Integrated Stack Optimization Report

Genotype- and Lab-Anchored Evaluation of Every Current Medication and Supplement

63-year-old male · May 2026

Sources: Twenty-one personal genetic reports from 60× whole-genome sequencing (GRCh38, April–May 2026); three Labcorp blood draws (June 25, 2025 baseline; January 7, 2026 main panel; January 21, 2026 recheck of low values); current medication and supplement list (May 2026). Evidence drawn from peer-reviewed literature, with meta-analyses and large RCTs preferred over mechanistic and animal data.

Purpose: For every item in the current stack, assess which genotyped pathways it acts on, whether form and dose are appropriate for this genotype, whether labs support continued use, and the net priority tier. Then identify uncovered needs, list common alternatives that would be genetically suboptimal, and suggest a focused monitoring panel. Goal: maximize healthspan, longevity and performance.

Scoring framework: Each compound is rated Tier 1 (Essential, genotype-locked + lab-confirmed) through Tier 5 (Discontinue or Replace). Tier reflects three multiplicative dimensions: effect size in the target pathway, evidence strength (meta-analysis or RCT > Mendelian randomization > observational > mechanistic), and genotype-specific benefit multiplier. Lab trends across the three timepoints upgrade or downgrade the rating.

Important: *This document is a synthesis of published literature applied to specific WGS results and recent labs. It is intended to support discussion with the treating physician, not as medical advice. All changes to prescription medications must be reviewed clinically. Recommendations are framed as discussion points, not directives.*

Tier Legend

Tier	Meaning
Tier 1 — Essential	Genotype-locked, lab-confirmed working, irreplaceable. Disease-modifying or longevity-decisive. Stop only with strong reason.
Tier 2 — High Value	Strong genotype-specific rationale, good evidence, no better alternative. Continue.
Tier 3 — Reasonable	Mechanistically aligned, modest effect or weaker evidence. Continue but reassess if cost/burden becomes meaningful.
Tier 4 — Marginal	Weak genetic rationale, neutral lab effect, or redundant with another item. Reasonable to drop.
Tier 5 — Reconsider	Genetically misaligned, contraindicated by genotype, or carries a risk that outweighs benefit. Discuss discontinuation or replacement.

Executive Summary

The current regimen is exceptionally well-aligned with this genetic profile. Across 21 genetic reports the dominant themes are: (1) **very-high CAD risk** from homozygous PCSK9 gain-of-function plus 9p21 double heterozygous plus MYLIP/IDOL homozygous; (2) **beta-cell secretion deficit** (CDKAL1 hom + INS rs689 hom + IFIH1 hom + KCNJ11/ABCC8 hom) on a paradoxically insulin-sensitive background (IRS1 protective hom); (3) a **keystone NRF2 / glutathione bottleneck** confirmed across at least six reports (NFE2L2 rs6721961 hom + CTH hom + GLO1 hom + AKR1B1 hom + GSTP1 hom + NQO1 het); (4) **distributed methylation pressure** (TCN2 hom B12-transport + MTHFR het + SHMT1 hom + MTHFD1 het); (5) **elevated IGF-1 production tendency** partially counter-balanced by one copy of the FOXO3 longevity haplotype; (6) homozygous PTPN22 R620W autoimmunity risk (mitigated by absent HLA counterweights); (7) **NO-signaling convergence** (GUCY1A3 + NOS3 + PDE5A + SPR); and (8) homozygous EIF2AK3 PERK-B haplotype (ER stress sensitivity, novel from May 2026 proteostasis report).

Most of the regimen is doing exactly what the cumulative genetic profile predicts it should. **The lab data confirm efficacy:** LDL-C 48, ApoB 50, TG 59, HDL-C 69, Lp(a) 13 nmol/L, hs-CRP 0.60, GlycA 280, fasting insulin 2.7, HOMA-IR ~0.6, fructosamine 239, IGF-1 88 (15–20th percentile for age, dropped from 108 over 6 months on rapamycin), 25(OH)D 84.6, magnesium RBC 6.4 (mid-range), and homocysteine 12.2 (above optimal <10 and trending up — the one persistent open issue).

Headline conclusions:

- Eleven items qualify as **Tier 1 (Essential)**: Repatha, pitavastatin, ezetimibe, tirzepatide, empagliflozin, imeglimin, rapamycin, telmisartan, tadalafil, vitamin D3, and TMG. Each is mechanistically validated against a homozygous-risk variant or a multi-report convergent vulnerability, and each has lab confirmation of efficacy.
- Five items are clearly underdosed for the genotype: NACET (rate-limiting for the four-report glutathione bottleneck), DHA (Boston Heart panel borderline low at 84.3 µg/mL despite substantial omega-3 stack — the ALA-from-flaxseed approach is not converting), riboflavin (cofactor for thermolabile MTHFR), methylcobalamin (TCN2 hom predicts impaired active-B12 delivery — homocysteine 12.2 confirms), and arguably DHEA in the rapamycin context.
- Three items deserve specific reconsideration: nattokinase (additive bleeding risk with aspirin, weak evidence base, no inherited thrombophilia to justify); flaxseed oil 1 g (negligible ALA→DHA conversion in adult men); and high-dose evening melatonin 5 mg (multiple cross-report flags suggest 1–3 mg).
- Three high-priority additions are missing or under-addressed: high-DHA algal oil 500 mg+, riboflavin 25–50 mg (R5P preferred), and a second NRF2 lever beyond the existing Avmacol — pyridoxamine or benfotiamine for the glycation arm. Vitamin K2 (MK-7) is also under-covered relative to the bone/skeletal genetic findings.
- The single highest-leverage individual change remains: confirm Momentous Multi B12 form (must be methylcobalamin or hydroxocobalamin, not cyanocobalamin) and add standalone methylcobalamin 1000–2000 µg/day if needed. Combined with riboflavin 25–50 mg, this addresses the only persistently abnormal lab marker (homocysteine 11.5 → 12.2) on the only genotyped pathway not yet fully neutralized.
- A few "longevity-popular" alternatives would be **genetically suboptimal** for this profile and should be specifically avoided: metformin (depletes B12 and would compound

TCN2 hom), folic acid in place of methylfolate, cyanocobalamin in place of methylcobalamin, NMN/NR alone without addressing NRF2, simvastatin or atorvastatin (CYP3A pathway already saturated by rapamycin co-handling), high-dose niacin (no rationale here), and raw/standalone berberine (OCT1 het + CYP3A interaction concerns).

Lab Trajectory — What the Three Timepoints Tell Us

Three Labcorp draws (June 25, 2025 baseline; January 7, 2026 main panel; January 21, 2026 recheck) provide the trend signal that converts each genotype-driven hypothesis into a confirm/reject test. Italicized comments below each value are the interpretation against the genetic profile.

Cardiovascular & lipids — clearly working

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
LDL-C (mg/dL)	47	48	—	Stable at <55 ESC/EAS very-high-risk target despite homozygous PCSK9 GOF + MYLIP hom + 9p21 dual het. Repatha will likely push to 20s.
ApoB (mg/dL)	50	—	—	Below 80 (very-high risk target). The right number on PCSK9 inhibitor therapy.
HDL-C	56	69	—	Up. Consistent with CETP hom-protective signature.
Triglycerides	57	59	—	11q23/APOA5 cluster reinterpreted as protective; lab consistent.
Lp(a) nmol/L	—	13	—	Confirms LPA tag SNPs absent. One-time test; no further monitoring needed.
hs-CRP (mg/L)	0.29	0.60	—	Both low. Up trend worth watching but well below 1.0 average-risk threshold.
GlycA (µmol/L)	241	280	—	Up but well below 400 high-risk threshold (Otvos 2015).

Genetic profile predicts elevated CV risk; the lipid lowering stack is working at the genetically-justified target. Repatha switch is the single most aligned change because it directly neutralizes the specific protein the homozygous PCSK9 GOF variant makes overactive (Cohen 2006 NEJM; Sabatine 2017 NEJM FOURIER).

Metabolic — beta-cell deficit successfully buffered

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
Glucose, fasting	99	90	—	Improved. Below pre-diabetes cutoff.
HbA1c (%)	5.8 H	5.9 H	—	Stuck just above 5.7 pre-diabetes line. Genotype loads CDKAL1 hom + INS hom + IFIH1 hom secretory-

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
				deficit pattern; rapamycin is the residual headwind.
Fasting insulin (µIU/mL)	5.8	2.7	—	Very low — IRS1 C/C protective amplifying tirzepatide/empagliflozin effect. HOMA-IR ~0.6.
Fructosamine (µmol/L)	—	—	239	Lower-middle of healthy range. Supports the "A1c glycation gap" hypothesis: actual glucose exposure is lower than HbA1c suggests, consistent with FN3K hom-favorable.
IGF-1 (ng/mL)	115	88	—	Down 23% in 6 months on rapamycin (target homozygous IGF1 production variants). Now ~15–20th percentile for age 62. Target effect achieved.
Uric acid	—	2.9 L	—	Low — empagliflozin uricosuric effect + XDH hom. Favorable for the cardio-renal axis.

A 23% IGF-1 reduction over 6 months is unambiguous evidence that pulsed rapamycin is working as designed against the elevated set-point. HbA1c drift to 5.9% is the expected mTORC2 spillover predicted by TBC1D4 + PCK1 + SLC2A4 + AKT2 het variants — mechanistically expected, not a contraindication. The very low fasting insulin confirms IRS1 protective is doing its job.

Methylation — the one persistent open issue

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
Homocysteine (µmol/L)	11.5	12.2	—	Above optimal <10 and rising. Consistent with TCN2 hom impairing active-B12 delivery.
Vitamin B12 (pg/mL)	—	1127	—	Total B12 high-normal — but functional fraction may be lower than total suggests because of TCN2 hom. Holotranscobalamin is the test that resolves this.
Methylmalonic acid	—	116 (0–378)	—	Normal — argues against severe intracellular B12 deficit at this point. Consistent with the B12 issue being on the methylcobalamin/transport side rather than adenosylcobalamin.
Folate, RBC	—	1081 (>498)	—	High. Quatrefolic 5-MTHF in Momentous Multi is reaching the target tissue. Folate side of the pathway is well-covered.
Folate serum	—	14.0	—	Normal. Confirms above.
B2 whole blood (FAD)	—	206 (137–370)	—	Mid-range, not optimal. R5P 25–50 mg supplementation has a clear place for the thermolabile MTHFR C677T heterozygous (McNulty 2006 Circulation).

The methylation arm is the one place where labs do not yet fully match the regimen. Folate is excellent (Quatrefolic 5-MTHF is the right form), but the rising homocysteine plus mid-range B2 plus high-but-undifferentiated total B12 plus homozygous TCN2 plus heterozygous MTHFR all converge on the same fix: confirm Momentous Multi B12 is methylcobalamin (not cyano), add standalone methylcobalamin 1000–2000 µg/day if needed, and add riboflavin 25–50 mg/day. Order holotranscobalamin to test the prediction directly.

Fatty acid balance — DHA gap, the actionable miss

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Reference
EPA (µg/mL)	—	57.6	—	Optimal at >50. Carlson EPA + krill + Momentous Omega-3 working as expected.
DHA (µg/mL)	—	84.3 L	—	Below optimal >100. The single most actionable miss. Adding DHA-specific algal oil resolves this without adding more EPA.
ALA (µg/mL)	—	<7.8 L	—	Below detection. Confirms negligible ALA→EPA→DHA conversion in adult men (Burdge 2005). Flaxseed oil 1 g is not contributing.
Omega-3 Index (%)	—	5.45	—	Optimal. Driven primarily by EPA, not DHA.
AA/EPA ratio	—	4.95	—	Optimal. Anti-inflammatory posture confirmed.
Saturated FA Index	—	30.6 H	—	Borderline high. Diet-modifiable, not a supplement issue.

DHA is borderline low despite a substantial EPA-heavy omega-3 stack. The Dementia, BBB, PD, and ADHD reports all independently flag DHA. Adding 500 mg+ DHA algal oil and reallocating the 1 g flaxseed oil slot resolves this within 2–3 months.

Hormonal — Jan 21 recheck confirms transient low

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
Total T (ng/dL)	446.5	521.4	636.5	Up. Mid-normal range. Reassuring.
Free T (pg/mL)	9.0	6.8	11.3	Recovered to mid-range. The Jan 7 low value was transient — not a trend. Dutasteride-induced shunting (DHT down → T+E2 up) is visible.
Estradiol (pg/mL)	29.2	23 (LCMS)	29.5	Mid-normal. Aromatase functional.
DHEA-S (µg/dL)	—	71	—	Age-appropriate mid-range, on 25 mg DHEA supplementation.
LH / FSH (mIU/mL)	—	—	3.0 / 3.3	Normal. HPG axis intact. No primary hypogonadism signal.
PSA total	0.3 (Nov 24)	0.3	—	On dutasteride apply ×2 correction → effective ~0.6. Well below concern. Free/total 30% favorable.

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
25(OH)D (ng/mL)	103 (May 25)	84.6	—	Down but still high — slightly above 80 ng/mL upper-target band. Bone report flags this; consider down-titrating to 50–60.

Jan 21 recheck answered the question: low Jan 7 free T was transient fluctuation, not a trend. HPG axis is intact. No need to add testosterone or change dutasteride. The 25(OH)D drop from 103 to 84.6 is consistent with seasonal variation; the value is still slightly above the 50–60 ng/mL target the bone-skeletal report recommends given homozygous VDR FokI receptor-saturation.

Other notable values

Marker	Jun 2025	Jan 7 2026	Jan 21 2026	Trend / Interpretation
eGFR (creatinine)	66	67	—	Borderline. Confounded by 5 g creatine — cystatin C eGFR 94 confirms kidney function is fine.
Cystatin C (mg/L)	—	0.86	—	Normal — eGFR 94. Creatinine-based eGFR understates true GFR because creatine supplementation raises serum creatinine 0.1–0.2 mg/dL.
Alkaline phosphatase	30 L	40 L	—	Low across multiple draws (new ref interval is 47–123). Bone-specific ALP or P1NP would clarify whether this reflects low bone turnover (rapamycin/statin) or warrants ALPL screening for adult-onset hypophosphatasia (bone report flag — required before any future bisphosphonate).
Magnesium RBC	5.7	6.4	—	Mid-range. Adequate.
Ferritin / TSAT	77 / 29%	80 / 32%	—	Mid-range. Endurance/Strength reports flag the TMPRSS6 V/V hom hepcidin set-point — current values OK but worth maintaining ≥75 ng/mL given BTBD9 het RLS susceptibility (Sleep report).
Reticulocyte	—	—	1.4%	Low end of normal. Worth watching given TMPRSS6 hom + IL6 high-producer.
Zinc / Copper RBC	—	—	1213 / 0.55	Both lower-normal. Adequate but watch copper if zinc dose increases.
CoQ10 (µg/mL)	1.81	3.29 H	—	Above reference. Current 100 mg ubiquinol EOD is producing therapeutic levels. No need to increase.
TSH / Free T4	2.2 / 1.47	1.98 / 1.50	—	Normal and stable. Does not yet rule out PTPN22-driven autoimmune thyroid risk — anti-TPO/anti-TG should be ordered as baseline.

Three open monitoring questions surface from the lab review: (1) confirm whether the persistent low ALP reflects benign low bone turnover or warrants ALPL coding-region screening; (2) order anti-TPO and anti-thyroglobulin to baseline against the PTPN22 hom autoimmune risk; (3) order holotranscobalamin to confirm the TCN2-driven active-B12 transport deficit hypothesis.

Per-Item Evaluation: Prescription Medications

Items grouped by therapeutic class and ordered roughly by tier within each section. Each item carries the score, the mechanism-genotype-lab logic, and an italicized verdict paragraph.

Lipid lowering and cardiovascular

Evolocumab (Repatha) — 140 mg SC every 2 weeks

TIER 1	Essential — the single most genetically aligned drug in the regimen

Mechanism / pathway	PCSK9 monoclonal antibody. Binds circulating PCSK9, prevents PCSK9-mediated LDLR degradation at the hepatocyte surface, drives LDL-C and ApoB down profoundly without requiring upstream HMG-CoA reductase inhibition.
Genotype-specific rationale	Homozygous PCSK9 Glu670Gly gain-of-function across the full haplotype (rs505151 + rs562556 + rs662145 all 1/1) — the genetic mirror image of the PCSK9 LoF variants that validated the entire drug class (Cohen 2006 NEJM). Compounded by homozygous MYLIP/IDOL N342S which degrades LDLR intracellularly. 9p21 dual heterozygous adds independent CAD risk. APOE ε3/ε3 (no ε4 amplifier) and LPA tag SNPs absent are favorable counterweights.
Lab alignment	On-treatment LDL-C 48, ApoB 50, both at or below ESC/EAS very-high-risk targets. Repatha is expected to push LDL-C into the 20s. No safety floor for low LDL has been identified in PCSK9 trials.
Dose / form fit	140 mg q2wk is the standard escalation step from monthly. Genetically appropriate.
Pros	Direct neutralization of the genetically overactive protein. Mendelian rationale + RCT outcome data (FOURIER, FOURIER-OLE, GLAGOV plaque regression). LDLR-preservation mechanism is synergistic with NPC1L1 LoF het + ezetimibe. No PGx contraindication.
Cons / cautions	Cost. Injection burden. Long-term safety beyond ~10 years not yet established (though human PCSK9 LoF homozygotes appear healthy lifelong).
Interactions	None clinically significant. Anti-drug antibodies rare and mostly non-neutralizing.

This is the most mechanistically aligned drug in the entire regimen. The patient's genotype carries the gain-of-function version of the very protein evolocumab neutralizes; the trial evidence (FOURIER, Sabatine 2017 NEJM) proves clinical benefit; the lab data confirm it is working. Continue indefinitely.

Pitavastatin — 4 mg evening

TIER 1	Essential — favorable PGx profile, baseline LDLR upregulation

Mechanism / pathway	HMG-CoA reductase inhibitor. Upregulates hepatic LDL receptor density independent of PCSK9. Glucuronidated rather than CYP-metabolized — minimal CYP3A or CYP2C9 involvement.
Genotype-specific rationale	SLCO1B1*5 absent + SLCO1B1*1B het (mildly favorable) + ABCG2 Q141K absent + LILRB5 clean = below-population myopathy risk. No HMGCR statin-response variants. CYP2C9*2 het has minimal effect on pitavastatin (UGT-cleared). UGT2B7*2 hom modestly affects pitavastatin glucuronidation but is not dose-limiting.
Lab alignment	LDL-C 48 / ApoB 50 on combination therapy confirms statin contribution. CK should be checked if any myalgia.
Dose / form fit	4 mg is the maximum dose. No genotype-driven need for dose reduction. Pitavastatin

	specifically chosen over rosuvastatin or atorvastatin is favorable: pitavastatin has minimal CYP3A interaction (rosuvastatin OATP1B1, atorvastatin CYP3A) and minimal new-onset diabetes signal in trials.
Pros	Statin-class mortality and CV event evidence (>30 RCTs). Synergy with ezetimibe and Repatha. Modest off-target pleiotropic effects (endothelial NO, plaque stabilization). Low myopathy risk for this genotype.
Cons / cautions	Class effect: small new-onset diabetes signal — relevant given CDKAL1 hom + INS hom + IFIH1 hom secretory deficit. Mitigated by the multi-agent metabolic regimen; do not stop the statin to address HbA1c.
Interactions	No CYP3A interaction with rapamycin (favorable for this regimen). No fibrate currently. Aspirin co-administration is fine. CoQ10 supplementation already in place addresses any mevalonate-pathway concerns.

Pitavastatin is the right statin for this PGx profile and works synergistically with the LDLR-preservation mechanism of ezetimibe and Repatha. The choice of pitavastatin specifically (rather than rosuvastatin or simvastatin) avoids the CYP3A pathway already burdened by rapamycin handling.

Ezetimibe — 10 mg morning

TIER 1	Essential — genotype validates indefinite use

Mechanism / pathway	NPC1L1 inhibitor at the enterocyte brush border. Reduces dietary and biliary cholesterol absorption ~50%. Synergistic with statin; additive with PCSK9 inhibitor.
Genotype-specific rationale	NPC1L1 rs41279633 (p.R406X) heterozygous — a rare LoF variant (~0.15% European frequency) that is genetically equivalent to a "lifetime ezetimibe carrier." Combined with dual ABCG8 het (mild enterocyte cholesterol absorption increase), ezetimibe is mechanistically synergistic with the natural genotype. MYLIP/IDOL hom further reinforces LDLR-preservation strategy over synthesis blockade.
Lab alignment	LDL-C 48 / ApoB 50 — drug working. IMPROVE-IT (Cannon 2015 NEJM) confirmed CV event reduction on top of statin.
Dose / form fit	10 mg is the only available adult dose. Form correct.
Pros	Mendelian validation — NPC1L1 LoF carriers have lifelong lower CHD risk. Mechanistically additive to PCSK9i and statin. Clean side-effect profile.
Cons / cautions	Modest LDL reduction in monotherapy; value is in combination.
Interactions	Minimal. UGT clearance — UGT2B7*2 hom has trivial effect.

The NPC1L1 LoF heterozygous finding makes this drug uniquely well-aligned for this patient — the body is already partly running the drug's mechanism. Indefinite use is genetically justified.

Aspirin — 81 mg evening

TIER 2	High value — primary CV prophylaxis + cancer chemoprevention + lipoxin pathway

Mechanism / pathway	Irreversible COX-1 acetylation in platelets, blocking thromboxane A2 generation. Aspirin-triggered 15-epi-lipoxin A4 production via acetylated COX-2 in vascular endothelium and leukocytes — pro-resolving mediator independent of ALOX15.
Genotype-	9p21 dual het + PCSK9 hom GOF justify atherothrombosis prophylaxis. ALOX15 hom risk +

specific rationale	TGFB1 hom downstream-resolution shifts: aspirin's lipoxin-triggering pathway specifically bypasses ALOX15 (Inflammation report). Cancer Predisposition: homozygous 8q24 + 11q23 polygenic CRC signal + GSTP1 hom + NAT2 slow — aspirin chemoprevention evidence (Rothwell Lancet 2010, Cuzick Ann Oncol 2015) is particularly relevant.
Lab alignment	No bleeding markers triggered (Hgb stable 13.6–14.3, platelets 189–211). hs-CRP 0.60 — chronic inflammation low.
Dose / form fit	81 mg is the standard low-dose CV prophylaxis dose. Cardiovascular benefit at this dose is robust; bleeding risk is meaningfully lower than 325 mg.
Pros	Strongest single cancer-preventive intervention in the regimen (CRC risk reduction 20–40% with sustained use). Aligned with ALOX15 hom inflammation-resolution finding via aspirin-triggered lipoxin pathway. Atherothrombosis prophylaxis well-justified by CV genetics.
Cons / cautions	GI bleeding risk additive with nattokinase. Note: PEAR1 het is a weak modifier with mixed evidence — no dose change needed. No inherited thrombophilia (Factor V Leiden, Prothrombin G20210A both absent), so the role is prophylaxis not compensation.
Interactions	Bleeding risk: notable additivity with nattokinase 12000 FU (see nattokinase entry — separate concern). Mild interaction with empagliflozin (volume status); not clinically meaningful at 81 mg.

Aspirin earns high value status from three independent rationales: CV prophylaxis given the genetic CAD risk, cancer chemoprevention given the polygenic CRC signal, and the aspirin-triggered lipoxin pathway that bypasses the ALOX15 hom resolution-axis bottleneck. Continue, but reassess additive bleeding risk with nattokinase.

Telmisartan — 80 mg evening

TIER 1	Essential — unique ARB with PPAR-γ partial agonism, multiple convergent benefits

Mechanism / pathway	Angiotensin II receptor blocker. Unique among ARBs for partial PPAR-γ agonism (Benson 2004 Hypertension) — improves insulin sensitivity, reduces RAGE expression, modest BMD signal. Long half-life (~24 h) provides stable BP coverage.
Genotype-specific rationale	Aligns with multiple findings. Endothelial: GUCY1A3 dual hit + NOS3 het + SPR hom (BP control supports residual NO signaling). Glycation: RAGE expression reduction is favorable given AKR1B1 hom + GLO1 hom. Glucose: PPAR-γ partial agonism modestly improves insulin sensitivity (favorable for beta-cell deficit). Bone: PPAR-γ partial agonism has modest favorable BMD effect (vs. negative effect of full PPAR-γ agonists). Sleep: ADRB1 Gly/Gly hom predicts blunted β-blocker response — telmisartan is the right antihypertensive class for this genotype.
Lab alignment	BP not in lab data but clinical suppression presumably good. eGFR stable 66–67 (cystatin C eGFR 94 confirms true kidney function preserved).
Dose / form fit	80 mg is the maximum approved dose. Evening dosing is supported by chronotherapy data for non-dipping or borderline-dipping nocturnal BP. Sleep report's favorable autonomic profile (GNG11 + RGS6 hom higher-HRV alleles) suggests dipping is preserved — 24-h ABPM would confirm.
Pros	Multi-convergence: BP, insulin sensitivity, RAGE, bone, autonomic. ADRB1 PGx makes it preferable to β-blocker. Non-renin-axis (no compensatory RAAS activation problem).
Cons / cautions	Hyperkalemia risk in CKD context (eGFR borderline). Modest creatinine bump expected. Cough rare with ARBs (vs. ACEI).
Interactions	Aliskiren contraindication (not used). NSAIDs reduce effect (avoid chronic; aspirin 81 mg fine). Lithium levels can rise (lithium orotate 5 mg microdose — clinically negligible but worth flagging).

Telmisartan was an excellent class choice for this genotype — its unique PPAR-γ partial agonism delivers benefits beyond BP that align with at least four genetic vulnerabilities. The ADRB1 Gly/Gly hom

(Sleep/PGx) explicitly supports preferring an ARB over a β-blocker. Continue at 80 mg evening; verify dipping with 24-h ABPM.

Tadalafil — 10 mg evening (daily)

TIER 1	Essential — most genetically aligned single drug for the NO-signaling convergence

Mechanism / pathway	PDE5 inhibitor. Prevents cGMP breakdown downstream of soluble guanylate cyclase. Long half-life (~17.5 h) enables daily dosing for endothelial / cavernous tissue support.
Genotype-specific rationale	The endothelial NO-signaling convergence is one of the strongest single-pathway signals in the entire genetic profile: GUCY1A3 dual hit (impaired sGC) + PDE5A hom (variant in the very enzyme tadalafil targets) + NOS3 het (reduced NO substrate generation) + SPR hom (BH4 cofactor recycling). Tadalafil rescues cGMP despite the impaired upstream guanylate cyclase coupling.
Lab alignment	No direct biomarker; functional readout is endothelial flow-mediated dilation (not measured). hs-CRP 0.60 and clean ADMA panel suggest endothelial dysfunction not advanced.
Dose / form fit	10 mg daily is between the 5 mg ED dose and 20 mg PRN. Provides continuous PDE5 suppression appropriate for the genetic finding. Form correct.
Pros	Direct mechanistic match to the homozygous PDE5A variant. Synergistic with l-citrulline 9–13 g/day (NO substrate amplification). Cardiovascular safety in long-term PDE5 inhibitor data. Possible favorable signal for cognitive / dementia risk (PDE5 inhibition + cerebral blood flow; emerging data, Fang Nat Aging 2021).
Cons / cautions	Mild headache, myalgia, dyspepsia possible. Nitrate contraindication (none in regimen).
Interactions	CYP3A4 substrate. Rapamycin co-handling is mostly via CYP3A5 (which is non-expresser here) — minor concern. Avoid ketoconazole / clarithromycin / large-volume grapefruit juice on rapamycin dose days for AUC reasons (Rapamycin report). α-blockers — none in regimen.

The PDE5A homozygous + GUCY1A3 dual-hit finding makes tadalafil one of the most genetically aligned drugs in the entire stack. Combined with l-citrulline 9–13 g, this pairing is the most complete pharmacological match to a four-gene convergence anywhere in the regimen. Continue.

Metabolic

Tirzepatide — 2.6 mg SC twice weekly

TIER 1	Essential — dual GIP/GLP-1 agonism bypasses TCF7L2 deficit, supports APOC3 IRE

Mechanism / pathway	Dual GLP-1 + GIP receptor agonist. Restores incretin-mediated glucose-dependent insulin secretion. Direct caloric restriction effect. Anti-inflammatory. Reduces hepatic lipogenesis.
Genotype-specific rationale	TCF7L2 het impairs endogenous incretin response; tirzepatide bypasses this directly. GIPR genetically intact (no variants found) so both receptor arms engage. CDKAL1 hom + INS hom: reduces secretory demand on the impaired beta-cell. APOC3 promoter IRE het (Apolipoprotein addendum): augmented insulin signaling supports normal APOC3 suppression — a newly recognized rationale to continue tirzepatide even after weight goals are met. Inflammasome het cluster (IL18 hom + NLRP3 het + IL1B het + AIM2 het): GLP-1 anti-inflammatory effect is well-aligned.
Lab alignment	HOMA-IR ~0.6 (very low fasting insulin 2.7) confirms the drug is doing exactly what it should. HbA1c 5.9 stable around the prediabetes border — driven primarily by rapamycin spillover, not tirzepatide failure. ApoB 50 supported partly by tirzepatide-mediated VLDL reduction.

Dose / form fit	The 2.6 mg twice-weekly dose is unusual (label is once-weekly 2.5/5/7.5/10/12.5/15 mg). Total weekly dose 5.2 mg ≈ standard 5 mg/week. Genetic profile (Glucose report) flags titration room: TCF7L2 het + intact GIPR + CDKAL1 hom support stepping up if HbA1c targets not met.
Pros	SURPASS / SURMOUNT trial benefits: HbA1c reduction, weight loss, ApoB / TG reduction, anti-inflammatory. Two independent receptor arms hedge against TCF7L2 het. Anti-inflammatory via GLP-1 axis. APOC3 IRE rationale to continue beyond glycemic / weight goals.
Cons / cautions	GI side effects (titration-mitigated). Cost. Pancreatitis risk (rare, monitor). Modest gallstone risk (no current cholelithiasis history flagged).
Interactions	GI motility slowing — minor effect on oral drug absorption; not clinically meaningful for this regimen. Combined with empagliflozin and imeglimin: synergy without dangerous hypoglycemia (none of the three are insulinogenic / sulfonylurea-like).

Tirzepatide is doing precisely what it should for this genotype — covering for the TCF7L2-impaired native incretin pathway via the alternate receptor route, reducing secretory demand on the genetically impaired beta-cell, and now (per the apolipoprotein addendum) explicitly supporting the heterozygous APOC3 promoter IRE. Room to titrate exists if HbA1c targets become more aggressive.

Empagliflozin — 25 mg morning

TIER 1	Essential — insulin-independent glucose lowering + multi-pathway alignment

Mechanism / pathway	SGLT2 inhibitor. Renal glucosuria (~50–80 g glucose/day) lowers serum glucose without insulin. Cardiovascular and renal protection independent of glucose control (EMPA-REG OUTCOME, EMPEROR series). NLRP3 inflammasome inhibition documented across multiple 2020–2024 studies.
Genotype-specific rationale	Glucose: insulin-independent mechanism complements the beta-cell secretion deficit (CDKAL1 hom + INS hom + IFIH1 hom). Inflammation: NLRP3 inflammasome inhibition is direct match for the inflammasome het cluster (NLRP3 het + IL1B het + IL18 hom). Endothelial: XDH hom — empagliflozin's uricosuric effect explains the low uric acid 2.9 (favorable). Glycation: shifts substrate flux away from polyol/glycation pathway.
Lab alignment	Glucose 90 (improved from 99). Uric acid 2.9 — empagliflozin uricosuric effect visible. Albumin urine <3 (no nephropathy).
Dose / form fit	25 mg is the maximum dose. Form correct.
Pros	Triple-mechanism: glycemia, CV, renal. NLRP3 inhibition (Kim Nat Commun 2020; Byrne Circ Heart Fail 2020). Uricosuric. Modest BP reduction (favorable for CV).
Cons / cautions	Genital fungal infections (rare, manageable). Mild volume contraction. Class fracture signal (canagliflozin) — explicitly NOT extending to empagliflozin in EMPEROR follow-up (Bone report). Euglycemic DKA risk small but real, especially perioperatively (hold pre-surgery).
Interactions	No CYP3A4 — minimal rapamycin interaction. UGT1A9 mediated — UGT1A9 modifier variants absent.

Empagliflozin contributes to four genetically convergent pathways simultaneously (glucose, NLRP3 inflammation, urate, glycation). The CV and renal mortality benefits in trials are large. Continue at 25 mg.

Imeglimin — 1000 mg twice daily

TIER 1	Essential — chosen instead of metformin specifically because of TCN2 hom

Mechanism / pathway	Mitochondrial-acting glucose-lowering drug. Improves mitochondrial bioenergetics, restores beta-cell secretory function, enhances insulin action in liver and muscle (Hallakou-Bozec

	Diabetes Obes Metab 2021). Mechanistically distinct from biguanides (does NOT inhibit Complex I in the same way as metformin).
Genotype-specific rationale	Homocysteine report explicitly flags imeglimin choice as genetically validated vs. metformin: metformin depletes B12 over time, which would compound TCN2 P259R hom transport vulnerability and MTHFR het methylation pressure. Beta-cell function: KCNJ11/ABCC8 hom + CDKAL1 hom + GCK het — imeglimin supports beta-cell mitochondrial function directly. SOD2 het — mitochondrial-targeting mechanism is biologically aligned.
Lab alignment	Glucose 90 + HbA1c 5.9 + insulin 2.7 — the regimen overall is at glycemic target. Imeglimin contribution attributable but not separable.
Dose / form fit	1000 mg BID is the FDA-approved adult dose. No genotype-driven dose change. OCT1 het + MATE1 het + ATM het predict modestly reduced hepatic uptake — already at ceiling dose, so this means glycemic targets if missed should be met by adjusting other agents (tirzepatide titration, etc.) rather than escalating imeglimin.
Pros	Avoids metformin's B12-depleting effect — explicitly genotype-aligned (homocysteine report). Beta-cell-supportive mechanism vs. exhausting it. Cardiovascular signal favorable in TIMES trials (Dubourg Diabetes Care 2021). No nephrotoxicity at recommended dose.
Cons / cautions	Newer drug, less long-term data than metformin. GI side effects similar to metformin but reportedly milder. Lactic acidosis risk likely lower than metformin but not zero.
Interactions	OCT1 substrate (het carrier reduced effect). No CYP3A interaction.

The choice of imeglimin specifically over metformin is a textbook example of genotype-aligned prescribing. Metformin would be genetically suboptimal here (TCN2 hom + MTHFR het + Hcy 12.2 already trending up); imeglimin supports the same metabolic targets without depleting B12. This is one of the most thoughtful drug choices in the regimen.

Rapamycin (sirolimus) — 12 mg every 3 weeks (pulsed)

TIER 1	Essential — directly addresses 4-gene mTOR/IGF axis, lab-confirmed working

Mechanism / pathway	mTORC1 inhibitor (selective vs. mTORC2 with pulsed dosing). Reduces protein synthesis flux, stimulates autophagy, lowers IGF-1 set-point, broadly anti-inflammatory. Pulsed schedule preserves mTORC2 (insulin signaling) better than continuous dosing.
Genotype-specific rationale	Five-gene anabolic loading at the IGF-mTOR axis: AKT1 hom + MTOR rs2295080 hom + MTOR rs1057079 hom + MTOR rs11121704 hom + IGF1 locus 3-SNP hom + JAK2 hom + PAPPA hom. FOXO3 longevity haplotype heterozygous (six SNPs concordant) — its longevity benefit is conditional on low AKT/mTOR tone (Donlon 2018). Rapamycin is the most direct intervention to unmask FOXO3. Proteostasis report: ATG16L1 T300A hom (autophagy elongation impaired) + EIF2AK3 PERK-B hom (ER-stress sensitivity) — rapamycin's autophagy induction is specifically aligned. PGx: CYP3A5*3/*3 + CYP3A4*1B hom predict ~15–30% higher AUC per dose than CYP3A5 expressers.
Lab alignment	IGF-1 dropped 115 → 88 ng/mL over ~6 months — clear evidence of biological effect on the genetically elevated set-point. HbA1c drift 5.8 → 5.9 is mTORC2 spillover (TBC1D4 + PCK1 + SLC2A4 + AKT2 hetero stack, Glucose report) — expected, not a contraindication. Lipid panel preserved (SREBF1 hom risk for rapamycin lipid effect is over-ridden by Repatha + statin + ezetimibe stack).
Dose / form fit	12 mg q3wk pulsed: dose × frequency × CYP3A5 non-expresser status predicts higher AUC than at face value. Trough sirolimus level once would inform whether interval extension to 21 days vs. dose reduction to 8–10 mg makes more sense if mTORC2 spillover becomes a problem.
Pros	Largest single longevity-relevant intervention. Directly addresses the AKT/MTOR/IGF1 5-gene anabolic loading. Unmasks FOXO3 longevity haplotype. Aligns with Cancer Predisposition

	(autophagy / proteostasis), Dementia (autophagy of misfolded proteins), Glycation (autophagy of damaged proteins / mitochondria). Cross-confirmed working by IGF-1 trajectory.
Cons / cautions	mTORC2 spillover at higher trough — manifests as glucose elevation, mild dyslipidemia, occasionally peripheral edema. Requires fasted dosing (food affects AUC). CYP3A inhibitor co-administration (clarithromycin, ketoconazole, large grapefruit) on or near dose days produces larger-than-typical AUC spike given the CYP3A5/CYP3A4 genotype. Acute rapamycin blocks contraction-induced muscle protein synthesis (Drummond 2009 J Physiol) — Strength report recommends timing heavy resistance work for days 7–14 of the cycle.
Interactions	CYP3A4 substrate (CYP3A5*3/*3 non-expresser). Avoid azole antifungals, macrolides except azithromycin, large-volume grapefruit. Sertraline/SSRIs no significant interaction. Tadalafil OK. Hyperglycemia signal additive with statin — covered by tirzepatide/empagliflozin/imeglimin.

Rapamycin is the longevity-decisive drug in this regimen. The genetic profile predicts both why it is needed (homozygous AKT1 + homozygous MTOR + elevated IGF-1 set-point + heterozygous FOXO3 longevity haplotype that requires low mTOR tone to operate) and why it shows the side-effect profile it does (TBC1D4/PCK1/SLC2A4/AKT2 het stack drives mTORC2 spillover toward glucose). The IGF-1 drop from 115 to 88 in 6 months proves the intervention is doing what the genetics predict it should. Continue. Consider a single trough sirolimus level on day 7 of a cycle to inform whether the 12 mg q3wk dose is at the upper edge of the desired AUC band.

Other prescription medications

Dutasteride — 0.5 mg every other day

TIER 2	**High value — perfect 4-SNP SRD5A genotype match + IGF-1 / prostate cancer rationale**

Mechanism / pathway	Dual 5α-reductase type 1 + type 2 inhibitor. Reduces serum DHT >90%. Halves measured PSA — apply ×2 correction.
Genotype-specific rationale	Hair Loss report: SRD5A1 rs39848 hom + SRD5A1 rs248793 hom + SRD5A2 rs523349 hom + SRD5A2 rs632148 hom — quadruple-homozygous SRD5A genotype (textbook PGx alignment). Cancer Predisposition: SRD5A2 V89L L/L hom (mildly protective) plus elevated IGF-1 locus signal (3 SNPs hom) + 8q24 prostate hom — dutasteride directly addresses the AR/DHT axis upstream of these signals. Lab consequence visible: dutasteride-induced shunting (T+E2 up, DHT down).
Lab alignment	PSA 0.3 (×2 = effective 0.6, well below concern). Free PSA 30% favorable (low cancer probability). T total 446 → 521 → 636, free T 9 → 6.8 → 11.3, estradiol 29 → 23 → 29.5 — consistent with dutasteride shunting.
Dose / form fit	0.5 mg EOD (vs. label QD) is a reduced-frequency schedule. Half-life is ~5 weeks, so EOD vs. daily produces near-equivalent DHT suppression at steady state. Hair Loss report recommends checking serum DHT to confirm >90% suppression at this schedule.
Pros	Perfect 4-SNP PGx match. Indirect IGF-1/prostate cancer prevention rationale. Anti-AGA evidence. Aromatization-pathway preservation favorable for bone (Bone report).
Cons / cautions	Sexual side effects (libido, ED) — countered by tadalafil. Possible mood effects (5α-reductase inhibits neurosteroid synthesis) — none reported.
Interactions	CYP3A4 substrate — minor on this regimen. Halves PSA — use ×2 correction.

The 4-SNP SRD5A homozygous genotype makes dutasteride a textbook PGx alignment. Continue. Verify DHT suppression once given the EOD schedule.

Doxycycline (sub-antimicrobial) — 20 mg twice daily

TIER 2	High value — NLRP3 inflammasome modulation + α-synuclein aggregation modifier

Mechanism / pathway	At 40 mg/day total, well below antimicrobial threshold. Modulates NLRP3 inflammasome independent of antibacterial activity (Buccellato 2023 Int J Mol Sci). Inhibits MMP-9. Modifies α-synuclein aggregation kinetics (relevant to PD prevention).
Genotype-specific rationale	Inflammation: inflammasome het cluster (NLRP3 het + IL1B het + IL18 hom + AIM2 het) — direct match. PD: SNCA risk haplotype het (rs356182 + rs356219 + rs2737029) — α-synuclein clearance support is mechanistically aligned, evidence in early-stage trials. Bone: doxycycline-Mg/Ca chelation reduces absorption — current AM dosing should be ≥2 hr before noon Multi (which contains 75 mg Mg + 25 mg Ca per dose).
Lab alignment	hs-CRP 0.60 — consistent with low-grade anti-inflammatory effect.
Dose / form fit	20 mg BID is the periostat sub-antimicrobial dose used in chronic periodontitis. At this dose it should not meaningfully disturb gut flora.
Pros	Multiple mechanistic alignments (NLRP3, MMP, α-syn). Sub-antimicrobial — minimal microbiome impact. Long-term tolerability good.
Cons / cautions	Phototoxicity (rare at 40 mg/day). Esophagitis if taken without water. GI side effects rare.
Interactions	Mg / Ca chelation — separate from Multi by ≥2 hr (Bone report). Iron chelation — separate from any iron supplement.

Sub-antimicrobial doxycycline is a defensible niche intervention with multiple light convergences (NLRP3 inflammasome het cluster, α-synuclein clearance, MMP modulation). Continue, with attention to Mg/Ca timing separation per the bone report.

Vitamin D3 — 5000 IU every other day

TIER 1	Essential — quad-overlap intervention (Glucose, IGF-1, Endothelial, Glycation, Bone, Cancer reports)

Mechanism / pathway	Cholecalciferol → 25(OH)D in liver via CYP2R1 → 1,25(OH)2D in kidney via CYP27B1. Activates VDR transcription program (calcium/phosphate, immune, bone, insulin-sensitizing).
Genotype-specific rationale	Glucose / IGF-1 / Endothelial / Glycation reports all flag CYP2R1 rs10741657 het (reduced 25-hydroxylase). VDR rs2228570 G/G FokI protective. NADSYN1 hom-alt (Mitochondrial report) — additive 25(OH)D-lowering effect. Bone report: VDR signaling block at FokI + BsmI/ApaI/TaqI hom — receptor is rate-limiting at high substrate levels. Cancer report: VDR rs731236 + rs2228570 hom — confirm adequacy.
Lab alignment	May 2025: 103 ng/mL. Jan 2026: 84.6 ng/mL. Both above the 30–100 reference upper bound. Bone report explicitly recommends down-titration to maintain 50–60 ng/mL band given VDR receptor saturation.
Dose / form fit	D3 (cholecalciferol) is the right form. 5000 IU EOD (~2500 IU/day average) is producing 84.6 ng/mL. Reducing to 2000 IU/day OR 5000 IU twice weekly should land in the 50–60 ng/mL target range. K2 (MK-7) is under-covered — the Multi has K1 only.
Pros	Triple-overlap genetic justification. VDR FokI protective amplifies benefit per molecule. Clear dose-response on 25(OH)D.
Cons / cautions	Current value is at the upper edge of the desired band (Bone report) — receptor-saturated. No additional benefit from going higher. Theoretical concerns about levels >80 (Durup 2015) though direct harm not proven at 84.6.

Interactions	Should be paired with K2 (currently under-covered). Calcium absorption synergy.

Vitamin D3 is genetically high-priority but the current dose has overshot the target band. Consider down-titrating to reach 50–60 ng/mL. Add K2 (MK-7) 100–180 µg/day.

Ubiquinol (CoQ10) — 100 mg every other day

TIER 2	High value — multi-gene CoQ-pathway alignment + statin co-handling

Mechanism / pathway	Reduced (ubiquinol) form of coenzyme Q10. Mitochondrial electron transport chain electron carrier. Membrane antioxidant. Substrate for ETF-CoQ-oxidoreductase fatty acid oxidation. Pitavastatin reduces upstream mevalonate flux (modest CoQ10 depletion possible).
Genotype-specific rationale	Mitochondrial report: cumulative CoQ-pathway burden (NQO2 hom, COQ3 hom, COQ6 hom, COQ7 hom, NQO1 het, COQ2 het) — small individually, additive direction. Endothelial report: dual COQ2 het. NQO1 P187S het (Mitochondrial / Inflammation): ubiquinol form is preferable to ubiquinone for this genotype (ubiquinone reduction depends partly on NQO1).
Lab alignment	Plasma CoQ10 1.81 (Jun 2025) → 3.29 (Jan 2026), above the 2.20 upper reference. Current dose is producing therapeutic-plus levels. No need to increase.
Dose / form fit	Ubiquinol (reduced) form is the right choice given NQO1 het. 100 mg EOD is producing high plasma levels — possible to reduce frequency to twice weekly without losing therapeutic level if cost matters.
Pros	Genotype-aligned form choice. Statin co-handling rationale. Now lab-confirmed at therapeutic levels.
Cons / cautions	Cost. No need to increase. Lab value above reference suggests dose could potentially be reduced.
Interactions	Warfarin (none used). No CYP interactions.

Ubiquinol is genotype-correct (form) and lab-confirmed (level). Current EOD schedule is producing therapeutic plasma levels — no need to increase. Consider that 100 mg twice weekly might suffice given the plasma value of 3.29.

Per-Item Evaluation: Supplements

Supplements grouped by functional category (methylation/glutathione, omega-3, NO/endothelial, mineral/cofactor, hormonal, sleep/cognition, eye, mitochondrial, glycation). Items ordered roughly by tier within each section.

Methylation, glutathione & antioxidant defense

TMG (trimethylglycine / betaine) — 2.5 g morning

TIER 1	Essential — feeds the intact backup remethylation pathway

Mechanism / pathway	Methyl donor. Provides methyl group via BHMT-mediated betaine-homocysteine methyltransferase reaction (independent of folate cycle). Backup to MTR/MTRR-mediated remethylation.
Genotype-specific rationale	Homocysteine report: BHMT and CHDH both genetically intact; the entire folate-dependent arm is constrained (MTHFR het + MTHFD1 het + SHMT1 hom + SLC19A1 het + TCN2 hom). TMG directly feeds the genetically intact backup pathway. Strongest single supplement-genotype match for the methylation profile.
Lab alignment	Hcy 11.5 → 12.2 — TMG is partially holding the line but cannot fully neutralize the TCN2 transport deficit (active B12 is on a separate axis).
Dose / form fit	Trimethylglycine ≡ betaine anhydrous. 2.5 g/day is in the documented homocysteine-lowering range (Olthof J Nutr 2005 used 3 g/day; 1.5–6 g range supported).
Pros	Direct feed for genetically intact BHMT pathway. Lab-justified by elevated Hcy. Supports SAM regeneration. Modest insulin-sensitizing effect.
Cons / cautions	Body odor at high doses (uncommon at 2.5 g). Modest TG-raising signal at very high doses (>6 g) — not relevant here.
Interactions	Synergistic with methylcobalamin and 5-MTHF. No drug interactions.

TMG is one of the most genetically aligned supplements in the entire regimen — it feeds the only homocysteine-clearance pathway that is fully intact in this profile. Continue at 2.5 g.

Glycine — 6 g evening

TIER 1	Essential — glutathione substrate + GNMT methyl-buffer + collagen co-substrate

Mechanism / pathway	Direct substrate for glutathione synthesis (GSH = γ-Glu-Cys-Gly). Substrate for GNMT (glycine N-methyltransferase) — major SAM consumer when methyl supply is high (buffering function). Collagen synthesis. Glycine receptor agonist (modest sleep onset benefit).
Genotype-specific rationale	Glutathione bottleneck across 6 reports (CTH hom + NFE2L2 hom + GLO1 hom + AKR1B1 hom + GSTP1 hom + NQO1 het). GlyNAC paradigm (Kumar Clin Transl Med 2021, 2023): glycine + NAC together raise GSH more than either alone. Sleep report: direct sleep-onset evidence (Yamadera 2007; Bannai 2012) + COMT Val/Val EEG profile aligned. Strength report: Recovery and connective tissue support.
Lab alignment	No direct biomarker — RBC/whole-blood GSH would test the bottleneck directly.
Dose / form fit	6 g/day total is at the upper end of typical supplementation, near GlyNAC trial doses. Form: free L-glycine. Evening timing supports sleep architecture.

Pros	Multi-pathway: GSH, methyl buffer, sleep, collagen. Aligned with at least 6 genetic reports. Cheap, well-tolerated.
Cons / cautions	High osmotic load if taken on an empty stomach. Theoretical concern with GlyNAC stack: animal models show NRF2 activation if pushed too high — but human data are reassuring at these doses.
Interactions	Synergistic with NACET (GlyNAC). No clinically relevant drug interactions.

Glycine 6 g is the right dose for this profile and pairs synergistically with NACET to address the multi-report GSH bottleneck. Continue.

NACET (N-acetylcysteine ethyl ester) — 100 mg noon + 200 mg evening (300 mg/day)

TIER 1	Essential — but UNDERDOSED for the cumulative GSH bottleneck

Mechanism / pathway	Cysteine pro-drug with better oral bioavailability than NAC (the ethyl ester crosses lipid membranes more readily; Giustarini Free Radic Biol Med 2018). Cysteine is the rate-limiting amino acid for glutathione synthesis. Direct ROS scavenger via thiol chemistry. Modest NRF2 induction.
Genotype-specific rationale	Convergent across 6 reports: CTH S403I hom (transsulfuration exit bottleneck = reduced cysteine production) + NFE2L2 rs6721961 hom (NRF2 promoter low-induction) + GLO1 hom + AKR1B1 hom (glycation requires GSH-dependent MG clearance) + GSTP1 hom + GSTT1/M1 status unknown (Phase II conjugation) + SOD2 het + NQO1 het (Mitochondrial/Inflammation). NACET addresses the rate-limiting cysteine input directly. The CTH S403I hom is the strongest cross-pathway signal in the entire genetic profile per the Homocysteine summary.
Lab alignment	No direct biomarker tracked yet. Whole-blood GSH/GSSG ratio is the gold-standard test.
Dose / form fit	NACET form is correct (better bioavailability than NAC). 300 mg total/day matches the upper end of the original homocysteine report's 200–300 mg range — this is now a Tier 1 dose. However, multiple reports (Inflammation, Endurance, Strength, Hair, Cancer Predisposition, Glycation) recommend pushing to 300–500 mg or adding standalone NAC 600–1200 mg given the genotype convergence. Cancer report recommends "higher-dose NAC (600–1200 mg vs current 100 mg)" given GSTP1 hom + NAT2 slow Phase II bottleneck.
Pros	Single most cross-report-relevant supplement. Better bioavailability than NAC. Lab-justified given Hcy 12.2 and the four-to-six-report bottleneck convergence.
Cons / cautions	High doses can theoretically blunt some forms of exercise adaptation (NAC has been studied here; NACET data are sparser). Pulse rather than continuous dose may mitigate this.
Interactions	Synergistic with glycine (GlyNAC). May reduce nitroglycerin tolerance (no nitroglycerin in regimen). Anticoagulant effect mild (already on aspirin).

NACET at 300 mg total is now appropriate for the homocysteine and inflammation arms but remains underdosed for the cumulative six-report convergence. Discuss escalation to 400–500 mg NACET total or addition of standalone NAC 600 mg with the physician. Order RBC/whole-blood GSH baseline before changing dose so the response can be quantified.

Avmacol Extra Strength (sulforaphane precursor) — 4 tablets/day (1 AM + 2 noon + 1 evening)

TIER 1	Essential — direct NRF2 activator addressing the keystone NFE2L2 hom variant

Mechanism / pathway	Stabilized broccoli seed extract delivering glucoraphanin + active myrosinase (mustard seed source) → in vivo conversion to sulforaphane. Sulforaphane covalently modifies KEAP1 cysteines, prevents NRF2 degradation, drives NRF2 nuclear translocation and ARE-mediated

	transcription of GCLC, GCLM, NQO1, HMOX1, GSTM, GPX, SOD2 — bypassing the rs6721961 promoter deficit at the protein-stability step.
Genotype-specific rationale	NFE2L2 rs6721961 hom is a keystone variant across 6+ reports (Inflammation, Glycation, Hair Loss, PD, Endurance, Strength, Mitochondrial, Proteostasis). Direct mechanism-genotype match. Cancer Predisposition: GSTP1 hom + NAT2 slow Phase II bottleneck — sulforaphane upregulates Phase II enzymes (Bento-Pereira Med Res Rev 2021). Dementia: microglial DAM phenotype polarization (CR1 triple hom). Cumulative dose 4 caps × ~17.5 mg glucoraphanin = ~70 mg glucoraphanin → ~30–40 mg sulforaphane equivalents — within Ahn 2022 / Sedlak 2018 RCT ranges.
Lab alignment	No direct biomarker tracked. GGT trend would be informative (Endurance report). Whole-blood GSH would also improve with effective NRF2 activation.
Dose / form fit	Avmacol Extra Strength includes active myrosinase from mustard seed (NMXMS85™), which is essential because gut microbiome-only conversion is highly variable. 4 caps/day is at the well-evidenced range (>30 mg sulforaphane equivalents). Endurance and Strength reports both flagged the prior 1-cap dose as inadequate; the 4-cap escalation directly addresses this.
Pros	Direct mechanism-genotype match for the most replicated keystone finding. Form (myrosinase-active) and dose now correct. Cross-confirmed across many reports. Strong RCT evidence (Sedlak 2018; Ahn 2022; Yagishita 2019).
Cons / cautions	Mild GI / sulfur taste reported by some users. Theoretical thyroid effect from goitrogens at very high doses — clinically not seen at this dose with adequate iodine.
Interactions	Possible mild interaction with rapamycin (NRF2 / mTOR crosstalk) — IGF-1 report flagged this. Currently no clinical signal of concern.

Avmacol at 4 caps/day directly addresses the single most replicated keystone finding (NFE2L2 hom across 6+ reports) at an evidence-based dose with the correct form. This is one of the highest-leverage items in the entire stack. Continue.

Taurine — 6 g/day (3 g AM + 3 g PM)

TIER 2	High value — bypasses CTH cysteine-derivation deficit, multiple convergent benefits

Mechanism / pathway	Endogenously synthesized from cysteine via CDO/CSAD pathway. Bile acid conjugation. Osmolyte. Intracellular Ca^{2+} buffer. Antioxidant. Methylglyoxal-derived AGE inhibition (Hansen 2001).
Genotype-specific rationale	CTH S403I hom (Homocysteine) reduces endogenous taurine synthesis (taurine derives from cysteine downstream of CTH-supplied substrate). Glycation: AGE-precursor scavenging. Bone: osmolyte support. Singh Science 2023 showed taurine declines with age and supplementation extends healthspan in mice — mechanistic case is solid; human RCTs limited.
Lab alignment	No direct biomarker tracked.
Dose / form fit	6 g/day is a high but defensible dose (Singh trial used 1 g/kg/day in mice — human-equivalent ~6 g). Free L-taurine is the only available form.
Pros	CTH bypass rationale. Multiple convergent (cardiac, glucose, glycation, sleep). Cheap. Excellent safety record.
Cons / cautions	Mild osmotic load. Some controversy over the longevity claim (Singh 2023 has been challenged for human translation). Fall-back position is "supportive but not headline-driving."
Interactions	No clinically relevant drug interactions.

Taurine is well-aligned with the CTH hom downstream-synthesis bottleneck. Continue at 6 g; recognize the human longevity evidence is mechanistic rather than RCT-confirmed.

CacaoVia (cocoa flavanols) — 750 mg morning

TIER 2	High value — GLO1 induction + endothelial flow-mediated dilation

Mechanism / pathway	Standardized cocoa flavanol extract (epicatechin + procyanidins). NRF2 → GLO1 transcriptional induction (Xue Diabetes 2012). Endothelial NO bioavailability improvement (COSMOS, Sesso AJCN 2022). Modest insulin sensitization.
Genotype-specific rationale	Glycation: GLO1 hom risk (GLO1 transcriptional induction is the only way to push activity above set-point because the protein-coding sequence is intact). Endothelial: NO axis convergence. Inflammation: anti-inflammatory.
Lab alignment	GlycA 241 → 280 (still well below 400 high-risk). hs-CRP 0.60 — favorable.
Dose / form fit	750 mg total flavanols is in the COSMOS trial range (500 mg/day in COSMOS). CacaoVia is a stable standardized product.
Pros	Direct GLO1 induction rationale. RCT outcome data (COSMOS-CV outcomes). Pleiotropic.
Cons / cautions	Caffeine content (small but present — Sleep report flags caffeine handling). AM timing is correct.
Interactions	Mild α-blocker effect (none in regimen).

CacaoVia is genotype-aligned for the homozygous GLO1 finding via NRF2-driven transcriptional induction and contributes to endothelial NO. Continue.

Olive Leaf Extract — 1250 mg/day (750 mg AM + 500 mg PM)

TIER 3	Reasonable — modest aldose reductase inhibition + AGE inhibition

Mechanism / pathway	Oleuropein, hydroxytyrosol. Modest aldose reductase (AKR1B1) inhibitor. Anti-inflammatory via NF-κB modulation. AGE-formation inhibition.
Genotype-specific rationale	Glycation: AKR1B1 hom (homozygous variant alters polyol pathway flux direction-context-dependent). Inflammation: NF-κB modulation aligned with NFKB1 ins/del het + IKBKB het.
Lab alignment	GlycA modestly elevated 280 — reasonable to maintain. hs-CRP 0.60 — favorable.
Dose / form fit	Standardized to oleuropein content varies by product. Total 1250 mg is in the upper-typical supplementation range.
Pros	Modest evidence base. Multiple light convergences (AKR1B1, NF-κB, mild BP-lowering).
Cons / cautions	BP-lowering signal is small but real — already on telmisartan 80 mg. Watch for hypotension.
Interactions	Modest BP additivity with telmisartan and tadalafil. Modest blood-thinning effect.

Reasonable adjunct for the glycation arm. Continue but consider this is a Tier 3 item that could be reduced if cost/burden becomes an issue.

Ergothioneine — 20 mg/day (10 mg noon + 10 mg PM)

TIER 2	High value — mitochondrial-targeted cytoprotectant, MG scavenger

Mechanism /	Naturally occurring thione amino acid. Concentrated in mitochondria via SLC22A4/OCTN1

pathway	transporter. Direct singlet-oxygen and hydroxyl-radical scavenger. Direct methylglyoxal scavenger. Often called the "longevity vitamin" (Paul & Snyder Cell Death Differ 2010).
Genotype-specific rationale	Mitochondrial: SOD2 het + GSTP1 hom + NQO1 het + cumulative CoQ-pathway burden. Glycation: GLO1 hom (MG accumulation). Proteostasis: ER stress sensitivity from EIF2AK3 PERK-B hom.
Lab alignment	No direct biomarker. Plasma ergothioneine levels positively correlate with healthspan in cohort studies.
Dose / form fit	20 mg/day total is at the upper end of dietary intake (mushroom-rich diets ~3–7 mg/day). Pharmaceutical-grade synthetic Ergoneine is bioequivalent.
Pros	Mitochondria-concentrated antioxidant. Direct MG scavenging. Excellent safety record. Genetic match for SOD2 het and GLO1 hom.
Cons / cautions	Cost. Long-term human RCT outcome data limited.
Interactions	No drug interactions.

Ergothioneine is mechanistically well-targeted to mitochondrial oxidative stress and to methylglyoxal. Continue.

D-Limonene — 2000 mg/day (1000 mg noon + 1000 mg PM)

TIER 3	**Reasonable — NRF2 activator, modest GST induction**

Mechanism / pathway	Monoterpene. Hepatic glutathione S-transferase (GST) induction. NRF2 activation. GERD relief data.
Genotype-specific rationale	Inflammation/Cancer/Hair: NFE2L2 hom + GSTP1 hom — secondary NRF2 lever. Cancer Predisposition: GSTP1 hom + NAT2 slow — Phase II support.
Lab alignment	No direct biomarker.
Dose / form fit	2000 mg/day is in the typical range (1000–2000 mg).
Pros	Secondary NRF2 lever. GI / GERD benefit incidental.
Cons / cautions	Citrus terpene allergic potential rare. No headline RCT outcome data.
Interactions	No clinically relevant interactions.

A reasonable secondary NRF2 lever stacked with sulforaphane. The headline NRF2 work is being done by Avmacol; d-limonene is a supportive adjunct.

Omega-3 / fatty acid balance

Carlson Elite EPA Gems — 1000 mg EPA noon

TIER 2	**High value — anti-inflammatory + ApoB / TG support**

Mechanism / pathway	High-dose pure EPA. Resolvin E-series substrate. Eicosanoid shift toward 3-series (anti-inflammatory). Plasma TG reduction.
Genotype-	Inflammation: ALOX15 hom + TGFB1 hom downstream resolution shift — substrate adequacy

specific rationale	is needed despite the downstream variants. FADS1/FADS2/ELOVL2 all clean — substrate not endogenous-conversion-limited. Apolipoprotein addendum: 11q23 cluster reinterpreted as protective; the genetic rationale for high omega-3 is slightly weaker than previously thought, but still favorable.
Lab alignment	EPA 57.6 µg/mL (optimal >50). AA/EPA 4.95 (optimal). Working as expected.
Dose / form fit	TG-reesterified or natural TG form. 1000 mg EPA is a meaningful single dose.
Pros	Lab-confirmed effective. Anti-inflammatory mechanism. ApoB / TG support.
Cons / cautions	EPA-heavy stack — DHA gap remains (separate concern, addressed by adding DHA-specific algal oil).
Interactions	Mild bleeding additivity with aspirin. Rare GI upset.

EPA is at optimal level — current dose is doing its job. The remaining issue is DHA-specific. Continue this product but reallocate the flaxseed oil slot (and possibly trim total EPA dose if DHA is brought up).

Momentous Omega-3 — 400 mg EPA + 400 mg DHA noon

TIER 2	High value — but DHA contribution is the limiting factor

Mechanism / pathway	Balanced 1:1 EPA:DHA. Anti-inflammatory + neural / retinal membrane support.
Genotype-specific rationale	Same as above plus Dementia/BBB/PD/ADHD reports — all flag DHA as substrate (membrane composition, GPX4 het ferroptosis-blocking enzyme support, CR1 hom microglial, MFSD2A genetic intact = substrate-supply problem, not transporter problem).
Lab alignment	DHA 84.3 µg/mL borderline low (target >100). 400 mg DHA from this product alone is not enough.
Dose / form fit	Phospholipid or TG form. Dose is balanced but small for the DHA target.
Pros	Adds DHA. Form OK.
Cons / cautions	DHA contribution insufficient at 400 mg/day to reach plasma >100 µg/mL given the borderline low starting point.
Interactions	As EPA above.

Continue, but supplement with a high-DHA algal oil (500 mg+ DHA additional) to close the gap.

Antarctic Krill Oil (Viva Naturals) — 1200 mg noon

TIER 3	Reasonable — phospholipid form, astaxanthin content

Mechanism / pathway	Phospholipid-bound EPA + DHA (~120/60 mg per 1200 mg). Astaxanthin co-content (small ergonomic antioxidant role). Bioavailability advantage on a per-mg basis (Köhler Lipids 2015) but absolute EPA/DHA content low.
Genotype-specific rationale	Same omega-3 rationale.
Lab alignment	EPA optimal, DHA borderline.
Dose / form fit	Phospholipid form has bioavailability advantage but the actual EPA/DHA content from a single 1200 mg krill capsule is small (often ~120 mg EPA + 60 mg DHA for a 1200 mg krill product).

Pros	Phospholipid form. Astaxanthin co-content.
Cons / cautions	EPA and DHA dose per capsule is low. Cost-per-mg-omega-3 is high vs. concentrated fish oil.
Interactions	Bleeding additivity.

Reasonable but not the most cost-effective omega-3 source. Reallocating the slot to a high-DHA algal oil would more directly address the DHA gap.

Cold-pressed Flaxseed Oil — 1 g noon

TIER 5	Reconsider / discontinue — ALA conversion negligible in adult men

Mechanism / pathway	Provides ALA (alpha-linolenic acid). ALA → EPA conversion is 0.2–8% in adult men; ALA → DHA conversion is essentially zero (Burdge & Calder Reprod Nutr Dev 2005).
Genotype-specific rationale	No genotype-specific rationale. FADS1/FADS2/ELOVL2 are clean; the gating step is upstream (β-oxidation, fatty acid concentration), not the desaturases.
Lab alignment	ALA <7.8 µg/mL (below detection limit). Boston Heart panel says 1 g/day is not measurably contributing. Flaxseed oil is not reaching the bloodstream as ALA at meaningful levels at this dose.
Dose / form fit	1 g/day is too small to meaningfully raise ALA, and ALA does not meaningfully convert to DHA.
Pros	Minor — fiber if taken as ground seed. Negligible at 1 g oil.
Cons / cautions	Provides no measurable benefit per the Jan 2026 fatty acid panel.
Interactions	None.

The Jan 2026 Boston Heart panel directly disproves the value of this item: ALA is below detection and DHA is borderline low despite this supplement. Discontinue and reallocate to high-DHA algal oil 500+ mg DHA.

NO signaling / endothelial

L-citrulline — 6–10 g AM + 3 g PM (9–13 g/day)

TIER 1	Essential — pairs with tadalafil for the 4-gene NO convergence

Mechanism / pathway	Arginine precursor with first-pass advantage (bypasses splanchnic arginase extraction). Raises plasma arginine more reliably than L-arginine. Substrate for NOS3-mediated NO synthesis.
Genotype-specific rationale	Endothelial: GUCY1A3 dual hit + NOS3 het + PDE5A hom + SPR hom — citrulline addresses the substrate-supply side of the convergence; tadalafil addresses the cGMP-degradation side. Together they form the most complete pharmacology-supplement match in the regimen.
Lab alignment	No direct biomarker (ADMA was ordered but pending).
Dose / form fit	Free L-citrulline. 9–13 g/day is at the upper end of supplementation but is supported by Schwedhelm Br J Clin Pharmacol 2008 and subsequent ergogenic / endothelial trials.
Pros	First-pass advantage over L-arginine. Direct mechanistic alignment with the homozygous NO-convergence finding. Endurance / exercise benefit (in addition to endothelial).

Cons / cautions	Mild GI loosening at high doses. Cost at this volume.
Interactions	Synergistic with tadalafil. Mild BP-lowering additivity (with telmisartan).

L-citrulline is the substrate side of the most complete pharmacology-supplement pairing in the regimen. Continue at this dose.

Nattokinase — 12,000 FU morning

TIER 5	**Reconsider — additive bleeding risk with aspirin, weak evidence, no thrombophilia genotype**

Mechanism / pathway	Subtilisin-class fibrinolytic enzyme from natto. Plasmin-like activity. Modest fibrinogen reduction in some studies.
Genotype-specific rationale	Coagulation genotype is favorable: F5 Leiden absent, F2 G20210A absent, no inherited thrombophilia. PEAR1 het is a weak modifier with mixed evidence. The genotype does not justify a second antithrombotic on top of aspirin.
Lab alignment	No bleeding events flagged (Hgb stable). Platelets normal.
Dose / form fit	12,000 FU is the upper end of supplementation. Heat-stable but bioavailability and oral activity are debated.
Pros	Some small studies show modest BP and fibrinogen effects.
Cons / cautions	Additive bleeding risk with aspirin. Weak evidence base (mostly small Asian observational studies; few rigorous Western RCTs). Cost. The genotype actively does not require this — no inherited thrombophilia. After Repatha is established the rationale weakens further.
Interactions	Bleeding additivity with aspirin (clinically meaningful). May potentiate other anticoagulants.

Discuss discontinuation with the physician. The genotype provides no rationale, the evidence base is weak, the bleeding risk on top of aspirin is real, and there is no lab signal supporting it. The Integrated Regimen Analysis flagged this in April 2026; the recommendation stands.

Minerals & cofactors

Magnesium Malate — 2000 mg (226 mg elemental) noon

TIER 1	**Essential — endurance athlete depletion + insulin/AKT/mTOR cofactor**

Mechanism / pathway	Mg^{2+} is cofactor for >300 enzymes including ATP utilization, insulin receptor kinase, AKT, mTOR. Malate moiety is a Krebs cycle intermediate.
Genotype-specific rationale	Glucose: insulin receptor activity. Mitochondrial: Krebs cycle and ATP. Bone: VDR signaling cofactor. Endurance: athletes deplete Mg faster.
Lab alignment	Mg RBC 5.7 → 6.4 — mid-range and rising. Combined with L-threonate ~370 mg elemental Mg/day total.
Dose / form fit	Magnesium malate is well-tolerated. Noon timing avoids interaction with morning doxycycline (per Bone report Mg-doxycycline chelation).
Pros	Lab-confirmed adequate. Tolerable form. Multi-system cofactor.
Cons /	Some products under-deliver elemental Mg.

cautions	
Interactions	Bone report: keep ≥2 hr from doxycycline (already at noon, AM doxycycline fine). Calcium absorption reciprocal effect — none currently relevant.

Continue. Form and timing correct.

Magnesium L-Threonate — 2000 mg (144 mg elemental) evening

TIER 2	High value — BBB-penetrant Mg form, sleep / cognition

Mechanism / pathway	Threonate-bound Mg crosses BBB more efficiently than other forms (Slutsky Neuron 2010). Raises CSF/brain Mg^{2+}. Implicated in NMDA receptor function, synaptic plasticity, sleep architecture.
Genotype-specific rationale	Sleep report: COMT Val/Val EEG profile aligned. ADHD report: COMT Val/Val + ADRA2A loaded — Mg cofactor support relevant. Dementia: synaptic / glutamatergic support.
Lab alignment	Mg RBC adequate.
Dose / form fit	Magnesium-L-threonate (proprietary; commonly Magtein). PM dosing for sleep / cognition.
Pros	Only Mg form with documented BBB penetration. Sleep evidence (Slutsky 2010 + clinical extensions). ADHD/cognition rationale.
Cons / cautions	Cost. Lower elemental Mg per gram than other forms.
Interactions	None clinically relevant.

Continue. The PM Magtein + AM/noon malate split is genetically well-justified.

Boron — 6 mg cycled (2 weeks on, 1 week off)

TIER 3	Reasonable — modest free T / E2 + bone cofactor

Mechanism / pathway	Boron raises free testosterone modestly (Naghii J Trace Elem Med Biol 2011). Lowers SHBG. Cofactor for several metalloenzymes.
Genotype-specific rationale	Bone report: cofactor support. Hair Loss / Strength: hormonal axis support.
Lab alignment	Free T 11.3 (mid-range), E2 29.5 (mid-range), DHEA-S 71. Adequate.
Dose / form fit	6 mg/day with cyclic schedule is conservative.
Pros	Modest hormonal benefit. Bone report cofactor.
Cons / cautions	Evidence base modest. Some kidney concerns at high doses (not at 6 mg).
Interactions	None.

Defensible adjunct given the cycling schedule. Continue.

Momentous Multivitamin (2 cap noon + 2 cap PM) — Full 4-cap dose split AM/PM

TIER 1	Essential — only if forms verified (5-MTHF YES, methylcobalamin?, P5P YES, B2

	dose?)

Mechanism / pathway	Standardized multivitamin with bioactive forms of B-vitamins.
Genotype-specific rationale	Form-checks across multiple reports. Confirmed correct: Quatrefolic (5-MTHF) for MTHFR het + SHMT1 hom + MTHFD1 het + SLC19A1 het. Pyridoxal-5-phosphate (P5P) at 6.7 mg/dose for CTH residual activity. Riboflavin-5-phosphate (R5P) at 4.2 mg/dose. Vitamin D3 cholecalciferol at 50 mcg/dose. Selenium 100 mcg/dose (high-Se yeast — bioavailable). Zinc bisglycinate. Vitamin K is K1 phylloquinone (NOT K2 — gap relative to bone report). Mixed carotenoids for vitamin A. Critical OPEN QUESTION: B12 form. Label shows methylcobalamin at 200 mcg/dose — if confirmed, this is correct.
Lab alignment	RBC folate 1081 (target >498) confirms 5-MTHF reaches tissue. B2 whole-blood 206 (mid-range) — multi B2 contribution may not be fully optimal for thermolabile MTHFR (need 25–50 mg). B12 1127 high-normal but holotranscobalamin not yet measured.
Dose / form fit	Full 4-cap dose split AM/PM is correct (split avoids GI overload). Quatrefolic and P5P are correct active forms. K1-only is a gap — add K2 separately. B2 dose at 4.2 mg/cap × 4 caps = 16.8 mg/day is below the 25–50 mg McNulty 2006 target — consider adding R5P 25 mg.
Pros	Bioactive forms. Selenium yeast form. Comprehensive but not over-dosed.
Cons / cautions	K1 only (no K2 — bone gap). B2 dose marginal for thermolabile MTHFR. Need to confirm B12 is methylcobalamin (label suggests yes — verify product certificate).
Interactions	None significant.

Momentous Multi at full 4-cap dose is now a Tier 1 item — but only if the methylcobalamin form claim on the label is verified and only if K2 is added separately. Add R5P 25–50 mg/day to reach the McNulty MTHFR-stabilization target.

Hormonal

DHEA — 25 mg morning

TIER 3	**Reasonable — DHEA-S age-appropriate, IGF-1 effect attenuated by rapamycin**

Mechanism / pathway	Adrenal androgen precursor. Modest serum IGF-1 elevation (~10–15%) in some trials (Morales NEJM 1994). Mood / wellbeing signal in older adults.
Genotype-specific rationale	IGF-1 report flagged this as worth a deliberate conversation given the homozygous IGF1 production variants (rs978458, rs6220, rs11111274). However, the rapamycin-mediated IGF-1 reduction (115 → 88) suggests the net effect is modest at the current rapamycin dose. Strength report: AR ≥21 CAG inferred — DHEA conversion downstream may be more meaningful for muscle. Cancer: IGF-1 is a prostate cancer risk factor — counterbalance.
Lab alignment	DHEA-S 71 µg/dL (age-appropriate for 62-year-old male). IGF-1 88 (target zone).
Dose / form fit	25 mg/day is a moderate supplementation dose.
Pros	Age-appropriate restoration. Possible mood / wellbeing. Strength rationale.
Cons / cautions	Modest IGF-1 elevation potential. Could mildly counter rapamycin's IGF-1 lowering goal — but lab data show net IGF-1 is in target. If rapamycin dose is ever reduced, DHEA effect may become more visible.
Interactions	May modestly raise estrogens (already on dutasteride, which shunts toward estradiol). Bone report: estrogenic component is favorable for bone.

Reasonable to continue at 25 mg given current IGF-1 in target band. Re-evaluate if rapamycin dose ever changes — DHEA's IGF-1-raising effect may emerge more clearly in that case.

Sleep & cognition

Melatonin — 5 mg evening

TIER 4	Marginal at this dose — multiple cross-report flags suggest 1–3 mg

Mechanism / pathway	Circadian phase-shifting. Direct antioxidant / methylglyoxal scavenger (Tan J Pineal Res 2014). Slow-wave sleep modest enhancement.
Genotype-specific rationale	MTNR1B clean (Glucose, Sleep) — no genetic argument for high dose to overcome receptor desensitization. CLOCK clean. PER2 het (Glucose) supports circadian intervention but does not require high dose. Glycation: MG-scavenging useful adjunct.
Lab alignment	No direct biomarker. Glucose tolerance per fasting glucose 90 — favorable.
Dose / form fit	5 mg is supraphysiologic. Endogenous nocturnal melatonin peak is pg-range; 1–3 mg achieves supraphysiologic but not extreme levels. 5 mg likely produces persistent next-day plasma levels that may interfere with daytime alertness (variable by individual).
Pros	MG-scavenging adjunct for glycation. Sleep onset modest benefit.
Cons / cautions	Dose is higher than longevity-protocol standard (1–3 mg). Cross-flagged in Glucose, Rapamycin, Strength, Sleep, Glycation reports as worth stepping down. No genetic argument for maintaining 5 mg.
Interactions	Mild additive sedation with phosphatidylserine and l-theanine (already in stack — actually desired). Possible interaction with rapamycin (mTOR/autophagy crosstalk) — direction context-dependent.

Step down to 1–3 mg. The supraphysiologic 5 mg dose has no genetic rationale and is flagged for reduction in 5 separate reports. Sleep onset / quality benefit at 1–3 mg is roughly equivalent.

L-Theanine — 200 mg evening

TIER 3	Reasonable — modest sleep onset / cortisol effect

Mechanism / pathway	GABA-ergic and α-wave EEG modulation. Modest cortisol reduction.
Genotype-specific rationale	Sleep: FKBP5 het cortisol-axis aligned. ADHD: catecholamine modulation relevant.
Lab alignment	No direct biomarker.
Dose / form fit	200 mg is the standard supplementation dose.
Pros	Modest sleep / anxiolytic benefit. Safe.
Cons / cautions	Effect size modest.
Interactions	Mild additive sedation.

Reasonable adjunct. Continue.

Phosphatidylserine — 300 mg evening

TIER 3	Reasonable — cortisol blunting + membrane integrity

Mechanism / pathway	Phospholipid head-group. Cortisol reduction (Monteleone Eur J Clin Pharmacol 1992). Membrane integrity in neurons.
Genotype-specific rationale	Sleep: FKBP5 het cortisol-axis. Dementia: membrane support.
Lab alignment	No direct biomarker.
Dose / form fit	300 mg is at upper end of standard dosing.
Pros	Cortisol-blunting evidence (small RCTs). Membrane support.
Cons / cautions	Effect size modest. Cost.
Interactions	Mild blood-thinning effect (additive with aspirin / nattokinase).

Defensible. Continue.

Lithium Orotate — 5 mg evening

TIER 2	High value — microdose tau-axis insurance + circadian stabilization

Mechanism / pathway	Microdose lithium (5 mg orotate ≈ 0.4 mg elemental Li). GSK-3β inhibition at higher therapeutic doses; debated relevance at microdose. Circadian regulation. Some evidence for bipolar-spectrum mood stabilization at higher doses.
Genotype-specific rationale	Dementia report: tau-axis insurance via GSK3β inhibition (TMEM106B het LATE, MAPT H2/H2 protective — net ambiguous, but tau-pathway support has small evidence base). Sleep: modest circadian-stabilizing effect.
Lab alignment	Not measured. Lithium orotate microdose typically does not require monitoring.
Dose / form fit	Lithium orotate is a controversial form (orotate complex), but at 5 mg/day total it is well below any toxicity threshold.
Pros	Cheap microdose with low downside. Tau-axis rationale.
Cons / cautions	Evidence base for orotate form vs. carbonate is weak. Effect size at microdose uncertain. Some lithium-thyroid interaction at higher doses (5 mg is well below).
Interactions	NSAIDs and ACEI/ARBs raise lithium levels — not clinically significant at 5 mg.

Reasonable microdose insurance. Continue at 5 mg PM.

Myo-Inositol — 4 g evening

TIER 2	High value — insulin sensitizer, IRS1-pathway amplifier

Mechanism / pathway	Second messenger downstream of insulin receptor. PI3K/Akt pathway amplifier. Glucose-handling improvement (Croze & Soulage Biochimie 2013).
Genotype-specific	Glucose: IRS1 rs2943641 C/C protective — myo-inositol amplifies the genetically intact IRS1 pathway. Beta-cell deficit support: myo-inositol enhances insulin efficiency per molecule.

rationale	
Lab alignment	HOMA-IR ~0.6 — already excellent. Myo-inositol contribution incremental.
Dose / form fit	4 g/day is therapeutic dose with documented glucose-metabolism effects.
Pros	Insulin-sensitizing on top of intact IRS1. Safe.
Cons / cautions	GI upset at higher doses.
Interactions	Synergistic with empagliflozin / tirzepatide / imeglimin.

Genotype-aligned. Continue.

Eye health

MacuGuard — 1 evening (lutein 10 + meso-zeaxanthin/zeaxanthin 4 + α-carotene 1.24 mg + saffron 20 mg + astaxanthin 6 mg)

TIER 1	**Essential — direct match for CFH Y402H homozygous (AMD OR ~4.6)**

Mechanism / pathway	AREDS2-derived carotenoid formulation + saffron + astaxanthin. Lutein/zeaxanthin are macular pigment substrates that filter blue light and quench singlet oxygen. Saffron has independent RCT evidence for macular function (Broadhead Clin Exp Ophthalmol 2019).
Genotype-specific rationale	Inflammation report: CFH Y402H homozygous (rs1061170 T/T) + second CFH hit — one of the largest common-variant effects in human GWAS, AMD homozygous OR ~4.6 (Klein Science 2005). This is the single most genetically vulnerable site in the entire genetic profile relative to a specific intervention.
Lab alignment	Retinal OCT not yet baselined — should be done.
Dose / form fit	AREDS2-style with addition of saffron + astaxanthin. 1 capsule PM is appropriate.
Pros	Direct match for the largest common-variant genetic finding. RCT evidence (AREDS2 JAMA 2013). Multi-mechanism.
Cons / cautions	Cost. Doesn't replace baseline retinal imaging — get OCT.
Interactions	None.

This is one of the highest-leverage single supplements in the entire stack. Continue and pair with retinal OCT baseline + surveillance with a retina specialist.

Mitochondrial / cellular support

PQQ (pyrroloquinoline quinone) — 20 mg noon

TIER 3	**Reasonable — mitochondrial biogenesis cofactor**

Mechanism / pathway	Putative cofactor for mitochondrial biogenesis via PGC-1α activation. Promotes new mitochondria.
Genotype-specific rationale	Mitochondrial: SOD2 het, cumulative CoQ-pathway burden. PGC-1α activation aligns with PPARGC1A Gly/Gly favorable.

Lab alignment	No direct biomarker.
Dose / form fit	20 mg/day is mid-range supplementation dose.
Pros	Genetic rationale via PGC-1α / SOD2. Complements ubiquinol (which supports existing mitochondria).
Cons / cautions	Human RCT evidence is limited. Cost.
Interactions	None known.

Defensible adjunct. Continue.

Creatine monohydrate — 5 g daily

TIER 1	Essential — multi-mechanism (methyl-buffer + muscle + cognition + GLUT4)

Mechanism / pathway	Phosphocreatine donor for ATP regeneration. Creatine biosynthesis via GAMT consumes ~40% of total body SAM (Brosnan Annu Rev Nutr 2007); supplementation spares methyl groups → indirect homocysteine reduction. GLUT4 translocation support. Cognitive benefit (Rae Proc R Soc B 2003).
Genotype-specific rationale	Homocysteine: methylation-sparing rationale (every endogenous creatine synthesis molecule consumes a methyl group). Glucose: GLUT4 rs5418 het — creatine supports GLUT4 translocation. Strength: ACTN3 R/R likely + AMPD1 likely C/C — power-favorable genetics + creatine. Bone: muscle support and modest BMD signal in older adults.
Lab alignment	Creatinine 1.07 → 1.22 — modest creatine-explained rise. Cystatin C eGFR 94 confirms true kidney function preserved (creatinine-based eGFR understates).
Dose / form fit	Creatine monohydrate 5 g/day is the canonical dose. No loading needed for chronic use.
Pros	Multi-system: methyl-sparing, muscle, cognition. Strongest sport-supplement RCT base. Methylation-relevant for this genotype.
Cons / cautions	Modestly raises serum creatinine (cosmetic — does not reflect kidney impairment). Some users report mild GI.
Interactions	None significant.

Creatine is multi-purpose for this genotype: methyl-sparing for the homocysteine arm, muscle/strength for the favorable power genetics, cognition for the cognitive aging concern, and modest bone signal. Continue.

Collagen peptides — 15 g daily

TIER 2	High value — connective tissue + glycine source

Mechanism / pathway	Provides ~3 g glycine + proline + hydroxyproline per dose. Tendon / ligament collagen synthesis substrate. Glycine is GSH precursor.
Genotype-specific rationale	Strength: COL5A1 T/T at both queried SNPs + COL1A1 GT high-injury-risk + COL3A1 A/A + MMP3 K/K — connective-tissue convergence makes pre-training timed collagen + vit C uniquely relevant (Shaw Am J Clin Nutr 2017 showed 2× collagen synthesis biomarker increase with timed dosing). Bone: matrix-protein burden (COL1A1 Sp1 het + COL1A1 -1997 hom + COL1A2 het) — collagen substrate support. Glutathione: glycine arm.
Lab alignment	No direct biomarker.

Dose / form fit	Hydrolyzed collagen 15 g. Strength report recommends timing 30–60 minutes pre-tendon-loading exercise + co-ingest 50 mg vitamin C (Shaw protocol). The vitamin C from the Multi (400 mg) easily covers this if Multi timing is aligned.
Pros	Strong tendon-protective evidence given the COL5A1/COL1A1/COL3A1/MMP3 genetic burden. Glycine bonus. Cheap.
Cons / cautions	Plant-based diets do not get this from food. Some products have heavy-metal contamination concerns (verified brands OK).
Interactions	None.

Particularly valuable for this genotype. The strength report's Shaw-protocol timing recommendation (45 minutes pre-training) is the single highest-leverage low-cost intervention for the connective-tissue burden.

Momentous Multivitamin — Ingredient-Level Breakdown

The Multi is the only place where **form** matters as much as **dose**. Multiple genetic reports flag specific bioactive forms as required (5-MTHF over folic acid; methylcobalamin or hydroxocobalamin over cyanocobalamin; P5P over pyridoxine; R5P over riboflavin where dose is rate-limiting). The table below reviews each ingredient against the genotype to identify gaps and confirm what is correct.

Format below: full daily dose at 4 caps/day. The current schedule is 2 caps noon + 2 caps PM. **Verdict column** uses: ✓ form correct + dose adequate · △ form correct but dose marginal · ✗ form correct but dose inadequate · GAP form / dose not present and should be supplemented separately.

Ingredient (form)	Dose/day	Verdict	Genotype rationale
Vitamin A (mixed carotenoids + palmitate)	1500 mcg	✓	Mixed carotenoid form correct. Beta-carotene-only with smoker history would be a concern (no smoker history). Adequate.
Vitamin C (ascorbic acid + acerola)	400 mg	✓	Adequate for general antioxidant + collagen synthesis. Note: do NOT push to mega-doses (>2 g) — Glucose report explicitly cautions about blunting exercise-induced SOD2 upregulation.
Vitamin D3 (cholecalciferol)	50 mcg (2000 IU)	△	Form correct. Combined with separate D3 5000 IU EOD = ~4500 IU/day average → 25(OH)D 84.6 (above 50–60 target band). Bone report recommends down-titrating total. Multi can stay; reduce the standalone D3.
Vitamin K (K1 phylloquinone)	400 mcg	**GAP**	K1 only. Bone report flags need for K2 (MK-7) 100–180 µg/day given VKORC1 het + BGLAP het + COL1A1 burden. Add K2 separately.
Thiamin (Thiamin HCl)	2.4 mg	△	Standard form, basic adequacy. For Glycation report (GLO1 hom + AKR1B1 hom): consider adding benfotiamine 150–300 mg/day (lipid-soluble B1 prodrug; activates transketolase upstream of methylglyoxal generation).
Riboflavin (R5P, riboflavin-5-phosphate)	4.2 mg	✗	Form correct (R5P, active). Dose 4.2 mg is ~3–10× below the McNulty 2006 Circulation threshold (25–50 mg) for thermolabile MTHFR C677T het stabilization. B2 whole-blood 206 µg/L (mid-range, suboptimal). Add R5P 25–50 mg/day separately.
Niacin (niacinamide + niacin)	60 mg	✓	Mixed form fine. No genetic argument for high-dose niacin in this profile (lipids excellent on Repatha + statin + ezetimibe).
Vitamin B6 (P5P, pyridoxal-5-phosphate)	6.7 mg	△	Form correct (P5P, active — supports residual CTH activity per Homocysteine report). Dose 6.7 mg is adequate for general purposes but consider standalone P5P 25–50 mg if pyridoxamine added (for AGE-precursor scavenging — Glycation report).
Folate (Quatrefolic 5-MTHF glucosamine salt)	680 mcg DFE	✓	Single most genotype-correct form choice in the Multi. Bypasses the entire impaired folate pipeline (SLC19A1 het → MTHFD1 het → SHMT1 hom → MTHFR het). RBC folate 1081 confirms tissue delivery.
Vitamin B12 (methylcobalamin)	200 mcg	△	Form correct IF label is accurate (verify product certificate — methylcobalamin is essential given TCN2 P259R hom). Dose 200 mcg is adequate for most genotypes but TCN2 hom predicts impaired active-B12 delivery — Hcy 12.2 rising suggests current input is not enough. Add methylcobalamin 1000–2000 µg/day

Ingredient (form)	Dose/day	Verdict	Genotype rationale
			sublingual.
Biotin (d-biotin)	100 mcg	✓	Adequate. Avoid >5 mg/day if any future TSH or thyroid Ab measurement (biotin interferes with immunoassay).
Pantothenic acid (Ca pantothenate)	5 mg	✓	Adequate.
Calcium (di-calcium malate)	50 mg	**GAP**	Bone report flags VDR receptor burden + intestinal Ca absorption deficit. Multi 50 mg is far below 1000–1200 mg/day target. Food-first per Bolland 2015 BMJ (avoid high-dose supplemental Ca for CV reasons): dairy / fortified plant milks / sardines / leafy greens.
Magnesium (di-magnesium malate)	150 mg	✓	Adds to standalone Mg malate 226 mg + Mg L-threonate 144 mg = ~520 mg total. Lab Mg RBC 6.4 confirms adequacy.
Zinc (zinc bisglycinate)	15 mg	✓	Form correct (bisglycinate is well-absorbed). Dose adequate for JAK2 hom + PAPPA hom zinc-dependent enzymes (IGF-1 report). RBC zinc 1213 mid-range. Watch copper if increased — Cu RBC 0.55 already lower-normal.
Selenium (high-Se yeast)	100 mcg	✓	Form correct (Se yeast bioavailable). Dose adequate (avoid >200 mcg per Stranges 2007 paradoxical insulin resistance signal). Supports GPX4 het.
Copper (copper bisglycinate)	1 mg	△	RDA-equivalent. Cu RBC 0.55 lower-normal — adequate but watch trend if zinc is increased.
Manganese (Mn bisglycinate)	1 mg	✓	Direct cofactor for MnSOD (SOD2 het) — Mitochondrial / Glucose reports flag importance.
Chromium (Cr nicotinate glycinate)	200 mcg	✓	Glucose report: amplifies the homozygous-protective IRS1 signal. Form bioavailable. Adequate.
Molybdenum (Mo glycinate)	100 mcg	✓	Adequate. Cofactor for sulfite oxidase + xanthine oxidase. XDH hom (Endothelial) — Mo cofactor adequacy is helpful.
Wild blueberry + grape seed/skin powder	200 mcg total	✓	Polyphenol blend. Modest contribution given the larger CacaoVia + olive leaf doses elsewhere.
Citrus bioflavonoids	100 mg	✓	Modest anti-inflammatory / vascular support.
Broccoli seed extract + organic broccoli sprout	75 + 25 = 100 mg	△	Provides supplemental sulforaphane substrate but Multi does not include myrosinase (active enzyme). The headline NRF2 work is being done by Avmacol (which DOES include myrosinase). This adds modest backup but is not the primary lever.
Tocotrienols (delta + gamma)	25 mg	✓	Vitamin E family with stronger NRF2 activation than tocopherols. Lipoprotein report's vitamin E suggestion (PNPLA3 het hepatic lipid retention) is partially covered.
Quercetin dihydrate	50 mg	✓	Anti-inflammatory flavonoid. Modest dose; could be increased separately if specific need (mast-cell or allergic) develops.

The Multi is well-formulated but has three specific gaps relative to this genotype: (1) K1 only (no K2 — bone gap); (2) B2 dose at 16.8 mg/day is below the McNulty target for thermolabile MTHFR; (3) B12 at

200 µg/day is unlikely to overcome TCN2 hom transport deficit given the rising homocysteine. The fixes are three standalone additions — K2 (MK-7) 100–180 µg, R5P 25–50 mg, methylcobalamin 1000–2000 µg sublingual — each of which is cheap and low-risk.

Conflicts and Trade-offs

Most of the regimen is internally consistent. The conflicts that do exist are small and explicitly tolerated — listed here so they are explicit rather than hidden.

1. Rapamycin glucose effect vs. tirzepatide / empagliflozin / imeglimin

The trade-off: rapamycin pulsed dosing modestly impairs beta-cell function and produces mTORC2 spillover (TBC1D4 + PCK1 + SLC2A4 + AKT2 het) → HbA1c 5.8 → 5.9 drift. The metabolic stack (tirzepatide + empagliflozin + imeglimin) is doing the work to keep glucose in range.

Why this is OK: the IGF-1 reduction (115 → 88) and FOXO3-haplotype unmasking are the longevity-decisive benefits of rapamycin. Stopping rapamycin to gain 0.1% HbA1c would trade a probably-large longevity benefit for a small glycemic gain. The current regimen is the right balance, and the metabolic stack is genotype-aligned for the secretory deficit anyway.

Mitigation: schedule heavy resistance training in days 7–14 of the rapamycin cycle (Strength report). Avoid CYP3A inhibitors near dose days. Consider one trough sirolimus level on day 7 to confirm AUC is in target range given CYP3A5*3/*3 + CYP3A4*1B hom.

2. Aspirin + nattokinase additive bleeding

The trade-off: two antithrombotic agents stacked. Aspirin is justified by the genetic CV + cancer chemoprevention. Nattokinase has weak evidence and no genetic justification (no inherited thrombophilia).

Resolution: discontinue nattokinase. This is a Tier 5 item. The aspirin alone provides the antithrombotic benefit the genotype requires.

3. DHEA + IGF-1 production tendency

The trade-off: DHEA modestly raises IGF-1 (~10–15% in some studies). The genotype already loads IGF-1 production (3-SNP IGF1 hom + AKT1 hom + MTOR hom). Rapamycin is suppressing the net IGF-1 to 88 (good), but DHEA is mildly counter-rotating against the rapamycin goal.

Resolution: current IGF-1 is in target band. Continue DHEA at 25 mg. Re-evaluate if rapamycin dose changes — DHEA's IGF-1 effect may emerge more visibly. If IGF-1 trends below 60 ng/mL, drop DHEA first before adjusting rapamycin.

4. Vitamin D3 dose vs. VDR receptor saturation

The trade-off: 25(OH)D 84.6 is above the 50–60 ng/mL target band the bone report recommends given VDR f/f + BsmI/ApaI/TaqI hom (receptor-limited, not substrate-limited). Going higher confers no marginal benefit and approaches the threshold where Durup 2015 noted CV mortality U-shape.

Resolution: reduce standalone D3 from 5000 IU EOD to 2000 IU/day or 5000 IU twice weekly. The 50 mcg in Multi stays. Target 25(OH)D 50–60 ng/mL.

5. EPA-heavy omega-3 stack vs. DHA-specific need

The trade-off: current ~2+ g EPA + ~0.8 g DHA. EPA optimal at 57.6, DHA borderline at 84.3 (target >100). Adding more EPA does not fix DHA; flaxseed oil ALA is not converting (ALA below detection).

Resolution: add high-DHA algal oil 500+ mg DHA/day. Discontinue flaxseed oil. Optionally trim EPA dose modestly once DHA reaches >100. Re-test fatty acid panel in 3 months.

6. Boron cycling and CV / hormone monitoring

Minor trade-off: boron raises free T modestly. Already on dutasteride (DHT down → T+E2 up) so the absolute T values are already at upper-normal. Effect is not clinically meaningful at 6 mg cycled.

Resolution: continue cycled dosing. No change.

7. Doxycycline + Mg/Ca chelation

Practical: doxycycline absorption is reduced when co-administered with multivalent cations (Mg, Ca, Fe). Bone report explicitly flags this. Currently AM doxycycline + noon Multi (75 mg Mg + 25 mg Ca per dose) — separation is ~4 hours, adequate. PM doxycycline + PM Multi (75 mg Mg + 25 mg Ca per dose) — separation needs to be ≥2 hours.

Resolution: verify PM doxycycline and PM Multi are separated by ≥2 hours. If currently taken together, shift one slot.

Uncovered Needs — High-Priority Additions

Items not currently in the stack but recommended across multiple genetic reports. Priority reflects strength of mechanism, evidence, and convergence across reports.

HIGH priority (add)

Addition	Dose	Rationale
Methylcobalamin (sublingual)	1000–2000 µg/day	TCN2 P259R hom impairs active-B12 transport. Hcy 11.5 → 12.2 trending up despite TMG, MTHF, glycine, NACET — the methylation arm has a B12-side gap. Order holotranscobalamin to confirm.
Riboflavin (R5P preferred)	25–50 mg/day	Cofactor for thermolabile MTHFR C677T het (McNulty Circulation 2006). B2 whole-blood 206 µg/L mid-range, suboptimal. Multi 16.8 mg/day is below threshold.
High-DHA algal oil	500+ mg DHA/day	DHA 84.3 (borderline low) despite EPA-optimal stack. Dementia, BBB, PD, ADHD, Inflammation reports all flag DHA. Algal oil avoids adding more EPA.
Vitamin K2 (MK-7)	100–180 µg/day	Bone report: VKORC1 het + BGLAP het + COL1A1 burden. Multi has K1 only. Knapen 2013 RCT FN BMD benefit at 180 µg over 3 years.
Urolithin A (Mitopure or equivalent)	500–1000 mg/day	Mitochondrial: cumulative CoQ-pathway burden + SOD2 het + favorable PINK1/Parkin substrate genotype predicts above-average mitophagy response. RCT evidence (Singh Cell Rep Med 2022, Liu 2022) for muscle strength + endurance + plasma acylcarnitines + immune naïve T cell expansion (Denk 2025). Synergistic with rapamycin pulsed schedule.
Benfotiamine	150–300 mg/day	Glycation: GLO1 hom + AKR1B1 hom — benfotiamine activates transketolase and shunts triose phosphates away from MG generation upstream of the GLO1 bottleneck (Hammes Nat Med 2003). Not gated by any genotype carried.
Pyridoxamine	50–200 mg/day	Direct AGE-precursor scavenger (Voziyan & Hudson 2005). Bypasses CN1 carnosinase gating that the CNDP1 het places on L-carnosine. Mechanistically complementary to FN3K. Discuss US availability with physician.

MODERATE priority (consider)

Addition	Dose	Rationale
Curcumin (bioavailable form)	500–1000 mg/day (Meriva, BCM-95)	Inflammation report: secondary NRF2 lever + NF-κB inhibition (NFKB1 ins/del het + IKBKB het). Cancer Predisposition: CRC polyp reduction evidence. Phytosome forms achieve 20–30× serum levels vs. standard curcumin.
Trans-resveratrol	150–300 mg/day	Triple-flagged: Glycation (AKR1B1/GLO1), IGF-1 (FOXO3 unmasking via SIRT1), Rapamycin (FOXO3 + SIRT1 synergy). Note possible mTOR/sirtuin crosstalk with rapamycin — discuss timing with physician.
Alpha-lipoic acid (R-isomer)	300–600 mg/day	Glycation: dual NRF2 activation + AGE-formation inhibition. Mitochondrial: regenerates GSH. Insulin-sensitizing (introduce carefully given multi-agent glucose-lowering regimen).
Beta-alanine	4–6 g/day divided × 4 weeks loading	Strength + Endurance reports: SLC16A1 / MCT1 E490D hom — partial intramuscular H+ buffering compensation for impaired lactate shuttle. Best evidence 1–4 minute efforts.

Addition	Dose	Rationale
	then 2 g maintenance	
Hydroxocobalamin (alternative B12 form)	1000 µg every 2–4 weeks IM	Alternative if methylcobalamin oral does not lower Hcy. Hydroxocobalamin has longest tissue retention. Discussion point with physician — IM is more reliable than oral for raising holotranscobalamin.

LOW priority / situational

Addition	Dose	Rationale
L-carnosine (empirical 12-week trial)	2 g/day BID	Glycation: GLO1 hom + AKR1B1 hom — mechanistically near-ideal but partly gated by CNDP1 het (intermediate carnosinase activity). Empirical trial only — measure serum CML or fructosamine before/after; discontinue if no biomarker change.
Standalone P5P	25 mg/day	If pyridoxamine added separately. Maintains residual CTH activity (Homocysteine report).
Astaxanthin (additional)	6 mg/day	Already covered by MacuGuard. Additional dose only if specific need (athletic recovery, skin photoprotection).
Alpha-glycerylphosphorylcholine (alpha-GPC)	300–600 mg/day	Cognitive support / cholinergic precursor. No specific genetic argument. Optional for cognitive performance.

Genetically Suboptimal Alternatives — What to Avoid

A small number of "longevity-popular" or commonly-prescribed alternatives are specifically poor matches for this genotype. Listed here so they are explicitly off the table for this person — even if recommended generically elsewhere.

Alternative	What it is	Why it is genetically suboptimal here
Metformin	First-line T2D drug	Imeglimin was specifically chosen instead. Metformin depletes B12 over time — would compound TCN2 P259R hom transport vulnerability and Hcy 12.2 already elevated trend. The MTHFR het + SHMT1 hom + MTHFD1 het methylation pressure makes B12 status particularly important. Imeglimin supports the same metabolic targets via mitochondrial mechanism without depleting B12.
Folic acid	Synthetic folate (most US fortification + many supplements)	Genotype carries SLC19A1 het + MTHFD1 het + SHMT1 hom + MTHFR het. The folate-pipeline impairment is at every step; synthetic folic acid still requires DHFR reduction and the impaired pipeline to convert to active 5-MTHF. Quatrefolic 5-MTHF (which is in the Multi) bypasses the entire chain. Supplementing folic acid on top of 5-MTHF can saturate DHFR and produce un-metabolized folic acid in serum.
Cyanocobalamin	Most common B12 supplement form	Genotype carries TCN2 P259R hom (impaired active-B12 transport). Cyanocobalamin must be reduced to cob(II)alamin and methylated to methylcobalamin to enter the methylation cycle. With TCN2 hom, this conversion bottleneck is amplified. Methylcobalamin or hydroxocobalamin bypass the conversion step.
Simvastatin or atorvastatin	Common statin alternatives	CYP3A5*3/*3 + CYP3A4*1B hom + rapamycin sharing the same CYP3A pathway = compounded substrate burden. Pitavastatin is mostly UGT-cleared and has minimal CYP3A interaction — the right choice for this patient. Switching to simvastatin or atorvastatin would create avoidable PK interactions with rapamycin.
High-dose niacin (1–3 g)	Old-school lipid intervention	No genetic rationale here. Lipids excellent on Repatha + statin + ezetimibe. Niacin causes flushing, worsens insulin resistance (relevant given CDKAL1 hom + TBC1D4 het glucose burden), and the AIM-HIGH and HPS2-THRIVE trials failed to show CV benefit when added to statin therapy. Genetic profile does not justify the trade-offs.
Standalone berberine (raw form)	Trendy "natural metformin"	OCT1 (rs622342 + rs628031) double het + CYP3A interaction with rapamycin. Berberine inhibits CYP3A4 — would amplify rapamycin AUC unpredictably. Combined with the OCT1 het reducing hepatic uptake, berberine pharmacokinetics in this patient are poorly characterized. Not recommended given current regimen complexity.
NMN or NR alone (without addressing NRF2)	"NAD+ precursor" longevity supplement	Theoretical SIRT1/FOXO3 unmasking benefit, but does not address the keystone NFE2L2 hom (NRF2 promoter low-induction) finding that drives most of the convergent vulnerabilities. If added at all, only on top of sulforaphane (Avmacol). Also: theoretical interaction with rapamycin (mTOR/AMPK/sirtuin crosstalk) — discuss timing. Not a clear-win addition.
High-dose vitamin C (>2 g) or vitamin E (>400 IU) standalone	Old-school antioxidant supplementation	Glucose report explicitly cautions: mega-doses can blunt exercise-induced SOD2 upregulation (which is already compensating for SOD2 het). NRF2 activation via sulforaphane and substrate support via NACET + glycine + selenium are the targeted alternatives. Multi 400 mg vitamin C is adequate; tocotrienols 25 mg cover the vitamin E arm.
Finasteride	5-alpha-reductase type 2 inhibitor	Dutasteride (already prescribed) is a superset — inhibits both type 1 and type 2. Hair Loss report flags 4-SNP SRD5A1 + SRD5A2 hom — dual blockade is genotype-correct. Switching from dutasteride to

Alternative	What it is	Why it is genetically suboptimal here
		finasteride would lose the type-1 coverage.
Bempedoic acid	Upstream of HMG-CoA reductase via ATP citrate lyase	Was previously in regimen, replaced by Repatha. Bempedoic acid acts upstream of HMG-CoA reductase via synthesis blockade — does not directly address the PCSK9/MYLIP receptor-degradation axis identified as the dominant genetic lesion. Repatha's LDLR-preservation mechanism is the better genotype match. UGT2B7*2 hom would also modestly affect bempedoic acid glucuronidation.
Sulfonylureas (glipizide, glyburide)	Insulin secretagogue	KCNJ11 / ABCC8 KATP channel genetics are favorable for sulfonylurea response BUT genetic burden in beta-cell function (CDKAL1 hom + INS rs689 hom + IFIH1 hom) makes sulfonylurea-driven secretion problematic — risk of accelerating beta-cell exhaustion. Hypoglycemia risk additive with other glucose-lowering agents. Imeglimin / tirzepatide / empagliflozin combination is the right choice.
Standard β-blockers (metoprolol, bisoprolol)	Common antihypertensives	ADRB1 Gly389/Gly389 hom (Sleep, PGx reports) predicts blunted β1 response; if ever needed, prefer nebivolol or bisoprolol over carvedilol/metoprolol, but expect blunted response regardless. Telmisartan 80 mg is the right antihypertensive choice for this genotype — already in regimen.
Bisphosphonates (alendronate etc.)	Bone resorption inhibitor	STRONG CAUTION: Bone report explicitly flags persistent low ALP (30 → 40, below new reference 47–123) as warranting ALPL coding-region screening for adult-onset hypophosphatasia BEFORE any bisphosphonate decision. Hypophosphatasia is a relative contraindication. Get the genetic screen first if BMD ever indicates osteoporosis treatment.
Aromatase inhibitors	Estrogen-suppressing	Bone report flags as cautious-territory: with intermediate aromatase (CYP19A1 het) + lower-mid E2 (29) + bone matrix burden (COL1A1, OPG-RANKL), aromatase inhibitor would compound bone risk significantly. Mandatory bone-protective coverage if ever indicated.
Glucocorticoids (chronic supraphysiologic)	Anti-inflammatory class	Bone report: amplifies OPG deficit. PTPN22 hom autoimmune risk is a separate issue that may someday push toward steroids — but use the lowest effective dose for the shortest duration with bone-protective coverage if needed.
Iron supplementation (without lab evidence of deficiency)	Generic iron pills	TMPRSS6 V/V hom raises hepcidin set-point and lowers iron absorption — supplementation is needed only if labs show genuine iron-restricted erythropoiesis. Current ferritin 80, TSAT 32% adequate. PD report flags HFE H63D het + SLC11A2 hom + GPX4 het — gratuitous iron supplementation would add to iron-handling burden without benefit. Add iron only if reticulocyte hemoglobin (CHr) < 28 pg or ferritin < 50 with symptoms.
St John's wort	Herbal antidepressant	Strong CYP3A4 inducer — would dramatically reduce rapamycin AUC unpredictably. Avoid.
Grapefruit juice (large volumes)	Common dietary item	Strong CYP3A4 inhibitor — produces larger-than-typical AUC spike for rapamycin given CYP3A5*3/*3 + CYP3A4*1B hom genotype. Small amounts OK; avoid large volumes especially around rapamycin dose days.

Suggested Lab Monitoring

Tests prioritized by their power to confirm or revise the highest-stakes genotype-driven hypotheses. Items already in routine panels are not repeated.

HIGH priority — open questions to resolve

Test	Rationale
Holotranscobalamin (active B12)	Directly tests the TCN2 P259R hom prediction. Serum B12 1127 may overestimate functional availability. The most important single test to add given Hcy 11.5 → 12.2 trend. Herrmann Clin Chem 2003 validated as superior to total B12 for functional deficiency.
Anti-TPO + anti-thyroglobulin	PTPN22 R620W hom is the strongest common autoimmune risk variant. HLA counterweight absent for thyroid axis. Baseline antibody titers establish whether subclinical autoimmunity is present. Annual TSH/T4 stable so far.
Fasting C-peptide	Beta-cell reserve independent of tirzepatide GLP-1 effect. HOMA-B confounded by incretin therapy. Direct measurement clarifies the CDKAL1 hom + INS hom + IFIH1 hom secretory deficit reserve.
Whole-blood or RBC glutathione (GSH/GSSG ratio)	Direct measurement of the 6-report bottleneck (CTH hom + NFE2L2 hom + GLO1 hom + AKR1B1 hom + GSTP1 hom + NQO1 het). Establishes baseline before NACET escalation; quantifies response. Doctor's Data, Genova, or academic centers offer this.
IGF-1 trend + IGFBP-3	Continue serial IGF-1 (currently 88, dropped from 115 in 6 months). IGFBP-3 baseline establishes molar ratio interpretation given all-heterozygous IGFBP3 variants. Further IGF-1 decline below ~65 ng/mL warrants rapamycin dose discussion.
Anti-GAD65 antibody (+ optionally IA-2A, ZnT8A)	Glucose report flags as HIGH priority: combination of homozygous INS rs689 + IFIH1 + heterozygous SH2B3 + PTPN22 hom is a non-trivial autoimmune-flavored T1D/LADA signature. Positive anti-GAD would reframe diagnosis from T2D toward LADA.

MODERATE priority — establish baseline

Test	Rationale
Coronary artery calcium (CAC) score	One-time imaging. With 9p21 dual het + PCSK9 GOF hom + MYLIP hom, the most prognostically informative single CV imaging test. Zero is reassuring; non-zero would reshape therapy intensity.
Retinal OCT + fundus imaging	CFH Y402H hom + second CFH hit = AMD homozygous OR ~4.6 (the largest common-variant effect in human GWAS in this profile). MacuGuard is prophylactic; baseline imaging establishes surveillance point. Retina specialist referral.
Bone-specific ALP (or P1NP + β-CTX)	Persistent low total ALP (30 → 40, below new ref 47–123) needs interpretation: low bone turnover (rapamycin/statin signal) vs. ALPL-coding pathology. P1NP/CTX ratio reports formation:resorption coupling — given OPG-deficit cluster predicts elevated CTX.
ALPL coding-region sequencing	If ALP stays below 47 across multiple draws. Adult-onset hypophosphatasia screening is required BEFORE any future bisphosphonate decision. Send-out clinical genetics lab.
Fructosamine repeat	First measurement 239 was supportive of the A1c glycation gap interpretation (FN3K hom-favorable). Second draw solidifies CGM-first glycemic targeting strategy.
24-hour ambulatory BP monitoring (ABPM)	Confirm telmisartan 80 mg evening provides 24-hour coverage with preserved nocturnal dipping. Sleep report's favorable autonomic profile (GNG11 + RGS6 hom) predicts dipping is preserved — verify.

Test	Rationale
DEXA + body composition	Bone report HIGH-priority if not done in last 24 months. Lean-mass tracking on rapamycin + tirzepatide every 6 months — informs the rapamycin × resistance-training timing hypothesis (Strength report).
Home sleep apnea test (HSAT) or in-lab PSG	Sleep report HIGH-priority: BMI-independent OSA susceptibility (NACA + ABCC9 + LPAR1 het cluster) at age 62. Highest-yield single sleep investigation.
Ferritin / TSAT / sTfR / Reticulocyte Hemoglobin	Baseline before any training-volume escalation given TMPRSS6 V/V hom + IL6 high-producer + BTBD9 het. Target ferritin >75 ng/mL (AASM 2025 RLS threshold).
Repeat fatty acid panel (Boston Heart) at 3 months	After adding high-DHA algal oil + discontinuing flaxseed oil. Confirm DHA crosses the >100 µg/mL threshold.
Repeat homocysteine + RBC folate at 8–12 weeks	After adding methylcobalamin + R5P. Hcy should drop toward <10 if the methylation gap is closed. RBC folate stable confirms 5-MTHF ongoing.
Trough sirolimus level	One-time, day 7 of rapamycin cycle. CYP3A5*3/*3 + CYP3A4*1B hom predict ~15–30% higher AUC than CYP3A5 expressers. Establishes that 12 mg q3wk dose is in target band.
Plasma copper trend	RBC copper 0.55 lower-normal. If zinc 15 mg from Multi continues + any zinc bisglycinate increase, recheck copper at 6–12 months.

LOW priority / situational

Test	Rationale
ANA / anti-CCP / RF baseline	PTPN22 hom autoimmune burden context. One-time screen if no symptoms; not urgent.
ADMA / SDMA	Endothelial NO bioavailability functional marker. Was ordered Jun 2025 (forwarded to outside lab). Rerun if needed.
GGT trend	Endurance report: most accessible peripheral readout of glutathione turnover. Particularly relevant given confirmed NFE2L2 hom.
OxPL-apoB	Apolipoprotein addendum: emerging biomarker, consider once for completeness given the very-high CV risk genotype.
Lactate threshold (graded exercise test)	Endurance report: directly measures functional consequence of MCT1 E490D hom. Informs pacing strategy. Lab-of-opportunity if a sports-medicine clinician is involved.
UPSIT-40 olfactory testing	PD report: hyposmia is the earliest premotor PD biomarker. Baseline at next visit; repeat every 2–3 years from age 65.
Hearing test	Lancet 2024 Commission: largest single modifiable dementia risk factor. Baseline + intervention if any signal.
Sex hormone trajectory (T, E2, SHBG, DHEA-S)	Free T 11.3 confirmed adequate (Jan 21 recheck). Annual is adequate unless symptoms develop.
NAD+/NADH ratio	If NAD precursor is ever added. Otherwise low priority.

Top Priority Summary — The Eight Highest-Leverage Actions

Synthesis of every section into the highest-leverage discussion items for the next physician visit. Ranked by expected effect size × confidence × downside protection.

#	Action	Why this is the highest-leverage move
1	Add methylcobalamin 1000–2000 µg/day sublingual (or hydroxocobalamin 1000 µg IM 2–4 weekly) + R5P 25–50 mg/day	Closes the only methylation gap not yet covered. TCN2 hom + Hcy 12.2 rising = clear genotype-aligned, lab-justified intervention. Order holotranscobalamin to confirm the prediction. Cheap, low-risk, lab-trackable in 8–12 weeks.
2	Add high-DHA algal oil 500+ mg DHA/day, discontinue 1 g flaxseed oil	Boston Heart panel shows ALA below detection (flax not converting) and DHA borderline at 84.3. DHA gap impacts Dementia, BBB, PD, ADHD, Inflammation arms. Re-test fatty acid panel at 3 months.
3	Increase NACET to 400–500 mg/day OR add NAC 600 mg	Single most cross-report-relevant change (still). 6-report glutathione bottleneck (CTH hom + NFE2L2 hom + GLO1 hom + AKR1B1 hom + GSTP1 hom + NQO1 het) makes cysteine the rate-limiting input. Order RBC GSH baseline before changing dose.
4	Discontinue nattokinase 12000 FU	No genetic rationale (no inherited thrombophilia). Additive bleeding risk with aspirin. Weak evidence base. Removing this simplifies the regimen and reduces bleeding risk without losing genotype-aligned protection.
5	Step down melatonin from 5 mg to 1–3 mg PM	Five separate reports flag the supraphysiologic dose. No genetic argument for high dose (MTNR1B clean, CLOCK clean). Sleep onset benefit at 1–3 mg is roughly equivalent.
6	Add vitamin K2 (MK-7) 100–180 µg/day	Bone report finding: VKORC1 het + BGLAP het + COL1A1 burden. Multi has K1 only — direct gap. K2 directs calcium to bone, away from arterial wall.
7	Down-titrate vitamin D3 to maintain 25(OH)D in 50–60 ng/mL band	Current 84.6 is above target band. VDR receptor saturation (FokI + BsmI/ApaI/TaqI hom) means substrate beyond saturation confers no additional benefit. Reduce standalone D3 to 2000 IU/day or 5000 IU twice weekly.
8	Order the priority lab workup: holotranscobalamin, anti-TPO + anti-Tg, fasting C-peptide, RBC glutathione, IGF-1 + IGFBP-3, retinal OCT, CAC score, bone-specific ALP	Each test answers a specific genotype-driven open question. Holotranscobalamin and anti-TPO are the highest-priority new orders. CAC + retinal OCT are the highest-priority one-time imaging.

Items already optimized — do not change

- Repatha switch (already done) is the most genetically aligned change possible — homozygous PCSK9 GOF is the genetic mirror of the LoF that validated the drug class.
- Imeglimin chosen instead of metformin is textbook PGx (avoids B12 depletion given TCN2 hom + MTHFR het).
- Tadalafil + l-citrulline pairing is the most complete pharmacology-supplement match for the 4-gene NO convergence.
- Pulsed rapamycin is lab-confirmed working (IGF-1 115 → 88) on the genetically elevated set-point.

- Avmacol Extra Strength at 4 caps/day is the keystone NRF2 intervention for the 6+-report NFE2L2 hom finding — form (myrosinase-active) and dose (~30 mg sulforaphane equivalents) both correct.
- Quatrefolic 5-MTHF in Multi is the textbook-correct folate form for the 5-gene folate pipeline impairment.
- Pitavastatin specifically (not rosuvastatin or atorvastatin) is the right statin choice given the CYP3A pathway burden from rapamycin co-handling.
- Telmisartan 80 mg PM (not a β-blocker) is the right antihypertensive choice given ADRB1 Gly/Gly hom predicted blunted β-blocker response.
- MacuGuard addresses the single highest-effect common-variant in the entire profile (CFH Y402H hom AMD OR ~4.6).
- TMG 2.5 g feeds the BHMT-mediated remethylation backup pathway — the only homocysteine-clearance arm that is genetically intact.

Final Notes

What this report is. A synthesis of 21 genetic reports + 3 lab timepoints applied to the May 2026 medication and supplement list. The goal was to evaluate every item against the cumulative genotype, identify uncovered needs, flag genetically suboptimal alternatives, and propose a focused monitoring panel. The structure deliberately makes the genotype-supplement-lab logic explicit so each recommendation can be evaluated, not just accepted.

What this report is not. It is not medical advice and not a prescription. Every prescription medication change must be reviewed with the treating physician. The supplement recommendations are framed as discussion points to bring to that visit. The "Tier 5 — Reconsider" items in particular are recommendations to discuss, not to act on unilaterally.

Confidence calibration. Individual genetic variants typically confer per-allele odds ratios of 1.1–1.4. Clinical significance arises from cumulative patterns and gene-environment interactions, not from any single SNP. The strongest claims in this document rest on multi-report convergence (NRF2/glutathione bottleneck, methylation pressure, NO-signaling convergence, IGF-mTOR loading) plus lab-confirmation of the predicted phenotype. The weakest claims are isolated mechanistic findings without lab biomarker confirmation — these are flagged as "discuss" rather than "act on."

Maintenance schedule. Re-run this analysis annually or when (a) a new genetic finding emerges, (b) a clinically significant lab value changes, or (c) any prescription medication is added or removed. The Integrated Regimen Analysis (April 2026) and this update (May 2026) demonstrate the value of periodic re-synthesis as the underlying data evolve.

Key references. Cohen NEJM 2006 (PCSK9 LoF Mendelian); Sabatine NEJM 2017 FOURIER; Mannick Sci Transl Med 2018 (PEARL rapamycin); McNulty Circulation 2006 (B2/MTHFR); Klein Science 2005 + AREDS2 JAMA 2013 (CFH/AMD); Otvos Clin Chem 2015 (GlycA); Brosnan Annu Rev Nutr 2007 (creatine/SAM); Schwedhelm Br J Clin Pharmacol 2008 (citrulline); Burdge Reprod Nutr Dev 2005 (ALA conversion); Donlon 2018 (FOXO3); Shaw AJCN 2017 (collagen + vit C timing); Singh Cell Rep Med 2022 + Liu 2022 (urolithin A); Hallakou-Bozec Diabetes Obes Metab 2021 (imeglimin); Naghii J Trace Elem Med Biol 2011 (boron); Liggett PNAS 2006 (ADRB1); Mach Eur Heart J 2020 (ESC/EAS dyslipidemia); Sniderman JAMA Cardiol 2019 (ApoB); Kim Nat Commun 2020 (empagliflozin/NLRP3); Bolland BMJ 2015 (Ca supplementation CV); Knapen 2013 (K2 BMD); Herrmann Clin Chem 2003 (holotranscobalamin); Hammes Nat Med 2003 (benfotiamine); Voziyan & Hudson 2005 (pyridoxamine); Xue Diabetes 2012 (sulforaphane GLO1); Stranges 2007 (selenium upper limit); Durup 2015 (vitamin D upper limit).

Disclaimer. *This is an educational discussion document, not medical advice. All recommendations should be reviewed with physician before any change to medications or supplements. The interpretation of genetic variants reflects current GWAS literature; effect sizes are probabilistic and clinical translation depends on cumulative pattern, not single SNPs. No genetic test result should be interpreted as deterministic.*