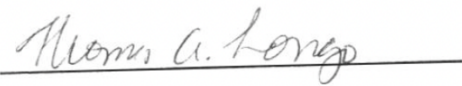


Exhibit 351

Rebuttal Expert Report Thomas Longo, M.D.

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A handwritten signature in cursive script, reading "Thomas A. Longo", is written over a horizontal line.

Thomas Longo, MD

Date: May 14, 2025

It is my opinion that Dr. Kates' definition of bladder cancer as an idiopathic disease by nature is not supported by the overwhelming majority of epidemiological literature. It is also my opinion that Dr. Kates' application of idiopathy as a "contributing risk" to the development of bladder cancer is not a scientifically accepted method of conducting a valid differential etiology.

I. Bladder Cancer is Not Considered Idiopathic by Nature

Idiopathic is defined by the National Cancer Institute as, "a disease of unknown cause."¹ In the context of differential etiology, idiopathic is a diagnosis of exclusion. Logically, it follows that a clinician would not begin the process of developing a differential etiology with an unknown cause. A patient's diagnosis is only considered "idiopathic" if, after examining potential risk factors, a cause remains undetermined.

Dr. Kates defines idiopathic as cases whose cause is "either spontaneous or not yet known".² I am not aware of any instance in my education, training, research, or clinical practice where I have encountered spontaneously occurring bladder cancer.

The term idiopathic appears nowhere in the National Comprehensive Cancer Network Guidelines for bladder cancer.³ The terms "idiopathic" and "idiopathy" are absent from the National Cancer Institute web page for bladder cancer.

Dr. Kates states that as many as 40% of bladder cancer cases are idiopathic. A brief review of more recent literature indicates that over 87% of bladder cancer cases could be attributed to either known preventable causes or known heritable mutations.⁴ Other studies also find that occupation or environmental toxic exposures are the cause of 20% of bladder cancers, though it is difficult to establish precise numbers due to the fact that bladder cancer develops years or decades after the exposure, even if the exposure itself was limited.⁵

As discussed throughout the literature, the strong association between modifiable risk factors and bladder cancer is itself the reason it is important to conduct a thorough differential etiology. A patient should be informed of potentially ongoing exposures which caused their cancer, so that they can avoid those exposures in the future.

¹ National Cancer Institute. *NCI Dictionary of Cancer Terms*. 2025. Available at <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/idiopathic>

² See e.g., *Dyer v United States* – Expert Report of Max Kates M.D. (Apr. 8, 2025)(p.13)

³ Flaig, T. W., et al (2024). NCCN Guidelines® Insights: Bladder Cancer, Version 3.2024: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*, 22(4), 216-225. <https://doi.org/10.6004/jnccn.2024.0024>

⁴ Al-Zalabani AH, Stewart KF, Wesselius A, Schols AM, Zeegers MP. Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. *Eur J Epidemiol*. 2016 Sep;31(9):811-51. doi: 10.1007/s10654-016-0138-6. Epub 2016 Mar 21.

⁵ Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. *Med Sci (Basel)*. 2020 Mar 13;8(1):15. doi: 10.3390/medsci8010015.

II. Idiopathy Cannot Be a Contributing Risk Factor in a Valid Differential Etiology

Keeping in mind that most bladder cancers are attributable to numerous well-known risk factors, a sound differential would begin with these likely causes, and examine the patient's history to identify exposures that would apply and then move forward. At the end of the process, if there is no apparent valid cause, the diagnosis can be considered idiopathic. Idiopathic is not a cause, but rather a word to denote an unknown cause. Thus, the label of idiopathic means that the search for etiology continues. Dr. Kates' differential is based upon falsely assuming the "idiopathic nature of bladder cancer" and unscientifically including it as one in a combination of causes of bladder cancer.

It is unscientific and illogical to conclude that idiopathy is a contributing cause of any disease, or that idiopathy and a combination of known risk factors caused a disease. As discussed, idiopathic means that there are *no* known risk factors present suggestive of causation. Therefore, if a patient's diagnosis is idiopathic, it stands alone. A bladder cancer patient's diagnosis is either attributable to exposure to known risk factors, or it is not. Idiopathic is a conclusion, not a contributing factor, in a valid differential etiology.

III. Obesity as a Bladder Cancer Risk Factor

Epidemiological studies have reported inconsistent associations between body mass index and bladder cancer risk. Body mass index usually tends to fluctuate overtime, but most studies used a single measure of BMI at baseline, which may not reflect usual adult weight. It is possible that the observed association between BMI and bladder cancer could be underestimated or overestimated due to unmeasured or residual confounding. Higher level of BMI tends to be associated with other unhealthy behaviors (e.g. lower levels of physical activity, higher alcohol consumption). Obesity is highly prevalent in our current population, and it may be harder to determine if it truly increases cancer risk because its presence is so widespread that it obscures the effect of other, possibly more influential, risk factors. This is especially true when the prevalent factor is also associated with other factors that have a stronger influence on cancer development.