Germline mutations in high penetrance genes are associated with worse clinical outcomes in patients with non–small cell lung cancer

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ABSTRACT

Objective: To determine the frequency of pathogenic mutations in high-penetrance genes (HPGs) in patients with non–small cell lung cancer (NSCLC) and identify whether such mutations are associated with clinicopathologic outcomes.

Methods: Patients with NSCLC who had consented to participate in a linked clinical database and biorepository underwent germline DNA sequencing using a next-generation sequencing panel that included cancer-associated HPGs and cancer risk–associated single nucleotide polymorphisms (SNPs). These data were linked to the clinical database to assess for associations between germline variants and clinical phenotype using Fisher’s exact test and multivariable logistic and Cox regression.

Results: We analyzed 151 patients, among whom 33% carried any pathogenic HPG mutation and 23% had a genetic risk score (GRS) >1.5. Among the patients without any pathogenic mutation, 31% were at cancer stage II or higher, compared with 55% of those with 2 types of HPG mutations (P = .0293); 40% of patients with both types of HPG mutations had cancer recurrence, compared with 21% of patients without both types (P = .0644). In multivariable analysis, the presence of 2 types of HPG mutations was associated with higher cancer stage (odds ratio [OR], 3.32; 95% CI, 1.10–9.93; P = .0228), increased recurrence of primary tumor (OR, 2.93; 95% CI, 1.07–7.94; P = .0327), shorter time to recurrence (hazard ratio [HR], 3.03; 95% CI, 1.14–8.00; P = .0119), and decreased cancer-specific (HR, 3.53; 95% CI, 1.35–9.08; P = .0039) and overall survival (HR, 2.44; 95% CI, 1.01–5.85; P = .0424). In multivariable analysis, the presence of 2 types of HPG mutations was associated with higher cancer stage (odds ratio [OR], 3.32; 95% CI, 1.10–9.93; P = .0228), increased recurrence of primary tumor (OR, 2.93; 95% CI, 1.07–7.94; P = .0327), shorter time to recurrence (hazard ratio [HR], 3.03; 95% CI, 1.14–8.00; P = .0119), and decreased cancer-specific (HR, 3.53; 95% CI, 1.35–9.08; P = .0039) and overall survival (HR, 2.44; 95% CI, 1.01–5.85; P = .0424).

Conclusions: The presence of mutations in HPGs is associated with higher cancer stage, increased risk of recurrence, and worse cancer-specific and overall survival in patients with NSCLC. Further large studies are needed to better delineate the role of HPGs in cancer recurrence and the potential benefit of adjuvant treatment in patients harboring such mutations. (JTCVS Open 2022;12:399-409)

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Advancements in our understanding of the somatic mutations in non–small cell lung cancer (NSCLC) has led to the development of targeted molecular therapy and immunotherapy, with practice-changing results. The role of the patient’s underlying genetic makeup also may have a significant impact on cancer development and outcomes, but this historically has received less attention than somatic driver mutations. The heritability of lung cancer was estimated at 18% in twin studies. Population-based studies also have implicated family history as a significant risk factor for lung cancer. Many questions regarding tumor biology cannot be answered based on somatic mutations alone: Why do some heavy smokers develop lung cancer while others do not? Why do some patients present with widely metastatic disease and others with a small primary tumor and a single metastasis? Why do cancers that are seemingly similar biologically have radically different outcomes in different patients?

Across a variety of cancers, pathogenic germline mutations in high-penetrance genes (HPGs) have been implicated in both an increased risk of developing cancer and the development of more aggressive cancers. Our group has published work showing how a targeted inherited cancer panel including HPGs and using single nucleotide polymorphisms (SNPs) to generate a polygenic genetic risk score (GRS) not only can help identify patients at increased risk of developing prostate cancer, but also is associated with worse clinical outcomes. 

Although research on germline mutations among lung cancer patients is in its early stages, recent evidence suggests that a considerably high proportion of lung cancer patients have germline pathogenic mutations in HPGs. Genes that have been associated with lung cancer include ATM, BRCA1, DIS3, ERCC2, FANC, MRE11A, PALB2, PIK3C2G, and XRCC2 in lung adenocarcinoma, and BRCA2, BRIP1, DIS3, FANCA, FANCC, MAP3K15, and PARP3 and lung squamous cell carcinoma.

In this study, we used a prospectively collected linked clinical database and biorepository along with next-generation sequencing (NGS) of DNA to analyze the prevalence of pathogenic mutations in HPGs and overall GRS in patients with NSCLC. We also assessed for any association between pathogenic mutations and clinicopathologic outcomes, including cancer stage, histologic grade, cancer recurrence, and overall survival (OS) and cancer-specific survival. It was our hypothesis that an increased prevalence of pathogenic HPG mutations and elevated GRS would be associated with worse clinical outcomes.

**METHODS**

**Study Population**

The study cohort comprised patients with either primary lung adenocarcinoma or squamous cell carcinoma, diagnosed between March 1, 2013, and November 1, 2017, who had consented to participate in a prospectively collected linked clinical database and biorepository and had either a blood or tissue sample from which DNA could be extracted. Patients had to be age ≥18 years at the time of diagnosis. This study was approved by the North Shore University HealthSystem Institutional Review Board (IRB EH18-162, March 20, 2018).

**Data Collection**

Clinicopathologic data, including age, sex, age at diagnosis, smoking history, clinical and pathologic stage, vital status, recurrence, and type of therapy, were obtained from a prospectively collected clinical database along with the electronic medical record and the institutional cancer registry.

**Genetic Analysis**

Germline DNA was sequenced using a targeted NGS panel targeting 355 HPGs and 23 SNPs associated with lung cancer risk (Online Data Supplement). HPGs are genes in which rare disruptive or protein-truncating variants confer a high risk of disease. The probes for capturing exon regions in these genes were manufactured by Roche NimbleGen. The SeqCap EZ Library SR User’s Guide (Roche) was followed for library preparation and capture of targeted sequences. Paired-end sequencing of 2 × 150 bp was performed on an Illumina NextSeq500 sequencer. The median coverage for the samples was at 300×.

Candidate HPGs evaluated in this study include those involved in DNA repair and/or cancer-related genes. Selection of DNA repair genes was based on the catalog of 178 human DNA repair genes, including genes involved in base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and nonhomologous end joining. Cancer-related genes were selected based on our review of published articles on susceptibility genes in all major types of cancer, including lung cancer. Cancer-related genes have a very broad range of functions, including those ubiquitously expressed, and participate in such fundamental processes as cell cycle regulation.

**Bioinformatics Analysis**

Paired-end reads were aligned to the GRCh37 version of the human genome using Burrows–Wheeler Aligner v0.7 to generate BAM files. After sorting the BAM files using samtools, polymerase chain reaction
duplicates were marked using Picard, and realignment around putative gaps was performed using the Genome Analysis Toolkit v3.2-2. Variant calling was performed with the Genome Analysis Toolkit Haplotype caller. ANNOVAR (http://annovar.openbioinformatics.org/en/latest/) and snpEff were used for annotating variants and for retrieving information on variants in the population-based studies, such as the 1000 Genomes Project (www.1000genomes.org), NHLBI-ESP 6500 exomes, ExAC (http://exac.broadinstitute.org/), and gnomAD (http://gnomad.broadinstitute.org/), and clinical databases, such as the Human Gene Mutation Database, and ClinVar. The pathogenicity of variants was defined based on American College of Medical Genetics and Genomics criteria. Specifically, pathogenic and likely pathogenic mutations are defined as (1) all protein-truncating mutations unless their allele frequency is ≥5% in any racial group in population databases or is reported as benign or likely benign in ClinVar, and (2) nonsynonymous changes if their allele frequency is <5% and reported as pathogenic and likely pathogenic mutations in ClinVar.

GRS
GRS, a population-standardized polygenic risk score (PMID: 31037745), was calculated based on 23 lung cancer risk-associated SNPs identified from previous genome-wide associated studies as

\[ GRS = \prod_{i=1}^{n} OR_i^{Wi} \]

\[ Wi = \frac{1}{\text{OR}_i} + 2f_i(1-f_i)\text{OR}_i+(1-f_i)^2 \]

where \( g_i \) is the genotype of SNP \( i \) in an individual (0, 1, or 2 risk alleles), \( OR_i \) is the odds ratio (OR) of SNP \( i \) estimated from external studies, and \( f_i \) is the risk allele frequency of SNP \( i \) based on gnomAD (non-Finnish European population). The GRS value can be interpreted as relative risk to the general population.

Statistical Analysis
The genomic data were linked to the corresponding clinical database. Because consent for the biorepository and clinical database was granted prior to the revised common rule outlining broad consent, the genetic data and the clinical data were kept separate and were linked only by an “honest broker,” which kept the investigators blinded to the link between genetic data and any protected health information.

With the blinded, linked data, we assessed for associations between germline mutations and clinical phenotype, including pathologic stage, tumor grade, and disease recurrence, using Fisher’s exact test. Recurrence rate was defined as any recurrence of the primary tumor. Time to recurrence was measured from the last day of definitive treatment to the documented first recurrence. OS and cancer-specific survival were measured from the date of diagnosis. No adjustments for multiple comparisons were made because of the small sample size with too few mutations and clinical events for adequate power. Univariate analyses of time to recurrence, OS, and cancer-specific survival were performed using the Kaplan–Meier method and log-rank test. Estimated 5-year survival rates were reported. Multivariable logistic regression and Cox regression were used to assess factors associated with clinical outcomes. OR was reported for logistic regression, and hazard ratio (HR) was reported for Cox regression. All statistical analyses were performed using SAS 9.4 (SAS Institute) with 2-tailed tests and a significance level of \( P < .05 \).

RESULTS
Demographics
We analyzed 151 patients with NSCLC for whom both genetic material and clinicopathologic data were available. Demographic and clinicopathologic data for the entire cohort are presented in Table 1. The majority of patients were at pathologic stage I (n = 96; 64%) with only 7 patients (4.6%) at pathologic stage IV. Twenty-seven patients (18%) were never smokers, and only 13 (9%) were current smokers. Thirty-eight patients (26%) had a family history of lung cancer, and 92 patients (65%) had a family history of other cancers. Most cancers were adenocarcinomas (n = 109; 72%). Thirty-five patients (35%) had documented recurrence of their primary cancer.

Genetic Analysis
We identified 50 patients (33%) who were carriers of any pathogenic mutation of HPGs, with 34 patients (23%) carrying a pathogenic mutation in a cancer-related gene, 38 (25%) harboring a pathogenic mutation in a DNA repair gene (25%), and 22 (15%) harboring a pathogenic mutation in a gene involved in both DNA repair and cancer-related functions (Table 2). The most common mutations were a GBA, MUTYH, or POLO mutation in 4 patients (3%) and either a CHEK2 or GJB2 mutation in 3 patients (2%). The mean GRS was 1.2; 34 patients (23%) had a GRS >1.5 and 16 (11%) had a GRS >2.0.

Clinicopathologic Outcomes
Both carrier status of a pathogenic HPG mutation and elevated GRS were associated with a higher pathologic stage, with the strength of the association varying based on the degree of genetic mutation (Figure 1, A). Among the patients with no pathogenic HPG mutation, 31% (31 of 101) presented at stage II or higher and 11% (11 of 101) were at stage III or higher. Among patients with a pathogenic mutation in either a cancer-related gene or a DNA repair gene but not both, 43% (12 of 28) were at stage II or higher and 21% (6 of 28) were at stage III or higher, a rate not statistically different from those without any mutations (\( P = .3069 \)). For patients who were carriers for both a cancer-related gene and a DNA repair gene pathogenic mutation, there was a significant clinical and statistical difference compared to patients without any mutation, with 55% (12 of 22) presenting at stage II or higher and 32% (7 of 22) presenting at stage III or higher (\( P = .0293 \)). When combined with an elevated GRS, the presence of any pathogenic HPG mutation showed the largest difference compared to those without any mutation (\( P = .0147 \)). Although only 11 patients had both an HPG mutation and a GRS >1.5, 8 of them (73%) were at stage II or higher and 4 (36%) were at stage III or higher. GRS alone was not associated with later stage at presentation. There was not significant association between HPGs or GRS and histologic grade.

We also looked at recurrence of the primary tumor and found a higher overall rate of recurrence in patients with a pathogenic HPG mutation compared with patients without an HPG mutation, with the degree of statistical significance varying according to the type of HPG mutation. Recurrence
data were available for the entire cohort. Nine patients where never disease-free and were excluded from the analysis. The clinical association was strongest in patients with pathogenic mutations in both a DNA repair gene and a cancer-related gene, as 8 out of the 20 patients (40\% ) harboring such mutations experienced recurrence, compared with only 20 of 97 patients (21\% ) without any pathogenic mutation, although the statistical association fell just below the preset threshold of significance ($P = .0644$) (Figure 1, B). Patients who were carriers of a pathogenic HPG mutation in either a cancer-related gene or a DNA repair gene had only a slightly higher rate of primary tumor recurrence compared with patients who were not carriers of any pathogenic HPG mutation (28\% [7 of 25] vs 21\%; $P = .4279$). Unlike stage at presentation, the combination of a pathogenic HPG mutation and elevated GRS did not have a meaningful clinical or statistical difference with respect to overall recurrence ($P = .6783$).

In addition to overall recurrence rate, we measured time to recurrence, OS, and cancer-specific survival (Figure 2). Among patients without any pathogenic HPG mutation, 80\% were free of recurrence at 5 years, compared with only 69\% of patients harboring a pathogenic mutation in either a cancer-related gene or a DNA repair gene but not both and only 55\% of patients harboring pathogenic mutations in both a cancer-related gene and a DNA repair gene ($P = .0330$ both vs none) (Figure 2, A). The 5-year OS rate for patients without any pathogenic mutation was 75\%, compared with 68\% for patients with only one type of mutation and 51\% for those harboring mutations in both a cancer-related gene and a DNA repair gene ($P = .0063$ both vs none) (Figure 2, B). The 5-year cancer-specific survival rate for patients without any pathogenic mutation was 86\%, compared with 77\% for patients

### TABLE 1. Patient characteristics

| Characteristic | Value |
|---------------|-------|
| Total patients | 151   |
| Age, y, mean ± SD | 69 ± 9 |
| Female sex, n (%) | 91 (60.3) |
| Race, n (%) |       |
| Caucasian | 135 (89.4) |
| African American | 4 (2.6) |
| Asian | 8 (5.3) |
| Other | 4 (2.6) |
| Smoking status, n (%) |       |
| Never smoker | 27 (17.9) |
| Former smoker | 111 (73.5) |
| Current smoker | 13 (8.6) |
| Pack-y smoked, median (IQR) (missing, n = 38) | 30 (21-50) |
| Previous history of lung cancer, n (%) | 7 (4.6) |
| Family history of lung cancer, n (%) (missing, n = 4) | 38 (25.9) |
| Family history of other cancer, n (%) (missing, n = 9) | 92 (64.8) |
| Topology, n (%) (missing, n = 3) |       |
| Upper lobe | 83 (56.1) |
| Middle lobe | 10 (6.8) |
| Lower lobe | 55 (37.2) |
| Histology, n (%) |       |
| Adenocarcinoma | 109 (72.2) |
| Squamous cell carcinoma | 42 (27.8) |
| Laterality, n (%) |       |
| Left | 61 (40.4) |
| Right | 90 (59.6) |
| Surgery type, n (%) |       |
| None | 7 (4.6) |
| Wedge | 20 (13.2) |
| Segmentectomy | 12 (7.9) |
| Lobectomy | 112 (74.2) |
| Complications, n (%) (missing, n = 10) | 46 (32.6) |
| Lymph node dissection, n (%) (missing, n = 4) | 141 (95.9) |
| Lymph nodes examined, n, median (IQR) | 13 (8-18) |
| Lymph nodes positive, n, median (range) (missing, n = 9) | 0 (0-7) |
| Surgical resection, n (%) (missing, n = 23) |       |
| R0 | 127 (99.2) |
| R1 | 1 (0.8) |
| R2 | 0 |
| AJCC pathologic staging, n (%) |       |
| pT stage |       |
| pT0 | 5 (3.3) |
| pT1 | 81 (53.6) |
| pT2 | 46 (30.5) |
| pT3-T4 | 19 (12.6) |
| pN stage |       |
| pN0 | 119 (78.8) |
| pN1 | 15 (9.9) |
| pN2 | 16 (10.6) |

### TABLE 1. Continued

| Characteristic | Value |
|---------------|-------|
| pN3 | 1 (0.7) |
| pM stage |       |
| pM0 | 147 (97.4) |
| pM1 | 4 (2.6) |
| Pathologic stage group, n (%) |       |
| I | 96 (63.6) |
| II | 31 (20.5) |
| III | 17 (11.3) |
| IV | 7 (4.6) |
| Lymphovascular invasion, n (%) (missing, n = 19) | 23 (17.4) |
| Tumor grade, n (%) (missing, n = 16) |       |
| Well differentiated | 44 (32.6) |
| Moderately/moderately to poorly differentiated | 50 (37.0) |
| Poorly differentiated | 41 (30.4) |
| Chemotherapy, n (%) | 49 (32.5) |

SD, Standard deviation; IQR, interquartile range; AJCC, American Joint Committee on Cancer.

(Continued)
with only one type of mutation and 65% for patients with mutations in both a cancer-related gene and a DNA repair gene ($P = .0020$ both vs none) (Figure 2, C).

Multivariable logistic and Cox regression analysis was performed on all clinical and genetic variables to assess for association with increased tumor grade, increased pathologic stage at presentation, recurrence of primary tumor, OS, and cancer-specific survival (Tables 3 and 4). None of the genetic variables were associated with increased tumor grade, although patients with squamous cell cancer were much more likely to have moderate to poor tumor grade (HR, 5.53; $P = .0032$). Harboring a mutation in both a DNA repair gene and a cancer-related gene was most strongly associated with presentation at higher stage (OR,
3.32; $P = .0228$), shorter time to recurrence (HR, 3.03; $P = .0119$), worse OS (HR, 2.44; $P = .0114$), and worse cancer-specific survival (HR, 5.53; $P = .0039$) compared with a lack of pathogenic mutation. We also found evidence of an association with any recurrence of the primary tumor (OR, 2.93; $P = .053$), although with a weaker statistical significance than the other clinical outcomes. Patients harboring only a mutation in either a DNA repair gene or a cancer-related gene did not show any statistically significant differences compared with those without any pathogenic mutation. GRS was not associated with any measured pathologic or clinical outcomes.

**DISCUSSION**

In this study of 151 patients with NSCLC, we found that more than 30% of the patients harbored a pathogenic...
mutation in an HPG, and nearly 25% had a GRS >1.5. We also identified an association between the presence of HPG pathogenic mutations and a more aggressive clinical phenotype. Patients who were carriers for pathogenic HPG mutations were more likely to present at a higher pathologic stage, had an increased likelihood of cancer recurrence and shorter time to recurrence, and had decreased OS and cancer-specific survival, with the strongest clinical and statistical associations seen in patients harboring pathogenic mutations across both cancer-related genes and DNA repair genes. Although GRS by itself was not associated with a more aggressive cancer phenotype, those patients who had both an HPG mutation and an elevated GRS were much more likely to present at a more advanced pathologic stage (Figure 3 and Video 1).

There are relatively few published studies on germline HPG mutations and NSCLC, and many of them had either small patient samples or used relatively small gene panels. One exception is a large study from China that looked at 1764 patients using a 381-gene NGS panel and found pathogenic or likely pathogenic mutations in 3.8% of the patients and in 25 different genes, the majority of which are involved in DNA repair pathways.12 A separate study of 1026 patients that used a much smaller 58-gene panel found pathogenic or likely pathogenic mutations in 4.7% of the patients. 9 Although neither of these studies looked at outcomes, the second study did look at family history. Patients with pathogenic or likely pathogenic mutations were more likely than patients without such mutations to have a first-degree relative who also had lung cancer. Compared with the general population, patients with lung cancer were nearly 18 times more likely to have a pathogenic or likely pathogenic mutation. These findings suggest that these mutations are associated with an increased risk of developing lung cancer. The most common mutations were in \( BRCA2 \), \( CHECK2 \),

### TABLE 3. Multivariable logistic regression analysis

| Variables                                      | Moderate to poor tumor grade | Pathologic stage II-IV | Recurrence of primary tumor |
|------------------------------------------------|-----------------------------|------------------------|-----------------------------|
|                                                | OR (95% CI) | \( P \) value | OR (95% CI) | \( P \) value | OR (95% CI) | \( P \) value |
| Female vs male                                 | 1.06 (0.43-2.59) | .8980 | 0.57 (0.27-1.20) | .1385 | 0.81 (0.35-1.89) | .6248 |
| Current or former smoker, yes vs no            | 1.26 (0.48-3.33) | .6407 | 1.05 (0.37-3.03) | .9259 | 1.93 (0.53-7.07) | .3230 |
| Histology, squamous cell vs adenocarcinoma     | 62.59 (3.99-982.72) | \textbf{.0032} | 1.44 (0.61-3.40) | .4080 | 1.07 (0.43-2.70) | .8845 |
| Lymphovascular invasion, yes vs no             | 1.73 (0.55-5.46) | .3508 | 5.93 (2.14-16.46) | \textbf{.0006} | 1.78 (0.60-5.35) | .3016 |
| Pathogenic HPG mutation                        |               |                         |               |                         |               |                         |
| Cancer-related or DNA repair vs none           | 1.21 (0.41-3.54) | .7304 | 1.80 (0.68-4.76) | .2361 | 1.06 (0.34-3.33) | .9198 |
| Cancer-related and DNA repair genes vs none    | 0.87 (0.22-3.48) | .8386 | 3.32 (1.18-9.31) | \textbf{.0228} | 2.93 (0.99-8.68) | .0527 |

Significant \( P \) values are in bold type. OR, Odds ratio; CI, confidence interval; HPG, high-penetrance gene.

### TABLE 4. Multivariable Cox regression analysis

| Variables                                      | Time to recurrence | Overall survival | Cancer-specific survival |
|------------------------------------------------|-------------------|------------------|-------------------------|
|                                                | HR (95% CI) | \( P \) value | HR (95% CI) | \( P \) value | HR (95% CI) | \( P \) value |
| Female vs male                                 | 0.79 (0.40-1.56) | .4938 | 0.64 (0.37-1.10) | .1062 | 0.70 (0.34-1.45) | .3366 |
| Current or former smoker, yes vs no            | 1.82 (0.61-5.41) | .2818 | 2.55 (0.82-7.94) | .1074 | 1.40 (0.42-4.68) | .5825 |
| Histology, squamous cell vs adenocarcinoma     | 1.26 (0.61-2.63) | .5365 | 1.80 (1.02-3.18) | \textbf{.0433} | 1.79 (0.83-3.84) | .1375 |
| Lymphovascular invasion, yes vs no             | 1.83 (0.71-4.76) | .2138 | 1.93 (0.95-3.90) | .0690 | 2.37 (0.90-6.23) | .0802 |
| Pathogenic HPG mutation                        |               |                         |               |                         |               |                         |
| Cancer-related or DNA repair vs none           | 0.85 (0.34-2.13) | .7230 | 1.87 (0.95-3.68) | .0706 | 2.01 (0.82-4.93) | .1257 |
| Cancer-related and DNA repair genes vs none    | 3.03 (1.28-7.20) | \textbf{.0119} | 2.44 (1.22-4.86) | \textbf{.0114} | 3.53 (1.50-8.34) | \textbf{.0039} |

Significant \( P \) values are in bold type. HR, Hazard ratio; CI, confidence interval; HPG, high-penetrance gene.
and ATM. In our study, we found a significantly higher proportion of patients—33%—who harbored an HPG mutation. Whether this is due to differences in the panels is unclear, although the larger study used a 381-gene panel, so that is unlikely to be the sole reason. Our population was mostly Caucasian, compared with an East Asian population in the Chinese studies, and further validation across more varied and larger populations will be necessary.

CHECK2 was also among the higher-frequency mutations in our study, but still represented only 2% of the total patients and 6% of patients with an HPG mutation.

Even fewer studies have examined the clinical impact of germline mutations in lung cancer. Reckamp and colleagues published a study in 2021 that looked a subset of mutations, specifically TP53/EGFR, BRCA2, Fanconi anemia (FA) genes, and non-FA DNA repair genes, in 187 patients with NSCLC. They found a similar proportion of patients with pathologic variants as we found in our study (26.7% vs 33%) and an earlier age of cancer onset depending on the gene mutation. The greatest impact was in patients with a BRCA2 mutation, in whom cancer was diagnosed a median of 12.2 years earlier than in patients without this mutation. TP53, EGFR, and FA genes all showed associations with earlier age of onset, whereas non-FA DNA repair genes were not associated with age of onset. A separate study of 12 different cancers and >4000 patients found that pathogenic germline mutations were associated with early age of onset across multiple cancers. In that study, lung cancer patients with a BRCA1 or BRCA2 mutation presented at a median age of 63 years, compared with 66 years for patients who did not carry a pathogenic mutation. An analysis of 119 patients with NSCLC looked the relationship between repair gene (ERCC1, XP, and XRCC1) and glutathione S-transferase gene (GSTP1, GSTT1, and GSTM1) SNPs and clinical outcomes, including response to platinum-based chemotherapy, treatment toxicity, and OS. In that study, SNPs within ERCC1 were associated with improved treatment response and

FIGURE 3. Graphical abstract summarizing the background, methods, major findings, and implications of this study. HPG, High-penetrance gene; GRS, genetic risk score.

VIDEO 1. Narrated PowerPoint presentation of the major findings of the study. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00351-5/fulltext.
better OS (9.8 months vs 14.1 months), whereas the combination of *ERCC1* and *XRCC1* polymorphisms was identified as a prognostic factor for improved OS in a Cox multivariable analysis.22

The clinical implications of our findings are unclear. As highlighted, this is a burgeoning field, and although the data presented here are intriguing, this study is merely a starting point for further research into the complex interplay between patients’ genetic risk and cancer outcomes. The outcomes on which we focused—stage at presentation, cancer recurrence, and OS and cancer-specific survival—are complex and lie at the intersection of numerous competing factors, including underlying patient genetics, epigenetic and environmental factors, tumor-specific factors, and social determinants of health. In the study reported by Lu and colleagues,10 germline mutations in *BRCA1* and *BRCA2* were associated with a greater frequency of somatic mutations across multiple cancers. This is especially relevant in light of several recently reported studies using serum biomarkers and tumor molecular profiling to identify patients at increased risk of cancer recurrence. Seder and colleagues23 used a panel of 47 biomarkers to accurately identify patients with early-stage cancer <4 cm who were at risk of recurrence with a negative predictive value of 83% and overall accuracy of 78%. A now commercially available product (DetermaRx; Oncocyte) uses a 14-gene panel (of tumor somatic mutations) and has been shown to very accurately predict recurrence and to guide adjuvant chemotherapy use in patients with stage I-IIA NSCLC.24,25

In future studies, we hope to study the interaction between somatic predictors of recurrence with a patient’s underlying genetic risk. This may allow us to better stratify which patients are at risk for recurrence and poor outcomes and which patients may respond best to the ever-increasing number of available therapies, and could serve as the next level of advancement in treating patients with lung cancer.

**Study Limitations**

Our study has several limitations. First, our population was relatively small, consisting of only 151 patients, the majority of whom were stage I, which may preclude generalization to the broader lung cancer population. Second, the overall frequency of pathogenic mutations and clinical events was small, and thus our results may be underpowered to show a statistically significant impact, especially in patients with only a single class of gene mutation. The mutation frequency in specific genes was even lower, leaving us unable to draw any specific conclusions with respect to specific mutations and clinicopathologic outcomes. Third, the targeted NGS panel was developed based on studies published before 2017, and as such, several newly reported lung cancer risk-associated SNPs were not analyzed, including the recent genome-wide associated study of Gabriel and colleagues.26

**CONCLUSIONS**

Our study is one of the first in a North American population to apply a large gene panel to patients with NSCLC. Unlike previous studies that correlated results with specific mutations, our study has demonstrated that genome-wide identification of pathogenic HPG mutations is associated with worse outcomes, most significantly in patients with mutations in multiple oncogenic pathways. Further studies, including larger studies and studies considering somatic variables, will help further define the role of genetic testing in the treatment of NSCLC (Video Abstract).

**Webcast**

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/1588.

**Conflict of Interest Statement**

The authors reported no conflicts of interest.

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Key Words: non–small-cell lung cancer, high penetrance gene, DNA repair, polygenic risk score, germline mutation

Discussion

Presenter: Dr Seth Krantz

Dr Chuong Hoang (Bethesda, MD). Thank you very much to the association for allowing me to discuss this abstract and paper. And I thank Dr Krantz for sending me the manuscript and slides ahead of time to review. This study in non–small cell lung cancer is quite unique and original. Dr Krantz and colleagues explored the clinical impact of gene mutations in the germline, and this was to identify accurate prognostic factors in lung cancer. And so, in this growing literature of population-based genomics, Dr Krantz has identified a subgroup of lung cancers that may require more specialized clinical decision making and/or unique therapies. We should acknowledge the excellent prospective clinical database and tissue bank established by his team at NorthShore, without which this study would not be possible.

I have two short questions that are basic to help all of us better understand your results today, Dr Krantz. Number one, I notice that your cohort was 90% Caucasian. So it’s not obvious if your clinical associations of outcome in lung cancer apply to all persons across a larger population regardless of race. And number two, can you explain more about the genetic risk, or the GRS? Exactly what information does this contain, and specifically, why was this parameter included for risk stratification in addition to the high-penetrance genes that you mentioned? The GRS greater than 1.5 was only relevant when analyzing stage at presentation and was not significant in the multivariate analysis that followed. I thank you very much, and I’ll yield the floor back to you to educate us all.

Dr Seth Krantz (Evanston, IL). Thank you very much for those questions. Yeah, in terms of the distribution of a population where it’s on the monogenic side, right, there are multiple mutations in each one of these genes. And you mentioned, specifically, race. We define that socially, right? And so, in terms of a biological impact on individual gene mutations, there are so many mutations at an individual gene level that probably doesn’t make a difference. Now, on a polygenic risk score per the GRS, the genetic risk score, there probably are differences in broad populations, which is why we see some differences in a large, predominantly East Asian population versus a Western population. It’s why you can go onto ancestry.com and it can tell me that I’m 99% Central European Jewish, right, based on a genome-wide polygenic risk score. But in terms of a monogenic risk, in terms of the individual gene mutations, there’s too much variation, with more variation within groups than between groups. And so, I don’t think that’ll have as significant an impact, but to the GRS it will.

And now to the genetic risk score, that’s a polygenic model, right? So even though we did a 355-gene panel for the high-penetrance genes, those are individual genes we’re looking at, as opposed to an overall score based on the number of SNPs that you have that creates an overall genetic risk score. And that’s based on genome-wide association studies. So, there’s good evidence in the literature that is predictive of development of cancer. And so our hypothesis that it would show an increased stage and be involved in recurrence, but we didn’t find that. The numbers are probably small. And we need to look at a broader population,
both precancer and a screening population, and probably in a larger set of patients across a variety of cancers in a variety of stages and a variety of populations, to see how that genetic risk score actually plays out and what the impact is.

But that combination, again, of monogenic individual genes within a genome-wide array, that polygenic score, probably will have an impact that we just didn’t see here, at least in recurrence.