BioCog AI Health Report

Comprehensive Genetic Analysis & Diagnostic Assessment

BIOCOGNITIVE ENGINES

Patient: Jane Doe **DOB:** 03/15/1990 **Sex:** Female **Report ID:** BCG-2026-SS-0042

Ordering Physician: Dr. Sarah Chen, MD **Report Date:** January 16, 2026

Patient Presentation:

35-year-old female with debilitating chronic fatigue (6 years), diffuse musculoskeletal pain without joint swelling (5 years), cognitive dysfunction and difficulty concentrating (4 years), and chronically unrefreshing sleep. Reports "heavy, tired eyes" at end of day (attributed to screen time), increased thirst requiring frequent water intake, and occasional cold-induced finger pallor. Stopped wearing contact lenses in mid-20s due to persistent discomfort. Episodic eye redness 2-3 times yearly (attributed to seasonal allergies). Currently carries diagnosis of fibromyalgia.

Prior Workup:

2019: Normal CBC, CMP, fasting glucose, TSH/Free T4 (3/19); borderline vit D 28—supplemented (6/19); nl ferritin (6/19). **2020:** Negative ANA, RF, Anti-CCP, normal ESR and CRP (8/20). **2021:** Normal vitamin D and B12 after supplementation (6/21); sleep study without significant apnea (10/21). **2022:** Normal lumbar spine X-ray (1/22); SPEP total protein 8.3 g/dL (upper limit); PHQ-9 score 8. Fibromyalgia diagnosis; started duloxetine 60mg daily with partial improvement.

ACTION ITEMS

Priority items for physician review and next steps

DIFFERENTIAL DIAGNOSES TO CONSIDER

DIAGNOSIS	RECOMMENDED NEXT STEPS	TREATMENT TO CONSIDER
Sjogren's Syndrome [info]	☐ Anti-SSA (Ro) antibodies ☐ Lip biopsy ☐ Schirmer test	• Local/systemic immunosuppressants
Ankylosing Spondylitis [info]	☐ MRI sacroiliac joints with STIR sequence	• NSAIDs continuous • TNF inhibitors if needed

ROUTINE GENOMIC ANALYSIS

CATEGORY	SUMMARY	STATUS
ACMG Secondary Findings	Screened 81 genes for well-established disease risks requiring action (BRCA, Lynch syndrome, FH, cardiomyopathies).	✓ No action required
Cardiac Risk Assessment	CAD PRS: 62nd percentile (average). AFib PRS: 71st percentile (slightly elevated).	✓ No action required
Drug-Gene Interactions	All tested pharmacogenes (CYP2C19, CYP2C9, CYP3A4, SLCO1B1) show normal metabolizer phenotypes.	✓ No action required

PATHOPHYSIOLOGY

Understanding how disease mechanisms produce patient symptoms

Diagnosis 1: Sjogren's Syndrome [more info]

SJOGREN'S SYNDROME PATHOPHYSIOLOGY

Sjogren's Syndrome is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands (primarily salivary and lacrimal), leading to sicca symptoms. However, the disease extends far beyond dry eyes and mouth—systemic manifestations include profound fatigue, widespread pain, and cognitive dysfunction ("brain fog") that can precede or dominate over sicca symptoms. The underlying mechanism involves aberrant B-cell activation and autoantibody production targeting glandular tissue.

In this patient, Sjogren's syndrome would explain the constellation of chronic fatigue (~6y), diffuse musculoskeletal pain, and cognitive dysfunction—all common extra-glandular manifestations. The minimal dry eyes (attributed to computer work) and increased thirst suggest early or subclinical glandular involvement. Female sex and age (35) match the typical demographic (9:1 female predominance). Long-standing contact lens intolerance (stopped in mid-20s) and increased dental cavities at the gum line (~2019) are subtle clues consistent with early sicca. Mother's history of "always had dry mouth" raises familial autoimmune susceptibility.

Against this hypothesis: ANA negative (though 30-40% of SS cases are ANA-negative), no severe dry mouth or difficulty swallowing dry foods, no documented parotid swelling, and minimal overt sicca symptoms overall.

Key confirmatory test: Anti-SSA/SSB antibodies (positive in 60-70% of primary SS) and Schirmer test/ salivary flow rate to document objective glandular dysfunction.

🧬 GENETIC BASIS

HLA-DQA1 — rs2187668 • Heterozygous • Risk Factor

The patient carries a heterozygous variant in HLA-DQA1, an MHC Class II molecule that presents glandular self-antigens to CD4+ T cells. This variant is associated with Sjogren's syndrome and directs autoimmune attack against salivary and lacrimal glands.

Present in ~12% of European population; ~5-6% of carriers with SSA+ status develop Sjogren's.[1]

STAT4 — rs7574865 • Homozygous • Risk Factor

Homozygous variant in STAT4, which enhances IL-12 signaling → Th1 differentiation → interferon-γ overproduction. The resulting chronic IFN-γ elevation explains systemic symptoms—fatigue, body aches, and brain fog are direct consequences of sustained interferon signaling.

Present in ~22% of European population; ~1-2% of carriers develop Sjogren's.[2],[3]

References: [1] Miceli-Richard C et al. Arthritis Rheum 2007;56:3989-94 • [2] Lessard CJ et al. Nat Genet 2013;45:1284-92 • [3] Khatri B et al. Nat Commun 2022;13:3601 • [gnomAD] Karczewski KJ et al. Nature 2020;581:434-443

Diagnosis 2: Ankylosing Spondylitis [more info]

ANKYLOSING SPONDYLITIS PATHOPHYSIOLOGY

Ankylosing Spondylitis (AS) is a chronic inflammatory arthritis primarily affecting the axial skeleton, characterized by sacroiliitis and progressive spinal fusion. Extra-articular manifestations include anterior uveitis (25-40% of patients), fatigue, and systemic inflammation. The IL-23/IL-17 pathway plays a central role in pathogenesis, with HLA-B27 being the strongest genetic risk factor (present in 90-95% of cases).

In this patient, AS could explain the episodic eye redness (2-3x/year, possible anterior uveitis), body aches, and chronic fatigue. The normal ESR/CRP does not exclude AS, as 40% of patients have normal inflammatory markers.

Against this hypothesis: Patient is HLA-B27 negative (present in 90% of AS patients, making this diagnosis significantly less likely), pain is diffuse rather than axial-predominant with no documented inflammatory back pain pattern (morning stiffness >30 minutes improving with activity), and female sex (AS 2-3x more common in males). The absence of HLA-B27 combined with atypical pain distribution makes AS a lower probability diagnosis.

Key confirmatory test: MRI sacroiliac joints with STIR sequence to detect active inflammation or bone marrow edema. Given HLA-B27 negativity and atypical presentation, a negative MRI would essentially rule out AS.

🧬 GENETIC BASIS

HLA-B27 — NEGATIVE ✓ rs4349859

The patient is **NEGATIVE** for HLA-B27, the strongest genetic risk factor for AS (present in 90-95% of cases). This significantly reduces the probability of AS.

Present in ~8% of European population; ~5-6% of HLA-B27+ individuals develop AS.[1],[2]

IL23R rs11209032 • Heterozygous • Risk Factor

A variant in IL23R is present, which is associated with spondyloarthritis independent of HLA-B27. This enhances IL-23 signaling → Th17 differentiation → IL-17 overproduction, potentially explaining entheseal inflammation (body aches) and anterior uveitis (episodic eye redness). However, without HLA-B27, this variant alone has limited penetrance.

Present in ~40% of European population; OR 1.2 for AS; <1% of carriers develop spondyloarthritis.[3],[4]

References: [1] Evans DM et al. Nat Genet 2011;43:761-7 • [2] Cortes A et al. Nat Genet 2013;45:730-8 • [3] Roberts AR et al. Ann Rheum Dis 2016;75:2166-72 • [4] gnomAD, Karczewski KJ et al. Nature 2020;581:434-443

CONFIRMATORY TESTS

Recommended testing to confirm or refute the differential diagnoses

Diagnosis 1: Sjogren's Syndrome

Anti-SSA (Ro) Antibodies

Purpose: Most important serological marker (60-70% sensitivity). Positive alone = 3 of 4 points needed.

SSA+	Add one functional test to confirm diagnosis.
SSA−	Does NOT exclude SS (30-40% seronegative). Proceed to lip biopsy.

Labial Salivary Gland Biopsy

Purpose: Gold standard for SS, especially seronegative. Focal lymphocytic sialadenitis with focus score ≥1.

Score ≥1	Combined with any functional test abnormality confirms SS even if seronegative.
Score <1	Does not support SS. Consider alternatives or monitor for early/subclinical disease.

Schirmer Test / Salivary Flow Rate

Purpose: Objective glandular function. Schirmer ≤5mm/5min or salivary flow <0.1mL/min. Supportive tests.

Abnormal	Combined with SSA+ or positive biopsy confirms diagnosis.
Normal	Does not exclude SS. Diagnosis can still be made with SSA+ plus positive biopsy.

Potential actionability: Local and/or systemic immunosuppressants if confirmed.

Diagnosis 2: Ankylosing Spondylitis

MRI Sacroiliac Joints (STIR Sequence)

Purpose: Detects active inflammation (bone marrow edema) before X-ray changes. Gold standard for early AS.

Active sacroiliitis	Confirms axSpA even without HLA-B27. Start continuous NSAIDs; TNF inhibitors if inadequate (60-80% improvement).
Normal	Essentially rules out AS given HLA-B27 negativity. Focus on alternative explanations.

⚠ **Note:** Given HLA-B27 negativity and atypical presentation, AS probability is low. Consider cost-effectiveness before ordering.

Potential actionability: NSAIDs continuous dosing; TNF inhibitors if needed.

APPENDIX

Supplementary information for reference — not required for clinical decision-making

SELECTED GENOMIC VARIANTS SUMMARY

GENE	VARIANT	POSITION (GRCH38)	ZYGOSITY	CLASSIFICATION	CONTEXT	REF
HLA-DQA1	rs2187668	chr6:32638107	Heterozygous	Risk Factor	DD1: Sjogren's	↗
STAT4	rs7574865	chr2:191099907	Homozygous	Risk Factor	DD1: Sjogren's	↗
IL23R	rs11209032	chr1:67259791	Heterozygous	Risk Factor	DD2: Ank. Spond.	↗
HLA-B*27	rs4349859	chr6:31353867	Negative	—	DD2: AS excluded	↗

Coordinates: GRCh38/hg38. ↗ = external database link. **Classification:** Risk factor = increased susceptibility; Negative = variant absent.

ADDITIONAL NOTES

> **Contact lens intolerance:** Stopped wearing contacts in mid-20s due to chronic discomfort and "eyes that always felt tired." Never formally evaluated; switched to glasses.

> **Dental history:** Increased cavity frequency beginning ~2019, concentrated at the gum line. Attributed to stress.

> **Incidental lab:** SPEP (2022) showed total protein at upper limit of normal (8.3 g/dL). Not flagged at the time.

> **Mother's history:** "Always had dry mouth," carried water bottles in her 60s. No formal diagnosis; deceased age 71.

HYPOTHESES RULED OUT

Condition	Why Ruled Out
Rheumatoid Arthritis	Negative RF, Anti-CCP (Aug 2020), no joint swelling or erosions documented.
Systemic Lupus	Negative ANA (Aug 2020); lacks malar rash, photosensitivity, serositis.
Hypothyroidism	Normal TSH/Free T4 (March 2019); fatigue pattern not consistent.
Vitamin D Deficiency	Borderline 28 ng/mL (2019), corrected (2021). Fatigue persisted despite correction.
B12 Deficiency	Normal B12 (June 2021); symptoms not explained by deficiency.
Iron Deficiency	Normal ferritin (June 2019); fatigue not due to iron deficiency.
Diabetes Mellitus	Normal fasting glucose (March 2019); thirst not explained by hyperglycemia.
Anemia	Normal CBC (March 2019); fatigue not due to low hemoglobin.
Sleep Apnea	Sleep study without significant apnea (October 2021).
Structural Spine Disease	Normal lumbar spine X-ray (Jan 2022); no degenerative changes.

CARDIAC POLYGENIC RISK SCORES

Polygenic risk scores aggregate common genetic variants to estimate disease susceptibility, expressed as population percentiles.

Condition	PRS Percentile	Risk Category	Interpretation
Coronary Artery Disease	62nd percentile	Average	Genetic risk within typical population range
Atrial Fibrillation	71st percentile	Slightly Elevated	Modestly increased genetic predisposition
Heart Failure	45th percentile	Average	Genetic risk within typical population range
Dilated Cardiomyopathy	58th percentile	Average	Genetic risk within typical population range

Risk categories: <20th = Low | 20th-80th = Average | 80th-95th = Elevated | >95th = High. PRS calculated using validated GWAS data.

ACMG SECONDARY FINDINGS (SF V3.2)

No reportable ACMG secondary findings identified.
The American College of Medical Genetics and Genomics (ACMG) recommends reporting pathogenic and likely pathogenic variants in 81 genes associated with highly penetrant conditions where early intervention may prevent or reduce morbidity/mortality.

Category	Genes Screened	Findings
Hereditary Cancer Syndromes	APC, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, TP53, and others (25 genes)	No pathogenic variants
Cardiovascular Conditions	MYBPC3, MYH7, KCNQ1, KCNH2, SCN5A, LDLR, and others (32 genes)	No pathogenic variants
Metabolic Conditions	GAA, GLA, OTC, and others (10 genes)	No pathogenic variants
Other Actionable Conditions	RYR1, CACNA1S, MUTYH, and others (14 genes)	No pathogenic variants

ACMG SF v3.2 (2023) includes 81 genes. Full gene list available upon request.

PHARMACOGENOMICS

Pharmacogenomic analysis identifies genetic variants that may affect drug metabolism, efficacy, or adverse reaction risk. Results generated using PharmCAT v3.0.1 with CPIC guidelines.

Drug Metabolism Enzymes

Gene	Genotype	Phenotype	Affected Medications
CYP2C19	*38/*38	Normal Metabolizer	Clopidogrel, PPIs, SSRIs, voriconazole
CYP2C9	*1/*1	Normal Metabolizer	Warfarin, NSAIDs, phenytoin
CYP3A4	*1/*1	Normal Metabolizer	Quetiapine, many others
SLC01B1	*1/*1	Normal Function	Statins (simvastatin, atorvastatin)

Interpretation Note: All tested pharmacogenes show normal function/metabolism phenotypes. Standard drug dosing is expected to be appropriate for this individual.

Analysis performed using PharmCAT v3.0.1. Recommendations based on CPIC guidelines.

Important Notice: This report is intended for use by qualified healthcare professionals and should be interpreted in conjunction with clinical findings, family history, and other diagnostic information. Genetic findings require clinical correlation and may warrant additional confirmatory testing. This analysis is not a substitute for professional medical advice, diagnosis, or treatment.