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Likelihood of Germline Mutation with Solitary Unilateral Retinoblastoma Based on Patient Age at Presentation. A Real-World Analysis of 482 Consecutive Patients.

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Likelihood of Germline Mutation with Solitary Unilateral Retinoblastoma Based on Patient Age at Presentation. A Real-World Analysis of 482 Consecutive Patients

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(*) indicates primary project advisor

(**) indicates another student who is declaring the same project as primary for SI

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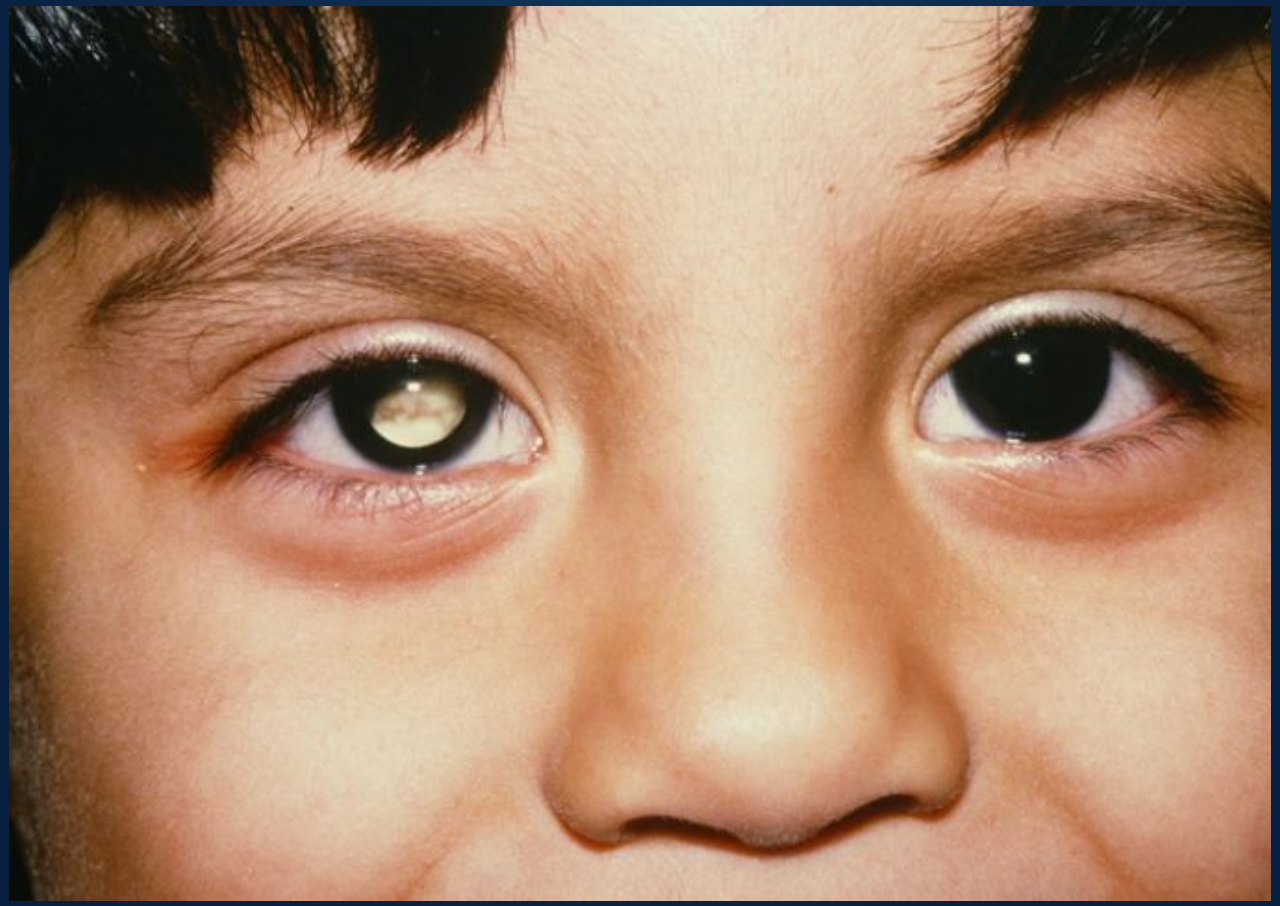
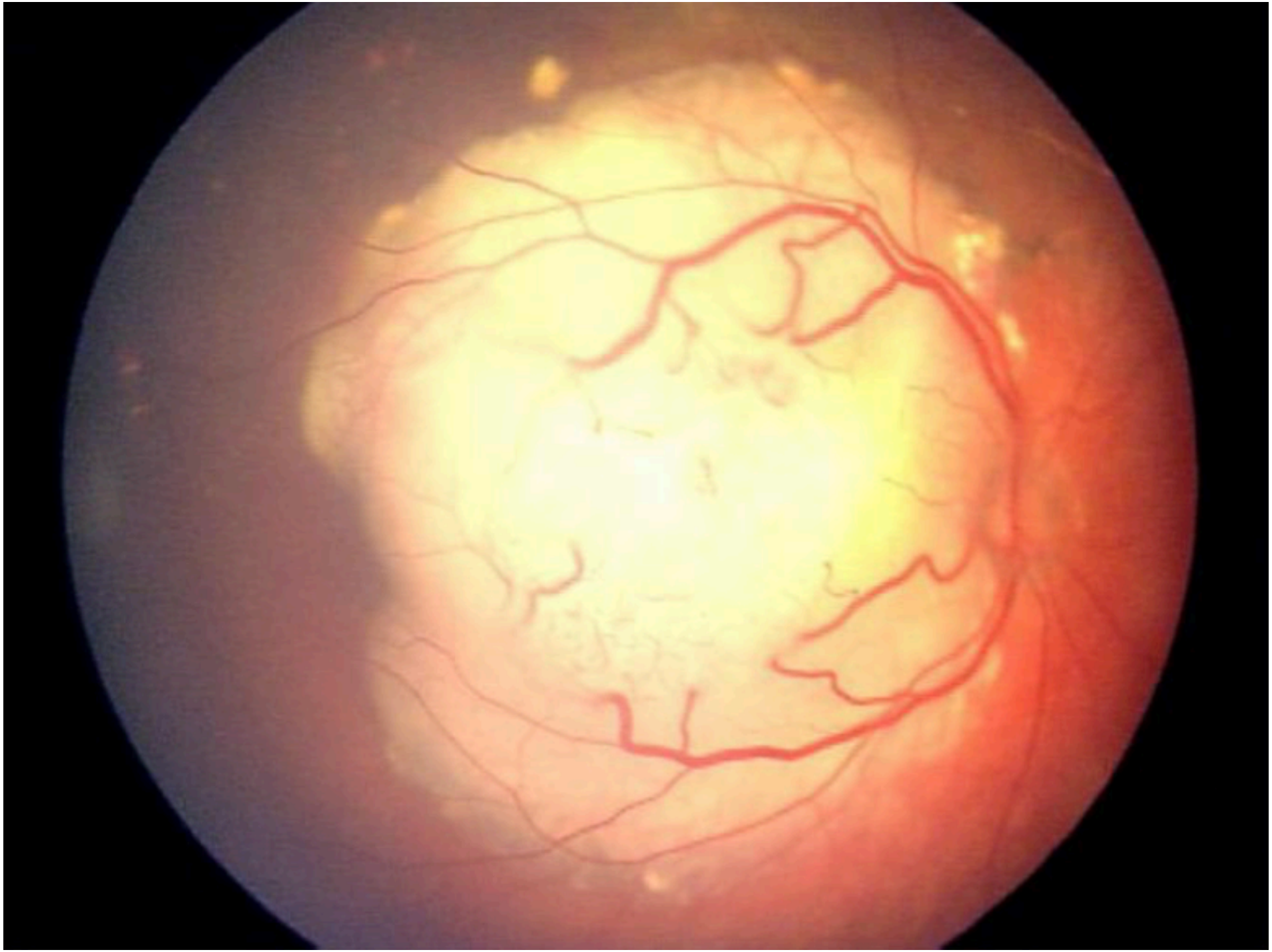
Introduction

- Retinoblastoma (Rb) is an ocular tumor common in children





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Introduction

- Bilateral presentation ± multifocal → Germline mutation
- Unilateral presentation → somatic mutation (?)
- Inheritance pattern is important for patient management
  - Germline → More conservative treatment (i.e. chemotherapy)
  - Somatic → Enucleation is common
- Previous studies: 7%-33% of solitary unilateral retinoblastomas are germline[1-7]
  - Problems: small sample size, patients were not followed long-term, and inclusion criteria only included genetic testing

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Objectives & Hypothesis

- Research Question
  - In children with unilateral retinoblastoma, what is the likelihood of germline mutation and does this likelihood vary based on age at initial presentation?
- Hypothesis
  - In children with unilateral retinoblastoma, there is a greater likelihood of germline mutation and this likelihood is greater in younger patients

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Approach & Results

- Study design: Retrospective chart review
- Data collection: Paper charts, excel, SAS Software Suite
- PICO:
  - 482 consecutive patients with solitary unilateral Retinoblastoma at Wills Eye Hospital between 1972 and 2020
  - Assessed the likelihood of germline inheritance based on age of presentation (≤1 year vs. >1 year old)
- Inclusion criteria: unilateral Rb & >1 month follow-up

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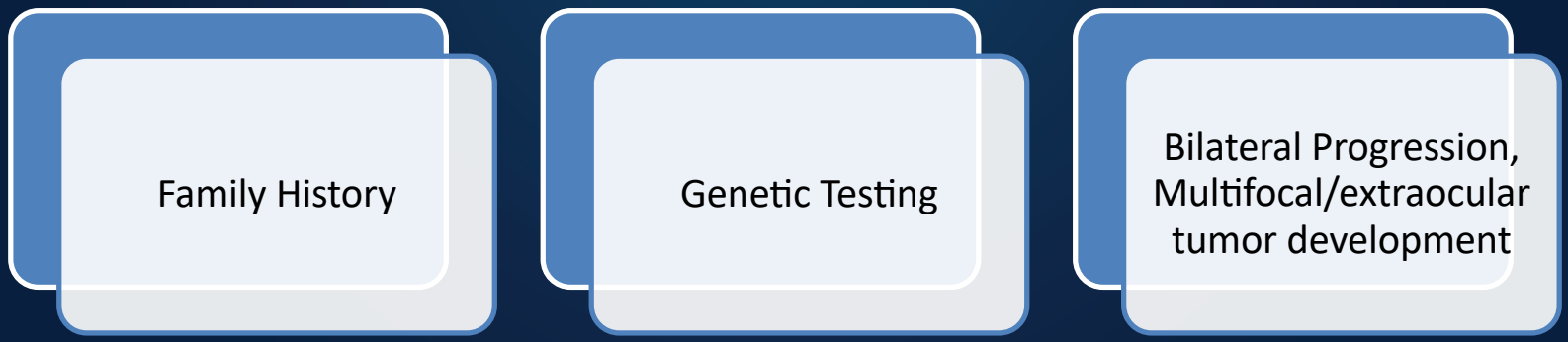
Approach & Results

- Germline inheritance deemed "likely" if:
  1. Family History
  2. Germline Positive test
  3. Multifocal/extraocular tumor development



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Approach & Results

- Analysis
  - Likelihood ratio Chi-square test
  - ANOVA and Odds Ratios for differences between age groups
- Findings
  - 465 of 482 patients had sufficient follow-up time
  - 16% (n=72) of all unilateral Rb patients were likely to have germline disease ($p<0.001$)
  - 29% of patients ≤1 year old demonstrated a greater likelihood of germline inheritance ($p=0.001$)
  - Compared to patients >1 year of age (n=339), patients ≤1 year of age (n=126) demonstrated a greater likelihood of germline inheritance ($p=0.001$, OR=2.96 [1.55-5.65])

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Approach & Results

Outcomes	Age 0-12 months (n= 132) [n (%)]	Age >12-24 months (n= 122) [n (%)]	Age >24-36 months (n= 97) [n (%)]	Age >36 months (n= 131) [n (%)]	*p*-value	Total (N= 482) [N (%)]
Follow-up*	n=126	n=119	n=93	n=127		n=465
Duration (months) Mean (median, range)	99.1 (64.9, 0.1-465.1)	86.7 (42.8, 0.1-495.2)	75.6 (52.3, 0.1-357.6)	60.0 (40.4, 0.1-472.9)	**0.010**	81.4 (50.0, 0.1-495.2)
Patients without follow-up visits	6 (5)	3 (2)	4 (4)	4 (3)	--	17 (4)
Family history of retinoblastoma						
Negative	119 (90)	118 (98)	96 (99)	128 (98)	**0.004**	461 (96)
Positive	13 (10)	3 (2)	1 (1)	3 (2)		20 (4)
Genetic status	n=95	n=89	n=66	n=83		n=333
Somatic	65 (68)	72 (81)	62 (94)	77 (93)	**<0.001**	276 (83)
Germline	30 (32)	17 (19)	4 (6)	6 (7)		57 (17)
Development of bilateral disease†	n=125	n=112	n=91	n=119		n=447
No	112 (90)	112 (100)	91 (100)	118 (99)	**0.035**	433 (97)
Yes	13 (10)	0 (0)	0 (0)	1 (1)		14 (3)
Development of new tumors†	n=125	n=112	n=91	n=119		n=447
No	109 (87)	112 (100)	89 (98)	116 (97)	0.214	426 (95)
Yes	16 (13)	0 (0)	2 (2)	3 (3)		21 (5)
Likely germline disease‡	n=126	n=117	n=93	n=126		n=462
No	89 (71)	100 (85)	86 (92)	115 (91)	**0.001**	390 (84)
Yes	37 (29)	17 (17)	7 (8)	11 (9)		72 (16)
High risk features at enucleation	n=50	n=72	n=65	n=75		n=262
Enucleation	44 (88)	60 (83)	47 (72)	60 (80)	0.159	211 (81)
Enucleation with adjuvant IVC	6 (12)	12 (17)	18 (28)	15 (20)		51 (19)
Metastasis†	n=125	n=113	n=91	n=121		n=450
No	125 (100)	111 (98)	91 (100)	119 (98)	0.364	446 (99)
Yes	0 (0)	2 (2)	0 (0)	2 (2)		4 (1)
Systemic location of metastasis						
Bone	0 (0)	2 (100)	0 (0)	1 (50)	---	3 (75)
Brain	0 (0)	0 (0)	0 (0)	1 (50)		1 (25)
Death†	n=125	n=112	n=91	n=121		n=449
Total number of patients	0 (0)	0 (0)	0 (0)	2 (2)	---	2 (<1)

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Approach & Results

Outcomes	Age 0-3 months (n= 23) [n (%)]	Age >3-6 months (n= 27) [n (%)]	Age >6-9 months (n= 42) [n (%)]	Age >9-12 months (n= 40) [n (%)]	*p*-value	Total (N= 132) [N (%)]
Follow-up*	n=23	n=26	n=40	n=37		n=126
Duration (months) Mean (median, range)	98.1 (66.3, 1.2-410.0)	94.5 (81.5, 0.1-376.9)	101.0 (58.7, 1.9-465.1)	101.0 (63.3, 1.9-408.1)	0.989	99.1 (64.9, 0.1-465.1)
Patients without follow-up visits	0 (0)	1 (4)	2 (5)	3 (8)	--	6 (5)
Family history of retinoblastoma						
Negative	15 (65)	27 (100)	38 (90)	39 (98)	**<0.001**	119 (90)
Positive	8 (35)	0 (0)	4 (10)	1 (3)		13 (10)
Genetic status	n=16	n=18	n=33	n=28		n=95
Somatic	5 (31)	14 (78)	24 (73)	22 (79)	**0.047**	65 (68)
Germline	11 (69)	4 (22)	9 (27)	6 (21)		30 (32)
Development of bilateral disease†	n=23	n=25	n=40	n=37		n=125
No	16 (70)	20 (80)	39 (98)	37 (100)	**0.001**	112 (90)
Yes	7 (30)	5 (20)	1 (3)	0 (0)		13 (10)
Development of new tumors†	n=23	n=25	n=40	n=37		n=125
No	15 (65)	20 (80)	38 (95)	36 (97)	**0.004**	109 (87)
Yes	8 (35)	5 (20)	2 (5)	1 (3)		16 (13)
Likely germline disease‡	n=23	n=25	n=40	n=37		n=126
No	9 (39)	20 (80)	31 (76)	29 (78)	**0.009**	89 (71)
Yes	14 (61)	5 (20)	10 (24)	8 (22)		37 (29)
High risk features at enucleation	n=7	n=16	n=15	n=12		n=50
Enucleation	7 (100)	15 (94)	13 (87)	9 (75)	0.087	44 (88)
Enucleation with adjuvant IVC	0 (0)	1 (6)	2 (13)	3 (25)		6 (12)
Metastasis†	n=23	n=25	n=40	n=37		n=125
No	23 (100)	25 (100)	40 (100)	37 (100)	---	125 (100)
Yes	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
Systemic location of metastasis						
Bone	0 (0)	0 (0)	0 (0)	0 (0)	---	0 (0)
Brain	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
Death†	n=23	n=25	n=40	n=37		n=125
Total number of patients	0 (0)	0 (0)	0 (0)	0 (0)	---	0 (0)

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Approach & Results

Outcomes	OR (95% CI)	p-value
Family history of retinoblastoma		
All Patients (≤1 year vs. >1 year)	2.33 (0.70-7.81)	0.171
Infants * (≤3 months vs. >3-12 months)	**5.10 (1.09-23.81)**	**0.038**
Genetic status Rb1 germline mutation		
All Patients (≤1 year vs. >1 year)	**2.91 (1.56 – 5.44)**	**0.001**
Infants (≤3 months vs. >3-12 months)	**7.60 (1.87 – 30.86)**	**0.005**
Development of bilateral disease†		
All Patients (≤1 year vs. >1 year)	**17.28 (2.07 – 144.26)**	**0.009**
Infants (≤6 months vs. >6-12 months)	**23.94 (2.35 – 244.33)**	**0.007**
Development of new tumors†		
All Patients (≤1 year vs. >1 year)	**6.89 (2.38 – 19.98)**	**<0.001**
Infants (≤6 months vs. >6-12 months)	**10.17 (2.28 – 45.30)**	**0.002**
Likely germline disease‡		
All Patients (≤1 year vs. >1 year)	**2.96 (1.55 – 5.65)**	**0.001**
Infants (≤3 months vs. >3-12 months)	**5.52 (1.93 – 15.83)**	**0.002**

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Conclusions

- Bilateral Rb is typically germline; inheritance of unilateral Rb is poorly understood
- Previous studies had small sample sizes and did not account for family history and development of bilateral tumors in the assessment of the real-world likelihood of unilateral Rb
- We found that 16% of 465 children with unilateral Rb likely have germline inheritance with a greater likelihood in children ≤1 year of age
- Implications: clinical management of germline Rb is treated more conservatively to preserve vision due to the greater likelihood of bilateral progression

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Future Directions

- What are the next steps for research and/or implementation?
- Implementing clinical assessments of unilateral Rb earlier may prove beneficial
  - Earlier detection of disease
  - Can influence management (targeted IAC vs enucleation) and preserve eyesight
- Our likelihood criteria can be incorporated into routine clinical assessment as opposed to just genetic testing

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