

ACOG District II Genetics Slides - Speaker's Notes

1. This presentation on hereditary cancer risk assessment was put together by a group of providers from ACOG District II including OB-GYNs, Gynecologic Oncologists, Geneticists, and Genetic Counselors, and hopes to serve as a foundation for OB-GYNs to understand the importance of their role in this process.
2. *READ AS IS.*
3. *READ AS IS.*
4. OB-GYNs have a crucial role to play in hereditary cancer risk assessment ... *READ SLIDE.*
5. We will spend just a few moments discussing some of the basics of cancer genetics, including inheritance, penetrance and expressivity, new mutations, recessive disease, and genetic changes in cancer.
6. *READ bullets and stress that not all cancer syndromes are autosomal dominant.*
7. *READ both sides and remind the audience that not every family or patient with a cancer susceptibility gene looks the same due to incomplete penetrance and variable expressivity.*
8. *Left Side:* New mutations are important because there may be no family history.

Right Side: SEVERAL of the cancer susceptibility genes we are testing for now have reproductive risks associated with them for recessive diseases in offspring.

9. ****Note that this slide is animated**** *READ BULLETS ...*
ADD THIS: Genetic tumor profiles are different, and in some cases, including the identification of *BRCA1* or *BRCA2* mutations in tumors, can indicate a high risk that the person has a germline genetic mutation. Indeed, the identification of a *BRCA1* or a *BRCA2* mutation in a tumor is now highlighted by the NCCN as an indication for genetic counseling and testing. This is not the case for all gene mutations identified in tumors.
10. *READ AS IS.*
11. Next, we will do a quick overview of some of the known hereditary cancer genes and syndromes, including *BRCA1* and *BRCA2*, Lynch Syndrome, Hereditary Diffuse Gastric Cancer, Li-Fraumeni Syndrome, and some other cancer risk genes and syndromes.
12. *READ BULLET POINTS FIRST ... For Picture:* And here is a pictorial representation of the complexity of one of the most well-known hereditary cancer genes, *BRCA1*, displaying various important regions of the gene and some of the many proteins it interacts with, several of which are coded for by OTHER hereditary cancer predisposition genes.
13. ****Note that this slide is animated**** Here we have a new patient: a young woman with no history of cancer herself, who is concerned about her cancer risk, but was previously reassured because she had no **maternal** family history of cancer (*could ask the audience what is wrong with that statement*). This astute new OB-GYN

inquires about the paternal history, and given the pattern, refers this patient to a genetic counselor, who assists the family in having the cousin with early-onset breast cancer referred for genetic counseling and testing ...

(CLICK TO SHOW MUTATION ...) With a mutation now identified in the family, these two unaffected women, ages 45 and 42, can then have informative genetic testing to assess their risks.

(CLICK TO SHOW CONCLUSIONS ...) This pedigree reminds us that the paternal family history is of equal importance; there is no maternal family history of cancer, but there was an ovarian and a pancreatic cancer on the paternal side. It also reminds us that it is important to choose the best family member to test since the cousin's positive result makes testing in unaffected relatives more informative, a concept that we will review in more detail in coming slides.

14. You may know a lot about *BRCA1* and *BRCA2* ... *REVIEW BULLETS ... (read types of cancer involved, and do not read all risk numbers).*

ADD: Risk numbers can differ depending on which gene the mutation is in, and we continue to learn more and more about these risks. Some very recent risk figures were published in JAMA in 2017, and are incorporated into the risk ranges given here.

15. ****Note that this slide is animated**** Here we have a young woman, indicated by the arrow, who is concerned about her cancer risks. She reports to her OB-GYN that her mother had some type of abdominal issue, either bleeding or maybe a gastric or colon cancer, but she doesn't know which because she was only five when her mother died. She also knows that her maternal grandmother had an unusual breast cancer, lobular, she thinks, around 45, and that her maternal great-grandmother had some kind of gastrointestinal cancer. This knowledgeable OB-GYN is already suspicious, but wants to learn more, so she asks about the other side of her mother's family. The patient reports that her maternal grandfather had some colon polyps, and had a brother who had a colon cancer at young age. These brothers' mother was also thought to have had uterine cancer in her 50's. Upon further questioning, the patient recalls that her sister has also had some colon polyps. Note that it is quite common for patients to be unsure about the exact type or age of onset of the cancers in their families, which can make assessment much more challenging. With red flags on both sides of the family, the OB-GYN sends this patient to a genetic counselor, who expresses concern about ...

(CLICK TO SHOW...) Lynch Syndrome on the maternal grandfather's side due to the polyps, colon, and uterine cancers, AND ALSO about ...

(CLICK TO SHOW...) hereditary diffuse gastric cancer on the maternal grandmother's side, due to the lobular breast cancer and suspected GI cancers. The genetic counselor assists the patient in connecting her maternal grandparents with genetics providers for assessment.

(CLICK TO SHOW CONCLUSIONS ...)

So this family reminds us of two things: first, ALWAYS check BOTH sides of the family—we do actually see families with more than one cancer syndrome, and second to note precancerous features like polyps, and pathologies like lobular breast cancer, when they are reported, since they can give clues too.

16. You may have heard about Lynch Syndrome or HNPCC (hereditary non-polyposis colorectal cancer). It can be caused by five different genes, and does have a recessive disease risk for a condition called CMMRD or BMMRD, which as described on a previous slide, is a rare and severe cancer syndrome characterized by a high risk of cancer starting in childhood, and many individuals with multiple primary cancers.

READ OTHER BULLETS, and then READ CANCER TYPES (not risk numbers) and remind the audience that risk numbers can differ depending on which gene the mutation is in.

17. Hereditary Diffuse Gastric Cancer is actually often diagnosed with diagnostic criteria based on clinical findings because *CDH1* gene mutations are not found in all families believed to have HDGC—this is why high risk screening is still warranted for those who meet the clinical criteria but do not have a mutation identified. We see increased cancer risks for diffuse gastric cancer and lobular breast cancer, so **pathology** can be very important in identifying this condition.
18. ****Note that this slide is animated**** Here, we have a young woman with a very early-onset breast cancer who is concerned about her future risks, especially given that her child has cancer. She is only aware of one relative with breast cancer. Upon further exploration, the OB-GYN notes quite a variety of early cancers in this family that raise concern, and refers this patient to a genetic counselor. The counselor tells the family that they meet criteria for Li-Fraumeni syndrome testing, and ...

(CLICK TO SHOW DX ...) further genetic testing confirms this diagnosis.

(CLICK TO SHOW CONCLUSIONS ...) This pedigree shows us that we won't always see a big cluster of the **same** cancer, but to also look for patterns of related cancers. Here, the breast cancer at a young age, along with the sarcoma, leukemia and brain tumor make us think about Li Fraumeni Syndrome.

19. Li-Fraumeni Syndrome is thought to be relatively rare, and has a large variety of types of associated tumors ...
READ BULLETS ...
NOTE: *STRESS that all women with breast cancer under age 31 should be offered genetic counseling and testing for Li Fraumeni Syndrome.*
20. *READ BULLETS ... (remind the audience that the **presentation's appendix includes detailed tables with risk figures**, and point out that there are a growing number of genes related to breast cancer risk, to gynecological cancer risk, and to other organ cancer risks as well. Don't read the gene lists.)*
21. ****Note that this slide is animated**** Sometimes there can be important clinical clues to pay attention to. Here we have a young woman who presents to her OB-GYN with some huge, impressive uterine fibroids, which require hysterectomy at 22. Although the patient doesn't volunteer any concerns about cancer, the OB-GYN gathers a history anyway and notes a similar presentation of fibroids in her mother, as well as a kidney cancer presenting at a relatively young age, and one other unknown type of cancer. The OB-GYN finds this a bit curious, and refers the patient for genetic counseling ...

The genetic counselor notes the skin findings, fibroids, and cancer and facilitates testing, (**CLICK TO SHOW Diagnosis ...**) and the patient is found to have HLRCC, Hereditary Leiomyomatosis and Renal Cell Cancer. This condition is characterized by benign tumors containing smooth muscle tissue (leiomyomas) in the skin and, in females, also in the uterus (fibroids). While uterine fibroids are very common in the general population, women with HLRCC tend to have numerous large fibroids that appear earlier than in the general population. In a patient like this, you would want to make sure that pathology from a myomectomy goes to a cancer center for analysis.

This condition is caused by mutations in the fumarate hydratase gene. In this condition, there is also an increased risk for renal cell (kidney) cancer. There is also a reproductive risk for autosomal recessive Fumarate Hydratase Deficiency.

22. ****Note that this slide is animated**** Again, thinking about clinical clues, here we have a young unaffected woman who is very concerned about her gynecological cancer risks, and reports that her mother had "ovarian
- Updated December 2017

cancer” at 25 years of age. Further exploration reveals two other later onset cancers of unknown type in the family, but knowing that all ovarian cancers warrant referral, the OB-GYN refers the patient to a genetic counselor. The counselor tracks down pathology reports, and finds that the mother had small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). The counselor is suspicious because SCCOHT accounts for ~1% of ovarian cancers with median age of onset at 24 years, and an estimated 43% of SCCOHTs are due to germline mutations, with greater than 98% of these being due to mutations in the SMARCA4 gene.

Genetic testing reveals **(CLICK TO SHOW Diagnosis ...) a SMARCA4 mutation in the patient.**

(CLICK TO SHOW MORE ...) Similar clinical clues can be seen in other conditions such as Cowden Syndrome, caused by *PTEN* mutations, which has a variety of clinical features including breast and GYN cancers, and the *RB1* gene, which causes both retinoblastoma and an increased risk of uterine leiomyosarcoma.

23. ****Note that this slide is animated**** Sometimes, we don’t just have to think about the GENE in question, but also about the specific genetic variants, and some of these variants are quite common in the general population which means they “POP UP” in test results quite a bit!! This young woman discusses her breast cancer risk with her OB-GYN, who notes that she had a cousin with an early-onset breast cancer. He refers the patient for genetic counseling, and genetic testing reveals **(CLICK TO SHOW Diagnosis ...) a CHEK2 mutation in the patient.**

Let’s take a look at some possible test results and their variable meanings ... **(CLICK TO SHOW MORE ...)**

Sometimes we see CHEK2 gene mutations where the specific gene change is important.

- I157T is a common mutation in the Finnish population, which confers a modest degree of breast & colon cancer risk, so it can be a challenge to determine how to use this test result in patient management since the increased cancer risk is less substantial than other mutations. In this particular family, we wouldn’t even know if this was related to the cousin having early-onset breast cancer or not, as it is possible that that woman’s breast cancer had a different etiology, and finding this *CHEK2* mutation could just be a coincidence. At this time, NCCN does specify that the I157T mutation appears to confer a lower risk, but does not make different management recommendations for *CHEK2* depending on which mutation is found.
- IN CONTRAST, 1100delC, which is a truncating mutation, is common in the northern European population, confers a clear **increased** breast & colon cancer risk, and its use in clinical management is much more clear.
- AND FINALLY, S428F is a mutation for which there are conflicting cancer risk reports, even among laboratories!! The jury is still out, and use in clinical management is very challenging

So this reminds us that sometimes it’s not just the GENE we need to think about, but the actual specific variation!!

OTHER Similar Examples of these common mutations we could see are things like ... **(CLICK TO SHOW ...)**

- The I1307K mutation in the APC gene. APC mutations often cause Familial Adenomatous Polyposis, with a very high risk of colon cancer, but the I1307K mutation, common in the Ashkenazi Jewish population, is thought to confer only about a doubling of colon cancer risk in that population, with an unclear risk in other populations.
- The *MUTYH* gene is also complex. Notably, there are some common Northern European mutations. Also notable is the issue that individuals with **TWO** *MUTYH* mutations are thought to have an increased risk

of colon cancer, but there has been a long debate about whether those with just ONE *MUTYH* mutation have increased risk or not.

24. This issue is complex and evolving ... *READ SLIDE AS IS.*
25. *READ AS IS.*
26. Next, we are going to talk about the OB-GYN and Family History, including current guidelines, liability, and family history collection.
27. Overall, many guidelines agree that OB-GYNs need to be gathering a cancer family history, and that it should be updated regularly. We definitely saw in the last group of case examples how important it was for the OB-GYN to be gathering that history.
28. One of the reasons we should all be thinking and talking about this is due to the liability exposure associated with a FAILURE to take a family history and recognize a possible hereditary risk. **READ THE BULLETS;** *quickly overview both cases.*
29. Again, we saw in those last cases that collecting a thorough family history is key ... *READ AS IS.*
30. These are examples, this is not an exhaustive list.
31. *READ AS IS.*
32. So now that we've thought about taking the family history and what conditions we might be looking for, let's discuss who should be referred, how to make those referrals, and other providers who offer testing.
33. *READ AS IS.*
34. How do you know who to refer after you gather the history? *READ BULLETS ... Mention that ACOG recommends the ACMG/NSGC document.*

ADD: Be on the lookout for updated documents, NCCN provides updates often.
35. Let's make note of some special issues that may arise ... *READ BULLETS.*
36. *Read SLIDE, and then summarize that guidelines agree that patients need to be seen by someone with EXPERTISE in cancer genetics.*
37. There are many options to connect with a genetics professional, whether it's locally in-person, or via the rapidly growing field of telegenetics.
38. When other providers do offer genetic testing ... *READ ALL BULLETS.*

39. We should all be aware that there is DOCUMENTED liability exposure when non-genetics professionals offer genetic testing. Examples include ... *READ BULLETS* ... we should all keep these issues in mind when making decisions about which providers are going to offer genetic testing.

40. *READ AS IS.*

41. So once a patient gets to the provider with expertise in genetics, what actually happens within those consultations? Let's take a look at the content and process of such consultations, the outcomes, and informed consent issues.

42. *READ AS IS.*

43. Within these consultations, the provider will ... *READ SLIDE.*

44. It is important that anyone offering genetic testing understand NYS consent laws for genetic testing ... *READ THE SLIDE ... stress consent is a process, not a piece of paper.*

NYS Consent Law FYI, DO NOT READ THIS!!

No person shall perform a genetic test on a biological sample taken from an individual without the prior written informed consent of such individual as provided in paragraph (b) of this subdivision, except as otherwise provided in paragraph (c) of subdivision two and by subdivision nine of this section. (b) Written informed consent to a genetic test shall consist of written authorization that is dated and signed and includes at least the following: (1) a general description of the test; (2) a statement of the purpose of the test; (2-a) a statement indicating that the individual may wish to obtain professional genetic counseling prior to signing the informed consent. (3) a statement that a positive test result is an indication that the individual may be predisposed to or have the specific disease or condition tested for and may wish to consider further independent testing, consult their physician or pursue genetic counseling; (4) a general description of each specific disease or condition tested for; (5) the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease. If no level of certainty has been established, this subparagraph may be disregarded; (6) the name of the person or categories of persons or organizations to whom the test results may be disclosed; (7) a statement that no tests other than those authorized shall be performed on the biological sample and that the sample shall be destroyed at the end of the testing process or not more than sixty days after the sample was taken, unless a longer period of retention is expressly authorized in the consent; and (8) the signature of the individual subject of the test or, if that individual lacks the capacity to consent, the signature of the person authorized to consent for such individual. (c) A general waiver, wherein consent is secured for genetic testing without compliance with paragraph (b) of this subdivision, shall not constitute informed consent. Notwithstanding the provisions of this section, for purposes of research conducted in accordance with the provisions of subdivision nine of this section, a general waiver for the use of samples for research may be granted which would authorize the use of samples for these research purposes. (d) Any further disclosure of genetic test results to persons or organizations not named on the informed consent shall require the further informed consent of the subject of the test. (e) Written consent by an individual for tests to be conducted on a biological sample and to the lawful possession and ownership of such sample by a laboratory shall not be deemed written informed consent for the performance of any genetic test on that sample, except as further provided in subdivision four of this section. (f) For medical research purposes, with the approval of an institutional review board and the written informed consent of the subject, samples may be kept for longer than sixty days and utilized for scientific research. The requirements of subparagraphs three, four and five of paragraph (b) of this subdivision may be modified by the institutional review board in case the research protocol does not permit such degree of specificity. - See more at: <http://codes.findlaw.com/nv/civil-rights-law/cvr-sect-79-.html#sthash.lq1Vzx94.dpuf>

45. In the end, these consultations should determine ... *READ BOX ...*

Remind the audience:

- STAT tests are sometimes needed if management decisions will be influenced by results, for example a patient who has a recent diagnosis of breast cancer may wish to have a mastectomy instead of a lumpectomy if she is *BRCA+*.
- DNA banking is sometimes used if a family member is near death, or if no appropriate genetic test is available now, but may be in the future.
- New York State has a laboratory test approval process through the Clinical Laboratory Evaluation Program (CLEP), and providers cannot order genetic tests that don't have NYS approval.

46. *READ AS IS.*

47. Now let's think a bit about how genetic tests are selected and interpreted, with a brief overview of genetic tests, genetic variants, and the interpretation and use of various test results.

48. *READ BULLETS, with this addition for bullet #1:*

Hereditary cancer genetic testing is a diagnostic tool. It is **not a screening** test because a positive hereditary cancer genetic test result **DIAGNOSES** a person with a specific medical condition without the need for any

further testing. A screening test, on the other hand, indicates some kind of increased risk which requires a follow up test to confirm.

49. We can think about test options from the most narrow in scope to the most broad, as shown in the diagram on the right. The narrowest scope test would be ... *READ ALL BULLETS* ...

NOTE: *Stress the last section that “professional organizations such as the NCCN and SGO have begun to recommend that multi-gene panels only be ordered in consultation with a genetics professional due to their intrinsic complexity.”*

50. No discussion of genetic testing is complete without talking about the possibility of genetic variants ... *READ ALL BULLETS* ... *stress that the ORDERING PROVIDER will be responsible for re-contacting patients if variants are reclassified over time.*

51. This chart can help us think about the ways genetic changes are classified.

- In the center, we have those “variants of uncertain significance” that we just discussed. With these, we do not do clinical testing for relatives, and we do not use them to make management decisions.
- Above that, we have likely pathogenic and definitely pathogenic mutations, and we basically treat these the same way: we do test at-risk relatives, and we do use them to make management choices.
- At the bottom, we have “likely benign” and “benign” variants, and we basically treat these the same: we do not use them to test other relatives, and we treat them as “no mutation detected” and don’t use them in management decisions.
- AGAIN, REMEMBER, these classifications CAN AND DO vary between different laboratories, and can change over time. It’s a good idea to see if **OTHER** CLIA certified labs will share their interpretation of variants in question in case there are discordant reports (as we had discussed with the *CHEK2 S428F* variant, where some labs call it pathogenic, and some labs call it a variant of uncertain significance).

52. After testing, the post-test consultation typically includes ... *READ BOX* ...

53. The appropriate interpretation of genetic test results is of utmost importance. For patients with a positive test result, where a pathogenic mutation is found, the result is conclusive: there are known cancer risks. *READ THE SLIDE* ...

NOTE: *Stress the comment that “if testing was ordered by another provider, always refer these patients to a genetics professional.”*

54. Clinical management for a mutation-positive patient is going to depend on the GENE and the ORGANS at risk ... *READ BOX* ...

NOTE: *Highlight the point that NCCN may **NOT** provide detailed management recommendations for all genes, and that for some cancer risk genes we don’t have as much data on lifetime cancer risks. A genetics consultation is prudent, and for many newly discovered or lower penetrance genes, genetics providers often need to do a literature search for current information because given the updates in panel testing, updated cancer risk data is being reported all the time.*

55. For patients with a variant of uncertain significance with no other known family mutation, the result is inconclusive ... *READ THE SLIDE* ...

56. Clinical management of patients with a VUS cannot be based on that test result; it must be based on their personalized cancer risk estimate ... *READ THE SLIDE ...*
57. ****Note that this slide is animated**** The interpretation of a negative genetic test result is much more complex. If we look at these two situations side by side, we can see why:
- On the right side, we have a family where we already know that there's a *BRCA1* mutation. We then test this 37 year old unaffected woman for the mutation in her family. We see that pre-test, her breast cancer risk was estimated at 43.5%. After testing negative, if there are no other family or personal risk factors, (which sometimes there are!!!) her breast cancer risk might come down to around (**CLICK TO HIGHLIGHT ...**): 15%. So here, since we know what causes the cancer in her family, and we have shown that she did not inherit that predisposition, her recalculated cancer risks are reduced enough (**CLICK TO HIGHLIGHT ...**) that she can follow general population screening guidelines.
 - On the left side, however, we have no previous genetic testing in the family. Same exact family history, same unaffected 37 year old woman, and a negative test result. We see her pre-test risk for developing breast cancer was about 33%, and post-test (**CLICK TO HIGHLIGHT ...**): only went down to 32% because we still do not know why the cancer in her family happened, and we thus have to manage her according to her family history and personal risk factors. (**CLICK TO HIGHLIGHT ...**): Patients in this situation often end up needing enhanced screening going forward. We should always think about whether we can test other family members to try to find the explanation for the cancers in the family.
 - So you can see that it really makes a huge difference whether you have a known mutation in the family or not, and it can be really valuable to try to get the people who have had cancer in the family tested first.
58. With that in mind, we can look at this summary of interpreting a negative result ... *READ BOX ...*
NOTE: *Stress the last statement that "If testing was ordered by another provider, many of these patients can still benefit from post-test consultations with genetics professionals."*
59. When we see patients with negative results, AGAIN ... we use personalized cancer risk estimates based on relevant risk factors using MODELS and epidemiological DATA ... *READ SLIDE ... (note that the bottom of the slide is a repeat from the VUS slide reminding us that some patients will warrant extra screening).*
60. What about patients who decline testing altogether ... how do we manage them clinically?? *READ SLIDE ... (note that the bottom of the slide is a repeat from the VUS slide reminding us that some patients will warrant extra screening).*
61. Some of the really complicated and new issues in genetic testing include ... *READ FULL BULLET LIST ... and stress that you should always refer to genetics professionals in these cases...*
62. ****Note that this slide is animated***** So let's take a moment to reflect back on all of the things that happen in a genetics consultation ... here we have a family with a young woman who is concerned about her family history of pancreatic and ovarian cancer. Her aunt is currently in hospice. Her OB-GYN, noting the significance of this history, refers her to a genetic counselor. The counselor discusses with the patient that the family meets criteria for genetic testing, but, as we have learned, the aunt would be the best person to test since she has cancer. The

patient is concerned that the aunt has very little time left and that the family may not be amenable to testing right now. With that information in mind, the counselor collaborates with the patient to answer each of these questions. (**CLICK TO REVEAL EACH of the 6 QUESTIONS AND ANSWERS ...**)

NOTE: Note that DNA banking is sometimes used in time-sensitive situations like this if the family does not wish to pursue immediate testing on an affected family member.

63. READ AS IS.

64. So finally, let's think a bit more about some clinical management issues, including the role of the OB-GYN, and collaborations with other providers.

65. With regard to the OB-GYN's specific role in **management** ... READ THE SLIDE ...

66. Many organizations support the involvement of a Gynecologic Oncologist in situations including ... READ RIGHT SIDE OF SLIDE ...

67. Collaboration with various other providers will also be important, including ... READ THE SLIDE ...

68. READ AS IS.

69. We've covered a lot today ... in brief conclusion ... READ THE SLIDE ...

70. ****Note that this slide is animated**** (**CLICK FOR EACH POINT ...**) READ SLIDE AS IS ...

71. We encourage you to see the appendix for summary tables for various genes and cancer risks. Questions on this project can be directed to ACOG District II.

72. Quickly display slides 73-77 as an FYI, and remind the audience the tables will be made available to them ...

TAKE QUESTIONS AND COMMENTS