

## Prevention and Reversal of Peripheral Neuropathy/Peripheral Arterial Disease

by

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### KEYWORDS

Peripheral Neuropathy; Peripheral Arterial Disease; Peripheral Vascular Disease; Neurodegeneration; Text Mining; Literature-Based Discovery; Information Technology; Treatments

### ABSTRACT

This monograph presents a five-step treatment protocol to prevent and reverse Peripheral Neuropathy (PN)/Peripheral Arterial Disease (PAD), 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*. Implementation of the five-step PN/PAD treatment protocol is as follows:

#### **FIVE-STEP TREATMENT PROTOCOL TO PREVENT AND REVERSE PN/PAD**

- Step 1:** Obtain a detailed medical and habit/exposure history from the patient.
- Step 2:** Administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms and degradation of executive functions
- Step 3:** Administer laboratory tests (blood, urine, imaging, etc)
- Step 4:** Eliminate ongoing PN/PAD contributing factors
- Step 5:** Implement PN/PAD treatments

This individually-tailored PN/PAD treatment protocol can be *implemented with the data currently available in the biomedical literature*. Additionally, while the methodology developed for this study was applied to comprehensive identification of diagnostics, contributing factors, and treatments for PN/PAD, it is general and applicable to any chronic disease/condition that, like PN/PAD, has an associated substantial research literature. Thus, the protocol and methodology developed to prevent or reverse PN/PAD can be used *to prevent or reverse any chronic disease* (with the possible exceptions of individuals with *strong genetic predispositions* to the disease in question or who have suffered *irreversible damage* from the disease).

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**DISCLAIMERS**

The views in this monograph are solely those of the author, and do not represent the views of the Georgia Institute of Technology.

This monograph is not intended as a substitute for the medical advice of physicians. The reader should regularly consult a physician in matters relating to his/her health and particularly with respect to any symptoms that may require diagnosis or medical attention. Any information in the monograph that the reader chooses to implement should be done under the strict guidance and supervision of a licensed health care practitioner.

## PREFACE

Why was this monograph written, what are its contents, what is new, who is the intended audience, and how will readers benefit from it?

### Motivation

Non-communicable diseases have overtaken communicable diseases as the leading cause of global mortality. The impacts of non-communicable disease expansion on healthcare and associated costs have been dramatic. In the USA, these costs, and how to deal with them, have become a central political issue.

The mainstream medical approach emphasizes treatments over prevention for non-communicable diseases. Given the expansion of non-communicable diseases, the present treatment-dominant approach is insufficient. More balance between treatment and prevention is required. Eliminating the actionable foundational causes of these diseases is at least as important as applying new treatments, if there is to be any hope for full or partial reversal of non-communicable diseases.

Toward that end, I developed the following systemic medical principle that would form the bedrock of a healing protocol for diseases: **At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective** (where "removal" encompasses "neutralization" in those cases where actual "removal" is not possible, and "restoration" encompasses restoration of *health* to the organ/tissue as well as restoration of *function*). To prevent disease, the actionable [foundational causes](#) that underlie the disease symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse disease (if irreversible damage has not been done and genetic predisposition to the disease in question is not a dominant factor), the preventive steps above need to be implemented as well. If the preventive protocols alone are inadequate for reversing disease progression, they need to be augmented by treatments. The first step in either disease prevention or reversal is to identify the full spectrum of potential foundational causes/contributing factors for the disease(s) of interest.

The present monograph identifies a wide spectrum of PN/PAD contributing factors, treatments, biomarkers, and symptoms/related diseases. It shows linkages among these categories, and especially the impacts of contributing factors and treatments on biomarkers and symptoms. The final product is a PN/PAD treatment protocol that can be tailored to the individual.

### Contents

The overall theme of the present monograph is preventing and reversing PN/PAD based on the systemic medical principle described above. The specific focus of the present monograph is identifying, categorizing, and analyzing the existing PN/PAD contributing factors and

treatments, and potential PN/PAD treatments. Identification of these existing and potential PN/PAD contributing factors, and potential PN/PAD treatments is based on analysis of many thousands of biomedical journal articles from the premier biomedical literature.

Moreover, identifying both PN/PAD contributing factors and treatments, in concert with identifying their impacts on specific PN/PAD biomarkers, symptoms, behaviors, performance, etc, allows PN/PAD treatment protocols to be tailored to each person's unique condition. This monograph presents the comprehensive PN/PAD treatment protocol I have developed, and provides illustrative examples of how the PN/PAD treatment protocol would be implemented. Sufficient data and text are presented to make this monograph self-contained.

There is a lengthy section in the present monograph describing

- 1) the [text mining](#)/information technology advances that allowed the existing PN/PAD contributing factors, and existing and potential PN/PAD treatments to be extracted efficiently from the large numbers of journal articles retrieved from the premier biomedical literature, and
- 2) the impacts of these contributing factors and treatments extracted from the literature.

Major advances were made in the text mining approach for extracting both existing and potential treatments, and existing contributing factors, from the biomedical literature (and their impacts). These advances could be applied to identifying existing and potential foundational causes for any disease from the literature as well.

### Novelty

While the individual existing and potential PN/PAD treatments identified in this monograph are "known", in the sense that they exist scattered throughout the published literature (although the *potential* PN/PAD treatments have not been previously associated with PN/PAD in the literature), they have not been integrated to the extent they are integrated in this monograph. The new "insights" in this monograph are:

- 1) the sheer number of existing PN/PAD contributing factors, and existing and potential PN/PAD treatments;
- 2) the sheer number of potential *combinations* of PN/PAD contributing factors and treatments that have to be identified and researched (many of whose individual components have not yet been identified);
- 3) the sheer number of PN/PAD biomarkers and symptoms that can be used as diagnostics to identify causes and treatments for individual patients;
- 4) the approach for discovering treatments from the non-PN/PAD literature, which allows both the *re-purposing of drugs* that have been used for treating other diseases and identification of non-drug substances that will correct the abnormal PN/PAD biomarker values and symptoms;

5) the PN/PAD treatment protocol that can be tailored to any individual patient.

### **Audience**

There are three communities to whom this monograph is targeted. First is the "PN/PAD prevention and reversal" community. This encompasses the public health community, the PN/PAD research community, medical practitioners involved clinically with PN/PAD prevention and reversal, healthcare support personnel for PN/PAD patients, and individuals interested in what the present approach has to offer (they should heed the warnings in the Disclaimer). The PN/PAD treatment taxonomies and discussions in Chapter 2, and the treatment protocol in Chapter 3, should be of particular interest to this community.

Second is the text mining and information technology community. This would cover the full spectrum of researchers interested in extraction of useful information from any type of text, since the techniques developed in this monograph can be readily adapted to extracting useful information from myriad types of biomedical and non-biomedical text. The concepts, algorithms, and discussions in Chapter 6 should be of special interest to this community.

Third is the broader medical and health policy community. While the findings in the present monograph relate specifically to PN/PAD prevention and reversal, the **methodology is applicable to prevention and reversal of any disease** that has an associated substantial research literature.

### **Benefits**

The interested reader of this monograph will gain a deeper understanding of the main contributing factors to, and treatments for, PN/PAD. The reader will also gain an understanding of the broad spectrum of rigorous actions required to prevent and/or reverse PN/PAD. Finally, and most importantly, the motivated reader will see that much of what is required to prevent and reverse PN/PAD **may be available in the here and now** (for those who have not suffered irreversible damage or do not have an overwhelming genetic predisposition for PN/PAD)!

Ronald N. Kostoff, 20 September 2019, Gainesville, VA

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## EXECUTIVE SUMMARY

### ES-1. Overview

The treatment protocol proposed for prevention and reversal of PN/PAD in the present monograph is based on the following systemic medical principle [Kostoff, Porter, Buchtel, 2018]: ***At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective.*** This principle is general, and applicable to prevention and reversal of *any* disease. The methodology that has been developed based on this principle is general, and applicable to any disease as well.

To prevent any disease, the [foundational causes](#) that underlie the disease symptoms and biomarkers need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse any disease (if irreversible damage from the disease has not been done and strong genetic predisposition to the disease is not a dominant factor), the preventive steps above need to be implemented, and [treatments](#) to reverse the disease progression need to be applied.

The efficacy of the methodology for preventing and reversing any disease depends on how thoroughly the foundational causes, treatments, biomarkers, and symptoms of the disease of interest have been identified. In the present monograph, a wide spectrum of existing PN/PAD foundational causes has been identified using a Literature-Related Discovery and Innovation (LRDI) methodology (see Chapter 6 for details of methodology). Additionally, a wide spectrum of existing (and a few newly discovered) PN/PAD treatments and PN/PAD symptoms and biomarkers has been identified. Combining these results allows development of a PN/PAD treatment protocol that can be tailored to individual patients. Most importantly, this PN/PAD treatment protocol (based on the systemic medical principal described above) is **available with the information at our disposal today!**

For a more detailed overview, see [Chapter 1](#).

### ES-2. Results

#### ES-2A. Existing PN/PAD Contributing Factors

[Table 7A-1](#) contains a list of the ~840 existing contributing factors (in the present monograph, 'cause' and 'contributing factor' are used interchangeably) identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these contributing factors are shown in [Table 2B-1](#). Because these are the highest frequency contributing factors, many will be very general.

**Table 2B-1 - Top Fifty Existing PN/PAD Contributing Factors**

<b>#RECORDS</b>	<b>CONTRIBUTING FACTOR</b>
2507	chemotherapy
2265	smoking
1140	High cholesterol diet
985	paclitaxel
821	HIV-1
745	dialysis
708	infections
683	viruses
570	cisplatin
570	trauma
545	depression
524	oxaliplatin
508	hemodialysis
503	Bortezomib
442	alcohol
393	alcohol consumption
378	highly active antiretroviral therapy
361	radiation
357	anesthesia
351	thalidomide
347	vincristine
340	peripheral nerve injury
337	lifestyle
332	leprosy
329	radiation therapy
324	taxanes
323	cyclophosphamide
314	hepatitis
296	Streptozotocin
230	carboplatin
217	platinum
201	chronic constriction injury
196	docetaxel
186	Hepatitis C Virus
184	antibiotics
162	doxorubicin
149	Arsenic
148	stavudine
140	5-fluorouracil
131	sedentary
125	advanced glycosylation end products
121	capecitabine
121	tuberculosis

119	zidovudine
118	latrogenic
118	Taxol
111	methotrexate
110	lenalidomide

Categorization and analysis of these contributing factors will be shown in the next section.

#### ES-2B. Factor Matrix of Existing Contributing Factors

Figure 2B-1 in the Excel workbook located under the same URL as the present monograph (FIGURES\_FOR\_MONOGRAPH.xlsx - listed under View/Open on the link page) contains a factor matrix of the existing PN/PAD contributing factors (click on first tab FIG 2B-1). The 29 factor headings are shown below in [Table 2B-2](#). This listing provides a convenient taxonomy for categorizing the myriad contributing factors identified. Figure 2B-1 lists the specific contributing factors that had the strongest influence in determining the theme of each of the 29 factors.

The main broad categories include:

- drugs (e.g., antiretroviral, chemotherapy, antifungal, antibiotics, antiarrhythmic/cardiovascular, statins [PN only]),
- pesticides/herbicides (e.g., dioxin, Chlorophenoxy herbicides, trichlorophenol, Paraquat, Trichlorfon, dichlorvos, mipafox, organophosphate pesticides, malathion, chlorpyrifos),
- infectious agents (e.g., bacteria, mycobacteria, viruses),
- occupational/industrial chemicals (e.g., organic solvents, hydrocarbons, dithiocarbamates, benzene, organotin, methyl n-butyl ketone),
- environmental pollutants (e.g., heavy metals, persistent organic pollutants, air pollution, bisphenol A),
- induced injury (e.g., lysophosphatidic acid, N-methyl-D-aspartate, Freund's adjuvant, partial sciatic nerve ligation),
- lifestyle (e.g., excess alcohol, recreational drugs, smoking, sedentary, high cholesterol diet)

**Table 2B-2 - Factor Matrix-based Categories for PN/PAD Contributing Factors**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - HIGHLY ACTIVE ANTIRETROVIRAL THERAPY</b>
<b>FACTOR 2 - CHEMOTHERAPY, ESPECIALLY TAXANES</b>
<b>FACTOR 3 - ANTIFUNGAL DRUGS</b>
<b>FACTOR 4 -</b>
<b>FACTOR 5A - CHEMOTHERAPY, CHRONIC MYELOGENOUS LEUKEMIA</b>
<b>FACTOR 5B - MYCOBACTERIA</b>
<b>FACTOR 6 - CHEMOTHERAPY, PROTEASOME INHIBITORS</b>
<b>FACTOR 7 - ALIPHATIC HYDROCARBONS</b>
<b>FACTOR 8 - HEPATITIS VIRUS AND DRUGS</b>
<b>FACTOR 9 - VIRUSES</b>
<b>FACTOR 10 - ORGANOPHOSPHATE PESTICIDES</b>
<b>FACTOR 11 - ANTIVIRAL DRUGS FOR AIDS</b>
<b>FACTOR 12A - OCCUPATIONAL CHEMICALS</b>
<b>FACTOR 12B - INFECTIOUS AGENTS</b>
<b>FACTOR 13 - ANTIARRHYTHMIC DRUGS</b>
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<b>FACTOR 17 - BACTERIA AND CHRONIC MYELOGENOUS LEUKEMIA DRUGS</b>
<b>FACTOR 18 - HEAVY METALS</b>
<b>FACTOR 19A - ENVIRONMENTAL POLLUTANTS</b>
<b>FACTOR 19B - HYDROCARBONS, MAINLY ALIPHATIC SOLVENTS</b>
<b>FACTOR 20 - HERBICIDES</b>
<b>FACTOR 21 - VACCINES</b>
<b>FACTOR 22 - CHEMOTHERAPY, ESPECIALLY VINCA ALKALOIDS AND TAXANES</b>
<b>FACTOR 23A - DITHIOCARBAMATES</b>
<b>FACTOR 23B - HYDROCARBONS, ESPECIALLY TOXIC ALCOHOLS</b>
<b>FACTOR 24 - CHEMOTHERAPY</b>
<b>FACTOR 25A - INDUCED INJURY</b>
<b>FACTOR 25B - LIFESTYLE</b>

ES-2C. Contributing Factors-Contributing Factors Matrix

To display the inter-relationships among the PN/PAD causes, all the causes identified are matrixed together in Figure 2B-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two causes defining the cell. Thus, smoking co-occurs with high cholesterol diet in 397 records (third column, second row).

ES-2D. Contributing Factors Related to PN and to PAD

While many of the contributing factors applied relatively equally to PN and PAD, some were focused exclusively on PN and others on PAD. To identify the relative contributions, the symptoms/diseases related to PN and to PAD were aggregated separately. [Table 7A-4](#) shows the numbers of records in which the contributing factors co-occur with PN and with PAD. The top fifty are shown in [Table 2B-5](#).

Causes shared more or less equally between PN and PAD include infections, trauma, alcohol, radiation, anesthesia, antibiotics, advanced glycation end products, Hepatitis C virus, spinal cord injury, burn, high fat diet, inactivity, environmental factors, arsenic, lipopolysaccharide, drug abuse, etc. Causes weighted toward PN include chemotherapy agents, radiation therapy, statins, chronic constriction injury, tuberculosis, antiviral agents, mycobacterium, pesticides, solvents, acrylamide, acetone, occupational exposures, etc. Causes weighted toward PAD include smoking, high cholesterol diet, dialysis, sedentary, lifestyle, air pollution, atenolol, etc.

**Table 2B-5 - Contributing Factors Relevant to PN and to PAD**

#RECORDS	CAUSE	#PN RECORDS	#PAD RECORDS
2507	chemotherapy	2315	119
2265	smoking	275	2124
1140	High cholesterol diet	261	1004
985	paclitaxel	874	69
821	HIV-1	696	134
745	dialysis	139	643
708	infections	391	393
683	viruses	548	182
570	cisplatin	515	20
570	trauma	269	260
545	depression	326	251
524	oxaliplatin	499	1
508	hemodialysis	105	428
503	Bortezomib	473	32
442	alcohol	232	230
412	statins	43	
393	alcohol consumption	266	147
378	highly active antiretroviral therapy	344	37
361	radiation	189	134
357	anesthesia	157	139
351	thalidomide	333	56
347	vincristine	328	11
340	peripheral nerve injury	229	18
337	lifestyle	78	283
332	leprosy	206	19

329	radiation therapy	245	50
324	taxanes	303	7
323	cyclophosphamide	288	80
314	hepatitis	267	142
296	Streptozotocin	273	40
230	carboplatin	215	5
217	platinum	194	6
201	chronic constriction injury	179	1
196	docetaxel	183	4
186	Hepatitis C Virus	155	107
184	antibiotics	101	102
162	doxorubicin	148	17
149	Arsenic	78	73
148	stavudine	143	3
140	5-fluorouracil	130	3
131	sedentary	34	108
125	advanced glycosylation end products	74	74
121	capecitabine	103	
121	tuberculosis	101	22
119	zidovudine	115	4
118	Iatrogenic	55	37
118	Taxol	103	3

### ES-2E. Existing PN/PAD Treatments

[Table 7A-5](#) contains a list of the existing PN/PAD treatments identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these treatments are shown in Table 2C-1. Because these are the highest frequency treatments, many will be very general.

**Table 2C-1 - Top Fifty Existing PN/PAD Treatments**

# RECORDS	TREATMENT
5105	surgery
3638	drug
2402	amputation
1920	revascularization
1766	inhibitor
1358	walking
1328	exercise
1308	artery bypass grafting
1228	angioplasty
828	stents
812	growth factor

754	insulin
745	dialysis
632	medications
588	operation
576	aspirin
567	analgesic
541	endovascular treatment
507	vascular surgery
499	implantation
489	angiogenesis
459	rehabilitation
450	bypass surgery
449	diet
447	glycemic control
420	Ligation
411	corticosteroid
382	catheter
370	statin
353	Clopidogrel
349	vascular endothelial growth factor
337	antiplatelet therapy
317	opioid
288	supplementation
266	coronary intervention
252	antihypertensive agents
242	Gabapentin
240	PNS
233	endarterectomy
233	pregabalin
228	antidepressant
221	anticoagulant
215	Cilostazol
207	vitamin B12
206	nerve growth factor
190	smoking cessation
189	Spinal Cord Stimulation
172	Gene therapy

### ES-2F. Factor Matrix of Existing Treatments

Figure 2C-1 in the Excel workbook located under the same URL as the present monograph (FINAL\_FIGURES.xlsx - listed under View/Open on the link page) contains a factor matrix of the existing PN/PAD (click on FIG 2C-1). The thirty factor headings are shown below in Table 2C-2. This listing provides a convenient taxonomy for categorizing the myriad



treatments identified. Figure 2C-1 lists the specific treatments that had the strongest influence in determining the theme of each of the thirty factors.

The main categories include:

- drugs (e.g., antidepressants, anticonvulsants, opioids, muscle relaxants, antiplatelet/antithrombotic/anticoagulant agents, calcium channel blockers, antihypertensive agents, serotonin reuptake inhibitors, endocannabinoid deactivation inhibitors, cannabinoids, dipeptidyl peptidase-4 inhibitors, etc);
- surgery (e.g., angioplasty, arterial bypass, stents, revascularization, amputation, spinal cord stimulation, deep brain stimulation, etc)
- supplements (e.g., omega-3 fatty acids, fish oil, antioxidants, Vitamin E, Vitamin C, Vitamin B12, alpha lipoic acid, biotin, Vitamin D, magnesium, etc)
- herbs (e.g., herbal medicines, Chinese herbs, Buyang Huanwu decoction, Guizhi-shaoyao-zhimu decoction, Huoxue Kangyuan decoction, Plantaginis Semen, Aucubin, Goshajinkigan, kampo, etc)
- angiogenesis (growth factors, cell therapy, etc)

**Table 2C-2 - Factor Matrix-based Categories for PN/PAD Treatments**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - ANTIDEPRESSANTS/ANTICONVULSANTS/OPIOIDS</b>
<b>FACTOR 2 - ANTIPLATELET/ANTITHROMBOTIC THERAPY</b>
<b>FACTOR 3 - ENDOCANNABINOID DEACTIVATION INHIBITORS</b>
<b>FACTOR 4 - ANTIHYPERTENSIVE AGENTS</b>
<b>FACTOR 5 - SEROTININ REUPTAKE INHIBITORS</b>
<b>FACTOR 6 - CANNABINOIDS/ANGIOGENESIS</b>
<b>FACTOR 7 - MUSCLE RELAXANTS</b>
<b>FACTOR 8 - ENDOVASCULAR TREATMENT</b>
<b>FACTOR 9A - CANNABINOIDS</b>
<b>FACTOR 9B - ANGIOGENESIS/GROWTH FACTORS/CELL THERAPY</b>
<b>FACTOR 10 - ANTICOAGULANTS</b>
<b>FACTOR 11 - ANTIEPILEPTICS/ANTICONVULSANTS</b>
<b>FACTOR 12 - ANTIHYPERTENSIVE AGENTS, ESPECIALLY ACE INHIBITORS</b>
<b>FACTOR 13 - PERIPHERAL NERVE REGENERATION AND PROTECTION</b>
<b>FACTOR 14 - OMEGA-3 FATTY ACIDS</b>
<b>FACTOR 15 - LOW-DENSITY LIPOPROTEIN REDUCTION THERAPY, ESPECIALLY STATINS</b>
<b>FACTOR 16 - NEUROPATHIC PAIN MANAGEMENT, ESPECIALLY OPIOIDS</b>
<b>FACTOR 17 - REPURPOSED THERAPIES FOR NEUROPATHY</b>
<b>FACTOR 18 - CALCIUM CHANNEL ANTAGONISTS</b>
<b>FACTOR 19 - CXCR4 ANTAGONISTS FOR NEUROPATHIC PAIN</b>
<b>FACTOR 20 - PHENOLS</b>

<b>FACTOR 21 - PROSTACYCLIN ANALOGUES</b>
<b>FACTOR 22A - GROWTH FACTORS</b>
<b>FACTOR 22B - CELL THERAPY</b>
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<b>FACTOR 24 - HERBAL MEDICINE</b>
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<b>FACTOR 27A - ANTIPLATELET/ANTITHROMBOTIC THERAPY</b>
<b>FACTOR 27B - ANTITHROMBOTIC/ANTICOAGULANT AGENTS</b>

### ES-2G. Treatment-Treatment Matrix

To display the inter-relationships among the PN/PAD treatments, all the treatments identified are matrixed together in Figure 2C-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two treatments defining the cell. Thus, walking co-occurs with drug in 122 records (second column, sixth row).

### ES-2H. Treatments related to PN and to PAD

While many of the treatments applied relatively equally to PN and PAD, some were focused exclusively on PN and others on PAD. To identify the relative contributions, the symptoms/diseases related to PN and to PAD were aggregated separately. [Table 7A-8](#) shows the numbers of records in which the treatments co-occur with PN and with PAD. The top fifty are shown in Table 2C-5.

**Table 2C-5 - Top Fifty Treatments Relevant to PN and to PAD**

<b>#RECORDS</b>	<b>TREATMENT</b>	<b>#PN RECORDS</b>	<b>#PAD RECORDS</b>
5105	surgery	1172	3427
3638	drug	2279	1321
2402	amputation	591	2064
1920	revascularization	56	1839
1766	inhibitor	951	813
1358	walking	304	1058
1328	exercise	229	1124
1308	artery bypass grafting	59	1154
1228	angioplasty	23	1149
828	stents	7	751
812	growth factor	377	426
754	insulin	467	465
745	dialysis	139	643
632	medications	320	338
588	operation	122	374
576	aspirin	33	552

567	analgesic	479	61
541	endovascular treatment	3	499
507	vascular surgery	17	466
499	implantation	69	393
489	angiogenesis	56	439
459	rehabilitation	149	262
450	bypass surgery	13	421
449	diet	239	233
447	glycemic control	333	247
420	Ligation	274	110
411	corticosteroid	328	148
382	catheter	41	297
370	statin		333
353	Clopidogrel	8	345
349	vascular endothelial growth factor	105	257
337	antiplatelet therapy	4	330
317	opioid	271	28
288	supplementation	160	124
266	coronary intervention		261
252	antihypertensive agents	36	238
242	Gabapentin	235	16
240	PNS	166	23
233	endarterectomy	2	222
233	pregabalin	230	5
228	antidepressant	203	27
221	anticoagulant	24	196
215	Cilostazol	6	211
207	vitamin B12	160	50
206	nerve growth factor	170	8
190	smoking cessation	9	184
189	Spinal Cord Stimulation	122	84
172	Gene therapy	37	128
172	IL-6	75	95
167	heparin	15	146

Treatments shared more or less equally between PN and PAD include insulin, growth factors, diet, antioxidants, folic acid, carnitine, cannabis, DHA, etc. Treatments weighted toward PN include analgesics, opioids, gabapentin, pregabalin, antidepressants, Vitamin B12, capsaicin, morphine, zidovudine, amitriptyline, alpha lipoic acid, carbamazepine, anthracycline, thiamine, etc. Treatments weighted toward PAD include revascularization, exercise, walking, artery bypass grafting, angioplasty, stents, aspirin, endovascular treatment, vascular surgery, angiogenesis, catheter, statins, clopidogrel, antiplatelet therapy, antihypertensive agents, warfarin, etc.

ES-2I. Potential PN/PAD Treatments from LRDI Discovery

The LRDI Discovery method outlined in section 6B5 and presented in detail in [Appendix 6-1](#) was used to identify potential PN/PAD treatment candidates. Even with the abbreviated query shown, hundreds of potential PN/PAD treatment candidates were retrieved (mid-August 2019), and thousands more could have been easily obtained with an expanded query. Ten of the candidates that were evaluated and validated for Discovery are shown in Table 2C-6. While combinations of two biomarkers were the criteria for retrieving potential PN/PAD treatment candidates, the impacts of the treatment on myriad other biomarkers were included in the retrieved article as well. All the biomarkers impacted by the candidate treatment (listed in the abstract) are shown in parentheses after the quoted material.

**Table 2C-6 - Potential Treatments for PN/PAD**1. *Dendrobium nobile* Lindl

"***DNLA*** [*Dendrobium nobile* Lindl. alkaloids] ***protects mice from CCl4 induced liver injury***, probably through the activation of the Nrf2 signaling pathway." [Li, Shiyue; Zhou, Jinxin; Xu, Shangfu; et al, 2019]

(biomarkers altered: oxidative stress, Nrf2, alanine aminotransferase, aspartate aminotransferase, malondialdehyde)

## 2. CPUY192018

"CPUY192018 exhibited cytoprotective effects by enhancing the Nrf2-ARE regulated antioxidant system and ***diminished the LPS-induced inflammatory response*** by hindering the ROS-mediated activation of the NF-kappaB pathway..... by activating Nrf2, CPUY192018 treatment balanced renal ***oxidative stress*** and suppressed inflammatory responses." [Lu, Meng-Chen; Zhao, Jing; Liu, Yu-Ting; et al, 2019]

(biomarkers: inflammation, oxidative stress, Nrf2, ROS, NF-kappaB)

3. Swertiamarin OR *Gentiana macrophylla* Pall

"Collectively, Swe [Swertiamarin] could be considered as a ***promising protective agent against cerebral I/R injury through suppressing oxidative stress by activation of the Nrf2 protective pathway***." [Wang, H. et al, 2019]

(biomarkers: apoptosis, oxidative stress, ROS, Nrf2, NQO1, HO-1)

4. *Malva sylvestris*

"***MS*** [*Malva sylvestris*] ***extract can protect the kidney against toxic effects of gentamicin, and thus, the degree of harmful effects of nephrotoxicity on remote organs including the liver will be decreased***." [Mohamadi Yarijani, Z. et al, 2019]

(biomarkers: oxidative stress, creatinine, urea-nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, malondialdehyde, inflammation, TNF-alpha, ICAM-1)

## 5. Avenathramide C

"***Avn C*** [Avenathramide C] ***protects normal human skin fibroblasts against oxidative stress and inflammatory response through NF-kappaB inhibition and Nrf2/HO-1 activation*** "

[Wang, C. and Eski, C.H, 2019]

(biomarkers: oxidative stress, free radical levels, inflammation, tumor necrosis factor-alpha, NF-kappaB, HO-1, Nrf2)

## 6. SK-119 OR (E)-5-oxo-1-(4-((2,4,6-trihydroxybenzylidene)amino)phenyl)pyrrolidine-3-

carboxylic acid

" ***Nrf2 Activation by SK-119*** [(E)-5-oxo-1-(4-((2,4,6-trihydroxybenzylidene)amino)phenyl)pyrrolidine-3-carboxylic acid] ***Attenuates Oxidative Stress, UVB, and LPS-Induced Damage*** " [Kahremany, S. et al, 2019]

(biomarkers: oxidative stress, Nrf2, inflammation, apoptosis)

7. pristimerin

" ***Pris*** [pristimerin] ***exerted protective activity against LPS-induced ALI*** [acute lung injury] ***via anti-oxidant, anti-inflammatory and anti-apoptotic pathways*** " [Shaaban, A.A. et al, 2018]

(biomarkers: inflammation, myeloperoxidase, lesions, oxidative stress, tumor necrosis factor-alpha, interleukin-6, apoptosis, Bax, caspase-3, Bcl2)

8. Astilbin

" ***Astilbin ameliorates cisplatin-induced nephrotoxicity through reducing oxidative stress and inflammation.*** " [Wang, S.-W. et al, 2018]

(biomarkers: oxidative stress, inflammation, apoptosis, ROS, NRF2, TNF-alpha, NF-kappaB, iNOS, COX-2)

9. Ac-YVAD-cmk

" ***Pharmacological*** [Ac-YVAD-cmk] ***Inhibition of Caspase-1 Ameliorates Cisplatin-Induced Nephrotoxicity through Suppression of Apoptosis, Oxidative Stress, and Inflammation in Mice.*** " [Kim, J.-Y. et al, 2018]

(biomarkers: caspase-1, blood urea nitrogen, creatinine, caspase-3, apoptosis, oxidative stress, inflammation)

10. Pterostilbene

" ***Protective Effects of Pterostilbene Against Myocardial Ischemia/Reperfusion Injury in Rats.*** " [Wu, M. et al, 2017]

(biomarkers: lactate dehydrogenase, creatine kinase-MB, oxidative stress, inflammation, Gas6, Axl, Bcl-2, Bax, apoptosis)

## ES-2J. Existing PN/PAD Characteristics

[Table 7A-9a](#) contains a list of the 757 existing biomarkers identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these biomarkers are shown in Table 2D-1a. Because these are the highest frequency biomarkers, many will be very general.

**Table 2D-1a - Top Fifty PN/PAD Biomarkers**

#RECORDS	BIOMARKER
2638	lesions
2536	inflammation
2320	toxicity
2277	nerve conduction velocity
2038	ankle brachial index
1549	blood pressure
1402	stenosis

1156	body mass index
1142	neurotoxic
1139	total cholesterol
1138	blood glucose levels
1091	degeneration
1061	hemoglobin A1c
932	blood flow
856	marker
841	proteins
748	atrophy
747	dorsal root ganglia
704	creatinine
700	oxygen
693	lipoprotein
671	growth factor
640	Schwann cell
616	demyelination
610	pain-free walking distance
549	C reactive protein
538	calcium
516	cytokine
499	triglycerides
495	low-density lipoprotein cholesterol
489	angiogenesis
455	axonal degeneration
435	Systolic blood pressure
426	circulation
425	high-density lipoprotein cholesterol
419	oxidative stress
413	plaque
412	occlusions
402	albumin level
399	glomerular filtration rate
391	ventricular ejection fraction
382	calcification
365	nerve damage
354	neurodegeneration
349	IgM
345	tumour necrosis factor-alpha
344	sodium
329	lipids

Areas emphasized include neurotoxicity, neurodegeneration, inflammation, oxidative stress, demyelination, angiogenesis, circulation, calcification.

[Table 7A-9b](#) contains a list of the existing symptoms/diseases identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these symptoms/diseases are shown in Table 2D-1b. Because these are the highest frequency contributing factors, many will be very general.

**Table 2D-1b - Top Fifty Existing PN/PAD Symptoms/Diseases**

#RECORDS	SYMPTOM/DISEASE
17050	neuropathy
13577	peripheral neuropathy
9627	diabetes mellitus
9078	artery disease
8114	peripheral artery disease
6967	peripheral vascular disease
5942	pain
5016	ischemia
3095	hypertension
3014	cancer
2969	atherosclerosis
2861	neuropathic pain
2612	stroke
2152	diabetic peripheral neuropathy
2071	infection
2056	myocardial infarction
2051	cardiovascular disease
1983	intermittent claudication
1913	polyneuropathy
1796	coronary artery disease
1585	heart disease
1571	type 2 diabetes mellitus
1547	critical limb ischemia
1533	diabetic foot ulcer
1519	Disorder
1440	heart failure
1135	weakness
879	neutropenia
878	cerebrovascular disease
833	sensory neuropathy
832	retinopathy
799	coronary heart disease
779	allodynia
769	disability
769	obesity
747	renal failure
731	thrombosis

705	ataxia
675	abdominal aortic aneurysm
660	nephropathy
645	angina
645	renal disease
625	Congestive heart failure
623	multiple myeloma
621	peripheral artery occlusive disease
618	bleeding
618	hyperalgesia
613	chronic kidney disease
612	vasculitis
607	ischemic heart disease

Diabetes, hypertension, infection, and obesity are of particular note.

#### ES-2K. Factor Matrix of Characteristics

Figure 2D-1a in the Excel workbook contains a factor matrix of the existing PN/PAD biomarkers. The 28 factor headings are shown below in Table 2D-2a. This listing provides a convenient taxonomy for categorizing the myriad biomarkers identified. Figure 2D-1a lists the specific biomarkers that had the strongest influence in determining the theme of each of the 28 factors.

**Table 2D-2a - Factor Matrix-based Categories for PN/PAD Biomarkers**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - PLASMA LIPIDS</b>
<b>FACTOR 2 - PROINFLAMMATORY CYTOKINES</b>
<b>FACTOR 3 - miRNA</b>
<b>FACTOR 4 - HEME BIOSYNTHESIS DEFICIENCY</b>
<b>FACTOR 5 - OXIDATIVE STRESS</b>
<b>FACTOR 6 - FIBRIN DEPOSITION</b>
<b>FACTOR 7A - GROWTH FACTORS</b>
<b>FACTOR 7B - ADVANCED GLYCATION END PRODUCTS</b>
<b>FACTOR 8 - KALLIKREIN-KININ SYSTEM</b>
<b>FACTOR 9 - APOLIPOPROTEINS</b>
<b>FACTOR 10 - FATTY ACIDS</b>
<b>FACTOR 11 - KIDNEY FILTERING</b>
<b>FACTOR 12 - PLATELET AGGREGATION</b>
<b>FACTOR 13 - PROINFLAMMATORY MONOCYTES</b>
<b>FACTOR 14 - AXONAL DEGENERATION</b>
<b>FACTOR 15 - MATRIX METALLOPROTEINASES</b>



<b>FACTOR 16 - ANTIBODIES</b>
<b>FACTOR 17 - VASCULAR CALCIFICATION</b>
<b>FACTOR 18 - B12/FOLATE DEFICIENCIES</b>
<b>FACTOR 19 - ENDOTHELIAL DYSFUNCTION</b>
<b>FACTOR 20 - ARTERIAL STIFFNESS</b>
<b>FACTOR 21 - RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS AND LIGANDS</b>
<b>FACTOR 22 - INSULIN DEFICIENCY</b>
<b>FACTOR 23A - CELL ADHESION MOLECULES</b>
<b>FACTOR 23B - ANTI-INFLAMMATORY CYTOKINES</b>
<b>FACTOR 24 - OXIDATIVE STRESS</b>
<b>FACTOR 25 - CARDIOVASCULAR DISEASE BIOMARKERS</b>
<b>FACTOR 26 - VIRAL DAMAGE MARKERS</b>

Figure 2D-1b contains a factor matrix of the existing PN/PAD symptoms/diseases. The 15 factor headings are shown below in in Table 2D-2b. This listing provides a convenient taxonomy for categorizing the myriad symptoms/diseases identified. Figure 2D-1b lists the specific symptoms/diseases that had the strongest influence in determining the theme of each of the 15 factors.

**Table 2D-2b - Factor Matrix-based Categories for PN/PAD Symptoms/Diseases**

<b>FACTOR HEADINGS</b>
<b>FACTOR 1 - REDUCED NEUROMUSCULAR CONTROL</b>
<b>FACTOR 2 - NON-PAIN DIABETES-RELATED SYMPTOMS/DISEASES</b>
<b>FACTOR 3 - MOTOR NEURON DISEASES</b>
<b>FACTOR 4 - NEUROPATHIC PAIN</b>
<b>FACTOR 5 - CANCER TREATMENT SIDE EFFECTS</b>
<b>FACTOR 6 - EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS</b>
<b>FACTOR 7 - POEMS SYNDROME</b>
<b>FACTOR 8 - ASSOCIATED MAJOR ORGAN DISEASES</b>
<b>FACTOR 9 - POLYNEUROPATHY</b>
<b>FACTOR 10 - ISCHEMIA</b>
<b>FACTOR 11 - DIABETIC NEUROPATHY</b>
<b>FACTOR 12 - INFECTION-RELATED AUTOIMMUNE DISEASES</b>
<b>FACTOR 13 - CARDIOVASCULAR DISEASES</b>
<b>FACTOR 14 - MYOCARDIAL INFARCTION SYMPTOMS</b>
<b>FACTOR 15 - ARTERY DISEASE</b>

#### ES-2L. Biomarker-Biomarker Matrix

To display the inter-relationships among the PN/PAD biomarkers, all the biomarkers identified are matrixed together in Figure 2D-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two biomarkers defining the cell.

ES-2M. Biomarkers related to PN and to PAD

While many of the biomarkers applied relatively equally to PN and PAD, some were focused more strongly on PN and others on PAD. To identify the relative contributions, the biomarkers related to PN and to PAD were aggregated separately. [Table 7A-12](#) shows the numbers of records in which the biomarkers co-occur with PN and with PAD. The top fifty are shown in Table 2D-5.

**Table 2D-5 - Top Fifty Biomarkers Relevant to PN and to PAD**

#RECORDS	TREATMENT	#PN RECORDS	#PAD RECORDS
2638	lesions	985	1503
2536	inflammation	1445	1143
2320	toxicity	2077	186
2277	nerve conduction velocity	2003	183
2038	ankle brachial index	93	1984
1549	blood pressure	334	1362
1402	stenosis	72	1274
1156	body mass index	378	868
1142	neurotoxic	980	37
1139	total cholesterol	261	1003
1138	blood glucose levels	685	625
1091	degeneration	874	167
1061	hemoglobin A1c	663	646
932	blood flow	167	802
856	marker	321	558
841	proteins	568	245
748	atrophy	633	93
747	dorsal root ganglia	631	28
704	creatinine	230	550
700	oxygen	184	536
693	lipoprotein	117	625
671	growth factor	318	344
640	Schwann cell	506	25
616	demyelination	536	56
610	pain-free walking distance	17	598
549	C reactive protein	68	507
538	calcium	249	274
516	cytokine	289	211
499	triglycerides	158	410
495	low-density lipoprotein cholesterol	70	461
489	angiogenesis	56	439
455	axonal degeneration	402	73
435	Systolic blood pressure	88	392
426	circulation	86	362
425	high-density lipoprotein cholesterol	105	386

419	oxidative stress	223	212
413	plaque	22	382
412	occlusions	3	358
402	albumin level	162	304
399	glomerular filtration rate	95	338
391	ventricular ejection fraction	33	366
382	calcification	45	346
365	nerve damage	238	32
354	neurodegeneration	305	42
349	IgM	325	46
345	tumour necrosis factor-alpha	225	126
344	sodium	229	114
329	lipids	92	255
322	heart rate	133	204
318	edema	205	120

Biomarkers shared more or less equally between PN and PAD include inflammation, blood glucose levels, hemoglobin A1c, growth factor, calcium, oxidative stress, nitric oxide, IL-6, reactive oxygen species, acetylcholine, lactate, urea, antioxidants, lipid peroxidation, advanced glycation end products, etc. Biomarkers weighted toward PN include nerve conduction velocity, neurotoxicity, atrophy, Schwann cell, demyelination, axonal degeneration, CD4, nerve fiber density, etc. Biomarkers weighted toward PAD include ankle brachial index, blood flow, pain-free walking distance, low density lipoprotein cholesterol, occlusions, ventricular ejection fraction, calcification, fibrinogen, carotid artery intima-media thickness, platelet aggregation, pulse pressure, etc.

#### ES-2N. Biomarkers Selected for Protocol

The final number of biomarkers identified in the present study was 757 ([Table 7A-9a](#)). To reduce this number of biomarkers to a manageable amount for the treatment protocol, a number of thematic categories were generated based on the results of the biomarker factor matrix (Figure 2D-1a) and other inputs. Then, phrases were selected to populate these categories based in part on 1) their rankings in the biomarker factor matrix, and on 2) their applicability to PN/PAD or PN or PAD ([Table 7A-12](#)), as discussed at the end of section 2D4.

Table 2D-6 contains the final list of biomarkers selected for the protocol. While each biomarker is listed for one category, many of the biomarkers will be applicable to multiple categories. The biomarkers highlighted in red are the highest priority for each category, based on the criteria described above.

**Table 2D-6 - Final List of Biomarkers for Treatment Protocol**

(Note: biomarkers highlighted in red are highest priority for category)

CATEGORY	BIOMARKER
ANTIBODIES	IgM
ANTIBODIES	IgA
ANTIBODIES	immunoglobulin
ANTIBODIES	IgG antibodies
ANTIBODIES	autoantibodies
ANTIBODIES	anti-ganglioside antibodies
ANTIBODIES	demyelination
ANTIBODIES	monoclonal antibodies
ANTIBODIES	glucuronic acid
ANTIBODIES	Chlamydia pneumoniae
ANTIBODIES	antinuclear antibodies
ART STIFFNESS	arterial stiffness
ART STIFFNESS	pulse wave velocity
ART STIFFNESS	pulse pressure
ART STIFFNESS	vascular stiffness
ART STIFFNESS	blood pressure
CALCIFICATION	calcium
CALCIFICATION	magnesium
CALCIFICATION	Zinc
CALCIFICATION	glutamine
CALCIFICATION	selenium
CALCIFICATION	glutamate
CALCIFICATION	calcification
CALCIFICATION	cadmium
CALCIFICATION	alkaline phosphatase
ENDOTHELIAL DYSFUNCTION	nitric oxide
ENDOTHELIAL DYSFUNCTION	L-arginine
ENDOTHELIAL DYSFUNCTION	nitric oxide synthase
ENDOTHELIAL DYSFUNCTION	arginine
ENDOTHELIAL DYSFUNCTION	endothelin-1
FOLATE DEFICIENCY	folic acid
FOLATE DEFICIENCY	folate deficiency
FOLATE DEFICIENCY	methionine
FOLATE DEFICIENCY	S-adenosylmethionine
FOLATE DEFICIENCY	Hcy
FOLATE DEFICIENCY	cysteine
FOLATE DEFICIENCY	methylmalonic acid
FOLATE DEFICIENCY	asymmetric dimethylarginine
GROWTH FACTORS	growth factor
GROWTH FACTORS	vascular endothelial growth factor
GROWTH FACTORS	fibroblast growth factor

GROWTH FACTORS	hepatocyte growth factor
GROWTH FACTORS	nerve growth factor
GROWTH FACTORS	fibroblast growth factor 23
GROWTH FACTORS	blood flow
GROWTH FACTORS	transforming growth factor beta
INFLAMMATION	C reactive protein
INFLAMMATION	IL-6
INFLAMMATION	Tumour necrosis factor-alpha
INFLAMMATION	IL1-beta
INFLAMMATION	Intercellular adhesion molecule-1
INFLAMMATION	IL-10
INFLAMMATION	neutrophils
INFLAMMATION	IL-8
INFLAMMATION	myeloperoxidase
INFLAMMATION	D-dimer
INFLAMMATION	IL-12
INFLAMMATION	Monocyte chemoattractant protein-1
INFLAMMATION	Interferon gamma
INFLAMMATION	TGFbeta
INFLAMMATION	IL-2
INFLAMMATION	matrix metalloproteinase 2
INFLAMMATION	matrix metalloproteinase 9
INFLAMMATION	COX-2
INFLAMMATION	IL-4
INFLAMMATION	IL-18
INFLAMMATION	IL-13
KIDNEY FUNCTION	urea
KIDNEY FUNCTION	blood urea nitrogen
KIDNEY FUNCTION	creatinine
KIDNEY FUNCTION	white blood cell
KIDNEY FUNCTION	uric acid
KIDNEY FUNCTION	bilirubin
KIDNEY FUNCTION	glomerular filtration rate
LIPIDS	high-density lipoprotein cholesterol
LIPIDS	total cholesterol
LIPIDS	triglycerides
LIPIDS	low-density lipoprotein cholesterol
LIPIDS	fibrinogen
LIPIDS	Lipoprotein(a)
LIPIDS	hemoglobin A1c
NEURODEGENERATION	myelinated fibers
NEURODEGENERATION	dorsal root ganglia
NEURODEGENERATION	nerve conduction velocity
NEURODEGENERATION	Schwann cell
NEURODEGENERATION	fiber loss

NEURODEGENERATION	atrophy
NEURODEGENERATION	nerve fiber density
OXIDATIVE STRESS	Reactive oxygen species
OXIDATIVE STRESS	glutathione
OXIDATIVE STRESS	superoxide dismutase
OXIDATIVE STRESS	malondialdehyde
OXIDATIVE STRESS	advanced glycation end products
OXIDATIVE STRESS	catalase
OXIDATIVE STRESS	glutathione peroxidase
OXIDATIVE STRESS	iNOS
OXIDATIVE STRESS	Hydrogen peroxide
OXIDATIVE STRESS	peroxynitrite
OXIDATIVE STRESS	NADPH oxidases
OXIDATIVE STRESS	TBARS
OXIDATIVE STRESS	4-hydroxy-2-nonenal
OXIDATIVE STRESS	Nrf2
OXIDATIVE STRESS	isoprostane
OXIDATIVE STRESS	NOx
OXIDATIVE STRESS	heme oxygenase 1
OXIDATIVE STRESS	oxidized low-density lipoprotein
OXIDATIVE STRESS	lipid hydroperoxides
OXIDATIVE STRESS	PON-1
OXIDATIVE STRESS	3-nitrotyrosine
OXIDATIVE STRESS	adenosine triphosphate
OXIDATIVE STRESS	creatine kinase
PLATELET ACTIVATION	arachidonic acid
PLATELET ACTIVATION	adenosine diphosphate
PLATELET ACTIVATION	P-selectin
PLATELET ACTIVATION	prothrombin
PLATELET ACTIVATION	thrombin
PLATELET ACTIVATION	L-selectin
PLATELET ACTIVATION	elastase
RAGE	RAGE
RAGE	carboxymethyl-lysine
RAGE	S100A12
RAGE	thromboxane
RAGE	NF-kappaB
RAGE	thromboxane A2
RAGE	phosphatidylinositol 3-kinase
RAGE	adenosine monophosphate
RAGE	caspase 3

The biomarkers highlighted in red are only a suggestion for testing prioritization. There is not strong consensus in the literature for many of these biomarkers, and clinicians should substitute biomarkers for testing they deem more appropriate. Also, there may be categories

listed that some clinicians believe are not relevant to specific patients, based on their medical histories. The biomarkers in these categories could be eliminated, thereby reducing the number of tests required. Conversely, there could be categories not listed in [Table 2D-6](#) that clinicians believe are important for specific patients. Biomarkers for these categories should be added as required. Three such categories not emphasized in Table 2D-6 are heavy metals, infections, and Vitamin deficiencies.

Heavy metals that can impact various segments of PN/PAD adversely include arsenic, cadmium, lead, mercury, and thallium. Infections/infectious agents that can impact various segments of PN/PAD adversely include human immunodeficiency virus (HIV), *Aggregatibacter actinomycetemcomitans*, *Borrelia burgdorferi*, *Brucella* spp., *C. pneumoniae*, *Campylobacter jejuni*, *Campylobacter rectus*, *Chlamydia pneumoniae*., *Chryseomonas*, *Clostridium botulinum*, *Collinsella*, *Corynebacterium diphtheriae*, *Cytomegalovirus*, *Eikenella corrodens*, Epstein-Barr virus, *Eubacterium*, *Fusobacterium nucleatum*, *H. influenzae*, *Helicobacter pylori*, Hepatitis C virus, *Herpes simplex virus*, *Human T-cell lymphotropic virus*, *M. pneumoniae*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Parvimonas micra*, *Parvimonas micros*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella nigrescens*, *Rabies virus*, *Roseburia*, *Streptococcus*, *Tannerella forsythia*, *Treponema denticola*, *Varicella-zoster virus*, *Veillonella*, *West Nile Virus* [Brizzi and Lyons, 2014; Budzynski et al, 2016]. Vitamin deficiencies include, but are not limited to, Vitamins B-1, B-12, C, D, E.

#### ES-2O. Matrix of PN/PAD Causes vs Biomarkers

Figure 2E-1 (Excel Workbook) displays the co-occurrences between the existing PN/PAD contributing factors and biomarkers. The cell numbers reflect the co-occurrences of the contributing factor and biomarker defining the cell.

The matrix is relatively dense starting at the upper left, and becomes increasingly sparse going to the lower right. There are approximately 630,000 cells in the matrix, of which about 16,000 have entries. That's an occupancy rate of slightly more than two percent. Why is this important? The cell numbers reflect, in part, the amount of research effort devoted (reported) to examining the relationship between the cause and the biomarker defining the cell. Cells that are blank may reflect that research has not been done on the cause and biomarker combination, and therefore could be excluding another potential cause. The message to be taken from this observation is far more research could be conducted on identifying potential causes if more biomarkers were included in the investigations.

#### ES-2P. Matrix of PN/PAD Treatments vs Biomarkers

Figure 2F-1 (Excel Workbook) displays the co-occurrences between the existing PN/PAD treatments and biomarkers. The cell numbers reflect the co-occurrences of the treatment and biomarker defining the cell.

### ES-3. Treatment Protocol to Prevent and Reverse PN/PAD

This section summarizes the recommended treatment protocol for preventing and reversing AD. There are five steps in the full treatment protocol, as shown in the following:

#### **FIVE-STEP TREATMENT PROTOCOL TO PREVENT AND REVERSE PN/PAD**

- Step 1:** Obtain a detailed medical and habit/exposure history from the patient.
- Step 2:** Administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms and degradation of functions
- Step 3:** Administer laboratory tests (blood, urine, imaging, etc)
- Step 4:** Eliminate ongoing PN/PAD contributing factors
- Step 5:** Implement PN/PAD treatments

These five steps will now be described in more detail.

**Step 1.** The first step in the protocol is to obtain a detailed medical and habit/exposure history from the PN/PAD patient. The patient would be provided a detailed questionnaire focusing mainly on practices and exposures that are potential PN/PAD contributing factors. The contributing factor component of the questionnaire would be based on [Table 7A-1](#), or, preferably, on a similar, but even more extensive, table derived from an expanded study.

**Step 2.** The second step in the protocol is to administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms. This would include tests for sensing, pain, gait, endurance, strength, etc, and for anxiety, depression, cognitive dysfunction, etc. The latter group of mood-related tests would have some overlap with the medical history on the initial questionnaire.

**Step 3.** The third step in the protocol is administration of laboratory tests (blood, urine, imaging, etc). Any abnormalities shown by these tests would help prioritize the PN/PAD contributing factors to be eliminated and PN/PAD treatments to be implemented. [Table 2D-6](#) contains the PN/PAD biomarkers selected for initial laboratory tests in the PN/PAD protocol. These PN/PAD biomarkers reflect the PN/PAD pathological themes and the major themes from the PN/PAD biomarker factor matrix (Figure 2D-1a). Based on the laboratory test results, the health practitioner could require further tests to gain detailed information on problematic areas.

**Step 4.** The fourth step in the protocol is to eliminate ongoing PN/PAD contributing factors. Unfortunately, as Figure 2E-1 shows, each PN/PAD contributing factor typically impacts many PN/PAD biomarkers, and each PN/PAD biomarker is typically impacted by many PN/PAD contributing factors. Thus, in the general case, PN/PAD biomarker values' abnormalities in the lab tests will not be uniquely related to specific PN/PAD contributing factors.



To circumvent this problem, a combined 'direct-identification' and 'reverse-engineering' approach that has the virtue of simplicity is proposed. The 'direct-identification' component consists of eliminating the PN/PAD contributing factors the patient listed on the initial medical/exposure questionnaire. The 'reverse-engineering' component

- 1) identifies all the patient's PN/PAD biomarkers with abnormal laboratory test values,
- 2) identifies the number of these abnormal PN/PAD biomarkers impacted by each PN/PAD contributing factor, then
- 3) prioritizes the PN/PAD contributing factors for elimination according to the number of PN/PAD biomarkers impacted by the PN/PAD contributing factors.

See section 3B4 to show how this prioritization, and further sub-prioritizations, would operate.

The recommended prioritization above is based on numbers of PN/PAD biomarkers impacted by each PN/PAD contributing factor. It does not:

- 1) distinguish between one record describing the impact (for a particular PN/PAD contributing factor) or ten records describing the impact,
- 2) distinguish among the strengths of impact described in different records, irrespective of the number of records describing the impact,
- 3) weight the PN/PAD biomarkers by relative importance,
- 4) incorporate the effects of contributing factor synergies.

This additional information could be used by the healthcare practitioner to modify the prioritization illustrated above.

In addition, there are some cases where 'reverse-engineering' may be more straightforward. For example, high serum or urine readings of heavy metals (such as cadmium or mercury) would identify specific targets for elimination. These would be the exception rather than the rule, in terms of specificity.

The above prioritization approach would serve as a proxy for the more comprehensive elimination of all 'low-hanging fruit' PN/PAD contributing factors, shown in [Table 3B-2](#). To the degree possible, the patient should strive to eliminate as many of these 'low-hanging fruit' PN/PAD contributing factors as possible. The combination of 1) lack of knowledge about harmful exposures (limiting what can be answered on the initial medical/exposure questionnaire) and 2) incompleteness of PN/PAD characteristics measured will result in 3) PN/PAD contributing factors not being identified through the complete testing/evaluation process. Eliminating as many of the 'low-hanging fruit' PN/PAD contributing factors as possible will

compensate partially for this lack of knowledge. Many of these items are under the patient's control, and can be readily eliminated, with proper motivation and discipline.

**Table 3B-2 - "Low-Hanging Fruit" Causes for Elimination**

**"LOW-HANGING FRUIT" RECOMMENDATIONS**

- 1) curb the dietary excesses, and remove the dietary deficiencies, identified in Table 7A-1, the medical questionnaire, and the lab tests;
- 2) eliminate food additives to the extent knowable and possible, including those dietary excesses that derive from food additives (excessive fat, sugar, salt);
- 3) minimize high temperature cooking and the subsequent increases in advanced glycation end products from certain susceptible foods, heterocyclic amines, acrylamide, and polycyclic aromatic hydrocarbons;
- 4) reverse the sedentary behavior patterns identified;
- 5) remove the foundational impediments to better sleep;
- 6) eliminate the use of 'recreational' drugs, including smoking and excessive alcohol;
- 7) eliminate the use of medicinal drugs shown to be potential PN/PAD contributing factors from Table 7A-1, unless these drugs are absolutely necessary;
- 8) minimize exposures to some hydrocarbons, such as n-hexane, methyl-n-butyl ketone, carbon disulfide, acrylamide, ethylene oxide, trichloroethylene, kerosene, polycyclic aromatic hydrocarbons (including those found in smoke), etc;
- 9) minimize exposures to some neurotoxic solvents, especially organic solvents;
- 10) minimize inhalation and ingestion exposures to pesticides, herbicides, insecticides, and fungicides;
- 11) minimize exposures to heavy metals in food, in water, and in the air;
- 12) minimize exposure to particulates, especially air pollution;
- 13) minimize exposures to ionizing radiation and non-ionizing non-visible radiation (such as cell phones, cell towers, WiFi, smart meters, etc.);
- 14) minimize chronic stress (mental/emotional/psychological);

There is an implicit assumption in some/many of these PN/PAD contributing factor elimination recommendations of a treatment implementation. For example, elimination of a high-fat diet (PN/PAD contributing factor) implies adoption of a low-fat diet (PN/PAD treatment).

**Step 5.** The fifth step in the protocol is to implement PN/PAD treatments. Because of risk associated with implementation of even single PN/PAD treatments, and the lack of knowledge of how overall risk increases (or decreases) because of treatment combination synergies, it is highly recommended that the *lowest-risk* treatments be implemented initially in parallel with required higher-risk treatments

Even among low-risk PN/PAD treatments, some prioritization may be possible. The approach recommended parallels that for eliminating PN/PAD contributing factors in Step 4. The approach is a hybrid of 'direct-identification' and 'reverse-engineering'. The 'direct-identification' component consists of identifying the patient's PN/PAD contributing factors from the medical/exposure questionnaire. Where applicable, PN/PAD treatments that are positive behaviors/habits would be substituted for the negative PN/PAD contributing factors under the patient's control. Thus, if the patient is eating a high AGEs diet, the PN/PAD 'treatment' would consist of substituting a low AGEs diet. If the patient is participating in minimal physical activities, he/she would be encouraged to participate in more physical activities.

The 'reverse-engineering' component would be based on the laboratory tests. In parallel with the approach in Step 4, PN/PAD treatments would be prioritized based on the number of abnormal PN/PAD biomarkers they would impact. The caveats of step 4 about relying on numbers of biomarkers impacted would apply here as well.

The specific PN/PAD treatments employed would be selected based on the medical questionnaire results, the clinical sensorimotor evaluation, and the lab tests results. Some of the following PN/PAD lowest-risk treatments shown in Table 3B-3 would (in practice) be substitutions for the PN/PAD contributing factors eliminated; others would be new activities implemented.

**Table 3B-3 - Lowest-Risk Treatments**

- Exercise (such as aerobic exercise, walking, resistance training, treadmill, calisthenics, stretching, balancing)
- Sleep Improvement (such as quiet environment, minimal light, minimal food before bedtime, maintain regular sleep schedule)
- Stress Reduction (such as tai chi, yoga, massage, aromatherapy, acupuncture, accupressure, sensory stimulation, physiotherapy, massage, reflexology, meditation)
- Diet - Choose foods high in
  - polyphenols (such as cloves, star anise, capers, curry powder, ginger, cinnamon, peppermint, oregano, sage, rosemary, thyme, basil, cocoa, tea, red wine, chokeberries, elderberries, blueberries, plums, cherries, black currants, blackberries, strawberries, raspberries, grapes, flaxseeds, celery seeds, chestnuts, hazelnuts, pecans, almonds, walnuts, olives, artichokes, chicory, red onion, spinach, broccoli, apples, pomegranates, peaches, apricots, olive oil, canola oil), especially flavonoids (such as apples, blueberries, strawberries, red grapes, cabbage, broccoli, onions, capers, dark chocolate, cocoa, tea, red wine), isoflavones/genistein (such as soybeans, natto, tempeh, tofu, miso), and anthocyanins (such as blackberries, black currants, blueberries, strawberries, cranberries, eggplant, cherries, prunes, raisins, and the darker versions of raspberries, cabbage, plums, radish, grapes, plums, apples, beans, beets, cabbage, onions, pears, wines)
  - Unrefined carbohydrates (such as whole grains, legumes, fruits, and uncooked

vegetables)

- DHA/omega-3 fatty acid (such as salmon, herring, mackerel, anchovy, sardine, trout, shark, swordfish, mussel, sea bass, pollock, whiting, flounder, sole, lobster, halibut, carp, oyster, crab, mullet, tuna, perch, snapper, shrimp, octopus)
- Vitamin B12/Folate (such as meat [beef liver, lamb, beef], fish [sardines, mackerel, salmon], dairy [feta cheese, cottage cheese], eggs, legumes [chickpeas, fermented soy, pinto beans, lentils], fruit [banana, avocado], vegetables [spinach, parsley, broccoli, beets, turnip, asparagus,])
- Vitamin C (such as fruits [guavas, acerola cherry, kiwifruit, rose hips, strawberries, oranges, papayas, vegetables [bell peppers, broccoli, tomatoes, snow peas, kale])
- Vitamin D (such as fish [sardines, salmon, mackerel, tuna], liver [beef, calf, cod liver oil], dairy [milk, yogurt]; most importantly, sunlight on exposed skin)
- Vitamin E (such as seeds [sunflower seeds, pumpkin seeds], nuts [almonds, hazelnuts, pine nuts], fish [abalone, salmon, trout], fruit [avocado, mango, kiwifruit], vegetables [red peppers, turnip greens, spinach, chard, squash, broccoli])
- lycopene (such as tomatoes, guavas, watermelon, papaya, grapefruit),
- oleic acid (such as nuts [almonds, peanuts, pecans, cashews, pistachios, hazelnuts] seeds [sesame, sunflower], avocados, olives, and vegetable oils [safflower, almond, olive, sesame, sunflower]),
- luteolin (such as dried oregano, celery seed, hot peppers, peppermint, sage, rosemary, juniper berries, thyme, radicchio, chinese celery),
- quercetin (such as capers, lovage leaves, elderberry juice, dock leaves, raddish leaves, arugula, dill weed, coriander, and fennel, cilantro, banana peppers, juniper berries, oregano, onions, carob flour, radicchio, red leaf lettuce, onions, watercress, raw, asparagus, kale, okra, cocoa powder, chia seeds)
- sulforaphane (such as broccoli sprouts, broccoli, cauliflower, kale, brussels sprouts, cabbage, collards, arugula, turnips)
- resveratrol (such as red wine, red grapes, peanut butter, pistachios, cocoa powder, dark chocolate, strawberries, blueberries, bilberries, cranberries)
- epigallocatechin-3-gallate (such as green tea, black tea, carob powder, apples, blackberries).

#### Caveats on diet:

- Many toxic/harmful substances enter the food supply during all phases of food growth, distribution, and processing. While foods should be selected to maximize the amounts of healing nutrients identified above, care must be taken to minimize the level of toxic additions to the food in parallel.
- Low-temperature cooking should be used to minimize production of AGEs and other harmful products (nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides) during the cooking process.

- Only low-mercury wild-caught fish should be used; these tend to be smaller fish, lower on the food chain.
- Grass-fed animals with no exogenous growth hormones or antibiotics should be used, if possible, since these harmful products could be passed through to the consumer.
- For fruits and vegetables normally eaten with skin, those that have not been sprayed with harmful pesticides and other toxic chemicals should be used.
- Heavy metals are a contributing factor for many neurodegenerative diseases, including AD. One source of heavy metal bioaccumulation in the body is through the food supply. Heavy metals can occur naturally in the soil in which food is grown, they can concentrate abnormally in soils from nearby industrial pollution or from precipitation of air pollution, they can preferentially absorb in different types of food, and, depending on the type of food, can be absorbed from the food processing and manufacturing process. Any of the above foods selected for PN/PAD prevention or treatment purposes should have heavy metal concentrations as low as possible.

A note about these dietary recommendations. In [Table 7A-5](#), herbs and plant extracts are associated with large numbers of records. One of the major reasons for this is their copious use in Traditional Chinese Medicine, which had significant representation in the PN/PAD database. Some of the concoctions that contained these substances had adverse side effects, which removed them from the desired low-risk category. Also, independent verification of many of these concoctions' impacts was not readily available. Therefore, they are not in the first-tier recommendations.

Additionally, many of these plant extracts, almost by definition, are not whole foods. The present monograph recommends whole foods containing the desired chemicals and nutrients (listed in Table 7A-5) preferentially in the above list. The full spectrum of phytochemicals contained in whole foods acts synergistically with the fragmented chemicals listed to provide far more protection. As stated in [Liu, 2003]: "the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods."

#### **ES-4. Health Policy**

The above PN/PAD treatment protocol has been developed based mainly on medical findings, especially as reported in the premier biomedical literature. Financial and political/policy considerations were not taken into account.

The protocol contains implicit assumptions that patients will be able to

- 1) pay for any expensive drugs (if necessary),
- 2) afford pesticide-free, and other harmful-chemical-free, foods,
- 3) leave jobs where the working environment is toxic,
- 4) move from residences where the environment is toxic, etc.

This flexibility might not be available to many patients with limited income and/or limited assets.

There is also the implicit assumption that, if one has sufficient assets and flexibility, toxin-free environments can be found and toxin-free lifestyles can be achieved. This assumption is open to question, as shown by the following example.

Probably the key exogenous contributing factor to the development of PN/PAD (and many other chronic diseases) is the incorporation of technology in all aspects of modern life without adequate regulation and safety testing [Kostoff, 2015; Kostoff, 2016]. To compound the problem, some/many of these new technologies are effectively mandated by government, and impossible to avoid, even if the PN/PAD patient is wealthy. One example follows, but it is reflective of myriad other technologies contributing in part to PN/PAD.

Wireless radiation technology has become ubiquitous in modern life (cell phones, WiFi, smart meters, etc.). Research has shown that wireless radiation in the cell phone radiofrequency part of the spectrum contributes to oxidative stress and inflammation [Kostoff and Lau, 2017; Chauhan et al, 2017; Kesari et al, 2013], among many other adverse effects. As the present PN/PAD study results show, oxidative stress and inflammation are key PN/PAD characteristics. Chronic exposure to wireless radiation would be a factor contributing to increase the incidence of PN/PAD (and many other chronic diseases in which these two characteristics are important).

Wireless radiation technology requires an infrastructure. For cell phones, the major infrastructure is cell towers. The Telecommunications Act of 1996 effectively mandates the construction of cell towers with no opposition allowed based on health considerations. As of this writing, the FCC is attempting to implement similar effective mandates for the next generation of mobile wireless technology, known as 5G. A million or more 'short' cell towers (in the USA alone) would be required for 5G implementation, since the propagation of radiation energy at the

high frequencies characteristic of 5G is poor, and the distances between 'short' cell towers is relatively small by necessity.

This means that populated areas will be blanketed (around the clock) with 3GHz-30GHz (or higher) radiofrequency radiation, in addition to the lower frequency radiation emitted from today's installed cell towers. This is a range of the frequency spectrum essentially untested for adverse health effects, especially over the long-term in humans, and especially in combination with other toxic stimuli [Kostoff and Lau, 2017]. It is no different in principle from a contractor proposing to spray the populated areas of the USA with Agent Orange around the clock, and the relevant government regulatory agency stating that no opposition to the spraying is allowed based on health considerations. In effect, **the USA Federal government is promoting/mandating an increase in rates of PN/PAD**, with the potential of this increase being very large.

Thus, there is a dichotomy in the relevant USA Federal policy. On the one hand, the Federal government is investing heavily in biomedical research to treat and reverse PN/PAD. On the other hand, the Federal government is allowing essentially unrestricted and inadequately regulated expansion of technologies that are important contributing factors to PN/PAD. Metaphorically, the Federal government is *drilling holes in the floor of the boat at the same time they are pumping water out of the boat!* These policies are diametrically opposed, and will limit the effectiveness of any PN/PAD treatment protocol, no matter how strictly followed.

#### **ES-5. Near-Term Implementation of Findings**

To gain operational experience with exploiting the findings in this monograph, clinical trials should be started in the near future. Given the limitations in knowing exposures to many potential PN/PAD contributing factors outlined above, these trials could start with incorporating the "[low-hanging fruit](#)" contributing factors that have been identified previously. These are potential PN/PAD contributing factors that could be estimated or measured relatively easily. If elimination of these PN/PAD contributing factors does not yield the results desired, then low-risk treatments could be instituted.

[References - Executive Summary](#)

## Chapter 1

### INTRODUCTION

#### 1A. Overview

Chapter 1 describes

- Basic principles of the treatment protocol
- Present and projected incidence and prevalence of Peripheral Neuropathy (PN)/Peripheral Arterial Disease (PAD) in our society
- Rationale for combining PN and PAD
- Mainstream medical approach to treating this disease
- Relationship of proposed approach to some segments of the mainstream medical approach.

This chapter ends with an outline of the monograph's structure and contents.

#### 1B. Basic Principles of Treatment Protocol

The treatment protocol proposed for prevention and reversal of PN/PAD in the present monograph is based on the following systemic medical principle [Kostoff, Porter, Buchtel, 2018]: **At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective.** This principle is general, and applicable to prevention and reversal of *any* disease. The methodology that has been developed based on this principle is general, and applicable to any disease as well.

To prevent any disease, the foundational causes that underlie the disease symptoms and biomarkers need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse any disease (if irreversible damage from the disease has not been done and strong genetic predisposition to the disease is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse the disease progression need to be applied.

The efficacy of the methodology for preventing and reversing any disease depends on how thoroughly the foundational causes, treatments, biomarkers, and symptoms of the disease of interest have been identified. In the present monograph, a wide spectrum of existing PN/PAD foundational contributing factors has been identified. Additionally, a wide spectrum of existing (and a few newly discovered) PN/PAD treatments and PN/PAD symptoms and biomarkers has been identified. Combining these results allows development of a PN/PAD treatment protocol that can be tailored to individual patients. Most importantly, this PN/PAD treatment protocol (based on the systemic medical principal described above) is ***available with the information at our disposal today!***



## 1C. Present and Projected PN/PAD Incidence and Prevalence

### 1C1. PN

PN refers to the range of clinical syndromes that involve damage to the peripheral nervous system, including motor, sensory, and autonomic fibers [Shields RW, 2010; NINDS, 2019]. If one nerve is damaged, the condition is referred to as mononeuropathy. If many nerves are involved, it is called polyneuropathy [UCSF, 2019].

Estimates of PN prevalence vary widely.

- Watson and Dyck: the prevalence of PN in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years [Watson and Dyck, 2015];
- Foundation for PN: an estimated thirty million Americans suffer from some type of PN [FPN, 2019];
- Western Neuropathy Association and University of California at San Francisco (UCSF): more than twenty million Americans suffer from some sort of PN [WNA, 2019; UCSF, 2019];
- Cioroiu and Brannagan: "Peripheral neuropathy is thought to affect approximately 24 % of the population over age 70" [Cioroiu and Brannagan, 2014].

The most prevalent types of PN are diabetic (~60%), ideopathic (~23%), chemotherapy-induced (~10%), HIV/AIDS-induced (~2%), other (~5%) [FPN, 2019].

More detailed information about symptoms, biomarkers, diagnoses, causes, treatments, and epidemiology of PN can be found in the following comprehensive PN review articles [e.g., Barrell and Smith, 2019; Saporta and Shy, 2015; Pascuzzi, 2009; England and Asbury, 2004; Hughes, 2002; Watson and Dyck, 2015; Hanewinkel, Ikram, and van Doorn, 2016] and in the following PN books [e.g., Donofrio, 2012; Smith and Bromberg, 2005; Barohn, 2013; Herskovitz, Scelsa, and Schaumburg, 2010; Thomas and Dyck, 2005; Dyck et al, 2010].

### 1C2. PAD

PAD is a circulatory problem involving narrowing of the peripheral arteries serving the legs, stomach, arms and head, affecting arteries in the legs most commonly [AHA, 2019; MC, 2019]. It is one of a number of terms used commonly to refer to arterial occlusive disease of the lower and upper extremities, including peripheral vascular disease (PVD), peripheral arterial occlusive disease, and arteriosclerosis obliterans [Campia, Gerhard-Herman, Piazza, et al, 2019]

Estimates of PAD prevalence vary somewhat.

- PAD affects around 13% of the Western population who are more than 50 years old [Morley, Sharma, Horsch et al, 2018];

- PAD has a reported prevalence of 15% in Australia, the USA, and other Western countries, and up to 30% when studied in older populations [Conte and Vale, 2018];
- PAD affects 12% to 20% of Americans 60 years and older, increasing to nearly 50% in those 85 years and older. Prevalence increases dramatically with age, and PAD disproportionately affects black persons. The global disease burden exceeds 200 million persons worldwide, and PAD increased in prevalence by 23.5% between 2000 and 2010 [Firnhaber and Powell, 2019];
- PAD prevalence in the United States is low in people 50 years and younger, while PAD rates increase sharply with age, reaching approximately 20% in octogenarians [Campia, Gerhard-Herman, Piazza, et al, 2019];
- PAD prevalence globally was ~118 million cases in 2017 and the number of incident cases was ~11 million, with two thirds of PAD prevalent cases being asymptomatic. Furthermore, PAD caused 515,600 years lived with disability. In 2017, ~70,000 people died from PAD, which represents ~56% increase compared with 2007 [Kengne and Echouffo-Tcheugui, 2019].

More detailed information about symptoms, diagnoses, causes, treatments, and epidemiology of PAD can be found in the following comprehensive PAD review articles [e.g., Firnhaber and Powell, 2019; Campia, Gerhard-Herman, Piazza, et al, 2019; Conte and Vale, 2018; Morley, Sharma, Horsch et al, 2018; Gerhard-Herman, Gornik, Barrett, et al, 2017] and in the following PAD books [e.g., Mohler and Jaff (Eds), 2017; Alonso, McManus, and Fisher, 2010; Kevil, Bir, and Pattillo, 2013; Zemaitis, Bah, Boll et al, 2019].

These projections may be strong under-estimates. PN and PAD have environmental components. There have been many potentially harmful and effectively un-regulated high-technology additions to the environment in the past few decades [Kostoff, Porter, and Buchtel, 2018; Kostoff, 2015] (e.g., wireless radiation, vaccine combinations, agricultural chemicals, etc., have expanded greatly). Because of latency delays, inadequate time has elapsed to show linkages between these potentially harmful environmental additions and changes in the incidence of PN/PAD in human populations. As will be shown in the present monograph, the adverse impact of (for example) recent potentially harmful environmental and dietary additions on PN/PAD biomarkers and symptoms ominously portends increased incidence and prevalence of PN/PAD in the future.

Many of the toxic stimuli that are contributing factors to PN/PAD also contribute to many other serious diseases [Kostoff, 2015]. Many of these diseases can be fatal, and may not have the multi-decadal latencies associated with some forms of PN and especially with PAD. Thus, these lethal diseases serve to cull out people who would have been high-risk candidates for PN/PAD had they lived. This culling out of high-risk individuals artificially depresses and masks the real incidence of PN/PAD had these high-risk people survived.

### 1D. Combining PN and PAD

Most of the PN or PAD contributing factor or treatment references examined addressed each disease/condition as a separate entity. However, since poor peripheral blood circulation characteristic of many forms of PAD would restrict adequate transport of nutrients (especially oxygen) to the peripheral neural system, potentially causing severe damage and destruction to the peripheral neural system, an argument could be made that PN and PAD should be treated as a combined entity. What is the evidence in the biomedical literature for this argument?

- "pathological alterations in chronic ischaemic neuropathy may be due to the combined effects of acute ischaemia/reperfusion and chronic hypoxia." [Nukada, vanRij, Packer et al, 1996];
- "These results support the presence of a mild sensory axonopathy in subjects with peripheral arterial disease." [Ugalde, Wineinger, Kappagoda et al, 1998];
- "There is a predominantly sensory neuropathy associated with chronic and critical limb ischemia. Neuropathic symptoms are often obscured by the effects of ischemia on other tissues. The neurophysiologic changes suggest that the underlying pathophysiology is a distal axonopathy affecting nerve fibers of all sizes. Measures of blood flow in the leg correlate with neurologic symptom scores, examination scores, and electrophysiologic testing." [Weinberg DH, Simovic D, Isner et al, 2001];
- "Patients with peripheral vascular disease are susceptible to neuropathy from chronic hypoxia." [Toursarkissian, Connaughton, D'Ayala et al, 2002];
- "chronic peripheral arterial occlusive disease causes axonal degeneration, resulting in axonal polyneuropathy." [Weber and Ziegler, 2002];
- "ischemia-related impairment in lower extremity nerve function may contribute to functional impairment and decline in people with PAD." [McDermott, 2015];
- "Subgroup analysis points towards a PAD-associated peripheral neuropathy independent of diabetes." [Lang, Schober, Rolke et al, 2006];
- "Incidence of CI-DSN [Chronic Idiopathic Distal Symmetric Neuropathy] is higher in individuals carrying vascular conditions. In men, the presence at baseline of peripheral artery disease is associated with a threefold increase in the risk of developing CI-DSN." [Baldereschi, Inzitari, Di Carlo et al, 2013];
- "Chronic ischemia in patients with peripheral arterial disease (PAD) represents a common medical problem. Neuropathic changes and pain caused by chronic ischemia are often found in the lower extremities of these patients. Pain in patients with chronic critical limb ischemia fulfill the criteria of neuropathic pain." [Lang, 2015];

The message from these studies, and many other similar studies not referenced, is clear. Restricted circulation characteristic of PAD deprives the peripheral nerves (and other peripheral micro and macro-structures) of adequate nutrients for optimal functioning and survival, especially, but not limited to, oxygen. This deprivation of adequate nutrient supplies to critical

organs, cells, and other biological structures, and the resulting pathology, is not limited to PN. In essentially every previous LRDI study I have performed examining myriad chronic diseases, poor blood circulation and the attendant nutrient deprivation to critical structures, has been a (typically under-emphasized) causal factor in the disease development and progression. Intake of the highest quality nutrients, by whatever route, will have limited effect on biological structure health if the logistics transport system (veins and arteries) is 1) not able to deliver these nutrients to the appropriate structures in a timely manner and is 2) not able to dispose of the metabolic waste products in a timely manner as well.

## 1E. Mainstream Medical Approach for PN/PAD

### 1E1. PN

The mainstream medical approach (and limitations) for PN is reflected in the comprehensive PN review articles and books cited above, and is addressed in more detail in the Background chapter, sections [5C1](#), [5C3](#), and [5E](#). While there are modest variations among authors, the treatments presented can be categorized in three main categories: related disease treatments; lifestyle changes; pain management. The selection of treatments depends on the perceived main causes of PN, if known.

Thus, if a patient has diabetes (which is associated with painful PN), emphasis is placed on addressing control/reversal of the diabetes. This is typically accomplished with a combination of lifestyle changes (especially dietary) and drugs. Other lifestyle changes may include the use of walking aids, and strict attention to proper foot care and proper footwear.

Pain management occupies much of the treatment literature for PN. It is mainly drug-based, with potential addition of dietary supplements. The main drug categories appear to be anticonvulsants, antidepressants, supplements, topicals, and analgesics.

### 1E2. PAD

The mainstream medical approach for PAD is reflected in the comprehensive PAD review articles and books cited above, and is addressed in more detail in the Background chapter, sections [5C2](#), [5C4](#), and [5E](#). However, the AHA/ACC guidelines referenced above [Gerhard-Herman, Gornik, Barrett et al, 2017] reflect a mainstream consensus approach to diagnosis and treatment of PAD, and these guidelines overlap strongly with recommendations contained in the referenced review articles and books.

For treatment, four broad categories are suggested in the AHA/ACC guidelines [Gerhard-Herman, Gornik, Barrett et al, 2017]: lifestyle changes; pharmacotherapy; exercise; surgery. The above reference suggests combination of some or all of the following, based in the results of the comprehensive diagnostic techniques:

- Antiplatelet, Statin, Antihypertensive Agents, and Oral Anticoagulation

- Smoking Cessation
- Glycemic Control
- Cilostazol, Pentoxifylline, and Chelation Therapy
- Homocysteine Lowering
- Influenza Vaccination
- Structured Exercise Therapy
- Prevention of wounds through patient education, foot examination, and prompt recognition of foot infection
- Endovascular surgical approaches

### 1E3. Limitations of high-technology mainstream medical approach

While lifestyle changes form part of the mainstream PN/PAD treatment protocol, including elimination of well-known causative factors, for the most part the mainstream PN/PAD treatment protocols are centered on pharmacotherapy and surgery. These typically high-technology treatments focus on removing/suppressing PN/PAD pathological symptoms, rather than removing the causes of these symptoms. These treatments (in the absence of comprehensive cause removal) have minimal success in reversing PN/PAD because they violate the systemic medical principle that forms the basis of the prevention and reversal methodology in this monograph.

The strategy of identifying symptoms as pathological mechanisms that must be suppressed or removed for healing is a mainstay of Western Medicine. However, another perspective is to view these symptoms in a positive light, as having two basic functions: serve as a warning signal that dysfunction exists and actions need to be taken to remove the cause of this dysfunction, and serve as a protective mechanism.

There are many examples in the biomedical literature supporting the concept of disease symptoms as warning signals and protective mechanisms, as shown by the following:

#### **EXAMPLES OF DISEASE SYMPTOMS AS PROTECTIVE MECHANISMS**

- "the down-regulation of energy metabolism in AD is a protective response of the neurons to the reduced level of nutrient and oxygen supply in the microenvironment" [Sun, Feng, Liang et al, 2012];
- "Neurofibrillary tangle formation as a protective response to oxidative stress in Alzheimer's Disease" [Nunomura, Takeda, Moreira et al, 2009];
- "Autophagy is a protective response to the oxidative damage to endplate chondrocytes in intervertebral disc" [Chen, Lv, Li et al, 2017];
- "loss of appetite in the acute phase of illness is indeed an adaptive, protective response that improves cell recycling (autophagy) and detoxification" [Schutz, Bally, Stanga et al, 2014];
- "Cataract is a self-defence reaction to protect the retina from oxidative damage" [Wegner and Khoramnia, 2011].

Along these same lines, Bredesen states in his 2017 book [Bredesen, 2017]: "Alzheimer's disease is actually a protective response to, specifically, three different processes: inflammation, suboptimal levels of nutrients and other synapse-supporting molecules, and toxic exposures." Other AD researchers have drawn similar conclusions. If Bredesen's view that the AD symptoms serve as a protective response against more serious damage is correct, then the mainline drug-based AD treatment approach of removing these pathologies/symptoms without removing their foundational causes comprehensively in parallel

- 1) effectively removes the protective shield reflected by these pathologies/symptoms and
- 2) exacerbates the progression of AD!

These conclusions are applicable to most, if not all, chronic diseases.

#### 1F. Approach Proposed in Present Monograph

The approach to prevention and reversal of PN/PAD proposed in the present monograph is 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 of disease to be effective.** To prevent PN/PAD, or any disease, the foundational causes that underlie the disease symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse PN/PAD (if irreversible damage has not been done and strong genetic predisposition to PN/PAD is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse progression (if necessary) need to be applied.

The approach in the present monograph is not constrained by hypotheses based primarily on symptoms/pathological mechanisms. Symptoms, pathological mechanisms, and other abnormal PN/PAD characteristics are used as a guidepost to identify causes to be eliminated and treatments to be implemented for individual patients. The present approach is based on cause and effect as evidenced in the premier biomedical literature. PN/PAD characteristics that exist in the biomedical literature are identified as comprehensively as possible, and then adverse changes in the values of these PN/PAD characteristics are related to potential underlying foundational causes. Preferably, the research findings will identify the biological mechanisms that link a foundational cause to its impact(s) on PN/PAD characteristics. However, even in the absence of such mechanisms, the linkage is retained. Beneficial changes in the values of these PN/PAD characteristics are related to potential treatments, again, whether or not the biological mechanisms that link treatments to positive impacts have been identified.

In the present monograph, the treatments identified cover research over the past ~thirty years. Treatments that have 'failed' in human clinical trials are not excluded. My reading of thousands of abstracts on laboratory experiments and clinical trials of potential PN/PAD 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;
- 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 humans who live in the real-world sea of myriad toxic exposures and animals who live in the very controlled environment of the laboratory are rarely, if ever, discussed.

As the present monograph will show, there are many hundreds of potential causes for PN/PAD (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 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 was able to reverse her own case of Multiple Sclerosis (MS) [Kostoff, 2012; Kostoff, 2015]. She used two main types of treatments: lifestyle changes (mainly dietary) to reverse the MS and neuromuscular electrical stimulation (NMES) to reverse the damage resulting from MS. **It was only when her diet achieved near-pristine status 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 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 PN/PAD treatments in the clinical trials of the past three decades cannot be ruled out. That is why even so-called 'failed' treatments in the present full-spectrum study of existing PN/PAD treatments have been included. 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 PN/PAD causes by themselves would have obviated the need for many of these PN/PAD treatments!***

For the comprehensive treatment process contained in this monograph, the first step in both PN/PAD prevention and reversal protocols is to identify the full spectrum of existing PN/PAD foundational causes/contributing factors. The second step (in parallel with the elimination of the actionable causes identified in the first step) is to identify existing and potential PN/PAD treatments that can be implemented to accelerate PN/PAD reversal. The remainder of the present monograph identifies a wide spectrum of existing PN/PAD foundational causes, existing and potential treatments, and PN/PAD 'characteristics' impacted by both PN/PAD causes and treatments. Then, these PN/PAD foundational causes, treatments, and characteristics are integrated, and a treatment protocol for preventing and reversing PN/PAD tailored to the individual is presented.

#### 1G. Structure of Remaining Monograph Chapters

\*[Chapter 2](#) presents Results, Discussion, and Conclusions from the PN/PAD study.

\*[Chapter 3](#) integrates the findings to outline an individualized Treatment Protocol for preventing and reversing PN/PAD, in selected cases.

\*[Chapter 4](#) contains Suggested Further Research, based on both the deficiencies and opportunities identified by this study.

\*[Chapter 5](#) contains the Background for the present study, including definitions of key terms.

\*[Chapter 6](#) presents the detailed Methodology used to identify existing and potential PN/PAD treatments, and existing PN/PAD contributing factors and characteristics.

\*[Chapter 7](#) contains full Tables.

\*[Chapter 8](#) contains the [References](#) for each chapter, and a comprehensive [Bibliography](#) of myriad PN/PAD references.

#### [References - Chapter 1](#)



## Chapter 2

### RESULTS, DISCUSSION, AND CONCLUSIONS

#### 2A. Overview

This chapter presents the results of data analyses, discussion of the findings, and conclusions. It contains lists of the existing PN/PAD causes, treatments, and characteristics. These lists undergo factor analyses, and the resultant factor matrices showing the myriad categories intrinsic to each list are presented. Beyond this factor matrix step, only the biomarker component of characteristics will be used. Square matrices of causes-causes, treatments-treatments, and biomarkers-biomarkers are then presented, to allow identification of closely related items in the same category. For PN/PAD treatments, illustrative examples of potential PN/PAD treatment discoveries are also presented.

Two matrices are then shown that link the existing PN/PAD causes, treatments, and biomarkers. The first matrix shows causes vs biomarkers, and the second matrix shows treatments vs biomarkers. Sample strings of data from each matrix are extracted to show how the matrix would be interpreted and used in practice. Finally, matrices of causes, treatments, and biomarkers vs PN and PAD display the approximate number of records of each item that could be assigned to PN and PAD.

#### 2B. PN/PAD Causes

##### 2B1. List of Existing PN/PAD Contributing Factors

[Table 7A-1](#) contains a list of the ~840 existing contributing factors identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these contributing factors are shown in Table 2B-1. Because these are the highest frequency contributing factors, many will be very general.

The usual practice when listing contributing factors, treatments, and characteristics in a document is to provide one or more references for each item listed. Because of the voluminous numbers of existing PN/PAD contributing factors, treatments, and characteristics identified in this study, thousands of references would be required. The approach that will be taken here is to list the search query in Pubmed format for any of these items, and the interested user can run the query to identify *all* the PN/PAD records in Pubmed that contain the item of interest. This allows the user to view all the evidence for selection of the item, not one or two selected references. It also insures the user will have access to the latest references containing the item, and not limited to references published months before the publication date of the monograph. For those who wish to use Thomson Reuters for this purpose, convert the Pubmed query to Thomson Reuters format.

To access the Pubmed records containing the item of interest, use the following:

{item of interest }

AND

(peripheral neuropathy [mh:noexp] OR "peripheral neuropathy" [tiab] OR peripheral arterial disease [mh] OR "peripheral arterial disease" [tiab] OR "peripheral vascular disease" [tiab])

One caveat. Thomson Reuters-Medline does not recognize the MeSH Heading "Peripheral Neuropathy". Instead, the MeSH Heading "Peripheral Nervous System Diseases" has to be substituted for the MeSH Heading "Peripheral Neuropathy" in Thompson Reuters.

So, if one wants to find the references showing Bortezomib as a contributing factor to PN/PAD, one would enter the following query into Pubmed:

Bortezomib

AND

(peripheral neuropathy [mh:noexp] OR "peripheral neuropathy" [tiab] OR peripheral arterial disease [mh] OR "peripheral arterial disease" [tiab] OR "peripheral vascular disease" [tiab])

**Table 2B-1 - Top Fifty Existing PN/PAD Contributing Factors**

#RECORDS	CONTRIBUTING FACTOR
2507	chemotherapy
2265	smoking
1140	High cholesterol diet
985	paclitaxel
821	HIV-1
745	dialysis
708	infections
683	viruses
570	cisplatin
570	trauma
545	depression
524	oxaliplatin
508	hemodialysis
503	Bortezomib
442	alcohol
393	alcohol consumption
378	highly active antiretroviral therapy
361	radiation
357	anesthesia
351	thalidomide

347	vincristine
340	peripheral nerve injury
337	lifestyle
332	leprosy
329	radiation therapy
324	taxanes
323	cyclophosphamide
314	hepatitis
296	Streptozotocin
230	carboplatin
217	platinum
201	chronic constriction injury
196	docetaxel
186	Hepatitis C Virus
184	antibiotics
162	doxorubicin
149	Arsenic
148	stavudine
140	5-fluorouracil
131	sedentary
125	advanced glycosylation end products
121	capecitabine
121	tuberculosis
119	zidovudine
118	iatrogenic
118	Taxol
111	methotrexate
110	lenalidomide

Categorization and analysis of these contributing factors will be shown in the next section.

## 2B2. Factor Matrix of Existing Causes

Figure 2B-1 in the Excel workbook located under the same URL as the present monograph (FIGURES\_FOR\_MONOGRAPH.xlsx - listed under View/Open on the link page) contains a factor matrix of the existing PN/PAD contributing factors (click on first tab FIG 2B-1). The 29 factor headings are shown below in Table 2B-2. This listing provides a convenient taxonomy for categorizing the myriad contributing factors identified. Figure 2B-1 lists the specific contributing factors that had the strongest influence in determining the theme of each of the 29 factors.

One of the challenges in combining the literatures for two different (but related) diseases/conditions is that some (very few) of the treatments for PAD are contributing factors to PN. Statins are one example, and modifications were made to compensate for this fact. Statins

are a **direct** contributing factor to PN in a modest number of applications. PN's main symptoms are numbness, tingling, and pain, and PN patients experience one or more of these symptoms.

Presence of these symptoms adversely impacts the quality and volume of walking, and therefore contributes to an increase in sedentary living (everything else being equal). Sedentary living is a **direct** contributing factor to PAD. Therefore, statins can be viewed as an **indirect** contributing factor to PAD. In summary, statins serve three roles: a **direct** treatment for PAD, a **direct** contributing factor to PN, and an **indirect** contributing factor to PAD. Since indirect contributing factors were not addressed in the present study, some modifications to the statin numbers were required to provide a more accurate picture.

Statins initially constituted Factor 4 in Figure 2B-2. However, this was misleading for the above reasons, so this factor was removed. For any of the treatments specific to PAD that contributed **directly** to PN, the PN contributing factor numbers should be substituted for the present treatment contributing factor numbers, and viewed as **indirect** contributing factors.

The main broad categories include:

- drugs (e.g., antiretroviral, chemotherapy, antifungal, antibiotics, antiarrhythmic/cardiovascular, statins [PN only]),
- pesticides/herbicides (e.g., dioxin, Chlorophenoxy herbicides, trichlorophenol, Paraquat, Trichlorfon, dichlorvos, mipafox, organophosphate pesticides, malathion, chlorpyrifos),
- infectious agents (e.g., bacteria, mycobacteria, viruses),
- occupational/industrial chemicals (e.g., organic solvents, hydrocarbons, dithiocarbamates, benzene, organotin, methyl n-butyl ketone),
- environmental pollutants (e.g., heavy metals, persistent organic pollutants, air pollution, bisphenol A),
- induced injury (e.g., lysophosphatidic acid, N-methyl-D-aspartate, Freund's adjuvant, partial sciatic nerve ligation),
- lifestyle (e.g., excess alcohol, recreational drugs, smoking, sedentary, high cholesterol diet)

Almost 60% of the total contributing factors were not included under the factors in Figure 2B-1, because of the factor loading values used to determine the cutoffs. Many had factor loadings too small to influence the themes of the factors, and the remainder were unit frequency (only terms with record frequencies greater than or equal to two were used to generate the factor matrix). The bulk of those not shown under the specific factors were chemicals and drugs, with a few related to lifestyle. However, even though a contributing factor had little influence in determining the theme of a factor, it could be very important in its impact on PN/PAD.

**Table 2B-2 - Factor Matrix-based Categories for PN/PAD Contributing Factors**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - HIGHLY ACTIVE ANTIRETROVIRAL THERAPY</b>
<b>FACTOR 2 - CHEMOTHERAPY, ESPECIALLY TAXANES</b>
<b>FACTOR 3 - ANTIFUNGAL DRUGS</b>
<b>FACTOR 4 -</b>
<b>FACTOR 5A - CHEMOTHERAPY, CHRONIC MYELOGENOUS LEUKEMIA</b>
<b>FACTOR 5B - MYCOBACTERIA</b>
<b>FACTOR 6 - CHEMOTHERAPY, PROTEASOME INHIBITORS</b>
<b>FACTOR 7 - ALIPHATIC HYDROCARBONS</b>
<b>FACTOR 8 - HEPATITIS VIRUS AND DRUGS</b>
<b>FACTOR 9 - VIRUSES</b>
<b>FACTOR 10 - ORGANOPHOSPHATE PESTICIDES</b>
<b>FACTOR 11 - ANTIVIRAL DRUGS FOR AIDS</b>
<b>FACTOR 12A - OCCUPATIONAL CHEMICALS</b>
<b>FACTOR 12B - INFECTIOUS AGENTS</b>
<b>FACTOR 13 - ANTIARRHYTHMIC DRUGS</b>
<b>FACTOR 14 - ORGANIC SOLVENTS</b>
<b>FACTOR 15 - FLUOROQUINOLONE ANTIBIOTICS, FOCUSED ON TUBERCULOSIS</b>
<b>FACTOR 16 - BACTERIA AND INDUSTRIAL CHEMICALS</b>
<b>FACTOR 17 - BACTERIA AND CHRONIC MYELOGENOUS LEUKEMIA DRUGS</b>
<b>FACTOR 18 - HEAVY METALS</b>
<b>FACTOR 19A - ENVIRONMENTAL POLLUTANTS</b>
<b>FACTOR 19B - HYDROCARBONS, MAINLY ALIPHATIC SOLVENTS</b>
<b>FACTOR 20 - HERBICIDES</b>
<b>FACTOR 21 - VACCINES</b>
<b>FACTOR 22 - CHEMOTHERAPY, ESPECIALLY VINCA ALKALOIDS AND TAXANES</b>
<b>FACTOR 23A - DITHIOCARBAMATES</b>
<b>FACTOR 23B - HYDROCARBONS, ESPECIALLY TOXIC ALCOHOLS</b>
<b>FACTOR 24 - CHEMOTHERAPY</b>
<b>FACTOR 25A - INDUCED INJURY</b>
<b>FACTOR 25B - LIFESTYLE</b>

### 2B3. Causes-Causes Matrix

To display the inter-relationships among the PN/PAD causes, all the causes identified are matrixed together in Figure 2B-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two causes defining the cell. Thus, smoking co-occurs with high cholesterol diet in 397 records (third column, second row).

As an example of all causes that co-occur with a selected cause, [Tables 7A-2](#) and [7A-3](#) show all causes that co-occur with with the phrases 'chemotherapy' and 'lifestyle', respectively. The top fifty causes from Tables 7A-2 and 7A-3 are shown in Tables 2B-3 and 2B-4,

respectively. The first column represents the total number of records for the specific cause, the second column is the cause name, and the third column is the number of records in which the cause co-occurs with 'chemotherapy'.

In Table 2B-3, the bulk of the other causes are chemotherapeutic agents, although other related terms such as radiation and depression are mentioned as well. Table 2B-4 covers a much broader range of concepts than Table 2B-3, since 'lifestyle' is a much broader concept than 'chemotherapy'. To understand the associations in more detail, the specific records enumerated in each cell of interest must be evaluated. The reader can manipulate the matrix in Figure 2B-2 to evaluate terms and relationships of personal interest.

It should be emphasized that 'chemotherapy' and 'lifestyle' are phrases that occur in the database. In these tables, they do not reflect category headings. As an example, 'smoking' co-occurs with 'lifestyle' 108 times, even though 'smoking' occurs in 2265 records in the total PN/PAD database, and 'lifestyle' occurs 337 times in the total PN/PAD database. Smoking is an obvious component of lifestyle, but it only co-occurs with the word 'lifestyle' about 5% of the time that the word 'smoking' occurs in the total database. Interestingly, 'smoking' co-occurs with the word 'lifestyle' about 1/3 the time that 'lifestyle' appears in the total database. Given that caveat, these co-occurrences give some idea of what a chemotherapy category would reflect and what a lifestyle category would reflect.

**Table 2B-3 - Top Fifty Co-occurrences of Chemotherapy with other Causes**

#RECORDS	CAUSE	#CO-OCCURENCES
2507	chemotherapy	2507
985	paclitaxel	630
570	cisplatin	392
524	oxaliplatin	347
324	taxanes	223
347	vincristine	190
329	radiation therapy	166
230	carboplatin	161
217	platinum	156
503	Bortezomib	144
196	docetaxel	133
361	radiation	115
323	cyclophosphamide	112
140	5-fluorouracil	97
162	doxorubicin	95
351	thalidomide	93
118	Taxol	70
121	capecitabine	69
86	alkaloids	64
76	Vinca alkaloids	60

96	gemcitabine	59
76	vinorelbine	50
74	etoposide	50
111	methotrexate	46
63	bevacizumab	45
56	epirubicin	41
54	ifosfamide	40
62	fluorouracil	40
61	eribulin	38
60	cancer therapy	34
545	depression	33
90	proteasome inhibitors	31
46	irinotecan	30
821	HIV-1	28
96	drug-induced	28
708	infections	27
37	vinblastine	26
31	bleomycin	25
58	ixabepilone	23
91	melphalan	21
683	viruses	20
184	antibiotics	20
23	mitomycin C	18
39	trastuzumab	17
110	lenalidomide	17
22	suramin	16
49	acetone	16

In Table 2B-3, specific chemotherapy agents tend to co-occur with chemotherapy when they appear in the PN/PAD database.

**Table 2B-4 - Top Fifty Co-occurrences of Lifestyle with other Causes**

#RECORDS	CAUSE	#CO-OCCURENCES
337	lifestyle	337
2265	smoking	108
131	sedentary	44
1140	High cholesterol diet	35
442	alcohol	18
545	depression	11
59	inactivity	11
393	alcohol consumption	10
2507	chemotherapy	9
745	dialysis	6
361	radiation	4

570	trauma	3
329	radiation therapy	3
31	bleomycin	2
821	HIV-1	2
708	infections	2
96	malnutrition	2
60	cancer therapy	2
12	red meat	2
683	viruses	2
28	vitamin D deficient	2
43	bariatric surgery	2
85	renal transplantation	2
83	axotomy	2
83	liver transplant	2
125	advanced glycosylation end products	2
73	coronary angioplasty	2
66	high fat diet	2
5	salt intake	2
46	irinotecan	1
20	folate deficient	1
296	Streptozotocin	1
82	burn	1
11	cocaine	1
18	organic solvent	1
21	Drug Abuse	1
74	etoposide	1
324	taxanes	1
37	interferon-alpha	1
985	paclitaxel	1
67	solvents	1
570	cisplatin	1
118	iatrogenic	1
65	Zinc	1
49	environmental factors	1

In Table 2B-4, while myriad lifestyle problems are mentioned at the higher frequencies (e.g., smoking, inactivity, recreational substances, poor diet), sedentary living stands out by co-occurring with lifestyle a significant fraction of the time it appears in the PN/PAD database. At lower frequencies, red meat and salt intake stand out for the same reasons as well.



## 2B4. Contributing Factors Related to PN and to PAD

While many of the contributing factors applied relatively equally to PN and PAD, some were focused exclusively on PN and others on PAD. To identify the relative contributions, the symptoms/diseases related to PN and to PAD were aggregated separately. [Table 7A-4](#) shows the numbers of records in which the contributing factors co-occur with PN and with PAD. The top fifty are shown in Table 2B-5.

Causes shared more or less equally between PN and PAD include infections, trauma, alcohol, radiation, anesthesia, antibiotics, advanced glycation end products, Hepatitis C virus, spinal cord injury, burn, high fat diet, inactivity, environmental factors, arsenic, lipopolysaccharide, drug abuse, etc. Causes weighted toward PN include chemotherapy agents, radiation therapy, statins, chronic constriction injury, tuberculosis, antiviral agents, mycobacterium, pesticides, solvents, acrylamide, acetone, occupational exposures, etc. Causes weighted toward PAD include smoking, high cholesterol diet, dialysis, sedentary, lifestyle, air pollution, atenolol, etc.

**Table 2B-5 - Contributing Factors Relevant to PN and to PAD**

#RECORDS	CAUSE	#PN RECORDS	#PAD RECORDS
2507	chemotherapy	2315	119
2265	smoking	275	2124
1140	High cholesterol diet	261	1004
985	paclitaxel	874	69
821	HIV-1	696	134
745	dialysis	139	643
708	infections	391	393
683	viruses	548	182
570	cisplatin	515	20
570	trauma	269	260
545	depression	326	251
524	oxaliplatin	499	1
508	hemodialysis	105	428
503	Bortezomib	473	32
442	alcohol	232	230
412	statins	43	
393	alcohol consumption	266	147
378	highly active antiretroviral therapy	344	37
361	radiation	189	134
357	anesthesia	157	139
351	thalidomide	333	56
347	vincristine	328	11
340	peripheral nerve injury	229	18
337	lifestyle	78	283
332	leprosy	206	19

329	radiation therapy	245	50
324	taxanes	303	7
323	cyclophosphamide	288	80
314	hepatitis	267	142
296	Streptozotocin	273	40
230	carboplatin	215	5
217	platinum	194	6
201	chronic constriction injury	179	1
196	docetaxel	183	4
186	Hepatitis C Virus	155	107
184	antibiotics	101	102
162	doxorubicin	148	17
149	Arsenic	78	73
148	stavudine	143	3
140	5-fluorouracil	130	3
131	sedentary	34	108
125	advanced glycosylation end products	74	74
121	capecitabine	103	
121	tuberculosis	101	22
119	zidovudine	115	4
118	Iatrogenic	55	37
118	Taxol	103	3

## 2C. PN/PAD Treatments

### 2C1. List of Existing PN/PAD Treatments

[Table 7A-5](#) contains a list of the existing PN/PAD treatments identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these treatments are shown in Table 2C-1. Because these are the highest frequency treatments, many will be very general. The references are identified using the same method as the contributing factors in section 2B-1.

**Table 2C-1 - Top Fifty Existing PN/PAD Treatments**

# RECORDS	TREATMENT
5105	surgery
3638	drug
2402	amputation
1920	revascularization
1766	inhibitor
1358	walking
1328	exercise
1308	artery bypass grafting

1228	angioplasty
828	stents
812	growth factor
754	insulin
745	dialysis
632	medications
588	operation
576	aspirin
567	analgesic
541	endovascular treatment
507	vascular surgery
499	implantation
489	angiogenesis
459	rehabilitation
450	bypass surgery
449	diet
447	glycemic control
420	Ligation
411	corticosteroid
382	catheter
370	statin
353	Clopidogrel
349	vascular endothelial growth factor
337	antiplatelet therapy
317	opioid
288	supplementation
266	coronary intervention
252	antihypertensive agents
242	Gabapentin
240	PNS
233	endarterectomy
233	pregabalin
228	antidepressant
221	anticoagulant
215	Cilostazol
207	vitamin B12
206	nerve growth factor
190	smoking cessation
189	Spinal Cord Stimulation
172	Gene therapy

Categorization and analysis of these treatments will be shown in the next section.

## 2C2. Factor Matrix of Existing Treatments

Figure 2C-1 in the Excel workbook located under the same URL as the present monograph (FINAL\_FIGURES.xlsx - listed under View/Open on the link page) contains a factor matrix of the existing PN/PAD (click on FIG 2C-1). The thirty factor headings are shown below in Table 2C-2. This listing provides a convenient taxonomy for categorizing the myriad treatments identified. Figure 2C-1 lists the specific treatments that had the strongest influence in determining the theme of each of the thirty factors.

The main categories include:

- drugs (e.g., antidepressants, anticonvulsants, opioids, muscle relaxants, antiplatelet/antithrombotic/anticoagulant agents, calcium channel blockers, antihypertensive agents, serotonin reuptake inhibitors, endocannabinoid deactivation inhibitors, cannabinoids, dipeptidyl peptidase-4 inhibitors, etc);
- surgery (e.g., angioplasty, arterial bypass, stents, revascularization, amputation, spinal cord stimulation, deep brain stimulation, etc)
- supplements (e.g., omega-3 fatty acids, fish oil, antioxidants, Vitamin E, Vitamin C, Vitamin B12, alpha lipoic acid, biotin, Vitamin D, magnesium, etc)
- herbs (e.g., herbal medicines, Chinese herbs, Buyang Huanwu decoction, Guizhi-shaoyao-zhimu decoction, Huoxue Kangyuan decoction, Plantaginis Semen, Aucubin, Goshajinkigan, kampo, etc)
- angiogenesis (growth factors, cell therapy, etc)

Almost 75% of the total treatments were not included under the factors in Figure 2C-1, because of the factor loading values used to determine the cutoffs. Many had factor loadings too low to influence the themes of the factors, and the remainder were unit frequency. The bulk of those not shown under the specific factors were drugs, herbs/plants, neural stimulation (rTMS, TENS, acupuncture, massage, EMF radiation, shock wave, ultrasound, etc), with a few related to lifestyle. Even though a treatment had little influence in determining the theme of a factor, it could be very important in its impact on PN/PAD.

**Table 2C-2 - Factor Matrix-based Categories for PN/PAD Treatments**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - ANTIDEPRESSANTS/ANTICONVULSANTS/OPIOIDS</b>
<b>FACTOR 2 - ANTIPLATELET/ANTITHROMBOTIC THERAPY</b>
<b>FACTOR 3 - ENDOCANNABINOID DEACTIVATION INHIBITORS</b>
<b>FACTOR 4 - ANTIHYPERTENSIVE AGENTS</b>
<b>FACTOR 5 - SEROTININ REUPTAKE INHIBITORS</b>
<b>FACTOR 6 - CANNABINOIDS/ANGIOGENESIS</b>
<b>FACTOR 7 - MUSCLE RELAXANTS</b>
<b>FACTOR 8 - ENDOVASCULAR TREATMENT</b>
<b>FACTOR 9A - CANNABINOIDS</b>
<b>FACTOR 9B - ANGIOGENESIS/GROWTH FACTORS/CELL THERAPY</b>
<b>FACTOR 10 - ANTICOAGULANTS</b>
<b>FACTOR 11 - ANTIEPILEPTICS/ANTICONVULSANTS</b>
<b>FACTOR 12 - ANTIHYPERTENSIVE AGENTS, ESPECIALLY ACE INHIBITORS</b>
<b>FACTOR 13 - PERIPHERAL NERVE REGENERATION AND PROTECTION</b>
<b>FACTOR 14 - OMEGA-3 FATTY ACIDS</b>
<b>FACTOR 15 - LOW-DENSITY LIPOPROTEIN REDUCTION THERAPY, ESPECIALLY STATINS</b>
<b>FACTOR 16 - NEUROPATHIC PAIN MANAGEMENT, ESPECIALLY OPIOIDS</b>
<b>FACTOR 17 - REPURPOSED THERAPIES FOR NEUROPATHY</b>
<b>FACTOR 18 - CALCIUM CHANNEL ANTAGONISTS</b>
<b>FACTOR 19 - CXCR4 ANTAGONISTS FOR NEUROPATHIC PAIN</b>
<b>FACTOR 20 - PHENOLS</b>
<b>FACTOR 21 - PROSTACYCLIN ANALOGUES</b>
<b>FACTOR 22A - GROWTH FACTORS</b>
<b>FACTOR 22B - CELL THERAPY</b>
<b>FACTOR 23 - GLYCOSAMINOGLYCANS</b>
<b>FACTOR 24 - HERBAL MEDICINE</b>
<b>FACTOR 25 - ANALGESICS/NSAIDs</b>
<b>FACTOR 26 - SUPPLEMENTATION</b>
<b>FACTOR 27A - ANTIPLATELET/ANTITHROMBOTIC THERAPY</b>
<b>FACTOR 27B - ANTITHROMBOTIC/ANTICOAGULANT AGENTS</b>

### 2C3. Treatment-Treatment Matrix

To display the inter-relationships among the PN/PAD treatments, all the treatments identified are matrixed together in Figure 2C-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two treatments defining the cell. Thus, walking co-occurs with drug in 122 records (second column, sixth row).

As an example of all treatments that co-occur with a selected treatment, [Tables 7A-6](#) and [7A-7](#) show all that co-occur with the phrases 'revascularization' and 'growth factor', respectively. The top fifty causes from [Tables 7A-6](#) and [7A-7](#) are shown in [Tables 2C-3](#) and [2C-](#)

4, respectively. The first column represents the total number of records for the specific treatment, the second column is the treatment name, and the third column is the number of records in which the treatment co-occurs with 'revascularization' or 'growth factor'.

In Table 2C-3, the bulk of the other treatments are invasive procedures, although other related treatment concepts such as drugs and exercise are mentioned as well. Table 2C-4 covers a much broader range of concepts than Table 2C-3, since 'growth factor' is a much broader concept than 'revascularization'. To understand the associations in more detail, the specific records enumerated in each cell of interest must be evaluated. The reader can manipulate the matrix in Figure 2C-2 to evaluate terms and relationships of personal interest.

**TABLE 2C-3 - Top Fifty Co-occurrences of Revascularization with other Treatments**

#RECORDS	TREATMENT	#CO-OCCURRENCES
1920	revascularization	1920
5105	surgery	776
2402	amputation	615
1228	angioplasty	403
828	stents	300
1308	artery bypass grafting	276
541	endovascular treatment	178
450	bypass surgery	127
507	vascular surgery	121
1358	walking	120
3638	drug	119
1328	exercise	117
1766	inhibitor	76
588	operation	73
576	aspirin	73
266	coronary intervention	71
499	implantation	71
337	antiplatelet therapy	68
233	endarterectomy	62
489	angiogenesis	59
745	dialysis	58
370	statin	56
353	Clopidogrel	54
382	catheter	52
812	growth factor	51
215	Cilostazol	44
632	medications	38
68	drug-coated balloons	33
190	smoking cessation	33
459	rehabilitation	31

107	cell therapy	31
57	nitinol stents	24
349	vascular endothelial growth factor	22
754	insulin	21
252	antihypertensive agents	20
172	Gene therapy	19
167	heparin	18
37	drug-eluting balloons	17
221	anticoagulant	17
447	glycemic control	16
420	Ligation	13
44	vorapaxar	13
36	stem cell therapy	13
35	directional atherectomy	12
449	diet	11
110	enzyme inhibitors	11
131	mononuclear cells	10
32	Orbital atherectomy	10
55	antithrombotic therapy	9

In Table 2C-3, the treatments that co-occur with revascularization a significant fraction of the time they appear in the PN/PAD database are specific types of vascular surgery (e.g., stents, bypass surgery, angioplasty).

**TABLE 2C-4 Top Fifty Co-occurrences of Growth Factor with other Treatments**

#RECORDS	TREATMENT	# CO-OCCURRENCES
812	growth factor	812
349	vascular endothelial growth factor	301
489	angiogenesis	216
206	nerve growth factor	174
3638	drug	103
1766	inhibitor	85
5105	surgery	82
172	Gene therapy	78
2402	amputation	61
52	hepatocyte growth factor	52
51	epidermal growth factor	51
1920	revascularization	51
150	hypoxia	31
420	Ligation	28
1358	walking	26
1328	exercise	25
107	cell therapy	25

754	insulin	23
24	bFGF	22
42	Neurotrophins	21
1308	artery bypass grafting	20
1228	angioplasty	18
33	neurotrophin-3	18
52	BDNF	17
28	GDNF	16
172	IL-6	15
131	mononuclear cells	15
215	Cilostazol	14
51	Mesenchymal Stem Cells	14
107	granulocyte colony-stimulating factor	12
411	corticosteroid	11
567	analgesic	11
499	implantation	11
449	diet	10
240	PNS	10
147	capsaicin	10
24	insulin-like growth factor-I	9
36	stem cell therapy	9
167	heparin	9
78	anthracycline	9
14	CNTF	8
189	Spinal Cord Stimulation	8
317	opioid	7
17	viral vectors	7
242	Gabapentin	7
447	glycemic control	7
288	supplementation	6

In Table 2C-4, treatments closely related to growth factor are the specific growth factors in the PN/PAD database.

#### 2C4. Treatments related to PN and to PAD

While many of the treatments applied relatively equally to PN and PAD, some were focused more strongly on PN and others on PAD. To identify the relative contributions, the symptoms/diseases related to PN and to PAD were aggregated separately. [Table 7A-8](#) shows the numbers of records in which the treatments co-occur with PN and with PAD. The top fifty are shown in Table 2C-5.



**Table 2C-5 - Top Fifty Treatments Relevant to PN and to PAD**

<b>#RECORDS</b>	<b>TREATMENT</b>	<b>#PN RECORDS</b>	<b>#PAD RECORDS</b>
5105	surgery	1172	3427
3638	drug	2279	1321
2402	amputation	591	2064
1920	revascularization	56	1839
1766	inhibitor	951	813
1358	walking	304	1058
1328	exercise	229	1124
1308	artery bypass grafting	59	1154
1228	angioplasty	23	1149
828	stents	7	751
812	growth factor	377	426
754	insulin	467	465
745	dialysis	139	643
632	medications	320	338
588	operation	122	374
576	aspirin	33	552
567	analgesic	479	61
541	endovascular treatment	3	499
507	vascular surgery	17	466
499	implantation	69	393
489	angiogenesis	56	439
459	rehabilitation	149	262
450	bypass surgery	13	421
449	diet	239	233
447	glycemic control	333	247
420	Ligation	274	110
411	corticosteroid	328	148
382	catheter	41	297
370	statin		333
353	Clopidogrel	8	345
349	vascular endothelial growth factor	105	257
337	antiplatelet therapy	4	330
317	opioid	271	28
288	supplementation	160	124
266	coronary intervention		261
252	antihypertensive agents	36	238
242	Gabapentin	235	16
240	PNS	166	23
233	endarterectomy	2	222
233	pregabalin	230	5
228	antidepressant	203	27
221	anticoagulant	24	196

215	Cilostazol	6	211
207	vitamin B12	160	50
206	nerve growth factor	170	8
190	smoking cessation	9	184
189	Spinal Cord Stimulation	122	84
172	Gene therapy	37	128
172	IL-6	75	95
167	heparin	15	146

Treatments shared more or less equally between PN and PAD include insulin, growth factors, diet, antioxidants, folic acid, carnitine, cannabis, DHA, etc. Treatments weighted toward PN include analgesics, opioids, gabapentin, pregabalin, antidepressants, Vitamin B12, capsaicin, morphine, zidovudine, amitriptyline, alpha lipoic acid, carbamazepine, anthracycline, thiamine, etc. Treatments weighted toward PAD include revascularization, exercise, walking, artery bypass grafting, angioplasty, stents, aspirin, endovascular treatment, vascular surgery, angiogenesis, catheter, statins, clopidogrel, antiplatelet therapy, antihypertensive agents, warfarin, etc.

#### 2C5. Potential PN/PAD Treatments from LRDI Discovery

The LRDI Discovery method outlined in section 6B5 and presented in detail in [Appendix 6-1](#) was used to identify potential PN/PAD treatment candidates. Even with the abbreviated query shown, hundreds of potential PN/PAD treatment candidates were retrieved (mid-August 2019), and thousands more could have been easily obtained with an expanded query. Ten of the candidates that were evaluated and validated for Discovery are shown in Table 2C-6. While combinations of two biomarkers were the criteria for retrieving potential PN/PAD treatment candidates, the impacts of the treatment on myriad other biomarkers were included in the retrieved article as well. All the biomarkers impacted by the candidate treatment (listed in the abstract) are shown in parentheses after the quoted material.

**Table 2C-6 - Potential Treatments for PN/PAD**

1. *Dendrobium nobile* Lindl

"***DNLA*** [*Dendrobium nobile* Lindl. alkaloids] ***protects mice from CCl4 induced liver injury***, probably through the activation of the Nrf2 signaling pathway." [Li, Shiyue; Zhou, Jinxin; Xu, Shangfu; et al, 2019]

(biomarkers altered: oxidative stress, Nrf2, alanine aminotransferase, aspartate aminotransferase, malondialdehyde)

2. CPUY192018

"CPUY192018 exhibited cytoprotective effects by enhancing the Nrf2-ARE regulated antioxidant system and ***diminished the LPS-induced inflammatory response*** by hindering the ROS-mediated activation of the NF-kappaB pathway..... by activating Nrf2, CPUY192018 treatment balanced renal ***oxidative stress*** and suppressed inflammatory responses." [Lu, Meng-

Chen; Zhao, Jing; Liu, Yu-Ting; et al, 2019]

(biomarkers: inflammation, oxidative stress, Nrf2, ROS, NF-kappaB)

3. Swertiamarin OR *Gentiana macrophylla* Pall

"Collectively, Swe [Swertiamarin] could be considered as a ***promising protective agent against cerebral I/R injury through suppressing oxidative stress by activation of the Nrf2 protective pathway.***" [Wang, H. et al, 2019]

(biomarkers: apoptosis, oxidative stress, ROS, Nrf2, NQO1, HO-1)

4. *Malva sylvestris*

"***MS [Malva sylvestris] extract can protect the kidney against toxic effects of gentamicin, and thus, the degree of harmful effects of nephrotoxicity on remote organs including the liver will be decreased.***" [Mohamadi Yarijani, Z. et al, 2019]

(biomarkers: oxidative stress, creatinine, urea-nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, malondialdehyde, inflammation, TNF-alpha, ICAM-1)

5. Avenathramide C

"***Avn C [Avenathramide C] protects normal human skin fibroblasts against oxidative stress and inflammatory response through NF-kappaB inhibition and Nrf2/HO-1 activation***"

[Wang, C. and Eski, C.H, 2019]

(biomarkers: oxidative stress, free radical levels, inflammation, tumor necrosis factor-alpha, NF-kappaB, HO-1, Nrf2)

6. SK-119 OR (E)-5-oxo-1-(4-((2,4,6-trihydroxybenzylidene)amino)phenyl)pyrrolidine-3-carboxylic acid

"***Nrf2 Activation by SK-119 [(E)-5-oxo-1-(4-((2,4,6-trihydroxybenzylidene)amino)phenyl)pyrrolidine-3-carboxylic acid] Attenuates Oxidative Stress, UVB, and LPS-Induced Damage***" [Kahremany, S. et al, 2019]

(biomarkers: oxidative stress, Nrf2, inflammation, apoptosis)

7. pristimerin

"***Pris [pristimerin] exerted protective activity against LPS-induced ALI [acute lung injury] via anti-oxidant, anti-inflammatory and anti-apoptotic pathways***" [Shaaban, A.A. et al, 2018]

(biomarkers: inflammation, myeloperoxidase, lesions, oxidative stress, tumor necrosis factor-alpha, interleukin-6, apoptosis, Bax, caspase-3, Bcl2)

8. Astilbin

"***Astilbin ameliorates cisplatin-induced nephrotoxicity through reducing oxidative stress and inflammation.***" [Wang, S.-W. et al, 2018]

(biomarkers: oxidative stress, inflammation, apoptosis, ROS, NRF2, TNF-alpha, NF-kappaB, iNOS, COX-2)

9. Ac-YVAD-cmk

"***Pharmacological [Ac-YVAD-cmk] Inhibition of Caspase-1 Ameliorates Cisplatin-Induced Nephrotoxicity through Suppression of Apoptosis, Oxidative Stress, and Inflammation in Mice.***" [Kim, J.-Y. et al, 2018]

(biomarkers: caspase-1, blood urea nitrogen, creatinine, caspase-3, apoptosis, oxidative stress, inflammation)

10. Pterostilbene

"***Protective Effects of Pterostilbene Against Myocardial Ischemia/Reperfusion Injury in Rats.***" [Wu, M. et al, 2017]

(biomarkers: lactate dehydrogenase, creatine kinase-MB, oxidative stress, inflammation, Gas6, Axl, Bcl-2, Bax, apoptosis)

2D. PN/PAD Characteristics

## 2D1. List of Existing PN/PAD Characteristics

Table [7A-9a](#) contains a list of the 757 existing biomarkers identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these biomarkers are shown in Table 2D-1a. Because these are the highest frequency biomarkers, many will be very general.

**Table 2D-1a - Top Fifty PN/PAD Biomarkers**

<b>#RECORDS</b>	<b>BIOMARKER</b>
2638	lesions
2536	inflammation
2320	toxicity
2277	nerve conduction velocity
2038	ankle brachial index
1549	blood pressure
1402	stenosis
1156	body mass index
1142	neurotoxic
1139	total cholesterol
1138	blood glucose levels
1091	degeneration
1061	hemoglobin A1c
932	blood flow
856	marker
841	proteins
748	atrophy
747	dorsal root ganglia
704	creatinine
700	oxygen
693	lipoprotein
671	growth factor
640	Schwann cell
616	demyelination
610	pain-free walking distance
549	C reactive protein
538	calcium
516	cytokine
499	triglycerides
495	low-density lipoprotein cholesterol
489	angiogenesis
455	axonal degeneration
435	Systolic blood pressure
426	circulation

425	high-density lipoprotein cholesterol
419	oxidative stress
413	plaque
412	occlusions
402	albumin level
399	glomerular filtration rate
391	ventricular ejection fraction
382	calcification
365	nerve damage
354	neurodegeneration
349	IgM
345	tumour necrosis factor-alpha
344	sodium
329	lipids

Areas emphasized include neurotoxicity, neurodegeneration, inflammation, oxidative stress, demyelination, angiogenesis, circulation, calcification.

[Table 7A-9b](#) contains a list of the existing symptoms/diseases identified in this study, and the numbers of records in which they appear, highest first. The top fifty of these symptoms/diseases are shown in Table 2D-1b. Because these are the highest frequency contributing factors, many will be very general.

**Table 2D-1b - Top Fifty Existing PN/PAD Symptoms/Diseases**

#RECORDS	SYMPTOM/DISEASE
17050	neuropathy
13577	peripheral neuropathy
9627	diabetes mellitus
9078	artery disease
8114	peripheral artery disease
6967	peripheral vascular disease
5942	pain
5016	ischemia
3095	hypertension
3014	cancer
2969	atherosclerosis
2861	neuropathic pain
2612	stroke
2152	diabetic peripheral neuropathy
2071	infection
2056	myocardial infarction
2051	cardiovascular disease
1983	intermittent claudication

1913	polyneuropathy
1796	coronary artery disease
1585	heart disease
1571	type 2 diabetes mellitus
1547	critical limb ischemia
1533	diabetic foot ulcer
1519	Disorder
1440	heart failure
1135	weakness
879	neutropenia
878	cerebrovascular disease
833	sensory neuropathy
832	retinopathy
799	coronary heart disease
779	allodynia
769	disability
769	obesity
747	renal failure
731	thrombosis
705	ataxia
675	abdominal aortic aneurysm
660	nephropathy
645	angina
645	renal disease
625	Congestive heart failure
623	multiple myeloma
621	peripheral artery occlusive disease
618	bleeding
618	hyperalgesia
613	chronic kidney disease
612	vasculitis
607	ischemic heart disease

Diabetes, hypertension, infection, and obesity are of particular note.

## 2D2. Factor Matrix of Characteristics

Figure 2D-1a in the Excel workbook contains a factor matrix of the existing PN/PAD biomarkers. The 28 factor headings are shown below in Table 2D-2a. This listing provides a convenient taxonomy for categorizing the myriad biomarkers identified. Figure 2D-1a lists the specific biomarkers that had the strongest influence in determining the theme of each of the 28 factors.

**Table 2D-2a - Factor Matrix-based Categories for PN/PAD Biomarkers**

<b>FACTOR HEADING</b>
<b>FACTOR 1 - PLASMA LIPIDS</b>
<b>FACTOR 2 - PROINFLAMMATORY CYTOKINES</b>
<b>FACTOR 3 - miRNA</b>
<b>FACTOR 4 - HEME BIOSYNTHESIS DEFICIENCY</b>
<b>FACTOR 5 - OXIDATIVE STRESS</b>
<b>FACTOR 6 - FIBRIN DEPOSITION</b>
<b>FACTOR 7A - GROWTH FACTORS</b>
<b>FACTOR 7B - ADVANCED GLYCATION END PRODUCTS</b>
<b>FACTOR 8 - KALLIKREIN-KININ SYSTEM</b>
<b>FACTOR 9 - APOLIPOPROTEINS</b>
<b>FACTOR 10 - FATTY ACIDS</b>
<b>FACTOR 11 - KIDNEY FILTERING</b>
<b>FACTOR 12 - PLATELET AGGREGATION</b>
<b>FACTOR 13 - PROINFLAMMATORY MONOCYTES</b>
<b>FACTOR 14 - AXONAL DEGENERATION</b>
<b>FACTOR 15 - MATRIX METALLOPROTEINASES</b>
<b>FACTOR 16 - ANTIBODIES</b>
<b>FACTOR 17 - VASCULAR CALCIFICATION</b>
<b>FACTOR 18 - B12/FOLATE DEFICIENCIES</b>
<b>FACTOR 19 - ENDOTHELIAL DYSFUNCTION</b>
<b>FACTOR 20 - ARTERIAL STIFFNESS</b>
<b>FACTOR 21 - RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS AND LIGANDS</b>
<b>FACTOR 22 - INSULIN DEFICIENCY</b>
<b>FACTOR 23A - CELL ADHESION MOLECULES</b>
<b>FACTOR 23B - ANTI-INFLAMMATORY CYTOKINES</b>
<b>FACTOR 24 - OXIDATIVE STRESS</b>
<b>FACTOR 25 - CARDIOVASCULAR DISEASE BIOMARKERS</b>
<b>FACTOR 26 - VIRAL DAMAGE MARKERS</b>

About 64% of the total biomarkers were not included under the factors in Figure 2D-1a, because of the factor loading values used to determine the cutoffs. Many had factor loadings too small to influence the themes of the factors, and the remainder were unit frequency. However, even though a biomarker had little influence in determining the theme of a factor, it could be very important in its impact on PN/PAD.

Figure 2D-1b contains a factor matrix of the existing PN/PAD symptoms/diseases. The 15 factor headings are shown below in in Table 2D-2b. This listing provides a convenient taxonomy for categorizing the myriad symptoms/diseases identified. Figure 2D-1b lists the specific symptoms/diseases that had the strongest influence in determining the theme of each of the 15 factors.

**Table 2D-2b - Factor Matrix-based Categories for PN/PAD Symptoms/Diseases**

<b>FACTOR HEADINGS</b>
<b>FACTOR 1 - REDUCED NEUROMUSCULAR CONTROL</b>
<b>FACTOR 2 - NON-PAIN DIABETES-RELATED SYMPTOMS/DISEASES</b>
<b>FACTOR 3 - MOTOR NEURON DISEASES</b>
<b>FACTOR 4 - NEUROPATHIC PAIN</b>
<b>FACTOR 5 - CANCER TREATMENT SIDE EFFECTS</b>
<b>FACTOR 6 - EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS</b>
<b>FACTOR 7 - POEMS SYNDROME</b>
<b>FACTOR 8 - ASSOCIATED MAJOR ORGAN DISEASES</b>
<b>FACTOR 9 - POLYNEUROPATHY</b>
<b>FACTOR 10 - ISCHEMIA</b>
<b>FACTOR 11 - DIABETIC NEUROPATHY</b>
<b>FACTOR 12 - INFECTION-RELATED AUTOIMMUNE DISEASES</b>
<b>FACTOR 13 - CARDIOVASCULAR DISEASES</b>
<b>FACTOR 14 - MYOCARDIAL INFARCTION SYMPTOMS</b>
<b>FACTOR 15 - ARTERY DISEASE</b>

### 2D3. Biomarker-Biomarker Matrix

To display the inter-relationships among the PN/PAD biomarkers, all the biomarkers identified are matrixed together in Figure 2D-2 (Excel Workbook). The cell numbers reflect the co-occurrences of the two biomarkers defining the cell.

As an example of all biomarkers that co-occur with a selected biomarker, [Tables 7A-10](#) and [7A-11](#) show all that co-occur with the phrases 'angiogenesis' and 'oxidative stress', respectively. The top fifty biomarkers from Tables 7A-10 and 7A-11 are shown in Tables 2D-3 and 2D-4, respectively. The first column represents the total number of records for the specific biomarker, the second column is the biomarker name, and the third column is the number of records in which the biomarker co-occurs with 'angiogenesis' or 'oxidative stress'.

**Table 2D-3 - Top Fifty Biomarkers Co-occurring with Angiogenesis**

<b>#RECORDS</b>	<b>BIOMARKER</b>	<b>#CO-OCCURRENCES</b>
489	angiogenesis	489
671	growth factor	190
278	vascular endothelial growth factor	131
932	blood flow	121
2536	inflammation	64
700	oxygen	43
841	proteins	42
516	cytokine	39
52	Angiogenic growth factors	39



80	fibroblast growth factor	39
81	Endothelial progenitor cells	36
318	nitric oxide	32
2038	ankle brachial index	29
610	pain-free walking distance	28
309	apoptosis	28
52	hepatocyte growth factor	25
856	marker	21
2320	toxicity	17
1138	blood glucose levels	16
426	circulation	16
284	endothelial dysfunction	14
115	nitric oxide synthase	14
419	oxidative stress	13
74	matrix metalloproteinase	13
29	fibroblast growth factor 2	12
2638	lesions	12
1549	blood pressure	11
318	edema	10
28	CD31	10
345	tumour necrosis factor-alpha	10
1402	stenosis	9
41	CD34	8
152	Reactive oxygen species	8
1091	degeneration	7
413	plaque	7
52	l-arginine	6
18	HIF-1alpha	6
42	thromboangiitis	6
51	epidermal growth factor	5
41	transforming growth factor beta	5
17	CXCR4	5
748	atrophy	5
412	occlusions	5
16	neoangiogenesis	5
26	miRNA	5
25	platelet-derived growth factor	5
2277	nerve conduction velocity	4
126	vitamin E deficiency	4
23	integrin	4
78	transcutaneous oxygen pressure	4

In Table 2D-3, the most closely related biomarkers are the myriad growth factors. When these growth factors appear in the PN/PAD database, they will co-occur with angiogenesis a significant fraction of the time.

**Table 2D-4 - Top Fifty Biomarkers Co-occurring with Oxidative Stress**

<b>#RECORDS</b>	<b>BIOMARKER</b>	<b>#CO-OCCURRENCES</b>
419	oxidative stress	419
2536	inflammation	117
700	oxygen	72
1138	blood glucose levels	60
152	Reactive oxygen species	53
119	glutathione	52
841	proteins	47
99	antioxidants	46
309	apoptosis	44
318	nitric oxide	44
69	superoxide dismutase	41
84	malondialdehyde	39
2277	nerve conduction velocity	37
69	lipid peroxidation	36
284	endothelial dysfunction	30
932	blood flow	30
693	lipoprotein	30
747	dorsal root ganglia	27
856	marker	27
640	Schwann cell	27
115	Mitochondrial dysfunction	26
2320	toxicity	25
1139	total cholesterol	23
1091	degeneration	23
1142	neurotoxic	22
495	low-density lipoprotein cholesterol	21
1061	hemoglobin A1c	20
671	growth factor	20
549	C reactive protein	20
65	advanced glycation end product	19
1549	blood pressure	18
329	lipids	18
354	neurodegeneration	18
538	calcium	17
345	tumour necrosis factor-alpha	17
516	cytokine	17
34	catalase	16
126	vitamin E deficiency	16
266	IL-6	16
185	insulin resistance	15
26	glutathione peroxidase	14
115	nitric oxide synthase	14

2038	ankle brachial index	14
33	oxidative damage	14
1156	body mass index	13
489	angiogenesis	13
261	high homocysteine	13
413	plaque	13
2638	lesions	12
616	demyelination	12

In Table 2D-4, the most closely related biomarkers are measures of oxidation and oxidants. Advanced glycation end products and catalase are closely related as well. To understand the associations in more detail, the specific records enumerated in each cell of interest must be evaluated. The reader can manipulate the matrix in Figure 2D-2 to evaluate terms and relationships of personal interest.

#### 2D4. Biomarkers related to PN and to PAD

While many of the biomarkers applied relatively equally to PN and PAD, some were focused more strongly on PN and others on PAD. To identify the relative contributions, the biomarkers related to PN and to PAD were aggregated separately. [Table 7A-12](#) shows the numbers of records in which the biomarkers co-occur with PN and with PAD. The top fifty are shown in Table 2D-5.

**Table 2D-5 - Top Fifty Biomarkers Relevant to PN and to PAD**

#RECORDS	TREATMENT	#PN RECORDS	#PAD RECORDS
2638	lesions	985	1503
2536	inflammation	1445	1143
2320	toxicity	2077	186
2277	nerve conduction velocity	2003	183
2038	ankle brachial index	93	1984
1549	blood pressure	334	1362
1402	stenosis	72	1274
1156	body mass index	378	868
1142	neurotoxic	980	37
1139	total cholesterol	261	1003
1138	blood glucose levels	685	625
1091	degeneration	874	167
1061	hemoglobin A1c	663	646
932	blood flow	167	802
856	marker	321	558
841	proteins	568	245
748	atrophy	633	93
747	dorsal root ganglia	631	28

704	creatinine	230	550
700	oxygen	184	536
693	lipoprotein	117	625
671	growth factor	318	344
640	Schwann cell	506	25
616	demyelination	536	56
610	pain-free walking distance	17	598
549	C reactive protein	68	507
538	calcium	249	274
516	cytokine	289	211
499	triglycerides	158	410
495	low-density lipoprotein cholesterol	70	461
489	angiogenesis	56	439
455	axonal degeneration	402	73
435	Systolic blood pressure	88	392
426	circulation	86	362
425	high-density lipoprotein cholesterol	105	386
419	oxidative stress	223	212
413	plaque	22	382
412	occlusions	3	358
402	albumin level	162	304
399	glomerular filtration rate	95	338
391	ventricular ejection fraction	33	366
382	calcification	45	346
365	nerve damage	238	32
354	neurodegeneration	305	42
349	IgM	325	46
345	tumour necrosis factor-alpha	225	126
344	sodium	229	114
329	lipids	92	255
322	heart rate	133	204
318	edema	205	120

Biomarkers shared more or less equally between PN and PAD include inflammation, blood glucose levels, hemoglobin A1c, growth factor, calcium, oxidative stress, nitric oxide, IL-6, reactive oxygen species, acetylcholine, lactate, urea, antioxidants, lipid peroxidation, advanced glycation end products, etc. Biomarkers weighted toward PN include nerve conduction velocity, neurotoxicity, atrophy, Schwann cell, demyelination, axonal degeneration, CD4, nerve fiber density, etc. Biomarkers weighted toward PAD include ankle brachial index, blood flow, pain-free walking distance, low density lipoprotein cholesterol, occlusions, ventricular ejection fraction, calcification, fibrinogen, carotid artery intima-media thickness, platelet aggregation, pulse pressure, etc.

## 2D5. Biomarkers Selected for Protocol

The final number of biomarkers identified in the present study was 757 (Table 7A-9a). To reduce this number of biomarkers to a manageable amount for the treatment protocol, a number of thematic categories were generated based on the results of the biomarker factor matrix (Figure 2D-1a) and other inputs. Then, phrases were selected to populate these categories based in part on 1) their rankings in the biomarker factor matrix, and on 2) their applicability to PN/PAD or PN or PAD (Table 7A-12), as discussed at the end of section 2D4.

Table 2D-6 contains the final list of biomarkers selected for the protocol. While each biomarker is listed for one category, many of the biomarkers will be applicable to multiple categories. The biomarkers highlighted in red are the highest priority for each category, based on the criteria described above.

**Table 2D-6 - Final List of Biomarkers for Treatment Protocol**

(Note: biomarkers highlighted in red are highest priority for category)

CATEGORY	BIOMARKER
ANTIBODIES	IgM
ANTIBODIES	IgA
ANTIBODIES	immunoglobulin
ANTIBODIES	IgG antibodies
ANTIBODIES	autoantibodies
ANTIBODIES	anti-ganglioside antibodies
ANTIBODIES	demyelination
ANTIBODIES	monoclonal antibodies
ANTIBODIES	glucuronic acid
ANTIBODIES	Chlamydia pneumoniae
ANTIBODIES	antinuclear antibodies
ART STIFFNESS	arterial stiffness
ART STIFFNESS	pulse wave velocity
ART STIFFNESS	pulse pressure
ART STIFFNESS	vascular stiffness
ART STIFFNESS	blood pressure
CALCIFICATION	calcium
CALCIFICATION	magnesium
CALCIFICATION	Zinc
CALCIFICATION	glutamine
CALCIFICATION	selenium
CALCIFICATION	glutamate
CALCIFICATION	calcification
CALCIFICATION	cadmium
CALCIFICATION	alkaline phosphatase
ENDOTHELIAL DYSFUNCTION	nitric oxide

ENDOTHELIAL DYSFUNCTION	l-arginine
ENDOTHELIAL DYSFUNCTION	nitric oxide synthase
ENDOTHELIAL DYSFUNCTION	arginine
ENDOTHELIAL DYSFUNCTION	endothelin-1
FOLATE DEFICIENCY	folic acid
FOLATE DEFICIENCY	folate deficiency
FOLATE DEFICIENCY	methionine
FOLATE DEFICIENCY	S-adenosylmethionine
FOLATE DEFICIENCY	Hcy
FOLATE DEFICIENCY	cysteine
FOLATE DEFICIENCY	methylmalonic acid
FOLATE DEFICIENCY	asymmetric dimethylarginine
GROWTH FACTORS	growth factor
GROWTH FACTORS	vascular endothelial growth factor
GROWTH FACTORS	fibroblast growth factor
GROWTH FACTORS	hepatocyte growth factor
GROWTH FACTORS	nerve growth factor
GROWTH FACTORS	fibroblast growth factor 23
GROWTH FACTORS	blood flow
GROWTH FACTORS	transforming growth factor beta
INFLAMMATION	C reactive protein
INFLAMMATION	IL-6
INFLAMMATION	Tumour necrosis factor-alpha
INFLAMMATION	IL1-beta
INFLAMMATION	intercellular adhesion molecule-1
INFLAMMATION	IL-10
INFLAMMATION	neutrophils
INFLAMMATION	IL-8
INFLAMMATION	myeloperoxidase
INFLAMMATION	D-dimer
INFLAMMATION	IL-12
INFLAMMATION	Monocyte chemoattractant protein-1
INFLAMMATION	Interferon gamma
INFLAMMATION	TGFbeta
INFLAMMATION	IL-2
INFLAMMATION	matrix metalloproteinase 2
INFLAMMATION	matrix metalloproteinase 9
INFLAMMATION	COX-2
INFLAMMATION	IL-4
INFLAMMATION	IL-18
INFLAMMATION	IL-13
KIDNEY FUNCTION	urea
KIDNEY FUNCTION	blood urea nitrogen
KIDNEY FUNCTION	creatinine
KIDNEY FUNCTION	white blood cell

KIDNEY FUNCTION	uric acid
KIDNEY FUNCTION	bilirubin
KIDNEY FUNCTION	glomerular filtration rate
LIPIDS	high-density lipoprotein cholesterol
LIPIDS	total cholesterol
LIPIDS	triglycerides
LIPIDS	low-density lipoprotein cholesterol
LIPIDS	fibrinogen
LIPIDS	Lipoprotein(a)
LIPIDS	hemoglobin A1c
NEURODEGENERATION	myelinated fibers
NEURODEGENERATION	dorsal root ganglia
NEURODEGENERATION	nerve conduction velocity
NEURODEGENERATION	Schwann cell
NEURODEGENERATION	fiber loss
NEURODEGENERATION	atrophy
NEURODEGENERATION	nerve fiber density
OXIDATIVE STRESS	Reactive oxygen species
OXIDATIVE STRESS	glutathione
OXIDATIVE STRESS	superoxide dismutase
OXIDATIVE STRESS	malondialdehyde
OXIDATIVE STRESS	advanced glycation end products
OXIDATIVE STRESS	catalase
OXIDATIVE STRESS	glutathione peroxidase
OXIDATIVE STRESS	iNOS
OXIDATIVE STRESS	Hydrogen peroxide
OXIDATIVE STRESS	peroxynitrite
OXIDATIVE STRESS	NADPH oxidases
OXIDATIVE STRESS	TBARS
OXIDATIVE STRESS	4-hydroxy-2-nonenal
OXIDATIVE STRESS	Nrf2
OXIDATIVE STRESS	isoprostane
OXIDATIVE STRESS	NOx
OXIDATIVE STRESS	heme oxygenase 1
OXIDATIVE STRESS	oxidized low-density lipoprotein
OXIDATIVE STRESS	lipid hydroperoxides
OXIDATIVE STRESS	PON-1
OXIDATIVE STRESS	3-nitrotyrosine
OXIDATIVE STRESS	adenosine triphosphate
OXIDATIVE STRESS	creatine kinase
PLATELET ACTIVATION	arachidonic acid
PLATELET ACTIVATION	adenosine diphosphate
PLATELET ACTIVATION	P-selectin
PLATELET ACTIVATION	prothrombin
PLATELET ACTIVATION	thrombin
PLATELET ACTIVATION	L-selectin

PLATELET ACTIVATION	elastase
RAGE	RAGE
RAGE	carboxymethyl-lysine
RAGE	S100A12
RAGE	thromboxane
RAGE	NF-kappaB
RAGE	thromboxane A2
RAGE	phosphatidylinositol 3-kinase
RAGE	adenosine monophosphate
RAGE	caspase 3

## 2E. Matrix of PN/PAD Causes vs Biomarkers

Figure 2E-1 (Excel Workbook) displays the co-occurrences between the existing PN/PAD contributing factors and biomarkers. The cell numbers reflect the co-occurrences of the contributing factor and biomarker defining the cell.

The matrix is relatively dense starting at the upper left, and becomes increasingly sparse going to the lower right. There are approximately 630,000 cells in the matrix, of which about 16,000 have entries. That's an occupancy rate of slightly more than two percent. Why is this important? The cell numbers reflect, in part, the amount of research effort devoted (reported) to examining the relationship between the cause and the biomarker defining the cell. Cells that are blank may reflect that research has not been done on the cause and biomarker combination, and therefore could be excluding another potential cause. The message to be taken from this observation is far more research could be conducted on identifying potential causes if more biomarkers were included in the investigations.

As an example of all contributing factors that co-occur with a biomarker, [Tables 7A-13](#) and [7A-14](#) show all the causes that co-occur with the phrases 'oxidative stress' and 'blood pressure', respectively. The top fifty contributing factors from Tables 7A-13 and 7A-14 are shown in Tables 2E-1 and 2E-2, respectively. The first column represents the total number of records for the specific contributing factor, the second column is the contributing factor name, and the third column is the number of records in which the contributing factor co-occurs with 'oxidative stress' or 'blood pressure'.

**Table 2E-1 - Top Fifty Causes that Co-occur with Oxidative Stress**

#RECORDS	CAUSE	#CO-OCCURRENCES
2507	chemotherapy	37
125	advanced glycosylation end products	32
296	Streptozotocin	31
2265	smoking	24
1140	High cholesterol diet	23



524	oxaliplatin	16
985	paclitaxel	11
149	Arsenic	10
745	dialysis	9
503	Bortezomib	9
347	vincristine	7
340	peripheral nerve injury	6
442	alcohol	6
508	hemodialysis	6
217	platinum	6
19	high glucose	6
66	high fat diet	6
14	Hydrogen peroxide	6
570	cisplatin	5
29	Ischemia-reperfusion	5
393	alcohol consumption	5
324	taxanes	5
201	chronic constriction injury	5
49	acetone	5
12	iron overload	4
18	streptozocin	3
570	trauma	3
26	metals	3
351	thalidomide	3
196	docetaxel	3
93	spinal cord injury	3
86	alkaloids	3
34	dichloroacetate	3
9	manganese	3
9	HFD	2
9	dithiocarbamates	2
9	allopurinol	2
140	5-fluorouracil	2
29	phenytoin	2
131	sedentary	2
83	axotomy	2
76	Vinca alkaloids	2
337	lifestyle	2
73	coronary angioplasty	2
821	HIV-1	2
65	Zinc	2
708	infections	2
545	depression	2

**Table 2E-2 - Top Fifty Causes that Co-occur with Blood Pressure**

#RECORDS	CAUSES	#CO-OCCURRENCES
2265	smoking	411
1140	High cholesterol diet	321
442	alcohol	55
337	lifestyle	53
745	dialysis	52
508	hemodialysis	44
393	alcohol consumption	38
545	depression	27
131	sedentary	20
22	atenolol	10
2507	chemotherapy	9
357	anesthesia	9
59	inactivity	9
15	lisinopril	7
96	malnutrition	7
821	HIV-1	6
14	enalapril	6
24	cadmium	5
85	renal transplantation	5
66	high fat diet	5
5	salt intake	5
44	Mercury	5
985	paclitaxel	4
683	viruses	4
39	lead exposure	4
323	cyclophosphamide	4
125	advanced glycosylation end products	4
42	hand-arm vibration	3
96	drug-induced	3
570	trauma	3
708	infections	3
73	coronary angioplasty	3
378	highly active antiretroviral therapy	3
361	radiation	3
43	bariatric surgery	3
3	felodipine	3
324	taxanes	2
24	immunization	2
201	chronic constriction injury	2
196	docetaxel	2
23	5-hydroxytryptamine	2

28	vitamin D deficient	2
21	vibration-induced	2
149	Arsenic	2
63	bevacizumab	2

As an example of all biomarkers that co-occur with a contributing factor, [Tables 7A-15](#) and [7A-16](#) show all biomarkers impacted by 'high cholesterol diet' and 'sedentary', respectively. The top fifty contributing factors from Tables 7A-15 and 7A-16 are shown in Tables 2E-3 and 2E-4, respectively.

**Table 2E-3 - Top Fifty Biomarkers Co-occurring with High Cholesterol Diet**

#RECORDS	BIOMARKER	#CO-OCCURRENCES
1139	total cholesterol	1139
693	lipoprotein	472
495	low-density lipoprotein cholesterol	386
499	triglycerides	340
425	high-density lipoprotein cholesterol	323
1549	blood pressure	321
1156	body mass index	209
1138	blood glucose levels	191
1061	hemoglobin A1c	169
2038	ankle brachial index	164
435	Systolic blood pressure	133
329	lipids	116
549	C reactive protein	96
2536	inflammation	93
704	creatinine	90
308	fibrinogen	72
402	albumin level	63
856	marker	60
125	apolipoprotein	59
147	lipid profile	57
175	diastolic blood pressure	51
1402	stenosis	50
399	glomerular filtration rate	48
413	plaque	41
2638	lesions	39
261	high homocysteine	39
185	insulin resistance	39
96	uric acid	36
162	glycated haemoglobin	34
110	waist circumference	33
94	Lipoprotein(a)	31

208	carotid artery intima-media thickness	30
2277	nerve conduction velocity	28
27	high total cholesterol	27
538	calcium	27
610	pain-free walking distance	27
92	albumin excretion rate	26
41	apolipoprotein B	26
210	fatty acid	23
419	oxidative stress	23
104	pulse pressure	22
841	proteins	22
266	IL-6	22
932	blood flow	21
382	calcification	21
284	endothelial dysfunction	20
39	apolipoprotein A-I	20
251	angiotensin converting enzyme	19
345	tumour necrosis factor-alpha	18
36	niacin	17

**Table 2E-4 - Top Fifty Biomarkers Co-occurring with Sedentary**

#RECORDS	BIOMARKER	#CO-OCCURRENCES
2038	ankle brachial index	31
1549	blood pressure	20
1156	body mass index	19
1139	total cholesterol	10
1138	blood glucose levels	10
2536	inflammation	9
30	body fat	9
549	C reactive protein	7
185	insulin resistance	7
1402	stenosis	6
1061	hemoglobin A1c	6
610	pain-free walking distance	6
425	high-density lipoprotein cholesterol	5
322	heart rate	5
932	blood flow	5
538	calcium	5
693	lipoprotein	5
495	low-density lipoprotein cholesterol	5
208	carotid artery intima-media thickness	5
110	waist circumference	4
856	marker	4
748	atrophy	4

700	oxygen	4
435	Systolic blood pressure	4
284	endothelial dysfunction	4
151	arterial stiffness	4
841	proteins	3
413	plaque	3
499	triglycerides	3
94	Lipoprotein(a)	3
318	nitric oxide	2
455	axonal degeneration	2
329	lipids	2
20	adenosine triphosphate	2
308	fibrinogen	2
2277	nerve conduction velocity	2
105	plasminogen activator inhibitor-1	2
222	weight loss	2
2638	lesions	2
38	vitamin K	2
516	cytokine	2
183	pulse wave velocity	2
419	oxidative stress	2
1091	degeneration	2
147	lipid profile	2
27	high total cholesterol	2
125	Vitamin D deficiency	2
10	low birth weight	2
32	insulin levels	1
107	lactate	1

## 2F. Matrix of PN/PAD Treatments vs Biomarkers

Figure 2F-1 (Excel Workbook) displays the co-occurrences between the existing PN/PAD treatments and biomarkers. The cell numbers reflect the co-occurrences of the treatment and biomarker defining the cell.

As an example of all treatments that affect a biomarker, Tables [7A-17](#) and [7A-18](#) show all the treatments that co-occur with with the phrases 'oxidative stress' and 'blood pressure', respectively. The top fifty treatments from Tables 7A-17 and 7A-18 are shown in Tables 2F-1 and 2F-2, respectively. The first column represents the total number of records for the specific treatment, the second column is the treatment name, and the third column is the number of records in which the treatment co-occurs with 'oxidative stress' or 'blood pressure', respectively.

**Table 2F-1 - Top Fifty Treatments that Co-occur with Oxidative Stress**

<b>#RECORDS</b>	<b>TREATMENT</b>	<b>#CO-OCCURRENCES</b>
3638	drug	49
99	antioxidants	46
1766	inhibitor	42
62	superoxide dismutase	38
754	insulin	30
812	growth factor	24
288	supplementation	21
1328	exercise	20
1358	walking	18
2402	amputation	17
126	vitamin E	16
449	diet	16
25	GSH	15
349	vascular endothelial growth factor	13
489	angiogenesis	13
34	vitamin C	12
5105	surgery	11
86	Alpha lipoic acid	11
745	dialysis	9
172	IL-6	9
447	glycemic control	9
14	antioxidant therapy	9
150	hypoxia	8
47	aldose reductase inhibitor	7
567	analgesic	6
189	Spinal Cord Stimulation	6
632	medications	6
252	antihypertensive agents	6
206	nerve growth factor	6
233	pregabalin	5
80	folic acid	5
1920	revascularization	5
28	N-acetylcysteine	5
190	smoking cessation	5
67	erythropoietin	5
25	nicotinamide	5
541	endovascular treatment	4
100	haemodialysis	4
370	statin	4
12	tempol	4
1228	angioplasty	4
266	coronary intervention	4
242	Gabapentin	4

25	curcumin	4
337	antiplatelet therapy	4
111	duloxetine	4
117	Vitamin D	3
207	vitamin B12	3
17	interleukin-10	3

**Table 2F-2 - Top Fifty Treatments Co-occurring with Blood Pressure**

#RECORDS	TREATMENT	#CO-OCCURRENCES
3638	drug	178
1328	exercise	149
252	antihypertensive agents	137
1766	inhibitor	122
5105	surgery	112
754	insulin	106
1358	walking	81
2402	amputation	74
447	glycemic control	71
1920	revascularization	67
632	medications	58
745	dialysis	52
576	aspirin	48
449	diet	47
190	smoking cessation	40
370	statin	36
1228	angioplasty	30
337	antiplatelet therapy	29
110	enzyme inhibitors	29
353	Clopidogrel	26
507	vascular surgery	22
58	angiotensin converting enzyme inhibitor	22
1308	artery bypass grafting	20
221	anticoagulant	19
812	growth factor	18
459	rehabilitation	16
33	ramipril	15
588	operation	12
233	endarterectomy	12
22	calcium antagonists	12
450	bypass surgery	11
489	angiogenesis	11
288	supplementation	11
215	Cilostazol	11

59	Testosterone	10
349	vascular endothelial growth factor	10
50	C-peptide	10
27	verapamil	10
17	amlodipine	10
117	Vitamin D	9
59	acetylsalicylic acid	9
172	Gene therapy	9
828	stents	9
50	Nicotine	9
12	hydrochlorothiazide	9
28	nifedipine	9
118	warfarin	8
16	losartan	8
21	calcium channel blocker	8

As an example of all biomarkers affected by a treatment, Tables [7A-19](#) and [7A-20](#) show all biomarkers impacted by 'exercise' and 'gabapentin', respectively. The top fifty biomarkers from Tables 7A-19 and 7A-20 are shown in Tables 2F-3 and 2F-4, respectively.

**Table 2F-3 - Top Fifty Biomarkers Co-occurring with Exercise**

#RECORDS	BIOMARKER	#CO-OCCURRENCES
610	pain-free walking distance	287
2038	ankle brachial index	210
700	oxygen	160
1549	blood pressure	149
932	blood flow	124
322	heart rate	84
2536	inflammation	67
1138	blood glucose levels	64
1402	stenosis	56
1156	body mass index	53
1139	total cholesterol	52
2638	lesions	49
1061	hemoglobin A1c	46
70	peak oxygen consumption	43
693	lipoprotein	40
495	low-density lipoprotein cholesterol	35
856	marker	35
435	Systolic blood pressure	34
426	circulation	33
251	angiotensin converting	29



	enzyme	
489	angiogenesis	28
329	lipids	28
549	C reactive protein	26
2277	nerve conduction velocity	23
499	triglycerides	23
78	transcutaneous oxygen pressure	23
61	oxygen saturation	23
308	fibrinogen	20
671	growth factor	20
284	endothelial dysfunction	20
419	oxidative stress	20
318	nitric oxide	20
185	insulin resistance	19
425	high-density lipoprotein cholesterol	19
107	lactate	19
28	phosphocreatine	19
748	atrophy	18
516	cytokine	16
538	calcium	15
266	IL-6	15
262	stenoses	15
151	arterial stiffness	14
841	proteins	14
413	plaque	14
278	vascular endothelial growth factor	14
222	weight loss	13
345	tumour necrosis factor-alpha	12
95	blood viscosity	12
168	platelet aggregation	12
147	lipid profile	11

**Table 2F-4 - Top Fifty Biomarkers Co-occurring with Gabapentin**

#RECORDS	BIOMARKER	#CO-OCCURRENCES
538	calcium	19
147	capsaicin	18
2536	inflammation	15
1142	neurotoxic	14
344	sodium	10
2320	toxicity	9
747	dorsal root ganglia	8

38	Noradrenaline	8
2277	nerve conduction velocity	6
318	edema	6
1138	blood glucose levels	5
671	growth factor	5
30	Gamma-aminobutyric acid	5
65	magnesium	5
122	mechanical hyperalgesia	5
119	glutathione	5
365	nerve damage	4
419	oxidative stress	4
195	thermal hyperalgesia	4
318	nitric oxide	3
704	creatinine	3
700	oxygen	3
263	vitamin B(12) deficiency	3
206	nerve growth factor	3
27	cholinesterase	3
152	Reactive oxygen species	3
126	glutamate	3
273	glycoprotein	2
1139	total cholesterol	2
222	weight loss	2
1549	blood pressure	2
1091	degeneration	2
54	glial fibrillary acidic protein	2
322	heart rate	2
349	IgM	2
40	myeloperoxidase	2
70	IL-10	2
27	cyclooxygenase 2	2
345	tumour necrosis factor-alpha	2
128	IL-1beta	2
25	Iron Deficiency	2
1156	body mass index	2
516	cytokine	2
12	anticardiolipin antibodies	2
20	folate deficiency	1
24	aspartate aminotransferase	1
99	antioxidants	1
18	caspase 3	1

## 2G. Under-representation of PN/PAD Causes, Treatments, and Characteristics

The previous sections of the present chapter have shown that, while the numbers of PN/PAD causes, treatments, and characteristics identified in the present monographs of the PN/PAD study are massive compared to any other study in the literature, these numbers are

1) a modest fraction of what could theoretically be extracted from the existing PN/PAD literature and

2) a very modest fraction of what could be extracted from both the existing PN/PAD literature and non-PN/PAD literature.

There are two main reasons for this. First, numbers of PN/PAD causes, treatments, and characteristics are under-reported in the biomedical literature (especially PN/PAD causes). Second, resource limitations restricted the numbers of PN/PAD causes, treatments, and characteristics that could be extracted from what is reported in the biomedical literature.

There are myriad reasons for under-reporting of PN/PAD causes, treatments, and characteristics. These include:

- lack of incentives for industry and government to sponsor research on PN/PAD causes from industrial products
- lack of incentives for some journals (especially those with sponsorship from industry or government) to publish research on PN/PAD causes from industrial products
- limited scope and variables measured in many research projects

There are also myriad reasons that extraction of PN/PAD causes, treatments, and characteristics from those reported in the biomedical literature was limited in the present study. Most reasons for limited extraction from the reported data are based on resource and time limitations for the study, but process, software, and data limitations played a role as well. These issues are discussed in the remainder of this chapter. For those readers who want to access the PN/PAD treatment protocols directly at this point, they can be found in [Chapter 3](#).

### 2G1. Under-reporting of PN/PAD Foundational Causes

#### 2G1a. Reduced incentives for sponsoring and reporting PN/PAD foundational causes

Chapter 9 of [Kostoff, 2015], and [Kostoff, 2016], contain many caveats showing why the numbers of PN/PAD (or any other chronic disease) [foundational causes](#) presented in [Table 7A-1](#) may be vast under-representations of the numbers of PN/PAD operational foundational causes. Summarily, many adverse events are not reported and published in the literature (e.g., see references 70-125 of [Kostoff, 2015]), or, if they are reported and published, many are not accessed due to inadequate search algorithms. The under-reporting occurs at the patient, doctor,

researcher, journal, corporate, and Federal agency levels, mainly because of myriad incentives (and few disincentives) for under-reporting. See Chapter 9 of [Kostoff, 2015], or [Kostoff, 2016], for further examples.

Under-reporting can be disguised through selective reporting of adverse events. For example, in a previous monograph focusing on AD causes [Kostoff, Zhang, Ma et al, 2017], we considered an endogenous substance to be a foundational cause if it was administered exogenously in lab tests for the purpose of better understanding its pathological mechanisms. There was a substantial amount of research reported on these intrinsically endogenous substances, and they were high-frequency in the literature (large numbers of records). These endogenous substances are typically not major industrial products, and therefore pose no threat to any industry if adverse effects are reported. As an example, in the AD causes monograph, there were many studies where Abeta was administered exogenously, in order to study its effects under more controlled conditions. Contrast this high level of effort on Abeta as an exogenous contributing factor to AD with the low level of research effort on the myriad harmful occupational and environmental substances and radiations.

In the same vein, for those foundational causes that are accepted as harmful (smoking, excess alcohol, etc), again, there is little reluctance for research funding into adverse effects. For potentially toxic substances that have not yet received public consensus as being harmful, industry and government research funds are sparse. This is reflected by the large number of very detailed foundational causes (typically specific chemicals, materials, or radiations) appearing in only one or two records in [Kostoff, 2015] and the present study.

So, while PN/PAD research on potential foundational causes may appear to be reasonable based on overall funding and levels of effort, the research effort/funding is highly skewed toward 'safe' research on already known harmful substances, and away from substances important to industry and government not yet proven to be toxic.

Apart from individual and organizational reluctance to identify adverse effects from products in which they are involved, a very important consideration limiting sponsor resources for identifying new contributing factors is the sheer number of experiments and epidemiological studies that would be required for comprehensive evaluation. This is especially true for the case of combinations of contributing factors, where adverse effects from each constituent may only show up as part of a combination, or may substantially worsen as part of a combination.

The reason few combinations are selected for study derives from combinatorics. Consider the number of possible combinations of two and three items in a list of  $n$  items. For  $n$  variables, and possible combinations of a subset of  $n$  consisting of  $r$  variables, the number of combinations is:  $C(n,r)=n!/(r!(n-r)!)$ , where  $!$  denotes the factorial function. For large  $n$ , and  $r$  small compared to  $n$ ,  $C(n,r)\sim n^r/r!$ . For large  $n$ ,  $C$  becomes a large number. How large? Consider the following.

It would be useful to identify those substances that, in isolation or in combination, could potentially impact PN/PAD or its surrogate endpoints, but have not been studied yet. There are many tens of thousands of items that could be potential candidates for study. Is there any way to narrow those down?

[Kostoff, 2015] examined contributing factors to ~4,000 diseases, and identified factors that contributed to 1) any of these diseases and 2) a threshold number of diseases. In [Kostoff, 2015], on the order of 800 substances that contributed to at least a threshold number of the ~4,000 diseases were identified. These 800 *pervasive* causes constituted about ten percent of the total number of causes (90% of which impacted less than the threshold number of diseases) identified for the ~4,000 diseases. The total number of causes identified for all diseases (~8,000) might be a good starting point for identifying additional potential PN/PAD causes. Why is this a reasonable assumption?

The various systems in the body are inter-related. The immune system, neural system, endocrine system, circulatory system, etc, are linked. There are research disciplines devoted to study of these linked systems (e.g., neuroimmunology, neuroimmunoendocrinology, etc). Most of the ~8,000 causes identified in [Kostoff, 2015] impacted one or more of these inter-related systems. Many of the studies focused on the impact of the test substance on (typically) one system only. It would be reasonable to expect that a substance impacting one of the systems above would have some level of impact on the other systems above, with some impacts being more significant than others.

Thus, the ~8,000 potential causes identified in [Kostoff, 2015], minus those that were identified in the present PN/PAD study, would be candidates for evaluation as potential AD causes. Subtracting the ~800 PN/PAD causes identified in the present study from the ~8,000 causes leaves on the order of ~7,200 items to be examined in isolation. Assume there were another 800 items evaluated for potential impacts on PN/PAD in other studies but were shown not to have an effect (in isolation, although we may want to examine them as part of a combination). We are then left with on the order of

- 1) ~7,200 substances to study in combination, and
- 2) ~6,400 of the initial ~7,200 substances to study in isolation.

This would include the case where the ~800 identified contributing factors in isolation could have a stronger effect in combination, for those cases where the combinations have not been studied.

The numbers of combinations of two and three for 7,200 test items,  $C(7200,2)$ ,  $C(7200,3)$ , are, according to the formula above for small  $r$ :

$$C(7200,2) \approx 26 \text{ million}$$

$$C(7200,3) \approx 62 \text{ billion}$$

These numbers are astronomical in any of the cases shown. Research on each of these combinations is a major resource and time effort, in the lab and/or in the field/clinic. There's no way all the combinations, or even the most relevant ones, can be run. Unfortunately, the myriad combinations of potentially toxic stimuli mirror the real world, not the potentially toxic stimuli acting in isolation. And, which combinations are important to a specific individual would be a function of that person's unique characteristics, such as genetic makeup.

## 2G1b. Resource limitations to identifying foundational causes

### 2G1b1. Existing foundational causes

Additionally, in the initial process of identifying the existing PN/PAD causes listed in [Table 7A-1](#), identification of the higher-frequency causes (including some relatively general causes) was quite comprehensive. There were many lower frequency causes identified through the linking terms, but the latter process was truncated because of time considerations. Unfortunately, as the record frequency of PN/PAD causes decreases, the number of discrete PN/PAD causes increases drastically. These lower frequency PN/PAD causes tended to be highly specific in chemical and radiation exposures from industrial practices, medical treatments, everyday personal exposures, etc. Thus, over and above the existing PN/PAD causes that have not entered the PN/PAD literature for the reasons described in the previous section, there are probably many hundreds of low-frequency PN/PAD causes in the literature that were not accessed due to our time/resource limitations.

### 2G1b2. Potential foundational causes

Another constraint imposed by this study's resource limitations was identification of potential PN/PAD foundational causes. The LRDI approach for identifying potential PN/PAD foundational causes (aka literature-related discovery) is analogous to that used for identifying potential PN/PAD treatments, shown in section 6B5 and [Appendix 6-1](#). Non-PN/PAD literatures are examined for causes that move the values of PN/PAD characteristics in some desired pre-determined direction, but these causes have not been identified in the PN/PAD literature. This LRDI-discovery approach was demonstrated in the chronic kidney disease (CKD) LRDI study [Kostoff and Patel, 2015]. It was clear from the voluminous retrievals in the CKD study that many hundreds of potential CKD contributing factors could be identified with the LRDI discovery process, and similar results for identifying PN/PAD causes would be expected from application of this LRDI discovery process to the non-PN/PAD biomedical literature.

### 2G1c. Limited research focus on identifying foundational causes

Further, in the epidemiological studies whose focus was on PN/PAD cause identification, only a finite number of PN/PAD causes to be identified were the objects of the research. PN/PAD causes that were operable, but not search targets, would not be identified.

### 2G1d. Research concentration on identifying foundational causes in isolation

Also, in both the epidemiology and laboratory studies, very few studies attempted to ascertain synergies resulting from combined potential contributing factors. These included factors that, when operating in isolation, produced no or miniscule harmful effects, but when operating in combination, produced very harmful effects. As a recent study shows, the potential impacts of contributing factor synergies could be substantial [Kostoff, Goumenou, Tsatsakis, 2018].

## 2G2. Under-reporting of PN/PAD Treatments

It was shown in section 2G1 that under-reporting of causes had two major components: technical and disincentives for reporting. Under-reporting of treatments is mainly due to technical reasons, since there are many incentives for sponsorship and publication of PN/PAD treatment research.

### 2G2a. Resource constraints

#### 2G2a1. Existing PN/PAD treatments limited

Existing PN/PAD treatments were identified in two ways primarily: visual examination of the high-frequency title and abstract phrases, and use of linking phrases (e.g., improve, restore, mitigate, etc) to identify low-frequency title and abstract phrases. As in the case of the existing PN/PAD causes, the numbers of existing PN/PAD treatments increased drastically as the frequency of appearance in the literature decreased. So, most of the existing PN/PAD treatments to be identified were in the region that required linking phrases to access. Because of resource constraints and time limitations, not all of the linking terms identified were used operationally. While this approach allowed identification of massive numbers of existing PN/PAD treatments, the limited use of linking terms meant that additionally massive numbers of existing PN/PAD treatments were not being identified. An expanded study could overcome this deficiency.

#### 2G2a2. Potential PN/PAD treatments limited

Resource constraints also limited the number of potential PN/PAD treatments that could be identified. These are treatments that influence PN/PAD characteristics in directions desired for PN/PAD reversal, and are currently being used for non-PN/PAD diseases. The LRDI discovery approach allows these potential PN/PAD treatments to be readily identified, and 're-purposed' for PN/PAD application. Exploratory analysis showed that voluminous treatments

from non-PN/PAD literatures had potential to be 're-purposed' for PN/PAD, but only a handful of potential PN/PAD treatments were presented in the present proof-of-principle demonstration.

#### 2G2b. Process, software, and database limitations

The linking term approach was indispensable for extracting existing PN/PAD treatments from the millions of PN/PAD abstract phrases, but it had intrinsic limitations. While many PN/PAD treatment phrases were in close proximity to linking terms, not all PN/PAD treatment phrases were. Some PN/PAD treatment phrases were slightly outside the four-word range of the software abstract phrases, while other PN/PAD treatment phrases were not associated with any of the linking terms identified in the present study.

The titles were searched initially for existing PN/PAD treatments, and then the abstracts were searched. Unfortunately, there were records in which the existing PN/PAD treatment occurred in full-text only, and not in the title or abstract. Full-text searching would overcome this limitation. However, not all biomedical records are available in full-text on the main biomedical databases, and the complexity of searching full-text increases substantially over searching titles or abstracts [Kostoff, 2010].

#### 2G3. Under-reporting of PN/PAD characteristics

The high-frequency PN/PAD characteristics were identified from visual examination of the abstract phrases in the retrieved PN/PAD database. The low frequency PN/PAD characteristics were identified and extracted with use of the linking terms developed for identifying and extracting treatments and contributing factors.

#### 2G3a. Process, software, and database limitations

Because of time and resource limitations, the characteristics identification process was terminated before all linking terms could be examined. Many of the comments made in the previous PN/PAD treatments section apply to PN/PAD characteristics as well.

While many PN/PAD characteristics phrases were in close proximity to linking terms, not all PN/PAD characteristics phrases were. Some PN/PAD characteristics phrases were slightly outside the four-word range of the software abstract phrases. In many cases, this was because PN/PAD characteristics phrases were used in one long sentence following one linking term (e.g., treatment X attenuated characteristic A, characteristic B, characteristic C, etc, where only characteristic A would be in the range of the software phrase length). Other PN/PAD characteristics phrases were not associated with any of the linking terms identified in the present study.

The titles were searched initially for existing PN/PAD characteristics, and then the abstracts were searched. Unfortunately, there were records in which the existing PN/PAD characteristics occurred in full-text only, and not in the title or abstract. This occurred much



more frequently than for treatments, since PN/PAD treatments tended to be the focus of the research more than the PN/PAD characteristics. Full-text searching would overcome this limitation. However, not all biomedical records are available in full-text on the main biomedical databases, and the complexity of searching full-text increases substantially over searching titles or abstracts [Kostoff, 2010].

### 2G3b. Experiment and epidemiology study limitations

In order for PN/PAD characteristics to be reported, they need to be identified and measured. Lab experiments targeted a handful of PN/PAD characteristics to be measured, typically selected for their relevance to the PN/PAD hypothesis being addressed by the researcher. Epidemiology studies used PN/PAD characteristics identified in medical records or stated on questionnaires. Every additional PN/PAD characteristic that is added to a lab experiment or epidemiology study translates into additional time and other resource expenditures. This effectively limits the number and scope of PN/PAD characteristics selected for any given lab experiment or epidemiological study.

The main point here is the PN/PAD characteristics in the biomedical literature that change based on PN/PAD causes or treatments will be a small fraction of all the PN/PAD characteristics that could have been measured and shown to have changed due to PN/PAD causes or treatments. This has strong implications on the populations of the PN/PAD causes-characteristics or PN/PAD treatments-characteristics matrices. The matrices presented above, massive as they are relative to any others that appear in the PN/PAD literature, are vastly underpopulated because of the limited scope of the epidemiological studies or lab experiments relative to breadth of PN/PAD characteristics examined.

### 2G3c. Resource limitations on identifying potential PN/PAD characteristics

While many hundreds of existing PN/PAD causes and treatments were identified in the present study, many hundreds more could have been identified if the limitations described above had been removed. Additionally, many more potential PN/PAD causes and treatments could have been identified by using the LRDI process to search non-AD literatures.

The same holds true for identifying potential PN/PAD characteristics. There are patterns/groupings of PN/PAD characteristics that could be used to search the non-AD literatures for groups of characteristics that include the PN/PAD group patterns, but may also contain other characteristics that were not included in the PN/PAD groups in the PN/PAD literature. Identifying potential PN/PAD characteristics was not explored in the present study, so it is not credible to make estimations of the magnitude of additional PN/PAD characteristics possible using this approach.

## 2G4. Impact of under-reporting of PN/PAD causes, treatments, and characteristics

What is the real-world impact from the under-reporting of PN/PAD causes, treatments, and impacts, as outlined above? As will be shown in the next chapter on PN/PAD treatment protocols, the PN/PAD protocols involve

- 1) measuring relevant PN/PAD characteristics for individual patients,
- 2) identifying causes to be removed based on that patient's PN/PAD characteristics' abnormalities, and
- 3) identifying PN/PAD treatments to be implemented based on that patient's PN/PAD characteristics' abnormalities.

Any deficiencies in not identifying, or mis-identifying, PN/PAD characteristics, causes, and treatments will translate into deficiencies of these PN/PAD protocols' effectiveness.

In the results presented so far in the present chapter, the PN/PAD treatment-biomarker (Figure 2F-1) and causes-biomarker matrixes (Figure 2E-1) have their axes ordered starting with largest numbers of records at top left, and decreasing numbers of records when proceeding rightwards and downwards. Both types of matrices are dense in the upper left region and very sparse in the lower right region. The PN/PAD treatment-biomarker matrix has a small percent of its cells populated with any records. Even for those cells that contain record numbers, the number of records they contain is a very small fraction (on average) of what they could theoretically contain. While an expanded study could increase both the density of the matrix and the length of the axes, it would offer little if any insight on the magnitude of the PN/PAD causes being suppressed by PN/PAD gatekeepers (e.g., sponsors, journals, etc).

## 2H. Conclusions

The LRDI-based text mining approach used for this study allowed identification of many hundreds of existing PN/PAD characteristics, contributing factors, and treatments, and a handful of potential treatments for illustrative purposes. These are far more characteristics, contributing factors, and treatments published in any other PN/PAD study, and they were obtained under the most severe resource constraints. An adequately resourced study could probably double the number of these existing PN/PAD items identified, and probably increase the number of potential PN/PAD treatments (and contributing factors and biomarkers) by at least an order of magnitude.

Given the massive numbers of potential contributing factors to PN/PAD, it is difficult to see how any treatment approach that does not incorporate full-spectrum elimination of the major contributing factors for a given patient can be effective in truly reversing PN/PAD. Some symptom management, especially for the near-term, can be done, but far more is possible.

Successful elimination of the main contributing factors requires three entities: the patient, the healthcare provider(s), and the government. The patient must have the motivation and will to heal. The provider(s) must have the motivation to provide the most accurate information and recommendations to the patient. And, the government must be willing to institute regulations that will protect the patient from exposure to many of the known PN/PAD contributing factors. All three of the above entities have much room for improvement if PN/PAD reversal is to be achieved.

[References - Chapter 2](#)

## Chapter 3

### TREATMENT PROTOCOL

#### 3A. Overview

In the present monograph, over 800 PN/PAD causes (depending on how one aggregates PN/PAD causes at different levels), over 1100 PN/PAD treatments (again, depending on aggregation), and about 1000 PN/PAD characteristics were identified. As stated repeatedly, an expanded study (including recommendations for study process improvement outlined throughout this monograph) could double these numbers of existing PN/PAD causes, treatments, and characteristics identified, or more. Additionally, the LRDI technique could be used to easily identify hundreds more potential PN/PAD causes, treatments, and characteristics.

Therefore, the challenge for developing a realistic PN/PAD treatment protocol is to

*1) reduce the numbers of PN/PAD characteristics to be measured, PN/PAD causes to be eliminated, and PN/PAD treatments to be implemented from*

*2) the many hundreds of measurable existing and potential PN/PAD characteristics, PN/PAD causes, and PN/PAD treatments identified to*

*3) reasonable numbers of PN/PAD characteristics to be measured, PN/PAD causes to be eliminated, and PN/PAD treatments to be implemented.*

The following sections of the present chapter outline the major components of the PN/PAD treatment protocol in chronological order. Adherence to this protocol should restore adequate functionality to a substantial number of PN/PAD patients; quantification of this hypothesis will require clinical trials for credible estimation. Strict adherence to this protocol should also prevent a substantial number of PN/PAD-prone cases from ever coming to fruition. A summary of the complete PN/PAD treatment protocol is contained in [section 3B6](#).

#### 3B. PN/PAD Treatment Protocol in Chronological Order

There are five steps in the full PN/PAD treatment protocol, as shown in Table 3B-1.

**Table 3B-1 - Five-Step Protocol to Prevent and Reverse PN/PAD**

#### **FIVE-STEP PROTOCOL TO PREVENT AND REVERSE PN/PAD**

- Step 1:** Obtain a detailed medical and habit/exposure history from the patient.
- Step 2:** Administer written and clinical performance tests to assess the severity of the higher-level symptoms and degradation of functions
- Step 3:** Administer laboratory tests (blood, urine, imaging, etc)
- Step 4:** Eliminate ongoing PN/PAD contributing factors
- Step 5:** Implement PN/PAD treatments

These five steps will now be described in more detail.

### 3B1. Medical History Questionnaire

**The first step** in the protocol is to obtain a detailed medical and habit/exposure history from the PN/PAD patient. The patient would be provided a detailed questionnaire focusing mainly on practices and exposures that are potential PN/PAD contributing factors. The PN/PAD contributing factor component of the questionnaire would be based on [Table 7A-1](#) or, preferably, on a similar table derived from an expanded study. In the latter case, there could be greater than 1,000 potential contributing factors identified.

Most of the questions would not be answerable. The patient might be able to answer a number of questions related to the lifestyle and iatrogenic components of Table 7A-1, and perhaps a few of the questions related to the occupational exposures component if these exposures were significant. However, most patients would probably not be able to identify past and present exposures to many hundreds of chemicals and radiations that are contributing factors to PN/PAD. The questionnaire would yield some idea of past and present relevant PN/PAD contributing factors for the patient, with much to be determined by further testing.

Thus, the patient would probably be able to provide some estimate of dietary components, sedentary behavior, sleep quality, recreational drug use, major medications taken and surgeries experienced, and perhaps exposures to pesticides, ionizing radiation, asbestos, etc, as part of their job. The patient would probably not be able to identify food additives ingested when they ate out, chemicals in their home from cleaning and new furniture, particulates and chemicals in the air they breathe, exposure to non-ionizing radiations, etc.

For those patients whose major PN/PAD contributing factors are in the readily identifiable category, their chances of reversing PN/PAD are reasonable (assuming irreversible damage has not been done and they do not have an overwhelming genetic predisposition to PN/PAD). For those patients whose major PN/PAD contributing factors are in the non-identifiable category, complete reversal would be much more of a challenge. Reversal for them may in fact require identification and elimination of far more of the PN/PAD contributing factors.

### 3B2. Assess Performance Observables

**The second step** in the protocol is to administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms. This would include tests for sensing, pain, gait, endurance, strength, etc, and for anxiety, depression, cognitive dysfunction, etc. The latter group of mood-related tests might have some overlap with the medical history on the initial questionnaire.

### 3B3. Administer Laboratory Tests

### 3B3a. Criteria for PN/PAD characteristics laboratory tests

**The third step** in the protocol is administration of laboratory tests (blood, urine, imaging, etc). Any abnormalities shown by these tests would help prioritize the PN/PAD contributing factors to be eliminated and PN/PAD treatments to be implemented in the streamlined protocol presented in this chapter.

In the present study, approximately 1000 PN/PAD characteristics were identified. Perhaps 25 percent were treatments and symptoms (whose abnormalities would be reflective of PN/PAD, and whose evaluation would be addressed by the procedures in section 3B2). The remaining ~75 percent were estimated to be laboratory-measurable quantities. It was also estimated these numbers of measurable PN/PAD characteristics could be at least doubled in an expanded study. Therefore, for a non-streamlined protocol, this step in the protocol could involve the administration of ~1500 lab tests (or more) to identify the full spectrum of abnormalities in these measured PN/PAD characteristics.

Given costs and other negative aspects of such tests, the number of tests would have to be reduced by more than an order of magnitude to be acceptable to both the patient and the healthcare practitioner. In other words, many hundreds of laboratory tests are too large to be practical, at the present time. The present protocol proposes a greatly reduced number of lab tests, selected for their ability to cover a wide swath of PN/PAD-related pathologies. Results from these core lab tests will help prioritize PN/PAD causes to be eliminated and PN/PAD treatments to be implemented.

The protocol approach is cause-and-effect based. The general biomarkers that tended to focus on a broad range of pathophysiological mechanisms (e.g., oxidative stress, inflammation, endothelial dysfunction, etc.) were selected, with input from the factor matrix-based categorization of key biomarker themes. Then, for each of the selected general biomarker categories, the biomarker-biomarker matrix of Figure 2D-2 was used to identify specific measurable biomarkers closely related to the theme of the general biomarker.

To reiterate, the final streamlined PN/PAD characteristics selected will encompass the pathologies viewed by the PN/PAD research community as important features of PN/PAD. Because of the inter-connectedness of major systemic networks (immune system, neural system, endocrine system, circulatory system, etc.), one would expect the myriad pathologies associated with the factors to have some relationship. Because of this ripple effect, important PN/PAD contributing factors and important PN/PAD treatments are expected to be systemic in their impact. This systemic impact would be reflected by

1) important PN/PAD contributing factors producing abnormalities in *many* of the factor-driven categories used as the basis for PN/PAD biomarkers selection, and

2) important PN/PAD treatments removing abnormalities in *many* of the factor-driven categories used as the basis for PN/PAD biomarkers selection.

### 3B3b. Sample recommendations for PN/PAD biomarkers laboratory tests

Based on the criteria for selecting potential PN/PAD biomarkers laboratory tests in the previous section, numbers of possible combinations were examined. Following is the combination selected for the present example. Different practitioners may interpret the source data differently, and modify the combinations. Some practitioners may want to modify the combinations to be more focused on PN or on PAD. Other modifications and additions could be expected after an expanded study was conducted.

[Table 2D-6](#) contains the PN/PAD biomarkers selected for initial laboratory tests in the PN/PAD protocol. The biomarkers are listed by category, with the highest priority biomarkers highlighted in red. These thematic categories were generated based on the results of the biomarker factor matrix (Figure 2D-1a) and other inputs. Then, phrases were selected to populate these categories based in part on 1) their rankings in the biomarker factor matrix, and on 2) their applicability to PN/PAD or PN or PAD ([Table 7A-12](#)), as discussed at the end of section 2D4. The PN/PAD characteristics are typically not uniquely related to the pathological themes. Usually, any one of the PN/PAD characteristics in the selected group will be related to multiple PN/PAD pathologies, and any one of the PN/PAD pathologies will be related to many of the PN/PAD characteristics.

The biomarkers highlighted in red are only a suggestion for testing prioritization. There is not strong consensus in the literature for many of these biomarkers, and clinicians should substitute biomarkers for testing they deem more appropriate. Also, there may be categories listed that some clinicians believe are not relevant to specific patients, based on their medical histories. The biomarkers in these categories could be eliminated, thereby reducing the number of tests required. Conversely, there could be categories not listed in [Table 2D-6](#) that clinicians believe are important for specific patients. Biomarkers for these categories should be added as required. Three such categories not emphasized in Table 2D-6 are heavy metals, infections, and Vitamin deficiencies.

Heavy metals that can impact various segments of PN/PAD adversely include arsenic, cadmium, lead, mercury, and thallium. Infections/infectious agents that can impact various segments of PN/PAD adversely include human immunodeficiency virus (HIV), *Aggregatibacter actinomycetemcomitans*, *Borrelia burgdorferi*, *Brucella* spp., *C. pneumoniae*, *Campylobacter jejuni*, *Campylobacter rectus*, *Chlamydia pneumoniae*., *Chryseomonas*, *Clostridium botulinum*, *Collinsella*, *Corynebacterium diphtheriae*, *Cytomegalovirus*, *Eikenella corrodens*, Epstein-Barr virus, *Eubacterium*, *Fusobacterium nucleatum*, *H. influenzae*, *Helicobacter pylori*, Hepatitis C virus, Herpes simplex virus, Human T-cell lymphotropic virus, *M. pneumoniae*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Parvimonas micra*, *Parvimonas micros*, *Porphyromonas*

gingivalis, Prevotella intermedia, Prevotella nigrescens, Rabies virus, Roseburia, Streptococcus, Tannerella forsythia, Treponema denticola, Varicella-zoster virus, Veillonella, West Nile Virus [Brizzi and Lyons, 2014; Budzynski et al, 2016]. Vitamin deficiencies include, but are not limited to, Vitamins B-1, B-12, C, D, E.

### 3B4. Recommend PN/PAD Contributing Factors to be Eliminated

#### 3B4a. Prioritization based on Causes-Biomarkers Matrix

**The fourth step** in the PN/PAD treatment protocol is elimination of as many of the ongoing PN/PAD contributing factors as possible. Once the laboratory tests have been completed, the abnormalities in the PN/PAD characteristics' values can be identified. This allows causes to be eliminated and treatments to be implemented.

However, identification of unique causes based on abnormal biomarker values is extremely difficult. As [Tables 2E-1](#) and [2E-2](#) show for oxidative stress and blood pressure, respectively there can be many causes that impact a given biomarker adversely. Thus, 'reverse-engineering' the abnormal PN/PAD biomarker values to identify candidate PN/PAD causes for elimination will be difficult. As these tables show, even if only one PN/PAD biomarker had abnormal values, there could be tens or hundreds of PN/PAD causes for this abnormality that could be identified through 'reverse-engineering' for potential elimination.

I propose a combined 'direct-identification' and 'reverse-engineering' approach that has the virtue of simplicity. The 'direct-identification' component consists of eliminating the PN/PAD contributing factors the patient listed on the initial medical/exposure questionnaire. The 'reverse-engineering' component

- 1) identifies all the patient's PN/PAD biomarkers with abnormal laboratory test values,
- 2) identifies the number of these abnormal PN/PAD biomarkers impacted by each PN/PAD contributing factor, then
- 3) prioritizes the PN/PAD contributing factors for elimination according to the number of PN/PAD biomarkers impacted by the PN/PAD contributing factors.

For example, suppose five of the PN/PAD characteristics measured show abnormal values: *high AGEs*, *low ATP*, *low BDNF*, *high Homocysteine*, *high IL-6*. Then, those PN/PAD contributing factors that impacted all five biomarkers would have first priority for elimination, those PN/PAD contributing factors that impacted four of the five biomarkers would have second priority for elimination, and so on down to PN/PAD contributing factors that impacted any one of the biomarkers.

The recommended prioritization above is based on numbers of PN/PAD biomarkers impacted by each PN/PAD contributing factor. It does not distinguish between one record



describing the impact (for a particular PN/PAD contributing factor) or ten records describing the impact. Irrespective of the number of records describing the impact, it does not distinguish among the strengths of impact described in different records. This additional information could be used by the healthcare practitioner to modify the prioritization approach presented above.

In addition, there are some cases where 'reverse-engineering' may be more straightforward. For example, high serum or urine readings of heavy metals (e.g., arsenic, cadmium, mercury) would identify specific targets for elimination. These would be the exception rather than the rule, in terms of specificity.

#### 3B4b. Prioritization based on "Low-Hanging Fruit"

The contributing factors to be eliminated identified from the causes-biomarkers matrix may be straight-forward, or they may be unknown in the absence of detailed environmental measurements. Some may be beyond the patient's control, such as fixed cell towers near one's residence.

Based on [Table 7A-1](#), there are a number of contributing factors that are mainly related to lifestyle, and are mainly within one's control to retain or eliminate. These have been termed "Low-Hanging Fruit", since they are probably the 'easiest' contributing factors to eliminate. Elimination of the "Low-Hanging Fruit", in parallel with the elimination of the contributing factors identified by the method of the previous section, would be most effective.

**Table 3B-2 - "Low-Hanging Fruit" Causes for Elimination****LOW-HANGING FRUIT RECOMMENDATIONS**

- 1) curb the dietary excesses, and remove the dietary deficiencies, identified in Table 7A-1, the medical questionnaire, and the lab tests;
- 2) eliminate food additives to the extent knowable and possible, including those dietary excesses that derive from food additives (excessive fat, sugar, salt);
- 3) minimize high temperature cooking and the subsequent increases in Advanced Glycation End Products from certain susceptible foods, Heterocyclic Amines, Acrylamide, and Polycyclic Aromatic Hydrocarbons;
- 4) reverse the sedentary behavior patterns identified;
- 5) remove the foundational impediments to better sleep;
- 6) eliminate the use of 'recreational' drugs, including smoking and excessive alcohol;
- 7) eliminate the use of medicinal drugs shown to be potential PN/PAD contributing factors from Table 7A-1, unless these drugs are absolutely necessary;
- 8) minimize exposures to some hydrocarbons, such as n-hexane, methyl-n-butyl ketone, carbon disulfide, acrylamide, ethylene oxide, trichloroethylene, kerosene, polycyclic aromatic hydrocarbons (including those found in smoke), etc;
- 9) minimize exposures to some neurotoxic solvents, especially organic solvents;
- 10) minimize inhalation and ingestion exposures to pesticides, herbicides, insecticides, and fungicides;
- 11) minimize exposures to heavy metals in food, in water, and in the air;
- 12) minimize exposure to particulates, especially air pollution;
- 13) minimize exposures to ionizing radiation and non-ionizing non-visible radiation (such as cell phones, cell towers, WiFi, smart meters, etc.);
- 14) minimize chronic stress (mental/emotional/psychological);

**3B4c. Prioritization Based on Remaining Indirect Causes**

In the prior two sections, the prioritizations were mainly based on removing different types of direct causes. But, there are cases where removing indirect causes would be beneficial.

For example, pesticides could be viewed as direct causes of PN/PAD, and they could be identified and removed by methods in 3B4a. Chemotherapy, however, is a direct cause of PN/PAD, and its elimination would exacerbate the cancer being treated. The indirect cause of PN/PAD in this case would be the cancer that is necessitating the use of chemotherapy, or, more specifically, those contributing factors that, for many people, resulted in the development of cancer. Removing those direct causes of cancer would obviate the need for chemotherapy, and is identical to removing the indirect causes of PN/PAD.

**3B5. Recommend PN/PAD Treatments to be Implemented****3B5a. Prioritization based on Treatments-Biomarkers Matrix**

**The fifth step** in the PN/PAD treatment protocol is implementation of the optimal number of treatments necessary for reversal. Once the laboratory tests have been completed, the abnormalities in the PN/PAD characteristics' values can be identified. This allows targeted treatments to be implemented.

However, identification of unique treatments based on abnormal biomarker values is extremely difficult. As [Tables 2F-1](#) and [2F-2](#) show for oxidative stress and blood pressure, respectively there can be many treatments that impact a given biomarker adversely. Thus, 'reverse-engineering' the abnormal PN/PAD biomarker values to identify candidate PN/PAD treatments for implementation will be difficult. As these tables show, even if only one PN/PAD biomarker had abnormal values, there could be tens or hundreds of PN/PAD treatments for this abnormality that could be identified through 'reverse-engineering' for potential implementation.

I propose a modified 'reverse-engineering' approach that has the virtue of simplicity. The modified 'reverse-engineering' component

- 1) identifies all the patient's PN/PAD biomarkers with abnormal laboratory test values,
- 2) identifies the number of these abnormal PN/PAD biomarkers impacted by each PN/PAD treatment, then
- 3) prioritizes the PN/PAD treatments for implementation according to a) the number of PN/PAD biomarkers impacted by the PN/PAD treatments and the risk level of the combination of treatments selected.

For example, suppose five of the PN/PAD characteristics measured show abnormal values: *high AGEs*, *low ATP*, *low BDNF*, *high Homocysteine*, *high IL-6*. Then, those PN/PAD treatments that impacted all five biomarkers and had low-risk would have first priority for elimination, those PN/PAD treatments that impacted four of the five biomarkers and had low-risk would have second priority for elimination, and so on down to PN/PAD treatments that impacted any one of the biomarkers and had low-risk.

The recommended prioritization above is based on numbers of PN/PAD biomarkers impacted by each PN/PAD treatment and the perceived treatment risk level. It does not distinguish between one record describing the impact (for a particular PN/PAD treatment) or ten records describing the impact. Irrespective of the number of records describing the impact, it does not distinguish among the strengths of impact described in different records. This additional information could be used by the healthcare practitioner to modify the prioritization approach presented above.

In addition, there are some cases where 'reverse-engineering' may be more straightforward. For example, high serum or urine readings of heavy metals (e.g., arsenic,

cadmium, mercury) or specific bacteria/viruses would identify specific targets for treatment implementation. These would be the exception rather than the rule, in terms of specificity.

### 3B5b. Prioritization based on Lowest-Risk Treatment

The treatments to be implemented from the treatments-biomarkers matrix may have different risk levels calculated in isolation, and perhaps enhanced risk levels when combined.

Based on [Table 7A-5](#), there are a number of treatments that are low risk, and are mainly within one's control to retain or eliminate. These have been termed "Lowest-Risk Treatments", since they are probably the 'easiest' treatments to implement. Implementation of these Lowest-Risk Treatments, in parallel with the implementation of treatments identified by the method of the previous section, would be most effective.

### 3B5c. Examples of lowest-risk PN/PAD treatments

The lowest-risk PN/PAD treatments mentioned in section 3B5b are shown in Table 3B-3. They would include, but not be limited to:

**Table 3B-3 - Lowest-Risk Treatments**

- Exercise (such as aerobic exercise, walking, resistance training, treadmill, calisthenics, stretching, balancing)
- Sleep Improvement (such as quiet environment, minimal light, minimal food before bedtime, maintain regular sleep schedule)
- Stress Reduction (such as tai chi, yoga, massage, aromatherapy, acupuncture, accupressure, sensory stimulation, physiotherapy, massage, reflexology, meditation)
- Diet - Choose foods high in
  - polyphenols (such as cloves, star anise, capers, curry powder, ginger, cinnamon, peppermint, oregano, sage, rosemary, thyme, basil, cocoa, tea, red wine, chokeberries, elderberries, blueberries, plums, cherries, black currants, blackberries, strawberries, raspberries, grapes, flaxseeds, celery seeds, chestnuts, hazelnuts, pecans, almonds, walnuts, olives, artichokes, chicory, red onion, spinach, broccoli, apples, pomegranates, peaches, apricots, olive oil, canola oil), especially flavonoids (such as apples, blueberries, strawberries, red grapes, cabbage, broccoli, onions, capers, dark chocolate, cocoa, tea, red wine), isoflavones/genistein (such as soybeans, natto, tempeh, tofu, miso), and anthocyanins (such as blackberries, black currants, blueberries, strawberries, cranberries, eggplant, cherries, prunes, raisins, and the darker versions of raspberries, cabbage, plums, radish, grapes, plums, apples, beans, beets, cabbage, onions, pears, wines)
  - Unrefined carbohydrates (such as whole grains, legumes, fruits, and uncooked vegetables)
  - DHA/omega-3 fatty acid (such as salmon, herring, mackerel, anchovy, sardine, trout, shark, swordfish, mussel, sea bass, pollock, whiting, flounder, sole, lobster, halibut, carp, oyster, crab, mullet, tuna, perch, snapper, shrimp,

octopus)

- Vitamin B12/Folate (such as meat [beef liver, lamb, beef], fish [sardines, mackerel, salmon], dairy [feta cheese, cottage cheese], eggs, legumes [chickpeas, fermented soy, pinto beans, lentils], fruit [banana, avocado], vegetables [spinach, parsley, broccoli, beets, turnip, asparagus,])
- Vitamin C (such as fruits [guavas, acerola cherry, kiwifruit, rose hips, strawberries, oranges, papayas, vegetables [bell peppers, broccoli, tomatoes, snow peas, kale])
- Vitamin D (such as fish [sardines, salmon, mackerel, tuna], liver [beef, calf, cod liver oil], dairy [milk, yogurt]; most importantly, sunlight on exposed skin)
- Vitamin E (such as seeds [sunflower seeds, pumpkin seeds], nuts [almonds, hazelnuts, pine nuts], fish [abalone, salmon, trout], fruit [avocado, mango, kiwifruit], vegetables [red peppers, turnip greens, spinach, chard, squash, broccoli])
- lycopene (such as tomatoes, guavas, watermelon, papaya, grapefruit),
- oleic acid (such as nuts [almonds, peanuts, pecans, cashews, pistachios, hazelnuts] seeds [sesame, sunflower], avocados, olives, and vegetable oils [safflower, almond, olive, sesame, sunflower]),
- luteolin (such as dried oregano, celery seed, hot peppers, peppermint, sage, rosemary, juniper berries, thyme, radicchio, chinese celery),
- quercetin (such as capers, lovage leaves, elderberry juice, dock leaves, raddish leaves, arugula, dill weed, coriander, and fennel, cilantro, banana peppers, juniper berries, oregano, onions, carob flour, radicchio, red leaf lettuce, onions, watercress, raw, asparagus, kale, okra, cocoa powder, chia seeds)
- sulforaphane (such as broccoli sprouts, broccoli, cauliflower, kale, brussels sprouts, cabbage, collards, arugula, turnips)
- resveratrol (such as red wine, red grapes, peanut butter, pistachios, cocoa powder, dark chocolate, strawberries, blueberries, bilberries, cranberries)
- epigallocatechin-3-gallate (such as green tea, black tea, carob powder, apples, blackberries).

#### Caveats on diet:

- Many toxic/harmful substances enter the food supply during all phases of food growth, distribution, and processing. While foods should be selected to maximize the amounts of healing nutrients identified above, care must be taken to minimize the level of toxic additions to the food in parallel.
- Low-temperature cooking should be used to minimize production of AGEs and other harmful products (nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides) during the cooking process.
- Only low-mercury wild-caught fish should be used; these tend to be smaller fish, lower on the food chain.
- Grass-fed animals with no exogenous growth hormones or antibiotics should be used, if possible, since these harmful products could be passed through to the consumer.

- For fruits and vegetables normally eaten with skin, those that have not been sprayed with harmful pesticides and other toxic chemicals should be used.
- Heavy metals are a contributing factor for many neurodegenerative and other chronic diseases, including PN/PAD. One source of heavy metal bioaccumulation in the body is through the food supply. Heavy metals can occur naturally in the soil in which food is grown, they can concentrate abnormally in soils from nearby industrial pollution or from precipitation of air pollution, they can preferentially absorb in different types of food, and, depending on the type of food, can be absorbed from the food processing and manufacturing process. Any of the above foods selected for PN/PAD prevention or treatment purposes should have heavy metal concentrations as low as possible.

A note about these dietary recommendations. In [Table 7A-5](#), herbs and plant extracts are associated with large numbers of records. One of the major reasons for this is their copious use in Traditional Chinese Medicine, which had significant representation in our PN/PAD database. Some of the concoctions that contained these substances had adverse side effects, which removed them from the desired low-risk category. Also, independent verification of many of these concoctions' impacts was not readily available. Therefore, they are not in the first-tier recommendations.

Additionally, many of these plant extracts, almost by definition, are not whole foods. The present monograph recommends whole foods containing the desired chemicals and nutrients (listed in [Table 7A-5](#)) preferentially in the above list. The full spectrum of phytochemicals contained in whole foods act synergistically with the fragmented chemicals listed to provide far more protection. As stated in [Liu, 2003]: "the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods."

### 3B6. Summary Treatment Protocol to Prevent and Reverse PN/PAD

This section summarizes the recommended treatment protocol for preventing and reversing PN/PAD. There are five steps in the full treatment protocol, as shown in the following:

#### **FIVE-STEP TREATMENT PROTOCOL TO PREVENT AND REVERSE PN/PAD**

- Step 1:** Obtain a detailed medical and habit/exposure history from the patient.
- Step 2:** Administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms and degradation of functions
- Step 3:** Administer laboratory tests (blood, urine, imaging, etc)
- Step 4:** Eliminate ongoing PN/PAD contributing factors
- Step 5:** Implement PN/PAD treatments

These five steps will now be described in more detail.

**Step 1.** The first step in the protocol is to obtain a detailed medical and habit/exposure history from the PN/PAD patient. The patient would be provided a detailed questionnaire focusing mainly on practices and exposures that are potential PN/PAD contributing factors. The contributing factor component of the questionnaire would be based on [Table 7A-1](#), or, preferably, on a similar, but even more extensive, table derived from an expanded study.

**Step 2.** The second step in the protocol is to administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms. This would include tests for sensing, pain, gait, endurance, strength, etc, and for anxiety, depression, cognitive dysfunction, etc. The latter group of mood-related tests would have some overlap with the medical history on the initial questionnaire.

**Step 3.** The third step in the protocol is administration of laboratory tests (blood, urine, imaging, etc). Any abnormalities shown by these tests would help prioritize the PN/PAD contributing factors to be eliminated and PN/PAD treatments to be implemented. [Table 2D-6](#) contains the PN/PAD biomarkers selected for initial laboratory tests in the PN/PAD protocol. These PN/PAD biomarkers reflect the PN/PAD pathological themes and the major themes from the PN/PAD biomarker factor matrix (Figure 2D-1a). Based on the laboratory test results, the health practitioner could require further tests to gain detailed information on problematic areas.

**Step 4.** The fourth step in the protocol is to eliminate ongoing PN/PAD contributing factors. Unfortunately, as Figure 2E-1 shows, each PN/PAD contributing factor typically impacts many PN/PAD biomarkers, and each PN/PAD biomarker is typically impacted by many PN/PAD contributing factors. Thus, in the general case, PN/PAD biomarker values abnormalities in the lab tests will not be uniquely related to specific PN/PAD contributing factors.

To circumvent this problem, a combined 'direct-identification' and 'reverse-engineering' approach that has the virtue of simplicity is proposed. The 'direct-identification' component consists of eliminating the PN/PAD contributing factors the patient listed on the initial medical/exposure questionnaire. The 'reverse-engineering' component

- 1) identifies all the patient's PN/PAD characteristics with abnormal laboratory test values,
- 2) identifies the number of these abnormal PN/PAD characteristics impacted by each PN/PAD contributing factor, then
- 3) prioritizes the PN/PAD contributing factors for elimination according to the number of PN/PAD characteristics impacted by the PN/PAD contributing factors.

Section 3B4 shows how this prioritization, and further sub-prioritizations, would operate.

The recommended prioritization above is based on numbers of PN/PAD characteristics impacted by each PN/PAD contributing factor. It does not:

- 1) distinguish between one record describing the impact (for a particular PN/PAD contributing factor) or ten records describing the impact,
- 2) distinguish among the strengths of impact described in different records, irrespective of the number of records describing the impact,
- 3) weight the PN/PAD characteristics by relative importance,
- 4) incorporate the effects of contributing factor synergies.

This additional information could be used by the healthcare practitioner to modify the prioritization illustrated above.

In addition, there are some cases where 'reverse-engineering' may be more straightforward. For example, high serum or urine readings of heavy metals (such as cadmium or mercury) would identify specific targets for elimination. These would be the exception rather than the rule, in terms of specificity.

The above prioritization approach would serve as a proxy for the more comprehensive elimination of all 'low-hanging fruit' PN/PAD contributing factors shown in [Table 3B-2](#). To the degree possible, the patient should strive to eliminate as many of these 'low-hanging fruit' PN/PAD contributing factors as possible. The combination of 1) lack of knowledge about harmful exposures (limiting what can be answered on the initial medical/exposure questionnaire) and 2) incompleteness of PN/PAD characteristics measured will result in 3) PN/PAD contributing factors not being identified through the complete testing/evaluation process. Eliminating as many of the 'low-hanging fruit' PN/PAD contributing factors as possible will



compensate partially for this lack of knowledge. Many of these items are under the patient's control, and can be readily eliminated, with proper motivation and discipline.

There is an implicit assumption in some/many of these PN/PAD contributing factor elimination recommendations of a treatment implementation. For example, elimination of a high-fat diet (PN/PAD contributing factor) implies adoption of a low-fat diet (PN/PAD treatment).

**Step 5.** The fifth step in the protocol is to implement PN/PAD treatments. Because of risk associated with implementation of single PN/PAD treatments, and the lack of knowledge of how overall risk increases because of treatment combination synergies, it is recommended that the *lowest-risk* treatments (e.g., [Table 3B-3](#)) be implemented initially in parallel with the required higher-risk treatments.

Even among low-risk PN/PAD treatments, some prioritization may be possible. The approach recommended parallels that for eliminating PN/PAD contributing factors in Step 4. The approach is a hybrid of 'direct-identification' and 'reverse-engineering'. The 'direct-identification' component consists of identifying the patient's PN/PAD contributing factors from the medical/exposure questionnaire. Where applicable, PN/PAD treatments that are positive behaviors/habits would be substituted for the negative PN/PAD contributing factors under the patient's control. Thus, if the patient is eating a high AGEs diet, the PN/PAD 'treatment' would consist of substituting a low AGEs diet. If the patient is participating in minimal physical activities, he/she would be encouraged to participate in more physical activities.

The 'reverse-engineering' component would be based on the laboratory tests. In parallel with the approach in Step 4, PN/PAD treatments would be prioritized based on the number of abnormal PN/PAD characteristics they would impact. The caveats of step 4 about relying on numbers of characteristics impacted would apply here as well.

The specific PN/PAD treatments employed would be selected based on the medical questionnaire results, the clinical sensorimotor evaluation, and the lab tests results. Some of the recommended lowest-risk PN/PAD treatments would (in practice) be substitutions for the PN/PAD contributing factors eliminated; others would be new activities implemented. See [Table 3B-3](#) for a partial list of these lowest-risk treatments.

### 3B7. Health policy impact on PN/PAD treatment protocol

The above PN/PAD treatment protocol has been developed based mainly on medical findings, especially as reported in the premier biomedical literature. Financial and political/policy considerations were not taken into account.

The protocol contains implicit assumptions that patients will be able to

- 1) pay for any expensive drugs (if necessary),

- 2) afford pesticide and other harmful chemical-free foods,
- 3) leave jobs where the working environment is toxic,
- 4) move from residences where the environment is toxic, etc.

This flexibility might not be available to many patients with limited income and/or limited assets.

There is also the implicit assumption that, if one has sufficient assets and flexibility, toxin-free environments can be found and toxin-free lifestyles can be achieved. This assumption is open to question, as shown by the following example.

Probably the key exogenous contributing factor to the development of PN/PAD (and many other chronic diseases) is the incorporation of technology in all aspects of modern life without adequate regulation and safety testing. To compound the problem, some/many of these new technologies are effectively mandated, and impossible to avoid, even if the PN/PAD patient is wealthy.

For example, wireless radiation technology has become ubiquitous in modern life (cell phones, WiFi, smart meters, etc). Research has shown that wireless radiation in the cell phone radiofrequency part of the spectrum contributes to oxidative stress and inflammation of the brain [Kostoff and Lau, 2017; Gulati et al, 2017; Chauhan et al, 2017; Kesari et al, 2013], among many other adverse effects. As our PN/PAD study results show, oxidative stress and inflammation are key PN/PAD characteristics. Chronic exposure to wireless radiation would be a factor contributing to increase the incidence of PN/PAD (and many other chronic diseases in which these two characteristics are important).

Wireless radiation technology requires an infrastructure. For cell phones, the major infrastructure is cell towers. The Telecommunications Act of 1996 effectively mandates the construction of cell towers with no opposition allowed based on health considerations. As of this writing, the FCC is attempting to implement similar effective mandates for the next generation of mobile wireless technology, known as 5G. A million or more 'short' cell towers (in the USA) would be required for 5G implementation, since the propagation of radiation energy at the high frequencies characteristic of 5G is poor, and the distances between 'short' cell towers is relatively small by necessity.

This means that populated areas will be blanketed (around the clock) with 3GHz-30GHz (or higher) radiofrequency radiation. This is a range of the frequency spectrum essentially untested for adverse health effects, especially over the long-term in humans, and especially in combination with other toxic stimuli [Kostoff and Lau, 2017]. It is no different in principle from a contractor proposing to spray the populated areas of the USA with Agent Orange around the clock, and the relevant government regulatory agency stating that no opposition to the spraying

is allowed based on health considerations. In effect, ***the USA government is mandating an increase in rates of PN/PAD***, with the potential of this increase being very large.

Thus, we have a dichotomy in the relevant USA Federal policy. On the one hand, the Federal government is investing heavily in biomedical research to treat and reverse PN/PAD. On the other hand, the Federal government is allowing essentially unrestricted and inadequately regulated expansion of technologies that are important contributing factors to PN/PAD. Metaphorically, the Federal government is *drilling holes in the floor of the boat at the same time it is pumping water out of the boat!* These policies are diametrically opposed, and will limit the effectiveness of any PN/PAD treatment protocol, no matter how strictly it is followed.

### [References - Chapter 3](#)

## Chapter 4

### SUGGESTED FURTHER RESEARCH

#### 4A. Identifying Additional PN/PAD Treatments and Contributing Factors

##### **RECOMMENDATION FOR EXPANDED STUDY**

This present monograph contains numerous recommendations for a follow-on expanded study. The context of the recommendations is typically to identify more (perhaps factors of two or three more) PN/PAD treatments, PN/PAD characteristics, and PN/PAD causes/contributing factors than are shown in the present monograph.

Some of the reviewers of this monograph have questioned why more PN/PAD treatments, characteristics, and causes/contributing factors are necessary. After all, the monograph has identified far more PN/PAD treatments, characteristics, and causes/contributing factors than any other published paper. Why are even more PN/PAD treatments, characteristics, and causes/contributing factors required and recommended?

The answer lies in the status of PN/PAD prevention and reversal. We have not solved the problem of preventing and reversing PN/PAD. We don't know the full extent of what is required to prevent and reverse the full spectrum of PN/PAD cases. How, then, can we make the assumptions that

- 1) the full spectrum of necessary diagnostics for every PN/PAD patient will be found within the ~1000 PN/PAD characteristics we have identified in this study,
- 2) the full spectrum of necessary treatments for every PN/PAD patient will be found within the ~1200 PN/PAD treatments we have identified in this study,
- 3) the full spectrum of necessary causes to be eliminated for every PN/PAD patient will be found within the ~800 PN/PAD causes/contributing factors we have identified in this study?

The PN/PAD protocol for preventing and reversing PN/PAD presented in this monograph represents a culling of the large numbers of diagnostics, treatments, and causes identified to more 'manageable' levels. It is imperative that this culling process

- 1) starts with the full complement of PN/PAD diagnostics, treatments, and causes identified in the biomedical literature, and then
- 2) proceeds to reduce these numbers to levels acceptable to both the healthcare and patient communities.

**I believe that the large numbers of PN/PAD diagnostics, treatments, and causes identified in the present monograph will be adequate to prevent and reverse many PN/PAD cases.** However, we cannot exclude the possibility that PN/PAD diagnostics, treatments, and causes existing in the biomedical literature, but not identified in the present monograph, will expand the number of PN/PAD cases that could be prevented or reversed.

#### 4A1. Identifying Additional Existing PN/PAD Contributing Factors and Treatments

The present study is more comprehensive than any of its predecessors with respect to identifying existing PN/PAD contributing factors and treatments and their consequences, based on the premier biomedical literature. However, the study has identified only the tip of the iceberg of existing PN/PAD contributing factors and treatments, and their consequences.

First, only a modest number of existing PN/PAD contributing factor and treatment linking terms were identified due to time and resource limitations. More research could be done to identify additional existing PN/PAD contributing factor and treatment linking terms, as well as identify combinations of existing PN/PAD contributing factor and treatment linking terms for better precision.

Second, not all the existing PN/PAD contributing factor or treatment linking terms identified were used to extract existing PN/PAD contributing factors and treatments and their impacts from the VP abstracts' phrases. An arbitrary cutoff of numbers of existing PN/PAD contributing factors and treatments was set. These limits were deemed adequate to present a wide spectrum of existing PN/PAD contributing factors and treatments without 1) overwhelming the reader and 2) prolonging the study unnecessarily. If more specific existing PN/PAD contributing factors or treatments are desired, the remaining linking terms can be used to query the VP abstracts for this purpose. Given the rate at which existing PN/PAD contributing factors and treatments were being identified with the linking term approach (especially at the lower frequencies of appearance in the biomedical literature), I would estimate the number of additional existing PN/PAD contributing factors and treatments possible using this approach would double or triple those identified presently.

Additionally, in order to access the record containing the existing PN/PAD contributing factor or treatment and its consequence(s), the existing PN/PAD contributing factor or treatment linking term had to be physically relatively close to the existing PN/PAD contributing factor or treatment impact. There were numerous records where an abstract sentence was of the form 'contributing factor X increased the occurrence of A, B, C, D.....' or 'treatment X reduced the occurrence of A, B, C, D.....'. The software would not have recognized the occurrence of B, C, and D because of software phrase length limitations. This problem could be eliminated by the use of Concordance software, where all words within some pre-specified distance of the existing PN/PAD contributing factor or treatment linking term would be displayed, and the additional existing PN/PAD contributing factor or treatment consequences extracted.

#### 4A2. Identifying Additional Potential PN/PAD Contributing Factors or Treatments

One straightforward way of identifying additional *potential* PN/PAD contributing factors or treatments is with use of the Discovery component of the literature-related discovery and innovation (LRDI) approach [Kostoff, 2012; Kostoff and Patel, 2014; Kostoff, Porter, and Buchtel, 2018]. Only a handful of these *potential* PN/PAD treatments (obtained with the LRDI

methodology outlined in [Chapter 6](#), and shown in [Table 2C-6](#)) were identified in the present monograph. An expanded study could identify many *hundreds* more of these *potential* PN/PAD treatments using the LRDI methodology, and this LRDI approach could be used to identify *potential* PN/PAD contributing factors and characteristics as well. This concept is discussed further in a 2018 monograph on the topic of treatment re-purposing [Kostoff, 2018a].

#### 4B. Institute Clinical Trials Combining Removal of Potential PN/PAD Contributing Factors with Implementation of PN/PAD Treatments

The prevention and treatment protocol for PN/PAD described in Chapter 3 requires patient diagnostics measurements, removal of causes based on abnormal diagnostics measurements, and implementation of treatments to normalize the abnormal diagnostics measurements.

To gain operational experience with exploiting the findings in the present monograph, clinical trials incorporating the above protocol should be started in the near future. One of the serious limitations in fully implementing the PN/PAD treatment protocol in section 3B6 is linking 1) the PN/PAD contributing factors to 2) the PN/PAD characteristics that deviate from the norm. As the results in [Chapter 2](#) show, there are many potential PN/PAD contributing factors in our environment and in our daily life to which we are exposed and of which we are unaware. We need to have the capability to measure the exposures to these toxic substances experienced by an individual, and section 4C describes a research opportunity to achieve this goal.

Given the limitations today in identification of personal exposures to many PN/PAD contributing factors, near-term clinical trials as recommended above could start with a broad-based removal of 'low-hanging fruit' PN/PAD causes/contributing factors identified in Table 3B-2.

#### 4C. Develop Measurement Devices for Potential PN/PAD Contributing Factor Exposures

As stated in section 4B, a key deficiency in implementing comprehensive PN/PAD cause removal for any individual is lack of knowledge of the myriad toxic stimuli to which the individual is being exposed continually. What is the full spectrum of potentially toxic chemicals in the water we drink, the air we breathe, the food we eat, and in contact with our skin? Further, what is the full spectrum of ionizing and non-ionizing, visible and non-visible, radiations to which we are exposed as a function of time? To answer these questions, we need devices that 1) can measure the full range of these toxic stimuli and 2) are convenient and portable. Producing such devices would require an extensive research and development effort, especially devices in a form that people would be motivated to wear and use.

#### [References - Chapter 4](#)

## Chapter 5

### BACKGROUND

#### 5A. Overview

This Background section consists of three parts: 1) studies to identify a broad spectrum of causes and treatments for PN/PAD; 2) text mining approaches that have been developed for identifying existing and potential disease contributing factors and treatments; 3) definitions of terms. Sections 5A-5E address the PN/PAD literature, Section 5F addresses the text mining literature, and Section 5G addresses the definitions.

PN refers to the range of clinical syndromes that involve damage to the peripheral nervous system, including motor, sensory, and autonomic fibers [Shields RW, 2010; NINDS, 2019]. If one nerve is damaged, the condition is referred to as mononeuropathy. If many nerves are involved, it is called polyneuropathy [UCSF, 2019].

PAD is a circulatory problem involving narrowing of the peripheral arteries serving the legs, stomach, arms and head, affecting arteries in the legs most commonly [AHA, 2019; MC, 2019]. It is one of a number of terms used commonly to refer to arterial occlusive disease of the lower and upper extremities, including peripheral vascular disease (PVD), peripheral arterial occlusive disease, and arteriosclerosis obliterans [Campia, Gerhard-Herman, Piazza, et al, 2019].

Poor peripheral blood circulation characteristic of many forms of PAD restricts adequate transport of nutrients (especially oxygen) to the peripheral neural system, potentially causing severe damage and destruction to the peripheral neural system and surrounding structures, suggesting that PN and PAD should be treated as a combined entity. Intake of the highest quality nutrients, by whatever route, will have limited effect on biological structure health if the logistics transport system (veins and arteries) is 1) not able to deliver these nutrients to the appropriate structures in a timely manner and is 2) not able to dispose of the metabolic waste products in a timely manner as well.

#### 5B. Present and Projected PN/PAD Incidence and Prevalence

##### 5B1. PN

Estimates of PN prevalence vary widely.

- Watson and Dyck: the prevalence of PN in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years [Watson and Dyck, 2015];
- Foundation for PN: an estimated thirty million Americans suffer from some type of PN [FPN, 2019];

- Western Neuropathy Association and University of California at San Francisco (UCSF): more than twenty million Americans suffer from some sort of PN [WNA, 2019; UCSF, 2019].

The most prevalent types of PN are diabetic (~60%), ideopathic (~23%), chemotherapy-induced (~10%), HIV/AIDS-induced (~2%), other (~5%) [FPN, 2019].

More detailed information about symptoms, biomarkers, diagnoses, causes, treatments, and epidemiology of PN can be found in the following comprehensive PN review articles [e.g., Barrell and Smith, 2019; Pascuzzi, 2009; England and Asbury, 2004; Hughes, 2002; Watson and Dyck, 2015] and in the following PN books [e.g., Donofrio, 2012; Smith and Bromberg, 2005; Barohn, 2013; Herskovitz, Scelsa, and Schaumburg, 2010; Thomas and Dyck, 2005; Dyck et al, 2010].

## 5B2. PAD

Estimates of PAD prevalence vary somewhat.

- PAD affects around 13% of the Western population who are more than 50 years old [Morley, Sharma, Horsch et al, 2018];
- PAD has a reported prevalence of 15% in Australia, the USA, and other Western countries, and up to 30% when studied in older populations [Conte and Vale, 2018];
- PAD affects 12% to 20% of Americans 60 years and older, increasing to nearly 50% in those 85 years and older. Prevalence increases dramatically with age, and PAD disproportionately affects black persons. The global disease burden exceeds 200 million persons worldwide, and PAD increased in prevalence by 23.5% between 2000 and 2010 [Firnhaber and Powell, 2019];
- PAD prevalence in the United States is low in people 50 years and younger, while PAD rates increase sharply with age, reaching approximately 20% in octogenarians [Campia, Gerhard-Herman, Piazza, et al, 2019];
- PAD prevalence globally was ~118 million cases in 2017 and the number of incident cases was ~11 million, with two thirds of PAD prevalent cases being asymptomatic. Furthermore, PAD caused 515,600 years lived with disability. In 2017, ~70,000 people died from PAD, which represents ~56% increase compared with 2007 [Kengne and Echouffo-Tcheugui, 2019].

More detailed information about symptoms, diagnoses, causes, treatments, and epidemiology of PAD can be found in the following comprehensive PAD review articles [e.g., Firnhaber and Powell, 2019; Campia, Gerhard-Herman, Piazza, et al, 2019; Conte and Vale, 2018; Morley, Sharma, Horsch et al, 2018; Gerhard-Herman, Gornik, Barrett, et al, 2017] and in the following PAD books [e.g., Mohler and Jaff (Eds), 2017; Alonso, McManus, and Fisher, 2010; Kevil, Bir, and Pattillo, 2013; Zemaitis, Bah, Boll et al, 2019].



These PN/PAD projections may be strong under-estimates. They are based mainly on extrapolations from the past. The large causative technology component of these projections reflects the adverse effects of *established* technologies. The results shown in [Chapter 2](#) reflect many *recently-implemented technologies* that could potentially contribute to PN/PAD.

PN and PAD have environmental components. There have been many potentially harmful and effectively un-regulated high-technology additions to the environment in the past few decades [Kostoff, Porter, and Buchtel, 2018; Kostoff, 2015] (e.g., wireless radiation, vaccine combinations, agricultural chemicals, etc., have expanded greatly). Because of latency delays before serious diseases emerge, inadequate time has elapsed to show linkages between these potentially harmful technology additions and changes in the incidence of PN/PAD (or myriad other chronic diseases) in human populations. Additionally, the synergetic adverse effects resulting from combinations of these new technologies are unknown, especially when used for long time periods [Kostoff, Goumenou, Tsatsakis, 2018]. As will be shown in the present monograph, the adverse impact of (for example) recent potentially harmful environmental and dietary additions on PN/PAD biomarkers and symptoms ominously portends increased incidence and prevalence of PN/PAD in the future.

Thus, the appropriate future projections of PN/PAD incidence and prevalence should consist of superposition of 1) a trend line reflective of past harmful exposures and positive health advances and 2) increasing incidence due to implementation of new potentially harmful technologies with decadal latency periods. The Precautionary Principle dictates that the impacts of these newer technologies on PN/PAD characteristics be considered when developing future incidence projections, especially in the longer-term.

Finally, many of the toxic stimuli that are contributing factors to PN/PAD also contribute to many other serious diseases [Kostoff, 2015]. Many of these diseases can be fatal, and may not have the multi-decadal latencies associated with some forms of PN and especially with PAD. Thus, these lethal diseases serve to cull out people who would have been high-risk candidates for PN/PAD had they lived. This culling out of high-risk individuals artificially depresses and masks the real incidence of PN/PAD had these high-risk people survived.

## 5C. PN/PAD Contributing Factor and Treatment Studies

### 5C1. PN Contributing Factor Studies

As shown in [Chapter 2](#), there are many published studies focusing on identifying one or a few contributing factors to PN. There are many fewer studies identifying a very broad spectrum of disease contributing factors, as was done in the previous LRDI-based prevention and reversal of chronic disease studies [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018]. The focus in the present section is to summarize the results from credible broad spectrum or meta analysis studies identifying myriad PN contributing factors.

Results from significant review studies of PN contributing factors are as follows:

- [Shields, 2010]: "Drugs that can induce polyneuropathies" (Table 1):

-Antibiotic (Chloramphenicol; Chloroquine; Dapsone; Didanosine; Ethambutol; Ethionamide; Isoniazid; Metronidazole; Nitrofurantoin; Savudine; Suramin)

-Sensorimotor (Zalcitabine)

-Chemotherapeutic (Cisplatin; Cytarabine; Docetaxel; Paclitaxel; Procarbazine; Vinblastine; Vincristine)

-Cardiovascular (Amiodarone; Captopril; Enalapril; Flecainide; Hydralazine; Perhexiline);

-Rheumatologic (Allopurinol; Colchicine; Gold; Indomethacin)

-Miscellaneous (Disulfiram; Interferon alfa; Lithium; Lovastatin; Phenytoin; Pyridoxine; Simvastatin; Thalidomide)

"Environmental and industrial toxins that cause polyneuropathy" (Table 2):

-Acrylamide; Allyl chloride; Arsenic; Carbon disulfide; Ethylene oxide; Hexacarbons; Lead; Mercury; Organophosphorus esters; Thallium; Trichloroethylene

- [FPN, 2019]: "There are many causes of peripheral neuropathy, including diabetes, chemo-induced neuropathy, hereditary disorders, inflammatory infections, auto-immune diseases, protein abnormalities, exposure to toxic chemicals (toxic neuropathy), poor nutrition, kidney failure, chronic alcoholism, and certain medications – especially those used to treat cancer and HIV/AIDS."
- [NINDS, 2019]: Causes of symptomatic acquired peripheral neuropathy include:

-Physical injury (trauma - e.g., automobile accidents, falls, sports, and medical procedures)

-Diabetes is the leading cause of polyneuropathy in the United States

-Vascular and blood problems that decrease oxygen supply to the peripheral nerves can lead to nerve tissue damage. Diabetes, smoking, and narrowing of the arteries from high blood pressure or atherosclerosis (fatty deposits on the inside of blood vessel walls) can lead to neuropathy

-Systemic (body-wide) autoimmune diseases can directly target nerves or cause problems when surrounding tissues compress or entrap nerves

-Hormonal imbalances can disturb normal metabolic processes, leading to swollen tissues that can press on peripheral nerves

-Kidney and liver disorders can lead to abnormally high amounts of toxic substances in the blood that can damage nerve tissue

-Nutritional or vitamin imbalances, alcoholism, and exposure to toxins can damage nerves and cause neuropathy. Vitamin B12 deficiency and excess vitamin B6 are the best known vitamin-related causes. Several medications have been shown to occasionally cause neuropathy

-Certain cancers and benign tumors cause neuropathy; tumors sometimes infiltrate or press on nerve fibers. Paraneoplastic syndromes can indirectly cause widespread nerve damage

-Chemotherapy drugs used to treat cancer cause polyneuropathy in an estimated 30 to 40 percent of users. Radiation therapy also can cause nerve damage, sometimes starting months or years later

-Infections can attack nerve tissues and cause neuropathy. Varicella-zoster virus, West Nile virus, cytomegalovirus, and herpes simplex target sensory fibers, causing attacks of sharp, lightning-like pain. Lyme disease can cause a range of neuropathic symptoms. The human immunodeficiency virus (HIV), which causes AIDS, can extensively damage the central and peripheral nervous systems. An estimated 30 percent of people who are HIV-positive develop peripheral neuropathy; 20 percent develop distal (away from the center of the body) neuropathic pain.

- [England and Asbury, 2004]:

#### Drugs

-Amiodarone; Chloramphenicol; Chloroquine; Colchicine; Dapsone; Disulfiram; Ethambutol; Hydralazine; Isoniazid; Metronidazole; Misonidazole; Nitrofurantoin; Nitrous oxide; Nucleosides (ddC, ddI, d4T); Phenytoin; Platinum (cisplatin); Pyridoxine (vitamin B-6); Suramin; Taxol; Thalidomide; Vincristine

#### Toxins

-Acrylamide monomer; Acrylamide polymer; Arsenic; Carbon disulphide; Diphtheria toxin; Ethylene oxide; Hexacarbons (n-hexane and methyl); Lead; Mercury (metallic and vapour); Organophosphates; Thallium; gold (aurothioglucose); perhexilene; allyl chloride; buckthorn berries

- [Saporta and Shy, 2015]:

Immune-Mediated Neuropathies: inflammatory (Guillain–Barré syndrome, CIDP and variants); vasculitic; paraproteinemic; paraneoplastic. Other neuropathies in which an inflammatory component can be identified include some infectious and metabolic neuropathies, including diabetic radiculoplexopathy

Infectious Neuropathies: Leprosy; HIV; Herpes Zoster; Lyme Disease; Diphtheria

Toxic Neuropathies:

-Antineoplastic agents (Vincristine, paclitaxel (Taxol®), cisplatin, suramin, thalidomide)

-Antimicrobials (Chloroquine, dapsone, isoniazid, metronidazole, nitrofurantoin)

-Cardiac medications (Amiodarone, perhexiline, hydralazine)

-Other medications (Colchicine, tacrolimus, gold salts, phenytoin, disulfiram (Antabuse®), pyridoxine (vitamin B6))

-Heavy metals (Lead, arsenic, mercury, thallium)

-Chemical compounds (Acrylamide, carbon disulfide, ethylene glycol, hexacarbons, organophosphate esters, vacor)

- [Karam and Dyck, 2015]

-Toxic Neuropathies Related to Drugs

--Chemotherapeutic Agents

---Vinca Alkaloids (vincristine, vinblastine, vinflunine, vinorelbine)

---Taxanes (paclitaxel, docetaxel, cabazitaxel)

---Platinum Derivates (cisplatin, carboplatin, oxaliplatin)

---Bortezomib

---Thalidomide

---Other Chemotherapy Agents Less Commonly Associated with Peripheral Neuropathy (Etoposide, teniposide, methotrexate, gemcitabine, fluorouracil, camptothecins, irinotecan, topotecan, cytosine

arabinoside)

--Antimicrobials

---Fluoroquinolone

---Linezolid

---Chloramphenicol

---Dapsone

- Ethambutol
- Metronidazole
- Nitrofurantoin
- Isoniazid
- Nucleoside Analogue Reverse Transcriptase Inhibitors (zalcitabine (ddC), didanosine (ddI), stavudine (d4T)).
- Chloroquine
- Cardiovascular Drugs
  - Amiodarone
  - Procainamide
  - Hydralazine
  - Perhexiline
  - Statins
- Other Drugs Associated with Peripheral Neuropathy
  - Disulfiram
  - Phenytoin
  - Pyridoxine
  - Gold
  - Colchicine
- Toxic Neuropathies Related to Heavy Metals
  - Thallium
  - Lead
  - Arsenic
  - Mercury

--Toxic Neuropathies Related to Industrial Agents

---Carbon Disulfide

---Dimethylamine Borane

---Ethylene Glycol, Diethylene Glycol, and Methanol

---n-Hexane

---Acrylamide

---Vacor

---Organophosphates

--Toxic Neuropathies Related to Biotoxins

---Ciguatera

---Tetrodotoxin

---Fruit Toxins: Buckthorn

---Pig Toxins

---Tick Paralysis

---Diphtheria Toxin

--Neuropathies Related to Alcohol

There is a thread of common PN risk factors running through the above (and many other) full spectrum surveys and meta-analyses. They can be classified into two types: associated and foundational. The associated risk factors include hypertension, diabetes, obesity, autoimmune diseases, kidney and liver disorders, cancers, tumors, and infectious diseases. The foundational risk factors are the many hundreds of foundational contributing factors that were identified in the present study.

Many of the PN articles in the core database focus on 1) the associated risk factors and 2) methods to modify them in a positive direction. Superficially, the number of associated risk factors is a relatively low number of "modifiable" risk factors (the authors of these review articles view them as "modifiable"). However, this "low number" is deceptive. Each of these associated risk factors could be classified as a chronic disease. As our previous LRDI studies on reversing chronic disease have shown [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018], as well as our comprehensive pervasive causes of disease study [Kostoff, 2015], there tend to be *many hundreds of foundational contributing factors for each of these diseases*. The

'treatments' proposed in most of the PN studies tend to be some combination of drugs/radiation/surgery for controlling the associated risk factors, sometimes accompanied by eliminating a few of the major foundational contributing factors.

This is in contrast to the approach of the present monograph, where the full spectrum of foundational factors that contribute directly to PN as shown in the core PN biomedical research articles are identified and proposed for elimination. While those foundational factors that contribute indirectly to PN through their contribution to the associated risk factors were not identified in the present study because of resource and time limitations, they could be identified and proposed for elimination in a well-resourced study. The factors that contribute **directly** to PN are identified through the *innovation* component of LRDI, and the factors that contribute **indirectly** to PN could be identified through the *discovery* component of LRDI.

## 5C2. PAD Contributing Factor Studies

As shown in Chapter 2, there are many published studies focusing on identifying one or a few contributing factors to PAD. There are many fewer studies identifying a very broad spectrum of disease contributing factors, as was done in the previous LRDI-based prevention and reversal of chronic disease studies [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018]. The focus in the present section is to summarize the results from credible broad spectrum or meta analysis studies identifying myriad PAD contributing factors.

Results from significant review studies of PAD contributing factors are as follows:

- [Campia, Gerhard-Herman, Piazza et al, 2019]

### Risk Factors for PAD

-cigarette smoking is associated with a 2- to 4-fold increased risk of PAD

-diabetes mellitus is associated with an approximately 2- to 4-fold increase in risk

-hypertension has reported odds ratios from 1.5 to 2.2

-association between dyslipidemia and peripheral artery disease appears to be multifaceted

--higher total cholesterol is associated with increased risk

--higher high-density lipoprotein (HDL) cholesterol is associated with decreased risk

- [Firnhaber and Powell, 2019]

Risk factors include:

hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, and smoking

- [Morley, Sharma, Horsch et al, 2018]

Risk factors include:

Smoking, diabetes, advancing age, black ethnicity, men are affected at a younger age than women, high fasting serum cholesterol level, hypertension, chronic kidney disease, high serum homocysteine.

- [Conte and Vale, 2018]

### **Risk Factors**

smoking, hypertension, hyperlipidaemia, diabetes mellitus, obesity, family history of vascular disease with smoking being the strongest.

Novel risk factors include increased inflammatory markers such as C-reactive protein, fibrinogen, and plasma homocysteine

### **Associated Conditions**

atrial fibrillation; congestive heart failure; obstructive sleep apnoea; chronic kidney disease.

- [Ruiz-Canela and Martínez-González, 2014]

Most important risk factors: smoking, diabetes, hypertension, and high low-density lipoprotein-cholesterol levels.

Metabolic syndrome, central and abdominal obesity, and poor sleep quality are also risk factors.

Novel risk factors or biomarkers are low serum 25-hydroxyvitamin D levels, hyperhomocysteinemia, low levels of serum bilirubin, total adiponectin, and lipoprotein-associated phospholipase. Several markers of inflammation, such as serum C-reactive protein and interleukin-6, have been found to be associated with symptomatic PAD independently of traditional cardiovascular risk factors. A graded direct dose-response relationship between inflammatory markers (C-reactive protein, fibrinogen and leukocyte count) and PAD has been found.

### **Environmental Risk Factors**

polycyclic aromatic hydrocarbons, Bisphenol A, organochlorine pesticides.

- [Abdulhannan, Russell, and Homer-Vanniasinkam, 2012]

PAD results from any disease causing stenosis or occlusion of the lower limb arteries, with atherosclerosis disease being the most common aetiology.

### **Risk factors**



race; male gender; increasing age; smoking; diabetes mellitus; hypertension; dyslipidaemia; hypercoagulable and hyperviscous states; hyperhomocysteinaemia; systemic inflammatory conditions and chronic renal insufficiency.

**Non-atherosclerotic causes of PAD:**

- Peripheral emboli
- Aneurysm thrombosis or thromboembolism (aortic, popliteal)
- Arteritis
  - Takayasu's disease
  - Thromboangiitis obliterans (Buerger's disease)
  - Giant cell arteritis
  - Polyarteritis nodosa
- Fibromuscular dysplasia
- Prior trauma or irradiation injury
- Aortic coarctation
- Endofibrosis of the external iliac artery (iliac artery syndrome in cyclists)
- Primary vascular tumours
- Pseudoxanthoma elasticum
- Young patients
  - Adventitial cyst of the popliteal artery
  - Popliteal entrapment
  - Persistent sciatic artery
    - [Hills, Shalhoub, Shepherd et al, 2009]

**Risk factors:**Non-modifiable:

- Increasing age
- Male gender

- Race
- Type 1 diabetes mellitus
- Positive family history
- Genotype
- Chronic renal insufficiency

Modifiable:

- Smoking
- Dyslipidaemia
- Hyperhomocysteinaemia
- Metabolic syndrome, type 2 diabetes mellitus or impaired glucose tolerance
- Hypertension
- Sedentary lifestyle
- Poor diet

There is a thread of common risk factors running through the above (and many other) full spectrum surveys and meta-analyses. They can be classified into two types: associated and foundational. The associated risk factors include hypertension, diabetes, obesity, dyslipidemia, renal insufficiency, systemic inflammation, hyperhomocysteinemia. The foundational risk factors identified in the studies referenced above include smoking, poor diet, poor sleep quality, but can be expanded to the many hundreds of foundational contributing factors that were identified in the present study.

Many of the PAD articles in the core database focus on the associated risk factors, and methods to modify them in a positive direction. Superficially, the number of associated risk factors is a relatively low number of "modifiable" risk factors (the authors of these review articles view them as "modifiable"). However, this "low number" is deceptive. Each of these associated risk factors could be classified as a chronic disease. As our previous LRDI studies on reversing chronic disease have shown [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018], as well as our comprehensive pervasive causes of disease study [Kostoff, 2015], there tend to be many hundreds of foundational contributing factors for each of these diseases. The 'treatments' proposed in most of the PAD studies tend to be some combination of drugs, surgery, diet, and exercise for controlling the associated risk factors, sometimes accompanied by eliminating a few of the major foundational contributing factors.

This is in contrast to the approach of the present monograph, where the full spectrum of foundational factors that contribute directly to PAD as shown in the core PAD biomedical research articles are identified and proposed for elimination. While those foundational factors that contribute indirectly to PAD through their contribution to the associated risk factors were not identified in the present study because of resource and time limitations, they could be identified and proposed for elimination in a well-resourced study. The factors that contribute **directly** to PAD are identified through the *innovation* component of LRDI, and the factors that contribute **indirectly** to PAD could be identified through the *discovery* component of LRDI.

### 5C3. PN Treatment Studies

As shown in Chapter 2, there are many published studies focusing on identifying one or a few treatments for PN. There are many fewer studies identifying a very broad spectrum of treatments, as was done in the previous LRDI-based prevention and reversal of chronic disease studies [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018]. The focus in the present section is to summarize the results from credible broad spectrum or meta analysis studies identifying myriad PN treatments.

Results from significant review studies of PN treatments are as follows:

- [Shields, 2010]

"In disorders attributed to underlying medical conditions, management is focused on the medical disorder. For example, optimizing glycemic control in diabetic polyneuropathy often stabilizes or improves the polyneuropathy."

"In patients with idiopathic immune-mediated polyneuropathies, specific immune-modulating therapies are often recommended (e.g., intravenous gamma globulin (IVIg), plasmapheresis)."

"Treatment of CIDP may begin with corticosteroid therapy. However, chronic IVIg or plasmapheresis, or both, are usually effective and obviate the need for long-term steroid therapy. Alternative therapies including azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate, and rituximab have also been used in patients who have not responded to initial standard therapies."

"Toxic polyneuropathies are managed by discontinuing the offending drug or removing the industrial toxin from the patient's environment."

Supportive therapies include use of various physical therapy and occupational therapy modalities including bracing, aids to ambulation, and ankle-foot orthoses.

Pain management centers on drugs, such as tricyclic antidepressants and a variety of antiepileptic drugs and membrane stabilizers. Specific drugs include:

-Antidepressants (Amitriptyline; Nortriptyline; Imipramine; Desipramine; Duloxetine; Venlafaxine)

-Antiepileptics (Gabapentin; Pregabalin; Carbamazepine; Oxycarbazepine; Lamotrigine; Topiramate)

-Miscellaneous (Mexiletine; Tramadol; Capsaicin)

All these drugs have side effects, listed in [Shields, 2010].

- [NINDS, 2019]

### **Addressing causes**

healthy lifestyle habits (maintaining optimal weight, avoiding toxic exposures, eating a balanced diet, correcting vitamin deficiencies, stopping smoking, appropriate regular exercise, maintaining strict control of blood glucose levels [diabetics]).

Controlling inflammatory and autoimmune conditions

immunosuppressive drugs (prednisone, cyclosporine, or azathioprine).

Plasmapheresis

Other drugs (rituximab; immunoglobulins, and antibodies).

### **Addressing symptoms**

Motor (hand or foot braces; orthopedic shoes; splints; tendon transfers; bone fusions).

Autonomic (standing up slowly and taking medications to improve blood pressure swings; acupuncture, massage, herbal medications, cognitive behavioral or other psychotherapy).

Sensory (medication; behavioral strategies).

Medications

-Antidepressants (Nortriptyline; newer serotonin-norepinephrine reuptake inhibitors such as duloxetine hydrochloride).

-Antiepileptics (gabapentin; pregabalin; topiramate; lamotrigine; carbamazepine; oxycarbazepine).

-Local anesthetics (Lidocaine patches or creams; capsaicin, bupivacaine).

-Narcotics (tapentadol)

Surgery (protruding disks; neurosurgical decompression).

Transcutaneous electrical nerve stimulation (TENS).

- [England and Asbury, 2004]

"Medical causes such as diabetes mellitus, renal insufficiency, hypothyroidism, vitamin B-12 deficiency, or systemic vasculitis need specific and active treatment. Immunemediated neuropathies such as Guillain-Barré syndrome or CIDP respond to specific treatments."

Medications for pain

- antiepileptic drugs (gabapentin, carbamazepine),
- antidepressants (amitriptyline, nortriptyline, and venlafaxine),
- other (tramadol, lidocaine, opioids)

Preventive and palliative management (weight reduction, assiduous foot care, good shoes, ankle-foot orthoses, walking aids, wrist splints).

- [Watson and Dyck, 2015]

### **Neuropathic pain management - combination approach**

#### Tier 1

- Anticonvulsants (Gabapentin, Pregabalin)
- Antidepressants (Amitriptyline, Nortriptyline, Duloxetine)
- Supplements (a-Lipoic acid, Acetyl-Lcarnitine)
- Topicals (Lidocaine, Capsaicin)

#### Tier 2

- Antidepressants (Venlafaxine)
- Analgesics (Tramadol)

#### Tier 3

- Analgesics (Tapentadol)
- Opioids

The approaches include:

- addressing the underlying diseases (e.g., diabetes, hypertension, etc) if known, usually with drugs;
- maintaining healthy lifestyles (diet, exercise, avoiding toxic substances, etc)
- palliative supportive measures (braces, splints, orthoses, etc)
- pain management (typically drug-based, although supplemented by complementary therapies in some cases)

This is in contrast to the approach of the present monograph, where two categories of treatments are used:

- identifying and eliminating the full spectrum of foundational causes that 1) contribute directly to PN as shown in the core PN biomedical research articles and 2) contribute indirectly to PN through their contribution to the associated risk factors (e.g., diabetes, hypertension, inflammation, etc), and
- implementing treatments that 1) focus directly on PN as shown in the core PN biomedical research articles, and 2) focus indirectly on PN through their actions on the associated risk factors.

The contributing factors and treatments that operate directly on PN are identified through the *innovation* component of LRDI, and the contributing factors and treatments that operate indirectly on PN are identified through the *discovery* component of LRDI.

#### 5C4. PAD Treatment Studies

As shown in Chapter 2, there are many published studies focusing on identifying one or a few treatments for PAD. There are many fewer studies identifying a very broad spectrum of treatments, as was done in the previous LRDI-based prevention and reversal of chronic disease studies [Kostoff and Patel, 2015; Kostoff, Porter, and Buchtel, 2018]. The focus in the present section is to summarize the results from credible broad spectrum or meta analysis studies identifying myriad PAD treatments.

Results from significant review studies of PAD treatments are as follows:

- [Gerhard-Herman, Gornik, Barrett, 2017]

Antiplatelet, Statin, Antihypertensive Agents, and Oral Anticoagulation

Smoking Cessation

Glycemic Control

Cilostazol, Pentoxifylline, and Chelation Therapy

Homocysteine Lowering

Influenza Vaccination

Structured exercise therapy

Minimizing tissue loss in patients with PAD

-Prevention of wounds through patient education, foot examination, and prompt recognition of foot infection is important to minimize tissue loss among patients with PAD.

Revascularization for claudication

-Endovascular Revascularization for Claudication

-Surgical Revascularization for Claudication

management of CLI:

-Revascularization for CLI

-Surgical Revascularization for CLI

-Wound Healing Therapies for CLI

- [Campia, Gerhard-Herman, Piazza, 2019]

**The goals of medical therapy for PAD include:**

-improvement of limb symptoms,

-exercise performance,

-quality of life,

-reduction of the risk of adverse cardiovascular events and limb events

**Recommended approach of medical therapy for PAD:**

Improvement of symptoms and quality of life

-Supervised exercise program

-Cilostazol

-Statins

-Revascularization

Reduction of risk of cardiovascular events

- Lifestyle modification
- Tobacco cessation
- Statins
- PCSK9 inhibitor (evolocumab)
- ACE-inhibitors/ARBs
- Aspirin or a thienopyridine
- PAR-1 antagonist (vorapaxar)
- Aspirin + low-dose rivaroxaban

Reduction of risk of limb events

- Statins
- PCSK9 inhibitor (evolocumab)
- PAR-1 antagonist (vorapaxar)
- Aspirin + low-dose rivaroxaban
  - [Finhaber and Powell, 2019]

**Lifestyle modification**

- Smoking cessation
- Supervised exercise therapy

**Drug therapy**

- Antiplatelet therapy
  - Aspirin
  - Clopidogrel
  - Ticagrelor
- Anticoagulant therapy
  - Rivaroxaban



--Aspirin

-Statin therapy

--Atorvastatin

-Antihypertensive therapy

--ACE inhibitors/ARBs

---Ramipril

---Telmisartan

-Medications to improve circulatory flow

--Cilostazol

### **Surgery**

-Revascularization

--bypass grafting

--endarterectomy

--angioplasty with stenting

- [Morley, Sharma, Horsch et al, 2018]

### **Primary Care**

#### Risk factor modification

Smoking cessation therapy

HbA1c control

Blood pressure control

Clopidogrel (or aspirin)

Atorvastatin

#### Symptom control

Supervised exercise therapy

Vasoactive drugs

-Naftidrofuryl oxalate

-Cilostazol

## **Secondary Care**

### Revascularization

-Stent

-Angioplasty

-Open surgery

### Non-invasive interventions

-Prostanoid infusions

- [Conte and Vale, 2018]

"The management of PAD focuses on two main goals: improving quality of life by reducing symptoms and reducing vascular morbidity and mortality."

### **Risk factor modification**

-smoking cessation

-pressure management

-lipid control

-weight loss

-exercise

-dietary interventions

### **Pharmacological therapies**

-lipid control with a statin

-blood pressure lowering with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy

--ramipril

-blood glucose control

-antiplatelet therapy

- aspirin
- clopidogrel
- symptom reduction
- phosphodiesterase-inhibitors
- cilostazol
- pentoxifylline
- prostaglandin E1

### **Interventional therapies**

- pharmacological thrombolysis
- percutaneous transluminal angioplasty (PTA) with or without stent insertion
- mechanical thrombectomy
- surgical bypass procedures.

These comprehensive PAD review articles show that the mainline prevention and treatment recommendations are relatively few. The recommendations include Lifestyle modifications (smoking cessation, improved diet, supervised exercise), Pharmacotherapy (Antiplatelet, Anticoagulant, Antihypertensive, Glycemic control, Lipid control), and Surgery (Endovascular, Open surgery).

This is in contrast to the approach of the present monograph, where two categories of treatments are used:

- identifying and *eliminating* the full spectrum of foundational causes that 1) contribute directly to PAD as shown in the core PAD biomedical research articles and 2) contribute indirectly to PAD through their contribution to the associated risk factors (e.g., diabetes, hypertension, inflammation, etc), and
- implementing treatments that 1) focus directly on PAD as shown in the core PAD biomedical research articles, and 2) focus indirectly on PAD through their actions on the associated risk factors.

The contributing factors and treatments that operate directly on PAD are identified through the *innovation* component of LRDI. The treatments that operate indirectly on PAD are identified through the *discovery* component of LRDI, and the contributing factors that operate

indirectly on PAD could be readily identified through the *discovery* component of LRDI in a well-resourced study.

#### 5D. Combining PN and PAD

Most of the PN or PAD contributing factor or treatment references examined addressed each disease/condition as a separate entity. However, since poor peripheral blood circulation characteristic of many forms of PAD would restrict adequate transport of nutrients (especially oxygen) to the peripheral neural system, potentially causing severe damage and destruction to the peripheral neural system, an argument could be made that PN and PAD should be treated as a combined entity. What is the evidence in the biomedical literature for this argument?

- "pathological alterations in chronic ischaemic neuropathy may be due to the combined effects of acute ischaemia/reperfusion and chronic hypoxia." [Nukada, vanRij, Packer et al, 1996];
- "These results support the presence of a mild sensory axonopathy in subjects with peripheral arterial disease." [Ugalde, Wineinger, Kappagoda et al, 1998];
- "There is a predominantly sensory neuropathy associated with chronic and critical limb ischemia. Neuropathic symptoms are often obscured by the effects of ischemia on other tissues. The neurophysiologic changes suggest that the underlying pathophysiology is a distal axonopathy affecting nerve fibers of all sizes. Measures of blood flow in the leg correlate with neurologic symptom scores, examination scores, and electrophysiologic testing." [Weinberg DH, Simovic D, Isner et al, 2001];
- "Patients with peripheral vascular disease are susceptible to neuropathy from chronic hypoxia." [Toursarkissian, Connaughton, D'Ayala et al, 2002];
- "chronic peripheral arterial occlusive disease causes axonal degeneration, resulting in axonal polyneuropathy." [Weber and Ziegler, 2002];
- "ischemia-related impairment in lower extremity nerve function may contribute to functional impairment and decline in people with PAD." [McDermott, 2015];
- "Subgroup analysis points towards a PAD-associated peripheral neuropathy independent of diabetes." [Lang, Schober, Rolke et al, 2006];
- "Incidence of CI-DSN [Chronic Idiopathic Distal Symmetric Neuropathy] is higher in individuals carrying vascular conditions. In men, the presence at baseline of peripheral artery disease is associated with a threefold increase in the risk of developing CI-DSN." [Baldereschi, Inzitari, Di Carlo et al, 2013];
- "Chronic ischemia in patients with peripheral arterial disease (PAD) represents a common medical problem. Neuropathic changes and pain caused by chronic ischemia are often found in the lower extremities of these patients. Pain in patients with chronic critical limb ischemia fulfill the criteria of neuropathic pain." [Lang, 2015];

The message from these studies, and many other similar studies not referenced, is clear. Restricted circulation characteristic of PAD deprives the peripheral nerves (and other peripheral micro and macro-structures) of adequate nutrients for optimal functioning and survival, especially, but not limited to, oxygen. This deprivation of adequate nutrient supplies to critical organs, cells, and other biological structures, and the resulting pathology, is not limited to PN. In essentially every previous LRDI study I have performed examining myriad chronic diseases, poor blood circulation and the attendant nutrient deprivation to critical structures, has been a (typically under-emphasized) causal factor in the disease development and progression. Intake of the highest quality nutrients, by whatever route, will have limited effect on biological structure health if the logistics transport system (veins and arteries) is 1) not able to deliver these nutrients to the appropriate structures in a timely manner and is 2) not able to dispose of the metabolic waste products in a timely manner as well.

#### 5E. Limitations of High-Technology Mainstream Medical Approach

While lifestyle changes form part of the PN/PAD treatment protocol, including elimination of well-known causative factors, for the most part the PN/PAD treatment protocols are centered on pharmacotherapy and surgery. These typically high-technology treatments focus on removing/suppressing PN/PAD pathological symptoms, rather than removing the causes of these symptoms. These treatments (in the absence of comprehensive cause removal) have minimal success in reversing PN/PAD because they violate the systemic medical principle that forms the basis of the prevention and reversal methodology in this monograph.

The strategy of identifying symptoms as pathological mechanisms that must be suppressed or removed for healing is a mainstay of Western Medicine. However, another perspective is to view these symptoms in a positive light, as having two basic functions: serve as a warning signal that dysfunction exists and actions need to be taken to remove the cause of this dysfunction, and serve as a protective mechanism.

There are many examples in the biomedical literature supporting the concept of disease symptoms as warning signals and protective mechanisms, as shown in the following box:

- "the down-regulation of energy metabolism in AD is a protective response of the neurons to the reduced level of nutrient and oxygen supply in the microenvironment" [Sun, Feng, Liang et al, 2012];
- "Neurofibrillary tangle formation as a protective response to oxidative stress in Alzheimer's Disease" [Nunomura, Takeda, Moreira et al, 2009];
- "Autophagy is a protective response to the oxidative damage to endplate chondrocytes in intervertebral disc" [Chen, Lv, Li et al, 2017];
- "loss of appetite in the acute phase of illness is indeed an adaptive, protective response that improves cell recycling (autophagy) and detoxification" [Schutz, Bally, Stanga et al, 2014];
- "Cataract is a self-defence reaction to protect the retina from oxidative damage" [Wegner and Khoramnia, 2011].

Along these same lines, Bredesen states in his 2017 book [Bredesen, 2017]: "Alzheimer's disease is actually a protective response to, specifically, three different processes: inflammation, suboptimal levels of nutrients and other synapse-supporting molecules, and toxic exposures." Other AD researchers have drawn similar conclusions. If Bredesen's view that the AD symptoms serve as a protective response against more serious damage is correct, then the mainline drug-based AD treatment approach of removing these pathologies/symptoms without removing their foundational causes comprehensively in parallel

- 1) effectively removes the protective shield reflected by these pathologies/symptoms and
- 2) exacerbates the progression of AD!

These conclusions are applicable to most, if not all, chronic diseases.

## 5F. Text Mining to Identify Causes and Treatments for Disease

### 5F1. Overview

The two main literature-based approaches for identifying existing and potential contributing factors to, or treatments for, PN/PAD (or any other disease) are "direct" and "indirect": "direct" can be viewed as analogous to Innovation, and "indirect" can be viewed as analogous to Discovery [Kostoff and Patel, 2015]. The direct approach identifies e.g. existing contributing factors (or treatments) that appear in the same article as PAD (e.g., *smoking* increases the risk for *PAD*) and link directly to PAD. The indirect approach identifies e.g. potential contributing factors (or treatments) to some disease/symptom other than PAD, then links this disease/symptom to PAD (e.g., *high-salt diet* increases the risk for *hypertension*, *hypertension* is strongly linked to *PAD*).

In the present PN/PAD monograph, only a handful of potential treatments for PN/PAD was presented (Discovery). Based on the retrieval of potential Discovery candidates by the Discovery query, voluminous discoveries of potential PN/PAD treatments (and contributing factors as well) are possible.

### 5F2. Literature Survey

The published text mining approach related most closely to that used in the present monograph can be found in our 2018 AD monograph [Kostoff, Porter, Buchtel, 2018] and [Kostoff, 2015]. In [Kostoff, 2015], three approaches were used to develop queries for identifying foundational causes for all diseases. The first approach used MeSH Qualifiers relevant to identifying foundational causes of disease (e.g., adverse effects, toxicity, pathogenicity, poisoning) to retrieve records from Pubmed for analysis. The second approach used generic MeSH terms related relatively unambiguously to foundational causes (e.g., "Drug-Related Side Effects AND Adverse Reactions"; Abnormalities, Drug Induced; Air Pollutants, Occupational; Amphetamine Related Disorders; Carcinogens; Chemical Warfare Agents;

Chemically-Induced Disorders, etc) to retrieve the records from Pubmed for analysis. The third approach used text terms (applied to the title field) to retrieve the records from Pubmed for analysis. This title query consisted of two parts: standalone terms (e.g., cardiotoxic\*, genotoxic\*, mutagenic, adverse-outcome, adverse-metabolic-effect\*, etc) and terms that are intersected with diseases (e.g., (expos\* OR induc\*) AND (cancer\* OR dermatitis)).

Other text mining approaches have been developed for generating literature-based discovery. They have been used mainly for identifying potential new treatments for disease, but the approaches used for identification of new treatments could be easily modified for identification of potential new foundational causes as well (e.g., [Kostoff, Porter, Buchtel, 2018]). In the past decade, a number of these semantic relation-based approaches have been promulgated:

- Cohen et al [Cohen, Widdows, Schvaneveldt et al, 2012] use semantic indexing to identify empirically sequences of relationships known as 'discovery patterns', such as "drug x INHIBITS substance y, substance y CAUSES disease z" that link pharmaceutical substances to diseases they are known to treat. These sequences are derived from semantic predications extracted from the biomedical literature, and subsequently utilized to direct the search for known treatments for a held out set of diseases.
- Hu et al [Hu, Zhang, Yoo et al, 2010] present a biomedical semantic-based association rule system that significantly reduces spurious/useless/biologically irrelevant connections through semantic filtering.
- Miller et al [Miller, Rindfleisch, Fiszman et al, 2012] advance the hypothesis of "cortisol as part of a mechanistic link elucidating the observed correlation between decreased testosterone in aging men and diminished sleep quality".
- Hristovski et al [Hristovski, Rindfleisch, Peterlin, 2013] emphasize semantic relations approaches to literature-based discovery.
- Sang et al [Sang, Yang, Li et al, 2015] develop a supervised learning based approach to generate hypotheses from biomedical literature, splitting the traditional processing of hypothesis generation with classic ABC model into AB model and BC model.
- Cameron et al [Cameron, Kavuluru, Rindfleisch et al, 2015] implement a context-driven, automatic subgraph creation method that captures multifaceted complex associations between biomedical concepts; given a pair of concepts, the method automatically generates a ranked list of subgraphs, which provide informative and potentially unknown associations between such concepts.
- Kastrin et al [Kastrin, Rindfleisch, Hristovski, 2016] mimic the process of literature-based discovery as a classification problem on a graph of MeSH terms, using unsupervised and supervised link prediction methods for predicting previously unknown connections between biomedical concepts.

Further variants on literature-based discovery can be found in the following articles: [Ahmed, 2016; Ahmed and Alhashmi, 2014, 2015; Cameron, Kavuluru, Rindflesch et al, 2015; Cohen, Widdows, Stephan et al, 2014; Dai, Li, Yang et al, 2019; Dong, Liu, Zhu et al, 2014; Gabetta, Larizza, Bellazzi, 2013; Han, Wang, Subhadarshini et al, 2012; Henry and McInnes, 2017; Hristovski, Kastrin, Dinevski et al, 2016; Hristovski, Kastrin, Dinevski et al, 2015; Hur, Sullivan, Schuyler et al, 2010; Ittipanuvat, Fujita, Kajikawa et al, 2012; Ittipanuvat, Fujita, Sakata et al, 2014; Kastrin, Rindflesch, Hristovski, 2014; Kim and Song, 2019; Korhonen, Guo, Baker et al, 2014; Liu, Fu, Jiang, 2016; Maver, Hristovski, Rindflesch et al, 2013; Miller, Rindflesch, Strohl et al, 2012; Ozgur, Xiang, Radev et al, 2010; Preiss and Stevenson, 2016; Preiss and Stevenson, 2017; Preiss, Stevenson, Gaizauskas, 2015; Pyysalo, Baker, Ali et al, 2019; Rastegar-Mojarad, Elayavilli, Li et al, 2015; Rastegar-Mojarad, Elayavilli, Wang et al, 2016; Ruch, 2010; Sang, Yang, Liu et al, 2018; Sebastian, 2014; Sebastian, Siew, Orimaye, 2017a; Sebastian, Siew, Orimaye, 2017b; Smalheiser, 2012; Smalheiser, 2017; Srinivasan, Blackburn, Mohamed et al, 2015; Vos, Aarts, van Mulligen et al, 2014; Workman, Fiszman, Rindflesch et al, 2014; Yamazaki, Onodera, Nakayama, 2013; Yang, Ju, Wong et al, 2017].

These approaches achieve neither the breadth nor the volume of Innovation and Discovery found in [Kostoff and Patel, 2015; Kostoff, 2015; Kostoff, Porter, and Buchtel, 2018], and the present study.

Other information technology approaches have been used to identify potential risk factors/contributing factors for specific diseases. They differ from the Discovery approaches above because of their focus on identifying the direct causes of disease as defined above. Examples of these information technology approaches include:

- training neural networks to identify risk factors for specific diseases/conditions [Wang, 2002; Amin, Agarwal, Beg, 2013; Ushida, Kato, Niwa et al; 2012; Ismaeel and Mikhail, 2016; Esfahani and Ghazanfari, 2017],
- machine learning-based methods to quantify risk factors for diseases/conditions [Barisic, Wilhelm, Stambuk et al, 2002; Du and Guo, 2005; Liao X, Kerr D, Morales et al, 2019; Berkowitz, Basu, Venkataramani et al, 2019],
- data based clustering and rule based prediction to identify risk factors for diseases/conditions [Rahaman and Hossain, 2013; Pfaff, Weller, Woetzel et al, 2004; Cole, Frankovich, Iyer et al, 2013; Gaskin, Pershing, Cole et al, 2016],
- Bayesian networks to identify risk factors [Rodin, Mosley, Clark et al, 2005; Koskela, Ryyananen, Soini, 2010; Zhao and Weng, 2011; Aussem, de Moraes, Corbex, 2012; Bertke, Meyers, Wurzelbacher et al, 2012; Ben-Assuli and Leshno, 2016; Li, Pang, Li et al, 2019]
- association rules to identify risk factors [Karaolis, Moutiris, Papaconstantinou et al, 2009; Ordonez and Zhao, 2011; Ramezankhani, Pournik, Shahrabi et al, 2015; Li, Zhang, Kang et al, 2017]



- decision trees to identify risk factors [Samanta, Bird, Kuijpers et al, 2009; Karaolis, Moutiris, Hadjipanayi et al, 2010; Marschollek, Goevercin, Rust et al, 2012; Kim, Kim, Won et al, 2012; Meng, Huang, Rao et al, 2013; Gonoodi, Tayefi, Saberi-Karimian et al, 2019; Shao, Chen, Li et al, 2019],
- text/data mining approaches [Friedman, Liu, Shagina, 2003; Anno, 2004; Tanaka, Aronson, Weeber, 2002; Turner, Arsevska, Brant et al, 2018; Pereira, Ito, Fonseca LM et al, 2017], and
- information technology approaches for identifying adverse events resulting from drugs and surgery [Garcia and Guzman, 2008; Golder, Loke, McIntosh, 2008; Golder and Loke, 2009; Tanon, Champagne, Contandriopoulos et al, 2010; Egan, MacLean, Sweeting et al, 2012; Golder and Loke, 2012; Golder, Loke, Zorzela, 2013; Sampson, Zhang, Morrison et al, 2006; Harbour, Fraser, Lefebvre et al, 2014; Waffenschmidt, Janzen, Hausner et al, 2013; Damarell, Tieman, Sladek et al, 2011; McKibbon, Wilczynski, Haynes, 2009; Haase, Follmann, Skipka et al, 2007; Golder, Wright, Loke, 2018].

## 5G. Definitions

### 5G1. PN/PAD Foundational Cause definition

The myriad causes of PN/PAD reported in this monograph are termed "foundational". A PN/PAD foundational cause is a tangible stimulus or behavior that can contribute to a PN/PAD symptom or a PN/PAD biomarker/characteristic change that reflects PN/PAD progression. Thus, selected drugs, chemicals, radiations, etc are tangible items and are viewed as 'foundational'. Diseases/symptoms such as diabetes and hypertension, while associated with or related to PN/PAD, are not viewed as 'foundational', since they are not tangible, but rather are driven by tangible contributing factors (high salt diet, high fat diet, high refined carbohydrate diet, etc). The expression '*contributing factor*' is used interchangeably with '*cause*' throughout this monograph.

A symptom(s)/disease(s) in a person exposed to toxic stimuli is the result of imbalance between the strength of the toxic stimuli and the person's innate ability to neutralize the effects of the toxic stimuli, including the genetic factors that were not included in this monograph. The two are not independent; the toxic stimuli can affect the capabilities of the defensive system to neutralize incoming toxic stimuli. Thus, the full spectrum of incoming toxic stimuli can be viewed as a "signature" of individual toxic stimuli, with different weightings assigned to each toxic stimulus, and the defense can also be viewed as a "signature", with different weightings assigned to the health of the body's defensive mechanisms. Whether a symptom/disease will materialize as a result of one or more incoming toxic stimuli depends on whether the defensive "signature" is able to neutralize the "signature" of the incoming toxic stimuli.

Thus, not every person who eats a high refined carbohydrate diet or undergoes chemotherapy for cancer develops PN, but some (more than expected randomly) do. There were a number of cases in the literature where relatively few people were reported to have adverse

reactions to a given toxic stimulus. Identifying the offensive-defensive "signature" relationships that allow toxic stimuli to translate into symptoms (within the context of understanding genetic polymorphisms and the resulting variations in biological pathways) will play a significant role in explaining why some people develop a disease and others do not when exposed to the same agent(s). Understanding the complex web of gene-environment interactions is the central challenge of modern medicine; identification of myriad individual toxic stimuli and defensive system deficiencies is the first step in this long journey.

For purposes of this monograph, a toxic stimulus is termed a (foundational) cause if the research author stated/implied/inferred the toxic stimulus was a cause and the information presented supported the research author's conclusion. However, this toxic stimulus was in all probability one component of a more complex offensive-defensive "signature" imbalance that resulted in the symptom(s) of interest.

### 5G2. PN/PAD Treatment definition

PN/PAD treatments are actions taken to modify PN/PAD characteristics/ symptoms/ biomarkers in desired directions. The most widely used PN/PAD treatments are myriad drugs for attenuating undesired symptoms and/or modifying undesired biomarker/characteristics changes. However, removal of PN/PAD contributing factors could be viewed as PN/PAD 'treatments' (e.g., cessation of smoking, cessation of excessive alcohol intake, cessation of high-fat diet, cessation of exposure to harmful chemicals, etc), since this action would modify PN/PAD characteristics in desired directions. Also, substitution of positive practices for PN/PAD contributing factors removed could be considered as PN/PAD 'treatments' (e.g., drinking more water as a substitute for high-fructose beverages, moving from high air pollution environments to low air pollution environments, replacing high-temperature cooking with low-temperature cooking, etc), again, since they modify PN/PAD characteristics in desired directions.

### 5G3. PN/PAD Characteristics definition

A PN/PAD characteristic is a measurable quantity associated with a test subject/patient whose changes in value may reflect changes in the progression or reversal of PN/PAD. The PN/PAD characteristics can be divided into three main categories as follows:

- Symptoms (e.g., pain, foot ulcer, muscle weakness, fatigue, numbness, poor balance, unsteady gait, etc);
- Biomarker/metabolic function (e.g., oxidative stress, neuroinflammation, axonal degeneration, etc); and
- Biomarker/metabolic metrics (e.g., C reactive protein, HDL cholesterol, blood glucose level, etc).

Each of the main categories, especially Symptoms, could be divided into sub-categories, if greater clarity is desired.

#### 5G4. Linking Term definition

Linking terms are words/phrases strongly associated with specific text concepts of interest. Linking terms tend to be more generic than the specific terms that are the main targets of text searching. There are relatively few linking terms compared to the large numbers of characteristics, causes, and treatments. Searching text for the known linking terms will allow the desired concepts of interest to be identified.

For the causes, treatments, and characteristics of interest in the PN/PAD study, linking terms are verbs strongly associated with PN/PAD causes, treatments, and characteristics. For PN/PAD treatments and characteristics in particular, some of the more useful linking terms identified included the following: treat\*, therap\*, prevent\*, protect\*, improv\*, reduc\*, attenuat\*, ameliorat\*, enhanc\*, revers\*, promot\*, alleviat\*, inhibit\*, remov\*, suppress\*, mitigat\*, restor\*, lower\*, preserv\*, regenerat\*, rescu\*, slow\*, neuroprotect\*, neurorestorati\*, decreas\*, increas\*, eliminat\*.

Not all these terms are of equal value, or efficiency in identifying the desired text concepts. Some of these terms had higher efficiencies of identifying the PN/PAD treatment consequences of interest (PN/PAD characteristics) than others. Terms like prevent\*, protect\*, improv\*, restor\*, alleviat\*, ameliorat\*, mitigat\*, etc, almost always gave the desired PN/PAD characteristics and the direction in which they changed as a result of PN/PAD treatment. Terms like decreas\*, increas\*, reduc\*, 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).

Linking terms for identifying PN/PAD causes include: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; -exposed [at end]; -related; -associated; -infected; abuse\*; toxicity; risk factors; deficiency; neurotoxicity; risk factor; causes; workers; toxic; occupational; intoxication; toxicities; neurotoxic; excessive; deficiencies; contributing factors; worker; contributing factor; occupation; overload.

#### 5G5. Text Mining definition

Text mining is the extraction of useful information from large volumes of text.

### [References - Chapter 5](#)

## Chapter 6

### METHODOLOGY

#### 6A. Overview and Strategy

##### 6A1. Overview

There are two main goals of the present study:

- identify the full spectrum of contributing factors, treatments, and biomarkers/symptoms (characteristics) for PN/PAD
- develop an individually-tailored treatment protocol that could be used for prevention and reversal of PN/PAD.

The operational objectives that contribute to these goals include:

- comprehensive identification of existing contributing factors to PN/PAD
- comprehensive identification of existing treatments available for PN/PAD
- comprehensive identification/discovery of potential treatments for PN/PAD
- comprehensive identification of specific existing PN/PAD characteristics impacted by each of these existing and potential contributing factors and treatments
- integration of the above PN/PAD contributing factors and treatments and their impacts to generate a protocol that will prevent and reverse PN/PAD, in selected cases.

Comprehensive identification of *potential* contributing factors to PN/PAD and comprehensive identification of specific *potential* PN/PAD characteristics impacted by each of these existing and potential contributing factors and treatments was not done in this study because of resource and time limitations.

Assume the existing and potential PN/PAD treatments can be related to their effects on the PN/PAD characteristics identified above, existing PN/PAD causes can be related to their effects on the same PN/PAD characteristics, and these PN/PAD characteristics are amenable to objective and subjective quantification. Then, a treatment protocol can be generated that identifies

- the amount that measured PN/PAD characteristics deviate from the norm for each PN/PAD patient
- the causes that have to be eliminated to restore the PN/PAD characteristic measurements back to the norm
- the treatments required to restore the PN/PAD characteristics back to the norm. This individually tailored protocol is discussed in more detail in Chapter 3.

The methodology employed in the present monograph identifies existing PN/PAD contributing factors, and existing and potential PN/PAD treatments that impact one or more of the myriad characteristics associated with PN/PAD, and existing PN/PAD characteristics whose values can move in predictable directions when stimulated by PN/PAD contributing factors and treatments.

#### 6A2. Strategy

**Table 6-1 - Approaches Used to Identify Causes/Treatments/Characteristics  
(Biomarkers/Symptoms)**

<b>APPROACH</b>			
<b>VISUAL INSPECTION ABSTRACT</b>	X	X	X
<b>LINKING TERMS TITLE</b>	X	X	X
<b>LINKING TERMS ABSTRACT</b>	X	X	X
<b>MESH TERMS UNAMBIGUOUS</b>	X	X	X
<b>MESH TERMS QUALIFIERS</b>	X	X	X
<b>DOT PRODUCT ABSTRACT</b>	X		
<b>CATEGORIES-----&gt;</b>	<b>CAUSES</b>	<b>TREATMENTS</b>	<b>CHARACTERISTICS</b>

The overall conceptual strategy for identifying existing PN/PAD causes, treatments, and characteristics was based upon the conceptual strategy used in [Kostoff, Porter, Buchtel, 2018], although the implementation of the conceptual strategy differed slightly as knowledge was gained during the evolution of the study.

The strategy components used in the present study are:

- Select source database (Medline/Pubmed was selected as the primary source database, although the Thomson-Reuters version was used when proximity searching was performed).
- Generate a core PN/PAD database (a Pubmed query was used to generate a core PN/PAD database).
- Retrieve records relevant to PN/PAD treatments, contributing factors, or characteristics from the core PN/PAD database (methods will be shown in following sections)
- Extract existing contributing factors, treatments, and characteristics from retrieved records (methods will be shown in following sections)

A combination of MeSH-based and text-based examination approaches was used to retrieve records relevant to PN/PAD treatments, contributing factors, and characteristics, and to extract the desired PN/PAD treatments, contributing factors, and characteristics from these

retrieved records. [Table 6-1](#) summarizes the specific approaches used to identify contributing factors, treatments, and characteristics. Because of resource limitations, not all approaches were applied to all targets.

## 6B. Methodology for Identifying Existing and Potential PN/PAD Contributing Factors, Treatments, and Characteristics

### 6B1. Overview

As stated above, a MeSH-based approach and a text-based approach were used in tandem to identify existing PN/PAD contributing factors, treatments, and characteristics. The text-based approach was developed and used because of the following MeSH-based approach limitations:

- 1) not all Medline records have MeSH terms assigned;
- 2) for those records with MeSH terms, the terms do not always form a comprehensive set;
- 3) for records with MeSH terms, the Qualifiers appended to the Heading are not always complete.

Thus, the text-based approach complements (and overlaps) the MeSH-based approach.

### 6B2. Identifying Existing PN/PAD Contributing Factors

#### 6B2a. Text-based Approach

##### 6B2a1. Visual Inspection

The text-based approach had three components: a visual inspection component, a [linking term](#) component, and a dot-product component. The parsed Abstract field, containing about 4,000,000 phrases reflecting the 43056 records that constituted the core PN/PAD database, was used for all three components. The visual inspection component involved reading the 30,000 highest frequency Abstract phrases, and selecting those phrases deemed to be candidate contributing factors. The Vantage Point (VP) software [VP, 2019] containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate contributing factor selected.

##### 6B2a2. Linking Term

To identify candidate contributing factors in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with contributing factors were generated through visually inspecting many records containing foundational contributing factors in the Titles, and identifying those terms that appeared frequently with the foundational contributing factors. The remainder of the parsed Abstract field

was searched with use of these linking terms. The additional candidate contributing factors were extracted from the retrieved phrases, and validated as contributing factors.

These linking terms included: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; -exposed [at end]; -related; -associated; -infected; abuse\*; toxicity; risk factors; deficiency; neurotoxicity; risk factor; causes; workers; toxic; occupational; intoxication; toxicities; neurotoxic; excessive; deficiencies; contributing factors; worker; contributing factor; occupation; overload.

### 6B2a3. Dot Product

While the visual inspection approach identifies comprehensively the higher-frequency foundational causes, the linking term approach is less efficient. Not all foundational causes are associated with the finite list of linking terms used. Even if a foundational cause is associated (in the same Abstract) with a linking term, the software effectively limits the proximity of the linking term/foundational cause to four words. Some foundational causes can be located much further away from a linking term than four words in an Abstract.

To identify additional foundational causes that may have slipped through the cracks from the visual inspection and linking term approaches, the dot product approach was developed. Approximately 12,350 potentially toxic substances from myriad other sources (including past foundational causes studies, government-approved lists of toxic substances, MeSH-derived causes, etc) were generated, and intersected with the ~4,000,000 Abstract phrases in the core PN/PAD literature. While the dot product approach was developed specifically for identifying causes, a similar approach could be used for identifying treatments, biomarkers, mechanisms, etc. Moreover, given that many authors don't place detailed substances in the Title or Abstract, there could be substantial benefits gained by using full-text rather than Abstracts.

### 6B2b. MeSH-based Approach

#### 6B2b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. Four were selected (after extensive validation) as producing highly relevant results when used in isolation: adverse effects, toxicity, pathogenicity, poisoning. A few limited combinations of the remaining MeSH Qualifiers were examined for the streamlined approach, but none were deemed to have sufficient relevance. All MeSH terms that contained at least one of these Qualifiers were extracted, and the related records examined for potential foundational causes. While this MeSH Qualifier linking approach was developed for,

and applied to, identifying existing foundational causes, it was easily modified for identifying existing treatments and biomarkers, and could be further modified for identifying mechanisms, etc.

## 6B2b2. MeSH Headings

MeSH Headings related relatively unambiguously to foundational causes were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for potential PN/PAD foundational causes.

Sample MeSH terms related relatively unambiguously to foundational causes included: "Drug-Related Side Effects AND Adverse Reactions"; Abnormalities, Drug Induced; Air Pollutants, Occupational; Amphetamine Related Disorders; Carcinogens; Chemical Warfare Agents; Chemically-Induced Disorders, etc.

Again, while this focused MeSH Heading approach was developed for identifying foundational causes, it was adapted to identifying treatments, and could be readily adapted to identifying biomarkers, mechanisms, etc.

## 6B3. Identifying Existing PN/PAD Treatments

### 6B3a. Text-based Approach

#### 6B3a1. Visual Inspection

The text-based approach had two components: a visual inspection component, and a linking term component. The parsed Abstract field, containing about 4,000,000 phrases, was used for both components. The visual inspection component involved reading the 30,000 highest frequency phrases, and selecting those phrases deemed to be candidate treatments. The Vantage Point (VP) software containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate treatment selected.

#### 6B3a2. Linking Term

To identify candidate treatments in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with treatments were generated through visually inspecting many records containing treatments in the Titles, and identifying those terms that appeared frequently with the treatments. The remainder of the



parsed Abstract field was searched with use of these linking terms. The additional candidate treatments were extracted from the retrieved phrases, and validated as treatments.

Some of the more useful linking terms identified included the following: treat\*, therap\*, prevent\*, protect\*, improv\*, reduc\*, attenuat\*, ameliorat\*, enhanc\*, revers\*, promot\*, alleviat\*, inhibit\*, remov\*, suppress\*, mitigat\*, restor\*, lower\*, preserv\*, regenerat\*, rescu\*, slow\*, neuroprotect\*, neurorestorati\*, decreas\*, increas\*, eliminat\*.

Not all these terms are of equal value, or efficiency in identifying the desired text concepts. Some of these terms had higher efficiencies of identifying the PN/PAD treatment consequences of interest (PN/PAD characteristics) than others. Terms like prevent\*, protect\*, improv\*, restor\*, alleviat\*, ameliorat\*, mitigat\*, etc, almost always were associated with treatments, and gave the desired PN/PAD characteristics and the direction in which they changed as a result of PN/PAD treatment. Terms like decreas\*, increas\*, reduc\*, 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).

### 6B3b. MeSH-based Approach

#### 6B3b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying treatments. For the initial Visual Inspection approach query, seven were selected (after extensive validation) as producing highly relevant results when used in isolation: diet therapy, drug therapy, prevention & control, radiotherapy, surgery, therapeutic use, therapy. A few limited combinations of the remaining MeSH Qualifiers were examined for the streamlined approach, but none were deemed to have sufficient relevance. All MeSH terms that contained at least one of these Qualifiers were extracted, and the related records examined for treatments.

#### 6B3b2. MeSH Headings

MeSH Headings related relatively unambiguously to treatments were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for candidate PN/PAD treatments.

Sample MeSH terms related relatively unambiguously to treatments included Treatment Outcome, Neuroprotective Agents, Nootropic Agents, Plant Extracts, Phytotherapy, Dietary Supplements, Drugs, Chinese Herbal, etc.

#### 6B4. Identifying Existing PN/PAD Characteristics

##### 6B4a. Text-based Approach

###### 6B4a1. Visual Inspection

The text-based approach had two components: a visual inspection component, and a linking term component. The parsed Abstract field, containing about 4,000,000 phrases, was used for both components. The visual inspection component involved reading the 30,000 highest frequency phrases, and selecting those phrases deemed to be candidate characteristics. The Vantage Point (VP) software containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate characteristic selected.

###### 6B4a2. Linking Term

To identify candidate characteristics in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with characteristics were generated through visually inspecting many records containing characteristics in the Titles, and identifying those terms that appeared frequently with the characteristics. The remainder of the parsed Abstract field was searched with use of these linking terms. The additional candidate characteristics were extracted from the retrieved phrases, and validated as characteristics.

For the streamlined approach, the linking terms used for identifying treatments were selected as the linking terms to be used for identifying characteristics. These linking terms included: treat\*, therap\*, prevent\*, protect\*, improv\*, reduc\*, attenuat\*, ameliorat\*, enhanc\*, revers\*, promot\*, alleviat\*, inhibit\*, remov\*, suppress\*, mitigat\*, restor\*, lower\*, preserv\*, regenerat\*, rescu\*, slow\*, neuroprotect\*, neurorestorati\*, decreas\*, increas\*, eliminat\*.

##### 6B4b. MeSH-based Approach

###### 6B4b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying

characteristics. None were identified as being unambiguously related to characteristics, and this approach was not pursued further.

#### 6B4b2. MeSH Headings

MeSH Headings related relatively unambiguously to characteristics were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The only MeSH term related relatively unambiguously to characteristics was Biomarkers.

#### 6B4c. Spinoff from Contributing Factor and Treatment Identification Approaches

Contributing factor or treatment records typically identify one or more characteristics that are impacted by the contributing factor(s) or treatment(s) in the record. In the present streamlined approach, most of the characteristics were identified during the validation process for a contributing factor or treatment. The records were read for validation, and any characteristics were then extracted from the record.

#### 6B5. Identifying Potential PN/PAD Treatments

Existing treatments identified in the present monograph were deemed successful when they moved the values of characteristics in desired directions. Thus, if high oxidative stress or high inflammation reflected an undesired disease state, then one component of a successful treatment for this undesired disease state would be reduction of oxidative stress or reduction of inflammation. One of the outcomes of the present study was identification of myriad characteristics and the directions in which they changed as a result of successful treatments.

For Discovery (identification of potential PN/PAD treatments), this process is reversed. A query is formed consisting of critical characteristics and the directions in which they would be changed if successful treatments were applied. This query is then applied to the full Medline database excluding the PN/PAD literature. Chemicals/radiations/supplements etc, and other forms of potential PN/PAD treatments are identified that move these characteristics in desired directions, and they are viewed as candidate potential PN/PAD treatments. A validation is performed to insure these candidate potential PN/PAD treatments are not part of the core PN/PAD literature.

The number of terms in the query could range from one to many. The more terms in the query, the more restricted the retrievals would be in volume and focus. The fewer terms in the query, the greater the chances for radical discovery, but the larger the volume of retrieval to be evaluated for validation.

As an example, consider the above case of an undesired disease state, characterized by high oxidative stress and high inflammation. A query would be generated, consisting of "reduce oxidative stress AND "reduce inflammation". All treatments for any disease in Medline (with the exception of PN/PAD) that reduced oxidative stress and reduced inflammation would be retrieved. After much experimentation, it was found that queries consisting of combinations of two biomarkers (with desired directions of change) provided a good balance between content of discovery and volume of retrieval.

The detailed methodology that was used in the present study is described in Appendix 6-1, and in the broader context of *treatment re-purposing* in [Kostoff, 2018].

#### 6B6. Identifying Potential PN/PAD Contributing Factors

Potential PN/PAD contributing factors were not identified in the present study because of time and resource limitations. However, the conceptual approach is the same as that for identifying potential PN/PAD treatments, with the exception that the directions in which characteristics changes are desired are reversed. In the example provided in section 6B5 for treatments, the query for identifying potential contributing factors would be "increase oxidative stress" AND "increase inflammation". All contributing factors for any disease in Medline (with the exception of PN/PAD) that increased oxidative stress and increased inflammation would be retrieved.

#### 6B7. Identifying Potential PN/PAD Characteristics

Potential PN/PAD characteristics were not identified in the present study because of time and resource limitations. If potential PN/PAD characteristics were desired, the identification concept would be to identify patterns of PN/PAD characteristics that tend to co-occur frequently in the PN/PAD literature, then use these patterns as a search query in the non-PN/PAD literature. New patterns may be identified in the non-PN/PAD literature consisting of the search query pattern plus additional characteristics not in the PN/PAD literature. These additional characteristics would then be candidates for discovery as new PN/PAD characteristics that not have been identified previously.

For example, IL-1 and IL-6 and TNF-alpha and NF-KappaB tend to co-occur in many PN/PAD articles relating to inflammation. These four terms would be combined as a query for the non-AD literature: "**IL-1 AND IL-6 AND TNF-alpha AND NF-KappaB**". Any records retrieved would be examined for additional characteristics, and these additional characteristics would be validated if they did not occur in the PN/PAD literature.

Myriad other patterns are possible. For example, existing PN/PAD treatments and existing PN/PAD causes move PN/PAD characteristics in known directions. Non-PN/PAD literatures could be searched for characteristics impacted by these known PN/PAD treatments and PN/PAD causes, and not contained in the core PN/PAD literature. Combinations of these

PN/PAD treatments and PN/PAD causes could be used to increase the likelihood that any new characteristics identified would have higher relevance to PN/PAD.

As a specific example, consider the following query that was demonstrated in the Alzheimer's Disease (AD) study [Kostoff, Porter, Buchtel, 2018]: (high-fat-diet\* NEAR/5 (increas\* OR decreas\*) AND chitosan NEAR/5 (increas\* OR decreas\*)) NOT alzheimer\*. This will retrieve all records reflecting an increase or decrease of characteristic values (in the non-AD literature) due to the presence of the existing AD cause "high-fat-diet" and the existing AD treatment "chitosan". Applying this query to the Medline database leads to the identification of a potential AD characteristic "mup17" (major urinary protein 17) [Wang, Zhang, Wang et al, 2017]. This potential AD characteristic is not found in the AD literature, but it is altered in one direction by an existing AD cause, and is altered in the opposing direction by an existing AD treatment. So, it might be a valuable characteristic for AD researchers to track.

## Appendices - Chapter 6

### Appendix 6-1 - PN/PAD Treatment Discovery Query

#### 6-1a. General strategy

As stated in 6B5, a query is formed consisting of critical characteristics and the directions in which they would be changed if successful treatments were applied. This query is then applied to the full Medline database excluding the PN/PAD literature. Chemicals/ radiations/ supplements etc, and other forms of potential PN/PAD treatments are identified that move these characteristics in desired directions, and they are viewed as candidate potential PN/PAD treatments. A validation is performed to insure these candidate potential PN/PAD treatments are not part of the core PN/PAD literature.

#### 6-1b. Specific approach

The most general form of the treatment discovery/repurposing query can incorporate any number of characteristics of interest. For PN/PAD, a two biomarker query was deemed adequate for demonstration purposes. The generic form of the two biomarker PN/PAD treatment discovery/repurposing query is

(A and B) not (C or D), where

A is a biomarker and its associated desired direction of change

B is another biomarker and its associated direction of change

C is the query used to retrieve the PN/PAD core literature

D is a list of existing PN/PAD treatments identified in the initial part of the PN/PAD study

Thus, the combination (A and B) retrieves ALL records from the biomedical literature that contain potential PN/PAD treatments based on the two desired characteristics A and B, while (C or D) subtracts those records and treatments associated with the PN/PAD core literature. The remainder is non-PN/PAD records with substances that could be candidate potential PN/PAD treatments, based on the requirement that A and B must be present.

Twenty of the 757 biomarkers identified in the PN/PAD study (through text mining techniques) were selected for the query. The query was run in Thompson-Reuters-Medline, since its search engine allows for proximity searching (e.g., [direction] within three words of [biomarker], or [direction] near/3 [biomarker]). In modular form, each query term is shown as follows:

#### 6-1b1. PN/PAD Characteristic-Linking Term units

**#1** - (reduc\* OR decreas\* OR prevent\* OR attenuat\* OR suppress\* OR alleviat\* OR ameliorat\*) near/3 "oxidative stress"

**#2** - (reduc\* OR decreas\* OR prevent\* OR attenuat\* OR suppress\* OR alleviat\* OR ameliorat\* OR inhibit\*) near/3 "advanced glycation end product"

**#3** - (reduc\* OR decreas\* OR prevent\* OR attenuat\* OR suppress\* OR alleviat\* OR ameliorat\*) near/3 ("hemoglobin a1c" OR "hba1c")

**#4** - (increase OR enhanc\* OR restor\*) near/3 "glomerular filtration rate"

**#5** - (modulat\* OR attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 ("il-6" OR "interleukin-6")

**#6** - (reduc\* OR decreas\* OR attenuat\* OR suppress\* OR inhibit\*) near/3 "creatin kinase"

**#7** - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "malondialdehyde"

**#8** - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "alkaline phosphatase"

**#9** - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "myeloperoxidase"

**#10** - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "blood urea nitrogen"

**#11** - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 ("beta 2 microglobulin" OR "beta-2 microglobulin" OR "beta-2-microglobulin")

#12 - (increas\* OR enhanc\* OR restor\*) near/3 "adenosine triphosphate"

#13 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 ("pge2" OR "Prostaglandin E2")

#14 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "cystatin c"

#15 - (increas\* OR enhanc\* OR restor\*) near/3 "Nrf2"

#16 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "gamma-glutamyltransferase "

#17 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "galectin-3"

#18 - (increas\* OR enhanc\* OR restor\*) near/3 "cyclic guanine monophosphate"

#19 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\* OR suppress\*) near/3 "aspartate aminotransferase "

#20 - (attenuat\* OR reduc\* OR inhibit\* OR decreas\*) near/3 "Glutamate carboxypeptidase II"

NOT

#21 - peripheral neuropathy [MeSH Heading-NO EXP] OR "peripheral neuropathy" [TOPIC] OR peripheral arterial disease [MeSH Heading] OR "peripheral arter\* disease" [TOPIC] OR "peripheral vascular disease" [TOPIC]

OR

Existing Treatments

#22 - ("revascularization" OR "walking" OR "artery bypass grafting" OR "angioplasty" OR "insulin" OR "dialysis" OR "aspirin" OR "endovascular treatment" OR "vascular surgery" OR "angiogenesis" OR "glycemic control" OR "corticosteroid" OR "catheter" OR "Clopidogrel" OR "thalidomide" OR "vascular endothelial growth factor" OR "balloon angioplasty" OR "CABG" OR "Gabapentin" OR "PNS" OR "endarterectomy" OR "pregabalin" OR "Cilostazol" OR "vitamin B12" OR "nerve growth factor" OR "smoking cessation" OR "IL-6" OR "heparin" OR "adenosine" OR "Electrical stimulation" OR "prednisone" OR "hypoxia" OR "capsaicin" OR "morphine" OR "SCS" OR "mononuclear cells" OR "rituximab" OR "Spinal Cord Stimulation" OR "vitamin E" OR "zidovudine" OR "plasmapheresis" OR "prednisolone" OR "warfarin" OR "Vitamin D" OR "duloxetine" OR "enzyme inhibitors" OR "Acupuncture" OR "pentoxifylline" OR "plasma exchange" OR "haemodialysis" OR "antioxidants" OR "IVIg" OR "lidocaine" OR "Prostaglandin" OR "gangliosides" OR "Amitriptyline" OR "Alpha lipoic acid" OR "carbamazepine" OR "folic acid" OR "anthracycline" OR "GM1" OR "leucovorin" OR

"dipyridamole" OR "thiamine" OR "Ticlopidine" OR "methylprednisolone" OR "drug-coated balloons" OR "near-infrared" OR "magnesium" OR "Zinc" OR "surgical decompression" OR "ethanol" OR "superoxide dismutase" OR "erythropoietin" OR "simvastatin" OR "Acetyl-L-carnitine" OR "acetylsalicylic acid" OR "hyperbaric oxygen" OR "Testosterone" OR "angiotensin converting enzyme inhibitor" OR "nitinol stents" OR "carnitine" OR "Pyridoxine" OR "BDNF" OR "hepatocyte growth factor" OR "iloprost" OR "immunosuppressive agents" OR "AA" OR "epidermal growth factor" OR "Mesenchymal Stem Cells" OR "peripheral blood mononuclear cells" OR "C-peptide" OR "Nicotine" OR "aldose reductase inhibitor" OR "atorvastatin" OR "azathioprine" OR "Ketamine" OR "vorapaxar" OR "Neurotrophins" OR "clonidine" OR "arginine" OR "ticagrelor" OR "aerobic exercise" OR "antiepileptic drugs" OR "valproic acid" OR "drug-eluting balloons" OR "glucocorticoid" OR "apheresis" OR "distal bypass" OR "niacin" OR "stem cell therapy" OR "venlafaxine" OR "Cannabinoids" OR "directional atherectomy" OR "nitroglycerin" OR "urokinase" OR "vitamin C" OR "ramipril" OR "tramadol" OR "Orbital atherectomy" OR "prasugrel" OR "covered stents" OR "l-carnitine" OR "progesterone" OR "amifostine" OR "Gamma-aminobutyric acid" OR "lamotrigine" OR "Lumbar sympathectomy" OR "Methylcobalamin" OR "phenytoin" OR "propionyl-L-carnitine" OR "electroacupuncture" OR "GDNF" OR "HMG-CoA" OR "nifedipine" OR "oxcarbazepine" OR "baclofen" OR "glutamine" OR "intermittent pneumatic compression" OR "Mexiletine" OR "verapamil" OR "botulinum toxin" OR "diphenhydramine" OR "growth hormone" OR "hormone replacement therapy" OR "massage" OR "minocycline" OR "sodium nitroprusside" OR "antimicrobial therapy" OR "cannabis" OR "curcumin" OR "GSH" OR "MK-801" OR "nicotinamide" OR "opiates" OR "Transcutaneous electrical nerve stimulation" OR "bFGF" OR "Goshajinkigan" OR "immunoglobulin therapy" OR "insulin-like growth factor-I" OR "omega-3 fatty acids" OR "pulse therapy" OR "docosahexaenoic acid" OR "EPO" OR "fish oil" OR "hypothermia" OR "alpha-tocopherol" OR "calcium antagonists" OR "cryoplasty" OR "NT-3" OR "prostanoids" OR "rapamycin" OR "topiramate" OR "Vitamin B1" OR "calcium channel blocker" OR "NSAIDs" OR "oxycodone" OR "phosphodiesterase inhibitor" OR "rivaroxaban" OR "tacrolimus" OR "bone marrow mononuclear cells" OR "fentanyl" OR "peripheral nerve stimulation" OR "alprostadil" OR "bufloxedil" OR "DAPT" OR "ezetimibe" OR "neuroactive steroids" OR "neurotrophin-3" OR "phentolamine" OR "serotonin reuptake inhibitors" OR "ascorbic acid" OR "balloon dilatation" OR "chelation therapy" OR "eicosapentaenoic acid" OR "indomethacin" OR "lithium" OR "muscle stimulation" OR "selenium" OR "amlodipine" OR "CXCR4" OR "interleukin-10" OR "laser therapy" OR "mycophenolate mofetil" OR "N-acetylcysteine" OR "NAC" OR "rifampin" OR "strength training" OR "thienopyridines" OR "viral vectors" OR "whole-body vibration" OR "androgen" OR "beraprost sodium" OR "ceftriaxone" OR "chlorambucil" OR "Coenzyme Q10" OR "epalrestat" OR "galanin" OR "losartan" OR "negative pressure wound therapy" OR "ozone" OR "PGE2" OR "pravastatin" OR "RTX" OR "acetaminophen" OR "digoxin" OR "glycosaminoglycan" OR "kampo" OR "lisinopril" OR "osteopontin" OR "sildenafil" OR "Streptokinase" OR "abciximab" OR "Aldehyde" OR "antioxidant therapy" OR "bivalirudin" OR "cimetidine" OR "CNTF" OR



"enalapril" OR "femoropopliteal in-stent restenosis" OR "fluoxetine" OR "memantine" OR "myo-inositol" OR "Org 2766" OR "phenylephrine" OR "Picotamide" OR "tapentadol" OR "TCA" OR "yohimbine" OR "ACTH" OR "Caffeine" OR "celecoxib" OR "dextromethorphan" OR "doxycycline" OR "etanercept" OR "FK506" OR "guanosine" OR "mecobalamin" OR "nortriptyline" OR "Olive oil" OR "sulodexide" OR "antihistamines" OR "beta-carotene" OR "betaine" OR "cyanocobalamin" OR "Dex" OR "ganglioside GM1" OR "Ginkgo biloba extract" OR "hydrochlorothiazide" OR "ketanserin" OR "Lovastatin" OR "prazosin" OR "retinoic acid" OR "sodium bicarbonate" OR "tempol" OR "anandamide" OR "chlorthalidone" OR "diclofenac" OR "EDTA" OR "phosphatidylcholine" OR "ruboxistaurin" OR "serotonin-norepinephrine reuptake inhibitors" OR "tea" OR "benfotiamine" OR "chloroquine" OR "desipramine" OR "fenofibrate" OR "glibenclamide" OR "GP IIB/IIIa inhibitors" OR "imipramine" OR "lentivirus" OR "melatonin" OR "mesenchymal stromal cells" OR "milnacipran" OR "PAR-1 antagonists" OR "plaque excision" OR "Ranitidine" OR "Resveratrol" OR "scrambler therapy" OR "tai chi" OR "thiazolidinediones" OR "uridine" OR "vitamin D3" OR "WIN 55,212-2" OR "allopurinol" OR "Angiogenic gene therapy" OR "benzodiazepine" OR "captopril" OR "Carvedilol" OR "clonazepam" OR "dabigatran" OR "Defibrotide" OR "electromagnetic field" OR "everolimus" OR "hydrogen sulfide" OR "levetiracetam" OR "methadone" OR "methylxanthine" OR "Paracetamol" OR "perindopril" OR "phlebotomy" OR "sunlight" OR "tafamidis" OR "tolrestat" OR "vitamin K antagonist" OR "all-trans retinoic acid" OR "amantadine" OR "Calcitriol" OR "D-penicillamine" OR "eptifibatide" OR "external counterpulsation" OR "hydrocortisone" OR "ibuprofen" OR "inositol" OR "KU-32" OR "lacosamide" OR "levothyroxine" OR "mannitol" OR "manual therapy" OR "Menhaden oil" OR "menthol" OR "muscimol" OR "nicotinic acid" OR "osteocalcin" OR "paroxetine" OR "pioglitazone" OR "placenta" OR "Protamine" OR "Sitagliptin" OR "taurine" OR "Tetrodotoxin" OR "thiols" OR "tirofiban" OR "TRPA1 antagonist" OR "7-nitroindazole" OR "acetylcysteine" OR "apixaban" OR "ATS" OR "Cannabidiol" OR "capsazepine" OR "coffee" OR "cortical stimulation" OR "cryotherapy" OR "DA-9801" OR "dexmedetomidine" OR "diltiazem" OR "factor Xa inhibitors" OR "gamma-globulin" OR "gamma-linolenic acid" OR "gemfibrozil" OR "Ghrelin" OR "Gliclazide" OR "histone deacetylase inhibitors" OR "Huangqi Guizhi Wuwu" OR "interferon-beta" OR "Isosorbide dinitrate" OR "linoleic acid" OR "MIRE" OR "neuromuscular electrical stimulation" OR "nimodipine" OR "papaverine" OR "Peripheral nerve decompression" OR "PGB" OR "plasminogen activators" OR "prostacyclin analogues" OR "quercetin" OR "retigabine" OR "riluzole" OR "sirolimus" OR "Viabahn endoprosthesis" OR "acarbose" OR "ancrod" OR "atopaxar" OR "Biotin" OR "CB1/CB2 agonist" OR "coumarin" OR "EGb 761" OR "erlotinib" OR "HC-030031" OR "hyaluronic acid" OR "hydromorphone" OR "Hydroxocobalamin" OR "liraglutide" OR "magnetic fields" OR "marijuana" OR "mesoglycan" OR "naltrexone" OR "nebivolol" OR "PARP inhibition" OR "relaxin" OR "salbutamol" OR "Sarpogrelate hydrochloride" OR "shockwave therapy" OR "THC" OR "Thiamine pyrophosphate" OR "thioctic acid" OR "trimetazidine" OR "Vitamin B complex" OR "Zilver PTX stent" OR "acetylcholine-induced" OR "adrenocorticotrophic hormone" OR "AMD3100" OR "Bezafibrate"

OR "cangrelor" OR "cholinesterase inhibitor" OR "clomipramine" OR "diazepam" OR "drug-coated stents" OR "edoxaban" OR "epoprostenol" OR "Exendin-4" OR "FAAH inhibitor" OR "Flunarizine" OR "Grape" OR "guanethidine" OR "haemodilution" OR "Hematin" OR "Heparin cofactor II" OR "hydrotherapy" OR "hydroxychloroquine" OR "hydroxyethyl starch" OR "Ibutilast" OR "Jinmaitong" OR "ketorolac" OR "moxibustion" OR "N-methyl-D-aspartate receptor antagonists" OR "naftidrofuryl oxalate" OR "NGX-4010" OR "P2Y12 inhibitor" OR "pralidoxime" OR "puerarin" OR "repetitive transcranial magnetic stimulation" OR "reteplase" OR "rheopheresis" OR "rofecoxib" OR "Sativex" OR "SCH 530348" OR "Shakuyaku-kanzo-to" OR "tadalafil" OR "telmisartan" OR "trigonelline" OR "triiodothyronine" OR "URB597" OR "VLTS-589" OR "17beta-estradiol" OR "4-methylcatechol" OR "acetazolamide" OR "adrenal medullary transplants" OR "agmatine" OR "Aliskiren" OR "allopregnanolone" OR "amikacin" OR "anakinra" OR "betamethasone" OR "bosentan" OR "canagliflozin" OR "catechin" OR "cefotaxime" OR "chelerythrine" OR "Cinacalcet" OR "ciprostone" OR "dextrophan" OR "dimercaprol" OR "dipyron" OR "donepezil" OR "doxepin" OR "enoxaparin" OR "evolocumab" OR "fluorocitrate" OR "GLP-1 receptor agonists" OR "glyceryl trinitrate" OR "hemin" OR "icariin" OR "IGF-II" OR "indobufen" OR "isoproterenol" OR "K-134" OR "lafutidine" OR "laser ablation" OR "linolenic acid" OR "Lycopene" OR "Maggot debridement therapy" OR "mangafodipir" OR "midodrine" OR "misoprostol" OR "molsidomine" OR "Netrin-1" OR "orexin-A" OR "percutaneous therapy" OR "pirenzepine" OR "probucol" OR "propentofylline" OR "protein kinase C inhibitors" OR "pyridine" OR "pyridostigmine" OR "quinidine" OR "Quinine" OR "reflexology" OR "rolipram" OR "ruthenium red" OR "S-Nitroso-N-acetylpenicillamine" OR "saponins" OR "Sodium nitrite" OR "Tanezumab" OR "Tang-Luo-Ning" OR "tetrahydrocannabinol" OR "thalamotomy" OR "Thymoquinone" OR "Tizanidine" OR "trandolapril" OR "troglitazone" OR "turmeric" OR "unsaturated fatty acids" OR "valsartan" OR "Waon therapy" OR "wortmannin" OR "ximelagatran" OR "zenarestat" OR "zonisamide" OR "2-(3-mercaptopropyl)pentanedioic acid" OR "2-AG" OR "A23187" OR "actovegin" OR "adrenergic agonists" OR "albendazole" OR "alpha-linolenic acid" OR "amiloride" OR "antitussive" OR "argatroban" OR "Aucubin" OR "becaplermin" OR "berberine" OR "bone marrow stem cells" OR "BPAU" OR "bupivacaine" OR "butyric acid" OR "caloric restriction" OR "candesartan" OR "carbenoxolone" OR "carotenoids" OR "caspase inhibitors" OR "charcoal" OR "chemical lumbar sympathectomy" OR "chlorpropamide" OR "chondroitinase ABC" OR "codeine" OR "cognitive behavior therapy" OR "cyproheptadine" OR "dermatan sulfate" OR "desferrioxamine" OR "desvenlafaxine" OR "dietary flaxseed" OR "diflunisal" OR "dihydroergotamine" OR "dimethyl fumarate" OR "ellagic acid" OR "epibatidine" OR "ethosuximide" OR "Fasudil" OR "fidarestat" OR "fingolimod" OR "fludrocortisone" OR "fluvoxamine" OR "fosfomycin" OR "fucoidan" OR "genistein" OR "green tea" OR "H-Wave device" OR "hexamethonium" OR "High-mobility group box-1 protein" OR "ifenprodil" OR "interferon alfa" OR "irbesartan" OR "ivermectin" OR "JZL184" OR "L-cysteine" OR "Lutonix drug-coated balloon" OR "Lyrica" OR "Metanx" OR "mifepristone" OR "mirtazapine" OR "N-acetyl-L-cysteine" OR "natalizumab" OR "Neostigmine" OR "olesoxime" OR "oxytocin" OR

"palmitoylethanolamide" OR "passive exercise" OR "PD98059" OR "pergolide" OR "phenols" OR "phosphatidylethanolamine" OR "Photobiomodulation" OR "pifithrin-mu" OR "Plantaginis Semen" OR "PLX-PAD" OR "polytetrafluoroethylene-covered stents" OR "probenecid" OR "pyrrolidine dithiocarbamate" OR "quinpirole" OR "ranolazine" OR "rotenone" OR "RU38486" OR "shear rate therapy" OR "sialidase" OR "Silybin" OR "SKPs" OR "tetrahydrobiopterin" OR "thermal ablation" OR "thymosin beta4" OR "Tongxinluo" OR "trimethylamine" OR "TSPO" OR "1,5-isoquinolinediol" OR "2,3-dimercapto-1-propanesulfonic acid" OR "2-MPPA)" OR "5-hydroxydecanoate" OR "Acidic fibroblast growth factor" OR "Aconitum" OR "Acorus calamus" OR "adenylate cyclase inhibitor" OR "ALDH Bright Cells" OR "Aleglitazar" OR "alfentanil" OR "alogliptin" OR "alpha-conotoxin Vc1.1" OR "alpha2-delta ligands" OR "AM424" OR "angelica" OR "anisodamine" OR "Anodyne Therapy System" OR "apomorphine" OR "Astragali" OR "Bee venom acupuncture" OR "Bimocloamol" OR "Biolimus" OR "bisoprolol" OR "BRX-220" OR "calcium gluconate" OR "calmangafodipir" OR "calpeptin" OR "carisoprodol" OR "Cerebrolysin" OR "cicaprost" OR "cinnamaldehyde" OR "Cobalt Chloride" OR "controlled reperfusion" OR "Cyclandelate" OR "cytidine" OR "Dark chocolate" OR "deferoxamine" OR "DHbetaE)" OR "dietary nitrate" OR "Dihydro-beta-erythroidine" OR "dihydropyridines" OR "diluted bee venom" OR "DMSO" OR "docosapentaenoic acid" OR "DRG stimulation" OR "DVC1-0101" OR "E2072" OR "egg white hydrolysate" OR "elcatonin" OR "electromagnetic neural stimulation" OR "electromagnetic radiation" OR "emodin" OR "ergocalciferol" OR "Ethoxyquin" OR "etodolac" OR "excimer laser ablation" OR "fibroblast growth factor 1" OR "Flupirtine" OR "fondaparinux" OR "gallic acid" OR "geldanamycin" OR "glutathione" OR "glycyrrhizin" OR "HGF plasmid DNA" OR "hypoxia-inducible factor-1alpha" OR "HIF-1alpha" OR "intravenous high-dose immunoglobulin" OR "kappa-opioid receptor agonist" OR "KRN5500" OR "KU-596" OR "leuprolide acetate" OR "linagliptin" OR "Lipid apheresis" OR "local ultrasound" OR "loperamide" OR "LV vectors" OR "maraviroc" OR "maximal strength training" OR "MEK inhibitors" OR "melanocortin" OR "metaxalone" OR "Methocarbamol" OR "methyl nicotinate" OR "Mibefradil" OR "monochromatic infrared photo energy" OR "MSG" OR "nalbuphine" OR "Neomycin" OR "neurofeedback" OR "niflumic acid" OR "nitrate consumption" OR "Nitrendipine" OR "nitric oxide donors" OR "norketamine" OR "NS1209" OR "nutrient deprivation" OR "Ocimum sanctum" OR "oestradiol" OR "oleic acid" OR "orange and blackcurrant juice" OR "Padma 28" OR "Paeoniae Radix" OR "percutaneous electrical nerve stimulation" OR "peripheral nerve grafts" OR "PFT-mu" OR "PGE1 alpha-cyclodestrina" OR "phosphonic acid" OR "Photoablation" OR "physostigmine" OR "pulsed infrared light therapy" OR "PXT3003" OR "pyrrolidine-2,5-dione" OR "radiofrequency thermocoagulation" OR "retroviral vectors" OR "rimonabant" OR "ropinirole" OR "Rotarex thrombectomy" OR "sacubitril/valsartan" OR "saxagliptin" OR "scopolamine" OR "selegiline" OR "Selesorb" OR "skin-derived precursors" OR "Snake venoms" OR "Sodium ferulate" OR "sodium glutamate" OR "sonothrombolysis" OR "spicamycin derivative" OR "sulforaphane" OR "Sumatriptan" OR "TDP1" OR "tiron" OR "tocotrienol" OR "Tranilast" OR "trapidil" OR "triamcinolone" OR "trifluoperazine" OR "tropisetron" OR "TX14(A)" OR "U-50,488H" OR

"ultrasonic therapy" OR "URB937" OR "vibro-medical insole" OR "1,3-dimethyl-2,6-dioxopurin-7-yl-alkylcarboxylic acids" OR "11beta-HSD1 inhibitors" OR "(25)Mg-PMC16" OR "3,3,5-trimethylcyclohexanol" OR "3-Aminobenzamide" OR "4-phenylbutyric acid" OR "5-phenyl-1-pentyne" OR "7-hydroxy-3,4-dihydrocadalin" OR "8-methoxypsoralen" OR "A-134974" OR "A-834735" OR "AC591" OR "Acanthopanax" OR "ACEA" OR "acellular dermal regenerative tissue" OR "Achyranthis bidentata Blume" OR "acipimox" OR "activation of Nrf2" OR "active treadmill walking" OR "ACY-1083" OR "adipose-tissue-derived stem cells" OR "AGGF1" OR "aktovegin" OR "Alfa LMW1" OR "alpha-chymotrypsin" OR "Alstonia scholaris" OR "AM1241" OR "AM1714" OR "ambroxol" OR "aminoguanidine hydrochloride" OR "aminophylline" OR "ampakines" OR "AMPK activators" OR "anthranilic acid" OR "antimycin" OR "Apligraf" OR "ARA 290" OR "arm-crank exercise" OR "ascorbyl palmitate" OR "AVP-923" OR "Azadirachta indica" OR "baicalein" OR "Baicalin" OR "BAIMAI-SAN" OR "BAK-PLO" OR "bendazac lysine" OR "benserazide" OR "bepreminogene perplasmid" OR "beta-caryophyllene" OR "betulinic acid" OR "bis(maltolato)oxovanadium IV" OR "blueberry" OR "blunt microdissection catheter" OR "borneol" OR "bovine lactoferrin" OR "BRL-50481" OR "BRLP-42" OR "bromelain" OR "bushi" OR "Butea monosperma" OR "Buyang Huanwu decoction" OR "Caffeic acid phenethyl ester" OR "calciparine" OR "calcium citrate" OR "calcium/magnesium infusion" OR "Calmare therapy" OR "Calmidazolium" OR "candoxatril" OR "Capnellene" OR "CD31(+) cell transplantation" OR "ceftaroline fosamil (CPT-F)" OR "CEP 03" OR "CEP protein adducts" OR "Chamomilla matricaria" OR "chemical ablation" OR "chlorogenic acid" OR "Chlorpheniramine" OR "cholecystokinin receptor antagonists" OR "cholecystokinin-8" OR "cholesterol-rich diet" OR "chromaffin cell grafts" OR "chuanxiong" OR "cinnamamide" OR "cinnamic acid" OR "circulator boot therapy" OR "citicoline" OR "COMP-Ang-1" OR "contrast-enhanced sonothrombolysis" OR "copper ions" OR "CQ" OR "crenotherapy" OR "Crocin" OR "cromakalim" OR "Crotoxin" OR "CX614" OR "CX729" OR "cyclobenzaprine" OR "Cymbalta" OR "Cystamine" OR "cytoflavin" OR "D-sorbitol" OR "daidzin" OR "daltroban" OR "danshen root" OR "Deguelin" OR "dexibuprofen" OR "Diallyl trisulfide" OR "dielectric barrier discharge plasma" OR "dietary folate intake" OR "dietary vitamin E" OR "diethylcarbamide" OR "dihydrolipoic acid" OR "dimethicone" OR "diphenyl diselenide" OR "dronabinol" OR "EAntS-GS" OR "Effexor" OR "Electroconvulsive shock" OR "electromagnetic therapy" OR "elinogrel" OR "emfilermin" OR "Entacapone" OR "Epac-inhibitor" OR "EPAS1 gene" OR "epicatechin gallate" OR "eplerenone" OR "ergothioneine" OR "erucic acid" OR "ESI-09" OR "estradiol valerate" OR "ethanethiol" OR "ethopropazine" OR "eugenol" OR "exogenous recombination IL-4" OR "extracorporeal shock wave therapy" OR "extract of date fruit" OR "felbamate" OR "Fenfluramine" OR "fenugreek extract" OR "Ferula assa-foetida" OR "ferulic acid" OR "Fexofenadine" OR "fluocinolone acetonide" OR "focused ultrasound" OR "fumonisins B1" OR "gadolinium chloride" OR "GCSB-5" OR "Gentiopicroside" OR "ginsenoside Rb1" OR "Guizhi-shaoyao-zhimu decoction" OR "Hachimi-jio-gan" OR "hedysari" OR "hemangioblasts" OR "Huoxue Kangyuan decoction" OR "Hydroxytyrosol" OR "hyperforin" OR "hypericin" OR "Ilepatril" OR "imatinib mesylate" OR "increased intake of

folate" OR "IND01" OR "INGAP peptide" OR "injectable biomaterial" OR "integrin-linked kinase" OR "Intention controlled Myo-Feedback)" OR "interval walking" OR "intrathecal opioid infusion" OR "IRE1alpha siRNA" OR "isoprenaline" OR "isopropyl myristate" OR "Isoxsuprine hydrochloride" OR "itaconic acid" OR "J147" OR "Jiaweibugan" OR "Juglans regia L." OR "kaempferol" OR "Kamishoyosan" OR "ketogenic diet" OR "Kv7 channel activator" OR "lactoferrin" OR "leupeptin" OR "levo-corydalmine" OR "Levocarnitine acetyl 150" OR "levorphanol" OR "LiCl" OR "ligustrazine" OR "Linalool" OR "Lithospermi radix" OR "LM11A-31" OR "lomitapide" OR "Lotrafiban" OR "low frequency acoustic waveform" OR "low frequency magnetic fields" OR "low glucose diet" OR "low-frequency contact ultrasound debridement" OR "LPP1" OR "Maltol" OR "mangiferin" OR "Manidipine" OR "maprotiline" OR "MCC-257" OR "mCPP" OR "MDA19" OR "Me6TREN" OR "meclizine" OR "MenSCs" OR "menstrual blood-derived stem cell" OR "metamizol/paracetamol" OR "methylsulfonylmethane" OR "metyrapone" OR "microRNA let-7g" OR "mindfulness meditation" OR "minoxidil" OR "MnDPDP" OR "MnL4" OR "Momordica cymbalaria" OR "monosialotetrahexosylganglioside" OR "monosodium glutamate" OR "morin" OR "MPV-2426" OR "N(6)-cyclopentyladenosine" OR "nabilone" OR "naringin" OR "NCX 6550" OR "nefopam" OR "neoline" OR "neprilysin" OR "nerve autografts" OR "Neuragen PN" OR "Neurotin" OR "NF3" OR "niclosamide" OR "nicorandil" OR "NM-702" OR "Nmnat" OR "Normicotine" OR "NSCs" OR "NT-702" OR "nylidrin" OR "oleanolic acid" OR "OP-1206" OR "pamoic acid" OR "pancreatic kininogenase" OR "parthenolide" OR "passive cycling" OR "pCK-HGF-X7" OR "PDE4B/7A dual inhibitor" OR "PDE5 inhibitor" OR "PDWHF" OR "pemirolast" OR "Peptide5" OR "percutaneous catheter-based therapies" OR "Phenoxodiol" OR "phenoxyphenyl pyridines" OR "phenyl-N-tert-butylnitron" OR "Picrorhiza kurroa" OR "piler-light" OR "piperine" OR "piroxican" OR "pitavastatin" OR "placental-derived adherent stromal cells" OR "plantar vibration" OR "pneumatic compression boot" OR "polaprezinc" OR "potassium channel openers" OR "prifinium bromide" OR "pRLX" OR "Procyclidine" OR "progestins" OR "progestogen therapy" OR "Prograf" OR "programmable neuro-stimulator" OR "propionylcarnitine" OR "propolis" OR "prosaposin-derived 14-mer peptide" OR "proxiphylline" OR "psoralen" OR "Pulsed radiofrequency ablation" OR "pulsed radiofrequency neuromodulation" OR "Punica granatum L" OR "Punicalagins" OR "pyrimethamine" OR "QR-333" OR "Quetiapine" OR "Racemic (R/S)-guaifenesin (1)" OR "rAd5/NR2B" OR "Recombinant Sema3A protein" OR "reparixin" OR "Ro5-4864" OR "rosemary" OR "Rosmarinic acid" OR "RSR13" OR "rutin" OR "safranal" OR "Salicylaldehyde" OR "salmon calcitonin" OR "salsalate" OR "Salvia officinalis" OR "Salvianolic acid B" OR "SAN-Gly" OR "Saposhnikovia divaricata Schiskin" OR "SDZ PCO-400" OR "sesame oil" OR "shellac" OR "silymarin" OR "SMC therapy" OR "SN gene therapy" OR "sodium hydrosulfide" OR "sodium sulfide" OR "sonication" OR "SP600125" OR "spironolactone" OR "SQ22536" OR "SR 57746A" OR "subsensory electrical stimulation" OR "SVF-enriched fat graft" OR "synthetic exendin-4" OR "T-cell-pre-stimulated monocytes" OR "Tanshinone" OR "TAT-CBD3A6K" OR "Terbinafine" OR "tetracyclines" OR "tetramethylpyrazine" OR "thenoyltrifluoroacetone" OR

"thiorphan" OR "thiosalicylic acid" OR "torsemide" OR "Trehalose" OR "Treprostini  
 diethanolamine" OR "tretinoin" OR "trimethoxy flavone" OR "TRPA1/PDE4B/PDE7A ligand"  
 OR "TT saponin" OR "Turpentine" OR "U 69593" OR "ulinastatin" OR "vascular regenerative  
 therapy" OR "Vernonia cinerea" OR "vitamin D2" OR "vitamin K2" OR "Vitis vinifera" OR  
 "VR-1 receptor modulators" OR "WR1065" OR "Xilonix" OR "xylazine" OR "yang-warming"  
 OR "Yiqi Huayu" OR "zaprinast" OR "Zhenqing Capsule" OR "ziconotide")

#### 6-1b2. Final Query

(#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12  
 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#2 AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR  
 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR  
 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#4 AND (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR  
 #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#5 AND (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR  
 #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#6 AND (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16  
 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

#7 AND (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17  
 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#8 AND (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18  
 OR #19 OR #20)) NOT (#21 OR #22)

(#9 AND (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR  
 #19 OR #20)) NOT (#21 OR #22)

(#10 AND (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR  
 #20)) NOT (#21 OR #22)

(#11 AND (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20))  
 NOT (#21 OR #22)

(#12 AND (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21  
 OR #22)

(#13 AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#14 AND (#15 OR #16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#15 AND (#16 OR #17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#16 AND (#17 OR #18 OR #19 OR #20)) NOT (#21 OR #22)

(#17 AND (#18 OR #19 OR #20)) NOT (#21 OR #22)

(#18 AND (#19 OR #20)) NOT (#21 OR #22)

(#19 AND (#20)) NOT (#21 OR #22)

### 6-1b3. Treatment Discovery Validation

Treatment discovery validation (or contributing factor or characteristic validation) is defined as the process of demonstrating that the candidate treatment has not been used or proposed for application to PN/PAD. This will be a function not only of the scope of PN/PAD assumed, but which databases are included in the definition of the PN/PAD literature.

The present study used the Pubmed version of Medline to retrieve the core PN/PAD literature, and used both the Pubmed and Thomson Reuters versions to determine previous use. All the treatment discoveries listed in the present monograph were not present in these versions of the PN/PAD literature.

There could be other ways to define the scope of PN/PAD. There are also many other databases that could be searched for validation purposes, including other literature indexes, patent databases, books, magazine articles not indexed in Pubmed or Thomson Reuters, etc. Thus, the present validation has to be viewed as limited, even though it is the method used, and the databases used, by most (if not all) of the literature-based discovery community. For discovery patenting purposes, or other purposes, more extensive validation and larger numbers of databases, may be required.

In summary, each candidate potential PN/PAD treatment retrieved using the above query required validation before becoming a potential PN/PAD treatment. The candidate potential PN/PAD treatment was intersected with the core PN/PAD literature, and was validated only after this intersection showed orthogonality.

A final note of interest. In the AD study [Kostoff, Porter, Buchtel, 2018], five potential AD treatment discoveries were shown as an illustrative example (ten were shown in the present study, in Chapter 2). While none of those five were retrieved with the single query used to generate the ten illustrative examples in the present monograph, all five turn out to be treatment discoveries in the PN/PAD study as well (they passed the final validation step). In those five examples, most of the biomarkers identified that changed in the desired directions were applicable to the PN/PAD study as well. Because of the biomarker identification experience gained in the AD study, the PN/PAD study generated about four times the number of biomarkers

compared to the AD study. Most of the AD biomarkers are contained within the list of PN/PAD biomarkers, especially those used for the actual AD discovery query.

[References - Chapter 6](#)



## Chapter 7

## TABLES

Table 7A-1 - Existing PN/PAD Contributing Factors

(CODE: #REC is the number of records that contain the phrase)

#REC	CONTRIBUTING FACTOR
2507	chemotherapy
2265	smoking
1140	High cholesterol diet
985	paclitaxel
821	HIV-1
745	dialysis
708	infections
683	viruses
570	cisplatin
570	trauma
545	depression
524	oxaliplatin
508	hemodialysis
503	Bortezomib
442	alcohol
	Statins [PN only]
393	alcohol consumption
378	highly active antiretroviral therapy
361	radiation
357	anesthesia
351	thalidomide
347	vincristine
340	peripheral nerve injury
337	lifestyle
332	leprosy
329	radiation therapy
324	taxanes
323	cyclophosphamide
314	hepatitis
296	Streptozotocin
230	carboplatin
217	platinum
201	chronic constriction injury
196	docetaxel
186	Hepatitis C Virus
184	antibiotics
162	doxorubicin

149	Arsenic
148	stavudine
140	5-fluorouracil
131	sedentary
125	advanced glycosylation end products
121	capecitabine
121	tuberculosis
119	zidovudine
118	iatrogenic
118	Taxol
111	methotrexate
110	lenalidomide
107	cytomegalovirus
106	arthroplasty
96	drug-induced
96	gemcitabine
96	malnutrition
96	NMDA
95	antiviral
93	didanosine
93	spinal cord injury
91	melphalan
91	zalcitabine
90	proteasome inhibitors
89	Staphylococcus
86	alkaloids
86	Mycobacterium
85	renal transplantation
83	axotomy
83	liver transplant
83	N-methyl-D-aspartate
83	organophosphate pesticides
82	burn
81	injury-induced
76	Vinca alkaloids
76	vinorelbine
74	etoposide
73	coronary angioplasty

67	solvents
66	high fat diet
65	Zinc
64	formalin
63	bevacizumab
62	fluorouracil
61	cyclosporin
61	eribulin
61	Mycobacterium leprae
	Simvastatin [PN only]
60	cancer therapy
59	Acrylamide
59	inactivity
59	naloxone
58	ixabepilone
56	epirubicin
55	Thallium
54	anticonvulsant
54	DDI
54	ifosfamide
54	linezolid
54	Pyridoxine
49	acetone
49	environmental factors
48	n-hexane
48	occupational exposure
	Atorvastatin [PN only]
47	Borrelia burgdorferi
47	brentuximab
46	carfilzomib
46	irinotecan
46	isoniazid
45	axonal injury
44	Mercury
44	metronidazole
43	bariatric surgery
43	gluten
43	lamivudine
42	hand-arm vibration
42	levodopa
39	lead exposure
39	partial sciatic nerve ligation
39	trastuzumab
38	bone marrow transplantation
38	herpesviruses
38	lipopolysaccharide

37	interferon-alpha
37	nevirapine
37	thiamine deficiency
37	vaccine
37	vinblastine
36	2',3'-dideoxycytidine
36	arachidonic acid
35	2,5-hexanedione
35	CSA
35	Freund's adjuvant
35	HTLV-1
34	dichloroacetate
34	hip arthroplasty
33	bupivacaine
32	AZT
32	efavirenz
32	pesticides
31	Amiodarone
31	bleomycin
31	carrageenan
31	gastrectomy
31	glucocorticoids
30	carbon monoxide
30	valproic acid
29	Chlamydia pneumoniae
29	Ischemia-reperfusion
29	phenytoin
28	cytotoxic agents
28	vitamin D deficient
27	adriamycin
27	bacterium
27	insecticide
27	varicella zoster virus
26	dapsone
26	metals
26	vitamin B12 deficiencies
25	cannabis
25	Epstein Barr virus
25	Infliximab
25	Iron Deficiency
25	neurotoxins
25	nitrous oxide
24	cadmium
24	Campylobacter jejuni
24	disulfiram
24	immunization

24	purine
23	5-hydroxytryptamine
23	copper deficiency
23	Cytosine Arabinoside
23	Helicobacter pylori
23	hepatitis B virus
23	hypothermia
23	mitomycin C
22	atenolol
22	ciprofloxacin
22	fluoroquinolone
22	heavy metals
22	infectious agents
22	spine surgery
22	suramin
21	Drug Abuse
21	gp120
21	lymphotropic virus
21	Retroviruses
21	tacrolimus
21	vibration-induced
20	colchicine
20	epothilone B
20	folate deficient
20	nutritional deficiency
20	pomalidomide
19	2',3'-dideoxyinosine
19	etanidazole
19	filgrastim
19	high glucose
19	hyperthermia
19	protease inhibitors
19	substance abuse
19	tamoxifen
19	tenofovir
19	traumatic brain injury
19	tumor necrosis factor (TNF)-alpha
18	cytarabine
18	lithium
18	organic solvent
18	parasite
18	rifampicin
18	streptozocin
17	amyloid beta
17	chlorpyrifos
17	cholecystokinin

17	fludarabine
17	interferon-gamma
17	itraconazole
17	Vindesine
17	voriconazole
16	interferons
	Pravastatin [PN only]
16	syphilis
15	cobalt
15	fungi
15	H1N1 vaccine
15	lisinopril
15	Streptokinase
14	aluminum
14	enalapril
14	Ganciclovir
14	Heroin
14	Hydrogen peroxide
14	Leflunomide
14	mechanical compression
14	mitoxantrone
14	Mycobacterium tuberculosis
13	carbon disulfide
13	Cremophor EL
13	etanercept
13	FK506
13	H. pylori
13	herbicide
13	toluene
12	cabazitaxel
12	ethambutol
12	Ethylene oxide
12	galactose
12	hydroxyurea
12	iron overload
12	L-tryptophan
	Lovastatin [PN only]
12	nilotinib
12	Panobinostat
12	Phenobarbital
12	Pseudomonas aeruginosa
12	red meat
12	SIV-infected
12	tobacco smoke
12	Trypanosoma cruzi
12	zinc deficient

11	3'-azido-3'-deoxythymidine
11	almitrine
11	Ara-C
11	cigarette smoke
11	cocaine
11	Coxsackie
11	cyanide
11	enterovirus
11	fructose
11	hydrogen sulfide
11	INH
11	tellurium
10	carbamate
10	chloroquine
10	coal
10	contaminants
10	cranial irradiation
10	environmental exposure
10	hypoxia-induced
10	idazoxan
10	lentivirus
10	lysophosphatidic acid
10	Misonidazole
10	naltrindole
10	phenol
10	proton pump inhibitor
10	sodium arsenite
10	sodium thiosulfate
10	tri-ortho-cresyl phosphate
9	air pollution
9	allopurinol
9	cetuximab
9	chronic stress
9	dithiocarbamates
9	HFD
9	indinavir
9	levofloxacin
9	manganese
9	methamidophos
9	neuroleptic
9	neurotoxicants
9	resiniferatoxin
9	ritonavir
9	Taxotere
9	topotecan
8	abdominal surgery

8	acetic acid
8	Agent Orange
8	amantadine
8	antipsychotics
8	Clioquinol
8	CS2
8	dietary deficiency
8	ergotamine tartrate
8	HCT
8	head trauma
8	L-dopa
8	methyl bromide
8	nitrofurantoin
8	pertussis toxin
8	pollutants
8	theophylline
8	vitamin B6 deficiency
7	Alemtuzumab
7	amphotericin B
7	atipamezole
7	BCNU
7	beam radiation
7	benznidazole
7	ciguatoxin
7	dacarbazine
7	dioxin
7	dust
7	estramustine phosphate
7	feline immunodeficiency virus
7	fine particulate matter
7	fluconazole
7	forskolin
7	ipilimumab
7	LCIG
7	methanol
7	methysergide
7	Nelarabine
7	pemetrexed
7	PNB
7	posaconazole
7	sevoflurane
7	Styrene
7	sweeteners
7	tetanus
7	Velcade
6	acyclovir

6	adalimumab
6	alloxan
6	dideoxyinosine
6	entecavir
6	flecainide
6	Germanium
6	hydrocarbon
6	LPA-induced
6	manual work
6	medication-induced
6	methyl mercury
6	Methylglyoxal
6	metoclopramide
6	mipafox
6	momelotinib
6	N2O
6	nedaplatin
6	pertuzumab
6	petroleum
6	podophyllin
6	procarbazine
6	quinolinic acid
6	Sorafenib
6	sorbinil
6	sugars
5	1-bromopropane
5	2',3'-dideoxy-3'-deoxythymidine
5	acitretin
5	atazanavir
5	bendamustine
5	Brucella
	Cerivastatin [PN only]
5	Chloroform
5	Cryptococcus
5	D-glucose
5	dasatinib
5	depolarization-induced
5	gasoline
5	gonadotropin-releasing hormone
5	hydroxychloroquine
5	insulin-induced
5	LY294002
5	malathion
5	meloxicam
5	mineralocorticoid
5	MPTP

5	omeprazole
5	palmitate
5	Porphyromonas gingivalis
5	propafenone
5	riboflavin deficiency
5	rofecoxib
5	salt intake
5	saquinavir
5	Sleep deprivation
5	Spirochetes
5	strontium ranelate
5	strychnine
5	traffic accidents
5	trichloroethylene
5	zymosan
4	2,3,7,8-tetrachlorodibenzo-p-dioxin
4	2-CdA
4	acrylonitrile
4	allyl isothiocyanate
4	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
4	anabolic steroids
4	CCNU
4	Chloramphenicol
4	diethylene glycol
4	diisopropyl phosphorofluoridate
	Fluvastatin [PN only]
4	folic acid deficiency
4	Fotemustine
4	gold salts
4	hydralazine
4	inorganic mercury
4	lactacystin
4	lapatinib
4	lomustine
4	mecamylamine
4	methyl methacrylate
4	methyl n-butyl ketone
4	mustard oil
4	N,N-diethyldithiocarbamate
4	NGF-induced
4	ofloxacin
4	ovariectomy
4	p-bromophenylacetylurea
4	paints
4	Perhexiline

4	phorbol 12-myristate 13-acetate
4	polychlorinated biphenyls
4	prions
4	psychological stress
4	Salinomycin
4	saxitoxin
4	sertraline
4	sofosbuvir
4	squatting position
4	thiotepa
4	Toxoplasma
4	Vp-16
4	West Nile virus
3	1,2-diacetylbenzene
3	2-bp
3	actinomycin D
3	Bisphenol
3	bradykinin-induced
3	carcinogens
3	citalopram
3	Corynebacterium
3	dactinomycin
3	daunorubicin
3	dimethyl sulfoxide
3	Enfuvirtide
3	Ertapenem
3	estrogen deficiency
3	ethyl acetate
3	felodipine
3	fialuridine
3	formaldehyde
3	gastric surgery
3	gefitinib
3	glue sniffing
3	glues
3	glutamate-induced
3	HSV-1
3	intermittent hypoxia
3	kainic acid
3	lysophosphatidylcholine
3	methamphetamine
3	montelukast
3	Mycobacterium avium
3	naproxen
3	natalizumab
3	nivolumab

3	pazopanib
3	phenelzine
3	physical trauma
3	pirarubicin
3	piroxicam
3	Polysorbate 80
3	pyrethroid
3	rabies vaccine
3	restraint stress
3	ruxolitinib
3	sotalol
3	Staurosporine
3	sunitinib
3	tegafur
3	teniposide
3	Theiler's murine encephalomyelitis virus
3	Treponema denticola
3	undernutrition
3	vorinostat
2	1,1,1-trichloroethane
2	1,2-Diethylbenzene
2	Abraxane
2	Adrenaline-induced
2	altretamine
2	ammonium chloride
2	amphetamine
2	auranofin
2	axitinib
2	benzene
2	benzimidazole
2	bexarotene
2	busulfan
2	cerebral artery occlusion
2	childhood infection
2	Chlamydomydia pneumoniae
2	Chlorophenoxy herbicides
2	CNS infections
2	cyclohexanone
2	daratumumab
2	DDT
2	dengue virus
2	desogestrel
2	dichlorvos
2	Diethylbenzene
2	Diphenylhydantoin

2	disopyramide
2	doxifluridine
2	environmental toxicants
2	epoxy resins
2	escitalopram
2	ethionamide
2	Ethylene glycol
2	ferric chloride
2	HDI
2	hexacarbons
2	hexamethylmelamine
2	hydrazine
2	Ibrutinib
2	imidazole
2	isonicotinic acid
2	Karwinskia humboldtiana
2	lansoprazole
2	lasalocid sodium
2	leptin deficiency
2	levonorgestrel
2	lopinavir
2	methyl ethyl ketone
2	methyllycaconitine
2	Mitochondrial toxins
2	MK-2206
2	moxifloxacin
2	mumps measles rubella vaccination
2	mycotoxins
2	N-methylolacrylamide
2	NaHS
2	naphthalene
2	nerve tissue vaccine
2	nitroimidazole
2	organochlorine pesticides
2	organotin
2	pancuronium bromide
2	Paraquat
2	Pefloxacin
2	pembrolizumab
2	pentanedioic acid
2	persistent organic pollutants
2	phenylmethylsulfonyl fluoride
2	poliovirus
2	ponatinib
2	procainamide
2	quinolone

2	raltegravir
2	ramucirumab
2	recreational drugs
2	REMSD
2	RFR
2	romidepsin
2	sepsis-induced
2	streptomycin
2	surgery-induced
2	TBE
2	Teriflunomide
2	Toxocara canis
2	Treponema pallidum
2	Trichlorfon
2	trichlorophenol
2	Trichloropropane
2	ultraviolet irradiation
2	uracil
2	vaccination against MD
2	valganciclovir
2	vitamin E deficient
2	western diet
2	xenobiotic
2	xylene
1	1,2,4-triethylbenzene)
1	1,2-diaminocyclohexane
1	1,3-diethylbenzene
1	1,3-dipropyl-8-cyclopentylxanthine
1	1,4-diethylbenzene
1	1-hydroxyphenanthrene
1	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
1	1-naphthyl N-methylcarbamate
1	2,2-dichlorovinyl dibutyl phosphate
1	2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate)
1	2,4,5-T
1	2,4-dichlorophenoxy
1	2,4-dinitrophenol
1	2-bromopropane
1	2-hydroxyfluorene
1	2-hydroxyphenanthrene
1	3,4-dihydroxyphenylglycolaldehyde
1	3,4-dimethyl-2,5-hexanedione
1	3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid

1	3-hydroxyfluorene
1	3-nitropropionic acid
1	3-NPA
1	6-OHDA
1	8-phenyltheophylline
1	acetylhydrazine
1	acetylisoniazid
1	aconitine
1	acrolein
1	Actinobacillus actinomycetemcomitans
1	Acute nerve injuries
1	ADI-PEG 20
1	adverse upper limb postures
1	aerosolize CNS tissue
1	AF64A
1	AG-012986
1	AlCl3
1	alpha-latrotoxin
1	aminoglycoside-induced
1	amprenavir
1	androgenic steroids
1	anti-tetanus vaccination
1	antimony
1	aprepitant
1	atherogenic diet
1	aurothioglucose
1	BMS-275183
1	BoNT/B
1	BoNT/D
1	bromate intoxication
1	buckthorn
1	Bunyaviridae
1	butyl acetate
1	C-4 methyl carbonate
1	C2-ceramide
1	cacodylic acid
1	Calmette Guerin (BCG) vaccination
1	Carbetimer
1	carbofuran
1	CGS 21595
1	chemical warfare agents
1	Chikungunya virus
1	chlorinated solvents
1	chlorofluorocarbon
1	chromium deficiency
1	chronic restraint stress

1	CP intoxication
1	cuprizone
1	Cycloleucine
1	cypermethrin
1	cytolethal distending toxin
1	darunavir
1	DEG intoxication
1	deltamethrin
1	dextroamphetamine
1	di-n-butyl-2,2-dichlorovinyl phosphate
1	diacetylhydrazine
1	dichlorohydrin
1	diclofenac sodium
1	dieldrin
1	Dimethylamine borane
1	Diocetyl phthalate
1	diquat
1	DMAB
1	DOPEGAL)
1	dronedarone
1	DSP-4
1	Dursban
1	dyes
1	efalizumab
1	Efudex)
1	erythrosin B
1	ethanolamine
1	ethyl chloride
1	Ethylene chlorohydrin
1	etonogestrel
1	ferric ammonium citrate
1	flavivirus
1	Flecainide acetate
1	Formic acid
1	fractalkine-induced
1	frequent monotonous movements
1	fuel oils
1	fungicides
1	gamma rays
1	gemifloxacin
1	gestodene
1	griseofulvin
1	guthion
1	GYKI 52466
1	Halaven
1	hantavirus



1	Harmine
1	hazardous chemicals
1	HCH
1	HPV vaccine
1	hydroquinone
1	ICI 118,551
1	indocyanine green-loaded boronated maltodextrin
1	indoxacarb
1	intoxication with Kh fruit
1	isofenphos
1	isopropanol
1	Ixempra
1	kerosene
1	keyboarding
1	L-tryptophan-induced
1	labetalol
1	lard
1	lauric acid
1	lomefloxacin
1	lorlatinib
1	Lyme vaccination
1	m-tolyl methylcarbamate
1	MAF intoxication
1	MBK
1	MD vaccination
1	megestrol acetate
1	metergoline
1	methomyl
1	methylcyclopentadienyl manganese tricarbonyl
1	mobile phones
1	N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine
1	n-heptane
1	N-methylformamide
1	n-propyl bromine
1	n-propylbromide
1	naphthoquinone
1	neuropathy-inducing drugs
1	Nimorazole
1	nintedanib
1	nitromethane
1	norbinaltorphimine
1	NP-polySA vaccine
1	O,O-diethyl O-3,5,6-trichloro-2-pyridyl

	phosphorothioate
1	OGD
1	oligomycin
1	OS-induced
1	OspA-vaccinated
1	oxychlorane
1	oxygen-glucose deprivation
1	p,p'-DDE
1	PAHs
1	pantoprazole)
1	perazine
1	Perfluorooctanoic acid
1	peroxisomal acyl-CoA oxidase deficiency
1	PFOA
1	phenothiazine
1	phosphamidon/mevinphos
1	phosphatidyl ethanolamine
1	phosphine
1	photosensitive dyes
1	phthalates
1	physical overload
1	piragliatin
	Pitavastatin [PN only]
1	polychlorinated dioxins
1	Polycyclic aromatic hydrocarbons
1	Pralatrexate
1	pronase
1	propylthiouracil
1	RA-induced
1	radiofrequency radiation
1	raltitrexed
1	rapeseed oil
1	refined carbohydrates
1	repeated mechanical trauma
1	repetitive work
1	Repin
1	Revlimid
1	rotenone-induced
1	roxarsone
1	S arvensis
1	S. occidentalis intoxication
1	samarium
1	selenium-deficient diet
1	silicones
1	Sinemet

1	Sodium 3,5,6-trichloropyridin-2-ol
1	sodium arsenate
1	sodium bromate
1	sulfonamide
1	sulindac
1	taenia solium
1	Tannerella forsythia
1	temozolomide
1	temsirolimus
1	teriparatide
1	tert-butylhydroperoxide
1	tetracaine
1	tetrachlorethylene
1	tetralin)
1	THP
1	trabectedin
1	trans fatty acids
1	trans-nonachlor
1	traumatic stress

1	trichloronit
1	Trichloroethane
1	tricresyl phosphate
1	trimethyltin
1	triphenyltin
1	trovafloxacin
1	TTR-induced
1	tungsten
1	vecuronium bromide
1	Videx
1	X-radiation
1	zileuton
1	Zoloft

**Table 7A-2 - Chemotherapy Co-Occurrences with other Causes**

(CODE: #CO-OCC is the number of co-occurrences of the two phrases)

#REC	CAUSE	#CO-OCC
2507	chemotherapy	2507
985	paclitaxel	630
570	cisplatin	392
524	oxaliplatin	347
324	taxanes	223
347	vincristine	190
329	radiation therapy	166
230	carboplatin	161
217	platinum	156
503	Bortezomib	144
196	docetaxel	133
361	radiation	115
323	cyclophosphamide	112
140	5-fluorouracil	97
162	doxorubicin	95
351	thalidomide	93
118	Taxol	70

121	capecitabine	69
86	alkaloids	64
76	Vinca alkaloids	60
96	gemcitabine	59
76	vinorelbine	50
74	etoposide	50
111	methotrexate	46
63	bevacizumab	45
56	epirubicin	41
54	ifosfamide	40
62	fluorouracil	40
61	eribulin	38
60	cancer therapy	34
545	depression	33
90	proteasome inhibitors	31
46	irinotecan	30
821	HIV-1	28
96	drug-induced	28
708	infections	27

37	vinblastine	26
31	bleomycin	25
58	ixabepilone	23
91	melphalan	21
683	viruses	20
184	antibiotics	20
23	mitomycin C	18
39	trastuzumab	17
110	lenalidomide	17
22	suramin	16
49	acetone	16
570	trauma	16
27	adriamycin	16
47	brentuximab	16
28	cytotoxic agents	14
18	cytarabine	13
2265	smoking	13
378	highly active antiretroviral therapy	12
332	leprosy	12
17	Vindesine	12
442	alcohol	11
393	alcohol consumption	10
19	tamoxifen	10
31	gastrectomy	10
121	tuberculosis	10
96	NMDA	10
201	chronic constriction injury	9
64	formalin	9
337	lifestyle	9
340	peripheral nerve injury	9
23	Cytosine Arabinoside	8
11	Ara-C	8
9	cetuximab	8
357	anesthesia	7
19	filgrastim	7
91	zalcitabine	7
83	N-methyl-D-aspartate	7
13	Cremophor EL	7
38	bone marrow transplantation	7
118	iatrogenic	6
14	mitoxantrone	6
9	Taxotere	6
9	topotecan	6
61	cyclosporin	6

20	epothilone B	6
54	anticonvulsant	6
54	Pyridoxine	6
6	procarbazine	6
296	Streptozotocin	6
25	cannabis	5
36	2',3'-dideoxycytidine	5
46	isoniazid	5
45	axonal injury	5
148	stavudine	5
10	cranial irradiation	5
149	Arsenic	5
37	interferon-alpha	5
30	valproic acid	4
26	metals	4
59	naloxone	4
7	pemetrexed	4
16	interferons	4
18	lithium	4
19	hyperthermia	4
67	solvents	4
6	nedaplatin	4
95	antiviral	4
27	bacterium	4
46	carfilzomib	4
119	zidovudine	4
29	phenytoin	4
17	amyloid beta	4
17	voriconazole	4
10	sodium thiosulfate	4
4	CCNU	4
4	lomustine	4
20	colchicine	3
19	tumor necrosis factor (TNF)-alpha	3
22	heavy metals	3
10	idazoxan	3
23	hypothermia	3
11	INH	3
86	Mycobacterium	3
745	dialysis	3
38	herpesviruses	3
1140	High cholesterol diet	3
7	Nelarabine	3
17	fludarabine	3
17	itraconazole	3

12	cabazitaxel	3
19	etanidazole	3
93	spinal cord injury	3
24	purine	3
7	BCNU	3
14	aluminum	3
65	Zinc	3
314	hepatitis	3
3	gefitinib	3
44	metronidazole	2
43	lamivudine	2
7	dacarbazine	2
39	partial sciatic nerve ligation	2
35	CSA	2
32	AZT	2
186	Hepatitis C Virus	2
31	carrageenan	2
31	glucocorticoids	2
6	pertuzumab	2
26	dapsone	2
12	Panobinostat	2
25	nitrous oxide	2
5	meloxicam	2
7	posaconazole	2
21	tacrolimus	2
5	bendamustine	2
6	metoclopramide	2
19	substance abuse	2
8	nitrofurantoin	2
107	cytomegalovirus	2
96	malnutrition	2
7	Velcade	2
93	didanosine	2
83	axotomy	2
83	liver transplant	2
82	burn	2
15	fungi	2
66	high fat diet	2
61	Mycobacterium leprae	2
7	beam radiation	2
59	Acrylamide	2
4	Fotemustine	2
59	inactivity	2
4	thiotepa	2
4	Vp-16	2
3	actinomycin D	2

3	daunorubicin	2
49	environmental factors	2
3	nivolumab	2
3	pirarubicin	2
3	Polysorbate 80	2
3	tegafur	2
2	MK-2206	2
6	Sorafenib	1
44	Mercury	1
7	methysergide	1
19	traumatic brain injury	1
48	n-hexane	1
21	gp120	1
7	PNB	1
9	manganese	1
12	hydroxyurea	1
54	linezolid	1
54	DDI	1
13	carbon disulfide	1
8	HCT	1
10	carbamate	1
7	sevoflurane	1
19	2',3'-dideoxyinosine	1
14	Mycobacterium tuberculosis	1
81	injury-induced	1
28	vitamin D deficient	1
9	levofloxacin	1
83	organophosphate pesticides	1
85	renal transplantation	1
34	dichloroacetate	1
125	advanced glycosylation end products	1
131	sedentary	1
8	pertussis toxin	1
508	hemodialysis	1
18	rifampicin	1
10	lentivirus	1
7	estramustine phosphate	1
8	pollutants	1
5	strontium ranelate	1
27	varicella zoster virus	1
30	carbon monoxide	1
35	HTLV-1	1
12	nilotinib	1

35	Freund's adjuvant	1
32	pesticides	1
7	Alemtuzumab	1
6	acyclovir	1
6	momelotinib	1
5	2',3'-dideoxy-3'-deoxythymidine	1
15	H1N1 vaccine	1
5	depolarization-induced	1
25	neurotoxins	1
31	Amiodarone	1
14	enalapril	1
14	Ganciclovir	1
7	fluconazole	1
14	Hydrogen peroxide	1
5	MPTP	1
4	allyl isothiocyanate	1
35	2,5-hexanedione	1
12	tobacco smoke	1
4	hydralazine	1
4	lactacystin	1
4	lapatinib	1
36	arachidonic acid	1
4	mecamylamine	1
4	NGF-induced	1
4	ovariectomy	1
4	psychological stress	1
4	Salinomycin	1
12	Ethylene oxide	1
4	Toxoplasma	1
23	5-hydroxytryptamine	1
12	zinc deficient	1
3	dactinomycin	1
12	ethambutol	1
3	dimethyl sulfoxide	1
3	fialuridine	1
38	lipopolysaccharide	1
29	Ischemia-reperfusion	1
9	indinavir	1

13	FK506	1
3	ruxolitinib	1
3	Staurosporine	1
3	sunitinib	1
6	dideoxyinosine	1
3	teniposide	1
3	vorinostat	1
2	Abraxane	1
2	altretamine	1
2	auranofin	1
2	axitinib	1
2	hexacarbons	1
2	hexamethylmelamine	1
2	methyllycaconitine	1
6	medication-induced	1
2	organotin	1
2	ramucirumab	1
2	streptomycin	1
1	1,2-diaminocyclohexane	1
1	Carbetimer	1
1	Halaven	1
1	megestrol acetate	1
1	N-methylformamide	1
1	raltitrexed	1
1	samarium	1
1	THP	1
1	trimethyltin	1

**Table 7A-3 - Lifestyle Co-Occurrences with other Causes**

#REC	CAUSE	#CO-OCC
337	lifestyle	337
2265	smoking	108
131	sedentary	44
1140	High cholesterol diet	35
442	alcohol	18
545	depression	11
59	inactivity	11
393	alcohol consumption	10
2507	chemotherapy	9
745	dialysis	6
361	radiation	4
570	trauma	3
329	radiation therapy	3
31	bleomycin	2
821	HIV-1	2
708	infections	2
96	malnutrition	2
60	cancer therapy	2
12	red meat	2
683	viruses	2
28	vitamin D deficient	2
43	bariatric surgery	2
85	renal transplantation	2
83	axotomy	2
83	liver transplant	2
125	advanced glycosylation end products	2
73	coronary angioplasty	2
66	high fat diet	2
5	salt intake	2
46	irinotecan	1

20	folate deficient	1
296	Streptozotocin	1
82	burn	1
11	cocaine	1
18	organic solvent	1
21	Drug Abuse	1
74	etoposide	1
324	taxanes	1
37	interferon-alpha	1
985	paclitaxel	1
67	solvents	1
570	cisplatin	1
118	iatrogenic	1
65	Zinc	1
49	environmental factors	1
14	Heroin	1
508	hemodialysis	1
10	contaminants	1
14	mechanical compression	1
9	ritonavir	1
4	psychological stress	1
3	physical trauma	1
2	recreational drugs	1

**Table 7A-4 - Contributing Factors Relevant to PN and to PAD**

#REC	CAUSE	#PN REC	#PAD REC
2507	chemotherapy	2315	119
2265	smoking	275	2124
1140	High cholesterol diet	261	1004
985	paclitaxel	874	69
821	HIV-1	696	134
745	dialysis	139	643
708	infections	391	393
683	viruses	548	182
570	cisplatin	515	20
570	trauma	269	260
545	depression	326	251
524	oxaliplatin	499	1
508	hemodialysis	105	428
503	Bortezomib	473	32
442	alcohol	232	230
412	statins	43	
393	alcohol consumption	266	147
378	highly active antiretroviral therapy	344	37
361	radiation	189	134
357	anesthesia	157	139
351	thalidomide	333	56
347	vincristine	328	11
340	peripheral nerve injury	229	18
337	lifestyle	78	283
332	leprosy	206	19
329	radiation therapy	245	50
324	taxanes	303	7
323	cyclophosphamide	288	80
314	hepatitis	267	142
296	Streptozotocin	273	40
230	carboplatin	215	5
217	platinum	194	6
201	chronic constriction injury	179	1
196	docetaxel	183	4
186	Hepatitis C Virus	155	107
184	antibiotics	101	102
162	doxorubicin	148	17
149	Arsenic	78	73
148	stavudine	143	3
140	5-fluorouracil	130	3
131	sedentary	34	108

125	advanced glycosylation end products	74	74
121	capecitabine	103	
121	tuberculosis	101	22
119	zidovudine	115	4
118	iatrogenic	55	37
118	Taxol	103	3
111	methotrexate	93	22
110	lenalidomide	102	19
107	cytomegalovirus	76	36
106	arthroplasty	36	48
96	drug-induced	86	15
96	gemcitabine	89	3
96	malnutrition	54	43
96	NMDA	84	3
95	antiviral	84	28
93	didanosine	88	2
93	spinal cord injury	56	37
91	melphalan	89	20
91	zalcitabine	91	2
90	proteasome inhibitors	79	3
89	Staphylococcus	33	67
86	alkaloids	83	3
86	Mycobacterium	62	4
85	renal transplantation	32	64
83	axotomy	42	2
83	liver transplant	65	17
83	N-methyl-D-aspartate	64	5
83	organophosphate pesticides	73	2
82	burn	46	32
81	injury-induced	64	2
76	Vinca alkaloids	75	1
76	vinorelbine	73	1
74	etoposide	68	9
73	coronary angioplasty	6	73
67	solvents	52	5
66	high fat diet	41	27
65	Zinc	44	17
64	formalin	56	1
63	bevacizumab	57	4
62	fluorouracil	57	1
61	cyclosporin	43	21
61	eribulin	57	2
61	Mycobacterium leprae	42	1
61	simvastatin	19	
60	cancer therapy	45	6



59	Acrylamide	49	2
59	inactivity	23	42
59	naloxone	50	2
58	ixabepilone	51	1
56	epirubicin	55	4
55	Thallium	21	33
54	anticonvulsant	49	2
54	DDI	53	1
54	ifosfamide	53	
54	linezolid	48	5
54	Pyridoxine	49	4
49	acetone	49	
49	environmental factors	23	32
48	n-hexane	45	
48	occupational exposure	35	2
47	atorvastatin	6	
47	Borrelia burgdorferi	34	5
47	brentuximab	45	1
46	carfilzomib	43	2
46	irinotecan	43	
46	isoniazid	43	2
45	axonal injury	32	4
44	Mercury	28	9
44	metronidazole	40	3
43	bariatric surgery	29	12
43	gluten	39	7
43	lamivudine	41	4
42	hand-arm vibration	17	2
42	levodopa	40	1
39	lead exposure	29	5
39	partial sciatic nerve ligation	35	
39	trastuzumab	38	1
38	bone marrow transplantation	29	7
38	herpesviruses	23	6
38	lipopolysaccharide	19	12
37	interferon-alpha	34	11
37	nevirapine	36	1
37	thiamine deficiency	34	4
37	vaccine	27	10
37	vinblastine	35	3
36	2',3'-dideoxycytidine	36	
36	arachidonic acid	7	27
35	2,5-hexanedione	32	
35	CSA	31	5
35	Freund's adjuvant	22	1
35	HTLV-1	32	8

34	dichloroacetate	27	9
34	hip arthroplasty	11	9
33	bupivacaine	9	8
32	AZT	31	2
32	efavirenz	31	3
32	pesticides	23	5
31	Amiodarone	24	9
31	bleomycin	26	4
31	carrageenan	24	
31	gastrectomy	29	1
31	glucocorticoids	21	17
30	carbon monoxide	13	19
30	valproic acid	27	2
29	Chlamydia pneumoniae		29
29	Ischemia-reperfusion	4	27
29	phenytoin	24	2
28	cytotoxic agents	25	7
28	vitamin D deficient	8	23
27	adriamycin	25	7
27	bacterium	15	11
27	insecticide	23	
27	varicella zoster virus	18	6
26	dapsone	21	1
26	metals	19	9
26	vitamin B12 deficiencies	23	3
25	cannabis	16	10
25	Epstein Barr virus	20	5
25	Infliximab	21	6
25	Iron Deficiency	19	9
25	neurotoxins	18	2
25	nitrous oxide	16	4
24	cadmium	5	16
24	Campylobacter jejuni	23	1
24	disulfiram	23	
24	immunization	18	5
24	purine	19	5
23	5-hydroxytryptamine	4	18
23	copper deficiency	16	1
23	Cytosine Arabinoside	20	2
23	Helicobacter pylori	9	16
23	hepatitis B virus	21	10
23	hypothermia	12	9
23	mitomycin C	22	1
22	atenolol	2	20
22	ciprofloxacin	14	8
22	fluoroquinolone	19	2

22	heavy metals	18	5
22	infectious agents	11	9
22	spine surgery	8	5
22	suramin	20	
21	Drug Abuse	10	16
21	gp120	20	1
21	lymphotropic virus	16	6
21	Retroviruses	15	6
21	tacrolimus	15	7
21	vibration-induced	12	
20	colchicine	16	7
20	epothilone B	19	1
20	folate deficient	14	6
20	nutritional deficiency	19	2
20	pomalidomide	17	4
19	2',3'-dideoxyinosine	18	
19	etanidazole	18	
19	filgrastim	16	3
19	high glucose	17	3
19	hyperthermia	11	2
19	protease inhibitors	14	8
19	substance abuse	11	7
19	tamoxifen	14	4
19	tenofovir	18	2
19	traumatic brain injury	14	12
19	tumor necrosis factor (TNF)- alpha	15	4
18	cytarabine	17	
18	lithium	16	
18	organic solvent	11	3
18	parasite	12	2
18	rifampicin	12	3
18	streptozocin	17	1
17	amyloid beta	11	3
17	chlorpyrifos	14	
17	cholecystokinin	16	1
17	fludarabine	16	1
17	interferon-gamma	10	3
17	itraconazole	15	2
17	Vindesine	17	1
17	voriconazole	13	3
16	interferons	14	3
16	pravastatin	2	
16	syphilis	12	3
15	cobalt	11	4
15	fungi	10	4

15	H1N1 vaccine	11	4
15	lisinopril	2	13
15	Streptokinase	1	12
14	aluminum	9	3
14	enalapril	6	9
14	Ganciclovir	11	
14	Heroin	10	3
14	Hydrogen peroxide	6	6
14	Leflunomide	14	1
14	mechanical compression	9	7
14	mitoxantrone	14	
14	Mycobacterium tuberculosis	12	1
13	carbon disulfide	10	3
13	Cremophor EL	12	1
13	etanercept	11	4
13	FK506	8	1
13	H. pylori	5	9
13	herbicide	11	1
13	toluene	12	
12	cabazitaxel	11	1
12	ethambutol	11	1
12	Ethylene oxide	9	2
12	galactose	11	
12	hydroxyurea	11	
12	iron overload	6	6
12	L-tryptophan	10	1
12	Lovastatin	4	
12	nilotinib	2	8
12	Panobinostat	10	1
12	Phenobarbital	10	1
12	Pseudomonas aeruginosa	6	10
12	red meat	4	7
12	SIV-infected	12	
12	tobacco smoke	2	10
12	Trypanosoma cruzi	8	1
12	zinc deficient	12	
11	3'-azido-3'-deoxythymidine	10	
11	almitrine	11	1
11	Ara-C	10	
11	cigarette smoke		10
11	cocaine	6	8
11	Coxsackie	10	1
11	cyanide	10	
11	enterovirus	7	3
11	fructose	9	2
11	hydrogen sulfide	5	6

11	INH	10	
11	tellurium	9	
10	carbamate	7	
10	chloroquine	7	3
10	coal	3	4
10	contaminants	7	5
10	cranial irradiation	8	
10	environmental exposure	3	5
10	hypoxia-induced	3	9
10	idazoxan	10	
10	lentivirus	7	2
10	lysophosphatidic acid	7	1
10	Misonidazole	10	
10	naltrindole	8	
10	phenol	5	2
10	proton pump inhibitor	4	6
10	sodium arsenite	10	
10	sodium thiosulfate	8	2
10	tri-ortho-cresyl phosphate	10	1
9	air pollution		8
9	allopurinol	5	5
9	cetuximab	8	
9	chronic stress	4	4
9	dithiocarbamates	8	
9	HFD	7	3
9	indinavir	9	
9	levofloxacin	8	
9	manganese	6	3
9	methamidophos	9	
9	neuroleptic	5	1
9	neurotoxicants	7	1
9	resiniferatoxin	7	
9	ritonavir	7	2
9	Taxotere	8	
9	topotecan	9	1
8	abdominal surgery	5	2
8	acetic acid	6	1
8	Agent Orange	7	1
8	amantadine	8	1
8	antipsychotics	4	5
8	Clioquinol	2	
8	CS2	6	2
8	dietary deficiency	8	1
8	ergotamine tartrate	1	7
8	HCT	3	5
8	head trauma	8	4

8	L-dopa	8	1
8	methyl bromide	5	
8	nitrofurantoin	6	1
8	pertussis toxin	5	3
8	pollutants	2	6
8	theophylline	1	6
8	vitamin B6 deficiency	7	1
7	Alemtuzumab	7	3
7	amphotericin B	3	3
7	atipamezole	6	
7	BCNU	7	
7	beam radiation	5	2
7	benznidazole	7	
7	ciguatoxin	4	
7	dacarbazine	7	
7	dioxin	6	
7	dust	5	
7	estramustine phosphate	7	1
7	feline immunodeficiency virus	5	3
7	fine particulate matter		6
7	fluconazole	4	2
7	forskolin	1	3
7	ipilimumab	7	1
7	LCIG	7	
7	methanol	5	2
7	methysergide	7	1
7	Nelarabine	6	
7	pemetrexed	6	
7	PNB	4	
7	posaconazole	6	1
7	sevoflurane	6	1
7	Styrene	5	
7	sweeteners	5	2
7	tetanus	6	
7	Velcade	7	
6	acyclovir	4	1
6	adalimumab	4	3
6	alloxan	6	1
6	dideoxyinosine	6	
6	entecavir	6	1
6	flecainide	5	
6	Germanium	5	
6	hydrocarbon	4	2
6	LPA-induced	5	
6	manual work	4	
6	medication-induced	6	1

6	methyl mercury	4	
6	Methylglyoxal	5	2
6	metoclopramide	6	1
6	mipaflox	6	
6	momelotinib	6	
6	N2O	4	
6	nedaplatin	6	
6	pertuzumab	6	
6	petroleum	5	2
6	podophyllin	5	
6	procarbazine	6	
6	quinolinic acid	3	3
6	Sorafenib	4	2
6	sorbinil	5	
6	sugars	4	2
5	1-bromopropane	4	
5	2',3'-didehydro-3'- deoxythymidine	4	
5	acitretin	4	
5	atazanavir	5	1
5	bendamustine	4	
5	Brucella	4	1
5	cerivastatin	1	
5	Chloroform	5	
5	Cryptococcus	2	2
5	D-glucose	2	3
5	dasatinib	2	2
5	depolarization-induced	5	
5	gasoline	4	
5	gonadotropin-releasing hormone	3	2
5	hydroxychloroquine	5	
5	insulin-induced	4	
5	LY294002	4	1
5	malathion	5	
5	meloxicam	5	
5	mineralocorticoid	2	3
5	MPTP	2	1
5	omeprazole	2	2
5	palmitate	4	2
5	Porphyromonas gingivalis		3
5	propafenone	5	
5	riboflavin deficiency	4	
5	rofecoxib	2	4
5	salt intake	1	5
5	saquinavir	5	

5	Sleep deprivation	4	
5	Spirochetes	4	
5	strontium ranelate	1	4
5	strychnine	5	
5	traffic accidents	2	1
5	trichloroethylene	5	
5	zymosan	4	1
4	2,3,7,8-tetrachlorodibenzo-p-dioxin	4	1
4	2-CdA	4	
4	acrylonitrile	4	
4	allyl isothiocyanate	4	1
4	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	4	
4	anabolic steroids	1	2
4	CCNU	4	
4	Chloramphenicol	3	1
4	diethylene glycol	4	
4	diisopropyl phosphorofluoridate	4	
4	fluvastatin	2	
4	folic acid deficiency	3	1
4	Fotemustine	3	
4	gold salts	4	1
4	hydralazine	3	1
4	inorganic mercury	3	
4	lactacystin	4	
4	lapatinib	4	
4	lomustine	4	
4	mecamylamine	4	
4	methyl methacrylate	2	2
4	methyl n-butyl ketone	4	
4	mustard oil	3	
4	N,N-diethyldithiocarbamate	4	
4	NGF-induced	3	
4	ofloxacin	2	1
4	ovariectomy	3	
4	p-bromophenylacetylurea	4	
4	paints	4	
4	Perhexiline	4	1
4	phorbol 12-myristate 13-acetate	1	2
4	polychlorinated biphenyls	3	1
4	prions	3	
4	psychological stress	4	1



4	Salinomycin	4	
4	saxitoxin	2	
4	sertraline	2	2
4	sofosbuvir	4	3
4	squatting position	2	1
4	thiotepa	4	1
4	Toxoplasma	4	
4	Vp-16	4	1
4	West Nile virus	4	2
3	1,2-diacetylbenzene	3	
3	2-bp	3	
3	actinomycin D	3	
3	Bisphenol		3
3	bradykinin-induced	3	1
3	carcinogens		2
3	citalopram	2	2
3	Corynebacterium	2	1
3	dactinomycin	2	
3	daunorubicin	3	
3	dimethyl sulfoxide	3	1
3	Enfuvirtide	3	
3	Ertapenem	2	1
3	estrogen deficiency		3
3	ethyl acetate	3	
3	felodipine		3
3	fialuridine	3	
3	formaldehyde	1	
3	gastric surgery	2	1
3	gefitinib	3	
3	glue sniffing	1	
3	glues	2	
3	glutamate-induced	3	
3	intermittent hypoxia		3
3	kainic acid	1	
3	lysophosphatidylcholine	1	2
3	methamphetamine	1	
3	montelukast	3	2
3	Mycobacterium avium	2	1
3	naproxen	2	3
3	natalizumab	3	2
3	nivolumab	3	
3	pazopanib	3	
3	phenelzine	3	
3	physical trauma	2	1
3	pirarubicin	3	
3	piroxicam	2	2

3	Polysorbate 80	2	
3	pyrethroid	2	
3	rabies vaccine	1	
3	restraint stress	3	
3	ruxolitinib	3	
3	sotalol	3	
3	Staurosporine	3	
3	sunitinib	2	1
3	tegafur	3	
3	teniposide	2	
3	Theiler's murine encephalomyelitis virus	1	
3	Treponema denticola		2
3	undernutrition		3
3	vorinostat	3	1
2	1,1,1-trichloroethane	2	
2	1,2-Diethylbenzene	2	
2	Abraxane	2	
2	Adrenaline-induced		2
2	altretamine	2	
2	ammonium chloride	1	1
2	amphetamine	1	1
2	auranofin	1	
2	axitinib	2	
2	benzene	2	
2	benzimidazole	1	1
2	bexarotene	1	
2	busulfan	2	1
2	cerebral artery occlusion	2	2
2	childhood infection		1
2	Chlamydomyces pneumoniae		2
2	Chlorophenoxy herbicides	2	
2	CNS infections	1	1
2	daratumumab	2	
2	desogestrel		2
2	dichlorvos	1	
2	Diethylbenzene	1	
2	Diphenylhydantoin	2	1
2	disopyramide	1	1
2	doxifluridine	2	1
2	environmental toxicants	1	
2	epoxy resins		2
2	escitalopram	1	1
2	ethionamide	2	
2	Ethylene glycol	1	
2	ferric chloride		2

2	HDI	2	
2	hexacarbons	2	
2	hexamethylmelamine	2	
2	hydrazine	1	
2	ibrutinib	2	1
2	imidazole	2	1
2	isonicotinic acid	2	
2	Karwinskia humboldtiana	1	
2	lansoprazole	2	
2	lasalocid sodium	1	
2	leptin deficiency	1	1
2	levonorgestrel		1
2	lopinavir	2	1
2	methyl ethyl ketone	2	
2	methyllycaconitine	1	1
2	Mitochondrial toxins	2	
2	MK-2206	2	
2	moxifloxacin	2	
2	mumps measles rubella vaccination	2	
2	mycotoxins	2	
2	N-methylolacrylamide	1	
2	NaHS	1	1
2	naphthalene	2	
2	nerve tissue vaccine	1	
2	nitroimidazole	2	
2	organochlorine pesticides	1	1
2	organotin	2	
2	pancuronium bromide	2	
2	Paraquat	2	
2	Pefloxacin	2	
2	pembrolizumab	2	
2	pentanedioic acid	2	
2	persistent organic pollutants	1	1
2	phenylmethylsulfonyl fluoride	2	
2	poliovirus	2	
2	ponatinib		1
2	procainamide	2	
2	quinolone	2	
2	raltegravir	2	
2	ramucirumab	2	
2	recreational drugs	2	1
2	REMSD	2	
2	romidepsin	2	
2	sepsis-induced		1
2	streptomycin	2	

2	surgery-induced	2	
2	TBE	2	
2	Teriflunomide	2	2
2	Toxocara canis		2
2	Treponema pallidum	2	
2	Trichlorfon	2	
2	trichlorophenol	2	1
2	Trichloropropane	2	
2	ultraviolet irradiation		1
2	uracil	2	
2	vaccination against MD	2	1
2	valganciclovir	2	
2	vitamin E deficient	1	
2	western diet		2
2	xenobiotic	2	
2	xylene	2	
1	1,2,4-triethylbenzene)	1	
1	1,2-diaminocyclohexane	1	
1	1,3-diethylbenzene	1	
1	1,4-diethylbenzene	1	
1	1-hydroxyphenanthrene		1
1	1-naphthyl N-methylcarbamate	1	
1	2,2-dichlorovinyl dibutyl phosphate	1	
1	2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate)	1	
1	2,4,5-T	1	1
1	2,4-dichlorophenoxy	1	
1	2,4-dinitrophenol	1	
1	2-bromopropane	1	
1	2-hydroxyfluorene		1
1	2-hydroxyphenanthrene		1
1	3,4-dihydroxyphenylglycolaldehyde	1	
1	3,4-dimethyl-2,5-hexanedione	1	
1	3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid	1	
1	3-hydroxyfluorene		1
1	3-nitropropionic acid	1	
1	3-NPA	1	
1	acetylhydrazine	1	
1	acetylisoniazid	1	
1	aconitine	1	
1	acrolein	1	
1	Actinobacillus		1

	actinomycetemcomitans		
1	Acute nerve injuries	1	
1	ADI-PEG 20	1	
1	adverse upper limb postures	1	
1	aerosolize CNS tissue	1	
1	alpha-latrotoxin	1	
1	aminoglycoside-induced	1	
1	amprenavir	1	
1	androgenic steroids		1
1	anti-tetanos vaccination	1	1
1	antimony		1
1	aprepitant	1	
1	atherogenic diet		1
1	aurothioglucose	1	
1	BMS-275183	1	
1	bromate intoxication	1	
1	buckthorn	1	
1	Bunyaviridae	1	
1	butyl acetate	1	
1	C-4 methyl carbonate	1	
1	C2-ceramide	1	
1	cacodylic acid		1
	Calmette Guerin (BCG)		
1	vaccination	1	
1	Carbetimer	1	
1	carbofuran	1	
1	CGS 21595	1	
1	chemical warfare agents	1	
1	Chikungunya virus	1	
1	chlorinated solvents	1	
1	chlorofluorocarbon	1	
1	chromium deficiency	1	
1	chronic restraint stress	1	
1	CP intoxication	1	
1	cuprizone	1	
1	Cycloleucine	1	
1	cypermethrin	1	
1	cytolethal distending toxin	1	
1	darunavir	1	
1	DEG intoxication	1	
1	dextroamphetamine	1	
	di-n-butyl-2,2-dichlorovinyl		
1	phosphate	1	
1	diacetylhydrazine	1	
1	dichlorohydrin	1	
1	dieldrin		1

1	Dimethylamine borane	1	
1	diquat	1	
1	DMAB	1	
1	DOPEGAL)	1	
1	dronedarone	1	
1	Dursban	1	
1	dyes	1	
1	efalizumab	1	1
1	Efudex)	1	
1	erythrosin B	1	1
1	ethanolamine	1	1
1	ethyl chloride	1	
1	Ethylene chlorohydrin	1	
1	ferric ammonium citrate	1	
1	flavivirus	1	
1	Flecainide acetate	1	
1	Formic acid	1	
1	fractalkine-induced	1	
1	frequent monotonous movements	1	
1	fuel oils	1	
1	gamma rays	1	
1	gemifloxacin	1	
1	gestodene		1
1	griseofulvin	1	
1	GYKI 52466	1	
1	Halaven	1	
1	hantavirus	1	
1	hazardous chemicals	1	
1	hydroquinone	1	
1	ICI 118,551	1	
1	indocyanine green-loaded boronated maltodextrin		1
1	indoxacarb	1	
1	isofenphos	1	
1	isopropanol	1	
1	kerosene	1	
1	keyboarding	1	
1	L-tryptophan-induced	1	
1	labetalol		1
1	lard	1	
1	lauric acid		1
1	lorlatinib	1	
1	Lyme vaccination	1	
1	m-tolyl methylcarbamate	1	
1	MAF intoxication	1	

1	MBK	1	
1	MD vaccination	1	
1	megestrol acetate	1	1
1	metergoline	1	
1	methomyl	1	
1	methylcyclopentadienyl manganese tricarbonyl	1	
1	N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine	1	
1	n-heptane	1	
1	N-methylformamide	1	
1	n-propyl bromine	1	
1	naphthoquinone	1	
1	neuropathy-inducing drugs	1	
1	Nimorazole	1	
1	nintedanib	1	
1	nitromethane	1	
1	NP-polySA vaccine	1	
1	O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate	1	
1	OGD		1
1	oligomycin	1	
1	OS-induced	1	
1	OspA-vaccinated	1	
1	oxychlorane		1
1	oxygen-glucose deprivation		1
1	p,p'-DDE		1
1	PAHs		1
1	pantoprazole)	1	
1	perazine	1	
1	Perfluorooctanoic acid		1
1	peroxisomal acyl-CoA oxidase deficiency	1	
1	PFOA		1
1	phenothiazine	1	
1	phosphamidon/mevinphos	1	
1	phosphatidyl ethanolamine	1	1
1	photosensitive dyes	1	
1	phthalates		1
1	physical overload	1	
1	piragliatin	1	
1	polychlorinated dioxins	1	
1	Polycyclic aromatic hydrocarbons		1
1	Pralatrexate	1	
1	pronase	1	

1	propylthiouracil	1	
1	RA-induced	1	
1	raltitrexed	1	
1	rapeseed oil	1	1
1	refined carbohydrates		1
1	repeated mechanical trauma	1	
1	repetitive work	1	
1	Repin	1	
1	Revlimid	1	
1	rotenone-induced	1	
1	S arvensis	1	
1	S. occidentalis intoxication	1	
1	samarium	1	
1	selenium-deficient diet	1	
1	silicones	1	
1	Sinemet	1	
1	Sodium 3,5,6-trichloropyridin-2-ol	1	
1	sodium arsenate	1	
1	sodium bromate	1	
1	sulfonamide	1	
1	sulindac	1	
1	Tannerella forsythia		1
1	temozolomide	1	
1	temsirolimus	1	
1	teriparatide	1	1
1	tert-butylhydroperoxide	1	
1	tetralin)	1	
1	trabectedin		1
1	trans fatty acids		1
1	trans-nonachlor		1
1	traumatic stress		1
1	trichlorat	1	
1	Trichloroethane	1	
1	trimethyltin	1	
1	triphenyltin	1	
1	TTR-induced	1	
1	tungsten		1
1	vecuronium bromide	1	
1	X-radiation	1	
1	zileuton	1	
1	Zolof		1



**Table 7A-5 - Existing PN/PAD Treatments**

#REC	TREATMENT
5105	surgery
3638	drug
2402	amputation
1920	revascularization
1766	inhibitor
1358	walking
1328	exercise
1308	artery bypass grafting
1228	angioplasty
828	stents
812	growth factor
754	insulin
745	dialysis
632	medications
588	operation
576	aspirin
567	analgesic
541	endovascular treatment
507	vascular surgery
499	implantation
489	angiogenesis
459	rehabilitation
450	bypass surgery
449	diet
447	glycemic control
420	Ligation
411	corticosteroid
382	catheter
370	statin
353	Clopidogrel
	vascular endothelial growth factor
349	
337	antiplatelet therapy
317	opioid
288	supplementation
266	coronary intervention
252	antihypertensive agents
242	Gabapentin
240	PNS
233	endarterectomy
233	pregabalin
228	antidepressant
221	anticoagulant

215	Cilostazol
207	vitamin B12
206	nerve growth factor
190	smoking cessation
189	Spinal Cord Stimulation
172	Gene therapy
172	IL-6
167	heparin
160	adenosine
156	Electrical stimulation
156	prednisone
150	hypoxia
147	capsaicin
144	morphine
131	mononuclear cells
126	vitamin E
119	zidovudine
118	plasmapheresis
118	prednisolone
118	warfarin
117	Vitamin D
111	duloxetine
110	anticonvulsants
110	enzyme inhibitors
107	cell therapy
	granulocyte colony-stimulating factor
107	
103	Acupuncture
103	pentoxifylline
101	plasma exchange
100	haemodialysis
99	antioxidants
98	IVIG
98	lidocaine
91	Prostaglandin
90	gangliosides
87	Amitriptyline
86	Alpha lipoic acid
80	carbamazepine
80	folic acid
78	anthracycline
78	GM1
77	dipyridamole
73	thiamine

71	Ticlopidine
69	methylprednisolone
68	drug-coated balloons
67	erythropoietin
67	near-infrared
65	magnesium
65	Zinc
63	surgical decompression
62	ethanol
62	superoxide dismutase
61	simvastatin
59	Acetyl-L-carnitine
59	acetylsalicylic acid
59	hyperbaric oxygen
59	Testosterone
	angiotensin converting enzyme inhibitor
58	
57	nitinol stents
55	antithrombotic therapy
55	carnitine
54	Pyridoxine
54	steroid therapy
52	BDNF
52	hepatocyte growth factor
52	iloprost
51	AA
51	epidermal growth factor
51	Mesenchymal Stem Cells
	peripheral blood mononuclear cells
51	
50	C-peptide
50	Nicotine
47	aldose reductase inhibitor
47	atorvastatin
47	azathioprine
45	Ketamine
44	vorapaxar
42	Neurotrophins
41	clonidine
40	arginine
40	ticagrelor
39	aerobic exercise
38	antiepileptic drugs
38	valproic acid
37	anesthetics
37	drug-eluting balloons

37	glucocorticoid
36	apheresis
36	distal bypass
36	niacin
36	stem cell therapy
36	venlafaxine
35	Cannabinoids
35	directional atherectomy
34	nitroglycerin
34	urokinase
34	vitamin C
33	neurotrophin-3
33	ramipril
33	tramadol
32	Orbital atherectomy
32	prasugrel
31	covered stents
31	L-carnitine
31	progesterone
30	amifostine
30	Gamma-aminobutyric acid
30	propionyl-L-carnitine
29	lamotrigine
29	Lumbar sympathectomy
29	Methylcobalamin
29	phenytoin
28	electroacupuncture
28	GDNF
28	N-acetylcysteine
28	nifedipine
28	oxcarbazepine
27	baclofen
27	glutamine
	intermittent pneumatic compression
27	Mexiletine
27	serotonin reuptake inhibitors
27	verapamil
26	botulinum toxin
26	diphenhydramine
26	growth hormone
26	hormone replacement therapy
26	massage
26	minocycline
26	sodium nitroprusside
25	antimicrobial therapy

25	cannabis
25	curcumin
25	GSH
25	MK-801
25	nicotinamide
25	opiates
25	Transcutaneous electrical nerve stimulation
24	bFGF
24	Goshajinkigan
24	immunoglobulin therapy
24	insulin-like growth factor-I
24	omega-3 fatty acids
24	pulse therapy
23	docosahexaenoic acid
23	fish oil
23	hypothermia
22	alpha-tocopherol
22	calcium antagonists
22	cryoplasty
22	prostanoids
22	rapamycin
22	topiramate
22	Vitamin B1
21	calcium channel blocker
21	NSAIDs
21	oxycodone
21	phosphodiesterase inhibitor
21	rivaroxaban
21	tacrolimus
20	bone marrow mononuclear cells
20	fentanyl
20	peripheral nerve stimulation
19	alprostadil
19	buflomedil
19	DAPT
19	ezetimibe
19	neuroactive steroids
19	phentolamine
18	ascorbic acid
18	balloon dilatation
18	chelation therapy
18	eicosapentaenoic acid
18	indomethacin
18	lithium
18	muscle stimulation

18	selenium
17	amlodipine
17	CXCR4
17	interleukin-10
17	laser therapy
17	mycophenolate mofetil
17	rifampin
17	strength training
17	thienopyridines
17	viral vectors
17	whole-body vibration
16	androgen
16	beraprost sodium
16	ceftriaxone
16	chlorambucil
16	Coenzyme Q10
16	deep brain stimulation
16	epalrestat
16	galanin
16	losartan
16	ozone
16	PGE2
16	pravastatin
16	RTX
15	acetaminophen
15	digoxin
15	glycosaminoglycan
15	kampo
15	lisinopril
15	osteopontin
15	sildenafil
15	Streptokinase
14	abciximab
14	Aldehyde
14	anti-inflammatory agents
14	antioxidant therapy
14	bivalirudin
14	cimetidine
14	CNTF
14	enalapril
14	femoropopliteal in-stent restenosis
14	Flavonoids
14	fluoxetine
14	herbal medicines
14	memantine

14	myo-inositol
14	Org 2766
14	phenylephrine
14	Picotamide
14	tapentadol
14	TCA
14	yohimbine
13	ACTH
13	Caffeine
13	celecoxib
13	dextromethorphan
13	doxycycline
13	etanercept
13	FK506
13	guanosine
13	mecobalamin
13	nortriptyline
13	Olive oil
13	sulodexide
12	all-trans retinoic acid
12	antihistamines
12	beta-carotene
12	betaine
12	cyanocobalamin
12	Dex
12	Ginkgo biloba extract
12	hydrochlorothiazide
12	ketanserin
12	Lovastatin
12	prazosin
12	sodium bicarbonate
12	tempol
11	anandamide
11	chlorthalidone
11	diclofenac
11	EDTA
11	phosphatidylcholine
11	ruboxistaurin
11	tea
10	benfotiamine
10	chloroquine
10	desipramine
10	fenofibrate
10	glibenclamide
10	GP IIb/IIIa inhibitors
10	imipramine

10	lentivirus
10	melatonin
10	mesenchymal stromal cells
10	milnacipran
10	PAR-1 antagonists
10	plaque excision
10	Ranitidine
10	Resveratrol
10	scrambler therapy
10	tai chi
10	thiazolidinediones
10	uridine
10	vitamin D3
10	WIN 55,212-2
9	allopurinol
9	Angiogenic gene therapy
9	benzodiazepine
9	captopril
9	Carvedilol
9	clonazepam
9	dabigatran
9	Defibrotide
9	electromagnetic field
9	everolimus
9	hydrogen sulfide
9	levetiracetam
9	methadone
9	methylxanthine
9	Paracetamol
9	perindopril
9	phlebotomy
9	sunlight
9	tafamidis
9	tolrestat
9	vitamin K antagonist
8	amantadine
8	Calcitriol
8	D-penicillamine
8	eptifibatide
8	external counterpulsation
8	hydrocortisone
8	ibuprofen
8	inositol
8	KU-32
8	lacosamide
8	levothyroxine

8	mannitol
8	manual therapy
8	Menhaden oil
8	menthol
8	muscimol
8	nicotinic acid
8	osteocalcin
8	paroxetine
8	pioglitazone
8	placenta
8	Protamine
8	Sitagliptin
8	taurine
8	Tetrodotoxin
8	thiols
8	tirofiban
8	TRPA1 antagonist
7	7-nitroindazole
7	acetylcysteine
7	apixaban
7	ATS
7	Cannabidiol
7	capsazepine
7	coffee
7	cortical stimulation
7	cryotherapy
7	DA-9801
7	dexmedetomidine
7	diltiazem
7	factor Xa inhibitors
7	gamma-globulin
7	gamma-linolenic acid
7	gemfibrozil
7	Ghrelin
7	Gliclazide
7	histone deacetylase inhibitors
7	Huangqi Guizhi Wuwu
7	interferon-beta
7	Isosorbide dinitrate
7	linoleic acid
7	MIRE
	neuromuscular electrical stimulation
7	nimodipine
7	papaverine
7	Peripheral nerve decompression

7	PGB
7	plasminogen activators
7	prostacyclin analogues
7	quercetin
7	retigabine
7	riluzole
7	sirolimus
7	Viabahn endoprosthesis
6	acarbose
6	ancrod
6	atopaxar
6	Biotin
6	CB1/CB2 agonist
6	coumarin
6	Egb 761
6	erlotinib
6	HC-030031
6	hyaluronic acid
6	hydromorphone
6	Hydroxocobalamin
6	liraglutide
6	magnetic fields
6	marijuana
6	mesoglycan
6	naltrexone
6	nebivolol
6	PARP inhibition
6	polyphenol
6	relaxin
6	salbutamol
6	Sarpogrelate hydrochloride
6	shockwave therapy
6	THC
6	Thiamine pyrophosphate
6	thioctic acid
6	trimetazidine
6	Vitamin B complex
6	Zilver PTX stent
5	acetylcholine-induced
5	adrenocorticotrophic hormone
5	AMD3100
5	Bezafibrate
5	cangrelor
5	cholinesterase inhibitor
5	clomipramine
5	diazepam

5	drug-coated stents
5	edoxaban
5	epoprostenol
5	Exendin-4
5	FAAH inhibitor
5	Flunarizine
5	Grape
5	guanethidine
5	haemodilution
5	Hematin
5	Heparin cofactor II
5	hydrotherapy
5	hydroxychloroquine
5	hydroxyethyl starch
5	Ibudilast
5	Jinmaitong
5	ketorolac
5	moxibustion
5	N-methyl-D-aspartate receptor antagonists
5	naftidrofuryl oxalate
5	NGX-4010
5	P2Y12 inhibitor
5	pralidoxime
5	puerarin
5	repetitive transcranial magnetic stimulation
5	reteplase
5	rheopheresis
5	rofecoxib
5	Sativex
5	SCH 530348
5	tadalafil
5	telmisartan
5	triiodothyronine
5	ultrasonic therapy
5	URB597
4	17beta-estradiol
4	4-methylcatechol
4	acetazolamide
4	adrenal medullary transplants
4	agmatine
4	Aliskiren
4	allopregnanolone
4	amikacin
4	anakinra

4	betamethasone
4	bosentan
4	canagliflozin
4	catechin
4	cefotaxime
4	chelerythrine
4	Cinacalcet
4	ciprostene
4	Del-1
4	dextrorphan
4	dimercaprol
4	Dioscorea nipponica Makino
4	dipyrrone
4	donepezil
4	doxepin
4	enoxaparin
4	evolocumab
4	fluorocitrate
4	GLP-1 receptor agonists
4	glyceryl trinitrate
4	hemin
4	icariin
4	IGF-II
4	indobufen
4	isoproterenol
4	K-134
4	lafutidine
4	laser ablation
4	linolenic acid
4	Lycopene
4	Maggot debridement therapy
4	mangafodipir
4	midodrine
4	misoprostol
4	molsidomine
4	Netrin-1
4	percutaneous therapy
4	pirenzepine
4	probucof
4	propentofylline
4	protein kinase C inhibitors
4	pyridine
4	pyridostigmine
4	quinidine
4	Quinine
4	reflexology

4	rolipram
4	ruthenium red
4	S-Nitroso-N-acetylpenicillamine
4	saponins
4	Sodium nitrite
4	Tanezumab
4	Tang-Luo-Ning
4	tetrahydrocannabinol
4	thalamotomy
4	Thymoquinone
4	Tizanidine
4	trandolapril
4	trigonelline
4	troglitazone
4	turmeric
4	unsaturated fatty acids
4	valsartan
4	Waon therapy
4	wortmannin
4	ximelagatran
4	zenarestat
4	zonisamide
3	2-(3-mercaptopropyl)pentanedioic acid
3	2-AG
3	A23187
3	actovegin
3	adrenergic agonists
3	albendazole
3	alpha-linolenic acid
3	amiloride
3	antitussive
3	argatroban
3	Aucubin
3	becaplermin
3	berberine
3	bone marrow stem cells
3	BPAU
3	bupivacaine
3	butyric acid
3	caloric restriction
3	candesartan
3	carbenoxolone
3	carotenoids
3	caspase inhibitors

3	charcoal
3	chemical lumbar sympathectomy
3	Chinese herbs
3	chlorpropamide
3	chondroitinase ABC
3	codeine
3	cognitive behavior therapy
3	CXCR4 antagonist
3	cyproheptadine
3	dermatan sulfate
3	desferrioxamine
3	desvenlafaxine
3	dietary flaxseed
3	diflunisal
3	dihydroergotamine
3	dimethyl fumarate
3	ellagic acid
3	epibatidine
3	ethosuximide
3	Fasudil
3	fidarestat
3	fingolimod
3	fludrocortisone
3	fluvoxamine
3	fosfomycin
3	fucoidan
3	genistein
3	H-Wave device
3	hexamethonium
3	High-mobility group box-1 protein
3	ifenprodil
3	interferon alfa
3	irbesartan
3	ivermectin
3	JZL184
3	L-cysteine
3	Lutonix drug-coated balloon
3	Lyrica
3	Metanx
3	mifepristone
3	mirtazapine
3	natalizumab
3	Neostigmine
3	olesoxime
3	orexin-A
3	oxytocin

3	palmitoylethanolamide
3	passive exercise
3	PD98059
3	pergolide
3	phosphatidylethanolamine
3	Photobiomodulation
3	pifithrin-mu
3	Plantaginis Semen
3	PLX-PAD
3	poloxamer 188
3	polytetrafluoroethylene-covered stents
3	probenecid
3	pyrrolidine dithiocarbamate
3	quinpirole
3	ranolazine
3	rotenone
3	Shakuyaku-kanzo-to
3	shear rate therapy
3	sialidase
3	SKPs
3	tetrahydrobiopterin
3	thermal ablation
3	thymosin beta4
3	Tongxinluo
3	trimethylamine
3	TSPO
2	1,5-isoquinolinediol
2	2,3-dimercapto-1-propanesulfonic acid
2	2-MPPA)
2	5-hydroxydecanoate
2	Acidic fibroblast growth factor
2	Aconitum
2	Acorus calamus
2	adenylate cyclase inhibitor
2	ALDH Bright Cells)
2	Aleglitazar
2	alfentanil
2	alogliptin
2	alpha-conotoxin Vc1.1
2	alpha2-delta ligands
2	AM424
2	angelica
2	anisodamine
2	Anodyne Therapy System

2	apomorphine
2	Astragali
2	Bimoclolmol
2	Biolimus
2	bisoprolol
2	blackcurrant juice
2	BRX-220
2	calcium gluconate
2	calmangafodipir
2	calpeptin
2	carisoprodol
2	Cerebrolysin
2	cicaprost
2	cinnamaldehyde
2	Cobalt Chloride
2	controlled reperfusion
2	Cyclandelate
2	cytidine
2	Dark chocolate
2	deferoxamine
2	DHbetaE)
2	dietary nitrate
2	Dihydro-beta-erythroidine
2	dihydropyridines
2	diluted bee venom
2	Dioscoreae rhizoma
2	DMSO
2	docosapentaenoic acid
2	DRG stimulation
2	DVC1-0101
2	E2072
2	egg white hydrolysate
2	elcatonin
2	electromagnetic neural stimulation
2	electromagnetic radiation
2	emodin
2	ergocalciferol
2	Ethoxyquin
2	etodolac
2	fibroblast growth factor 1
2	Flupirtine
2	fondaparinux
2	gallic acid
2	geldanamycin
2	glutathione



2	glycyrrhizin
2	HGF plasmid DNA
2	hypoxia-inducible factor-1alpha (HIF-1alpha)
2	intravenous high-dose immunoglobulin
2	kappa-opioid receptor agonist
2	KRN5500
2	KU-596
2	leuprolide acetate
2	linagliptin
2	loperamide
2	LV vectors
2	maraviroc
2	maximal strength training
2	MEK inhibitors
2	melanocortin
2	metaxalone
2	Methocarbamol
2	methyl nicotinate
2	Mibefradil
2	monochromatic infrared photo energy
2	monosodium glutamate
2	nalbuphine
2	Neomycin
2	neurofeedback
2	niflumic acid
2	nitrate consumption
2	pyrrolidine-2,5-dione
2	Snake venoms
1	25)Mg-PMC16
1	3,3,5-trimethylcyclohexanol
1	3-Aminobenzamide
1	4-phenylbutyric acid
1	5-phenyl-1-pentyne
1	7-hydroxy-3,4-dihydrocadalin
1	8-methoxypsoralen
1	A-134974
1	A-834735)
1	AC591
1	Acanthopanax
1	ACEA
1	acellular dermal regenerative tissue
1	Achyranthis bidentata Blume

1	acipimox
1	activation of Nrf2
1	active treadmill walking
1	ACY-1083
1	adipose-tissue-derived stem cells
1	AGGF1
1	aktovegin
1	Alfa LMW1
1	alpha-chymotrypsin
1	Alstonia scholaris
1	AM1241)
1	AM1714
1	ambroxol
1	aminoguanidine hydrochloride
1	aminophylline
1	ampakines
1	AMPK activators
1	anthranilic acid
1	antimycin
1	Apligraf
1	ARA 290
1	arm-crank exercise
1	ascorbyl palmitate
1	AVP-923
1	Azadirachta indica
1	baicalein
1	Baicalin
1	BAIMAI-SAN
1	BAK-PLO
1	bendazac lysine
1	benserazide
1	bepermingene perplasmid
1	beta-caryophyllene
1	betulinic acid
1	bis(maltolato)oxovanadium IV
1	blueberry
1	blunt microdissection catheter
1	borneol
1	bovine lactoferrin
1	BRL-50481
1	BRLP-42)
1	bromelain
1	bushi
1	Butea monosperma
1	Buyang Huanwu decoction
1	Caffeic acid phenethyl ester

1	calciparine
1	calcium citrate
1	calcium/magnesium infusion
1	Calmare therapy
1	Calmidazolium
1	candoxatril
1	Capnellene
1	ceftaroline fosamil (CPT-F)
1	CEP 03
1	CEP protein adducts
1	Chamomilla matricaria
1	chemical ablation
1	chlorogenic acid
1	Chlorpheniramine
1	cholecystokinin receptor antagonists
1	cholecystokinin-8
1	cholesterol-rich diet
1	chromaffin cell grafts
1	chuanxiong
1	cinnamamide
1	cinnamic acid
1	circulator boot therapy
1	citicoline
1	COMP-Ang-1
1	contrast-enhanced sonothrombolysis
1	copper ions
1	CQ
1	crenotherapy
1	Crocine
1	cromakalim
1	Crotoxin
1	CX614
1	CX729
1	cyclobenzaprine
1	Cymbalta
1	Cystamine
1	cytoflavin
1	D-sorbitol
1	daidzin
1	daltroban
1	danshen root
1	Deguelin
1	dexibuprofen
1	Diallyl trisulfide

1	dielectric barrier discharge plasma
1	dietary folate intake
1	dietary vitamin E
1	diethylcarbamazine
1	dihydrolipoic acid
1	dimethicone
1	diphenyl diselenide
1	dronabinol
1	EAntS-GS
1	Effexor
1	Electroconvulsive shock
1	electromagnetic therapy
1	elinogrel
1	emfilermin)
1	Entacapone
1	Epac-inhibitor
1	EPAS1 gene
1	epicatechin gallate
1	eplerenone
1	ergothioneine
1	erucic acid
1	ESI-09
1	estradiol valerate
1	ethanethiol
1	ethopropazine
1	eugenol
1	exogenous recombination IL-4
1	extracorporeal shock wave therapy
1	extract of date fruit
1	felbamate
1	Fenfluramine
1	fenugreek extract
1	Ferula assa-foetida
1	ferulic acid
1	Fexofenadine
1	fluocinolone acetonide
1	fumonisin B1
1	gadolinium chloride
1	GCSB-5
1	Gentiopicroside
1	ginsenoside Rb1
1	Guizhi-shaoyao-zhimu decoction
1	Hachimi-jio-gan
1	hedysari

1	hemangioblasts
1	Huoxue Kangyuan decoction
1	Hydroxytyrosol
1	hyperforin
1	hypericin
1	Ilepatril
1	imatinib mesylate
1	immunoabsorber
1	increased intake of folate
1	IND01
1	INGAP peptide
1	injectable biomaterial
1	integrin-linked kinase
1	Intention controlled Myo-Feedback)
1	interval walking
1	intrathecal opioid infusion
1	IRE1alpha siRNA
1	isoprenaline
1	isopropyl myristate
1	Isoxsuprine hydrochloride
1	itaconic acid
1	J147
1	Jiaweibugan
1	Juglans regia L.
1	kaempferol
1	Kamishoyosan
1	ketogenic diet
1	Kv7 channel activator
1	lactoferrin
1	leupeptin
1	levo-corydalmine
1	Levocarnitine acetyl 150
1	levorphanol
1	LiCl
1	ligustrazine
1	Linalool
1	Lithospermi radix
1	LM11A-31
1	lomitapide
1	Lotrafiban
1	low frequency acoustic waveform
1	low frequency magnetic fields
1	low glucose diet
1	low-frequency contact ultrasound debridement

1	LPP1
1	Maltol
1	mangiferin
1	Manidipine
1	maprotiline
1	MCC-257
1	mCPP
1	MDA19
1	Me6TREN
1	meclizine
1	medical herbs
1	menstrual blood-derived stem cell
1	metamizol/paracetamol
1	methylsulfonylmethane
1	metyrapone
1	microRNA let-7g
1	mindfulness meditation
1	minoxidil
1	MnDPDP
1	MnL4
1	Momordica cymbalaria
1	monosialotetrahexosylganglioside
1	morin
1	MPV-2426
1	N(6)-cyclopentyladenosine
1	nabilone
1	naringin
1	NCX 6550
1	nefopam
1	neoline
1	neprilysin
1	nerve autografts
1	Neuragen PN
1	Neurotin
1	NF3
1	niclosamide
1	nicorandil
1	NM-702
1	Nmnat)
1	Nornicotine
1	NSCs
1	NT-702
1	nylidrin
1	oleanolic acid
1	OP-1206

1	pamoic acid
1	pancreatic kininogenase
1	parthenolide
1	passive cycling
1	pCK-HGF-X7
1	PDE4B/7A dual inhibitor
1	PDE5 inhibitor
1	PDWHF
1	pemirolast
1	Peptide5
1	percutaneous catheter-based therapies
1	phenols
1	Phenoxodiol
1	phenoxyphenyl pyridines
1	phenyl-N-tert-butylnitron
1	Picrorhiza kurroa
1	piler-light
1	piperine
1	piroxican
1	pitavastatin
1	placental-derived adherent stromal cells
1	plantar vibration
1	pneumatic compression boot
1	polaprezinc
1	potassium channel openers
1	prifinium bromide
1	pRLX
1	Procyclidine
1	progestins
1	progestogen therapy
1	Prograf
1	programmable neuro-stimulator
1	propolis
1	prosaposin-derived 14-mer peptide
1	proxiphylline
1	psoralen
1	Pulsed radiofrequency ablation
1	pulsed radiofrequency neuromodulation
1	Punica granatum L
1	Punicalagins
1	pyrimethamine
1	QR-333

1	Quetiapine
1	Racemic (R/S)-guaifenesin (1)
1	rAd5/NR2B
1	Recombinant Sema3A protein
1	reparixin
1	Ro5-4864
1	rosemary
1	Rosmarinic acid
1	RSR13
1	RU38486
1	rutin
1	safranal
1	Salicylaldehyde
1	salmon calcitonin
1	salsalate
1	Salvia officinalis
1	Salvianolic acid B
1	SAN-Gly
1	Saposhnikovia divaricata Schislin
1	SDZ PCO-400
1	sesame oil
1	shellac
1	Silybin
1	silymarin
1	SMC therapy
1	SN gene therapy
1	sodium hydrosulfide
1	sodium sulfide
1	SP600125
1	spironolactone
1	SQ22536
1	SR 57746A
1	subsensory electrical stimulation
1	SVF-enriched fat graft
1	synthetic exendin-4
1	T-cell-pre-stimulated monocytes
1	Tanshinone
1	TAT-CBD3A6K
1	Terbinafine
1	tetracyclines
1	tetramethylpyrazine
1	thenoyltrifluoroacetone
1	thiorphan
1	thiosalicylic acid
1	torseamide
1	Trehalose

1	Treprostinil diethanolamine
1	tretinoin
1	trimethoxy flavone
1	TRPA1/PDE4B/PDE7A ligand
1	TT saponin
1	Turpentine
1	U 69593
1	ulinastatin
1	vascular regenerative therapy
1	Vernonia cinerea
1	vitamin D2
1	vitamin K2
1	Vitis vinifera

1	VR-1 receptor modulators
1	WR1065
1	Xilonix
1	xylazine
1	yang-warming
1	Yiqi Huayu
1	zaprinast
1	Zhenqing Capsule
1	ziconotide

**TABLE 7A-6 - Revascularization Co-Occurrences with other Treatments**

#REC	TREATMENT	#CO-OCC
1920	revascularization	1920
5105	surgery	776
2402	amputation	615
1228	angioplasty	403
828	stents	300
1308	artery bypass grafting	276
541	endovascular treatment	178
450	bypass surgery	127
507	vascular surgery	121
1358	walking	120
3638	drug	119
1328	exercise	117
1766	inhibitor	76
588	operation	73
576	aspirin	73
266	coronary intervention	71
499	implantation	71
337	antiplatelet therapy	68
233	endarterectomy	62
489	angiogenesis	59
745	dialysis	58
370	statin	56
353	Clopidogrel	54
382	catheter	52
812	growth factor	51
215	Cilostazol	44
632	medications	38
68	drug-coated balloons	33
190	smoking cessation	33
459	rehabilitation	31
107	cell therapy	31
57	nitinol stents	24
	vascular endothelial growth factor	22
349	insulin	21
754	antihypertensive agents	20
252	Gene therapy	19
172	heparin	18
167	drug-eluting balloons	17
37	anticoagulant	17
221	glycemic control	16
447	Ligation	16
420		13

44	vorapaxar	13
36	stem cell therapy	13
35	directional atherectomy	12
449	diet	11
110	enzyme inhibitors	11
131	mononuclear cells	10
32	Orbital atherectomy	10
55	antithrombotic therapy	9
	femoropopliteal in-stent restenosis	8
14		8
17	amlodipine	8
22	prostanoids	8
77	dipyridamole	8
189	Spinal Cord Stimulation	7
11	chlorthalidone	7
567	analgesic	7
52	iloprost	7
36	distal bypass	7
118	warfarin	7
31	covered stents	7
40	ticagrelor	6
19	DAPT	6
	angiotensin converting enzyme inhibitor	6
58		6
103	pentoxifylline	6
150	hypoxia	6
51	Mesenchymal Stem Cells	6
15	lisinopril	6
10	plaque excision	5
59	hyperbaric oxygen	5
67	near-infrared	5
172	IL-6	5
20	bone marrow mononuclear cells	5
	intermittent pneumatic compression	5
27		5
61	simvastatin	5
8	external counterpulsation	5
21	rivaroxaban	5
47	atorvastatin	4
71	Ticlopidine	4
52	hepatocyte growth factor	4
14	abciximab	4
15	Streptokinase	4
14	bivalirudin	4

21	calcium channel blocker	4
59	acetylsalicylic acid	4
22	cryoplasty	4
160	adenosine	4
34	nitroglycerin	4
34	urokinase	4
30	propionyl-L-carnitine	4
51	AA	3
36	apheresis	3
7	Viabahn endoprosthesis	3
4	percutaneous therapy	3
21	phosphodiesterase inhibitor	3
91	Prostaglandin	3
6	Zilver PTX stent	3
5	SCH 530348	3
100	haemodialysis	3
27	verapamil	3
3	Lutonix drug-coated balloon	3
10	mesenchymal stromal cells	2
288	supplementation	2
24	bFGF	2
36	niacin	2
14	Aldehyde	2
7	sirolimus	2
107	granulocyte colony-stimulating factor	2
103	Acupuncture	2
5	drug-coated stents	2
32	prasugrel	2
10	GP IIb/IIIa inhibitors	2
19	alprostadil	2
62	superoxide dismutase	2
8	eptifibatide	2
18	balloon dilatation	2
3	fucoidan	2
50	Nicotine	2
3	passive exercise	2
2	controlled reperfusion	2
156	prednisone	1
4	enoxaparin	1
10	PAR-1 antagonists	1
156	Electrical stimulation	1
25	Transcutaneous electrical nerve stimulation	1
25	nicotinamide	1
4	probucol	1

15	osteopontin	1
39	aerobic exercise	1
7	acetylcysteine	1
25	cannabis	1
17	laser therapy	1
317	opioid	1
4	laser ablation	1
59	Testosterone	1
4	canagliflozin	1
4	bosentan	1
5	reteplase	1
10	thiazolidinediones	1
6	trimetazidine	1
22	rapamycin	1
55	carnitine	1
19	ezetimibe	1
17	thienopyridines	1
17	viral vectors	1
33	ramipril	1
8	tirofiban	1
5	epoprostenol	1
9	perindopril	1
101	plasma exchange	1
16	androgen	1
4	evolocumab	1
9	allopurinol	1
7	plasminogen activators	1
14	enalapril	1
7	cryotherapy	1
29	Lumbar sympathectomy	1
9	captopril	1
9	Carvedilol	1
4	Cinacalcet	1
16	losartan	1
28	N-acetylcysteine	1
28	nifedipine	1
12	hydrochlorothiazide	1
5	P2Y12 inhibitor	1
4	glyceryl trinitrate	1
19	buflomedil	1
7	factor Xa inhibitors	1
9	everolimus	1
5	hydrotherapy	1
15	digoxin	1
26	diphenhydramine	1
26	growth hormone	1

26	hormone replacement therapy	1
15	glycosaminoglycan	1
12	tempol	1
26	sodium nitroprusside	1
4	trandolapril	1
3	argatroban	1
3	bone marrow stem cells	1
	peripheral blood mononuclear cells	
51		1
18	chelation therapy	1
14	Picotamide	1
2	Acidic fibroblast growth factor	1
2	Biolimus	1
2	bisoprolol	1

9	vitamin K antagonist	1
2	nitrate consumption	1
1	blunt microdissection catheter	1
1	cholesterol-rich diet	1
1	circulator boot therapy	1
1	estradiol valerate	1
	percutaneous catheter-based therapies	
1		1
1	spironolactone	1
1	torseamide	1
1	Xilonix	1



**TABLE 7A-7 - Growth Factor Co-Occurrences with other Treatments**

#REC	TREATMENT	#CO-OCC
812	growth factor	812
349	vascular endothelial growth factor	301
489	angiogenesis	216
206	nerve growth factor	174
3638	drug	103
1766	inhibitor	85
5105	surgery	82
172	Gene therapy	78
2402	amputation	61
52	hepatocyte growth factor	52
51	epidermal growth factor	51
1920	revascularization	51
150	hypoxia	31
420	Ligation	28
1358	walking	26
1328	exercise	25
107	cell therapy	25
754	insulin	23
24	bFGF	22
42	Neurotrophins	21
1308	artery bypass grafting	20
1228	angioplasty	18
33	neurotrophin-3	18
52	BDNF	17
28	GDNF	16
172	IL-6	15
131	mononuclear cells	15
215	Cilostazol	14
51	Mesenchymal Stem Cells	14
107	granulocyte colony-stimulating factor	12
411	corticosteroid	11
567	analgesic	11
499	implantation	11
449	diet	10
240	PNS	10
147	capsaicin	10
24	insulin-like growth factor-I	9
36	stem cell therapy	9
167	heparin	9
78	anthracycline	9

14	CNTF	8
189	Spinal Cord Stimulation	8
317	opioid	7
17	viral vectors	7
242	Gabapentin	7
447	glycemic control	7
288	supplementation	6
588	operation	6
103	pentoxifylline	6
51	peripheral blood mononuclear cells	6
59	hyperbaric oxygen	6
59	Acetyl-L-carnitine	5
20	bone marrow mononuclear cells	5
576	aspirin	5
67	erythropoietin	5
450	bypass surgery	5
156	Electrical stimulation	5
233	pregabalin	5
228	antidepressant	5
632	medications	5
382	catheter	4
65	Zinc	4
9	Angiogenic gene therapy	4
22	rapamycin	4
26	growth hormone	4
86	Alpha lipoic acid	4
117	Vitamin D	4
80	folic acid	3
12	all-trans retinoic acid	3
4	Tanezumab	3
26	diphenhydramine	3
31	progesterone	3
4	4-methylcatechol	3
30	propionyl-L-carnitine	3
54	Pyridoxine	3
14	cimetidine	3
61	simvastatin	3
541	endovascular treatment	3
353	Clopidogrel	3
47	aldose reductase inhibitor	3
80	carbamazepine	3
29	lamotrigine	3
55	carnitine	2

78	GM1	2
118	warfarin	2
9	electromagnetic field	2
22	topiramate	2
190	smoking cessation	2
87	Amitriptyline	2
21	tacrolimus	2
4	Del-1	2
4	Netrin-1	2
91	Prostaglandin	2
7	DA-9801	2
337	antiplatelet therapy	2
27	glutamine	2
52	iloprost	2
4	IGF-II	2
507	vascular surgery	2
2	Acidic fibroblast growth factor	2
6	erlotinib	2
16	PGE2	2
21	NSAIDs	2
4	wortmannin	2
828	stents	2
27	serotonin reuptake inhibitors	2
15	osteopontin	2
65	magnesium	2
25	cannabis	2
3	PD98059	2
207	vitamin B12	2
103	Acupuncture	2
25	curcumin	2
2	fibroblast growth factor 1	2
126	vitamin E	2
118	plasmapheresis	2
73	thiamine	2
111	duloxetine	2
3	fucoidan	1
28	electroacupuncture	1
3	passive exercise	1
28	oxcarbazepine	1
14	TCA	1
25	Transcutaneous electrical nerve stimulation	1
8	Protamine	1
98	lidocaine	1
10	lentivirus	1
745	dialysis	1

26	massage	1
370	statin	1
17	laser therapy	1
459	rehabilitation	1
26	minocycline	1
59	Testosterone	1
7	Peripheral nerve decompression	1
252	antihypertensive agents	1
13	celecoxib	1
8	taurine	1
6	trimetazidine	1
221	anticoagulant	1
110	enzyme inhibitors	1
8	Tetrodotoxin	1
24	Goshajinkigan	1
69	methylprednisolone	1
8	thiols	1
22	prostanoids	1
24	omega-3 fatty acids	1
6	hyaluronic acid	1
23	docosahexaenoic acid	1
7	PGB	1
13	mecobalamin	1
5	AMD3100	1
13	Olive oil	1
31	covered stents	1
13	sulodexide	1
62	ethanol	1
	angiotensin converting enzyme inhibitor	1
58		1
6	naltrexone	1
67	near-infrared	1
28	N-acetylcysteine	1
6	polyphenol	1
18	ascorbic acid	1
18	eicosapentaenoic acid	1
18	indomethacin	1
71	Ticlopidine	1
4	linolenic acid	1
50	C-peptide	1
7	dexmedetomidine	1
21	calcium channel blocker	1
4	pyridostigmine	1
7	diltiazem	1
160	adenosine	1
6	shockwave therapy	1

8	ibuprofen	1
4	trandolapril	1
34	nitroglycerin	1
16	beraprost sodium	1
41	clonidine	1
5	Exendin-4	1
11	ruboxistaurin	1
51	AA	1
8	lacosamide	1
10	benfotiamine	1
7	Gliclazide	1
36	apheresis	1
10	fenofibrate	1
1	cholesterol-rich diet	1
40	arginine	1
4	donepezil	1
7	interferon-beta	1
15	acetaminophen	1
15	kampo	1
15	sildenafil	1
38	antiepileptic drugs	1
4	turmeric	1
4	unsaturated fatty acids	1
21	phosphodiesterase inhibitor	1
3	A23187	1
38	valproic acid	1
3	Aucubin	1
3	becaplermin	1
6	Hydroxocobalamin	1
3	carbenoxolone	1
3	caspase inhibitors	1
100	haemodialysis	1
3	High-mobility group box-1 protein	1
6	liraglutide	1
5	tadalafil	1
4	protein kinase C inhibitors	1
3	Photobiomodulation	1
3	Shakuyaku-kanzo-to	1
3	Tongxinluo	1
8	placenta	1
2	angelica	1
10	vitamin D3	1
31	l-carnitine	1
2	calcium gluconate	1
30	amifostine	1

2	glutathione	1
2	HGF plasmid DNA	1
2	LV vectors	1
30	Gamma-aminobutyric acid	1
1	adipose-tissue-derived stem cells	1
1	Apligraf	1
1	bepreminogene perplasmid	1
1	bis(maltolato)oxovanadium IV	1
1	CEP 03	1
1	CEP protein adducts	1
1	cholecystokinin-8	1
14	tapentadol	1
1	Deguelin	1
1	dielectric barrier discharge plasma	1
1	EPAS1 gene	1
29	phenytoin	1
1	injectable biomaterial	1
1	Kamishoyosan	1
1	Lithospermi radix	1
1	MCC-257	1
1	NF3	1
1	pCK-HGF-X7	1
1	PDE5 inhibitor	1
18	balloon dilatation	1
110	anticonvulsants	1
1	T-cell-pre-stimulated monocytes	1
1	Tanshinone	1
99	antioxidants	1
1	vascular regenerative therapy	1
1	WR1065	1

**TABLE 7A-8 - Treatments Relevant to PN and to PAD**

#REC	TREATMENT	#PN REC	#PAD REC
5105	surgery	1172	3427
3638	drug	2279	1321
2402	amputation	591	2064
1920	revascularization	56	1839
1766	inhibitor	951	813
1358	walking	304	1058
1328	exercise	229	1124
1308	artery bypass grafting	59	1154
1228	angioplasty	23	1149
828	stents	7	751
812	growth factor	377	426
754	insulin	467	465
745	dialysis	139	643
632	medications	320	338
588	operation	122	374
576	aspirin	33	552
567	analgesic	479	61
541	endovascular treatment	3	499
507	vascular surgery	17	466
499	implantation	69	393
489	angiogenesis	56	439
459	rehabilitation	149	262
450	bypass surgery	13	421
449	diet	239	233
447	glycemic control	333	247
420	Ligation	274	110
411	corticosteroid	328	148
382	catheter	41	297
370	statin		333
353	Clopidogrel	8	345
349	vascular endothelial growth factor	105	257
337	antiplatelet therapy	4	330
317	opioid	271	28
288	supplementation	160	124
266	coronary intervention		261
252	antihypertensive agents	36	238
242	Gabapentin	235	16
240	PNS	166	23
233	endarterectomy	2	222
233	pregabalin	230	5
228	antidepressant	203	27

221	anticoagulant	24	196
215	Cilostazol	6	211
207	vitamin B12	160	50
206	nerve growth factor	170	8
190	smoking cessation	9	184
189	Spinal Cord Stimulation	122	84
172	Gene therapy	37	128
172	IL-6	75	95
167	heparin	15	146
160	adenosine	56	106
156	Electrical stimulation	87	37
156	prednisone	139	48
150	hypoxia	52	116
147	capsaicin	129	14
144	morphine	121	6
131	mononuclear cells	59	76
126	vitamin E	80	42
119	zidovudine	115	4
118	plasmapheresis	106	26
118	prednisolone	90	19
118	warfarin	14	107
117	Vitamin D	48	76
111	duloxetine	110	4
110	anticonvulsants	105	6
110	enzyme inhibitors	6	105
107	cell therapy	4	99
107	granulocyte colony-stimulating factor	77	25
103	Acupuncture	90	10
103	pentoxifylline	14	95
101	plasma exchange	90	19
100	haemodialysis	31	77
99	antioxidants	53	47
98	IVIg	84	16
98	lidocaine	71	10
91	Prostaglandin	29	60
90	gangliosides	84	6
87	Amitriptyline	84	5
86	Alpha lipoic acid	83	11
80	carbamazepine	70	4
80	folic acid	33	46
78	anthracycline	71	4
78	GM1	73	9
77	dipyridamole	5	74
73	thiamine	68	4
71	Ticlopidine	2	71

69	methylprednisolone	52	21
68	drug-coated balloons	1	66
67	erythropoietin	46	26
67	near-infrared	5	61
65	magnesium	51	13
65	Zinc	44	17
63	surgical decompression	49	5
62	ethanol	55	6
62	superoxide dismutase	41	21
61	simvastatin		41
59	Acetyl-L-carnitine	53	5
59	acetylsalicylic acid	1	58
59	hyperbaric oxygen	17	44
59	Testosterone	27	40
58	angiotensin converting enzyme inhibitor	6	55
57	nitinol stents		48
55	antithrombotic therapy		54
55	carnitine	25	30
54	Pyridoxine	49	4
54	steroid therapy	40	18
52	BDNF	39	4
52	hepatocyte growth factor	6	47
52	iloprost	2	50
51	AA	9	40
51	epidermal growth factor	39	8
51	Mesenchymal Stem Cells	9	39
51	peripheral blood mononuclear cells	31	21
50	C-peptide	32	26
50	Nicotine	13	37
47	aldose reductase inhibitor	45	5
47	atorvastatin		41
47	azathioprine	41	18
45	Ketamine	39	5
44	vorapaxar		44
42	Neurotrophins	32	2
41	clonidine	33	8
40	arginine	21	16
40	ticagrelor		40
39	aerobic exercise	22	18
38	antiepileptic drugs	36	2
38	valproic acid	33	2
37	anesthetics	24	8
37	drug-eluting balloons		32
37	glucocorticoid	29	16

36	apheresis	8	29
36	distal bypass	1	34
36	niacin	11	26
36	stem cell therapy	1	33
36	venlafaxine	34	3
35	Cannabinoids	32	
35	directional atherectomy		33
34	nitroglycerin	1	30
34	urokinase	5	29
34	vitamin C	12	23
33	neurotrophin-3	27	3
33	ramipril		33
33	tramadol	30	3
32	Orbital atherectomy		29
32	prasugrel	1	32
31	covered stents		29
31	l-carnitine	14	19
31	progesterone	25	3
30	amifostine	23	
30	Gamma-aminobutyric acid	27	2
30	propionyl-L-carnitine	1	30
29	lamotrigine	29	2
29	Lumbar sympathectomy	3	24
29	Methylcobalamin	29	1
29	phenytoin	24	2
28	electroacupuncture	22	3
28	GDNF	20	
28	N-acetylcysteine	16	9
28	nifedipine	5	21
28	oxcarbazepine	28	1
27	baclofen	22	3
27	glutamine	25	
27	intermittent pneumatic compression		26
27	Mexiletine	27	2
27	serotonin reuptake inhibitors	21	3
27	verapamil	4	21
26	botulinum toxin	20	3
26	diphenhydramine	25	
26	growth hormone	15	12
26	hormone replacement therapy	8	19
26	massage	18	7
26	minocycline	24	4
26	sodium nitroprusside	11	17
25	antimicrobial therapy	15	15
25	cannabis	16	10

25	curcumin	19	7
25	GSH	17	5
25	MK-801	19	
25	nicotinamide	22	6
25	opiates	21	6
25	Transcutaneous electrical nerve stimulation	16	9
24	bFGF	10	15
24	Goshajinkigan	22	1
24	immunoglobulin therapy	22	1
24	insulin-like growth factor-I	18	6
24	omega-3 fatty acids	8	15
24	pulse therapy	18	8
23	docosahexaenoic acid	11	12
23	fish oil	4	18
23	hypothermia	12	9
22	alpha-tocopherol	15	7
22	calcium antagonists	2	21
22	cryoplasty		19
22	prostanoids	3	19
22	rapamycin	15	7
22	topiramate	21	
22	Vitamin B1	21	3
21	calcium channel blocker	6	16
21	NSAIDs	15	6
21	oxycodone	21	1
21	phosphodiesterase inhibitor	2	20
21	rivaroxaban	1	20
21	tacrolimus	15	7
20	bone marrow mononuclear cells	1	18
20	fentanyl	13	3
20	peripheral nerve stimulation	18	2
19	alprostadil	4	16
19	buflomedil	1	18
19	DAPT		18
19	ezetimibe		18
19	neuroactive steroids	15	2
19	phentolamine	13	4
18	ascorbic acid	11	6
18	balloon dilatation		15
18	chelation therapy	8	11
18	eicosapentaenoic acid	3	15
18	indomethacin	10	7
18	lithium	16	
18	muscle stimulation	9	5
18	selenium	10	8



17	amlodipine	1	17
17	CXCR4	10	7
17	interleukin-10	14	4
17	laser therapy	13	4
17	mycophenolate mofetil	14	9
17	rifampin	11	3
17	strength training	3	13
17	thienopyridines		17
17	viral vectors	1	11
17	whole-body vibration	15	3
16	androgen	8	5
16	beraprost sodium	2	15
16	ceftriaxone	10	2
16	chlorambucil	16	1
16	Coenzyme Q10	15	3
16	deep brain stimulation	12	3
16	epalrestat	16	1
16	galanin	9	
16	losartan	2	13
16	ozone	2	13
16	PGE2	7	7
16	pravastatin		14
16	RTX	11	5
15	acetaminophen	9	6
15	digoxin	2	15
15	glycosaminoglycan	2	14
15	kampo	13	1
15	lisinopril	2	13
15	osteopontin	2	13
15	sildenafil	7	9
15	Streptokinase	1	12
14	abciximab		14
14	Aldehyde	9	6
14	anti-inflammatory agents	11	4
14	antioxidant therapy	3	13
14	bivalirudin		11
14	cimetidine	13	1
14	CNTF	10	2
14	enalapril	6	9
14	femoropopliteal in-stent restenosis		14
14	Flavonoids	6	8
14	fluoxetine	11	4
14	herbal medicines	11	1
14	memantine	13	1
14	myo-inositol	12	1

14	Org 2766	14	
14	phenylephrine	7	6
14	Picotamide	1	14
14	tapentadol	13	1
14	TCA	10	5
14	yohimbine	13	
13	ACTH	11	
13	Caffeine	5	9
13	celecoxib	6	4
13	dextromethorphan	12	2
13	doxycycline	11	1
13	etanercept	11	4
13	FK506	8	1
13	guanosine	6	4
13	mecobalamin	12	
13	nortriptyline	13	1
13	Olive oil	2	12
13	sulodexide	1	12
12	all-trans retinoic acid	9	3
12	antihistamines	11	3
12	beta-carotene	2	10
12	betaine	6	6
12	cyanocobalamin	11	2
12	Dex	11	
12	Ginkgo biloba extract	4	8
12	hydrochlorothiazide	3	10
12	ketanserin	3	8
12	Lovastatin		8
12	prazosin	7	5
12	sodium bicarbonate	6	7
12	tempol	5	6
11	anandamide	7	2
11	chlorthalidone		11
11	diclofenac	7	1
11	EDTA	3	8
11	phosphatidylcholine	7	3
11	ruboxistaurin	11	5
11	tea	4	3
10	benfotiamine	10	
10	chloroquine	7	3
10	desipramine	10	2
10	fenofibrate	7	8
10	glibenclamide	8	4
10	GP IIb/IIIa inhibitors		10
10	imipramine	10	
10	lentivirus	7	2

10	melatonin	5	1
10	mesenchymal stromal cells		10
10	milnacipran	9	
10	PAR-1 antagonists		10
10	plaque excision		9
10	Ranitidine	10	
10	Resveratrol	7	3
10	scrambler therapy	9	
10	tai chi	10	
10	thiazolidinediones	6	10
10	uridine	7	3
10	vitamin D3	3	7
10	WIN 55,212-2	10	
9	allopurinol	5	5
9	Angiogenic gene therapy	1	9
9	benzodiazepine	6	2
9	captopril		9
9	Carvedilol	2	8
9	clonazepam	9	
9	dabigatran		9
9	Defibrotide	1	9
9	electromagnetic field	8	1
9	everolimus	3	5
9	hydrogen sulfide	4	5
9	levetiracetam	8	
9	methadone	6	1
9	methylxanthine	1	8
9	Paracetamol	7	4
9	perindopril		9
9	phlebotomy	1	8
9	sunlight	6	5
9	tafamidis	9	
9	tolrestat	9	
9	vitamin K antagonist		8
8	amantadine	8	1
8	Calcitriol	1	7
8	D-penicillamine	7	1
8	eptifibatide	1	8
8	external counterpulsation		8
8	hydrocortisone	7	1
8	ibuprofen	5	1
8	inositol	6	2
8	KU-32	8	
8	lacosamide	8	1
8	levothyroxine	6	2
8	mannitol	3	4

8	manual therapy	3	1
8	Menhaden oil	8	2
8	menthol	5	3
8	muscimol	7	
8	nicotinic acid	2	6
8	osteocalcin		7
8	paroxetine	6	3
8	pioglitazone	7	5
8	placenta	2	5
8	Protamine	2	7
8	Sitagliptin	3	7
8	taurine	8	1
8	Tetrodotoxin	6	
8	thiols	6	3
8	tirofiban		8
8	TRPA1 antagonist	8	1
7	7-nitroindazole	5	
7	acetylcysteine	3	4
7	apixaban		7
7	ATS	4	4
7	Cannabidiol	7	1
7	capsazepine	5	
7	coffee	2	5
7	cortical stimulation	5	
7	cryotherapy	2	4
7	DA-9801	7	
7	dexmedetomidine	6	
7	diltiazem	1	6
7	factor Xa inhibitors		7
7	gamma-globulin	4	1
7	gamma-linolenic acid	6	2
7	gemfibrozil	2	6
7	Ghrelin	5	2
7	Gliclazide	5	3
7	histone deacetylase inhibitors	7	
7	Huangqi Guizhi Wuwu	5	
7	interferon-beta	6	1
7	Isosorbide dinitrate	4	3
7	linoleic acid	3	3
7	MIRE	7	
7	neuromuscular electrical stimulation	1	4
7	nimodipine	6	1
7	papaverine	2	5
7	Peripheral nerve decompression	7	1
7	PGB	7	

7	plasminogen activators	1	6
7	prostacyclin analogues		7
7	quercetin	6	2
7	retigabine	6	
7	riluzole	6	1
7	sirolimus	1	5
7	Viabahn endoprosthesis		7
6	acarbose	3	4
6	ancrod		6
6	atopaxar		6
6	Biotin	5	1
6	CB1/CB2 agonist	5	
6	coumarin	3	2
6	EGB 761	1	5
6	erlotinib	6	
6	HC-030031	5	2
6	hyaluronic acid	3	2
6	hydromorphone	4	2
6	Hydroxocobalamin	4	
6	liraglutide	3	3
6	magnetic fields	4	
6	marijuana	6	
6	mesoglycan		6
6	naltrexone	6	
6	nebivolol		6
6	PARP inhibition	6	1
6	polyphenol	4	3
6	relaxin	1	5
6	salbutamol	3	2
6	Sarpogrelate hydrochloride	1	6
6	shockwave therapy	1	6
6	THC	5	2
6	Thiamine pyrophosphate	6	1
6	thioctic acid	6	
6	trimetazidine		6
6	Vitamin B complex	6	
6	Zilver PTX stent		4
5	acetylcholine-induced	1	5
5	adrenocorticotrophic hormone	4	
5	AMD3100	4	2
5	Bezafibrate		5
5	cangrelor		5
5	cholinesterase inhibitor	4	
5	clomipramine	4	1
5	diazepam	4	
5	drug-coated stents		5

5	edoxaban		5
5	epoprostenol		5
5	Exendin-4	4	1
5	FAAH inhibitor	4	
5	Flunarizine	1	3
5	Grape	3	
5	guanethidine	5	
5	haemodilution		5
5	Hematin	5	
5	Heparin cofactor II		5
5	hydrotherapy	4	2
5	hydroxychloroquine	5	
5	hydroxyethyl starch		5
5	Ibudilast	5	1
5	Jinmaitong	5	1
5	ketorolac	3	2
5	moxibustion	4	1
5	N-methyl-D-aspartate receptor antagonists	4	1
5	naftidrofuryl oxalate		5
5	NGX-4010	5	
5	P2Y12 inhibitor		5
5	pralidoxime	5	
5	puerarin	4	2
5	repetitive transcranial magnetic stimulation	4	
5	reteplase		5
5	rheopheresis	1	4
5	rofecoxib	2	4
5	Sativex	5	1
5	SCH 530348		5
5	tadalafil	4	2
5	telmisartan		5
5	triiodothyronine	1	3
5	ultrasonic therapy	2	2
5	URB597	5	
4	17beta-estradiol	3	
4	4-methylcatechol	4	
4	acetazolamide	2	2
4	adrenal medullary transplants	3	
4	agmatine	4	
4	Aliskiren	1	4
4	allopregnanolone	3	
4	amikacin	4	1
4	anakinra	3	1
4	betamethasone	4	

4	bosentan		4
4	canagliflozin		3
4	catechin	1	2
4	cefotaxime	1	1
4	chelerythrine	3	1
4	Cinacalcet		4
4	ciprostene		4
4	Del-1		4
4	dextrorphan	4	
4	dimercaprol	3	
4	Dioscorea nipponica Makino	4	
4	dipyrrone	1	1
4	donepezil	3	1
4	doxepin	4	2
4	enoxaparin		4
4	evolocumab		4
4	fluorocitrate	4	
4	GLP-1 receptor agonists	3	3
4	glyceryl trinitrate		3
4	hemin	4	
4	icariin	4	
4	IGF-II	3	1
4	indobufen		4
4	isoproterenol	2	2
4	K-134		4
4	lafutidine	4	
4	laser ablation		3
4	linolenic acid	3	1
4	Lycopene	2	2
4	Maggot debridement therapy		3
4	mangafodipir	4	
4	midodrine	4	1
4	misoprostol		4
4	molsidomine		4
4	Netrin-1		3
4	percutaneous therapy		3
4	pirenzepine	4	
4	probucol		3
4	propentofylline	4	
4	protein kinase C inhibitors	4	1
4	pyridine	3	
4	pyridostigmine	3	1
4	quinidine	3	2
4	Quinine	3	2
4	reflexology	4	
4	rolipram	2	

4	ruthenium red	4	
4	S-Nitroso-N-acetylpenicillamine	4	
4	saponins	2	
4	Sodium nitrite	1	4
4	Tanezumab	4	
4	Tang-Luo-Ning	4	
4	tetrahydrocannabinol	4	1
4	thalamotomy	3	
4	Thymoquinone	3	1
4	Tizanidine	2	
4	trandolapril	2	3
4	trigonelline	4	
4	troglitazone	1	3
4	turmeric	1	3
4	unsaturated fatty acids	2	3
4	valsartan	1	3
4	Waon therapy		4
4	wortmannin	3	
4	ximelagatran	1	4
4	zenarestat	4	
4	zonisamide	4	1
3	2-(3-mercaptopropyl)pentanedioic acid	2	
3	2-AG	3	
3	A23187		2
3	actovegin	2	1
3	adrenergic agonists	2	
3	albendazole	1	2
3	alpha-linolenic acid		3
3	amiloride	1	2
3	antitussive	3	
3	argatroban		3
3	Aucubin	2	1
3	becaplermin	2	3
3	berberine	3	2
3	bone marrow stem cells		3
3	BPAU	3	
3	bupivacaine	2	2
3	butyric acid	3	1
3	caloric restriction	1	2
3	candesartan	2	2
3	carbenoxolone	2	1
3	carotenoids	3	
3	caspase inhibitors	2	
3	charcoal	2	



3	chemical lumbar sympathectomy		3
3	Chinese herbs	2	
3	chlorpropamide	3	3
3	codeine	3	1
3	cognitive behavior therapy	2	1
3	CXCR4 antagonist	2	1
3	cyproheptadine	3	
3	dermatan sulfate		3
3	desferrioxamine	3	
3	desvenlafaxine	3	
3	dietary flaxseed		3
3	diflunisal	3	
3	dihydroergotamine	1	3
3	dimethyl fumarate	3	1
3	ellagic acid	3	
3	epibatidine	2	
3	ethosuximide	3	
3	Fasudil	1	1
3	fidarestat	3	
3	fingolimod	3	1
3	fludrocortisone	3	1
3	fluvoxamine	2	1
3	fosfomycin	3	
3	fucoidan		3
3	genistein	2	2
3	H-Wave device	3	
3	hexamethonium		2
3	High-mobility group box-1 protein	2	1
3	ifenprodil	1	2
3	interferon alfa	3	3
3	irbesartan	1	3
3	ivermectin	2	
3	JZL184	3	
3	L-cysteine	3	
3	Lutonix drug-coated balloon		3
3	Lyrica	3	
3	Metanx	3	
3	mifepristone	3	
3	mirtazapine	3	
3	natalizumab	3	2
3	Neostigmine	3	
3	olesoxime	3	
3	orexin-A	3	
3	oxytocin	2	1
3	palmitoylethanolamide	3	1
3	passive exercise		2

3	PD98059	3	
3	pergolide	2	1
3	phosphatidylethanolamine	2	
3	Photobiomodulation	3	
3	pifithrin-mu	3	
3	Plantaginis Semen	3	
3	PLX-PAD		3
3	poloxamer 188		3
3	polytetrafluoroethylene-covered stents		3
3	probenecid	3	
3	pyrrolidine dithiocarbamate	3	
3	quinpirole	3	
3	ranolazine		3
3	rotenone	3	
3	Shakuyaku-kanzo-to	3	
3	shear rate therapy		3
3	sialidase	2	
3	SKPs	1	
3	tetrahydrobiopterin	1	2
3	thermal ablation		2
3	thymosin beta4	3	
3	Tongxinluo	3	
3	trimethylamine	2	1
3	TSPO	2	1
2	1,5-isoquinolinediol	2	
2	2,3-dimercapto-1-propanesulfonic acid	2	
2	2-MPPA)	2	
2	5-hydroxydecanoate	2	
2	Acidic fibroblast growth factor	1	1
2	Aconitum	2	
2	Acorus calamus	2	
2	adenylate cyclase inhibitor	1	1
2	ALDH Bright Cells)		2
2	Aleglitazar	1	1
2	alfentanil	1	1
2	alogliptin		2
2	alpha-conotoxin Vc1.1	2	
2	alpha2-delta ligands	2	
2	AM424	2	
2	angelica	1	
2	anisodamine	1	
2	Anodyne Therapy System	2	
2	apomorphine	2	1
2	Astragali	1	

2	Bimoclolmol	2	1
2	Biolimus		1
2	bisoprolol	1	1
2	blackcurrant juice		2
2	BRX-220	2	
2	calcium gluconate	2	
2	calmangafodipir	2	
2	calpeptin	2	
2	carisoprodol	1	1
2	Cerebrolysin	1	
2	cicaprost		2
2	cinnamaldehyde	2	
2	Cobalt Chloride	2	
2	controlled reperfusion		2
2	Cyclandelate		2
2	cytidine	2	
2	Dark chocolate		2
2	deferoxamine	2	
2	DHbetaE)	1	
2	dietary nitrate		2
2	Dihydro-beta-erythroidine	1	1
2	dihydropyridines		2
2	diluted bee venom	2	
2	Dioscoreae rhizoma	2	
2	DMSO	2	
2	docosapentaenoic acid		2
2	DRG stimulation	2	
2	DVC1-0101		2
2	E2072	2	
2	egg white hydrolysate	2	
2	elcatonin	2	
2	electromagnetic neural stimulation	2	
2	electromagnetic radiation		1
2	emodin	2	
2	ergocalciferol		1
2	Ethoxyquin	2	
2	etodolac	2	
2	fibroblast growth factor 1		2
2	Flupirtine	1	1
2	fondaparinux		2
2	gallic acid	2	
2	geldanamycin	1	
2	gluthatione	2	
2	glycyrrhizin	2	
2	HGF plasmid DNA		2

2	hypoxia-inducible factor-1alpha (HIF-1alpha)		2
2	intravenous high-dose immunoglobulin	2	
2	kappa-opioid receptor agonist	2	
2	KRN5500	2	
2	KU-596	2	
2	leuprolide acetate		1
2	linagliptin	1	2
2	loperamide	2	
2	maraviroc	1	1
2	maximal strength training		2
2	MEK inhibitors	2	
2	melanocortin	2	
2	metaxalone	1	
2	methyl nicotinate	2	
2	Mibefradil	2	
2	monochromatic infrared photo energy	2	
2	monosodium glutamate	1	1
2	nalbuphine	2	
2	Neomycin	1	
2	neurofeedback	2	
2	niflumic acid	1	1
2	nitrate consumption		2
2	pyrrolidine-2,5-dione	2	1
2	Snake venoms	2	
1	25)Mg-PMC16	1	
1	3,3,5-trimethylcyclohexanol		1
1	3-Aminobenzamide	1	
1	4-phenylbutyric acid	1	
1	5-phenyl-1-pentyne	1	
1	7-hydroxy-3,4-dihydrocadalin	1	
1	8-methoxypsoralen		1
1	A-134974	1	
1	AC591	1	
1	Acanthopanax	1	
1	ACEA	1	
1	acellular dermal regenerative tissue	1	1
1	Achyranthis bidentata Blume	1	
1	acipimox	1	
1	activation of Nrf2	1	
1	ACY-1083	1	
1	AGGF1		1
1	aktovegin		1

1	Alfa LMW1		1
1	alpha-chymotrypsin	1	
1	Alstonia scholaris	1	
1	AM1714	1	
1	aminoguanidine hydrochloride	1	
1	aminophylline		1
1	ampakines	1	
1	AMPK activators	1	
1	anthranilic acid	1	
1	antimycin	1	
1	Apligraf	1	
1	ARA 290	1	
1	arm-crank exercise		1
1	ascorbyl palmitate	1	
1	AVP-923	1	1
1	Azadirachta indica	1	
1	baicalein	1	
1	Baicalin	1	
1	BAIMAI-SAN	1	
1	BAK-PLO	1	
1	bendazac lysine	1	
1	benserazide	1	
1	bepermingene perplasmid		1
1	beta-caryophyllene	1	
1	betulinic acid	1	
1	bis(maltolato)oxovanadium IV		1
1	borneol	1	
1	bovine lactoferrin	1	
1	BRL-50481	1	
1	BRLP-42)	1	1
1	bromelain	1	
1	bushi	1	
1	Butea monosperma	1	
1	Caffeic acid phenethyl ester	1	
1	calciparine		1
1	calcium citrate	1	
1	calcium/magnesium infusion	1	
1	Calmare therapy	1	
1	Calmidazolium	1	
1	candoxatril	1	
1	Capnellene	1	
1	ceftaroline fosamil (CPT-F)		1
1	CEP 03		1
1	CEP protein adducts		1
1	Chamomilla matricaria	1	
1	chemical ablation		1

1	chlorogenic acid		1
1	Chlorpheniramine	1	
1	cholecystinin receptor antagonists	1	
1	cholecystinin-8	1	
1	cholesterol-rich diet		1
1	chromaffin cell grafts	1	
1	circulator boot therapy		1
1	citicoline	1	
1	COMP-Ang-1	1	
1	contrast-enhanced sonothrombolysis		1
1	copper ions	1	1
1	CQ		1
1	crenotherapy		1
1	Crocin	1	
1	cromakalim		1
1	Crotoxin	1	
1	CX614	1	
1	CX729	1	
1	Cymbalta	1	1
1	Cystamine	1	
1	cytoflavin	1	
1	D-sorbitol	1	
1	daidzin	1	
1	daltroban		1
1	Deguelin	1	
1	dexibuprofen	1	
1	dielectric barrier discharge plasma		1
1	dietary folate intake		1
1	dietary vitamin E	1	
1	diethylcarbamazine		1
1	dihydrolipoic acid	1	1
1	diphenyl diselenide	1	
1	dronabinol	1	
1	EAntS-GS	1	
1	Effexor	1	
1	Electroconvulsive shock	1	
1	electromagnetic therapy		1
1	elinogrel		1
1	emfilermin)	1	
1	Entacapone	1	
1	Epac-inhibitor	1	
1	EPAS1 gene		1
1	epicatechin gallate	1	

1	eplerenone	1	1
1	ergothioneine	1	
1	erucic acid	1	
1	ESI-09	1	
1	estradiol valerate		1
1	ethanethiol	1	
1	ethopropazine	1	
1	eugenol	1	
1	exogenous recombination IL-4	1	
1	extracorporeal shock wave therapy	1	
1	extract of date fruit	1	
1	felbamate	1	
1	Fenfluramine	1	
1	fenugreek extract	1	
1	Ferula assa-foetida	1	
1	ferulic acid	1	
1	Fexofenadine	1	
1	fluocinolone acetonide	1	
1	fumonisin B1	1	
1	gadolinium chloride	1	
1	GCSB-5	1	
1	Gentiopicroside	1	
1	Guizhi-shaoyao-zhimu decoction	1	1
1	Hachimi-jio-gan		1
1	hemangioblasts		1
1	Hydroxytyrosol	1	
1	hyperforin	1	
1	hypericin	1	
1	Ilepatril	1	
1	imatinib mesylate		1
1	immunoabsorber	1	1
1	increased intake of folate		1
1	IND01	1	
1	INGAP peptide	1	
1	injectable biomaterial		1
1	interval walking		1
1	intrathecal opioid infusion	1	
1	IRE1alpha siRNA	1	
1	isoprenaline		1
1	isopropyl myristate	1	
1	Isoxsuprine hydrochloride		1
1	itaconic acid		1
1	J147	1	
1	Jiaweibugan	1	
1	Juglans regia L.	1	

1	kaempferol	1	
1	Kamishoyosan	1	
1	ketogenic diet	1	
1	Kv7 channel activator	1	
1	lactoferrin	1	
1	levo-corydalmine	1	
1	Levocarnitine acetyl 150	1	
1	levorphanol	1	1
1	LiCl	1	
1	ligustrazine	1	
1	Linalool	1	
1	Lithospermi radix	1	
1	LM11A-31	1	
1	lomitapide		1
1	Lotrafiban		1
1	low frequency acoustic waveform		1
1	low frequency magnetic fields	1	
1	low glucose diet		1
1	LPP1	1	
1	Maltol	1	
1	mangiferin	1	
1	Manidipine	1	1
1	maprotiline	1	
1	MCC-257	1	
1	mCPP	1	
1	MDA19	1	
1	Me6TREN		1
1	meclizine	1	
1	medical herbs	1	
1	metamizol/paracetamol		1
1	methylsulfonylmethane	1	
1	metyrapone	1	
1	microRNA let-7g		1
1	mindfulness meditation	1	
1	minoxidil	1	
1	MnDPDP	1	
1	MnL4	1	
1	Momordica cymbalaria	1	
1	monosialotetrahexosylganglioside	1	
1	morin	1	
1	MPV-2426	1	
1	N(6)-cyclopentyladenosine	1	
1	nabilone	1	
1	naringin	1	
1	NCX 6550		1
1	nefopam	1	



1	neoline	1	
1	neprilysin	1	
1	Neuragen PN	1	
1	NF3		1
1	niclosamide	1	
1	nicorandil	1	
1	NM-702		1
1	Nmnat)	1	
1	Nornicotine	1	
1	NT-702		1
1	nylidrin		1
1	oleanolic acid	1	
1	OP-1206	1	1
1	pamoic acid	1	
1	pancreatic kininogenase	1	
1	parthenolide	1	
1	pCK-HGF-X7		1
1	PDE4B/7A dual inhibitor	1	
1	PDE5 inhibitor	1	
1	PDWHF		1
1	pemirolast	1	
1	Peptide5	1	
1	percutaneous catheter-based therapies		1
1	phenols		1
1	Phenoxodiol	1	
1	phenoxyphenyl pyridines	1	
1	phenyl-N-tert-butylNitron	1	
1	Picrorhiza kurroa	1	
1	piler-light		1
1	piperine	1	
1	piroxican	1	
1	pitavastatin		1
1	placental-derived adherent stromal cells		1
1	plantar vibration	1	
1	pneumatic compression boot	1	1
1	polaprezinc	1	
1	potassium channel openers	1	1
1	prifinium bromide	1	
1	pRLX		1
1	Procyclidine	1	
1	progestins		1
1	progestogen therapy		1
1	Prograf	1	
1	propolis	1	

1	prosaposin-derived 14-mer peptide	1	
1	proxiphylline	1	
1	psoralen		1
1	Pulsed radiofrequency ablation	1	
1	pulsed radiofrequency neuromodulation	1	
1	Punica granatum L	1	
1	Punicalagins	1	
1	pyrimethamine	1	
1	QR-333	1	
1	Quetiapine	1	
1	Racemic (R/S)-guaifenesin (1)	1	
1	rAd5/NR2B	1	
1	Recombinant Sema3A protein	1	
1	reparixin	1	
1	Ro5-4864	1	
1	rosemary	1	
1	Rosmarinic acid	1	
1	RSR13		1
1	RU38486	1	
1	rutin	1	
1	safranal	1	
1	Salicylaldehyde	1	
1	salmon calcitonin	1	
1	salsalate	1	1
1	Salvia officinalis	1	
1	Salvianolic acid B	1	
1	SAN-Gly	1	
1	Saposhnikovia divaricata Schiskin	1	
1	SDZ PCO-400		1
1	sesame oil	1	
1	shellac		1
1	Silybin	1	
1	silymarin	1	1
1	SN gene therapy		1
1	sodium hydrosulfide		1
1	sodium sulfide		1
1	SP600125	1	
1	spironolactone		1
1	SQ22536	1	
1	SR 57746A	1	1
1	subsensory electrical stimulation	1	
1	synthetic exendin-4	1	
1	T-cell-pre-stimulated monocytes		1
1	Tanshinone	1	

1	TAT-CBD3A6K	1	
1	Terbinafine		1
1	tetracyclines	1	
1	tetramethylpyrazine	1	
1	thenoyltrifluoroacetone		1
1	thiorphan	1	
1	thiosalicylic acid	1	
1	torse mide		1
1	Trehalose	1	
1	Treprostinil diethanolamine		1
1	tretinoin		1
1	trimethoxy flavone	1	
1	TRPA1/PDE4B/PDE7A ligand	1	
1	TT saponin	1	
1	Turpentine	1	1
1	U 69593	1	
1	vascular regenerative therapy		1
1	Vernonia cinerea	1	
1	vitamin K2		1
1	Vitis vinifera	1	
1	VR-1 receptor modulators	1	
1	WR1065	1	
1	Xilonix		1
1	yang-warming	1	
1	Yiqi Huayu	1	
1	Zhenqing Capsule	1	
1	ziconotide	1	

**TABLE 7A-9a - Existing PN/PAD Biomarkers**

# REC	BIOMARKER
2638	lesions
2536	inflammation
2320	toxicity
2277	nerve conduction velocity
2038	ankle brachial index
1549	blood pressure
1402	stenosis
1156	body mass index
1142	neurotoxic
1139	total cholesterol
1138	blood glucose levels
1091	degeneration
1061	hemoglobin A1c
932	blood flow
856	marker
841	proteins
748	atrophy
747	dorsal root ganglia
704	creatinine
700	oxygen
693	lipoprotein
671	growth factor
640	Schwann cell
616	demyelination
610	pain-free walking distance
549	C reactive protein
538	calcium
516	cytokine
499	triglycerides
495	low-density lipoprotein cholesterol
489	angiogenesis
455	axonal degeneration
435	Systolic blood pressure
426	circulation
425	high-density lipoprotein cholesterol
419	oxidative stress
413	plaque
412	occlusions
402	albumin level
399	glomerular filtration rate
391	ventricular ejection fraction
382	calcification
365	nerve damage
354	neurodegeneration
349	IgM
345	tumour necrosis factor-alpha
344	sodium
329	lipids
322	heart rate
318	edema
318	nitric oxide
309	apoptosis
308	fibrinogen
284	endothelial dysfunction
283	denervation
278	vascular endothelial growth factor
273	glycoprotein
266	IL-6
263	vitamin B(12) deficiency
262	stenoses
261	high homocysteine
251	angiotensin converting enzyme
247	amyloid
240	myelinated fibers
237	vibration perception threshold
222	weight loss
210	fatty acid
208	carotid artery intima-media thickness
206	nerve growth factor
202	T-cell
197	autoantibodies
195	thermal hyperalgesia
193	CD4
186	proinflammatory cytokine
185	insulin resistance
183	pulse wave velocity

175	diastolic blood pressure
170	nerve regeneration
168	platelet aggregation
162	glycated haemoglobin
159	lymphocytes
158	nerve fiber density
154	B-cell
152	Reactive oxygen species
151	arterial stiffness
147	capsaicin
147	lipid profile
135	platelet activation
128	IL-1beta
126	glutamate
126	Transthyretin
126	vitamin E deficiency
125	apolipoprotein
125	Vitamin D deficiency
123	acetylcholine
122	mechanical hyperalgesia
119	glutathione
118	compound muscle action potential
115	Mitochondrial dysfunction
115	nitric oxide synthase
115	white blood cell
114	creatine
110	waist circumference
108	creatinine clearance
107	lactate
106	von Willebrand factor
105	plasminogen activator inhibitor-1
104	pulse pressure
104	thrombin
103	urea
102	atherosclerotic plaque
102	IgA
101	vasculopathy
100	intercellular adhesion molecule-1
99	antioxidants
98	calcitonin gene-related peptide
96	uric acid

95	blood viscosity
94	Lipoprotein(a)
92	albumin excretion rate
92	substance P
84	fiber loss
84	malondialdehyde
81	Endothelial progenitor cells
81	orthostatic hypotension
80	fibrin
80	fibroblast growth factor
80	folic acid
78	transcutaneous oxygen pressure
74	creatine kinase
74	matrix metalloproteinase
74	thromboxane
73	thiamine
72	systemic sclerosis
70	IL-10
70	peak oxygen consumption
69	lipid peroxidation
69	prostacyclin
69	superoxide dismutase
69	troponin
68	D-dimer
66	mRNA levels
65	advanced glycation end product
65	magnesium
65	Zinc
64	anti-neutrophil cytoplasmic antibody
64	erythrocyte sedimentation rate
64	Red Blood Cell
61	monoclonal antibodies
61	oxygen saturation
61	P-selectin
60	heat shock
60	rheumatoid factor
59	acetylsalicylic acid
59	nitrogen
58	methionine
58	Neutrophils

55	Ca(2+)
55	Venous occlusion
54	glial fibrillary acidic protein
53	chemokines
53	Tissue Plasminogen Activator
52	Angiogenic growth factors
52	BDNF
52	hepatocyte growth factor
52	l-arginine
52	MetS
51	cardiac troponin T
51	epidermal growth factor
51	glucose metabolism
51	prothrombin
50	NF-kappaB
49	adenosine diphosphate
49	bone mineral density
49	cytochrome c
49	monocyte chemoattractant protein-1
49	protein kinases
48	bilirubin
48	thymidine
48	urinary albumin/creatinine ratio
47	glycosylation
45	neuronal damage
44	adiponectin
44	alanine
44	carbon dioxide
44	Mercury
43	erythrocytes
42	leucocytes
42	myelin basic protein
42	neuroinflammation
42	phosphorus
42	thromboangiitis
41	alkaline phosphatase
41	apolipoprotein B
41	CD34
41	free radicals
41	N-terminal pro-brain

	natriuretic peptide
41	transforming growth factor beta
40	arginine
40	DBP
40	dopamine
40	myeloperoxidase
40	sorbitol
39	apolipoprotein A-I
39	bacterial infection
39	cyclic AMP
39	endothelial damage
38	connexin 32
38	glycine
38	Noradrenaline
38	vitamin K
37	blood urea nitrogen
37	E-selectin
37	endothelin-1
37	matrix metalloproteinase 9
36	arachidonic acid
36	heme
36	IgG antibodies
36	niacin
35	glycogen
35	HCY
35	IL-8
35	interferon gamma
34	actin
34	catalase
34	cystatin C
34	histamine
34	Streptococcal
33	anti-ganglioside antibodies
33	catecholamine
33	cerebral ischemia
33	ferritin
33	glial activation
33	hypoperfusion
33	oxidative damage
32	anti-MAG antibodies
32	insulin levels
32	polyunsaturated fatty acids

31	parathyroid hormone
31	progesterone
30	beta 2 microglobulin
30	body fat
30	Gamma-aminobutyric acid
29	acetylcholinesterase
29	adenine
29	asymmetric dimethylarginine
29	Chlamydia pneumoniae
29	fibroblast growth factor 2
29	laminin
29	phospholipids
28	albumin/creatinine
28	brain atrophy
28	carotid-femoral pulse wave velocity
28	CD31
28	matrix metalloproteinase 2
28	Osteoprotegerin
28	phosphocreatine
28	Tau
28	thromboxane A2
27	antinuclear antibodies
27	Apolipoprotein E
27	cholinesterase
27	cyclooxygenase 2
27	epinephrine
27	GDNF
27	glutamine
27	high total cholesterol
27	methylmalonic acid
27	RAGE
27	vascular reactivity
26	Endothelin
26	glutathione peroxidase
26	growth hormone
26	HMG-CoA reductase
26	Hydrogen peroxide
26	leptin
26	miRNA
25	amyloid beta
25	cysteine
25	GP IIb/IIIa

25	Helicobacter pylori
25	Iron Deficiency
25	platelet-derived growth factor
25	sulfatide
24	aspartate aminotransferase
24	cadmium
24	IL-4
23	copper deficiency
23	immune activation
23	integrin
23	peroxynitrite
23	transferrin
22	CD8
22	lipase
22	Vitamin B1 deficiency
21	bradykinin
21	Escherichia coli
21	glutamic acid
21	methicillin-resistant Staphylococcus aureus
21	Oxidized low-density lipoprotein
21	prostate-specific antigen
20	acylcarnitine
20	adenosine triphosphate
20	aldosterone
20	arterial obstruction
20	CD40 ligand
20	folate deficiency
20	insulin-like growth factor I
20	thromboxane B2
20	transaminases
19	Ccl2
19	riboflavin
19	serum calcium
19	thrombomodulin
19	vascular calcifications
18	amyloid fibrils
18	c-Fos
18	caspase 3
18	docosahexaenoic acid
18	eicosapentaenoic acid
18	endothelial activation

18	estradiol
18	heme oxygenase 1
18	HIF-1alpha
18	luminal diameter
18	NADPH oxidases
18	renin
18	selenium
17	5-hydroxytryptamine
17	aortic pulse wave velocity
17	arterial compliance
17	bone density
17	compound motor action potential
17	CXCR4
17	cytomegalovirus infection
17	dehydration
17	desmin
17	elastin
17	excitotoxicity
17	High-mobility group box 1
17	IL-2
17	lactic acid
17	lead levels
17	porphobilinogen
17	prothrombin time
16	androgen
16	factor Xa
16	galanin
16	neoangiogenesis
16	PGE2
16	phytanic acid
16	proline
16	pyridoxal
15	activated partial thromboplastin time
15	calcium phosphate
15	calpain
15	cholestanol
15	cortisol
15	digoxin
15	DNA polymerase gamma
15	osteopontin
14	anti-GM1 antibody

14	antithrombin III
14	CD68
14	choline
14	CNTF
14	Fas
14	fos
14	MMA
14	myo-inositol
14	porphyrin
14	TBARS
13	atheromatous plaque
13	ceruloplasmin
13	complement levels
13	cyclic guanine monophosphate
13	E. coli
13	elastase
13	Fetuin-A
13	leucine
13	Lipoprotein-associated phospholipase A2
13	Neopterin
13	RNA levels
13	thyroxine
13	transglutaminase
13	vasopressin
12	adipokine
12	anticardiolipin antibodies
12	arterial calcifications
12	beta-carotene
12	C1q
12	calcineurin
12	caspases
12	Chondroitin sulfate
12	hydrogen sulfide
12	IgE
12	insulin deficiency
12	MEP
12	mitogen-activated protein kinases
12	NOx
12	PBMCs
12	Proteus
12	sE-selectin
12	spirochete
11	anti-gliadin antibodies



11	Coxsackie
11	dendritic cells
11	dipeptidyl peptidase
11	excitatory amino acids
11	fructose
11	gamma-glutamyltransferase
11	histidine
11	IL-12
11	Myelin breakdown
11	Pseudomonas aeruginosa
11	Resistin
10	ammonia
10	AMPA
10	apolipoprotein(a)
10	cathepsins
10	cotinine
10	Glutamate carboxypeptidase II
10	glycogen synthase
10	low birth weight
10	lysophosphatidic acid
10	Nrf2
10	polyglutamine
10	S-adenosylmethionine
10	threonine
10	tryptophan
9	adenosine monophosphate
9	alpha-synuclein
9	anticholinesterase
9	Aortic augmentation index
9	beta-galactosidase
9	BNP levels
9	BSA
9	CD133
9	cystathionine beta-synthase
9	deoxyuridine
9	enolase
9	fibrin D-dimer
9	fungi
9	heparan sulfate
9	iodine
9	low testosterone

9	phenylalanine
9	squalene
9	staphylococcal
9	vascular stiffness
8	arterial dilatation
8	Aspergillus
8	Butyrylcholinesterase
8	CBM
8	coagulation activation
8	corticosterone
8	glucagon
8	gonadotropin
8	inositol
8	isoprostane
8	leukotrienes
8	osteocalcin
8	paraoxonase-1
8	phosphates
8	Retroviruses
8	S100 beta
8	somatostatin
8	taurine
8	thyrotropin
7	4-hydroxy-2-nonenal
7	aldehyde dehydrogenase
7	amines
7	angiotensin II type 1
7	CD14
7	coronary calcification
7	HIV RNA levels
7	horseradish peroxidase
7	linoleic acid
7	monomethylarsonic acid
7	neuropilin-1
7	OX-42
7	phosphatidylinositol 3-kinase
7	thrombospondin
7	TNFR2
6	alcohols
6	arterial elasticity
6	citrulline
6	Cu
6	dimethylarsinic acid
6	factor XIII
6	fibroblast growth factor

	23
6	FVII
6	glucuronic acid
6	GRP78
6	histone deacetylase 6
6	IL-18
6	kallikrein
6	lipid hydroperoxides
6	Methylglyoxal
6	N-acetylglucosamine
6	neurotoxic esterase
6	oxygen radicals
6	pentraxin
6	pERK
6	prolactin
6	quinolinic acid
6	Telomerase
6	transketolase
5	Acetylcarnitine
5	apolipoprotein A-II
5	apolipoprotein B-100
5	CD11c
5	CD16
5	CD86
5	cyclin D1
5	deoxyhemoglobin
5	dihydrotestosterone
5	galectin-3
5	Glyoxalase 1
5	guanosine monophosphate
5	Guanylate Cyclase
5	hyperphosphorylation
5	IL-13
5	inosine
5	L-selectin
5	lipofuscin
5	luteinizing hormone
5	monoamine oxidase
5	omega-3 index
5	perforin
5	phenyl valerate
5	platelet factor 4
5	pregnenolone
5	pristanic acid
5	retinol

5	sphingosine
5	thiocyanate
5	YKL-40
4	Adrenomedullin
4	amyloid precursor protein
4	angiogenin
4	angiotensinogen
4	apolipoprotein B-48
4	apolipoprotein C-III
4	arterial tonometry index (RHI)
4	beta-endorphin
4	chromogranin
4	dehydroepiandrosterone
4	dynactin
4	endopeptidases
4	erythrocyte aggregation
4	GHb
4	glutathione transferase
4	glycated albumin
4	homovanillic acid
4	hydroxymethylbilane synthase
4	IgG4-positive plasma cells
4	IL-17
4	IL-22
4	indole
4	Janus kinase 2
4	mannose
4	metallothionein
4	myostatin
4	nitrogen oxide
4	Nox2
4	S100A12
4	Sirtuin 1
4	SO2
4	soluble guanylyl cyclase
4	succinate dehydrogenase
4	tetrahydrobiopterin
4	tissue inhibitors of metalloproteinases
4	ubiquinone
4	valvular calcification
4	vasoactive intestinal

	peptide
3	acetaldehyde
3	acyl-CoA oxidase
3	Allograft inflammatory factor-1
3	arginase
3	B vitamin deficiency
3	brain iron accumulation
3	butyric acid
3	CFU
3	chorionic gonadotropin
3	connective tissue growth factor
3	CXCL10
3	eosinophil cationic protein
3	factor XII
3	Fusobacterium
3	glucagon-like peptide 1
3	Glucokinase
3	glutathione reductase
3	GTP cyclohydrolase
3	hemosiderin
3	hydroperoxide
3	hydroxyl radical antioxidant capacity
3	hyperoxia
3	iron deposition
3	kynurenine
3	LXR
3	m-calpain
3	mandelic acid
3	methemoglobin
3	mu-calpain
3	N-acetylaspartate
3	neurite loss
3	neurotensin
3	NF68
3	nicotinamide mononucleotide
3	Nociceptin
3	phosphatidylserine
3	PINK1
3	pipecolic acid
3	pregnancy-associated plasma protein-A

3	ryanodine
3	S-adenosylhomocysteine
3	sCD163
3	serum nitrate
3	sTWEAK
3	trimethylamine
3	waist-to-height ratio
3	xanthine oxidase
2	3-nitrotyrosine
2	32P
2	acid phosphatase
2	adenosine deaminase
2	adenosine kinase
2	adenyl cyclases
2	agrin
2	aminolevulinic acid
2	aminopeptidases
2	apoB/apoA-I ratio
2	apolipoprotein A-IV
2	apolipoprotein AI-CIII-AIV gene cluster
2	aspartic acid
2	campesterol
2	carboxymethyl-lysine
2	Cardiometabolic index (CMI)
2	caspase 9
2	CCL4
2	Ceramide antibody levels
2	cyclin-dependent kinase 5
2	deoxyguanosine
2	deoxypyridinoline
2	docosapentaenoic acid
2	endostatin
2	estrone
2	follicle stimulating hormone
2	glutaredoxin
2	herpes simplex virus 1
2	hippuric acid
2	histone deacetylases
2	hydroxyproline
2	Janus kinase 1
2	JC virus
2	Ketones

2	kininase II
2	kininogen fractions
2	kynurenic acid
2	measles virus
2	midkine
2	miR-130a
2	miR-210
2	miR-27b
2	MuSK
2	omentin-1 level
2	phenylglyoxylic acid
2	polymorphonuclear neutrophils
2	Prevotella intermedia
2	protein tyrosine phosphatases
2	pyruvic acid
2	saturated fatty acid
2	suPAR level
2	tachykinins
2	transcription factor CHOP
2	TREM-1
2	vitamin C deficiency
2	Wnt5a
1	1,1-Diphenyl-2-picrylhydrazyl
1	1,7-dimethylxanthine
1	25-hydroxycholesterol
1	27-hydroxycholesterol
1	3,4-dihydroxyphenylacetic acid
1	3,4-dihydroxyphenylglycol
1	3,5,3'-triiodothyronine
1	4-pyridoxic acid
1	5-bromo-2'-deoxyuridine
1	7-ketocholesterol
1	8-hydroxyguanosine
1	8-oxoguanine
1	adenylate kinase
1	aniline hydroxylase
1	Anti-Mullerian hormone
1	antiphospholipids-induced
1	apolipoprotein D

1	Apolipoprotein L1
1	aryl hydrocarbon hydroxylases
1	bacterial endotoxins
1	benzo(a)pyrene
1	beta-mannosidase
1	calcium-dependent protein kinase
1	caspase 12
1	caspase 8
1	catechol-O-methyltransferase
1	CgA
1	complement C3b
1	complex II deficiency
1	complex IV deficiency
1	cyclic ADP-ribose
1	cyclooxygenase 1
1	cystathionine gamma-lyase
1	cysteinylglycine
1	dihydroxyphenylalanine
1	DL-alpha-tocopherol
1	elevated copper
1	Ferric iron
1	gamma-glutamylcysteine
1	gamma-tocopherol
1	glutaminase
1	glyceraldehyde
1	glyoxal
1	granzymes
1	hemopexin
1	hexokinase
1	High adiponectin
1	histone acetyltransferases
1	homocysteic acid
1	hypochlorite
1	isobutanol
1	keratins
1	L-ascorbic acid
1	lathosterol
1	NADH dehydrogenase
1	Nepsilon-(carboxymethyl)lysine
1	o-xylene

1	oncostatin
1	oxysterols
1	p-cresol
1	p300-CBP-associated factor
1	pancreatic polypeptide
1	Perlecan
1	Peroxiredoxins
1	phosphorylases
1	polyamines
1	polyQ
1	protoporphyrin IX

1	prulifloxacin
1	psychosine
1	pyrrole
1	pyruvate carboxylase
1	S-nitrosoglutathione
1	sex steroid hormones
1	ulifloxacin
	Urine kidney injury molecule-1

**TABLE 7A-9b - Existing PN/PAD Symptoms/Diseases**

# REC	SYMPTOM/DISEASE
17050	neuropathy
13577	peripheral neuropathy
9627	diabetes mellitus
9078	artery disease
8114	peripheral artery disease
6967	peripheral vascular disease
5942	pain
5016	ischemia
3095	hypertension
3014	cancer
2969	atherosclerosis
2861	neuropathic pain
2612	stroke
2152	diabetic peripheral neuropathy
2071	infection
2056	myocardial infarction
2051	cardiovascular disease
1983	intermittent claudication
1913	polyneuropathy
1796	coronary artery disease
1585	heart disease
1571	type 2 diabetes mellitus
1547	critical limb ischemia
1533	diabetic foot ulcer
1519	Disorder
1440	heart failure
1135	weakness
879	neutropenia
878	cerebrovascular disease
833	sensory neuropathy
832	retinopathy
799	coronary heart disease
779	allodynia
769	disability
769	obesity
747	renal failure
731	thrombosis
705	ataxia
675	abdominal aortic aneurysm
660	nephropathy

645	angina
645	renal disease
625	Congestive heart failure
623	multiple myeloma
621	peripheral artery occlusive disease
618	bleeding
618	hyperalgesia
613	chronic kidney disease
612	vasculitis
607	ischemic heart disease
602	restenosis
578	chronic obstructive pulmonary disease
578	fatigue
566	Charcot-Marie-Tooth disease
560	anemia
545	depression
521	thrombocytopenia
503	dyslipidemia
497	numbness
456	Hyperglycemia
455	nausea
444	sclerosis
441	hypersensitivity
433	atrial fibrillation
417	balance
412	chronic pain
400	mononeuropathy
391	lymphoma
389	rheumatoid arthritis
388	End stage renal disease
387	autonomic neuropathy
385	dementia
380	axonal neuropathy
379	mechanical allodynia
376	vomiting
373	gangrene
363	myopathy
362	palsy
360	hypercholesterolemia
358	diarrhea
354	ischemic stroke

352	Guillain-Barre syndrome
345	carpal tunnel syndrome
343	hyperlipidemia
332	leprosy
319	type 1 diabetes mellitus
314	hepatitis
308	renal insufficiency
306	encephalopathy
305	demyelinating peripheral neuropathy
304	motor neuropathy
303	Coronary Syndrome
295	neurological symptoms
285	neurologic disease
284	muscle weakness
280	Atherothrombosis
275	arrhythmia
273	inflammatory demyelinating polyneuropathy
271	metabolic syndrome
266	systemic lupus erythematosus
257	stiffness
254	amyloidosis
250	left ventricular hypertrophy
249	peripheral sensory neuropathy
249	radiculopathy
247	fractures
244	myelopathy
231	fibrosis
227	microalbuminuria
224	diabetic retinopathy
220	hypotension
213	multiple sclerosis
205	coronary disease
202	paresthesia
199	constipation
199	monoclonal gammopathy
190	proteinuria
187	diabetic nephropathy
187	Mixed Cryoglobulinemia
187	Sjogren's syndrome
179	nerve dysfunction

178	arterial hypertension
169	demyelinating polyradiculoneuropathy
169	sensorimotor polyneuropathy
165	Mononeuritis
162	angina pectoris
160	axonopathy
158	lung disease
157	Parkinson's disease
157	renal dysfunction
152	autoimmune disease
150	albuminuria
150	hypoxia
149	liver disease
149	sensorimotor neuropathy
147	hyperplasia
133	erectile dysfunction
126	renal impairment
125	artery calcification
124	vasculitic neuropathy
123	amyotrophic lateral sclerosis
123	systemic atherosclerosis
120	axonal polyneuropathy
119	hypothyroidism
119	myocardial ischemia
117	neurodegenerative disease
113	Alzheimer's disease
113	POEMS syndrome
110	atherosclerotic vascular disease
110	Osteoporosis
107	carotid artery disease
107	peripheral polyneuropathy
107	reactive hyperemia
103	neuromuscular disease
103	optic neuropathy
102	impaired glucose tolerance
101	endocrinopathy
101	Macrovascular disease
88	motor neuron disease
86	cerebral infarction

84	arterial stenosis
84	metastatic disease
80	atherogenesis
78	dysesthesia
77	macroglobulinemia
76	acquired immunodeficiency syndrome
75	Hyperhomocysteinemia
73	left ventricular dysfunction
73	peripheral atherosclerosis
72	complex regional pain syndrome
72	microvascular disease
70	dysphagia
70	polyarteritis nodosa
69	HIV disease
69	organ damage
68	granulomatosis
68	neuroarthropathy
67	eosinophilia
67	Restless legs syndrome
66	vascular calcification
65	hypoglycemic
65	polyangiitis
63	Churg-Strauss syndrome
61	amyloidotic polyneuropathy
61	neurodegenerative disorders
59	metabolic disease
58	impaired renal function
56	celiac disease
56	Crohn's disease
55	demyelinating disease
54	coronary atherosclerosis
54	inflammatory bowel disease
54	macroalbuminuria
53	sleep apnea
52	nephrotic syndrome
51	carotid atherosclerosis
48	gammopathies
47	connective tissue disease

47	proliferative retinopathy
46	cardiac autonomic neuropathy
43	Buerger's disease
43	Lyme disease
41	arteriosclerosis obliterans
41	polyvascular disease
41	vascular dysfunction
38	cutaneous vasculitis
37	Fabry disease
37	Miller Fisher syndrome
33	hypercoagulability
31	hypoalbuminemia
31	mitochondrial diseases
31	muscle ischemia
30	Castleman's disease
30	diplopia
30	Hansen's disease
29	Behcet's disease
29	chronic liver disease
28	sicca syndrome
26	hyperuricemia
25	gluten sensitivity
25	peripheral ischemia
21	Hypereosinophilic syndrome
20	aortic stiffness
18	coronary artery stenosis
17	normoalbuminuria
16	kidney dysfunction
15	CLTI
14	dysmetria
12	malaria
12	mechanical stress
12	rheumatoid vasculitis
11	hypomagnesemia
11	neurone disease
10	neurosyphilis
10	social isolation
9	low physical activity
8	bulbar palsy
8	Hyperfibrinogenemia
6	hypercapnia
6	Wolfram



**Table 7A-10 - Angiogenesis Co-Occurrences with other Biomarkers**

# RECORDS	BIOMARKER	# CO-OCCURRENCES
489	angiogenesis	489
671	growth factor	190
278	vascular endothelial growth factor	131
932	blood flow	121
2536	inflammation	64
700	oxygen	43
841	proteins	42
516	cytokine	39
52	Angiogenic growth factors	39
80	fibroblast growth factor	39
81	Endothelial progenitor cells	36
318	nitric oxide	32
2038	ankle brachial index	29
610	pain-free walking distance	28
309	apoptosis	28
52	hepatocyte growth factor	25
856	marker	21
2320	toxicity	17
1138	blood glucose levels	16
426	circulation	16
284	endothelial dysfunction	14
115	nitric oxide synthase	14
419	oxidative stress	13
74	matrix metalloproteinase	13
29	fibroblast growth factor 2	12
2638	lesions	12
1549	blood pressure	11
318	edema	10
28	CD31	10
345	tumour necrosis factor-alpha	10
1402	stenosis	9
41	CD34	8
152	Reactive oxygen species	8
1091	degeneration	7
413	plaque	7
52	l-arginine	6
18	HIF-1alpha	6
42	thromboangiitis	6
51	epidermal growth factor	5
41	transforming growth factor beta	5
17	CXCR4	5
748	atrophy	5

412	occlusions	5
16	neoangiogenesis	5
26	miRNA	5
25	platelet-derived growth factor	5
2277	nerve conduction velocity	4
126	vitamin E deficiency	4
23	integrin	4
78	transcutaneous oxygen pressure	4
168	platelet aggregation	4
186	proinflammatory cytokine	4
128	IL-1beta	4
640	Schwann cell	4
101	vasculopathy	4
1156	body mass index	3
185	insulin resistance	3
18	heme oxygenase 1	3
55	Venous occlusion	3
13	cyclic guanine monophosphate	3
20	arterial obstruction	3
6	oxygen radicals	3
61	monoclonal antibodies	3
15	osteopontin	3
99	antioxidants	3
17	High-mobility group box 1	3
36	heme	3
329	lipids	3
7	neuropilin-1	3
69	prostacyclin	3
435	Systolic blood pressure	3
202	T-cell	3
33	cerebral ischemia	3
37	matrix metalloproteinase 9	3
1061	hemoglobin A1c	3
266	IL-6	3
7	thrombospondin	2
1139	total cholesterol	2
747	dorsal root ganglia	2
693	lipoprotein	2
6	Telomerase	2
549	C reactive protein	2
4	angiogenin	2
16	proline	2
2	endostatin	2
53	chemokines	2
2	Wnt5a	2
35	IL-8	2

354	neurodegeneration	2
344	sodium	2
308	fibrinogen	2
283	denervation	2
50	NF-kappaB	2
206	nerve growth factor	2
49	monocyte chemoattractant protein-1	2
170	nerve regeneration	2
123	acetylcholine	2
119	glutathione	2
26	growth hormone	2
107	lactate	2
106	von Willebrand factor	2
105	plasminogen activator inhibitor-1	2
104	thrombin	2
102	atherosclerotic plaque	2
100	intercellular adhesion molecule-1	2
94	Lipoprotein(a)	2
84	malondialdehyde	2
39	cyclic AMP	2
69	lipid peroxidation	2
66	mRNA levels	2
65	Zinc	2
37	E-selectin	2
37	endothelin-1	2
28	matrix metalloproteinase 2	2
9	beta-galactosidase	2
1142	neurotoxic	1
616	demyelination	1
538	calcium	1
495	low-density lipoprotein cholesterol	1
24	IL-4	1
29	acetylcholinesterase	1
20	insulin-like growth factor I	1
29	asymmetric dimethylarginine	1
27	vascular reactivity	1
154	B-cell	1
25	cysteine	1
80	fibrin	1
48	thymidine	1
80	folic acid	1
162	glycated haemoglobin	1
183	pulse wave velocity	1
197	autoantibodies	1
29	laminin	1

39	bacterial infection	1
26	HMG-CoA reductase	1
14	MMA	1
70	peak oxygen consumption	1
26	Hydrogen peroxide	1
18	estradiol	1
69	superoxide dismutase	1
38	connexin 32	1
17	elastin	1
114	creatine	1
65	advanced glycation end product	1
65	magnesium	1
33	hypoperfusion	1
27	cyclooxygenase 2	1
34	actin	1
251	angiotensin converting enzyme	1
261	high homocysteine	1
61	oxygen saturation	1
27	RAGE	1
102	IgA	1
273	glycoprotein	1
19	Ccl2	1
52	MetS	1
365	nerve damage	1
58	Neutrophils	1
12	adipokine	1
12	arterial calcifications	1
12	insulin deficiency	1
10	lysophosphatidic acid	1
10	Nrf2	1
41	alkaline phosphatase	1
9	CD133	1
9	heparan sulfate	1
8	glucagon	1
8	Retroviruses	1
7	CD14	1
17	excitotoxicity	1
7	phosphatidylinositol 3-kinase	1
135	platelet activation	1
7	TNFR2	1
6	kallikrein	1
402	albumin level	1
6	prolactin	1
26	leptin	1
5	CD16	1
5	CD86	1

5	Glyoxalase 1	1
5	sphingosine	1
4	Adrenomedullin	1
45	neuronal damage	1
4	IL-22	1
4	SO2	1
3	arginase	1
3	GTP cyclohydrolase	1
3	NF68	1
3	serum nitrate	1
47	glycosylation	1
2	protein tyrosine phosphatases	1
18	NADPH oxidases	1
1	Perlecan	1
1	polyamines	1

**Table 7A-11 - Oxidative Stress Co-Occurrences with other Biomarkers**

#REC	BIOMARKER	#CO-OCC
419	oxidative stress	419
2536	inflammation	117
700	oxygen	72
1138	blood glucose levels	60
152	Reactive oxygen species	53
119	glutathione	52
841	proteins	47
99	antioxidants	46
309	apoptosis	44
318	nitric oxide	44
69	superoxide dismutase	41
84	malondialdehyde	39
2277	nerve conduction velocity	37
69	lipid peroxidation	36
284	endothelial dysfunction	30
932	blood flow	30
693	lipoprotein	30
747	dorsal root ganglia	27
856	marker	27
640	Schwann cell	27
115	Mitochondrial dysfunction	26
2320	toxicity	25
1139	total cholesterol	23
1091	degeneration	23
1142	neurotoxic	22
495	low-density lipoprotein cholesterol	21
1061	hemoglobin A1c	20
671	growth factor	20
549	C reactive protein	20
65	advanced glycation end product	19
1549	blood pressure	18
329	lipids	18
354	neurodegeneration	18
538	calcium	17
345	tumour necrosis factor-alpha	17
516	cytokine	17

34	catalase	16
126	vitamin E deficiency	16
266	IL-6	16
185	insulin resistance	15
26	glutathione peroxidase	14
115	nitric oxide synthase	14
2038	ankle brachial index	14
33	oxidative damage	14
1156	body mass index	13
489	angiogenesis	13
261	high homocysteine	13
413	plaque	13
2638	lesions	12
616	demyelination	12
610	pain-free walking distance	12
278	vascular endothelial growth factor	11
499	triglycerides	10
41	free radicals	10
308	fibrinogen	10
42	neuroinflammation	10
186	proinflammatory cytokine	10
399	glomerular filtration rate	9
26	Hydrogen peroxide	9
23	peroxynitrite	8
47	glycosylation	8
36	heme	8
18	NADPH oxidases	8
455	axonal degeneration	7
158	nerve fiber density	7
426	circulation	7
14	TBARS	7
210	fatty acid	7
10	Nrf2	7
8	isoprostane	7
206	nerve growth factor	6
45	neuronal damage	6
49	protein kinases	6
704	creatinine	6
12	NOx	6
18	heme oxygenase 1	6

151	arterial stiffness	6
80	folic acid	5
748	atrophy	5
425	high-density lipoprotein cholesterol	5
39	endothelial damage	5
74	matrix metalloproteinase	5
102	atherosclerotic plaque	5
51	glucose metabolism	5
96	uric acid	5
49	cytochrome c	5
382	calcification	5
115	white blood cell	5
147	lipid profile	5
21	Oxidized low-density lipoprotein	5
50	NF-kappaB	5
6	lipid hydroperoxides	5
52	l-arginine	5
154	B-cell	4
263	vitamin B(12) deficiency	4
69	prostacyclin	4
29	asymmetric dimethylarginine	4
40	myeloperoxidase	4
60	heat shock	4
105	plasminogen activator inhibitor-1	4
37	endothelin-1	4
208	carotid artery intima-media thickness	4
18	caspase 3	4
33	ferritin	4
7	4-hydroxy-2-nonenal	4
344	sodium	4
122	mechanical hyperalgesia	4
84	fiber loss	4
6	oxygen radicals	4
104	pulse pressure	4
100	intercellular adhesion molecule-1	4
52	MetS	3
44	adiponectin	3

26	leptin	3
318	edema	3
147	capsaicin	3
73	thiamine	3
128	IL-1beta	3
42	leucocytes	3
107	lactate	3
365	nerve damage	3
59	nitrogen	3
123	acetylcholine	3
19	Ccl2	3
125	Vitamin D deficiency	3
125	apolipoprotein	3
55	Ca(2+)	3
1402	stenosis	3
70	IL-10	3
195	thermal hyperalgesia	3
13	ceruloplasmin	3
183	pulse wave velocity	3
66	mRNA levels	3
237	vibration perception threshold	3
27	glutamine	3
8	paraoxonase-1	3
106	von Willebrand factor	3
126	glutamate	3
21	bradykinin	3
98	calcitonin gene-related peptide	2
29	phospholipids	2
92	substance P	2
81	Endothelial progenitor cells	2
28	CD31	2
74	thromboxane	2
65	magnesium	2
65	Zinc	2
28	Tau	2
18	selenium	2
26	growth hormone	2
61	oxygen saturation	2
61	P-selectin	2
27	cyclooxygenase 2	2
54	glial fibrillary acidic protein	2
53	chemokines	2

52	hepatocyte growth factor	2
27	RAGE	2
48	bilirubin	2
27	vascular reactivity	2
43	erythrocytes	2
41	alkaline phosphatase	2
40	arginine	2
402	albumin level	2
40	sorbitol	2
391	ventricular ejection fraction	2
16	pyridoxal	2
322	heart rate	2
14	MMA	2
35	HCY	2
35	IL-8	2
17	CXCR4	2
34	actin	2
283	denervation	2
29	acetylcholinesterase	2
240	myelinated fibers	2
222	weight loss	2
29	adenine	2
32	insulin levels	2
175	diastolic blood pressure	2
170	nerve regeneration	2
12	adipokine	2
162	glycated haemoglobin	2
159	lymphocytes	2
8	arterial dilatation	2
135	platelet activation	2
126	Transthyretin	2
8	taurine	2
17	excitotoxicity	2
7	neuropilin-1	2
6	arterial elasticity	2
6	Cu	2
104	thrombin	2
101	vasculopathy	2
5	galectin-3	2
4	Nox2	2
3	hydroxyl radical antioxidant capacity	2
2	glutaredoxin	2

25	cysteine	1
41	transforming growth factor beta	1
68	D-dimer	1
40	DBP	1
40	dopamine	1
20	folate deficiency	1
20	insulin-like growth factor I	1
19	riboflavin	1
39	bacterial infection	1
25	Helicobacter pylori	1
52	Angiogenic growth factors	1
13	atheromatous plaque	1
38	glycine	1
38	Noradrenaline	1
25	platelet-derived growth factor	1
37	blood urea nitrogen	1
37	E-selectin	1
27	Apolipoprotein E	1
37	matrix metalloproteinase 9	1
19	thrombomodulin	1
72	systemic sclerosis	1
14	fos	1
24	cadmium	1
15	DNA polymerase gamma	1
51	cardiac troponin T	1
28	carotid-femoral pulse wave velocity	1
94	Lipoprotein(a)	1
27	high total cholesterol	1
29	laminin	1
34	cystatin C	1
34	histamine	1
27	methylmalonic acid	1
14	myo-inositol	1
20	aldosterone	1
33	cerebral ischemia	1
103	urea	1
33	glial activation	1
23	transferrin	1
49	monocyte	1



	chemoattractant protein-1	
15	cholestanol	1
108	creatinine clearance	1
22	lipase	1
58	methionine	1
58	Neutrophils	1
26	Endothelin	1
12	beta-carotene	1
12	caspases	1
12	insulin deficiency	1
110	waist circumference	1
12	sE-selectin	1
11	gamma-glutamyltransferase	1
10	ammonia	1
29	Chlamydia pneumoniae	1
10	tryptophan	1
9	cystathionine beta-synthase	1
9	low testosterone	1
168	platelet aggregation	1
30	beta 2 microglobulin	1
20	CD40 ligand	1
8	S100 beta	1
26	HMG-CoA reductase	1
70	peak oxygen consumption	1
202	T-cell	1
247	amyloid	1
251	angiotensin converting enzyme	1
6	GRP78	1
273	glycoprotein	1
42	thromboangiitis	1
6	Telomerase	1
6	transketolase	1
55	Venous occlusion	1
4	apolipoprotein C-III	1
4	erythrocyte aggregation	1
4	glutathione transferase	1

4	metallothionein	1
17	aortic pulse wave velocity	1
4	Sirtuin 1	1
3	acetaldehyde	1
3	CXCL10	1
3	glutathione reductase	1
3	GTP cyclohydrolase	1
3	hydroperoxide	1
16	neoangiogenesis	1
3	iron deposition	1
3	LXR	1
3	neurotensin	1
2	deoxyguanosine	1
435	Systolic blood pressure	1
2	miR-130a	1
2	miR-210	1
2	miR-27b	1
2	polymorphonuclear neutrophils	1
2	TREM-1	1
2	vitamin C deficiency	1
1	1,1-Diphenyl-2-picrylhydrazyl	1
1	cyclooxygenase 1	1
1	elevated copper	1
1	gamma-glutamylcysteine	1
1	L-ascorbic acid	1
1	Nepsilon-(carboxymethyl)lysine	1

**Table 7A-12 - Biomarkers Relevant to PN and to PAD**

# REC	TREATMENT	#PN REC	#PAD REC
2638	lesions	985	1503
2536	inflammation	1445	1143
2320	toxicity	2077	186
2277	nerve conduction velocity	2003	183
2038	ankle brachial index	93	1984
1549	blood pressure	334	1362
1402	stenosis	72	1274
1156	body mass index	378	868
1142	neurotoxic	980	37
1139	total cholesterol	261	1003
1138	blood glucose levels	685	625
1091	degeneration	874	167
1061	hemoglobin A1c	663	646
932	blood flow	167	802
856	marker	321	558
841	proteins	568	245
748	atrophy	633	93
747	dorsal root ganglia	631	28
704	creatinine	230	550
700	oxygen	184	536
693	lipoprotein	117	625
671	growth factor	318	344
640	Schwann cell	506	25
616	demyelination	536	56
610	pain-free walking distance	17	598
549	C reactive protein	68	507
538	calcium	249	274
516	cytokine	289	211
499	triglycerides	158	410
495	low-density lipoprotein cholesterol	70	461
489	angiogenesis	56	439
455	axonal degeneration	402	73
435	Systolic blood pressure	88	392
426	circulation	86	362
425	high-density lipoprotein cholesterol	105	386
419	oxidative stress	223	212
413	plaque	22	382
412	occlusions	3	358
402	albumin level	162	304
399	glomerular filtration rate	95	338

391	ventricular ejection fraction	33	366
382	calcification	45	346
365	nerve damage	238	32
354	neurodegeneration	305	42
349	IgM	325	46
345	tumour necrosis factor-alpha	225	126
344	sodium	229	114
329	lipids	92	255
322	heart rate	133	204
318	edema	205	120
318	nitric oxide	114	188
309	apoptosis	203	86
308	fibrinogen	24	292
284	endothelial dysfunction	44	251
283	denervation	202	40
278	vascular endothelial growth factor	89	202
273	glycoprotein	187	75
266	IL-6	107	157
263	vitamin B(12) deficiency	198	68
262	stenoses	6	248
261	high homocysteine	58	215
251	angiotensin converting enzyme	31	223
247	amyloid	213	50
240	myelinated fibers	199	30
237	vibration perception threshold	225	55
222	weight loss	162	81
210	fatty acid	118	92
208	carotid artery intima-media thickness	12	197
206	nerve growth factor	170	8
202	T-cell	152	41
197	autoantibodies	153	48
195	thermal hyperalgesia	177	3
193	CD4	177	19
186	proinflammatory cytokine	110	72
185	insulin resistance	76	148
183	pulse wave velocity	16	158
175	diastolic blood pressure	41	161
170	nerve regeneration	87	7
168	platelet aggregation	10	161
162	glycated haemoglobin	117	103

159	lymphocytes	104	40
158	nerve fiber density	154	8
154	B-cell	126	35
152	Reactive oxygen species	84	68
151	arterial stiffness	11	132
147	capsaicin	129	14
147	lipid profile	53	123
135	platelet activation	3	134
128	IL-1beta	83	37
126	glutamate	98	9
126	Transthyretin	122	7
126	vitamin E deficiency	80	42
125	apolipoprotein	27	96
125	Vitamin D deficiency	52	81
123	acetylcholine	74	46
122	mechanical hyperalgesia	114	2
119	glutathione	92	24
118	compound muscle action potential	90	9
115	Mitochondrial dysfunction	99	16
115	nitric oxide synthase	63	46
115	white blood cell	37	81
114	creatine	69	44
110	waist circumference	29	93
108	creatinine clearance	38	83
107	lactate	59	46
106	von Willebrand factor	11	99
105	plasminogen activator inhibitor-1	6	98
104	pulse pressure	12	96
104	thrombin	2	99
103	urea	50	67
102	atherosclerotic plaque	2	102
102	IgA	91	18
101	vasculopathy	51	64
100	intercellular adhesion molecule-1	20	84
99	antioxidants	53	47
98	calcitonin gene-related peptide	73	7
96	uric acid	26	80
95	blood viscosity	26	75
94	Lipoprotein(a)	8	92
92	albumin excretion rate	55	74
92	substance P	71	10
84	fiber loss	76	15

84	malondialdehyde	48	35
81	Endothelial progenitor cells	6	79
81	orthostatic hypotension	63	30
80	fibrin	10	70
80	fibroblast growth factor	17	67
80	folic acid	33	46
78	transcutaneous oxygen pressure	5	75
74	creatine kinase	52	25
74	matrix metalloproteinase	22	57
74	thromboxane	3	70
73	thiamine	68	4
72	systemic sclerosis	26	49
70	IL-10	40	28
70	peak oxygen consumption	12	58
69	lipid peroxidation	37	31
69	prostacyclin	6	66
69	superoxide dismutase	46	23
69	troponin	5	69
68	D-dimer	2	68
66	mRNA levels	45	17
65	advanced glycation end product	41	39
65	magnesium	51	13
65	Zinc	44	17
64	anti-neutrophil cytoplasmic antibody	58	46
64	erythrocyte sedimentation rate	47	34
64	Red Blood Cell	17	47
61	monoclonal antibodies	41	14
61	oxygen saturation	7	54
61	P-selectin	2	60
60	heat shock	50	10
60	rheumatoid factor	51	32
59	acetylsalicylic acid	1	58
59	nitrogen	25	39
58	methionine	29	27
58	Neutrophils	29	31
55	Ca(2+)	41	10
55	Venous occlusion	6	53
54	glial fibrillary acidic protein	41	6
53	chemokines	32	18
53	Tissue Plasminogen Activator		50
52	Angiogenic growth factors	5	50

52	BDNF	39	4
52	hepatocyte growth factor	6	47
52	l-arginine	12	36
52	MetS	7	47
51	cardiac troponin T	4	51
51	epidermal growth factor	39	8
51	glucose metabolism	28	31
51	prothrombin	8	47
50	NF-kappaB	34	17
49	adenosine diphosphate	3	46
49	bone mineral density	27	30
49	cytochrome c	45	4
49	monocyte chemoattractant protein-1	11	31
49	protein kinases	36	12
48	bilirubin	27	26
48	thymidine	43	4
48	urinary albumin/creatinine ratio	15	42
47	glycosylation	38	19
45	neuronal damage	41	12
44	adiponectin	13	37
44	alanine	35	11
44	carbon dioxide	10	31
44	Mercury	28	9
43	erythrocytes	20	17
42	leucocytes	6	37
42	myelin basic protein	36	3
42	neuroinflammation	39	3
42	phosphorus	9	34
42	thromboangiitis	1	38
41	alkaline phosphatase	18	22
41	apolipoprotein B	4	39
41	CD34	12	31
41	free radicals	19	25
41	N-terminal pro-brain natriuretic peptide	1	41
41	transforming growth factor beta	17	28
40	arginine	21	16
40	DBP	7	37
40	dopamine	26	9
40	myeloperoxidase	16	29
40	sorbitol	35	3
39	apolipoprotein A-I	12	26
39	bacterial infection	21	22

39	cyclic AMP	21	14
39	endothelial damage	10	34
38	connexin 32	37	
38	glycine	35	3
38	Noradrenaline	32	6
38	vitamin K	3	33
37	blood urea nitrogen	17	25
37	E-selectin	8	30
37	endothelin-1	9	26
37	matrix metalloproteinase 9	15	25
36	arachidonic acid	7	27
36	heme	28	8
36	IgG antibodies	26	14
36	niacin	11	26
35	glycogen	27	5
35	HCY	10	27
35	IL-8	8	30
35	interferon gamma	22	7
34	actin	21	10
34	catalase	22	10
34	cystatin C	7	29
34	histamine	25	4
34	Streptococcal	17	20
33	anti-ganglioside antibodies	29	1
33	catecholamine	15	11
33	cerebral ischemia	8	33
33	ferritin	9	24
33	glial activation	31	1
33	hypoperfusion	7	27
33	oxidative damage	16	16
32	anti-MAG antibodies	31	1
32	insulin levels	22	15
32	polyunsaturated fatty acids	8	21
31	parathyroid hormone	9	21
31	progesterone	25	3
30	beta 2 microglobulin	18	14
30	body fat	9	22
30	Gamma-aminobutyric acid	27	2
29	acetylcholinesterase	21	5
29	adenine	21	6
29	asymmetric dimethylarginine	1	27
29	Chlamydia pneumoniae		29
29	fibroblast growth factor 2	10	20
29	laminin	19	4
29	phospholipids	12	20

28	albumin/creatinine	7	25
28	brain atrophy	21	7
28	carotid-femoral pulse wave velocity	3	23
28	CD31	4	27
28	matrix metalloproteinase 2	11	20
28	Osteoprotegerin	6	27
28	phosphocreatine	5	24
28	Tau	20	8
28	thromboxane A2		27
27	antinuclear antibodies	23	16
27	Apolipoprotein E	8	16
27	cholinesterase	17	1
27	cyclooxygenase 2	17	9
27	epinephrine	6	16
27	GDNF	19	
27	glutamine	25	
27	high total cholesterol	5	26
27	methylmalonic acid	25	3
27	RAGE	16	14
27	vascular reactivity	9	19
26	Endothelin	8	19
26	glutathione peroxidase	16	8
26	growth hormone	15	12
26	HMG-CoA reductase	10	19
26	Hydrogen peroxide	11	14
26	leptin	13	14
26	miRNA	8	18
25	amyloid beta	16	6
25	cysteine	14	11
25	GP IIb/IIIa		25
25	Helicobacter pylori	9	18
25	Iron Deficiency	19	9
25	platelet-derived growth factor	9	18
25	sulfatide	23	2
24	aspartate aminotransferase	17	9
24	cadmium	5	16
24	IL-4	14	10
23	copper deficiency	16	1
23	immune activation	17	9
23	integrin	10	11
23	peroxynitrite	18	6
23	transferrin	12	12
22	CD8	19	4
22	lipase	13	10



22	Vitamin B1 deficiency	21	3
21	bradykinin	6	12
21	Escherichia coli	14	8
21	glutamic acid	19	4
21	methicillin-resistant Staphylococcus aureus	4	19
21	Oxidized low-density lipoprotein	2	17
21	prostate-specific antigen	19	3
20	acylcarnitine	10	7
20	adenosine triphosphate	11	10
20	aldosterone	6	14
20	arterial obstruction	2	19
20	CD40 ligand	3	16
20	folate deficiency	14	6
20	insulin-like growth factor I	16	4
20	thromboxane B2	1	19
20	transaminases	19	5
19	Ccl2	10	7
19	riboflavin	17	1
19	serum calcium	6	16
19	thrombomodulin	4	15
19	vascular calcifications		16
18	amyloid fibrils	16	2
18	c-Fos	15	
18	caspase 3	16	1
18	docosahexaenoic acid	7	11
18	eicosapentaenoic acid	3	15
18	endothelial activation	2	16
18	estradiol	2	15
18	heme oxygenase 1	11	7
18	HIF-1alpha	4	17
18	luminal diameter		18
18	NADPH oxidases	8	11
18	renin	7	13
18	selenium	10	8
17	5-hydroxytryptamine	4	12
17	aortic pulse wave velocity	1	17
17	arterial compliance		17
17	bone density	10	8
17	compound motor action potential	12	2
17	CXCR4	10	7
17	cytomegalovirus infection	14	6
17	dehydration	10	5
17	desmin	15	2

17	elastin	3	15
17	excitotoxicity	14	3
17	High-mobility group box 1	9	11
17	IL-2	10	6
17	lactic acid	8	4
17	lead levels	10	2
17	porphobilinogen	17	
17	prothrombin time	4	13
16	androgen	8	5
16	factor Xa		16
16	galanin	9	
16	neoangiogenesis		16
16	PGE2	7	7
16	phytanic acid	15	
16	proline	13	4
16	pyridoxal	10	5
15	activated partial thromboplastin time		15
15	calcium phosphate	4	11
15	calpain	12	2
15	cholestanol	15	3
15	cortisol	4	8
15	digoxin	2	15
15	DNA polymerase gamma	14	1
15	osteopontin	2	13
14	anti-GM1 antibody	12	3
14	antithrombin III	3	13
14	CD68	6	7
14	choline	8	4
14	CNTF	10	2
14	Fas	8	4
14	fos	9	2
14	MMA	13	2
14	myo-inositol	12	1
14	porphyrin	14	2
14	TBARS	9	5
13	atheromatous plaque		12
13	ceruloplasmin	5	5
13	complement levels	12	7
13	cyclic guanine monophosphate	2	8
13	E. coli	8	6
13	elastase	2	11
13	Fetuin-A	2	13
13	leucine	10	1
13	Lipoprotein-associated		13

	phospholipase A2		
13	Neopterin	6	8
13	RNA levels	11	1
13	thyroxine	8	4
13	transglutaminase	11	2
13	vasopressin	1	10
12	adipokine	2	10
12	anticardiolipin antibodies	6	7
12	arterial calcifications		10
12	beta-carotene	2	10
12	C1q	10	4
12	calcineurin	9	5
12	caspases	10	
12	Chondroitin sulfate	8	2
12	hydrogen sulfide	5	7
12	IgE	10	5
12	insulin deficiency	12	2
12	MEP	10	
12	mitogen-activated protein kinases	10	2
12	NOx	1	11
12	PBMCs	7	4
12	Proteus	4	6
12	sE-selectin	3	10
12	spirochete	9	1
11	anti-gliadin antibodies	11	4
11	Coxsackie	10	1
11	dendritic cells	3	7
11	dipeptidyl peptidase	4	8
11	excitatory amino acids	10	1
11	fructose	9	2
11	gamma-glutamyltransferase	5	9
11	histidine	9	1
11	IL-12	5	6
11	Myelin breakdown	11	
11	Pseudomonas aeruginosa	6	9
11	Resistin	3	8
10	ammonia	6	2
10	AMPA	10	
10	apolipoprotein(a)		10
10	cathepsins	5	5
10	cotinine		9
10	Glutamate carboxypeptidase II	9	1
10	glycogen synthase	10	

10	low birth weight	3	8
10	lysophosphatidic acid	7	1
10	Nrf2	7	2
10	polyglutamine	10	
10	S-adenosylmethionine	5	5
10	threonine	9	1
10	tryptophan	8	1
9	adenosine monophosphate	4	4
9	alpha-synuclein	6	
9	anticholinesterase	9	1
9	Aortic augmentation index		9
9	beta-galactosidase	5	3
9	BNP levels	1	9
9	BSA	8	1
9	CD133	1	9
9	cystathionine beta-synthase	3	7
9	deoxyuridine	9	
9	enolase	7	1
9	fibrin D-dimer		9
9	fungi	5	3
9	heparan sulfate	3	8
9	iodine	4	5
9	low testosterone	5	7
9	phenylalanine	7	2
9	squalene	7	
9	staphylococcal	5	6
9	vascular stiffness	1	9
8	arterial dilatation		7
8	Aspergillus	3	4
8	Butyrylcholinesterase	6	
8	CBM	4	4
8	coagulation activation		8
8	corticosterone	6	
8	glucagon	6	5
8	gonadotropin	5	2
8	inositol	6	2
8	isoprostane	2	6
8	leukotrienes	3	4
8	osteocalcin		7
8	paraoxonase-1	2	6
8	phosphates	5	3
8	Retroviruses	5	3
8	S100 beta	7	1
8	somatostatin	8	2
8	taurine	8	1

8	thyrotropin	5	2
7	4-hydroxy-2-nonenal	1	6
7	aldehyde dehydrogenase	4	4
7	amines	4	3
7	angiotensin II type 1	2	6
7	CD14	2	5
7	coronary calcification		7
7	HIV RNA levels	7	
7	horseradish peroxidase	3	1
7	linoleic acid	3	3
7	monomethylarsonic acid	1	6
7	neuropilin-1	2	4
7	OX-42	6	
7	phosphatidylinositol 3-kinase	6	1
7	thrombospondin		7
7	TNFR2	4	4
6	alcohols	6	2
6	arterial elasticity		6
6	citrulline	3	3
6	Cu	2	2
6	dimethylarsinic acid	2	4
6	factor XIII		6
6	fibroblast growth factor 23		6
6	FVII		6
6	glucuronic acid	6	
6	GRP78	3	2
6	histone deacetylase 6	6	1
6	IL-18	3	3
6	kallikrein		6
6	lipid hydroperoxides		6
6	Methylglyoxal	5	2
6	N-acetylglucosamine	5	1
6	neurotoxic esterase	6	
6	oxygen radicals	1	3
6	pentraxin		6
6	pERK	4	1
6	prolactin	3	3
6	quinolinic acid	3	3
6	Telomerase	2	4
6	transketolase	6	
5	Acetylcarnitine	1	4
5	apolipoprotein A-II	1	3
5	apolipoprotein B-100	1	4
5	CD11c	1	4
5	CD16	1	3

5	CD86	2	3
5	cyclin D1	2	1
5	deoxyhemoglobin		5
5	dihydrotestosterone	1	4
5	galectin-3	2	4
5	Glyoxalase 1	3	2
5	guanosine monophosphate	1	2
5	Guanylate Cyclase		4
5	hyperphosphorylation	4	
5	IL-13	2	4
5	inosine	2	2
5	L-selectin		5
5	lipofuscin	4	
5	luteinizing hormone	2	4
5	monoamine oxidase	3	2
5	omega-3 index		5
5	perforin	4	1
5	phenyl valerate	5	
5	platelet factor 4		5
5	pregnenolone	5	
5	pristanic acid	5	1
5	retinol	1	3
5	sphingosine	3	1
5	thiocyanate	3	2
5	YKL-40		5
4	Adrenomedullin	2	2
4	amyloid precursor protein	4	1
4	angiogenin	2	3
4	angiotensinogen	1	4
4	apolipoprotein B-48	1	3
4	apolipoprotein C-III		4
4	arterial tonometry index (RHI)		4
4	beta-endorphin	3	
4	chromogranin	3	2
4	dehydroepiandrosterone	3	2
4	dynactin	4	
4	endopeptidases	3	3
4	erythrocyte aggregation	2	3
4	GHb	4	3
4	glutathione transferase	4	
4	glycated albumin	3	4
4	homovanillic acid	4	1
4	hydroxymethylbilane synthase	4	
4	IgG4-positive plasma cells	4	2

4	IL-17	3	1
4	IL-22	2	2
4	indole	2	3
4	Janus kinase 2	3	1
4	mannose	3	2
4	metallothionein	2	
4	myostatin	1	3
4	nitrogen oxide	1	3
4	Nox2		4
4	S100A12		4
4	Sirtuin 1	2	2
4	SO2		3
4	soluble guanylyl cyclase	2	
4	succinate dehydrogenase	3	1
4	tetrahydrobiopterin	2	2
4	tissue inhibitors of metalloproteinases		4
4	ubiquinone	3	1
4	valvular calcification		4
4	vasoactive intestinal peptide	1	
3	acetaldehyde	3	
3	acyl-CoA oxidase	2	
3	Allograft inflammatory factor-1	3	
3	arginase	1	1
3	B vitamin deficiency	3	1
3	brain iron accumulation	2	1
3	butyric acid	3	1
3	CFU	1	2
3	chorionic gonadotropin	1	1
3	connective tissue growth factor	1	2
3	CXCL10	3	
3	eosinophil cationic protein	3	2
3	factor XII		3
3	Fusobacterium	3	3
3	glucagon-like peptide 1	1	2
3	Glucokinase	2	2
3	glutathione reductase	3	
3	GTP cyclohydrolase	1	2
3	hemosiderin	2	3
3	hydroperoxide		3
3	hydroxyl radical antioxidant capacity		3
3	hyperoxia		3

3	iron deposition	2	
3	kynurenine	2	
3	LXR	3	
3	m-calpain	2	
3	mandelic acid	2	1
3	methemoglobin	2	2
3	mu-calpain	3	
3	N-acetylaspartate	3	1
3	neurite loss	3	1
3	neurotensin	3	1
3	NF68	3	
3	nicotinamide mononucleotide	3	
3	Nociceptin	2	
3	phosphatidylserine	1	2
3	PINK1	3	
3	pipecolic acid	2	
3	pregnancy-associated plasma protein-A		3
3	ryanodine	1	2
3	S-adenosylhomocysteine	1	2
3	sCD163	1	2
3	serum nitrate	1	3
3	sTWEAK		3
3	trimethylamine	2	1
3	waist-to-height ratio	1	2
3	xanthine oxidase	1	2
2	3-nitrotyrosine	2	
2	<sup>32</sup> P	2	
2	acid phosphatase	1	
2	adenosine deaminase	1	
2	adenosine kinase	2	
2	adenylyl cyclases	1	
2	agrin	1	
2	aminolevulinic acid	2	
2	aminopeptidases		2
2	apoB/apoA-I ratio		2
2	apolipoprotein A-IV	1	1
2	apolipoprotein AI-CIII-AIV gene cluster		2
2	aspartic acid	2	
2	campesterol	1	1
2	carboxymethyl-lysine		2
2	Cardiometabolic index (CMI)		2
2	caspase 9	1	



2	CCL4	2	
2	cyclin-dependent kinase 5	2	
2	deoxyguanosine	2	
2	deoxyypyridinoline	2	
2	docosapentaenoic acid		2
2	endostatin		2
2	estrone		2
2	follicle stimulating hormone	2	1
2	glutaredoxin		2
2	herpes simplex virus 1	1	1
2	hippuric acid	1	1
2	histone deacetylases	1	
2	hydroxyproline	1	2
2	Janus kinase 1	2	
2	JC virus	2	1
2	Ketones	2	
2	kininase II		2
2	kininogen fractions		2
2	kynurenic acid	2	
2	measles virus	1	
2	midkine		2
2	miR-130a		2
2	miR-210		2
2	miR-27b		2
2	MuSK	1	
2	omentin-1 level		2
2	phenylglyoxylic acid	1	
2	polymorphonuclear neutrophils		2
2	Prevotella intermedia		2
2	protein tyrosine phosphatases		2
2	pyruvic acid	1	
2	saturated fatty acid	2	
2	suPAR level		2
2	tachykinins	1	
2	transcription factor CHOP	2	
2	TREM-1		2
2	vitamin C deficiency		2
2	Wnt5a		2
1	1,1-Diphenyl-2-picrylhydrazyl	1	
1	1,7-dimethylxanthine		1
1	25-hydroxycholesterol		1
1	27-hydroxycholesterol		1

1	3,4-dihydroxyphenylacetic acid	1	
1	3,4-dihydroxyphenylglycol	1	
1	3,5,3'-triiodothyronine	1	
1	5-bromo-2'-deoxyuridine	1	
1	7-ketocholesterol		1
1	8-hydroxyguanosine		1
1	8-oxoguanine	1	
1	adenylate kinase	1	
1	aniline hydroxylase	1	
1	Anti-Mullerian hormone		1
1	antiphospholipids-induced	1	1
1	apolipoprotein D	1	
1	Apolipoprotein L1		1
1	aryl hydrocarbon hydroxylases	1	
1	bacterial endotoxins		1
1	benzo(a)pyrene	1	
1	beta-mannosidase	1	
1	calcium-dependent protein kinase	1	
1	caspase 12	1	
1	caspase 8	1	
1	catechol-O-methyltransferase	1	
1	CgA	1	1
1	complement C3b	1	
1	complex II deficiency	1	
1	complex IV deficiency	1	
1	cyclic ADP-ribose	1	
1	cyclooxygenase 1		1
1	cystathionine gamma-lyase	1	
1	cysteinylglycine		1
1	dihydroxyphenylalanine	1	
1	DL-alpha-tocopherol	1	
1	elevated copper	1	
1	Ferric iron	1	1
1	gamma-glutamylcysteine	1	
1	gamma-tocopherol		1
1	glutaminase	1	
1	glyceraldehyde	1	
1	glyoxal	1	
1	granzymes	1	
1	hexokinase	1	
1	High adiponectin	1	1
1	histone acetyltransferases	1	

1	homocysteic acid		1
1	hypochlorite		1
1	isobutanol	1	
1	L-ascorbic acid		1
1	lathosterol		1
1	NADH dehydrogenase		1
1	Nepsilon-(carboxymethyl)lysine	1	
1	o-xylene		1
1	oncostatin	1	
1	oxysterols		1
1	p-cresol		1
1	p300-CBP-associated factor		1
1	pancreatic polypeptide	1	
1	Perlecan		1
1	Peroxiredoxins		1
1	phosphorylases	1	
1	polyamines		1
1	polyQ	1	
1	prulifloxacin		1
1	psychosine	1	
1	pyruvate carboxylase	1	
1	S-nitrosoglutathione		1
1	sex steroid hormones	1	
1	ulifloxacin		1
1	Urine kidney injury molecule-1		1

**Table 7A-13 - Causes Co-Occurring with Oxidative Stress**

#REC	CAUSE	#CO-OCC
2507	chemotherapy	37
125	advanced glycosylation end products	32
296	Streptozotocin	31
2265	smoking	24
1140	High cholesterol diet	23
524	oxaliplatin	16
985	paclitaxel	11
149	Arsenic	10
745	dialysis	9
503	Bortezomib	9
412	statins	7
347	vincristine	7
340	peripheral nerve injury	6
442	alcohol	6
508	hemodialysis	6
217	platinum	6
19	high glucose	6
66	high fat diet	6
14	Hydrogen peroxide	6
570	cisplatin	5
29	Ischemia-reperfusion	5
393	alcohol consumption	5
247	leading cause	5
324	taxanes	5
201	chronic constriction injury	5
49	acetone	5
12	iron overload	4
18	streptozocin	3
570	trauma	3
26	metals	3
351	thalidomide	3
196	docetaxel	3
93	spinal cord injury	3
86	alkaloids	3
34	dichloroacetate	3

9	manganese	3
9	HFD	2
9	dithiocarbamates	2
9	allopurinol	2
140	5-fluorouracil	2
29	phenytoin	2
131	sedentary	2
83	axotomy	2
76	Vinca alkaloids	2
337	lifestyle	2
73	coronary angioplasty	2
821	HIV-1	2
65	Zinc	2
708	infections	2
545	depression	2
61	simvastatin	2
683	viruses	2
22	heavy metals	2
10	sodium arsenite	2
30	carbon monoxide	2
13	herbicide	2
4	N,N-diethyldithiocarbamate	2
3	Bisphenol	2
2	epoxy resins	2
2	Paraquat	2
30	valproic acid	1
24	cadmium	1
29	Chlamydia pneumoniae	1
90	proteasome inhibitors	1
24	disulfiram	1
357	anesthesia	1
11	cigarette smoke	1
85	renal transplantation	1
47	atorvastatin	1
10	lentivirus	1
5	mineralocorticoid	1
83	organophosphate pesticides	1

11	cyanide	1
81	injury-induced	1
314	hepatitis	1
46	carfilzomib	1
23	Helicobacter pylori	1
186	Hepatitis C Virus	1
14	aluminum	1
28	HMG-CoA reductase inhibitors	1
7	sevoflurane	1
64	formalin	1
6	metoclopramide	1
45	axonal injury	1
5	palmitate	1
22	atenolol	1
5	Sleep deprivation	1
12	tobacco smoke	1
60	cancer therapy	1
8	dietary deficiency	1
32	pesticides	1
31	Amiodarone	1
58	ixabepilone	1
42	levodopa	1
22	infectious agents	1
54	anticonvulsant	1
5	zymosan	1
7	fine particulate matter	1
20	folate deficient	1
54	Pyridoxine	1
20	nutritional deficiency	1

4	hydralazine	1
96	drug-induced	1
4	phorbol 12-myristate 13-acetate	1
4	prions	1
96	malnutrition	1
3	citalopram	1
16	pravastatin	1
8	pollutants	1
2	REMSD	1
1	3-nitropropionic acid	1
1	3-NPA	1
1	acrolein	1
1	AlCl <sub>3</sub>	1
1	atherogenic diet	1
1	diquat	1
1	ferric ammonium citrate	1
1	tert-butylhydroperoxide	1
# Records		oxidative stress

**Table 7A-14 - Causes Co-Occurring with Blood Pressure**

#REC	CAUSE	#CO-OCC
2265	smoking	411
1140	High cholesterol diet	321
442	alcohol	55
337	lifestyle	53
745	dialysis	52
508	hemodialysis	44
393	alcohol consumption	38
412	statins	37
545	depression	27
247	leading cause	23
131	sedentary	20
22	atenolol	10
2507	chemotherapy	9
357	anesthesia	9
59	inactivity	9
15	lisinopril	7
96	malnutrition	7
821	HIV-1	6
14	enalapril	6
24	cadmium	5
85	renal transplantation	5
66	high fat diet	5
5	salt intake	5
44	Mercury	5
985	paclitaxel	4
683	viruses	4
39	lead exposure	4
323	cyclophosphamide	4
125	advanced glycosylation end products	4
28	HMG-CoA reductase inhibitors	4
61	simvastatin	4
47	atorvastatin	4
42	hand-arm vibration	3
96	drug-induced	3
570	trauma	3
708	infections	3
73	coronary	3

	angioplasty	
378	highly active antiretroviral therapy	3
361	radiation	3
43	bariatric surgery	3
3	felodipine	3
324	taxanes	2
24	immunization	2
201	chronic constriction injury	2
196	docetaxel	2
23	5-hydroxytryptamine	2
28	vitamin D deficient	2
21	vibration-induced	2
149	Arsenic	2
63	bevacizumab	2
314	hepatitis	2
67	solvents	2
119	zidovudine	1
118	iatrogenic	1
107	cytomegalovirus	1
37	interferon-alpha	1
96	gemcitabine	1
37	nevirapine	1
37	thiamine deficiency	1
19	tenofovir	1
93	spinal cord injury	1
7	dust	1
23	Helicobacter pylori	1
14	Heroin	1
89	Staphylococcus	1
14	Hydrogen peroxide	1
111	methotrexate	1
570	cisplatin	1
524	oxaliplatin	1
83	liver transplant	1
18	organic solvent	1
34	dichloroacetate	1
11	fructose	1
7	Alemtuzumab	1
11	INH	1
7	sweeteners	1

5	mineralocorticoid	1
6	manual work	1
340	peripheral nerve injury	1
332	leprosy	1
65	Zinc	1
31	Amiodarone	1
14	Leflunomide	1
21	Drug Abuse	1
61	cyclosporin	1
7	fine particulate matter	1
329	radiation therapy	1
296	Streptozotocin	1
31	glucocorticoids	1
30	carbon monoxide	1
230	carboplatin	1
13	H. pylori	1
29	Chlamydia pneumoniae	1
56	epirubicin	1
55	Thallium	1
29	Ischemia-reperfusion	1
29	phenytoin	1
10	contaminants	1
217	platinum	1
186	Hepatitis C Virus	1
184	antibiotics	1
49	environmental factors	1
6	Methylglyoxal	1
27	insecticide	1
11	cyanide	1
5	omeprazole	1
9	air pollution	1

26	metals	1
20	nutritional deficiency	1
5	gasoline	1
11	cigarette smoke	1
148	stavudine	1
15	cobalt	1
14	aluminum	1
11	cocaine	1
4	paints	1
3	Bisphenol	1
121	tuberculosis	1
3	intermittent hypoxia	1
2	disopyramide	1
2	epoxy resins	1
2	ramucirumab	1
2	recreational drugs	1
2	sepsis-induced	1
2	Teriflunomide	1
2	western diet	1
1	antimony	1
1	labetalol	1
1	Perfluorooctanoic acid	1
1	PFOA	1
1	tungsten	1

**Table 7A-15 - Biomarkers Co-Occurring with High Cholesterol Diet**

#REC	BIOMARKER	#CO-OCC
1139	total cholesterol	1139
693	lipoprotein	472
495	low-density lipoprotein cholesterol	386
499	triglycerides	340
425	high-density lipoprotein cholesterol	323
1549	blood pressure	321
1156	body mass index	209
1138	blood glucose levels	191
1061	hemoglobin A1c	169
2038	ankle brachial index	164
435	Systolic blood pressure	133
329	lipids	116
549	C reactive protein	96
2536	inflammation	93
704	creatinine	90
308	fibrinogen	72
402	albumin level	63
856	marker	60
125	apolipoprotein	59
147	lipid profile	57
175	diastolic blood pressure	51
1402	stenosis	50
399	glomerular filtration rate	48
413	plaque	41
2638	lesions	39
261	high homocysteine	39
185	insulin resistance	39
96	uric acid	36
162	glycated haemoglobin	34
110	waist circumference	33
94	Lipoprotein(a)	31
208	carotid artery intima-media thickness	30
2277	nerve conduction velocity	28
27	high total cholesterol	27
538	calcium	27
610	pain-free walking	27

	distance	
92	albumin excretion rate	26
41	apolipoprotein B	26
210	fatty acid	23
419	oxidative stress	23
104	pulse pressure	22
841	proteins	22
266	IL-6	22
932	blood flow	21
382	calcification	21
284	endothelial dysfunction	20
39	apolipoprotein A-I	20
251	angiotensin converting enzyme	19
345	tumour necrosis factor-alpha	18
36	niacin	17
183	pulse wave velocity	17
516	cytokine	17
391	ventricular ejection fraction	17
426	circulation	16
237	vibration perception threshold	16
103	urea	15
106	von Willebrand factor	15
95	blood viscosity	14
125	Vitamin D deficiency	14
126	vitamin E deficiency	14
115	white blood cell	14
108	creatinine clearance	13
640	Schwann cell	13
52	MetS	13
322	heart rate	13
44	adiponectin	13
105	plasminogen activator inhibitor-1	13
102	atherosclerotic plaque	13
222	weight loss	12
1091	degeneration	12
151	arterial stiffness	12
100	intercellular adhesion molecule-1	11
26	HMG-CoA reductase	10



318	nitric oxide	10
40	DBP	10
263	vitamin B(12) deficiency	9
48	urinary albumin/creatinine ratio	9
59	nitrogen	9
99	antioxidants	9
168	platelet aggregation	8
27	Apolipoprotein E	7
80	folic acid	7
616	demyelination	7
671	growth factor	7
33	ferritin	7
128	IL-1beta	6
2320	toxicity	6
42	phosphorus	6
455	axonal degeneration	6
84	malondialdehyde	6
186	proinflammatory cytokine	6
28	Osteoprotegerin	6
9	squalene	6
29	phospholipids	6
37	blood urea nitrogen	6
1142	neurotoxic	5
18	endothelial activation	5
48	bilirubin	5
41	N-terminal pro-brain natriuretic peptide	5
53	Tissue Plasminogen Activator	5
412	occlusions	5
28	albumin/creatinine	5
39	endothelial damage	5
37	E-selectin	5
22	lipase	5
32	polyunsaturated fatty acids	5
29	Chlamydia pneumoniae	5
65	magnesium	5
114	creatine	5
66	mRNA levels	5
262	stenoses	5

748	atrophy	4
747	dorsal root ganglia	4
44	alanine	4
119	glutathione	4
30	body fat	4
278	vascular endothelial growth factor	4
68	D-dimer	4
344	sodium	4
24	aspartate aminotransferase	4
26	growth hormone	4
69	lipid peroxidation	4
74	creatine kinase	4
72	systemic sclerosis	4
70	IL-10	4
42	leucocytes	4
51	glucose metabolism	4
18	docosahexaenoic acid	4
14	antithrombin III	4
15	cholestanol	4
23	transferrin	4
273	glycoprotein	3
365	nerve damage	3
197	autoantibodies	3
193	CD4	3
700	oxygen	3
123	acetylcholine	3
135	platelet activation	3
18	eicosapentaenoic acid	3
41	alkaline phosphatase	3
64	Red Blood Cell	3
41	transforming growth factor beta	3
25	Helicobacter pylori	3
26	glutathione peroxidase	3
80	fibrin	3
37	endothelin-1	3
318	edema	3
69	superoxide dismutase	3
354	neurodegeneration	3
34	cystatin C	3
21	Oxidized low-density lipoprotein	3
31	progesterone	3
28	carotid-femoral pulse	3

	wave velocity	
13	Lipoprotein-associated phospholipase A2	3
12	beta-carotene	3
6	IL-18	3
5	pregnenolone	3
64	erythrocyte sedimentation rate	2
40	arginine	2
15	calcium phosphate	2
61	P-selectin	2
489	angiogenesis	2
38	vitamin K	2
69	troponin	2
59	acetylsalicylic acid	2
309	apoptosis	2
202	T-cell	2
36	arachidonic acid	2
18	selenium	2
195	thermal hyperalgesia	2
52	l-arginine	2
35	HCY	2
19	serum calcium	2
34	catalase	2
27	vascular reactivity	2
17	aortic pulse wave velocity	2
69	prostacyclin	2
51	cardiac troponin T	2
33	oxidative damage	2
32	insulin levels	2
55	Venous occlusion	2
26	leptin	2
40	myeloperoxidase	2
20	adenosine triphosphate	2
26	Endothelin	2
13	ceruloplasmin	2
49	monocyte chemoattractant protein-1	2
13	Fetuin-A	2
101	vasculopathy	2
13	thyroxine	2
61	monoclonal antibodies	2
12	sE-selectin	2

11	gamma-glutamyltransferase	2
11	Resistin	2
10	apolipoprotein(a)	2
159	lymphocytes	2
6	alcohols	2
47	glycosylation	2
5	apolipoprotein A-II	2
5	luteinizing hormone	2
43	erythrocytes	2
5	YKL-40	2
4	apolipoprotein B-48	2
4	valvular calcification	2
3	LXR	2
3	waist-to-height ratio	2
2	apolipoprotein AI-CIII-AIV gene cluster	2
2	campesterol	2
2	Cardiometabolic index (CMI)	2
38	connexin 32	1
23	copper deficiency	1
27	methylmalonic acid	1
15	osteopontin	1
58	methionine	1
58	Neutrophils	1
52	BDNF	1
81	Endothelial progenitor cells	1
20	insulin-like growth factor I	1
36	IgG antibodies	1
283	denervation	1
16	pyridoxal	1
247	amyloid	1
35	IL-8	1
22	CD8	1
240	myelinated fibers	1
13	atheromatous plaque	1
206	nerve growth factor	1
22	Vitamin B1 deficiency	1
21	bradykinin	1
33	anti-ganglioside antibodies	1
14	CD68	1
49	bone mineral density	1

170	nerve regeneration	1
17	arterial compliance	1
20	thromboxane B2	1
152	Reactive oxygen species	1
17	bone density	1
16	neoangiogenesis	1
28	phosphocreatine	1
31	parathyroid hormone	1
16	PGE2	1
20	acylcarnitine	1
19	riboflavin	1
45	neuronal damage	1
16	factor Xa	1
20	arterial obstruction	1
29	asymmetric dimethylarginine	1
27	antinuclear antibodies	1
20	CD40 ligand	1
115	nitric oxide synthase	1
17	IL-2	1
44	Mercury	1
104	thrombin	1
13	Neopterin	1
13	RNA levels	1
102	IgA	1
12	adipokine	1
12	arterial calcifications	1
42	myelin basic protein	1
12	hydrogen sulfide	1
12	NOx	1
42	neuroinflammation	1
11	Coxsackie	1
27	cholinesterase	1
11	Myelin breakdown	1
17	lactic acid	1
27	cyclooxygenase 2	1
10	cathepsins	1
10	cotinine	1
9	Aortic augmentation index	1
9	BNP levels	1
9	cystathionine beta-synthase	1
9	heparan sulfate	1
9	low testosterone	1

84	fiber loss	1
8	glucagon	1
8	gonadotropin	1
8	leukotrienes	1
8	paraoxonase-1	1
8	S100 beta	1
8	thyrotropin	1
7	angiotensin II type 1	1
7	coronary calcification	1
7	HIV RNA levels	1
7	horseradish peroxidase	1
7	monomethylarsonic acid	1
41	CD34	1
6	dimethylarsinic acid	1
6	factor XIII	1
6	FVII	1
6	GRP78	1
41	free radicals	1
6	pentraxin	1
6	prolactin	1
81	orthostatic hypotension	1
5	dihydrotestosterone	1
5	lipofuscin	1
19	thrombomodulin	1
5	omega-3 index	1
74	matrix metalloproteinase	1
5	retinol	1
74	thromboxane	1
25	sulfatide	1
4	apolipoprotein C-III	1
4	beta-endorphin	1
4	endopeptidases	1
4	nitrogen oxide	1
4	ubiquinone	1
73	thiamine	1
3	brain iron accumulation	1
14	TBARS	1
3	NF68	1
65	advanced glycation end product	1
2	apoB/apoA-I ratio	1
2	apolipoprotein A-IV	1

65	Zinc	1
18	luminal diameter	1
64	anti-neutrophil cytoplasmic antibody	1
2	follicle stimulating hormone	1
2	herpes simplex virus 1	1
2	midkine	1
2	omentin-1 level	1
2	suPAR level	1
1	25-hydroxycholesterol	1

1	27-hydroxycholesterol	1
1	7-ketocholesterol	1
1	aniline hydroxylase	1
1	benzo(a)pyrene	1
1	gamma-tocopherol	1
1	lathosterol	1
1	oxysterols	1
1	Peroxiredoxins	1

**Table 7A-16 - Biomarkers Co-Occurring with Sedentary**

#REC	BIOMARKER	#CO-OCC
2038	ankle brachial index	31
1549	blood pressure	20
1156	body mass index	19
1139	total cholesterol	10
1138	blood glucose levels	10
2536	inflammation	9
30	body fat	9
549	C reactive protein	7
185	insulin resistance	7
1402	stenosis	6
1061	hemoglobin A1c	6
610	pain-free walking distance	6
425	high-density lipoprotein cholesterol	5
322	heart rate	5
932	blood flow	5
538	calcium	5
693	lipoprotein	5
495	low-density lipoprotein cholesterol	5
208	carotid artery intima-media thickness	5
110	waist circumference	4
856	marker	4
748	atrophy	4
700	oxygen	4
435	Systolic blood pressure	4
284	endothelial dysfunction	4
151	arterial stiffness	4
841	proteins	3
413	plaque	3
499	triglycerides	3
94	Lipoprotein(a)	3
318	nitric oxide	2
455	axonal degeneration	2
329	lipids	2
20	adenosine triphosphate	2
308	fibrinogen	2
2277	nerve conduction velocity	2
105	plasminogen activator inhibitor-1	2
222	weight loss	2

2638	lesions	2
38	vitamin K	2
516	cytokine	2
183	pulse wave velocity	2
419	oxidative stress	2
1091	degeneration	2
147	lipid profile	2
27	high total cholesterol	2
125	Vitamin D deficiency	2
10	low birth weight	2
32	insulin levels	1
107	lactate	1
345	tumour necrosis factor-alpha	1
344	sodium	1
70	peak oxygen consumption	1
309	apoptosis	1
80	folic acid	1
39	apolipoprotein A-I	1
283	denervation	1
278	vascular endothelial growth factor	1
273	glycoprotein	1
266	IL-6	1
747	dorsal root ganglia	1
262	stenoses	1
104	pulse pressure	1
251	angiotensin converting enzyme	1
104	thrombin	1
240	myelinated fibers	1
69	lipid peroxidation	1
704	creatinine	1
17	arterial compliance	1
671	growth factor	1
49	bone mineral density	1
101	vasculopathy	1
69	troponin	1
640	Schwann cell	1
66	mRNA levels	1
96	uric acid	1
489	angiogenesis	1
118	compound muscle action potential	1

175	diastolic blood pressure	1
170	nerve regeneration	1
49	monocyte chemoattractant protein-1	1
51	cardiac troponin T	1
29	Chlamydia pneumoniae	1
158	nerve fiber density	1
65	Zinc	1
53	Tissue Plasminogen Activator	1
402	albumin level	1
84	malondialdehyde	1
26	growth hormone	1
16	pyridoxal	1
16	factor Xa	1
80	fibrin	1
42	thromboangiitis	1

126	vitamin E deficiency	1
125	apolipoprotein	1
382	calcification	1
12	adipokine	1
9	low testosterone	1
8	CBM	1
8	corticosterone	1
8	gonadotropin	1
6	pERK	1
6	prolactin	1
6	Telomerase	1
5	luteinizing hormone	1

**Table 7A-17 - Treatments Co-Occurring with Oxidative Stress**

#REC	TREATMENT	#CO-OCC
3638	drug	49
99	antioxidants	46
1766	inhibitor	42
62	superoxide dismutase	38
754	insulin	30
812	growth factor	24
288	supplementation	21
1328	exercise	20
1358	walking	18
2402	amputation	17
126	vitamin E	16
449	diet	16
25	GSH	15
349	vascular endothelial growth factor	13
489	angiogenesis	13
34	vitamin C	12
5105	surgery	11
86	Alpha lipoic acid	11
745	dialysis	9
172	IL-6	9
447	glycemic control	9
14	antioxidant therapy	9
150	hypoxia	8
47	aldose reductase inhibitor	7
567	analgesic	6
189	Spinal Cord Stimulation	6
632	medications	6
252	antihypertensive agents	6
206	nerve growth factor	6
233	pregabalin	5
80	folic acid	5
1920	revascularization	5
28	N-acetylcysteine	5
190	smoking cessation	5
67	erythropoietin	5
25	nicotinamide	5
541	endovascular treatment	4

100	haemodialysis	4
370	statin	4
12	tempol	4
1228	angioplasty	4
266	coronary intervention	4
242	Gabapentin	4
25	curcumin	4
337	antiplatelet therapy	4
111	duloxetine	4
117	Vitamin D	3
207	vitamin B12	3
17	interleukin-10	3
6	PARP inhibition	3
36	apheresis	3
147	capsaicin	3
16	epalrestat	3
30	propionyl-L-carnitine	3
29	Methylcobalamin	3
9	phlebotomy	3
27	glutamine	3
14	Aldehyde	3
576	aspirin	3
167	heparin	3
73	thiamine	3
8	thiols	3
14	Flavonoids	3
382	catheter	2
317	opioid	2
160	adenosine	2
65	magnesium	2
65	Zinc	2
18	selenium	2
13	guanosine	2
103	Acupuncture	2
8	TRPA1 antagonist	2
62	ethanol	2
17	CXCR4	2
228	antidepressant	2
7	acetylcysteine	2
40	arginine	2
6	polyphenol	2
5	puerarin	2
4	mangafodipir	2
215	Cilostazol	2

36	venlafaxine	2
11	tea	2
7	quercetin	2
16	ozone	2
8	taurine	2
29	lamotrigine	2
61	simvastatin	2
29	phenytoin	2
59	Acetyl-L-carnitine	2
10	melatonin	2
5	Heparin cofactor II	2
7	Gliclazide	2
7	Huangqi Guizhi Wuwu	2
26	growth hormone	2
9	allopurinol	2
6	HC-030031	2
55	carnitine	2
450	bypass surgery	2
420	Ligation	2
52	hepatocyte growth factor	2
4	saponins	2
2	1,5-isoquinolinediol	2
2	calmangafodipir	2
71	Ticlopidine	1
12	beta-carotene	1
18	chelation therapy	1
12	betaine	1
63	surgical decompression	1
6	nebivolol	1
59	hyperbaric oxygen	1
59	Testosterone	1
58	angiotensin converting enzyme inhibitor	1
4	Tang-Luo-Ning	1
54	Pyridoxine	1
9	sunlight	1
52	iloprost	1
51	AA	1
51	Mesenchymal Stem Cells	1
51	peripheral blood mononuclear cells	1
47	atorvastatin	1

45	Ketamine	1
5	hydrotherapy	1
42	Neurotrophins	1
41	clonidine	1
1308	artery bypass grafting	1
6	liraglutide	1
39	aerobic exercise	1
38	antiepileptic drugs	1
38	valproic acid	1
37	anesthetics	1
588	operation	1
507	vascular surgery	1
22	alpha-tocopherol	1
6	THC	1
4	midodrine	1
11	phosphatidylcholine	1
8	placenta	1
11	ruboxistaurin	1
16	Coenzyme Q10	1
34	nitroglycerin	1
353	Clopidogrel	1
7	nimodipine	1
4	protein kinase C inhibitors	1
10	benfotiamine	1
33	tramadol	1
7	gamma-linolenic acid	1
22	rapamycin	1
10	desipramine	1
31	l-carnitine	1
16	pravastatin	1
30	amifostine	1
6	thioctic acid	1
22	topiramate	1
9	Carvedilol	1
7	Ghrelin	1
21	NSAIDs	1
13	Caffeine	1
8	KU-32	1
8	lacosamide	1
131	mononuclear cells	1
10	lentivirus	1
28	oxcarbazepine	1
13	celecoxib	1
13	dextromethorphan	1
10	mesenchymal stromal	1



	cells	
27	Mexiletine	1
27	serotonin reuptake inhibitors	1
110	anticonvulsants	1
5	Jinmaitong	1
110	enzyme inhibitors	1
7	PGB	1
4	catechin	1
13	sulodexide	1
91	Prostaglandin	1
26	sodium nitroprusside	1
10	Resveratrol	1
8	menthol	1
90	gangliosides	1
87	Amitriptyline	1
4	Sodium nitrite	1
25	opiates	1
4	anakinra	1
4	donepezil	1
80	carbamazepine	1
14	fluoxetine	1
24	insulin-like growth factor-I	1
14	herbal medicines	1
8	paroxetine	1
14	myo-inositol	1
4	Thymoquinone	1
4	trigonelline	1
4	turmeric	1
4	zonisamide	1
3	amiloride	1
3	caloric restriction	1
3	carotenoids	1
3	dihydroergotamine	1
3	ellagic acid	1
3	fludrocortisone	1
3	Metanx	1
3	PLX-PAD	1
3	rotenone	1
5	pralidoxime	1
2	Astragali	1
18	ascorbic acid	1
2	Dark chocolate	1
2	deferoxamine	1
2	egg white hydrolysate	1

1	3-Aminobenzamide	1
1	Acanthopanax	1
1	Achyranthis bidentata Blume	1
1	activation of Nrf2	1
1	antimycin	1
1	ascorbyl palmitate	1
1	dihydrolipoic acid	1
1	epicatechin gallate	1
1	eugenol	1
1	ferulic acid	1
1	GCSB-5	1
1	ginsenoside Rb1	1
1	hemangioblasts	1
1	Jiaweibugan	1
1	Juglans regia L.	1
1	LiCl	1
1	Linalool	1
1	Maltol	1
1	MnDPDP	1
1	MnL4	1
1	Momordica cymbalaria	1
1	morin	1
1	naringin	1
1	NF3	1
1	niclosamide	1
1	phenyl-N-tert-butylnitron	1
1	placental-derived adherent stromal cells	1
1	Punica granatum L	1
1	Punicalagins	1
1	QR-333	1
1	Rosmarinic acid	1
1	rutin	1
1	Salvianolic acid B	1
1	Saposhnikovia divaricata Schiskin	1
1	Silybin	1
1	Vernonia cinerea	1

**Table 7A-18 - Treatments Co-Occurring with Blood Pressure**

#REC	TREATMENT	#CO-OCC
3638	drug	178
1328	exercise	149
252	antihypertensive agents	137
1766	inhibitor	122
5105	surgery	112
754	insulin	106
1358	walking	81
2402	amputation	74
447	glycemic control	71
1920	revascularization	67
632	medications	58
745	dialysis	52
576	aspirin	48
449	diet	47
190	smoking cessation	40
370	statin	36
1228	angioplasty	30
337	antiplatelet therapy	29
110	enzyme inhibitors	29
353	Clopidogrel	26
507	vascular surgery	22
58	angiotensin converting enzyme inhibitor	22
1308	artery bypass grafting	20
221	anticoagulant	19
812	growth factor	18
459	rehabilitation	16
33	ramipril	15
588	operation	12
233	endarterectomy	12
22	calcium antagonists	12
450	bypass surgery	11
489	angiogenesis	11
288	supplementation	11
215	Cilostazol	11
59	Testosterone	10
349	vascular endothelial growth factor	10
50	C-peptide	10
27	verapamil	10
17	amlodipine	10

117	Vitamin D	9
59	acetylsalicylic acid	9
172	Gene therapy	9
828	stents	9
50	Nicotine	9
12	hydrochlorothiazide	9
28	nifedipine	9
118	warfarin	8
16	losartan	8
21	calcium channel blocker	8
541	endovascular treatment	7
103	pentoxifylline	7
15	lisinopril	7
9	perindopril	7
24	omega-3 fatty acids	7
160	adenosine	6
14	enalapril	6
207	vitamin B12	6
150	hypoxia	5
126	vitamin E	5
100	haemodialysis	5
67	near-infrared	5
47	atorvastatin	4
52	hepatocyte growth factor	4
99	antioxidants	4
61	simvastatin	4
420	Ligation	4
55	antithrombotic therapy	4
266	coronary intervention	4
11	chlorthalidone	4
411	corticosteroid	3
382	catheter	3
91	Prostaglandin	3
52	iloprost	3
67	erythropoietin	3
189	Spinal Cord Stimulation	3
65	magnesium	3
15	digoxin	3
77	dipyridamole	3
156	Electrical stimulation	3
71	Ticlopidine	3

39	aerobic exercise	3
8	Sitagliptin	3
10	thiazolidinediones	3
34	vitamin C	3
6	nebivolol	3
147	capsaicin	3
9	captopril	3
51	AA	3
41	clonidine	3
26	sodium nitroprusside	3
62	superoxide dismutase	3
172	IL-6	3
103	Acupuncture	3
7	diltiazem	3
8	Calcitriol	3
5	telmisartan	3
567	analgesic	3
499	implantation	3
4	trandolapril	3
3	alpha-linolenic acid	3
228	antidepressant	2
9	dabigatran	2
111	duloxetine	2
7	apixaban	2
26	growth hormone	2
26	hormone replacement therapy	2
8	pioglitazone	2
13	Caffeine	2
4	ciprostene	2
25	Transcutaneous electrical nerve stimulation	2
36	niacin	2
80	folic acid	2
4	Aliskiren	2
14	anti-inflammatory agents	2
14	antioxidant therapy	2
22	prostanoids	2
242	Gabapentin	2
167	heparin	2
32	prasugrel	2
21	rivaroxaban	2
19	ezetimibe	2
12	tempol	2

18	ascorbic acid	2
10	fenofibrate	2
59	hyperbaric oxygen	2
4	valsartan	2
9	Carvedilol	2
3	dietary flaxseed	2
3	irbesartan	2
2	dietary nitrate	2
2	dihydropyridines	2
6	relaxin	1
37	drug-eluting balloons	1
37	glucocorticoid	1
36	apheresis	1
14	abciximab	1
4	dimercaprol	1
206	nerve growth factor	1
36	venlafaxine	1
6	hydromorphone	1
156	prednisone	1
5	NGX-4010	1
34	urokinase	1
6	Hydroxocobalamin	1
10	vitamin D3	1
6	liraglutide	1
33	tramadol	1
4	canagliflozin	1
119	zidovudine	1
5	ketorolac	1
31	l-carnitine	1
31	progesterone	1
8	tirofiban	1
14	Flavonoids	1
30	propionyl-L-carnitine	1
4	quinidine	1
14	herbal medicines	1
7	riluzole	1
29	phenytoin	1
28	electroacupuncture	1
17	strength training	1
17	thienopyridines	1
107	cell therapy	1
14	phenylephrine	1
27	baclofen	1
4	linolenic acid	1
27	intermittent pneumatic compression	1

17	viral vectors	1
9	Defibrotide	1
98	IVIG	1
98	lidocaine	1
4	Sodium nitrite	1
16	beraprost sodium	1
86	Alpha lipoic acid	1
26	massage	1
26	minocycline	1
80	carbamazepine	1
10	glibenclamide	1
4	isoproterenol	1
6	trimetazidine	1
4	glyceryl trinitrate	1
9	methylxanthine	1
6	Biotin	1
13	guanosine	1
73	thiamine	1
24	bFGF	1
13	mecobalamin	1
69	methylprednisolone	1
13	Olive oil	1
4	probutol	1
65	Zinc	1
5	hydrotherapy	1
23	fish oil	1
4	molsidomine	1
12	beta-carotene	1
16	deep brain stimulation	1
62	ethanol	1
8	menthol	1
9	vitamin K antagonist	1
7	factor Xa inhibitors	1
7	neuromuscular electrical stimulation	1
21	NSAIDs	1
21	oxycodone	1
55	carnitine	1
7	nimodipine	1
12	ketanserin	1
4	GLP-1 receptor agonists	1
20	fentanyl	1
12	prazosin	1
19	alprostadil	1
19	buflomedil	1

12	sodium bicarbonate	1
8	osteocalcin	1
51	epidermal growth factor	1
19	phentolamine	1
5	edoxaban	1
18	balloon dilatation	1
5	lbudilast	1
5	epoprostenol	1
7	gemfibrozil	1
8	hydrocortisone	1
4	Tizanidine	1
45	Ketamine	1
15	kampo	1
4	Waon therapy	1
40	arginine	1
3	candesartan	1
3	chlorpropamide	1
40	ticagrelor	1
3	dimethyl fumarate	1
3	fingolimod	1
3	fludrocortisone	1
3	ifenprodil	1
18	muscle stimulation	1
3	ranolazine	1
2	bisoprolol	1
15	osteopontin	1
18	selenium	1
2	ergocalciferol	1
2	HGF plasmid DNA	1
2	linagliptin	1
2	monosodium glutamate	1
2	nitrate consumption	1
1	blueberry	1
1	cromakalim	1
1	Cymbalta	1
1	electromagnetic therapy	1
1	estradiol valerate	1
1	Linalool	1
1	lomitapide	1
1	low glucose diet	1
1	SDZ PCO-400	1

**Table 7A-19 - Biomarkers Co-Occurring with Exercise**

#REC	BIOMARKER	#CO-OCC
610	pain-free walking distance	287
2038	ankle brachial index	210
700	oxygen	160
1549	blood pressure	149
932	blood flow	124
322	heart rate	84
2536	inflammation	67
1138	blood glucose levels	64
1402	stenosis	56
1156	body mass index	53
1139	total cholesterol	52
2638	lesions	49
1061	hemoglobin A1c	46
70	peak oxygen consumption	43
693	lipoprotein	40
495	low-density lipoprotein cholesterol	35
856	marker	35
435	Systolic blood pressure	34
426	circulation	33
251	angiotensin converting enzyme	29
489	angiogenesis	28
329	lipids	28
549	C reactive protein	26
2277	nerve conduction velocity	23
499	triglycerides	23
78	transcutaneous oxygen pressure	23
61	oxygen saturation	23
308	fibrinogen	20
671	growth factor	20
284	endothelial dysfunction	20
419	oxidative stress	20
318	nitric oxide	20

185	insulin resistance	19
425	high-density lipoprotein cholesterol	19
107	lactate	19
28	phosphocreatine	19
748	atrophy	18
516	cytokine	16
538	calcium	15
266	IL-6	15
262	stenoses	15
151	arterial stiffness	14
841	proteins	14
413	plaque	14
278	vascular endothelial growth factor	14
222	weight loss	13
345	tumour necrosis factor-alpha	12
95	blood viscosity	12
168	platelet aggregation	12
147	lipid profile	11
115	white blood cell	11
412	occlusions	11
74	thromboxane	10
344	sodium	10
747	dorsal root ganglia	9
175	diastolic blood pressure	9
183	pulse wave velocity	9
283	denervation	9
52	MetS	9
402	albumin level	9
261	high homocysteine	8
365	nerve damage	8
69	prostacyclin	7
42	leucocytes	7
391	ventricular ejection fraction	7
152	Reactive oxygen species	7
210	fatty acid	7

208	carotid artery intima-media thickness	7
162	glycated haemoglobin	7
135	platelet activation	6
399	glomerular filtration rate	6
158	nerve fiber density	6
84	malondialdehyde	6
126	vitamin E deficiency	6
125	apolipoprotein	6
186	proinflammatory cytokine	6
102	atherosclerotic plaque	5
114	creatine	5
1091	degeneration	5
30	body fat	5
100	intercellular adhesion molecule-1	5
110	waist circumference	5
61	P-selectin	5
59	acetylsalicylic acid	5
105	plasminogen activator inhibitor-1	5
52	L-arginine	5
41	CD34	5
20	acylcarnitine	5
382	calcification	4
74	creatine kinase	4
80	fibroblast growth factor	4
55	Venous occlusion	4
81	Endothelial progenitor cells	4
49	monocyte chemoattractant protein-1	4
237	vibration perception threshold	4
69	troponin	4
147	capsaicin	4

128	IL-1beta	4
125	Vitamin D deficiency	4
51	cardiac troponin T	4
41	apolipoprotein B	4
51	prothrombin	4
115	Mitochondrial dysfunction	4
26	HMG-CoA reductase	4
69	superoxide dismutase	4
35	glycogen	4
99	antioxidants	4
53	Tissue Plasminogen Activator	3
21	bradykinin	3
80	fibrin	3
20	arterial obstruction	3
96	uric acid	3
65	magnesium	3
2320	toxicity	3
1142	neurotoxic	3
704	creatinine	3
69	lipid peroxidation	3
68	D-dimer	3
616	demyelination	3
455	axonal degeneration	3
37	E-selectin	3
44	carbon dioxide	3
20	adenosine triphosphate	3
27	vascular reactivity	3
42	phosphorus	3
29	asymmetric dimethylarginine	3
104	pulse pressure	3
318	edema	3
115	nitric oxide synthase	3
309	apoptosis	3
101	vasculopathy	3
273	glycoprotein	3
28	thromboxane A2	3
36	niacin	3

18	NADPH oxidases	2
52	hepatocyte growth factor	2
51	glucose metabolism	2
49	cytochrome c	2
247	amyloid	2
240	myelinated fibers	2
28	albumin/creatinine	2
48	urinary albumin/creatinine ratio	2
41	N-terminal pro-brain natriuretic peptide	2
40	arginine	2
40	DBP	2
40	myeloperoxidase	2
126	glutamate	2
39	endothelial damage	2
27	high total cholesterol	2
37	endothelin-1	2
35	interferon gamma	2
118	compound muscle action potential	2
33	oxidative damage	2
13	elastase	2
104	thrombin	2
12	beta-carotene	2
8	phosphates	2
32	insulin levels	2
170	nerve regeneration	2
94	Lipoprotein(a)	2
92	albumin excretion rate	2
20	thromboxane B2	2
7	neuropilin-1	2
81	orthostatic hypotension	2
6	kallikrein	2
5	Acetylcarnitine	2
5	CD11c	2
5	CD86	2
5	L-selectin	2
3	waist-to-height ratio	2

2	Cardiometabolic index (CMI)	2
70	IL-10	2
14	choline	2
58	Neutrophils	2
52	Angiogenic growth factors	2
640	Schwann cell	1
26	miRNA	1
20	aldosterone	1
263	vitamin B(12) deficiency	1
206	nerve growth factor	1
202	T-cell	1
195	thermal hyperalgesia	1
193	CD4	1
20	CD40 ligand	1
154	B-cell	1
17	bone density	1
123	acetylcholine	1
33	hypoperfusion	1
119	glutathione	1
106	von Willebrand factor	1
15	cortisol	1
102	IgA	1
24	aspartate aminotransferase	1
15	digoxin	1
65	advanced glycation end product	1
65	Zinc	1
17	lactic acid	1
64	Red Blood Cell	1
19	riboflavin	1
72	systemic sclerosis	1
28	Osteoprotegerin	1
14	antithrombin III	1
44	alanine	1
27	cyclooxygenase 2	1
17	aortic pulse wave velocity	1
21	Oxidized low-density lipoprotein	1
27	glutamine	1

28	carotid-femoral pulse wave velocity	1
74	matrix metalloproteinase	1
17	arterial compliance	1
27	RAGE	1
38	vitamin K	1
29	fibroblast growth factor 2	1
29	Chlamydia pneumoniae	1
43	erythrocytes	1
26	Endothelin	1
36	arachidonic acid	1
66	mRNA levels	1
36	IgG antibodies	1
55	Ca(2+)	1
58	methionine	1
26	growth hormone	1
35	IL-8	1
22	CD8	1
59	nitrogen	1
34	catalase	1
26	Hydrogen peroxide	1
26	leptin	1
49	bone mineral density	1
12	adipokine	1
49	adenosine diphosphate	1
12	insulin deficiency	1
12	PBMCs	1
11	dendritic cells	1
11	fructose	1
11	gamma-glutamyltransferase	1
11	IL-12	1
11	Myelin breakdown	1
10	glycogen synthase	1
9	adenosine monophosphate	1
9	CD133	1
9	low testosterone	1
8	CBM	1
8	corticosterone	1
8	inositol	1

50	NF-kappaB	1
7	CD14	1
18	c-Fos	1
6	arterial elasticity	1
6	citrulline	1
41	alkaline phosphatase	1
6	Telomerase	1
16	PGE2	1
24	IL-4	1
5	CD16	1
41	free radicals	1
22	lipase	1
5	retinol	1
4	apolipoprotein C-III	1
4	myostatin	1
4	Nox2	1
3	hydroperoxide	1
3	hydroxyl radical antioxidant capacity	1
3	methemoglobin	1
3	N-acetylaspartate	1
3	serum nitrate	1
27	Apolipoprotein E	1
3	xanthine oxidase	1
15	calpain	1
2	polymorphonuclear neutrophils	1
2	TREM-1	1
1	cyclooxygenase 1	1
1	NADH dehydrogenase	1



**Table 7A-20 - Biomarkers Co-Occurring with Gabapentin**

#REC	BIOMARKER	#CO-OCC
538	calcium	19
147	capsaicin	18
2536	inflammation	15
1142	neurotoxic	14
344	sodium	10
2320	toxicity	9
747	dorsal root ganglia	8
38	Noradrenaline	8
2277	nerve conduction velocity	6
318	edema	6
1138	blood glucose levels	5
671	growth factor	5
30	Gamma-aminobutyric acid	5
65	magnesium	5
122	mechanical hyperalgesia	5
119	glutathione	5
365	nerve damage	4
419	oxidative stress	4
195	thermal hyperalgesia	4
318	nitric oxide	3
704	creatinine	3
700	oxygen	3
263	vitamin B(12) deficiency	3
206	nerve growth factor	3
27	cholinesterase	3
152	Reactive oxygen species	3
126	glutamate	3
273	glycoprotein	2
1139	total cholesterol	2
222	weight loss	2
1549	blood pressure	2
1091	degeneration	2
54	glial fibrillary acidic protein	2
322	heart rate	2
349	IgM	2

40	myeloperoxidase	2
70	IL-10	2
27	cyclooxygenase 2	2
345	tumour necrosis factor-alpha	2
128	IL-1beta	2
25	Iron Deficiency	2
1156	body mass index	2
516	cytokine	2
12	anticardiolipin antibodies	2
20	folate deficiency	1
24	aspartate aminotransferase	1
99	antioxidants	1
18	caspase 3	1
14	choline	1
354	neurodegeneration	1
18	c-Fos	1
309	apoptosis	1
19	Ccl2	1
26	Hydrogen peroxide	1
283	denervation	1
278	vascular endothelial growth factor	1
118	compound muscle action potential	1
266	IL-6	1
115	Mitochondrial dysfunction	1
16	galanin	1
84	malondialdehyde	1
52	BDNF	1
81	orthostatic hypotension	1
52	hepatocyte growth factor	1
14	TBARS	1
115	nitric oxide synthase	1
80	folic acid	1
2638	lesions	1
856	marker	1
17	CXCR4	1
841	proteins	1

22	lipase	1
34	catalase	1
186	proinflammatory cytokine	1
185	insulin resistance	1
22	Vitamin B1 deficiency	1
108	creatinine clearance	1
107	lactate	1
40	sorbitol	1
69	lipid peroxidation	1
48	thymidine	1
158	nerve fiber density	1
69	superoxide dismutase	1
499	triglycerides	1
49	cytochrome c	1
495	low-density lipoprotein cholesterol	1
34	histamine	1

49	protein kinases	1
40	dopamine	1
44	alanine	1
65	advanced glycation end product	1
126	vitamin E deficiency	1
33	ferritin	1
16	PGE2	1
123	acetylcholine	1
103	urea	1
44	Mercury	1
16	androgen	1
11	fructose	1
9	deoxyuridine	1
8	S100 beta	1
4	beta-endorphin	1

[References - Chapter 7](#)

## Chapter 8

### REFERENCES AND BIBLIOGRAPHY

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