Genetics Webinar Follow-up Questions

1. Low-grade serous carcinoma --what are the chances of it being hereditary. I have stage III ovarian cancer; I`m 36. My Dad`s mother had it at age 27. My oncologist told me this cancer is rarely hereditary. But is it really a coincidence?

Your physician is correct, low-grade serous ovarian carcinoma is rarely hereditary; however rare is not never. This may be an instance where you might consider having testing done. It will likely be negative, but may be a good idea to rule out the issue. You can find inexpensive genetic testing at JScreen.org, or you can check with me at genetics@sharsheret.org.

2. Any suggestions for proactively caring for my young children and BRCA genetics?

You should think about training your children in visiting their doctor for regular checkups, healthy eating, and exercise. You can share information about genetic risk with them in a developmentally appropriate way. We have information about speaking to your children about genetics on our website https://sharsheret.org/product/how-do-i-tell-my-children-about-my-cancer-gene/.

3. (1) Are there other gene mutations besides *BRCA1* and *BRCA2* that could lead to breast cancer? (2) Can breast cancer occur without mutations on the *BRCA1* and *BRCA2* genes?

How many other gene mutations besides those found in *BRCA1* and *BRCA2* could contribute to breast cancer or other cancers? How much can we rely on genetic DNA testing for breast cancer?

There are other gene mutations that predispose to breast cancer, including but not limited to *ATM, CHEK2, PALB2, PTEN, & TP53*. There are also genetic changes that we don't yet know how to find that may predispose to breast cancer. Most breast cancer is unrelated to *BRCA1* and *BRCA2*, and most women who get breast cancer have no family history. Genetic testing is a reliable way to find out about inherited breast cancer. If a mutation is identified, you can rely on the result.

4. I was told I had familial pancreatic cancer, even though I had ovarian cancer. Please explain the implications for me and my children.

If there is pancreatic cancer and ovarian cancer in the same family, there might be a genetic change that is causing this. Even when no hereditary cause is identified, we might think the cancer is inherited just based on family history. You should follow up with a genetics specialist to help determine the best approach to familial cancer.

5. Dana-Farber is the only place that offers Lynch Syndrome coordination for patient screenings. Does Sharsheret know of anyone else who can support patients with screenings and yearly management?

There are not many centers that provide this type of care, it can be complicated to get all of the biggest experts available at one location. Those with Lynch syndrome need to use several different specialists for all of the care they need. You can try asking a genetic counselor or physician in your area to see if they know of programs nearby. Find a genetic counselor at www.nsgc.org, scroll down the page until the orange find a counselor arrow appears.

6. I tested positive for *CHEK2*, and I am post breast cancer by three years. The geneticist at the time said she did not advise that my 2 adult daughters get tested because they may be prohibited from two types of insurance, one being life insurance. What is your feeling about this response? Both daughters will begin getting yearly mammograms at age 35.

There are three types of insurance that can be impacted by genetic testing: life insurance, disability insurance, and long term care insurance. Individuals may want to get their insurance lined up before they have genetic testing. However, be careful that fear of insurance discrimination doesn't prevent you or your daughter from getting the care that you all need.

7. Latest updates and findings for Parp Inhibitors like Lynparza.

PARP inhibitors are a targeted treatment that can benefit women with cancer. They may be used as a targeted treatment for those whose cancer has deficits in DNA repair, specifically HRD, or homologous repair deficiency.

8. What are the updated tests that weren't in the BRCA panel 15-20 years ago?

There are dozens more genes available for testing; these are genes that may predispose to cancers like breast, ovarian, prostate, pancreatic, melanoma, uterine, and colon. Many updated tests include other genes that can cause more rare cancers. Panels range in size from less than 10 genes to almost 100. In the larger panels, some of the genes tested may have limited evidence that they cause cancer. For a few other genes, there may not be any proven method of risk reduction for those who are carriers.

9. I`d like to understand how to explain my sons` risk if they inherited *BRCA1*. Also, I`d like information regarding problems they might encounter having a genetic mutation in their medical record.

The risk for men to develop cancer is relatively small with *BRCA1*. There is an increased risk for male breast, prostate, and pancreatic cancer. There are three types of insurance that can be impacted by genetic testing: life insurance, disability insurance, and long term care insurance. Individuals may want to get their insurance lined up before they have genetic testing. It is important that your sons know about their risk even if they are planning to wait to be tested.

10. Looking for any mutations I may have that may be drug targeted.

In general, it is testing of the tumor itself which points out mutations that may be targeted by a specific drug or treatment. You can ask your doctor if you would benefit from biomarker testing of your tumor.

11. My daughter had a positive genetic test. At what age should she have double mastectomy? My daughter is 35; I (her mother) had breast cancer at 28 and 30; both breasts removed. At 69 I was diagnosed with fallopian tube cancer; and am currently in remission. My daughter has one child and wants a second child.

There is no recommended age to have a risk reducing bilateral mastectomy. Some women may choose to continue to have a regular mammogram alternating with an MRI instead. Your daughter may be able to have another child, but she needs to discuss the various options with her physician.

12. Is IVF with PGD becoming more common among young people who find out that they carry abnormal genes?

Base on the many questions Sharsheret receives about this topic, it appears that this option is being considered by more of our callers. IVF (In vitro fertilization) with PG-T (preimplantation genetic testing) involves harvesting eggs and sperm in order to create embryos in the lab. Those embryos may be biopsied and tested for mutations. Parents may then choose to implant only embryos that don't carry the BRCA mutation to avoid passing the mutation to the next generation.

13. How are BRCA 2 mutation carriers screened for pancreatic cancer?

Screening for pancreatic cancer is a complex decision, and is often pursued after age 50 for those with a family history of pancreatic cancer. The screening might involve an endoscopic ultrasound and an MRI of the pancreas called an MRCP. These tests are best done under the auspices of a study, since the benefit to the patients is not yet well proven.

14. I tested BRCA positive in 2014, and am a survivor of a rare type of ovarian cancer. When should test be repeated? If repeated, what will I gain?

Those whose results are positive don't usually need to have an upgraded test except in special circumstances. Please check with your healthcare provider or contact Sharsheret at genetics@sharsheret.org.

15. The genetic variant known as c.2559C>T (p.Gly853Gly) was detected in one of the patient`s *PALB2* genes. They said it was not fully determined yet to cause Hereditary Breast CA Syndrome. What is the recent research?

This sounds like it is a variant of uncertain significance. These common findings mean that something is a little different from the usual in your DNA, and scientists are not sure if it is important or not. Research continues to find out the implications of these types of findings, and your ordering physician should be in touch with you if the classification of your variant is changed. If you have further questions about variants of uncertain significance, you can check with Sharsheret at genetics@sharsheret.org.

16. My husband has prostate cancer and the CHEK2 variant that is less serious than some. Concern is for him and my 2 adult daughters who need to get tested.

Please ask your healthcare provider or call Sharsheret to find out about the specifics of your CHEK2 or other variant.

17. How early should I get my daughter tested to see if she has the BRCA mutation? If positive, what are the next steps?

We don't recommend testing for those at risk to test positively for BRCA mutations until age 25, when something can be done differently to care for them. Those who plan to begin having children should also consider testing, even if they are under 25, since it is possible to use IVF and embryo screening to avoid passing the mutation to the next generation.

18. Can you please explain what an ATM mutation means for prevention?

Those with an ATM mutation should consider having an annual breast MRI beginning at age 40, or 10 years younger than the earliest age of diagnosis of breast cancer in the family, whichever is earlier. They may also consider pancreatic cancer screening, probably after age 50.

19. Is the BRCA 2 gene an aggressive mutation? I am scared of recurrence after ovarian cancer! My oncologist does not recommend double mastectomy.

I think a mutation in BRCA2 is a serious, maybe not an aggressive mutation. Most physicians recommend waiting some time after ovarian cancer treatment to consider a double mastectomy, and some might not recommend it at all. These decisions are made differently by individuals in consultation with their healthcare providers.

20. I have the CHEK2 gene, and have several family members on my father's side who have had breast cancer. Besides the usual checkups and keeping a healthy diet, what else can I do to reduce my risk?

You might consider having an annual breast MRI if you are not already doing that. Be sure to get plenty of exercise, and avoid regular alcohol consumption.

21. Future studies- how to participate. Percentage chance of future secondary, non-related cancers in the first 10 years after diagnosis of breast.

A great study to participate in for those with an inherited mutation is the PROMPT study, https://clinicaltrials.gov/ct2/show/NCT02665195
If you are looking for other studies in which to participate, please check FORCE, https://www.facingourrisk.org/research-clinical-trials

22. Please discuss Primary Peritoneal cancer. My mom had a complete hysterectomy and 9 years later was diagnosed with this type of cancer, which is treated like ovarian cancer.

Rarely, women who have had a total hysterectomy, and are *BRCA1* or *BRCA2* positive, develop a cancer called primary peritoneal. It develops from the cells that line the pelvic cavity and behaves like ovarian cancer. It is not known why this happens.

23. HRD what is it? HRD positive what is?

HRD stands for homologous repair deficiency, and it means the tumor cells are having trouble repairing DNA mistakes. It is found on a specialized test done on tumor cells. When it is present, the patient may benefit from taking a targeted medicine called a PARP inhibitor.

24. My mother tested negative for the BRCA gene but was diagnosed with bilateral breast cancer and an aggressive uterine cancer. She had surgery for both and they caught it early enough so prognosis is good and she will need radiation only no chemotherapy as of now. Should her children get tested for the gene etc? Or is it not necessary?

It depends. If she was tested only for BRCA1 and BRCA2, she might need an updated test. Also, children may inherit mutations from both parents. If one parent's result is negative, the children are not in the clear for a possible hereditary cancer gene mutation.

25. Would the speaker be able to address how drinking alcohol, or specifically wine, could or could not increase your risk for cancers?

Alcohol is thought to increase the risk for many cancers, including breast cancer. It doesn't matter if it is wine, beer or liquor. There is no known safe amount, so those concerned should limit their alcohol consumption.

26. I am positive for the *ATM* variant and my physician who ordered this test a while back didn't know what if anything that signified. Are there next steps I should be taking?

It depends on whether you have a true mutation in ATM or an uncertain variant. You need to check with a genetics expert to review your result to help determine next steps. Please feel free to be in touch with Sharsheret, genetics@sharsheret.org

27. How important is it to test for every different breast cancer variance if BRCA is not found?

For many people it will not make any difference, since typically nothing is identified. However, for those who do find something, it can make a big difference! Please remember the story from our caller Marcy!

28. Do you recommend that all adults be screened for the 70+ dominant cancers? How about the recessive genes?

Most hereditary cancer genes are inherited dominantly; only one mutation is necessary to be at high risk for cancer. There are however, a few that are inherited recessively, where one needs to have 2 mutations to have the high risk for cancer. As the cost of genetic testing continues to decline, it can make sense for people to be screened for hereditary cancer even in the absence of family history. It's especially important if one is of Ashkenazi Jewish descent. Anyone planning to become pregnant should have carrier screening to reduce the risk of disease to their offspring. Many of these disorders are inherited in a recessive manner, like Tay Sachs.

29. I have a question re: insurance coverage for genetic testing

Insurance often covers the cost of genetic testing. Many labs offer a $250 cash price for those whose insurance won't cover the cost.

30. In one of the previous slides titled "PTEN - Cowden syndrome" it references "Lifetime Risks of Cancer for Patients with PHTS" …… what is the acronym PHTS stand for, and how does it relate to PTEN - Cowden syndrome?

PHTS stands for PTEN hamartoma tumor syndrome. Often, hamartoma is the tumor type seen in individuals with PTEN mutations.

31. Is it possible to carry multiple "bad genes/mutations??" BRCA and Lynch etc?

Yes, it is very possible. Most of the time, the risks are not additive. So if there is a 10-12% risk of ovarian cancer with Lynch, and a 25-45% risk of ovarian cancer with BRCA1, the risk will be the higher number, 25-45, not the combined number, 35-57%.

32. Do the tests offered by commercial companies like 23andme include BRCA?

23andme may include BRCA testing, but it isn't full sequencing of the gene. Only 3 of the thousands of mutations that might be present are detected by their testing. The three mutations are the ones that are seen more commonly in the Ashkenazi Jewish population. Since 23andme's testing is not considered "medical grade", positive results need to be confirmed with test offered by healthcare providers.

33. My Ambry Genetics testing came back Negative No Clinically Significant Variants Detected. (I do have stage 2 breast cancer) So question is do I dismiss the genetic testing or take a next step?

No need to dismiss the result. It means that it's unlikely that your breast cancer is related to the genes that were tested. It may still be hereditary, but related to genes we don't know how to look for yet. It's also possible that the breast cancer was not inherited, but is related to lifestyle factors, exposures or chance.