

Appendix 1 – Protocol for Preventing or Reversing Chronic Disease

The first author has developed a protocol over the past decade for preventing or reversing chronic disease based on the following systemic medical principle: “at the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective”^[1]. The protocol methodology refines the age-old principles of both reducing harm in addition to providing treatment, and allows better identification of factors that contribute to the disease process (so that they may be eliminated if possible). These contributing factors are expansive and may include a combination of Lifestyle choices (diet, exercise, smoking), iatrogenic and biotoxin exposures, environmental/occupational exposures, and psychosocial stressors. This strategy exploits the existing literature to identify patterns of biologic response using biomarkers from various modalities of diagnostic testing to capture a much broader list of potential contributing factors.

Existing inflammatory bowel diseases (IBD) Biomarker Identification to Remove Contributing Factors and Implement Treatment

The initial protocol steps are diagnostic. The main output of these diagnostics will be identification of the biomarker levels and symptoms that reflect abnormalities, and the directions of change required to eliminate these abnormalities. In the present study, hundreds of general and specific biomarkers and symptoms were identified from the core IBD literature. The highest frequency (based on numbers of record appearances) biomarkers and symptoms were extracted, and are listed in Table 1 (highest frequency items first, reading down each column before proceeding to the next column). They are not necessarily consensus biomarkers. They are biomarkers whose values were altered by a treatment or contributing factor, and reported in the core IBD literature.

There is some redundancy (*e.g.*, spelled-out version of a biomarker and its acronym) in the tables, since these are actual search terms, and they would retrieve different amounts of records. If unique biomarker concepts are desired, the similar terms can be combined. The purpose of the table shown here is to illustrate the breadth of biomarkers identified.

Table 1 Highest frequency existing inflammatory bowel diseases biomarkers/symptoms

Inflammation	Mucin	Fibrinogen
Weight	CD4	Vitamin B12
Diarrhea	Colon length	Vascular endothelial growth factor
TNF-alpha	IL-2	Bone density
T cells	Bloody diarrhea	Transferrin
C-reactive protein	Mucosal damage	Arachidonic acid
Abdominal pain	Mycobacterium avium	Occludin
Lymphocytes	CD4(+) T cells	Erythrocytes
Calprotectin	Nitric oxide synthase	Lymphoid cells
Macrophages	Wall thickening	Lipid peroxidation
Crohn's disease activity index	Eosinophils	Calcineurin
IL-6	Bowel movements	CD8
Weight loss	Tight junction	CD14
IL-10	Th17 cells	Matrix metalloproteinases
Apoptosis	CD4+ T cells	TLR2
Mucosal inflammation	TGF-beta	White blood cell count
Ulcers	Helicobacter pylori	E-cadherin
Permeability	Epithelial barrier function	Elastase
Albumin	ANCA	PGE2
Fibrosis	IL23R	Catalase
Myeloperoxidase	Intestinal flora	IL-5
Body weight	FoxP3	Actin
Leukocyte	STAT3	Tight junctions
Fecal calprotectin	iNOS	Bcl-2
IL-1beta	Platelet count	Homocysteine

Neutrophils	Alkaline phosphatase	IgE
Anemia	COX-2	Lactobacilli
Barrier function	Mast cells	Substance P
Body mass index	Fibroblasts	Folic acid
IFN-gamma	Glycoprotein	MUC2
NF-kappaB	Cholesterol	Leukotriene B4
Erythrocyte sedimentation rate	Vitamin D deficiency	NLRP3
Vitamin D	White blood cell	Caspase-3
IgG	Glucose	GSH
Proinflammatory cytokines	Cell death	Histamine
<i>Escherichia coli</i>	Single nucleotide polymorphism	IL-1Ra
Iron	Allele frequencies	Fibrin
Intestinal microbiota	IL-17A	CD40
Epithelial barrier	Protein level	Epithelial permeability
Nitric oxide	Superoxide dismutase	CD68
IgA	Heparin	Glutathione peroxidase
Oxidative stress	ICAM-1	MCP-1
Fatty acids	Malondialdehyde	MMP-9
Hemoglobin	IgM	Prothrombin
IL-8	Protein kinase	Akt
Dendritic cells	Body weight loss	Bilirubin
Mycobacterium	IL-13	Free radicals
Bone mineral density	T-cells	IgG4
Calcium	Intestinal fibrosis	Lipoprotein
Rectal bleeding	Immune function	IgG antibodies
Autophagy	Intestinal epithelial barrier	Tryptophan

Interferon-gamma	Antineutrophil cytoplasmic antibodies	Oxidative damage
IL-17	IL-22	CD25
MPO	Single-nucleotide polymorphisms	IL-21
Intestinal permeability	Folate	NOD1
Regulatory T cells	Bowel wall thickness	Triglycerides
Tissue damage	Bifidobacterium	Erythropoietin
Autoantibodies	Faecalibacterium	IL-33
IL-4	Bile acid	TNFSF15
Collagen	C. difficile	Claudin-1
IL-12	CD8+	Hydrogen peroxide
Iron deficiency	IL-18	Phospholipids
Edema	Anti-inflammatory cytokines	MAdCAM-1
Fecal microbiota	Lipids	S100A12
Toll-like receptor	miRNAs	Bax
Granulocytes	Nuclear factor-kappaB	Claudin-2
Colonic epithelial cells	B12	fecal lactoferrin
Wall thickness	Ferritin	Fusobacterium
IL-23	Epstein-Barr virus	Caspase-1
Treg	Barrier integrity	P-selectin
TLR4	Creatinine	Leukocyte count
IL-1	Mycobacteria	CD86
Reactive oxygen species	Metalloproteinases	VCAM-1
Interleukin-10	Treg cells	Acetylcholine
Glutathione	Barrier dysfunction	C3
mRNA levels	Cell differentiation	Colon weight

Because of the sheer volume of the metrics presented in this Appendix (biomarkers, contributing factors, treatments), adding specific references for each would have been overwhelming for the reader. Instead, if the reader wants to track down the initial documents from which the metrics of interest were taken, it is recommended the reader use the following query (written in PubMed search form):

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(inflammatory bowel diseases [mh] OR crohn disease [mh] OR colitis, ulcerative [mh] OR "inflammatory bowel disease*" [ti] OR crohn-disease [ti] OR crohn's-disease [ti] OR "ulcerative colitis" [ti] OR IBD [ti]) AND "metric of interest" [tiab]
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This query is the intersection of the core IBD literature and the metric of interest. As an example, if the reader wants a broad understanding of Infliximab's performance as an IBD treatment, the reader would enter the following query into PubMed (the query is easily modified for other search engines, such as SCI-Medline (Clarivate)):

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(inflammatory bowel diseases [mh] OR crohn disease [mh] OR colitis, ulcerative [mh] OR "inflammatory bowel disease*" [ti] OR crohn-disease [ti] OR crohn's-disease [ti] OR "ulcerative colitis" [ti] OR IBD [ti]) AND "Infliximab" [tiab]
```

On 19 April 2020, this query was entered into PubMed. It retrieved 4686 documents, which would allow the interested reader to examine the full scope of the biomedical community's experience with application of Infliximab to IBD. This breadth of information would be of far more use to the interested reader than any one or two references.

Existing IBD Contributing Factor Identification

The protocol requires identifying and eliminating those factors that contribute to the disease, and specifically those factors that contribute to the abnormal levels of biomarkers and abnormal symptoms identified by the initial diagnostics. In the three chronic disease studies examined using the disease

prevention and reversal protocol^[1], anywhere from 500-1000 existing factors that contribute to the disease could be identified. As the text mining techniques have become refined, identification of more existing contributing factors (especially those that appear in records at very low frequencies) became possible, and the higher number is probably more reflective of what should be expected for serious chronic diseases. Unless (at least) the major contributing factors to the disease of interest applicable to any individual are removed, it is difficult to see how any treatments can be effective, much less help reverse the disease.

As in the case of biomarkers, the contributing factors are not necessarily consensus contributing factors. They are contributing factors (identified in one or more studies) whose author(s) believed their impact on biomarkers and symptoms reflected their potential contribution to initiating or exacerbating IBD.

Some/many other studies of these potential contributing factors reported in the literature may not have found them to be potential contributing factors to IBD. There can be many reasons that these other biomedical papers did not report adverse IBD effects from the items listed below as potential contributing factors: (1) the research conducted in the other studies was poor, or the research conducted in the study that reported the contributing factors was poor; (2) there were windows in parameter space in which the reported contributing factors had adverse effects on IBD, and the other papers operated outside these windows; and (3) authors of the studies that found no adverse effects on IBD from these contributing factors had a pre-determined agenda to find no adverse effects, especially for contributing factors that had commercial, military, or political sensitivity^[2-5].

With such large numbers of contributing factors being identified, could any useful patterns be gleaned from this very disparate data? It became clear that a first-order categorization of the contributing factors could be achieved mechanistically. The contributing factors were divided into six categories (with some overlap): Lifestyle; Iatrogenic; Biotoxins; Occupational/Environmental; Psychosocial/Socioeconomic; Genetics. The latter category was not pursued further in the studies, since the thrust was contributing factors over which patients or government had (in theory) some control currently. The categories proved

useful for presenting results.

The next question was whether there were a few latent categories that would explain the larger structure. It soon became evident that the bulk of contributing factors to disease were 1) the products of modern and semi-modern technology, especially technology that was effectively unregulated, and from 2) the spinoffs of this modern technology (such as sedentary living, staring at computer screens all day, *etc.*). These latent categories have been described in more detail elsewhere^[6].

The present study did not focus on identifying large numbers of contributing factors to IBD, since its focus was discovery of treatments that could be repurposed for IBD. However, in the course of the study, a number of the leading existing IBD contributing factors were identified. The highest frequency existing IBD contributing factors are listed in Table 2, in order to give the reader a small sampling of what could be obtained from a full-blown IBD reversal protocol study. The IBD contributing factors in Table 2 are phrases (from the core IBD record Abstracts) listed in order of the frequency of records in which they appeared; i.e., most studied. There tends to be less uniformity in descriptions of contributing factors than biomarkers or treatments.

Table 2 Highest frequency existing inflammatory bowel diseases contributing factors

Smoking	Lipopolysaccharides	High cholesterol
Stress	Dinitrobenzene	Listeria spp
Antibiotics	Psychosocial stress	Low fibre
Dextran sulfate sodium	Sedentary	Mercury
Tuberculosis	Carrageenan	Pasta
Fat	Emulsifiers	Spicy food
Clostridium difficile	High-fat diet	Sucrose intake
Malnutrition	Industrialization	Advanced glycation end product

Mycobacterium	Air pollution	Aluminosilicate
Cytomegalovirus	Alcohol abuse	Bacille Calmette-Guerin vaccination
<i>E. coli</i>	Urbanization	Benzo[a]pyrene
Milk	Peroxynitrite	Candida tropicalis
Acetic acid	Diclofenac	Carboxymethylcellulose
Etanercept	Fluoride	Ceramic
Vitamin D deficiency	Fructose	Circadian disruption
Vaccines	Polyols	Dimethylhydrazine
Epstein-Barr virus	Toxoplasma gondii	Fructooligosaccharides
Sugar	Long-chain fatty acids	Galactooligosaccharides
NSAIDs	Soft drinks	Heavy metal
Mycobacterium avium subspecies paratuberculosis	Omega-6 fatty acids	High carbohydrate diet
Saccharomyces cerevisiae	Red meat	High salt diet
Fungi	Silica	Hydrazine
Infectious agents	Animal fat	Low fiber intake
Non-steroidal anti-inflammatory drugs	Atypical mycobacteria	Mycotoxins
Yeast	Sulphate-reducing bacteria	Nitrogen dioxide
Indomethacin	Titanium dioxide	Paramyxoviridae
Lactose	Emotional stress	Perfluorooctanoic acid
Oral contraceptives	Fast food	Pertussis vaccine
Mannitol	Margarine	Polydextrose
Mycophenolate mofetil	Refined sugar	Polysorbate-80
Gluten	Fructans	Printers
Trinitrobenzenesulfonic acid	Ipilimumab	Restraint stress

Hydrogen peroxide	Refrigeration	Sausages
Meat	Saturated fat	Second-hand cigarette smoke
Fusobacterium	Sorbitol	Splenda
Candida albicans	Aluminum	Thickeners
Dairy products	Bitter	Urban upbringing
Aspirin	Maltodextrin	Indoor work
Polysaccharides	Particulate matter	Low helminths
Rituximab	Processed foods	Maltitol
Linoleic acid	Dinitrochlorobenzene	Managerial occupations
Western diet	Fried foods	Metalware
Campylobacter jejuni	2,4-dinitrochlorobenzene	Office workers
Caesarean section	Klebsiella microbes	Sales workers
Isotretinoin	PFOA	Selenium-deficient diet
Poor sleep	Refined carbohydrates	Sulfur dioxide
Bacteroides vulgatus	Silicates	Tile workers
Fat intake	Wood	Ultrafine particles
Hydrogen sulfide	Artificial sweeteners	White collar workers
Eggs	Bakers	Xylitol
Food additives	Bedroom sharing	

It is easy to state a principle that contributing factors should be eliminated before true disease reversal or even effective treatment is possible. It is more difficult to identify these factors from text, much more difficult to measure one's exposure to these potential contributing factors, and much much more difficult to actually eliminate them. As a first step, it would be valuable to identify those contributing factors over which one has substantial control to eliminate (if one so chooses), and especially those that would be *relatively easy and safe to eliminate*. Based on the three disease reversal studies that were done so far, a group of

contributing factors having this property (and appearing in all three disease reversal studies) was identified^[1]. It is reasonable to assume many (if not all) would apply to IBD as well, although specific changes to eliminate these contributing factors should be implemented under the guidance and strict supervision of one's healthcare practitioner.

Existing IBD Treatment Identification

The protocol requires identifying and implementing those treatments that will correct (to the extent possible) the abnormal biomarker levels and abnormal symptoms identified in the initial diagnostics. The three chronic disease studies examined so far identified anywhere from 500-1000 existing treatments for the disease of interest (these are large numbers, as stated in the previous reference to Appendix 3^[1]). Improvement in the LRDI text mining techniques has resulted in more existing treatments being identified (especially those that appear in records at very low frequencies), and the higher number is probably more reflective of what should be expected for serious chronic diseases.

In the current study, some effort was placed on identifying existing IBD treatments, although not as much effort as would have been placed in a full-blown disease reversal study. The main value of having identified these existing treatments (in the present IBD treatment discovery study) was that subtraction of records containing these treatments from the query retrieval would reduce the noise/signal ratio of the retrieval. The highest frequency existing IBD treatments identified are listed in Table 3. Some are mainline treatments used widely in medical practice for IBD; most are procedures used in laboratory studies to alter biomarker values in desired directions.

Table 3 Highest frequency existing inflammatory bowel diseases treatments

Infliximab	Allopurinol	Bone	marrow
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		transplantation
Proctocolectomy	Olsalazine	Adrenomedullin
Azathioprine	MMX	Vasoactive intestinal peptide
Adalimumab	Etanercept	Saccharomyces boulardii
Colectomy	Cannabis	Naltrexone
Dextran	Fish oil	Glucagon-like peptide-2
Vitamin D	Adenosine	Germinated Barley
Mesalazine	Mercaptopurine	Etrolizumab
Thiopurine	Mesenchymal stromal cells	Adacolumn
Vedolizumab	Ciprofloxacin	Tryptophan
Ultrasound	Beclomethasone dipropionate	Salazosulfapyridine
Probiotics	Seton	Methylprednisolone
5-Aminosalicylic Acid	Hematopoietic stem cell Transplantation	Linoleic acid
Enteral nutrition	Glutamine	Inosine
Mesalamine	Balsalazide	Granulocyte-monocyte apheresis
Iron	Monocyte Apheresis	FK506
Budesonide	Helminths	Cannabinoids
Methotrexate	Acupuncture	Ca ²
6-mercaptopurine	Yersinia	Bilirubin
Tacrolimus	VSL#3	Somatostatin
Fecal microbiota transplantation	Selenium	Rituximab
Ustekinumab	Resveratrol	Phosphatidylcholine
Corticosteroids	Isotretinoin	Peptidoglycan
Leukocytapheresis	Hyperbaric oxygen	Octreotide

Interleukin-10	Thioguanine	Low molecular weight heparin
Glucocorticoid	Short-chain fatty acids	Laparotomy
ATG16L1	Opioid	Lactobacillus acidophilus
Lactoferrin	Mycophenolate mofetil	Flavonoids
Sulfasalazine	Factor XIII	Baicalin
Golimumab	Pentasa	Antisense Oligonucleotide
Certolizumab pegol	Faecalibacterium prausnitzii	Rosiglitazone
Prednisolone	Ciclosporin	Lichen Planus
Helicobacter pylori	Monocyte adsorption apheresis	Leukocyte apheresis
Curcumin	Chitosan	Indigo naturalis
6-thioguanine	Ursodeoxycholic acid	Granulocyte colony-stimulating factor
5-ASA	Smoking cessation	Carbon monoxide
Stem Cell Transplantation	Lactococcus lactis	Adipose-derived stem cells
Appendectomy	Erythropoietin	Triptolide
Thalidomide	Melatonin	Olive oil
Mesenchymal stem cells	Cytapheresis	Muramyl dipeptide
Nicotine	Alicaforsen	L-arginine
Butyrate	Vitamin D3	Hypnotherapy
Moxibustion	Lactobacillus plantarum	<i>Escherichia coli</i> nissle 1917
Hidradenitis suppurativa	GM-CSF	Eicosapentaenoic acid
CT-P13	Ghrelin	Clostridium butyricum
Zinc	Ferric carboxymaltose	Boswellia serrata
Tofacitinib	Estrogen	Akkermansia muciniphila
Natalizumab	Trichuris suis	Vitamin E
Aminosalicylates	Secukinumab	Sodium butyrate

CD14	Remicade	Sargramostim
Metronidazole	Lactulose	Quercetin
Heparin	Lactic acid bacteria	N-Acetylcysteine
Bifidobacterium	Granulocytapheresis	Magnesium
Sulphasalazine	Berberine	Lactobacillus rhamnosus
Interleukin-2	Asacol	Keratinocyte growth factor
Rifaximin	Alkaline phosphatase	Huangqin
Laparoscopy	Dexamethasone	

The existing treatments identified in these previous chronic disease reversal studies, as well as the present IBD study, range from very-low risk to high-risk. Analogous to identifying contributing factors relatively easy to eliminate that were common to these chronic disease studies, 'low-risk' treatments have been identified for early application^[1]. Again, any IBD patient who wants to pursue these 'low-risk' treatments should do so only under strict supervision and guidance of his/her healthcare practitioner.

Appendix 2 - Detailed Treatment Repurposing Methodology using LRDI

Literature-Related Discovery (LRD) for Treatment Repurposing (TR)

Literature-Related Discovery (the discovery component of LRDI) is a systematic approach to bridging unconnected disciplines based on text mining procedures^[7,8]. In the LRD context, discovery is linking two or more literature concepts that have heretofore not been linked (*i.e.*, disjoint), in order to produce novel, interesting, plausible, and intelligible knowledge. In the medical arena, LRD can be used for identifying potentially new treatments for a disease (aka Treatment Repurposing (TR)), identifying potentially new contributing factors for a disease, identifying new biomarkers for a disease, *etc.* 'New' means previously non-existent in the core biomedical literature for the disease of interest.

Structure of Treatment Repurposing Literature

TR is the application of 1) an existing treatment for one or more diseases to 2) diseases or symptoms of interest other than the disease(s) or symptom(s) for which the treatment was developed and/or used initially. Many comprehensive reviews of one component of TR, drug repurposing/repositioning, have been published recently, and these have been summarized^[9].

Overview of LRD-TR Methodology

Treatments of disease or contributing factors to disease result in changes to myriad markers in the body. Some examples in general include:

- *general biomarkers (*e.g.*, neuroinflammation, neurodegeneration, DNA damage, mitochondrial dysfunction, oxidative stress, neurotransmission dysfunction; olfactory dysfunction, glutamate uptake, glucose homeostasis, *etc.*);
- *specific biomarkers (*e.g.*, CRP, IL-1, IL-4, IL-6, ATP, B12, B6, BACE-1, Bax, Bcl-2, BDNF, c-AMP, caspase, folate, GLP-1, GSK-3, *etc.*);
- *symptoms (*e.g.*, abdominal pain, diarrhea, rectal bleeding, insomnia, ataxia, dysphagia, *etc.*);
- *performance (*e.g.*, memory, learning, cognition, *etc.*);

*behaviors (*e.g.*, apathy, depression, anxiety, aggression, agitation, *etc.*);
*others.

The TR discovery approach presented in this article consists of a two-stage process:

Stage 1: Identify critical markers associated with a disease of interest (IBD, in the present case), and identify how the values of those markers change when treatments are operable.

Stage 2: Search the non-disease-of-interest literature (non-IBD literature) for potential treatments that will change the markers of interest in the desired direction.

Stage 1

Identify critical markers and their directions of change associated with existing IBD treatments

Stage 1 of the IBD study identified 1) existing IBD treatments and 2) markers (mainly biomarkers) whose changes from the norm were associated with the existing IBD treatments. The following multiple approaches were used to identify these existing IBD treatments and their associated markers, since no one approach was fully comprehensive.

Visual Inspection

A Visual Inspection approach was used, which consisted of reading the thousands of high frequency abstract phrases in the core IBD literature, and selecting those that appeared to be treatments for IBD. During this process, and in the subsequent confirmatory process that validated the selection of existing IBD treatments, non-biomedical terms were identified that were closely associated with the existing IBD treatments (shown in the next section). These non-biomedical terms could then be (and were) used as 'linking terms', to target phrases (among the millions of abstract phrases) that had high probability of being/including existing IBD treatments.

Linking Term

Diverse linking term approaches have been developed to target records with high probability of containing existing treatments for the disease of interest^[1], but only text terms were used for the IBD study. They proved to be more than adequate, and included: treat*, therap*, prevent*, protect*, improv*, reduc*, attenuat*, ameliorat*, enhanc*, revers*, promot*, alleviat*, inhibit*, remov*, suppress*, mitigat*, restor*, lower*, preserv*, regenerat*, rescu*, slow*.

These linking terms were especially valuable for accessing existing low-frequency IBD treatments (reported infrequently) not accessible from visual inspection of the high-frequency phrases. Some of these linking terms had higher efficiencies of identifying the treatment consequences of interest than others. Terms like prevent*, protect*, improv*, restor*, alleviat*, ameliorat*, mitigat*, *etc.*, almost always gave the desired IBD markers and the direction in which they changed as a result of treatment. Terms like decreas*and increas* (used initially, then abandoned), reduc*, slow*, *etc.*, could go either way. The former group of terms had the 'sense' of improvement, while the latter group of terms reflected change (positive or negative) and may or may not have reflected improvement.

The total number of existing IBD treatments identified by the above approaches (from the premier biomedical literature and validated) numbered about 800-900, depending on how the existing IBD treatments were aggregated. In all the approaches to identifying existing IBD treatments shown above, the initial existing IBD treatments selected were confirmed and validated by detailed reading of the relevant abstracts. Reasons for the large numbers of existing treatments identified are presented in Appendix 3.

During the confirmation and validation process, one or (usually) more record abstracts containing the candidate existing IBD treatment term were read, and other relevant data in the abstract were recorded. These data included biomarkers, symptoms, and behaviors impacted by the treatment(s), and the directions in which these markers were moved (increased, decreased, *etc.*) associated with the treatment. In some/many of these records, one or more existing IBD contributing factor(s) were also identified, as well as the myriad markers associated with the existing IBD contributing factor(s) and the directions

of change these markers experienced associated with the existing IBD contributing factor(s). Some of these contributing factor-related data were also recorded. More existing treatments could have been identified, but identification of approximately 800-900 existing IBD treatments was deemed sufficient for purposes of this paper.

Stage 2

Search the non-disease-of-interest literature for potential treatments that will change the markers of interest in the desired direction.

Text mining of the IBD biomedical literature (especially records focused on treatments) identified the critical markers associated with IBD, and identified the directions in which these critical markers needed to change for potential IBD alleviation. For example, critical general biomarkers for IBD and their desired directions of change included 'reduce oxidative stress', 'reduce inflammation', 'improve barrier function', *etc.* Critical specific biomarkers for IBD and their desired directions of change included 'reduce CRP', 'increase IL-10', 'enhance FoxP3', 'reduce IFN-gamma', *etc.*

From these markers and their desired directions of change for effective treatment of IBD, a query was developed to (1) identify potential IBD treatments from (2) treatments used in the non-IBD literature. The non-IBD biomedical literature was then searched for records that contained at least two IBD markers (that moved in the appropriate direction in conjunction with a treatment), in order to keep the retrieval volume manageable. Even then, the retrieval was voluminous, indicating the wealth of potential IBD treatment repurposing possible from an expanded well-resourced study.

The general form of the query was (1) combinations of the markers and their desired directions of change followed by (2) negation of records that contained existing IBD treatments. The specific query used will be shown after the following paragraph.

Finally, there are no restrictions on the numbers of treatments that could be repurposed for any disease of interest. For example, assume that a patient has been diagnosed with a specific disease, characterized by three abnormal biomarker

values. The query could be applied to identify/discover (1) one treatment that would bring all three of the biomarkers back to normal; or (2) one treatment that would bring two of the biomarkers back to normal and one treatment that would bring the third biomarker back to normal; or (3) three treatments, each of which would bring one of the biomarkers back to normal. Obviously, the repurposed treatments in (2) and (3) would have to be compatible, but the technique offers a wide variety of options.

Specific Query used to Retrieve Candidate Novel Treatments for IBD

ENTER THE FOLLOWING IN SCI-MEDLINE: SEARCH THE TOPIC FIELD

#1 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 (IFN-gamma OR interferon-gamma OR IFNgamma)

#2 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 (IL-1beta OR interleukin-1beta OR "IL-1 beta" OR IL-6 OR interleukin-6)

#3 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("C-reactive protein" OR CRP OR NF-kappaB OR nf-kb)

#4 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("toll-like receptor 4" OR TLR4)

#5 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (IL-10 OR interleukin-10 OR IL10)

#6 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (IL-4 OR interleukin-4 OR IL4)

#7 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (FoxP3 OR Foxp3+)

#8 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("intercellular adhesion molecule-1" OR ICAM-1)

#9 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("vascular cell adhesion molecule 1" OR VCAM-1)

#10 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat*

OR ameliorat*) near/3 ("inducible nitric oxide synthase" OR iNOS)

#11 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("reactive oxygen species" OR ROS)

#12 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 ("lipid *peroxid*")

#13 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 (malondialdehyde OR MDA OR myeloperoxidase OR MPO)

#14 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (glutathione OR GSH)

#15 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 ("nuclear factor-erythroid 2 related factor 2" OR Nrf2)

#16 - (reduc* OR decreas* OR prevent* OR attenuat* OR suppress* OR alleviat* OR ameliorat*) near/3 (permeability)

#17 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 ("barrier function" OR "barrier integrity")

#18 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 ("tight junction*")

#19 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (claudin-1 OR occludins OR ZO-1 OR "zonula occludens-1")

#20 - (enhanc* OR increas* OR improv* OR protect* OR restor*) near/3 (hemoglobin)

ENTER THE FOLLOWING TWENTY BIOMARKER COMBINATORIAL IN
SCI-MEDLINE

(#1 AND #2) OR (#1 AND #3) OR (#1 AND #4) OR (#1 AND #5) OR (#1 AND #6)
OR (#1 AND #7) OR (#1 AND #8) OR (#1 AND #9) OR (#1 AND #10) OR (#1
AND #11) OR (#1 AND #12) OR (#1 AND #13) OR (#1 AND #14) OR (#1 AND
#15) OR (#1 AND #16) OR (#1 AND #17) OR (#1 AND #18) OR (#1 AND #19) OR
(#1 AND #20) OR (#2 AND #3) OR (#2 AND #4) OR (#2 AND #5) OR (#2 AND
#6) OR (#2 AND #7) OR (#2 AND #8) OR (#2 AND #9) OR (#2 AND #10) OR (#2

AND #11) OR (#2 AND #12) OR (#2 AND #13) OR (#2 AND #14) OR (#2 AND #15) OR (#2 AND #16) OR (#2 AND #17) OR (#2 AND #18) OR (#2 AND #19) OR (#2 AND #20) OR (#3 AND #4) OR (#3 AND #5) OR (#3 AND #6) OR (#3 AND #7) OR (#3 AND #8) OR (#3 AND #9) OR (#3 AND #10) OR (#3 AND #11) OR (#3 AND #12) OR (#3 AND #13) OR (#3 AND #14) OR (#3 AND #15) OR (#3 AND #16) OR (#3 AND #17) OR (#3 AND #18) OR (#3 AND #19) OR (#3 AND #20) OR (#4 AND #5) OR (#4 AND #6) OR (#4 AND #7) OR (#4 AND #8) OR (#4 AND #9) OR (#4 AND #10) OR (#4 AND #11) OR (#4 AND #12) OR (#4 AND #13) OR (#4 AND #14) OR (#4 AND #15) OR (#4 AND #16) OR (#4 AND #17) OR (#4 AND #18) OR (#4 AND #19) OR (#4 AND #20) OR (#5 AND #6) OR (#5 AND #7) OR (#5 AND #8) OR (#5 AND #9) OR (#5 AND #10) OR (#5 AND #11) OR (#5 AND #12) OR (#5 AND #13) OR (#5 AND #14) OR (#5 AND #15) OR (#5 AND #16) OR (#5 AND #17) OR (#5 AND #18) OR (#5 AND #19) OR (#5 AND #20) OR (#6 AND #7) OR (#6 AND #8) OR (#6 AND #9) OR (#6 AND #10) OR (#6 AND #11) OR (#6 AND #12) OR (#6 AND #13) OR (#6 AND #14) OR (#6 AND #15) OR (#6 AND #16) OR (#6 AND #17) OR (#6 AND #18) OR (#6 AND #19) OR (#6 AND #20) OR (#7 AND #8) OR (#7 AND #9) OR (#7 AND #10) OR (#7 AND #11) OR (#7 AND #12) OR (#7 AND #13) OR (#7 AND #14) OR (#7 AND #15) OR (#7 AND #16) OR (#7 AND #17) OR (#7 AND #18) OR (#7 AND #19) OR (#7 AND #20) OR (#8 AND #9) OR (#8 AND #10) OR (#8 AND #11) OR (#8 AND #12) OR (#8 AND #13) OR (#8 AND #14) OR (#8 AND #15) OR (#8 AND #16) OR (#8 AND #17) OR (#8 AND #18) OR (#8 AND #19) OR (#8 AND #20) OR (#9 AND #10) OR (#9 AND #11) OR (#9 AND #12) OR (#9 AND #13) OR (#9 AND #14) OR (#9 AND #15) OR (#9 AND #16) OR (#9 AND #17) OR (#9 AND #18) OR (#9 AND #19) OR (#9 AND #20) OR (#10 AND #11) OR (#10 AND #12) OR (#10 AND #13) OR (#10 AND #14) OR (#10 AND #15) OR (#10 AND #16) OR (#10 AND #17) OR (#10 AND #18) OR (#10 AND #19) OR (#10 AND #20) OR (#11 AND #12) OR (#11 AND #13) OR (#11 AND #14) OR (#11 AND #15) OR (#11 AND #16) OR (#11 AND #17) OR (#11 AND #18) OR (#11 AND #19) OR (#11 AND #20) OR (#12 AND #13) OR (#12 AND #14) OR (#12 AND #15) OR (#12 AND #16) OR (#12 AND #17) OR (#12 AND #18) OR (#12 AND #19) OR (#12 AND #20) OR

(#13 AND #14) OR (#13 AND #15) OR (#13 AND #16) OR (#13 AND #17) OR
(#13 AND #18) OR (#13 AND #19) OR (#13 AND #20) OR (#14 AND #15) OR
(#14 AND #16) OR (#14 AND #17) OR (#14 AND #18) OR (#14 AND #19) OR
(#14 AND #20) OR (#15 AND #16) OR (#15 AND #17) OR (#15 AND #18) OR
(#15 AND #19) OR (#15 AND #20) OR (#16 AND #17) OR (#16 AND #18) OR
(#16 AND #19) OR (#16 AND #20) OR (#17 AND #18) OR (#17 AND #19) OR
(#17 AND #20) OR (#18 AND #19) OR (#18 AND #20) OR (#19 AND #20)

ENTER THE FOLLOWING CORE IBD LITERATURE TERMS INTO
SCI-MEDLINE

MeSH

inflammatory bowel diseases OR crohn disease OR colitis, ulcerative

OR

TOPIC

"inflammatory bowel disease*" OR crohn-disease OR crohn's-disease OR
"ulcerative colitis" OR IBD

ENTER THE FOLLOWING EXISTING TREATMENT TERMS IN TOPIC FIELD IN
SCI-MEDLINE

"1,25-Dihydroxycholecalciferol" OR "1,25Dihydroxyvitamin D" OR
"1,25-dihydroxyvitamin D3" OR "21-aminosteroid tirilazad mesylate" OR
"25-hydroxyvitamin D3 1alpha-hydroxylase adoptive gene" OR
"2-methoxy-N-((6-(1-methyl-4-(methylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,
3-b] pyridin-7-yl)pyridin-2-yl)methyl)acetamide" OR "3,3'-Diindolylmethane" OR
"3,4-oxo-isopropylidene-shikimic acid" OR
"3-[(dodecylthiocarbonyl)-methyl]-glutarimide" OR "4-aminosalicylic acid" OR
"4-methoxy-5-hydroxycanthin-6-one" OR "4SC-101" OR
"4-vinyl-2,6-dimethoxyphenol" OR "5-amino salicylic acid" OR
"5'-aminosalicylate" OR "5-aminosalicylate" OR "5-aminosalicylates" OR
"5-aminosalicylic acid" OR "5-amino-salicylic acid" OR "5-ASA" OR "6-Gingerol"
OR "6-heteroaryl-amino-2,4,5-trimethylpyridin-3-ols" OR "6-mercaptapurine" OR

"6-thioguanine" OR "8-Gingerol" OR "Abelmoschus manihot" OR "abrilumab"
OR "ABT-874" OR "Acacia ferruginea" OR "Acarbose" OR "Acellular Bordetella
pertussis vaccine" OR "Acer palmatum thumb." OR
"Acetyl-11-keto-beta-boswellic acid" OR "Aconitum laciniatum" OR "ACTH" OR
"Actinidia arguta" OR "acupuncture" OR "Adacolumn" OR "adacolumn
granulocytapheresis" OR "adalimumab" OR "Adelmidrol" OR "adenosine" OR
"adenovirus expressing IL-18 antisense mRNA" OR "adrenomedullin" OR
"adsorptive leucocytapheresis" OR "AE-941" OR "Aedes aegypti" OR "Agave
americana Linn." OR "AJM300" OR "Akkermansia muciniphila" OR
"alanyl-glutamine" OR "Alequel" OR "Alicaforsen" OR "All Trans Retinoic Acid"
OR "Allicin" OR "Alliin" OR "Allium sativum" OR "allopurinol" OR "Allyl
Isothiocyanate" OR "allyl sulfides" OR "Aloe vera" OR "Aloperine" OR
"alopolysaccharide" OR "alpha-Chitin nanofibrils" OR "alpha-eleostearic acid"
OR "Alpha-interferon" OR "Alpha-lipoic acid" OR "Alpha-Tocopheryl
Succinate-Conjugated G5 PAMAM Dendrimer" OR "aminosalicylate" OR
"aminosalicylates" OR "amlodipine" OR "Amomum villosum" OR
"Amphipterygium adstringens" OR "Anakinra" OR "Andecaliximab " OR
"Andrographis paniculata" OR "Andrographolide" OR "Angelica gigas Nakai"
OR "Angelica sinensis" OR "Antileukotrienic N-arylethyl-2-arylamides" OR
"Anti-NKG2D mAb" OR "antisense oligonucleotide" OR "APC 2059" OR
"apilimod mesylate" OR "Appendectomy" OR "Apple peel" OR "apple
procyanidins" OR "Apremilast" OR "Argon plasma coagulation" OR
"Armamentarium" OR "Armillarisin A" OR "Aronia Berry" OR "Aronia
melanocarpa" OR "Artemisia absinthium" OR "Artemisinin" OR "Artesunate" OR
"Artrofoon" OR "asacol" OR "Ascorbic acid" OR "Asiatic acid" OR "Astragaloside
II" OR "Astragaloside IV" OR "astragalus polysaccharides" OR "ATG16L1" OR
"ATG4B/autophagin-1" OR "atorvastatin" OR "Autologous bone marrow-derived
mesenchymal stromal cell" OR "Averrhoa bilimbi L." OR "AVX-470" OR
"Ayurvedic" OR "azathioprine" OR "Bacillus coagulans SANK 70258" OR
"Bacillus Superoxide Dismutase" OR "Bacterial beta-(1,3)-glucan" OR "Bacterial
beta-glucuronidase" OR "Bacteroides thetaiotaomicron" OR "baicalin" OR

"Baizhu Shaoyao" OR "balsalazide" OR "Banxia xiexin" OR "Basiliximab" OR "Batimastat" OR "Bauhinia tomentosa" OR "Bawei Xilei Powder" OR "Bawei Xileisan" OR "beclometasone dipropionate" OR "beclomethasone dipropionate" OR "belatacept" OR "Berberine" OR "Berberis lycium" OR "beta-D-Mannuronic Acid" OR "beta-sitostanol ester" OR "Betel nut" OR "BGN4" OR "bifidobacteria" OR "bifidobacterium" OR "Bifidobacterium bifidum" OR "Bifidobacterium infantis" OR "Bifidobacterium longum" OR "Bifidobacterium longum" OR "Bilberries" OR "BIRB 796" OR "Bisindole Alkaloid Caulerpin" OR "bismuth subsalicylate" OR "black cumin oil" OR "Blueberry" OR "BMP-7" OR "bolinaquinone" OR "Bombax malabaricum DC" OR "bone marrow transplantation" OR "Bortezomib" OR "Boswellia serrata" OR "Brazilian red propolis" OR "BRG1" OR "Briakinumab" OR "Broccoli" OR "bromelain" OR "Brucea javanica" OR "Bruguiera gymnorrhiza (L.) Lam." OR "BT-11" OR "budesonide" OR "busulfan" OR "Butyrate" OR "Butyric Acid " OR "Butyricoccus pullicaecorum" OR "BX661A" OR "cA2" OR "CAD" OR "Caffeic acid phenethyl ester" OR "Calcipotriol" OR "Calculus Bovis Sativus" OR "calendula officinalis" OR "Calpastatin" OR "camostat mesilate" OR "Cannabinoids" OR "cannabis" OR "canola oil" OR "canolol" OR "Caprylic acid" OR "Carbohydrate Monotony" OR "carbon monoxide" OR "Carbonic Anhydrase I" OR "carboxamidotriazole" OR "Carboxypeptidase E " OR "cardamonin" OR "Cardiotrophin-1" OR "Carnosol " OR "Carpolobia lutea G. Don " OR "Carvedilol" OR "caspase-3 fusion proteins" OR "Cassia obtusifolia" OR "Casticin" OR "Catechin-7-O-beta-D-glucopyranoside" OR "Cathelicidin gene therapy" OR "Caulerpa" OR "cavidine" OR "CB-01-05-MMX" OR "CBLB502" OR "CD40 antisense oligonucleotide" OR "CDP571" OR "CDP870" OR "Cecropin A" OR "Cefepime" OR "celastrol" OR "Celecoxib" OR "cell-surface mucin" OR "Cellulose supplementation" OR "certolizumab pegol" OR "ceruloplasmin" OR "Chaga mushroom" OR "cheese whey protein" OR "chelidonic acid" OR "Chickpea" OR "Childhood helminth exposure" OR "Chitosan" OR "Chitosan oligosaccharide" OR "Chlorogenic Acid" OR "chloroquine" OR "Cholecalciferol" OR "Cholera toxin" OR "Cholestyramine" OR "chondroitin sulfate" OR "Chrysin"

OR "Cicer arietinum L." OR "Ciclosporin" OR "Cimzia" OR "cinnamaldehyde"
OR "ciprofloxacin" OR "Citrus aurantium" OR "Citrus junos Tanaka" OR "Citrus
sinensis" OR "clarithromycin" OR "Clerodane Diterpene" OR "clofazimine" OR
"Clostridium butyricum" OR "Clostridium tyrobutyricum" OR "CMP33" OR
"cocoa" OR "COG112" OR "colchicine" OR "colectomy" OR "Colicin-like
bacteriocins" OR "copper zinc superoxide dismutase" OR "Cordia dichotoma" OR
"Cordia vignei" OR "Cordyceps militaris" OR "Coriolus versicolor " OR
"CORM2" OR "Cortistatin" OR "Costus root granules" OR "Cottonseed Oil" OR
"cranberry" OR "crocin" OR "CSA13" OR "c-Src peptide" OR "CTLA-4Ig" OR
"CT-P13" OR "curcumin" OR "curcuminoid pyrazoles" OR "CuZn SOD" OR
"CX-10" OR "Cx601" OR "CXCL8(3-72)K11R/G31P" OR "Cyanidin-3-glucoside"
OR "Cyanocobalamin" OR "cyclic home elemental enteral alimentation" OR
"cyclophosphamide pulse" OR "cyclophosphane pulse-therapy" OR "Cyclosporin
A " OR "cystatin C" OR "cytapheresis" OR "Daclizumab" OR "Daidzein" OR
"Daikenchuto" OR "Da-Jian-Zhong-Tang" OR "Dandelion root extract" OR
"dapson" OR "darvadstrocel" OR "Dead Sea environment" OR "decursin" OR
"dehydroepiandrosterone" OR "dehydrolovastatin " OR "Demethyleneberberine"
OR "Dendrobium Officinale" OR "Deoxyschizandrin" OR "Desmethylbellidifolin"
OR "Desmoglein 2" OR "Dexamethasone" OR "dextran" OR "DHA" OR "DHEA"
OR "Diallyl trisulfide" OR "diaminodiphenylsulfone" OR "dietary glutathione"
OR "Dimethyl sulfoxide" OR "DIMS0150" OR "Diphenyl diselenide" OR
"diphtheria toxin" OR "DMARDs" OR "DMBT1" OR "Docosapentaenoic acid" OR
"DPA" OR "DR3" OR "duodenal seal oil" OR "*E. coli* Nissle" OR "EB 1089" OR
"ecabet sodium" OR "Echinacea angustifolia" OR "Echinacea spp." OR
"eculizumab" OR "edelfosine" OR "Efalizumab" OR "EGCG" OR "EHLJ7" OR
"eicosapentaenoic acid" OR "Eldelumab" OR "ellagic acid" OR "ellagic
acid-enriched pomegranate" OR "eltrombopag" OR "embelin" OR "Emodin" OR
"Emu oil " OR "Encenicline" OR "Enprostil" OR "Enterococcus faecalis EF-2001"
OR "epicatechin" OR "epigallocatechin-3-gallate" OR "Epiisopiloturine" OR
"Erbin" OR "ertapenem" OR "ES-62" OR "*Escherichia coli* Nissle 1917" OR
"estrogen" OR "Etanercept" OR "ethacridine lactate" OR "etidronate" OR

"etoricoxib" OR "Etrolizumab" OR "Eubacterium limosum" OR "Eucheuma cottonii" OR "everolimus" OR "EW-7197" OR "extra virgin olive oil" OR "factor XIII" OR "FADD" OR "Faecalibacterium prausnitzii" OR "Fasting-Mimicking Diet" OR "Fc-fused PD-L1" OR "Febuxostat " OR "fecal bacteriotherapy" OR "Fecal Microbiota Transplantation" OR "Feijoa " OR "Fenofibrate" OR "Fermentable Carbohydrate Restriction" OR "fermented grain" OR "fermented rice" OR "Fermented Rice Bran" OR "Ferric carboxymaltose" OR "Ferric maltol" OR "Ferulic acid" OR "Ficus carica" OR "Filgotinib" OR "Fish oil " OR "FK506" OR "FKBP11 " OR "Flaxseed" OR "Flos Ionicerae" OR "Flt3 ligand" OR "fludarabine" OR "Flunixin" OR "Fluoxetine" OR "Flupentixol-Melitracen" OR "FTY720" OR "Fufangkushen" OR "Fumigaclavine C " OR "fusidic acid" OR "Galacto-oligosaccharides" OR "galangin" OR "Galectin-1" OR "Gallic acid " OR "gallotannin corilagin " OR "garden cress seed oil" OR "Garidisan" OR "Garlic oil" OR "Gegen Qinlian" OR "Gelatin tannate" OR "Geniposide" OR "Genistein" OR "Gentamicin" OR "Gentianella acuta" OR "gentiopicroside" OR "Gepon" OR "geraniol" OR "Geranylgeranylacetone" OR "Germ therapy with IL-10" OR "germinated barley" OR "ghrelin" OR "Ginkgo biloba" OR "ginsenoside Rd" OR "GL1001" OR "glatiramer acetate" OR "GLM" OR "GLP2-2G-XTEN" OR "Glucosylceramide" OR "gluten-free diet" OR "Glyceollins" OR "Glycyrrhetic Acid" OR "GMA" OR "GM-CSF" OR "Goji Berry" OR "gold nanoparticles" OR "golimumab" OR "granulocytapheresis" OR "granulocyte" OR "Granulocyte and monocyte adsorption apheresis" OR "granulocyte apheresis" OR "granulocyte colony-stimulating factor" OR "granulocyte macrophage-colony stimulating factor" OR "Granulocyte Monocyte Adsorption Apheresis" OR "granulocyte/monocyte adsorptive apheresis" OR "granulocyte-colony stimulating" OR "Granulocyte-monocyte apheresis" OR "Granulomonocytapheresis" OR "Grape Pomace" OR "grape seed extract " OR "grape seeds" OR "green tea" OR "Grifola frondosa" OR "GSK-1605786" OR "GSK2586184" OR "guar gum" OR "guben yichang" OR "guggulsterone" OR "Guselkumab" OR "Gymnema sylvestre" OR "H. attenuatum Choisy" OR "HE3286" OR "Heald Silastic Anal Stent" OR "Helicobacter pylori" OR

"Heligmosomoides polygyrus bakeri" OR "Helminth therapy" OR "Helminths"
OR "Heparin" OR "heparin--a" OR "herbal" OR "Herb-partitioned moxibustion"
OR "herbs-partitioned moxibustion" OR "Hev b 13" OR "hidradenitis
suppurativa" OR "histamine receptor ligands" OR "HMPL-004" OR "honey" OR
"Honey Polyphenols" OR "Huangkui Lianchang" OR "Huang-lian-Jie-du" OR
"Huangqin" OR "Human filarial proteins" OR "Humira" OR "hydrogen-rich
saline" OR "Hydrogen-rich water" OR "hydroquinone zonarol " OR
"Hydroxychloroquine" OR "hydroxynaphthoquinone" OR "hyperbaric oxygen"
OR "hyperbaric oxygenation" OR "Hypnosis" OR "hypnotherapy" OR "Hypoxis
hemerocallidea corm" OR "ibandronate" OR "ICAM-1 antisense oligonucleotides"
OR "IgG4-Guided Exclusion Diet" OR "Iguratiomod" OR "IL-10 therapy" OR
"IL-27 recombinant bacteria" OR "IL2-caspase 3" OR "IL-35 recombinant protein"
OR "IL-37b gene transfer" OR "ileo-rectal anastomosis" OR "ilomastat" OR
"imiquimod" OR "immunoglobulin G enemas" OR "Indicaxanthin" OR "indigo
naturalis" OR "indirubin" OR "Inflectra" OR "Infliximab" OR "Inonotus obliquus
polysaccharide" OR "interleukin-10 gene therapy" OR "interleukin-4 gene
therapy" OR "interleukin-4 gene transfer" OR "intravenous immunoglobulins" OR
"intravenous iron" OR "iron replacement " OR "IS-741" OR "isatin" OR
"isorhamnetin" OR "isotretinoin" OR "itraconazole" OR "IVIG" OR "Ixekizumab"
OR "Jianpi Qingchang" OR "Jiechangning" OR "JTE907" OR "jujube" OR
"Kaempferol " OR "KAG-308" OR "Kampo" OR "Kangfuxin" OR "kefir grain
Lactobacillus" OR "Keratinocyte growth factor" OR "Ketotifen" OR "kininogen"
OR "KIOM-MA128" OR "Kireno" OR "Kiwifruit" OR "Kolaviron" OR "krill oil"
OR "Kuijieling" OR "kuijiening plaster" OR "Lacteol Fort" OR "Lactic acid
bacteria" OR "Lactobacillus acidophilus" OR "Lactobacillus bulgaricus OLL1181"
OR "Lactobacillus casei DN-114 001" OR "Lactobacillus paracasei subsp. paracasei
B21060" OR "Lactobacillus plantarum" OR "Lactobacillus plantarum 21" OR
"Lactobacillus plantarum K68" OR "Lactobacillus plantarum Sanriku-SU7" OR
"Lactobacillus reuteri" OR "Lactobacillus reuteri F-9-35" OR "Lactobacillus
rhamnosus" OR "Lactococcus lactis" OR "Lactococcus lactis subsp. cremoris FC
" OR "lactulose" OR "lafutidine" OR "Lagerstroemia speciosa" OR "laparoscopy"

OR "laparotomy" OR "Laquinimod" OR "laquinimod D-alpha-tocopheryl polyethylene glycol-1000 succinate polymeric micelles" OR "Lateolabrax maculatus" OR "LB-9" OR "lecithinized superoxide dismutase" OR "Leflunomide" OR "lenalidomide" OR "lentinan" OR "Lentinus edodes beta-glucans" OR "Lepidium sativum" OR "Let-7b" OR "leukocytapheresis" OR "Leukocyte adsorptive apheresis" OR "leukocyte apheresis" OR "lichen planus" OR "Licochalcone A" OR "lidocaine" OR "Limonin" OR "linalool" OR "linoleic acid" OR "liriodendrin" OR "LK 423" OR "Lonicera japonica" OR "loperamide" OR "loratadine" OR "losartan" OR "low molecular weight heparin" OR "LRH-1" OR "Lupeol" OR "Luteolin" OR "lycopene" OR "Lyprinol" OR "M10" OR "M2000" OR "Maggot protein" OR "magnesium lithospermate B" OR "magnetic silica mesoporous particles" OR "malva parviflora l." OR "Mangiferin" OR "Mangosteen" OR "Maqui berry" OR "Maresin 1" OR "mastiha" OR "matrine" OR "Matriptase" OR "Maxipime" OR "mCRAMP-encoding plasmid " OR "Mekabu" OR "Mepolizumab" OR "Mercaptopurine" OR "mesalamine" OR "mesalazine" OR "Mesna" OR "metallic enteral endoprosthesis" OR "Metformin" OR "methadone" OR "Methane-Rich Saline" OR "methotrexate" OR "Methyl jasmonate" OR "Methylococcus capsulatus" OR "methylprednisolone" OR "methylthioadenosine" OR "metronidazole" OR "mexiletine" OR "MG132" OR "MICA*A4" OR "Misoprostol " OR "MLN0002" OR "MMF" OR "MMX" OR "mongersen" OR "monocyte adsorption apheresis" OR "monocyte apheresis" OR "Monofloral honey" OR "Morinda officinalis" OR "Moringa oleifera root" OR "Moxibustion" OR "mucoadhesive azopolymer" OR "Mumiju" OR "Muramyl dipeptide" OR "muscovite" OR "mycophenolate mofetil" OR "Mycophenolate sodium" OR "myricetin" OR "Myrrh" OR "N-(3', 4'-dimethoxycinnamonyl) anthranilic acid " OR "N-3 fatty acids" OR "N-3 polyunsaturated fatty acid" OR "n3 polyunsaturated fatty acids" OR "n-3 polyunsaturated fatty acids" OR "N-acetyl-L-cysteine" OR "naltrexone" OR "naringenin" OR "Naringin" OR "Natalizumab" OR "natural interferon-beta" OR "NCB-02" OR "NCIMB 41856" OR "Neferine" OR "Neoral" OR "Neorogioltriol " OR "NF-kappa B decoy oligonucleotides" OR "nicotine" OR "Nigella sativa" OR "Nimbolide" OR

"nimesulide" OR "NLRP1" OR "NLRP12" OR "nonanoic acid" OR "Noripurum EV" OR "Norisoboldine" OR "Notoginsenoside R1" OR "Novaferon" OR "NOVOX" OR "NS6180" OR "nucleotide synthesis enzyme CAD" OR "NUR77" OR "Nv-52" OR "Oat beta-glucan" OR "octreotide" OR "oleic acid" OR "Oleuropein" OR "Oligomannan" OR "Oligonol" OR "olive leaf" OR "olive oil" OR "Olmesartan" OR "olsalazine" OR "Omalizumab" OR "Omega-3 fatty acids" OR "Opioid" OR "Opuntia dillenii Haw." OR "Oridonin" OR "Ornidazole" OR "Oroxindin" OR "ox bile" OR "Oxymatrine" OR "oxypurinol" OR "Ozone" OR "P. subpeltata Ortega" OR "PACAP" OR "paeoniflorin" OR "Palm oil tocotrienol" OR "Palmitoylethanolamide" OR "Papaverine" OR "Paraoxonase-1" OR "Parthenolide" OR "Passiflora edulis peel" OR "PDA001" OR "PDA-001" OR "Peanut shell extract" OR "Peficitinib" OR "pegfilgrastim" OR "Pelargonidin 3-glucoside" OR "pembrolizumab" OR "Pentadecapeptide BPC 157" OR "Pentasa" OR "Peony" OR "Peptidoglycan" OR "Periplaneta americana" OR "petrosaspongiolide M." OR "PF-00547659" OR "PGRN" OR "phenantrolin" OR "phloretin" OR "Phosphatidylcholine" OR "Phosphorylcholine-tuftsins" OR "phthalimido-desmuramyl-dipeptide compound" OR "piceatannol" OR "Pien Tze Huang" OR "Pingwei San" OR "piperine" OR "Pirfenidone" OR "Pistacia lentiscus" OR "Plaquenil" OR "polaprezinc" OR "polycurcumin" OR "Polydatin" OR "polydextrose" OR "polyenylphosphatidylcholine" OR "polyethylene glycosylated porcine glucagon" OR "Polygonum cuspidatum Siebold" OR "Polypectomy" OR "polyunsaturated fatty acids" OR "Portulaca" OR "Portulaca oleracea L" OR "potassium iodide" OR "pravastatin" OR "prednisolone" OR "prednisolone metasulphobenzoate" OR "proctocolectomy" OR "Proglumide" OR "Prohibitin" OR "propionyl-L-carnitine" OR "Propionyl-L-carnitine hydrochloride" OR "Protectin D1n-3 DPA" OR "Protein-bound polysaccharide-K" OR "protocatechuic acid" OR "psychoanalytic treatment" OR "Pterocarpus marsupium" OR "Pulsatilla" OR "Pulsatillae Radix" OR "Pulvis Fellis Suis" OR "purslane" OR "pycnogenol" OR "Pyridostigmine Bromide" OR "Qing Chang Hua Shi" OR "Qing Hua Chang Yin" OR "Qingchang Wenzhong" OR "quercetin" OR "R68070" OR "radon" OR "rapamycin" OR "Rauvolfia verticillata" OR

"Rauwolfia verticillata" OR "RDP58" OR "Rebamipide" OR "Recombinant alfa-2 interferon" OR "Recombinant erythropoietin" OR "recombinant factor VIIa" OR "recombinant growth hormone" OR "recombinant human erythropoietin" OR "Recombinant human interleukin 10" OR "recombinant human interleukin-11" OR "Recombinant human MFG-E8" OR "recombinant interferon alfa-2b" OR "Recombinant interleukin 10" OR "Recombinant Thrombomodulin" OR "Red Alga Laurencia" OR "Red Ginseng" OR "Remicade" OR "Repifermin" OR "resistant starch" OR "resolvin D5n-3 DPA" OR "Resolvin E1" OR "resveratrol" OR "RHB-104" OR "Rheum tanguticum" OR "Rhizophora apiculata" OR "Rhubarb Peony" OR "rHuKGF" OR "Ridogrel" OR "rifabutin" OR "rifaximin" OR "Risankizumab" OR "ritonavir" OR "rituximab" OR "Rivastigmine" OR "Ro 48-5695" OR "Ro60" OR "Roflumilast" OR "Roseburia" OR "rosiglitazone" OR "rosuvastatin" OR "rSj16" OR "rutin" OR "rutoside" OR "ruxolitinib" OR "rWbL2" OR "Saccharomyces boulardii" OR "saireito" OR "Salazosulfapyridine" OR "sanguinarine" OR "Sanhuang Shu'ai" OR "Sanshensancao" OR "Sarcodon aspratus" OR "sargramostim" OR "SB203580" OR "schisandrin B" OR "schizophyllan" OR "Scutellariae radix" OR "Sea Bass" OR "Seaweeds" OR "secukinumab" OR "selectie granulocyte" OR "selenium" OR "semapimod" OR "Semen Coicis" OR "Serp in B1" OR "Sesbania grandiflora" OR "Seton" OR "SEW2871" OR "SGK1" OR "SGLT-1" OR "Shark fin" OR "Shenzhu Capsule" OR "Shikonin" OR "shogaol" OR "Shuxuening" OR "Sijunzi" OR "sildenafil citrate" OR "silver-coated glass beads" OR "simvastatin" OR "Si-Ni-San" OR "sinomenine" OR "sirolimus" OR "Siropins" OR "Sirtuin 1" OR "SM934" OR "Smad nuclear interacting protein 1" OR "Small bowel transplantation" OR "Smoking Cessation" OR "SOCS1" OR "sodium alginate" OR "Sodium Butyrate" OR "sodium fluoride" OR "sofosbuvir" OR "somatostatin" OR "sophocarpine" OR "Sour Cherry" OR "Soy protein" OR "Soy sterol esters" OR "SP140" OR "SP600125" OR "SpaceOAR" OR "Spinacia oleracea" OR "Spirulina platensis" OR "Srf" OR "St. John's wort" OR "Stool transplantation" OR "Streptococcus thermophilus" OR "Streptococcus thermophilus ST28" OR "Streptokinase" OR "streptokinase therapy" OR "Strontium chloride" OR "Structured physical

activity" OR "Substance-P" OR "Sugar Cane" OR "Sulfasalazine" OR "Sulphasalazine " OR "sunitinib" OR "syngingic acid" OR "TA-2711E" OR "Tacrolimus" OR "Tacrolimus enema" OR "Tagetes erecta L" OR "tamarind xyloglucan" OR "tannin albuminate" OR "Tanshinone IIA" OR "Taurine" OR "taurolidine" OR "Tauroursodeoxycholate" OR "Tauroursodeoxycholic acid" OR "TCM differential" OR "Teduglutide" OR "Telmisartan" OR "tenascin-C" OR "Tenovil" OR "Tetomilast" OR "Tetramethylpyrazine" OR "thalidomide" OR "thalidomide analogues" OR "Thespesia populnea" OR "Thioguanine" OR "thiopurine" OR "Thrombospondin peptide ABT-898" OR "Thrombospondin-1 type 1" OR "tinzaparin" OR "tioguanine" OR "TNF-alpha B cell epitope MAP vaccine" OR "tobramycin" OR "Tocotrienol-Rich Fraction" OR "Tofacitinib" OR "tolerogenic dendritic cells" OR "topical 0.5% nicotine cream" OR "Topical butyrate" OR "Topical glutamine" OR "total body irradiation" OR "Tou Nong San" OR "tranilast" OR "trans-delta-Viniferin" OR "Transfection of IL-10 expression vectors" OR "Triazolopyridines" OR "Trichuris suis" OR "Trichuris suis ova" OR "trigonelline" OR "Tripterygium glycoside" OR "Tripterygium wilfordii Hook" OR "Tripterygium wilfordii polyglycoside" OR "Tripterygium Wilfordii poly-glycoside" OR "Triptolide" OR "tropisetron" OR "tryptophan" OR "TSG-6" OR "Turmeric" OR "TV-5010" OR "TX527" OR "TY-51469" OR "Tyrosol" OR "ubiquinol" OR "Ulmus macrocarpa hance" OR "ultrasound" OR "unfractionated heparin" OR "UR-1505" OR "urocortin" OR "Ursodeoxycholic acid" OR "Ursolic acid" OR "ustekinumab" OR "vasoactive intestinal peptide" OR "vasoactive intestinal polypeptide-immunoreactive" OR "VCAM-1 antisense oligonucleotides" OR "vedolizumab" OR "VEGF164b" OR "VEGF-C" OR "vercirnon" OR "Veronica polita" OR "Vitamin A" OR "Vitamin D" OR "Vitamin D3" OR "vitamin E" OR "Vitex negundo" OR "VPR-254" OR "VSL#3" OR "whey protein" OR "Withania somnifera root" OR "WKYMVm" OR "Wormwood" OR "XG-102" OR "Yersinia" OR "Yoghurt" OR "Yunnan Baiyao" OR "Yuzu" OR "Zanthoxylum bungeanum" OR "Zeolite" OR "Zhenrenyangzang" OR "zhikang" OR "Zileuton" OR "Zinc gluconate" OR "Ziziphora clinopoides" OR "Ziziphus spina-christi" OR "ZnO" OR "Zoledronic acid" OR "bowel" OR "intestinal" OR

"colitis" OR "colon" OR "colonic" OR "gastrointestinal" OR "ileal" OR
"colorectal" OR "colectomy" OR "intestine" OR "colonoscopy" OR "anastomosis"
OR "rectal" OR "ileum" OR "perianal" OR "proctocolectomy" OR "ileostomy" OR
"anal" OR "rectum" OR "gastroenterology" OR "pouchitis" OR "pouch-anal" OR
"anastomotic" OR "colonoscopic" OR "pancolitis" OR "proctitis" OR "ileoanal"
OR "ileocolonoscopy" OR "adenomatous polyposis" OR "ileocolic" OR
"gastroenterologist" OR "proctectomy"

ENTER THE FOLLOWING (RETRIEVAL MINUS NEGATION TERM) QUERY IN
SCI-MEDLINE

#21 NOT (#22 OR #23)

Appendix 3 - Definition of Treatments used for Reversal Protocol and Present Study

Treatments can be viewed generally as actions taken to improve health. Existing treatments in the IBD study were defined mainly as any positive actions taken to improve health reported in the core IBD literature. These treatments ranged from laboratory experiments on non-human species to successful clinical trials and commercial usage. A very large number of existing treatments were identified in the present study, as well as all three chronic disease and prevention studies performed previously. In all these studies, the treatments identified included research over the past approximately two-three decades. Treatments that have 'failed' in human clinical trials were not excluded. The reason for retaining these 'failed' treatments is as follows:

Reading of thousands of abstracts on laboratory experiments and clinical trials of potential chronic disease treatments has shown: (1) *in vitro* experiments typically performed on cells tend to have reasonably positive outcomes, at least for those papers that surface in the peer-reviewed published literature; (2) *in vivo* experiments typically performed on rodents (but other small animals as well) tend to also have reasonably positive outcomes, albeit somewhat less than *in vitro* experiments; and (3) when these potential treatments reach the human clinical trial stage, especially the later phases, the success rates plummet!

The explanation for this discrepancy given most often is the species difference. Humans are different from rodents *et al*, and their physiological responses to stimuli are different as well. However, the toxic experiential and exposure background differences between; (1) humans who live in the real-world sea of myriad toxic exposures; and (2) animals who live in the very controlled and relatively pristine environment of the laboratory are rarely, if ever, discussed.

For the present study, and especially for the more extensive three chronic diseases studied previously, there were many hundreds of potential contributing factors identified (ranging from Lifestyle to Occupational/Environmental exposures). For a given individual, some causes have happened in the past, and

are no longer happening, but their damage trail remains. Other causes are ongoing, have caused damage, and continue to cause damage.

Why would anyone expect a human being with such a toxic history to respond to a potential treatment the same way that a laboratory animal raised in a controlled and relatively pristine environment would respond to that treatment? Furthermore, why would anyone expect a human being with such a toxic history to respond to a potential treatment the same way that another human being without such a toxic burden would respond to that treatment?

Consider the example of Dr. Terri Wahls, an M.D. who (by her own account) was able to reverse her own case of MS (Multiple sclerosis)^[6,10]. She used two main types of treatments; lifestyle changes (mainly dietary) to reverse the MS, and NMES (Neuromuscular Electrical Stimulation) to reverse the damage resulting from MS. It was only when her diet achieved substantial improvement that the NMES produced positive effects.

While Dr. Wahls' experience represents one data point only, it is a very powerful data point. Consider its implications. Suppose a clinical trial were conducted to evaluate the potential for NMES to reverse the damage from MS. Suppose further that Dr. Wahls' dietary-dominant contributing factor to MS and her reaction to NMES were typical of the participants in such a clinical trial. If the participants did not address their diet (with the rigor shown by Dr. Wahls) during the clinical trial, they would not respond positively to the NMES (as was the case for Dr. Wahls initially). The trial would be interpreted as a failure of NMES. However, in this hypothetical example, the NMES ineffectiveness is not the reason for the clinical trial's lack of success. Failure to remove the cause of the disease and subsequent damage is the problem! Failure to remove cause as a reason for the very limited success of myriad treatments in the clinical trials of the past three decades cannot be ruled out.

That is why even so-called 'failed' treatments were included in the studies of the three chronic diseases, and are included in the present study under existing treatments shown in Appendices 1 and 2. It cannot be stated conclusively which treatments failed because; (1) they were intrinsically ineffective; or (2) their

beneficial effects were overwhelmed by the strong negative effects of the ongoing causes remaining operable. In fact, it is unknown whether comprehensive, timely, and thorough removal of the relevant contributing factors for each of the three diseases (and IBD) by themselves would have obviated the need for many of these treatments!

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