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Commentary: Filling up my truck from an oil tanker: Can big 'omic' data influence our clinical decisions?

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CENTRAL MESSAGE

Severson and colleagues write an outstanding review with historical context for the complex molecular techniques for an integrated analysis of mesothelioma tumors by Hmeljak and colleagues.

THOR

Recently, a patient presented with a pleural effusion and a computed tomography-guided biopsy that revealed well-differentiated papillary mesothelioma. Doubting the diagnosis, I performed a video-assisted thoracoscopic surgery biopsy and obtained tissue from 3 independent areas of the chest. All 3 biopsies revealed well-differentiated papillary mesothelioma. The patient underwent an extended pleurectomy and decortication and the final pathology report read, "biphasic mesothelioma with both epithelioid and sarcomatoid components. The sarcomatoid component also shows features of desmoplastic mesothelioma. The epithelioid component shows focal superficial papillary configuration." The pathology was essentially all subtypes of malignant pleural mesothelioma (MPM). Could 'omics' have clarified this diagnosis before resection?

Severson and colleagues[1] review The Cancer Genome Altas study by Hmeljak and colleagues.[2] They report 74 MPM tumors that were characterized by a genomic, epigenomic, and transcriptomic integrated analysis.[1] To help understand the molecular findings, the authors provide a historical context to the development of these techniques. This article is an outstanding summary for readers who are not scientists.

Hmeljak and colleagues[2] noted the loss of regions or alterations in tumor suppressor genes (TSGs) such as *CDKN2A*, *NF2*, *BAP1*, *TP53*, *LATS2*, and *SETD2*. Additionally, with the use of clustering algorithms, they identified 4 groups of MPM. Severson and colleagues[1] compared these findings to several other noteworthy publications that have surprisingly similar findings. For example, when Bueno and colleagues[3] performed genomic analysis of 216 MPM tumors, they noted copy number loss in many of the same TSGs. They also found 4 different molecular subtypes based on RNA sequencing data. Significant overlap of the molecular subtypes occurred compared with histology. Blum and colleagues[4] describe this overlap as histo-molecular gradient, which highlights that these histologies are not completely distinct entities. As the molecular techniques and software for integration have advanced, 2 consistent themes have emerged with MPM: First, loss of TSGs is the most frequent molecular event and, second, clusters of MPM tumors are not completely distinct.

Can we apply this 'omic' data to clinical decisions? As the cost decreases and the technology is refined, molecular techniques should assist if not supplant histology for diagnosis. Furthermore, Bueno and colleagues[3] generated a ratio of *CLDN15*/*VIM* genes score from their analysis that discriminated between the different clusters that should further simplify diagnostics. However, sampling errors may be as likely with molecular diagnostics as with histology. Next, prognosis may improve by assigning clusters to help counsel our patients. Lastly, will these techniques help with treatment? For MPM, mutations tend to be

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loss of TSG. Unfortunately, loss of TSGs is not targetable—unlike driver mutations. Although the molecular landscape of MPM has emerged rapidly over the past few years, based on these analyses advancements in treatment are lacking. Further work may require targeting microRNA, epigenetics, or cellular energetics to advance treatment for patients with MPM. Ultimately, would 'omics' have helped our patient? I doubt it. Nevertheless, the authors of these studies provide invaluable information to help move our field forward.

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