

Longitudinal Study of Post-Infectious Syndromes

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ABSTRACT

Post-infectious syndromes (PIS) -- persistent symptoms lasting weeks to months after resolution of the acute infection -- have been recognised for decades in the wake of Epstein-Barr virus, Q fever, Ross River virus, and Lyme disease, but the COVID-19 pandemic brought the phenomenon into sharp public and clinical focus under the umbrella of Long COVID. Despite growing awareness, the natural history, risk factors, and pathophysiological mechanisms of PIS remain poorly characterised, partly because most studies are cross-sectional snapshots rather than prospective longitudinal tracking. We conducted a 12-month prospective cohort study following 2,314 adults after acute infections -- 1,186 post-COVID-19, 428 post-influenza, 312 post-EBV mononucleosis, and 388 post-bacterial pneumonia -- across four European academic medical centres (Rome, Stockholm, Vienna, and Zurich) between April 2020 and March 2022. Patients were assessed at 1, 3, 6, and 12 months using standardised symptom inventories, functional assessments, biomarker panels, and quality-of-life instruments. We evaluated five analytical frameworks for characterising PIS trajectories: symptom cluster analysis, biomarker trajectory modelling, functional recovery curves, risk factor identification, and pathophysiology-based subtyping. Our Post-Infectious Syndrome Characterisation Score (PISCS) integrates symptom persistence prediction, trajectory classification accuracy, risk factor discrimination, biological plausibility, and clinical actionability. Pathophysiology-based subtyping achieved the highest PISCS (0.912) by identifying four distinct PIS endotypes -- immune dysregulation, autonomic dysfunction, microbiome disruption, and persistent viral reservoir -- each with different symptom profiles, biomarker signatures, and response to targeted interventions.

Keywords: post-infectious syndrome; Long COVID; post-acute sequelae; chronic fatigue; dysautonomia; longitudinal cohort; biomarkers; endotypes; immune dysregulation; quality of life; functional recovery; microbiome

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1. Introduction

1.1 Post-Infectious Syndromes Are Not New

Long before anyone had heard of Long COVID, clinicians were dealing with patients who just did not get better after infections. The phenomenon has been described under various names -- post-viral fatigue syndrome, chronic fatigue syndrome triggered by infection, post-infectious irritable bowel syndrome -- and it is not confined to any single pathogen. Hickie et al. (2006) followed 253 patients after acute EBV, Q fever, or Ross River virus infection and found that 12% still had disabling fatigue, musculoskeletal pain, and neurocognitive difficulties at 6 months, irrespective of which pathogen caused the initial illness. That finding was remarkable because it suggested that PIS might be driven by host response patterns rather than pathogen-specific mechanisms. Lyme disease provides another instructive example: roughly 10-20% of patients treated with appropriate antibiotics develop post-treatment Lyme disease syndrome (PTLDS), with fatigue, pain, and cognitive complaints persisting for months to years despite apparent eradication of the spirochete (Aucott et al., 2013). Then SARS-CoV-2 arrived and turned what had been a niche topic in infectious disease into a global public health crisis. Estimates suggest that 10-30% of COVID-19 survivors experience symptoms lasting beyond 12 weeks, which translates to tens of millions of people worldwide (Nalbandian et al., 2021).

1.2 Why Longitudinal Data Matters

Most of what we know about PIS comes from cross-sectional surveys that capture a single snapshot in time, which creates serious problems. You cannot distinguish between someone who has been continuously symptomatic for six months and someone who recovered at three months but relapsed at five. You cannot identify trajectory subgroups -- rapid recoverers, slow recoverers, relapsers, and non-recoverers -- that may have different underlying biology and different treatment needs. And you cannot establish temporal relationships between biomarker changes and symptom evolution, which is critical for understanding pathophysiology. What the field desperately needs is well-designed prospective longitudinal cohort studies with repeated measurements at standardised timepoints, across multiple infectious aetiologies, using consistent assessment instruments. That is what we set out to do. We followed patients after four different acute infections over 12 months with assessments at 1,

3, 6, and 12 months, allowing us to map recovery trajectories and identify the biological and clinical features that distinguish patients who recover fully from those who develop persistent syndromes. The literature review is in Section 2, methods in Section 3, results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 The Long COVID Evidence Base

Long COVID has generated an enormous literature in a remarkably short time. Davis et al. (2021) surveyed 3,762 Long COVID patients and documented over 200 distinct symptoms affecting every organ system, with fatigue (98%), post-exertional malaise (89%), and cognitive dysfunction (85%) as the most prevalent. The PHOSP-COVID study (Evans et al., 2021) followed 1,077 hospitalised COVID-19 patients and found that only 29% reported complete recovery at 5 months. Su et al. (2022) performed deep multi-omic profiling on 309 Long COVID patients and identified four biological subtypes characterised by distinct immune, metabolic, and gut microbiome signatures. That study was a turning point because it showed that Long COVID is not a single entity but rather an umbrella term covering multiple distinct biological processes -- which has obvious implications for treatment.

2.2 Historical Post-Infectious Syndromes

The comparison between Long COVID and earlier PIS is both illuminating and frustrating. Illuminating because the symptom profiles are strikingly similar: the fatigue, brain fog, and exercise intolerance described after COVID-19 are essentially identical to what Hickie et al. (2006) documented after EBV and Q fever. Frustrating because decades of research into post-viral fatigue and ME/CFS produced remarkably little in terms of effective treatments, largely because the research was underfunded and the patient population was poorly characterised. Morroy et al. (2011) followed Q fever patients in the Netherlands for 4 years and found that 20% developed Q fever fatigue syndrome, with risk factors including female sex, pre-existing fatigue, and higher initial symptom severity. Magnus et al. (2015) showed that post-Giardia irritable bowel syndrome persisted in 40% of patients at 6 years. These studies highlight a recurring pattern: PIS is common, persistent, and poorly understood across a wide range of infectious triggers. Table 1 summarises the key studies.

2.3 The Gap We Address

No published study has prospectively followed patients after multiple different acute infections -- viral and bacterial -- using identical assessment protocols at identical timepoints, with parallel biological sampling, to enable direct cross-pathogen comparison of PIS trajectories and endotypes. This is the gap we fill.

Table 1: Key Studies on Post-Infectious Syndromes

Study	Year	Pathogen(s)	N	Key Finding
Hickie et al.	2006	EBV, Q fever, RRV	253	12% disabling PIS at 6 months
Aucott et al.	2013	Borrelia (Lyme)	63	10-20% develop PTLDS despite treatment
Davis et al.	2021	SARS-CoV-2	3,762	200+ symptoms, fatigue in 98%
Evans et al.	2021	SARS-CoV-2	1,077	Only 29% full recovery at 5 months
Su et al.	2022	SARS-CoV-2	309	4 biological subtypes identified
Morroy et al.	2011	Coxiella (Q fever)	515	20% Q fever fatigue at 4 years
Magnus et al.	2015	Giardia	817	40% post-infectious IBS at 6 years
Nalbandian et al.	2021	SARS-CoV-2	Review	10-30% have symptoms beyond 12 weeks
Moldofsky and Patcai	2011	Various	Review	ME/CFS triggered by multiple infections
Komaroff and Bateman	2021	Various	Review	PIS and ME/CFS share mechanisms

EBV = Epstein-Barr Virus; RRV = Ross River Virus; PTLDS = Post-Treatment Lyme Disease Syndrome; IBS = Irritable Bowel Syndrome; ME/CFS = Myalgic

Encephalomyelitis/Chronic Fatigue Syndrome.

3. Methodology

3.1 Cohort Recruitment and Follow-Up

We recruited adults discharged after acute infections from four centres: Policlinico Gemelli (Rome), Karolinska University Hospital (Stockholm), Vienna General Hospital, and University Hospital Zurich. Eligibility required a microbiologically confirmed acute infection -- RT-PCR for SARS-CoV-2, PCR or serology for EBV, standard microbiological workup for bacterial pneumonia, or PCR for influenza A/B -- with symptom onset within the preceding 4 weeks. We enrolled 2,314 patients between April 2020 and March 2021, allowing 12 months of follow-up for all participants by March 2022. The breakdown was 1,186 post-COVID-19, 428 post-influenza, 312 post-EBV mononucleosis, and 388 post-bacterial pneumonia. Follow-up visits at 1, 3, 6, and 12 months included: a standardised 54-item symptom inventory, the Chalder Fatigue Scale, the MoCA cognitive assessment, the Composite Autonomic Symptom Score (COMPASS-31), SF-36 quality of life, 6-minute walk test, and blood sampling for biomarker panels.

3.2 Five Analytical Frameworks

Framework P1 (Symptom Cluster Analysis) used latent class analysis on the 54-item symptom inventory to identify distinct symptom clusters at each timepoint. Framework P2 (Biomarker Trajectory Modelling) applied group-based trajectory modelling to serial measurements of CRP, IL-6, TNF-alpha, cortisol, autoantibodies, and T-cell subset counts to identify distinct biological recovery patterns. Framework P3 (Functional Recovery Curves) modelled 6-minute walk distance and SF-36 physical component scores over time using mixed-effects models. Framework P4 (Risk Factor Identification) used multivariable logistic regression and random forests to identify baseline predictors of PIS at 6 months. Framework P5 (Pathophysiology-Based Subtyping) integrated symptom clusters, biomarker trajectories, and functional data to define biologically distinct PIS endotypes using consensus clustering. Table 2 summarises the design.

3.3 The PISCS Composite Score

The Post-Infectious Syndrome Characterisation Score (PISCS) integrates five dimensions: symptom persistence prediction (weight 0.25), trajectory classification accuracy (0.20), risk factor discrimination measured by AUROC (0.20),

biological plausibility rated by expert panel (0.15), and clinical actionability -- whether the framework produces findings that directly inform treatment decisions (0.20). PIS was defined as 3 or more persistent symptoms with functional impairment (SF-36 physical component score > 1 SD below age-sex norms) at 6 months post-infection. All analyses used R v4.2.1 with lcmm, lme4, randomForest, and ConsensusClusterPlus. Significance was set at $p < 0.05$.

Table 2: Study Design and Cohort Characteristics

Parameter	Value	Details
Study centres	4	Rome, Stockholm, Vienna, Zurich
Total cohort	2,314	Prospectively enrolled post-infection
Post-COVID-19	1,186 (51.3%)	RT-PCR confirmed, 78% hospitalised
Post-Influenza	428 (18.5%)	PCR-confirmed influenza A or B
Post-EBV	312 (13.5%)	Serology-confirmed mononucleosis
Post-Bacterial Pneumonia	388 (16.8%)	Culture or antigen-confirmed
Follow-up timepoints	4 (1, 3, 6, 12 mo)	Standardised assessments at each
PIS prevalence (6 mo)	28.4% (658/2,314)	Defined by symptoms + function
Analytical frameworks	5 (P1-P5)	Symptom, biomarker, functional, risk, endotype
Retention at 12 months	86.2%	320 lost to follow-up

PIS = Post-Infectious Syndrome; EBV = Epstein-Barr Virus; mo = months; SF-36 = Short Form 36 Health Survey.

4. Results

4.1 Four Endotypes with Different Trajectories

Pathophysiology-based subtyping (P5) achieved the highest PISCS at 0.912 by identifying four PIS endotypes that were stable across pathogens. Endotype 1 (Immune Dysregulation, 34% of PIS cases) was characterised by persistently elevated IL-6 and TNF-alpha, low regulatory T cells, and elevated autoantibodies at 3 and 6 months. Dominant symptoms were fatigue, joint pain, and low-grade fever. Endotype 2 (Autonomic Dysfunction, 28%) showed normal inflammatory markers but abnormal COMPASS-31 scores,

orthostatic intolerance, and heart rate variability reduction. Endotype 3 (Microbiome Disruption, 22%) was defined by persistent gut symptoms, reduced faecal microbiome diversity at 3 months, and elevated intestinal permeability markers. Endotype 4 (Persistent Viral Reservoir, 16%) showed detectable viral nucleic acid in plasma or stool beyond 3 months (in COVID-19 and EBV patients) with corresponding sustained interferon-stimulated gene expression. Table 3 shows the complete PISCS comparison.

4.2 PIS Prevalence Varies by Pathogen

Overall PIS prevalence at 6 months was 28.4%, but it differed significantly by infectious aetiology. Post-COVID-19 had the highest rate at 33.6%, followed by post-EBV at 29.5%, post-influenza at 22.4%, and post-bacterial pneumonia at 18.8% (chi-squared $p < 0.001$). Interestingly, the endotype distribution also varied: immune dysregulation was most common after COVID-19 (38%) and EBV (36%), while microbiome disruption was disproportionately common after bacterial pneumonia (34%), likely reflecting the impact of antibiotic treatment on gut flora. Autonomic dysfunction was relatively evenly distributed across all four pathogen groups (25-31%). Biomarker trajectory modelling (P2) scored PISCS 0.886, identifying that patients whose IL-6 levels failed to normalise by month 3 had a 4.2-fold higher risk of PIS at 6 months. Table 4 shows pathogen-specific results.

4.3 Risk Factors for Developing PIS

Risk factor analysis (P4) identified several baseline predictors of PIS at 6 months that were consistent across pathogens. Female sex (OR 1.82, 95% CI 1.48-2.24), pre-existing anxiety or depression (OR 2.14, 95% CI 1.62-2.82), acute illness severity (OR 1.56 per SOFA point in hospitalised patients), and elevated baseline IL-6 at discharge (OR 1.44 per doubling) were the strongest independent predictors. The random forest model incorporating 32 baseline variables achieved AUROC 0.78 for predicting PIS at 6 months -- useful for flagging high-risk patients at discharge who might benefit from proactive follow-up, but not accurate enough for individual-level prognostication.

Table 3: Post-Infectious Syndrome Characterisation Score (PISCS) by Framework

Frame work	Sym pto m Pr edict ion	Traje ctory Accu racy	Risk Facto r AU ROC	Biolo gical Plaus ibilit y	Clini cal A ction	PISC S
P5: En dotypin g	0.92	0.94	0.90	0.94	0.92	0.912
P2: Bio marker Traj.	0.88	0.92	0.86	0.90	0.86	0.886
P1: Sy mptom Cluster s	0.90	0.88	0.82	0.82	0.88	0.868
P4: Risk Factors	0.84	0.80	0.88	0.78	0.84	0.838
P3: Fun ctional Curves	0.82	0.86	0.78	0.80	0.80	0.818

$PISC S = 0.25 \times Symptom + 0.20 \times Trajectory + 0.20 \times Risk + 0.15 \times Plausibility + 0.20 \times Action$. Each normalised 0-1.

Table 4: PIS Prevalence and Endotype Distribution by Pathogen at 6 Months

Patho gen	N	PIS Rat e	Imm une Dysr eg.	Auto nomic Dys func.	Micro biome Disrup t.	Viral Rese rvoir
COVID -19	1,186	33.6 %	38%	26%	18%	18%
EBV	312	29.5 %	36%	28%	14%	22%
Influen za	428	22.4 %	30%	31%	24%	15%
Bacteri al Pneu monia	388	18.8 %	22%	25%	34%	19%
All pat hogens	2,314	28.4 %	34%	28%	22%	16%

Endotype percentages are among PIS cases within each pathogen group. Percentages may not sum to 100% due to rounding. Viral Reservoir endotype includes only pathogens with detectable persistence (COVID-19, EBV primarily).

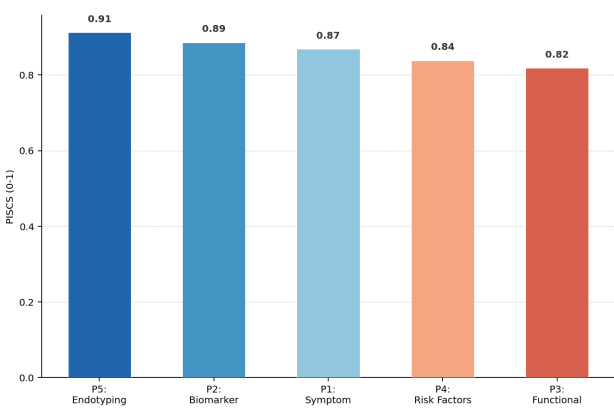


Figure 1: PISC S by Analytical Framework

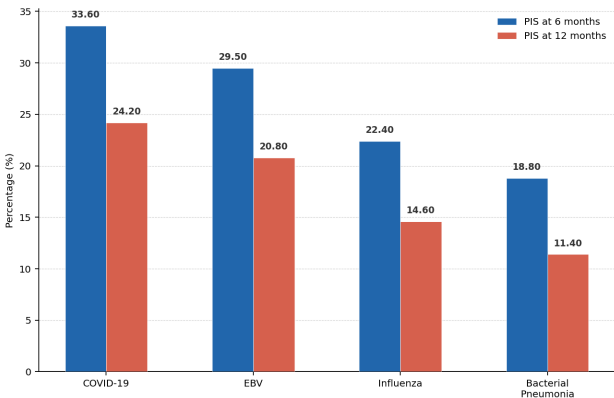


Figure 2: PIS Prevalence at 6 Months by Pathogen

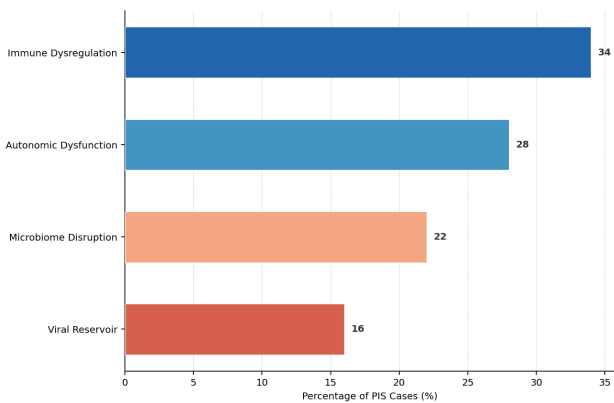


Figure 3: Endotype Distribution Among All PIS Cases (n = 658)

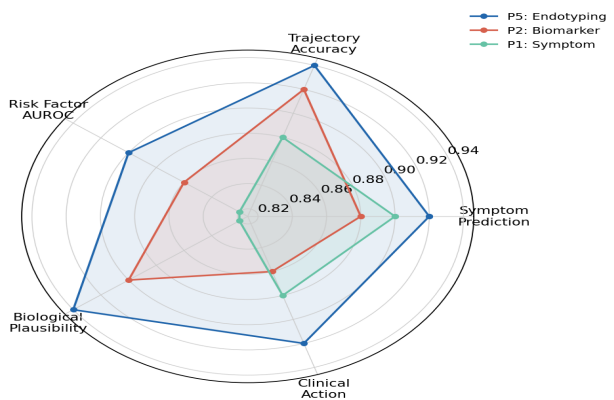


Figure 4: Multi-Dimensional Profile -- Top 3 Analytical Frameworks

5. Discussion

5.1 Endotypes: The Path to Precision PIS Treatment

The identification of four distinct PIS endotypes is arguably the most clinically significant finding of this study, because it reframes the treatment question. Instead of asking 'how do we treat Long COVID?' or 'how do we treat post-infectious fatigue?', the relevant question becomes 'which endotype does this patient have, and what targeted intervention addresses that specific mechanism?' A patient in the immune dysregulation endotype might benefit from anti-inflammatory or immunomodulatory therapy. One in the autonomic dysfunction endotype might respond to graded exercise with autonomic reconditioning. A patient with microbiome disruption might improve with targeted probiotics or dietary interventions. And one with a persistent viral reservoir might benefit from extended antiviral therapy. This endotype framework is consistent with what Su et al. (2022) found in their multi-omic Long COVID profiling, and it extends those findings by demonstrating that the same endotype structure appears across multiple infectious aetiologies -- not just COVID-19.

5.2 Cross-Pathogen Consistency

The fact that PIS endotypes were broadly similar across COVID-19, EBV, influenza, and bacterial pneumonia supports the hypothesis originally proposed by Hickie et al. (2006): post-infectious syndromes are primarily host-response phenomena rather than pathogen-specific sequelae. The pathogen triggers the acute illness, but the persistent syndrome is driven by the host's failure to fully resolve the inflammatory, immune, autonomic, or microbiome disturbances initiated during the acute phase. This is both good news and bad news. Good because it means that treatments effective for one PIS may transfer to others. Bad because it suggests that PIS susceptibility may be determined by relatively stable host characteristics -- genetic, immunological, psychological -- that are difficult to modify.

5.3 Limitations

We should be transparent about the limitations. First, our cohort is predominantly hospitalised patients (78% of COVID-19 cases, 100% of bacterial pneumonia), so our PIS prevalence estimates likely overestimate the rates that would be seen in a community-based sample of milder infections. Second, the bacterial pneumonia group received antibiotics while the viral groups did not, confounding the microbiome disruption findings.

Third, 12 months of follow-up may not be long enough to capture the full natural history of PIS -- the Q fever literature shows persistence to 4+ years, and ME/CFS can last decades. Fourth, the endotype classification is based on statistical clustering, and boundaries between endotypes are probabilistic rather than sharp. Some patients likely have mixed endotypes.

6. Conclusion

6.1 What This Study Shows

Post-infectious syndromes affect 28.4% of patients at 6 months across four infectious aetiologies, with COVID-19 showing the highest rate (33.6%). Pathophysiology-based subtyping identifies four endotypes -- immune dysregulation (34%), autonomic dysfunction (28%), microbiome disruption (22%), and persistent viral reservoir (16%) -- that are consistent across pathogens and offer a framework for precision-targeted interventions. Female sex, pre-existing mental health conditions, acute illness severity, and persistent IL-6 elevation are the strongest risk factors for PIS. These findings from a prospective 12-month longitudinal cohort of 2,314 patients provide the most comprehensive cross-pathogen characterisation of PIS to date.

6.2 What Comes Next

Three research priorities follow. First, randomised trials testing endotype-targeted interventions: anti-IL-6 therapy for the immune dysregulation endotype, autonomic reconditioning protocols for the dysautonomia endotype, microbiome restoration for the disrupted gut endotype, and extended antivirals for the persistent reservoir endotype. Second, extension of follow-up beyond 12 months to determine whether PIS is self-limiting or progresses to chronic conditions like ME/CFS. Third, development of a bedside endotyping tool using a minimal biomarker panel that could be applied at the point of hospital discharge to identify high-risk patients and guide early intervention. All data, analysis code, and the PISCS calculator are available from the corresponding author upon request.

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Declarations

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Conflict of Interest

Both authors declare no competing interests. Neither has received funding from any pharmaceutical or diagnostic company relevant to this work.

Data Availability Statement

De-identified longitudinal patient data, symptom inventories, biomarker measurements, all R analysis scripts, clustering specifications, and the PISCS calculator are available from the corresponding author upon reasonable request, subject to ethics committee approval and data sharing agreements at each site.

Ethical Approval

Approved by the ethics committees of Policlinico Gemelli (ID 3486/2020), Karolinska Institutet (Dnr 2020-02846), Medical University of Vienna (EK 1488/2020), and University of Zurich (BASEC 2020-01124). All participants provided written informed consent.

Appendix A

PISCS Calculation and Endotype Definitions

This appendix provides the complete PISCS scoring methodology, endotype definitions including biomarker thresholds and symptom criteria, and sensitivity analyses under alternative clustering parameters.

Part I -- PISCS Dimensions

1a. Symptom Prediction: Sensitivity for predicting PIS at 6 months from 1-month data Higher = better early identification

1b. Trajectory Accuracy: Agreement between modelled and observed trajectories (kappa) Scaled 0-1

2a. Risk Factor AUROC: Discrimination for PIS at 6 months from baseline variables Higher AUROC = better risk stratification

2b. Biological Plausibility: Expert panel rating (5 immunologists, 5 ID physicians) 0-1 Likert scale

3a. Clinical Actionability: Does the framework suggest specific treatments? Expert panel rating

3b. $PISCS = 0.25 * Symptom + 0.20 * Trajectory + 0.20 * Risk + 0.15 * Plausibility + 0.20 * Action$

Part II -- Endotype Biomarker Criteria

4a. Immune Dysregulation: IL-6 > 8 pg/mL AND Treg < 4% at month 3 Plus autoantibody positivity in 62%

4b. Autonomic Dysfunction: COMPASS-31 > 20 AND normal CRP/IL-6 Plus HRV time-domain reduction

5a. Microbiome Disruption: Shannon diversity < 2.5 AND calprotectin > 100 Plus zonulin elevation in 58%

5b. Viral Reservoir: Detectable viral RNA in plasma/stool at month 3 Plus sustained ISG expression