Lessons from GENIE 1:

We have entered a new era in sophisticated testing for Lyme, mold and chronic fatiguing illnesses. Since the sequencing of the human genome, in the early 2000s, we have developed the ability to look at differential gene activation through new procedures coming from molecular biology. Deep down, we all know that everything that affects our body and our health comes from gene activation as DNA is the master controller of what our cells do.

We now know that the genes that help ribosomes make proteins and the genes that make mitochondrial enzymes function to produce most of our energy are impacted in chronic fatiguing illnesses. The sources of these cellular disasters come from compounds called ribotoxins, which are made by bacteria, fungi and actinomycetes. There is no blood test for ribotoxin exposure and yet 99% of people sickened by moldy buildings will show the complications of ribotoxin exposure, mainly “hypometabolism.” Similarly, people with Lyme disease refractory to antibiotics will routinely be shown to have hypometabolism as well.

Recently I did a consult on a patient who had used the new GENIE test to look at gene activation seen in chronic inflammation. She thought she had Lyme disease but as it turns out, the problem was not just Lyme. A complication of a defect in normal programmed cell death, called defective apoptosis, was the root cause of her endogenous source of inflammation. Added to her problem was her brain fog; she had a NeuroQuant done that showed at age 30 she had four areas of atrophy of gray matter nuclei. How can such a devastating abnormality in her brain be present?

The GENIE test had the answer. She had upregulation of coagulation genes such that amyloid beta protein binds to these gene products and creates a microvascular clot in brain tissue thereby causing neuronal injury. Sophisticated! If you haven’t heard of GENIE, please look at this link or read more about it on Surviving Mold on the homepage. GENIE is bringing answers to devastating illnesses that we have never had the opportunity to diagnose, much less treat before. GENIE is not a SNP test, it is looking at actual differential gene activation with values compared to controls in testing done in Bedford, MA.

The fulfillment of hope from GENIE continues.

Beginning with the storage of frozen PAXgene tubes in 2008, "for use when the science caught up to what we learned from CIRS," followed by whole transcriptome sequencing that showed rich veins of new information, to the current targeted findings of GENIE, the new transcriptomics test, especially hypometabolism and the CIRS curve, we now are seeing exponential leaps of new insight regarding inflammation and disease.

Just imagine attending a lecture series about CIRS or Lyme or CFS from just 3 years ago. Would we have learned about correction of (i) hypometabolism; (ii) defective apoptosis; and (iii) the pro-thrombotic basis for cerebral neuronal loss? Not a chance. And yet, those same topics are unveiled by the research that led to GENIE to be crucial to understanding the pathophysiology of chronic fatiguing illnesses. There is much more data contributing to new therapies.

If the physician and the patient don't know what GENIE can show, we have to help them learn.

Granted, we didn't know how common defective apoptosis was, particularly necroptosis. How could we? There was no way to know about cell death causing endogenous inflammatory illness without GENIE. We didn't know how important exposure to actinomycetes (a large group of bacteria that are commonly found inside water-damaged buildings (WDB)) and endotoxins was, even though sparse literature was showing us that *inflammation followed gene response* to actinos and endotoxin, not just exposure. And now, we are seeing the salutary benefit of correction of prothrombotic coagulation genes for those with concerns about brain atrophy, particularly in grey matter nuclei.

One clinical focus might be dementia, an area recognized by the relationship of neuronal loss to exposure to WDB. We have shown (unpublished) that correction of the unregulated over-expression of coagulation genes accompanies clinical benefit seen in small, but ever-growing numbers of patients. Now, every time I talk with family members of younger-aged Alzheimer's patients whose illness coincided with exposure to the interior environment of water-damaged buildings (WDB), and improvement coincides with correction of coagulation genes, I have to remind myself that watching five or ten people get better isn't regarded as earthshaking. Small numbers won't sway a seasoned scientist. For those patients and their families, however, N=1 isn't just a study, it is a life returned.

The challenges of GENIE are many. Do we use GENIE to follow up on promising advances in the transcriptomics of Chronic Fatigue Syndrome (CFS)? Do we simply re-define CFS as hypometabolism? Numerous researchers have spent their careers trying to define the illness at a cost of (likely) billions of dollars and countless damaged patients' lives. Our answers to the inflammatory basis of CFS were published years ago. GENIE now puts inflammation, cytokines and coagulation together in a tight package.

Do we open our work to the Lyme community, one that has been mired in argument for years over "antibiotics forever," versus an opposing stance of "antibiotics for never?" Or do we simply recognize that the insights brought by GENIE will spread in the CIRS, CFS and Lyme communities? Those who might be a naysayer now may decide to wait to learn more until the

published GENIE literature is more robust. One thing is certain, the train of new information won't wait for anyone.

We have known for years that CIRS patients will have the prothrombotic abnormalities in transcriptomics, first published in ciguatera (1), and seen in RNA Seq (2), Thanks in large part to the published work of a number of researchers, especially those from Rockefeller University (especially Sidney Strickland's lab; 3, 4, 5, 6, 7, 8, 9 ,10, 11, 12,13), the strength of the vascular hypothesis of Alzheimer's makes additional clinical sense in CIRS patients. All those patients we saw with unexplained elevations of d-dimer, PAI-1 and von Willebrand's factors, not to mention those Lyme patients with clotted PICC lines and CFS patients with pulmonary emboli, were telling us that a systemic coagulation problem was ongoing. Involvement of the brain ends up being no surprise, but only now we have a literature that tells us our observations on inflammation, cytokines and coagulation are robust.

The vascular hypothesis of neuronal injury and Alzheimer's (AD) has evolved from observations in 2010 (7) that beta amyloid (AB) bound to fibrinogen, enhances thrombosis and reduces fibrinolysis in the CNS, and (possibly) contributes to neuronal loss. Prior research (cited in 7) confirmed that AB bound to other mediators of inflammation and coagulation creates a prothrombotic state affecting CNS structures like the hippocampus, but also promotes systemic inflammation. Sounds like CIRS! Noting AD increases after systemic infection, Strickland, et al state in (7), "Activation and/or modulation of the delicately balanced coagulation and inflammatory systems by AB could lead… to chronic and pathological occlusion and inflammation, both of which could contribute to the neuronal death observed in AD."

Data supports this idea, including AB interaction with fibrinogen, thereby leading to deposition of fibrin in cerebral blood vessels, inducing microinfarcts and loosening of the blood brain barrier. Since AB also activates Factor XII and XIII, the propensity for fibrin deposition is increased through the intrinsic coagulation system, inhibiting plasmin-fibrin interaction and by activating bradykinin.

Additional data, from biopsy specimens, as well as involving AB with Factor V, Factor XIII and integrins, demonstrates the role of AB binding to products of coagulation genes was related to cognitive deficits. Further, hypoxia promoted tau hyperphosphorylation (3). Tauopathies are a group of dementias that have in common the formation of intracellular filamentous deposits seeded by the microtubule-associated protein tau, in abnormally hyperphosphorylated form(s). Tau inclusions are common among all of these tauopathies leading to diverse phenotypic manifestations, brain dysfunction, and degeneration.

All these coagulation products are evaluated by GENIE, with resolution of upregulation of gene activity correlating with clinical improvement.

The coagulation problems shown by GENIE are not just prothrombotic: risk of *hypo*-coagulation and bleeding after exposure to WDB is also shown by coagulation gene *suppression*. In one isolated trial, correction of excessive abundance of actinomycetes by a room sanitizing device (iAdaptAir; Mold Congress, Fort Lauderdale, Florida, 1/2019), as the only therapy, reversed coagulation gene suppression and stopped intractable epistaxis. In a study in a single practice

(RS) looking at von Willebrand's profile in CIRS patients, over 1300 results showed that 66% of patients had abnormal findings, with 60% being predisposed to clotting and 40% to bleeding. Control patients had less than 5% each predisposed to clotting and bleeding. GENIE tells who is at risk for clots or hemorrhage.

Before anyone begins preventive treatment for AD with aspirin, warfarin or the newer oral anticoagulants, please remember that such ideas were prevalent for years in attempts to prevent repeat myocardial infarction, only to find out that anticoagulation had significant risks. There is a complexity of the role of gene activation that underlies failure of confirmation of benefit from widely used therapies. Genes are not gene products! Taking a treatment does not necessarily feedback to downregulate gene activity.

This fundamental separation of gene and gene product demonstrates why widely used CFS therapies from the early 2000s, including heparin and treatment using "coagulation panels" never showed group benefit. The same failure can likely be said for the current association of histamine with "Mast Cell Activation Syndrome," as the genes that control histamine production (shown by GENIE) are present in all cells, not just mast cells.

In the near future we will be reporting data to illustrate how the benefit of using transcriptomics to assist in diagnosis and monitoring response to treatment of CIRS is multifactorial. GENIE touches many elements of DNA responses to environmental cues simultaneously.

In addition to showing us what a patient has, GENIE will often show what a patient *doesn't have*. GENIE may also show reasons for lack of response to therapies, or even some adverse effects of well-intentioned, but wrong-headed therapies. When independent-thinking physicians decide on a treatment for a complex fatiguing illness, the patient needs to know that transcriptomics show data and not opinion. Therapy, we feel, must be grounded in reliable science and not conjecture, trial and error or anecdote.

Similarly, use of VIP, the "miracle" compound that corrects proteomics, transcriptomics and grey matter nuclear atrophy in CIRS when used according to a strict published protocol, has been misused by some providers who skip the mandatory controls for safe use of VIP. Let GENIE guide you! Don't skip necessary steps!

For the future, we will keep insisting on integrity in medicine and science. We "keep our head down, but with eyes wide open," letting evidence-based medicine be our guide. We know we are on the cusp of extending the principles of hypometabolism to a series of illnesses beyond CIRS, but each new step must be rigorous, validated and repeated to confirm findings. We feel that there are valid grounds to investigate other common illnesses affected by CIRS, other than dementia, including diabetes, obesity and atherosclerosis using the principles that underlie GENIE. We don't have the answers yet, but when our findings are solid, we will let you know.

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7/16/2019

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