Genetic susceptibility studies of lymphoma may serve to identify at risk populations and clarify important disease mechanisms. This review considered all studies published through October 2006 on the contribution of genetic polymorphisms in the risk of lymphoma. Numerous studies implicate the role of genetic variants that promote B-cell survival and growth with increased risk of lymphoma. Several reports including a large pooled study by InterLymph, an international consortium of non-Hodgkin lymphoma (NHL) case-control studies, found positive associations between variant alleles in TNF-308G>A and IL10-3575T>A genes and risk of diffuse large B-cell lymphoma. Four studies reported positive associations between a GSTT1 deletion and risk of Hodgkin and non-Hodgkin lymphoma. Genetic studies of folate-metabolizing genes implicate folate in NHL risk, but further studies that include folate and alcohol intakes are needed. Links between NHL and genes involved in energy regulation and hormone production and metabolism may provide insights into novel mechanisms implicating neuro- and endocrine-immune cross-talk with lymphomagenesis. However, this links will need replication in larger populations. Numerous studies suggest that common genetic variants with low penetrance influence lymphoma risk, though replication studies will be needed to eliminate false positive associations.

Key words: lymphoma, genetic susceptibility, SNP, NHL, polymorphisms.
B-cell development that may lead to pre-neoplastic changes relevant to lymphoma.

**Normal B-cell development and genetic instability: potential underlying mechanisms of lymphomagenesis**

B-cells differentiate from hematopoietic stem cells within the bone marrow and their maturation occurs in several stages involving genetic recombination and mutation to generate high affinity antibodies. Recombinase activating gene (RAG) proteins initiate DNA double-strand breaks allowing a fixed set of gene segments variable, diversity, joining (VDJ) to recombine to produce B-cell receptors specific for antigen. During this process, chromosomal translocations and mutations involving the immunoglobulin heavy (IgH) and light (IgL) chain genes and the T-cell receptor genes are common that can deregulate several oncogenes. Further translocations and mutations can occur following antigenic dependent clonal expansion in the lymph nodes involving somatic hypermutation and class switching. These translocations and somatic mutations can disrupt B-cell homeostasis and lead to proliferation, blocked differentiation and immortalization of B-cells. Genetic factors that impair DNA repair can increase the likelihood of these pre-neoplastic lesions. Genomic lesions in B-cells that are not initially lethal could later be modulated by environmental (i.e., infectious agents), epigenetic (i.e., chromosomal hypo- or hypermethylation), disease (i.e., autoimmune disease), and genetic factors (i.e., genetic polymorphisms) that promote B-cell survival and proliferation, and may lead to the development and progression of lymphoma (Figure 1). Below we discuss how genetic polymorphisms may play a contributory role in this process.

**Candidate gene association studies of lymphoma**

The majority of candidate genes that have been investigated to date can be categorized into functional groups based on their potential biologic relevance. One group includes genes that influence DNA integrity and methylation. Polymorphisms in these genes could modulate the rate of chromosomal translocations, efficiency of DNA repair and DNA methylation status. Another major group involves genes that alter B-cell survival and growth including pro-inflammatory and regulatory cytokine genes, and genes involved in innate immunity, oxidative stress, energy regulation and hormone production. Another group are genes involved in xenobiotic metabolism. Risk alleles found in these pathways may provide clues to identify potential lymphomagens. On the basis of these studies, several gene variants have been associated with NHL and some have been replicated in more than one study suggesting their significance in lymphomagenesis. A summary of results from these studies is listed in Table 1 ([Supplementary online](#)) with particular emphasis on those that reported positive findings.

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**Genetic polymorphisms that modify DNA integrity and methylation patterns influence lymphoma risk**

SNPs in genes involved in DNA double-strand break and repair

The highrisk of lymphoproliferative disorders in individuals carrying germline mutations in the ataxia telangiectasia, mutated (ATM), and Nijmegen breakage syndrome (NBS1) genes that involve syndromes associated with aberrant DNA double-strand break repair (DSBR) underscores the relevance of this pathway in lymphomagenesis. Single nucleotide polymorphisms (SNPs) that hinder DNA repair mechanisms can increase the likelihood of pre-neoplastic lesions that may be relevant to lymphoma. For example, the WRN gene plays a crucial role in DNA DSBR and in other repair pathways. Mutations in this gene are associated with the autosomal recessive disorder, Werner syndrome, characterized by premature aging. More common genetic variants in WRN have been associated with NHL in two U.S. studies. Specifically, the Arg and Ile alleles of two non-synonymous SNPs in the WRN gene (Cys1367Arg, Val114Ile) were underrepresented in NHL cases. Polymorphisms in five other non-homologous end joining /DNA DSBR genes (LIG4, RAG1, BRCA1, BRCA2, XRCC3) and in the DNA DSBR checkpoint gene, TP53, also have been associated with NHL or specific subtypes. These studies highlight the relevance of genetic polymorphisms that may impede DNA DSBR, important during normal B-cell maturation in the bone marrow or as a result of humoral immune response to antigen in germinal centers, in the risk of lymphoma. Alkylation agents and other chemicals, oxidative stress, ionizing radiation and viruses provide other means to compromise genomic integrity. Mammalian cells have evolved numerous defense mechanisms to counter-balance these threats. Mismatch repair recognizes and repairs misplaced nucleotides and, if defective, can lead to microsatellite instability and neoplastic transformation. Two small studies report positive associations with a SNP in the mismatch repair gene, MSH2 (-6T>C), with NHL, suggesting the potential relevance of this mechanism. However, there is limited and sometimes contradictory evidence for the role of base excision repair and nucleotide excision repair pathways and lymphoma risk.

**Genetic polymorphisms in one-carbon metabolism and risk of lymphoma**

Epigenetic silencing of tumor suppressor and B-cell specific genes is an important mechanism in hematopoietic malignancies. Genetic variants that influence methylation processes may promote lymphoma by mechanisms that involve hypo- or hypermethylation of proto-oncogenes or tumor suppressor genes, respectively, or through viral re-activation. Folate deficiency or genetic variation in folate metabolic pathways can influence DNA methylation patterns and also impede DNA synthesis and repair mechanisms. 5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate metabolic pathway.
that catalyzes the production of 5-methyltetrahydrofolate, a major donor of one-carbon units for DNA synthesis and methylation processes (Supplementary online Figure 1). A 677C>T SNP in the MTHFR gene, associated with enzyme thermolability, 17 may hinder DNA methylation and shift the flux of one-carbon units toward purine and DNA synthesis and repair. Several NHL studies have examined polymorphisms involved in folate metabolism, although results have been inconsistent. 18-26

Similar discrepancies also have been reported for polymorphisms in the thymidylate synthase (TYMS) and methionine synthase (MTR) genes. TYMS plays a critical role in maintaining balanced supplies of deoxynucleotides required for DNA synthesis (Figure 1 supplementary online). Impairments of this enzyme have been associated with chromosome damage and fragile site induction. 27,28 A polymorphic 28-bp double (versus triple) repeat in the promoter region and a 6-bp deletion in the 3'UTR of the TYMS gene hinders TYMS gene expression and mRNA stability that may increase the rate of DNA double-strand breaks and chromosomal translocations. Positive associations with NHL have been reported for the 28-bp double repeat in an Asian study 29 and with the triple repeat in a British study, 19 but no associations were found in a U.S. study. 18 Furthermore, the 6-bp deletion has been positively 30 and inversely 31 associated with NHL. MTR catalyzes the remethylation of homocysteine to methionine. The Gly allele of a SNP in the MTR gene (MTR 2756A>G, Asp919Gly), associated with lower homocysteine levels than the Asp allele, was inversely associated with lymphoma subtypes in Caucasians 24-26 and positively associated with NHL in another Caucasian study 19 and in an Asian population. 30,31

Findings involving folate-metabolizing genes suggest a role for folate in lymphomagenesis that may involve DNA methylation and repair infidelity. The inconsistent findings in some studies may result from differences in folate status across populations since the influence of genetic variation on disease risk may be modified by folate status. Therefore, studies are needed that consider the complex interrelationship between genetics, folate intake, vitamin B₁₂, and other factors that may affect vitamin B status such as alcohol.

SNPs that alter B-cell survival and growth influence lymphoma risk

Studies suggest that chronic inflammation may enhance lymphocyte neoplastic transformation by promoting proliferation and survival of mutated cells through activation of nuclear factor (NF)-κB and AP-1 response genes. 32 Obesity, autoimmune disease, infection, chemical exposures, and other inflammatory mediators that exacerbate oxidative stress can induce chronic inflammation. SNPs in genes involved in these processes may also play an important role in the pathogenesis of lymphoid neoplasms (Figure 2 online).

SNPs in pro-inflammatory cytokine genes influence risk of lymphoma

In perhaps the most noteworthy NHL risk alleles reported to date are SNPs in the tumor necrosis factor (TNF) and interleukin (IL) 10 genes, reported by InterLymph, an international consortium of lymphoma epidemiological case-control studies. 33 Researchers found that the TNF -308AA genotype conferred 25% and 65% increased risks for NHL and DLCL respectively. 33 Similarly, polymorphisms in the IL10 distal (+575A>T) and proximal promoter (-1082A>G) regions, specifically the low IL-10 producer -575A and -1082G alleles, were associated with modest increases in DLCL, but not FL risk. TNF-α, mainly produced by mast cells, macrophages and other immune cells, is a pro-inflammatory immunoregulatory cytokine and a key
mediator of lymphocyte responses, natural killer cell activity and dendritic cell maturation. Elevated TNF-α expression augments anti-apoptotic behavior in B-cells through NF-κB activation that induces several anti-apoptotic factors including members of the Bcl2 family, cellular inhibitors of apoptosis, and cell cycle regulators29 (Figure 2 online). The TNF –308A allele has been associated with higher constitutual and inducible expression of TNF-α,30 and increased susceptibility for rheumatoid arthritis and Sjogren syndrome.31 IL-10 is a potent immunoregulatory cytokine of T-cells produced by monocytes and lymphocytes that hinders the inflammatory response by inducing apoptosis in mast cells and macrophages, thus inhibiting TNF-α production.32 Genetic factors that up-regulate TNF-α or down-regulate IL-10 may provide a pro-inflammatory milieu that favors lymphomagenesis. Recent studies exploring other TNF and IL10 variants and haplotypes found further evidence for associations with NHL.33-35 However, a number of studies reported conflicting results for another TNF variant (–357C>T).36-42 The TNF gene is located on chromosome 6p21 in the human leukocyte antigen (HLA) class III region in close proximity to several other immunoregulatory factors. Inconsistent results in variant-disease associations located in this region may be the result of population differences in linkage disequilibrium between the studied variant and the causal variant elsewhere in the HLA region. Fine mapping of the HLA region will help to clarify this and should be a major objective in future genetic studies of NHL. IL-6 is a pro-inflammatory cytokine involved in regulation of immune defense mechanisms through initiation of acute phase responses. IL-6 serum levels have been positively associated with adiposity and type 2 diabetes, and elevated levels have been detected in HL patients. Studies by InterLymph found no association between an IL6 promoter polymorphism (-174G>C) and NHL risk.33 However, inverse associations have been reported between the -174C allele and risk of young adult HL,43 young adult nodular lymphocyte predominant HL and T-cell lymphoma,37,38 but no associations have been found for multiple myeloma or CLL.44 Inverse associations also have been reported between the IL6 –174C allele and systemic-onset juvenile chronic arthritis45 and Kaposi sarcoma in HIV-positive men.46 An anti-inflammatory phenotype for the IL6 –174C allele has been recently described involving elevated apolipoprotein (Apo)-C1 levels and reduced heat shock protein 60 autoantibodies and platelet factor 4 protein levels in serum of healthy adults.47 Thus, the protective effects of the IL6 –174C allele for HL suggest the relevance of inflammatory and pro-oxidative processes in HL that will require further investigation.

SNPs in the innate immunity genes, toll-like receptor 4 (TLR4) and caspase recruitment domain family, member 15 (CARD15/NOD2), influence lymphoma risk

NOD2 and TLR4 are pro-inflammatory mediators integral as a first line of defense against viral and bacterial infection, providing non-specific protection against numerous pathogens. NOD2 directs antimicrobial activity through a NF-κB-mediated pathway of inflammation and apoptosis.48 A rare CARD15 C insertion at nucleotide 1007 results in a premature stop codon that has been linked to autoimmune disorders such as Crohn’s disease and psoriasis,51 and to an excess risk of lymphoma.52 Furthermore, studies by the InterLymph consortium found that this insertion was associated with an elevated, but imprecise, risk estimate for NHL (OR=2.3, 95% CI 0.12–135).53 Yet another polymorphism in CARD15 (Arg702Trp) was recently associated with an elevated risk of MALT lymphoma among H. pylori infected individuals.54 Recent studies describe a CARD15 C insertion phenotype associated with reduced intestinal expression of α- and β-defensins55 that may compromise the intestinal antimicrobial barrier. The link between Crohn’s disease and NHL and the association of NHL, and the CARD15 variants, suggest that antigenic challenges to lymphoid tissue in the gastrointestinal tract can alter immune system responses and influence disease risk. Thus, further study of CARD15 mutations and the role of defensins in NHL may be warranted.

The TLR4 gene facilitates pro-inflammatory cytokine release by human cells in response to lipopolysaccharide, and mediates tolerance and B-cell activation. A TLR4 polymorphism (Asp299Gly) in the extracellular domain weakens receptor signaling and reduces IL-12 and IFNγ levels. The TLR4 299Gly allele was inversely associated with risk of gastric MALT lymphoma56 and DLCL,57 and positively associated with MALT lymphoma and HL.58 Nieters et al. also reported that a –16933T>A SNP in the TLR2 gene, another important pattern recognition receptor involved in the resolution of inflammation, increased risk of HL. These studies suggest that SNPs in TLR signaling pathways may differentially affect risk of lymphoma subtypes, but will require replication in larger study populations. Furthermore, two studies reported that a functional variant (His165Arg) of an important innate immune response gene, the receptor for the FC portion of immunoglobulin G (FCGR2A), conferred an elevated NHL risk.59-60 The Arg variant might favor lymphomagenesis based on impaired immunoglobulin G2-mediated phagocytosis61 and promotion of antibody-based inflammation.62

Oxidative stress genes are implicated in NHL

Reactive oxygen species (ROS) are implicated in several inflammatory conditions and in cancer risk. Phagocytic macrophages and neutrophils are the initial inflammatory response against infectious agents and antigens. These cells undergo a respiratory burst, where the membrane-bound enzymes, NADPH-oxidase and nitric oxide synthase (NOS), produce superoxide anion radicals and nitric oxide radicals. The Leu/Leu genotype of a non-synonymous SNP in the nitric oxide synthase gene (NOS2A Ser608Leu), located in a functionally relevant domain, has been associated with gastric cancer56 and a 2 to 3-fold increased risk
Glutathione peroxidase is one of the most important antioxidant enzymes, manganese SOD (SOD2), is induced by the pro-inflammatory cytokines, IL-1 and TNF-α. The variant Ala allele of a non-synonymous SNP in SOD2 (Val16Ala) that increases ROS scavenging was associated with a marginal increased risk of B-cell lymphomas. However, a pooled analysis of 1,593 NHL cases and 2,517 controls found no association of this variant with overall NHL risk, but homozygosity for the 16A allele was associated with decreased MZL risk. In the same study, a variant in glutathione peroxidase 1 (GPX1 Pro197Leu) conferred 25% and 33% increased risks of NHL and FL respectively. Glutathione peroxidase is one of the most important antioxidant enzymes in humans that catalyzes the detoxification of hydrogen peroxide. These studies implicate pro-oxidant mechanisms that enhance free radical damage in increasing disease susceptibility. This may be particularly relevant in lymphocytes where chronic inflammation may increase the risk of neoplastic changes characteristic of the marginal-zone lymphomas.

**SNPs in energy regulation genes are implicated in risk of NHL**

An association between obesity and hematolymphopoietic cancers has been seen, with increased risks reported for NHL, leukemia and multiple myeloma. Obesity is associated with impaired immune function and generalized inflammation characterized by increased circulation of pro-inflammatory mediators such as leptin, TNF-α, IL-6, C-reactive protein and reduced levels of the anti-inflammatory peptide, ghrelin. Links between NHL and polymorphisms in the leptin (LEP), leptin receptor (LEPR), neuropeptide Y (NPY) and ghrelin (GHRL) genes may provide new insights into mechanisms of lymphomagenesis involving neuro-immune cross-talk. NPY acts on the central nervous system as a strong appetite stimulator controlled by positive and negative feedback actions of ghrelin and leptin respectively to regulate energy balance. Obesity upsets this fine balance, resulting in leptin resistance, and elevated leptin and reduced ghrelin production. Leptin, NPY and ghrelin also exert major influences on humoral and cellular immune functions. Notably, leptin promotes proinflammatory cytokine release, anti-apoptotic behavior in lymphocytes and oxidative stress. NPY suppresses innate immunity through natural killer cell activity inhibition, and increases adhesion, chemotaxis, phagocytosis and superoxide anion production in macrophages. Ghrelin stimulates growth hormone release and inhibits proliferation of inflammatory cytokines.

In a U.S. study, Skibola et al. found that the G allele for a SNP in the promoter region of the LEP gene (19A>G) gave up to a 2-fold increased risk of NHL, particularly FL. Further, gene-gene interaction was reported between LEP -2548G>A and LEPR Gln223Arg polymorphisms. Similar associations were observed in a U.K. study that found a 50% reduced FL risk associated with the LEP -19AA genotype and a 90% increased risk of FL among women associated with the LEPR 223ArgArg genotype. In the U.S. study population, four closely linked NPY variants were associated with up to a two-fold increased risk for NHL and FL. Of these, an NPY 1128T>C functional SNP may be particularly relevant as it has been associated with elevated NPY levels, enhanced angiogenesis, and lymphocyte proliferation. Furthermore, two variants in the GHRL (4427G>A and 5179A>G) gave 20-70% reduced risks for NHL, especially for DLCL, though no associations were found in the functionally relevant Leu72Met SNP percent that has been associated with reduced BMI and abdominal visceral fat. These studies further implicate obesity in the pathogenesis of NHL that may involve its adverse action on immune system functions.

**SNPs in genes involved in sex hormone production and metabolism influence lymphoma risk**

Other less obvious but noteworthy loci linked to lymphoma are SNPs in genes that influence sex hormone production and metabolism. Prolactin and estrogens, important in female reproduction, also function as immune modulators that affect apoptosis, activation and proliferation of immune cells, and promote B-cell proliferation and survival. Elevated prolactin levels have been associated with progression of hematological diseases such as AML and NHL. Two studies investigating SNPs in the CYP17A1 gene that encodes a key enzyme involved in estrogen and testosterone synthesis reported that the homozygous variant for a CYP17A1 347C>C SNP conferred a 40% increase in NHL risk, particularly for DLCL, where risks for the –34CC genotype were ~2-fold. The CYP17 –34CC genotype has been previously associated with elevated serum dehydroepiandrosterone sulphate and estradiol levels. Skibola et al. also found that SNPs in the catechol-O-methyltransferase (COMT) gene, involved in estrogen metabolism, and in the prolactin (PRL) gene, that influences lymphocyte prolactin levels, were associated with lymphoma risk. These results highlight a potential role of sex hormones in lymphoid tissue proliferation and ultimate neoplastic transformation.

**Limited evidence for detoxification genes in risk of lymphoma**

Glutathione S-transferases (GSTM1, GSTT1, GSTP1) are involved in the detoxification of a wide range of carcinogens, including benzene, organochlorine compounds, organophosphate pesticides, tobacco smoke, chemotherapeutic agents and reactive oxygen species. Deletion polymorphisms in GSTM1 (GSTM1*0) and GSTT1 (GSTT1*0)
result in loss of enzymatic activity. Evidence of higher risk of NHL and HL in GSTT1 null homozygotes was reported in several studies. Proposed mechanisms could include impaired neutralization of reactive oxygen species or reduced deactivation of carcinogenic intermediates of polycyclic aromatic hydrocarbons. No associations were found between GSTM1 and GSTT1 polymorphisms and NHL risk. Homozygous variants of a paraoxonase-1 (PON1) Gln192Arg SNP that determines efficiency of hydrolysis and detoxification of specific organophosphates was associated with a 2.5-fold elevated NHL risk. The 192Arg allele also has been implicated in organophosphate toxicity in sheep farmers that dip animals in the pesticide diazinon. Another study found no effect of the Gln192Arg variant, but an increased risk of FL and T-NHL associated with a non-synonymous PON1 Leu55Met variant. Single reports also suggest some relevance of genetic variants in phase I cytochrome P450 enzymes (CYP1B1, CYP2E1) and epoxide hydrolase 1 (EPHX1) in the etiology of lymphomas. These enzymes metabolize benzene, ethanol, halogenated solvents and xenobiotic epoxide substrates, respectively. N-acetyltransferase enzymes, NAT1 and NAT2, catalyze the metabolism of aromatic and heterocyclic amines via N- or O-acetylation. One large study found a 60% increased risk associated with the NAT1*10/10 genotype and a 20% increased risk in intermediate and rapid NAT2 acetylators compared to slow acetylators. Interestingly, among intermediate/rapid acetylators, NHL risk was specifically elevated among current smokers compared with non-smokers (OR=2.44, 95% CI=1.15-5.20) highlighting the importance of combined gene-environment analysis. Other smaller studies found only limited evidence for a role of NAT1 and NAT2 variants in lymphomagenesis.

Despite their crucial role in activation of potential carcinogens and detoxification of putative environmental lymphomagens, with the exception of GSTT1*0, there are few genetic data on the contribution of xenobiotic metabolizing genes in the pathogenesis of lymphomas even in occupationally exposed populations.

**Additional studies needed to explore the HLA region**

The HLA region located on chromosome 6 (6p21.3) has now been mapped and approximately 220 genes have been defined. Many of these genes encode proteins involved in immune and inflammatory responses such as TNF, LTA, heat shock protein 70 and PRL. Few studies have explored the association of HLA genes with lymphoid malignancies; existing reports are mainly for HL. Two consecutive markers, D6S265 and D6S510, located in the HLA class I region have been identified as susceptibility loci for EBV-positive HL. Furthermore, some studies have identified HL-associated HLA class II susceptibility alleles. What has emerged from these studies is that HLA-DPB1*0301 appears to give susceptibility and DPB1*0201 resistance to HL. Also, HLA class II DRB1*1501 and DQB1*0602 alleles, or linked loci, may increase risk of sporadic and familial HL. Thus far, few studies have explored the association of HLA polymorphisms with NHL risk and results have been inconclusive. Fine map genotyping in the HLA region may help to clarify the significance of variability in this region for HL and other lymphoma subtypes.

**Genome screens**

Few genome screens for lymphoma have been performed to date. Recently, a genome-wide linkage search of 115 families segregating CLL with or without additional B-cell lymphoproliferative disorders found evidence for a major susceptibility locus on the pericentric
region of chromosome 11 (chr11p11)." Linkage was suggested for four other chromosomal regions (5q22-23, 6p22, 10q25, and 14q32). Furthermore, a genome screen on 44 high-risk families for HL identified strong linkage on chromosome 4 (near marker D4S394) and suggestive linkage on chromosomes 2 and 11. Larger studies involving dense mapping in these regions and more exploratory studies involving whole genome scans for NHL will help to describe disease mechanisms and identify relevant pathways. To this end, plans for collaborative genome scan studies involving InterLymph consortium investigators are currently underway.

Conclusions
Case-control association studies provide further support for a genetic component to lymphomas. These studies suggest that disease mechanisms involving faulty DNA repair and genetic and environmental factors that deliver positive signals for B-cell survival and proliferation play important roles in lymphomagenesis (Figure 2). However, some genetic associations presented in this review may be false positive associations due to population stratification, improper control selection, genotyping error or other underlying causes. To date, most association studies have been limited by population size, restricting the potential investigation of gene-gene and gene-environment interactions. Larger collaborative studies using dense mapping to refine candidate regions, and exploratory studies involving whole genome scans followed by replication and multi-center pooled analyses will help to eliminate false positive findings, further clarify disease mechanisms and identify relevant pathways. InterLymph’s successful identification of two susceptibility alleles in TNF and IL10 highlight the importance of consortia to validate biomarkers, particularly related to NHL subtypes. A thorough exposure assessment using biomarkers and the WHO-defined classification of lymphoma subtypes will also be needed to assess gene-environment interactions. Functional studies such as animal knockout or knockdown models and cellular models will help verify actual disease-predisposing variants to establish that the identified causal variant alters function and that the sequence change contributes to the illness phenotype. To summarize, these studies will broaden our current understanding of important mechanistic pathways involved in lymphomagenesis and provide clues about environmental agents and lifestyle exposures that contribute to disease risk that may be translated to NHL screening, prevention or treatment regimens.

Authors’ Contributions
CFS and AN wrote the manuscript; JDC contributed to the table designs and legends.

Conflict of Interest
The authors reported no potential conflicts of interest.

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