NeurAbilities Healthcare

Neurabilities NeuroGenomics Service Peer-to-Peer Notes

Client:
Date: 3/20/2023
Patient:
DOB: 1/3/1942 (81y)
Service level: Basic Standard **Comprehensive**
Test/lab: WGS singleton/Variantyx
Off-target: Requested by adult patient, Dr.

Summary of the discussion:

Referral:

8/7/22

Dr. Boles,

I am referring this patient for genetic testing recommendation with Variantyx and then peer-to-peer consult.

Patient has an extensive past history of "unusual" symptoms and testing. He keeps an indexed website of the history of his symptoms, testing, and treatment (unusualsymptom.info) which is fairly thorough - especially so for the period before 2013, when I began to see him. Below is a list of interventions/treatments and their impact on his main symptoms. Main symptoms:

1. Fatigue: He started with vague, slowly progressive fatigue symptoms in the 1960's, with post-exertional malaise, muscle discomfort, and fibromyalgia. Onset of fatigue was not associated with any specific illness or events. When he started seeing me in 2013, his fatigue had progressed to the point that he was on total disability and essentially had 4 hours of 50-60% functionality per day and could walk approximately 1 square block. Now, he has 8 hours per day of >75% function and can walk >1 mi on level. He cannot do any aerobic exercise.
   He has lived in the same rent-controlled apartment for over 40 years. The apt flooded roughly once per year for 30 years, but not has not flooded for the last 4-5 years, after the sewer drainage for the building was fixed. No other water damage and no visible mold. He has 2 HEPA filters in his house, which helped his fatigue and muscle "buzzing" a little.

2. Muscle "Buzzing": Beginning in 1971, he developed onset of complex muscle "buzzing"/tightness/discomfort/pain/fatigue with washing. This complex effect on the muscles in the area washed is not stimulated by dry washing or rubbing (ie. it requires

water), is not affected by temperature of water or the absence/presence of soaps or shampoos, in the past, he would intermittently have red lines/dermatographia in the pattern of the washing/rubbing (but this stopped in the early 2000's). Improvements in his mood and general fatigue have not improved this symptom. No urticaria or parasthesias other than the buzzing/vibration effect in the muscles along with pain/tightness/fatigue. This symptom progressed to the point that by 2007 he was washing only small parts of his body in rotation every 5 days, since that was how long the pain and fatigue would last after the washing and he would be able to wash another part of his body. Starting Lamictal and supplementation with oral and IM magnesium, after RBC levels of magnesium were found to be low, all improved this symptom so that by 2013 he was able to take a full shower once per week with 5 days of decreasing fatigue after washing and 1-2 small, regional washes during the week. At that time, he was still requiring opiate pain medication when he washed but this has not been needed over the last 5-6 years, with gradual overall improvements.

fiber neuropathy.

3. Depression – long-standing for over 40 years, onset roughly correlating to the onset of his fatigue. See below for impact of multiple medications and other interventions on this.
4. Misc:
    a. Urological – he has had gradually increasing prostate size over the last 10-15 years. Despite treatment with medications, he now he has 3-4x/night nocturia, persistent large residual urine volumes, and frequent low-grade UTI's, of which only symptomatic ones are treated with antibiotics.

Patient information:

Chief complaints:

1. Fatigue
2. Myalgia/buzzing

Family history:

None; no chronic pain, no immunodeficiency phenotype

Non-genetic test results:

Carnitine: low by report prior to supplementation

MitoSwab: RC-I 1.4 low, RC-IV 0.44 nl, CS 4.56 low nl

NCV/EMG: normal

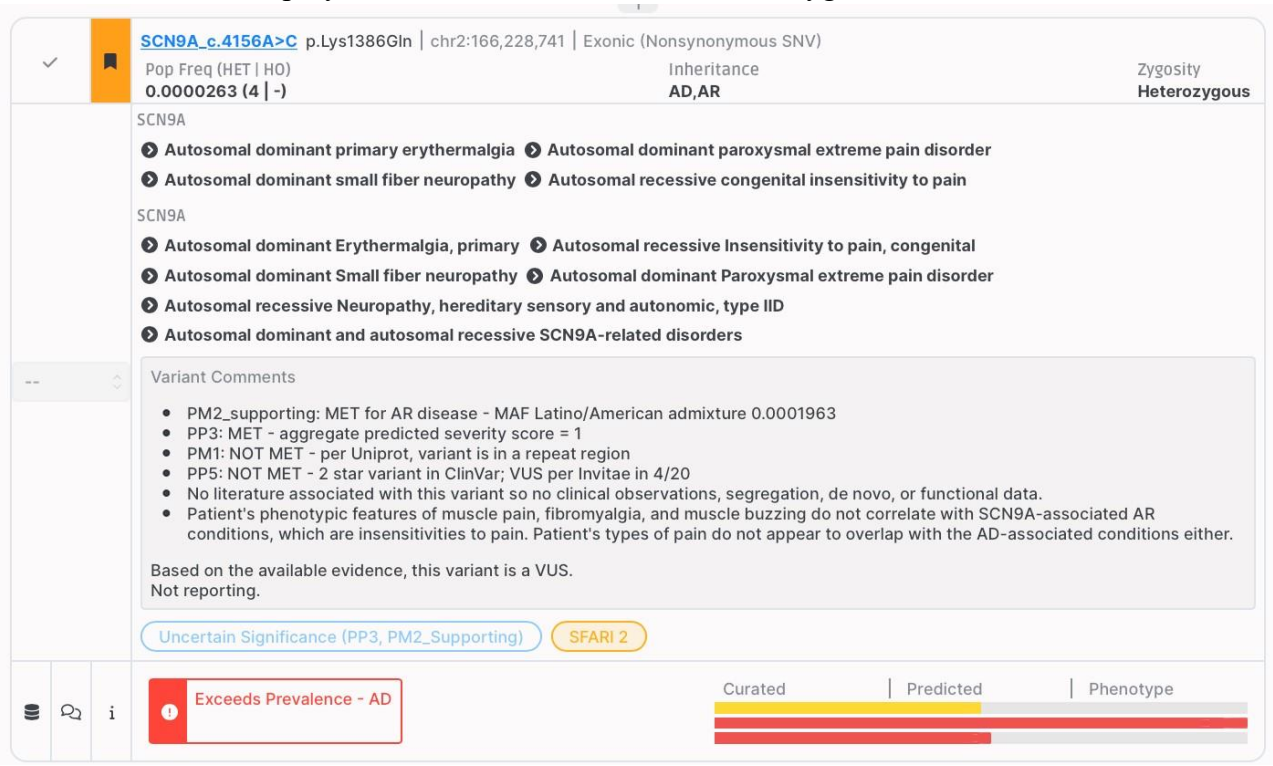
Genetic test results:

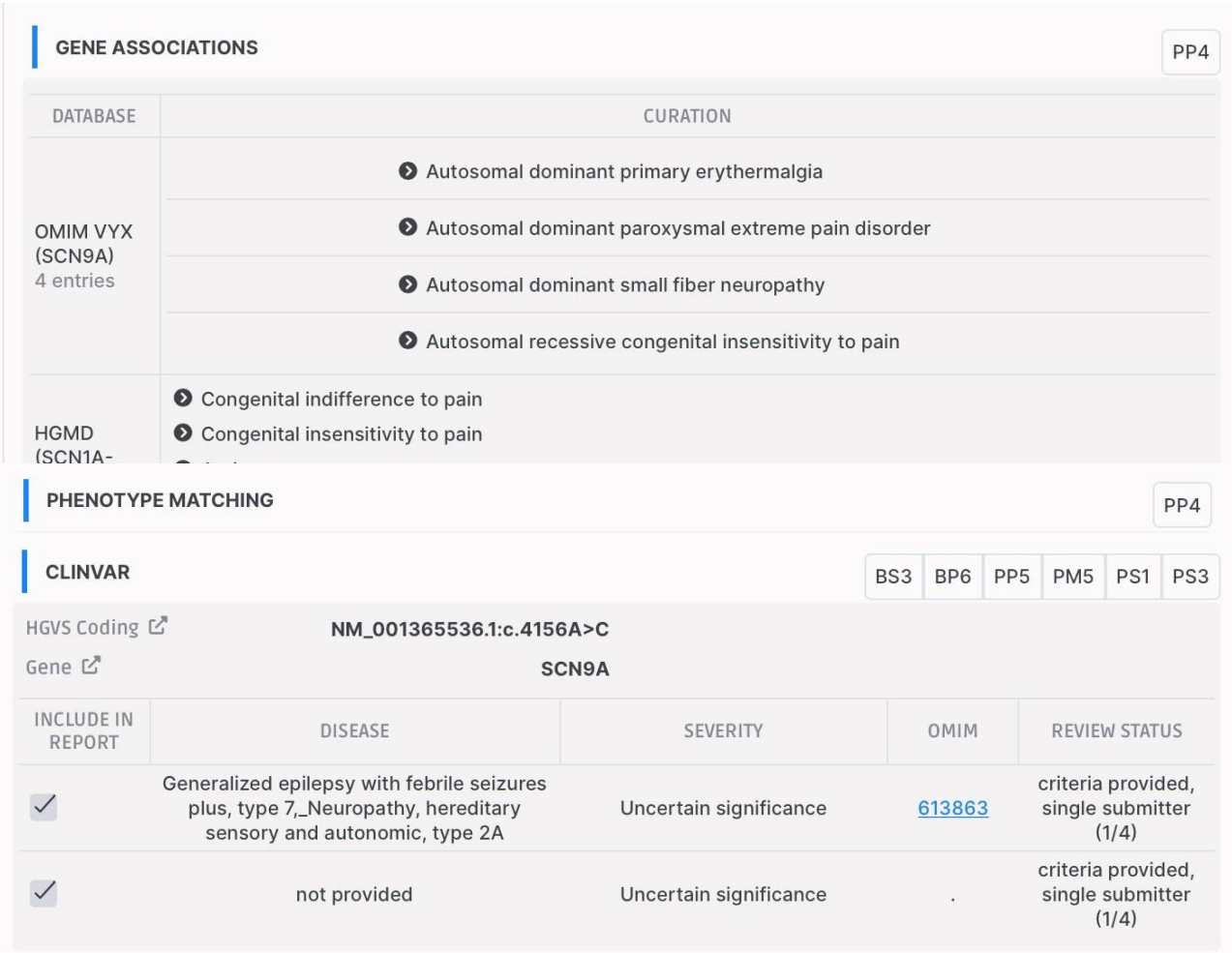
Official laboratory report:

Comprehensive Sequence Re-analysis - Variants of potential interest:

Functional disease gene list: ATP1A2, ATP1A3, ATXN8OS, CACNA1A, CACNA1S, CDK8, CHAMP1, CLCN1, CNR1, COQ2, GFAP, GLA, GLS2, HMBS, INF2, KCNH2, KCNJ18, KCNK18, KIF1B, INF2, MAP1B, MEFV, OCM, OPRM1, OTC, PMP22, POGZ, POLG, PPM1D, PRRT2, RYR2, SCN1A, SCN2A, SCN4A, SCN9A, SCN10A, SCN11A, SH3TC2, SLC1A3, SLC2A1, TNFRSF1A, TNFRSF1B, TNXB, TRAP1, TRPA1, TRPC3, TRPV1, TUBB3

SCN9A c.4156A>C, p.Lys1386Gln, ch2:166,228,741, heterozygous:





Coverage 17/19

COMPUTATIONAL AND PREDICTIVE

BP4 BP7 PP3

Aggregate Predicted Severity Score **1**	MutationTaster 0.999877,D	SIFT 0.001,D	MetaLR 0.962,D
SpliceRF -	PhyloP 1.061,D	FATHMM -4.97,D	GERP++ 4.13,D
SpliceADA -	PhastCons 1.0,D	LRT 7e-06,D	MetaSVM 1.0897,D
	MutationAssessor 3.02,D	Siphy 12.4612,B	Curated Severity Code 4

POPULATION DATA

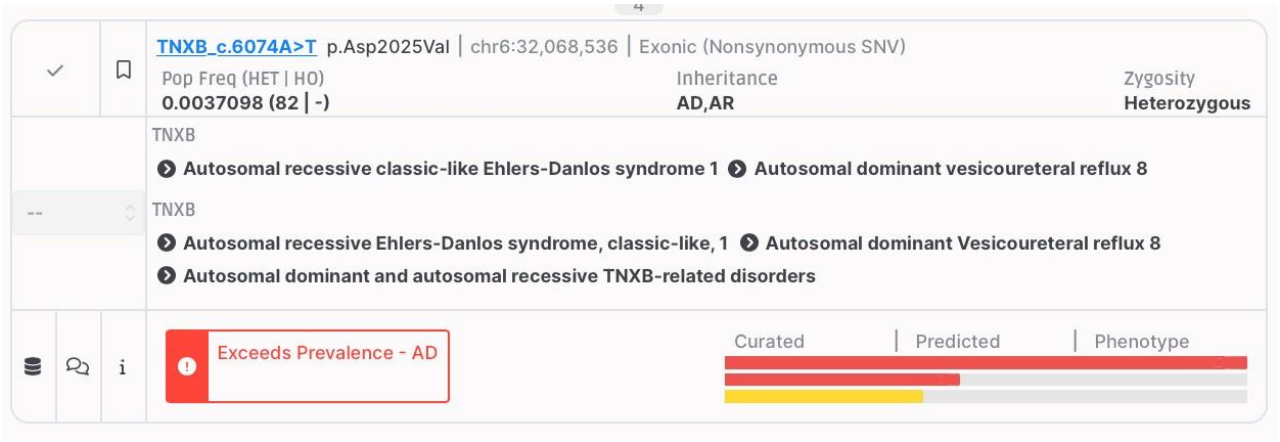
BA1 BS1 BS2 PM2 PS4

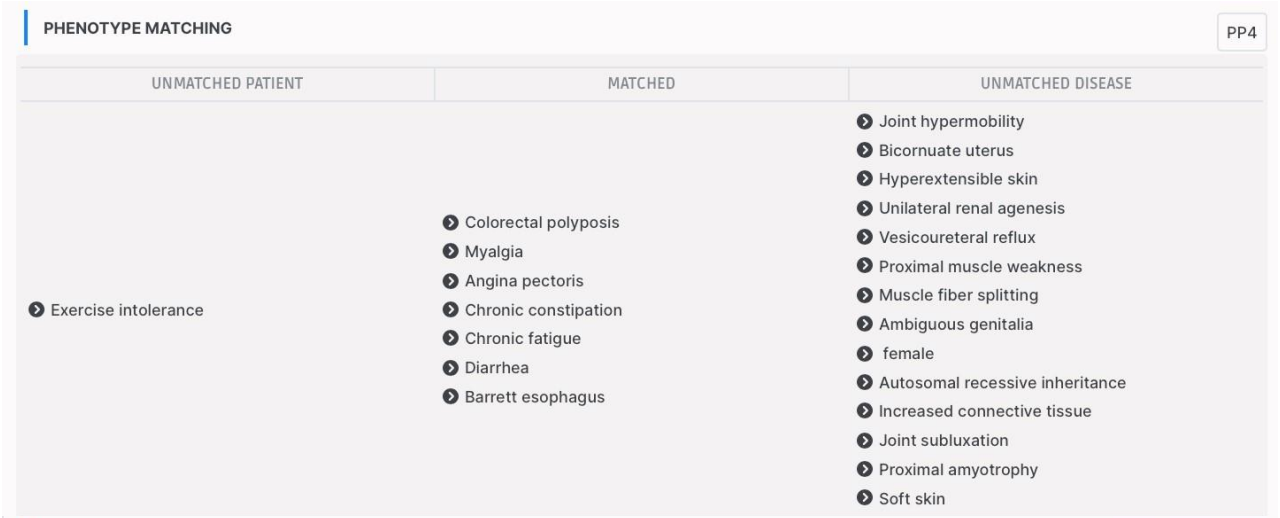
Date Range Specific PAF

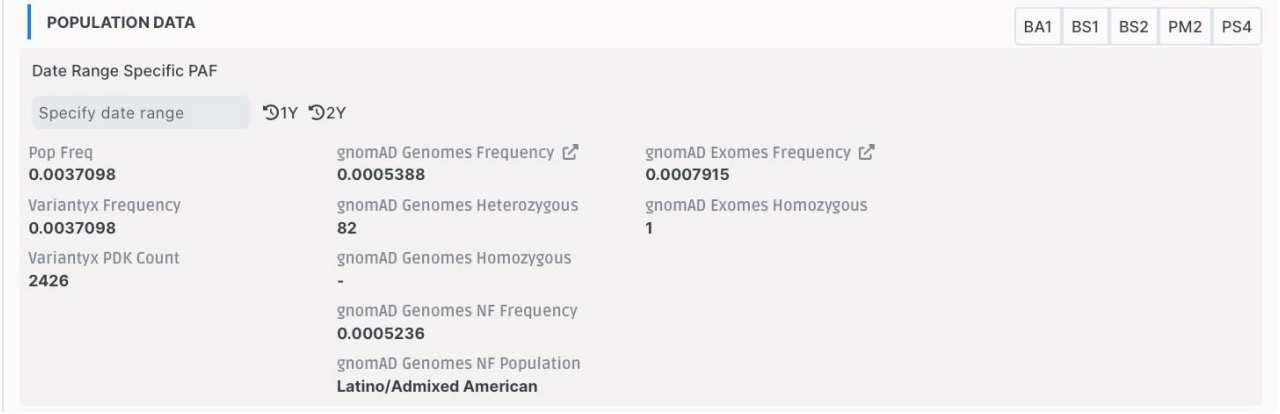
Specify date range 1Y 2Y

Pop Freq 0.0000263	gnomAD Genomes Frequency 0.0000263	gnomAD Exomes Frequency 0.0000146
Variantyx Frequency -	gnomAD Genomes Heterozygous 4	gnomAD Exomes Homozygous 0
Variantyx PDK Count -	gnomAD Genomes Homozygous -	
	gnomAD Genomes NF Frequency 0.0001963	
	gnomAD Genomes NF Population Latino/Admixed American	

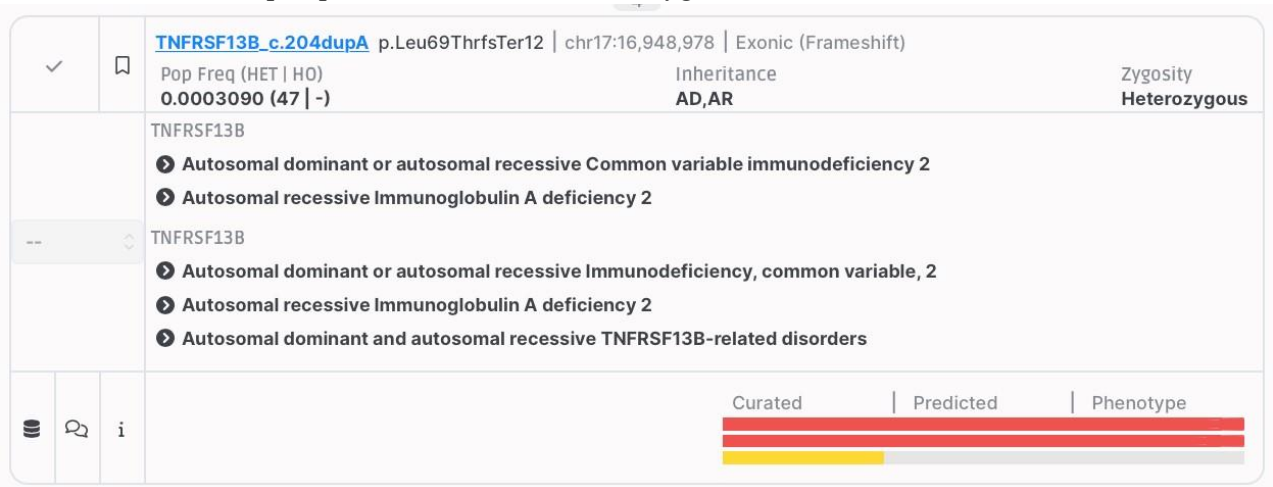
TNXB c.6074A>T, p.Asp2025Val, chr6:32,068,536, heterozygous:

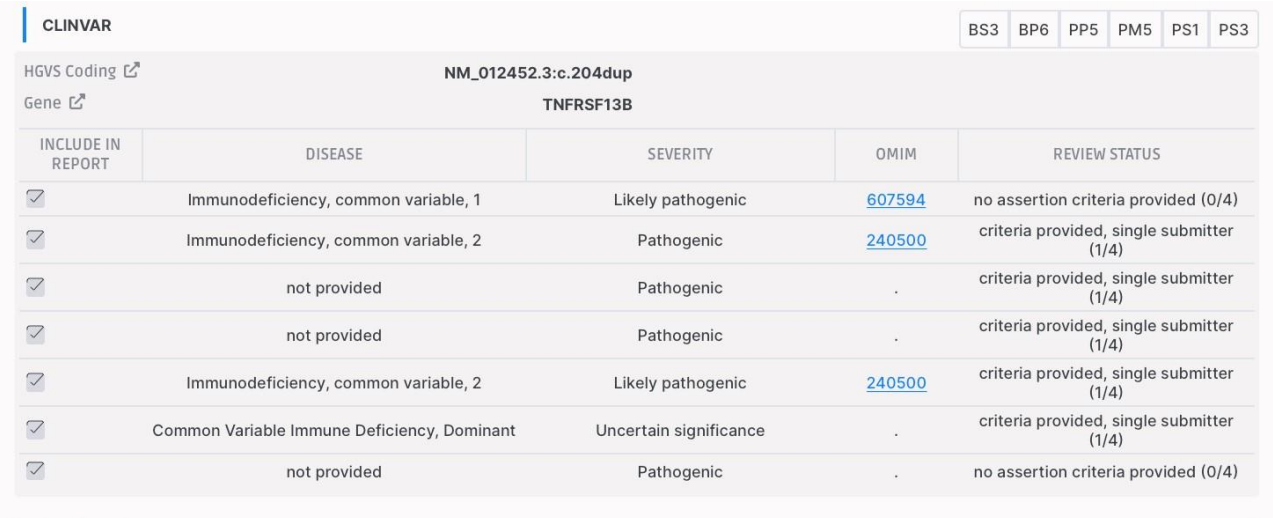






TNFRSF13B c.204dupA, p.Leu69ThrfsTer12, heterozygous:





INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS
☑	Immunodeficiency, common variable, 1	Likely pathogenic	607594	no assertion criteria provided (0/4)
☑	Immunodeficiency, common variable, 2	Pathogenic	240500	criteria provided, single submitter (1/4)
☑	not provided	Pathogenic	.	criteria provided, single submitter (1/4)
☑	not provided	Pathogenic	.	criteria provided, single submitter (1/4)
☑	Immunodeficiency, common variable, 2	Likely pathogenic	240500	criteria provided, single submitter (1/4)
☑	Common Variable Immune Deficiency, Dominant	Uncertain significance	.	criteria provided, single submitter (1/4)
☑	not provided	Pathogenic	.	no assertion criteria provided (0/4)

<u>Per our discussion today</u>:

- SCN9A c.4156A>C, p.Lys1386Gln, ch2:166,228,741, heterozygous:
  - This variant is highly likely to alter protein function as it is very rare in humans, highly conserved, and predicted as such by computer algorithms.
  - Variants in this gene can result in small fiber neuropathy with exaggerated sensation, including pain and fatigue. Other sensations I have seen in patients with variants in this gene include tinnitus and interstitial cystitis. Erythroderma is also then described.
  - This variant is an excellent fit for the disease in this patient, and thus is highly likely contributing in a polygenic/multifactorial manner.
- TNXB c.6074A>T, p.Asp2025Val, chr6:32,068,536, heterozygous:
  - This variant is likely to alter protein function as it is rare in humans, conserved, and predicted as variably such by computer algorithms.
  - Variants in this gene can result in Ehlers-Danlos syndrome-like issues, including dysautonomia.

    - This variant is a potential risk factor for fatigue in this patient, via vascular hypotension.
- TNFRSF13B c.204dupA, p.Leu69ThrfsTer12, heterozygous:
    - This variant results in protein loss of function, and assessed as Pathogenic. o Variants in this gene can result in common variable immunodeficiency.
    - This variant shows poor clinical correlation to the phenotype in this patient, however, it is possible that low immunoglobulin levels are a contributing factor in his disease.

Potential management issues for consideration:

- Consider SCN9A-targeted medications:
    - Gabapentin, duloxetine, sertraline, amitriptyline
- Consider increasing mitochondrial cocktail. The potential conflict of interest was discussed.

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