GULF WAR ILLNESS

Increased butyrate priming in the gut stalls microbiome associated-gastrointestinal inflammation and hepatic metabolic reprogramming in a mouse model of Gulf War Illness.

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Most of the associated pathologies in Gulf War Illness (GWI) have been ascribed to chemical and pharmaceutical exposures during the war. Since an increased number of veterans complain of gastrointestinal (GI), neuroinflammatory and metabolic complications as they age and there are limited options for a cure, the present study was focused to assess the role of butyrate, a short chain fatty acid for attenuating GWI-associated GI and metabolic complications. Results in a GWI-mouse model of permethrin and pyridostigmine bromide (PB) exposure showed that oral butyrate restored gut homeostasis and increased GPR109A receptor copies in the small intestine (SI). Claudin-2, a protein shown to be upregulated in conditions of leaky gut was significantly decreased following butyrate administration. Butyrate decreased TLR4 and TLR5 expressions in the liver concomitant to a decrease in TLR4 activation. GW-chemical exposure showed no clinical signs of liver disease but a significant alteration of metabolic markers such as SREBP1c, PPAR-α, and PFK was evident. Liver markers for lipogenesis and carbohydrate metabolism that were significantly upregulated following GW chemical exposure were attenuated by butyrate priming in vivo and in human primary hepatocytes. Further, Glucose transporter Glut-4 that was shown to be elevated following liver complications were significantly decreased in these mice after butyrate administration. Finally, use of TLR4 KO mice completely attenuated the liver metabolic changes suggesting the central role of these receptors in the GWI pathology. In conclusion, we report a butyrate specific mechanistic approach to identify and treat increased metabolic abnormalities in GWI veterans with systemic inflammation, chronic fatigue, GI disturbances, metabolic complications and weight gain.

CHRONIC FATIGUE SYNDROME

Patients with chronic fatigue syndrome do not score higher on the autism-spectrum quotient than healthy controls: Comparison with autism spectrum disorder.

Bileviciute-Ljungar I[1,2], Maroti D[1], Bejerot S[3].

Scand J Psychol. **2018 May 8**. doi: 10.1111/sjop.12451. PMID: 29738079. [Epub ahead of print]

Clinically, there is an overlap of several symptoms of chronic fatigue syndrome (CFS) and autism spectrum disorder (ASD), including fatigue; brain "fog"; cognitive impairments; increased sensitivity to sound, light, and odour; increased pain and tenderness; and impaired emotional contact. Adults with CFS (n = 59) or ASD (n = 50) and healthy controls (HC; n = 53) were assessed with the Autism-Spectrum Quotient (AQ) in a cross-sectional study. Non-parametric analysis was used to compare AQ scores among the groups. Univariate analysis of variance (ANCOVA) was used to identify if age, sex, or diagnostic group influenced the differences in scores. Patients with ASD scored significantly higher on the AQ than the CFS group and the HC group. No differences in AQ scores were found between the CFS and HC groups. AQ results were influenced by the diagnostic group but not by age or sex, according to ANCOVA. Despite clinical observations of symptom overlap between ASD and CFS, adult patients with CFS report few autistic traits in the self-report instrument, the AQ. The choice of instrument to assess autistic traits may influence the results.

HEADACHE and MIGRAINE

Comparing the Effects of Atorvastatin With Sodium Valproate (Divalproex) on Frequency and Intensity of Frequent Migraine Headaches: A Double-blind Randomized Controlled Study.

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Clin Neuropharmacol. **2018 May/Jun**;41(3):94-97. doi: 10.1097/WNF.0000000000000280. PMID: 29746282.

OBJECTIVES: To evaluate the prophylactic effects of atorvastatin on frequency, intensity, and duration of migraine attacks compared with sodium valproate.

METHODS: In this randomized, double-blind, single-center controlled trial, patients with 6 to 15 migraine attacks per month, which were candidates of preventive treatment, were recruited. The patients were randomly allocated into 2 groups. The first group (A) received atorvastatin 40 mg daily, and the second group (B) received sodium valproate 500 mg daily. All patients were visited each month and followed up for 3 months. The characteristics of migraine headaches including frequency, intensity, and duration of attacks were recorded, as well as the number of analgesics taken per each attack and probable adverse effects.

RESULTS: From 100 patients enrolled in the study, 18 cases were excluded owing to adverse effects (2 cases) or lost to follow-up (16 cases). From 82 patients who completed the trial, 46 and 36 were in group A (atorvastatin) and group B (sodium valproate), respectively. Mean age of the patients was not significantly different in the 2 arms of the study (33.56 ± 8.51 in group A and 33.25 ± 9.91 years in group B, P = 0.877). Number, duration, and intensity of attacks and number of analgesics taken during attacks decreased significantly in both groups in monthly follow-ups. However, there was no statistically significant difference between 2 arms of the study in terms of attenuation in the characteristics of migraine attacks. On the other hand, patients in group A suffered fewer adverse effects compared with group B.

CONCLUSIONS: This study indicates that atorvastatin could be an alternative for sodium valproate in migraine prophylaxis with comparable efficacy and fewer adverse effects. Multicenter studies with larger sample size are recommended.

Acupuncture therapy in treating migraine: results of a magnetic resonance spectroscopy imaging study.

Gu T[1,2], Lin L[3], Jiang Y[4], Chen J[1], D'Arcy RC[2,5,6], Chen M[1], Song X[2,5,6].

J Pain Res. **2018 Apr 27**;11:889-900. doi: 10.2147/JPR.S162696. PMCID: PMC5931197. eCollection 2018.

Background: Acupuncture has been proven to be effective as an alternative therapy in treating migraine, but the pathophysiological mechanisms of the treatment remain unclear. This study investigated possible neurochemical responses to acupuncture treatment.

Patients and methods: Proton magnetic resonance spectroscopy imaging was used to investigate biochemical levels pre- and post-acupuncture treatment. Participants (N=45) included subjects diagnosed with: 1) migraine without aura; 2) cervicogenic headache; and 3) healthy controls. Participants in the two patient groups received verum acupuncture using acupoints that target migraine without aura but not cervicogenic headache, while the healthy controls received a sham treatment. All participants had magnetic resonance spectroscopy scans before and after the acupuncture therapy. Levels of brain metabolites were examined in relation to clinical headache assessment scores.

Results: A significant increase in *N*-acetylaspartate/creatine was observed in bilateral thalamus in migraine without aura after the acupuncture treatment, which was significantly correlated with the headache intensity score.

Conclusion: The data demonstrate brain biochemical changes underlying the effect of acupuncture treatment of migraine.

HEADACHE and MIGRAINE (Continued)

The causal role of smoking on the risk of headache. A Mendelian randomization analysis in the HUNT Study.

Johnsen MB[1,2,3], Winsvold BS[2,4], Børte S[1,2], Vie GÅ[5], Pedersen LM[2], Storheim K[2], Skorpen F[6], Hagen K[7,8], Bjørngaard JH[5, 9], Åsvold BO[3,10], Zwart JA[1,2,4].

Eur J Neurol. **2018 May 10**. doi: 10.1111/ene.13675. PMID: 29747220. [Epub ahead of print]

BACKGROUND: Headache has been associated with various lifestyle- and psychosocial factors, one of which is smoking. The aim of the present study was to investigate whether the association between smoking intensity and headache is likely to be causal.

METHOD: 58 316 participants from the Nord-Trøndelag Health Study (HUNT) with information on headache status were genotyped for the rs1051730 C>T single-nucleotide polymorphism (SNP). The SNP was used as an instrument for smoking intensity in a Mendelian randomization (MR) analysis. Association between rs1051730 T alleles and headache was estimated by odds ratios (OR) with 95% confidence intervals (CI). Additionally, we investigated the association between the SNP and migraine or non-migrainous headache vs. no headache. All analyses were adjusted for age and sex.

RESULTS: There was no strong evidence that the rs1051730 T allele was associated with headache in ever smokers (OR 0.99, 95% CI 0.95-1.02). Similarly, there was no association between the rs1051730 T allele and migraine or non-migrainous headache vs. no headache.

CONCLUSION: Findings from this study do not support that there is a strong causal relationship between smoking intensity and any type of headache. Larger MR studies are required to examine whether higher smoking quantity can lead to a moderate increase in the risk of headache subtypes.

Prediction of vascular abnormalities on CT angiography in patients with acute headache.

Alons IME[1], Goudsmit BFJ[2], Jellema K[1], van Walderveen MAA[3], Wermer MJH[2], Algra A[4,5,6].

Brain Behav. **2018 May 9**:e00997. doi: 10.1002/brb3.997. PMID: 29741225. [Epub ahead of print]

OBJECTIVES: Patients with acute headache increasingly undergo CT-angiography (CTA) to evaluate underlying vascular causes. The aim of this study is to determine clinical and non-contrast CT (NCCT) criteria to select patients who might benefit from CTA.

METHODS: We retrospectively included patients with acute headache who presented to the emergency department of an academic medical center and large regional teaching hospital and underwent NCCT and CTA. We identified factors that increased the probability of finding a vascular abnormality on CTA, performed multivariable regression analyses and determined discrimination with the c-statistic.

RESULTS: A total of 384 patients underwent NCCT and CTA due to acute headache. NCCT was abnormal in 194 patients. Among these, we found abnormalities in 116 cases of which 99 aneurysms. In the remaining 190 with normal NCCT we found abnormalities in 12 cases; four unruptured aneurysms, three cerebral venous thrombosis', two reversible cerebral vasoconstriction syndromes, two cervical arterial dissections and one cerebellar infarction. In multivariable analysis abnormal NCCT, lowered consciousness and presentation within 6 hr of headache onset were independently associated with abnormal CTA. The c-statistic of abnormal NCCT alone was 0.80 (95% CI: 0.75-0.80), that also including the other two variables was 0.84 (95% CI: 0.80-0.88). If NCCT was normal no other factors could help identify patients at risk for abnormalities.

CONCLUSIONS: In patients with acute headache abnormal NCCT is the strongest predictor of a vascular abnormality on CTA. If NCCT is normal no other predictors increase the probability of finding an abnormality on CTA and diagnostic yield is low.

CHRONIC PAIN

Exploring psychological mechanisms of clinical response to an internet-delivered psychological pain management program.

Gandy M[1], Karin E[1], Jones M[1], McDonald S[1], Sharpe L[2], Titov N[1], Dear BF[1].

Eur J Pain. **2018 May 13**. doi: 10.1002/ejp.1239. PMID: 29754439. [Epub ahead of print]

BACKGROUND: The evidence for Internet-delivered pain management programs for chronic pain is growing, but there is little empirical understanding of how they effect change. Understanding mechanisms of clinical response to these programs could inform their effective development and delivery.

METHODS: A large sample (n = 396) from a previous randomised controlled trial of a validated internet-delivered psychological pain management program, the Pain Course, was used to examine the influence of three potential psychological mechanisms (pain acceptance, pain self-efficacy, fear of movement/re-injury) on treatment-related change in disability, depression, anxiety and average pain. Analyses involved generalised estimated equation models for clinical outcomes that adjusted for co-occurring change in psychological variables. This was paired with cross-lagged analysis to assess for evidence of causality. Analyses involved two time-points, pre-treatment and post-treatment.

RESULTS: Changes in pain-acceptance were strongly associated with changes in three (depression, anxiety and average pain) of the four clinical outcomes. Changes in self-efficacy were also strongly associated with two (anxiety and average pain) clinical outcomes. These findings suggest participants were unlikely to improve in these clinical outcomes without also experiencing increases in their pain self-efficacy and pain acceptance. However, there was no clear evidence from cross-lagged analyses to currently support these psychological variables as direct mechanisms of clinical improvements. There was only statistical evidence to suggest higher levels of self-efficacy moderated improvements in depression.

CONCLUSIONS: The findings suggest that, while clinical improvements are closely associated with improvements in pain acceptance and self-efficacy, these psychological variables may not drive the treatment effects observed.

Pain Agreements and Healthcare Utilization in a Veterans Affairs Primary Care Population: A Retrospective Chart Review.

Kay C[1,2,3], Wozniak E[4], Ching A[5,6], Bernstein J[6].

Pain Ther. **2018 May 11**. doi: 10.1007/s40122-018-0098-5. PMID: 29752701. [Epub ahead of print]

INTRODUCTION: The prevalence of chronic pain is enormous. In America, the management of chronic pain and opioids remains a critical focus. Guidelines recommend pain agreements as part of the management of chronic pain and opioids; however, evidence of improvement in patient outcomes is lacking. An aspect of patient outcome includes utilization of healthcare resources, such as emergency department visits and hospitalizations. It remains uncertain whether the use of pain agreements lessens healthcare utilization.

METHODS: Retrospective chart review of a Midwest Veterans Affairs primary care clinic. Subjects were veterans on chronic opioids between 1 April 2014 and 1 April 2015. Outcome measures included emergency department visits, hospitalizations, clinic visits, telephone triage, telephone/secure messages, and nurse visits.

RESULTS: The charts of 635 veterans on chronic opioids were reviewed. Of these, 295 were on a pain agreement. There were no significant differences in demographics, medical, or psychiatric diagnoses between patients with and without pain agreements. There were significant differences in opioid schedule and number of opioids based on pain agreement ($p < 0.01$). Patients on pain agreements did not utilize healthcare resources less than patients without a pain agreement. In fact, patients on pain agreements were likely to have more telephone calls, secure messages, and nurse visits compared with patients not on an agreement ($p = 0.02$).

CONCLUSIONS: Pain agreements are becoming standard of care for chronic pain management. However, there continues to be a lack of evidence demonstrating improvement in healthcare outcomes with their use, despite guideline recommendations. Further studies are needed to examine specific patient outcomes, such as overdose and death, in regard to pain agreements.

FUNDING: Advancing a Healthier Wisconsin-Patient-Centered Outcomes Research Program.

CHRONIC PAIN (Continued)

Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial.

Webster LR[1], Michna E[2], Khan A[3,4], Israel RJ[5], Harper JR[5].

Pain Med. **2017 Aug 1**;18(8):1496-1504. doi: 10.1093/pm/pnx148. PMCID: PMC5914419.

Objective: Methylnaltrexone, a peripherally acting μ-opioid receptor antagonist, alleviates opioid-induced constipation. Understanding its long-term safety and efficacy profile in patients with chronic noncancer pain is warranted given the persistence of opioid-induced constipation.

Methods: In this phase 3, multicenter, open-label trial, adults with chronic noncancer pain (N = 1034) received subcutaneous methylnaltrexone 12 mg once daily for 48 weeks.

Results: The most common adverse events were gastrointestinal related (e.g., abdominal pain, diarrhea, nausea) and were mild to moderate in intensity. Only 15.2% of patients discontinued because of an adverse event. Serious cardiac-related adverse events occurred in nine patients. Of the seven instances of major adverse coronary events reported, three were adjudicated after external review; all instances occurred in patients with cardiovascular risk factors. Methylnaltrexone elicited a bowel movement within four hours in 34.1% of the injections throughout the 48-week treatment period.

Conclusions: Change from baseline in mean weekly bowel movement rate, Bowel Movement Straining Scale score, Bristol Stool Scale score, and mean percentage of patients with complete evacuation from baseline to week 48 were significantly improved ($P < 0.001$ for all). Long-term subcutaneous methylnaltrexone was well tolerated, with no new safety concerns, and provided consistent opioid-induced constipation relief in patients with chronic noncancer pain.

Potentially traumatic events, PTSD and post-traumatic stress spectrum in patients with fibromyalgia.

Conversano C[1], Carmassi C[2], Bertelloni CA[2], Marchi L[3], Micheloni T[3], Carbone MG[2], Pagni G[2], Tagliarini C[2], Massimetti G[2], Bazzichi LM[4], Dell'Osso L[2].

Clin Exp Rheumatol. **2018 Apr 24**. PMID: 29745889. [Epub ahead of print]

OBJECTIVES: Fibromyalgia (FM) is defined as a severe, chronic, non-articular rheumatic condition characterised by widespread musculoskeletal pain, hyperalgesia and generalised tender points, in the absence of inflammatory or structural musculoskeletal abnormalities. Pain is the predominant symptom, allodynia and hyperalgesia are common signs. Extreme fatigue, impaired cognition and non-restorative sleeping difficulties coexist in addition to other somatic symptoms. Several studies suggest there is a meaningful relationship between FM and the psychological symptoms of depression and post-traumatic stress disorder (PTSD). PTSD is a mental disorder that can develop after a person has been exposed to a traumatic event, characterised by a specific set of symptoms including re-experiencing of the event, avoidance and numbing and arousal. The present study investigates the impact of lifetime potentially traumatic events, including losses, and of post-traumatic stress symptoms on the severity of illness in patients with fibromyalgia (FM).

METHODS: Sixty-one patients with FM, diagnosed according to the American College of Rheumatology criteria, were consecutively enrolled at the Unit of Rheumatology, University of Pisa, Italy. Assessments included: the SCID-5 and the Trauma and Loss Spectrum Self-Report (TALS-SR) lifetime version.

RESULTS: 21.3% of the subjects (n=13) met the criteria for "partial" PTSD: 57.4% criterion B, 42.6% criterion C, 31.1 criterion D and 44.3% criterion E. Fibromyalgia patients without PTSD reported significantly lower scores in all domains compared to the patients with partial PTSD, the latter ones reporting significantly lower scores in all domains compared to full PTSD with the exception of domain I. In particular, these differences were noticeable in Domain VI and Domain VIII.

CONCLUSIONS: The results of the study show that fibromyalgic patients with PTSD report more potentially traumatic events, avoidance symptoms, numbing, arousal, maladaptive coping and personality characteristics compared to patients with partial or without PTSD; these results could indicate that loss and/or trauma events represent a risk factor for the development of symptoms of FM in genetically predisposed individuals.

CHRONIC PAIN (Continued)

Correlates of Sexual Functioning and Relationship Satisfaction Among Men and Women Experiencing Chronic Pain.

Finn E[1], Morrison TG[2], McGuire BE[1].

Pain Med. **2018 May 1**;19(5):942-954. doi: 10.1093/pm/pnx056. PMID: 29741742.

Background: The aims of the study were to 1) examine the prevalence of sexual functioning difficulties in a chronic pain sample; 2) identify correlates of sexual functioning and relationship satisfaction utilizing pain variables (pain severity and pain interference) and psychological variables (mood, pain-related cognitions, self-efficacy, self-esteem, body-image); and 3) investigate possible sex differences in the correlates of sexual functioning and relationship satisfaction.

Method: Two hundred sixty-nine participants were recruited online from chronic pain organizations, websites, social media sites, and discussion forums. Those who met criteria for inclusion were presented with a variety of measures related to pain, sexual functioning, and relationship satisfaction (for those in a relationship), as well as cognitive and affective variables.

Results: Participant mean age was 37 years, and the majority were female, heterosexual, and currently in a relationship. High levels of pain severity and interference from pain, fatigue, depression, anxiety, stress, and body image concerns were reported, along with low levels of self-esteem and pain self-efficacy. In addition, substantial proportions of male (43%) and female (48%) respondents had scores indicative of sexual problems. Exploratory hierarchical regression analyses revealed that, for women, age and relationship satisfaction (which were both treated as covariates) as well as depression emerged as statistically significant correlates of sexual functioning (i.e., women who were older and reported greater levels of depression and less satisfaction with their current relationship indicated poorer sexual functioning). When relationship satisfaction was the criterion measure, age and sexual functioning (again, treated as covariates) and perceived stress emerged as significant (i.e., women who were older, reported poorer sexual functioning, and reported greater perceived stress also indicated being less satisfied with their current relationship). For male participants, age emerged as the only statistically significant correlate of sexual functioning (i.e., older men reported poorer functioning). In terms of relationship satisfaction, self-esteem was the lone significant correlate variable (men who reported lower self-esteem also were less satisfied with their current relationship).

Conclusions: Some sex differences were evident in the variables that predict sexual difficulties and relationship satisfaction among those suffering from chronic pain. Of note is that when psychological variables were considered, pain-specific physical variables (e.g., pain severity and activity limitations) accounted for very little additional variance.

OTHER RESEARCH OF INTEREST

Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response.

Faraco G[1], Brea D[1], Garcia-Bonilla L[1], Wang G[1], Racchumi G[1], Chang H[1], Buendia I[1], Santisteban MM[1], Segarra SG[1], Koizumi K[1], Sugiyama Y[1], Murphy M[1], Voss H[2], Anrather J[1], Iadecola C[3].

Nat Neurosci. **2018 Feb**;21(2):240-249. doi: 10.1038/s41593-017-0059-z. Epub 2018 Jan 15. PMID: 29335605.

A diet rich in salt is linked to an increased risk of cerebrovascular diseases and dementia, but it remains unclear how dietary salt harms the brain. We report that, in mice, excess dietary salt suppresses resting cerebral blood flow and endothelial function, leading to cognitive impairment. The effect depends on expansion of TH17 cells in the small intestine, resulting in a marked increase in plasma interleukin-17 (IL-17). Circulating IL-17, in turn, promotes endothelial dysfunction and cognitive impairment by the Rho kinase-dependent inhibitory phosphorylation of endothelial nitric oxide synthase and reduced nitric oxide production in cerebral endothelial cells. The findings reveal a new gut-brain axis linking dietary habits to cognitive impairment through a gut-initiated adaptive immune response compromising brain function via circulating IL-17. Thus, the TH17 cell-IL-17 pathway is a putative target to counter the deleterious brain effects induced by dietary salt and other diseases associated with TH17 polarization.

OTHER RESEARCH OF INTEREST (Continued)

Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016.

Jones CM[1], Einstein EB[2], Compton WM[2].

JAMA. **2018 May 1**;319(17):1819-1821. doi: 10.1001/jama.2018.2844. PMID: 29715347

Full text of JAMA Research Letter:

Drug overdose deaths are at unprecedented levels in the United States [1].Prescription opioids have been the most common drug involved in overdose deaths, but heroin and synthetic opioids (primarily illicit fentanyl) are increasingly implicated in overdoses [2].In addition, synthetic opioids are increasingly found in illicit drug supplies of heroin, cocaine, methamphetamine, and counterfeit pills [3].To date, the involvement of synthetic opioids in overdose deaths involving other drugs is not well characterized, limiting the ability to implement effective clinical and public health strategies. Using 2010-2016 mortality data, we describe recent trends for synthetic opioid involvement in drug overdose deaths .

Prodromal symptoms of multiple sclerosis in primary care.

Disanto G[1], Zecca C[1], MacLachlan S[2], Sacco R[1], Handunnetthi L[3], Meier UC[4], Simpson A[2], McDonald L[5], Rossi A[6], Benkert P[7], Kuhle J[8], Ramagopalan SV[5], Gobbi C[1].

Ann Neurol. **2018 May 8**. doi: 10.1002/ana.25247. PMID: 29740872. [Epub ahead of print]

OBJECTIVE: Early diagnosis and treatment initiation significantly influence long term disability outcome in multiple sclerosis (MS). We aimed at identifying prodromal symptoms of MS in primary care settings.

METHODS: This was a nested case-control study comparing the occurrence of various symptoms in MS patients vs controls at 0-2, 2-5 and 5-10 years before index date (first MS record). A total of 10,204 incident MS cases were identified within the UK Clinical Practice Research Datalink (CPRD) between 01/01/1987 and 28/02/2016 (median (IQR) age=47 (39-57) years, females=7,308 (71.6%)). Patients were matched to 39,448 controls with no MS record by sex, year of birth, general practitioner and year of registration (age=47 (39-56), females=28,248 (71.6%)). Odds ratios (OR) with 95% confidence intervals (CI) were calculated using conditional logistic regression.

RESULTS: MS patients had significantly higher risk of presenting up to 10 years prior to index date with gastric, intestinal, urinary and anorectal disturbances, anxiety, depression, insomnia, fatigue, headache and various types of pain. MS risk progressively increased with each additional symptom presented (0-2 years: OR=1.51, 95%CI=1.47-1.55, p<0.001; 2-5 years: OR=1.29, 95%CI=1.25-1.33, p<0.001; 5-10 years: OR=1.20, 95%CI=1.15-1.26, p<0.001). Sensitivity analyses in patients with age at index <40 years and no neurological disturbances prior to symptoms of interest showed consistent results.

INTERPRETATION: Various clinical disturbances precede MS diagnosis by several years, supporting a prodromal phase to the disease and improving our clinical knowledge of early MS. Integrating these symptoms in the diagnostic procedure may help earlier disease identification.

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