

CDKN2A PATHOGENIC VARIANTS IDENTIFIED IN PATIENTS TESTED WITH A 25-GENE HEREDITARY CANCER PANEL

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BACKGROUND

- Pathogenic variants in *CDKN2A* are associated with a predisposition to both melanoma and pancreatic cancer. Patients identified to carry pathogenic variants are appropriate for modified medical management such as clinical skin exams and consideration of pancreatic cancer screening.^{1,2}
- The aim of this analysis was to highlight the personal and family histories of patients with pathogenic variants in *CDKN2A*, as the histories alone for many of these patients would not have been an indicator for *CDKN2A* testing.

METHODS

- We identified patients positive for pathogenic variants in *CDKN2A* as an outcome of clinical testing with a 25-gene hereditary cancer panel reported between September 20, 2013 and February 13, 2015.
- These patients were identified as being appropriate for testing via the panel due to a personal and/or family history of cancer; the majority of which (53/57) met NCCN testing criteria for Hereditary Breast and Ovarian Cancer syndrome (HBOC),³ Lynch syndrome (LS),⁴ or Familial Adenomatous Polyposis (FAP).⁴
- Clinical history data was obtained via healthcare provider report on the test request forms.

RESULTS

- 57 patients were found to carry a pathogenic variant in *CDKN2A*; 55 in the p16INK4A (p16) protein and 2 in the p14ARF (p14) protein.
- 31/57 (54.4%) patients reportedly had no personal (Figure 1) or family history (Figure 2) of either melanoma or pancreatic cancer (Table 1).
- Only 12/57 (21.1%) patients would have met widely-accepted guidelines for *CDKN2A* testing: personal/family history of two or more melanomas, or at least one melanoma and at least one instance of pancreatic cancer.¹
 - Three patients were listed as having one or more relatives with “skin cancer.” These were not counted as melanomas in our analysis.

Table 1: Personal and Family History Among Patients with a Pathogenic Variant in *CDKN2A*

Personal/Family Cancer History	p16	p14	Total
Pancreatic	4 (7.3%)	1 (50.0%)	5 (8.8%)
1 Melanoma (No Pancreatic)	9 (16.4%)	0	9 (15.8%)
>1 Melanoma (No Pancreatic)	6 (10.9%)	0	6 (10.5%)
Pancreatic and Melanoma	6 (10.9%)	0	6 (10.5%)
Other	30 (54.5%)	1 (50.0%)	31 (54.4%)
Total	55	2	57

Figure 1. Personal History of Patients with a Pathogenic Variant in *CDKN2A*

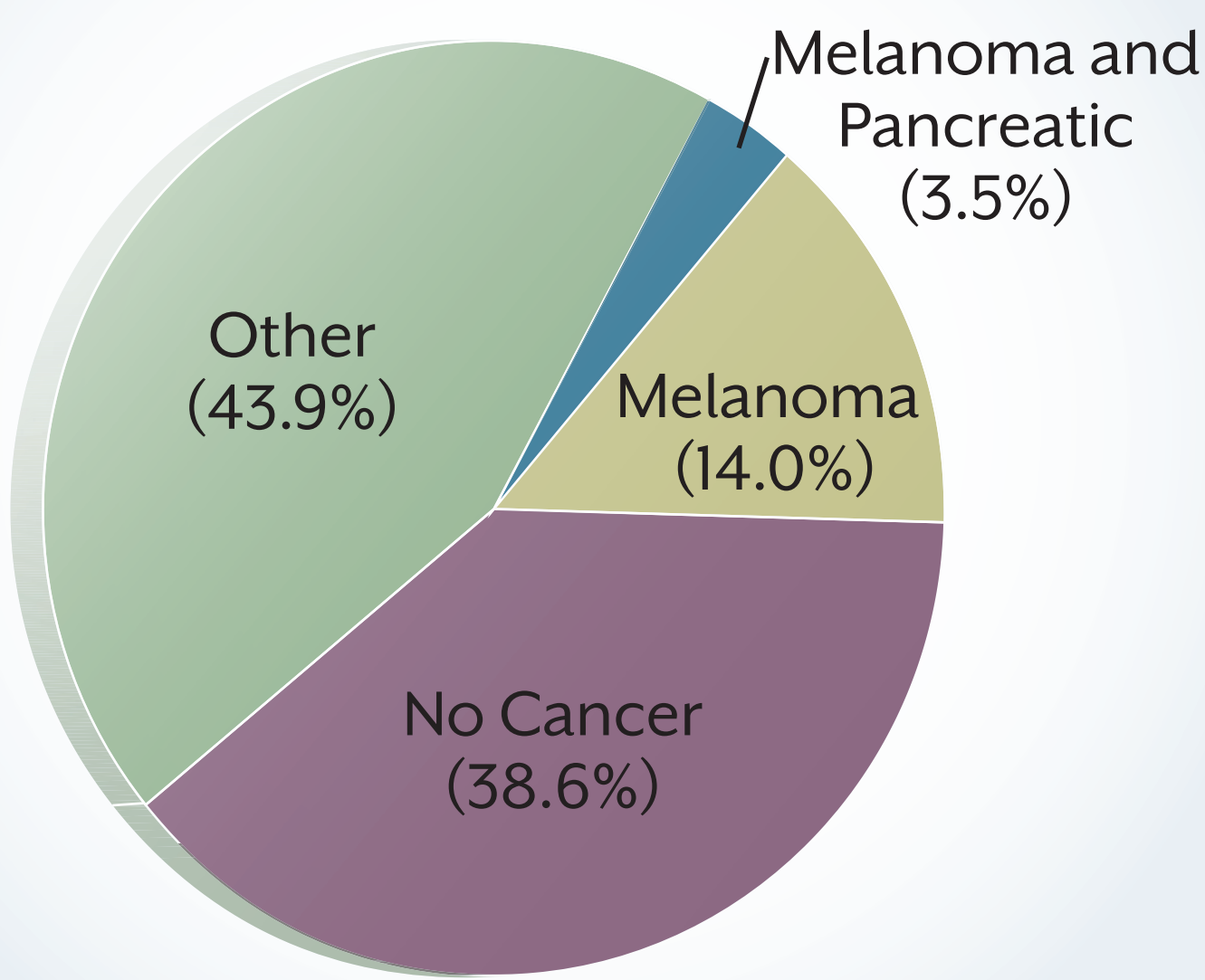
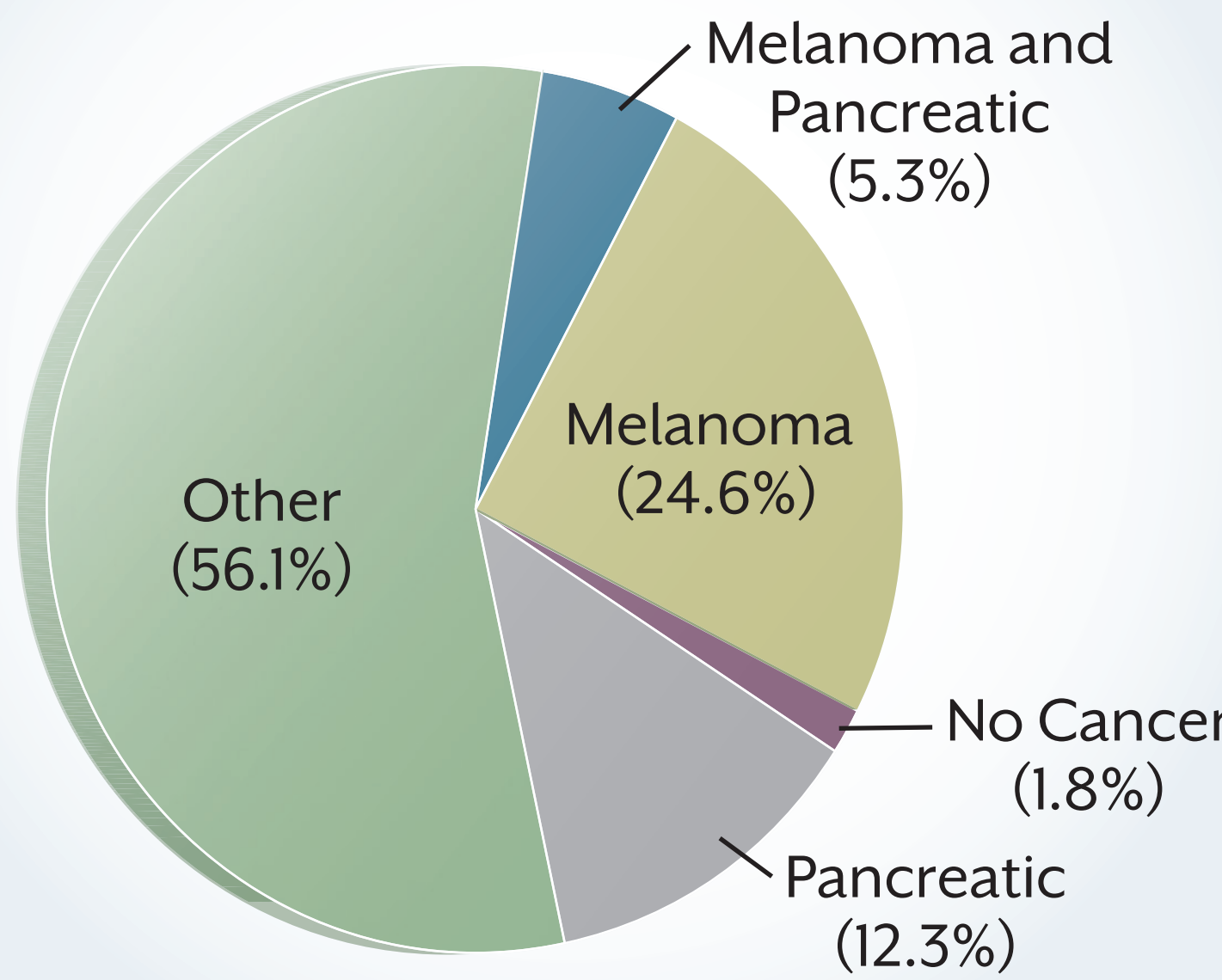


Figure 2. Family History of Patients with a Pathogenic Variant in *CDKN2A*



- Six patients were found to carry a pathogenic variant in another gene in addition to *CDKN2A* (Table 2).
- None of these six patients were reported to have any personal or family history of melanoma or pancreatic cancer that may have been explained by these additional pathogenic variants.

Table 2: Patients with Two Pathogenic Variants

Genes	n
<i>CDKN2A, PALB2</i>	2
<i>CDKN2A, APC</i>	1
<i>CDKN2A, ATM</i>	1
<i>CDKN2A, BRCA1</i>	1
<i>CDKN2A, BRCA2</i>	1

CONCLUSIONS

- In this cohort, while the majority of patients met NCCN testing criteria for syndrome-specific testing (HBOC, LS, or FAP) due to personal and/or family history of cancer, a minority (21.1%) met widely-accepted guidelines for *CDKN2A* testing alone.
- Six patients were identified to carry a pathogenic variant in a different gene in addition to the pathogenic variant identified in *CDKN2A* as a result of multi-gene panel testing.
- These findings illustrate the utility of multi-gene panel testing for hereditary cancer predisposition, as this approach can identify patients and families who are candidates for interventions to mitigate risks caused by pathogenic variants that would not have otherwise been identified.

REFERENCES

1) Champine M, et al. Genetic Counseling and Testing for Hereditary Melanoma: An Updated Guide for Dermatologists. Hereditary Genetics. 2013;S2: 004. 2) Canto MI, et al. International CAPS Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013; 62:339-347. 3) Daly M, et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology. 2014. 4) Provenzale D, et al. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Clinical Practice Guidelines in Oncology. 2014.