

Characteristics and Clinical Correlations of Likely Mosaic Large Rearrangements Identified by a Hereditary Pan-Cancer NGS Panel Test

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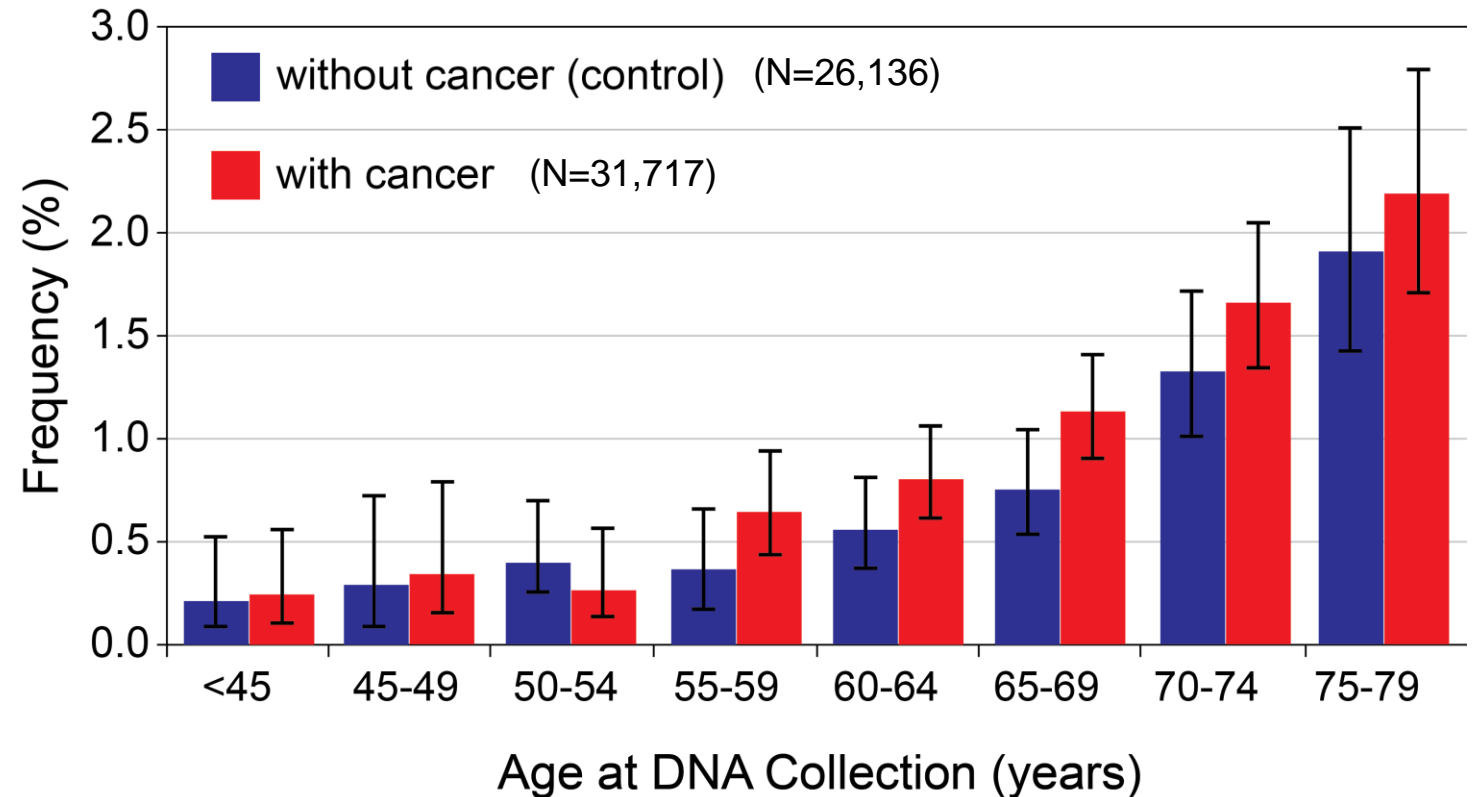
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Financial Disclosure

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Mosaic Chromosomal Abnormalities Increase with Age and Cancer Diagnoses

- Mosaic chromosomal abnormalities found in ~0.8% of individuals
- Mosaic chromosomal abnormalities:
 - Increase with age
 - More frequent in individuals with solid tumor
 - Confer ~10-fold higher risk for hematological malignancies (Laurie et al., *Nat Genet.* 2012;44(6): 642–650)



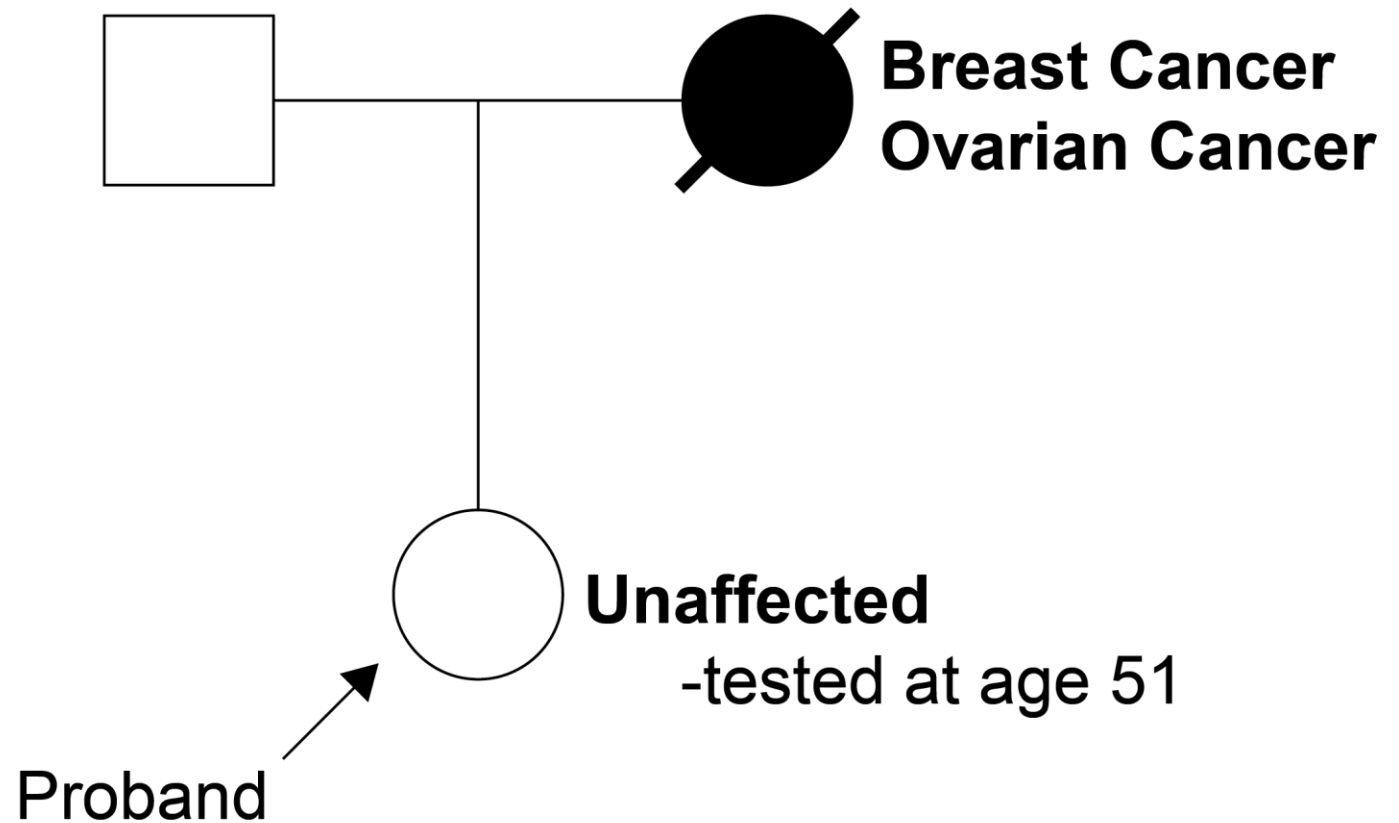
[Adapted from Jacobs et al., *Nat Genet.* 2012;44(6):651-8]

Study Aims

1. What is the frequency of mosaic large rearrangements (LRs) detected on the hereditary pan-cancer panel?
2. What are the characteristics of mosaic LRs compared to apparent germline LRs?
3. Are there any associations between mosaic LRs and aging, personal history of solid tumors, and/or hematological malignancies?

Clinical Case – Cancer History

- Patient underwent hereditary cancer panel testing due to clinical suspicion of hereditary breast and ovarian cancer (HBOC) based on family history



Likely Mosaic Large Rearrangements are Detectable by NGS Dosage Analysis

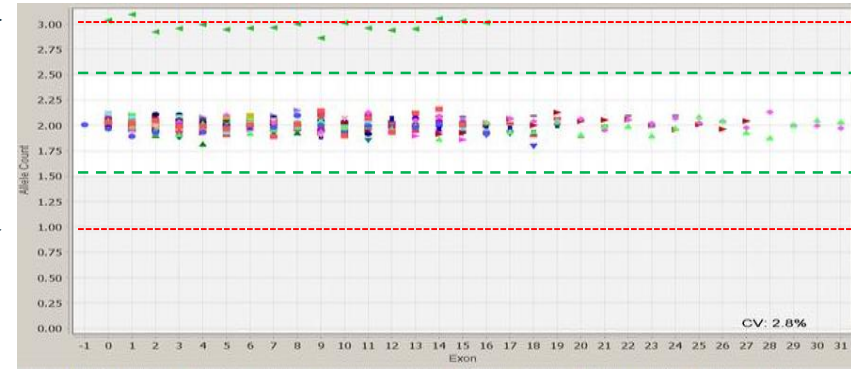
Germline
Deletion



Duplication

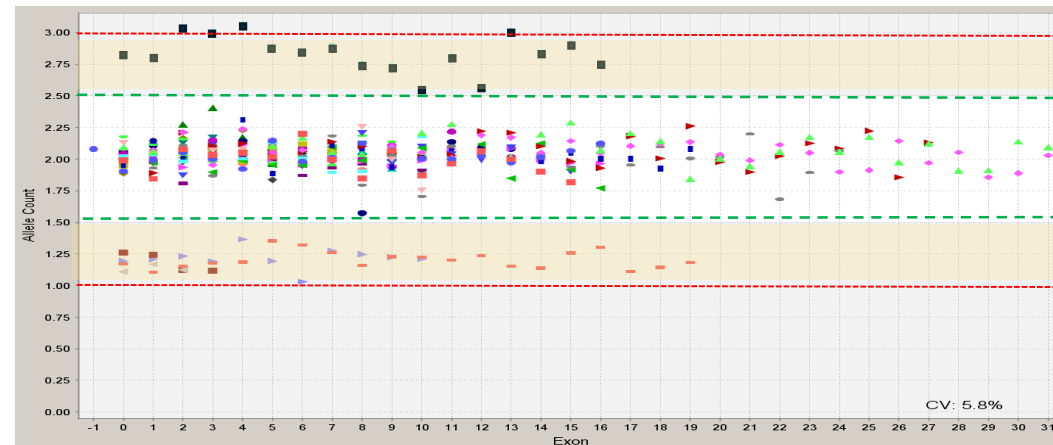
Normal

Deletion



Germline
Duplication

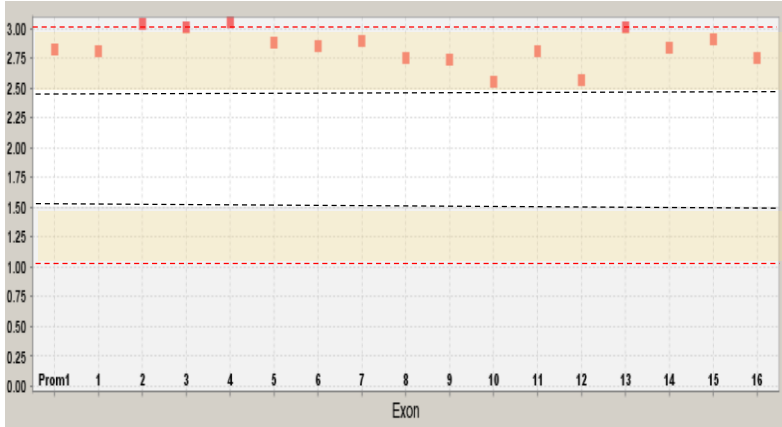
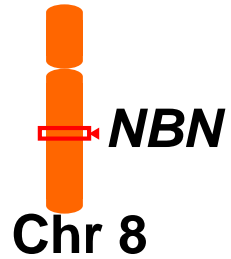
Clinical
Case



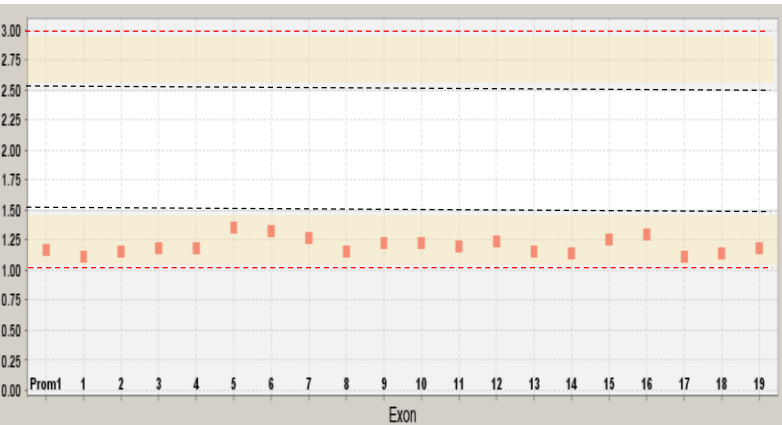
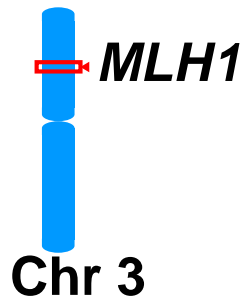
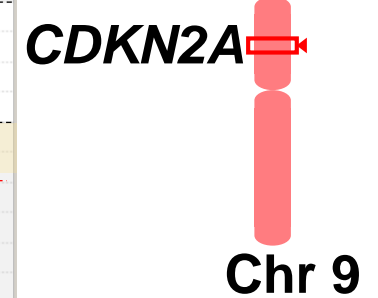
Mosaic

Mosaic

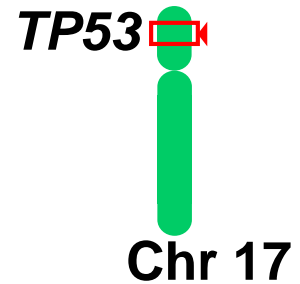
Multiple Mosaic Large Rearrangements are Present in the Clinical Case



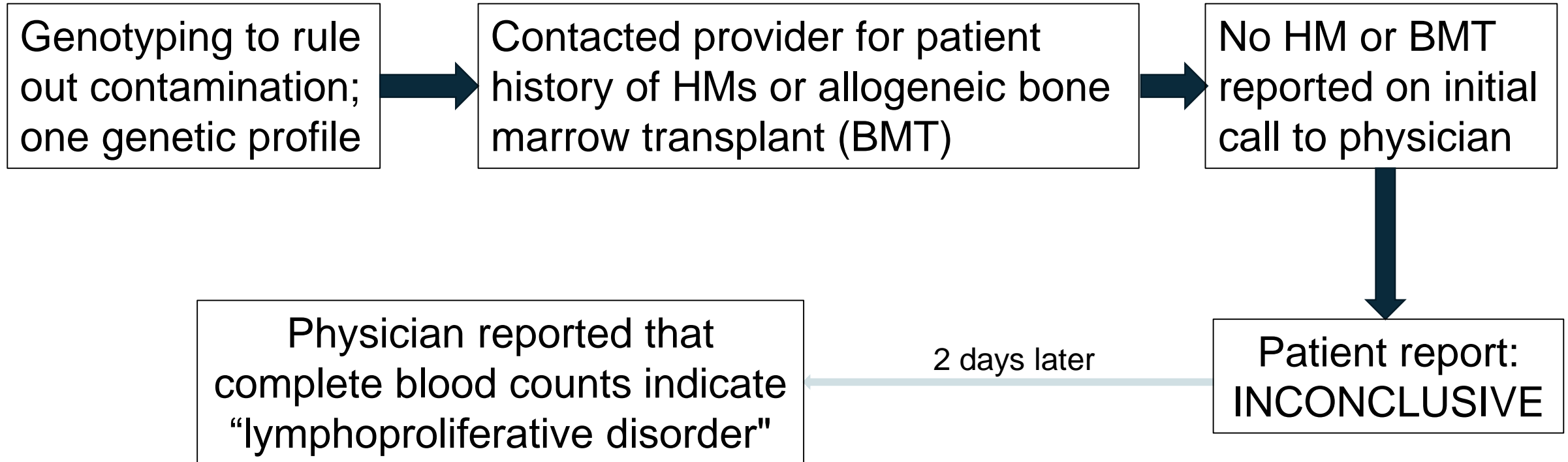
← Mosaic →
Normal
← Mosaic →



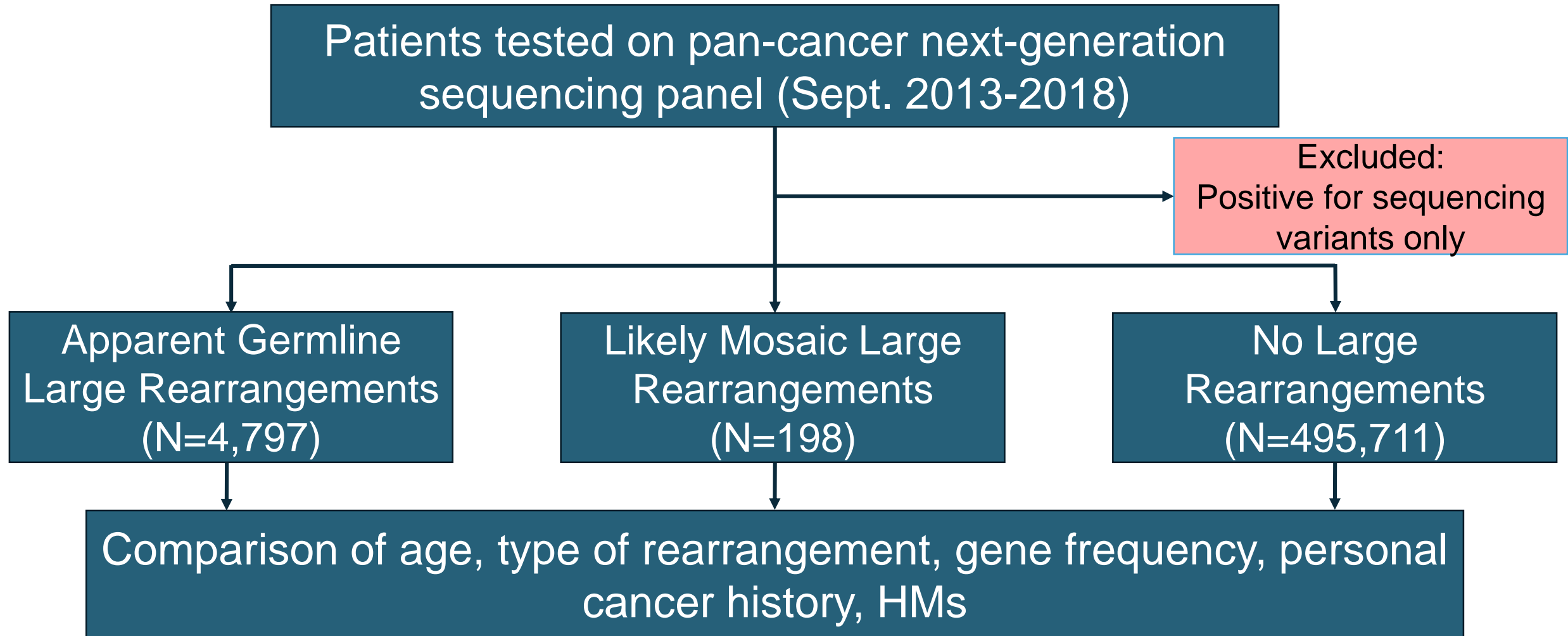
← Mosaic →
Normal
← Mosaic →



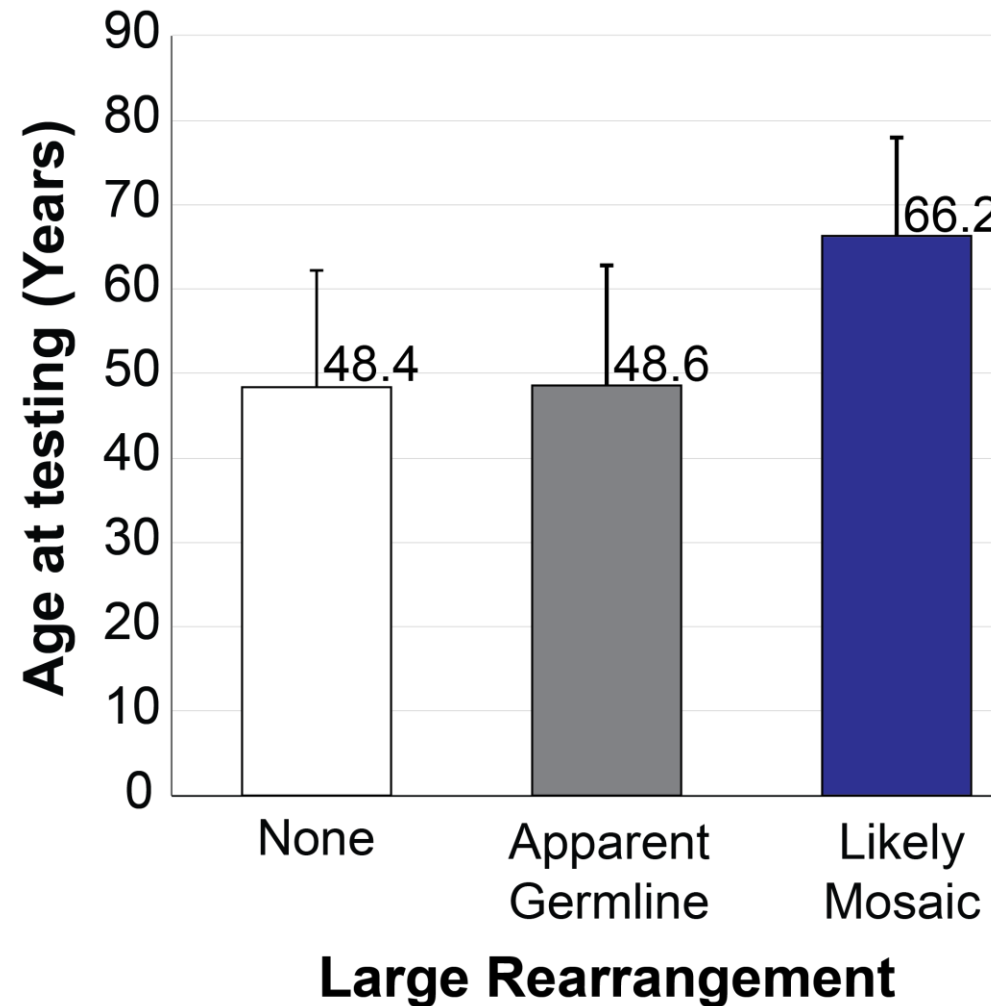
Additional Steps to Investigate Abnormal Results: Clinical Case



Study Design

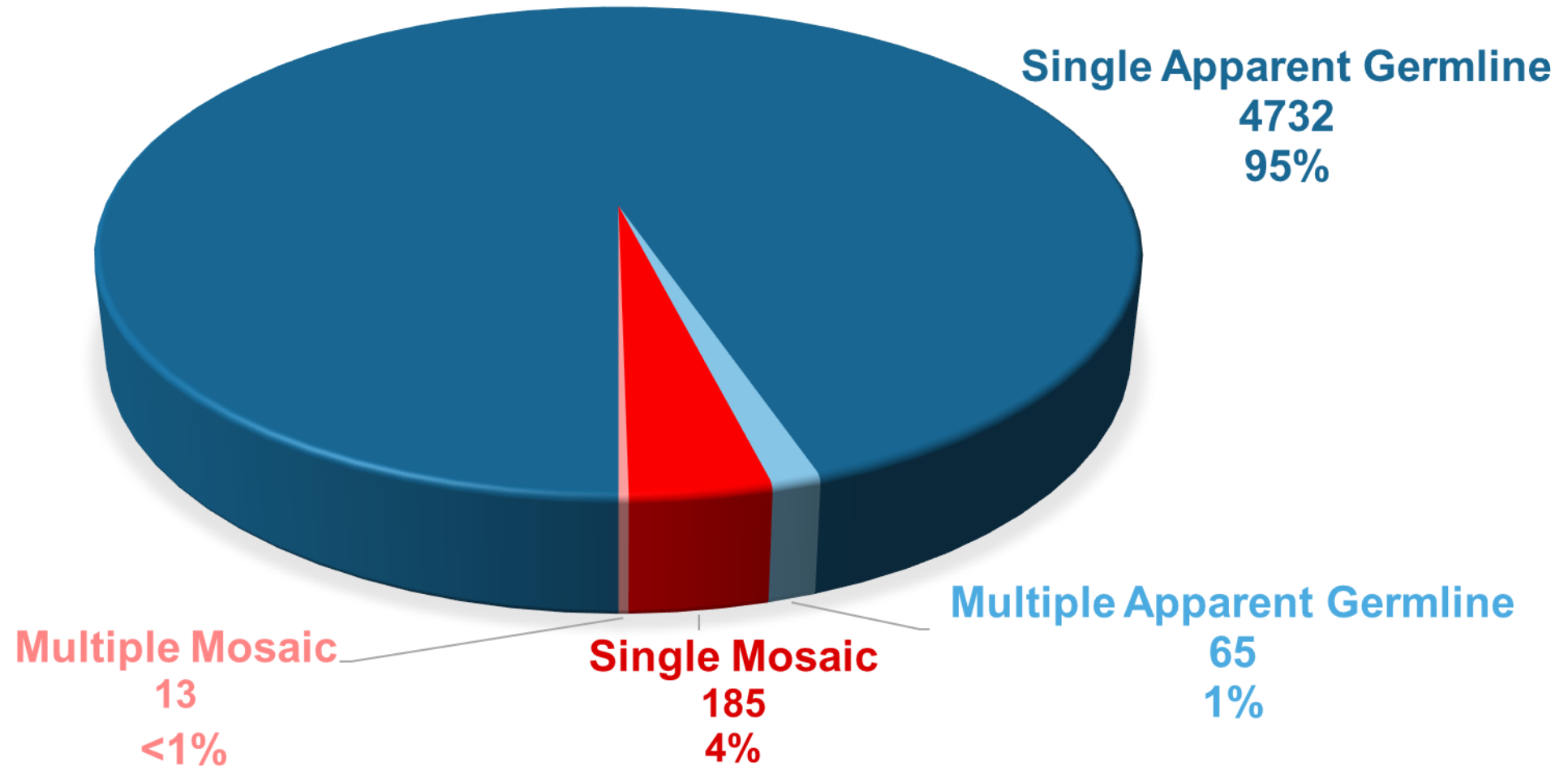


Likely Mosaic Large Rearrangements are Detected at Older Ages

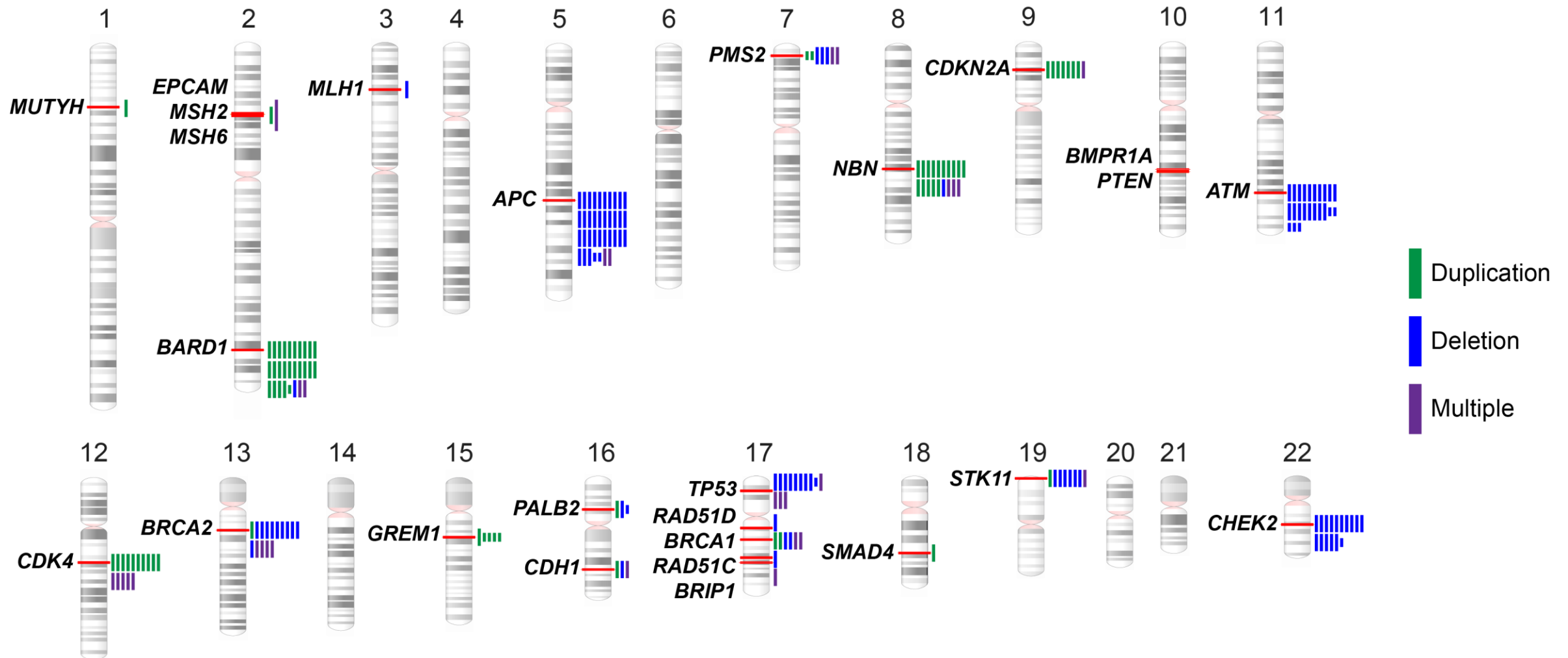


Apparent Germline LRs are More Common than Likely Mosaic LRs

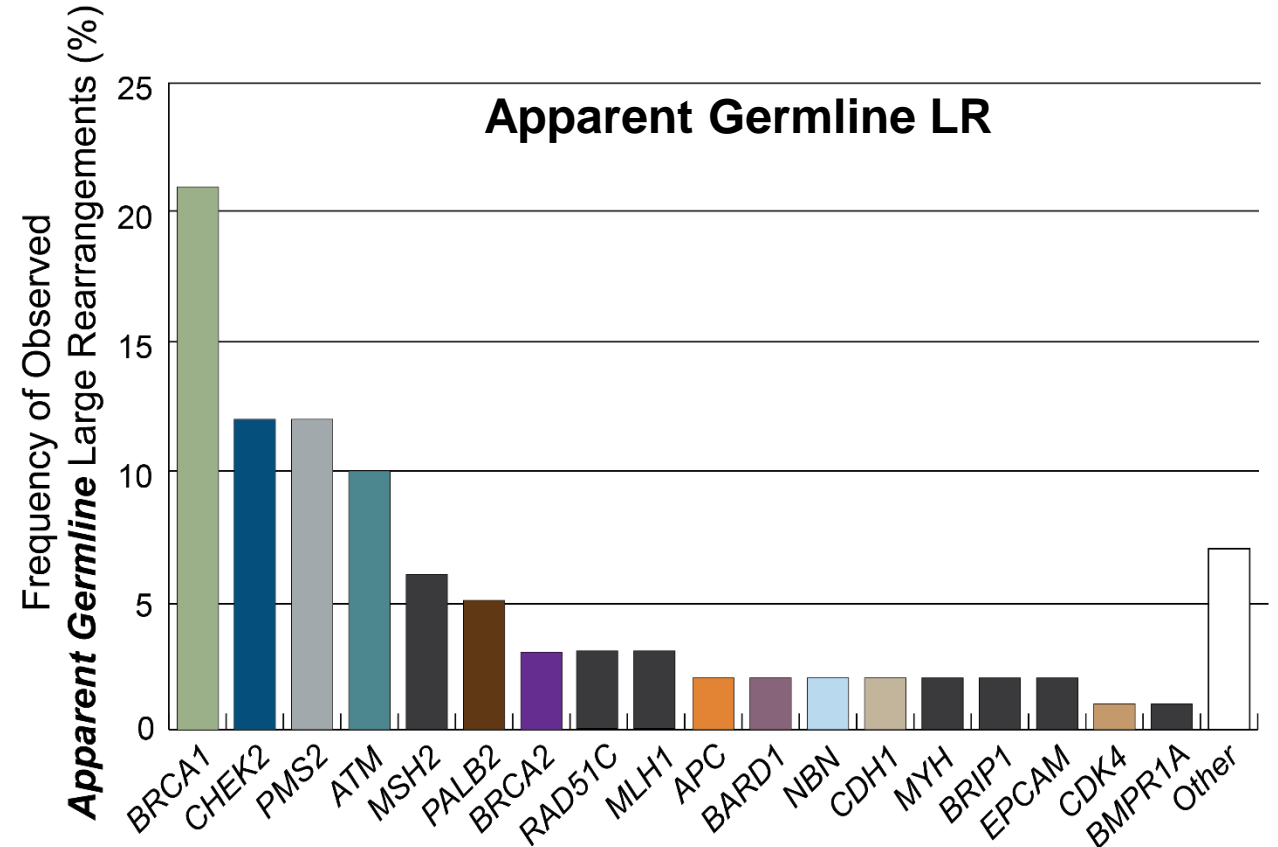
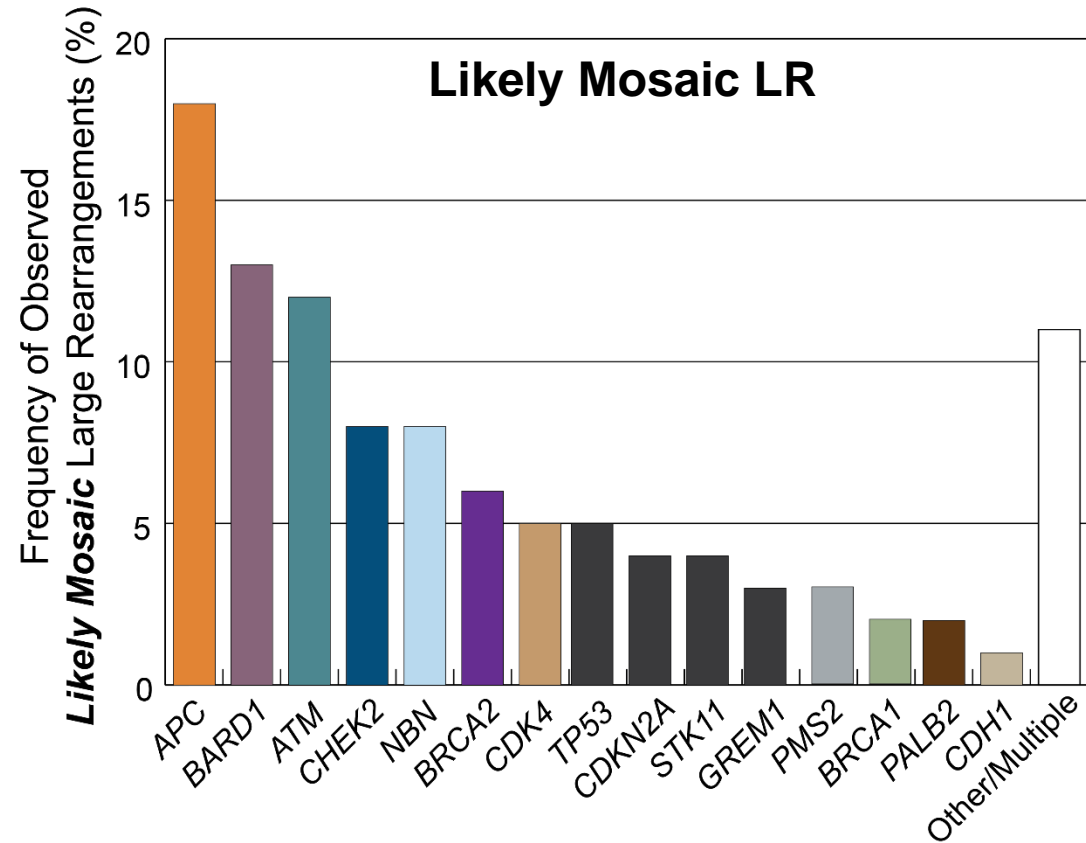
~4% of patients with large rearrangements (LRs) have at least one likely mosaic LR.



Distribution of Observed Likely Mosaic LRs

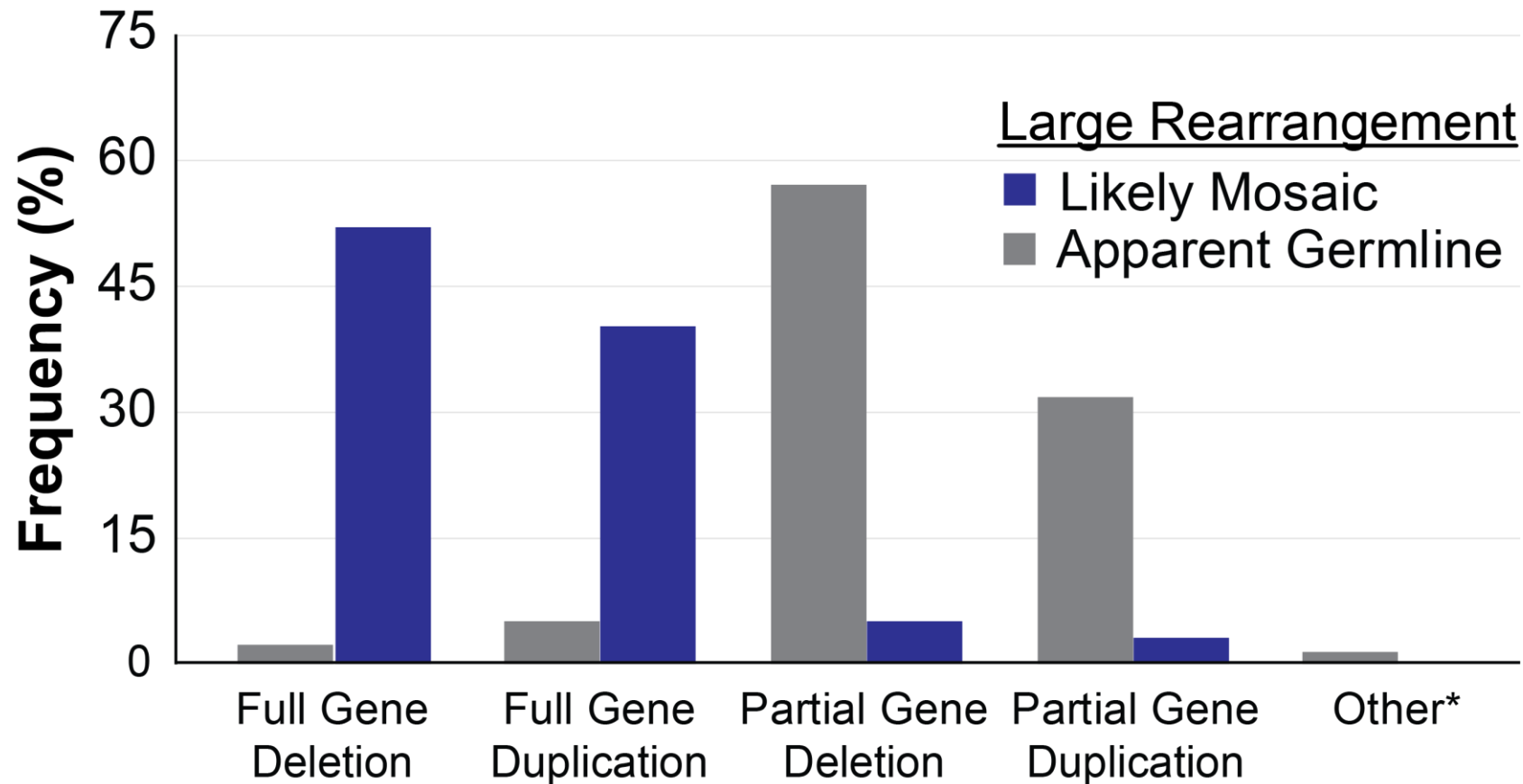


Likely Mosaic and Apparent Germline LRs have Different Gene Distributions



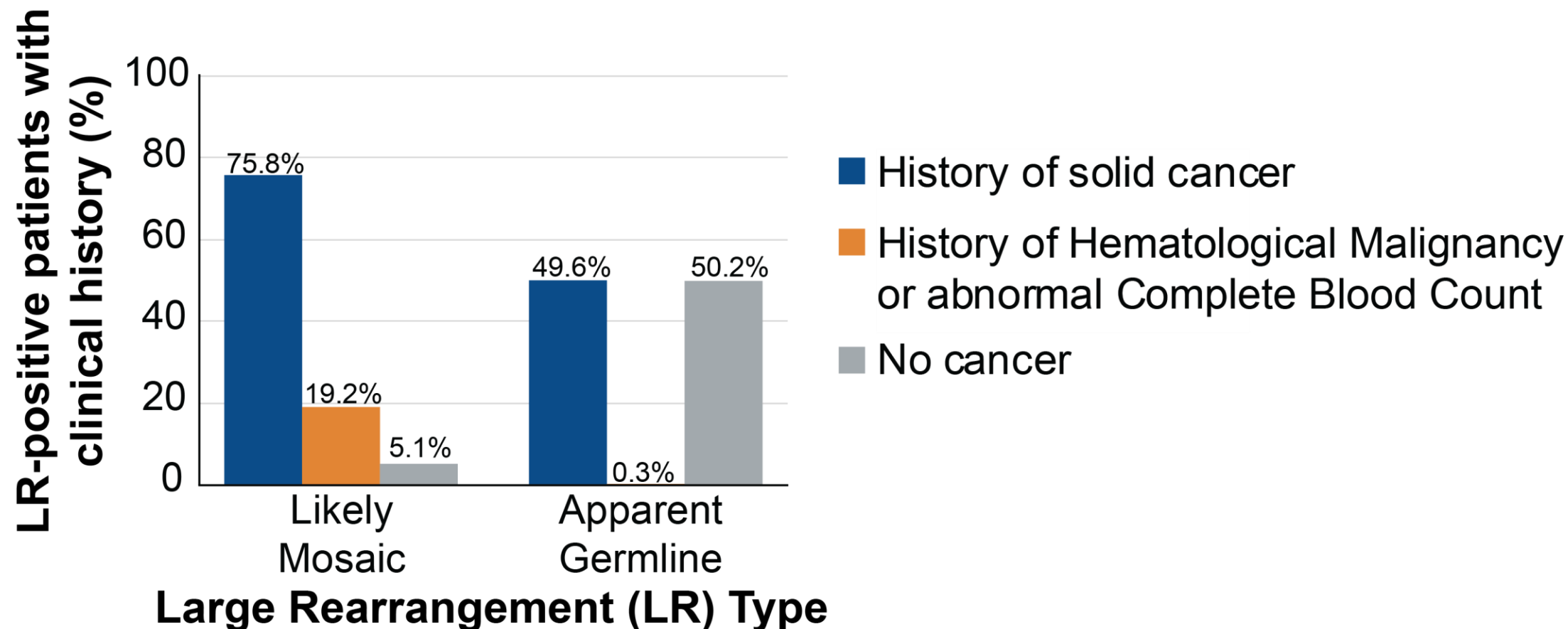
Dark grey bars indicate genes not shared in common between likely mosaic and apparent germline.

The Types of Likely Mosaic and Apparent Germline LRs are Distinct



*Includes inversion, triplication, and complex large rearrangements (LRs)

Likely Mosaic LRs are Associated with Hematological Malignancy



Hematological Malignancies (HM) are Found in Patients with Likely Mosaic LR in Many Genes

Gene	Chr.	Total Patients w/ mosaic LR (N)	Subset with HM (N, %)
<i>SMAD4</i>	<i>18q21.2</i>	1	1 (100%)
Multiple	Multiple	13	8 (61.5%)
<i>CDK4</i>	<i>12q14.1</i>	10	5 (50.0%)
<i>TP53</i>	<i>17p13.1</i>	9	4 (44.4%)
<i>GREM1</i>	<i>15q13.3</i>	5	2 (40.0%)
<i>BRCA2</i>	<i>13q13.1</i>	11	3 (27.3%)
<i>BRCA1</i>	<i>17q21.31</i>	4	1 (25.0%)
<i>ATM</i>	<i>11q22.3</i>	23	4 (17.4%)
<i>CHEK2</i>	<i>22q12.1</i>	16	2 (12.5%)
<i>BARD1</i>	<i>2q35</i>	26	3 (11.5%)
<i>APC</i>	<i>5q22.2</i>	35	4 (11.4%)
<i>NBN</i>	<i>8q21.1</i>	16	1 (6.3%)

Frequently observed in HM patients

Conclusions

- Likely mosaic large rearrangements (LRs) accounted for ~4% (198/4995) of all LRs detected by the multigene pan-cancer panel, and had a gene distribution that was distinct from that of apparent germline LRs.
- Patients with likely mosaic LRs are significantly older, and had a significantly higher prevalence of solid cancers and hematological malignancies than those carrying apparent germline LRs.

Conclusions

- In patients with likely mosaic large rearrangement (LR) findings, it is important to follow up with the provider to identify patients who may have undiagnosed or unreported hematological malignancies.
- Additional investigation is needed to more precisely establish the clinical importance of likely mosaic LRs, particularly in association with solid tumors and hematological malignancies.

Acknowledgements

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