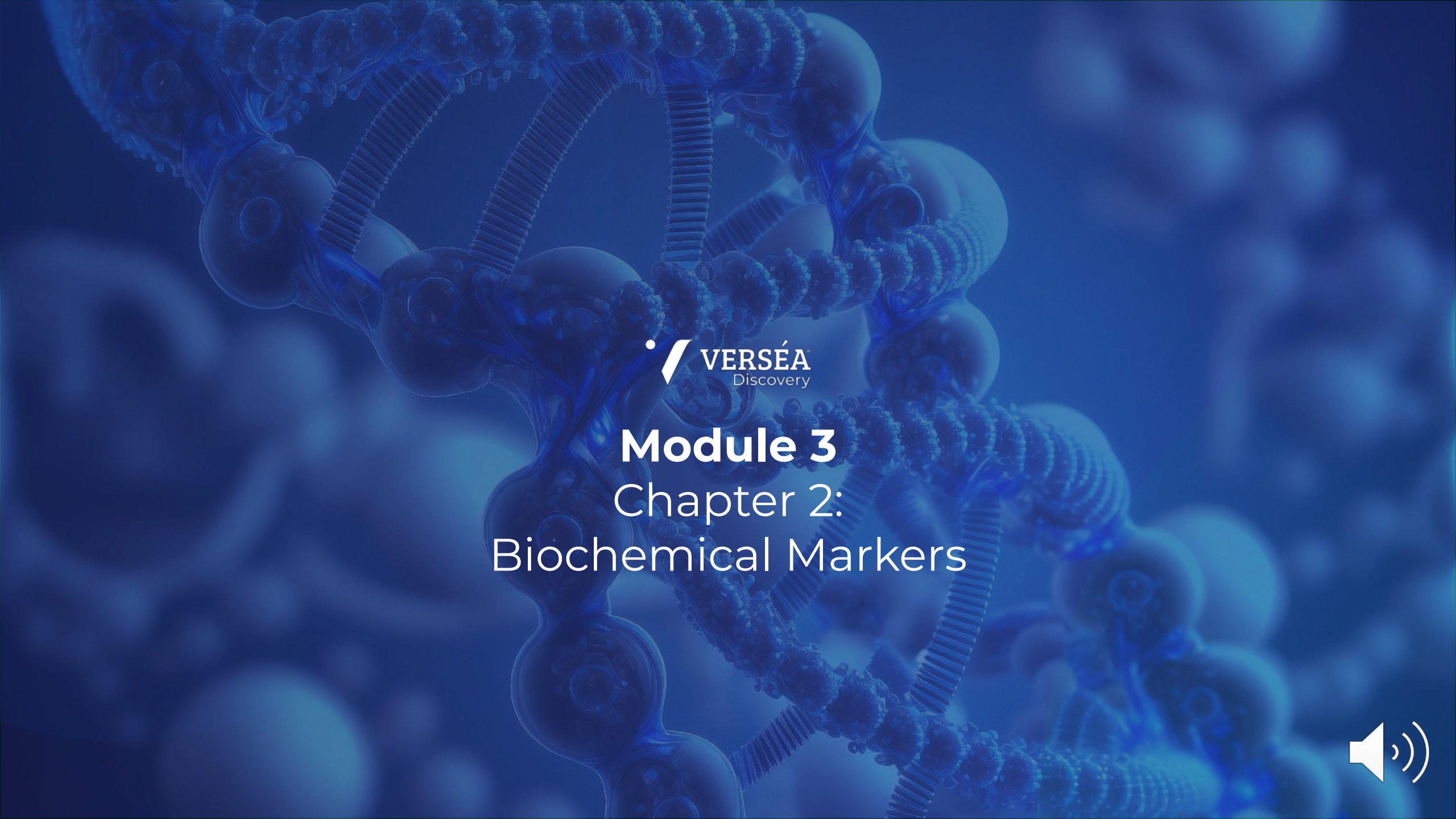
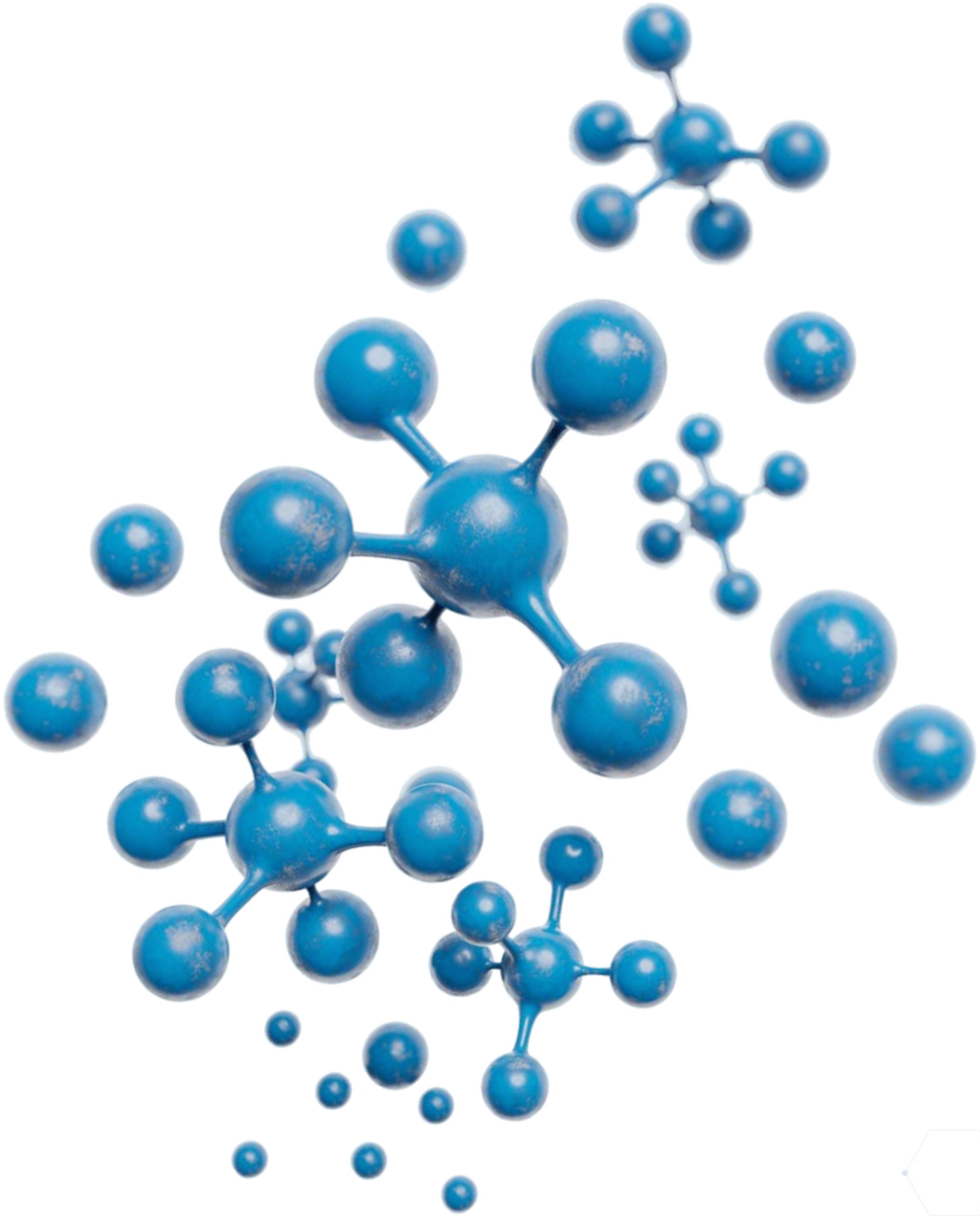



# Module 3

## Chapter 2:
## Biochemical Markers



# Biochemical Markers

Metabolic screening studies in blood and urine are useful for determining whether an individual with suspected primary mitochondrial disease or secondary dysfunction from multifactorial disease has evidence of mitochondrial dysfunction.

## Common Markers

Comprehensive chemistry panel, complete blood count with differential, blood lactate and pyruvate, ammonia, creatine kinase, hemoglobin A1C, plasma amino acid analysis, caritine and acylcarnitine profile, lipoprotein profile, hormone screening studies, and urine studies such as urinalysis, urine organic acid analysis, and urine amino acid analysis.

Caution must be used when interpreting these findings, as any alterations identified will not be specific to mitochondrial disease and are typically not diagnostic.

# Commonly Utilized Markers

## Organic Acid Test

One option for assessing mitochondrial function is an organic acid test. This evaluates the metabolites from digestion, assimilation, metabolism, and the production of ATP. The preferred specimen is a urine collection; these metabolites are more easily extracted from urine than plasma.

Ethylmalonate, adipate, and suberate are reflective of beta-oxidation. L-carnitine is necessary for carrying long-chain fatty acids across the mitochondrial membrane. If L-carnitine levels are inadequate, beta-oxidation might alternatively take place in peroxisomes, creating elevated levels of adipate and suberate. Ethylmalonate, a breakdown product of butyrate, is also dependent on L-carnitine.

Elevated succinate, fumarate, and malate may indicate inefficient energy production as they are part of mitochondrial oxidation. Markers indicative of carbohydrate metabolism are pyruvate, lactate, and beta-hydroxybutyrate. Metabolites of the citric acid cycle, some of which were mentioned previously, can also indicate variations in energy production.

## Amino Acid Test

Amino acid quantification can be performed on blood (plasma or serum)

Elevated plasma alanine may be a useful indicator of long-standing pyruvate accumulation.

Other amino acids whose elevations have been associated with mitochondrial dysfunction include proline, glycine, and sarcosine

It is important to remember that these tests are not diagnostic, but they can help guide treatment options and evaluate progress.
They again provide the potential of something that may or may not be.

# Limitations of Biomarker Testing

Mitochondrial disease patients may have normal lactate and pyruvate levels except when undergoing a metabolic crisis or following exercise.

Many patients with mitochondrial disease consistently have normal or only minimally elevated lactic acid levels.

Elevations of plasma lactate and/or pyruvate levels may be seen in a range of conditions other than primary mitochondrial disease, including spurious elevation due to poor collection or handling techniques, physiological elevation as a result of secondary mitochondrial dysfunction, which may occur in a wide range of systemic diseases and metabolic disorders, and nutritional deficiency of thiamine.

Pyruvate is quite unstable, necessitating blood specimens to be immediately transferred (i.e., within 30 seconds after drawing) into 8% perchlorate on ice and analyzed. Depending on sample handling, pyruvate levels may increase or decrease and are elevated in the immediate postprandial period.

Elevated alanine is low-sensitive to mitochondrial disease, as it may only be elevated at certain times, such as during physiologic stress or regression.

Amino Acid test results may indeed be affected by various conditions, including improper specimen handling, hemolysis, and dietary intake. Improperly stored specimens cause artifactual elevations in glutamate (especially in relation to glutamine), aspartate, and ornithine, with decreases in glutamine, cysteine, asparagine, and homocysteine.

Carnitine testing is limited by false negatives in individuals with total carnitine deficiency and elevations in carnitine-treated patients, as well as in cases where the biochemical abnormality is mild or of fluctuating severity.