We have successfully diagnosed and treated thousands of chronic inflammatory response syndrome (CIRS) patients, but these diagnoses were based on lab tests that looked at a small number of proteins. Now we are embarking on groundbreaking medical technology that will unlock critical information from within the human genome. We want to examine the fundamental basis of CIRS at the source, i.e. gene expression.

DNA is the brain of the cell: it directs all processes in all organisms and contains a remarkably complex blueprint of how the cell will react in health and disease. Human DNA contains tens of thousands of genes, or discrete components, that direct the functions needed to survive. To carry out these functions, copies of genes (called messenger RNA) are made and then turned into proteins, which are the molecules that perform the work intended by the gene. The amount of any given protein is in constant flux, trying to meet the changing demands the body experiences throughout the days, weeks and years. We can characterize many illnesses with abnormal levels of specific proteins but proteins are difficult to measure on a large scale so we can only guess at a few that might be abnormal. Instead, we now measure the intermediate step between the DNA and protein—the protein-coding messenger RNA (mRNA)—for all proteins the cell intends to use as well as others that arise from different kinds of RNA, called non-protein coding RNA. This process lets us access information on thousands of both protein coding and non-protein coding genes from one tube of blood, using a technique called RNA Sequencing. This is our CIRS Genomic Assay.

"Monitoring gene expression over the duration of illness gives us an overview of whether therapies effectively address the root cause."
This new assay uses RNA sequencing to focus on the abnormal gene expression found in white blood cells of CIRS patients. The gene activity in white blood cells will quickly change as a result of varying environmental exposures, such as the presence of a pathogen, or inflammation. Based on proprietary research, we have identified the abnormal expression of important genes involved in the inflammatory process. With this new data, we can monitor these genes during therapies, which is important to understanding the totality of correction, and better understand individual pathology by looking at metabolic pathways affected by abnormal gene activation.

For example, we have recently identified many genes that are abnormally expressed in the blood of CIRS patients, including a group of genes coding for defensins, which are anti-microbial peptides. These peptides keep bacteria found in our bodies from spreading systemically by coating mucosal layers, for example along the inside of the gut or in our airways and nasal passages. We've also identified the role of CD69, which is importantly linked with TGF beta-1 activity, and granzymes, which are cytotoxic proteases also found elevated in patients with autoimmune disease and infections. In fact, we have identified hundreds of genes that can impact CIRS pathology. Now with our CIRS Genomic Assay we can easily monitor the *expression* levels of these genes in a single test. We don't simply say if a given kind of DNA is present, such as what we see in 23and me, we look at the

activity of the gene, its regulation and metabolic effects.

When we can identify the irregular expression of these genes in CIRS patients, we can then use those patterns to help diagnose a given condition. This assay puts together diagnostic and prognostic information, and also tells us if a pathologic condition persists at the root level, even when patients begin to feel better. Because gene expression underlies protein expression, and we can monitor all genes with one assay, it is groundbreaking in the understanding and management of complex illness. Monitoring gene expression over the duration of illness gives us an overview of whether therapies effectively address the root cause. If the therapy simply interferes with protein function, but does not actually correct the aberrant gene expression, the illness will reappear when the therapy is removed. By examining the roots—the gene expression—we can better understand when a therapy will be durable.