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SMARCB1-Retained and SMARCB1-Deficient SNUC are Genetically Distinct: A Pilot Study Using RNA Sequencing

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Abstract

Background Understanding the genetic basis for the molecular classification of sinonasal undifferentiated carcinoma (SNUC) based on SMARCB1 may improve our understating regarding the nature of the disease. The objective of the study was to compare the genetic profile of SMARCB1-retained (SR-SNUC) and SMARCB1-deficient SNUC (SD-SNUC).

Methods Formalin-fixed, paraffin-embedded tissue from treatment-naive patients with SNUC were selected. Three cases of SR-SNUC, four cases of SD-SNUC, and four samples of nontumor tissue (control samples) were selected. Ribonucleic acid (RNA) sequencing was performed.

Results SR-SNUC had a higher number of variants (1 variant for every 15,000 bases) compared with SD-SNUC (1 variant every 29,000 bases). The ratio of missense to silent mutation ratio was higher for SR-SNUC (0.8) as compared with SD-SNUC (0.7). Approximately 1,500 genes were differentially expressed between SR-SNUC and SD-SNUC. The genes that had a higher expression in SR-SNUC included TPD52L1, B3GNT3, GFY, TJP3, ELL3, CYP4F3, ALDH3B2, CKMT1B, VIPR1, SLC7A5, PPP2R2C, UPK3B, MUC1, ELF5, STY7, and H2AC14. The gene that had a higher expression in SD-SNUC was ZFHX4. Most of these genes were related to either protein translation or immune regulation. The most common ($n = 3$, 75%) mechanisms of loss of SMARCB1 gene in SD-SNUC was loss of heterozygosity.

Conclusion RNA sequencing is a viable and informative approach for genomic profiling of archival SNUC samples. Both SR-SNUC and SD-SNUC were noted to have distinct genetic profiles underlying the molecular classification of these diseases.

Keywords
- SMARCB1
- SNUC
- RNA sequencing
- INI-1
- sinonasal cancer

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Introduction

Sinonasal undifferentiated carcinoma (SNUC) is currently defined by the World Health Organization (WHO) as "undifferentiated epithelial neoplasm lacking evidence of squamous or glandular differentiation by histology and immunophenotyping."[1] This has led to SNUC being a heterogeneous group of undifferentiated tumors that lack reliable histopathological markers and has wide variation in survival outcomes ranging from 6 to 75%.[2–6]

The accuracy of diagnosis of SNUC depends not only on the pathologists' acumen to recognize distinct morphological characteristics but also on the extent of the diagnostic markers (immunohistochemical, electron microscopic, molecular/genetic) tested. Additionally, the current literature remains equivocal about the survival outcomes for SNUC which make it particularly hard for a clinician to prognosticate this aggressive tumor. Thus, SNUC is associated with both diagnostic and prognostic challenges and hence, there is a need for novel molecular markers with both diagnostic and prognostic potential.

One of the latest diagnostic markers that has been defined for SNUC is SMARCB-1/INI-1. SMARCB1 is a tumor suppressor gene that is constitutively expressed in all eukaryotic cells. Previous research has noted the prognostic significance of SMARCB1 wherein it was noted that the SNUC patients that had retained SMARCB1 expression had better prognosis with lower recurrence rates and lower mortality rates, while patients deficient in SMARCB1 expression had worse prognosis with higher recurrence and higher mortality rate (67%).[7]

Understanding the genetic basis for this molecular classification (based on SMARCB1) may improve our understating regarding the nature of the disease and thus in turn improve the diagnostic and prognostic accuracy. It might also assist in improving the precision of treatment. The objective of the study was to compare the genetic profile of SMARCB1-retained SNUC (SR-SNUC) and SMARCB1-deficient SNUC (SD-SNUC) by (1) assessing the differential expression of genes, (2) identifying the distinct biologic processes and genes, and (3) understanding the mechanism of SMARCB1 gene loss in SD-SNUC.

Methodology

Institutional review board approval was obtained from Thomas Jefferson University Hospital.

Sample Selection

All cases of SNUC which were diagnosed between 2007 and 2018 at a single tertiary care center were identified ($n = 14$). Samples were divided into SR-SNUC and SD-SNUC based on immunohistochemical staining for SMARCB1. Clinicopathological outcomes of these 14 patients have been published by our research group as part of a previous study (the results of which have been described in brief in the Discussion section below).[7]

To assess the genetic profiles, out of the 14 patients, only those that were treatment naive and had adequate tissue available for testing were selected ($n = 7$). Formalin-fixed, paraffin-embedded tissue (FFPE) was used. Three cases of SR-SNUC and four cases of SD-SNUC were included as "cases." The control samples consisted of four specimens with normal sinonasal tissue from noncancer patients.

Ribonucleic Acid Extraction and Sequencing

Ribonucleic acid (RNA) extraction from FFPE was performed using next-generation QIAGEN kits using the protocol as per manufacturer's instructions. Complementary deoxyribonucleic acid library was created. Overall, the samples had acceptable levels of alignment and tumor purity (►**Table 1**).

Illumina TruSeq RNA Exome libraries were sequenced using Illumina NovaSeq 6000 using 2×100 bp-end chemistry and the reads (in FASTQ format) were aligned to human genome version GRCh38 with Gencode v37 transcript annotations using the RSEM-STAR pipeline.[8,9] The quality assessment of alignments was performed using Qualimap 2 software.[10] The differential gene expression (DGE) was assessed using DESeq2 package in R/Bioconductor software.[11] The core analysis of DGE was done using the Ingenuity Pathway Analysis software (QIAGEN Inc). Additional annotations for tumor suppressor and oncogenes were performed using the Tumor Suppressor Gene Database 2.0 and the COSMIC Cancer Gene Census. STAR was used to assess the genomic alignments. Mutations (base substitutions, small insertions, and deletions) were used using Freebayes v1.3.6. Biological processes associated with DGEs were assessed via Gene Ontology (GO) analysis using the gene set enrichment analysis software. Thresholds of 1.5 absolute fold change and false discovery rate (FDR)-corrected p-value of 0.05 were used for statistical analysis.[12]

Results

The three groups of samples—SR-SNUC, SD-SNUC, and controls—were compared based on various parameters.

1. Variant analysis:

(a) Frequency and type of variants: On analyzing the frequency of the variants among all three groups it was noted that SR-SNUC had the highest number of variants. The total variants seen in SR-SNUC was almost twice that of SD-SNUC. The frequency for SR-SNUC was 1 variant for every 15,000 based, while SD-SNUC had 1 variant every 29,000 bases and control samples had the least number of variants (1 in every 35,000 bases). The most common type of variant was single-nucleotide polymorphism among all three groups

Table 1 Comparison of alignment and tumor purity levels

Parameters analyzed	SR-SNUC	SD-SNUC	Control
Proportion of read pairs properly aligned	88%	94%	93%
Tumor purity score (*using ESTIMATE*)[30]	70%	90%	NA

Abbreviations: SD-SNUC, SMARCB1-deficient SNUC; SNUC, sinonasal undifferentiated carcinoma; SR-SNUC, SMARCB1-retained SNUC.

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Table 2 Comparison of type and frequency of variants

Type	SR-SNUC	SD-SNUC	Controls
Single-nucleotide polymorphism (SNP)	165,983	88,915	71,678
Multiple-nucleotide polymorphism (MNP)	13,357	6,433	5,898
Insertion	10,102	4,455	3,336
Deletion	13,490	5,920	4,546
Mixed	1,537	701	615
Total	204,469	106,424	86,073

Abbreviations: SD-SNUC, SMARCB1-deficient SNUC; SNUC, sinonasal undifferentiated carcinoma; SR-SNUC, SMARCB1-retained SNUC.

Table 3 Comparison of functional class of variants

Functional class	SR-SNUC	SD-SNUC	Controls
Missense	33,753 (44%)	38,724 (43%)	32,279 (44%)
Nonsense	688 (0.9%)	342 (0.4%)	208 (0.3%)
Silent	42,132 (55%)	50,160 (56%)	40,924 (56%)

Abbreviations: SD-SNUC, SMARCB1-deficient SNUC; SNUC, sinonasal undifferentiated carcinoma; SR-SNUC, SMARCB1-retained SNUC.

of samples. The rest of the details of the type of variant have been shown in ►**Table 2**.

(b) Functional class: Based on the functional class of the variants, it was noted that the ratio of the missense to silent mutation ratio was highest for SR-SNUC (0.8) as compared with SD-SNUC (0.7) and control samples (0.7). Also, among the different classes of variants, the proportion of nonsense mutation was highest for SR-SNUC. The details are provided in ►**Table 3**.

2. Differentially expressed genes:

On analyzing the number of differentially expressed genes, it was found that approximately 1,500 genes were differentially expressed between SR-SNUC and SD-SNUC. In comparison to SR-SNUC, SMARCB1 gene was five times downregulated in SD-SNUC ($p < 0.002$). Similarly, 1,422 genes were differentially expressed between SR-SNUC and control samples, while 1,773 genes were differentially expressed between SD-SNUC and control samples. In comparison to control samples, SMARCB1 gene was five times downregulated in SD-SNUC ($p < 0.001$).

On comparing the SR-SNUC and SD-SNUC it was noted that 420 genes were upregulated in SD-SNUC, while 300 genes were downregulated in SD-SNUC in comparison to SR-SNUC (►**Fig. 1**).

Among the 1,500 genes that were differentially expressed, the genes that were able to accurately discriminate between SR-

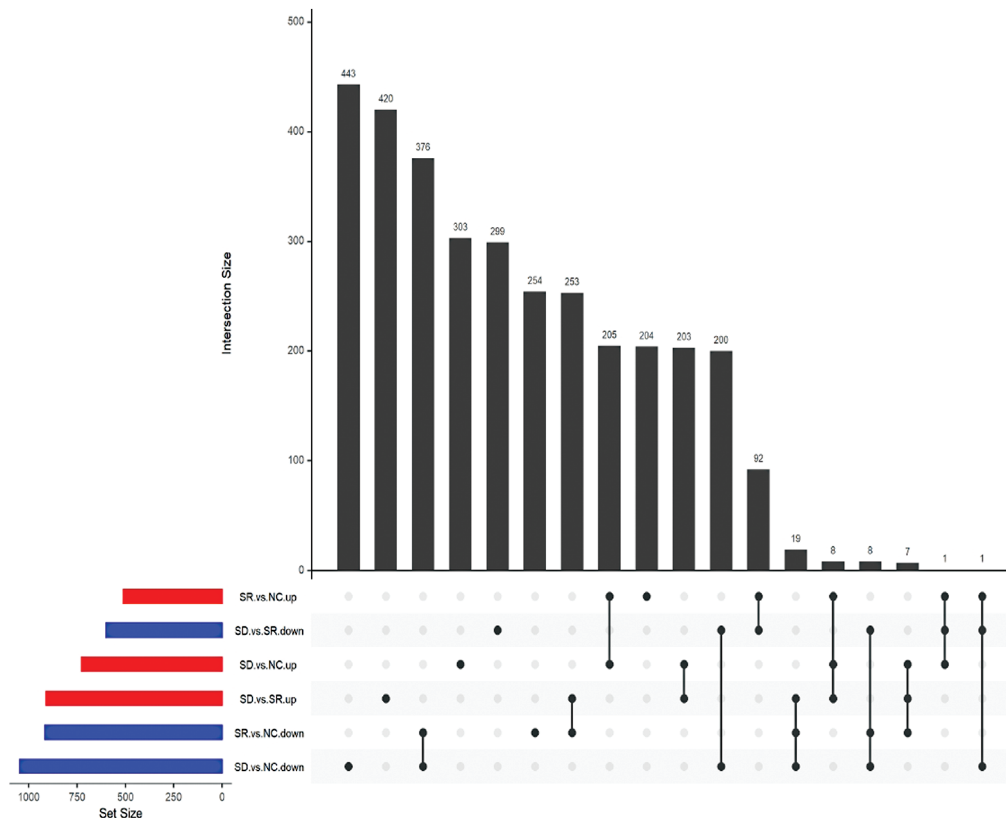

Fig. 1 Denotes the differential expression of gene sets. (The total gene sets on the left bottom corner are arranged in ascending order, while the intersection size is denoted on the *x*-axis in descending order. The red boxes denote the upregulated genes and blue boxes denote the downregulated genes.)

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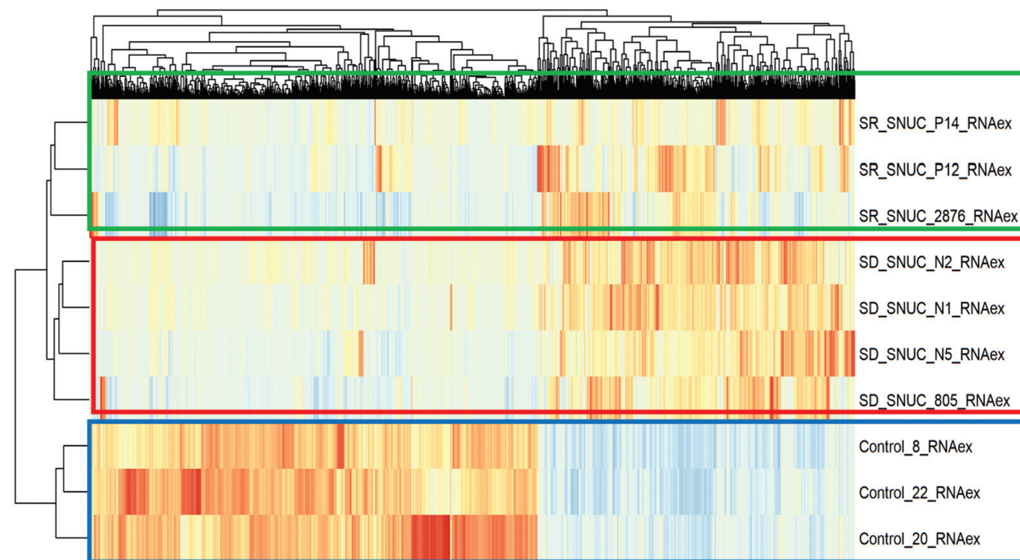

Fig. 2 Denotes the heat map of the gene expression of the samples. (The upper 1/3rd of the map denotes the SMARCB1-retained [SR-sinonasal undifferentiated carcinoma [SNUC]] [green box], the middle 1/3rd [red box] denotes the SMARCB1-deficient SNUC [SD-SNUC], and the bottom 1/3rd [blue box] represents control sample. The higher color intensity denotes higher level of clustering. Red denotes the upregulated genes while blue denotes the downregulated genes.)

SNUC and SD-SNUC were analyzed (i.e., area under the curve $= 1$, FDR < 0.05, absolute fold change of at least 1.5). The genes that had a *higher expression in SR-SNUC* included TPD52L1, B3GNT3, GFY, TJP3, ELL3, CYP4F3, ALDH3B2, CKMT1B, VIPR1, SLC7A5, PPP2R2C, UPK3B, MUC1, ELF5, STY7, and H2AC14. The gene that had a *higher expression in SD-SNUC* was ZFHX4.

3. Unsupervised clustering:

Unsupervised cluster analysis was performed to understand whether SR-SNUC and SD-SNUC can be differentiated based on their gene expression patterns obtained from the above-mentioned list of gene that were differentially expressed. It was noted that both types of tumors have a very distinct pattern compared with control samples. More interestingly, both SR-SNUC and SD-SNUC were noted to naturally self-separate into distinct heat map patterns denoting distinct gene expression (►**Fig. 2**).

4. Biologic and ingenuity pathways:

Several biological processes related to the enriched genes were noted to be distinct between SR-SNUC and SD-SNUC. Most of the processes were related to either protein translation or immune regulation. The distinct biologic processes related to enriched genes have been listed in ►**Table 4**.

To better understand the immune biology, signaling, and functional perturbations during tumor development, the ingenuity pathway analysis was performed. The distinct ingenuity pathways between different samples have been shown in ►**Table 5**.

5. Mechanism of loss of SMARCB1 gene in SD-SNUC:

On analyzing the SD-SNUC samples, it was noted that the most common mechanisms of loss of SMARCB1 gene was loss of heterozygosity ($n = 3$) and homozygous deletion of exon 1 ($n = 1$).

Discussion

In a previous study comparing the clinical outcomes of SR-SNUC and SD-SNUC, it has been shown that the loss of *SMARCB1* expression confers an overall worse prognosis.[7]

Table 4 Comparison of distinct biological processes

Gene ontology term	FDR value
SRP-dependent cotranslational protein targeting to membrane[a]	8.49E-20
Nuclear-transcribed mRNA catabolic process, nonsense-mediated decay[a]	1.32E-18
Viral transcription	1.32E-18
rRNA processing[a]	1.92E-16
Complement activation[b]	5.04E-16
Translational initiation[a]	7.44E-16
Complement activation, classical pathway[b]	1.57E-15
Translation[a]	1.14E-14
Fc-gamma receptor signaling pathway involved in phagocytosis[b]	4.80E-09
Receptor-mediated endocytosis[b]	4.12E-08
Regulation of immune response[b]	1.37E-06
Fc-epsilon receptor signaling pathway[b]	2.29E-05
Proteolysis[a]	5.87E-03
Positive regulation of B cell activation[b]	7.75E-03
Ribosomal small subunit assembly[a]	9.56E-03

Abbreviations: FDR, false discovery rate; mRNA, messenger ribonucleic acid; rRNA, ribosomal ribonucleic acid; SRP, signal recognition particle.
[a]The biological processes related to protein synthesis.
[b]Biological processes related to immune regulation.

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Table 5 Comparison of ingenuity pathways

SR-SNUC versus SD-SNUC	SR-SNUC versus controls	SD-SNUC versus controls
eIF2 signaling	Kinetochore metaphase signaling pathway	Kinetochore metaphase signaling pathway
mTOR signaling	IL-15 signaling pathway	Mitotic roles of Polo-like kinase
Regulation of eIF4 and p70S6K signaling	Nicotine degradation II pathway	Nicotine degradation II pathway
Neuropathic pain signaling in dorsal horn neurons	Nicotine degradation III pathway	Cell cycle: G2/M DNA damage checkpoint regulation

Abbreviations: DNA, deoxyribonucleic acid; IL, interleukin; SD-SNUC, SMARCB1-deficient SNUC; SNUC, sinonasal undifferentiated carcinoma; SR-SNUC, SMARCB1-retained SNUC.

In the study, 14 cases of SNUC were evaluated out of which 57% ($n = 8$) were SR-SNUC, while the remaining 43% ($n = 6$) were SD-SNUC. Although there was no statistically significant difference between the groups based on clinicopathological features and treatment modalities, SD-SNUC showed poorer prognosis. SD-SNUC showed higher recurrence (75 vs. 17%) and mortality (67 vs. 14%) (hazard rate = 8.562; $p = 0.05$) rates. Patients with SR-SNUC were noted to develop local recurrence ($n = 1$), while patients with SD-SNUC showed all three patterns of recurrent disease—local ($n = 1$), regional ($n = 1$), and metastatic ($n = 1$). Patient with SD-SNUC had poorer overall survival (OS) ($p = 0.07$) and poorer disease-free survival (DFS) ($p = 0.02$) on Kaplan–Meier curves. Both OS (28.82 ± 31.15 vs. 53.24 ± 37.50) and DFS durations (10.62 ± 10.26 vs. 43.79 ± 40.97) were consistently worse for SD-SNUC. Five-year survival probabilities were lower for SD-SNUC (0.33 vs. 0.85). Overall, 62% of patients (86% of SR-SNUC and 33% of SD-SNUC) were alive at the time of completion of the study.

Based on the distinct clinical outcomes of this study it is imperative to understand the molecular basis of the two types of SNUC—SR-SNUC and SD-SNUC. Although there are a few studies[13–15] describing the molecular characteristics of SNUC, to our knowledge this is the first study comparing the genetic makeup of the two types of SNUC based on SMARCB1 status. This absence of SMARCB1 in some of the non-sinonasal cancer has been used as a molecular marker for targeted therapies in several clinical trials.[16–18] These trials include targeted therapies like EZH2 inhibitors, histone deacetylase inhibitors, and CDK4 inhibitors. Tazemetostat is one such agent which is an oral selective EZH2 inhibitor that has shown some effectiveness in treating some of the SMARCB-1-deficient malignancies.[16] If these trials are successful, then it is possible to use SMARCB1 as a molecular marker for diagnosis, prognosis, and therapeutic purpose for SNUC. Therefore, it is critical to understand the molecular profiles of the various types of SNUC since it may help to better understand the molecular pathways and in turn may aid in identifying therapeutic targets.

To better characterize the molecular and genetic makeup of the two subtypes of SNUC, we used multiple parameters including frequency and class of variants, heat map patterns of gene expression, biological processes, and ingenuity pathways. We also noted the enriched genes in each tumor subtype. Overall, we found that all these parameters were distinct between the two subtypes of SNUC. Therefore, it is likely that loss of SMARCB1 in SD-SNUC triggers separate genetic pathways which in turn produce a distinct subtype of SNUC. At least one of the reasons for the dissimilar clinical outcomes between SR-SNUC and SD-SNUC could be related to the distinct genetic makeup of the two tumor subtypes. Also, it is unclear why SD-SNUC showed higher number of variants as compared with SR-SNUC and needs further validation. Also, this might just be reinforcing of the idea that they are truly different diseases.

It is worthwhile to note that the SD-SNUC cases in our study represent tumors that are now classified in the latest (5th edition) WHO Classification of Head and Neck Tumors as SMARCB1-deficient sinonasal carcinoma, which is the most common subtype of SWI/SNF complex-deficient sinonasal carcinoma.[19] SMARCB1-deficient carcinoma is a novel type of sinonasal cancer that was first reported in 2014 and mentioned in the differential diagnosis of SNUC in the 4th edition of the WHO Classification of Head and Neck Tumors in 2017.[19–23] Morphologically these tumors can appear basaloid, eosinophilic, squamoid, or even undifferentiated (as in our cases of SD-SNUC). Also, similar to what we found with SD-SNUC, SMARCB1-deficient sinonasal carcinoma is noted to be aggressive with poor prognosis. The other SNUC variant described in our study, SR-SNUC, probably represents a diverse group of tumors that likely harbor other molecular abnormalities.

Among the several genes that were accurately able to distinguish between the two subtypes of SNUC, it was noted that ZFHX4 gene was upregulated in SD-SNUC. Multiple studies have shown that ZFHX4 is a poor prognostic marker for several cancer types.[24,25] Conversely, vasoactive intestinal polypeptide type-I receptor (VIPR1) overexpression has been reported to play a critical role in hindering tumor growth and metastasis in some cancer types.[26] It remains to be seen if these enriched genes in SNUC have a similar mechanism of action.

Gene ontologies and biologic processes were analyzed to better delineate the biological features of SNUC. Of all the gene ontologies enriched in SNUCs, most of them were related to either protein synthesis or immune regulation. SNUC is an aggressive tumor with high mitotic rate.[27,28] This could possibly be the reason for upregulation of pathways related to protein synthesis. The higher proportion of enriched GO related to immune regulation is probably a

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reflection of the changes in the immune regulation in the tumor microenvironment.[29] Further studies are needed to analyze the changes in tumor microenvironment and if immunotherapy could be integrated into the multidisciplinary treatment strategies for personalized cancer treatment.

To summarize, based on the various parameter analyzed, both subtypes of SNUC—SR-SNUC and SD-SNUC—were observed to have distinct genetic makeup which likely is a reason for their distinct clinical behavior. This genetic difference could provide promising leads for improving therapeutic precision for patients with SNUC.

We acknowledge the limitations of the study, namely, the small sample size. Additionally, RNA sequencing only measures transcribed portion of the genome and not the regulatory portion. Therefore, further studies need to be conducted with broad-based sequencing, that is, whole genome sequencing and exome sequencing. Additionally, considering SNUC is a rare sinonasal tumor, we propose that for further studies a multi-institutional rare tumor registry could be used to increase the sample size.

Conclusion

This is the first study comparing the genetic profiles of both SMARCB1-retained and SMARCB1-deficient SNUC. Both SD-SNUC and SD-SNUC were noted to have distinct genetic profiles. Further large-scale studies are required to better delineate molecular characterization of the subtypes of SNUC.

Presentation
Oral presentation at North American Skull base society (NASBS) annual meeting at Phoenix, Arizona on February 18–20, 2022.

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Conflict of Interest
None declared.

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