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Article

Analyzing the effects of genetic mutations in BRCA1, BRCA2, BARD1, and MLH1 in causing different cancers

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SUMMARY

Although many studies have identified individual cancer-associated genes, there is still a gap in understanding which genes contribute broadly across multiple cancer types and how interactions between these genes influence cancer development when examined within the same analysis. Understanding these relationships is important because identifying the genes that contribute most significantly to cancer development may improve early detection, prevention, and targeted treatment strategies. We chose four genes commonly linked to cancer (BRCA1, BRCA2, BARD1, and MLH1) and hypothesized that mutations in the BRCA1 and BRCA2 genes would be associated with a higher number of cancer types and more severe mutation classifications compared to mutations in BARD1 and MLH1, given their central roles in DNA repair and genomic stability and their well-documented links to a broad range of hereditary cancers, whereas BARD1 functions primarily in partnership with BRCA1 and MLH1 is more narrowly tied to mismatch repair–associated cancers. Using publicly available CRISPR gene knockout data from the Broad Institute's Dependency Map (DepMap), gene relationships via protein-protein interactions from the STRING database visualized through Metascape, and mutation data from the NIH ClinVar database to test how often cancer cell lines had genetic dependencies associated with these specific genes, we found that BRCA1 and BRCA2 had mutations occurring most frequently across cancer types, with indications of the BRCA1-BRCA2-BARD1 complex possibly contributing to this pattern of high mutation frequency among BRCA1, BRCA2, and BARD1. These findings can be used to improve cancer prevention and treatment strategies.

INTRODUCTION

Cancer is the second leading cause of death among people in the United States, accounting for over 600,000 deaths in 2024 (1). Moreover, 20 million cancer cases were diagnosed in 2022 alone, with these numbers predicted to increase by 77% by 2050 (2). Certain types of cancer can be caused by genetic mutations that code for proteins that regulate the cell cycle, particularly tumor-suppressor genes (genes that prevent uncontrolled cell division) and oncogenes (genes that promote cell division and survival) (3). When mutated, the cell cycle is disrupted, leading to the uncontrolled growth as cells become stuck in mitosis and become cancerous (4). These cells can build up on top of each other, forming tumors that can become harmful once they undergo metastasis, preventing essential life processes from occurring (5). By targeting these specific genes, cancer could be prevented, treated, or cured in people who are more prone to cancer or currently battling cancer (6).

However, a knowledge gap exists regarding which genes to primarily target to prevent cancer (7). For example, some genes theorized to be involved in cancer are also linked to non-malignant conditions like Cowden's syndrome rather than only a type of cancer (8). Moreover, there is still uncertainty within the genes linked to cancer, as they do not always drive cancer when mutated and there is incomplete knowledge of the genes' specific functions and mutations. For example, the *ATM* gene is known to cause a rare hereditary condition known as ataxia-telangiectasia, but is also linked to breast, ovarian, pancreatic, skin, and prostate cancers when mutated (9). This demonstrates that the presence of a mutation within these genes is insufficient to determine malignancy (10).

Rather than addressing the underlying cause of each mutation, our study analyzed large-scale genomic data to identify which genes were most consistently linked to a wide range of cancers, informing drug development and prioritization. This approach begins to address this knowledge gap by highlighting which type of gene or combination of genes are most strongly associated with cancer.

We used DepMap's (Broad Institute's Dependency Map) genome-wide CRISPR-Cas9 knockout screenings of over 1000 different cancer cell lines, Metascape's gene annotation and relation tools, and ClinVar's classification of mutation pathogenicity to analyze which gene or relations of genes had the broadest associations across cancers through mutation susceptibility (11, 12, 13). We selected four genes: *BRCA1* (a tumor suppressor gene), *BRCA2* (a tumor suppressor gene), *BARD1* (an oncogene), and *MLH1* (a tumor suppressor gene). *BRCA1* is known as the "breast cancer 1" gene and *BRCA2* is known as the "breast cancer 2" gene. They are both normally involved with the maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair and are commonly linked with breast cancer when mutated (14). *BARD1* is known as the "BRCA1 associated RING domain 1" gene which interacts with *BRCA1* and may be an essential aspect of *BRCA1* tumor suppression (14). *MLH1* is known as the "mutL homolog 1" gene and is part of the DNA mismatch repair system, found frequently mutated in hereditary nonpolyposis colon cancer (14). These genes were chosen as each gene represents one of the two types of genes that have the potential to cause cancer and have been identified to be prominent genes linked to cancer consistently (evident through identification by the FORCE database), allowing us to determine which type of gene is most likely to have greater associations to cancer as compared to others, and had in-depth research to conduct our analysis (8).

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We hypothesized that *BRCA1* and *BRCA2* would have stronger associations with a wider range of cancers and higher mutations rates than *BARD1* and *MLH1* because *BRCA1* and *BRCA2* play central roles in DNA damage repair and maintaining genomic stability, and mutations in these genes have been extensively linked to hereditary breast, ovarian, and several other cancers (13). In contrast, *BARD1* primarily functions in partnership with *BRCA1*, while *MLH1* is more specifically involved in DNA mismatch repair pathways associated with a narrower range of cancers (13). Through DepMap, we utilized the CRISPR-Cas9 knockout screening data to identify gene dependencies in cancer cell lines (11). We then collected and used significance testing to analyze which had the most significant associations to cancer. These scores were combined with ClinVar's classification data to determine the general harmfulness of each gene by comparing pathogenic and benign tumor mutations (13). Then, we used Metascape to determine the possible relationships between each gene, indicating whether only one gene or a combination of genes is associated with the different types of cancer when mutated (12). We found that each of the genes contributed significantly to each different type of cancer chosen.

RESULTS

The goal of this study was to determine which cancer-associated genes showed the strongest and widest-ranging associations across different cancer types. We hypothesized that *BRCA1* and *BRCA2* would demonstrate stronger associations with a broader range of cancers and higher mutation frequencies than *BARD1* and *MLH1* because of their central roles in DNA repair and maintaining genomic stability. To test this hypothesis, we analyzed publicly available CRISPR-Cas9 gene knockout data from the DepMap database to examine how cancer cell lines responded when each gene was knocked out (11). The rationale behind this approach was that genes more essential to cancer cell survival or growth would produce larger changes in cell viability when disrupted. Because the selected genes differ in both gene type (tumor-suppressor gene versus oncogene-associated pathway involvement) and mechanisms of action, some genes were expected to show stronger associations with certain cancers than others (15).

Using the DepMap Chronos scores, we performed an ANOVA Single Factor test to determine whether there were differences between the effects of individually knocking out *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* on cancer cell line survival and growth. The Chronos scores measured how dependent each cancer cell line was on a specific gene, with lower scores indicating that knocking out the gene had a stronger negative effect on cell survival or proliferation. Each gene was analyzed independently across the selected cancer cell lines, and the average scores found represent the overall dependency patterns observed for each gene within a cancer type **(STable 1)**.

For most cancer cell lines, knocking out the four genes produced significantly different effects on cancer cell survival and growth, suggesting that some genes contributed more strongly than others depending on the cancer type, indicated by their very low p-values (most <0.001) ($\alpha = 0.05$, Single Factor ANOVA, **STable 1**). In many cancers, *BRCA1* and *BRCA2* knockouts produced stronger reductions in cancer cell survival compared to *BARD1* and *MLH1*. These findings are consistent with the known biological roles of the genes, as *BRCA1* and *BRCA2* are strongly involved in DNA repair and are commonly associated with hereditary breast and ovarian cancers, *BARD1* is often associated with ovarian cancer, and *MLH1* is primarily associated with DNA mismatch repair and colorectal cancers (14).

In contrast, Intracholecystic Papillary Neoplasm did not show significant differences between the effects of the four gene knockouts. This suggests that cancer cell survival in this cancer type may not depend more heavily on one of these genes over the others, unlike many of the other cancer cell lines analyzed. Instead, the genes may contribute more equally to this cancer type, or additional genes and biological pathways not included in this study may play a larger role. More biological testing would have to be done to better understand this result.

To determine which gene had the most significant associations to cancers, we aggregated and graphed ClinVar's mutation classification for each gene (**Figure 1**) (13). In comparing each of the counts, we saw that *BRCA1* and *BRCA2* had the most associations to different types of cancer, as there were more pathogenic mutations recorded as compared to the rest of the genes–*BRCA1* with 3,892 pathogenic mutations (around 26% of its mutations) and *BRCA2* with 4,771 pathogenic mutations (around 33% of its mutations) **(Figure 1a, Figure 1b)**. Meanwhile, *MLH1* had 1,505 pathogenic mutations (around 26% of its mutations) **(Figure 1c)**. However, there was some confusion evident within the graph for *BARD1*, as many of its mutation classification data–1,969 mutations (around 87% of its mutations)–were marked as uncertain significance, indicating that there is a chance for *BARD1* to have more associations to cancer as compared to *BRCA1*, *BRCA2*, and *MLH1* **(Figure 1d)**.

To clear this confusion, we used DepMap again to identify whether the selected genes showed strong correlations in their dependency patterns across cell lines (11). Specifically, Pearson correlation coefficients were analyzed to determine whether cancer cell lines that were highly dependent on one gene also tended to be highly dependent on another, with those around 0.5 (after the absolute value of the coefficient was taken) indicative of a strong relationship. *BRCA1* was seen to have a Pearson correlation (before the absolute value was taken) of 0.558 with *BARD1*, indicating a strong, positive relationship with *BARD1*, indicating that they could be working together. To identify this relationship, Metascape's gene annotation and interaction analysis tool was used to identify the potential protein-protein interactions between the selected genes and related biological pathways **(Figure 2)** (12). *BRCA1*, *BRCA2*, and *BARD1* were found to be involved in multiple shared DNA repair and cell cycle regulation pathways, including the BRCA1-BRCA2-BARD1 DNA damage complex III and BRCA1-BRCA2-BACH1 DNA damage complex I. The enrichment analysis also identified pathways related to DNA repair, ATR-mediated cellular response to DNA damage, and the Fanconi anemia pathway, further supporting the close functional relationship between these genes.

These findings suggest that the uncertain significance mutation classifications for *BARD1* could possibly been attributed to its functional interactions with *BRCA1* and *BRCA2* rather than completely independent activity. Because *BRCA1*, *BRCA2*, and *BARD1* work together in DNA repair and cell cycle regulation pathways that help prevent cancer,

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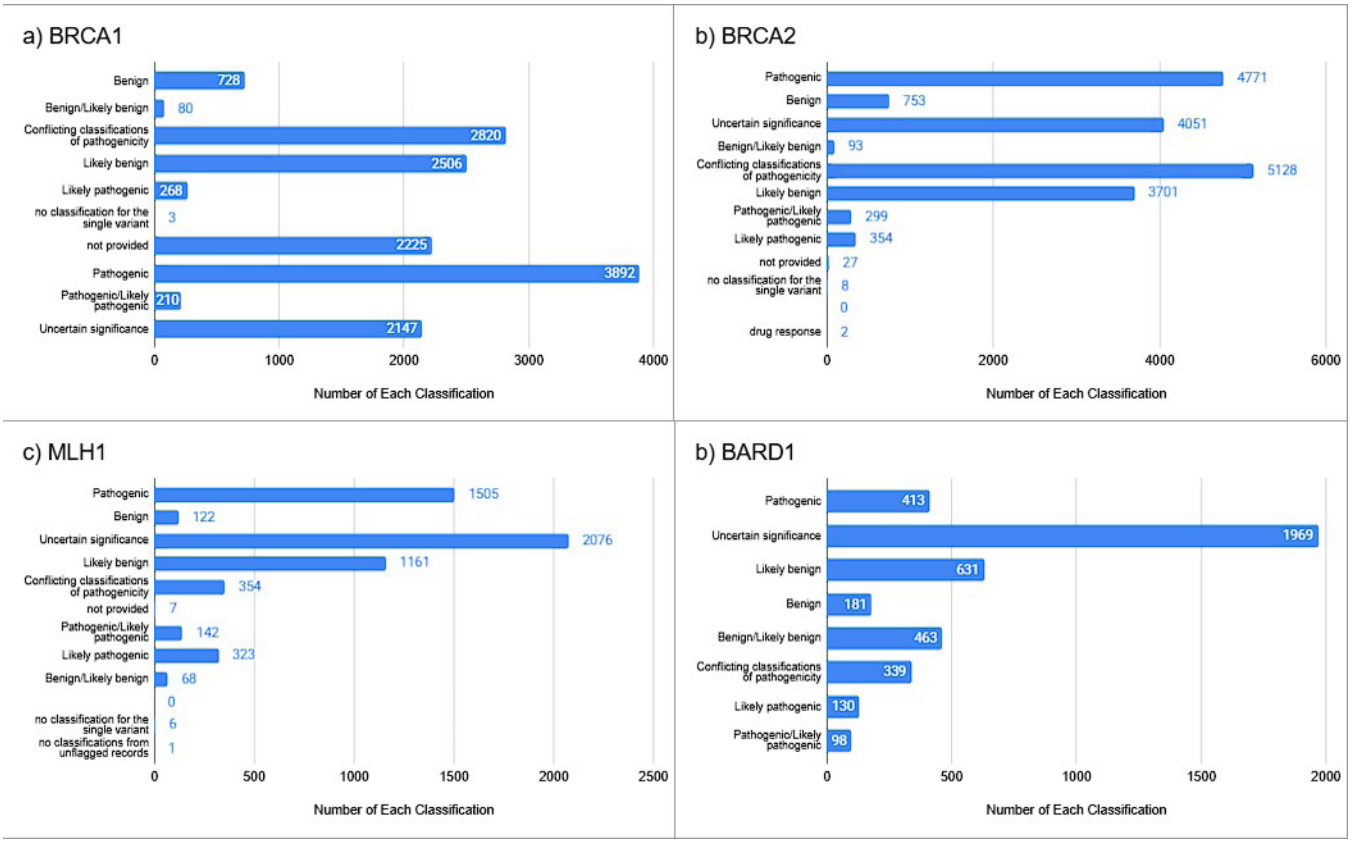

Figure 1: Distribution of ClinVar mutations classifications for *BRCA1* (a), *BRCA2* (b), *MLH1* (c), and *BARD1* (d). Horizontal bar graphs show the number of variants within each clinical significance classification category. The y-axis displays the different mutations classification categories, including pathogenic, likely pathogenic, benign, likely benign, uncertain significance, and conflicting classifications of pathogenicity, while the x-axis shows the number of variants within each category for the respective gene. Data was compiled from the ClinVar database for each respective gene.

mutations affecting one component of the complex may influence the function of the others. This interaction may also help explain why many *BARD1* mutations are classified as variants of uncertain significance, as some mutation effects could overlap with or be characterized primarily as *BRCA1* or *BRCA2*-related dysfunction instead (16). This interpretation is consistent with previous findings, as *BARD1* is known as BRCA1-associated RING domain 1 (14).

In contrast, *MLH1* was not identified within the BRCA1-BRCA2-BARD1 interaction complexes, suggesting that MLH1 may contribute to cancer development through more independent mismatch repair pathways rather than through the same coordinated DNA damage repair complexes **(Figure 2)**. These results support the conclusion that *BRCA1*, *BRCA2*, and *BARD1* have more closely related functional associations across cancers compared to *MLH1*.

DISCUSSION

This study found that *BRCA1* and *BRCA2* showed stronger and broader associations across multiple cancer types compared to *BARD1* and *MLH1*, supporting the original hypothesis. CRISPR knockout dependency data from DepMap suggested that *BRCA1* and *BRCA2* often had greater effects on cancer cell survival and growth, while the Metascape interaction analysis indicated that *BRCA1*, *BRCA2*, and *BARD1* may function together within shared DNA repair complexes. These findings suggest that interactions between genes involved in DNA damage repair pathways may contribute to the widespread associations of *BRCA1* and *BRCA2* across cancers.

A limitation of this study was the cancer cell lines used within the DepMap's CRISPR knockout gene database (11). These cell lines do not account for differences present as a result of race, sex, age, etc (17). These differences could have led to different results for which genes were associated with the most cancers. Future studies could address this limitation by incorporating more demographically diverse cancer datasets, patient-derived tumor samples, or stratified analyses comparing gene dependencies across demographic groups. Additionally, diseases with fewer than five CRISPR knockout entries were excluded from the analysis, which may have affected the overall results.

Another limitation involved the ClinVar mutation classification data. Because ClinVar classifications are submitter-dependent and may contain conflicting interpretations, the reported mutation classifications should be interpreted cautiously. In this study, "pathogenic" classifications reflected reported clinical associations rather than direct proof that a mutation caused a specific cancer. Furthermore, ClinVar did not consistently specify which cancer types were associated with individual mutations, making it difficult to determine whether a gene was broadly

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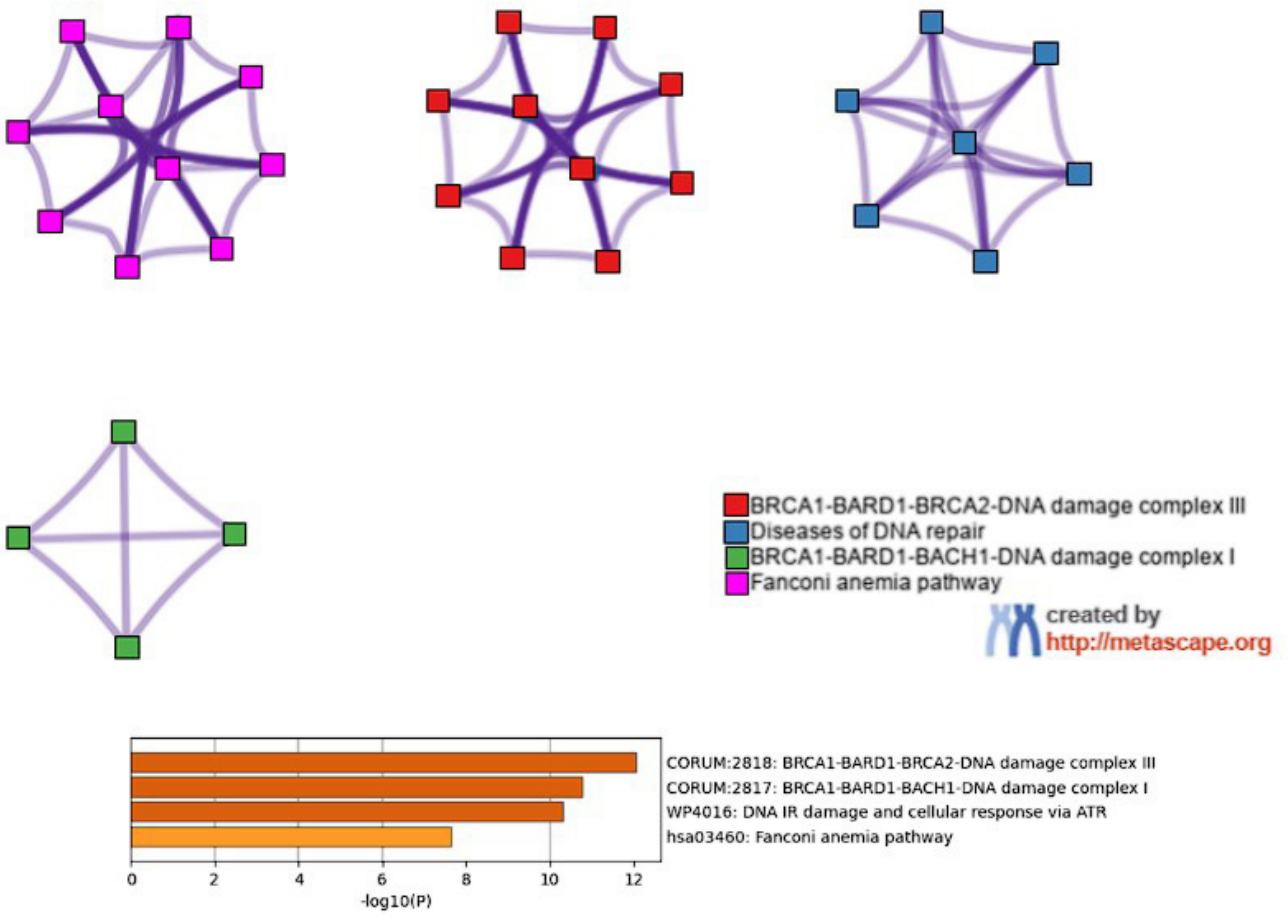

Figure 2. Gene interaction networks and enrichment significance values generated using Metascape for *BRCA1*, *BRCA2*, BARD1, and MLH1. Interaction network graphs display the relationships between the genes based on shared biological pathways, protein-protein interactions, and functional associations identified by Metascape. Each connecting line between genes represents an interaction or association identified within the database. Accompanying graphs display the corresponding −log10(*p*-value) enrichment scores calculated by Metascape for each interaction network. The y-axis represents the specific interaction or enrichment category analyzed, while the x-axis represents the −log10(*p*-value), where larger values indicate greater statistical significance of the interaction or pathway enrichment.

associated with multiple cancers or primarily linked to a single cancer type, such as breast cancer.

The presence of gene interaction complexes, such as the BRCA1-BRCA2-BARD1 complex, may have also complicated the interpretation of mutation effects. Because these genes function together in shared DNA repair and cell cycle regulation pathways, some mutations may overlap functionally, making it difficult to determine whether observed effects were primarily associated with one gene or with the complex as a whole. This may help explain why *BARD1* contained many variants of uncertain significance and why mutations within the complex could sometimes be attributed more strongly to *BRCA1* or *BRCA2*, which have been studied more extensively. As a result, differences in the amount of available research on each gene may have introduced bias into how mutations were classified and interpreted.

These results indicate that some of the genes have more associations to cancers when mutated as compared to others (18). To more conclusively determine which genes had the possibility of causing more types of cancer, we identified the gene with the most cases of severe mutations that were linked to the most different types of cancer. From this data, it was found that *BRCA1* and *BRCA2* had the potential to cause the most different types of cancer, which aligns with past data on these genes (19). The *BARD1* gene had the most recorded instances of uncertain significance, indicating *BARD1* could be working with other genes, making it seem to have more associations to cancer when mutated **(Figure 1b)**. Thus, we graphed the interactions between each gene **(Figure 2)**. The BRCA1-BRCA2-BARD1 complex (used for DNA repair through homologous recombination) may have played a role in why *BARD1* had so much uncertain significance as its mutations could have mutated this complex entirely, linking it to more cancers. For example, the BRCA1-BRCA2-BARD1 complex could have mutated, leading to errors in homologous recombination, allowing the possibility to cause cancer (20).

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In contrast, the *MLH1* gene showed fewer broad associations across cancer types and appeared to function more independently from the BRCA1-BRCA2-BARD1 interaction complex. This finding is consistent with the primary role of *MLH1* in DNA mismatch repair pathways rather than homologous recombination repair (14). The results suggest that *MLH1* mutations may be more strongly associated with specific cancers, particularly colorectal and other mismatch repair-related cancers, rather than contributing broadly across many cancer types. Therefore, while *MLH1* remains an important cancer-associated gene, its effects may be more pathway-specific and less interconnected with the broader DNA repair complexes identified for *BRCA1*, *BRCA2*, and *BARD1*.

This information could be used in future research to determine which genes or types of genes could be targeted to prevent or cure cancer. However, further research must be done to fully draw these conclusions and determine which genes or types of genes should be targeted to prevent or cure cancer. For example, laboratory experiments targeting these specific genes or testing mutations within these genes in mice could obtain more conclusive results in what type of gene, which gene itself, and which gene interaction causes the most types of cancer (21). Overall, the results of this study suggest that *BRCA1* and *BRCA2* have broader associations across multiple cancer types compared to *BARD1* and *MLH1*, while interactions between *BRCA1*, *BRCA2*, and *BARD1* may influence how these genes contribute to cancer development. These findings highlight the importance of both individual gene function and gene interactions in understanding cancer progression. Ultimately, this knowledge can be applied to advancing our understanding of cancer and drug development.

MATERIALS AND METHODS

Gene dependency scores for *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* were downloaded from the DepMap database along with the associated diseases linked to mutations in each gene (11). The data was sorted alphabetically, and diseases with fewer than five gene dependency score entries were removed in order to focus on more prevalent diseases and improve computational performance. The dependency scores for each disease were then compiled, and a Single Factor ANOVA test was performed for each disease to determine whether significant differences existed between the dependency scores of the four genes, resulting in a list of *p*-values **(STable 1)**. Next, mutation data for *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* was downloaded from ClinVar (13). The mutation classifications were organized alphabetically in a spreadsheet, and formulas were used to count the frequencies of the different mutation severity classifications. These data were then visualized using bar graphs to compare the relative numbers of severe mutations among the genes. Finally, Metascape's gene annotation tool was used to analyze interactions between *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* by inputting the list of genes into the software (12). Metascape generated interaction networks based on the STRING protein-protein interaction database, which were downloaded as JPG images and analyzed to compare the varying levels of interaction between the genes **(Figure 2)** (21).

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APPENDIX

Disease	ANOVA Calculated *P*-Value Between the Means of *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* DepMap Chronos Gene Effect Scores
Acute Myeloid Leukemia	3.22E-15
Anaplastic Thyroid Cancer	6.14E-6
B-Lymphoblastic Leukemia/Lymphoma	4.10E-12
Bladder Urothelial Carcinoma	<0.001
Cervical Squamous Cell Carcinoma	1.20E-11
Colorectal Adenocarcinoma	<0.001
Cutaneous Squamous Cell Carcinoma	1.48E-5
Diffuse Glioma	<0.001
Embryonal Tumor	1.27E-7
Endometrial Carcinoma	<0.001
Esophageal Squamous Cell Carcinoma	<0.001
Esophagogastric Adenocarcinoma	<0.001
Ewing Sarcoma	<0.001
Head and Neck Squamous Cell Carcinoma	<0.001
Hepatocellular Carcinoma	<0.001
Intracholecystic Papillary Neoplasm	9.98E-2
Intraductal Papillary Neoplasm of the Bile Duct	<0.001
Invasive Breast Carcinoma	<0.001
Liposarcoma	1.43E-5
Lung Neuroendocrine Tumor	<0.001
Mature B-Cell Neoplasms	<0.001
Mature T and NK Neoplasms	5.03E-8
Melanoma	<0.001

Myeloproliferative Neoplasms	3.97E-9
Nerve Sheath Tumor	1.79E-4
Neuroblastoma	<0.001
Non-Seminomatous Germ Cell Tumor	1.42E-3
Non-Small Cell Lung Cancer	<0.001
Ocular Melanoma	1.02E-5
Osteosarcoma	1.13E-11
Ovarian Epithelial Tumor	<0.001
Pancreatic Adenocarcinoma	<0.001
Pleural Mesothelioma	1.35E-12
Prostate Adenocarcinoma	1.88E-2
Renal Cell Carcinoma	1.33E-15
Rhabdoid Cancer	7.49E-7
Rhabdomyosarcoma	4.29E-7
Synovial Sarcoma	9.82E-3
T-Lymphoblastic Leukemia/Lymphoma	1.55E-2
Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	1.02E-4

STable 1: Table of ANOVA test results calculated from DepMap's gene dependency scores for each gene and the respective cancerous disease. For each cancerous disease, a one-way ANOVA Single Factor test was used to compare the dependency scores of *BRCA1*, *BRCA2*, *BARD1*, and *MLH1* simultaneously, producing a single *p*-value per disease rather than separate p-values for each gene. A significance level of $p < 0.05$ was used to determine statistically significant differences among the four genes' dependency scores within each disease.