference Institute Chemical Products Liability and Environmental Litigation, April 2010. The fundamental purpose of a medical monitoring program is to detect diseases which are sub-clinical, to provide knowledge or additional chance of cure for the participant. *See* OSHA-Medical Screening and Surveillance, Introductory Materials. Recovery for screening tests is NOT based on a physical injury or impact. Thus, by definition, a medical monitoring claimant has no existing physical injury, disease or symptom of disease. *Id.*; See also Exhibit C.

The Perrine/DuPont medical monitoring class agreed to a thirty-year Medical Monitoring Program to facilitate the testing necessary to detect disease associated with heavy metal exposure in the early stages in order to maximize the most meaningful treatment or management of disease. By imposing such restrictive limitations to the most effective screening tool for the diagnosis of lung cancer is essentially denying the class of their settlement. Furthermore, having the program Claims Administrator propose a definition for the term "medical necessity" for a competent physician seems to give the appearance of the practice of medicine. Thus, this counsel strongly advocates that paragraph 7 regarding factors which satisfy medical necessity, including "Signs and Symptoms" and "Medical History" be deleted from the proposed CT Guidelines. Rather, that all participating claimants receive an initial low-dose chest CT scan as a part of their medical monitoring to determine baseline data. Further, that the CT scan frequency for each claimant should be based exclusively upon the recommendation of the treating physician in consideration of the claimants proximity (Zone) and exposure to the heavy metals from the smelting facility.

II. DEFERENCE TO THE PRELIMINARY BUDGET FOR MEDICAL MONITORING PROGRAM EXPENDITURES FROM NOVEMBER 1, 2011 TO AUGUST 31, 2011 SHOULD BE GIVEN TO THE CLAIMS ADMINISTRATOR'S PROJECTIONS, GIVEN HIS ROLE AND PREVIOUS EXPERIENCE.

With regard to the projected calculations of the budget, specifically the expenditures in the November 1, 2011 through August 31, 2011 and bridge funding component, this counsel defers to the calculations offered by the Claims Administrator. This Court Ordered a pay-as-you-go approach as the most appropriate and equitable way to fund the Medical Monitoring Program, so that it would be based upon actual experience and costs incurred over time. *See* January 4, 2011 Final Order Approving Settlement and January 18, 2011 Final Order Setting Forth the Scope and Operation of the Medical Monitoring Plan. If the Claims Administrator over budgets at any given time, DuPont will have the benefit of carrying the surplus forward. Accordingly, no money will be lost.

DuPont objects to the figures offered by the Claims Administrator, particularly the CT Scan budget, as creating a "pot of money" for discretionary tests, under which his office is not equipped to monitor. However, this is exactly why the Court engaged Mr. Gentle as Claims Administrator. Mr. Gentle has the previous experience of administering and managing settlements in other class actions involving "pots of money". In fact, it was Mr. Gentle who advocated the "pay-go" approach and this Court indicated that "the precise mechanism by which any amounts are escrowed, how the escrow is replenished, how funds are disbursed and other similar matter should be evaluate by the Special Master, who should in turn make a prompt recommendation to the Court." See Feb. 25, 2008 Final Order Regarding the Scope, Duration and Cost of the Medical Monitoring Plan at 14.

Accordingly, Mr. Gentle should be given the latitude to provide his highly educated estimate on the projected budgetary expenses at issue for the constructive operation of the program. It is the recommendation of this counsel that the Preliminary Budget for post-implementation expenses associated with the program totaling $4,535,873.12- [comprising of the $2,407,835.93 monitoring costs without CT scans costs (*including* the $26,524.57 in bridge funding to CTIA for Sept. and Oct. 2011) and $2,128,037.19 Incremental Ct Scan costs] be approved by the Court.

III. THE CLAIMS ADMINISTRATOR'S RULES GOVERNING THE "MINOR-NO" AND "INACTIVE" CLAIMANT SHOULD BE ADOPTED BY THE COURT IN TOTAL.

As discussed herein, the Final Order Approving Settlement entered January 4, 2011 and the parties MOU, mandated that DuPont pay for a medical monitoring program for the class claimants for a period for thirty years. The Final Order Setting Forth The Scope and Operation of the Medical Monitoring Plan entered January 18, 2011, set forth the details of the establishment of the plan. The class members were notified of details regarding how to register for the Medical Monitoring Program via letter and registration form sent from the Perrine DuPont Settlement Claims Office on February 15, 2011. *See* Exhibit D. Specifically, the claimants were notified that they had the *opportunity* to participate in the program and that participation was *voluntary*. The correspondence provided that "If you are eligible and elect to participate in the Medical Monitoring program, that you *can* be medically tested free of charge shortly after registering, and every 2 years thereafter, for a total monitoring period of 30 years. The *voluntary* screen exam for participants will involve. . ." *Id.* at 3 (emphasis added). Neither the correspondence provided to the class, nor the Orders of the Court

which incorporated the MOU, required that participant avail himself to the program testing biannually. Thus, claimant medical monitoring participation was a negotiated right, not a requirement.

Accordingly, the Claims Administrator proposes two rules to govern those claimants who (1) initially chose to participate, yet become inactive over time, and (2) claimants who were minors at the time of registration and were precluded from enrollment by their parent/guardians actions (whether by marking "no" or failure to show for appointments). The proposed rule regarding the "inactive" claimants provides in essence that the claimant be provided biennial correspondence regarding the program, and invites the claimant to reactivate his/her participation status by providing written good cause for the lapse. The proposed rule regarding the "minor-no" claimants, provides that the upon turning 18, the claimant will be notified by the Claims Administrator of the program and afforded an opportunity to participate by responding affirmatively. It is proposed that both the "inactive" and "minor-no" claimants continue to receive biennial correspondence regarding the program availability for the duration of the thirty years.

DuPont raised an objection to the proposed rule, however, the specifics of the objection are unclear. Additionally, DuPont has not provided an alternative method of treating said claimants. As mentioned herein, the Perrine/DuPont class members fought for over six years for their medical monitoring program- it is their settlement. While it is hopeful that all claimants actively participate, there were no written mandates or conditional requirements that a claimant participate at every screening. Further, given the legal incapacity of the minor claimants, they had no real ability to exercise free will in terms of enrollment or meaningful participation in the program. Accordingly, it is only reasonable that the claimants who initially registered to participate in the program (whether

active or inactive), as well as, the minor-no claimants continue to have the opportunity to employ the Medical Monitoring Program for their thirty year option as outlined by the Claims Administrator Rules.

Respectfully submitted,

Meredith H. McCarthy, W.Va. Bar 7540
Guardian Ad Litem for class members that are minors or incompetent adults
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Bridgeport, WV 26330
(304) 842-9401

CERTIFICATE OF SERVICE

I, Meredith H. McCarthy, do hereby certify that I have this 21th day of September 2011, given notice of the filing of the foregoing *Submission of Guardian Ad Litem Regarding The Preliminary CT Rule and Preliminary Medical Monitoring Budget* upon the following counsel of record, by hand delivery or by depositing a true copy thereof in the United States Mail, postage prepaid, in envelopes addressed to:

Edgar C. Gentle, III, Esq.
c/o Spelter Vol. Fire Dept. Office
55 B. Street
P.O. Box 257
Spelter, WV 26438
Claims Administrator

Virginia Buchannan, Esq.
Levin, Papantonio, Thomas, Mitchell, Raffety & Proctor, P.A.
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Meredith H. McCarthy

West Virginia University
SCHOOL OF MEDICINE

Anticipated health effects of the contamination of Spelter, WV and surrounding communities with arsenic, cadmium, and lead, and recommendations for medical monitoring.

March 30, 2007

The residents in the area around Spelter have been exposed to arsenic, cadmium, and lead an extended time. There are clear associations between arsenic, cadmium, and lead with significantly increased risks of developing disease, primarily cancers. IARC lists arsenic and cadmium in Group 1 (Carcinogenic to Humans). Lead is listed in Group 2A (Probably Carcinogenic to Humans). Additionally, there have been several studies documenting increased cancer risk around smelter sites[1,2,3,4] where similar exposures have occurred.

I have reviewed the Dr. Kornberg's Initial report of November 11, 2005 as well as his rebuttal report of March 3, 2006. I concur with most of Dr. Kornberg's conclusions and recommendations, however I have several updates to both focus the exams to those conditions associated with the arsenic, cadmium and lead exposures as well as to update the science to reflect new technology available for medical monitoring.

DEFINITION OF GEOGRAPHICAL TERMS

Dr Brown, in his incremental cancer risk map, shows the residual contamination across the class area. There are three distinct areas within the class area, separate in their degree of contamination, and thus the risk to the residents in those areas.

- **Zone 1** ≡ The area delineated by Dr. Brown as within the $5x10^{-4}$ incremental risk contour for developing cancer.
- **Zone 2** ≡ The area between the 5×10^{-4} incremental risk contour and the 1×10^{-4} incremental risk contour.
- **Zone 3** ≡ The area within the class area but outside the 1×10^{-4} cumulative incremental risk contour.

The residents in all areas have a significantly increased risk of developing disease based upon their residence and exposures in the area. The toxic and carcinogenic effects of all

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[1] Brown LM, Pottern LM, Blot WJ. Lung Cancer in Relation to Environmental Pollutants Emitted from Industrial Sources. Environmental Research Vol 34, 250-261.

[2] Pershagen G. *Lung Cancer Mortality among Men Living near an Arsenic-Emitting Smelter*. American Journal of Epidemiology, Volume 122, Number 4, *Pp. 684-694*

[3] ATSDR Public Health Assessment for National Zinc Company in Bartlesville, OK., Viewable at http://www.atsdr.cdc.gov/HAC/PHA/zinc/nzc_p2.html#PUBLIC

[4] Tokudome S, Kuratsune M. A cohort study on mortality from cancer and other causes among workers at a metal refinery. Int J Cancer. 1976 Mar 15;17(3):310-7.

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Exhibit A

three of these agents are cumulative and additive[5]. As such, the longer one is exposed, and the more different toxins, the greater the likelihood of developing disease.

Arsenic is associated with cancers of the skin, lung, bladder, kidney, and liver. Cadmium accumulates in the kidney and can cause renal damage and ultimately renal failure. Cadmium is also a carcinogen, associated with cancer of the lung and kidney. There is also some evidence suggesting cancer of the prostate. Lead is associated with cancers of the lung, brain, stomach, and kidney. Additionally, elevated blood lead causes cognitive and behavioral difficulties and is a disease in its own right.

In response to these facts, I propose the following medical monitoring program for the residents of the affected area.

Residency Time Requirement

- For residents within Zone 1, an accumulation of one year of residence shall be required for entry into medical monitoring.
- For residents in the Zone 2, the accumulation of three years of residence in the class area shall be required for entry into medical monitoring.
- For residents in the Zone 3, the accumulation of five years of residence in the class area shall be required for entry into medical monitoring.
- Once a resident has qualified for entry into medical monitoring based upon their residence in the area, they shall remain in medical monitoring for 40 years past the remediation of their residence.

BASIS FOR THE RESIDENCY TIME RECOMMENDATIONS

My goal is to ensure that residents with a significantly increased risk are offered medical monitoring. However, reasonableness demands establishing a threshold for the minimum residency requirement. I also believe that it is appropriate to be moderate at each decision point.

In his report, Dr. Komberg did calculations to estimate risk using the difference between the measured soil Arsenic levels to calculate the incremental risk, and concluded that 277 days of exposure would be required to reach an "action level". This was adequate to demonstrate the presence of increased risk, however more precise calculations of risk are now available on Dr. Brown's map titled "Incremental Total Cancer Risk for All Pathways" (copy attached as Appendix A), and these are the basis of the minimum residency time requirements for entry into the medical monitoring program delineated here.

General logic:

Based solely upon the risk of skin cancer from arsenic exposure via ingestion, and lung cancer from arsenic and cadmium inhalation, Dr. Brown has calculated the total cancer risk from the exposures in the class area. Clearly there are multiple additional cancer risks for the exposed population from the arsenic, cadmium, and lead that are not

[5] EPA Risk Assessment Guidance for Superfund Volume I Human Health Evaluation Manual (Part A), sections 8.2.2 and 8.3; viewable at http://www.epa.gov/oswer/riskassessment/ragsa/pdf/ch8.pdf

included in these calculations, which would only increase the calculated risk. Starting with the 30 year total risk from Dr Brown's model, I calculated the time duration that would expose a person to a 1:100,000 risk of developing these two cancers for each of the zones.

Calculations:
Using a simple proportion, with the goal of calculating the total risk then the proportion was solved for time (X)

$$\frac{\text{Total Risk}}{\text{30 Years}} = \frac{\text{Significant Risk}}{X}$$

$$X \times \text{Total Risk} = \text{30 Years} \times \text{Significant Risk}$$

$$X = \frac{\text{30 Years} \times \text{Significant Risk}}{\text{Total Risk}}$$

Zone 1 (Inner)

$$X = \frac{30 \text{ Years} \times 10^{-5}}{1 \times 10^{-3}} = \frac{30 \times 10^{-5} \text{ Years}}{1 \times 10^{-3}} = 0.3 \text{ Years} = 109.5 \text{ Days}$$

Zone 1 (Outer)

$$X = \frac{30 \text{ Years} \times 10^{-5}}{5 \times 10^{-4}} = \frac{30 \times 10^{-5} \text{ Years}}{5 \times 10^{-4}} = 0.6 \text{ Years} = 217 \text{ Days}$$

Zone 2

$$X = \frac{30 \text{ Years} \times 10^{-5}}{1 \times 10^{-4}} = \frac{30 \times 10^{-5} \text{ Years}}{1 \times 10^{-4}} = 3 \text{ Years}$$

Zone 3

$$X = \frac{30 \text{ Years} \times 10^{-5}}{7 \times 10^{-5}} = \frac{30 \times 10^{-5} \text{ Years}}{7 \times 10^{-5}} = 4.28 \text{ Years}$$

Notes and codicils about residency time:

1. The contours on the map indicate that the area within the contour is at or above the listed risk. Thus, while a few residents just inside the contour line may have the risk level equal to the listed contour, most of the residents within the contour are exposed to a higher risk than that portrayed by the contour.

2. The exposure at individual residences will end only with the remediation of the contamination in the residences. Thus residence time calculations will end with the remediation of each individual residence.
3. The waste piles were capped in 2004, thus residence time in any home whose construction or installation was begun in 2005 or later would be excluded from the time calculations for medical monitoring, due to the much lower likelihood of the presence of large quantities of contaminated dust within the residence (although soil exposure risk remains).

I believe that it is appropriate to include moderating measures at each point in setting the minimum residency time.

Moderating measures used in calculating residency time included:

1. Using 1:100,000 as the threshold for "significant risk", rather than 1:1,000,000, which is a more common threshold.
2. The model discussed by Dr. Brown includes only skin cancer risk from arsenic and lung cancer risk from arsenic and cadmium. There are significant additional cancer risks that are not considered in this calculation. Thus, the actual cancer risk would be greater if these additional risks were considered.
3. The residence time was rounded up to the next reasonable interval (i.e. full year).
4. No cancer risk for lead was considered in the model

Moderating measures in medical surveillance program:

1. Only diseases clearly associated with arsenic, cadmium, and lead are monitored for.
2. Testing is limited to diseases and medical tests clearly supported by the literature or general medical practice.

GENERAL PRINCLPLES:

Once the entry criteria has been satisfied, the monitoring program shall be the same for all medical monitoring group members, except for differences by member age mentioned below.

Medical monitoring shall be conducted every 2 years for members of the medical monitoring group once entry criteria are met. While this spacing could miss some rapidly developing diseases, it will catch most diseases, and will not significantly increase the risk to the patients from the testing.

Medical monitoring shall continue until 40 years past the end of exposure. Generally this would be either 40 years beyond moving out of the class area or 40 years after their residence is remediated. This is based on the usual latencies of the diseases of interest.

Any resident whose residency within the class area ended more than 40 years ago, and has not resided within the class area within the past 40 years, shall be excluded from the medical monitoring eligibility.

Remediation

The residents in this community have been exposed to arsenic, cadmium, and Lead from the Spelter smelter site through breathing plant emissions during operations, soil contamination, exposure to fugitive emissions from the waste piles, living in houses contaminated with dust from the plant, soil contamination around their residence, incidental soil and dust ingestion, and consumption of contaminated vegetables, and perhaps drinking water contaminated by emissions from the plant site.

While clearly not of the magnitude as during smelter operations, exposure to arsenic, cadmium, and lead is ongoing for residents in the community. Several interventions have been undertaken to limit exposure, including extinguishing the fires in the piles, limiting access to the waste piles, and the capping of the piles to limit fugitive emissions, and establishment of municipal water for the affected area. I would encourage that additional interventions be undertaken to decrease or eliminate the exposure through the remaining routes. This would include remediating the homes to remove contaminated dust from the living spaces as well as the dust reservoir areas within the home (attic, basement, etc.), and remediating the soil around the residences.

Diseases considered to be related to the exposures from Spelter site. (Unfortunately, medical monitoring is not possible for all diseases associated with these exposures)

Arsenic[6,7]
Skin Cancer
Lung Cancer
Bladder Cancer
Kidney Cancer

Cadmium[8]
Lung Cancer
Kidney Cancer
Decreased Renal Function[9]
Renal Failure
Bone Fragility

Lead[10,11]
Plumbism (Lead Poisoning) – Having elevated whole blood lead is a disease in itself, causing mental retardation, poor school performance, and behavioral problems. In

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[6] Ferreccio C, Sancha AM. Arsenic exposure and its impact on health in Chile. J Health Popul Nutr. 2006 Jun;24(2):164-75
[7] IARC Monograph on Cadmium, viewed at http://monographs.iarc.fr/ENG/Monographs/vol23/volume23.pdf
[8] IARC Monograph on Cadmium, viewed at http://monographs.iarc.fr/ENG/Monographs/vol58/volume58.pdf
[9] NIOSH Worker Notification Program; Cadmium Recovery Workers (Cadmium); Viewed at: http://www.cdc.gov/niosh/pgms/worknotify/cadmium.html#estimated
[10] IARC Monograph on Lead, viewed at http://monographs.iarc.fr/ENG/Monographs/vol23/volume23.pdf
[11] IARC Monograph on Lead, viewed at http://monographs.iarc.fr/ENG/Monographs/vol87/volume87.pdf

children, there is clear evidence of this effect at levels well below the CDC action level of 10 µg/dl.
Lung Cancer
Stomach Cancer[12]
Kidney Cancer
Decreased Renal Function[13]
Renal Failure[13]
Bone Fragility
Loss of teeth
Hypertension
Increased rates of criminal activity[14,15]

There are several additional cancers that have been proposed as due to lead exposure, but for which I do not yet find the literature compelling. At the present I would not recommend screening for these diseases, but I would recommend a review of the literature in several years to consider these conditions.
Brain Cancer
Stomach Cancer
Rectal Cancer
Prostate Cancer
Colon Cancer

General flow for each surveillance exam:

1. Laboratory (Blood and Urine) and Chest CT obtained
2. Await results from studies (likely < 2 weeks)
3. Brief history, physical examination, and review of the results by a Physician
    a. Referral to specialist for positive findings in diseases associated with the exposures (paid for by screening program)
    b. Referral to PCP for findings not associated with the exposures

The screening examination will be the same for all participants, except

- Start screening chest CT scans at age 35 (none below age 35)
- No CT scans of anyone who is pregnant or possibly pregnant. Urine pregnancy test for females age 35-55 prior to scan unless surgical sterilization.
- Below age 15, screen ONLY whole blood lead (capillary or veinous)

[12] Steenland K, Boffetta P. Lead and cancer in humans: where are we now? Am J Ind Med. 2000 Sep;38(3):295-9.
[13] Ekong EB, Jaar BG, Weaver VM. Lead-related nephrotoxicity: a review of the epidemiologic evidence. Kidney Int. 2006 Dec;70(12):2074-84. Epub 2006 Oct 25
[14] Needleman HL, McFarland C, Ness RB, Fienberg SE, Tobin MJ. Bone lead levels in adjudicated delinquents. A case control study. Neurotoxicol Teratol. 2002 Nov-Dec;24(6):711-7
[15] Stretesky PB, Lynch MJ. The relationship between lead exposure and homicide. Arch Pediatr Adolesc Med. 2001 May;155(5):579-82.

General Screening Examination:

- Single Breath Hold High Resolution Low Dose CT scan of the Chest[16] (>= age 35)
- Urine Collection for:
  a. Urinalysis (Dip)
  b. Urine Rapid Pregnancy (Females age 35 – 55, unless surgical sterilization)
  c. Urine Cytology
  d. Urine Beta-2-microglobulin
- Blood collection for:
  a. Creatinine
  b. BUN (Blood Urea Nitrogen)
  c. Calculated glomerular filtration rate (GFR)
  d. Whole Blood Lead
- Stool Blood (Hemoccult)
  a. Dispense Hemoccult cards at time of blood/urine collection
  b. Patient to return cards at physician exam
- Physician examination/Interaction
  a. Record vital signs, including Blood Pressure
  b. Skin examination (head to toe, for skin cancer)
  c. HEENT exam, focus on dentition and mucosa
  d. Peripheral motor function (wrist & ankle extensors)
  e. Develop and review Hemoccult cards
  f. Review results of blood and urine screening
  g. Review CT scan results
  h. Order re-testing or make referrals based upon findings

Urinary System (Kidney & Bladder)

Screening exam:

- Urinalysis (dip stick)
- Urine Cytology
- Urine Beta-2 microglobulin
- BUN and Creatinine
- Calculated Glomerular Filtration Rate

Follow-up examination (Blood on UA or positive cytology)

- Consultation with Urologist (2 office visits)
- Repeat Urinalysis
- Cystoscopy with biopsy
- CT scan of Abdomen

Follow-up examination (Beta-2 microglobulin or BUN/Creatinine elevated)

- Consultation with a nephrologists (2 office visits)
- Repeat Urinalysis

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16 Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. JAMA. 2007 Mar 7;297(9):953-61

- Repeat BUN/Creatinine
- Labwork to look for other causes of kidney failure
  - Blood Glucose
  - ESR

Lungs

Medical Surveillance Examination (For persons >= age 35); Perform every 2 years

- Single-breath-hold, high-resolution, low-exposure, CT scan of the chest

First Cycle Positives

- Repeat same CT scan several months later
- Consultation with ordering physician to review changes over time and refer as appropriate

Subsequent Cycle Positives

- Consultation with a pulmonologist (2-3 office visits)
- Repeat CT scan several Months later
- Lung Biopsy
  - By Cardiothoracic surgeon or
  - Pulmonologist, depending upon the location of the lesion within the lungs

Plumbism (Lead Poisoning)

Screening Examination

- Whole Blood Lead
  - Medical Action Level (above which additional investigation is needed):
    - Children (<18 Years Old): 10 µg/dl
    - Adults (>18 years old): 30 µg/dl
  - Neuropsychiatric Action Level (above which neuropsychiatric evaluation is needed):
    - Children (<18 Years Old): 5 µg/dl
    - Adults (>18 years old): 20 µg/dl

    Note: Repeat neuropsychiatric evaluation is not needed unless >25% increase in measured whole blood lead

Medical Follow-up examination

- Consultation with medical toxicologist/Environmental Medicine Specialist (4 office visits)
- Repeat whole blood lead (veinous) (Children 15%, Adults 15%)
  - If elevated, refer for evaluation and possible treatment
- Zinc Protoporphyrin
- Complete Blood Count
- Bone x-ray fluorescence testing to assess body burden

Neuropsychiatric follow-up

- Formal neuropsychiatric evaluation

Skin

Screening Examination

- Head-to-toe examination of the skin by the screening physician as part of the physical examination.

Follow-up examination

- Consultation with Dermatologist (1-2 visits)
- Biopsy by dermatologist if indicated

GI system (stomach, intestines, rectum)

Screening Examination

- Stool Hemoccult, cards distributed at blood/urine collection, developed at physician follow examination
- Follow-up examination
  - Refer to PCP for evaluation for colon disease
  - IF negative colon disease workup, then re-enter screening program to look for stomach cancer
    - Refer to Gastroenterologist for stomach evaluation
    - EGD (Endoscopic Gastroduodenoscopy)

Overall medical surveillance assumptions:

- Participation in the entire program is voluntary, and that a participant can choose to participate or discontinue participation at any time.
- That there will be one (or a small number) of physicians from the community supervising the medical monitoring program and performing the physical examinations. This is to ensure that the physician is familiar with the program, the diagnosis of the diseases of concern, and to ensure consistency.
- For the first cycle, the patients must have pre-testing access to a knowledgeable clinician (physician or nurse) be discuss the risks and benefits of the proposed testing
- That medical testing without physician interpretation of the results is inappropriate for the well being of the participant
- That the ideal is for a physician visit for results interpretation (and physical examination) following testing
- That without the physician examination, key portions of the evaluation will be missed, and that the physical examination is critical to identifying some of the diseases of concern.
- That any participant who fails to participate in the post-testing physician evaluation will receive a letter communicating their test results, and any recommendations for follow-up.
- In all cases, the evaluating physician shall have the freedom to repeat any test if there is evidence of a lab error or if no other clinical evidence is found to support the diagnosis suggested by the test result.
- If a patient has had any of the recommended tests within the past 6 months, and the written results these can be provided, those tests will not be repeated, and the patient-provided results used for the screening program.

- That following diagnosis with a disease of interest, the screening for that disease will cease, but other screenings will/could continue
- That some test results can be caused by multiple diseases. The interpreting physician will be charged with figuring these cases out.
- Despite targeted testing, it is possible conditions will be detected by the testing that are not related to the exposure. When that happens, the participant will be referred to their Primary Care Physician for follow-up and treatment.
- Workup of positive test results will continue until the determination of exposure-related or non-exposure-related can be made
- As soon as a non-exposure-related condition is identified, the patient will be referred to their PCP. The screening for the disease of interest will continue unmodified. This referral will occur each screening cycle. The patient can decline the referral if they deem it unnecessary.
- A patient with an abnormal finding related to the exposures will be referred to the appropriate specialist with each screening cycle. The patient can decline the referral if they deem it unnecessary.
- That a central repository of the screening, referrals, and outcomes data will be maintained, and depersonalized data made available for epidemiological evaluations. It is clear from my literature review in preparing this document that there is incomplete scientific evidence in the literature on screening programs, participation rates, referral rates, etc. This data could serve as the basis for answering many of these scientific questions.
- The screening program described here is based upon the best available medical knowledge in 2007. While I would not propose changing the diseases being monitored for, it is likely that in the future new technology or better understandings within medicine will require the updating of this protocol. This protocol should be reviewed periodically by the administering physician to ensure that the screenings and follow-up described here remain consistent with best medical practice.

Commentary on the differences between Dr. Kornberg's proposal and this recommendation.

Overall, I concur with Dr. Kornberg's assessment of the nature of the exposure as well as the diseases of concern associated with these exposures. My opinion differs from his only in the details.

1) The only disease caused by all three of the exposures is lung cancer. Dr Kornberg recommended screening for lung cancer using chest x-rays. Unfortunately, by the time most lung cancers are large enough to be detected by chest x-ray they are incurable. Over the past several years there have been promising results from the use of low dose CT scans to screen for early lung cancers. This technology allows for the identification of much smaller tumors and the 3-D imaging makes it much easier to differentiate cancers from other lung lesions.

2) Some of the testing proposed by Dr Kornberg was aimed at biomonitoring (monitoring levels in blood, urine, or hair) to assess for the presence of the Arsenic, Lead, and Cadmium. I fully support monitoring whole blood lead since an elevated blood Lead is a disease in its own right. However, for arsenic and cadmium I do not believe biomonitoring would be useful clinically. There are two reasons.

   a. First, at this point the exposures are lower level chronic exposures, and the available biomonitoring tests are designed to monitor acute exposures, such as monitoring pre- and post-shift urinary cadmium for cadmium workers to assess the efficacy of employer control measures.
   b. The second reason is that the presence of the exposures has been established, and there could be a false sense of security (or even confusion) generated by low values on the biomonitoring tests. The risks of disease persist, whatever biomonitoring levels are found.

3) Dr Kornberg seemed to be offering options for the evaluating physician to add or subtract tests from the screening examination. To actually make this work, it would be necessary to have two visits with the physician, which would clearly add to the complexity of implementing the program. Efficiently looking for the diseases of interest is the key, but making the screening program practical to implement is also quite important. Thus, for the "general screening examination" my goal is to establish criteria that are very easy to implement (such as age) as the only differentiating factor for what tests each patient needs. A standardized testing regimen will allow the ordering of the tests to be handled by an administrative person, and allow the physician to focus on the interpretation of the tests and examining the patients. I would concur with Dr Kornberg's recommendation that current (< 6 months old) test results could be used in place of repeating the test.

4) There were several aspects of the screening examination proposed by Dr Kornberg that are good general medical surveillance, but not directly related to long term exposure to arsenic, cadmium, or lead. I have tried to focus the examination and eliminate these tests. For example, he includes an electrocardiogram (ECG), however, I am not able to directly associate ECG changes with the arsenic, cadmium, or lead at the levels likely to be found in this population.

In Summary, it is my recommendation that on the basis of their exposures in Spelter and the remaining class area that there is a significantly increased risk of developing disease, and that medical monitoring is necessary to look for these diseases.

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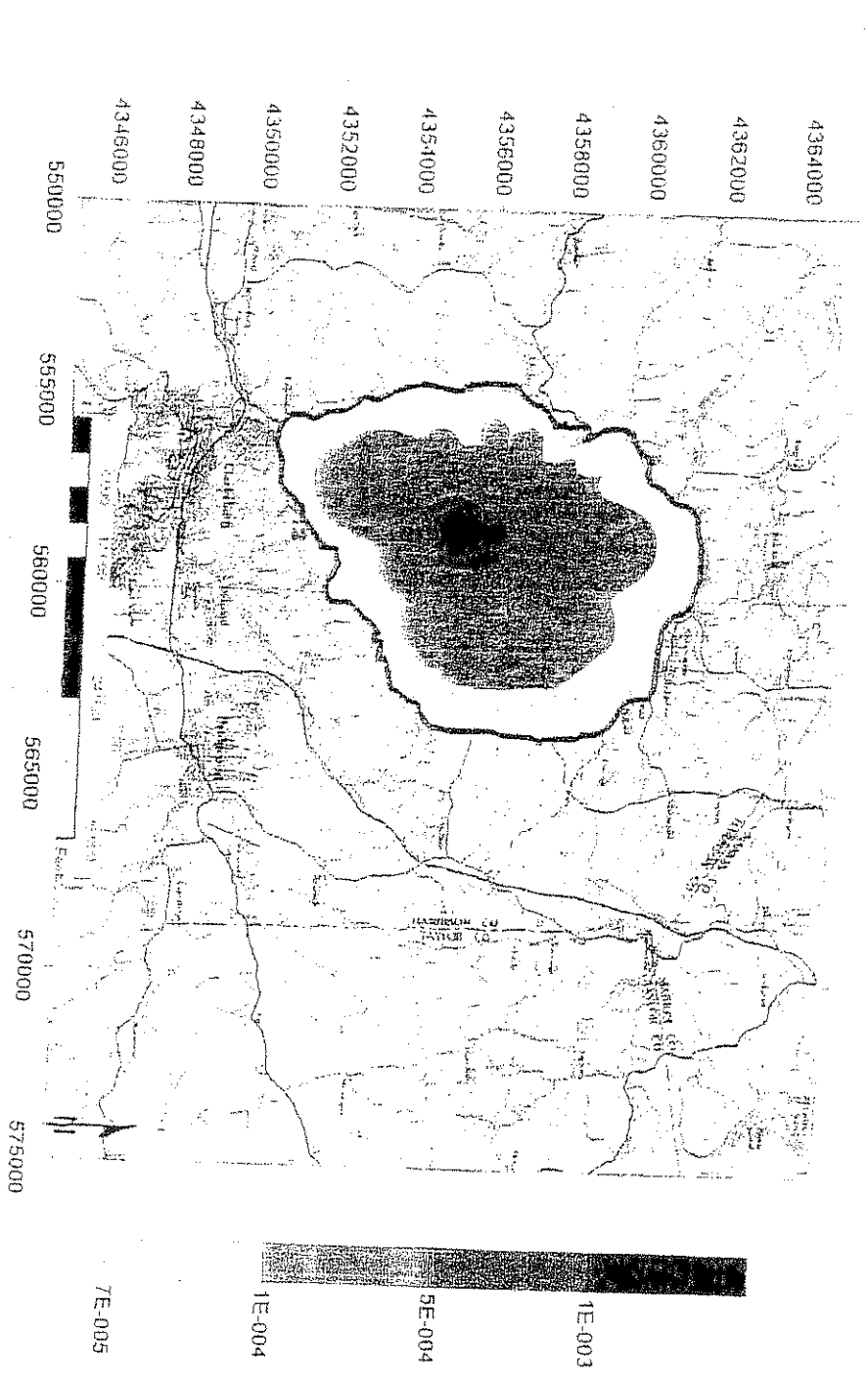
APPENDIX A - MEDICAL MONITORING



MEDICAL SURVEILLANCE GUIDELINES AND RECOMMENDATIONS

FOR THOSE INDIVIDUALS RESIDING PREVIOUSLY AND PRESENTLY WITHIN THE AREA ENVIRONMENTALLY IMPACTED BY THE SPELTER ZINC SMELTER BETWEEN APPROXIMATELY 1910 AND THE PRESENT

James P. Kornberg, MD, Sc.D.
COHBI Physicians, P.C.
November 11, 2005

Lenora Perrine, Carolyn Holbert, Waunona Messinger, Rebeccah Morlock, Anthony Beezel, Mary Ellen Montgomery, Mary Luzader, Truman R. Desist, Larry Beezel, and Joseph Bradshaw, individuals residing in West Virginia, on behalf of themselves and all others similarly situated,

Plaintiffs

Circuit Court
Harrison County, West Virginia
Case No. 04-C-296-2

VS.

E.I. DU PONT DE NEMOURS AND COMPANY, a Delaware corporation doing business in West Virginia, MEADOWBROOK CORPORATION, a Dissolved West Virginia corporation, MATTHIESSEN & HEGELER ZINC COMPANY, INC., a dissolved Illinois corporation Formerly doing business in West Virginia, NUZUM TRUCKING COMPANY, a West Virginia corporation, T. L. DIAMOND & COMPANY, INC. a New York Corporation doing business in West Virginia and JOSEPH PAUSHEL, an individual residing In West Virginia,

Defendants

Background

Beginning in 1910 and continuing without interruption for the next 95 years until the present, persons living within a scientifically definable, exposure impact region around the previously and now extinct zinc smelter in Spelter, West Virginia have been exposed to a variety of extremely toxic elements and compounds.

The sources and pathways of these toxic substances have been varied. While the smelter was operational from 1911 through approximately 1971[1,2], emissions from the stack, fugitive airborne entrainment from materials and fires in nearby waste piles, exposures from contaminated soils adjacent to dwellings and exposure to household dust, including that in attics have all contributed to adverse dose accumulation among exposed persons. Following the conversion of the primary smelter facility to secondary operations, exposure continued in essentially the same manner with a reduced contribution from stack emissions.

Among the broad spectrum foreseeable toxic species that crossed the plant site boundary and intruded into the living spaces of the plants' neighbors, the most important that have been considered for the purposes of medical surveillance are the heavy metals:

- Arsenic
- Cadmium
- Lead

These metals have very diverse adverse effects upon the human body. Collectively, they can interfere with the homeostasis of virtually every organ system to one degree or another, can cause cancer and can disrupt normal reproductive function, including embryonic and fetal growth and development.

The assigned scope of work for the Spelter Smelter case included:

- Determination of whether there exists the justification for medical surveillance for all exposed persons living for a prescribed length of time within a scientifically defined region around the Smelter facility.

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[1] DuPont Corporate Remediation Group, 2000, Site Characterization Report: Spelter Smelter Site, Spelter, West Virginia: Final Project Report D6CB7260, June, 2000.
[2] DuPont Corporate Remediation Group, 2001, Supplemental Site Characterization Report: Spelter Smelter Site, Spelter, West Virginia: Final Project Report 44D6CB7260, February, 2001.

- If, upon finding the justification for medical surveillance, then determination of the elements of medical surveillance for qualified, exposed persons, utilizing acceptable methodology.

- Prescribing guidelines for the implementation of the initial phases of medical surveillance and defining options for surveillance participants who may need follow-up care.

Determination of Whether There Exists Justification for Medical Surveillance

Under the provisions of what has come to be called the *Bower Test* within West Virginia law, the necessary prerequisites for plaintiff reimbursement for medical monitoring costs have been defined[3]. The *Bower Test* requires that the plaintiff must prove that:

1. he or she, relative to the general population, has been significantly exposed;

2. to a proven hazardous substance[4]

3. through the tortuous conduct of the defendant;[5]

4. as a proximate result of the exposure, plaintiff has suffered an increased risk of contracting serious latent disease[6];

5. the increased risk of disease makes it reasonably necessary for the plaintiff to undergo periodic diagnostic medical examinations different from what would be prescribed in the absence of exposure;[7]

and

6. monitoring procedures exist…that make the early detection of disease possible.[8]

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[3] 206 W. Va. 133, 522 S.E. 2d 424, p.9.
[4] The plaintiff must present scientific evidence demonstrating a probable link between exposure to a particular compound and human disease.
[5] Item 3 involves a legal argument that extends beyond the scope of the applied medical expertise in this report.
[6] …plaintiff is not required to show that a particular disease is certain or even likely to occur as a result of exposure. All that must be demonstrated is that the plaintiff has a significantly increased risk of contracting a particular disease relative to what would be the case in the absence of exposure. Importantly, "[n]o particular level of quantification is necessary to satisfy this requirement."
[7] Diagnostic testing must be "reasonably necessary" in the sense that it must be something that a qualified physician would prescribe based upon the demonstrated exposure to a particular toxic agent.
[8] Importantly, this provision does NOT require that the early identification of disease must be associated with the mitigation or the otherwise curing or curtailing of the disease.

It is clear that with the exception of item three, the remaining elements of the *Bower Test*, can and must be addressed from an Environmental Engineering or Industrial Hygiene (the first part of element 1) and Environmental Medical (the second part of element 1 and elements 2, 4, 5 and 6) point(s) of view.

Element 1 - SIGNIFICANT EXPOSURE

In this context, the concept "significant exposure" requires that, first, there be exposure (first part of Element 1) and, next that such exposure be "significant" (second part of Element 1).

Exposure, in this case, has been proven scientifically, based upon actual measurement of smelter specific chemical species that have been found, by a combination of direct measurements[9,10] and modeling[11], in the air, within the homes (attic dust) and within the soils adjacent to the homes of persons neighboring the smelter site. "Exposure" means that these species have been and are biologically available to persons living within the immediate vicinity of the smelter by the routes of inhalation, ingestion, and, to a lesser degree, skin absorption.

Environmental Engineering/Industrial Hygiene Opinion: ***Within a reasonable degree of Environmental Engineering/Industrial Hygiene Certainty, there has been "exposure" to Spelter Smelter specific chemical species among persons living and working within a scientifically defined, exposure impact area within the vicinity of the Smelter. Such "exposure" began as early as 1911 and continues until the present time.***

The above referenced "exposure" has been "significant." From an environmental medical standpoint, "significant" means "toxicologically significant," or stated in other terms, such exposure has the capacity to cause acute, subacute and/or chronic illness and/or the capacity to cause an increase in the risk of developing such illness.

Within the context of valid, scientifically acceptable modeling, exposures to increased levels (above background) of carcinogenic species (to be discussed) are accompanied, in a mathematically linear fashion, by increased risk of developing both individually and within populations, certain specific clinical endpoints, such as solid, organ-specific malignancies[12,13]. Such increased levels of exposure to qualified carcinogens have been demonstrated in this case.

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[9] Flowers, G. C., "Heavy Metal Contamination and Zinc Smelting in the Spelter, West Virginia Area," A Report Submitted to Levin, Papantonio, et.al., February 16, 2005.
[10] SI Group, L.P., "Final Report, Dust Sampling Harrison County, West Virginia, June and August, 2005, prepared for Levin, Papantonio, et. al., October 17, 2005.
[11] Dr. James H. Stewart, "Plaintiffs' Expert Report," prepared for Levin, Papantonio, et. al., November, 2005.
[12] Sullivan, J.B. and Krieger, G.R., **Clinical and Environmental Health and Toxic Exposures**, Lippincott, Williams & Wilkins, Philadelphia, 2001, p. 87-88.

Environmental Medical Opinion: ***Within a reasonable degree of Environmental Medical Certainty, the "exposures" that have occurred to toxic substances, specifically, cancer causing agents, have been and are "significant," because such exposures have the capacity to cause an increase in the risk of very serious clinical endpoints such as the development of organ specific malignancies.***

Given the preceding two opinions, it is probable that Element 1 of the Bower Test has been met.

Element 2 - EXPOSURE TO A PROVEN HAZARDOUS SUBSTANCE

In this context, the hazardous substances of interest are:

- Arsenic
- Cadmium
- Lead

In order to demonstrate that these substances are "hazardous," it is necessary to show that there is scientific evidence linking them to the development of human disease. Without exaggeration, one can offer thousands of references to prove that these substances are "hazardous." To meet this criterion, however, simply consider the following abbreviated list of adverse effects:

- **Arsenic:** Among other symptoms and diseases, arsenic is known to cause:

  - acute, severe gastrointestinal symptoms, following ingestion. Such symptoms may lead to renal, respiratory, cardiovascular, and central nervous system damage, often resulting in death after as little as a two gram exposure.[14]

  - Survivors of sub-lethal exposures to arsenic may be left with bone marrow suppression, hemolysis, hepatomegaly, melanosis and polyneuropathy, usually, more severe in the sensory than in the motor nerves.

  - The long-term effects of arsenic exposure include pigmentation changes in the

[13] Kaldor, J.M. and Day, N.E., "Mathematical Models in Cancer Epidemiology," Chapter 9 in Schottenfeld, D. and Fraumeni, J.F., editors, **Cancer Epidemiology and Prevention, 2nd Edition**, Oxford University Press, New York, New York, 1996.

[14] Environmental Health Criteria 224, **Arsenic and Arsenic Compounds**, 2nd Edition, IPCS, World Health Organization, 2001, p. 234

skin, hyperkeratosis, cancers of the skin, nasal passages, lung, and bladder, among other cancers, and suspicion of kidney cancer, along with perforation of the nasal septum,[15,16] peripheral vascular disease, cardiac disease, cerebrovascular disease, hypertension, diabetes, neurotoxicity and reproductive toxicity[17,18,19,20,21,22,23].

- **Cadmium:** Among other symptoms and diseases, cadmium is known to cause:

-acute, severe, gastrointestinal effects following ingestion, including rapid onset of severe nausea, vomiting and abdominal pain. This poisoning may lead to renal damage with development of proteinuria, renal glucosuria, aminoaciduria, hypercalciuria, phospaturia and polyuria. "Among cadmium – exposed persons in the general environment, the mean urine beta-2-microglobulin was elevated.[24]"

- Exposure to cadmium fumes by inhalation can lead to severe nasal, upper respiratory and pulmonary symptoms, along with chest pain, dizziness, headache, cough, dyspnea, vomiting, chills, nausea and diarrhea. Cadmium fume pneumonitis can lead to pulmonary fibrosis and a persistent restrictive pulmonary defect.

- Chronic toxicity associated with cadmium exposure is usually related to renal and pulmonary damage, along with damage to the skeletal system secondary to increased calcium excretion.

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[15] HESIS Fact Sheet, "Wood Preservatives Containing Arsenic and Chromates," California Department of Health Sevices, Richmond, California; <http://www.dhs.ca.gov/ohb/HESIS/arsen2.htm>
[16] Environmental Health Criteria 224, **Arsenic and Arsenic Compounds**, 2nd Edition, IPCS, World Health Organization, 2001, p. 387.
[17] Ibid., p.234-345.
[18] Nriagu, Jerome O., editor, **Arsenic in the Environment, Part II: Human Health and Ecosystem Effects**, Volume 27, Wiley Series in Advances in Environmental Science and Technology, New York, 1994, Chapter
[19] NIOSH, **Criteria for Occupational Exposure to Inorganic Arsenic, (New Criteria – 1975**, NIOSH 75-149, p. 14.
[20] Sullivan, J.B. and Krieger, G.R., **Clinical and Environmental Health and Toxic Exposures**, Lippincott, Williams & Wilkins, Philadelphia, 2001, p.858.
[21] Carson, B.L. et. Al., **Toxicology and Biological Monitoring of Metal in Humans, Including Feasibility and Need**, Lewis Publishers, Inc., Chelsea, Michigan, 1986, p. 27.
[22] Lauwerys, R.R. and Hoet, P., **Industrial Chemical Exposure Guidelines for Biological Monitoring, 2nd Edition** Lewis Publishers, Inc., Chelsea, Michigan, 1993, p. 21.
[23] Ryan, R.P. and Terry, C.E., editors, **Toxicology Desk Reference, The Toxic Exposure and Medical Monitoring Index, 4th Edition**, Taylor and Francis, Washington, D.C., Volume 1, 1997-1998, p. 261.
[24] Environmental Health Criteria 134, **Cadmium**., IPCS, World Health Organization, 1992., <www http://www.inchem.org/documents/ehc/ehc/ehc134.htm>.

- Chronic cadmium exposure has been linked to cancer of lung, the prostate, the kidneys and the stomach.[25,26,27,28,29].

- **Lead:** Among other symptoms and diseases, lead is known to cause:

- acute, severe gastrointestinal effects following ingestion, including headache, irritability, lassitude, nausea, arthralgias, myalgias, abdominal pain (lead colic), paresthesias and motor weakness[30].

- Exposure to lead can lead to the "poisoning " of certain enzyme systems in the human body, including those responsible for the synthesis of hemoglobin, the integrity of cell membranes and those affecting steroid metabolism.

There are a myriad of long term, adverse serious health effects, secondary to lead exposure. They involve virtually every major organ system in the human body. Specifically, lead can cause damage to the central and peripheral nervous systems especially in children. Adverse effects can also be seen in the cardiovascular system, the endocrine system, the reproductive systems, and the renal system, the latter exposure leading, among other outcomes, to Fanconi's syndrome (the loss of protein, amino acids and phosphate in the urine). Damage to these systems can lead to specific outcomes that include hypertension, chronic interstitial nephritis, hypothyroidism, decreased fertility, spontaneous abortion, reduced and abnormal sperm counts and morphology, stillbirths and increased infant mortality.[31,32,33,34]

At present, the collective scientific evidence has lead various agencies to disagree regarding the carcinogenicity of inorganic lead. The EPA[35] and IARC[36] (International Agency for Research on Cancer – Lyon, France) have classified lead as a probable human carcinogen; whereas, ACGIH[37] (The American Conference of Governmental Industrial Hygienists) has classified lead as a "Confirmed Animal Carcinogen with Unknown Relevance to Humans," and

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[25] Sullivan, J.B. and Krieger, G.R., **Clinical and Environmental Health and Toxic Exposures**, Lippincott, Williams & Wilkins, Philadelphia, 2001, p.889.
[26] NIOSH, **Criteria for Occupational Exposure to Cadmium**, NIOSH 76-192, p. 8.
[27] Carson, B.L., 1986, p. 51.
[28] Lauwerys, R.R., 1993 p. 32.
[29] Ryan, R.P., 1997-1998, p. 545.
[30] Sullivan, J.B., 2001, p. 879.
[31] Sullivan, J.B., 2001 p. 879.
[32] Carson, B.L., 1986, p. 128.
[33] Lauwerys, R. R., p.55.
[34] Ryan, R. P. 1997-1998, p. 1513.
[35] <www.epa.gov/iris/subst/0277.htm>
[36] <www-cie.iarc.fr/htdocs/announcements/vol87.htm>
[37] ACGIH, **2004 Guide to Occupational Exposure Values**, Signature Publications, Cincinnati, Ohio, 2004, p.83

> OSHA has not given lead a "Ca" (carcinogen) designation. The literature considers foreseeable carcinogenic outcomes to involve the lung, trachea, and stomach[38], along with kidney and brain[39].

Environmental Medical Opinion: ***Within a reasonable degree of Environmental Medical probability, the metals, Arsenic, Cadmium and Lead are "hazardous" substances, in the sense that there is abundant scientific evidence linking exposure to each of these metallic elements to the development of human disease.***

Element 3 – THE TORTUOUS CONDUCT OF THE DEFENDANT

The proof of this element is outside of the scope of Occupational and Environmental Medical Expertise and will, therefore, be deferred to Plaintiff's legal counsel.

Element 4 – INCREASED RISK OF SUFFERING LATENT DISEASE

Strictly speaking and within the EPA carcinogen risk assessment paradigm, exposure to any amount of a smelter-specific carcinogen, such as arsenic or cadmium will result in an increased risk of developing latent disease[12].

In particular, in the case of arsenic exposure, one can anticipate an increased risk of cancers of the:

Bladder [40,41,42]

Bone Marrow [41,42, 43]

Bronchus [40]

Buccal Cavity [42,43]

Kidney [41,42,43]

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[38] Ryan, R.P. 1997-1998, p. 1516.
[39] < http://www-cie.iarc.fr/htdocs/announcements/vol87.htm>
[40] Ryan, R.P. 1997-1998, p. 265-266.
[41] Sullivan, J.B. 2001, p. 862.
[42] Environmental Health Criteria 224, **Arsenic and Arsenic Compounds**, 2nd Edition, IPCS, World Health Organization, 2001, p. 284-286.
[43] Enterline, P. E., et. al, "Cancers Related to Exposure to Arsenic at a Copper Smelter," Occup Environ. Med 1995 **52**, (28-32).

Liver [41,42]

Lung [40,41,42,43]

Lymphoma [41]

Pharynx [43]

Prostate [41]

Rectum [42,43]

Skin [40,41,42]

Trachea [40]

In the case of cadmium exposure, one can anticipate an increased risk of cancers of the:

Genito-urinary tract [44]

Kidney [45]

Lung [45,46]

Prostate [44,45,46]

Respiratory System [44]

Stomach [45]

The proof of the assertion that any exposure will result in an increased risk of latent disease rest within the notion, adopted by the USEPA, that exposures to any cancer causing agent, especially above the background level, will result in a linear increase in the risk of developing cancer[12].

Environmental Medical Opinion: ***Within a reasonable degree of Environmental Medical probability, given the preceding, since it is probable that there exist many carcinogen exposed persons who have either worked and/or have lived within a scientifically defined exposure***

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[44] Ryan, R.P. 1997-1998, p. 524.
[45] Sullivan, J.B., 2001, p. 894.
[46] Lemen, R.A., et. al., "Cancer Mortality Among Cadmium Production Workers," in **Occupational Carcinogenesis**, Annals of the New York Academy of Sciences, ANYAA9 271 1-516(1976), p. 273

impact area in proximity to the Spelter Smelter, it is, therefore, probable that such persons have sustained an increased risk of developing latent disease.

Element 5 – GIVEN THE INCREASED RISK OF DISEASE, THERE EXISTS THE REQUIREMENT FOR MEDICAL TESTING THAT IS DIFFERENT FROM THAT WHICH WOULD BE REQUIRED IN THE ABSENCE OF EXPOSURE.

Most of the medical testing that will be employed to provide proactive surveillance is designed to detect early changes in those exposed persons who are at increased risk for the development of cancer or other smelter-compound specific morbidity. Many of the tests employed in this program are customized to such a degree that they would not be utilized for any other purpose, in the absence of such exposure and without the accompanying increased risk of disease.

It is anticipated, for example that there will be a recommendation for the measurement of beta-2-microglobulins in the urine of those persons exposed to cadmium[47]. This test is one that is fairly specific for the detection of early impairment of proximal tubular function. It is, clearly, not a test that would be routinely performed or recommended for persons unless they were to have been exposed to cadmium.

Another obvious example is related to the recommendation that persons exposed to arsenic and cadmium undergo urinary testing for the presence of arsenic and cadmium in the urine. It is nearly self-evident that such testing is different from that which would be required or recommended in the absence of such exposure.

Environmental Medical Opinion: ***Within a reasonable degree of Environmental Medical probability, the elements of medical surveillance for those persons adversely exposed to emissions from the Spelter Smelter will be specific to the established surveillance protocol. Such testing elements, moreover, will be different from any foreseeable testing for those persons, in the absence of their having sustained smelter exposure and in the absence of their having incurred the associated increased risk of disease***

Stated more simply, if such exposed persons had never sustained exposure and had never sustained an increased risk of developing smelter specific diseases, then these persons would not be expected to have developed the need to undergo such an unusual battery of tests.

Element 6 – MONITORING PROCEDURES EXIST THAT MAKE THE EARLY DETECTION OF DISEASE POSSIBLE.

[47] Ryan, R.P. 1997-1998, p. 526.

There are wide arrays of testing options that can and will be employed in the proposed medical monitoring program that are specifically designed to reveal changes at points in time that are among the very earliest stages of disease. In the case of the development of progressive renal disease secondary to cadmium exposure, for example, it is probable that routine urinalysis will first show the presence of protein, such as albumin, in the urine. Simultaneous screening for the presence of low molecular weight proteinuria will demonstrate the presence of elevations in beta 2 microglobulins. "Beta-2 microglobulin has been the most extensively studied and is thought to be the most sensitive test for renal dysfunction."[48]

Other tests will be performed that are also useful in the detection of early stage disease. The ECG (electrocardiogram), for example, is clearly a useful tool in discovering early cardiovascular disease by demonstrating impairments in the performance of the heart's electrical conducting system. Other examinations, for example, the PA and lateral chest x-ray, may demonstrate a very small tumor at a stage when it can be easily resected.

Environmental Medical Opinion: ***Within a reasonable degree of Environmental Medical probability, it is clear that several monitoring procedures, including laboratory and special tests, exist and will be utilized in an effort to make an early diagnosis of disease for which exposed persons are at risk.***

Overall Environmental Medical and Environmental Engineering/Industrial Hygiene Opinion:

The preceding discussion has confirmed that the general population living near the Spelter Smelter has been significantly exposed to hazardous material (including arsenic, cadmium and lead) that has originated from the smelter operations and the immediately surrounding plant property. This exposure has resulted in an increased risk of developing serious latent disease in the exposed population. This risk of serious disease requires that the exposed population participate in a medical monitoring program that includes tests that the exposed group would not need but for having sustained this serious exposure. These tests are designed to allow for the early detection of serious disease and are expected to benefit the participants in the medical monitoring program.

Eligibility Criterion for an Exposed Person's Inclusion in the Medical Monitoring Program

Pragmatically, it has been decided that entry into the medical surveillance program should be made in the absence of consideration of one's having lived in the midst of an area that is high in naturally occurring arsenic. In other words, entry into this program should be based upon one's dose accumulation of "enriched" arsenic or, namely, that arsenic that is above background and attributable to the smelter only.

It is proposed that the prerequisite of sustaining a certain level of exposure (E) for a certain period of time (Tp) must be the fundamental eligibility criteria for inclusion within the medical monitoring program.

Simply stated, one must have sustained an "eligible dose" (De) equal to (E) times (Tp) before one can enter the medical monitoring program.

The question arises that if one knows the level of exposure (E) and one has established the dose above which one should be eligible for medical surveillance (De), then, how can one determine the permissible time (Tp) after which one is eligible for inclusion within a medical surveillance program? The answer is, simply, that since (De) = (E) (Tp); if one knows E, then, one can determine Tp by simply dividing De by E.[49]

Our approach to deriving De is based upon adherence to the well established methodology of credible governmental and private agencies and the instructional and experiential principles associated with the specialty practice of Occupational and Environmental Medicine. It is anticipated that (E) will be provided by direct measurement or by capable and probable mathematical modeling.

It is well established that the eligibility of a worker to participate in a medical surveillance program is based upon that person's exposure to any toxic agent in question at levels that exceed the toxic agent's "Action Level."[50,51] The Action Level (AL) of a particular substance may be specified as a fraction of the maximum time-weighted average (TWA) exposure to a given substance that must never be exceeded[52]. Usually when specified, the Action Level is 50% of that maximum TWA.

If, for example the maximum TWA or PEL for a solvent found in paint strippers, like methylene chloride (MC), is 25 ppm, then the Action Level for MC is 12.5 ppm. The Action Level, then, is that level of exposure above which the exposed person is eligible for medical monitoring. This

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[49] If De = (E)(Tp); then Tp = (De)/(E)

[50] Kornberg, J.P., **The Workplace Walk-Through,** Lewis Publishers, Chelsea, Michigan, 1992.
Page 83: ***"The Action Level (AL) is the TWA [time-weighted average] exposure level below the PEL [permissible exposure level] or REL [recommended exposure level] but above which medical surveillance should commence. If true, representative exposure levels are consistently below the Action Level, medical surveillance may be optional. The Action Level is often set at 50% of the PEL or REL.***

[51] Johns Hopkins Safety Manual; Policy Number HSE 702. "Glossary of Terms For Material Safety Data Sheets," 09/16/05.
Action Level: The exposure level (concentration in air) at which OSHA regulations to protect employees take effect (29CFR1910.1001-1047); e.g. workplace air analysis, employee training, medical monitoring and recordkeeping. Exposure at or above action level is termed occupational exposure. Exposure below this level can be harmful. This level is generally half the PEL."

[52] for example the Permissible Exposure Limit (PEL) or the Threshold Limit Value (TLV).

concept is codified in federal regulations for many substances and, in practice, is usually 50% of the maximum TWA.

It is simple to see that associated with the "exposure" Action Level is also a "dose" Action Level. The "dose" Action Level is simply that "dose" over a lifetime of exposure that represents one half of the "dose" to which one may be permitted to be exposed over, for example a working lifetime of exposure. In the case of the OSHA Action Level, the associated lifetime of exposure would be, for example, 40 years. Thus, in the case of exposure to MC, for example, the maximum dose over a working lifetime to which one may be exposed is 25 ppm times 40 years or 1000 ppm-years. The dose-associated Action Level or, namely, that dose above which one must been afforded medical monitoring over his or her working lifetime is 50% of the maximum dose to which one may have been exposed. Thus, the Action Level for the MC dose is 0.5 times 1000 ppm-years or 500 ppm-years. Thus, if a worker was to have accumulated a dose of MC that exceeded 500 ppm-years, then, he or she must been afforded medical monitoring.

It is reasonable and methodologically sound to apply this same principle to determining the temporal eligibility criterion for inclusion in a medical monitoring program for persons environmentally exposed to smelter-specific toxic substances.

Based upon EPA modeling for Soil Screening Levels, there has been established the concept of the risk based concentration (RBC). The RBC for ingested carcinogens is that level to which one may be exposed over a period of 30 years without incurring a risk of greater than one in a million (above background) of developing a specific cancer. In the case of arsenic, the RBC is 0.43 ppm[53]. Since there are 10950 days in 30 years, then, the maximum ingested dose of arsenic that one may accumulate without exceeding the personal additional risk of one in a million of developing lung cancer is 0.43 ppm times 10950 days or 4708.5 ppm-days.

It is logical and reasonable to apply the concept of an Action Level to this lifetime dose by stating that one should be afforded the benefit of medical surveillance if one has accumulated a dose of arsenic in excess of 50% of the EPA maximum permitted lifetime dose associated with exposure to arsenic. In other words, if one has accumulated 0.5 times 4708.5 ppm-days or approximately, 2354.25 ppm-days, then, one should be eligible for inclusion in a medical monitoring program.

Within the framework of the questions proposed above, in the first paragraph, it is stipulated, then, that De = 2354.25ppm-days.

Given the above reasoning, then, one can see that, if, for example, one has been exposed to a level of arsenic of, say, 25 ppm or stated otherwise, E = 25 ppm, then, if such exposure were sustained for 2354.25 ppm-days divided by 25 ppm or exactly 94.17 days, then, one should be

[53] Risk Based Concentrations published by Region III EPA dated 10/25/05 <http://www.epa.gov/reg3hwmd/risk/human>

eligible for inclusion in a medical monitoring program after being exposed for that length of time.[54]

Environmental Medical Opinion: ***Invoking EPA logic and methodology, and one's clinical judgment as a Board Certified Occupational and Environmental Health physician, it is reasonable to conclude that a member of the exposed population should be eligible for medical monitoring if one were to accumulate an ingested dose of arsenic of 2354.25 ppm-days. (i.e. De = 2354.25 ppm-days).***

Modeling[55] provided by Environmental Health and Engineering (EH&E) in Newton, Massachusetts has demonstrated that within the un-impacted "Control Area" south and west of the Spelter smelter, the 95% confidence intervals for exposures to soil arsenic ranged from 3.3 – 17.3 ppm with a geometric mean of 7.5 ppm. Within the scientifically defined area, impacted by the smelter, the 95% confidence intervals for exposures to soil arsenic ranged from 3.91 – 25.8 ppm with a geometric mean of 9.9 ppm.

The preceding data can be interpreted as follows:

- The soils in the "Control Area" contain the un-impacted, concentration of arsenic, absent any contribution from the smelter. The upper end of the 95% confidence interval (i.e. 17.3 ppm) represents the near-maximum concentration of arsenic in the soil in the "Control Area."

- The soils in the "Impacted Area" contain concentrations of arsenic secondary to the effects of non-smelter related processes (including "nature") plus the effects of contamination from the Spelter Smelter. The upper end of the 95% confidence interval (i.e. 25.8 ppm) represents the near-maximum concentration of arsenic in the "Impacted Area."

- It is logical to conclude that the difference between 25.8 ppm and 17.3 ppm (or, namely, 8.5 ppm), as described above, would represent a conservative arsenic contribution from the smelter. 8.5 ppm is not the largest smelter contribution that could be expected. A larger near-maximum smelter contribution would be derived by subtracting 3.3 ppm from 25.8 ppm to derive a smelter contribution of 22.5 ppm..

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[54] It should be clear that exposure by ingestion for 94.17 days at a level of 25 ppm would cause one to accumulate a dose of 94.17 days times 25 ppm or 2354.25 ppm-days. This number, 2354.25 ppm-days, is equal to 50% of the EPA lifetime "allowable" dose of arsenic. Stated otherwise: If Tp = 94.17 days and E = 25 ppm , then De = (Tp) (E) or De = (94.17 days) (25 ppm) = 2354.25 ppm-days.

[55] Dr. James H. Stewart, "Plaintiffs' Expert Report," prepared for Levin, Papantonio, et. al., November, 2005.

Environmental Medical Opinion: *- In summary, it is concluded that the 8.5 ppm arsenic concentration is a conservative measure of the arsenic enrichment in the impacted area secondary to the effects of the smelter. Within the scope of the medical surveillance eligibility paradigm described at the beginning of this section, E= 8.5 ppm*

Since Tp = (De)/(E) and De = 2354.25 ppm-days

Then:

Tp = (2354.25 ppm-days)/(8.5 ppm)

Tp = 276.97 or about 277 days.

Within the scope of the model and assumptions described within this section, an exposed person must have lived within the smelter- impacted region for 277 days before he or she will have sustained exposure to "enriched arsenic" at a level sufficient to have created a dose equivalent to 2354.25 ppm-days or the dose threshold defined as pre-requisite to entering the medical surveillance program. This program is defined in detail in the Attachment to this report.

Further Considerations Regarding the Degree of Smelter Contamination Within the Environmentally Impacted Area Near the Smelter Site.

The above analysis was based upon consideration of the effects of arsenic in the soil in contaminating the area near the smelter site. This analysis does not represent the actual extent and degree of adverse heavy metal impact within the areas under consideration.

In order to develop a more complete picture of the potential for adverse health effects among exposed persons who will participate in the medical monitoring program, the following information is provided to augment the environmental database for the benefit of both surveillance health professionals and surveillance participants.

- In December 1995, a U.S. EPA Site Assessment Technical Assistance (SATA) team conducted an investigation of the smelter site. The SATA team characterized the site by taking biased soil samples at 50 different locations[56,57]

  A total of 25 samples were collected from the railings pile, 15 samples from the

[6] EPA, 1995. Trip Report - Spelter Smelter Site, Spelter, Harrison County, West Virginia. "Site Assessment Technical Assistance Team." US Environmental Protection Agency, Washington, D.C., 1995.
[7] ATSDR, 1996. Health Consultation: Spelter Smelter Site (CR#3#WV) Spelter, West Virginia. May 8, 1996.

hiking/biking trail, and 10 from adjacent residential areas[57] .

All of the samples were analyzed for arsenic, cadmium, and lead, and five samples were analyzed for total Priority Pollutant metals. The results of the analyses indicated that high levels of cadmium and lead were both found on and off of the smelter site, and high levels of arsenic were present on the smelter site[56].

The lead levels ranged from 400 ppm to 6,100 ppm in the tailings pile, 120 ppm to 6,900 ppm in the hiking/biking trail, and 44 ppm to 2,600 ppm in the residential areas. The cadmium concentrations were 4.2 ppm to 36 ppm in the tailings pile, 3.7 ppm to 36 ppm in the hiking/biking trail, and 4.2 to 39 ppm in the residential areas. The arsenic levels ranged from were 320 ppm to 3,500 ppm in the tailings pile, 200 ppm in the hiking/biking trail, and 33 ppm in the residential areas. Zinc concentrations in the tailings pile ranged between 23,000 ppm to 55,000 ppm, 6,000 ppm in the hiking/biking trail, and 3,900 ppm in the residential areas[57].

- In December 2003, July 2004, and January 2005, George C. Flowers, Ph.D., performed comprehensive soil contamination assessments by collecting 917 surficial soil samples in communities in relative proximity to the Spelter smelter site.

  The communities were divided into three geographical areas: (a) Spelter-Meadowbrook, Erie, and Hepzibah area; (b) Gypsy area; and (c) Lumberport area.

  All of the soil samples were analyzed for arsenic, cadmium, lead, and zinc. A total of 626 soil samples were collected in the Spelter-Meadowbrook, Erie, and Hepzibah area. This area was the closest to the smelter and sustained the greatest impact from air emissions and fugitive dusts from the tailings pile.

  Analyses of the samples revealed the following: (a) arsenic concentrations ranged from a minimum of 1 ppm to a maximum of 480 ppm; (b) cadmium levels ranged from a minimum of 0.25 ppm to a maximum of 850 ppm; (c) lead concentrations ranged from a minimum of 5.1 ppm to a maximum of 13,000 ppm; and (d) zinc levels ranged from a minimum of 65 ppm to maximum of 310,000 ppm.[9]

- With respect to the Gypsy area, a total of 215 soil samples were collected. Results of the analyses of the soil samples found the following: (a) arsenic concentrations ranged from a minimum of 2.8 ppm to a maximum of 44 ppm; (b) cadmium levels ranged from a minimum of 0.25 ppm to a maximum of 24 ppm; (c) lead concentrations ranged from a minimum of 14 ppm to a maximum of 1,900 ppm; and zinc levels ranged from a minimum of 48 ppm to maximum of 8,500 ppm. Regarding the Lumberport area, a total of 99 soil samples were collected in this area. Analyses of the samples revealed the following: (a) arsenic concentrations ranged from a minimum of 2.2 ppm to a maximum of 23 ppm; (b) cadmium levels ranged from a minimum of 0.25 ppm to a maximum of 2.4 ppm; (c) lead concentrations ranged from a minimum of 9.1 ppm to a maximum of 420 ppm;

and (d) zinc levels ranged from a minimum of 47 ppm to maximum of 1,200 ppm.[9]

- Overall, for all locations combined, the results of the Flowers' study reported the following:

  (a) arsenic: 383 samples (42%) had arsenic levels that were greater than 10 ppm and 573 (62%) samples had arsenic concentrations above background;

  (b) cadmium: 115 samples (13%) had cadmium levels that were greater than 10 ppm and 796 (87%) samples had cadmium concentrations above background;

  (c) lead: 327 samples (36%) had lead levels that were greater than 100 ppm and 810 (88%) samples had lead concentrations above background;

  and

  (d) zinc: 731 samples (80%) had zinc levels that were greater than 200 ppm and 883 (96%) samples had zinc concentrations above background.[9]

- A study was performed in June 2005, where 82 dust and air samples were collected from 15 sample locations around Spelter, West Virginia. Samples included 13 bulk attic dust samples, 15 attic dust wipe samples, 16 living area dust wipe samples, 10 living area ashed wipe samples, and 28 air particulate samples. All of the samples were analyzed for arsenic, cadmium, lead, and zinc.

  The results of the sampling study revealed the following results and are quoted almost verbatim:

  (a) Arsenic was detected at elevated concentrations in all 15 attic dust wipe samples and in all 13 bulk attic dust samples. The concentration of arsenic in each of the bulk attic samples exceeded the risk-based exposure level for arsenic of 0.39 mg/kg. Arsenic was detected in all 10 living area ashed wipe samples. Arsenic was detected in one of the air particulate samples at a concentration above the Region III EPA risk-based concentration of 0.00041 $\mu g/m^3$

  (b) Cadmium was detected at elevated concentrations in all 15 attic dust wipe samples and all 13 bulk attic dust samples. The concentration of cadmium in each of the bulk attic dust samples exceeded the risk-based exposure level for cadmium of 37 mg/kg. Cadmium was detected at elevated concentrations in six of the 10 living area ashed wipe samples. Cadmium was detected in five of the air particulate samples at concentrations above the Region III EPA risk-based concentration limit of 0.00099 $\mu g/m^3$ (SI Group LP, 2005);

  (c) Lead was detected at elevated concentrations in all 15 attic dust wipe samples and in all 13 bulk attic dust samples. The concentration of lead in each of the bulk attic dust samples exceeded the risk-based exposure level for lead of 400 mg/kg.

Lead was detected at elevated concentrations in seven of the 10 living area ashed wipe samples. Lead was detected in thirteen of the air particulate samples at concentrations above the Region III EPA risk-based concentration of 1.5 $\mu g/m^3$ (SI Group LP, 2005);

and

(d) Zinc was elevated at elevated concentrations in all 15 attic dust wipe samples in all 13 bulk attic dust samples. The concentration of zinc in each of the bulk attic dust samples exceeded the risk-based exposure level for zinc of 23,000 mg/kg. Zinc was detected at elevated concentrations in five of the 10 living area ashed wipe samples. Zinc was detected in twenty-four of the 28 air particulate samples. None of the measured zinc concentrations in the air exceeded the Region III EPA risk-based concentration limit of 1,100 $\mu g/m^3$. [10]

- The SI Group LP (2005) study found that "Toxic metal contamination was found in all sampled locations." The study indicated that the following conclusions could be drawn from the results, which are quoted verbatim:

(a) "Elevated metal concentrations were found in the living space samples and the attic samples.

" (b) "At all properties sampled, the concentration of one or more of the toxic metals exceeded the regulatory limits.

" (c) "Based on the distribution of sample locations throughout the neighborhood north and northwest of the former facility in Spelter, all properties have likely been contaminated with toxic metals.

" (d) "The ratio of metals was used to define a fingerprint of the metals in the dust. This fingerprint is consistent with the soils and tailings material at the smelter.

" (e) "Based on the metal ratios, the dust sampled in the attics of each of these properties is from the same source as the dust in the indoor living space.

" (f) "The concentrations of lead in the dust in the homes cannot be attributed to lead based paint sources.

and

(g) "The presence of toxic metal concentrations in the homes indicates an on-going source of contamination." [10]

ATTACHMENT

ELEMENTS OF SURVEILLANCE

RECOMMENDED MEDICAL EVALUATIONS AND DIAGNOSTIC TESTS FOR THE SURVEILLANCE OF PERSONS LIVING IN PROXIMITY TO THE FORMER ZINC SMELTER IN SPELTER, WEST VIRGINIA

Introduction

During the ninety years of its operation as a primary and secondary zinc smelter, the former smelter in Spelter, West Virginia, has caused significant and widespread contamination of the air, soil, household dust, surface water, and/or groundwater from arsenic, cadmium, and lead, at the former smelter site (EPA, 1995a, 1996a; Weston RF, 1997; DuPont CRG, 2003b, 2003c, 2003d, 2003e, 2003f); in the Town of Spelter (EPA, 1995a, 1996a; Flowers GC, 2005; SI Group LP, 2005); and in surrounding areas (Flowers GC, 2005; SI Group LP, 2005). These results are consistent with a number of published environmental and epidemiological studies that have documented contamination of the air, soil, household dust, and/or water in neighborhoods and communities from the polluting effects of nonferrous metals smelters (Landrigan PJ et al., 1975a, 1975b; Landrigan PJ et al., 1976; Landrigan & Baker, 1981; Baker EL Jr et al., 1977a, 1977b).

As a direct result of the widespread heavy metals contamination that exists in and around Spelter, West Virginia, persons living in proximity to the former zinc smelter are at an increased risk of developing symptoms, medical conditions, cancer, adverse reproductive outcomes, and developmental defects in their offspring from their past, current, and future exposures to, at least, arsenic, cadmium, and lead.

As a corollary to this exposure, the main body of this report has outlined the rational for the justification and the creation of a medical monitoring program for exposed persons.

This Attachment to the main report will set forth recommended medical evaluations and diagnostic tests for the surveillance of exposed persons living in the scientifically defined environmentally impacted region near the former zinc smelter in Spelter, West Virginia.

Organ System Specific Assessment

The elements of the medical surveillance program are defined by the nature of the hazardous materials to which the participants are exposed. These elements may be specified by:

- The contents and directives of federal, state, or local regulations.
- The science that has been customarily promulgated by qualified researchers, teachers and authors.

and

- The recommendations of qualified clinicians with appropriate practical experience in the fields of Occupational and Environmental Medicine and Toxicology.

Under the past and present exposure circumstances, associated with the Spelter smelter, it is clear that the surveillance elements associated with exposures to arsenic, cadmium and lead will define the surveillance directives of this program. The final design of this program will identify a "Core" evaluation that will be administered to all persons at the outset of the program. The components of the "Core" evaluation will de defined by those surveillance elements[1] collectively associated with exposures to arsenic, cadmium and lead.

The following sections define those organ-system specific recommendations for each of these heavy metals. Unless otherwise specified, all identified components will be part of the "Core" evaluation given to each person.

Selected components that are not part of the "Core" evaluation may or may not be administered to the surveillance participant. The final decision regarding whether to proceed with these tests is "Determined by the Responsible Physician – "DBRP" These tests will be identified by the acronym "DBRP" in parenthesis following the name of the test.

Periodicity

It is anticipated that following the Core Evaluation, follow-up routine assessment will occur annually. The elements of subsequent surveillance evaluations will need to be determined; although, it is anticipated that X-rays will not be repeated more frequently than every five years, unless there is an important clinical indication to repeat these tests.

Duration

The duration of this medical surveillance program will need to be determined; but it is anticipated that this program will remain in operation for no less than 40 years.

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[1] Both recommended and required by statute

Data Handling and Maintenance

All surveillance data will managed with the highest regard to the preservation of medical confidentiality and consistent with all applicable state and federal laws. It is anticipated that there will be a need for epidemiological oversight of the data gathered during this surveillance program.[1] It will be suggested that such oversight will be provided by a non-profit organization, such a university-based department of public health and preventive medicine (epidemiology and biostatistics).

Upon receiving permission from the surveillance participant, all medical surveillance results will be shared with the surveillance participant's personal physician.

Administrative Oversight

Administrative oversight for this medical surveillance program should be provided by a physician who is board certified in General Preventive Medicine, Occupational and Environmental Medicine or Clinical Toxicology.

It will be seen that certain tests in the medical surveillance program can be deferred, if the surveillance participant has had an equivalent test performed within a certain period of time and can produce the results of that test (e.g. If a person has undergone an ECG within the past 60 days and can produce the results of that test, it may not be necessary for the participant to repeat that recommended test). It is emphasized that the privilege of deferring a recommended test can be overridden by the examining physician at any time. That is - notwithstanding the participant' having undergone the same exam just a short time ago, the examining MD may deem it necessary to obtain the same test again, if warranted by the participant's medical presentation. (e.g. The physician may be told by the participant – "I am having chest pain every night;" thus, obtaining another ECG would still make sense, even if the participant just had one taken the day before.)

Elements of Surveillance

Medical, Surgical and Occupational History

[1] For epidemiological purposes, all medical data will be stripped of personal identification markers and information

A comprehensive medical, surgical and occupational history will be obtained by the completion of self-administrable history forms and the subsequent review, in a one on one manner, between the examining health professional and the surveillance participant.

During the interview with the health professional, emphasis will be placed upon those questions with relevance to the adverse effects of exposure to arsenic, cadmium and lead.

Emphasis shall also be placed upon obtaining a comprehensive work history, along with a detailed reproductive history.

Physical Examination

A comprehensive physical examination will be performed, with emphasis upon examining those organ-systems most at risk from exposure to arsenic, cadmium and lead.

The physical examination will be performed by a board certified physician, preferably in the specialties of Family Medicine, Internal Medicine, Clinical Toxicology, or Occupational and Environmental Medicine.

Hematology (serum and blood)[3]

- SMA-25[4] (including GGTP)
- CBC with differential and RBC indicies[5]
- Peripheral Smear Evaluation
- Blood Arsenic
- Blood Cadmium

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[3] These tests may be deferred, if the participant has had an equivalent examination within the past 30 days and can produce copies of his or her results.

[4] If liver enzymes (e.g. SGOT, SGPT) are elevated above normal and/or if the liver is swollen (hepatomegaly), then further evaluation and tests of the liver should be performed. A CT-scan with contrast is frequently performed in order to evaluate the liver.

[5] If a person has anemia based upon the results of the CBC, then further blood tests should be performed in order to diagnose the specific type of anemia (i.e., hemolytic, hyperchromic, macrocytic, et al.).

- Blood Lead;
- ZPP (Zinc Protoporphyrin)
- Thyroid Function Test (TSH) (DBRP)
- Prostate Specific Antigen (PSA) (DBRP)[6]
- Serum protein electrophoresis (DBRP)
- Immuno-fixation Electrophoresis (DBRP)
- Freeze and Hold Serum (Equivalent to two Red Top Tubes – Contingency Surveillance for Minimum of 90 days)

Urine[7]

- Urinalysis with microscopic examination
- Urine creatinine
- Urine beta2-microglobulin
- Urine for arsenic
- Urine for cadmium
- Urine for lead
- Urine N-acetyl beta glucosaminidase (DBRP)
- Urine retinol binding protein (DBRP)

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[6] Obtain for males over age 40, unless there is a family history of prostate cancer, in which case the PSA may be obtained at an earlier age.

[7] These tests may be deferred, if the participant has had an equivalent examination within the past 30 days and can produce copies of his or her results. If there is proteinuria, or hematuria or if there are elevated levels of beta2-microglobulin, n-acetyl-glucosaminidase and/or retinol-binding protein, following the performance of a baseline GFR (glomerular filtration rate), an IVP should be considered in order to rule-in or rule-out kidney damage, nephritis, and/or cancer of the bladder, urinary tract, and kidney.

Stool[8]

- Examination (analysis) of stool for occult blood. (Age > 40); (Age < 40, then DBRP)

Hair/Nails[9]

- Scalp/Pubic hair analysis for arsenic, cadmium or lead (DBRP)

Lungs[10]

- Baseline pulmonary function test[11]
- PA and lateral chest X-ray[12]
- Sputum cytology (DBRP)

Nervous System[13]

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[8] If blood is found in stool, then a colonoscopy should be performed.

[9] Using a very experienced and competent laboratory, hair analysis can be performed and can be useful in determining a measure of previous heavy metal exposure. It is also possible to compare levels of metals from the scalp hair and pubic hair washings to draw conclusions regarding the potential for environmental contamination and exposure.

[10] If significant symptoms (e.g..blood in sputum, chest pain, reduction in pulmonary function) of respiratory illness (lung cancer) are reported and/or identified during the history and physical examination, CT-Scan of the chest (lungs) should be performed.

[11] At a minimum, obtain FEV1, and FVC.

[12] This test may be deferred, if the participant has had an equivalent examination within the past six months (non-smoker) or three months (smoker) and can produce his or her films.

[13] If neurological, central nervous system, and/or peripheral nervous system symptoms are reported and/or identified during the history and physical examination, further evaluation by a neurologist should be undertaken in order to assess and to determine the extent of the neurological problems (e.g. tremor, numbness, peripheral neuropathy, and

- EMG (Electromyogram) (DBRP)
- NCV (Nerve Conduction Study) (DBRP)[14]

Heart and Vessels[15]

- 12 Lead Electrocardiogram (DBRP)

Skeletal System[16]

- Tests to Determine Bone Density (DBRP)

Cancer

Peer-reviewed epidemiological studies have reported statistically significant increases in risk and/or in mortality from: (a) lung cancer, among persons exposed to arsenic through inhalation; and bladder cancer, kidney cancer, liver cancer, lung cancer, and skin cancer, among persons exposed to arsenic through oral ingestion; (b) kidney cancer, lung cancer, and prostate cancer among individuals exposed to cadmium through inhalation; and (c) kidney cancer and lung cancer among persons exposed to lead through inhalation. If a person manifests signs and symptoms, therefore, that are consistent with any of the foregoing types of cancer, additional medical evaluations and diagnostic tests will be ordered.

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[14] If peripheral nervous system symptoms (peripheral neuropathy, i.e., numbness and/or tingling in fingers, hands, arms, toes, feet, and/or legs), are identified, NCV (nerve conduction studies) and, EMG (electromyography), should be administered in order to determine the extent of the peripheral nervous system effects (e.g. nerve denervation, nervous system impairment, and loss.).

[15] This test may be deferred if the participant has undergone an equivalent examination within the past 60 days and can produce the tracing. If cardiovascular abnormalities (e.g. hypertension, non-diabetic-induced peripheral vascular disease, and pericarditis) appear on physical examination, further evaluation by a cardiologist should be undertaken in order to assess and to determine the extent of the cardiovascular effects. A toxicologist or occupational and environmental medicine physician should ascertain whether these symptoms or findings can be related to exposures to heavy metals (arsenic, cadmium and/or lead).

[16] Peer-reviewed epidemiological studies and case reports have reported skeletal effects from exposure to cadmium. If symptoms of skeletal effects, such as osteoporosis, osteomalacia, brittle bones, fractures (with and without trauma), and/or changes in bone density are suspected or have occurred, additional diagnostic tests should be performed to assess bone density. Measurement of bone density at the forearm just above the wrist by single photon absorptiometry that uses a bone density scanner should be performed. To evaluate actual or suspected bone fractures, X-rays or CT-scans of the appropriate site(s) (bones) should be performed

August 19, 2011

Edgar C. Gentle, III, Esq.

Special Master

Perrine Medical Monitoring Plan, Product of the Perrine DuPont Settlement

Dear Mr. Gentle,

I am a medical consultant with experience in academics, private practice and Medical Management. My education includes a BS in Chemistry, a Medical Doctorate and an MBA. I have additional training in Nuclear Medicine with Board Certification. I have research experience with over 30 publications and a book chapter and over 10 years of experience in reviewing medical claims for medical appropriateness based on medical literature.

I have been asked to review the CT Scan Utilization Guidelines dated November 1, 2011. There are also several Exhibits that are referenced that I have reviewed including:

- Exhibit 1-CT Scan Utilization Protocols
- Exhibit 2-Class Area Map
- Exhibit 3-Paragraph C, page 2, of Memorandum of Understanding
- Exhibit A-Publication of USFDA
- Exhibit B-ACR Practice Guidelines
- Exhibit C-American College of Radiology September 2002 Statement on CT Screening Exams

In my review, I note many inconsistencies related to the information provided and the question at hand.

The first referenced publication under background in the Utilization guidelines is the Publication of the USFDA. First, this publication relates to Whole Body CT scanning in a normal population. It is my understanding that we are addressing Chest CT Scanning in high risk populations and not whole body scanning in normal populations; therefore this article is not applicable. It also is dated March 2003-

more than 8 years ago and is not up to date with the medical literature especially the recent New England Journal article published August 4, 2011 titled, "Reducing Lung-Cancer Mortality with Low-Dose Computed Tomography Screening". Additionally, the article does reference, "that CT screening of high-risk individuals for specific diseases such as lung cancer or colon cancer is currently being studied, but results are not yet available". The study they are referencing is the National Lung Screening Trial (NLST). The data from this study is what the New England Journal article is based on. Therefore, it is my opinion that this reference has no standing because it is addressing a different modality (whole body CT scanning versus specific areas), is outdated and even references that studies are coming in the future that are now available.

The next reference is to Exhibit B-the ACR Practice guideline. The practice guidelines included are for the performance of pediatric and adult chest radiography which is a Chest x-ray. I understood the matter we were discussing is CT scanning in high risk individuals and therefore

an article on Chest x-rays would be a completely different modality and certainly not applicable to this question. The practice guideline is out of date with the most recent medical literature cited in 2005 and the guideline revised in 2006. The other practice guideline in the exhibit was ACR practice guideline for performing FDG-PET/CT in Oncology. An FDG PET/CT utilizes positron emission tomography to assess metabolic activity in different tumors using flourodeoxyglucose, a radioactive sugar. The CT in PET/CT refers to the anatomic registration portion of the metabolic study and again is a completely different modality than CT scanning in high-risk lung cancers. These guidelines are dated 2007 and are therefore dated in this continually evolving field.

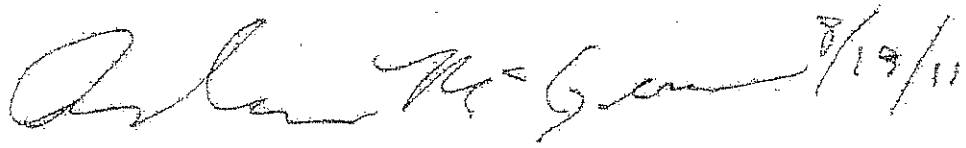
The CT scan guidelines that are quoted I believe are taken from the chest radiography practice guidelines and therefore are not applicable to another modality and neither is the reference to the American College of Radiology Board of Chancellors issued statement since it is referencing total body computed (CT) screening for patients with no

symptoms or a family history suggesting disease and we are addressing a different modality CT Scanning of the chest in patients with a high risk of cancer related to their exposure to the heavy metal contamination at issue in this litigation.

The guidelines that are listed (II. Guidelines, Page 2) are said to be based on these references that I have discussed above and therefore to base the guidelines on references about different tests than the one we are interested in and with medical references that are very out dated is not appropriate.

It is by opinion that according to the paragraph c, page 2 of the Memorandum of Understanding that was included as exhibit 3, CT scans should be provided as diagnostically medically necessary because of the high risk of the possible exposure to the heavy metal contamination at issue in this litigation. I base this on the August 4th 2011 article from the New England Journal "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening" based on

the National Lung Screening Trial (NLST). This article relates directly to this issue because it addresses a large population (53,454) that is at similar high risk of lung cancer (30 pack year history of smoking) to your patients with heavy metal exposure as noted in Exhibit 2-Class Area Maps. The mortality in these similar at risk individuals was 20% less if they had CT scans than if just chest x-ray surveillance. This article is up to date and particularly on point to this situation. It is my opinion that because of this study all participants should have a CT Scan as part of their surveillance because it is medically necessary in a high risk population with possible exposure to heavy metal contaminants.



Andrea H McGuire, MD, MBA

West Virginia University
School of Medicine

Virginia Buchanan, Esq. & Farrest Taylor, Esq.
Levin Papantonio Thomas Mitchell Rafferty & Proctor, P.A.
316 South Baylen Street Suite 600
Pensacola, FL 32502-5996

Re: Perrine v. Dupont

Date: December 9, 2010

In response to a proposed settlement agreement in this matter, you have advised me that CT scans would be allowed only if they are "diagnostically medically necessary, as determined by a competent physician, as relevant to possible exposure to heavy metal contamination at issue in this litigation". This is significant difference from the proposed every-other-year CT scans of the chest recommended in the initial program proposal. You have requested that I review the CT scan portion of the program and that a revised recommended schedule for CT scans be developed concordant with this wording.

At the present time, the best available test to screen for lung cancer remains the low-dose screening CT scan. Recent preliminary data released by the National Lung Cancer Screening Team supports the efficacy of low-dose screening CT scan in detecting lung cancers earlier than is possible via other means and demonstrating improved survival. The dose of radiation in a low-dose screening CT scan used in this study is estimated at 20-25% that of a diagnostic CT scan, and will likely continue to decrease as the technology improves. There is not yet any data on the optimum frequency of CT scanning to screen high-risk persons for lung cancer.

The purpose of a medical monitoring program is to detect diseases which are sub-clinical, to provide knowledge or additional chance of cure for the participant. By definition, this means it would not be necessary to have symptoms to be screened. Testing which is based solely upon symptoms would occur without any medical monitoring program and should be outside of the construct of a program aimed at detecting subclinical disease. I believe that diagnostically medically necessary CT scans for the participants can be estimated purely on the basis of the exposure, without the need for the participant to be symptomatic.

Within the affected area in this community, three geographic areas with different levels of contamination have been identified. These different areas are reflected in different residency time requirements for plan entry. Those living in zone 1 have a much greater exposure and risk of disease per unit time compared to those living in zones 2 or 3. It could be reasonable to develop this program such that there is a different frequency of CT scans recommended for each zone, based upon the relative levels of contamination in each zone. It is understood that there will be a science committee that will develop the final plan, and various permutations of this option have been considered.

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Exhibit C

My estimate is that participants in Zone 1 will need a diagnostic CT scan every 2-4 years, participants in zone 2 will need a CT scan every 4-8 years, and participants in zone 3 will need a scan approximately every 10 years.

Dr. Jackson provides the following estimates relative to the percentage of the participants in each zone based upon 2005 data:

	Zone1	Zone 2	Zone 3
Percentages	12.3%	30.2%	57.5%

Doing the math over a 30 year period:

Zone 1 (using every 3 years) = 11 CT Scans x 12.3% = 1.353 Scans

Zone 2 (using every 6 years) = 6 CT Scans x 30.2% = 1.812 Scans

Zone 3 (using every 10 years) = 4 CT Scans x 57.5% = 2.3 Scans

Summing these would yield 5.465 scans over the 30 year period of the program to "the average participant", or one scan every 5.489 years. For the purposes of estimating costs, this should be rounded to one scan every 6 years (on average).

I am not recommending any change in the entry criteria for the program. It is my recommendation that the initial CT scan (to occur with the first cycle of testing if the participant is currently over age 35, or with the first cycle of testing after a participant turns 35) be done for all participants. This will both allow for identification of current occult disease, and will provide baseline information, to support future testing of that participant.

In the original documents, I provided estimates for "leakage" of participants from the program, including both voluntary withdrawls and that which was due to diagnosis of diseases of interest. I believe that it would be simplest, and medically reasonable, to assume that the "leakage rates" due to voluntary and diagnosis-related withdrawls would remain unchanged from the prior estimates. Over time, lung cancers will present themselves clinically (although at a less curable stage), and this would still result in the participant leaving this aspect of the program at about the same rate as previously estimated.

Please contact me if you have any questions about these opinions/recommendations.

Charles L. Werntz III, D.O., MPH, FACOEM
Associate Professor, Clinical Emphasis
Program Director - Osteopathic Occupational Medicine Residency

PERRINE DUPONT SETTLEMENT CLAIMS OFFICE
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perrinedupont@gtandslaw.com

February 15, 2011

Re: Registration* for Medical Monitoring Program and Property Clean-Up Program

Dear Potential Medical Monitoring or Property Program Class Member,

THIS LETTER INVITES YOU TO A TOWN MEETING AT THE SPELTER, WEST VIRGINIA, FIRE STATION, WHERE WE WILL HELP YOU WITH YOUR PAPERWORK TO DETERMINE IF YOU ARE A MEMBER OF EITHER OF THESE CLASSES.

On January 4, 2011, a settlement between DuPont and members of two classes was approved by the Circuit Court of Harrison County. The approved settlement establishes two distinct plaintiff classes – a medical monitoring class and a property class. Ed Gentle has been appointed as the Claims Administrator for both classes. On January 18, 2011, the Court approved the medical monitoring program. Based upon information currently available to me, you may be a member of one or both of these classes. We will help you fill out your medical monitoring registration* form. Each Class Member must fill out a form. We will have extra copies at the town meeting or we can mail them to you. If you are a member of the property class, you will have an opportunity to discuss possible options available to address impacted properties within the class area. The Court Orders and a Class Area Map can be viewed at the settlement website at www.perrinedupont.com.

Here is the Town Meeting Schedule:

If Your Last Name Begins With	Your Town Meeting Is (You have the option to come to either the morning or the afternoon session. You are not required to attend both.)
A through B	February 28, 2011, 9:00 am or 2:00 pm
C through D	March 1, 2011, 9:00 am or 2:00 pm
E through G	March 2, 2011, 9:00 am or 2:00 pm
H through I	March 3, 2011, 9:00 am or 2:00 pm
J through L	March 4, 2011, 9:00 am or 2:00 pm
M through N	March 7, 2011, 9:00 am or 2:00 pm
O through R	March 8, 2011, 9:00 am or 2:00 pm
S	March 9, 2011, 9:00 am or 2:00 pm
T through Z	March 10, 2011, 9:00 am or 2:00 pm
Make Up Day (If you were unable to attend on your designated day, you may come on this day.)	March 11, 2011, 9:00 am or 2:00 pm

*Registration means proving medical monitoring Class membership. It does not require participation in the medical monitoring program.

If you cannot attend your scheduled town meeting, feel free to attend any other listed meeting. If you are disabled or otherwise unable to attend, please call us and we can review the Settlement with you over the phone or may be able to come visit you. It is not necessary that you attend one of these town meetings in order to complete the registration forms to determine whether or not you are eligible to participate in either the Medical Monitoring or Property Clean Up Classes. If you do not attend one of the town meetings, you can still complete the enclosed registration* form and mail it back to me at the above address or place it in the drop box at my office.

Below is a brief description of the Medical Monitoring Program and the Property Clean-Up Design town meeting.

A. THE MEDICAL MONITORING PROGRAM

Enclosed is your registration* form.

If you qualify as an eligible class member for medical monitoring you are entitled to receive two benefits: a cash payment and medical monitoring for a period of up to 30 years. In order to determine your eligibility, you must complete the enclosed eligibility registration form and you must choose whether you wish to receive both medical monitoring and cash benefits, or just the cash payment only. Once we have verified your eligibility, an initial cash payment of **$200** will be given to you and you may receive an additional cash payment later this year, depending upon the total number of participants in this program. You do not need to sign up for medical monitoring in order to receive this additional cash payment. The amount of the cash payment will be the same regardless of whether you choose to participate in the Medical Monitoring program. Additionally, you will begin to receive free medical monitoring for a period of up to 30 years if you choose to receive this benefit. Please note that if you don't apply to receive the medical monitoring by filling out the enclosed form by August 31, 2011, you will forever waive your right to receive that benefit.

As you may know, under this Settlement, the Honorable Thomas A. Bedell, Circuit Judge of Harrison County, West Virginia, has approved a 30 year Medical Monitoring program for individuals who lived in Zone 1 of the Class Area (see enclosed map attached to form) for at least 1 year, Zone 2 for at least 3 years, or Zone 3 for at least 5 years.**

To register* for the Medical Monitoring Program, a Class Member needs to fill out the enclosed Registration Form and provide the requested supplemental documents proving residency if you have them.

---

*Registration means proving medical monitoring Class membership. It does not require participation in the medical monitoring program.

** As long as the Class Member has continuously lived in the Class Area prior to reaching the minimum residence requirement, a Class Member's number of years of residence in each zone are added to determine if the number of years has been met. For example, if a Class Member lived ½ year in Zone 1 and 1 ½ years in Zone 2, he or she would qualify for Medical Monitoring, having spent 50% of the time required in each Zone.

At the town meeting, we will help you complete the form. You may bring the completed form to our office at the Perrine DuPont Settlement Claims Office, located at the Spelter Volunteer Fire Department, 55 B Street, Spelter, West Virginia, 26438 (a drop box is provided if we are closed), or mail it to The Perrine DuPont Settlement Claims Office, Attn: Edgar C. Gentle, Claims Administrator, c/o The Spelter Volunteer Fire Department Office, P.O. Box 257, Spelter, West Virginia, 26428, or e-mail the form to perrinedupont@gtandslaw.com. We must receive the completed form and the supplemental documents proving residency by August 31, 2011, or you will receive nothing.

If you are eligible and elect to participate in the Medical Monitoring program, then you can be medically tested free of charge shortly after registering*, and every 2 years thereafter, for a total monitoring period of 30 years. The voluntary screening exam for participants will involve only a whole blood test for those below age 15, and blood and urine monitoring for those from 15 to 35. In addition to blood and urine tests, class members age 35 or older may receive prescribed non-routine CT scans. All participants age 15 or less in the Medical Monitoring program will be tested for lead poisoning, skin cancer and gastrointestinal system problems.

No routine CT scans shall be performed as part of the Medical Monitoring program. CT scans shall be provided that are diagnostically medically necessary as determined by a competent physician as relevant to possible exposure to heavy metal contamination at issue in the Settlement.

After each screening, you will receive the confidential test results, and you will be entitled to a free physician office visit, where you will be allowed to discuss your medical history, have a physical exam, and review your test results with the physician.

If there is a positive finding of disease possibly associated with exposure to zinc, cadmium, arsenic or lead, you will be referred to a medical specialist for treatment. For other disease findings, the physician will also recommend treatment. The Settlement does not provide funding for actual medical treatment, and follow up treatment will not be paid for out of the Medical Monitoring program.

In the enclosed Medical Monitoring Registration* Form, we encourage you to recommend a Medical Clinic in the Class Area (with the major towns being Lumberport, Spelter, Arlington, Hepzibah, Shinston and Meadowbrook) in order to conduct the Medical Monitoring or provide the physician office visits.

Although it is not required, we also encourage you to provide the names and addresses of relatives and friends who have left the Class Area, so we can invite them to participate in this program.

*Registration means proving medical monitoring Class membership. It does not require participation in the medical monitoring program.

To efficiently carry out the Medical Monitoring process, which will involve reminders provided to you on your tests to be scheduled every two years, a confidential database protected by HIPAA and subject to a confidentiality agreement and other privacy laws will be maintained and will not be available to persons outside of the Medical Monitoring network without your prior permission. The Court will take the steps necessary to ensure that your private information stay private. The steps will include the use of confidentiality and protective orders and limitations on access to the database and/or identifying information. Refer to the January 18, 2011 Order at Paragraph 4.

B. PROPERTY CLEAN-UP PROGRAM DESIGN TOWN MEETING

Under the Settlement, **$34 Million** is to be used to help clean up impacted properties in the Class Area, which has 2,800 parcels, except that the ineligible Grasselli properties*** are not included. If you own a parcel in the Class Area other than a Grasselli property, you are a Property Class Member, and you will be encouraged to participate in the design of the property clean-up. The target contaminants are zinc, cadmium, arsenic and lead. At the town meetings, our clean-up expert, Marc Glass, will describe for you the impact of these metals on the Class Area, and we will welcome your suggestions on how to address the impacted properties in the area.

We will send you a follow-up property clean-up questionnaire after the town meetings. We will ask the Court to have a Fairness Hearing and decide how to design and carry out the property remediation program.

We look forward to meeting you and to your participation in this Settlement if you qualify as a Class Member.

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*Registration means proving medical monitoring Class membership. It does not require participation in the medical monitoring program.

** As long as the Class Member has continuously lived in the Class Area prior to reaching the minimum residence requirement, a Class Member's number of years of residence in each one are added to determine if the number of years has been met. For example, if a Class Member lived ½ year in Zone 1 and 1 ½ years in Zone 2, he or she would qualify for Medical monitoring, having spent 50% of the time required in each Zone.

***A list of these properties is on our website and will be available at the town meetings.

If you have any questions, please come by our office, call us, or send an email.

Yours very truly,

Ed Gentle,
Claims Administrator
(304) 622-7443
1-800-345-0837 (toll free)
Perrinedupont@gtandslaw.com

ECGIII/kjm
Enclosure

PERRINE DUPONT SETTLEMENT CLAIMS OFFICE
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MEDICAL MONITORING REGISTRATION* FORM

FILL OUT A SEPARATE FORM FOR EACH PERSON REGISTERING*

This Medical Monitoring Program only applies to Class Members who lived in the Class Area (See Attached Map) for the minimum time, as explained in Paragraph A on Page 6 and 7 of the January 18, 2011 Order approving the Medical Monitoring program, and as explained in the February 15, 2011 letter mailed to you with this form.**

COMPLETE AND RETURN THIS FORM BY HAND DELIVERY, MAIL OR E-MAIL TO THE ADDRESS AT THE TOP OF THIS PAGE NO LATER THAN AUGUST 31, 2011

For HELP with this form, visit our Office in Spelter (office hours are 9 to 5, Monday through Friday), call (304) 622-7443 or 1-800-345-0837, view our website at www.perrinedupont.com, or email us at perrinedupont@gtandslaw.com.

I. REQUIRED PARTICIPATION DECISION: YOU CAN USE THE MEDICAL MONITORING PROGRAM AND GET YOUR CASH PAYMENT OR YOU CAN JUST REGISTER* AND GET YOUR CASH PAYMENT ANYWAY

CHECK ONE OF THE FOLLOWING TWO BOXES:

☐ **YES, I wish to have Medical Monitoring available if I choose to use it, and want my cash payment.**

☐ **NO, I do not wish to use Medical Monitoring, and want my cash payment. If I check this box, I forever waive my right to be medically tested. The amount of the cash payment will be the same regardless of whether or not you choose to participate in the Medical Monitoring program.**

II. REQUIRED CLASS MEMBER INFORMATION

LAST NAME ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ FIRST NAME ☐☐☐☐☐☐☐☐☐☐☐☐ MI ☐

CURRENT ADDRESS ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

CITY ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ STATE ☐☐ ZIP CODE ☐☐☐☐☐

* Registration means proving medical monitoring Class membership. It does not require participation in the Medical Monitoring program.

**The Court Order can be found on the Settlement website at www.perrinedupont.com.

Social Security Number ☐☐☐-☐☐-☐☐☐☐

Birth Date ☐☐/☐☐/☐☐☐☐

III. REQUIRED PROOF OF LIVING IN THE CLASS AREA

PLEASE LIST ALL OF YOUR RESIDENCE ADDRESSES IN THE CLASS AREA (SEE ATTACHED MAP) WHERE YOU LIVED, TELL US WHEN YOU LIVED THERE, AND IF YOU WERE A CHILD AT THE TIME, PLEASE PROVIDE THE NAMES OF YOUR CUSTODIAL PARENT OR GUARDIAN AT THE TIME.

CLASS AREA ADDRESS:	DATES: FROM - UNTIL	CUSTODIAL PARENT OR GUARDIAN: (IF APPLICABLE)

Current Telephone Numbers: (___)_____ **(Home)** (___)_____ **(Cell)**

For additional addresses, attach a separate sheet of paper.

For each residence, to the extent you can, please attach proof that you lived there, and for how long, such as a school report card, medical bill, deed, lease, power bill, old check with the address, or the first page of income tax returns for each claimed year. Other documents you may use are in the attached table. We will also consider any other documents that show you lived in the Class Area.

We will also try to obtain the proof from outside sources that you lived in the class area to the extent possible. For adults, source documents will include class area voter registration rolls, Class Area ad valorem property tax records, Class Area Medical Clinic patient rolls, and Class Area utility billing records. For children, source documents will include Class Area school registration rolls and Class Area Medical Clinic patient rolls.

TO HELP US VERIFY THAT YOU LIVED IN THE CLASS AREA, PLEASE COMPLETE THE FOLLOWING TABLE:

Dates: From	Until	Class Area School Attended:

Dates: From	Until	Your Primary Care Doctor or Dentist:

IV. OPTIONAL ADDITIONAL REQUESTED INFORMATION- NOT NECESSARY TO RECEIVE CASH PAYMENT OR TO RECEIVE MEDICAL MONITORING

PLEASE LIST DOCTORS OR MEDICAL CLINICS IN OR NEAR THE CLASS AREA THAT YOU RECOMMEND TO CONDUCT MEDICAL MONITORING. WE WANT TO USE MEDICAL PROVIDERS THAT YOU TRUST.

Name	Address	Phone

PLEASE LIST BELOW THE NAMES AND ADDRESSES OF RELATIVES OR ACQUAINTANCES WHO HAVE LIVED IN THE CLASS AREA AND HAVE MOVED AWAY FROM THE CLASS AREA.

NAME:	ADDRESS:

IF YOU NEED ADDITIONAL SPACE TO ANSWER ANY OF THE QUESTIONS ON THIS FORM, PLEASE USE ADDITIONAL SHEETS OF PAPER AND ATTACH TO THIS REGISTRATION FORM.

VERY IMPORTANT - THIS REGISTRATION FORM CONTINUES ON THE NEXT PAGE

V. REQUIRED CERTIFICATION AND SIGNATURE – MUST BE WITNESSED

The undersigned hereby swears under penalty of perjury that all of the information provided herein is true and accurate.

Adult claimants must sign unless incompetent.
For Minor Claimants, the Custodial Parent or Guardian must sign.
For Incompetent Adult Claimants, the Guardian or Conservator must sign.

_____ Date: __ __ / __ __ / __ __ __ __

CLASS MEMBER SIGNATURE

WITNESS SIGNATURE:

_____

WITNESS NAME:

_____

WITNESS ADDRESS:

_____

_____

DOCUMENTS THAT MAY BE USED TO PROVE *HOW LONG YOU LIVED IN THE CLASS AREA*

Children - Type of Documents for Proving Residency
Birth Certificate
School/Day Care Records
Medical Records
Parents/Guardians Tax Records Listing Dependants
Lease Agreements Listing Children as Occupants
Government Benefits/Public Assistance Documents
Insurance Documents
DHR/Guardianship/Other Government Program Documents Showing Residency
Police Records/Other Court Records
Church Enrollment Records
Passport
Employment Rolls if of Employment Age
Extracurricular Activities - Sports, Clubs, Library Cards, Etc.

Adults - Type of Documents for Proving Residency
Real Estate Tax Documents
Driver's License
Other DMV Records
Passport
Employment Rolls
Utility Bills
Insurance
Medical Records
Government Benefit/Public Assistance Documents
Deeds
Lease Agreements
Tax Records
Church Enrollment Records
Bank Records
DHR/DA Other Government Program Documents Showing Residency
Police Records/Other Court Records
Gym Membership

Referenced Materials Attached

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   Lung Cancer: Diagnosis and Management, Lauren G. Collins, et al.

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   The Early Diagnosis of Lung Cancer, Petty, T.L.

5. N. Eng. J. Med. 2011; 365: 395-409, Aug. 4, 2011
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6. Oncologist 2001; 6(2):147-52, Feb. 2001
   Early Lung Cancer Action Project: A Summary of the Findings on Baseline Screening, Henschke C.L., et al.

7. N. Eng. J. Med. (2006); 355(17): 1763-71, Oct. 26, 2006
   Survival of Patients with Stage I Lung Cancer Detected on CT Screening, The International Early Lung Cancer Action Program Investigators

8. ABC News Medical Unit
   * CT Scans For Smokers Could Lower Lung Cancer Deaths by 20%, Courtney Hutchinson, Video
   * Hospitals Offering Lung Cancer CT Scans, June 29, 2011

9. American Conference Institute Chemical Products Liability and Environment Litigation., April 2010
   What is Medical Monitoring?, Jerome R. Doak

10. Occupational Safety and Health Administration (29 CFR 1910)
    Medical Screen and Surveillance: Introduction

Lung Cancer: Diagnosis and Management

LAUREN G. COLLINS, M.D., CHRISTOPHER HAINES, M.D., ROBERT PERKEL, M.D., and ROBERT E. ENCK, M.D.
Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Lung cancer is the leading cause of cancer-related death in the United States, with an average five-year survival rate of 15 percent. Smoking remains the predominant risk factor for lung cancer. Lung cancers are categorized as small cell carcinoma or non–small cell carcinoma (e.g., adenocarcinoma, squamous cell carcinoma, large cell carcinoma). These categories are used for treatment decisions and determining prognosis. Signs and symptoms may vary depending on tumor type and extent of metastases. The diagnostic evaluation of patients with suspected lung cancer includes tissue diagnosis; a complete staging work-up, including evaluation of metastases; and a functional patient evaluation. Histologic diagnosis may be obtained with sputum cytology, thoracentesis, accessible lymph node biopsy, bronchoscopy, transthoracic needle aspiration, video-assisted thoracoscopy, or thoracotomy. Initial evaluation for metastatic disease relies on patient history and physical examination, laboratory tests, chest computed tomography, positron emission tomography, and tissue confirmation of mediastinal involvement. Further evaluation for metastases depends on the clinical presentation. Treatment and prognosis are closely tied to the type and stage of the tumor identified. For stages I through IIIA non–small cell carcinoma, surgical resection is preferred. Advanced non–small cell carcinoma is treated with a multimodality approach that may include radiotherapy, chemotherapy, and palliative care. Chemotherapy (combined with radiotherapy for limited disease) is the mainstay of treatment for small cell carcinoma. No major organization recommends screening for early detection of lung cancer, although screening has interested researchers and physicians. Smoking cessation remains the critical component of preventive primary care. (Am Fam Physician 2007;75:56-63. Copyright © 2007 American Academy of Family Physicians.)

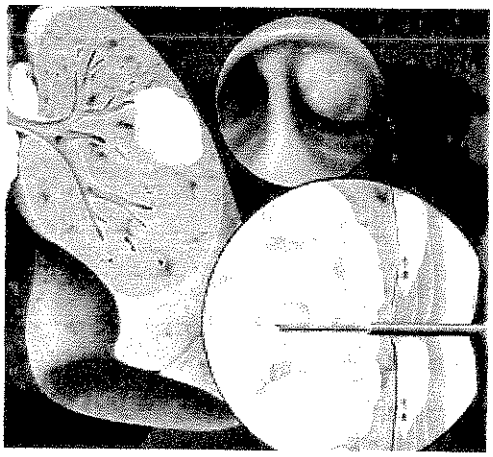


ILLUSTRATION BY MARK LEFKOWITZ

▶ **Patient information:** A handout on smoking cessation is available at http://familydoctor.org/161.xml.

Lung cancer is the leading cause of cancer-related death in the United States. In 2006, the disease caused over 158,000 deaths—more than colorectal, breast, and prostate cancers combined.[1] Although death rates have begun to decline among men in the United States, the lung recently surpassed the breast as the most common origin of fatal cancer in women.[2] Because one fourth of adults smoke, lung cancer will remain a problem for many years.[2] Despite advances in lung cancer therapy, the average five-year survival rate is only 15 percent.[3] Adenocarcinoma has surpassed squamous cell carcinoma as the most common histologic type of lung carcinoma,[4,5] and early metastasis has become increasingly common.

Risk Factors

Smoking is the predominant risk factor for lung cancer (relative risk [RR] = 10 to 30 compared with nonsmokers)[3,6]; smoking is directly linked to lung cancer in 90 percent of women and 79 percent of men.[7] Secondhand smoke exposure is also a risk factor.[8,9] Approximately 3,000 adults die each year from exposure to secondhand smoke, with a dose-response relationship between duration and intensity of exposure.[10,11]

The most common occupational risk factor for lung cancer is exposure to asbestos (RR = 6)[7]; the RR for smokers who are exposed to asbestos approaches 60.[12] Other common occupational and environmental causes of lung cancer include exposure to radon, arsenic, chromium, nickel, vinyl chloride, and ionizing radiation.[13] Preexisting nonmalignant lung diseases, such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and tuberculosis also are associated with increased lung cancer rates.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Patients with central lung tumors should undergo flexible bronchoscopy.	C	27, 28
Patients with peripheral lung tumors who are not surgical candidates should undergo transthoracic needle aspiration.	C	27, 28
Patients undergoing mediastinal staging for lung cancer should receive chest computed tomography plus positron emission tomography.	C	34, 35
There is insufficient evidence to recommend for or against routine screening for lung cancer.	C	40-42
For lung cancer prevention, smokers should be offered nicotine replacement therapy, bupropion (Wellbutrin), nortriptyline (Pamelor), and counseling for smoking cessation.	A	50-53

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 13 or http://www.aafp.org/afpsort.xml.

Pathology

To facilitate treatment and prognostic decisions, lung cancer is categorized as small cell carcinoma or non–small cell carcinoma. Light microscopy is used to further differentiate lung cancer into four major and several minor histologic classes (*Table 1*[14,15]).[16] The major histologic classes are adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma.

Adenocarcinomas are histologically heterogeneous peripheral masses that metastasize early, and often occur in patients with underlying lung disease.[17] Squamous cell carcinomas typically are centrally located endobronchial masses that may present with hemoptysis, postobstructive pneumonia, or lobar collapse. Unlike adenocarcinomas, squamous cell carcinomas generally metastasize late in the disease course.[18]

Small cell carcinomas are clinically aggressive; are usually centrally located with extensive mediastinal involvement; and are associated with early extrathoracic metastases, including paraneoplastic syndrome. Despite their responsiveness to chemotherapy, small cell carcinomas often are advanced at the time of diagnosis, and patients have a poor prognosis.[19]

Large cell carcinomas are poorly differentiated. These tumors are large peripheral masses associated with early metastases.[17]

Clinical Presentation

Although approximately 10 percent of lung cancers in asymptomatic patients are detected on chest radiographs, most patients are symptomatic when diagnosed.[19] Patients may present with the nonspecific systemic symptoms of fatigue, anorexia, and weight loss, or with direct signs and symptoms caused by the primary tumor or intrathoracic or extrathoracic spread (*Table 2*[20]). A minority of patients present with paraneoplastic syndromes.

PRIMARY TUMOR

Chest discomfort, cough, dyspnea, and hemoptysis are common manifestations of a primary tumor. Cough secondary to an endobronchial mass or postobstructive pneumonia occurs in up to 75 percent of patients.[20] Dyspnea occurs in up to 60 percent of patients and may be caused by a tumor occluding the airway.[20] Intermittent, aching chest discomfort occurs in approximately 50 percent of patients at diagnosis.[20] Hemoptysis is found in up to 35 percent of patients with symptoms from a primary tumor.[20] Although acute bronchitis is the most common

TABLE 1
Histologic Classification of Lung Cancer

Class	Prevalence (%)	Subtypes
Adenocarcinoma	40	Acinar, bronchioalveolar, papillary, solid carcinoma with mucus formation, mixed
Squamous cell carcinoma	25	—
Small cell carcinoma	20	Pure small cell carcinoma, combined small cell carcinoma
Large cell carcinoma	10	Large cell neuroendocrine, basaloid, lymphoepithelial-like, large cell with rhabdoid phenotype
Adenosquamous carcinoma	< 5	—
Carcinoid	< 5	—
Bronchial gland carcinoma	< 5	—

Information from 14 and 15.

TABLE 2
Common Lung Cancer Manifestations

Primary tumor	**Extrathoracic spread**
Chest discomfort	Bone pain, fracture
Cough	Confusion, personality change
Dyspnea	Elevated alkaline phosphatase level
Hemoptysis	Focal neurologic deficits
Intrathoracic spread	Headache
Chest wall invasion	Nausea, vomiting
Esophageal symptoms	Palpable lymphadenopathy
Horner syndrome	Seizures
Pancoast's tumor	Weakness
Phrenic nerve paralysis	Weight loss
Pleural effusion	
Recurrent laryngeal nerve paralysis	
Superior vena cava obstruction	

Information from reference 20.

cause of hemoptysis, lung cancer should be suspected in patients older than 40 who present with hemoptysis.[20]

INTRATHORACIC SPREAD

Forty percent of patients diagnosed with lung cancer initially present with signs and symptoms of intrathoracic spread. Intrathoracic spread is caused by direct extension of the tumor or lymphangitic spread.

Hoarseness from recurrent laryngeal nerve paralysis occurs in 2 to 18 percent of patients.[20] Phrenic nerve paralysis may present with dyspnea or an elevated left hemidiaphragm on a chest radiograph.[20] A superior pulmonary sulcus tumor (Pancoast's tumor) may present with Horner syndrome and is characterized by a brachial plexopathy and pain along the involved nerve roots.[21] Chest wall invasion often presents with persistent, pleuritic pain. Pleural effusions may present with dyspnea, decreased breath sounds, and dullness to percussion.[22] Esophageal obstruction may cause dysphagia. Superior vena cava obstruction is characterized by facial swelling and plethora and by dilated veins on the upper torso, shoulders, and arms.[23] Although pericardial involvement often is found at autopsy, patients seldom present with symptomatic pericardial effusion or tamponade.[24]

EXTRATHORACIC SPREAD

Nearly one third of patients with lung cancer present with signs and symptoms of extrathoracic spread.[20] Common metastatic sites include bones, liver, adrenal glands, lymph nodes, brain, and spinal cord.

Nonspecific symptoms of extrathoracic spread include weakness and weight loss. Bone metastasis often presents with pain, fracture, or elevated alkaline phosphatase level and usually involves the long bones or vertebrae. Palpable lymphadenopathy, particularly in the supraclavicular fossa, suggests metastasis. Ten percent of patients present with brain metastasis heralded by headache, nausea, vomiting, focal neurologic deficits, seizures, confusion, or personality changes.[25] Although liver involvement is common, transaminase elevation is relatively rare.

PARANEOPLASTIC SYNDROMES

Approximately 10 percent of patients with lung cancer develop systemic symptoms related to paraneoplastic syndromes. This is caused by the release of bioactive substances produced by the tumor or in response to the tumor. Symptoms may precede the diagnosis, appear late in the disease course, or suggest recurrence.

Common endocrine syndromes include hypercalcemia, syndrome of inappropriate antidiuretic hormone, and Cushing's syndrome. Digital clubbing and hypertrophic pulmonary osteoarthropathy are common skeletal manifestations. Less well-defined neurologic syndromes include Lambert-Eaton myasthenic syndrome, peripheral neuropathy, and cortical cerebellar degeneration.[26]

Diagnosis

TISSUE DIAGNOSIS

There are a variety of techniques to assist physicians in obtaining an accurate tissue diagnosis *(Table 3[27])*. Selecting the most appropriate test usually requires consultation with a pulmonologist, interventional radiologist, or thoracic surgeon. In patients with apparent early non–small cell carcinomas, who are surgical candidates, thoracotomy is the recommended test for tissue diagnosis and staging. In patients with presumed small cell or metastatic non–small cell carcinomas, the diagnosis should be made using the most convenient and least invasive method available (e.g., thoracentesis of a pleural effusion, excisional biopsy of an accessible node, bronchoscopy, transthoracic needle aspiration).[27]

Several options are available when the type and stage of the cancer are less clear, including sputum cytology, flexible bronchoscopy, and transthoracic needle aspiration. Sputum cytology is a noninvasive test that may be useful in identifying centrally located tumors. The test detects 71 percent of central tumors but less than 50 percent of peripheral tumors[27]; therefore, further testing must follow a negative result.

Flexible bronchoscopy (employing bronchial washings, brushings, and biopsies) often is the test of choice in patients with central tumors, with a combined sensitivity of 88 percent in these patients.[28] Despite the

TABLE 3
Methods for the Tissue Diagnosis of Lung Cancer

Diagnostic method	*Sensitivity (%)*	*Specificity (%)*	*Indication*	*Comments*
Sputum cytology (at least three specimens)	Central tumors: 71 Peripheral tumors: < 50	99	Central tumor and hemoptysis	Noninvasive; further testing needed after negative result
Thoracentesis	80	> 90	Pleural effusion	—
Excisional biopsy of an accessible node	—	—	Palpable lymphadenopathy	—
Flexible bronchoscopy with or without transbronchial needle aspiration	Central tumors: 88 Peripheral tumors: 60 to 70	90	Central or peripheral tumor and mediastinal lymphadenopathy	Fluoroscopic or CT guidance; transbronchial needle aspiration improves sensitivity in peripheral tumors
Transthoracic needle aspiration	Peripheral tumors: 90	97	Peripheral tumor in nonsurgical candidates or when transbronchial needle aspiration is inconclusive	Fluoroscopic or CT guidance; the assistance of a cytopathologist improves diagnostic yield
Video-assisted thoracoscopy	—	—	Small peripheral tumors (< 2 cm in diameter), pleural tumors, or pleural effusions	May prevent the need for thoracotomy
Thoracotomy	—	—	Only clearly resectable tumors	Recommended for diagnosis and treatment of early non–small cell carcinoma

CT = computed tomography.

Information from reference 27.

addition of fluoroscopic and computed tomography (CT) guided transbronchial needle aspiration, the sensitivity of bronchoscopy falls to 70 percent in patients with peripheral tumors and even lower in patients with a tumor less than 2 cm in diameter.[28,29] Pneumothorax and bleeding are serious but uncommon complications of transbronchial needle aspiration.[29]

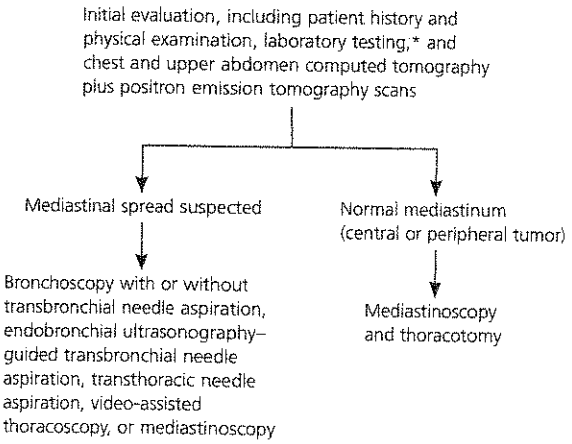
Transthoracic needle aspiration has been shown to be more sensitive than bronchoscopy in patients with peripheral lung tumors and may be used when transbronchial needle aspiration is inconclusive or in patients who are not surgical candidates.[28] Transthoracic needle aspiration is routinely guided by fluoroscopy or CT, and the assistance of a cytopathologist increases the diagnostic yield. The most common complication of transthoracic needle aspiration is pneumothorax (25 to 30 percent), but the procedure rarely requires chest tube insertion.[29]

Video-assisted thoracoscopy is a newer modality that may be used to sample small peripheral tumors (less than 2 cm in diameter), pleural tumors, or pleural effusions for diagnostic or staging purposes.[30]

STAGING

After establishing a tissue diagnosis, a thorough staging work-up, including metastatic evaluation (*Figure 1*[27,29-32])

Metastatic Evaluation of Lung Cancer



NOTE: *After the metastatic evaluation, a staging classification should be determined* (Table 4).

**—Laboratory tests should include complete blood count and electrolyte, calcium, hepatic transaminases, and alkaline phosphatase levels.*

Figure 1. Algorithm for the metastatic evaluation of lung cancer.

Information from references 27 and 29 through 32.

TABLE 4
Staging Classifications for Lung Cancer

Stage	*Description*
Non–small cell carcinoma (TNM staging system)	
Local	
IA (T1N0M0)	T1: 3 cm or less in diameter; surrounded by lung or pleura; does not invade main bronchus
IB (T2N0M0)	T2: more than 3 cm in diameter; may invade pleura; may extend into main bronchus but remains 2 cm or more distal to carina; may cause segmental atelectasis or pneumonitis
IIA (T1N1M0)	N1: involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes
Locally advanced	
IIB (T2N1M0 and T3N0M0)	T3: invasion of chest wall, diaphragm, pleura, or pericardium; main bronchus less than 2 cm distal to carina; atelectasis of entire lung
IIIA (T1N2M0, T2N2M0, T3N1M0, and T3N2M0)	N2: involvement of ipsilateral mediastinal or subcarinal nodes
IIIB (T1-4N3M0)	N3: involvement of contralateral nodes or any supraclavicular nodes
Advanced	
IIIB (T4N1-3M0)	T4: invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; separate tumor nodules; malignant pleural effusion
IV (T1-4N1-3M1)	Distant metastasis
Small cell carcinoma	
Limited	Disease confined to the ipsilateral hemithorax
Extensive	Disease with metastasis beyond the ipsilateral hemithorax

TNM = tumor-nodes-metastasis.

Adapted with permission from Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med 2004;350:382.

and staging classification, should be performed to determine the presence of metastasis and to identify surgical resection candidates.

Initial evaluation for metastasis can be performed by the primary care physician and includes a detailed history; physical examination; complete blood count; and levels of electrolyte, calcium, hepatic transaminases, and alkaline phosphatase. More than 80 percent of patients with an abnormality on evaluation have metastatic disease.[31] Patients presenting with anorexia, weight loss, and fatigue have an especially poor prognosis.[33]

Noninvasive radiographic imaging with chest CT and positron emission tomography (PET) scans is routinely performed in patients with suspected metastatic lung cancer. Chest and upper abdomen CT scans may reveal hilar and mediastinal adenopathy and liver or adrenal involvement. Although CT accuracy is 88 percent (80 percent sensitive, 100 percent specific) in the mediastinum, staging is enhanced by PET.[34] Integrated CT/PET scanners appear to have better test characteristics than CT or PET alone.[35]

In patients with suspected mediastinal disease, the remainder of the mediastinal staging evaluation usually is performed in consultation with subspecialists and may include bronchoscopy with or without transbronchial needle aspiration, endobronchial ultrasonography–guided transbronchial needle aspiration, transthoracic needle aspiration, video-assisted thoracoscopy, or mediastinoscopy. The clinical presentation dictates the use of additional staging measures. Abdominal CT, bone scanning, and brain magnetic resonance imaging are usually recommended in patients with small cell carcinoma because of the high likelihood of metastatic disease.

After the metastatic evaluation is complete, the staging classification *(Table 4[36])* can be determined based on the type of tumor identified and the presence or absence of metastatic disease. Non–small cell carcinoma is categorized using the TNM (tumor-nodes-metastasis) staging system, whereas small cell carcinoma is categorized as limited disease confined to the ipsilateral hemithorax or as extensive disease with metastasis beyond the ipsilateral hemithorax.[16]

FUNCTIONAL EVALUATION

The final component of the diagnostic assessment is a functional evaluation of the patient. Evaluation of performance and pulmonary status should be completed before discussing treatment options. Pulmonary function testing, specifically forced expiratory volume in one second (FEV_1) and carbon monoxide diffusion in the lung (DLCO) measurements, is a helpful predictor of morbidity and mortality in patients undergoing lung resection.[15]

Patients with an FEV_1 or DLCO value less than 80 percent of predicted require additional testing. This

includes calculation of postresection pulmonary reserve (with ventilation and perfusion scans or by accounting for the number of segments removed); cardiopulmonary exercise testing (with a maximum volume of oxygen utilization [VO_2max] measurement); and arterial blood gas sampling (with an oxygen saturation in arterial blood [S_{aO2}] measurement). Patients with a predicted postoperative FEV_1 or DLCO value less than 40 percent and a VO_2max value less than 10 mL per kg per minute or an S_{aO2} value less than 90 percent are at high risk of perioperative death or complications.[36]

Treatment and Prognosis

Treatment differs according to the histologic type of cancer, the stage at presentation, and the patient's functional evaluation (*Table 5*[36]). Surgery is the treatment of choice for patients with stage I through IIIA non–small cell carcinoma.[37] Recent data suggest that preoperative chemotherapy improves survival in patients with non–small cell carcinoma.[38] For patients undergoing complete resection and no preoperative chemotherapy, adjuvant chemotherapy is standard. Randomized controlled clinical trials should address the issue of preoperative versus postoperative adjuvant treatment.[38]

Treatment for unresectable non–small cell carcinoma may involve radiotherapy and chemotherapy. The role of targeted therapies, specifically the antivascular endothelial growth factor agent bevacizumab (Avastin), has been examined in patients with advanced stage (IIIB and IV) nonsquamous carcinoma. Bevacizumab combined with chemotherapy increased survival compared with chemotherapy alone.[39] Chemotherapy (combined with radiotherapy in limited stage disease) is the mainstay of treatment for small cell carcinoma.[37]

Palliative and hospice care are important end-of-life treatment modalities. The primary care physician can help patients determine what options may be most appropriate. *Table 6* includes hospice and palliative care resources.

Screening

Although studies have assessed screening with sputum cytology, routine chest radiography, and low-dose CT, no study has demonstrated that screening improves survival, and no major organization currently endorses lung cancer screening.[40] In 2004, the U.S. Preventive Services Task Force concluded that although there is fair evidence that screening may allow for earlier detection of lung cancer, there is poor evidence to suggest that any screening strategy decreases mortality.[41] With no proven effect of screening on mortality rates, there is concern that screening may cause overdiagnoses and unnecessary anxiety, radiation exposure, and expense.[42]

Several large randomized controlled trials designed to evaluate the effect of screening on mortality are

TABLE 5
Treatment of Lung Cancer According to Stage

Stage	*Primary treatment*	*Adjuvant therapy*	*Five-year survival rate (%)*
Non–small cell carcinoma			
I	Resection	Chemotherapy	60 to 70
II	Resection	Chemotherapy with or without radiotherapy	40 to 50
IIIA (resectable)	Resection with or without preoperative chemotherapy	Chemotherapy with or without radiotherapy	15 to 30
IIIA (unresectable) or IIIB (involvement of contralateral or supraclavicular lymph nodes)	Chemotherapy with concurrent or subsequent radiotherapy	None	10 to 20
IIIB (pleural effusion) or IV	Chemotherapy or resection of primary brain metastasis and primary T1 tumor	None	10 to 15 (two-year survival)
Small cell carcinoma			
Limited disease	Chemotherapy with concurrent radiotherapy	None	15 to 25
Extensive disease	Chemotherapy	None	< 5

Adapted with permission from Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med 2004;350:388.

TABLE 6
Hospice and Palliative Care Resources

American Academy of Hospice and Palliative Medicine Web site: http://www.aahpm.org
American Board of Hospice and Palliative Medicine Web site: http://www.abhpm.org
American Pain Society Web site: http://www.ampainsoc.org
Americans for Better Care of the Dying Web site: http://www.abcd-caring.org
Approaching Death: Improving Care at the End of Life Publisher: The National Academies Press
Before I Die: Medical Care and Personal Choices Web site: http://www.wnet.org/bid/index.html
City of Hope Pain/Palliative Care Resource Center Web site: http://www.cityofhope.org/prc
Dying Well: Defining Wellness Through the End of Life Web site: http://www.dyingwell.org
End of Life/Palliative Education Resource Center Web site: http://www.eperc.mcw.edu
EndLink Resource for End of Life Care Education Web site: http://endlink.lurie.northwestern.edu

underway.[43,44] Until these results become available, there is insufficient evidence to recommend for or against routine screening.

Prevention

Perhaps the primary care physician's most important role is preventing lung cancer by encouraging smoking cessation. The most effective cessation therapies (with quit rates ranging from 16 to 21 percent) are nicotine replacement, bupropion (Wellbutrin), nortriptyline (Pamelor), and structured telephone counseling.[45-53] Combining nicotine replacement, bupropion, and social or behavioral support can increase the quit rate to 35 percent.[54] Informal counseling by physicians has also been shown to modestly increase quit rates.[55,56]

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In the Balance

Screening for Lung Cancer: For Patients at Increased Risk for Lung Cancer, It Works

James R. Jett, MD; and David E. Midthun, MD

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Abstract

A 62-year-old woman with a history of well-controlled hypertension presents for routine follow-up. She is asymptomatic and feels well. She has jogged 3 miles 3 times weekly for years, with no recent change in exercise tolerance. She has a 30-pack-year history of cigarette smoking but stopped smoking 10 years ago. There is no personal or family history of cancer.

Physical examination is normal. She read a recent study that found a benefit to screening for lung cancer with computed tomography and inquires whether you think screening is appropriate for her. What should you recommend?

Screening for lung cancer is not currently recommended, even in persons at high risk for this condition. Most patients with lung cancer present with symptomatic disease that is usually at an incurable, advanced stage. The recently reported NLST (National Lung Screening Trial) showed a 20% decrease in deaths from lung cancer in high-risk persons undergoing screening with low-dose computed tomography of the chest compared with chest radiography.

The high-risk group included in the trial comprised asymptomatic persons aged 55 to 74 years, with smoking history of at least 30 pack-years. Screening with low-dose computed tomography detected more cases of early-stage lung cancer and fewer cases of advanced-stage cancer, confirming that screening has shifted the stage of cancer at diagnosis and provides more persons with the opportunity for curative treatment. Although computed tomography screening has risks and limitations, the 20% decrease in deaths is the single most dramatic decrease ever reported for deaths from lung cancer, with the possible exception of smoking cessation. Physicians should offer computed tomography screening for lung cancer to patients who fit the high-risk profile defined in the NLST.

Would we recommend that a 62-year-old woman with a 30-pack-year history of smoking undergo screening for lung cancer with low-dose computed tomography (LDCT)? Yes, but we would also discuss the potential risks and limitations as well as the potential benefits of screening before scheduling the test. If the patient currently smoked, we would strongly recommend a smoking cessation consultation and schedule it before or concurrent with LDCT (1). Smoking cessation significantly reduces the risk for lung cancer over time (2).

Most persons with lung cancer present with symptomatic disease at an advanced stage (stage III or IV) and at that point have little chance of curative treatment (3). Only 15% of patients with lung cancer in the United States are diagnosed with early-stage (stage I or II) disease, which is usually discovered incidentally on chest imaging studies done for other reasons (3, 4). Five-year survival with localized (early-stage) disease is 50% but only 4% in those with distant (stage IV) disease (3).

The NLST (National Lung Screening Trial) was a randomized, controlled trial of

LDCT versus chest radiography screening in persons at high risk for lung cancer (5). High-risk persons were defined as being 55 to 74 years of age; having a smoking history of at least 30 pack-years; and, in former smokers, having quit smoking in the past 15 years. Participants received baseline and annual screening for 2 additional years and were followed for a median of 6.5 years. The patient framing our discussion meets the eligibility criteria for the NLST.

In the computed tomography (CT) group of the NLST, 63% of cases of lung cancer diagnosed from a positive finding on a screening test were stage I and 70% were stage I or II (early stage). In 92.5% of cases, stage I lung cancer was treated with surgery (5). Treatment of stage I lung cancer offers the best chance of cure, with a 5-year survival rate of 70% to 80% (6). In the NLST, the LDCT group had fewer cases of stage IV cancer than did the chest radiography group at the second and third rounds of screening. These data show that, compared with chest radiography, screening with LDCT can shift the diagnosis of cancer from advanced- to early-stage disease and provide a better opportunity for curative treatment.

Screening with LDCT showed a 20% decrease in lung cancer deaths compared with chest radiography. To date, screening with chest radiography has not been shown to be superior to no screening. Patients who choose CT screening must understand that screening will diminish but not eliminate their chance of death due to lung cancer.

In the CT screening group, 356 deaths from lung cancer occurred (247 per 100 000 person-years) compared with 443 deaths (309 per 100 000 person-years) in the chest radiography group. This 20% decrease in lung cancer deaths is arguably the single greatest advance in decreasing lung cancer deaths ever reported, with the possible exception of smoking cessation (2).

The NLST also demonstrated an all-cause mortality reduction of 6.7%, although this predominantly resulted from reducing deaths from lung cancer. Lung cancer caused 60% of the 121 excess deaths in the chest radiography group (5).

Screening for lung cancer has been shown to be a "teachable moment" for smoking cessation. Quit rates of smokers participating in screening trials have exceeded the 4% background quit rate per year in smokers. The 1-year quit rate for smokers in CT screening trials varies from 12% to 20% (7-9). To date, studies have not shown an increased smoking rate in persons with negative screening results and indicate that participants are not using negative findings to rationalize continuing or resuming smoking.

The lay media and opponents of screening have emphasized the risk for cancer from medical imaging studies but have routinely failed to quantify real risk. The radiation dose associated with CT screening of the chest is generally less than 2 mSv, whereas the dose of standard non-contrast-enhanced chest CT is 7 mSv (10).

Investigations of the NLST have estimated that the risk for radiation exposure from LDCT screening in 55-year-old smokers is 1 to 3 deaths from lung cancer per 10 000 persons screened and 0.3 new cases of breast cancer per 10 000 women screened. The cumulative mortality reduction in the NLST was 30 cases of lung cancer per 10 000 persons screened. The benefit-risk ratio clearly demonstrates benefit (5, 11, 12). The American College of Radiology and the Radiological Society of North America have rated the additional lifetime risk for fatal cancer from LDCT as "very low" (1 per 10 000 to 1 per 100 000 persons) (www.radiologyinfo.org).

If results from the initial LDCT are negative, should this 63-year-old former smoker have additional yearly LDCT screening, and if so, for how long? The NLST participants underwent 3 yearly CTs. The 3 rounds of screening did not demonstrate a substantial decrease in the cases of lung cancer per year (270, 168, and 211, respectively). An additional 367 cases of lung cancer were detected in the CT group in the 5-year follow-up period after the initial 3 years of screening. The cumulative rate of new cases of and deaths from lung cancer did not decrease

during the 8 years of observation after participants were randomly assigned to the CT or chest radiography screening group (5). Therefore, the NLST data support yearly screening for at least 3 to 5 years; perhaps by that time, new information will be available to guide decisions on the length and frequency of screening.

We recommend LDCT screening for this high-risk patient on the basis of age and smoking history alone. In the future, we are likely to use a lung cancer risk prediction algorithm to better assess individual likelihood of developing lung cancer.

Persons at higher risk are more likely to benefit from screening. Current risk prediction models are approximately 70% accurate (13–15). A risk model recently developed on the basis of the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) accounts for the age, education level, body mass index, family history of lung cancer in first-degree relatives, history of chronic obstructive pulmonary disease, recent history of chest radiography, smoking status (current or former), pack-years smoked, and smoking duration (16, 17).

Each component contributed to the accuracy of the model. The risk model had good accuracy with an area under the receiver-operating characteristic curve for predicting lung cancer of 0.805. When the model was used in an external validation sample, the area under the receiver-operating characteristic curve was 0.784 for predicting the 9-year risk for lung cancer. This model does not work well for predicting risk in never-smokers.

Refinement of future models may include the presence or absence of genetic susceptibility variants for lung cancer (18–22). Extensive investigation is under way for serum biomarkers associated with lung cancer that are also likely to improve risk models (23–26). Measured pulmonary function data compared with a history of chronic obstructive pulmonary disease also will further augment risk prediction models (27–29).

In summary, we recommend LDCT screening for this patient at high risk for lung cancer to decrease her risk for death from this condition. Medicare and insurance companies presently do not reimburse patients for LDCT screening, but this decision is likely to change on the basis of the NLST results. The positive trial results strongly advocate that physicians discuss CT screening with patients who fit the risk profile of the NLST.

Screening should be done when desired by an informed patient only in a center with expertise in interpreting imaging studies, evaluating lung nodules, and diagnosing and treating lung cancer. We do not recommend that CT screening be done at the neighborhood shopping mall or medical facility without the appropriate expertise to pursue the results and maximize the benefits of this testing (30, 31).

Article and Author Information

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1870.

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Related Article

In the Balance:

Screening for Lung Cancer: It Works, but Does It *Really* Work?
Gerard A. Silvestri

Ann Intern Med September 5, 2011 E-364; published ahead of print September 5, 2011,

Abstract Full Text

Principles and practice of lung cancer: the official reference text of the IASLC By Harvey I. Pass, David P. Carbone, David H. Johnson

Lung cancer remains the leading cause of cancer related mortality in the United States, with 160,390 deaths projected for 2007.[1] Lung cancer accounts for the largest number of cancer deaths worldwide as well, with an estimated 1.3 million deaths in 2005.[2] These dismal numbers reflect persistent national and global challenges to lung cancer control.

Cancer control in general relies upon prevention, early detection, and treatment. Advances in the treatment of lung cancer, including minimally invasive surgery and targeted molecular therapies, have a limited impact on the burden of lung cancer because of the fact that most cancers continue to be diagnosed at an advanced stage. The presence of symptoms at the time of diagnosis is associated with a high probability of advanced disease. The failure of screening with chest radiography and sputum cytopathology to impact lung cancer mortality suggests that detection of asymptomatic disease is necessary but not sufficient to achieve this goal. A resurgence of interest in early detection has followed the widespread availability of chest computed tomography (CT). Although this technology has proven superior

the general population to ensure that the majority has the opportunity to receive appropriate preventive measures. Investigators have used such an approach to identify and recruit subjects into an ongoing chest CT screening trial,[7] and we have previously reviewed the criteria for a population-based approach to early lung cancer detection.[8] In contrast to breast or colon cancer, where the major defining risk factor is age, the profound risk associated with tobacco use allows for a powerful and economical additional selection factor to enrich for lung cancer risk. Other risk factors of lung cancer exist, however, and these collectively account for about 10% of lung cancer diagnoses. Which preventive measures should be applied to which specific subgroups of the population are questions that ongoing studies will help to address, but the answers will likely be dynamic as novel approaches are developed. This chapter will review contemporary lung cancer prevention strategies with a focus on their potential for implementation at a population level.

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Dis Mon. 2001 Jun;47(6):204-64.

The early diagnosis of lung cancer.

Petty TL.

Abstract

Lung cancer is the most common fatal malignancy in both men and women, both in the United States and elsewhere in the world. Today, **lung cancer** is most often diagnosed on the basis of symptoms of advanced disease or when chest x-rays are taken for a variety of purposes unrelated to **lung cancer** detection. Unfortunately, in the United States no **society** or governmental agency recommends screening, even for patients with high risks, such as smokers with airflow obstruction or people with occupational exposures, including asbestos. The origins of this negative attitude toward **lung cancer** screening are found in 3 studies sponsored by the National **Cancer** Institute in the mid-1970s and conducted at Johns Hopkins University School of Medicine, the Mayo Clinic, and the Memorial Sloan-Kettering Center. These studies concluded that early identification of **lung cancer** through chest x-rays and cytologic diagnosis of sputum did not alter disease-specific mortality. However, patients with earlier stage disease were found through screening, which resulted in a higher resectability rate and improved survival in the screening group compared with a control group of patients receiving ordinary care. Patients in the control group often received annual chest x-rays during the course of this study, which was the standard of care at the time. Thus no true nonscreening control group resulted. The patients at highest risk were not enrolled in this study. No specific amount of pack-years of smoking intensity was required. Only men were screened. The studies were inadequately powered to show an improvement in mortality rate of less than 50%. Ninety percent of **lung cancer** occurs in smokers. The prevalence of **lung cancer** is 4 to 6 times greater when smokers have airflow obstruction than with normal airflow, when all other background factors, including smoking history, occupational risk, and family history, are the same. Screening heavy smokers (ie, > or = 30 pack-years) with airflow obstruction (forced expiratory volume in one second < 70% of normal) will yield 2% or more patients with **lung cancer** (prevalence cases) and, over the course of 5 years, probably from 2% to 3% of patients with additional cancers, yielding an overall incidence of 5%. New technologies include low-dose helical computed tomographic scans for **small** peripheral adenocarcinomas that cannot yet be visualized by standard chest x-rays and cytologic diagnosis of sputum for central squamous **cell** lesions. These tests are complementary. A new health care initiative, the National **Lung** Health Education Program, recommends spirometric testing for all smokers 45 years or older, as well as for patients with symptoms of **lung cancer**. Screening for **lung cancer** in such patients will find many cancers at an early stage when they are amenable to cure. Today, we have the knowledge and the technology that could change the outcome of **lung cancer**.

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ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team

N Engl J Med 2011; 365:395-409 August 4, 2011

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Lung cancer is an aggressive and heterogeneous disease.[1,2] Advances in surgical, radiotherapeutic, and chemotherapeutic approaches have been made, but the long-term survival rate remains low.[3] After the Surgeon General's 1964 report on smoking and health, mortality from lung cancer among men peaked and then fell; among women, the peak occurred later and a slight decline has occurred more recently.[4] Even though the rate of heavy smoking continues to decline in the United States,[5] 94 million current or former smokers remain at elevated risk for the disease,[6] and lung cancer remains the leading cause of death from cancer in this country.[3] The prevalence of smoking is substantially higher in developing countries than in the United States, and the worldwide burden of lung cancer is projected to rise considerably during the coming years.[7]

Although effective mass screening of high-risk groups could potentially be of benefit, randomized trials of screening with the use of chest radiography with or without cytologic analysis of sputum specimens have shown no reduction in lung-cancer mortality.[8] Molecular markers in blood, sputum, and bronchial brushings have been studied but are currently unsuitable for clinical application.[8] Advances in multidetector computed tomography (CT), however, have made high-resolution volumetric imaging possible in a single breath hold at acceptable levels of radiation exposure,[9] allowing its use for certain lung-specific applications. Several observational studies have shown that low-dose helical CT of the lung detects more nodules and lung cancers, including early-stage cancers, than does chest radiography.[8] Therefore, the National Cancer Institute (NCI) funded the National Lung Screening Trial (NLST), a randomized trial, to determine whether screening with low-dose CT, as compared with chest radiography, would reduce mortality from lung cancer among high-risk persons. The NLST was initiated in 2002.[10] In October 2010, the available data showed that there was a significant reduction with low-dose CT screening in the rates of both death from lung cancer and death from any cause. We report here the findings of the NLST, including the performance characteristics of the screening techniques, the approaches used for and the results of diagnostic evaluation of positive screening results, the characteristics of the lung-cancer cases, and mortality. A comprehensive description of the design and operations of the trial, including the collection of the data and the acquisition variables of the screening techniques, has been published previously.[10]

METHODS

Trial Oversight

The NLST, a randomized trial of screening with the use of low-dose CT as compared with screening with the use of chest radiography, was a collaborative effort of the Lung Screening Study (LSS), administered by the NCI Division of Cancer Prevention, and the American College of Radiology Imaging Network (ACRIN), sponsored by the NCI Division of Cancer Treatment and Diagnosis, Cancer Imaging Program. Chest radiography was chosen as the screening method for the control group because radiographic screening was being compared with community care (care that a

participant usually receives) in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov number, NCT00002540).[11] The NLST was approved by the institutional review board at each of the 33 participating medical institutions. The study was conducted in accordance with the protocol; both the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org.

Participants

We enrolled participants from August 2002 through April 2004; screening took place from August 2002 through September 2007. Participants were followed for events that occurred through December 31, 2009 (Fig. 1 in the Supplementary Appendix, available at NEJM.org).

Eligible participants were between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years. Persons who had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year were excluded. A total of 53,454 persons were enrolled; 26,722 were randomly assigned to screening with low-dose CT and 26,732 to screening with chest radiography. Previously published articles describing the NLST[10,12] reported an enrollment of 53,456 participants (26,723 in the low-dose CT group and 26,733 in the radiography group). The number of enrolled persons is now reduced by 2 owing to the discovery of the duplicate randomization of 2 participants.

Participants were enrolled at 1 of the 10 LSS or 23 ACRIN centers. Before randomization, each participant provided written informed consent. After the participants underwent randomization, they completed a questionnaire that covered many topics, including demographic characteristics and smoking behavior. The ACRIN centers collected additional data for planned analyses of cost-effectiveness, quality of life, and smoking cessation. Participants at 15 ACRIN centers were also asked to provide serial blood, sputum, and urine specimens. Lung-cancer and other tissue specimens were obtained at both the ACRIN and LSS centers and were used to construct tissue microarrays. All biospecimens are available to researchers through a peer-review process.

Screening

Participants were invited to undergo three screenings (T0, T1, and T2) at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Participants in whom lung cancer was diagnosed were not offered subsequent screening tests. The number of lung-cancer screening tests that were performed outside the NLST was estimated through self-administered questionnaires that were mailed to a random subgroup of approximately 500 participants from LSS centers annually. Sample sizes were selected to yield a standard error of 0.025 for the estimate of the proportion of participants undergoing lung-cancer screening tests outside the NLST in each group. For participants from ACRIN centers, information on CT examinations or chest radiography performed outside the trial was obtained, but no data were gathered on whether the examinations were performed as screening tests.

All screening examinations were performed in accordance with a standard protocol, developed by medical physicists associated with the trial, that specified acceptable characteristics of the machine and acquisition variables.[10,13,14] All low-dose CT scans were acquired with the use of multidetector scanners with a minimum of four channels. The acquisition variables were chosen to reduce exposure to an average effective dose of 1.5 mSv. The average effective dose with diagnostic chest CT varies widely but is approximately 8 mSv.[10,13,14] Chest radiographs were obtained with the use of either screen-film radiography or digital equipment. All the machines used for screening met the technical standards of the American College of Radiology.[10] The use of new equipment was allowed after certification by medical physicists.

NLST radiologists and radiologic technologists were certified by appropriate agencies or boards and completed training in image acquisition; radiologists also completed training in image quality and standardized image interpretation. Images were interpreted first in isolation and then in comparison with available historical images and images from prior NLST screening examinations. The comparative interpretations were used to determine the outcome of the examination. Low-dose CT scans that revealed any noncalcified nodule measuring at least 4 mm in any diameter and radiographic images that revealed any noncalcified nodule or mass were classified as positive, "suspicious for" lung cancer. Other abnormalities such as adenopathy or effusion could be classified as a positive result as well. Abnormalities suggesting clinically significant conditions other than lung

cancer also were noted, as were minor abnormalities. At the third round of screening (T2), abnormalities suspicious for lung cancer that were stable across the three rounds could, according to the protocol, be classified as minor abnormalities rather than positive results.

Results and recommendations from the interpreting radiologist were reported in writing to the participant and his or her health care provider within 4 weeks after the examination. Since there was no standardized, scientifically validated approach to the evaluation of nodules, trial radiologists developed guidelines for diagnostic follow-up, but no specific evaluation approach was mandated.

Medical-Record Abstraction

Medical records documenting diagnostic evaluation procedures and any associated complications were obtained for participants who had positive screening tests and for participants in whom lung cancer was diagnosed. Pathology and tumor-staging reports and records of operative procedures and initial treatment were also obtained for participants with lung cancer. Pathology reports were obtained for other reported cancers to exclude the possibility that such tumors represented lung metastases. Histologic features of the lung cancer were coded according to the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3),[15] and the disease stage was determined according to the sixth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.[16] At ACRIN sites, additional medical records were also obtained for a number of substudies, including studies of health care utilization and cost-effectiveness.[16]

Vital Status

Participants completed a questionnaire regarding vital status either annually (LSS participants) or semiannually (ACRIN participants). The names and Social Security numbers of participants who were lost to follow-up were submitted to the National Death Index to ascertain probable vital status. Death certificates were obtained for participants who were known to have died. An end-point verification team determined whether the cause of death was lung cancer. Although a distinction was made between a death caused by lung cancer and a death that resulted from the diagnostic evaluation for or treatment of lung cancer, the deaths from the latter causes were counted as lung-cancer deaths in the primary end-point analysis. The members of the team were not aware of the group assignments (see Section 2 in the Supplementary Appendix).

Statistical Analysis

The primary analysis was a comparison of lung-cancer mortality between the two screening groups, according to the intention-to-screen principle. We estimated that the study would have 90% power to detect a 21% decrease in mortality from lung cancer in the low-dose CT group, as compared with the radiography group. Secondary analyses compared the rate of death from any cause and the incidence of lung cancer in the two groups.

Event rates were defined as the ratio of the number of events to the person-years at risk for the event. For the incidence of lung cancer, person-years were measured from the time of randomization to the date of diagnosis of lung cancer, death, or censoring of data (whichever came first); for the rates of death, person-years were measured from the time of randomization to the date of death or censoring of data (whichever came first). The latest date for the censoring of data on incidence of lung cancer and on death from any cause was December 31, 2009; the latest date for the censoring of data on death from lung cancer for the purpose of the primary end-point analysis was January 15, 2009. The earlier censoring date for death from lung cancer was established to allow adequate time for the review process for deaths to be performed to the same, thorough extent in each group. We calculated the confidence intervals for incidence ratios assuming a Poisson distribution for the number of events and a normal distribution of the logarithm of the ratio, using asymptotic methods. We calculated the confidence intervals for mortality ratios with the weighted method that was used to monitor the primary end point of the trial,[17] which allows for a varying rate ratio and is adjusted for the design. The number needed to screen to prevent one death from lung cancer was estimated as the reciprocal of the reduction in the absolute risk of death from lung cancer in one group as compared with the other, among participants who had at least one screening test. The analyses were performed with the use of SAS/STAT[18] and R[19] statistical packages.

Interim analyses were performed to monitor the primary end point for efficacy and futility. The analyses involved the use of a weighted log-rank statistic, with weights increasing linearly from no weight at randomization to full weight at 4 years and thereafter. Efficacy and futility boundaries were built on the Lan–DeMets approach with an O'Brien–Fleming spending function.[20] Interim analyses

were performed annually from 2006 through 2009 and semiannually in 2010.

An independent data and safety monitoring board met every 6 months and reviewed the accumulating data. On October 20, 2010, the board determined that a definitive result had been reached for the primary end point of the trial and recommended that the results be reported.[21] The board's decision took into consideration that the efficacy boundary for the primary end point had been crossed and that there was no evidence of unforeseen screening effects that warranted acting contrary to the trial's prespecified monitoring plan. The NCI director accepted the recommendation of the data and safety monitoring board, and the trial results were announced on November 4, 2010.

RESULTS

Characteristics of the Participants

The demographic characteristics and smoking history of the participants were virtually identical in the two groups (Table 1). As compared with respondents to a 2002–2004 U.S. Census survey of tobacco use[22] who met the NLST eligibility criteria for age and smoking history, NLST participants were younger, had a higher level of education, and were more likely to be former smokers.[12] As of December 31, 2009, vital status was known for 97% of the participants in the low-dose CT group and 96% of those in the radiography group. The median duration of follow-up was 6.5 years, with a maximum duration of 7.4 years in each group.

TABLE 1

Selected Baseline Characteristics of the Study Participants.

Adherence to Screening

The rate of adherence to the screening protocol across the three rounds was high: 95% in the low-dose CT group and 93% in the radiography group. Among LSS participants in the radiography group, the average annual rate of helical CT screening outside the NLST during the screening phase of the trial was 4.3%, which was well below the 10.0% rate estimated in the trial power calculations.

Results of Screening

In all three rounds, there was a substantially higher rate of positive screening tests in the low-dose CT group than in the radiography group (T0, 27.3% vs. 9.2%; T1, 27.9% vs. 6.2%; and T2, 16.8% vs. 5.0%) (Table 2). The rate of positive tests in both groups was noticeably lower at T2 than at T0 or T1 because the NLST protocol allowed tests showing abnormalities at T2 that were suspicious for cancer but were stable across all three rounds to be categorized as negative with minor abnormalities. During the screening phase of the trial, 39.1% of the participants in the low-dose CT group and 16.0% of those in the radiography group had at least one positive screening result. The percentage of all screening tests that identified a clinically significant abnormality other than an abnormality suspicious for lung cancer was more than three times as high in the low-dose CT group as in the radiography group (7.5% vs. 2.1%).

TABLE 2

Results of Three Rounds of Screening.

Follow-up of Positive Results

More than 90% of the positive screening tests in the first round of screening (T0) led to a diagnostic evaluation (Table 3). Lower rates of follow-up were seen at later rounds. The diagnostic evaluation most often consisted of further imaging, and invasive procedures were performed infrequently. Across the three rounds, 96.4% of the positive results in the low-dose CT group and 94.5% of those in the radiography group were false positive results. These percentages varied little by round. Of the total number of low-dose CT screening tests in the three rounds, 24.2% were classified as positive and 23.3% had false positive results; of the total number of radiographic screening tests in the three rounds, 6.9% were classified as positive and 6.5% had false positive results.

TABLE 3

Diagnostic Follow-up of Positive Screening Results in the Three Screening Rounds.

Adverse Events

Adverse events from the actual screening examinations were few and minor. The rates of complications after a diagnostic evaluation procedure for a positive screening test (listed by category in Table 1 in the Supplementary Appendix) were low; the rate of at least one complication was 1.4% in the low-dose CT group and 1.6% in the radiography group (Table 4). A total of 0.06% of the positive screening tests in the low-dose CT group that did not result in a diagnosis of lung cancer and 11.2% of those that did result in a diagnosis of

TABLE 4

lung cancer were associated with a major complication after an invasive procedure; the corresponding percentages in the radiography group were 0.02% and 8.2%. The frequency of major complications varied according to the type of invasive procedure. A total of 16 participants in the low-dose CT group (10 of whom had lung cancer) and 10 in the radiography group (all of whom had lung cancer) died within 60 days after an invasive diagnostic procedure. Although it is not known whether the complications from the diagnostic procedure caused the deaths, the low frequency of death within 60 days after the procedure suggests that death as a result of the diagnostic evaluation of positive screening tests is a rare occurrence.

Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.

Incidence, Characteristics, and Treatment of Lung Cancers

A total of 1060 lung cancers (645 per 100,000 person-years) were diagnosed in the low-dose CT group, as compared with 941 (572 per 100,000 person-years) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). In the low-dose CT group, 649 cancers were diagnosed after a positive screening test, 44 after a negative screening test, and 367 among participants who either missed the screening or received the diagnosis after their trial screening phase was over (Table 5). In the radiography group, 279 cancers were diagnosed after a positive screening test, 137 after a negative screening test, and 525 among participants who either missed the screening or received the diagnosis after their trial screening phase was over. Figure 1A shows the cumulative number of lung cancers through December 31, 2009, according to the screening group. Detailed calculations of sensitivity, specificity, positive predictive value, and negative predictive value are not reported here.

TABLE 5

In each group, the percentage of stage IA and stage IB lung cancers was highest among cancers that were diagnosed after a positive screening test (Table 5). Fewer stage IV cancers were seen in the low-dose CT group than in the radiography group at the second and third screening rounds (Table 2 in the Supplementary Appendix). Low-dose CT screening identified a preponderance of adenocarcinomas, including bronchioloalveolar carcinomas. Although the use of the term bronchioloalveolar carcinoma is no longer recommended,[23] while the NLST was ongoing, the term was used to denote in situ, minimally invasive, or invasive adenocarcinoma, lepidic predominant (i.e., neoplastic cell growth restricted to preexisting alveolar structure). In both groups, many adenocarcinomas and squamous-cell carcinomas were detected at either stage I or stage II, although the stage distribution was more favorable in the low-dose CT group than in the radiography group (Table 6). Small-cell lung cancers were, in general, not detected at early stages by either low-dose CT or radiography. A total of 92.5% of stage IA and stage IB cancers in the low-dose CT group and 87.5% of those in the radiography group were treated with surgery alone or surgery combined with chemotherapy, radiation therapy, or both (Table 3 in the Supplementary Appendix).

Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening.

FIGURE 1

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.

TABLE 6

Lung-Cancer–Specific Mortality

After the accrual of 144,103 person-years in the low-dose CT group and 143,368 person-years in the radiography group, 356 and 443 deaths from lung cancer in the two groups, respectively, had occurred, corresponding to rates of death from lung cancer of 247 and 309 deaths per 100,000 person-years, respectively, and a relative reduction in the rate of death from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). Figure 1B shows the cumulative number of deaths from lung cancer in the two screening groups through January 15, 2009. When only participants who underwent at least one screening test were included, there were 346 deaths from lung cancer among 26,455 participants in the low-dose CT group and 425 deaths among 26,232 participants in the radiography group. The number needed to screen with low-dose CT to prevent one death from lung cancer was 320.

Histologic Type of Lung Cancers in the Two Screening Groups, According to Tumor Stage.

Overall Mortality

There were 1877 deaths in the low-dose CT group, as compared with 2000 deaths in the radiography group, representing a significant reduction with low-dose CT screening of 6.7% (95% CI,

1.2 to 13.6) in the rate of death from any cause (P=0.02). We were unable to obtain the death certificates for two of the participants in the radiography group who died, but the occurrence of death was confirmed through a review by the end-point verification team. Although lung cancer accounted for 24.1% of all the deaths in the trial, 60.3% of the excess deaths in the radiography group were due to lung cancer (Table 7). When deaths from lung cancer were excluded from the comparison, the reduction in overall mortality with the use of low-dose CT dropped to 3.2% and was not significant (P=0.28).

TABLE 7

Cause of Death on the Death Certificate, According to Screening Group.

DISCUSSION

In the NLST, a 20.0% decrease in mortality from lung cancer was observed in the low-dose CT group as compared with the radiography group. The rate of positive results was higher with low-dose CT screening than with radiographic screening by a factor of more than 3, and low-dose CT screening was associated with a high rate of false positive results; however, the vast majority of false positive results were probably due to the presence of benign intrapulmonary lymph nodes or noncalcified granulomas, as confirmed noninvasively by the stability of the findings on follow-up CT scans. Complications from invasive diagnostic evaluation procedures were uncommon, with death or severe complications occurring only rarely, particularly among participants who did not have lung cancer. The decrease in the rate of death from any cause with the use of low-dose CT screening suggests that such screening is not, on the whole, deleterious.

A high rate of adherence to the screening, low rates of lung-cancer screening outside the NLST, and thorough ascertainment of lung cancers and deaths contributed to the success of the NLST. Moreover, because there was no mandated diagnostic evaluation algorithm, the follow-up of positive screening tests reflected the practice patterns at the participating medical centers. A multidisciplinary team ensured that all aspects of the NLST were conducted rigorously.

There are several limitations of the NLST. First, as is possible in any clinical study, the findings may be affected by the "healthy-volunteer" effect, which can bias results such that they are more favorable than those that will be observed when the intervention is implemented in the community.[24] The role of this bias in our results cannot be ascertained at this time. Second, the scanners that are currently used are technologically more advanced than those that were used in the trial. This difference may mean that screening with today's scanners will result in a larger reduction in the rate of death from lung cancer than was observed in the NLST; however, the ability to detect more abnormalities may result only in higher rates of false positive results.[25] Third, the NLST was conducted at a variety of medical institutions, many of which are recognized for their expertise in radiology and in the diagnosis and treatment of cancer. It is possible that community facilities will be less prepared to undertake screening programs and the medical care that must be associated with them. For example, one of the most important factors determining the success of screening will be the mortality associated with surgical resection, which was much lower in the NLST than has been reported previously in the general U.S. population (1% vs. 4%).[26] Finally, the reduction in the rate of death from lung cancer associated with an ongoing low-dose CT screening program was not estimated in the NLST and may be larger than the 20% reduction observed with only three rounds of screening.

Radiographic screening rather than community care (care that a participant usually receives) was chosen as the comparator in the NLST because radiographic screening was being evaluated in the PLCO trial at the time the NLST was designed.[11] The designers of the NLST reasoned that if the PLCO trial were to show a reduction in lung-cancer mortality with radiographic screening, a trial of low-dose CT screening in which a community-care group was the control would be of less value, since the standard of care would have become screening with chest radiography. Nevertheless, the choice of radiography precludes a direct comparison of low-dose CT with community care. Analysis of the subgroup of PLCO participants who met the NLST criteria for age and smoking history indicated that radiography, as compared with community care, does not reduce mortality from lung cancer.[27] Therefore, a similar reduction in lung-cancer mortality would probably have been observed in the NLST if community care had been chosen instead for the control group.

In addition to the high rate of false positive results, two other potentially harmful effects of low-dose CT screening must be mentioned. Overdiagnosis, a major source of controversy surrounding low-dose CT lung-cancer screening, results from the detection of cancers that never would have become symptomatic.[28] Although additional follow-up would be necessary to measure the magnitude of

overdiagnosis in the NLST, a comparison of the number of cancers diagnosed in the two trial groups suggests that the magnitude of overdiagnosis with low-dose CT as compared with radiographic screening is not large. The other harmful effect, the association of low-dose CT with the development of radiation-induced cancers, could not be measured directly, is a long-term phenomenon, and must be assessed in future analyses.[29]

A number of smaller, randomized trials of low-dose CT screening are under way in Europe.[30-36] Because none of these trials have sufficient statistical power to detect a reduction in lung-cancer mortality of the magnitude seen in the NLST, it is expected that meta-analyses of the findings from these trials will be performed. The European studies are gathering types of data that were not collected by the NLST and will be able to address additional questions about low-dose CT screening, including the best strategies for the management of nodules observed with screening.[37]

The observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions. Will populations with risk profiles that are different from those of the NLST participants benefit? Are less frequent screening regimens equally effective? For how long should screening continue? Would the use of different criteria for a positive screening result, such as a larger nodule diameter, still result in a benefit? It is unlikely that large, definitive, randomized trials will be undertaken to answer these questions, but modeling and microsimulation can be used to address them. Although some agencies and organizations are contemplating the establishment of lung-cancer screening recommendations on the basis of the findings of the NLST, the current NLST data alone are, in our opinion, insufficient to fully inform such important decisions.

Before public policy recommendations are crafted, the cost-effectiveness of low-dose CT screening must be rigorously analyzed. The reduction in lung-cancer mortality must be weighed against the harms from positive screening results and overdiagnosis, as well as the costs. The cost component of low-dose CT screening includes not only the screening examination itself but also the diagnostic follow-up and treatment. The benefits, harms, and costs of screening will all depend on the way in which low-dose CT screening is implemented, specifically in regard to the eligibility criteria, screening frequency, interpretation threshold, diagnostic follow-up, and treatment. For example, although there are currently only about 7 million persons in the United States who would meet the eligibility criteria for the NLST, there are 94 million current or former smokers[6] and many more with secondhand exposure to smoke or other risk factors. The cost-effectiveness of low-dose CT screening must also be considered in the context of competing interventions, particularly smoking cessation. NLST investigators are currently analyzing the quality-of-life effects, costs, and cost-effectiveness of screening in the NLST and are planning collaborations with the Cancer Intervention and Surveillance Modeling Network to investigate the potential effect of low-dose CT screening in a wide range of scenarios.

Other strategies for early detection of lung cancer — in particular, molecular markers in blood, sputum, and urine, which can be studied in specimens that were obtained as part of ACRIN's NLST activities and are available to the research community — may one day help select persons who are best suited for low-dose CT screening or identify persons with positive low-dose CT screening tests who should undergo more rigorous diagnostic evaluation.

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The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article.

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SOURCE INFORMATION

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A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

Appendix

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Early Lung Cancer Action Project: A Summary of the Findings on Baseline Screening

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ABSTRACT

Purpose. **The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low radiation dose computed tomography (low-dose CT) in persons at high-risk for lung cancer.**

Methods. **Since starting in 1993, the ELCAP has enrolled 1,000 asymptomatic persons, 60 years of age or older, with at least 10 pack-years (1 pack per day for 10 years, or 2 packs per day for 5 years) of cigarette smoking, no prior cancer, and medically fit to undergo thoracic surgery. After a structured interview and informed consent, baseline chest radiographs and low-dose CT were obtained on each subject. The diagnostic work-up of screen-detected noncalcified pulmonary nodules (NCN) was guided by ELCAP recommendations which included short-term high-resolution CT follow-up for the smallest nodules.**

Baseline Results. **On low-dose CT at baseline compared to chest radiography, NCN were detected three times as commonly (23% versus 7%), malignancies four times as commonly (2.7% versus 0.7%), and stage I malignancies six times as commonly (2.3% versus 0.4%). Of the 27 CT-detected cancers, 96% (26/27) were resectable; 85% (23/27) were stage I, and 83% (19 of the 23 stage I) were not seen on chest radiography. Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCN; 27 had a malignant and one a benign NCN. Another three individuals underwent biopsy outside of the ELCAP recommendations; all had benign NCNs. No one had thoracotomy for a benign nodule.**

Conclusion. **Baseline CT screening for lung cancer provides for detecting the disease at earlier and presumably more commonly curable stages in a cost-effective manner.** ***The Oncologist*** *2001;6:147-152*

INTRODUCTION

In the United States, the cure rate of lung cancer is a dismal 10%, and the 5-year survival rate is only slightly higher than the cure rate. In stage I lung cancer, by contrast, the 5-year survival rate upon resection is as high as 70%; but if left unresected, that rate is again of the order of a mere 10% [1, 2]. While these rates imply that the cure rate of lung cancer can be substantially enhanced by screening and its associated earlier intervention, results of randomized trials have been interpreted as indicating that this is not the case [3].

This paradox points to the possibility that the negative results of the randomized trials were a consequence of flaws in their design, execution and/or analysis. To quantify the full effect of screening in a randomized trial, the experimental regimen of screening and early intervention is to be contrasted with no screening; close adherence to those regimens is to be achieved in the implementation of the protocol; the analysis is to focus on the ratio of the respective rates of death from lung cancer in the relevant subsegment of the total period of follow-up in which the full effect of screening and early intervention can be expected to prevail [4]. These requirements were not met in the one and only randomized trial that contributed to the various authoritative recommendations against roentgenographic (CXR) screening for lung cancer [3]. In that trial [5], the experimental regimen of CXR screening every 4 months was contrasted with the routine Mayo Clinic recommendation, which at that time

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was to perform annual screening for high-risk persons; the rates of adherence to these two regimens were about 75% and 50%, respectively [6], and the analysis never focused on the relevant subsegment of follow-up. Moreover, the experimental regimen of quarterly screening in the Mayo study was so weak that it led to the detection of resectable malignancy in only 29% of the cases of lung cancer [5].

Our review of the previous studies of lung cancer screening led us to the conclusion that resection of screen-detected early-stage lung cancer commonly is curative, and that this has already been demonstrated beyond question [1, 2, 4]. Inspired by the enhanced potential of computerized tomography (CT) in screening for lung cancer, we developed the study design to assess the usefulness of annual CT screening for lung cancer in 1992 [7] and started baseline screening in 1993. The principal objective of the Early Lung Cancer Action Project (ELCAP) was to assess the extent to which the screening shifts the distribution of diagnosed cancers toward smaller sizes and thus toward earlier stages. We refer to this as the diagnostic mission. An added major objective, the interventive mission, was to quantify the curability of lung cancer as it depends on tumor size and disease stage at diagnosis. Both of these objectives may be taken to refer to all lung cancers diagnosed under screening, irrespective of whether the diagnosis actually is prompted by the screening or interim symptoms. The diagnostic and interventive components jointly determine the overall rate of curability for cases detected under screening. To us, therefore, the real question remaining to be answered by the ELCAP is whether the diagnostic shift towards smaller and earlier-stage lung cancers and the resultant gain in curability are large enough to provide for cost-effective screening, given suitable specifications of both the screening regimen and its recipients.

The results of baseline screening have been published in *The Lancet* [8]. Here we present a summary review of these findings.

Enrollment

Enrollment into the ELCAP was confined to a cohort of 1,000 persons (522 at Cornell University Medical College and 478 at New York University Medical Center), 60 years of age or older with a history of at least 10 pack-years of cigarette smoking, no history of cancer (other than nonmelanotic skin cancer), and fit to undergo thoracic surgery. Fit to undergo thoracic surgery means that the candidate does not require oxygen and can hold his/her breath for up to 20 seconds while obtaining the CT scan.

Baseline screening, initiated in 1993, was completed in 1998. Of the 1,000 persons at high risk for lung cancer that were enrolled, 46% were females, 54% males; 91% were white, 5% African-American, and 2% Hispanic (2% other). Median age at admission was 67 years, the median number of pack-years of smoking was 45, and the history of asbestos exposure was positive in 14%.

The Screening Test

The screening test was defined in terms of the equipment, how the images are viewed, and by whom they are read. Finally, the definition of the test also includes the results, both positive and negative for the test.

At baseline, a posterior-anterior and lateral standard CXR was obtained using Insight (Kodak; Rochester, NY) film. At baseline, low-dose CT (LDCT) images were obtained using a HighSpeed Advantage scanner (GE; Milwaukee, WI) at 140 kVp, 40 mA, 2:1 pitch with a collimation (slice thickness) of 10 mm. The images, covering the entire lung region, were acquired in a single breath-hold at end-inspiration following hyperventilation, and they were reconstructed with overlapping 5-mm intervals.

While images were initially read on film, 12 images per film, the readings were done on monitors once they became available with the images being viewed one at a time using maximum magnification. Two dedicated chest radiologists, each one blinded to the reading of the other, read the images. The respective findings with regard to the presence and number of nodules were separately recorded and then discussed, and the consensus findings were documented for the study. When the two readers could not reach a consensus, the case was presented to a third expert reader, and the adjudicated reading became the final one.

A positive test result at baseline was defined as the presence of one to six noncalcified nodules (NCN). If no NCN were identified, the result was classified as negative. Instances of more than six NCN, diffuse bronchiectasis and/or ground-glass opacities were classified as diffuse disease.

For all instances of positive results, defined characteristics of the relevant nodules were recorded: size (length and width), location (lobe), and calcification (benign, other). A nodule was classified as noncalcified if it did not show a "benign pattern of calcification" [9]. The following definitions were used: size was defined as the average of length and width.

Other measures were also obtained, but not analyzed for purposes of this paper. They were: distance from the costal pleura, shape (round, non-round), edge (smooth, non-smooth), and texture (pure ground-glass, other); location as peripheral if any part of the nodule was within 2 cm of the costal margin, otherwise central; shape as round if the nodule's width-to-length ratio was greater than two-thirds, otherwise non-round; and texture as pure ground-glass if the nodule did not obscure the lung parenchyma and had no solid component, otherwise "other."

Post-Test Work-Up

Recommendations were made for the work-up of positive results of baseline and annual repeat screening. However, it was not a requirement for the validity of the ELCAP that these recommendations be followed, as long as the final diagnosis became firmly established. Thus, the decision as to how to proceed was left to the referring physician, and the actual work-up was recorded. If malignancy was diagnosed and resectable, lobar resection was coupled with complete mediastinal lymph node dissection and labeling of all lymph node stations, and the deflated lung was palpated for any additional nodules. All cytologic and histologic findings from any biopsy or surgical procedure were documented.

For the instances in which NCN were detected on the baseline LDCT, additional deployment of a standard-dose, diagnostic CT scan of the chest with high-resolution imaging (HRCT) of the nodule(s) was recommended for management purposes. For all nodules detected on HRCT, the same nodule characteristics previously specified were documented. If the HRCT demonstrated benign calcifications not identified in the LDCT, both in terms of extent and distribution, in a nodule with smooth edges whose size was less than 20 mm, the nodule was considered to be benign.

If those criteria were not met by all of the NCN detected in the subject, the ELCAP protocol recommended further work-up according to the size of the largest nodule:

A) For NCN 5 mm or less in size (average of length and width), follow-up by HRCT 3 months later, and given no growth, at 6, 12, and 24 months. If no growth was noted over 2 years, the nodule was considered to be benign.

B) For NCN 6-10 mm in size, assessment on a case-by-case basis of the possibility of obtaining a biopsy using either percutaneous transthoracic CT-guided fine-needle aspiration or video-assisted thoracoscopic biopsy procedures. For instances of no biopsy, follow-up for growth, as described above.

C) For NCN 11 mm or more in size, biopsy according to current standards of care, by fine needle aspiration, video-assisted thoracoscopy, bronchoscopy, or a combination of these.

Results

Chest radiography found 68 subjects with one to six NCN, among whom fewer than half (33) actually had a nodule on LDCT. The remaining 35 subjects had false-positive chest radiography-detected nodules as they were not real but merely apparent ones caused by a confluence of shadows. LDCT identified 233 subjects as having one to six NCN; in only 33 of these subjects was the nodule(s) also apparent on chest radiography.

Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCN; 27 had a malignant nodule and one had a benign one. Another three individuals underwent biopsy outside of the ELCAP recommendations; all had benign nodules. No one had thoracotomy for a benign nodule. The diagnostic work-up was based on the size and appearance of the nodules. Those of suspicious appearance with non-smooth edges, for the most part NCN 10 mm or larger in size, were identifiable on the LDCT or baseline HRCT, and immediate biopsy was confidently recommended for these. In smaller nodules, documented growth was recommended as a prerequisite for biopsy, based on follow-up HRCT when compared with baseline HRCT. Additionally, given the concern about overdiagnosis, that is, the detection of malignancies whose growth is so slow that death is caused by diseases other than lung cancer, we determined growth per se, as well as the rate of growth in the smaller malignancies, using careful HRCT measurements [10, 11]. The growth rate of the smaller malignancies was all within the known range for malignant tumors of the lung [12-14] (Fig. 1).

Among the 233 subjects with one to six NCN found on LDCT, 27 (12%) had a nodule-associated malignancy. Among the 68 subjects with one to six NCN found on chest radiography, only seven (10%) were found to have a malignancy; therefore, 20 (74%) of the CT-detected malignancies were not seen on chest radiography. On the other hand, all of the chest radiographic-detected malignancies were detected on LDCT. Of these 27 CT-detected malignancies, 85% (23) were stage I and 83% (19/23) of them were missed on chest radiographs. The sizes of the CT-detected malignancies were 2-5 mm for one, 6-10 mm for 14, 11-20 mm for eight, and greater than 20 mm for four.

Pathologically, one of the nodule-associated malignancies was classified as an atypical carcinoid, one as a squamous-cell carcinoma, three as mixed squamous-adenocarcinoma, three as bronchioloalveolar carcinoma, two malignancies (in one lobe) were found in one person, one of them classified as adeno-squamous carcinoma and the other as bronchioloalveolar carcinoma, and the remaining 18 were classified as adenocarcinoma.

Discussion

In summary, on baseline screening, NCN were detected three times as commonly (23% versus 7%), malignancies four times as commonly (2.7% versus 0.7%), and stage I malignancies six times as commonly (2.3% versus 0.4%). Careful assessment of growth, and more particularly, growth rates prior to any invasive procedures permitted identification of

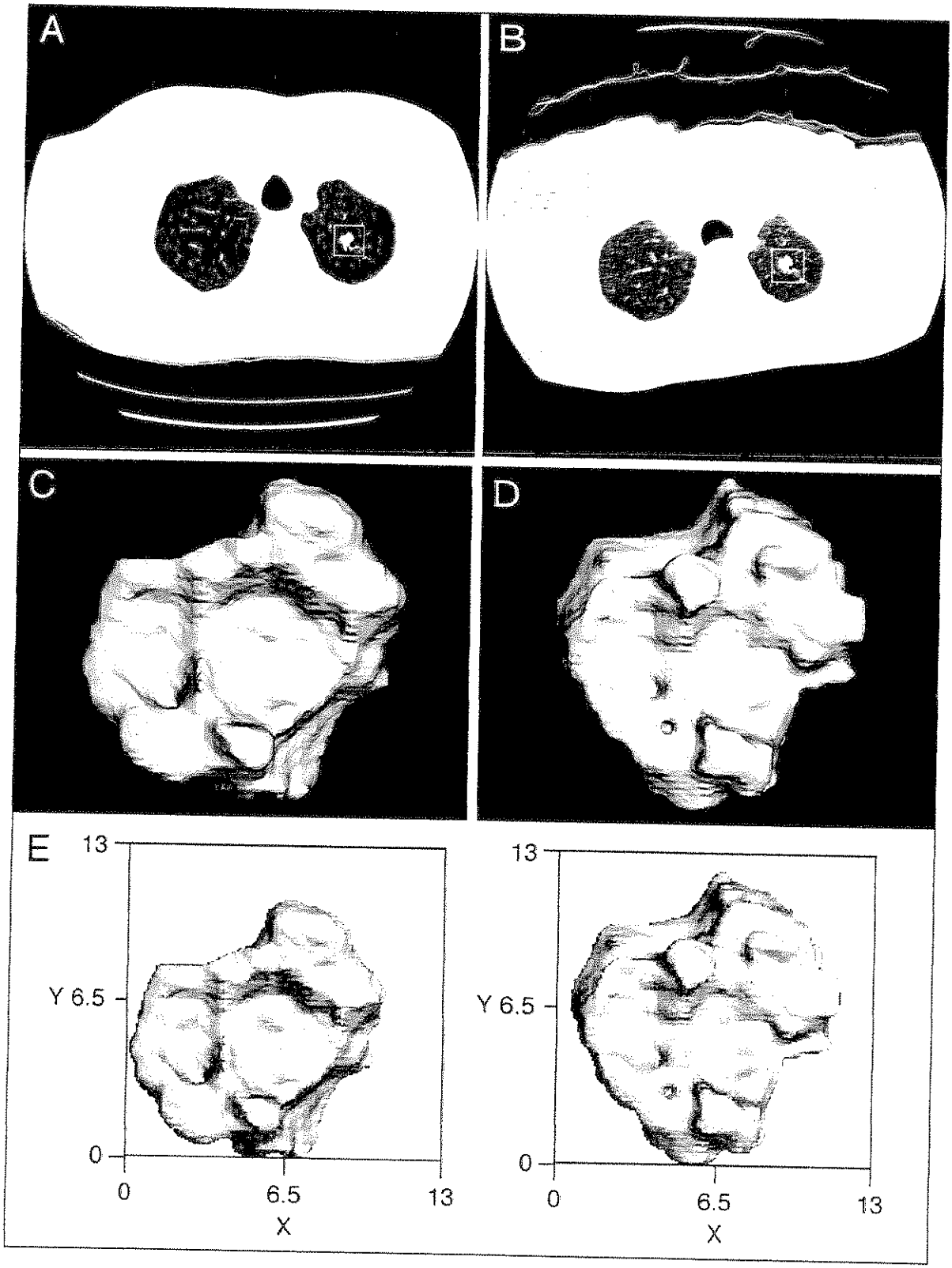

Figure 1. HRCT obtained at time of initial detection of the left upper lobe NCN (A). *Repeat HRCT of the nodule obtained 20 days later (B). Three-dimensional reconstruction of the nodule at time of the initial CT (C) and three months later (D). Initial volume was 240 mm³ and on repeat CT, it was 314 mm³, a marked change of 31% when compared with the normal variation of 2%. The resulting doubling time was 51 days. The growth is best documented by viewing the nodule at both times on the same grid (E).*

the malignancies without anyone undergoing lobectomy for benign disease. We thus showed that baseline screening markedly enhanced the detection of small NCN and confirmed our expectation that, relative to traditional chest radiography, CT-based screening markedly enhances the detection of lung cancer at earlier and more curable stages relative to what is known to prevail in the absence of screening.

The diagnostic distribution was markedly shifted toward earlier stages and smaller sizes as we found 22 (80%) of the 27 nodule-associated malignancies to be of stage IA. This is in marked contrast to 7% of all those diagnosed with lung cancer as seen by the cases in the End Results and Surveillence Registry, a national registry sponsored by the National Cancer Institute. The mobile CT screening study by *Sone et al.* [15] also showed that LDCT markedly enhanced the detection of malignancies; 10 times as many were detected on CT as on CXR. Their overall malignancy rates were lower than ours, predominately due to the fact that they screened individuals from the general population, not high-risk people.

Translation of this diagnostic distribution to its corresponding overall rate of curability under screening requires information on the stage- and size-specific rates of curability. The 5-year survival rate of stage IA non-small-cell malignancies of size less than 20 mm, detected by CT, has been reported to exceed 90% [16, 17] suggesting a curability rate of these malignancies in excess of 80%. Curability of the screen-detected small but later-stage non-small cell and limited stage small-cell malignancies is yet to be quantified.

As these results and inferences mainly pertain to very small lesions, the question of overestimation on the grounds of potential "overdiagnosis" is prone to arise. Convincing evidence against overdiagnosis for lung cancer detected by traditional radiography was given by *Flehinger et al.* [1] and *Sobue et al.* [2]. But as the CT-detected lesions are distinctly smaller, the concern remains legitimate; and indeed, it was a concern of ours. In an effort to avoid the problem, we naturally have been very careful with the pathologic (cytologic and histologic) criteria for rule-in diagnosis of malignancy; but beyond this, we had interim growth in all cases, and this was supplemented by documentation of further growth before biopsy. As it turned out, all cytologic diagnoses of malignancy (rule-in) were confirmed by the histologic specimens from surgery; and further, all of the calculated rates of growth were in accord with those of definite cancers of the lung [12-14]. Ultimately, once there are sufficiently many cases that, for various reasons, were not resected within the ELCAP and its "sister" projects, it will be possible to empirically estimate the proportions overdiagnosed (specific to size), if any.

Following the ELCAP recommendations, only a single biopsy of a benign NCN, 18 mm in size, was performed. Another three subjects underwent biopsy despite the ELCAP recommendations for follow-up HRCT as no growth could be documented, and all of these had a benign nodule. No subject had lobectomy for a benign NCN. Thus, our recommendations, intended to prevent overuse of invasive procedures and their attendant morbidity and cost, turned out to be quite successful.

For evaluation of annual CT screening for lung cancer, our baseline results must be supplemented by the results of annual repeat LDCT screenings in the subjects in whom no malignant nodules were detected on baseline screening. This will provide data on the frequency of finding new nodules, the frequency with which these are malignant, and, eventually their cure rate. We expect to find few instances of new nodules with a rate of about five malignancies per 1,000 subjects on each 1-year repeat CT screening, with the majority of these in nodules whose size is 10 mm or less. We are pursuing this repeat screening in all subjects whose baseline screening was negative or positive with a diagnosis of benign nodules.

We plan to incorporate smoking cessation programs into our future screening program, as we found that review of the LDCT with those subjects who were still smoking provided considerable motivation for smoking cessation [18]. Additional considerations for future investigations, in conjunction with future CT screenings, include chemoprevention and perhaps even chemotherapy, possibly administered by inhalation rather than oral or intraveneous methods.

Even if a given regimen of CT screening for lung cancer, perhaps a variant of the one addressed in the ELCAP, does serve to raise the overall rate of curability for lung cancer among the screenees, this does not in and of itself justify the use of that regimen of screening. It needs to be applied on indications such that the prospect of early diagnosis and its associated curability translate to a gain in life expectancy sufficient to justify the cost of the "screening," that is, of the screening test together with the result-contingent definitive diagnostics. The issues here are somewhat complex, but it is evident that, with suitable specifications of both the screening and its recipients, the cost of life-year saved can be as low as $10,000 or even lower [19]. Such a cost per life-year saved is well below that for existing programs of screening for breast cancer [20] or cervical cancer [21] and well below the benchmark of $50,000 used in the U.S.

The particulars of potential screening for lung cancer constitute, at present, an actively evolving topic in respect to all of its principal elements—the screening test(s), the diagnostic work-up of screening positives, intervention on early cancer, and identification of suitable candidates for

screening. The accruing evidence from the ELCAP and others [22], while still insufficient, is continuing to heighten the prospects for cost-effective screening for the cancer that is now the main cause of cancer deaths in both genders.

ACKNOWLEDGMENT

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Early Lung Cancer Action Project: A Summary of the Findings on Baseline Screening

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Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

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IN 1993, THE EARLY LUNG CANCER ACTION Project (ELCAP) initiated a study of the early diagnosis of lung cancer in cigarette smokers with the use of annual screening with spiral computed tomography (CT).[1,2] The principal finding was that more than 80% of persons given a diagnosis of lung cancer as a result of annual CT screening had clinical stage I cancer.[3] This result has been confirmed by others[4] who have adopted the updated protocol.[5,6] The question remains, however, whether early intervention in such patients is sufficiently effective to justify screening large asymptomatic populations who are at risk for lung cancer.[7,8] We report the results of all patients in the study with stage I lung cancer detected with the use of spiral CT screening, including those who underwent surgical resection.

METHODS

Screening was defined according to the International ELCAP (I-ELCAP) protocol[6] so that data from participating institutions could be pooled. Each institution was required to document the initiation of screening in each participant and all subsequent screenings of that participant for as long as the screening continued, transmit the data and images to the coordinating center at Weill Medical College of Cornell University by means of the study's Web-based management system for CT screening for lung cancer,[9] submit pathological specimens to the coordinating center, and follow quality-assurance procedures specified by the protocol. All participants gave written informed consent, and the institutional review board at each participating institution approved the protocols (Fig. 1).

The protocol specified a common regimen of screening but allowed each participating institution to specify its criteria for enrollment. The regimen included the technical variables for the initial low-dose spiral CT scan, which were the same for the baseline and annual screenings. However, the definition of a positive result on the initial CT scan and the diagnostic workup leading to a diagnosis of lung cancer were different for the baseline screening and annual screening.

For baseline screening, a positive result on the initial low-dose CT scan was defined as the identification of at least one solid or partly solid noncalcified pulmonary nodule 5 mm or more in diameter, at least one nonsolid noncalcified pulmonary nodule 8 mm or more in diameter, or a solid endobronchial nodule.[10] If none of the noncalcified nodules identified met the study criteria for a positive result or if the test was negative, CT was repeated 12 months later. The diameter of the nodule was defined as the average of the length and width of the cross-sectional area of the largest nodule in the CT images. The consistency of the nodule was defined as solid if the nodule obscured the entire lung parenchyma, partly solid if it obscured part of the lung parenchyma, and nonsolid if it obscured none of the parenchyma.[11] If the result was positive, the type of workup depended on the diameter of the largest nodule. For nodules 5 to 14 mm in diameter, the preferred option was to perform another CT at 3 months; if the images showed growth of the nodule,[12] then biopsy, ideally by fine-needle aspiration, was to be performed, whereas if there was no growth, the workup was stopped. The other option was to perform positron-emission tomography (PET) immediately, and if the results were positive, biopsy was to be performed; otherwise, CT was to be performed at 3 months. For nodules 15 mm in diameter or larger (whether solid, partly solid, or nonsolid), immediate biopsy was an option in addition to the options already specified for smaller nodules. When infection was suspected, a 2-week course of antibiotics followed 1 month later by CT was an alternative to all the options mentioned,[13] and if no resolution or growth was observed, biopsy was to be performed; otherwise, the workup was stopped. For all participants for whom the workup was stopped or for whom the biopsy did not lead to a diagnosis of lung cancer, CT was to be repeated 12 months after the baseline CT.

For annual screenings, a positive result was considered to be any newly identified noncalcified nodule, regardless of size. If no new nodule was identified, CT was to be repeated 12 months later. If one or more new nodules were identified, the workup depended on the diameter of the largest nodule. If all nodules were less than 3.0 mm in diameter, or if the largest nodule was more than 3.0 mm but less than 5.0 mm in diameter, CT 6 or 3 months later, respectively, was to be performed. If no growth was seen in any of the nodules, the workup was stopped. If at least one of the noncalcified nodules was 5.0 mm or larger in diameter, then an immediate 2-week course of a broad-spectrum antibiotic was prescribed, followed 1 month later by CT. If the nodules showed no

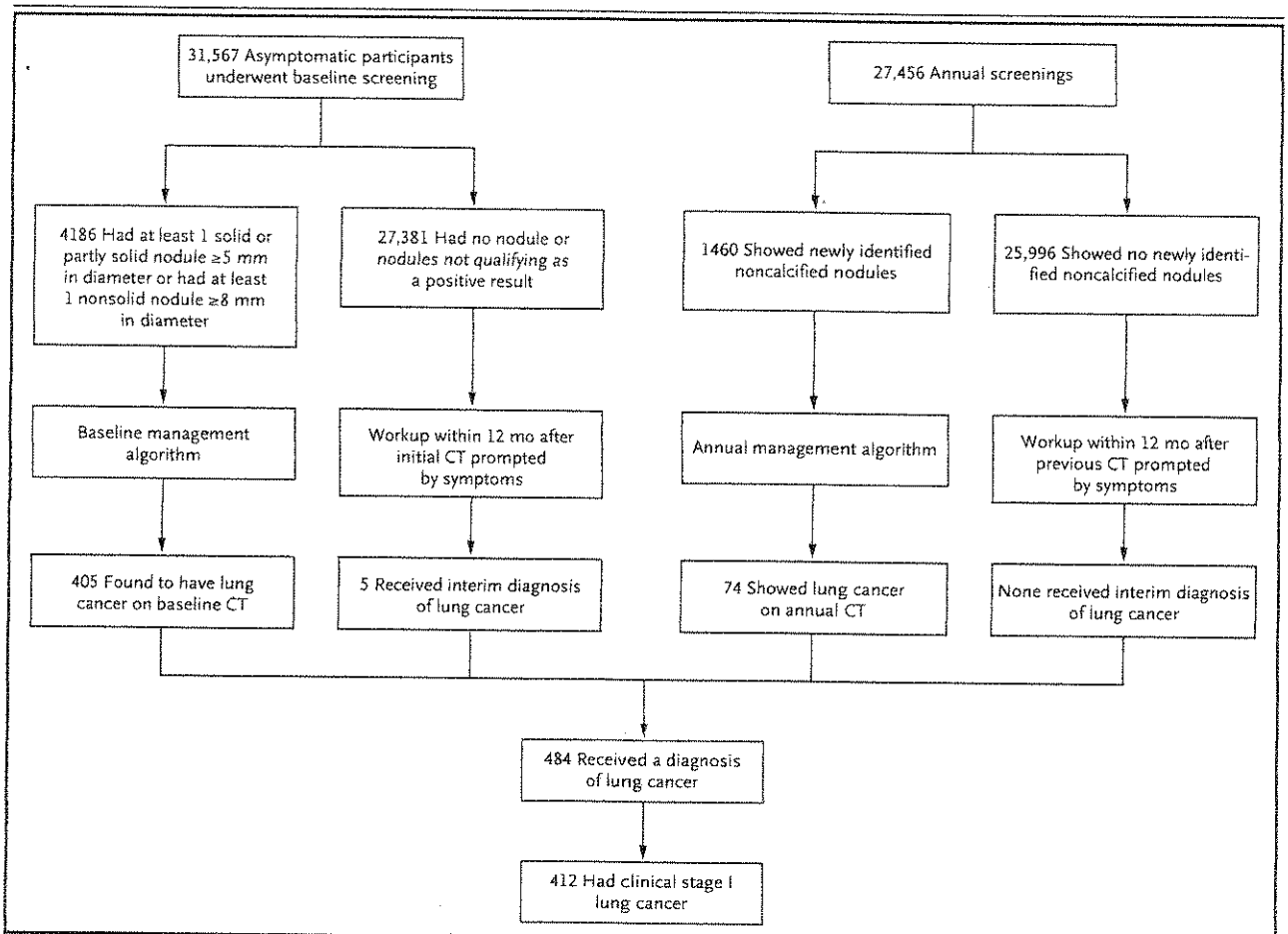

Figure 1. **Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT.**
A description of the I-ELCAP management algorithm for baseline CT and repeated CT screening is available in the study protocol.[6]

resolution or growth, biopsy was to be performed; otherwise, the workup was stopped. PET was an alternative to immediate biopsy; if the result was positive, biopsy was to follow. If the result was indeterminate or negative, CT was to be performed 3 months later, and if the scans showed growth, biopsy was to follow. Otherwise, the workup was stopped. For all patients for whom the workup was stopped or when biopsy did not result in a diagnosis of lung cancer, CT was to be repeated 12 months after the previous annual CT.

The protocol provided recommendations for the diagnostic workup in participants with a positive result on CT, with the decision regarding how to proceed left to each participant and the referring physician. The I-ELCAP protocol did not require that its recommendations for the workup of a nodule be followed, but it did require a firmly established final diagnosis of lung cancer and documentation of the workup in the management system. After the diagnosis of lung cancer was established, the type of intervention, if any, was left to the discretion of the participant and the physician. Documentation in the management system of the timing and type of intervention, if any, and follow-up with respect to manifestations of spread or death up to 10 years after diagnosis, were required.

A total of 31,567 asymptomatic men and women underwent baseline screening between 1993 and 2005 (median, 2001). The participants, who were 40 years of age and older, were at risk for lung cancer because of a history of cigarette smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to secondhand smoke without having smoked themselves; in Azumi, Japan, they participated as part of the annual health screening program (Table 1). All partici-

Table 1. I-ELCAP Participants, According to the Smoking Status, Exposure to Secondhand Smoke, and Occupational Exposures.

Program	Participants (N=31,567)
	no. (%)
Azumi Health Care Program in Japan	
Current or former smokers	3,087 (10)
Persons who had never smoked with exposure to secondhand smoke	3,299 (10)
Programs in the United States, Europe, Israel, and China	
Current or former smokers	23,052 (73)
Persons who had never smoked	
Occupational exposure*	1,690 (5)
Exposure to secondhand smoke with or without family history of lung cancer	439 (1)

* This category includes exposure to asbestos, beryllium, uranium, or radon.

pants were considered fit to undergo thoracic surgery. A total of 27,456 annual screenings were conducted between 1994 and 2005 (median, 2002), each of which was performed 7 to 18 months after the previous screening. At baseline, the median age of the participants was 61 years (range, 40 to 85), and the median number of pack-years of smoking was 30 (range, 0 to 141); on annual CT, the median values were an age of 62 years (range, 41 to 86) and 35 pack-years (range, 0 to 141). Among the participants, 13% (4186 of 31,567) who underwent baseline CT and 5% (1460 of 27,456) who underwent annual CT had a positive result that required immediate further workup. A biopsy of a pulmonary nodule as recommended in the protocol was performed in 535 of the participants with a positive result on the baseline or annual CT and led to a diagnosis of malignant disease in 492 of the participants (lung cancer was diagnosed in 479 and lymphoma or metastases from cancers other than lung cancer in 13) and no evidence of malignant disease in 43. The diagnosis was classified as having been identified during baseline screening when the nodule was first identified on the baseline CT, even for cases not meeting the criteria for a positive result, regardless of when the diagnosis was made. When the nodule was first identified on an annual CT, it was attributed to the annual screening. If the result on the baseline or annual CT was negative and a diagnostic workup was subsequently prompted by suggestive symptoms (or incidental findings) before the next scheduled annual CT, the finding was classified as an interim diagnosis. To fully document interim diagnoses of lung cancer, the protocol required that each enrolled participant who had not returned for the next scheduled screening be contacted 1 year after the previous screening. If contact could not be made either directly or through relatives of the participant, the referring physician was contacted to ascertain whether a diagnosis of lung cancer had been made.

We determined the distribution of the baseline and annual screenings and the resulting diagnoses according to age and median pack-years of cigarette smoking (Table 2). Each diagnosis of lung cancer was classified according to clinical stage with the use of standard criteria based on the clinical examination and the results of imaging.[14] The presence or absence of lymph-node (N) and distant metastases (M) was assessed on the most recent CT obtained before diagnosis and from PET (performed in 166 of the 484 participants who received a diagnosis of lung cancer). The cancer was classified as N0M0 if on CT the widths of all mediastinal lymph nodes were less than 10 mm and no hilar lymph nodes or distant metastases were identified (and PET, if performed, showed no abnormal uptake). For the purpose of this study, stage I cancers included those classified as N0M0 with more than 1 adenocarcinoma so long as all adenocarcinomas were 30 mm or less in diameter.[6]

The specimens obtained from participants who underwent surgical resection were examined at each institution according to the I-ELCAP pathology protocol,[15] which specified the preparation of the specimen and the findings that were to be documented by the pathologist at the hospital where the resection was performed. The protocol also specified the review process: a five-member pathology-review panel consisting of expert pulmonary pathologists was to reach a consensus diagnosis for each case of cancer and identify lymph-node involvement, additional cancers, and pleural, lymphatic, vascular, bronchial, and basement-membrane invasion by the cancer. For 22 of the 411 participants who underwent resection (5%), specimens could not be obtained from a nonparticipating hospital, and the panel therefore reviewed the detailed surgical and pathological reports for the relevant information.

All patients given a diagnosis of lung cancer were followed annually by the principal investigator and by the study coordinator at each participating institution, who submitted the information

Table 2. Frequency Distribution of Lung-Cancer Diagnoses on Baseline and Annual CT Screening, According to Age and Median Pack-Years of Cigarette Smoking.

Age	Baseline Screening			Annual Screening		
	Smoking History	No. Screened	Diagnosis of Lung Cancer	Smoking History	No. Screened	Diagnosis of Lung Cancer
	median pack-yr		*no. (%)*	*median pack-yr*		*no. (%)*
40–49 yr	15	4,066	8 (<1)	20	1,324	1 (<1)
50–59 yr	28	9,948	67 (1)	30	6,678	7 (<1)
60–69 yr	38	12,184	206 (2)	40	11,879	29 (<1)
70–79 yr	38	4,840	116 (2)	40	6,692	33 (<1)
80–86 yr	30	529	13 (2)	37	883	4 (<1)
Total	30	31,567	410 (1)*	35	27,456	74 (<1)

* The number includes five participants with interim diagnoses.

required by the protocol to the coordinating center. When a participant was known to have died, the date and cause were obtained from the participant's physician, family members, or both. Death resulting from treatment was considered to have been caused by lung cancer. Follow-up from diagnosis to death from lung cancer, the last contact, or May 30, 2006, whichever came first, was documented for each participant. The duration of follow-up ranged from 1 to 123 months (median, 40).

Kaplan–Meier curves were calculated for lung-cancer–specific survival as of the date of diagnosis, irrespective of the type of treatment, including no treatment, for all participants with lung cancer, irrespective of the stage of the cancer, and for the subgroup with clinical stage I cancer. Survival curves were also calculated for participants who underwent resection of clinical stage I cancer within 1 month after diagnosis and those who did not receive treatment. On the basis of these curves, we estimated the 10-year survival rates. The curves were constructed with the use of SAS statistical software (version 8), which also produced the standard error for the estimates.

RESULTS

Baseline screening of 31,567 asymptomatic persons who were at risk for lung cancer and annual screening of 27,456 resulted in the diagnosis of lung cancer in 405 and 74 participants, respectively (Fig. 1). Another five participants received interim diagnoses of lung cancer that were prompted by the development of symptoms within 12 months after the baseline screening. Of these 484 participants given a diagnosis of lung cancer, 411 underwent resection; 57 received radiation, chemotherapy, or both; and 16 received no treatment. Because survival rates among the participants who underwent baseline screening and those who underwent annual screening did not differ significantly, Kaplan–Meier estimates of lung-cancer–specific survival were calculated for all 484 participants (Fig. 2). The estimated 10-year survival rate for all participants, regardless of tumor stage and treatment, was 80% (95% confidence interval [CI], 74 to 85); as of May 2006, 75 of the 484 participants had died of lung cancer, including 2 who died within 4 weeks after surgery, yielding an operative mortality rate of 0.5% (2 of 411 participants).

Of the 484 participants who received a diagnosis of lung cancer, 412 (85%) had clinical stage I lung cancer. In this subgroup, the estimated 10-year survival rate regardless of treatment was 88% (95% CI, 84 to 91); as of May 2006, 39 of these 412 patients had died of lung cancer. Of these 412 participants, 375 had undergone surgical resection (284 lobectomy, 60 wedge resection, 21 segmentectomy, and 10 bilobectomy); 29 did not undergo resection but received chemotherapy, radiation, or both; and the remaining 8 did not receive treatment. Figure 2 also shows the lung-cancer–specific survival rate among the 302 participants who underwent resection within 1 month after diagnosis, among whom the estimated 10-year survival rate was 92% (95% CI, 88 to 95). All eight untreated patients died within 5 years after diagnosis.

Among the 412 participants with clinical

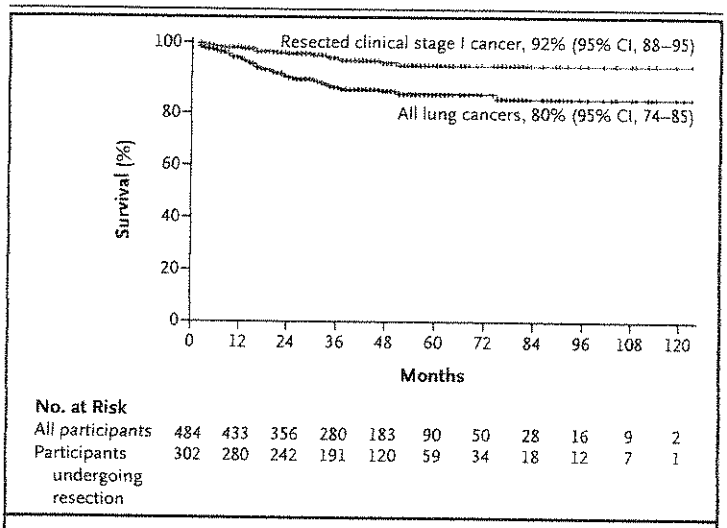

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

Table 3. Types of Cancer among 412 Participants with Clinical Stage I Lung Cancer Detected on Baseline or Annual CT Screening.

Type of Cancer	Diagnosed on Baseline Screening (N = 348)	Diagnosed on Annual Screening (N = 64)
	no. of participants	
Adenocarcinoma		
Bronchioloalveolar subtype	20	1
Other subtypes	243	30
Squamous cell	45	14
Adenosquamous	3	0
Non–small-cell*	5	2
Neuroendocrine		
Atypical carcinoid	2	1
Large cell	15	8
Small cell	9	7
Other	6	1

* If this cell type cannot be differentiated, the category is known as "not otherwise specified."

stage I cancer, the distribution according to the type of cell is shown in Table 3. The median tumor diameter was 13 mm at baseline and 9 mm on annual CT. The pathology-review panel confirmed the diagnosis of clinical stage I cancer in the specimens obtained from the 375 participants who underwent resection according to World Health Organization criteria of 2004.[16] With regard to spread or invasion (Table 4), the panel identified lymph-node metastases (hilar or ipsilateral mediastinal) in 28 participants (7%) and more than one cancer, either in the same or in different lobes, in another 35 (9%). Among the remaining participants, each with a solitary cancer, the panel identified invasion of the pleura in 62 (17%); bronchial, vascular, or lymphatic invasion or a combination in another 28 (7%); invasion of the basement membrane alone in 203 (54%), and no invasion in the remaining 19 (5%). (Because of rounding, percentages may not total 100.) Thus, of the 375 participants who underwent resection, 347 had pathological stage I cancer, and their estimated 10-year survival rate was 94% (95% CI, 91 to 97).

DISCUSSION

In making decisions about instituting CT screening for lung cancer, a major consideration is the outcome of treating a cancer detected on screening. In our study, the estimated 10-year lung-cancer–specific survival rate among the 484 participants with disease diagnosed on CT, regardless of the stage at diagnosis or type of treatment (including no treatment), was 80% (95% CI, 74 to 85) (Fig. 2). Among the 412 participants with clinical stage I lung cancer — the only stage at which cure by surgery is highly likely — the estimated 10-year survival rate was 88% (95% CI, 84 to 91), and among those with clinical stage I lung cancer who underwent surgical resection within 1 month after the diagnosis, the rate was 92% (95% CI, 88 to 95). The diagnosis of lung cancer of one type or another was verified by a panel of five expert pulmonary pathologists. In our series, the operative mortality rate was low — 0.5% — and was less than the 1.0% reported with lobectomy in a large cooperative study.[17]

Sobue et al.[18] reported a 5-year survival rate of 100% in their series of 29 patients who underwent resection after pathological stage I cancer was detected on CT. Before CT screening, reports based on registries showed 10-year survival rates of 80% among 17 patients with pathological stage I lung cancer 20 mm or less in diameter[19] and 93% among 35 patients with pathological stage I cancer less than 10 mm in diameter.[20] The National Cancer Institute's Surveillance, Epidemiology, and End

Table 4. Extent of Spread of Cancer in 375 Participants Who Underwent Resection of Clinical Stage I Lung Cancer According to Whether Cancer was Detected on Baseline or Annual CT Screening.

Extent of Spread	Diagnosed on Baseline Screening (N=320)	Diagnosed on Annual Screening (N=55)
	no. of participants	
Metastases to lymph nodes	22	6
No metastases to lymph nodes		
More than 1 cancer	29	6
Solitary cancer with invasion		
Pleural invasion	51	11
No pleural invasion but lymphatic, vascular, or bronchial spread (or a combination)	24	4
Basement membrane only	175	28
Solitary cancer without invasion	19	0

Results (SEER) registry, the largest U.S. cancer registry, reported an 8-year survival rate of 75% among patients with pathological stage I cancer with nodules less than 15 mm in diameter who had undergone resection.[8] Although the lung cancers in these three series were not detected on CT screening, most were presumably incidentally detected on imaging performed for other reasons in people who had no symptoms of lung cancer.

CT screening according to the I-ELCAP regimen can detect clinical stage I lung cancer in a high proportion of persons when it is curable by surgery. In a population at risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer. In comparison, in the United States at present, annually approximately 173,000 persons are diagnosed with lung cancer and 164,000 deaths are attributed to this disease,[21] so that approximately 95% of those who are diagnosed with lung cancer die from it.

Are these results sufficiently effective to justify screening people who are at risk of lung cancer? As compared with mammographic screening for breast cancer, for lung cancer the rates of detection among the participants in this study who were 40 years of age and older were 1.3% on baseline CT screening and 0.3% on annual screening (Table 2), values that were slightly higher than those for the detection of breast cancer (0.6 to 1.0% on baseline screening) and similar to those for annual screening (0.2 to 0.4%) among women 40 years of age and older.[22] The rate of cancer detection depends on the risk profile of those undergoing screening; the higher the risk, the more productive the screening. Thus, as expected, CT screening of the original participants in ELCAP, who were former and current smokers 60 years of age and older,[1,2] was more productive in detecting lung cancer (detection rates, 2.7% on baseline screening and 0.6% on annual screening) than among participants in the expanded study. The cost of low-dose CT is below $200,[23-26] and surgery for stage I lung cancer is less than half the cost of late-stage treatment.[26,27] Using the original ELCAP data and the actual hospital costs for the workup, we found CT screening for lung cancer to be highly cost-effective.[23] Other estimates of the cost-effectiveness of CT screening for lung cancer for various risk profiles[24-26,28] are similar to that for mammography screening.[29,30]

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Drs. Henschke and Yankelevitz report receiving royalties from Cornell Research Foundation as inventors of methods to assess tumor growth and regression on imaging tests for which pending patents are held by Cornell Research Foundation and licensed to General Electric. No other potential conflict of interest relevant to this article was reported.

APPENDIX

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Iguassu Falls, Brazil

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ABCNEWS

Hospitals Offering Lung Cancer CT Scans

June 29, 2011

Using CT scans to screen smokers for lung cancer cuts the risk of death from the disease by 20 percent, according to a new study by the National Cancer Institute published in the New England Journal of Medicine.

Meanwhile, medical centers across the country currently offer lung cancer screening programs for high-risk patients and pack-a-day smokers. Below is a list of institutions that offer such services.

CALIFORNIA

Cedars-Sinai Medical Center, Los Angeles

Cedars-Sinai Medical Center performs lung cancer screenings and is currently developing a formal program to help patients in Southern California who have CT results showing one or more small pulmonary nodules.

CONNECTICUT

Yale University Cancer Center, New Haven, Conn.

Smilow Cancer Hospital at Yale-New Haven and Yale Cancer Center offer screening for people at high risk of developing lung cancer through the Thoracic Oncology Program. CT scans are read by dedicated radiologists and any suspicious areas are reviewed by a multidisciplinary team of lung cancer experts.

COLORADO

National Jewish Hospital, Denver

National Jewish offers low-dose helical CT screening to patients at high risk for lung cancer. Thus far, patients have only been seen via internal referrals and/or on a self-pay premise.

University of Colorado Hospital, Denver

University of Colorado Hospital is developing a lung cancer screening program for high-risk patients based on the NLST trial results. However, until official recommendations regarding lung cancer screening are made by the U.S. Preventative Services Task Force next year, the hospital does not anticipate that insurance companies will cover lung cancer screening costs.

FLORIDA

Moffitt Cancer Center, Tampa, Fla.

Moffitt Cancer Center plans to develop a lung cancer screening program with spiral CT later this year.

University of Miami Miller School of Medicine, Miami, Fla.

The Miller School of Medicine will be offering a screening program at University of Miami's Sylvester

Comprehensive Cancer Center.

GEORGIA

Emory University Hospital, Atlanta

Emory University Hospital is offering lung cancer CT screening beginning on Aug. 1, 2011.

ILLINOIS

Northwestern Memorial Hospital, Chicago

Northwestern Memorial offers a lung cancer CT screening program for patients considered at high risk for lung cancer. The Northwestern Pulmonary Nodule Clinic provides appropriate monitoring and diagnostic intervention for individuals in whom the CT screening reveals indeterminate or suspicious lung nodule(s).

Rush University Medical Center, Chicago

Rush University Medical Center offers a lung cancer screening program.

MARYLAND

Johns Hopkins Medical Institution, Baltimore

Johns Hopkins offers spiral CT lung cancer screening per the NIH/NCI guidelines. Hopkins is the only Maryland hospital that participated in the National Lung Screening Trial.

MASSACHUSSETTS

Brigham and Women's Hospital, Boston

Brigham and Women's Hospital's Department of Radiology offers lung cancer CT screening to eligible patients. Current or former long-term smokers over the age of 50 can speak with their doctor about the scan and eligible patients can undergo a scan with a doctor's referral.

MICHIGAN

University of Michigan Comprehensive Cancer Center, Ann Arbor, Mich.

The University of Michigan Comprehensive Cancer Center is developing a lung screening program for high-risk patients based on the NLST trial results.

MINNESOTA

Abbott Northwestern Hospital, Minneapolis, Minn.

Abbott Northwestern Hospital offers low-dose CT lung cancer screening to patients aged 55-74 and who have smoked at least one pack of cigarettes per day for 30 years.

Mayo Clinic, Rochester, Minn.

Mayo Clinic offers low dose CT in patients at high risk for lung cancer in an attempt to identify cancer at its earliest stages.

NEW YORK

Continuum Cancer Centers of New York

Continuum partners with Beth Israel Medical Center, Roosevelt Hospital, St. Luke's Hospital and New York Eye and Ear Infirmary. Beth Israel currently has a screening program. Philanthropy support defrays some of the cost of the screenings for patients, as this screening is currently not covered by insurance.

Memorial Sloan-Kettering Cancer Center, New York

Memorial Sloan-Kettering Cancer Center offers low-dose helical CT screening for people with no history of cancer or who have been cancer-free for five years, aged 55-74, and who have smoked at least one pack of cigarettes per day for 30 years (30 pack years).

Mount Sinai Medical Center, New York

Mount Sinai Medical Center offers low-dose CT scanning for lung cancer screening in high-risk patients. Mount Sinai's Lung Disease and Lung Cancer Treatment Programs ensure a seamless transition to the best possible care should it become necessary.

NORTH CAROLINA

Wake Forest Baptist Medical Center, Winston-Salem, NC

Wake Forest Baptist Medical Center offers lung cancer screening with low-dose spiral CT scanning. Patients who are aware and interested can call a toll-free number to set up an appointment: (877) 243-0563.

OHIO

University Hospitals Seidman Cancer Center, Cleveland

University Hospitals Seidman Cancer Center offers $99 lung cancer screenings to patients aged 55-74, who have smoked at least one pack of cigarettes per day for 30 years and to other high-risk patients.

PENNSYLVANIA

Temple University Hospital, Philadelphia

Temple University Hospital offers a lung cancer prevention (smoking cessation), annual low-dose CT screening program and nodule work-up program.

Thomas Jefferson University Hospital, Philadelphia

Thomas Jefferson University Hospital offers lung cancer screening and a Pulmonary Nodule Clinic for patients with suspicious screening results.

TEXAS

MD Anderson Cancer Center, Houston

MD Anderson Cancer Center offers lung cancer screening for smokers over the age of 50 who have smoked the equivalent of one pack of cigarettes a day for at least 20 years. Along with screening, MD Anderson offers risk assessment counseling for those who do not have lung cancer and low-cost tobacco cessation programs to help smokers quit.

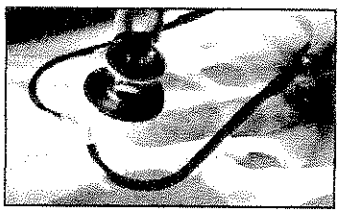
WASHINGTON, D.C.

Georgetown University Hospital, Washington, D.C.

Georgetown University Hospital offers a lung cancer screening program to patients over the age of 55 who have smoked at least one pack of cigarettes per day for 30 years. Georgetown University Hospital's comprehensive Lung Cancer Program provides the full spectrum of available and emerging radiation, chemotherapy and surgical options and support services. It uses a multi-disciplinary approach to treatment and has potential access to a variety of clinical research trials.

SAFETY AND HEALTH TOPICS

Medical Screening and Surveillance



Introduction

Medical screening and medical surveillance are two fundamental strategies for optimizing employee health. Although the terms are often used interchangeably, they are quite distinct concepts. Medical screening is, in essence, only one component of a comprehensive medical surveillance program. The fundamental purpose of screening is early diagnosis and treatment of the individual and thus has a *clinical focus*. The fundamental purpose of surveillance is to detect and eliminate the underlying causes such as hazards or exposures of any discovered trends and thus has a *prevention focus*. Both can contribute significantly to the success of worksite health and safety programs. However OSHA "medical surveillance" requirements are generally clinically focused (e.g.,medical and work histories, physical assessment, biological testing) with information obtained from the clinical processes used in the monitoring and analysis elements of medical surveillance.

Medical screening and surveillance are addressed in specific standards for the general industry.

OSHA Standards

This section highlights OSHA standards, directives (instructions for compliance officers), and standard interpretations (official letter related to medical screening and surveillance.

Note: Twenty-five states, Puerto Rico and the Virgin Islands have OSHA-approved State Plans and have adopted their own standa most part, these States adopt standards that are identical to Federal OSHA. However, some States have adopted different standar have different enforcement policies.

General Industry (29 CFR 1910)

- 1910 Subpart H, Hazardous materials
  - 1910.120, Hazardous waste operations and emergency response [related topic page]
- 1910 Subpart I, Personal protective equipment [related topic page]
  - 1910.134, Respiratory protection [related topic page]
- 1910 Subpart Z, Toxic and hazardous substances [related topic page]
  - 1910.1001, Asbestos [related topic page]
    - Appendix H, Medical surveillance guidelines for asbestos (Non-mandatory)
  - 1910.1003, 13 Carcinogens (4-nitrobiphenyl, etc.)
  - 1910.1004, alpha-Naphthylamine
  - 1910.1006, Methyl chloromethyl ether

- 1910.1007, 3,3'-Dichlorobenzidine (and its salts)
- 1910.1008, bis-Chloromethyl ether
- 1910.1009, beta-Naphthylamine
- 1910.1010, Benzidine
- 1910.1011, 4-Aminodiphenyl
- 1910.1012, Ethyleneimine
- 1910.1013, beta-Propiolactone
- 1910.1014, 2-Acetylaminofluorene
- 1910.1015, 4-Dimethylaminoazobenzene
- 1910.1016, N-Nitrosodimethylamine
- 1910.1017, Vinyl chloride
- 1910.1018, Inorganic Arsenic [related topic page]
  - Appendix C, Medical surveillance guidelines
- 1910.1025, Lead [related topic page]
- 1910.1027, Cadmium [related topic page]
- 1910.1028, Benzene [related topic page]
  - Appendix C, Medical surveillance guidelines for benzene
- 1910.1029, Coke oven emissions
  - Appendix B, Industrial hygiene and medical surveillance guidelines
- 1910.1030, Bloodborne pathogens [related topic page]
- 1910.1043, Cotton dust [related topic page]
- 1910.1044, 1,2-dibromo-3-chloropropane
  - Appendix C, Medical surveillance guidelines for DBCP
- 1910.1045, Acrylonitrile
  - Appendix C, Medical surveillance guidelines for acrylonitrile
- 1910.1047, Ethylene oxide [related topic page]
  - Appendix C, Medical surveillance guidelines for ethylene oxide (Non-mandatory)
- 1910.1048, Formaldehyde [related topic page]
- 1910.1050, Methylenedianiline
  - Appendix C, Medical surveillance guidelines for MDA
- 1910.1450, Occupational exposure to hazardous chemicals in the laboratories

Directives

- National Emphasis Program – Microwave Popcorn Processing Plants. CPL 03-00-005, (2007, July 27). Also available as a 21(policies and procedures for implementing a National Emphasis Program to identify and reduce or eliminate exposures to but microwave popcorn manufacturing facilities.
- OSHA Medical Surveillance Regulations -- Genetic Testing. STD 01-23-004 [STD 1-23.4], (1980, August 22). Provides an int(that require medical surveillance programs specifying a medical history with family and occupational background, including
- Search all available directives.

Standard Interpretations

- Medical surveillance is not required for terminated employees. (1984, February 29).
- Access to employee exposure and medical records. (1997, October 29).
- OSHA policy regarding medical surveillance requirements. (1987, August 6).

- Respiratory protection, medical surveillance, and training requirements under HAZWOPER. (2002, September 24).
- HAZWOPER medical examinations must be offered at a reasonable time and without cost to the employee. (2002, Septemb
- Search all available standards interpretations.

Medical Screening

Medical screening is a method for detecting disease or body dysfunction before an individual would normally seek medical care. Sc administered to individuals without current symptoms, but who may be at high risk for certain adverse health outcomes. The follov about medical screening and clinical evaluation.

- Screening and Surveillance: A Guide to OSHA Standards [365 KB PDF*, 40 pages]. OSHA Publication 3162, (2000). Provides and implement the screening and surveillance requirements of the OSHA standards.
- *Proceedings of the VIIth International Pneumoconioses Conference.* US Department of Human Health Services (DHHS), Nat and Health (NIOSH) Publication No. 90-108.
  - Part I. (1988, August).
  - Part II. (1990, November).

Clinical Evaluation

- Wiley Online Library. *American Journal of Industrial Medicine.* 37.1(2000, January): 1-157. Offers a series of clinical practice for clinicians, on a variety of occupational diseases.
- Specific Medical Tests or Examinations Published in the Literature for OSHA-Regulated Substances. National Institute for Oc (NIOSH). Lists the specific medical tests published in the literature for OSHA regulated substances and includes updates of (NIOSH/OSHA recommendations.

Related Literature

- Murthy, L.I. and W.E. Halperin. "Medical Screening and Biological Monitoring: A Guide to the Literature for Physicians." *Jour Environmental Medicine* 37.2(1995, February): 170-184. Summarizies recommended medical tests (including biologic monit as well as OSHA and the National Institute for Occupational Safety and Health (NIOSH). Provides guidance to occupational l pertinent literature.
- Terry, T.M. and G. Ryan. "Making Sense of OSHA Standards with Medical Requirements: Part 1." *Applied Occupational and* March): 144-148.

Medical Surveillance

Medical surveillance is the analysis of health information to look for problems that may be occurring in the workplace that require t surveillance serves as a feedback loop to the employer. Surveillance may be based on a single case or sentinel event, but more typ group of employees being evaluated to look for abnormal trends in health status. Surveillance can also be conducted on a single er results helps to identify potential problem areas and the effectiveness of existing worksite preventive strategies. The following reso information including specific hazards and surveillance guidelines.

- Surveillance. National Institute for Occupational Safety and Health (NIOSH) Safety and Health Topic.
- Indicators for Occupational Health Surveillance. Centers for Disease Control and Prevention (CDC), Morbidity and Mortality \ 7, (2007, January 19).
- Health Hazard Evaluations. National Institute for Occupational Safety and Health (NIOSH). NIOSH conducts investigations o workplace to determine whether any substance normally found in the place of employment has potentially toxic effects in s
- The Work-Related Lung Disease Surveillance Report, 2002. US Department of Human Health Services (DHHS), National Inst Health (NIOSH) Publication No. 2003-111, (2002). Provides national and state-specific data of pneumoconiosis and other w
- TLV/BEI Resources. American Conference of Governmental Industrial Hygienists (ACGIH). This organization of government biological exposure indices for use which can be used for criteria for evaluating biological samples collected for medical surv
- Tracking Occupational Injuries, Illnesses, and Hazards: The NIOSH Surveillance Strategic Plan. US Department of Human H Institute for Occupation Safety and Health (NIOSH) Publication No. 2001-118, (2001, January). Also available as a 209 KB F process to assess current surveillance needs and to identify its goals for the next decade. The Surveillance Strategic Plan is
- Best Practices in Workplace Surveillance: Identification and Tracking of Workplace Injury, Illness, Exposures, and Hazards. (

Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH). Includes presentations and handout mate

- Medical Surveillance Manual [411 KB PDF, 75 pages]. US Department of Defense (DoD). Provides minimum standard help occupational health professionals and others recognize and evaluate health risks associated with specific workpl
  - General Information. Chapter 1. Describes the general requirements for medical surveillance, types of examin
  - Medical Surveillance for OSHA-Regulated Exposures. Chapter 2. Describes OSHA related medical surveillance.
  - Medical Surveillance Endorsed by the Department of Defense. Chapter 3. Includes additional medical surveilla where OSHA does not provide guidance.
- National Occupational Exposure Survey Analysis of Management Interview Responses. US Department of Human Hea Institute for Occupation Safety and Health (NIOSH) Publication No. 89-103, (1998, March). Provides data on the exte exposure to chemical, physical, and biological agents.
- A Guide for the Management, Analysis, and Interpretation of Occupational Mortality Data. US Department of Human Institute for Occupational Safety and Health (NIOSH) Publication No. 90-115, (1990, September). Provides guidelines interested in occupational mortality surveillance.
- National Occupational Exposure Survey Sampling Methodology. US Department of Human Health Services (DHHS), N Safety and Health (NIOSH) Publication No. 89-102, (1990, February). Describes the method used to select the sampl estimation techniques used to project survey data to national estimates.
- For additional information, see OSHA's Safety and Health Topics Pages on:
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Additional Information

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Other Resources

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What Is Medical Monitoring - Document Transcript

1. WHAT IS MEDICAL MONITORING? AND WHEN IS A MOTION TO DISMISS ADVISABLE? American Conference Institute Chemical Products Liability and Environmental Litigation April 28-29, 2010 · Chicago, IL JEROME R. DOAK jrdoak@jonesday.com Jones Day · 2727 North Harwood Street Dallas, Texas 75201 · 214-969-2977 Copyright © 2010 As of March 31, 2010

2. I. MEDICAL MONITORING: WHAT IT IS, WHAT IT IS NOT A. What Is "Medical Monitoring"? "Medical monitoring" is a relatively new theory of liability in which persons with no ascertainable injuries or symptoms seek to recover the costs of screening for health problems caused by exposure to hazardous substances. The alleged "injury" in medical monitoring lawsuits is most often characterized as an increased risk of disease, and the alleged damages are the costs of "monitoring" for disease. Instead of monetary damages, some plaintiffs ask for so-called "equitable" relief in the form of a court-funded and court-established medical monitoring program. In our view, such "programs" of medical monitoring amount to no more than disguised requests for monetary relief. As currently framed by the courts that recognize medical monitoring, tort liability for medical monitoring arises when a person is involuntarily exposed to a hazardous substance, due to a defendant's negligence, thereby creating an increased risk of the person's developing some future disease, for which there is a cost-effective and medically efficacious screening test that will assist in the early detection and effective treatment of the targeted disease.1 Courts in a handful of states have recognized medical monitoring in the absence of a present physical injury either as an independent tort claim or as a theory of "remedy" that substitutes for injury in otherwise traditional negligence claims. Other courts have outright rejected medical monitoring without present injury, while in many states medical monitoring remains an open question. B. Medical Testing Terminology While common word usage refers to medical screening tests without differentiation, a more precise word usage is important in medical monitoring cases because the categories have different legal meanings. In our experience, the proper use and understanding of the terms is the foundation for the legal discussions. • Medical monitoring claims are different from diagnostic testing, which is medical testing to determine the extent of a known injury (or to confirm symptoms). Victims of a traumatic physical impact, for example, may need diagnostic testing to evaluate the extent of physical injuries. 1 See, e.g., Hansen v. Mountain Fuel Supply Co., 858 P.2d 970, 979-80 (Utah 1993); Redland Soccer Club, Inc. v. Dep't of the Army, 696 A.2d 137, 145-46 (Pa. 1997). 2

3. Traditionally, a plaintiff who has suffered a traumatic physical impact (such as a plane crash2 or motorbike accident3) may recover the costs of diagnostic testing, although the extent and severity of his injuries may not be readily apparent.4 This is not the same thing as awarding medical monitoring damages in the absence of any present injury. But medical monitoring plaintiffs at times will rely improperly on cases awarding the cost of diagnostic testing as precedent supporting their claims. • Medical monitoring claims are different from surveillance testing, which is medical testing to monitor the status of a known, existing disease or injury (or to test for a re-emerging disease, such as for a cancer patient in remission). For example, personal-injury plaintiffs with an existing physical injury often seek to recover future medical expenses that include surveillance testing. Traditionally, a plaintiff with an existing physical injury may recover the costs of surveillance testing.5 That is not the same thing as awarding medical monitoring damages in the absence of any present injury. But medical monitoring plaintiffs at times will rely improperly on cases awarding the cost of surveillance testing as precedent supporting their claims. • Screening is the type of testing implicated in medical monitoring cases. Screening is medical testing of an asymptomatic individual to check for the presence of disease.6 Recovery for screening tests is not based on a physical injury or impact; by definition, a medical monitoring plaintiff has no existing physical injury, disease, or symptom of disease. 2 Friends For All Children, Inc. v. Lockheed Aircraft Corp., 746 F.2d 816 (D.C. Cir. 1984) (although supposedly adopting medical monitoring, case involved a plane crash where passengers received one-time diagnostic testing to determine scope of their injuries). 3 Bower v. Westinghouse Elec. Corp., 522 S.E.2d 424, 430 (W. Va. 1999) (analyzing the hypothetical example of a motorbike accident); Hansen, 858 P.2d at 977-78 (same). 4 See RESTATEMENT (SECOND) TORTS § 919, ill. 1 (1979). 5 See, e.g., Metro-N. Commuter R.R. Co. v. Buckley, 521 U.S. 424, 438 (1997). 6 "For the purpose of defining screening, a person is asymptomatic if, at the time screening is done, he or she has no known signs or symptoms of the target condition. . . . The crucial point is that, at the time of screening, neither the patient nor the practitioner is aware of any signs or symptoms of the target condition." DAVID M. EDDY, M.D., PH.D. (ED.), COMMON

SCREENING TESTS 1-2 (1991). 3

4. Traditionally, compensation for the screening of asymptomatic individuals with no existing injury or disease (but rather an increased risk of disease) was not recoverable because of the usual tort law requirement that the plaintiff must show a present physical injury (or impact). But medical monitoring seeks recovery for these types of screening tests without a present physical injury. Such screening tests are those implicated in the legal theory of "medical monitoring." C. The Elements of a Claim for Medical Monitoring Plaintiffs have framed medical monitoring claims as both causes of action and remedies. Courts allowing recovery for medical monitoring as a new cause of action have embraced sometimes-varying elements of proof to establish the tort.7 The plaintiffs' bar has sometimes convinced courts to allow recovery for medical monitoring by describing it as merely a remedy.8 An amalgamation of these elements of proof—taken from various cases—is: • Exposure to a Proven Hazardous Substance. Most courts hold that the exposure must be "significant."9 Some courts have defined a "significant exposure" as one that is "greater than normal background levels."10 And at least one court has held that to be deemed significant, the exposure must also be direct and discrete; otherwise it "is impossible to approximate or quantify the extent to which [the plaintiff] may have encountered the substance . . . ."11 The substance must have been proven hazardous to human health.12 7 See, e.g., Redland Soccer Club, 696 A.2d at 145-46; Hansen, 858 P.2d at 979-80; In re Paoli R.R. Yard PCB Litig., 916 F.2d 829 (3d Cir. 1990). 8 See, e.g., Bourgeois v. A.P. Green Indus., Inc., 716 So. 2d 355 (La. 1998), superseded by LA. CIV. CODE ANN. art 2315 (2005); Potter v. Firestone Tire & Rubber Co., 863 P.2d 795 (Cal. 1993). 9 See, e.g., In re W. Va. Rezulin Litig., 585 S.E.2d 52, 73 (W. Va. 2003); In re Paoli R.R. Yard PCB Litig., 916 F.2d at 852; Bower, 522 S.E.2d at 433. 10 Bourgeois, 716 So. 2d at 360; Redland Soccer Club, Inc., 696 A.2d at 145. 11 Theer v. Philip Carey Co., 628 A.2d 724, 733 (N.J. 1993) (noting that a claim for medical monitoring should not be available "for plaintiffs who have not experienced direct and hence discrete exposure to a toxic substance"). 12 See Bourgeois, 716 So. 2d at 360 ("[T]he substance to which a plaintiff is exposed must have been proven hazardous to human health."); Bower, 522 S.E.2d at 433 ("The plaintiff 4

5. • Exposure Caused by the Defendant's Negligence. The defendant must have breached a duty owed to the plaintiff, which resulted in exposure.13 • Exposure Created an Increased Risk of Contracting a Serious Latent Disease. Most courts purport to require that the increased risk of disease be "significant,"14 but no particular level of quantification appears necessary to satisfy the requirement of significantly increased risk; for example, courts do not appear to require that the plaintiff prove he or she has a probability of actually contracting the disease.15 Some courts, however, have held that the plaintiff's increased risk must be greater than the chances of members of the public at large of developing the disease (so that exposures suffered by the entire population do not form the basis of medical monitoring claims).16 (continued...) must present scientific evidence demonstrating a probable link between exposure to a particular compound and human disease."). 13 See In re Welding Fume Prods. Liab. Litig., 245 F.R.D. 279, 292 (N.D. Ohio 2007); Abuan v. Gen. Elec. Co., 3 F.3d 329, 334 (9th Cir. 1993); In re W. Va. Rezulin Litig., 585 S.E.2d at 59 ("West Virginia law allows a cause of action for the recovery of medical monitoring costs, 'where it can be proven that such expenses are necessary and reasonably certain to be incurred as a proximate result of a defendant's tortious conduct.'") (internal citations omitted). 14 See Meyer v. Fluor Corp., 220 S.W.3d 712, 718 (Mo. 2007) ("[A] plaintiff can obtain damages for medical monitoring upon a showing that the plaintiff has a significantly increased risk of contracting a particular disease relative to what would be the case in the absence of exposure.") (internal quotes omitted); In re Paoli R.R. Yard PCB Litig., 916 F.2d at 852; Redland Soccer Club, Inc., 696 A.2d at 145 (expert's testimony based on increased cancer risk of one in a million); Bower, 522 S.E.2d at 433; Hansen, 858 P.2d at 979 (The term "significantly increased risk," however, is misleading because "[n]o particular level of quantification is necessary . . . ."); Bourgeois, 716 So. 2d at 360 (finding that any exposure "greater than normal background levels" is sufficient); see also Metro-N. Commuter R.R. Co., 521 U.S. at 427 (The plaintiffs' experts characterized the increased risk as one to five percent.); cf. In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 793-95 (3d Cir. 1994) (Paoli II) (noting that although the EPA set an acceptable cancer risk at one in 100,000, plaintiffs' expert testified that everyone, even those with PCBs in their blood at levels as low a one part per billion, should receive medical monitoring). 15 Hansen, 858 P.2d at 979; Bower, 522 S.E.2d at 433; Donovan v. Philip Morris USA, Inc., 914 N.E.2d 891, 901 (Mass. 2009). 16 See, e.g., Bourgeois, 716 So. 2d at 361. 5

Screening Test. Courts reason that if no such test exists, the potential plaintiff is not harmed until the onset of the actual illness.18 If a test is later developed that will detect the disease, a plaintiff would retain the right to demonstrate at some later date the effectiveness of the test and be compensated for using it.19 • Demonstrated Clinical Benefit of Early Detection and Diagnosis. Many courts have held that there must be a proven clinical benefit in the early detection and effective treatment of the targeted disease, i.e., that "an existing treatment, administered before the illness becomes apparent to a layperson, is effective in curing or ameliorating the consequences of the illness."20 A few courts, however, have held that a plaintiff need not demonstrate that a treatment currently exists because it would unfairly prevent a plaintiff from taking advantage of future developments in medical science.21 One court has even held that the benefit to a plaintiff is nothing more than "certainty as to his fate, whatever it might be. Even if there is no treatment available, the plaintiff could get his affairs in order and make peace with estranged loved ones or with his religion."22 • Screening Test Is Medically Advisable. Courts have held that the medically advisable test "must be shown to be 'consistent with contemporary scientific principles' and 'reasonably necessary.'"23 This 17 See, e.g., Theer, 628 A.2d at 733 (noting that there were "multiple factors that contribute to any future injuries that [plaintiff] may have" and plaintiff's "exposure to asbestos, when coupled with her chronic smoking, make it difficult to determine if there is a direct correlation between the asbestos exposure and future medical costs"). 18 See, e.g., Hansen, 858 P.2d at 979. 19 Hansen, 858 P.2d at 979 n.12; Bower, 522 S.E.2d at 433. 20 See Hansen, 858 P.2d at 979-80; see also Donovan, 914 N.E.2d at 901. 21 See Redland Soccer Club, Inc., 696 A.2d at 146 n.8; Bower, 522 S.E.2d at 433-34. 22 See Bower, 522 S.E.2d at 434 (internal quotations omitted). 23 Hansen, 858 P.2d at 980 (quoting Ayers v. Township of Jackson, 525 A.2d 287, 309 (N.J. 1987)); see also Meyer, 220 S.W.3d at 718. 6

7. means, in part, that the specific screening test must be medically advisable for the particular plaintiff.24 A few courts have held for various reasons that this element is not required. In holding that plaintiffs need not make this showing, The Supreme Court of West Virginia in 1999 explained that: [w]hile there obviously must be some reasonable medical basis for undergoing diagnostic monitoring, factors such as financial cost and frequency of testing need not necessarily be given significant weight. Moreover, the requirement that diagnostic testing must be medically advisable does not necessarily preclude the situation where such a determination is based, at least in part, upon the subjective desires of a plaintiff for information concerning the state of his or her health.25 • Exposure Warrants Screening Beyond What Otherwise Would Be Recommended. Courts have required, for a medical monitoring claim, that the screening be greater than that recommended for the public generally.26 II. OVERVIEW OF STATE LAW ON MEDICAL MONITORING While some courts have recognized a cause of action or remedy for medical monitoring, at least an equal number of courts have rejected medical monitoring claims because the claimants lacked a cognizable injury. The trend has now turned against recognizing the claim, with six of the last eight state supreme courts deciding that the lack of sufficient injury precludes recovery in tort. 24 Bourgeois, 716 So. 2d at 361 ("Plaintiff must show that administration of the diagnostic test is medically advisable for him or her specifically."); Hansen, 858 P.2d at 980 ("[I]t is not enough that early detection and treatment are shown to be theoretically beneficial. It also must be shown that administration of the test to a specific plaintiff must be medically advisable for that plaintiff."). 25 Bower, 522 S.E.2d at 433. 26 In re Fosamax Prods. Liab. Litig., 248 F.R.D. 389, 394 (S.D.N.Y. 2008) (applying Florida and Pennsylvania law). 7

8. A. State Supreme Courts Adopting Medical Monitoring27 • New Jersey. Ayers v. Township of Jackson, 525 A.2d 287, 312 (N.J. 1987) (recognized claim for medical monitoring in toxic tort case with 339 plaintiffs whose well water was contaminated by an illegally operated landfill), limited by Theer v. Philip Carey Co., 628 A.2d 724 (N.J. 1993), and further limited by Sinclair v. Merck & Co., Inc., 948 A.2d 587, 593-94 (N.J. 2008) (rejecting medical monitoring for future risk of harm associated with pain medication because state's Product Liability Act requires physical injury). • Utah. Hansen v. Mountain Fuel Supply Co., 858 P.2d 970, 979 (Utah 1993) (recognized claim for medical monitoring in case involving occupational asbestos exposure). • California. Potter v. Firestone Tire & Rubber Co., 863 P.2d 795, 823, 824-25 (Cal. 1993) (recognized claim for medical monitoring in case involving asymptomatic landowners whose water was contaminated by carcinogens from disposal of toxic waste at a landfill). • Pennsylvania. Redland Soccer Club, Inc. v. Department of the Army, 696 A.2d 137, 145-46 (Pa. 1997) (recognized claim for medical monitoring in case involving 148 plaintiffs exposed to toxic substances at a contaminated landfill converted into a park and soccer fields). • Louisiana. Bourgeois v. A.P. Green Industries, Inc., 716 So. 2d 355, 360-61 (La. 1998) (recognized claim for medical monitoring in case

brought by asymptomatic plaintiffs occupationally exposed to asbestos), superseded by LA. CIV. CODE ANN. art. 2315 (2005). • West Virginia. Bower v. Westinghouse Electric Corp., 522 S.E.2d 424, 426, 432-33 (W. Va. 1999) (recognized claim for medical monitoring in case of occupational exposure to toxic substances from a two-acre pile of debris from light bulb manufacturers). • Missouri. Meyer v. Fluor Corp., 220 S.W.3d 712, 717-20 (Mo. 2007) (recognized claim for medical monitoring in a case involving children exposed to emissions from a lead smelter). • Massachusetts. Donovan v. Philip Morris USA, Inc., 914 N.E.2d 891, 900-03 (Mass. 2009) (recognized claim for medical monitoring based on 27 Louisiana now rejects medical monitoring by statute. LA. CIV. CODE ANN. art. 2315 (2005). 8

9. evidence of subcellular or other physiological changes caused by smoking that substantially increased risk of contracting lung cancer). B. State Supreme Courts Rejecting Medical Monitoring • Nevada. Badillo v. American Brands, Inc., 16 P.3d 435, 440-41 (Nev. 2001) (rejecting claim for medical monitoring in a case alleging exposure to second-hand cigarette smoke). • Alabama. Hinton v. Monsanto Co., 813 So. 2d 827, 829-30 (Ala. 2001) (rejecting claim for medical monitoring in a case alleging exposure to PCBs). • Kentucky. Wood v. Wyeth-Ayerst Laboratories, 82 S.W.3d 849, 852, 857-58 (Ky. 2002) (rejecting claim for medical monitoring in case alleging harmful effects of appetite-suppressant diet drugs). • Michigan. Henry v. Dow Chemical Co., 701 N.W.2d 684, 686, 691 (Mich. 2005) (rejecting claim for medical monitoring in a case of alleged exposure to dioxin discharges from chemical plant). • Mississippi. Paz v. Brush Engineered Materials, Inc., 949 So. 2d 1, 4-5, 12, 20-21 (Miss. 2007) (declining to recognize an action for medical monitoring in a case alleging beryllium exposure). • Oregon. Lowe v. Philip Morris USA, Inc., 183 P.3d 181, 184-185 (Or. 2008) (refusing to recognize a significantly increased risk of contracting lung cancer as a cognizable injury in case seeking medical monitoring for cigarette smokers). C. United States Supreme Court's Examination of Medical Monitoring The United States Supreme Court has rejected medical monitoring in the context of a FELA claim in a case that has been often cited by courts rejecting medical monitoring: • Metro-North Commuter Railroad Co. v. Buckley, 521 U.S. 424, 428, 439, 442-44 (1997) (reversing a ruling that allowed an exposed, but uninjured, asbestos plaintiff to pursue a medical monitoring under an FELA claim, because (i) the plaintiff, despite a "massive, lengthy, and tangible" exposure, had no compensable injury that would allow medical monitoring costs as a traditional element of damages, and (ii) allowing recovery for medical-monitoring costs in the absence of physical injury would create a number of "systemic harms" for courts, the tort system, and society). 9

10.III. MOTION TO DISMISS STRATEGY In medical monitoring lawsuits, defense lawyers must decide whether to file a motion to dismiss for failure to state a claim. This evaluation requires a careful weighing of the risks of an unsuccessful motion to dismiss, with its potential negative impact on class certification, against the obvious advantages of prevailing on the motion to dismiss. The jurisdiction's class certification law and the chances of later defeating class certification must also go into the mix when defense counsel decides whether an early motion to dismiss is a good idea. A. Risks and Potential Disadvantages • Our experience indicates that it is usually more difficult to win a motion to dismiss in a proposed class action. We suspect this is because courts can be more reluctant to dismiss a proposed class action, which potentially could impact a large number of individuals, than they would be to dismiss a lawsuit brought on behalf of a single individual. • The idea of medical monitoring claims, in the abstract, can be appealing to the court. Judges, like most people, are concerned about toxic exposures that we all encounter in our daily lives, and they may be inclined to think that diagnosing a latent disease early will always lead to a better medical outcome. • Recent public outcry over the new mammogram guidelines may also be a factor to consider in weighing the strategy of a motion to dismiss. • If a defendant files a motion to dismiss but does not prevail, the plaintiff will gain momentum as a result. This kind of momentum can make it more difficult for the defendant to defeat class certification later. For example, a trial court may interpret an interlocutory decision affirming the denial of a motion to dismiss as a signal that a class action should be certified. B. Advantages • Many states have existing precedent on the injury requirement for tort claims that can be used successfully in an argument that medical monitoring claims should not be recognized. 10

11.• Defendants should now also consider whether the plaintiff's complaint fails to meet the heightened pleading standards required in recent Supreme Court decisions.28 C. Defining the Injury In jurisdictions that have not yet decided whether to recognize a medical monitoring claim, the most hotly contested issues may be whether plaintiffs must demonstrate the existence of injury—and what constitutes an injury. In an attempt to circumvent

cases in a number of ways, with varying degrees of success. • Present, physical harm is traditionally required to establish a cognizable injury under negligence and product liability theories. Indeed, "[f]rom the beginnings of our negligence jurisprudence, 'injury' has been synonymous with 'harm' and connotes physical impairment or dysfunction, or mental upset, pain and suffering resulting from such harm."29 Recent opinions from both state and federal courts confirm this understanding.30 In June 2008, the Supreme Court of New Jersey affirmed the dismissal of a medical monitoring claim brought against the manufacturer of the pain killer VIOXX by interpreting the state's Product Liability Act as requiring a "personal physical injury,"31 and in August 2008 the United States District Court for the Western District of Missouri dismissed a medical monitoring claim brought against the maker of a medical device because there was no proof of physical injury.32 Most medical monitoring plaintiffs, however, argue that something less than present, physical harm is required. 28 Ashcroft v. Iqbal, 129 S. Ct. 1937, 1949-50 (2009); Bell Atl. Corp. v. Twombly, 550 U.S. 544, 556-58 (2007). 29 James A. Henderson, Jr. & Aaron D. Twerski, Asbestos Litigation Gone Mad: Exposure-Based Recovery for Increased Risk, Mental Distress, and Medical Monitoring, 53 S.C. L. REV. 815, 841-42 (2002). 30 See, e.g., Ratliff v. Mentor, 569 F. Supp. 2d 926, 928-29 (W.D. Mo. 2008); Sinclair, 948 A.2d at 593-96. 31 Sinclair, 948 A.2d at 595. 32 Ratliff, 569 F. Supp. 2d at 928-29. The Ratliff opinion declined to extend the Missouri Supreme Court's Meyer decision, (allowing medical monitoring for potential latent injuries resulting from exposure to toxic substances), to the product liability claim asserted by the Ratliff plaintiff. Id. 11

12.• Exposure alone is typically insufficient to constitute an injury. The Michigan Supreme Court, for example, recently reversed and remanded a case for entry of summary judgment on a medical monitoring claim, reasoning: if plaintiffs' claim is that by virtue of their potential exposure to [a hazardous substance] they have suffered an 'injury,' in that any person so exposed would incur the additional expense of medical monitoring, then their claim is also precluded as a matter of law, because Michigan law requires an actual injury to person or property as a precondition to recovery under a negligence theory.33 • "Subcellular" and "subclinical" injuries have been rejected by many courts as non-cognizable injuries. Such alleged injuries are viewed with skepticism, because the supposed "harm" is uncertain.34 As a 2005 decision put it, "a 'subclinical' condition, lacking in any contemporaneous physiological manifestations, is not a cognizable 'injury' under applicable tort law."35 The Supreme Judicial Court of Massachusetts, however, recently held that "subcellular or other physiological changes" provided a sufficient proof of "impact" to warrant medical monitoring, citing to the traumatic physical impact cases where diagnostic testing was allowed and referred to by those courts as "medical monitoring."36 • Increased risk, coupled with exposure, has been asserted successfully as an injury in a few cases. In 2004, for example, the Supreme Court of West Virginia, which first recognized medical monitoring in 1999,37 described the injury this way: 33 Henry v. Dow Chem. Co., 701 N.W.2d 684, 689 (Mich. 2005) (emphasis added). 34 See, e.g., Rainer v. Union Carbide Corp., 402 F.3d 608 (6th Cir. 2005) (holding that subcellular damage to workers from radiation exposure did not constitute a present physical injury sufficient to support a Price-Anderson Act claim). 35 Parker v. Brush Wellman, Inc., 377 F. Supp. 2d 1290 (N.D. Ga. 2005); Burns v. Jaquays Min. Corp., 752 P.2d 28, 31 (Ariz. Ct. App. 1987) ("Allowing plaintiffs to sue [for medical monitoring] for injuries when the disease is still subclinical would be an abrogation of the discovery rule."). 36 Donovan, 914 N.E.2d at 900-01. 37 Bower, 522 S.E.2d at 432-33 (W. Va. 1999). 12

13.The injury that underlies a claim for medical monitoring — just as with any other cause of action sounding in tort — is the invasion of any legally protected interest. The specific invasion of a legally protected interest in a medical monitoring claim consists of a significantly increased risk of contracting a particular disease relative to what would be the case in the absence of exposure.38 Similarly, the United States Court of Appeals for the Sixth Circuit in 2005 found that the plaintiff had standing to assert a claim for medical monitoring associated with a cardiac medical device, describing the injury as a risk of future harm: Instead of the injury in an enhanced risk claim [being] the anticipated harm itself and the injury in a medical monitoring claim [being] the cost of the medical care that will, one hopes, detect that injury we think it more accurate to find the increased risk of future harm is the injury in both types of cases. The difference lies in the remedy sought by the plaintiff.39 A number of cases, however, have gone the other way. For example, the Alabama Supreme Court in 2001 rejected a medical-monitoring claim based on increased risk from exposure to PCBs, reasoning that "a cause of action based on nothing more than an increased risk . . . would result in . . . cases [being decided] based upon nothing more than speculation and conjecture."40 And in May 2008, the Supreme Court of Oregon affirmed the

dismissal of a medical-monitoring claim brought against tobacco companies. According to the court, the proposed class representative's allegation that "exposure to defendants' products has significantly increased the risk that she will 38 State ex rel. Chemtall Inc. v. Madden, 607 S.E.2d 772, 785 (W. Va. 2004) (internal quotations and citations omitted). 39 Sutton v. St. Jude Med. S.C., Inc., 419 F.3d 568, 572 (6th Cir. 2005) (Tennessee law) (internal quotations and citations omitted). 40 Hinton v. Monsanto Co., 813 So. 2d 827, 829-30 (Ala. 2001). 13

14.contract lung cancer sometime in the future" was an insufficient injury to maintain a cause sounding in negligence.41 • The cost of medical monitoring as a purely economic injury also has been successfully asserted. Traditionally, the "economic loss" rule prohibits tort recovery based purely on economic losses for a product's defects or failures, resulting in no personal injury to the plaintiff or damage to plaintiff's other property.42 The theory behind the rule is that contract law is "regarded as the exclusive source for ascertaining when a seller is subject to liability for damages if the claim is based on intangible economic loss not attributable to physical injury to person or harm to a tangible thing other than the defective product itself."43 Despite this generally accepted economic losses doctrine, some courts still permit medical monitoring claims based purely on economic losses. The Illinois Court of Appeals in 2003, in a case brought by family members of children allegedly exposed to lead paint, equated medical expenses of screening for lead poisoning with medical expenses for treatment of an actual physical injury: [i]f a defendant's breach of duty makes it necessary for a plaintiff to incur expenses to determine if he or she has been physically injured, we find no reason why the expense of such an examination is any less a present injury compensable in a tort action than the medical expenses that might be incurred to treat an actual physical injury caused by such a breach of duty.44 In 2007, the Missouri Supreme Court agreed, holding that "[t]he injury for which compensation is sought is not a present physical injury. Instead, medical monitoring damages compensate the plaintiff for the quantifiable 41 Lowe v. Philip Morris USA, Inc., 183 P.3d 181, 184-185 (Or. 2008); see also Paz v. Brush Engineered Materials, Inc., 949 So. 2d 1, 5 (Miss. 2007) ("Mississippi law does not recognize a claim for medical monitoring based on increased risk of future disease."). 42 See MDU Res. Group v. WR Grace & Co., 14 F.3d 1274, 1279 n.6 (8th Cir. 1993); Apollo Group, Inc. v. Avnet, Inc., 58 F.3d 477, 480 (5th Cir. 1995). 43 Spring Motors Distributors, Inc. v. Ford Motor Co., 489 A.2d 660, 673 (N.J. 1985) (citing W. PROSSER & W. PAGE KEETON, HANDBOOK OF THE LAW OF TORTS § 95A at 680 (5th ed. 1984). 44 Lewis v. Lead Indus. Ass'n, Inc., 793 N.E.2d 869, 874 (Ill. App. Ct. 2003); In re Paoli R.R. Yard PCB Litig., 916 F.2d at 850 ("The injury in a medical monitoring claim is the cost of the medical care that will, one hopes, detect the injury."). 14

15.costs of periodic medical examinations reasonably necessary for the early detection and treatment of latent injuries caused by the plaintiff's exposure to toxic substances."45 In a 2005 opinion, however, the Michigan Supreme Court rejected an economic injury argument, reasoning: It is no answer to argue, as plaintiffs have, that the need to pay for medical monitoring is itself a present injury sufficient to sustain a cause of action for negligence. In so doing, plaintiffs attempt to blur the distinction between "injury" and "damages." While plaintiffs arguably demonstrate economic losses that would otherwise satisfy the "damages" element of a traditional tort claim, the fact remains that these economic losses are wholly derivative of a possible, future injury rather than an actual, present injury. A financial "injury" is simply not a present physical injury, and thus not cognizable under our tort system. Because plaintiffs have not alleged a present physical injury, but rather, "bare" damages, the medical expenses plaintiffs claim to have suffered (and will suffer in the future) are not compensable.46 At times, plaintiffs have switched theories of injury in the same case. In Lowe v. Philip Morris USA, Inc., for example, after plaintiffs unsuccessfully argued to the trial court that a significantly increased risk of contracting lung cancer was sufficient harm to state a negligence claim, they later argued on appeal that the economic cost of the medical monitoring constituted a present injury.47 Neither argument carried the day with the Oregon Court of Appeals or the Oregon Supreme Court.48 D. Impact of the Science on Motion to Dismiss The state of the science can affect the chances of success on a motion to dismiss. If the proposed medical screening test is not widely recommended in the medical community, defendants should attempt to educate the court on this issue as part of the motion to dismiss. 45 Meyer, 220 S.W.3d at 718 ("A physical injury requirement is inconsistent with the reality of latent injury and with the fact that the purpose of medical monitoring is to facilitate the early diagnosis and treatment of latent injuries caused by exposure to toxins."). 46 Henry, 701 N.W.2d at 691 (emphasis in original). 47 Lowe, 183 P.3d at 184 (Or. 2008). 48 Id. at 184-87. 15

16.IV. CONCLUSION Medical monitoring continues to be raised in complaints across the country. Because only fourteen state supreme courts have spoken on the matter, the issue of cognizable injury is likely to be the most contested issue in the next decade, as plaintiffs continue to ask courts to depart from traditional principles of tort recovery. Defendants facing medical monitoring claims should carefully consider the risk of losing a motion to dismiss when deciding whether to file such a motion. If defendants choose to file a motion to dismiss, they should take care to see that the plaintiff specifically defines the alleged injury and the type of medical testing that is being requested. DLI-6295059v2 16