Case 1: *BRCA1* and *BRCA2* mutation-related ovarian cancer

Janet is 58 years old and has a recent history of abdominal pain and bloating. Her primary care physician obtained a CT scan of her abdomen and pelvis. The scan showed a pelvic mass, thickening of the omentum (a fatty apron that hangs from the colon), and fluid accumulation (ascites). Janet was referred to a gynecologic oncologist due to the concern for a gynecologic malignancy. Her gynecologic oncologist performed surgery to remove the uterus, fallopian tubes, ovaries, and the visible tumor on other surfaces and to stage her cancer. The final pathology report diagnosed stage III high-grade serous ovarian cancer.

After recovering from her surgery, Janet started the adjuvant chemotherapy that her oncologist recommended. She was surprised that her oncologist also recommended that she undergo genetic risk evaluation and testing. She did not think she was at risk for an inherited susceptibility to cancer since she has no family history of breast, colon, or ovarian cancer. She has concerns about the cost of genetic testing and the impact that it might have on her insurance status. Her 30-year-old daughter, Susan, has been having a hard time accepting Janet's cancer diagnosis. Janet worries that a result showing an inherited mutation might be too overwhelming for Susan.

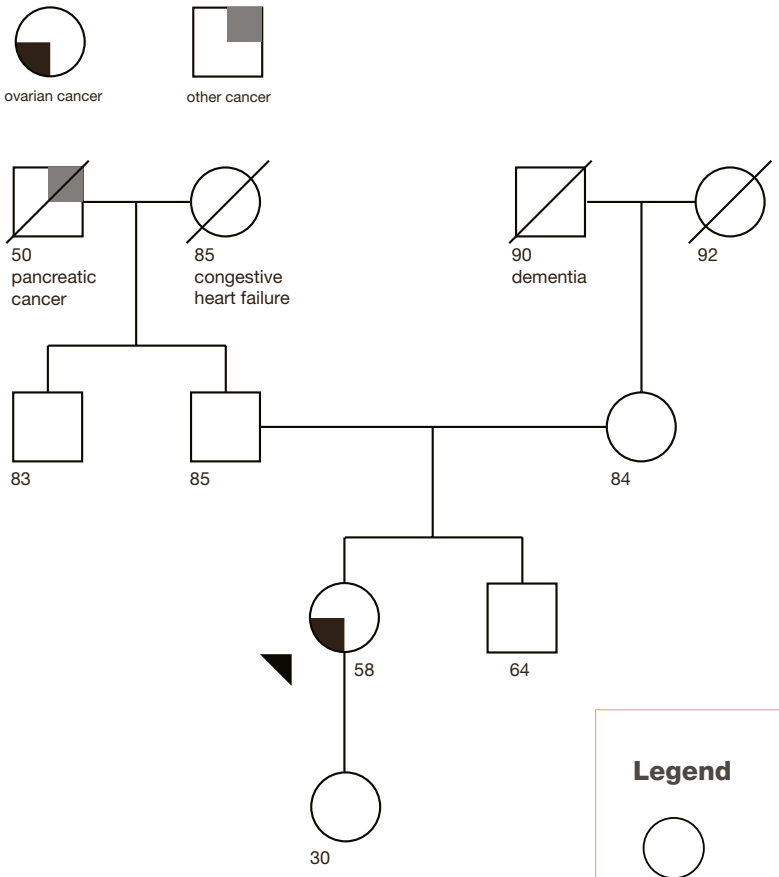
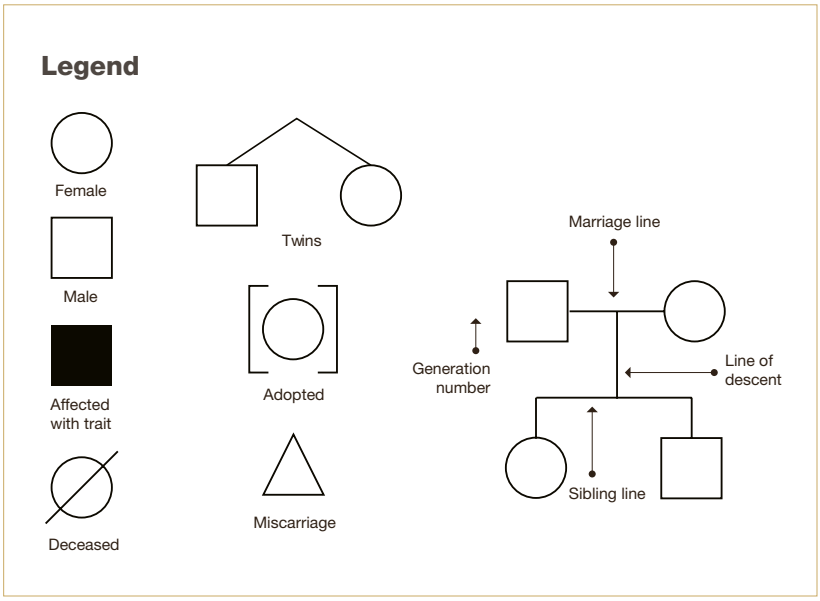


Fig. 1.
Janet's pedigree, or family history tree. Often inherited patterns will show multiple family members with cancer, cancer at young ages and cancer in several generations but one-third (about 30%) of women who have ovarian cancer and an inherited genetic risk do not have a strong family history.



Why is Janet's oncologist recommending genetic risk evaluation and testing for her?

About 20% of women with ovarian, fallopian tube, or primary peritoneal cancer carry an inherited mutation in *BRCA1, BRCA2, MSH2, MLH1, MSH6, PMS2, EPCAM, BRIP1, RAD51C, RAD51D, PALB2*, and/or *BARD1*. Increased hereditary risk is associated with young age at diagnosis, family history of breast and/or ovarian cancer, and some ethnicities such as Ashkenazi Jewish ancestry. However, most experts feel these factors do not need to be present to recommend testing, since at least one-third of women with hereditary ovarian cancer have none of these risk factors. All histologic types of invasive (not borderline) epithelial ovarian cancers should prompt consideration of referral for genetic risk evaluation and testing. Mucinous ovarian cancer represents a potential exception since it has not been shown to be part of hereditary breast and ovarian cancer (HBOC) syndrome and is rarely seen in Lynch syndrome. Genes that are part of HBOC syndrome increase the risk of breast cancer, ovarian cancer, and other cancers. The genes involved in Lynch syndrome increase the risk of colon, endometrial, ovarian, and other cancers.

What types of genetic tests are available to Janet?

Traditionally, genetic testing has been performed for 1 to 2 genes at a time, starting with the gene(s) considered most likely to be involved based on the patient's personal and family history. The testing looks for germline changes (mutations) in genes, meaning that the changes are in every cell and can be passed on to children. This process can be expensive and time-consuming if multiple genes are tested. More recently, multi-gene panel tests have been developed that include anywhere from a handful to several dozen cancer predisposition genes. These panels have the advantage of testing for many potential gene mutations simultaneously at a lower cost than traditional testing. Because so many genes in a panel are being investigated, however, there is also a higher likelihood of diagnosing a variant of uncertain significance (VUS), which is a genetic change without any clear association with a health problem. Changes in a gene that are known to be associated with a health problem like cancer are called deleterious mutations or pathogenic variants. According to the National Comprehensive Cancer Network (NCCN) 2019 guidelines, all women with epithelial ovarian, fallopian tube, and primary peritoneal cancer should be offered genetic risk evaluation and testing. The Society of Gynecologic Oncology (SGO) has endorsed that recommendation. NCCN guidelines include the statement that "when more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective." Many experts would consider HBOC an example of an inherited syndrome where multiple genes can explain the disease pattern seen.

Clinical recommendations like enhanced cancer screening or risk-reducing surgery are reserved for those individuals who have a deleterious mutation or who have a strong family cancer history. Because most VUS are ultimately found not to be associated with health problems, medical decisions should not be based on the presence of a VUS. The decision to pursue gene-by-gene testing versus panel testing is a complex one that benefits from discussion with a genetics professional. In addition to germline testing, patients may benefit from having the tumor itself tested for mutations. Mutations that occur in the tumor are called somatic mutations and cannot be passed through the family (unlike germline mutations). Knowledge of either germline or somatic mutations may help direct treatment.

How might the genetic test results affect Janet's treatment? Would they affect her eligibility for clinical trials?

Janet's treatment might be affected in several ways if genetic testing shows a gene mutation. Survival from ovarian cancer is higher for women who have a *BRCA1* or *BRCA2* mutation compared with those who do not have a mutation, at least partially due to the fact that *BRCA1* and *BRCA2* mutation-related ovarian cancer may be more sensitive to platinum chemotherapy. If her ovarian cancer goes into remission, the presence of a *BRCA1* or *BRCA2* mutation might influence her decision to receive enhanced breast cancer screening. She might choose to take a PARP inhibitor as part of maintenance therapy or treatment if her ovarian cancer recurs. This new class of drugs called PARP inhibitors is particularly effective in women with *BRCA1* and *BRCA2* mutations. Currently, 3 PARP inhibitor drugs are FDA-approved in the United States for use in women with ovarian cancer in specific clinical situations. This is an active area of research with ongoing clinical trials and frequent updates to the indications for PARP inhibitors, so consultation with an oncologist who is an expert in their use is recommended for ovarian cancer patients.

References

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