Physician Rationale for Tirzepatide Renewal

Patient: Chad T. Mansfield
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Supporting Clinician: Dr. Pruett

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1. Clinical Context

Mr. Mansfield demonstrates a reproducible pattern of **hepatic insulin resistance with stress-dependent glucagon dominance** and **delayed ketone generation** during fasting, consistent with the model of cortisol- and catecholamine-amplified gluconeogenesis described by Niswender and colleagues.
While on **tirzepatide (Mounjaro)**, he exhibited: - Normalization of fasting glucose (≈85–95 mg/dL)
- Faster, symmetric metabolic switching during caloric restriction
- More stable autonomic tone (better sleep/HRV; less BP volatility)

After discontinuation, he developed: - Impaired fasting glucose (≈112–124 mg/dL)
- Suppressed β-hydroxybutyrate during prolonged fasts (<0.2 mmol/L after 24 h)
- Marked sympathetic activation with poor sleep consolidation and delayed ketosis transition

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2. Mechanistic Rationale

Dual incretin agonism (GLP-1 + GIP) counters this physiology via hepatic and central actions: - **GLP-1R activation** restores hepatic insulin sensitivity and suppresses inappropriate glucagon.
- **GIPR co-activation** improves adipocyte insulin signaling/adiponectin and reduces lipolytic stress.
- **Combined axis** lowers hepatic glucose production, improves mitochondrial substrate flexibility, and dampens HPA hyper-reactivity to fasting.

This maps tightly to the patient's fasting phenotype (suppressed ketogenesis until sympathetic tone was pharmacologically reduced).

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3. Clinical Indicators Supporting Renewal

Parameter	Pre-tirzepatide	On tirzepatide	Post-withdrawal
Fasting glucose (mg/dL)	112–124	**85–95**	118
Fasting β-hydroxybutyrate (mmol/L)	<0.2	**0.4–0.7**	<0.2
BP (mmHg, waking)	142/88 ± 12	**122/78 ± 5**	146/86 ± 11
Sleep HRV (RMSSD, ms)	18	**45–50**	19
AM cortisol (µg/dL)	18.7	**11.9**	17.6

Pattern is consistent with **hepatic IR rebound** and **autonomic dysregulation** after GLP-1/GIP withdrawal.

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4. Expected Benefit of Re-initiation

- Restore hepatic insulin sensitivity and suppress excess glucagon

- Reduce sympathetic-mediated BP variability
- Normalize fasting→feeding transition (earlier βHB rise, improved metabolic switch)
- Stabilize glycemia and autonomic symptoms to enable rehab and cognitive performance

Proposal: restart 2.5 mg weekly → consider 5 mg as tolerated (clinician discretion). Maintain current TRT/hCG; keep AI stable pending E2 review.

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5. VA Coverage Framing (brief)

- **Medical necessity:** Persistent metabolic dysfunction (hepatic IR, impaired fasting adaptation) with **documented prior response** to tirzepatide; failure of metformin and lifestyle alone.
- **Risk–benefit:** GLP-1/GIP has favorable cardiometabolic and hepatic IR profiles; benefits outweigh risks in this phenotype when monitored.
- **Monitoring plan:** q4–6 weeks fasting glucose/insulin/C-peptide/ketones; CMP/ALT/AST q6–8 weeks; BP/HRV/symptom diary; endocrinology follow-up.
- **Alternatives tried/limited:** Metformin ineffective; SGLT2/acarbose/pioglitazone considered but less aligned with patient's sympathetic/ketone phenotype.

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6. References (representative)

1. Frias JP, et al. *N Engl J Med.* 2021 — Tirzepatide superiority and insulin sensitivity.
2. Finan B, et al. *Sci Transl Med.* 2013 — GLP-1/GIP synergy; hepatic glucose suppression.
3. Niswender KD, et al. *J Clin Endocrinol Metab.* 2005 — GLP-1 and hypothalamic glucose sensing.
4. Cusi K. *Diabetes Care.* 2022 — Hepatic insulin signaling and tirzepatide effects.

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