THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

# Next Generation Sequencing Panel for Hereditary Lymphoma

**Clinical Features:**
Lymphomas are cancers originating from the lymphoid tissues, and can be divided into two broad categories, Hodgkin lymphoma and non-Hodgkin lymphoma, which can be differentiated by their cellular pathology. Hodgkin lymphoma (HL) is characterized by the presence of neoplastic binucleated B-cells called Reed-Steinberg cells [1]. Exposure to Epstein Barr virus is associated with increased risk of HL [1]. In addition, familial HL has also been described, and first degree relatives of a patient with HL having an increased risk of developing the condition [2, 3]. Non-Hodgkin lymphoma (NHL) is a diverse group of more than 50 types of lymphoma that arise from the lymphoid tissues but do not contain Reed-Steinberg cells, each with distinct morphological, cytogenetic, genetic and clinical features [1]. Exposure to Epstein Barr virus and HIV are associated with increased risk of NHL; the contribution of other lifestyle factors and exposures remains unclear. Families with high rates of NHL have also been described, indicating a hereditary component in some cases [1]. In addition, first degree relatives of patients with NHL have a 1.5-3 fold increased risk of developing the condition, again indicating a genetic component to disease susceptibility [1]. Chronic lymphocytic leukemia (CLL) is considered a subtype of NHL. A 3- to 8.5-fold increased risk of CLL among first-degree relatives of probands has been reported [1]. Patients with primary immunodeficiency also have elevated risk to lymphoma [4].

*Our Hereditary Lymphoma and Immunodeficiency Panel includes mutation analysis of all 34 genes listed below.*

| Comprehensive Hereditary Lymphoma and Immunodeficiency Panel | | | |
|---|---|---|---|
| ACD* | CHEK2 | KLHDC8B | MLH1 |
| MSH2 | MSH6 | NPAT | PMS2 |
| POT1 | TERF2IP | TP53 | BRCA2 |
| ADA | ATM | BRCA1 | CTLA4 |
| CARD11 | CASP10 | CD27 (TNFRSF7) | IKZF1 |
| DOCK8 | FAS (TNFRSF6) | FASLG | NF1 |
| ITK | MAGT1 | NBN (NBS1) | SH2D1A (SAP) |
| PIK3CD | PRF1 | RECQL3 (BLM) | |
| STXBP2 | TNFRSF13B (TACI) | WAS | |

## Cancer/Tumor Susceptibility Syndromes

| Gene | Clinical Features |
|---|---|
| ACD | Guo Y *et al.* (2014) reported germline mutations of *ACD*, the gene encoding telomere protein TPP1 in Inherited bone marrow failure [5]. A pathogenic variant in *ACD* has also been described in a family with chronic lymphocytic leukemia [6]. Hoyeraal-Hreidarsson syndrome can also be caused by a germline mutation in *ACD* [7]. |
| CHEK2 [OMIM# 604373] | Variants in *CHEK2* have been associated with a phenotype similar to Li-Fraumeni syndrome [8], which is characterized by increased susceptibility to a number of different cancers including breast cancer, soft-tissue sarcoma, brain tumors, adrenocortical carcinoma and leukemias. Other cancers may also be observed. Ruijs *et al* (2009) identified four families with a Li-Fraumeni-like phenotype and a heterozygous mutation in *CHEK2*; one family included two individuals with Hodgkins lymphoma [9]. |
| MLH1 [OMIM# 120436] MSH2 [OMIM# 609309] MSH6 [OMIM# 600678] PMS2 [OMIM# 600259] | Biallelic mutations in DNA mismatch repair genes *MLH1, MSH2, MSH6* and *PMS2* are associated with a disorder called constitutional mismatch repair-deficiency syndrome (CMMR-D) [10]. CMMR-D is associated with increased risk of childhood cancers, including hematological malignancies (15%), brain tumors (48%), and gastrointestinal cancers (32%) [11]. The most prevalent hematological malignancies observed are NHL and acute lymphoblastoid leukemia [10]. The median age of diagnosis for patients who develop lymphoma is 5 years [10]. Patients may also exhibit features typically associated with neurofibromatosis type 1, such as café au lait spots or neurofibromas [10]. Heterozygous mutations in the *MLH1, MSH2, MSH6* and *PMS2* genes are associated with Lynch syndrome, an autosomal dominant condition with increased risk of a number of different types of malignancies, including colon, endometrial, ovarian and stomach cancer [10]. |
| NF1 [OMIM# 613113] | Mutations in *NF1* are associated with neurofibromatosis 1 (NF1), an autosomal dominant neurocutaneous disorder associated with increased risk of both benign and malignant tumors [12]. The |

| | |
|---|---|
| | most common malignancies include gliomas, peripheral nerve sheath tumors, juvenile myelomonocytic leukemia, pheochromocytoma, gastrointestinal stromal tumors, rhabdomyosarcoma, and malignant triton tumors [12]. Patients also have an increased relative risk of childhood NHL of 10 [13]. |
| NPAT [OMIM# 601448] | A heterozygous mutation in NPAT has been described in fours cousins who all presented between the ages of 22 and 26 with nodular lymphocyte predominant Hodgkin lymphoma [14]. |
| POT1 [OMIM# 606478] | Germline heterozygous pathogenic variants in *POT1* have been recently reported in thyroid cancer, breast cancer, renal cell carcinoma, colorectal cancer and familial chronic lymphocytic leukemia [6, 15]. A *POT1* mutation has been recently reported implicating defective telomere end fill-in and telomere truncations in Coats plus [16]. |
| TERF2IP [OMIM# 605061] | Mutations in *TERF2IP* have been described in patients with familial melanoma and familial chronic lymphocytic leukemia [6, 17]. |
| TP53 [OMIM# 191170] | Heterozygous mutations in *TP53* are associated with Li-Fraumeni syndrome (LFS), a cancer susceptibility disorder [18]. The most common cancers associated with LFS are soft tissue sarcomas, osteosarcomas, pre-menopausal breast cancer, brain tumors, adrenocortical carcinomas and leukemias [18]. A number of other cancers, including Hodgkin and non-Hodgkin lymphomas, have also been described in families with LFS [18]. |

## Immunodeficiency and Autoimmune Disorders

| Gene | Clinical Features |
|---|---|
| ADA [OMIM# 102700] | Mutations in the *ADA* gene are associated with autosomal recessive severe combined immunodeficiency, which is associated with defective T and B cell function [19]. This condition has been associated with a 5% risk of NHL [19, 20]. |
| CASP10 [OMIM# 601762] | Heterozygous germline mutations in *CASP10* are associated with autoimmune lymphoproliferative syndrome (ALPS). Patients with ALPS frequently present with fulminant Epstein-Barr viral infection, hypogammaglobulinemia, or lymphoma [21]. |
| CD27 (TNFRSF7) [OMIM#186711] | Homozygous or compound heterozygous mutations in *CD27* are associated with lymphoproliferative syndrome. The phenotype can vary significantly, from asymptomatic borderline-low hypogammaglobulinemia, to a full-blown symptomatic systemic inflammatory response with life-threatening EBV-related complications, including hemophagocytic lymphohistiocytosis, a lymphoproliferative disorder, and malignant lymphoma requiring stem cell transplantation [22, 23] |
| CTLA4 [OMIM#123890] | Heterozygous germline mutations in *CTLA4* are associated with ALPS characterized by autoimmune thrombocytopenias and abnormal lymphocytic infiltration of nonlymphoid organs, including the lungs, brain, and gastrointestinal tract, resulting in enteropathy [24]. |
| DOCK8 [OMIM#611432] | Autosomal recessive hyper-IgE recurrent infection syndrome is caused by homozygous or compound heterozygous mutation in the *DOCK8* gene [25]. |
| FAS (TNFRSF6) [OMIM# 134637] | ALPS type 1A is caused by heterozygous mutations in the *FAS* gene [26]. The disorder is caused by defective lymphocyte apoptosis and is associated with chronic lymphadenopathy and splenomegaly, and autoimmune cytopenias [26]. ALPS is associated with a 51-fold increased risk of Hodgkin lymphoma, and a 14-fold risk of non-Hodgkin lymphoma. The average of symptom onset is 5 years, and the average age of lymphoma diagnosis is 28 years [26]. |
| FASLG [OMIM#134638] | Heterozygous mutations in *FASLG* are associated with ALPS type 1 B [27]. |
| ITK [OMIM#186973] | Mutations in *ITK* are associated with an autosomal recessive form of lymphoproliferative syndrome [28, 29]. |
| IKZF1 [OMIM#606023] | A germline *IKZF1* mutation can cause an autosomal dominant form of common variable immunodeficiency (CVID) that is associated with a striking decrease in B-cell numbers, and is a predisposition to B-cell precursor acute lymphoblastic leukemia, pancytopenia and autoimmune diseases [30, 31]. |
| MAGT1 [OMIM#300715] | Mutations in *MAGT1* are associated with X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia [32, 33] |
| PIK3CD [OMIM#602839] | Heterozygous mutations in *PIK3CD* are associated with immunodeficiency characterized by onset of recurrent sinopulmonary and other infections in early childhood [34, 35]. |
| SH2D1A (SAP) [OMIM# 300490] | X-linked lymphoproliferative syndrome-1 (XLP1) is caused by mutations in the *SH2D1A* gene. XLP1 is associated extreme sensitivity to Epstein Barr virus, which leads to severe or fatal infection mononucleosis, acquired hypogammaglobulinemia and a 20% risk of lymphoma [1, 36]. Female carriers are typically asymptomatic [37]. |
| TNFRSF13B (TACI) [OMIM# 604907] | Mutations in *TNFRSF13B* are one cause of CVID, which is a heterogeneous disorder characterized by impaired production of antibodies after vaccination or antigen exposure, and reduced serum levels of IgG, IgA and IgM [38]. Symptoms can include chronic sinopulmonary infections [38]. First clinical manifestations typically occur in childhood or adolescence [38]. Mellemkjaer *et al.* (2002), identified 4 cases of NHL out of 176 CVID patients, indicating a 6-fold increase in NHL incidence compared to the general population [39]. Mutations in *TNFRSF13B* may be inherited in an autosomal dominant or recessive manner, and penetrance is incomplete [38]. |
| WAS [OMIM# 300392] | Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency caused by mutations in the *WAS* gene. Clinical findings may include thrombocytopenia with small platelets, recurrent otitis media, and |

| | |
|---|---|
| | eczema. The majority of patients are diagnosed in early childhood. The risk of lymphoreticular malignancies such as lymphoma is 13%. |

## Multisystem Disorders

| Gene | Clinical Features |
|---|---|
| ATM [OMIM# 607585] | Biallelic mutations in *ATM* are associated with ataxia telangiectasia (A-T), which is characterized by childhood onset progressive cerebellar ataxia, telangiectasias of the conjunctivae, immunodeficiency and increased risk of cancer [40]. The overall lifetime risk of cancer is 30-40%, with 40% of tumors being NHL, and approximately 5% being HL. Other associated cancers include leukemia, gastric cancer, breast cancer and medulloblastoma [40]. |
| NBN (NBS1) [OMIM# 602667] | Mutations in *NBN* are associated with the rare autosomal recessive disorder Nijmegen breakage syndrome (NBS). Features of NBS include microcephaly, dysmorphic facial features, immunodeficiency, chromosomal instability, and increased cancer susceptibility. In a series of 55 patients, 29% developed lymphoma, which was the most common cancer observed in the cohort [41]. Age of onset ranged from 1-22 years [41]. Biallelic mutations in *NBN* have also been associated with aplastic anemia [42]. |
| RECQL3 (BLM) [OMIM# 604610] | Mutations in *RECQL3* are associated with Bloom syndrome, an autosomal recessive disorder characterized by growth deficiency, immunodeficiency, sun-sensitive erythema and cancer susceptibility [43]. The lifetime risk of cancer for Bloom syndrome patients is 20% [44], including a 13% risk of NHL and a 1% risk of HL [1]. Other cancer risks include colorectal, breast, larynx and skin cancers [44]. |

## Other disorders

| Gene | Clinical Features |
|---|---|
| BRCA1 [OMIM#113705] | Germline mutations in *BRCA1* increase the risks of breast or ovary cancer and all other cancers including Hodgkin's and non-Hodgkin's lymphoma[45, 46] |
| BRCA2 [OMIM#600185] | Germline mutations in *BRCA2* increase the risks of breast or ovary cancer and all other cancers including Hodgkin's and non-Hodgkin's lymphoma[45, 46] |
| CARD11 [OMIM# 607210] | Recurrent somatic mutations in the *CARD11* gene have previously been identified in tumor samples from diffuse large B-cell lymphoma [47, 48]. A heterozygous germline missense mutation in *CARD11* has also been described in a family with hereditary polyclonal B cell lymphocytosis and splenomegaly [49]. B cell lymphocytosis is a condition that resembles chronic lymphocytic leukemia, and can be difficult to clinically distinguish from lymphoma. |
| KLHDC8B [OMIM# 613169] | Salipante *et al* (2009) identified a family with multiple individuals with HL, where disease segregated with a chromosomal translocation that disrupted the *KLHDC8B* gene [50]. In three other families with HL a variant in the 5' untranslated region of the *KLHDC8B* gene was found to segregate with the disease phenotype [50]. |
| PRF1 [OMIM# 170280] | Biallelic mutations in *PRF1* are associated with familial hemophagocytic lymphohistiocytosis-2 (FHL2), a life-threatening disorder caused by uncontrolled proliferation of CD25+ T-cells and activation of macrophages that phagocytose blood cells [51]. Symptoms can include fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, and hypofibrinogenemia [51]. Onset is typically in infancy, however late onset cases have also been described [52]. Clementi *et al* (2005) identified biallelic *PRF1* mutations in 4 out of 29 patients with HL or NHL who also had clinical features of hemophagocytic lymphohistiocytosis [53]. In addition, 4 patients had a heterozygous mutation in the *PRF1* gene. |
| STXBP2 [OMIM# 601717] | Biallelic *STXBP2* mutations have been described in patients with familial hemophagocytic lymphohistiocytosis-5 (FHL5), a genetic disorder of lymphocyte cytotoxicity that typically presents within the first two years of life [54]. Atypical cases with later onset in adulthood have also been described [54]. Associated complications of hemophagocytic lymphohistiocytosis (HLH) can include immunodeficiency, granulomatous lung or liver disease, encephalitis or lymphoma. Rohr *et al* described one individual with biallelic *STXBP2* mutations who presented with Hodkin lymphoma at age 6 years, 2 years prior to first onset of HLH [54]. |

## Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology

and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

## Hereditary Lymphoma and Immunodeficiency Panel (34 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $4000 |
| CPT codes: | 81406 and 81407 |
| Turn-around time: | 4-6 weeks |

***Note: We cannot bill insurance for this test.***

**Results:**

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Inherited Bone Marrow Sequencing Panel. All abnormal results are reported by telephone or email.

***For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.***

**References:**


1. Churpek, J.E. and K. Onel, *Heritability of hematologic malignancies: from pedigrees to genomics.* Hematol Oncol Clin North Am, 2010. **24**(5): p. 939-72.
2. Goldin, L.R., et al., *Familial aggregation of Hodgkin lymphoma and related tumors.* Cancer, 2004. **100**(9): p. 1902-8.
3. Kerzin-Storrar, L., et al., *Incidence of familial Hodgkin's disease.* Br J Cancer, 1983. **47**(5): p. 707-12.
4. van der Werff Ten Bosch, J. and M. van den Akker, *Genetic predisposition and hematopoietic malignancies in children: Primary immunodeficiency.* Eur J Med Genet, 2016. **59**(12): p. 647-653.
5. Guo, Y., et al., *Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1.* Blood, 2014. **124**(18): p. 2767-74.
6. Speedy, H.E., et al., *Germline mutations in shelterin complex genes are associated with familial chronic lymphocytic leukemia.* Blood, 2016.
7. Kocak, H., et al., *Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1.* Genes Dev, 2014. **28**(19): p. 2090-102.
8. Vahteristo, P., et al., *p53, CHK2, and CHK1 genes in Finnish families with Li-Fraumeni syndrome: further evidence of CHK2 in inherited cancer predisposition.* Cancer Res, 2001. **61**(15): p. 5718-22.
9. Ruijs, M.W., et al., *The contribution of CHEK2 to the TP53-negative Li-Fraumeni phenotype.* Hered Cancer Clin Pract, 2009. **7**(1): p. 4.
10. Wimmer, K. and J. Etzler, *Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg?* Hum Genet, 2008. **124**(2): p. 105-22.
11. Bakry, D., et al., *Genetic and clinical determinants of constitutional mismatch repair deficiency syndrome: report from the constitutional mismatch repair deficiency consortium.* Eur J Cancer, 2014. **50**(5): p. 987-96.
12. Yohay, K., *Neurofibromatosis type 1 and associated malignancies.* Curr Neurol Neurosci Rep, 2009. **9**(3): p. 247-53.
13. Stiller, C.A., J.M. Chessells, and M. Fitchett, *Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study.* Br J Cancer, 1994. **70**(5): p. 969-72.
14. Küppers, R., *NPAT mutations in Hodgkin lymphoma.* Blood, 2011. **118**(3): p. 484-5.
15. Wilson, T.L., et al., *A new POT1 germline mutation-expanding the spectrum of POT1-associated cancers.* Fam Cancer, 2017.
16. Takai, H., et al., *A POT1 mutation implicates defective telomere end fill-in and telomere truncations in Coats plus.* Genes Dev, 2016. **30**(7): p. 812-26.
17. Aoude, L.G., et al., *Nonsense mutations in the shelterin complex genes ACD and TERF2IP in familial melanoma.* J Natl Cancer Inst, 2015. **107**(2).
18. K, S., et al., *Li-Fraumeni Syndrome.*, 1999 Jan 19 [updated 2013 Apr 11], GeneReviews: University of Washington, Seattle.
19. Segel, G.B. and M.A. Lichtman, *Familial (inherited) leukemia, lymphoma, and myeloma: an overview.* Blood Cells Mol Dis, 2004. **32**(1): p. 246-61.
20. Mueller, B.U. and P.A. Pizzo, *Cancer in children with primary or secondary immunodeficiencies.* J Pediatr, 1995. **126**(1): p. 1-10.
21. Li, P., et al., *Updated Understanding of Autoimmune Lymphoproliferative Syndrome (ALPS).* Clin Rev Allergy Immunol, 2016. **50**(1): p. 55-63.
22. Alkhairy, O.K., et al., *Novel mutations in TNFRSF7/CD27: Clinical, immunologic, and genetic characterization of human CD27 deficiency.* J Allergy Clin Immunol, 2015. **136**(3): p. 703-712 e10.
23. Salzer, E., et al., *Combined immunodeficiency with life-threatening EBV-associated lymphoproliferative disorder in patients lacking functional CD27.* Haematologica, 2013. **98**(3): p. 473-8.
24. Kuehn, H.S., et al., *Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4.* Science, 2014. **345**(6204): p. 1623-7.
25. Zhang, Q., et al., *Combined immunodeficiency associated with DOCK8 mutations.* N Engl J Med, 2009. **361**(21): p. 2046-55.
26. Straus, S.E., et al., *The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis.* Blood, 2001. **98**(1): p. 194-200.
27. Stray-Pedersen, A., et al., *Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders.* J Allergy Clin Immunol, 2017. **139**(1): p. 232-245.
28. Huck, K., et al., *Girls homozygous for an IL-2-inducible T cell kinase mutation that leads to protein deficiency develop fatal EBV-associated lymphoproliferation.* J Clin Invest, 2009. **119**(5): p. 1350-8.
29. Linka, R.M., et al., *Loss-of-function mutations within the IL-2 inducible kinase ITK in patients with EBV-associated lymphoproliferative diseases.* Leukemia, 2012. **26**(5): p. 963-71.
30. Kuehn, H.S., et al., *Loss of B Cells in Patients with Heterozygous Mutations in IKAROS.* N Engl J Med, 2016. **374**(11): p. 1032-43.
31. Hoshino, A., et al., *Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations.* J Allergy Clin Immunol, 2016.
32. Li, F.Y., et al., *XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus.* Blood, 2014. **123**(14): p. 2148-52.
33. Dhalla, F., et al., *Identification of a novel mutation in MAGT1 and progressive multifocal leucoencephalopathy in a 58-year-old man with XMEN disease.* J Clin Immunol, 2015. **35**(2): p. 112-8.
34. Lucas, C.L., et al., *Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency.* Nat Immunol, 2014. **15**(1): p. 88-97.
35. Angulo, I., et al., *Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage.* Science, 2013. **342**(6160): p. 866-71.
36. Coffey, A.J., et al., *Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene.* Nat Genet, 1998. **20**(2): p. 129-35.
37. Palendira, U., et al., *Molecular pathogenesis of EBV susceptibility in XLP as revealed by analysis of female carriers with heterozygous expression of SAP.* PLoS Biol, 2011. **9**(11): p. e1001187.
38. Almejún, M.B., et al., *Immunological characteristics and two novel mutations in TACI in a cohort of 28 pediatric patients with common variable immunodeficiency.* J Clin Immunol, 2012. **32**(1): p. 89-97.

39. Mellemkjaer, L., et al., *Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study.* Clin Exp Immunol, 2002. **130**(3): p. 495-500.
40. Meyn, M.S., *Ataxia-telangiectasia, cancer and the pathobiology of the ATM gene.* Clin Genet, 1999. **55**(5): p. 289-304.
41. *Nijmegen breakage syndrome. The International Nijmegen Breakage Syndrome Study Group.* Arch Dis Child, 2000. **82**(5): p. 400-6.
42. Shimada, H., et al., *First case of aplastic anemia in a Japanese child with a homozygous missense mutation in the NBS1 gene (I171V) associated with genomic instability.* Hum Genet, 2004. **115**(5): p. 372-6.
43. Kaneko, H. and N. Kondo, *Clinical features of Bloom syndrome and function of the causative gene, BLM helicase.* Expert Rev Mol Diagn, 2004. **4**(3): p. 393-401.
44. Arora, H., et al., *Bloom syndrome.* Int J Dermatol, 2014. **53**(7): p. 798-802.
45. Friedenson, B., *BRCA1 and BRCA2 Pathways and the Risk of Cancers Other Than Breast or Ovarian.* MedGenMed, 2005. **7**(2): p. 60.
46. Yossepowitch, O., et al., *BRCA1 and BRCA2 Germline Mutations in Lymphoma Patients.* http://dx.doi.org/10.1080/1042819021000040332, 2009.
47. Zhang, J., et al., *Genetic heterogeneity of diffuse large B-cell lymphoma.* Proc Natl Acad Sci U S A, 2013. **110**(4): p. 1398-403.
48. Lohr, J.G., et al., *Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing.* Proc Natl Acad Sci U S A, 2012. **109**(10): p. 3879-84.
49. Snow, A.L., et al., *Congenital B cell lymphocytosis explained by novel germline CARD11 mutations.* J Exp Med, 2012. **209**(12): p. 2247-61.
50. Salipante, S.J., et al., *Mutations in a gene encoding a midbody kelch protein in familial and sporadic classical Hodgkin lymphoma lead to binucleated cells.* Proc Natl Acad Sci U S A, 2009. **106**(35): p. 14920-5.
51. George, M.R., *Hemophagocytic lymphohistiocytosis: review of etiologies and management.* J Blood Med, 2014. **5**: p. 69-86.
52. Nagafuji, K., et al., *Perforin gene mutations in adult-onset hemophagocytic lymphohistiocytosis.* Haematologica, 2007. **92**(7): p. 978-81.
53. Clementi, R., et al., *A proportion of patients with lymphoma may harbor mutations of the perforin gene.* Blood, 2005. **105**(11): p. 4424-8.
54. Rohr, J., et al., *Atypical familial hemophagocytic lymphohistiocytosis due to mutations in UNC13D and STXBP2 overlaps with primary immunodeficiency diseases.* Haematologica, 2010. **95**(12): p. 2080-7.


***Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS***