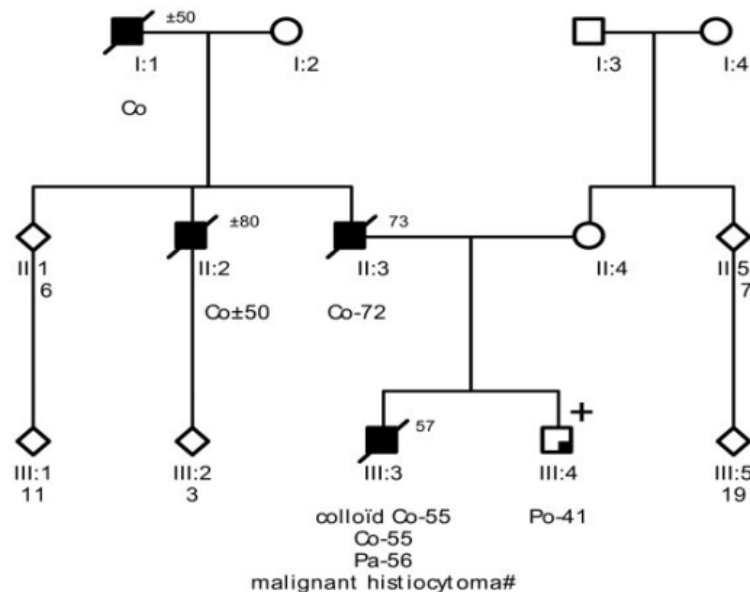
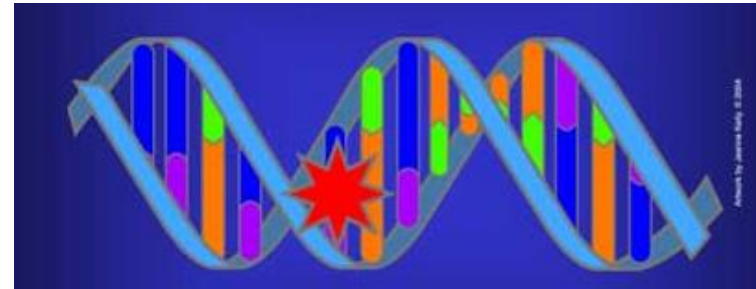


# Hereditary cancer

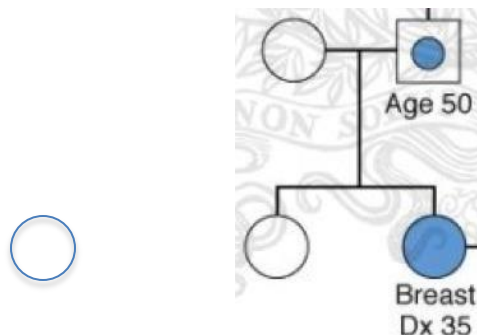
# Hereditary vs acquired changes

- Cancer is always a genetic disease
  - Somatic mutations acquired
- Cancer mutations are sometimes inherited
  - Germline

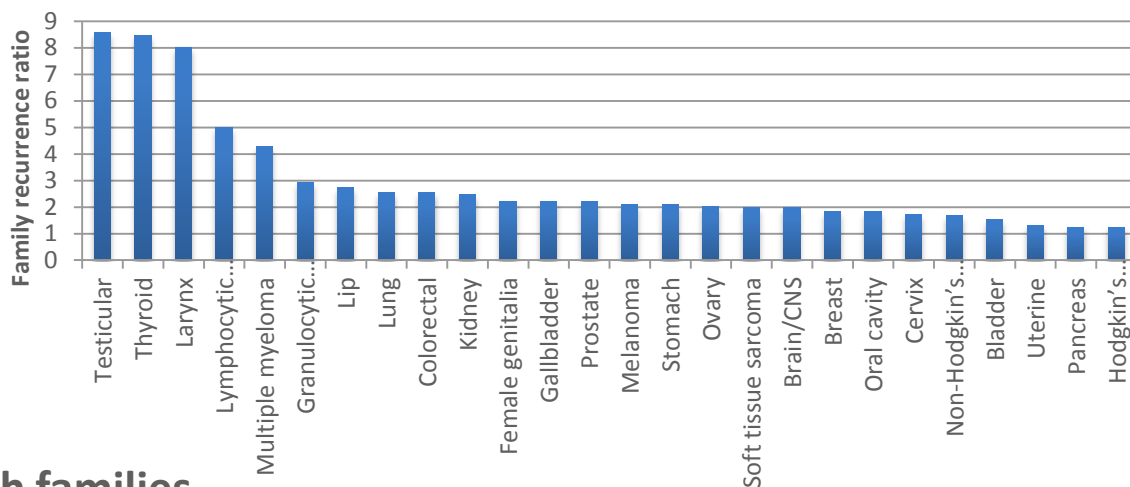


# Heritability of cancers

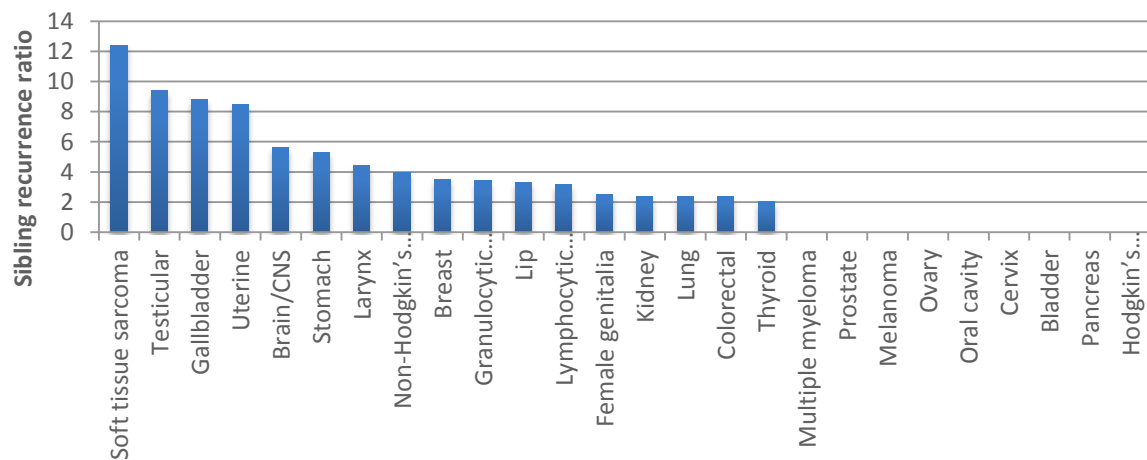
## Familial Recurrence Risk



## FRR (total) from Utah families



## FRR (sibling) from Swedish families

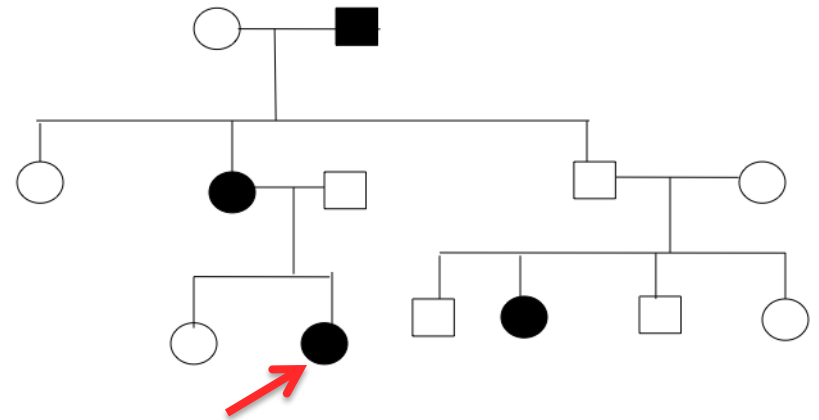


## Testicular cancer

Risk to sibling of affected individual is 8-9 times higher than risk in the general population

# Minimum elements for adequate family history of cancer

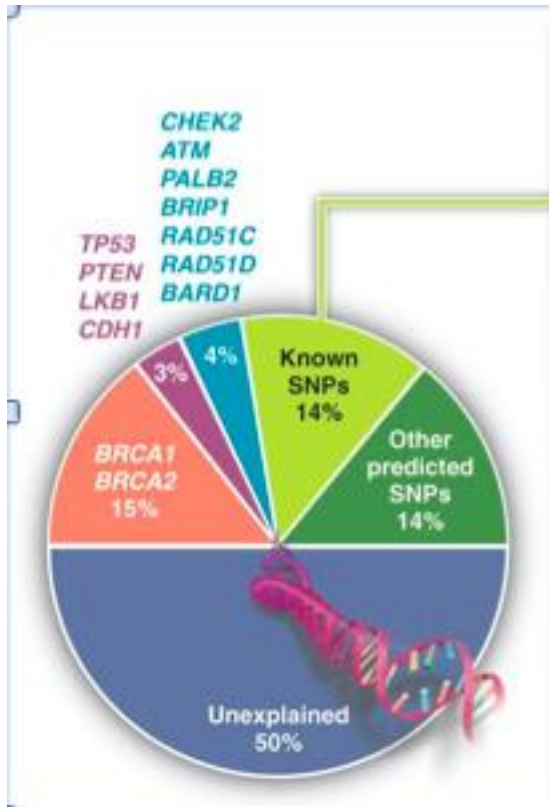
- Taken at diagnosis and updated regularly
- 1<sup>st</sup> and 2<sup>nd</sup> degree relatives
- Ask the following questions about each member of the family who has cancer:
  - Type of primary cancer
  - Age at diagnosis of primary
  - Lineage (maternal or paternal)
  - Ethnicity
  - Results of any genetic testing



# Features of hereditary cancers

- In the individual patient:
  - Multiple primary tumors in the same organ or different organs
  - Bilateral primary tumors in paired organs or multifocality within a single
  - Younger-than-usual age at tumor diagnosis
  - Tumors with rare histology
  - Tumors occurring in the sex not usually affected
- In the patient's family:
  - First-degree relatives with same tumor history

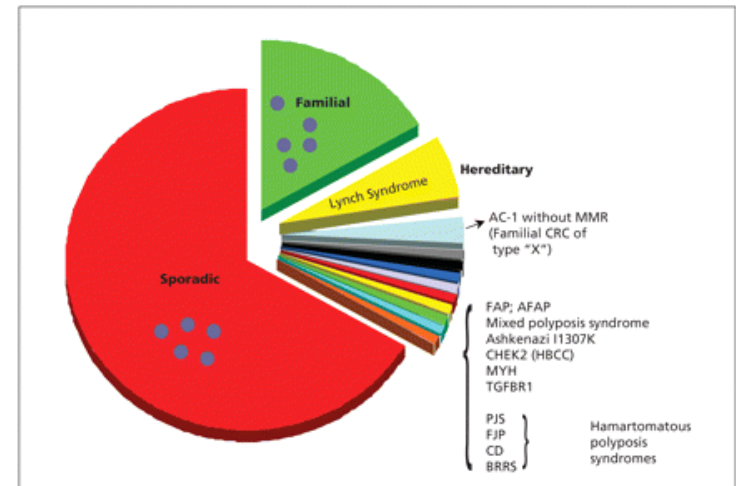
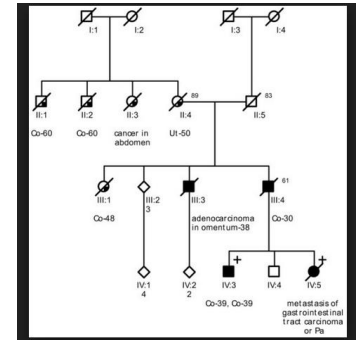
# Genetic basis of hereditary breast cancer



- First degree family history increases risk 2-fold
- Only 5-10% of breast cancer is hereditary
- Inheritance is complex at the disease level, but some individual genes behave in Mendelian fashion
- BRCA1/2 – Hereditary Breast and Ovarian Cancer

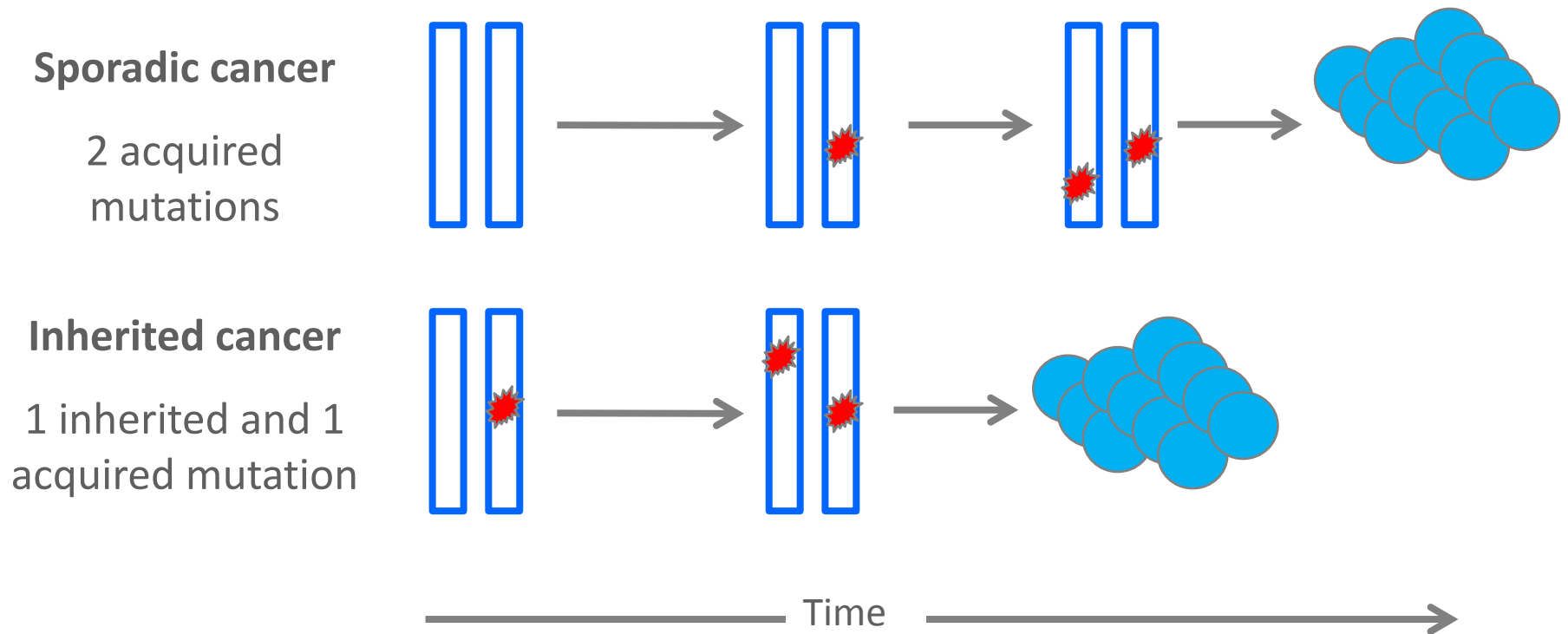
# Genetic basis of hereditary colon cancer

- Family history increases risk 2-4 fold
- Familial adenomatous polyposis (FAP)
  - Mutations in APC gene
- HNPCC – Lynch Syndrome
  - Mutations in DNA repair enzyme genes MLH1, MSH2, MSH6, PMS1, or PMS2
  - accounts for 2%–5% of the total burden of colorectal cancer



# Knudson's 2 Hit hypothesis for tumor suppressor genes

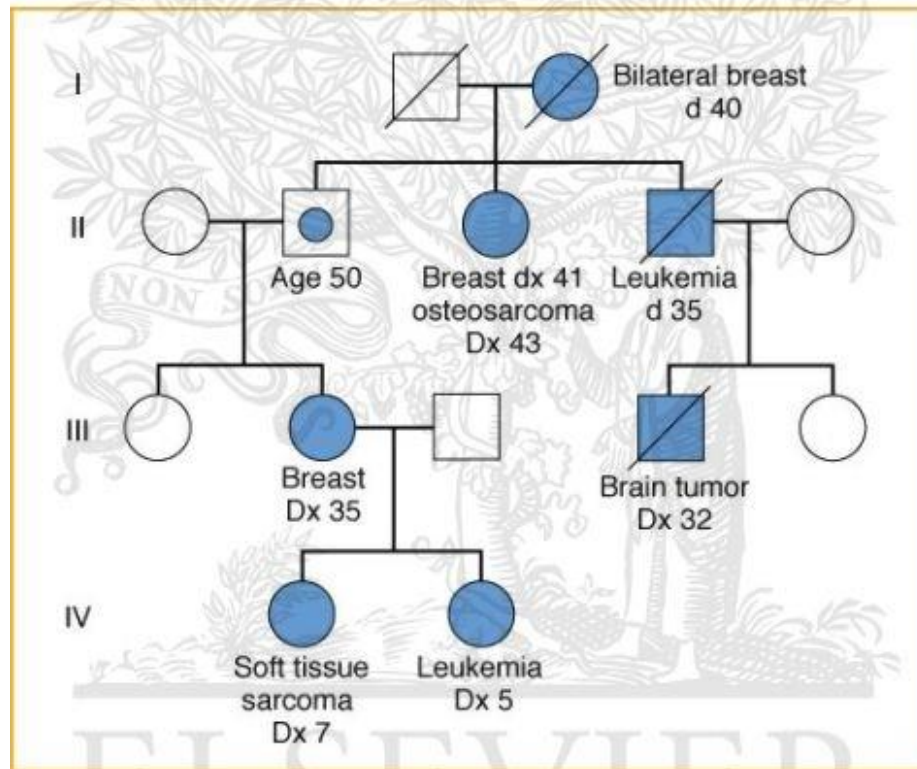
- Tumor suppressors are recessive at cellular level
- Inherited cancers behave as dominant trait



# Familial cancer syndromes

| Cancer                                                                   | Syndrome                                                 | Associated Gene               |
|--------------------------------------------------------------------------|----------------------------------------------------------|-------------------------------|
| Leukemias and lymphomas                                                  | Ataxia telangiectasia                                    | <i>ATM</i>                    |
| All cancers                                                              | Bloom syndrome                                           | <i>BLM</i>                    |
| Breast, ovarian, pancreatic, and prostate cancers                        | Breast-ovarian cancer syndrome                           | <i>BRCA1, BRCA2</i>           |
| Breast, thyroid and endometrial cancers                                  | Cowden syndrome                                          | <i>PTEN</i>                   |
| Colorectal cancer                                                        | Familial adenomatous polyposis (FAP)                     | <i>APC</i>                    |
| Melanoma                                                                 | Familial atypical multiple mole–melanoma syndrome (FAMM) | <i>CDKN2A</i>                 |
| Retinal cancer                                                           | Familial retinoblastoma                                  | <i>RB1</i>                    |
| Leukemia                                                                 | Fanconi's anemia                                         | <i>FACC, FACA</i>             |
| Colorectal cancer                                                        | Hereditary nonpolyposis colorectal cancer/Lynch syndrome | <i>MLH1, MSH2, MSH6, PMS2</i> |
| Pancreatic cancer                                                        | Hereditary pancreatitis/familial pancreatitis            | <i>PRSS1, SPINK1</i>          |
| Leukemias, breast, brain and soft tissue cancers                         | Li-Fraumeni                                              | <i>TP53</i>                   |
| Pancreatic cancers, pituitary adenomas, benign skin and fat tumors       | Multiple endocrine neoplasia 1                           | <i>MEN1</i>                   |
| Thyroid cancer, pheochromocytoma                                         | Multiple endocrine neoplasia 2                           | <i>RET, NTRK1</i>             |
| Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers | Peutz–Jeghers syndrome                                   | <i>STK11/LKB1</i>             |
| Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys         | von Hippel-Lindau syndrome                               | <i>VHL</i>                    |
| Kidney cancer                                                            | Wilms' tumor                                             | <i>WT1</i>                    |
| Skin cancer                                                              | Xeroderma pigmentosum                                    | <i>XPD, XPB, XPA</i>          |

# Li Fraumeni pedigree



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# When to seek genetic counseling

**Table 2.** Cancers for Which Genetic Counseling and Testing Should Be Considered, Even in Absence of Family History\*

| Tumor Diagnosis                                                                                                                                                                                                                                                                               | Genetic Loci                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <b>Common adult cancers</b>                                                                                                                                                                                                                                                                   |                                                                            |
| Triple-negative (ER/PR/HER2-neu negative) breast cancer, particularly if diagnosed at age < 60 years <sup>20</sup>                                                                                                                                                                            | <i>BRCA1/BRCA2</i>                                                         |
| Epithelial ovarian, fallopian tube, or primary peritoneal cancer (most commonly, high-grade serous histology) <sup>21</sup>                                                                                                                                                                   | <i>BRCA1/BRCA2</i>                                                         |
| Colorectal cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of <i>MLH1</i> promoter and somatic <i>BRAF</i> mutation) <sup>22,23</sup> | <i>MLH1/MSH2/MSH6/PMS2/EPCAM</i>                                           |
| Endometrial cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of <i>MLH1</i> promoter <sup>24</sup>                                     | <i>MLH1/MSH2/MSH6/PMS2</i>                                                 |
| <b>Rare tumors</b>                                                                                                                                                                                                                                                                            |                                                                            |
| Adrenocortical carcinoma, <sup>25</sup> choroid plexus carcinoma <sup>26</sup>                                                                                                                                                                                                                | <i>TP53</i>                                                                |
| Pheochromocytoma, paraganglioma <sup>27</sup>                                                                                                                                                                                                                                                 | <i>VHL, RET, multiple SDH loci</i>                                         |
| Retinal or cerebellar hemangioblastoma, endolymphatic sac tumor <sup>28</sup>                                                                                                                                                                                                                 | <i>VHL</i>                                                                 |
| Medullary thyroid cancer <sup>29</sup>                                                                                                                                                                                                                                                        | <i>RET</i>                                                                 |
| <b>Pediatric cancers</b>                                                                                                                                                                                                                                                                      |                                                                            |
| Retinoblastoma <sup>28,30</sup>                                                                                                                                                                                                                                                               | <i>RB1</i>                                                                 |
| Optic pathway tumor, malignant peripheral nerve sheath tumor, juvenile myelomonocytic leukemia <sup>28</sup>                                                                                                                                                                                  | <i>NF1</i>                                                                 |
| Atypical teratoid/rhabdoid tumor <sup>28</sup>                                                                                                                                                                                                                                                | <i>INI1/SMARCB1</i>                                                        |
| Acoustic or vestibular schwannomas <sup>28</sup>                                                                                                                                                                                                                                              | <i>NF2</i>                                                                 |
| Pulmonary pleuroblastoma <sup>31</sup>                                                                                                                                                                                                                                                        | <i>DICER1</i>                                                              |
| Multiple gastrointestinal polyps <sup>32</sup>                                                                                                                                                                                                                                                | <i>BMPR1A, SMAD4, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, APC, STK11, MYH</i> |

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

\*The cancer types included here are examples of those more commonly encountered by the oncology provider. This list is not intended to be exhaustive and should not be interpreted as guidance to limit the consideration of additional counseling or testing to only those identified. Furthermore, as an increasing number of genes become discovered, this list is likely to change with time.

# Should my patient undergo genetic testing?

**Table 3.** Risk Assessment Tools to Guide Referral for Comprehensive Genetic Evaluation

| Disease                                          | Gene                    | Models/Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lynch syndrome <sup>33,34</sup>                  | <i>MLH1, MSH2, MSH6</i> | PREMM model:<br><a href="http://premm.dfci.harvard.edu">http://premm.dfci.harvard.edu</a><br>MMRPRO model:<br><a href="http://bcb.dfci.harvard.edu/bayesmendel/mmrproqa.html">http://bcb.dfci.harvard.edu/bayesmendel/mmrproqa.html</a>                                                                                                                                                                                                                                                                                                                                                                                                |
| Breast and ovarian cancer syndrome <sup>35</sup> | <i>BRCA1, BRCA2</i>     | BRCAPRO model:<br><a href="http://bcb.dfci.harvard.edu/bayesmendel/brcapro.php">http://bcb.dfci.harvard.edu/bayesmendel/brcapro.php</a><br>PENN2 model:<br><a href="http://www.afcri.upenn.edu/itacc/penn2">http://www.afcri.upenn.edu/itacc/penn2</a><br>MYRIAD risk calculator and prevalence tables:<br><a href="http://www.myriadtests.com/provider/brca-mutation-prevalence.htm">http://www.myriadtests.com/provider/brca-mutation-prevalence.htm</a><br>BOADICEA Cambridge University Web site:<br><a href="http://ccge.medschl.cam.ac.uk/boadicea/web-application/">http://ccge.medschl.cam.ac.uk/boadicea/web-application/</a> |
| Melanoma <sup>36</sup>                           | <i>CDKN2A</i> (p16)     | MELAPRO model:<br><a href="http://bcb.dfci.harvard.edu/bayesmendel/melapro.php">http://bcb.dfci.harvard.edu/bayesmendel/melapro.php</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Pancreatic cancer <sup>37</sup>                  |                         | PANCPRO model:<br><a href="http://bcb.dfci.harvard.edu/bayesmendel/pancpro.php">http://bcb.dfci.harvard.edu/bayesmendel/pancpro.php</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Li-Fraumeni syndrome <sup>38</sup>               | <i>TP53</i>             | CHOMPRET criteria:<br><a href="http://jco.ascopubs.org/content/27/26/e108.full.pdf">http://jco.ascopubs.org/content/27/26/e108.full.pdf</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Cowden syndrome <sup>39</sup>                    | <i>PTEN</i>             | PTEN risk model:<br><a href="http://www.lerner.ccf.org/gmi/ccscore/">http://www.lerner.ccf.org/gmi/ccscore/</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

# Resources for locating cancer genetics specialists

**Table A1.** Resources for Locating Cancer Genetics Specialists

| Resource                                                    | Web Site                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| National Society of Genetic Counselors                      | <a href="http://www.nsgc.org/tabid/68/Default.aspx">http://www.nsgc.org/tabid/68/Default.aspx</a>                                                                                                                                                               |
| National Cancer Institute Cancer Genetic Services Directory | <a href="http://www.cancer.gov/cancertopics/genetics/directory">http://www.cancer.gov/cancertopics/genetics/directory</a>                                                                                                                                       |
| American College of Medical Genetics Provider Directory     | <a href="http://www.acmg.net/GIS/Disclaimer.aspx">http://www.acmg.net/GIS/Disclaimer.aspx</a>                                                                                                                                                                   |
| American Board of Medical Genetics                          | <a href="http://www.abmg.org/pages/searchmem.shtml">http://www.abmg.org/pages/searchmem.shtml</a>                                                                                                                                                               |
| American Board of Genetic Counselors                        | <a href="https://abgcmember.goamp.com/Net/ABGCWcm/Find_Counselor/ABGCWcm/PublicDir.aspx?hkey=0ad511c0-d9e9-4714-bd4b-0d73a59ee175">https://abgcmember.goamp.com/Net/ABGCWcm/Find_Counselor/ABGCWcm/PublicDir.aspx?hkey=0ad511c0-d9e9-4714-bd4b-0d73a59ee175</a> |

# Genetic testing for known cancer susceptibility genes

- A negative test result is no guarantee that cancer WILL NOT develop
- A positive test result is no guarantee that cancer WILL develop
- Risk management strategies for a positive test (e.g. BRCA1 – breast cancer)
  - Surveillance
  - Hormone therapy
  - Lifestyle changes
  - Prophylactic surgery

# Question

- Cancer is primarily due to which type of mutations, somatic or germline?

# Answer

- Cancer is always a somatic disease; only 5-10% of cancers are inherited.