GENIE

A Gene Expression Assay

colab
SERVICES

Contents

About GENIE

GENIE is a gene expression test, known technically as a gene transcriptomic test. GENIE stands for Gene Expression: Inflammation Explained.

Performed on a single blood specimen the test is an mRNA assay on white blood cells that considers 188 genes. Each of the roughly 105 markers on the test report is reported as the average of the activity of up to around 10 genes.

GENIE development came from complete transcriptome sequencing of Chronic Inflammatory Response Syndrome (CIRS) patients. From 20,000 protein coding and 30,000 non-protein coding genes it was noted that 1900 were expressed differently to controls. Nanostring was chosen as the reproducible platform for the test, and the number of genes was reduced from 1900 to 173 with 15 housekeeping genes.

GENIE is currently a research-only test, so all patients are de-identified to allow research to continue on the test. Now in its seventh iteration the markers change slightly as the research further defines the optimal genes to assay.

As Progene DX note about the GENIE:

"We know now that transcriptomics has a unique contribution to diagnosis and treatment of chronic illnesses, as it is here that we see (i) unusual levels of gene activity; (ii) failure of regulation; (iii) and the fundamental changes caused by therapies that lead to correction of pathophysiology. Moreover, by comparing the patient to himself over time; or by comparing cases to controls, we can use transcriptomics as a diagnostic and prognostic tool of far greater sophistication than blood tests (proteomics) alone….. Transcriptomics gives us the ability to see chronic illnesses in a new light".

In 2020 the test became available in Europe via Colab Services Ltd.

As GENIE is currently a research-only assay Colabs recommend that it is used in conjunction with other testing and consideration of client's symptoms to support clinical decision-making.

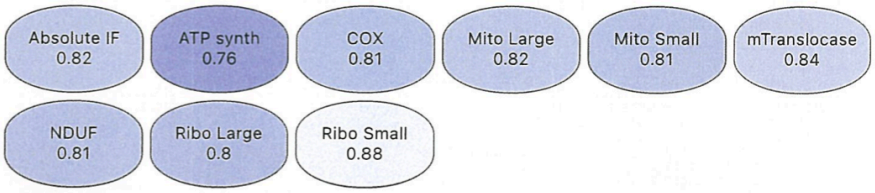
Sample Report

Latest Update Report October 2024

GENIE REPORT - *Gene Expression:Inflammation Explained*

1) Metabolism

Ratio for metabolic gene families compared to normal controls. 1 equals control value.

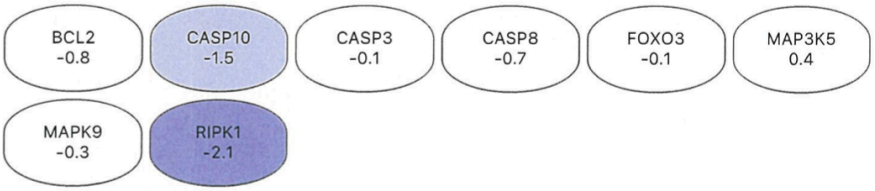


2) Insulin

The system that controls circulating blood sugar as well as sugar entry into the cell including binding proteins, receptors and growth factors.

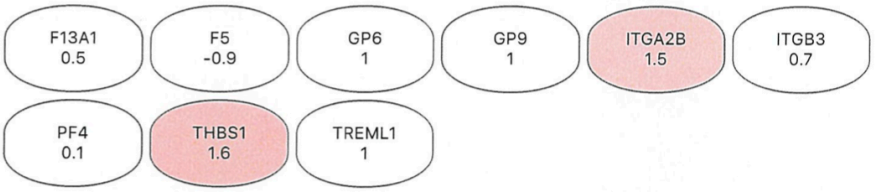
3) Apoptosis

Can be triggered by mild cellular injury and by various factors internal or external to the cell; the damaged cells are then disposed of in an orderly fashion.



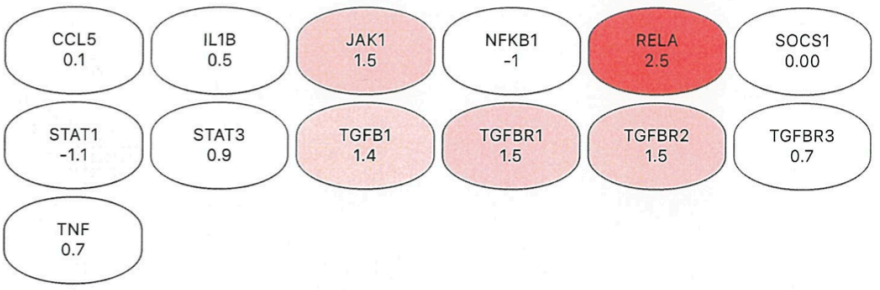
4) Coagulation

Also known as clotting is the process by which blood changes from a liquid to a gel forming a blood clot. It potentially results in hemostasis.



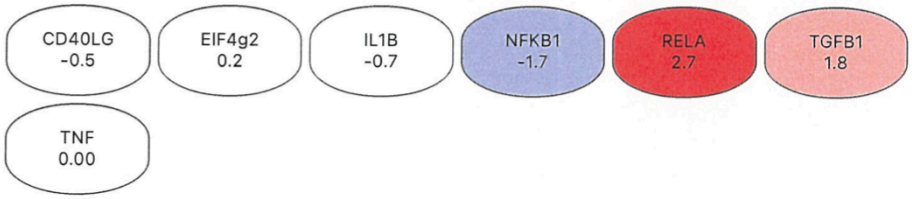
5) Cytokines

Signaling molecules that direct immune function.



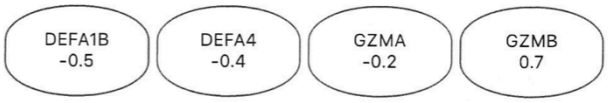
6) Lyme

These genes were found to be changed in patients with acute and post antibiotics Lyme disease.



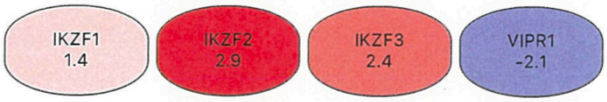
7) GZMS/DEF

Granzymes are proteases used by NK and Cytotoxic T cells to destroy unhealthy cells. Defensins are antimicrobial peptides.



8) Ikaros

A family of transcription factors important for lymphocyte proliferation and senescence.



9) MAP Kinase

MAPKs are involved in directing cellular responses to a diverse array of stimuli.

10) Toll Receptors

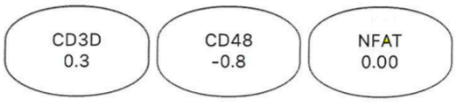
Membrane receptors important in recognition of microorganisms.

11) B Cells

Most often associated with antibody production.

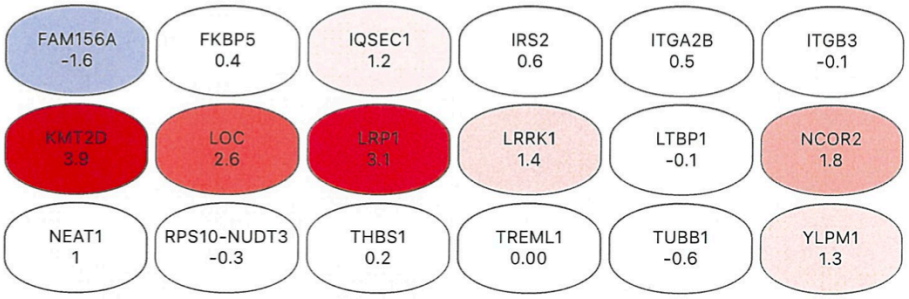
12) T Cells

Most often associated with cell to cell combat and immunosynapse with APCs.



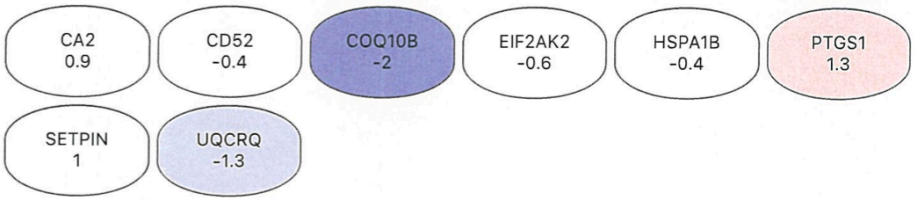
13) CIRS Biomarkers - UP

Genes important to CIRS typically found upregulated



14) CIRS Biomarkers

Genes important to CIRS

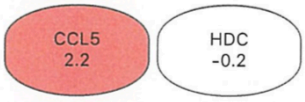


15) PTSD

Post Traumatic Stress Disorder

16) Histamine

Inlflammatory vasodilator



17) Cytoskeleton

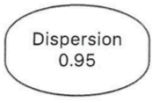
Interlinking protein filaments that support cellular structure.

18) Treg

Regulatory T cell membrane receptors

19) Dispersion

Variance of normalization. Scores below 1 are best.



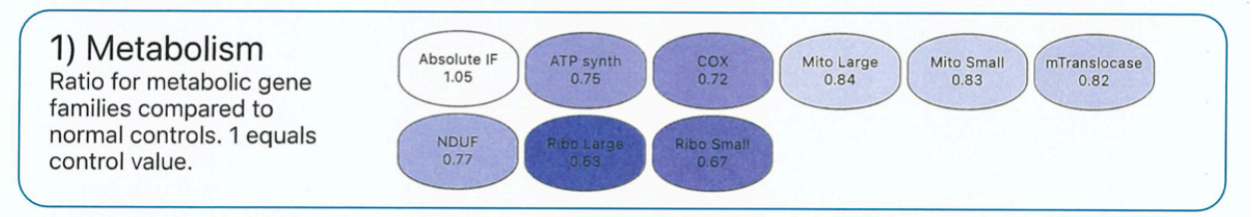
Key Concepts

The key results patterns that are taking research priority are as follows:

Firstly, does the result show hypo-metabolism. In particular suppression of ribosomal genes found in large and small sub-units in those who have not started a therapeutic protocol. Mitochondrial genes include electron transport genes, inner and outer membrane protein transport genes and ATP synthase genes. Both large and small mitoribosome sub-units are also reported on.

When we see hypo-metabolism, especially when the ribosomes are down-regulated, this is potentially occurring due to ribotoxin exposure. Gene expression is the result of gene activity being dialled up or down, and this can occur as a result a response to our environment, and to other biochemical processes such as methylation, acetylation, phosphorylation, ubiquitylation, or simply due to lifestyle factors such as stress.

On the GENIE report down regulation (under-expression) of genes is illustrated with the colour blue; the darker the blue the more down-regulation. Up-regulation (over-expression) is illustrated with the colour red; again the higher the value the darker the colour.



The report image above showed gene under-expression illustrated by shades of blue. The darker the blue the lower the value and the greater the under-expression/down-regulation. Typically CIRS clients tend to have the darkest blue in the Ribos large result.

What is being seen through data from research on the GENIE is that specific patterns are being seen in those with chronic illness, and that patterns also reflect the stage of therapy.

To date the research is pointing to:

- Ciguatera exposure associating with prothrombotic abnormalities
- Actinomycetes exposure associating with up-regulation of TGFB1 and/or TGFB Receptors 1,2 and 3, especially if MAP kinase are also up-regulated
- Mycotoxin exposure associating with MAP kinase (and possibly TLR2 and 4)
- Endotoxin exposure associating with CD14 and TLR4 up-regulation

Results can indicate that further environmental testing could be warranted.

Downstream Associations with Hypo-metabolism

Alongside Section 1 showing down-regulated results we may expect to see in a typical CIRS case:

- Increased coagulation- more up-regulation in section 4
- Increased cytokine activity- more up-regulation in section 5
- Possible increase in MAP kinase activity. Any elevations are significant
- More than 4 areas of increased activity in section 13, the CIRS Biomarkers section
- Increased markers in section 19 the cytoskeleton section

At this time in the research process it seems that the more entrenched the chronic illness the more the results are less prone to individual fluctuations. Research undertaken with mycotoxin-related results showed that if there was no hypo-metabolism as a result of the exposure then changes would normalise within a couple of weeks.

GENIE can therefore be used to further define who is a CIRS case and who isn't

In addition to the CIRS-related results GENIE may also prove useful when considering:

- Glycolysis pathway changes that can indicate increased risk of insulin resistance and increased risk of reduced pyruvate (which when coupled with hypo-metabolism may result in increased lactate/LDH)

- Cognitive decline. Perhaps the driving factor in developing GENIE was understanding links to cognitive decline seen in those with chronic inflammatory processes. When more than 4 coagulation results are up-regulated this increases the risk of cognitive decline and up-regulation in tubulins in the Cytoskeleton Section 17. In such cases referral for volumetric MRI could be warranted

- Defensin up-regulation in Section 7 can indicate ongoing bacterial or viral infection

- Lyme disease has a signature in Section 7, which was based on the work of Bouquet and Chiu from 2016

- Histamine; genes that control histamine are present in all nucleated cells, not just mast cells when CCL5 is up-regulated. Histamine Decarboxylase (HDC) is also reported on the GENIE test. HDCis involved in the conversion of l-histidine to histamine

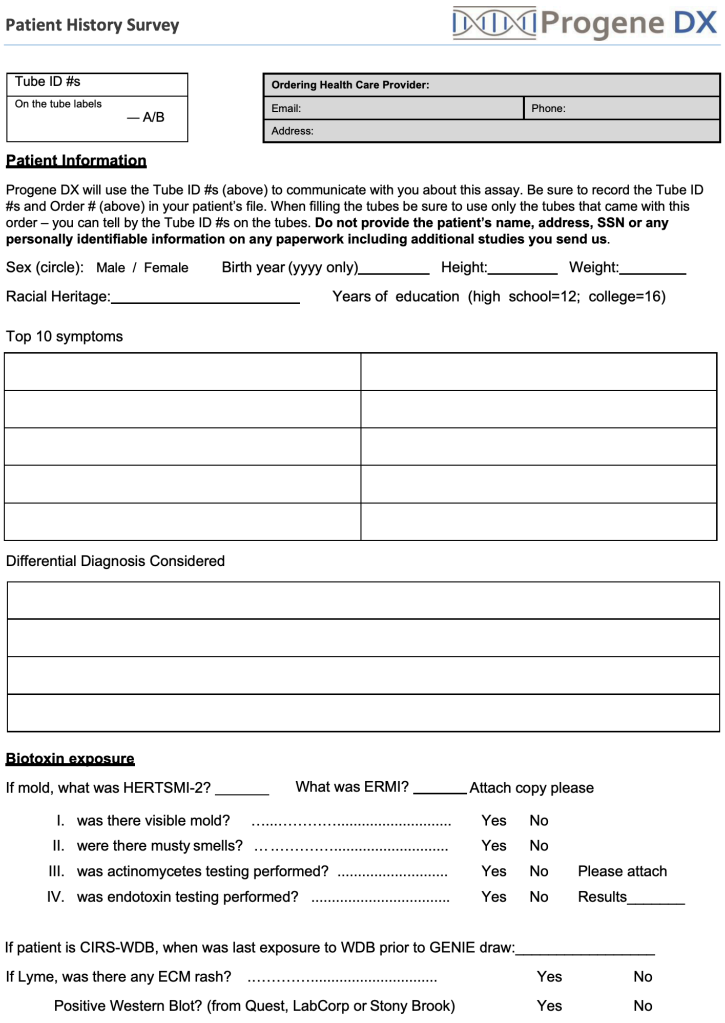
- If AKT/mTOR show an abnormal result and HIFA1 is also up-regulated then further investigation such as echocardiogram could be considered to rule out pulmonary hypertension

- If FKBP5 is up-regulated then additional history relating to PTSD may be warranted

Patient History Survey

The Patient History Survey form is filled in for each GENIE sample sent to Progene DX. This form is essential for research processes.

The form is double-sided with key symptoms and environmental exposure history on page one and staging plus any laboratory test results required on page two.



Patient History Survey — Progene DX

Tube ID #s
On the tube labels — A/B

Ordering Health Care Provider:	
Email:	Phone:
Address:	

Patient Information

Progene DX will use the Tube ID #s (above) to communicate with you about this assay. Be sure to record the Tube ID #s and Order # (above) in your patient's file. When filling the tubes be sure to use only the tubes that came with this order – you can tell by the Tube ID #s on the tubes. **Do not provide the patient's name, address, SSN or any personally identifiable information on any paperwork including additional studies you send us**.

Sex (circle): Male / Female Birth year (yyyy only)_____ Height:_____ Weight:_____

Racial Heritage:_____ Years of education (high school=12; college=16)

Top 10 symptoms

Differential Diagnosis Considered

Biotoxin exposure

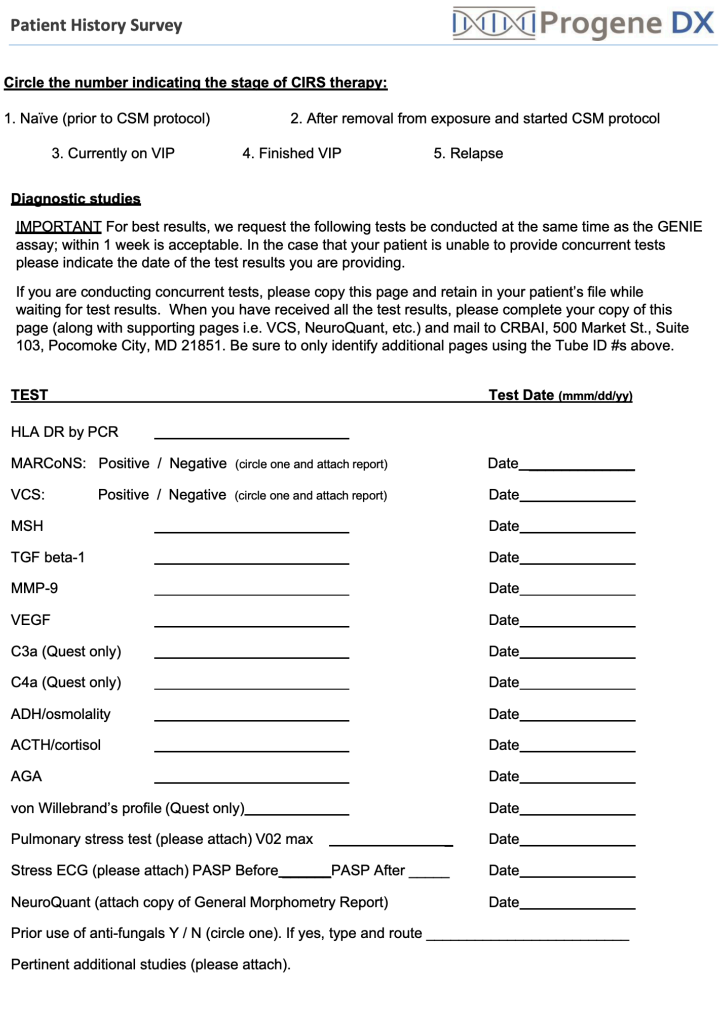
If mold, what was HERTSMI-2? _____ What was ERMI? _____Attach copy please

I. was there visible mold? ..... Yes No
II. were there musty smells? ..... Yes No
III. was actinomycetes testing performed? ..... Yes No Please attach
IV. was endotoxin testing performed? ..... Yes No Results_____

If patient is CIRS-WDB, when was last exposure to WDB prior to GENIE draw:_____

If Lyme, was there any ECM rash? ..... Yes No

Positive Western Blot? (from Quest, LabCorp or Stony Brook) Yes No



Patient History Survey — Progene DX

Circle the number indicating the stage of CIRS therapy:

1. Naïve (prior to CSM protocol) 2. After removal from exposure and started CSM protocol
3. Currently on VIP 4. Finished VIP 5. Relapse

Diagnostic studies

IMPORTANT For best results, we request the following tests be conducted at the same time as the GENIE assay; within 1 week is acceptable. In the case that your patient is unable to provide concurrent tests please indicate the date of the test results you are providing.

If you are conducting concurrent tests, please copy this page and retain in your patient's file while waiting for test results. When you have received all the test results, please complete your copy of this page (along with supporting pages i.e. VCS, NeuroQuant, etc.) and mail to CRBAI, 500 Market St., Suite 103, Pocomoke City, MD 21851. Be sure to only identify additional pages using the Tube ID #s above.

TEST		Test Date (mmm/dd/yy)
HLA DR by PCR	_____	
MARCoNS: Positive / Negative (circle one and attach report)		Date_____
VCS: Positive / Negative (circle one and attach report)		Date_____
MSH	_____	Date_____
TGF beta-1	_____	Date_____
MMP-9	_____	Date_____
VEGF	_____	Date_____
C3a (Quest only)	_____	Date_____
C4a (Quest only)	_____	Date_____
ADH/osmolality	_____	Date_____
ACTH/cortisol	_____	Date_____
AGA	_____	Date_____
von Willebrand's profile (Quest only)	_____	Date_____
Pulmonary stress test (please attach) V02 max	_____	Date_____
Stress ECG (please attach) PASP Before_____PASP After _____		Date_____
NeuroQuant (attach copy of General Morphometry Report)		Date_____

Prior use of anti-fungals Y / N (circle one). If yes, type and route _____

Pertinent additional studies (please attach).

CIRS Staging

GENIE can also be utilised to help place results on a timeline, allowing for tracking of progress through a therapeutic programme:

Stage 1: Still in exposure with evidence of hypo-metabolism and before any intervention has been undertaken

Stage 2: After the initial steps of the programme some hypo-metabolism may still be seen

Stage 3: If VIP has been started (if required/available)

Stage 4: After completion of VIP (if required/available)

Consideration of GENIE testing

For clients who have Chronic Fatigue, Cardiovascular History, early stage Cognitive changes and/or possible biotoxin exposure then GENIE could be considered.

Dr Shoemaker's 37 Question roster can be utilised to ascertain whether a client has 8 or more symptom clusters with at least one positive result, out of a possible 13. Each of the boxes below relates to a different symptom cluster.

If an adult patient has 8 or more clusters of symptoms with a positive result, the likelihood of CIRS exceeds 95%. For children it is more than 6 clusters. When combined with Visual Contrast Sensitivity (VCS) deficits symptom clusters can yield an accuracy of 98% for blood work returning positive for Biotoxin exposure.

37 most frequent symptoms		
Fatigue	Unusual skin sensitivity	Red eyes
Weak	Tingling	Blurred vision
Decreased assimilation of new knowledge	Shortness of breath	Sweats (night)
Aches	Sinus congestion	Mood swings
Headaches	Static shocks	Ice-pick pain
Light sensitivity	Vertigo	Abdominal pain
Memory Impairment	Cough	Diarrhoea
Decreased word finding	Excessive Thirst	Numbness
Difficulty concentrating	Confusion	Tearing of the eyes
Joint pain	Appetite swings	Disorientation
AM Stiffness	Difficulty regulating body temp.	Metallic taste
Cramps	Increased urinary frequency	

GENIE can also be used for those with specific concerns related to any of the sections in the report, and for clients with vague symptom presentation that has been ongoing for some time, especially if there are concerns over an ongoing infection.

Ordering GENIE

GENIE can be ordered by registered practitioners via the Colab Services Ltd Website: www.colabeu.com

or by emailing info@colabeu.com

If your client also requires a blood draw not at your own clinic then Colabs can assist with organising this along with the shipping. If you would like training on how to ship on dry ice Colabs can also facilitate this for you.

Important Information about the draw/shipping

Draw

The blood draw needs to take place between 9am-12pm. GENIE is drawn into 2 PAXgene tubes. Those with significant hypo-metabolism tend to produce less RNA so having two tubes filled to the line is essential to ensure processing can be completed. PAX tubes are designed to pull 2.5mL of blood under ideal conditions.

Post-draw the whole blood samples must sit for 4 hours, upright, and then transferred to the freezer prior to shipping.

Full draw instructions are supplied with the kit.

Shipping

GENIE samples must be kept frozen until being shipped on dry ice. Colabs can assist with facilitating dry ice and will organise both the dry ice delivery and onward courier collection to Progene DX.

Results take around 4-6 weeks to return.

Resources

https://www.progenedx.com

https://www.cirsx.com
(Quarterly online Conference focusing on GENIE including one live event annually considering the wider CIRS picture)

The Art and Science of CIRS, Shoemaker RC, McMahon SW, Heyman A, ISBN: 978-1-0983359-2-2 (available via survivingmold.com)

https://www.survivingmold.com

Dooley M, McMahon S.A Comprehensive Review of Mold Research Literature from 2011-2018. Internal Medicine Review. Vol 6; Page 1. https://www.survivingmold.com/Downloads/Dooley-McMahon_Final_Publication_-_3-30-2020.pdf

Ryan J, Shoemaker R. RNA-Seq on patients with chronic inflammatory response syndrome (CIRS) treated with vasoactive intestinal peptide (VIP) shows a shift in metabolic state and innate immune functions that coincide with healing. Medical Research Archives, 2017, 4: 1. https://www.survivingmold.com/Publications/MRA_GENOMIC

Shoemaker R, McMahon S, Heyman A, Lark D, van der Westhuizen M, Ryan J. Treatable metabolic and inflammatory abnormalities in Post COVID Syndrome (PCS) define the transcriptomic basis for persistent symptoms: Lessons from CIRS.. Medical Research Archives vol 9 issue 7. 2021

Shoemaker RC. Metabolism, molecular hypometabolism and inflammation: Complications of proliferative physiology include metabolic acidosis, pulmonary hypertension, T reg cell deficiency, insulin resistance and neuronal injury. Trends in Diabetes and Metabolism Vp; 3: 1-15 2020

https://www.survivingmold.com/Publications/Surviving_Mold_Actinobacteria_8_24_21_1.pdf