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COMMENTARY

Genetic Testing in Metastatic Breast Cancer in the USA: A Podcast

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ABSTRACT

This podcast highlights the importance of genetic testing in patients with metastatic breast cancer, with a specific focus on germline or inherited breast cancer susceptibility gene (*BRCA*) mutations. In the USA, national guidelines recommend that all patients with recurrent or metastatic breast cancer should be offered genetic testing for germline breast cancer susceptibility gene 1 or 2 (*BRCA1* or *2*) mutations to identify patients potentially suitable for treatment with a poly(ADP-ribose) polymerase inhibitor. However, a retrospective study indicated that only 43% of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer who may be eligible for genetic testing have undergone germline *BRCA1* or *2* testing. Therefore, a large national effort is required to offer genetic testing to more patients with recurrent or metastatic breast cancer. The aim of this podcast is to provide physicians with information to support the early engagement of patients in discussions about genetic testing, and guidance on how to manage patient concerns about the potential implications of testing. Here, a healthcare professional discusses germline genetic testing with a patient advocate and answers questions regarding the importance of testing in patients with metastatic breast cancer. Furthermore, the authors discuss what it means to receive a positive or negative result for a germline *BRCA* mutation and the impact this may have on the patient and their family members. Overall, the authors emphasize the importance of healthcare professionals providing every patient with metastatic breast cancer with the relevant information about genetic testing so that patients can make informed decisions. Podcast Audio and Infographic available for this article.

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Keywords: Breast cancer; *BRCA1*; *BRCA2*; Genetic testing; Patient experience

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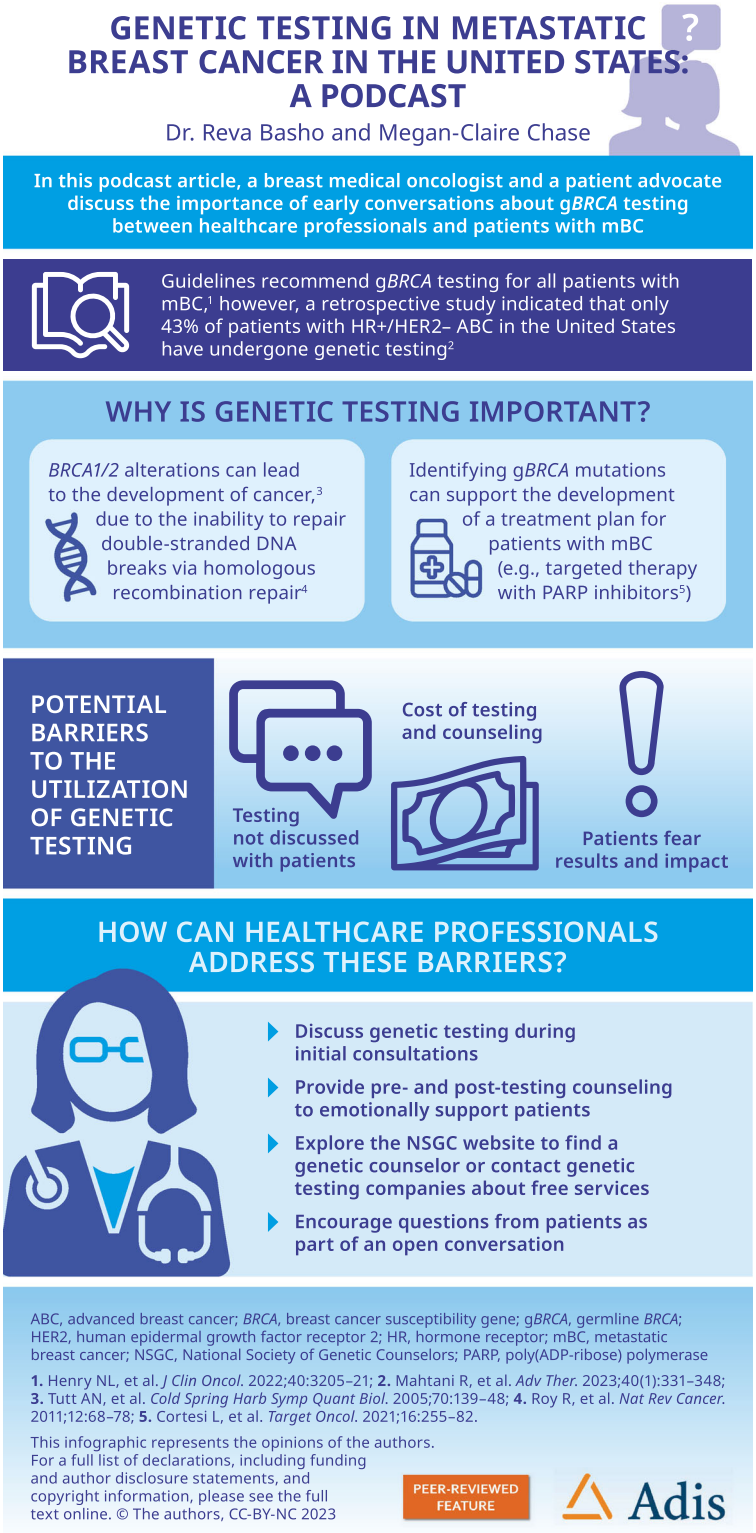
Infographic



Key Summary Points

Despite recommendations in current national guidelines, genetic testing for germline breast cancer susceptibility gene (*BRCA*) mutations is not discussed with many patients with metastatic breast cancer.

Our podcast emphasizes the importance of early conversations between healthcare providers and patients with metastatic breast cancer about germline *BRCA* testing and how these results can influence treatment decisions, for example, regarding treatment with poly(ADP-ribose) polymerase inhibitors. As the implications of having a germline *BRCA* mutation can have an emotional impact on patients, we share insights into how healthcare providers can navigate these discussions with their patients and what the results may mean for a patient's family members.

Finally, this podcast offers advice to help healthcare providers appropriately tailor conversations about germline *BRCA* testing with their patients.

DIGITAL FEATURES

This article is published with digital features, including an infographic and a podcast audio file, to facilitate understanding of the article. To view digital features for this article go to: https://doi.org/10.6084/m9.figshare.23978775.

PODCAST TRANSCRIPT

Dr. Reva Basho (RB)
Megan-Claire Chase (M-CC)

RB: Hello! My name is Dr. Reva Basho, and I am a Breast Medical Oncologist, and a director of the Women's Cancer Program at the Ellison Institute in California. I am thrilled to be joined today by Megan-Claire Chase, a 6-year breast cancer survivor and patient advocate. Hello Megan-Claire!

M-CC: Hello, Dr. Basho! Thank you for that kind introduction. Yes! Aside from being a 6-year breast cancer survivor and patient advocate, I am also the Breast Cancer Program Director for SHARE Cancer Support. I look forward to speaking with you during this podcast and delving deeper into the topic of genetic testing in metastatic breast cancer.

RB: Great! As Megan-Claire just mentioned, we will use this podcast to discuss the importance of offering genetic testing to your patients with metastatic breast cancer and how essential it is to have fully informed conversations so that patients can make educated decisions on whether to undergo genetic testing. We will specifically focus on germline or inherited breast cancer susceptibility gene (*BRCA*) mutations, although genetic testing for patients with metastatic breast cancer is not limited to these genes.

Despite evidence-based guidelines supporting genetic testing for patients with metastatic breast cancer [1], one retrospective analysis of data collected between October 2019 and March 2020 found that only 43% of patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in the United States, who may be eligible for genetic testing, have undergone germline breast cancer susceptibility gene 1 or 2 (*BRCA1* or *2*) testing [2].

Furthermore, a different study proposed that women who were diagnosed with breast cancer 5–20 years ago were less likely to be offered genetic testing due to a lack of awareness and availability, but may still benefit from genetic testing [3]. Thus, a large national effort [3] is required to offer genetic testing to a greater

number of patients with recurrent or metastatic breast cancer.

We hope our discussion will emphasize the importance of healthcare providers offering genetic testing to their patients with metastatic breast cancer and guidance on how these results can influence treatment decisions.

Similarly, we aim to give physicians insights into the specific questions their patients with metastatic breast cancer are likely to ask and the answers they need to fully understand the process of genetic testing and its implications. In addition to discussing the benefits of genetic testing and the process, we will look at the impact these results can have on a patient's mental health and the risk of a family member inheriting a genetic mutation. Megan-Claire, is there anything else you would add to this?

M-CC: I would just like to second the importance of this topic and how essential it is for patients to be offered genetic testing and to be fully informed of the process, as well as the outcomes, through conversations with their doctor. Genetic testing results have the potential to negatively impact patients and their families, and so, being equipped with the appropriate knowledge and support from their doctor can help guide them through a very challenging time in their lives.

To Dr Basho's earlier comment, I also hope that this podcast will spark more physicians to initiate these conversations on genetic testing and help empower patients to ask any difficult questions they may have. There is often confusion for patients between genetic testing and biomarker testing, so perhaps we could first define the key differences between the two.

RB: I agree with that. That is a great place to start, Megan-Claire!

Genetic testing analyzes deoxyribonucleic acid (DNA) in the blood or saliva to identify inherited mutations that can predispose a person to cancer [4]. The results of genetic testing can help healthcare providers tailor treatment decisions and ensure that patients' family members understand their own risk for developing cancer and how preventative measures can be undertaken to reduce this risk [4].

Conversely, biomarker testing uses tumor tissue or blood to identify genes or proteins in the tumor that can be used to determine treatment choice, and in turn, may predict how a patient will respond to treatment [4]. In addition, tumor biomarkers can be used to stage and/or classify a tumor [5].

Currently, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) acknowledge that "results from genetic testing may have therapeutic implications" in the metastatic setting and "germline mutations in *BRCA1* or *2* have proven clinical utility and therapeutic impact" [1]. As such, these guidelines (NCCN Guidelines) recommend that all patients with recurrent or metastatic breast cancer should be offered genetic testing for germline *BRCA1* or *2* mutations to identify patients potentially suitable for treatment with a poly(ADP-ribose) polymerase, or PARP, inhibitor [1, 6]. It is worth noting that these guidelines (NCCN Guidelines) and indications are US-based and may therefore vary in other jurisdictions.

It is important for healthcare professionals to have an open conversation with their patients about the rationale for genetic testing; the process of genetic testing, so that patients are fully aware of how testing is carried out; what the results mean for them; and how to cope with what the results may potentially mean for their families. These conversations also provide the opportunity to actively address any concerns and questions patients undoubtedly will have before opting to undergo genetic testing.

Sample collection for genetic testing can vary depending on what gene mutations are being looked for, but for germline *BRCA* testing, patients are asked to give blood or saliva, which will then be analyzed by laboratory staff for the presence of these mutations [7]. Both the doctor and the patient will receive a copy of the results [7]. These results can help determine whether a patient's breast cancer is hereditary and can also be used by the doctor and the patient to help tailor treatment discussions and decisions.

M-CC: That's good to know, Dr. Basho, and it sounds like the sample collection process for the testing of genetic *BRCA* mutations is straightforward for patients. I am sure this differs between health centers, but is there a

particular time that doctors would initiate a conversation with their patients on genetic testing, and at what point in a patient's treatment pathway can they expect to receive testing?

RB: That is a good question, Megan-Claire, as often these conversations on genetic testing can be delayed due to the limited time doctors have with their patients. In addition, when a patient receives their metastatic breast cancer diagnosis, the first consultations are generally needed to help patients understand their diagnosis and treatment options, so conversations about genetic testing can be hard to fit in here.

That said, it is important that healthcare professionals ensure that they make time during these initial appointments, since the results of genetic testing play a critical role in informing treatment options. Likewise, if prior genetic testing has not been conducted, genetic testing should be offered and discussed when metastatic breast cancer is diagnosed.

M-CC: I agree. There are often many questions that patients would like to discuss before the idea of genetic testing is even raised, so why is it so important that patients receive genetic testing when there are many other things to focus on at such a life-changing time?

RB: There is a great importance to genetic testing as the treatment landscape for metastatic breast cancer, and breast cancer in general, is evolving so rapidly. It is important for healthcare professionals to tailor their patients' treatment to optimize their outcomes. For example, there are two Food and Drug Administration (FDA)-approved PARP inhibitors for the treatment of germline *BRCA*-mutated breast cancer: olaparib and talazoparib [8]. Olaparib is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting [9]. Patients with hormone receptor-positive breast cancer should have been treated with prior endocrine therapy, or have been considered inappropriate for endocrine therapy [9].

Talazoparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, locally advanced or metastatic breast cancer [10]. The OlympiAD study resulted in a 2.8-month median progression-free survival benefit with olaparib monotherapy compared to standard chemotherapy [11]. Similarly, the EMBRACA study reported a 3-month median progression-free survival benefit in the talazoparib group compared with the standard chemotherapy group [12].

In the final analysis of both OlympiAD and EMBRACA studies, olaparib and talazoparib did not improve overall survival over standard chemotherapy [13, 14]. Thus, both studies showed a modest but discernible benefit of PARP inhibitors compared to chemotherapy in the treatment of metastatic breast cancer.

Despite these modest outcomes, PARP inhibitors offer a chemotherapy-sparing oral treatment option for patients and have a role as a biomarker-specific targeted therapy in patients with advanced or metastatic breast cancer.

To receive olaparib or talazoparib, the presence of germline *BRCA* mutations must be confirmed by an FDA-approved companion diagnostic, and thus, being aware of whether or not a patient with metastatic breast cancer has a germline *BRCA* mutation allows physicians to ensure that they are considering this therapy in patients for whom it would be appropriate.

Olaparib is also approved for adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer, who have been treated with neoadjuvant or adjuvant chemotherapy [9]. The OlympiA study, which evaluated 1 year of olaparib in the adjuvant setting in this group of patients, reported a significant improvement in 4-year invasive disease-free survival and overall survival in patients treated with adjuvant olaparib compared to placebo [15]. The adjuvant setting represents a setting where the addition of PARP inhibitors has resulted in significant improvement in outcomes in patients with germline *BRCA* mutations [15].

M-CC: I can see why it is critical to undergo genetic testing, but from my point of view, it is equally important that patients are emotionally supported through the process of genetic

testing, which leads me to my next question. As you mentioned previously Dr. Basho, both the doctor and the patient receive a copy of the results, but who sits down with the patient and discusses what these results mean?

RB: It is important to mention that pretesting counseling is recommended for patients, so they know exactly why genetic testing is being offered and what the potential implications of the results are.

The National Society of Genetic Counselors' website can help the provider or patient find a genetic counselor who can offer in-person or virtual counseling services. Once the patient receives the results from genetic testing, usually either the doctor themselves or someone with expertise in this area, such as a genetic counselor, will sit down with the patient and go through these. In either instance, the healthcare professional involved will support a patient through the questions they may have. It is important for patients to have a full understanding of the type of results they can receive from genetic testing so they can be prepared to deal with all potential outcomes.

It is helpful for us as healthcare professionals to have an idea of the type of questions that patients may ask. It would be great if we could get a patient's perspective on what you, as a patient advocate, understand are concerns that patients can have related to genetic testing results, Megan-Claire. Perhaps we can run through two scenarios: what to expect if a patient receives a positive result for a *BRCA* mutation, and then what to expect if a patient receives a negative result.

M-CC: That would be ideal. Perhaps we could first focus on receiving the news that a patient has a positive result for a *BRCA* mutation since this may raise the greatest concern among patients. I think, as a patient, I would first like to know, what does a germline *BRCA* mutation actually mean and how will this impact me as a patient and my cancer journey?

RB: As you say Megan-Claire, receiving the news of being positive for a *BRCA* mutation can be worrying for patients, so it is important that their doctor fully explains the implications of these mutations. However, it is important to note that these mutations are hereditary, and patients have no control over whether they have these or not, and so should understand that lifestyle factors did not cause these mutations.

Wild type or non-mutated *BRCA1* and *BRCA2* are tumor suppressor genes important for repairing double-strand DNA breaks via homologous recombination repair, which in turn helps prevent tumor development [16]. Mutations in *BRCA1* or *BRCA2* mean that the repair process of DNA damage is much more error-prone, which can introduce mutations and genetic instability, resulting in cancer [17, 18].

BRCA1 and *BRCA2* are the most likely affected genes in hereditary breast and ovarian cancer [19]. If you have a family history of breast or ovarian cancer, it is possible that you and your family members may have a *BRCA1* and/or *BRCA2* mutation, as these mutations have a 50% chance of being passed on from parent to child [16, 19, 20]. For people with mutations in *BRCA1*, the estimated cumulative risk of developing breast cancer by 80 years of age is 72%, and 69% for patients with *BRCA2* mutations [20].

Pooled cross-sectional data have shown that less than one-third of women with a history of breast cancer who are eligible for genetic testing have discussed genetic testing with their healthcare professional [3]. Even fewer still of those eligible were advised to undergo genetic testing, and of these, just 15% completed the testing [3].

As we discussed previously, presence of germline *BRCA1* or *2* mutations can indicate sensitivity to PARP inhibitors. This is because alterations in *BRCA1* or *2* rely more heavily on PARP1 to repair DNA damage [21]. PARP inhibitors trap PARP on DNA, preventing the repair of single-strand breaks, which in turn leads to irreparable double-strand DNA breaks and ultimately cell death via synthetic lethality [22]. Additional agents targeting the DNA damage response pathway are also in clinical trials, and presence of these and other mutations may qualify patients for those clinical trials.

M-CC: You mention there about the likelihood of family members also having mutations in their *BRCA1* and/or *BRCA2* genes if a patient

is found to be *BRCA* positive. If I were to put myself in that person's shoes, I would feel worried and scared to deliver this news to other members of my family. It would be a difficult and emotional conversation to have. How can I ensure my family receives support? Would they need to undergo genetic testing to confirm they definitely have these mutations?

RB: Your doctor or genetic counselor should talk through the support options available for your family members, which could include directing them to available support groups [23]. If members of your family choose to test for the presence of a *BRCA* mutation, genetic screening may be available, although this is typically not recommended for children under 18 years old [23].

M-CC: If other family members do decide to undergo genetic testing, what would this mean for them if they turn out to be positive for *BRCA1* or *BRCA2* mutations? Is there anything they could do to help minimize their chances of developing cancer?

RB: It is very natural to be concerned about what genetic testing would mean for your family, and their healthcare professionals should share measures that could be taken to help reduce the likelihood of developing cancer if a *BRCA1* or *BRCA2* mutation is detected. Regular screening for certain cancers is imperative in patients with known *BRCA* mutations, so it is important to discuss a plan with the doctor. This could include screening of breast using MRI or a mammogram, among other tests, to help detect evidence of disease in its early stages [24]. In addition, making healthy lifestyle choices, including keeping a healthy weight and exercising regularly, may reduce the chance of developing cancer [24].

It must be said, though, that the presence of a germline *BRCA* mutation does not mean that you will definitely get cancer at some point in your life, but there is a higher risk, which is why it is important to listen to the advice of your doctor.

M-CC: Turning to our second scenario, what can a patient expect if their test results come back negative for germline *BRCA* mutations? Is that good news?

RB: Having a negative test for germline *BRCA* mutations means that your breast cancer was not caused by a hereditary mutation in *BRCA1* or *BRCA2*, but it is possible that another gene mutation is driving cancer development [19]. As mentioned before, there are other gene mutations that can be tested for, so it is important that your doctor discusses whether any further genetic testing is available [19].

M-CC: Previously you mentioned the use of PARP inhibitors for patients with metastatic breast cancer and germline *BRCA1* or *BRCA2* mutations. However, will a negative result for germline *BRCA* mutations mean patients are offered different therapy options?

RB: Yes. Healthcare professionals should have a detailed discussion with their patients about treatment options, as these will be guided by the results of genetic testing. For example, for patients who have hormone receptor-positive, HER2-negative metastatic breast cancer, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in combination with hormone therapy are standard of care [25]. Further, a different targeted biologic therapy may be offered if further genetic testing uncovers a different type of mutation [25].

There is also a third potential result which healthcare professionals may discuss with their patients. This is a variant of uncertain significance, which is where a process of genetic testing has identified a mutation in either *BRCA1* and/or *BRCA2*, but it is uncertain whether that mutation has driven tumor development [19].

In this scenario, healthcare professionals should discuss with their patients whether further testing can be offered, if appropriate [19]. Do you have any questions on this, Megan-Claire?

M-CC: This is interesting. If a patient with breast cancer is found to have a variant of uncertain significance, will this still be something they need to inform their family of?

RB: Potentially. The patient's doctor should discuss this further and may suggest this is something that they should still share with their family [19].

M-CC: I think that having a variant of uncertain significance would be unsettling, particularly with respect to having no clear

answer as to whether it increases cancer risk. Are genetic variants of uncertain significance common? What do you say to a patient who feels concerned about this?

RB: Based on the ClinVar database, it is estimated that approximately 37% of *BRCA1* and 45% of *BRCA2* unique variants are recorded as variants of uncertain significance, and thus, there is a need to reclassify these variants by their pathogenicity [26] in order to tailor treatment and improve patient management [27].

Patients should note that the American College of Medical Genetics and Genomics guidelines specify that "a variant of uncertain significance should not be used in clinical decision-making," and that efforts should be made to "resolve the classification of the variant as pathogenic or benign" in order to appropriately "use the molecular testing information in clinical decision-making." [28].

M-CC: Are variants of uncertain significance ever reclassified? How has the knowledge about variants changed over time?

RB: As more information is gathered over time, variants of uncertain significance can often be reclassified. Several functional assays have been developed over recent years to help determine the pathologic features of variants [26, 27]. However, it should be noted that in some instances, a lack of data makes it impossible to reach a conclusion, and the variant may not be reclassified [29].

Where it is possible to reclassify variants of uncertain significance, it has been suggested that 91% were reclassified as a benign variant, or likely benign variant, and not driving the development of cancer, whereas only 9% were reclassified as pathogenic or likely to be pathogenic [30].

Megan-Claire, are there any other questions you feel a patient would ask regarding the results that could be received following germline *BRCA* genetic testing?

M-CC: Thanks, Dr. Basho. This is all helpful information to know. I can see the benefits and importance of genetic testing, but I think patients will be concerned about the financial impact. Is genetic testing or genetic counseling something that would be covered by insurance?

RB: Since genetic testing is recommended for patients with metastatic disease [1], it is generally supported with either minimal or no charge [31, 32]. Additionally, healthcare providers can enquire about genetic counseling with the companies used for germline testing, as many of these companies provide patients access to genetic counseling resources that are usually offered at no additional charge to a patient.

M-CC: Well, that is good to know, Dr. Basho.

RB: Great! Before we wrap up our podcast, Megan-Claire, have you any further thoughts on what we have discussed?

M-CC: Well, it is great to have had this discussion with you today, Dr. Basho. This conversation helped to increase my awareness and knowledge of what a patient can expect from the process of germline *BRCA* genetic testing and how to manage the outcomes. That said, if patients have friends who also have metastatic breast cancer and who have not had conversations with their doctor regarding genetic testing, could you offer some advice to these patients on how they can initiate these discussions with their physician?

RB: Absolutely! We want to ensure that patients have this knowledge of genetic testing so they can talk it through with their doctor. We also hope to equip healthcare professionals with the knowledge they need to discuss genetic testing with their patients with metastatic breast cancer in a timely manner, and subsequently increase the number of patients who undergo germline *BRCA* testing.

My advice would be to have the person ask their doctor if undergoing germline *BRCA* testing would be appropriate for them given their diagnosis. Often patients are apprehensive about asking their doctor questions, but this is important to do so that both the doctor and the patient can work together to deliver the best possible outcomes. I also encourage oncologists to routinely discuss genetic testing as it pertains to each individual patient during the initial consultation, so that the process of testing can be initiated early when indicated.

M-CC: Thanks, Dr. Basho. This is helpful advice and will hopefully get the ball rolling in ensuring this testing is actively discussed

between every patient with metastatic breast cancer and their doctor.

RB: Are there any other questions you would like to raise before we wrap up today's discussion, Megan-Claire?

M-CC: This was a fantastic discussion, Dr. Basho. Receiving a diagnosis of metastatic breast cancer is scary and comes with enormous stress on the patient as they try to navigate next steps. I hope this information about the benefits, importance, and impact of genetic testing for metastatic breast cancer patients sparks meaningful conversations between healthcare providers and their patients.

RB: I absolutely agree. It is really helpful to better understand the patient's perspective, and I hope that this discussion will help physicians engage patients early in decisions regarding genetic testing and discuss with them the potential implications of testing. Ultimately, this can increase the testing rate to better align with the national guidelines (NCCN Guidelines) [1] and ensure integration of genetic testing results into the determination of appropriate treatment options for patients with metastatic breast cancer.

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