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CAN BIOMARKERS AND GENETICS HELP PREDICT THE FUTURE OF MALIGNANT PLEURAL MESOTHELIOMA?

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Introduction

The unremitting march of asbestos-related mesothelioma case filings continues across the country. For the patient, the medical community, and the defendants, finding ways to predict, diagnose, alter, and treat this horrific malady are front and center. This article focuses on evolving and cutting-edge medical science that offers hope in forecasting one variety of this dreadful disease.

Background

Malignant pleural mesothelioma (“MPM”) is a fatal cancer primarily affecting workers exposed to asbestos fibers. Despite predictions of decline in incidences of mesothelioma, global incidences are increasing. Schneider, Marc A., et al., *Glycodelin is a potential novel follow-up biomarker for malignant pleural mesothelioma*, *Oncotarget*, Vol. 7, No. 44, p. 71285 (October 4, 2016), available at [http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path\[\]=12474&pubmed-linkout=1](http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=12474&pubmed-linkout=1). Occupational studies demonstrate that inhalation of asbestos produces asbestosis, malignant mesothelioma, lung, and other cancers. Baumann, Francine and Carbone, Michele, *Environmental risk of mesothelioma in the United States: An emerging concern – epidemiological issues*, *J. of Toxicology and Environmental Health, Part B*, Vol. 19, Nos. 5-6, pp. 231-249 (2016), p. 231, available at <http://dx.doi.org/10.1080/10937404.2016.1195322>. The Occupational Safety and Health Administration (“OSHA”) began regulating occupational exposure in the early 1970s; in 1989 the U.S. Environmental Protection Agency banned most asbestos-containing products. *Id.*



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Early detection of malignant pleural mesothelioma is essential for a more favorable prognosis. Schneider, *supra* at 71285. However, it remains difficult to diagnose MPM due to its various histologic patterns and cytomorphic appearances with different variations. Since the day it was defined, malignant pleural mesothelioma has been included on the list of tumors with ever-changing differential diagnoses. Sahin, Nurhan, et al., *The Role of CD90 in the Differential Diagnosis of Pleural Malignant Mesothelioma, Pulmonary Carcinoma and Comparison with Calretinin*, *Pathol. & Oncol. Res.*, Vol. 23, Issue 3, pp. 487-491 (July 2017).

Mechanisms to help diagnose this difficult tumor as early as possible include identifying new and specific biomarkers which may indicate the likelihood of developing this disease. Further, recent research into a possible genetic link to MPM may also yield earlier diagnoses and treatment options.

If biomarkers indicating the likelihood of developing malignant pleural mesothelioma can be identified, the disease can be diagnosed and treated much earlier.

Biomarkers

Biomarkers are distinct biochemical, genetic, or molecular characteristics indicating a particular biological condition or process. If biomarkers indicating the likelihood of developing malignant pleural mesothelioma can be identified, the disease can be diagnosed and treated much earlier. As indicated above, early diagnosis increases the chances of a favorable prognosis. To date several biomarkers have been analyzed, but few can be said to be reliable. Ledda, Caterina and Rapisarda, Venerando, *Letter to the editor: "Malignant Pleural Mesothelioma: The Need to Move from Research to Clinical Practice,"* *Archives of Medical Research*, Vol. 47, Issue 5, p. 407 (July 2016), available at <http://www.arcmedres.com/article/S0188-4409%2816%2930137-0/pdf>. Recently, two promising biomarkers have been discovered: (1) glycodelin and (2) circulating microRNAs.

1. Glycodelin

Glycodelin is a protein found in the uterus and is well-characterized during menstruation and pregnancy. Schneider, *supra* at 71286. Its official name is progestagen-associated endometrial protein ("PAEP"). Recent data have shown the involvement of glycodelin in several tumors, including ovarian cancer, breast cancer, and melanoma. *Id.*

Researchers have examined whether glycodelin is expressed and secreted by malignant pleural mesothelioma, rendering

glycodelin useful as a potential biomarker for early diagnosis. Researchers have also examined whether glycodelin can be used to monitor tumor response to treatment.

The presence of glycodelin was investigated in the serum of patients with benign and malignant thoracic diseases. *Id.* Most patients did not show increased glycodelin **except** those with malignant pleural mesothelioma. *Id.* Glycodelin serum concentrations were also compared to those of soluble mesothelin-related peptide ("SMRP"), a known malignant pleural mesothelioma biomarker, in untreated mesothelioma patients and in patients with pleurisy. Glycodelin and the SMRP serum concentrations were increased in mesothelioma patients compared to pleurisy patients. *Id.* Although neither SMRP nor glycodelin alone were significant factors for overall survival of the patient, combining both factors strongly increased the prognostic value. *Id.* at 71288-71289. Further, glycodelin concentration levels before therapy were higher than after the first therapy, and frequently increased during follow-up until the patient's death. *Id.* at 71289. Both glycodelin and glycodelin A, an immunosuppressive form of glycodelin which suppresses the body's immune response, were strongly expressed in malignant pleural mesothelioma tissue. *Id.* at 71290-71291. Indeed, strong expression levels of glycodelin A in the tumor appear to have a positive effect on overall survival of malignant pleural mesothelioma patients, possibly because glycodelin A may reduce the inflammation caused by the disease. *Id.* at 71293.

What does all of this mean? Increased glycodelin concentrations were found in patients with malignant pleural mesothelioma. Indeed, these levels were higher than in benign diseases such as chronic obstructive pulmonary disease ("COPD") and pleurisy. Analyses indicated that glycodelin reached values that were comparable to or better than other known biomarkers for malignant pleural mesothelioma. Thus, glycodelin might be used as a supportive biomarker for malignant pleural mesothelioma when diagnosis of this disease is difficult. Further, using glycodelin in conjunction with SMRP serum has been suggested to predict mesothelioma occurrence. This suggested use of glycodelin for early diagnosis is further supported by the finding of one patient in the pleurisy group, who had the highest glycodelin serum concentration and was later diagnosed with malignant pleural mesothelioma. *Id.* at 71291. In sum, glycodelin might be a feasible serum marker for the diagnosis and monitoring of this cancer.

2. Circulating microRNAs

In addition to glycodelin, recent studies have also identified using microRNAs ("miRNAs") to screen, diagnose, and follow-up cases of malignant pleural mesothelioma. Bononi, Ilaria, et

al., *Circulating microRNAs found dysregulated in ex-exposed asbestos workers and pleural mesothelioma patients as potential new biomarkers*, *Oncotarget*, Vol. 7, No. 50, pp. 82700-82711 (2016), available at <https://doi.org/10.18632/oncotarget.12408>. RNA plays a role in gene expression. While the majority of miRNAs are located within the cell, some miRNAs, called circulating miRNAs, are found outside the cell in the extracellular environment.

Researchers compared circulating miRNAs in serum samples of (1) malignant pleural mesothelioma patients previously exposed to asbestos; (2) workers previously exposed to asbestos without disease; and (3) healthy subjects. *Id.* at 82706. They found that the total number of circulating miRNAs in each group was different -- high differences in miRNA expression profiles in all three groups were identified. More miRNAs were expressed in healthy subjects than in those with mesothelioma or those previously exposed to asbestos without disease. Results indicate a general down-regulation (decrease) of miRNAs in tumors compared to normal tissues, leading the authors to speculate that exposure to asbestos fibers may induce dysregulation of the immune system. *Id.*

Scientific studies on these biomarkers have yet to be finalized to recognize those with the highest sensitivity and specificity.

However, can mutations in other genes predict the risk of other types of cancer, particularly mesothelioma? The answer, at least with respect to mesothelioma, is sort of.

Genetics

The link between genetic mutations and the incidence of cancer is particularly well known due to the finding that a genetic mutation in the BRCA1 or BRCA2 gene causes an increased risk of breast cancer. However, can mutations in other genes predict the risk of other types of cancer, particularly mesothelioma? The answer, at least with respect to mesothelioma, is sort of.

BAP1 Tumor Predisposition Syndrome (“*BAP1*-TPDS”) is associated with an increased risk for certain cancers, including malignant mesothelioma. Pilarski, Robert, et al., *BAP1 Tumor Predisposition Syndrome*, Gene Reviews (Internet), Seattle, WA: University of Washington, Seattle (October 13, 2016), available at <https://www.ncbi.nlm.nih.gov/books/NBK390611/>. *BAP1* is a tumor suppressor gene. Germline (inherited) mutations in the *BAP1* gene are associated with a hereditary tumor predisposition syndrome that occurs in family members with several cancer types, including malignant mesothelioma, which is the second most frequent cancer (22%) identified in *BAP1*-TPDS. *Id.* The median age of onset of malignant me-

sothelioma in individuals with *BAP1*-TPDS was significantly earlier (55-58 years) than the age of sporadic onset of malignant mesothelioma (68-72 years). *Id.* Although survival in persons with *BAP1*-related malignant mesothelioma may be significantly longer than people with other types of *BAP1*-related cancers, the data are not consistent or conclusive. *Id.* Growing evidence suggests that *BAP1* pathogenic variants interact with environmental asbestos exposure to increase the risk for malignant mesothelioma. *Id.* Germline (inherited) *BAP1* pathogenic variants have been identified in 6% to 20% of individuals with familial mesothelioma. *Id.*

Although the occurrence of malignant mesothelioma in clusters among blood relatives suggests increased genetic susceptibility, a recent study analyzing *BAP1* in four families with multiple mesothelioma cases to investigate possible *BAP1* alterations associated with an inherited cancer syndrome found differently. Ascoli, Valeria, et al., *Mesothelioma Families Without Inheritance of a BAP1 Predisposing Mutation*, *Cancer Genetics*, Vol. 209, Issue 9, pp. 381-387 (2016), available at [http://www.cancerjournal.org/article/S2210-7762\(16\)30221-6/pdf](http://www.cancerjournal.org/article/S2210-7762(16)30221-6/pdf). The study found that malignant mesothelioma cases in the same family should be considered equivalent to sporadic, and not inherited, malignant mesothelioma. *Id.* at 386. Although the *BAP1* gene was altered, the alterations were in somatic (non-inherited) cells, not germline (inherited) cells *Id.* at 383. These non-inherited genomic *BAP1* alterations are common in malignant mesothelioma. *Id.* at 386.

Findings from families described in this study without a predisposing germline *BAP1* mutation are similar to those reported by other investigators. *Id.* at 385. Most family clusters have asbestos exposure and a family history of malignancies other than those typical of *BAP1*-TPDS, suggesting that other genetic or epigenetic factors may be responsible for the high incidence of malignant mesothelioma in these families. *Id.* at 385-386. On the whole, researchers have not discounted the possibility of a genetic link between genes and malignant mesothelioma.

Early Diagnosis

The earlier a disease is diagnosed, the better the prognosis. Currently immuno-histochemical markers are used to differentiate malignant mesothelioma from benign mesothelial proliferations, but differentiating between malignant mesothelioma and lung cancer in the pleura remains especially difficult. Sahin, *supra* at 1. The World Health Organization recommends combining at least two positive and at least two negative markers for the pathologic diagnosis of malignant mesothelioma. *Id.* However, use of new markers is required to diagnose difficult cases.

Stem cells, or those which can differentiate into specialized cells, have been reported to be useful in the beginning causes of cancer and malignant mesothelioma. *Id.* at 2. The role of cancer stem cells in the initiation and progression of certain cancers has led investigators to inquire into their role in the differential diagnosis and prognosis of malignant mesothelioma.

In particular, CD90 is a glycoprotein mainly released by white blood cells and is a marker of cancer stem cells. *Id.* Researchers investigated whether CD90 can be used to differentiate between malignant mesothelioma and lung carcinomas, and whether it was better than Calretinin, the diagnostic marker primarily used to diagnose mesothelioma. *Id.*

Contrary to previous reports suggesting the use of CD90 as a differential diagnosis marker for malignant mesothelioma, new research found that CD90 had low specificity for that disease. Such low specificity renders its use inadequate to use as a differential diagnosis marker. *Id.* at 4.

The role of cancer stem cells in the initiation and progression of certain cancers has led investigators to inquire into their role in the differential diagnosis and prognosis of malignant mesothelioma.

Practice Pointers

Defense counsel should search the Plaintiff's medical records for the presence and increase of Glycodelin, glycodelin A, progesterone-associated endometrial protein, soluble mesothelin-related peptide, and a decrease in miRNAs, all of which appear to be bio-markers for mesothelioma. Additionally, established genetic mutations in the BRCA1 or BRCA2 genes, or a diagnosis of *BAP1* Tumor Predisposition Syndrome (*BAP1*-TPDS), may also be telling in the prediction, diagnosis, and treatment of MPM.

Conclusion

Malignant mesothelioma is a fatal cancer which presents with numerous deceptions. Thus far, science has been unsuccessful in combating this disease. However, recent research investigating and identifying possible ways to predict and earlier diagnose this disease are a promising addition to the medical and legal arsenal battling this continuing war.