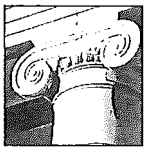

Toward a Defense of Mesothelioma Cases on Causation: Implications of Genetics

A Commentary by Mark G. Zellmer
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Today's defendants in asbestos litigation often face plaintiffs' claims that they have contracted mesothelioma from exposure to low or even doubtful doses of asbestos. In fact, from the defense perspective, one might suspect that the disease begets the exposure rather than the exposure causing the disease.

In such situations, the following points are important:

- Spontaneous mesothelioma occurs without exposure to asbestos or other environmental causes.
- Epidemiology regarding various fiber types, whether chrysotile, amosite, crocidolite or tremolite, fails to demonstrate and rather shows a lack of materially increased risk from low dose exposure to asbestos.
- Individual genetics rather than asbestos exposure explain why many people with low or doubtful exposure get mesothelioma.
- Although susceptibility to the oncogenic effects of asbestos may explain why some people who are substantially exposed get mesothelioma while others do not, proof is lacking that genetic predisposition causes people to be susceptible to mesothelioma from low dose asbestos exposure.

Low Doses and Spontaneous Mesothelioma

No one should be mistaken about this point: mesothelioma occurs without asbestos exposure and without other environmental exposures such as radiation or erionite.[1] In 1982, to study how mesothelial tumors may differ depending upon whether the tumor was or was not associated with asbestos, Hirsch and others identified cases of mesothelioma in which they were able to eliminate any possible exposure to asbestos.[2]

McDonald and McDonald went further using backward extrapolation from the rates of mesothelioma, particularly among females, to determine the background rate of spontaneous mesothelioma. Their conclusion was that the background rate of mortality from spontaneous mesothelioma was 1-2 per million of population.[3]

Numerous epidemiological studies demonstrate that a threshold exists for the occurrence of mesothelioma from asbestos exposure and that low doses of exposure are not causative.[4] For example, if chrysotile in fact causes mesothelioma, it has no observable effect to cause mesothelioma at least at 15 f/cc-years and more likely closer to 500 f/cc-years.[5] Despite the use of asbestos materials throughout naval ships, particularly amosite insulation, only the engine crew was at increased risk of mesothelioma.[6] Study of the Wittenoom crocidolite miners and millers found no excess incidence of mesothelioma per 10,000 man-years among those who worked three months or less.[7]
A study of the vermiculite workers found a statistically significant, increased relative risk of mesothelioma only when exposures exceeded 44 f/cc-years.[8]

As a result the question arises, if mesothelioma occurs without asbestos exposure or occurs only when the dose of exposure is significant, what is causing the mesothelioma? For a number of such cases, the answer may come from genetics.

Genetic Predisposition: Inherited Cancer Syndromes as a Cause of Mesothelioma Independent of Asbestos[9]

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The importance of hereditary, genetic predisposition to the development of a tumor is obvious considering the legal standards of causation. Looking to the Restatement, causation is not proven and in fact rebutted "if the harm would have been sustained even if the actor had not been negligent."[10] A genetic predisposition provides the basis for a finding that the harm would have been sustained in any event. The Restatement in the second subsection of this same provision provides that two causes, either sufficient to cause the result, is appropriate proof of causation.[11] If the cumulative exposure to asbestos is simply too small to cause the disease, this subsection has no applicability.

Tumors of various types occur due to inherited, genetic predispositions. As research has progressed, more of these cancer syndromes are being identified in both children and adults.[12] In fact 5-10 percent of tumors occur as a result of monogenic predispositions while another 30-50 percent occurs due to polygenic predispositions.[13] Mesothelioma, caused by one of a number of genetic predispositions, is not any different. Hirsch et al postulated already in 1982 the possibility of a natural disease process to explain spontaneous or idiopathic mesothelioma.[14]

As these issues are further analyzed, it will be clear these inherited cancer syndromes predispose people to a number of cancers including mesothelioma. There are common cellular and molecular pathways that lead to these tumors from these syndromes, including mesothelioma. Despite this commonality, asbestos is not even associated with most of the other types of cancers to which people with these syndromes are predisposed. If asbestos is not a necessary element in the causation of these other cancers, it should also not be an element in the cause of mesothelioma among those with inherited cancer syndromes and lacking sufficient asbestos exposure. In simplest terms, no matter what plaintiff lawyers and their experts tell us, mesothelioma is not some unique type of cancer associated only with asbestos and utterly divorced from a person's genetic makeup; instead, it is a tumor associated with and can be caused by genetic factors unrelated to asbestos exposure.[15]

TP53/Li-Fraumeni

In 1969, Frederick Li and Joseph Fraumeni first described the most clearly established, hereditary, tumor predisposition. It is an autosomal dominant pattern of various tumors including soft tissue sarcoma, breast cancer, brain tumors, adrenocortical carcinoma, leukemia, lymphoma, and melanoma as well as lung, prostate, pancreatic, and ovarian, kidney, testicular, laryngeal, head and neck cancers.[16] The Li-Fraumeni Syndrome, as it is now known, is a germline mutation in the TP53 gene, which controls cell growth and division and "encodes" or produces the tumor suppressor protein p53.[17]

Cancer among those with the mutation often contract cancer relatively early in life, but the mutation is also associated with late onset as well.[18] In 2001, in one cohort, approximately 180 families and individuals had been identified with the TP53 mutation.[19] Classic Li-Fraumeni Syndrome is clinically defined as follows:[20]

- A person, labelled the "proband," with a sarcoma before the age of 45;
- A first degree relative with any cancer before age 45;
- Another first or second-degree relative with any cancer before age 45 or a sarcoma at any age.

Subsequently, researchers have identified a "Li-Fraumeni like" Syndrome in which the patient has the TP53 mutation and suffers two cancers.[21]

Although chance must always be considered as an explanation for an association between a disease and a possible cause, researchers have concluded that "chance as the explanation for the familial association of sarcomas with other cancers" can be "formally excluded."[22] Numerous studies have demonstrated a significantly increased incidence of cancer for families and persons with Li-Fraumeni Syndrome.[23] Fifty percent of individuals with the TP53 mutation developed some sort of cancer by age 30. The risk over a lifetime in men is 70 percent while almost 100 percent in women. Having the TP53 mutation and contracting a

malignant tumor carries a cumulative probability of 57 percent that such person will develop a second cancer within 30 years of the first cancer.[24]

Li-Fraumeni Syndrome is now accepted as leading to malignant mesothelioma, particularly peritoneal mesothelioma.[25] The authors reported a woman, age 60, with the TP53 genetic mutation and relatives meeting the clinical definition of the classic syndrome who contracted peritoneal mesothelioma.[26] Li-Fraumeni-like Syndrome was discovered in a woman, age 54, with the TP53 mutation and coexistent endometrial cancer and peritoneal mesothelioma.[27]

BAP1

In 2010 Carbone et al identified BAP1 as a germline mutation creating an autosomal dominant cancer syndrome.[28] BRCA1 the associated protein 1 (BAP1) constitutes a tumor suppressor gene located on chromosome 3p21. Its mutation was found to be associated with increased risk of malignant mesothelioma and other neoplasms. The prevalence of cancer among a BAP1-mutated cohort is seven times greater than among the non-mutated cohort, 63 percent compared to 9 percent respectively. Other cancers in this syndrome include melanoma (uveal and cutaneous), lung, breast, renal and MBAIT.[29]

Some who have the BAP1 mutation and contracted mesothelioma have also had some dose of possible asbestos exposure. Family members in one instance had no occupational exposure but lived in residences with only trace amounts of chrysotile asbestos, leading the authors to ask "whether a genetic factor alone is sufficient for [malignant mesothelioma] development in these families."[30] In another instance two family members had occupational exposure and died of mesothelioma. The other family member who had the BAP1 mutation may have had take-home exposure from the other family members.[31] Both the dose of cumulative exposure and its contribution to the cause of mesothelioma in any of these family members is unknown.

Hence, the question arises whether BAP1 is an independent factor in the cause of mesothelioma or whether asbestos is a necessary addition to cause the disease. Science has directed efforts to answer such questions. A group reviewed pathology from 52 mesothelioma patients exhibiting the BAP1 mutation and compared it to indicia of exposure to asbestos. They found no statistically significant association between the BAP1 mutation and asbestos exposure.[32] Furthermore, researchers have studied asbestos exposure or the lack thereof among families with mesothelioma and prior history of cancer.[33] Any exposure to asbestos in these instances appears to be a chance occurrence unrelated to the cause of the mesothelioma. "[T]he asbestos associations comparing individuals with a family history with those without a history do not differ statistically so the appearance of an effect may be due to chance."[34]

In 2013 Carbone et al noted that the percentage of malignant tumors among the mutated BAP1 cohort had risen to 69.74 percent. They also explained that tumors among those affected with the BAP1 syndrome tended to but did not always suffer from the occurrence cancer at a somewhat younger age. Those with the BAP1 mutation who did not have cancer were all younger than age 55.[35] To the extent that these cancers also occur in the general population at a reasonable rate, the authors recommended larger population studies to prove the relationship causal.[36] However, as mesothelioma is a rare disease, the findings on mesothelioma are persuasive.

Carbone et al opined that mesothelioma as well as uveal and cutaneous melanoma in people with the mutation had common pathways controlled by BAP1 in the development of these malignancies.[37] In addition, already in 2012, Carbone et al found that 21 percent of persons with the BAP1 mutation contracted mesothelioma while no one in the non-mutated group had contracted the disease.[38] In 2013 they calculated a relative risk of 28.95 for mesothelioma among the BAP1 mutated cohort.[39] This can be compared to the findings on the Selikoff insulator cohort. Although the cohort is larger, the determination that 10 percent

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of the Selikoff insulator cohort contracted mesothelioma was sufficient to conclude that asbestos caused the incidence of mesothelioma among those workers. The even higher percentage associated with BAP1 is persuasive as proof that BAP1 is a cause of mesothelioma.

More than one researcher has found the BAP1 mutations in persons with mesothelioma, but without asbestos exposure.[40] Because the latency period is simply too short for the induction of an asbestos-related mesothelioma, the occurrence of that disease in children or adolescents, although exceedingly unfortunate, is instructive. Taylor et al published the occurrence of diffuse malignant peritoneal mesothelioma in an adolescent boy, age 16, with evidence of the BAP1 mutation and without any direct or indirect asbestos exposure.[41]

NF2/Neurofibromatosis Type 2

Neurofibromatosis Type 2 is a dominantly inherited tumor predisposition syndrome. NF2 refers to the tumor suppressor gene on chromosome 22q12. It provides the capability to produce an amino acid protein "595" also known as "Merlin."[42]

Significantly, this gene has suffered mutation in approximately 40-50 percent of mesotheliomas and is important to its tumorigenesis.[43] Bianchi et al opined that "[o]ur findings clearly implicate NF2 in malignant mesothelioma tumorigenesis. . ."[44]

The NF2 mutation predisposes to a number of tumor types including bilateral vestibular Schwannomas of the eighth cranial nerve and other brain tumors (meningiomas and ependymomas) as well as melanoma and carcinoma of the breast and colon.[45] The "commonly deleted" chromosomal areas in malignant mesothelioma overlap with the same sites often lost in other tumors.[46] No literature links these tumors with asbestos exposure except for possibly colon cancer for which such evidence is vanishingly close to non-existent. As a result it is easily conceivable that the pathways to induct these other tumors not related to asbestos exposure should be similar to the pathways that would induct mesothelioma without any substantial asbestos exposure.

Studies of mice with NF2 and only some exposed to asbestos showed greater, but not exclusive, tumor development among the asbestos exposed mice.[47] In addition, Baser et al found two individuals with long term employment in asbestos exposed occupations (22 and 25 years) both who contracted mesothelioma and had the NF2 mutation.[48] The authors noted that the evidence was "insufficient . . . to determine if . . . constitutional NF2 mutation confers an elevated risk of mesothelioma to asbestos-exposed people . . ."[49]

Genetic Susceptibility — A Red Herring

Plaintiffs attempt to perpetrate a myth that mesothelioma is somehow unique among tumors when it is not. When presenting a low dose case and confronting defendant's argument of a lack of causation, plaintiff's counsel seeks refuge in a simple, but specious argument: plaintiff or decedent contracted mesothelioma because he was especially susceptible to contracting the disease from small doses of inhaled asbestos. This argument appeals to the time honored tort principle of the plaintiff with the "egg shell" skull, meaning that a defendant takes his plaintiff as he finds him.[50] For application of this principle, plaintiff must prove that he had the egg shell skull or a special sensitivity to a toxin, likely a simple proposition in the personal injury context but a far more complex problem of proof in an asbestos or toxic tort case.

Plaintiff seldom offers proof of the predicate, rather offering an assertion that he was in fact susceptible, simply because he has the disease. The real issue is not just susceptibility, but susceptibility to what dose.

Only small numbers of people exposed to asbestos contract mesothelioma.[51] Insulators are well known to be at an elevated risk of mesothelioma due to the amount of their greater exposure to asbestos than many other occupations.[52] At the end of 1986, slightly in excess of 9 percent of deaths among the Selikoff insulator cohort were due to mesothelioma.[53] As a result all persons who contract mesothelioma due to asbestos exposure, even those highly exposed, have some probable, genetic susceptibility.[54]

That hardly provides any insight into low dose exposure as an alleged cause of mesothelioma. Plaintiff should prove that (1) some genetic abnormality causes susceptibility to mesothelioma from a low dose, not just any dose of asbestos exposure and (2) plaintiff or decedent in fact has this genetic characteristic. Without such evidence, plaintiff's claim that his mesothelioma came from a susceptibility to a low dose exposure is mere speculation and conjecture. In the Hanford Nuclear Reservation Litigation, plaintiffs argued that they were all sensitive to radiation exposure and thereby developed thyroid cancer. The argument failed because plaintiffs could not offer scientific proof of such sensitivity.[55] Science supports this view that genetic make-up will cause some people to contract mesothelioma without asbestos exposure or independent of low dose exposure to asbestos while genetic susceptibility explains why some people but not others with significant occupational exposure to asbestos contract mesothelioma. In 2013 a number of authors

endeavored to determine the potential impact of genetics as a cause of mesothelioma.[56] At the outset, the authors noted that only 5-17 percent of individuals "heavily exposed to asbestos" ultimately develop malignant pleural mesothelioma. This occurrence would thereby imply that a "genetic component" contributes to the etiology of the disease. They studied 392 cases of mesothelioma and 367 controls in Italy and another approximately equal number in Australia. The tissue of the cases and controls were tested for 330,879 different SNPs.[57] Among the Italian cohort, the authors determined exposure to asbestos based upon occupational history. The exposure was divided into three groups: high exposure subjects were asbestos cement and asbestos textile workers, insulators, shipyard workers and dockers; low exposure subjects were others with lesser expected occupational exposure such as pipefitters, boilermakers, laborers, and electricians; and the final category of subjects was no/unlikely exposure. Matullo et al discovered that 10 selected SNPs made "an independent contribution" to the causation of malignant pleural mesothelioma, in some instances, more than doubling the risk of the disease. They also found that occupational exposure in association with these SNPS, both high and low exposure, substantially increased the risk of mesothelioma.[58] Interestingly, some of the SNPs, namely FOXK1 and THRB, are related to the BAP1 gene. The authors concluded "genetic risk factors" should be taken into account in the "risk profile of people with a high exposure to asbestos."[59]

Most of the talk about a special susceptibility to mesothelioma from low dose exposure comes from experiments on mice with the dominant BAP1 mutation. Some researchers found that mice with the BAP1 mutation contracted mesothelioma in greater proportion if exposed to relatively low doses.[60] Of course what is found in animals may not apply to humans. In addition, it is especially difficult to compare levels and doses of exposure to asbestos between mice and men. This is especially true when the mice are exposed through direct injection into the peritoneum while human exposure almost invariably comes from inhalation. Certainly, a dose from injection into the peritoneum of a mouse cannot be correlated to a dose through human inhalation. Most tellingly, finding an increased number of cases of peritoneal mesothelioma in mice from low doses is inconsistent with human experience. Prolonged and heavy exposure, not a low dose exposure, is necessary to cause peritoneal mesothelioma in humans.[61] Similar to the Hanford Litigation, plaintiffs in asbestos cases assert susceptibility but fail to offer proof that a plaintiff has a particular genetic condition and that such condition has made him individually susceptible to mesothelioma from a low dose exposure. This is not surprising. No scientific literature has made such a link in humans.

Methods of Genetic Testing[62]

Likely the most common method to assess a genetic condition is cytogenic testing. A technician draws blood from which white blood cells, particularly the T lymphocytes, are separated. Cells from other tissue, including bone marrow and biopsy specimens, may also be used. The cells are cultured for several days. The chromosomes are spread and fixed on a slide and then stained to allow identification of each chromosome. Fluorescent in situ hybridization, known as "FISH," bathes the chromosomes in fluorescent molecules to identify abnormalities, including those associated with inherited cancer syndromes.

There are two other methods. Biochemical testing examines the proteins rather than the genes. Testing requires material with the proteins present, being blood, urine, or cerebrospinal fluid. Measurements of protein activity reveal chromosomal issues. As proteins degrade rapidly, precise specifications for such testing must be followed.

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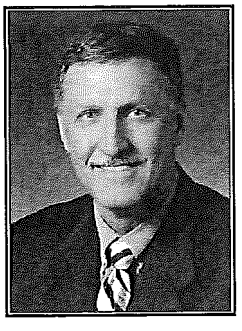

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Molecular or direct DNA testing requires a small sample of almost any tissue, but the gene sequence to be examined must be known in advance. Molecular testing utilizes a number of different technologies to determine the gene sequence sought.

Obtaining the necessary tissue will require a court order. A biopsy sample may be helpful and may possibly be sufficient if it has both normal and neoplastic tissue; however, a blood sample may be necessary to obtain clearly normal tissue or if biopsy specimens are not available. Although drawing blood is of course minimally invasive, plaintiff may argue otherwise. A trial court confronted this issue in California faced with a young man claimed to be deathly afraid of needles. The court allowed the testing, including drawing blood, reasoning that the defendant had a right to present a defense.[63]

Bringing It Altogether: Industrial Hygiene, Family History and Genetic/Molecular Testing

Separating an asbestos-caused mesothelioma from a spontaneous mesothelioma caused by genetics depends upon any one of a number of factors:

- The alleged dose of asbestos exposure;
- Identification of the mutation in normal and/or tumor tissue of plaintiff/decedent;
- Identification of the mutation in tissue of first degree relatives;
- Occurrence of cancer in first and second degree relatives.

Of course, failure to discover a genetic predisposition will not mean that a low dose caused the mesothelioma; instead, revealing a genetic predisposition is a much more persuasive explanation for a jury about why a person has mesothelioma.[64]

There are a number of steps in preparation of the defense. First, based upon a thorough deposition of plaintiff's exposure witnesses, an industrial hygienist must calculate the dose through a retrospective dose assessment. Second, a medical expert should be well versed in the scientific and medical literature and prepared to testify that the dose calculated by the hygienist is not sufficient to expose plaintiff to any materially increased risk of mesothelioma and in fact did not cause the mesothelioma. Third, from deposition and review of medical records, counsel and defense experts must establish any family history of cancer among blood relatives as well as any prior or concurrent cancer suffered by plaintiff. Fourth, defendant should perform genetic testing on plaintiff's tissues. This may require a court order for a blood sample.[65] Fifth, defendant must be prepared to present a genetics expert to opine that a genetic predisposition is the cause of plaintiff's mesothelioma.

A successful development of such a defense provides an opportunity to rebut plaintiff's unscientific siren song that a small dose of exposure from defendant's product or premises caused plaintiff's mesothelioma.

Footnotes

[1] The term, "spontaneous," is similar to the term, "idiopathic." The former suggests that the tumor occurred without environmental inducement. The latter term implies the same, but literally means the cause is unknown. Plaintiffs often complain that idiopathic mesothelioma is a "litigation" defense with no basis in fact; however, textbooks refer to "idiopathic" as a cause of mesothelioma. Thurlbeck W. et al. Pathology of the Lung. (Thieme Medical Publishers, New York: 1995) at 1086.

[2] Hirsch A. et al. "Features of Asbestos-exposed and Unexposed Mesothelioma." American Journal of Industrial Medicine. Vol. 3 (1982) at 413, 421.

[3] McDonald J.C. et al. "The Epidemiology of Mesothelioma in Historical Context." European Respiratory Journal. Vol. 9 (1996) at 1932, 1937; Ilgren and Wagner also provides a complete discussion about the occurrence of spontaneous mesothelioma. Ilgren et al. "Background Incidence of Mesothelioma: Animal and Human Evidence." Regulatory Toxicology and Pharmacology." Vol. 13. (1991) at 133.

[4] Various well known researchers on the hazards of asbestos exposures have already found evidence of a threshold below which the risk of mesothelioma is non-existent or at least vanishingly small, i.e. low enough that it is neither measurable nor meaningful. E. Ilgren et al. "Asbestos Related Mesothelioma: Evidence for a Threshold in Animals and Humans." Regulatory Toxicology and Pharmacology. Vol. 13 (1991) at 116, 119. K. Browne in Parkes Occupational Lung Disorders (Butterworth, Heineman: 1982) at 481.

[5] Pierce, J.S. et al "An Evaluation of Reported No-Effect Chrysotile Asbestos Exposures for Lung Cancer and Mesothelioma." Critical Reviews in Toxicology. Vol. 38 (2008) at 191, 193, 194-204.

[6] Strand L. et al. "Asbestos-Related Cancers Among 28,300 Military Servicemen in the Royal Norwegian Navy." American Journal of Industrial Medicine, Vol. 53 (2010) at 64-71.

[7] Hobbs, M.S.T. et al "The Incidence of Pneumoconiosis, Mesothelioma and Other Respiratory Cancer In Men Engaged in Mining and Milling Crocidolite in Western Australia." Biological Effects of Mineral Fibers Vol. 92 (1980) at 615, 619.

[8] Larson, M.S. et al. "Vermiculite Worker Mortality: Estimated Effects of Occupational Exposure to Libby Amphibole." Journal of Occupational and Environmental Medicine, Vol. 52(5) (May 2010) at 555, 558.

[9] Some explanation of the concepts of genetics may be helpful.

- All normal human cells except the sperm and the egg contain 23 pairs of chromosomes. The sperm and the egg each contain only one set. Each chromosome contains many genes. The DNA sequences in the cells and hence in the chromosomes are the instructions for cell activity.

- The genome is the totality of all genes of an organism plus non-coded regions of chromosomes such as chromosomal structure. In humans, the genes are 2 percent of the genome which is approximately 20,000 to 25,000 genes.

- A somatic mutation is a genetic alteration, not inherited from parents, but acquired by a cell and then passed to the progeny of that cell, i.e. from cell to cell. A somatic mutation may not have and often does not have an environmental cause. Epigenetic refers to an external modification to DNA that may turn genes off or on but does not modify the DNA sequence itself.

- Germline refers to inherited characteristics. Although the distinction is a bit artificial because some overlap occurs, cells in a germline are called germ cells while all other cells are somatic cells.

- Genetic diseases from abnormalities in the chromosomes (deletion, modification, addition) can occur due to inheritance or due to random events in formation of reproductive cells. The latter is more frequent.

- "Autosomal dominant" refers to inheritance of a genetic characteristic on one of the non-sex chromosomes, including predisposition to a disease, occurring when an individual inherits one copy of a dominant gene from one parent. Dominant inheritance means an abnormal gene from one parent can cause the characteristic, even though the matching gene from the other parent is normal.

- "Autosomal recessive" refers to inheritance of a genetic characteristic, including predisposition to a disease, occurring only when both genes in the pair of non-sex chromosomes are affected, i.e. it must come from both parents.

- There are three other methods by which reproduction passes genetic conditions: mitochondrial transmission (only females can pass the condition but it passes to both male and female offspring); X-linked dominant trait (passed from females mainly to female offspring but sometimes male offspring); and X-linked recessive trait (passed to males more than females; both parents must have the gene to pass to a daughter while only a mother is necessary to pass the condition to a son). These last three are not germane to the discussion in this article.

For a more in depth discussion of this and other concepts of genetics and genetic diseases and conditions, see Genetic Alliance/ District of Columbia Department of Health. Understanding Genetics: A District of Columbia Guide for Patient and Health Professionals (2010).

[10] Restatement (Second) of Torts, Section 432(2) (1965); Restatement (Third) of Torts, Section 26 (2014).

[11] Id.

[12] McBride K. et al. "Li-Fraumeni Syndrome: Cancer Risk Assessment and Clinical Management." Clinical Oncology. Vol. 11 (2014) at 260.

[13] Lubinski J. et al. "Molecular Basis of Inherited Predisposition for Tumors."Acta Biochimica Polonica. Vol. 49(3) (2001) at 571.

[14] Hirsch, supra. at 421.

[15] The genetic syndromes discussed herein should not be considered to be exclusive. If plaintiff/decedent does not have one of these syndromes, it does not mean that asbestos was the cause of the mesothelioma. These syndromes are further proof that asbestos did not cause the disease. Further genetic syndromes will almost certainly be discovered in the future.

[16] Li F. et al. "A Cancer Family Syndrome in Twenty-four Kindred." Cancer Research. Vol. 48 (1988) at 5358; McBride, supra. at 262.

[17] McBride, supra.

[18] Ruijs M. et al. "Late-onset Common Cancers in a Kindred with an Arg213Gin TP53 Germline Mutation." Familial Cancer. Vol. 5 (2006) at 169.

[19] Birch J. et al. "Relative Frequency and Morphology of Cancers in Carriers of Germline TP53 Mutations." Oncogene. Vol. 20 (2001) at 4621, 4623.

[20] Celeen W. "Malignant Peritoneal Mesothelioma in a Patient with Li-Fraumeni Syndrome." Journal of Clinical Oncology. Vol. 29(17) (2011) at 503.

[21] Chao A. et al. "Molecular Characteristics of Endometrial Cancer Coexisting with Peritoneal Malignant Mesothelioma in Li-Fraumeni-like Syndrome." BMC Cancer. Vol. 15(8) (2015) at 1.

[22] Li, supra. at 5361.

[23] McBride, supra.

[24] Chao, supra. at 4-5

[25] Ceelen, supra.

[26] Id. Six first degree relatives with cancer in three generations: astrocytoma, chondrosarcoma, leiomyosarcoma, gastric adenocarcinoma/breast cancer (same relative), two spinal schwannomas and colorectal cancer.

[27] Chao, supra. It is interesting that Wilm's tumor is strongly identified with TP53 mutations since mesothelioma is often positive for WT-1 immuno-histochemical staining. Birch, supra. at 4625.

[28] Carbone M. et al. "BAP1 Cancer Syndrome: Malignant Mesothelioma, Uveal and Cutaneous Melanoma and MBAITs." Journal of Transitional Medicine. Vol. 10 (2010) at 10.1186/1479-5876-10-179 (hereinafter "Carbone, JTM ").

[29] Id.

[30] Testa J. et al. "Connecting Molecular Pathways to Hereditary Cancer Syndromes." 2013 ASCO Educational Book at 81, 82.

[31] Sonja-Klebe et al. "BAP1 Hereditary Cancer Predisposition Syndrome: A Case Report and Review of Literature." Biomarker

Research, Vol. 3 (2015) at 14, 15. The authors did not discuss whether those occupationally exposed had high or low exposure occupations, something quite material to the sufficiency of take home exposure to cause mesothelioma.

[32] Azrt L. et al. "BAP1 Protein is a Progression Factor in Malignant Pleural Mesothelioma." Pathology and Oncology Research. Vol. 20 (2014) at 145, 148, 149.

[33] Heineman E. "Mesothelioma, Asbestos, and Reported History of Cancer in First Degree Relatives." Cancer. Vol. 77(3) (1996) at 549, 554.

[34] Id. at 553.

[35] Carbone M. et al. "BAP1 and Cancer." National Cancer Review. Vol. 13(3) (March 2013) at 153, 155 (hereinafter, "Carbone, NCR, supra").

[36] Id.

[37] Id. at 158.

[38] Carbone, JTM, supra.

[39] Carbone, NCR, supra at 155.

[40] Wiesner T. "Toward an Improved Definition of the Tumor Spectrum Associated with BAP1 Germline Mutations." Journal of Clinical Oncology. ico.ascopubs.org/content/30/32/e337.full.

[41] Taylor S. "Malignant Peritoneal Mesothelioma in an Adolescent Male with BAP1 Deletion." Journal of Pediatric Hematology and Oncology. Vol 37 (5) (2015) at 323. For a further discussion of both sides of this argument, see Sneddon S. et al. BAP1 Mutations in Mesothelioma: Advances and Controversies, "Current Pulmonology Reports. DOI: 10.1007/s13665-016-0132-1. Due to "the many reports of cases of mesothelioma where there has been no evidence . . . of asbestos exposure . . . it is postulated that there may be genetic factors associated with the risk of mesothelioma." However, the authors note that in a family with the BAP1 mutation, the family members with asbestos exposure got mesothelioma while the family member without asbestos exposure got a different tumor. The dose was not discussed; hence, this hardly answers the question since no one denies that asbestos in high enough doses can cause mesothelioma.

[42] Yokoyama, T. et al. "YAP1 Is Involved in Mesothelioma Development and Negatively Regulated by Merlin Through Phosphorylation." Carcinogenesis. Vol. 59(11) (2008) at 2139; Monteiro de Assis, L.V. at al. "The Role of Key Genes and Pathways Involved in the Tumorigenesis of Malignant Mesothelioma." Biochimica et Biophysica Acta. Vol. 1845 (2014) at 232, 236-237.

[43] Monteiro, supra . at 237. Silencing the gene occurs in only a subset of mesothelioma cell lines. Deguen B. et al. "Heterogeneity of Mesothelioma Cell Lines as Defined by Altered Genomic Structure and Expression of the NF2 Gene." International Journal of Cancer Vol. 77(4) (1998) at 554.

[44] Bianchi A. et al. "High Frequency of Inactivating Mutations in the Neurofibromatosis Type 2 Gene (NF2) in Primary Malignant Mesothelioma." Proceedings of the National Academy of Sciences USA. Vol. 92 (1995) at 10856.

[45] Monteiro, supra; Bianchi A., supra. at at 10854.

[46] Murthy S. et al. "Asbestos, Chromosomal Deletions, and Tumor Suppressor Gene Alterations in Human Malignant Mesothelioma." Journal of Cellular Physiology. Vol. 180 (1999) at 150, 155.

[47] Id.

[48] Baser M. et al. "Neurofibromatosis 2 (NF2) and Malignant Mesothelioma in a Man with a Constitutional NF2 Missense Mutation." Familial Cancer. Vol. 4 (2005) at 321.

[49] Id. at 322. To the extent that this evidence might suggest that NF2 mutations increase the risk of an asbestos caused mesothelioma, the occurrence of mesothelioma was only at substantial doses.

[50] Colonial Inn Motor Lodge, Inc. v. Gay, 288 Ill.App.3d 32, 45, 680 N.E.2d 407, 416 (1997); Heppner v. Atchison, Topeka, and Santa Fe Ry. Co., 297 S.W.2d 497, 504 (Mo. 1956).

[51] C. Bianchi et al. "Susceptibility and Resistance in the Genesis of Asbestos-related Mesothelioma." Indian Journal of Occupational and Environmental Medicine. Vol. 12, part 2 (August, 2008) at 57, 59.

[52] J.C. McDonald et al. "The Epidemiology of Mesothelioma in Historical Context." European Respiratory Journal. Vol. 9 (1996) at 1932, 1937 (insulators' odds ratio reflecting the risk of mesothelioma is 46).

[53] I. Selikoff et al. "Asbestos-Associated Deaths among Insulation Workers in the United States and Canada, 1967-1987." Annals of the New York Academy of Sciences. Vol.643 (1991) at 1, 7 (458 deaths from mesothelioma compared to 4951 total deaths).

[54] Bianchi, supra, at 59.

[55] In re Hanford Nuclear Reservation Litigation, No. CY-91-3015-AAM, 1998 WL 775340, at 64-65.

[56] Matullo G. et al. "Genetic Variants Associated with Increased Risk of Malignant Pleural Mesothelioma: A Genome-Wide Association Study." PlosOne. http://dx.doi.org/10.1371/journal.pone.0086 1253 (April 13, 2013).

[57] SNP is a single nucleotide polymorphism (pronounced "snip"), essentially a variant in the DNA. Although SNPs, may contribute to genetic make-up, they are not genes. Some SNPs, particularly those occurring in areas between the genes, may have little effect on human condition. Other SNPs occur in the genes and are associated with any number of genetic differences among humans including susceptibility and response to disease.

[58] OR of 45.28 for high exposure and OR of 15.31 for low exposure.

[59] The authors noted the limitations to this study. No single marker "reached the genome-wide significance threshold." There was heterogeneity of the SNPs identified as significant in the Italian cohort compared to the Australian cohort.

[60] Napolitano A. et al. "Minimal Asbestos Exposure in Germline BAP1 Heterozygous Mice Is Associated with Disregulated Inflammatory Response and Increased Risk of Mesothelioma." Oncogene. Vol. 35 (2016) at 1996, 1998; Xu J. et al. "Germline Mutation

of BAP1 Accelerates Development of Asbestos-induced Malignant Mesothelioma." Cancer Research., Vol. 74 (2014) at 4388; Carbone, NCR, supra at 158.

[61] Hemminike, K. et al. "Time Trends and Occupational Risk Factors for Pleural Mesothelioma in Sweden." Journal of Occupational and Environmental Medicine. Vol. 45(4) (April 2003) at 456 (peritoneal mesothelioma requires higher exposure); Hobbs, M.S.T. et al "The Incidence of Pneumoconiosis, Mesothelioma and Other Respiratory Cancer in Men Engaged in Mining and Milling Crocidolite in Western Australia." Biological Effects of Mineral Fibers Vol. 92 (1980) at 615, 619 (pleural mesothelioma occurring at cumulative exposures above 6 f/cc-years and peritoneal mesothelioma occurring at cumulative exposures above 16 f/cc-years); Roggli, V. et al. "Malignant Mesothelioma and Occupational Exposure to Asbestos: A Clinicopathological Correlation of 1445 Cases." Ultrastructural Pathology, Vol. 26(2) (March-April 2002) at 55 (peritoneal tumors predominate with heavier exposure); Selikoff, supra. (40 percent more peritoneal than pleural cases of mesothelioma among the heavily exposed Selikoff insulator cohort); Marinaccio, A. et al. "Incidence of Extrapleural Malignant Mesothelioma and Asbestos Exposure, from the Italian National Register." Occupational Environmental Medicine. Vol. 67 (2009) at 760 (studies comparing the degree of exposure with occupation and ultimate site of mesothelioma indicate the peritoneal site as being associated with longer and more intense exposure); Fonte, R. et al. "Asbestos-Induced Peritoneal Mesothelioma in a Construction Worker." Environmental Health Perspectives. Vol. 112 (51) (April, 2004) at 616 (peritoneal mesothelioma seems to require "a particularly intense and prolonged exposure"); Roggli, V. "The Role of Analytical SEM in the Determination of Causation in Malignant Mesothelioma." Ultrastructural Pathology. Vol. 30(1) (2006) at 31 (greater exposure is necessary to cause peritoneal mesothelioma).

[62] Genetic Alliance/ District of Columbia Department of Health. Understanding Genetics: A District of Columbia Guide for Patient and Health Professionals (2010) at 82-83.

[63] San Francisco Examiner, June 7, 1994 at www.nwitimes.com.

[64] In addition, a genetic predisposition may explain why a person has mesothelioma regardless of his or her exposure, minimal or substantial.

[65] Whether tissue or a blood sample can be obtained from first or second degree relatives and would be beneficial to this analysis is not addressed.