Case 1: *BRCA1*- and *BRCA2*-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 (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, and ovaries, as well as to remove the visible tumor on other surfaces and staging 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 counseling 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.

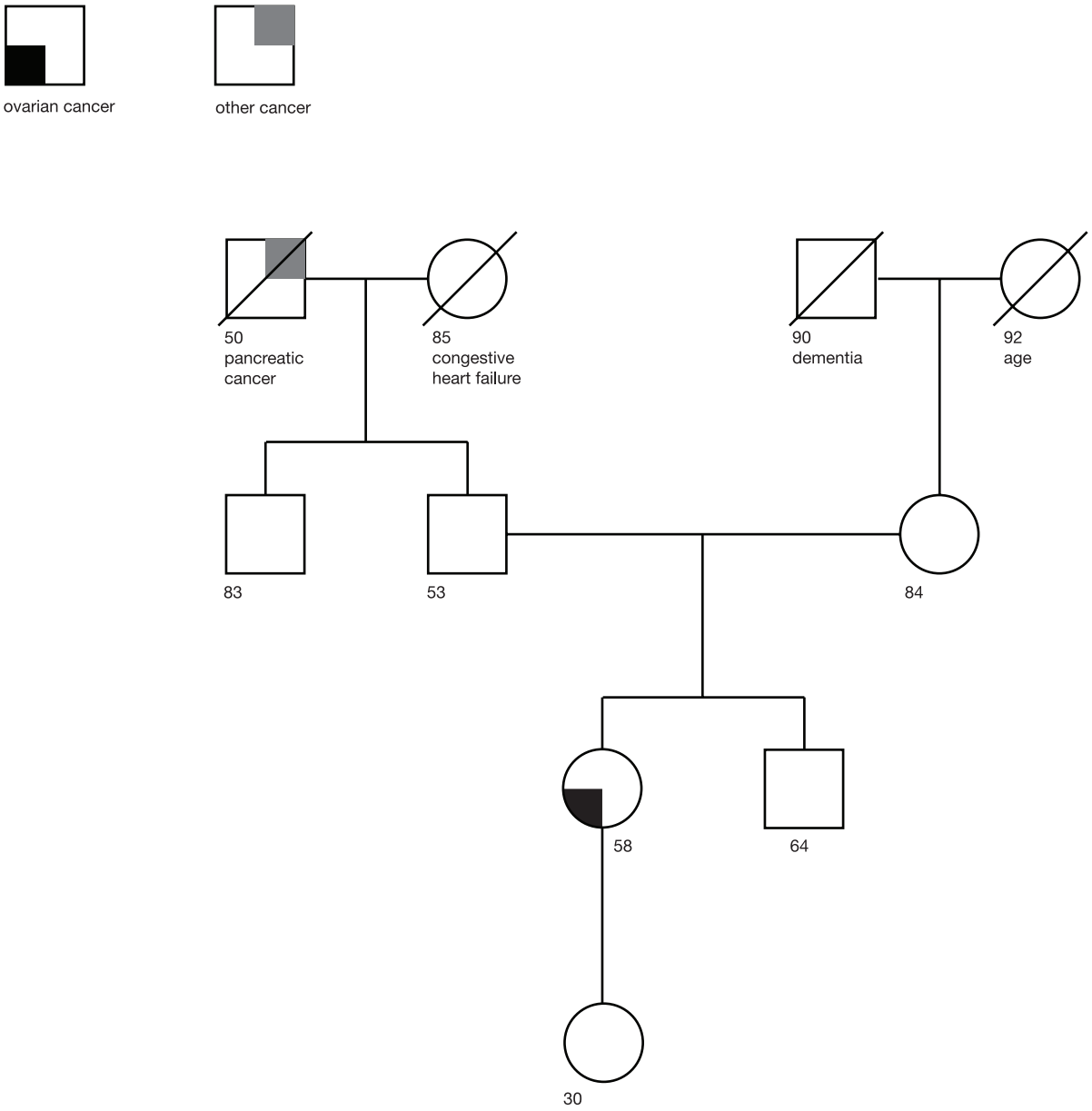

Fig. 1.

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.

Questions

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

All women with epithelial ovarian, fallopian tube, and primary peritoneal cancer have been recommended to undergo genetic counseling and testing since the National Comprehensive Cancer Network (NCCN) issued its 2011 guidelines. The Society of Gynecologic Oncology (SGO) has endorsed that recommendation. It is based on data that about 20 percent of women with these cancers 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. These factors do not need to be present in order to make testing reasonable 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 for referral to genetic counseling and testing. Mucinous ovarian cancer represents a rare exception since it has not been routinely shown to be part of hereditary breast and ovarian cancer or Lynch syndromes. Genes that increase the risk of breast cancer as well as ovarian cancer are part of hereditary breast and ovarian cancer (HBOC) syndrome. Those genes that increase the risk of colon, endometrial and ovarian cancer are associated with Lynch syndrome.

What types of genetic tests are available to Janet?

Traditionally, genetic testing has been performed one or two 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 they are in every cell and can be passed on to children. This process can be expensive and time-consuming if multiple genes could be involved. 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 to 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.

Clinical recommendations like enhanced cancer screening or risk-reducing surgery are reserved for those individuals who are found to 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 and 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 also 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 she is found to have a gene mutation. If she was found to have a *BRCA1* or *BRCA2* mutation, for example, and her ovarian cancer goes into remission, she might choose to receive enhanced breast cancer screening. Survival from ovarian cancer is improved in women who have a *BRCA1* or *BRCA2* mutation compared with those who do not have a mutation, and *BRCA1*- and *BRCA2*-related ovarian cancer may be more sensitive to platinum chemotherapy. This may affect treatment options for her. If her ovarian cancer recurs, she might be eligible for treatment with a class of drugs called PARP inhibitors that are particularly effective in women with *BRCA1* and *BRCA2* mutations. Currently, the PARP inhibitor, olaparib, is FDA-approved in the United States for women with recurrence of ovarian cancer after three previous lines of therapy if they carry a germline *BRCA1* or *BRCA2* mutation. However, clinical trials with PARP inhibitors might be available for women in other clinical settings, such as mutations in genes other than *BRCA1*and *BRCA2*, fewer prior treatment regimens, or somatic mutations in their tumor rather than in the germline.

References

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