
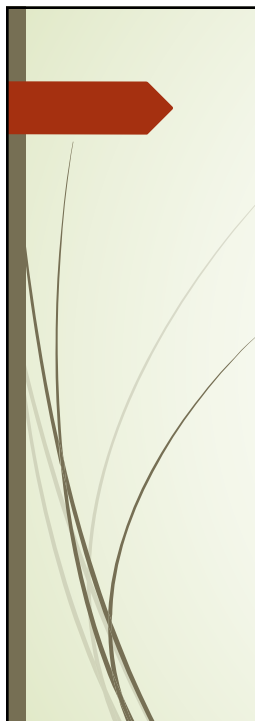


Separating CIRS: WDB, PLS, CFS, FIBRO, POST-COVID

RITCHIE SHOEMAKER MD
CIRSX 1/2024




1

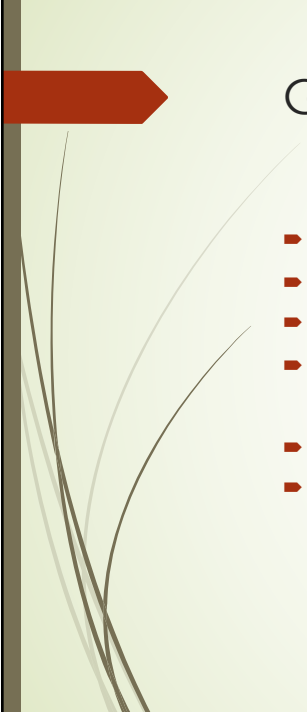


CONFLICTS OF INTEREST

- CONSULTANT TO AIR ANSWERS
- ROYALTIES FROM SALES DERIVED FROM IP
 - SURVIVING MOLD
 - PROGENEDX




2

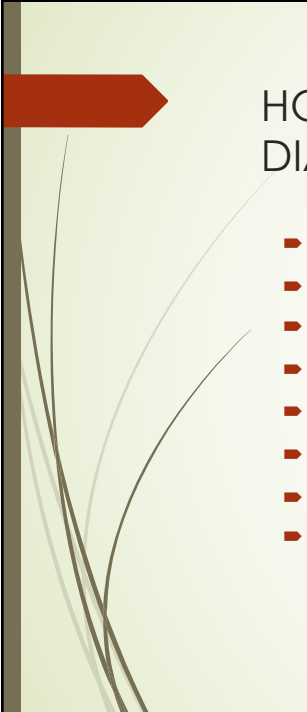


GOALS

- ▶ REVIEW CIRS, ITS CASE DEFINITION
- ▶ SIMILARITIES AND DIFFERENCES WITH CIRS, PLS, POST-COVID, CFS, FIBRO
- ▶ MITOCHONDRIAL DYSFUNCTION AND BLOCKADE OF PYRUVATE UPTAKE
- ▶ RIBOSOMAL INJURY AND CFI
 - ▶ CFI SHOEMAKER, HEYMAN AND RYAN 2017 IMR 1-30
- ▶ INTRODUCE HYPOMETABOLISM; HOW TO DIAGNOSE AND TREAT IT
- ▶ PINPOINT VCS, GENIE AND NQ AS KEYS SEEN IN CIRS




3



HOW CAN WE PERFORM DIFFERENTIAL DIAGNOSIS TO SPECIFICALLY DIAGNOSE CFI


- ▶ UNDERSTAND EXPOSURE AND **BIOMARKERS**
- ▶ LOOK FOR DIFFERENCES IN PRESENTATION
- ▶ USE VALIDATED VCS!
- ▶ LOOK FOR DIFFERENCES IN SYMPTOMS
- ▶ LOOK FOR DIFFERENCES IN LABS
- ▶ LOOK FOR DIFFERENCES IN NEUROQUANT
- ▶ LOOK FOR DIFFERENCES IN GENIE
- ▶ A PATIENT CAN HAVE MULTIPLE TYPES OF CIRS



4

CLUES TO MICROBIAL GROWTH IN WDB

- ▶ A(w); ACTIVITY OF WATER IS ECOLOGICAL DEFINING FEATURE
- ▶ XEROPHILES A(w) 0.55-0.65 WALLEMIA SEBI
- ▶ INTERMEDIATES A. VERSICOLOR, A PENICILLIODES .65-.80
- ▶ WET FUNGI STACHYBOTRYS (14 outdoor species), CHAETOMIUM 0.9-1.0
- ▶ MUSTY SMELLS: BACTERIA AND ACTINOBACTERIA; GEOSMIN
- ▶ VISIBLE GROWTH, R/O SOOT!
- ▶ SPECIES DETERMINED BY LICENSED LAB; NGS AND PCR
- ▶ FORGET ABOUT GENUS-ONLY LAB TESTING
- ▶ AIR SAMPLES ARE NOT USEFUL IN CIRCS



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A LITTLE MOLD WON'T HURT ANYONE



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VISUAL CONTRAST SENSITIVITY (VCS)

- ▶ PERHAPS THE BEST BIOMARKER FOR CIRS
- ▶ NON-INVASIVE, REPRODUCIBLY RELIABLE
- ▶ SHOWS REDUCTION OF FLOW IN CAPILLARIES
 - ▶ DUAL LASER RETINAL FLOWMETER
 - ▶ RETINA; NEURAL RIM OF OPTIC NERVE HEAD
- ▶ FIRST BIOMARKER FOR PFIESTERIA
- ▶ 92% + IN ALL CIRS ILLNESSES; USE AT AGE 8
- ▶ PRESENT AT 36 HOURS OF ONSET OF BOTH ACUTE ILLNESS AND RELAPSE
- ▶ TREATMENT CORRELATED WITH CORRECTION OF CAPILLARY FLOW



7

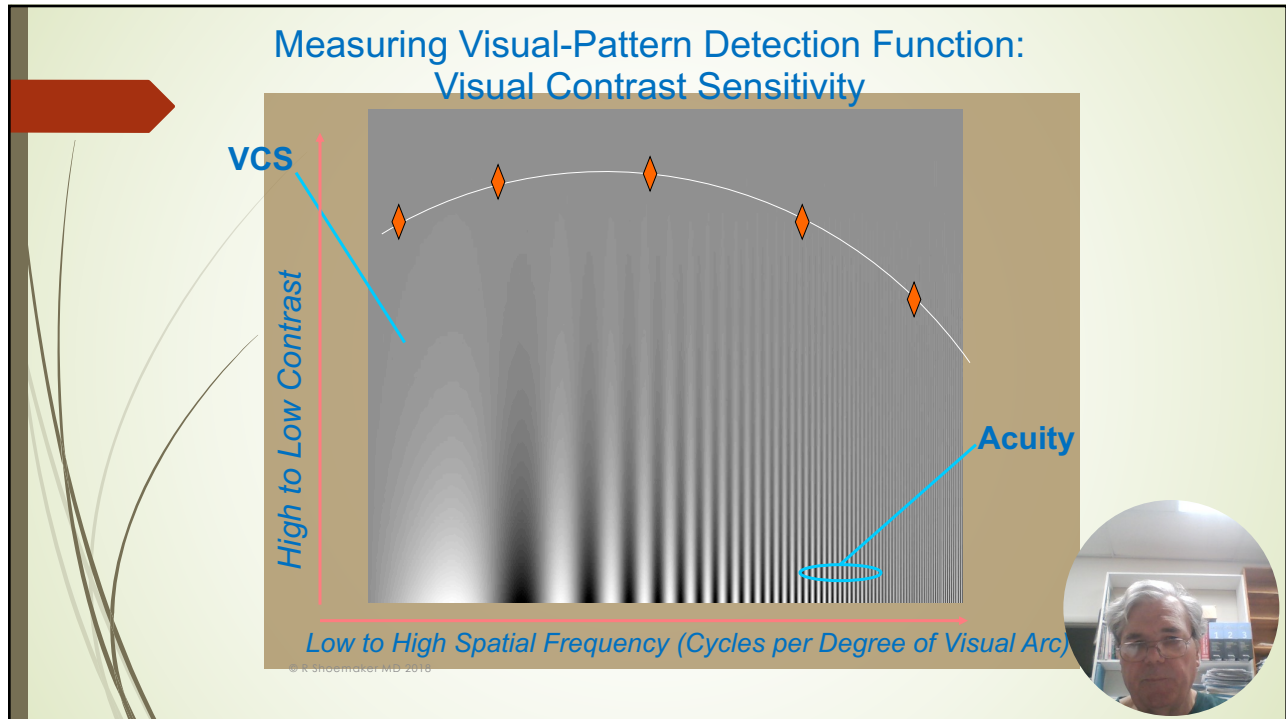
Start with VCS if starting DX and RX

- ▶ Best test of functional vision
- ▶ Old test from neurotoxicology
- ▶ On-line versions vary
- ▶ Diagnostic at baseline and essential for follow-up (especially hyperacute)
- ▶ Correlates with **INTENSIFICATION** in Lyme, MARCoNS

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EXPOSURE AND SUSCEPTIBILITY-1

- LOOK FOR WATER-DAMAGED BUILDINGS BEFORE ILLNESS ONSET
- HOMES, OFFICES, SCHOOLS, GYMS, RESTAURANTS, SUMMER CABINS, HOTELS, AIRPLANES OVER 30,000 FEET FOR MORE THAN AN HOUR, FLOODED CARS, HURRICANES AND FLOODS; (open windows and doors too)
- ROLE OF HLA DR BY PCR: 11-3-52B, 4-3-53, 13-3-52A, 14-5-52B THE DREADED
- LESS SEVERE HAPLOTYPES 7-2,3-53, 13-6-52A,B,C; 17-2,3-52A,B,C
- LITTLE RACIAL DIFFERENCES EXCEPT FOR 4-4-53 LATINO; 18-4-52A,B,C AFRICAN
- MSH DEFICIENCY (BIZARRE NORMAL RANGES!); < 35 AT LC

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EXPOSURE 2

- ▶ WDB SOURCES ARE THE SAME IN HUMID CLIMATES AND DRY
 - ▶ ASPERGILLUS PENICILLIOIDES ARE UBIQUITOUS IN HAWAII, TROPICS
- ▶ WATER INTRUSION: CAULK, FLASHING, CHIMNEYS, ROOFS, SOFFITS
 - ▶ CONSTRUCTION DEFECTS PLAGUE NEW CONSTRUCTION
- ▶ INDOOR WATER: LEAKS, WOODPILES, CONSTRUCTION MATERIALS
- ▶ HUMAN CONTRIBUTION: BREATHING, KITCHEN AND BATH EXHAUST
 - ▶ ACTINOBACTERIA MOVE; TRI-METHYL AMINE PHEROMONES
- ▶ SEWER GAS
- ▶ SUBTERRANEAN AREAS: DON'T TRUST CONDITIONING! TEST!



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EXPOSURE 3

- ▶ DINOFLAGELLATES
 - ▶ REEF FISH; CIGUATERA, CHATTONELLA, KARENIA, PFIESTERIA
- ▶ HUGE CONTROVERSY ABOUT LYME
- ▶ GROWING RECOGNITION OF CYANOBACTERIA WITH USE OF NGS
 - ▶ EVERY STATE HAS A FRESH WATER BODY GROWING CYANOS
- ▶ NO DATA FROM BIOMARKERS IN CFS AND FIBROMYALGIA
- ▶ POST COVID BEGINS WITH INFLAMMATORY DROP IN MSH
- ▶ PRIMING EVENT ACTIVATES GENE RESPONSE TO ENVIRONMENT!
 - ▶ DO THE GENIE TO BE SURE NOT ACQUIRED ENDOTOXIN OR ACTINO
- ▶ DISCLAIMER: NO BROAD-BASED PAPER ON COVID ON HLA/GENIE/M



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EXPOSURE 4: TICK-BORNE ILLNESSES

- ▶ POST LYME PRIMING UNDERLIES 15-6-51, 16-5-51, 4-3-53, 11-3-52B
 - ▶ 20% OF CONTROLS HAVE THESE GENES; AT RISK!!
- ▶ MSH DEFICIENCY IS ACQUIRED; HLA + FASTER; HLA - SLOWER
- ▶ BABESIA CAN PRODUCE APICOMPLEXAN GPI, BIOTOXIN IN MALARIA
 - ▶ UNKNOWN RE SARCOCYSTIS AND EIMERIA. GPI IS ESSENTIAL FOR TOXO
 - ▶ IGG AND IGM FOR BABESIA FALSE POSITIVES!
- ▶ EHRlichia NOT KNOWN TO MAKE A TOXIN
- ▶ SAM DONTA RECEIVED A US PATENT IN 90'S FOR Bb, A LYME BIOTOXIN
- ▶ PLS IS A CIRS AS WE WILL SEE



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ALWAYS CONTROVERSY IN LYME/PLS

- ▶ I USE ECM RASH, INCLUDING HEMORRHAGIC
- ▶ > 5 CM
- ▶ PHYSICIAN OBSERVED
- ▶ IGM AND IGG FROM RWJ OK; BASED ON NORVECT 2015
- ▶ I USE NEUROQUANT SMALL PUTAMEN AND LARGE R THALAMUS
- ▶ I USE TRANSCRIPTOMICS 2016 BOUQUET, ALCOTT AND CHIU
 - ▶ UNTREATED HAS UNIQUE ID; TREATED NOT TESTED BEYOND 6 MONTHS



15

The Norvect Study OSLO 2015 SHOEMAKER, HEYMAN, ET AL

- ▶ 187 scans
- ▶ 8 medical practices
- ▶ Patients' scans sent in for consult
- ▶ Data collated by NQ by areas; clinical impression; basis; key findings
- ▶ Variables included practice assessment; multinuclear atrophy and exposure assessment



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Results

- ▶ By NQ Lyme: criteria met by 36; Lyme neg 151
- ▶ By clinical Lyme: + 102; not Lyme 71; (14) not classified
- ▶ By NQ mold: 116; not mold 71
- ▶ By clinical mold: + 90; neg 50, not classified 47
- ▶ Correlation NQ/+clinical Lyme= 36/102
- ▶ Correlation NQ/- clinical Lyme= 151/71
- ▶ Correlation NQ mold/+ clinical=116/90
- ▶ Correlation neg NQ mold/-clinical 71/50



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Results 2

- ▶ If + ECM, N=14, NQ + in 13
- ▶ If Quest WB + N=10, IgM, NQ + in 6
- ▶ If Quest WB + N= 9, IgG, NQ + in 6
- ▶ If Igenex + IgM, N=42, NQ + in 3
- ▶ If Igenex + IgG, N= 42, NQ + in 1
- ▶ Multinuclear atrophy 1.62 in CIRS-WDB; PLS shows 2.38



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T-reg changes in Lyme by stage

	Control	Base	Post Abx	Post CIRS
N=	13	34	29	31
TGFB	3621	6782	8967	4890
C4a	3886	8149	6710	4120
C3a	124	1284	384	410
i-Treg	4.66	2.94	3.02	4.16
t-Treg	4.25	2.44	2.98	3.86



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CLINICAL PRESENTATION/SYMPTOMS

- **RASH** IN WBD 20%; PLS HAVE HISTORY OF ECM 35-70% VARIABLE
- NO RASH IN CFS, FIBRO, DINOS, CYANOS, BABESIA
- **FEVER** NONE EXCEPT ACUTE LYME
- **ESR** IN ACUTE LYME; OTHERS NONE/VARIABLE IN PLS
- **SYMPTOMS**: WEAKNESS, FATIGUE, BRAIN FOG, HEADACHE, RESPIRATORY ILLNESS, ACHING, BLURRED VISION, UNUSUAL PAIN, GI UPSET, ABDOMINAL PAIN, MOOD SWINGS, APPETITE SWINGS, NIGHT SWEATS, POLYURIA, DIZZINESS, METALLIC TASTE AND MORE, ALL TYPICALLY FOUND
- **VCS** AND CLUSTER TOGETHER SHOW 98.5% ACCURACY FOR CIRS



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Biotoxin symptoms by organ systems

- Fatigue, weak (1)
- Headache (2)
- Aches, cramps (3)
- Unusual, sharp, claw, electrical pain, ice-pick pain (4)
- Light sens, redness, blurring, tearing (5)
- SOB, cough, sinus (6)
- Abdominal pains, secretory diarrhea (7)
- Joints, AM stiff (8)
- Exec. cognitive memory concentration. Word assimilation, confusion, disorientation (9)
- Mood, appetite, sweats, temp regulation (10)
- Thirst, pee, shocks (11)
- Numbness, tingling, taste (12)
- Vertigo, tremor, skin (13)

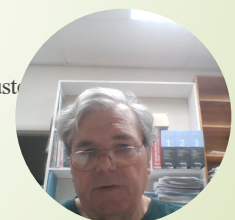
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CLUSTER ANALYSIS OF SYMPTOMS

1. Fatigue
 2. Weak, assimilation, aching, headache, light sensitivity
 3. Memory, word finding
 4. Concentration
 5. Joint, AM stiffness, cramps
 6. Unusual skin sensations, tingling
 7. Shortness of breath, sinus congestion
 8. Cough, thirst, confusion
 9. Appetite swings, body temperature regulation, urinary frequency
 10. Red eyes, blurred vision, sweats, mood swings, ice-pick pains
 11. Abdominal pain, diarrhea, numbness
 12. Tearing, disorientation, metallic taste
 13. Static shocks, vertigo
- A positive cluster analysis for biotoxin illness is presence of 8 or more of 13 clusters



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Chronic cognitive abnormalities in CIRS patients

- ▶ Executive cognitive functions
 - ▶ Recent memory
 - ▶ Concentration
 - ▶ Word finding; assimilation of new knowledge
 - ▶ Confusion; disorientation

NOT SPECIFIC FOR A GIVEN BIOTOXIN ILLNESS

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WHAT ABOUT COVID AND CIRS?

- ▶ INFLAMMATORY VIRAL DISEASE
- ▶ SETS OFF CYTOKINE STORM
- ▶ A CLASSIC PRIMING EVENT
- ▶ WELL PATIENTS GOT INFECTED
- ▶ MASSIVE INNATE IMMUNE RESPONSE FOLLOWED
- ▶ SURVIVORS ARE AT RISK FOR PROGRESSIVE IMMUNE RESPONSE
- ▶ GENIE SHOWS ACUTE POST-COVID TO BE IDENTICAL TO CHRONIC CIRS
 - ▶ BCL2 SHOWS PRIOR COVID (OR HIV)
- ▶ ACTIVATION OF SPECIFIC CAUSATION PATHWAYS, ESPECIALLY TGFBR 1, 2
 - ▶ ENDOS: CD14, TLR 2, TLR4
- ▶ ILLNESS FROM WDB IS PRIMED; ENDOS AND ACTINOS GO WILD



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ONE PAPER FROM SHOEMAKER, LARK AND HEYMAN WON'T CONVINCE CDC

- 24 PATIENTS WITH POST-COVID SYMPTOMS
- CLUSTER +, VCS + MSH LOW, TGF BETA-1 HIGH
- MOLECULAR HYPOMETABOLISM + 100%
- PROLIFERATIVE PHYSIOLOGY + 90%
- SPECIFIC CAUSATION 63% FOR ENDOTOXINS
- SPECIFIC CAUSATION 54% FOR ACTINOBACTERIA
- WE NEED DUST SAMPLES FROM EACH HOME
- STILL WAITING...



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LABS DO NOT SEPARATE ILLNESSES-1 COMMON ABNORMALITIES

- HLA DR: SAME
- MSH DEFICIENCY: SAME
- ACTH/CORTISOL DYSREGULATION: SAME
- ADH/OSMO: SAME
- C4 α , TGF BETA-1, MMP9: SAME
- VEGF: SAME
- AGA: SAME; VWF SAME
- CMP: 60% HAVE WIDENED ANION GAP; CLUE TO METABOLIC ACID
- LEADING TO PROLIFERATIVE PHYSIOLOGY AND HYPOMETABOLISM



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LABS DO NOT SEPARATE ILLNESSES-2 COMMON NORMALITIES

- ▶ CBC, CHEM-18: SAME
- ▶ CHOLESTEROL, LIPIDS, TSH: SAME
- ▶ IGG LEVELS: SAME
- ▶ D-DIMERS + IN DVT, PE: SAME
- ▶ FERRITIN: SAME
- ▶ EBV: SAME, THOUGH CFS DOCS HAVE BEEN CHASING VIRAL SOURCE
- ▶ ANA: FALSE POSITIVES



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LABS ARE ABNORMAL FOR GENETIC ILLNESS; INNATE IMMUNE ACTIVATION-1

- ▶ ILLNESSES ARE NOT ACQUIRED IMMUNITY
- ▶ WE EXPECT TO FIND DEFECTIVE ANTIGEN PRESENTATION, WE DO
 - ▶ T CELL SYNAPSE < 0 = 95%
- ▶ WE EXPECT TO SEE MOLECULAR HYPOMETABOLISM; WE DO
- ▶ WE EXPECT TO FIND PROLIFERATIVE PHYSIOLOGY, WE DO
- ▶ WE EXPECT TO FIND CD3D LOW, WE DO
- ▶ WE EXPECT TO FIND T REGULATORY CELL DEFICIENCY, WE DO
- ▶ WE EXPECT TO FIND CYTOKINE UPREGULATION, WE DO
- ▶ WE EXPECT TO FIND VASCULAR SOURCE OF COGNITIVE DECLINE, WE DO
- ▶ WE EXPECT TO FIND CYTOSKELETAL DEFECTS IN **MICROTUBULES, THEREBY**
CREATING DIEBACK CNS DEGENERATIVE DISEASE, WE DO TUBA4A



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THE INFLAMMATORY DATA DOESN'T GUESS MULTISYSTEMS, MULTI-SYMPOMS

- HLA CONFERS SUSCEPTIBILITY
- MSH DEFICIENCY CONVEYS LACK OF NEUROPEPTIDE REGULATION
 - CYTOKINE STORMS
 - C4a COUNTLESS DISORDERS ON MOLECULAR BASIS
- ADH AND ACTH DYSREGULATED
- MMP9 NERVE, MUSCLE, BRAIN, LUNG AND BLOOD
- VEGF VASCULAR DYSREGULATION
- COMMON GI LOOSE JUNCTIONS; SEE LIPTON AND CATANIA
- HYPOTHALAMIC SYMPTOMS MOOD, APPETITE, NIGHT SWEATS
- BUT WHAT ABOUT METABOLISM?



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WHERE ARE WE IN SEPARATION?

- WE KNOW THAT INFLAMMATION AND METABOLIC INJURY CAN LEAD TO IMMUNE INJURY SHARED BY CIRS ASSOCIATED ILLNESSES
- GENIE LETS US DEFINE THE IMMUNE FEATURES OF CIRS
- BUT WHERE DOES BRAIN INJURY COME IN? BRAIN ON FIRE?
- NO, BRAIN ON ICE!!
- 3/23 1800 GENIES AND 800 NEUROQUANTS SHOW DISTINCTLY DIFFERENT FINGERPRINTS OF BRAIN INJURY (OUR 3 AUTHORS STIRRING THE POT)
- FINALLY, WE CAN SHOW WDB AND LYME ARE DIFFERENT BEYOND BITE
- CFS AND FIBRO ARE THE SAME, BUT NO BIOMARKERS
- POST-COVID IS TOO NEW TO CONVINCE THE SKEPTIC



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CLUES TO COMMONALITY OF CIRCS MIGHT LIE WITH RIBOTOXINS

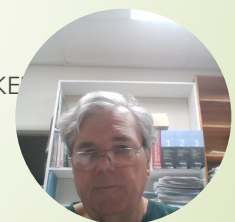
- ▶ RIBOSOMAL INJURY FROM SMALL MOLECULE RIBOTOXINS, RIBOSOMAL INHIBITORY PROTEINS (RIP)
- ▶ ACTINOBACTERIA LEAD THE LIST, ENDOTOXINS SECOND AND FUNGI LAST
 - ▶ ROLE OF BETA GLUCANS ACTIVATING DECTIN-1 AND -2 COULD CREATE RIP
- ▶ WE KNOW RIBOTOXINS EXIST BUT NOT EVEN GENIE CAN DETECT THEM
- ▶ EVOLUTIONARILY CONSERVED SARCIN-RICIN LOOP
- ▶ **SPECIFIC CAUSATION** IN FAB



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WRAPPING UP SEPARATING CIRCS-1

- ▶ NQ SEPARATES CIRCS-WDB ACTINO, ENDO AND MOLD
 - ▶ SPECIFIC CAUSATION FOR ALL THREE ON GENIE
 - ▶ NO DATA PUBLISHED ON BETA GLUCANS
- ▶ NQ SEPARATES PLS
- ▶ ECM SEPARATES ACUTE LYME; WB STILL SUSPECT
- ▶ GENIE SEPARATES PRIOR COVID AND ACUTE POST-COVID
- ▶ FIBRO AND CFS: THE SAME CFS PROTEOMES
 - ▶ SCHUTZER S, NATELSON B, ET AL. ANNALS MED, 2023 55:1-7 2208372
- ▶ 2009 PEDS CFS THE SAME AS CIRCS, CASE CONTROLS, 8 BIOMARKE



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SUMMARY

- ▶ WE SHALL NOT CEASE FROM EXPLORATION
- ▶ AND THE END OF ALL OUR EXPLORING
- ▶ WILL BE TO ARRIVE WHERE WE STARTED
- ▶ AND KNOW THE PLACE FOR THE FIRST TIME
 - ▶ TS ELIOT
- ▶ SO IT IS WITH CIRS, A RAPIDLY EVOLVING FIELD
- ▶ ONE THING IS CERTAIN, WHEN NEXT WE MEET
- ▶ THERE WILL BE MORE BIOMARKERS TO EXPLORE



33



THANKS TO

- ▶ DAVID LARK, CO-AUTHOR ON 10 PAPERS
- ▶ ANDY HEYMAN, CO-AUTHOR ON PAPERS, A TEXTBOOK, COUNTLESS CONFERENCE TALKS AND YEARS OF TEACHING
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- ▶ AND CHERYL LAURENCE-SHOEMAKER FOR INSPIRATION

34