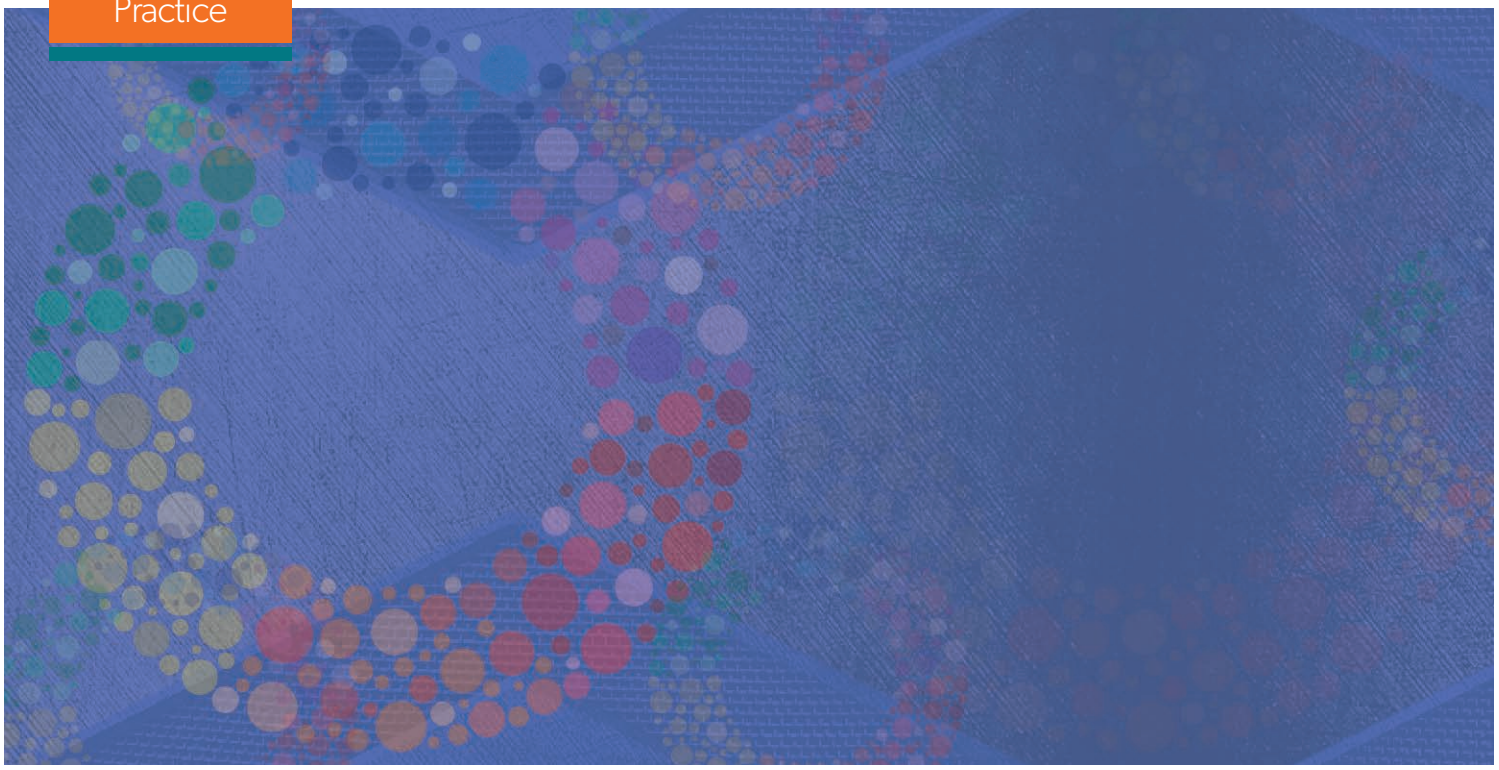


The Impact of Structural Variants and Co-Occurring Variants on Cancer Therapy Prioritization

The ability to better detect structural variants has created challenges for oncologists as they work to stay on top of what such variants mean for patient treatment, according to a recent panel discussion.

By Colin O'Connor

IMPROVEMENTS in nucleic acid sequencing technology have made the routine detection of structural alterations such as gene fusions, amplifications, and genomic instability signatures possible. In particular, the clinical relevance of gene fusions has expanded, resulting in US Food and Drug Administration-approved and clinically supported treatment options. Additionally, the increased use of comprehensive genomic analyses has the potential to inform a broad range of co-occurring somatic and germline alterations that may be associated with hereditary disease, therapeutic selection, and primary and acquired resistance to treatments.

However, this technological progress has increased clinical challenges for oncologists as they try to keep up with therapeutic opportunities and understand how to prioritize treatment options amid other biomarker-informed therapies that could also potentially benefit patients based on their comprehensive genomic profiling results.

This report summarizes the third session of the *Precision Oncology News* Virtual Molecular Tumor Board Series, sponsored by PGDx, in which the panel addressed the challenges and opportunities surrounding structural and co-occurring variants within the context of four clinical cases.

The panel included Aneesa Al-Soodani, variant scientist at Intermountain Healthcare; Derrick Haslem, medical oncologist and director of medical oncology at Intermountain Healthcare; Porscha Johnson Williams, medical oncology clinical pharmacy specialist at Northside Hospital of Atlanta; and Christine Walko, program lead for the precision medicine program at Moffitt Cancer Center.

Introduction to structural variants

Structural variants are defined as alterations in DNA that are one kilobase and larger, Johnson Williams began. These modifications include inversions, translocations, and insertions and deletions. Fusions occur when a gene region is "cut and pasted" into another gene and can result in a protein that is activated in the absence of a ligand and uncontrolled cell proliferation. However, Johnson Williams said, not all fusions have functional consequences or are targetable. Important fusions include BCR-ABL, ALK-EML4, FGFR1-TACC1, ETV6-NTRK3, and RET fusions.

Fusions can drive cancers in many different organs, so comprehensive genomic profiling should be used to uncover possible fusions to identify potential pan-cancer treatments for the patient, she said (see **Figure 1** for selected FDA-approved therapies targeting fusions).

Exon skipping is another structural variant that can occur when alterations result in exons being excluded during mRNA splicing. Johnson Williams gave an example in which exon 14 of the MET gene is skipped, resulting in a protein that is not degraded as normal. Thus, the MET receptor is constantly available, leading to cellular proliferation. MET exon 14 skipping is seen in three to four percent of non-small cell lung cancer patients, most commonly in older patients, females, and former or current smokers.

Case #1: Non-small cell lung cancer, 76-year-old female

Haslem presented the case of a 76-year-old woman with non-small cell lung cancer who presented to the emergency department after a fall and was found to have a mass in the right lung in X-rays (see **Figure 2**). The patient began standard therapy with carboplatin/paclitaxel and radiation. She was then hospitalized with fevers and failure to thrive, during which treatment was paused. Scans showed mixed response to treatment and therapy was changed to pembrolizumab. The patient then developed bilateral pulmonary emboli, and an echocardiogram revealed a large pericardial fusion, with cytology revealing malignant cells consistent with a lung primary. The brain MRI showed no evidence of disease. Scans showed pleural effusions that had significantly increased in size with near complete atelectasis of the right lung, and the patient began second-line chemotherapy with gemcitabine.

Pleural fluid and a fine needle aspiration specimen were analyzed with comprehensive genomic profiling with both DNA and RNA data, which is often used to detect variants such as exon skipping and fusions that appear in RNA transcripts. Walko emphasized the importance of RNA data for confirming structural variants, noting that DNA changes may not always translate to functional protein changes, so RNA data can help ensure that oncologists are not prescribing therapies targeting mutations that are not driving the cancer.

Al-Soodani reviewed the profiling results. The patient's tumor mutational burden (TMB)

Selected FDA approved fusion-targeted therapy		
Gene	**Drug**	**Disease Indication**
ALK	Alectinib, Brigatinib, Ceritinib, Lorlatinib	NSCLC
ALK, ROS1	Crizotinib, Ceritinib (off-label)	NSCLC
FGFR	Erdafitinib/Pemigatinib	Urothelial Carcinoma/Cholangiocarcinoma
NTRK	Larotrectinib	Solid Tumors
NTRK, ROS1	Entrectinib	Solid Tumors, NSCLC
RET	Pralsetinib, Selpercatinib	NSCLG, MTC

Figure 1

Non-Small Cell Lung Cancer
76-year-old, Female

History of Present Illness and Previous Treatments:

Pt presented to the ED after a fall. X-ray revealed a medical R Lung mass.

Pt began treatment with combination radiation therapy and carbo/paclitaxel. Pt was hospitalized with failure to thrive and fevers. Treatment was paused during hospitalization.

Scans showed mixed response, treatment changed to pembrolizumab.

Pt developed bilateral pulmonary emboli. ECHO revealed a large pericardial effusion. Cytology revealed malignant cells consistent with lung primary.

Brain MRI showed NED. Scans showed pleural effusion Significantly increasing in size with near complete atelectasis of the right lung. Began treatment with gemcitabine.

Specimen Sequenced:

Pleural fluid, FNA

Immunotherapy and Other Biomarkers:

1. TMB: High (10.2 mut/MB)
2. MSI: Negative (1.6% unstable sites)
3. PD-L1: Positive (TPS: 90%)

Known Variants:

1. SUPT7L-ALK fusion transcript
2. MET exon 14 skipping
3. CDK4 copy number gain (17 copies)
4. MDM2 copy number gain (8 copies)
5. FGF5 copy number gain (6 copies)
6. SMARCB1 p.L231Afs*50 (22% VAF)
7. TP53 p.V157A (63% VAF)

Non-Actionable Variants & VUS:

1. MSH6 p.C1269Y (37% VAF)
2. IRS1 p.E939K (25% VAF)
3. FLT4 p.Q736* (48% VAF)
4. DAXX p.R273W (48% VAF)
5. CTCF p.Q418R (31% VAF)

Figure 2

was high at 10.2 mutations per megabase, microsatellite instability (MSI) was negative, and PD-L1 was positive.

The patient's tumor harbored several structural variants, including a SUPT7L-ALK fusion. "This specific fusion has not been characterized in the literature but, based on other ALK fusions that are activating and oncogenic, because it retains the kinase domain, it is predicted to be activating like an EML4-ALK," she explained. Profiling also discovered MET exon 14 skipping. Additionally, there was a CDK4 amplification, which has been correlated with increased CDK4 protein expression and implicated in cell proliferation and tumor growth. Likewise, the patient's MDM2 amplification has been correlated with increased protein and P53 inactivation and shown to have a role in cell proliferation, invasion, and metastasis. A copy number gain was also found in FGF5. Lastly, profiling discovered a frameshift in SMARCB1 upstream of the binding domain, which may lead to upregulation of several downstream proteins and inhibition of CDK4 or CDK6.

Therapy considerations include immunotherapy as indicated by the high TMB and positive PD-L1 scores, ALK inhibitors to potentially target the SUPT7L-ALK fusion, and MET inhibitors targeting the exon 14 skipping. Lastly, CDK4/6 inhibitors could be considered to target the CDK4 amplification and SMARCB1 frameshift.

"At first glance, I would be really excited because it seems like there are a lot of options here that I'd be able to present to my patient," Haslem said. In particular, the high TMB and positive PD-L1 are suggestive of response to checkpoint inhibitor immunotherapy. However, closer examination reveals why this patient has not responded to pembrolizumab, he said: the literature is increasingly suggesting that cancers with MDM2 amplification are resistant to checkpoint inhibitors. "This, I think, points to the fact that the use of next-generation sequencing of biomarkers is really exciting, but it does require some effort and some expertise to be able to interpret those rather than just see it as a laundry list of options," he said.

Cervical Cancer
81-year-old, Female

History of Present Illness and Previous Treatments:

Pt presented to the ED after 4-month history of abdominal pain and recent vaginal bleeding. Ultrasound showed an ovarian cystic type mass with uterine enlargement.

Biopsy confirmed carcinoma cervical in origin. Began radiation treatment to control vaginal bleeding.

PET/CT showed large hypermetabolic mass invading the bladder and retroperitoneal, mediastinal and hilar lymphadenopathy.

Completed 3rd round of radiation therapy. Began carboplatin/paclitaxel and bevacizumab. Treatment held due to ongoing rectal bleeding.

CT scan show increasing size of pelvic mass and accompanying adenopathy. New small lung nodules.

Began treatment with pembrolizumab.

Specimen Sequenced:

Right pelvic mass, biopsy

Immunotherapy and other Biomarkers:

1. TMB: High (17 mut/MB)
2. MSI: Negative (0.8% unstable sites)
3. PD-L1: Expression (CPS: 10)

Known Variants:

1. FGFR3-TACC3 fusion transcript
2. ATM c.6453-1G>C (26%VAF)
3. RAD51D p.E104* (21% VAF)
4. ARID1A p.Q944 (21 %VAF)
5. PIK3CA p.E542K (46%VAF)
6. ESR1 p.S559T (36% VAF)

Non-actionable Variants & VUS:

1. MTOR p.E706Q (21% VAF)
2. SPTA1 p.D1634H (30% VAF)
3. PDGFRA p. 1535F (47% VAF)
4. FGFR4 p.G193R (44% VAF)
5. PALB2 p.D772N (2% VAF)

Figure 3

Haslem would be excited about using the ALK inhibitor crizotinib to target the SUPT7L-ALK fusion and MET exon skipping, he said.

Johnson Williams added that it's important to consider patient fitness, and that the inhibitors under consideration would likely be better tolerated than traditional chemotherapy.

Case #2:
Cervical cancer, 81-year-old female

Haslem presented the case of an 81-year-old woman who presented to the emergency department after four months of abdominal pain and vaginal bleeding (see **Figure 3**). Ultrasound showed an ovarian mass that was biopsied and revealed carcinoma of cervical origin. The patient underwent three rounds of radiation to control vaginal bleeding. PET/CT scanning showed a large hypermetabolic mass invading the bladder as well as retroperitoneal, mediastinal, and hilar lymphadenopathy. After the third round of radiation, the patient began systemic therapy with carboplatin/paclitaxel and bevacizumab. Treatment was withheld following rectal bleeding and a CT scan showed an increase in the size of the pelvic mass. New lung nodules were also discovered and assumed to be metastatic disease, and the patient began treatment with pembrolizumab. Biopsy from the pelvic mass was analyzed with comprehensive genomic profiling.

Al-Soodani reviewed the biomarkers. TMB was high and PD-L1 expression was positive, but MSI was negative.

The analysis discovered an activating, oncogenic FGFR3-TACC3 rearrangement that can induce anchorage-independent growth in soft agar, and tumors with this rearrangement are usually invasive, rapidly growing, high grade, and positive for glioma stem cell markers, she explained. The patient's ATM splice site mutation is likely inactivating and oncogenic, as is the RAD512 truncation and ARID1A truncation. The PIK3CA hotspot mutation results in increased PIK3CA activity, inducing an invasive phenotype. The ESR1 mutation has not been characterized, Al-Soodani said, though another substitution at the same site has been characterized as activating, so this mutation is also likely activating.

Therapy considerations include immunotherapy for the high TMB and positive PD-L1 expression. FGFR-family inhibitors in clinical trials or approved in other tumor types may be effective in targeting the FGFR3 fusion, Al-Soodani said. "Futibatinib, infigratinib, and pemigatinib are FDA-approved for cholangiocarcinoma with FGFR2 fusions or other

rearrangements. The FGFRs are pretty similar," she continued, "so targeting them with general FGFR TKIs may be a consideration."

PARP inhibitors can target the ATM, RAD51B, and ARID1A mutations, and PI3K or mTOR inhibitors can target the PIK3CA mutation.

The panelists agreed that prescribing an FGFR inhibitor off label is a strong option. Walko asked Halsem how he would decide which FGFR inhibitor to prescribe, noting that she would look at the potency of each, her familiarity with each, and the indications the drugs are approved for and how similar they are to this patient's situation. Haslem agreed with Walko's reasoning, saying that he would opt for erdafitinib, largely because that is the FGFR inhibitor he has the most experience with. He also said, as it is approved for use in patients with an FGFR3 fusion in bladder cancer, it may be easier to convince payors to approve its use in this patient.

Haslem noted that the reason FGFR inhibitors aren't approved for cervical cancer is because there aren't many cases of cervical cancer with FGFR variants to study in clinical trials. Walko added that it's important to explain to the patient why a drug may not be approved for use with their cancer. "If you're discussing this with a patient and they happen to go on and look up the drug erdafitinib and see that it's only approved in bladder cancer and ask why, [you should emphasize] that we have to do these clinical trials and we have to have a certain number of people to get on the trials to show that they work," she said. "And when you have these really, really rare instances, it doesn't mean that the drug isn't going to work in this patient's type. It's just it's uncommon and therefore it's going to be really challenging to do the clinical trial."

Case #3: Head and neck cancer, 60-year-old male

Haslem reviewed the case of a 60-year-old man who presented with a persistent sore throat and was found to have a fixed left tonsillar mass extending to the medial pterygoids and the base of the tongue (see **Figure 4**). Surgical pathology on biopsy and resection showed a moderately differentiated keratinizing, HPV-negative squamous cell carcinoma of the oral pharynx. A nasogastric tube was inserted, and the patient began standard chemoradiotherapy with carboplatin and 5-FU. PET/CT scan showed a moderate response to therapy after the treatment, but then also noted some development of bilateral pulmonary nodules indicative of metastatic disease. A lung biopsy was analyzed with comprehensive genomic profiling.

The tumor's TMB was low, and MSI and PD-L1 statuses were negative. The tumor had an amplification of ERBB2, which codes for HER2. HER2 amplifications can lead to excessive proliferation and tumor formation, Al-Soodani explained, and can play a role in several types of cancer in addition to breast cancer. Additionally, a region containing co-localized genes CCND1, FGF3, FGF4, and FGF19 has been copied seven times, and there was an ATM splice site alteration.

Immunotherapy markers were all negative, indicating that checkpoint inhibition is not a strong option. HER2 inhibitors are available to target the HER2 amplification, and CDK4/6 inhibitors can target the CCND1 amplification. FGFR inhibitors may be useful in targeting the FGF amplifications, and PARP inhibitors could target the ATM splice site alteration, Al-Soodani said.

Johnson Williams began by acknowledging that the patient's NG tube complicates treatment with oral agents. "At my institution, we don't really let this deter us," she said, as medications can be suspended for delivery by tube, but medications with IV administration should be considered.

"When I see an ERBB2 copy number alteration with a copy number gain of 23 copies, I get excited that this patient will likely respond to HER2 inhibitors. I would start with trastuzumab in this particular patient," Haslem said, noting that trastuzumab's IV formula would simplify potential administration problems, that the drug is well tolerated, and that he has ample experience with the drug. His second choice would be PARP inhibitors targeting the ATM mutation.

However, treating the amplification of CCND1, FGF3, FGF4, and FGF19 is not as compelling, Haslem said, as there is no strong data about that alteration. Walko agreed, saying it can sometimes be important to take options off the table if clinical trial data does not seem to support use. "I think we shouldn't just offer something because it could maybe, perhaps, from a biological standpoint, make sense," she said. "We do owe our patients better in terms of really interpreting the data and trying to help them understand why we're balancing risk and efficacy."

Head and Neck Cancer
60-year-old, Male

History of Present Illness and Previous Treatments:

Pt underwent laryngoscopy with left tonsillectomy for persistent sore throat and was found to have a fixed left tonsillar mass extending to the medial pterygoids and base of tongue.

CT neck showed enlarged enhancing lesion within the oral cavity, lateralized in left glossotonsillar sulcus, involving the intrinsic muscle on the left and the left faucial tonsil. Bilateral lymphadenopathy noted.

Surgical pathology showed moderately-diffused, keratinizing, HPV (p16)-negative SCC of the oropharynx.

NG tube inserted and began CRT with carbo/5-FU.

PET/CT showed moderate response to therapy, but internal development of multiple bilateral pulmonary nodules; highly suspicious.

Specimen Sequenced:

Lung biopsy

Immunotherapy and other Biomarkers:

1. TMB: Low 4 mut/MB)
2. MSI: Negative
3. PD-L1: Negative

Known Variants:

1. ERBB2 copy number gain (23 copies)
2. CCND1 copy number gain (7 copies)
3. FGF3, FGF4, and FGF19 copy number gain (7 copies)
4. ATM c8089+2T>G (32%VAF)
5. TP53 p. P151H (14% VAF)
6. TP53 p.R342* (15% VAF)

Non-actionable Variants & VUS:

1. ASXL1 p.G464fs*12 (5.9% VAF)
2. EPHA3 p. V983M (50% VAF)
3. FANCG p.S387fs*9 (63% VAF)
4. MTAP c.348-2A>G (33% VAF)
5. MUTYH p.Y165C (49% VAF)

Figure 4

Non-Small Cell Lung Cancer
74-year-old, Male

History of Present Illness and Previous Treatments:

Pt presented to his primary care provider for regular follow-up. Provider ordered a screening CT scan of his lungs given his 50 pack-year history of smoking. A CT scan revealed a 7.5 cm mass in the left upper lobe.

He underwent a CT-guided biopsy of the mass. Pathology revealed an adenosquamous carcinoma. A PET/CT confirmed PET avidity of the left upper lobe 7.5 cm mass and identified PET avid left supraclavicular adenopathy, mediastinal lymphadenopathy, and contralateral right upper lobe and left lower lobe masses.

Clinically, the patient appears to have a T4 N3 M1, stage Va, non-small cell lung cancer.

Plans to start treatment with carboplatin/pemetrexed/pembrolizumab.

Specimen Sequenced:

Left lung mass, biopsy

Immunotherapy and other Biomarkers:

1. TMB: High (22 mut/MB)
2. MSI: Negative (2.5% unstable sites)
3. PD-L1: Positive (TPS: 10%)

Known Variants:

1. KIT copy number gain (10 copies)
2. PDGFRA copy number gain (8 copies)
3. WHSC1L1-FGFR1 fusion transcript
4. RPS6KB1-VMP1 fusion transcript
5. TP53 p.E294* (80% VAF)

Non-actionable Variants & VUS:

1. SPTA1 pQ2107K (42% VAF)
2. LRP1B pL3010H (17% VAF)
3. MST1 p.R34H (8% VAF)
4. TSHR p.L629M (27% VAF)
5. PALB2 p.L100F (52% VAF)
6. SMAD2 p.T372A (25% VAF)

Figure 5

Case #4: Non-small cell lung cancer, 74-year-old male

The final case was of a 74-year-old man with a history of smoking who presented for a regular checkup and screening CT scan of the lungs (see **Figure 5**). The scan discovered a 7.5 cm mass in the left upper lobe. Biopsy revealed adenosquamous carcinoma. PET/CT confirmed PET avidity in the left upper lobe and identified supraclavicular mediastinal lymphadenopathy and a contralateral right upper lobe mass, as well as another left lower lobe mass. The patient plans to start treatment with standard carboplatin, pemetrexed, and pembrolizumab, and the left lung mass biopsy was profiled with comprehensive genomic profiling.

The tumor had high TMB and positive PD-L1 expression, but negative MSI. KIT and PDGFRA were both amplified. KIT is considered to be a proto-oncogene, Al-Soodani explained, and activating mutations in KIT can lead to tumorigenesis. PDGFRA amplifications have also been associated with various malignancies. The patient's WHSC1L1-FGFR1 fusion is predicted to be activating and oncogenic, as is the RPS6KB1-VMP1 fusion.

Possible therapies include immunotherapy for the high TMB and positive PD-L1 status, and various tyrosine kinase inhibitors are available to target the

Audience Q&A

The discussion was followed by a brief question-and-answer session with the audience. The following has been lightly edited for clarity and length.

Turna Ray: Can you comment on whether the patients that we discussed today received tumor and normal testing and how TMB thresholds were calibrated, whether they were cancer agnostic or set to a specific histology?

Aneesa Al-Soodani: No, these are advanced-stage biopsies and just tumor-only samples that were sequenced for these specific cases today. The TMB threshold for these was tumor agnostic at 10 mutations per megabase just based on the FDA's approval of pembrolizumab. But there is literature out there that suggests in the future it won't be tumor agnostic. I know, for example, in lung cancer and ovarian cancer, the data is very different for when you start to respond to immunotherapy. And I think it could be lower for non-small cell lung cancer compared to maybe a higher threshold for ovarian, for example. I don't know the exact numbers, but I think in the future when we get more data, the thresholds will no longer be tumor agnostic, but we don't have the data yet to definitively say for this very new biomarker that's being used for immunotherapy whether that'll be the case.

Turna Ray: With regard to the cervical cancer case, the mutation in PIK3CA had a variant allele frequency of around 50 percent while the other actionable variants were lower. Do you have any comments on that? And did you make sure to rule out any interference coming from the pseudogene on chromosome 22 that has over 95 percent homology with PIK3CA exon 9?

Aneesa Al-Soodani: Sometimes, if you see differing VAFs, it could be heterogeneity within the tumor. So maybe one clone has just been overtaking that region where the biopsy was taken. So, it's a combination of heterogeneity and where you took the biopsy. Maybe if you just moved a couple of inches to the left, the VAFs would be very different. And sometimes with PIK3CA, it leads to transforming capabilities in a tumor. So that clone might just have a survival advantage over the other clones in the tumor. So that's usually how I think of differing VAFs, high ones at 50 or over and then lower ones in the 10 percent region. And as far as pseudogenes, I haven't looked at this in detail, but I do know that these targeted panels often take into account that there's a pseudogene present and try to isolate the specific gene that you're looking at, so you don't have to worry about picking up a pseudogene.

Turna Ray: In the absence of a known variant, how do you predict the potential of a variant of uncertain significance? And what do you use to make those predictions? Is there a database or do you use something that's publicly available?

Christine Walko: Whenever I have VUSs that come back on a report that I'm interpreting, I will go through and look at the genes that may catch the eye of the prescribing physician or the main provider – like BRCA1, BRCA2, EGFR, anything that may kind of make them think that we may have a targeted therapy – and then I will go into ClinVar. We actually have a system built into our workflow database that will pull that information out, especially for the BRCA1s and BRCA2s and other genes that are associated with homologous recombination. So I will use ClinVar as my main initial stop to see, first of all, if it is reported in there and what information is there.

Is it benign? Is it likely benign? Is it likely pathogenic? Is it truly uncertain? Is it a mixed

KIT and PDFGRA amplifications, Al-Soodani said. FGFR inhibitors can treat the FGFR fusion, and the mTOR inhibitors may treat the RPS6KB1 fusion as it is involved in the mTOR pathway.

Haslem said that the standard therapy the patient is starting on is the best option to begin with, as the patient should be relatively fit and can handle chemotherapy, and his immunotherapy markers predict response to pembrolizumab. If the patient were to continue progressing, Haslem said he would target KIT with a tyrosine kinase inhibitor. "Those are probably our oldest targeted therapies that we have out there that have the most experience," he said. "And now we have second and third generations of these TKIs. We have really well-defined side effect profiles of these drugs. And they are really easy to administer and get in situations like this." PMQ

Derrick Haslem, MD

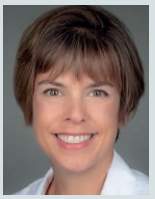
Medical Oncologist & Director of Medical Oncology, Intermountain Healthcare

Derrick Haslem is a medical oncologist and director of medical oncology for Intermountain Healthcare. He is a board-certified specialist in internal medicine and medical oncology with expertise in targeted therapy. Derrick received his medical degree from the University of Utah School of Medicine and residency and fellowship training at the University of Utah Medical Center.

Turna Ray

Managing Editor, Precision Oncology News

Turna Ray has been covering the personalized medicine and molecular diagnostics industries for *GenomeWeb* since 2006. She closely tracks the evolving regulatory, reimbursement, and business environment for precision medicine products. In 2019, she became managing editor of *Precision Oncology News* and now guides coverage for the newly launched *Precision Medicine Online*.



Christine Walko, PharmD, BCOP, FCCP

Associate Member, Department of Individualized Cancer Medicine, Program

Lead for the Precision Medicine Program, Moffitt Cancer Center

Christine M. Walko is an associate member in the Department of Individualized Cancer Medicine and program lead for the Precision Medicine Program at Moffitt Cancer Center. She received her Doctor of Pharmacy from Duquesne University in Pittsburgh. She completed a pharmacy practice residency at Virginia Commonwealth University Health System/Medical College of Virginia Hospitals in Richmond, Virginia. She also completed a hematology/oncology specialty residency at the University of North Carolina Hospitals and Clinics and a hematology/oncology fellowship at the University of North Carolina School of Pharmacy in Chapel Hill, North Carolina. She is a board-certified oncology pharmacist.

Colin O'Connor

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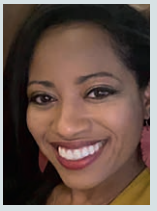
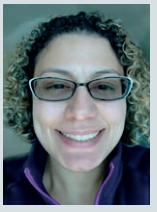
Colin O'Connor is the custom content editor at GenomeWeb. He writes and edits content in partnership with sponsors in the omics, in vitro diagnostics, and precision medicine fields. He was hired in 2021 to manage and grow GenomeWeb's new custom content business. Before joining GenomeWeb, Colin worked in press relations for the Science family of journals. He has a master's degree in science writing from Johns Hopkins University and a bachelor's in biology from Georgetown University. He also serves on the board of alumni editors as the senior copy and research editor for The Science Writer, a web magazine that publishes work by current students of the Johns Hopkins science writing program. He lives in Washington, DC with his partner, Sasha, and their cat, Rocket.



Porscha Johnson Williams, PharmD

Medical Oncology Clinical Pharmacy Specialist, Northside Hospital of Atlanta

Porscha Johnson Williams is a graduate of the University of North Carolina at Chapel Hill and received her Doctor of Pharmacy degree from Howard University College of Pharmacy. She furthered her training through the completion of a post-doctoral clinical pharmacy fellowship in hematology/oncology and critical care at Howard University Hospital. Currently, Porscha practices as a medical oncology clinical pharmacy specialist at Northside Hospital of Atlanta where she specializes in caring for medical oncology and bone marrow transplant patient populations. She collaborates with a multidisciplinary team for treatment decisions, and develops and maintains chemotherapy and supportive care protocols, policies, and procedures according to cutting-edge research within the field. Furthermore, Porscha oversees and contributes to many hospital-wide and department initiatives, the development and delivery of educational material and presentations to all disciplines, as well as serves as an independent consultant for pharmacogenomics to ensure exceptional care for all patients.



Aneesa Al-Soodani, PhD

Variant Scientist, Intermountain Precision Genomics

Aneesa Al-Soodani obtained her BS in biology from the University of Portland and her PhD in molecular biosciences from Washington State University. Her dissertation focused on the regulation of DNA double-strand break repair in the laboratory of Dr. Chengtao. Aneesa then went on to serve as a post-doctoral scholar at the University of Utah chemistry department where she investigated the transcriptional regulation of a family of methyl-binding proteins in prostate cancer. She is now a variant scientist at Intermountain Precision Genomics where she classifies and curates genomic variants. She is passionate about utilizing complex datasets for clinical applications.

bag? And what are the different assay companies that are reporting these different outcomes? And what was the date that the assertion was made into ClinVar? And then, ultimately, if we might be thinking about targeting something that could be uncertain or likely pathogenic, then we will always involve our genetic counselors and our clinical geneticists to have a discussion about that and weigh that evidence against the patients' additional options. But ClinVar is really where I start. I will say it's pretty uncommon to find something in the VUS section, but that does differ on how the different assays themselves will classify it. So, it's always a great question to look at and consider all of your evidence.

Turna Ray: Were copy number signatures that indicate homologous recombination deficiency assessed in the RAD51D ATM-altered cases to support PARP inhibitor therapy?

Aneesa Al-Soodani: It's my understanding that HRD is only used in ovarian, is that your understanding? We didn't have an ovarian cancer case today.

Christine Walko: It's only validated in ovarian cancer currently. However, some of the commercial assays will report it regardless of cancer type. Other commercial assays will report it only for ovarian cancer or perhaps a high-grade serous endometrial. If others are on this call who are working in this area, I cannot wait to see your data. Because I think this question really gets to: How do we identify patients who are going to respond to PARP inhibitors? How do we find out if this ATM and this RAD51D, and even perhaps that ARID1A, are driving the tumor? Does it have a homologous recombination signature? And I think the data is just very limited outside of ovarian cancer right now. If we can understand the phenotype of the tumor, the phenotype may trump the genotype.

If it's telling us that, yes, it is dependent on homologous recombination, and that if we can validate that that is a predictor for PARP inhibitors and even platinum therapy if you have the information that the patient responded really well to platinum therapy, that could also lead you to believe that there's more of a homologous recombination signature going on. But this is definitely an area that I really hope will have more answers and more validated data such that perhaps the HRD score may be closer to tumor mutational burden in the future where we'll be able to normalize it for different cancer types. So, again, if you're working in that area, your work is so valuable, and I can't wait to see it.