I) RESEARCH PROPOSAL

MHPG TESTING AS A BIOMARKER IN PSYCHIATRY: TOWARD PRECISION DIAGNOSIS AND TREATMENT

Applicant: Percy Naranjo, MD, MPH
Proposed Program: Doctoral Degree in Psychiatry/Neuroscience
Institution: University of California – ___ / University of Florida
Title: *MHPG Testing as a Biomarker in Psychiatry: Toward Precision Diagnosis and Treatment*

1. Background and Rationale

Psychiatry still lacks reliable biological markers to complement clinical observation. 3-Methoxy-4-hydroxyphenylglycol (MHPG), the principal metabolite of norepinephrine, reflects central noradrenergic activity. Research has linked MHPG to depression, bipolar disorder, schizophrenia, and suicidality, yet its practical use in clinical psychiatry remains unvalidated.

Establishing MHPG as a biomarker could help predict treatment response, identify high-risk patients, and refine diagnostic subgroups. This aligns with the broader movement toward **precision psychiatry**.

2. Research Question and Hypotheses

Research Question: Can MHPG serve as a clinically useful biomarker for diagnosis and treatment response in major psychiatric disorders?

Hypotheses:

1. Baseline MHPG levels differ between MDD, bipolar disorder, and schizophrenia.
2. Longitudinal changes in MHPG correlate with treatment response.
3. Lower MHPG levels predict suicidality risk.

3. Objectives

- **Primary:** Assess diagnostic and prognostic value of MHPG testing in psychiatric patients.
- **Secondary:**
    - Compare plasma vs. CSF measurements.
    - Explore correlations with standard psychiatric rating scales.
    - Evaluate MHPG as a predictor of suicidality.

4. Methods

Design: Prospective, observational study.
Participants: Adults (18–65) with MDD, bipolar disorder, or schizophrenia (DSM-5), plus matched healthy controls. Estimated N ≈ 60–80 per patient group + 40 controls.
Procedures:

- Baseline: psychiatric assessment, rating scales (HAM-D, YMRS, PANSS), plasma MHPG measurement.

- Follow-up: repeat MHPG at 4, 8, 12 weeks of treatment.
- Subset: optional CSF sampling.
  Analysis: ANOVA/regression for group differences, ROC analysis for predictive utility.

5. Ethical Considerations

- IRB approval and informed consent required.
- HIPAA compliance for confidentiality.
- Suicide-risk participants safeguarded through clinical monitoring and referral.

6. Expected Outcomes

- Clarify diagnostic differences in MHPG across disorders.
- Determine whether MHPG changes track with treatment response.
- Provide groundwork for integrating biomarkers into psychiatric practice.

7. Significance

This study may establish MHPG as a clinically valuable biomarker. Potential applications include:

- Improving diagnostic precision.
- Predicting pharmacological response.
- Identifying high-risk patients earlier.
- Contributing to the field of **precision psychiatry**.

8. Applicant's Preparation

- MD with training in pathology and psychiatry.
- Licensed physician in **California and Florida**.
- MPH with expertise in clinical research design and epidemiology.
- Positioned to bridge laboratory science, psychiatry, and translational research.

9. Timeline (3–4 Years)

- Year 1: Protocol refinement, IRB approval, pilot data.
- Years 2–3: Recruitment and data collection.
- Year 4: Data analysis, publications, dissertation.

Selected References

- Maas JW. *The Metabolism of Norepinephrine in Human Subjects: Studies with MHPG.* Arch Gen Psychiatry. 1975.

- Mann JJ et al. *Biological markers in suicide and depression.* CNS Spectrums. 2006.
- Meyer JH, et al. *Biomarkers in Psychiatry: Toward Precision Medicine.* J Clin Psychiatry. 2017.

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II) RESEARCH PROPOSAL

SALIVARY MHPG AS A NON-INVASIVE BIOMARKER OF STRESS-RELATED DISORDERS

Applicant: Percy Naranjo, MD, MPH
Proposed Program: Doctoral Degree in Psychiatry/Neuroscience
Institution: University of California – ___ / University of Florida
Title: *Salivary MHPG as a Non-Invasive Biomarker of Stress-Related Disorders*

1. Background and Rationale

Stress-related disorders (generalized anxiety disorder, panic disorder, PTSD) are prevalent, disabling, and often underdiagnosed. Objective biomarkers are lacking; diagnosis relies mainly on subjective self-report and clinical scales.

3-Methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, reflects locus coeruleus activity. While plasma and CSF MHPG have been studied in mood and psychotic disorders, less is known about **salivary MHPG**.

Saliva testing offers a non-invasive, repeatable, and patient-friendly alternative. If validated, salivary MHPG could support real-time monitoring of stress and anxiety states, with applications from clinical psychiatry to mobile health tools.

2. Research Question and Hypotheses

Research Question: Can salivary MHPG serve as a biomarker for stress-related psychiatric disorders, including anxiety and panic disorder?

Hypotheses:

1. Patients with panic disorder, generalized anxiety disorder, or PTSD exhibit higher baseline salivary MHPG than healthy controls.
2. Salivary MHPG levels increase during acute anxiety/panic episodes.
3. Salivary MHPG changes correlate with validated stress/anxiety rating scales.

3. Objectives

- **Primary Objective:** Assess the utility of salivary MHPG in differentiating patients with stress-related disorders from healthy controls.

- **Secondary Objectives:**
    - Measure acute salivary MHPG changes during laboratory stress tests.
    - Correlate salivary MHPG with established scales (HAM-A, CAPS-5, Panic Disorder Severity Scale).
    - Explore feasibility of portable salivary MHPG testing for real-world monitoring.

4. Methods

Design: Case-control + stress-provocation study.

Participants:

- N ≈ 120 (40 anxiety disorders, 40 PTSD/panic disorder, 40 controls).
- Inclusion: DSM-5 diagnosis, age 18–65.
- Exclusion: major medical illness, substance abuse, medications affecting noradrenergic metabolism.

Procedures:

- **Baseline saliva collection** (morning, standardized conditions).
- **Stress provocation:** Trier Social Stress Test (TSST) or equivalent standardized challenge.
- **Follow-up collections:** immediately after, +20 min, +60 min.
- **Measures:** salivary MHPG (HPLC or ELISA), psychological scales.

Analysis:

- Group comparisons (ANOVA, regression).
- ROC analysis for diagnostic accuracy.
- Within-subject analysis of stress-provoked changes.

5. Ethical Considerations

- IRB approval required.
- Stress tasks limited to validated, safe paradigms.
- Informed consent with clear disclosure of procedures.

6. Expected Outcomes

- Establish baseline salivary MHPG differences between stressed and control populations.
- Show acute sensitivity of MHPG to stress challenges.

- Demonstrate feasibility of non-invasive biomarker monitoring in psychiatry.

7. Significance

- Non-invasive biomarker development could transform stress-related psychiatry.
- Salivary MHPG testing could be adapted into **point-of-care devices** (similar to glucose strips), enabling **real-time monitoring** in clinics, emergency rooms, or even home settings.
- This translational research bridges neuroscience, psychiatry, and public health innovation.

8. Applicant's Preparation

- MD with training in pathology and psychiatry.
- Medical licenses in **California and Florida**.
- MPH with research and epidemiology expertise.
- Strong foundation for laboratory–clinical integration.

9. Timeline (3–4 Years)

- Year 1: Assay optimization, pilot saliva studies.
- Years 2–3: Full cohort recruitment, stress-challenge experiments.
- Year 4: Data analysis, publications, dissertation.

Selected References

- Maas JW, Hattox SE. *Plasma and Saliva MHPG: Correlates in Human Stress Response.* Biol Psychiatry, 1989.
- Southwick SM, et al. *Neurobiology of Posttraumatic Stress Disorder.* J Clin Psychiatry, 1999.
- Strawn JR, et al. *The Neurobiology of Anxiety Disorders: Noradrenergic Contributions.* CNS Drugs, 2010.