NGS Panel for Hereditary Cancer Syndromes and Cancer Targeted Therapy - Felicitas Lacbawan

Female Speaker:
Sure. Okay. Welcome, good afternoon, everyone, to the February genetics webinar. Today we're very pleased to have as our presenter, Dr. Felicitas Lacbawan, who is the medical director of genetics at Quest Diagnostics Nichols Institute. Today she'll be presenting Next-Gen Sequencing Panel Testing for Hereditary Cancer Syndromes and for Cancer-Targeted Therapy. And before she begins, I would just like to remind everyone, please mute your line during the presentation, and we will open up the conversation at the end of the presentation for questions. And as always, the webinar is being recorded. So Dr. Lacbawan, it's all yours.

Felicitas Lacbawan:
Thank you, Heather. Good afternoon everyone. It's a pleasure to present to you this topic for today, and hopefully it will be helpful in your individual companies or offices.

So -- sorry for that. So understanding the application NGS Panel Testing for Hereditary Cancer Syndromes and Cancer-Targeted Therapy, I would try to cover as much in terms of the content of the NGS panels, how they're put together, how they can be validated, what are the guidelines that are controlling or burning the use of this test panel. As well, both in germ line as well as symptomatic cancers.

So for -- based on the 2015 cancer facts-- American Cancer Society, there are areas beyond the United States where there are more than 100,000 cases per year. And that is actually in California, Florida, New York, and Texas. The ten most primary cancer sites are prostate, breast, female -- cancer, lung cancer, colon, rectum, uterus and pretty much -- some of this -- or, except prostate -- a lot of this are part of the hereditary cancer syndrome.

By distribution, 80 percent of cancers are sporadic, meaning that there's no germline mutation or inherited gene that's causing the cancer. Ten to 15 percent are familial, meaning that they occur in families and they could be low penetrance and they need a gene environment interaction or both to cause cancer. The -- five to ten percent, though, are inherited cancers, and they arise from high-penetrant germline mutations. So inherited -- inheriting a genetic mutation or pathogenic variant doesn't meant that the patient or the person who has the variant has cancer. But it increases his or her risk. The most common heredity cancers are breast, ovarian, colorectal, and prostate cancer.

Understanding if cancer is due to an inherited pathogenic mutation can help start by the risk of developing cancer, and it also helps determine options for cancers function as governed by guidelines and possibly therapy. Some cancer risks for common cancers are more or less variable, but it actually is around the range of almost 40 to 80 percent [unintelligible] hereditary and--versus the general population.

As an example, breast cancer -- BRCA2 has four in 10, versus BRCA1, which is six in ten chances of developing cancer by the age of 70. So what are the red flags of inherited cancer in a family or in an individual? So cancer in two or more closely related relatives; multiple

generations affected by -- depending on what type of cancer there is; and early age of diagnosis, multiple primary tumors, bilateral or rare cancers, as well as consolation of tumors consistent with specific cancer syndromes, and certain ethnic backgrounds, like the Ashkenazi Jewish panel -- I mean, cancers can be a clue that there is an inherited susceptibility gene.

So this patient's family history is the one good clue that something is happening in the family that could be inherited. With improvement or advances in technology, the costs for genome has drastically changed since 2007, and with that, the massive parallel sequencing or next-generation sequencing has briefly propelled the use of this technology in a lot of Sanger-based sequencing. And that we can also utilize that technology to interrogate several genes at a time.

So right now, we -- when we talk about sequencing, we would be able to do several things. We can do risk management, depending on the diagnostic test that actually is used for a certain gene panels, or certain genes. And we can use it also for screening when we apply it to high-risk patients and identify the disease early before the cancer occurs. And also for diagnosis, when we would want to ascertain what kind of cancer that patient has, and staging, of course, as well as therapy selection. And I would expound on the therapy selection when I get to the solid tumors. And, of course, moratorium for efficacy.

The workflow for cancer gene panel pretty much is similar to any next-generation sequencing. What varies is actually the input or the source of DNA or the RNA. So normally for germlines cancer panel testing, we use broad. There are some times when you would use exogene if you know that there's systematic mutations that could be subtracted you would have a germline mutation from removing the thematic mutations. And sometimes -- rarely, though -- this is not just published but definitely if there is a germline mutation that can be followed missing circulating with DNA. But right now, most of the cancer germline panels are run using blood. So just so kind of we -- so after DNA struction or RNA struction, the [unintelligible] prep is done, and then the target enrichment is something that is important to remember, because this is where different laboratories really differ. And depending on how they capture the DNA or the RNA, pretty much that could give you the sensitivity specificity, as well as the depth of coverage and also the type of coverage within the whole gene, whether they include the promoter sites or the other genetic material structure within the gene.

So then after that sequencing can be normally done, depending on what platform is available in that laboratory, and of course, the other thing that differentiates its blood would be the informatics of being using, meaning the informatics pipeline. Because that would actually differ in each of the laboratories that do certain DNA panels. The reporting is also something that is made different in the lab. So just a review: The normal or the more common tests that one can do if BRCA1, BRCA2, and therefore breast, ovarian cancer and the most common high-risk breast cancer susceptibility syndrome, because they occur in one in 300 to one in 800 individuals, more-so in Ashkenazi Jewish, where they have one in 40 individuals. so the cancer risk by age 70 for BRCA1, BRCA2 mutation carriers without personal history of cancer is – reflected in the stable. So for female breast cancer with BRCA1 mutation, it's up to 65 percent, and for BRCA2, it's up to 47 percent. And for ovarian cancer, 39 percent for BRCA1 and 17 percent for BRCA2. And for male breast cancer, more-so on BRCA2, it's 6.8 percent.

So there are other hereditary breast cancer genes, and every year there are more than 200,000 women in the U.S. that are diagnosed with breast cancer. I mentioned earlier that it is mostly BRCA1, BRCA2, but there are certain genes which are highlighted in this figure, like TP53, PTEN, STK11, CDH1 and PALB2 that are also responsible for breast cancer in around 4 percent of cases.

So gene suggest increased risk for breast cancer, as I mentioned earlier, are -- can be included with BRCA1, BRCA2 in the panel, and that increases the number or the presence of cases that can be detected with that panel. So why are they included in a panel? Pretty much, one would understand that breast cancer tumor genesis, it actually affects DNA repair. That is BRCA1 and 2 and check two, chromatin remodeling for BRCA1 and -- as well as protein [unintelligible]. There is cell cycle regulation is regulated by P53 and apoptosis, or cell death, by PTEN [unintelligible] cell proliferation.

so if genes participate or the products of these genes participate in tumor genesis in different ways, and that actually is the reason why they are put in certain panels for BRCA testing or for the variant cancer testing. Can I just -- hold on a second.

[laughter]

We're recording, sorry.

Hussein Noorani:
You probably need to go back now.

Felicitas Lacbawan:
Sorry for that. I have a competing lecture on the other side. So just to show the venn diagram on BRCA1 and BRCA2, they actually form complexes with the [unintelligible] complex. And they do repair DNA that are damaged and they also promote chromosome stability. So I wouldn't belabor some of this component, but just showing the fact that there are certain genes that interact with BRCA1 and BRCA2, and these are the Fanconi genes as well as the ATM and PALB2.

So BRCA1, BRCA2, we know it's hereditary breast and ovarian cancer syndrome. TP53 is actually responsible for lethal many syndromes, PTEN for the Hamartoma tumor syndrome, which includes Cowden syndrome; and then CDH1 for hereditary diffused cancer--gastric cancer, and Peutz-Jeghers syndrome for STK11 and PALB2 with associated breast cancer.

In terms of lifetime risk for breast cancer, TP53 has a relative risk of 6.4 times when you have a mutation, a pathogenic mutation and likely pathogenic mutation for TP53. And then PTEN we have ,for breast cancer, 85 percent approximately at the age of 70 years of age; CDH1, lobular breast cancer risk of 39 percent to 52 percent by age 80 years of age; and STK11, breast cancer risk of 45 percent by age 70 and PALB2 breast cancer of 35 percent by age 70.

Then, as I mentioned earlier, too, there are several other cancers that can be associated with the different genes. And for TP53, bone, connective tissue, brain, pancreas, colon and liver are also

increased in patients who have TP53 mutations. And for Cowden, besides breast, one can have thyroid, endometrial, renal, colorectal and melanoma. And, of course, hereditary diffused gastric cancer in males and females may differ. And then Peutz-Jeghers for gastrointestinal cancer, including pancreatic cancer, 11 percent by age 70. So the NCCM guideline actually gives a very well-defined criteria for testing based on age, family history, personal history. And pretty much, I wouldn't read through the whole criteria but it does tell you who are to be tested, and that within the family you can actually identify who needs to be tested after an individual in the family has been documented to have a mutation.

And of course, within the NCCN guidelines, there are also admonishment guidelines for women and men who have the mutation. And ranging from breast examination, MRI, as well as other procedures that would prevent development of associated cancers within the family or within the patient.

So this table just summarizes what are the guidelines that are out there and probably justifies why this NGS panels are really offered to individuals who really fulfill the genetic testing criteria. So for BRCA1, BRCA2 and TP53 as well as PTEN, NCCN guidelines have the Genetic Familial High-Risk Assessment breast-ovarian. And for CDH1, there's an International Gastric Cancer Linkage of Consortium cancers guidelines. And although STK11 and PALB2 don't have genetic testing criteria, NTCN has genetic formula and high-risk assessments for colorectal in STK11, as well as ACS has recommended guidelines for PALB2.

So why expanded menu -- remember I'd mentioned the BRCA1, BRCA2 explains 15 to 20 percent of hereditary breast cancer cases. And with additional genes, which are TP53, PTEN, CBH-1 and STK11 and PALB2, which are mostly probably not just high penetrants, but moderate to high penetrants. Breast cancer susceptibility genes can explain up to 4.5 percent of hereditary breast cancers. So that in itself justifies the fact that the seven genes can be put together as initial screens for patients with breast cancer that will fulfill genetic testing criteria. So I mentioned that PALB2 is an emerging gene, and pretty much right now, there are more reports of PALB2 positive breast cancer patients.

So it looks like that should be enough, but not really because there are other genes that are actually responsible for breast cancer risk, also. And just summarizing the fact that when will you use the panel versus just BRCA1, BRCA2 depending on the family history, one can actually prioritize BRCA1, BRCA2 it's mostly hereditary breast cancer variants. And -- but if there is a mixture within the same family of certain other cancers, one can opt to take the seven genes or even a 34-gene, which, actually, I can explain. Okay, so right now in certain laboratories, there is just BRCA1, BRCA2 as complete coding exome sequencing. And that can be just a comprehensive BRCA1, BRCA2. There are times when a family member has been tested with the single mutation or variant within the family, especially in Ashkenazi Jewish families where they have specifically any one of this common mutations. Then they can just be screened for that type of mutation.

The other thing that can happen is that if the family is Ashkenazi Jewish*, that then the Ashkenazi Jewish screen is negative one can order a reflex for the comprehensive so that the whole exomes of BRCA1 and BRCA2 can be tested. Single side means that within the family,

there's a known pathogenic mutation, so when ordering a test, the clinician can just order that specific mutation so that the lab doesn't have to sequence the whole BRCA1 or BRCA2 gene. And then there are times in the early days where rearrangements were not tested. One can also do just a rearrangement if the BRCA1, BRCA2 were sequenced earlier and not the rearrangement.

Then I mentioned that the seven-gene panel, we can call expanded panel. And who are the cases that would need those -- this panel? It depends. Sometimes when the family history is not very specific and not focusing or directing the test to just BRCA1, BRCA2, then you can order a seven-gene panel, including BRCA1, BRCA2, TP53, PTEN, CBH11, STK11 and PALB2. You can do a reflex also, and you can just do BRCA1, BRCA2. Then later on if it's negative and it's still -- the patient has some other family members involved, you can do a reflex of the five genes. Or just the five genes if BRCA1, BRCA2 was earlier tested and there were no point mutations, deletions or duplications.

Then comes the bigger panel. And this has been up and coming in different laboratories. And I'm just showing you what we have, but pretty much the reason why they are put together is because they can have-- the only breast cancer. Here we have the 7-gene panel that I discussed earlier, but then within the other genes, which are actually -- chances are they're low to moderate risk and low penetrants -- they can also cause breast cancer and some other cancers like ovarian cancer and -- or this other genes which are actually [unintelligible] syndrome genes, they can also cause breast cancer. And I'll discuss a paper that was just published and just to show you that there is some reason why cancer predisposition panel is bigger compared to the more high-end [unintelligible] genes because of the different conditions that can be tested for the 34-gene panel.

So here is the paper by Desmond, and it was just published recently by the journal Oncology, 2015. And pretty much, you have different labs here. We have -- there are 34 genes in two laboratories and 25 genes in one laboratory, and here's what the gene panel that this study did. They actually included 1,064 cases, which are BRCA1 and 2 negative, and they went through all the testing and found that there are 53 of those from 24 cases that are positive for other genes other than BRCA1, BRCA2. And significantly, actually, affected management as well as familial testing. So it does support the need or the use for multiple gene panels. And pretty much, the advantage of having this multiple gene panel is you would have a lower turnaround time, and you cover several genes at a time. However, just to iterate some of the differences in the different panels that are being offered out there, one would need to understand that they were validated in different ways depending on the platform that they were ran. And at the same time, there should be an accuracy sensitivity, specificity, limits of detection for each of the labs that had validated this test. One very important thing to consider, too, is that only the panel -- the content of the panel itself, but also the assay design and the genes that are included in that panel. Because there are certain genes that are actually very difficult to do massive parallel sequencing, because they can have pseudogenes. And I just gave one -- two genes here, the check 2 and the PMS2 pseudogenes can complicate sequencing.

So if the laboratory is offering these two genes, pretty much one can ask them what are the ways that they had improved on so that they are sure that they are not sequencing the pseudogenes, but

rather the real gene. And then, of course, the third one here were -- laboratories do optimize their conditions in terms of capturing the real exonic sequence, as well as the flunking sequence using RNA dates or some other ways of capturing the sequence of interest. Because there are times when there are some mutonic sequences that are commonly affected in some genes. And those need to be -- I'm sorry. I don't -- I think I'm disconnected. I don't see any slides on my – sorry -- . Got it.

So we've all missed the technicality within the assay design. One should understand that there's also difference between using tissue and blood. And the mechanism for capturing low-copy number variants, as well as addressing multi-systems. And the other part is also the type of mutation or rearrangement that one actually can see using that assay. Because some assays would not be detecting the CMBs, as well as large rearrangement. More-so for massive-parrallel sequencing, [unintelligible] repeats are difficult to actually identify, although they don't occur in some -- in most of the genes that we have and they prefer the NGS panels for cancer.

And again, sequencing performance and quality metrics need to be understood as well as I mentioned earlier. The bi-informatics pipeline also important because some bi-informatics pipeline actually do not detect small violations and they can be missed.

So at any rate once you have a pipeline that is working and annotation and classification is pretty much standard. However, in different laboratories also multiple data-based sources are something to highlight. There are publicly available mutation databases, and some of them are reported or recorded here in this slide. So everybody can use those, but there are certain private databases that others can query and consortia and other companies that are actually in participation or in collaboration with other foreign laboratories.

So those are the things that can happen in terms of annotation and variations in annotation. But hopefully with more public databases and more publications, pretty much every -- or most of the bias can be annotated similarly. There are multiple reviews for BUS and pathogenic cases in most laboratories, and anything that can be reclassified within a certain period of time can be done by the lab and contact the clinician who had ordered the test. Co-segregation family studies can help in the [unintelligible] reclassification, and I think some labs are doing those. And, of course, pretty much most of the labs or all of the labs are doing final interpretation by board-certified directors who are experienced in interpretation.

So in a breast cancer report, besides the fact that the turnaround time is important, one can reflect the options within 21 days of – at least within our lab, and the interpretation summary, depending on which lab you are sending your tests, it's pretty much -- they are categorized and highlighted and all of the ACMG guidelines are utilized. So that actually is the germline side of cancer sequencing. I'm shifting to solid tumors and if you have any questions, we'll take it at the end of the talk.

so solid tumors -- many of you probably have -- if you remember in med school or at least the theory that you have to have a double hit to have tumors or you have an environmental factor that effects a previous mutation within the tumor-producing genes before you can have tumor. And that becomes a little more of a challenge in terms of testing. And that we have solid tumors

with multiple genes and path rates being altered. Suppressor genes as well as oncogenes being affected. And with that, a lot of therapies have been affected, targeting specific genes as well as other molecules within the cells that could help prevent cell proliferation or induce cell death. And, of course, clinical annotation as well as clinical utility must establish before testing can be offered.

So the clinical view of cancer -- one can see the different stages or the different cell activity that can be affected during tumor formation, and that basically you're either inducing proliferation, preventing death of the cell, or pretty much there is a driver mutation within that sack of cells that actually causes the proliferation of that cell. So here is just giving you a broad view of cancer, and what are the possible inhibitors or therapies that can be developed to target specifically those activities within the cell that produce cancer?

So cancer pathways and targeted treatments: Most of you must have -- you must have heard of a lot of receptor antagonists, [unintelligible] inhibitors and some of this other gene products that can be inhibited within the intercellular part of the cell. And any part or any protein within this pathways can be inhibited or, depending on what the mutation or variants that can occur, they can actually have a constitutional activation of that receptor leading to self-proliferation or some inhibition of eye proptosis. And this actually just summarizes the fact that there are several receptors, cell receptors that can be shared by different cancers, and that certain drugs or emerging therapeutic agents can be used to target certain cancers. And they can also be used in some other non-specific cancers, depending on the target.

So just to give you an example, lung cancer Erlotinib is one of the drugs that can be used for treatment of lung cancer. And it is pretty much inhibiting the EGFR-mutated receptor action. So again, just -- you can probably look at the slides again, but I don't need to belabor the point that several genes responsible for tumor genesis are shared by a lot of solid tumors. And there are specific solid tumors that -- they're very much really more related to a specific tumor, but again, since they share different genes, they can have driver mutations in different solid tumors, then one can use a targeted mutation for that specific gene project.

For lung cancer, pretty much -- and some solid cancers -- they have at least a dozen of shared genes that one can target, and that's rationally why some of the hot spots that are commercially available are being used in different laboratories. And, of course, for lung, melanoma, breast and colorectal, here are all the genomes that are actually being targeted by some commercially available and some IVG diagnostic kits. And that in itself pretty much -- because of the hot spots, one can easily direct or target that particular cancer based on the cancer profile.

So in most next-generation sequencing, there are several targeted actionable genes. For us, we have a 34-gene panel, and it is applicable to all solid tumors, and it's annotated directed at FDA-approved drugs. And sometimes with the more or the less common genes, we have clinical trials that are available. And most of the other labs, as well as us, we actually can suggest which of these clinical trials can be used depending on the variants that are actually identified after the sequencing. So, for next-generation sequencing for a solid tumor, one can use FFPE tissue, small bioethanase, and sometimes there are tests that one can use some other types of cells. But for the most part, it's FFPE.

As an example, lung cancer. So there are treatment options based on the lecture profile as I alluded to earlier, and specifically for lung cancer, if you have an EGF or exome 18, 19, 21 mutation, you can use -- or Erlotinib -- and for the other mutations, an EGFR as well as some positive care mutations for 12, 13 and 51. This drug cannot be used because it's non-responsive. So this table just gives you a flavor of the different antibodies or the different drugs that can actually antagonize the driver mutations, and here are the different genes here based on the mutations, and then here are all the different [inaudible] for each of the different gene-specific mutations that can occur in lung cancer, specifically the non-small-cell lung cancer.

So in most cases, these are the ones that are targeted for diagnostic or profile. So for lung cancer, essentially it's EGFR, BRAF, and ALK. Some have ROS1, [unintelligible] as well as Her2 mutation detection. And for colorectal, Kras and Levitra. And for melanoma, [unintelligible]. So for the ones that are not commonly associated with hot spots and are very negative in this more hotspot-directed and less number of genes that are commonly tested, one can use a [unintelligible] panel that can encompass more genes that are actually causing driver mutations that are associated with cancer. So again, this is level-one association between gene and academia-approved therapies. And ranging from Bref,EGFR, HREF, Cip, RET [nintelligable]and NREF. And here are all the tumor types here, ranging from melanoma to colorectal cancer, and then the association of the different mutations that can occur whether they are sensitive or resistant to the specific drugs on column two.

This can be the table where we refer the more common changes that are associated with the different cancer types, as well as the genes that are aided to targeted therapy. And here's a larger-- actually, listing of gene targeting. And again, it could be that any of these genes on the far left, they're actually more suited for genes on the far left. Any of these genes can form mutations, and any of these genes can confer resistance or sensitivity, depending on what is the mutation. And the treatment can be identified or dictated depending on which gene is affected and what the mutation is.

Okay. So what are the clinical applications of NGS multigene cancer panel? Despite mild relief for cancer patients with few or no standard treatment options remaining, and this is sometimes after identifying the hot spots or the ones that are available out there. And that-- if the patient doesn't respond to treatment, given that initial stratification, the oncologist can be assisted in deciding on potential effective drugs or clinical trials that can be utilized by the patient. So most of the multigene cancer panels are actually for solid tumor, all solid tumor types. And pretty much, it could be either a metastatic or a locally advanced [unintelligible] on presentation. And when no actionable mutation is based on guidelines, then you can use this gene panel to actually get some of the other drugs that are pretty much under clinical trial or emerging into the market.

They can be used for small specimens, and they can be used for both recurrent and metastatic diseases, as well as tumor of unknown origin or primary origin, and some rare tumors with no specific standard of care can also be analyzed in this platform. But of course, results need to be guided in terms of how they could actually be used. And the evolving concept now varies with patients, clinicians, guideline committees as well as payers. And pretty much, within the contextual stage of the disease, whether it's primary or metastatic within the tumor type, the

guidelines and FDA-approved drug labels, as well as inclusions for clinical trials and anticipation of additional genes and lead-ins in the near future needs to be there. And it is not a binary action. It is actually a continuum of evidence, because the tumor can evolve, especially when there's metastases. And in that -- some of the drugs are quite new, and they're just emerging. And I think one of the best things about whether you target the primary tumor and knowing the genetic profile of that primary tumor, one can also understand what the next treatment would be if there's a system to know drugs.

So this is pretty much like any other NGS cancer panels. There's some that have all the 400, 100 genes that there is. But pretty much, they're the more common genes and, as I mentioned earlier, interrogating them simultaneously gives you an advantage of knowing some of the other driver mutations that are not very common. And it's actually enhanced compared to some of the other platforms that are readily available, including sangers sequencing. With NGS, one can also multiply patient samples, and that reduces costs of testing and also, hopefully, it actually reduces reimbursement in patient costs out-of-pocket. And that you could also do sequencing packages of sequencing and modify the content after verification of the panel that was previously developed.

So most of the panels are -- because of the technical considerations, they can use some other sequencing like -- sequencers like the proton or the PGM. And they can use, as I mentioned earlier, ultimate specimen like SNA and other cells. So specimen flow after surgery in the OR or after FNA, one can use any of the tissue types and transported for pseudo-pathology department. It could be that the tissue is prepared and formally fixed. And it could be that they prepare the tissue blocks, and then from the tissue blocks sections, one can extract DNA and then quantify and proceed to DNA capture and enrichment, and pretty much, DNA sequencing. So just to give you a flavor -- mutation distributions in common cancer types, pretty much from melanoma, colorectal, lung and breast, they're not truly that variable, but just to show that they can have ranging from no mutations to actually four variants within the same tissue and one can actually prioritize which driver mutations can be targeted, and that also just to mention that germline versus somatic testing, theres' a little bit of a challenge in terms of using tissue. And I will sort of give that part next after this slide.

So how do we do annotations for tissue? Similarly, there are actually databases that are publicly available, but a lot of cancer centers and the [unintelligible], some of the other cancer centers have their own mutation databases. And also there are available mutation databases that are publicly available, but they're not curated there well. So one should know -- and this is common knowledge in most labs -- that some of the publicly curated databases are not as good. But one needs to understand that this is a very dynamic field, and it could be that that mutation, particular mutation is not available in terms of classification at the moment, but pretty much with all the other data sharing, one can identify exactly -- or at least classify -- a mutation based on information from the different databases, as well as different publications that are available.

So mutations are identified, clinical relevance are given based on is out there in terms of literature. As I mentioned earlier, there are national/international guidelines that actually give us more information on how to treat or manage patients, and that the tumor type and additional tumor type can also be tested and gives us more treatment options depending on what drug has

been used previously. And, of course, the ones that are up and coming and there are known FDA-approved drugs that are available for that patient, the patient can be identified to join clinical trials. And mentioned earlier, if evidence are all based on publication as well as available mutation databases for the solid tumors.

But it's not as simple as the germline. Pretty much primary tumors are heterogeneous, and depending on how much tumor or how much of that particular tumor you have on your sample that would be the mutation or the variant that one can detect, and so therefore, at times, sampling would be a good thing to do. Metastases also can defer from primaries. And I mentioned earlier that tumors can grow, and they become resistant and that, depending on what clone is present, if one predominant clone is present in the primary tumor and that has been targeted by a drug early on, then that could have been really wiped out. But a secondary clone can be more resistant and be present or detected within the next testing. And again, as I probably would allude to, and more importantly with solid tumors, the copy number is very -- the lower copy number mutations are very critical also to detect. And so sensitivity is also a requirement for the validation of this kind of test. So again, individuals with cancer can have multiple tests, and that, of course, reimbursement is also an issue in terms of using next-generation sequencing base tests.

So there are other approaches out there that are commercially available in some laboratories. They have larger panels ranging from hundred genes to 400 genes, and it could be that you could use whole exome sequencing or genome sequencing with or without comparison to germline, and that could be probably something that some labs would eventually be able to offer. The more evolving or the more -- the hot one now is actually you could buy a C or circulating pre-tumor DNA, and it's got its own pros and cons. But it could be used for monitoring, as well as drug selection if it is validated properly.

So in summary, with all these advances, the past years we have access to genetic testing for cancer predisposition, as well as solid tumor genetic profiling. There are important technical advances, but there are also differences in different laboratories, so they may vary in terms of performance. And that one should be wary about how these tests were designed, and the platforms that are used. And pretty much they can be probably gathered from the laboratories that are actually offering this test, and that the other distinguishing or the different shading or points for the different labs that offered solid tumor as well as germline mutation analysis is the databases that they used at the same time, there are a lot of recent publications on clinical utility of multiple gene panels. And I alluded to one of the more recent ones. And that overall, the field of genetic testing for predisposition to cancer is becoming fundamentally important and providing clinical validity and utilities. And it does give hope to some of the patients who don't have the FDA with FDA-drug sensitive cancers. And in that -- nowadays, since we can do genetic profiling of tissue, one can be guided on which drug can be used, and that the targeted therapy will be better use than a shotgun therapy.

So with that, I think I have ten minutes for question and answer. Thank you very much.

Female Speaker:
Thank you Dr. Lacbawan. Is there anyone that has a question?

Bob Wildin:
Hi, this is Dr. Bob Wildin from NHGRI. That was a fantastic presentation. I came in about 15 minutes late, but I really enjoyed that. I have a question about the cancer predisposition genes, and sort of the historical part of that. So we think of BRCA1 and BRCA2 as fairly well-established, and clinically useful. And do you think that that's because they are more common and more -- or because they are -- it was sort of first to discovery and first to market? Or is it because it is fundamentally more powerful than the other genes on the panel that you talked about?

Felicitas Lacbawan:
Okay, at least for breast cancer, the — in our experience, it's pretty much a dimension -- it is the more common one in terms of -- I'm talking about experience in terms of the seven-gene panel. And it is the more common BRCA1 and BRCA2 still are the most-common mutations that we find. And in that, of course, there are some emerging or low-to-moderate penetrant genes like check-2 and PALB2 that we are actually getting more cases on. But I guess because the other thing, too, is because BRCA1, BRCA2 has been tested longer, and who knows -- I mean, most always would stay the most common one and the more dominant gene associated for breast cancer and ovarian.

Bob Wildin:
Then it's not fundamentally different than the others? It's just sort of more common and has a longer track record?

Felicitas Lacbawan:
I would say that is true for now. I guess the more testing or the more individuals are getting tested with the larger panels, we can understand more, probably. Because -- the other -- I'm a clinical geneticist, too. But cancer is, to me, well you're not testing a lot of other possible cancer syndromes. We are just testing mostly you have alluded to the one because BRCA1, BRCA2 is the most associated one, and it's more commonly tested. So again, will that landscape change? Maybe. And if you know more, probably you can share more.

Bob Wildin:
No, no, I'm just -- it just struck me that, you know, we think a lot about BRCA1 and BRCA2, and there's a lot of publicity. And there was, you know, myriad genetics and a lot of publicity into it, and that's not true of most of the other genes that are sort of coming to light now. So it kind of got this head start. It is a fairly high penetrance area, which also helps it, too. And I guess what I'm trying to point out is that we, I think, unconsciously make a division between BRCA1 and BRCA2 and then all the rest. And I'm not sure that, from a clinical standpoint, that that's fair.

Felicitas Lacbawan:
And I'm with you on that. It's -- I think because the other thing too is that because we have more experience and we have more families that have been tested, we get all this referrals most -- I mean, not just from programs within a family, but actually the ones that have been, I mean, had relatives who have been tested before. So --

Bob Wildin:
Which is another interesting point about that category of testing, is it has [unintelligible] effects. So even if you might use the panel and the pro-band, once you find, you know, associated mutations, then you can do targeted testing and the results at much lower cost.

Felicitas Lacbawan:
That's right. Precisely.

Male Speaker:
Hi, this is Dan [unintelligible] in Horizon [spelled phonetically]. Thanks for the presentation, it was very interesting. I have a question about your comments regarding the recent studies talking about clinical utilities for the tumor panels. and I think that one of the challenges we face in developing medical policy is using the right outcomes when it comes to demonstrating clinical utility, and I think the concern I had with these studies is that they really didn't look at any kind of hard outcomes. And I'm using this in comparison to what we've seen. I think it was called the Sheba* Trial, which was several months ago.

And that was, I think, the closer to the right kind of study design we'd be looking for where the results of the panel would guide therapy, and then we'd look at hard outcomes. Where as these panels in general oncology -- so one of them looked at, perhaps, increasing the yield of abnormalities. Which is relevant, but certainly doesn't demonstrate clinical utility when it comes to changing outcomes. And then the other trial was looking at -- oh yeah, actually I think it looked for targeted mutations, but when they actually looked at what happened with Dr. Vishal, they found that very, very few patients actually did get the recommended targeted therapy. So are there other trials that -- I mean, so far -- am I misunderstanding these recent trials? And the second question is: Are there other trials that you think would be more convincing, consistent with looking for hard outcomes?

Felicitas Lacbawan:
So let's -- I think I don't know -- the clinical actionability papers by Desmond and company or the coworkers, it is a multi-centered trial. And it's actually -- they actually have demonstrated that 4 percent of their cases have significantly changed in terms of management. So I think that's, like, one of the more -- to this day --

[end of transcript]