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How Should Persistent Symptoms Not Fully Explained by Diagnosis Be Studied? A Protocol for Scope, Observational Language, and Dual-Track Safety

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Abstract

Some patients continue to experience symptoms and impaired daily function after receiving a diagnosis or completing multiple investigations. These experiences arise in different situations—including residual symptoms of established disease, an evolving differential diagnosis, functional syndromes, and changes after infection or treatment—and should not be collapsed into one cause or a new disorder. This protocol proposes a way to preserve those differences while observing features that diagnostic labels may miss: sequence of onset, symptoms that change together, daily context, loss of function, and response to treatment over time. Two paths remain active. One continues appropriate medical differential diagnosis and reassessment as symptoms, red flags, and trajectories change. The other records patient-important symptoms and function, treatment exposure, and harm without waiting for perfect diagnostic closure. Contemporary research and lived experience are read alongside East Asian primary texts, commentaries and cases, and Korean, Chinese, and Japanese clinical traditions without assuming that their concepts are equivalent. Whether Korean-medicine observations add value must be tested by asking if they improve reproducibility, prediction, or clinical decisions beyond diagnoses and standard measures alone. This is a research design, not a screening tool, treatment recommendation, or efficacy claim.

Keywords: persistent physical symptoms · diagnostic uncertainty · multisystem symptoms · longitudinal phenotyping · Korean medicine · patient-important outcomes

Which patient experiences are we trying to study?

Diagnosis is essential for detecting risk, selecting treatment, and communicating between clinicians. A single label, however, does not fully encode symptom sequence, coupled variation, triggers and relievers, functional loss, interactions among multiple conditions, or individual treatment response. This protocol designs a complementary structure for studying clinical information that remains after diagnosis; it does not replace diagnostic classification.

“Diagnostic remainder” is not the name of a disease or patient group. It is a meta-term for an observational space under-described by current classifications, specialties, and records. Persistent physical symptoms, medically unexplained symptoms, functional somatic disorders, and ICD-11 bodily distress disorder differ in definition and theoretical commitment and will not be used interchangeably.

Questions this research must answer

- Create a versioned terminology ledger of definitions, scope, overlap, and stigma risks in contemporary terms.
- Define research strata that do not collapse heterogeneous states into one cause, including rules for movement between strata over time.
- Formalise dual-track safety that maintains diagnostic openness alongside symptom- and function-focused therapeutic research.
- Develop a minimum longitudinal observational grammar beyond labels and symptom sums, then evaluate feasibility.
- Test the reproducibility and incremental clinical decision value of Korean-medicine observations beyond baseline models.

Keeping different causes distinct

Strata are not mutually exclusive diagnoses. A person may occupy more than one or move between them over time. Analyses will report stratum-specific and pooled results together.

- Residual or disproportionate symptoms with established disease
- Evolving differential diagnosis, including early, intermittent, rare, or progressive disease
- Recognised functional syndrome or disorder
- Post-infectious, post-injury, treatment-related, or medication-related state
- Symptom clusters varying together across body systems
- Phenotypes dependent on activity, posture, sleep, meals, temperature, menstruation, work, or other contexts
- Explanatory gaps arising from fragmented records, specialty silos, or access to care

Two paths: continuing diagnosis while caring for symptoms

Track A continues differential diagnosis, investigation, referral, and reassessment in response to new symptoms, red flags, objective progression, and changing trajectories. Condition-specific red flags will link to current specialist guidance and referral pathways rather than a new universal checklist. Previous normal investigations do not close later reassessment.

Track B records patient-important symptoms and function, life context, treatment exposure, adverse events, and reasons for discontinuation without waiting for perfect diagnostic certainty. Improvement does not establish diagnosis or mechanism; natural variation, regression to the mean, expectation, selection, concurrent treatment, and confounding by indication must be considered. Neither track closes the other.

What should be observed over time?

Events and relations are preserved instead of compressed into one score. Candidate v0.1 fields include symptom onset, offset, intensity, quality and body region; diurnal, seasonal, menstrual, and peri-infectious timing; coupled and sequential symptoms; triggers and relievers; patient-selected functional goals; necessary objective observations; Korean-medicine examination items; treatment composition, dose, duration, changes and co-interventions; patient-important outcomes and harms; and missingness and reliability.

- Use cognitive interviews to examine patient language and recording burden.
- Separate inter-rater and intra-rater reliability from temporal stability and responsiveness.
- Match observation frequency to symptom timescale and burden, without post-hoc optimisation.

How different knowledge traditions are read together

Contemporary clinical epidemiology, physiology, pharmacology, qualitative research, lived experience, East Asian primary texts, commentaries and cases, Korean medicine, Chinese clinical traditions and formula/herb-presentation approaches, and Japanese Kampo are searched as independent lanes. Editions, translations, commentaries, and later reconstructions remain separate, and every substantive claim links to a source and passage.

Relations are typed as quotation, inheritance, transformation, clinical exemplification, analogy without correspondence, operational correspondence, support, qualification, contradiction, mechanistic bridge, or testable translational hypothesis. Lexical or impressionistic similarity cannot establish identity between classical concepts and modern mechanisms.

Does this approach actually lead to better decisions?

The first stage scopes terminology and observation-set feasibility; it is not an efficacy analysis. Later discovery and confirmation data will be separated, with bootstrap stability, temporal validation, and external-site validation planned to limit unstable clustering. Missing-data mechanisms and multiplicity will be disclosed, and exploratory subgroups will not be labelled established phenotypes.

Baseline models comprise diagnoses, standard symptom and function measures, necessary investigations, and routine clinical information. Temporal, contextual, network, and Korean-medicine observations are added sequentially. Evaluation includes calibration, Brier score, decision-curve net benefit, patient-important outcomes, harms, and between-site reproducibility—not discrimination alone. Candidate fields are retired if they add no value or increase harm.

Patient safety and open assessment

The current stage concerns public literature and study design only. Patient-level data, research reuse of existing charts, prospective registries, biospecimens, and digital tracking will not begin before separate ethics review, consent or waiver justification, data minimisation, access controls, and retention and destruction plans.

Advancement to v1.0 requires review by independent clinicians, methodologists, source-text and case experts, and people contributing lived-experience perspectives. Public critiques, author responses, and revision history remain linked to the same research object. Baekrokdam's local experience is labelled a source of questions and is not promoted into evidence of representativeness, causality, or efficacy.

When this research should stop or change course

- Reduce or retire the observational grammar if it adds no information about patient-important outcomes or decisions beyond diagnoses and standard measures.
- Do not use phenotypes clinically if they do not reproduce across assessors, time, and sites.
- Exclude Korean-medicine observations from the intended use if they fail to improve calibration or decision utility, or increase harm.
- Outputs include a terminology ledger, phenomenon-vocabulary atlas, minimum observation set, negative and counter-hypothesis maps, feasibility study, validation protocol, and public assessment record.

Declarations

Author contributions (CRediT)	Yeonseung Choe: Conceptualization, Methodology, Clinical framing, Research-system design · Baekrokdam Research Commons (BRC): Investigation, Data curation, Writing – original draft
Data availability	This stage uses public literature only. The terminology ledger, retrieval log, source–passage–claim relations, and protocol amendments are intended for release with the outputs. No patient data have been collected.
Funding	No external funding.
Competing interests	Baekrokdam Research Commons (BRC) originated at Baekrokdam Korean Medicine Clinic and has associated clinical and operational interests. Local observations and Korean-medicine treatment hypotheses are not treated as evidence before independent external review and separate effectiveness testing.
AI use disclosure	AI tools assisted search planning, candidate-source organisation, structuring, and drafting. AI is not an author. Human editors remain responsible for citation existence, content and fitness, clinical safety, and final judgments. Prompts and material change records are intended for release with formal v1.0.
Ethics	This work concerns public literature and study design and contains no patient data. Chart audits, registries, interviews, biospecimens, and digital tracking will not begin before separate ethics review and privacy design.

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