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I, Samantha Freeze, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Genetic Testing and Counseling Practices for Patients with Retinoblastoma at Cincinnati Children’s Hospital Medical Center

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Genetic Testing and Counseling Practices for Patients with Retinoblastoma at Cincinnati Children's Hospital Medical Center

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Master of Science
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by
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Abstract

**Background:** Retinoblastoma is the most common primary ocular cancer in childhood with an incidence of 1/15,000-1/20,000. Retinoblastoma tumors are associated with mutations in both copies of the Retinoblastoma 1 (RB1) tumor suppressor gene located on chromosome 13q14. Genetic testing and counseling for RB1 mutations is important for diagnosis of hereditary retinoblastoma and risk assessment in relatives. At this time, it is unclear if all patients with retinoblastoma receive genetic testing and genetic counseling. **Methods:** Seventy-four patients diagnosed with retinoblastoma and seen at Cincinnati Children’s Hospital Medical Center from January 1, 2000-August 1, 2015 were selected for participation in this study. Retrospective chart review was used to identify the genetic testing and counseling provided. Criteria for optimal genetic counseling included documentation of 5 of the 6 essential elements of genetic counseling cancer risk assessment as outlined in the 2012 article titled “Essential Elements of Genetic Cancer Risk Assessment” by Riley et al. **Results:** Documentation of genetic testing was identified in the 63.1% of patient charts. 36/74. Either a genetic counselor or medical geneticist saw 48.6% of patients. Involvement of a genetics professional was found to increase the likelihood of receiving genetic testing (p<.001). Documentation of optimal genetic counseling was identified in 33.3% of charts seen by genetics professional. Genetic testing uptake and documentation of optimal genetic counseling has improved over time. **Conclusions:** Inclusion of a genetics professional in the care for patients with retinoblastoma increases the likelihood of receiving genetic testing. Documentation of the essential elements of genetic counseling cancer risk assessment is suboptimal and may or may not reflect actual services provided. **Keywords:** retinoblastoma, RB1, genetic testing, genetic counseling
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Introduction

Retinoblastoma is the most common primary ocular cancer in childhood (Dommering et al., 2012) with an incidence of 1 in 15,000-20,000 live births (Aerts et al., 2006). Retinoblastoma tumors typically develop in pediatric patients before the age of five years and may be in one (unilateral) or both (bilateral) eyes. Retinoblastoma tumors are associated with mutations in both copies of the Retinoblastoma 1 (RB1) tumor suppressor gene located on chromosome 13q14. An individual who inherits a cancer-predisposing RB1 mutation is at much greater risk of acquiring a second mutation and developing retinoblastoma (Lohmann & Gallie, 1993) compared to individuals where both mutations are acquired sporadically. Individuals with germline RB1 mutations are also at an increased risk for developing secondary primary tumors such as pinealoma, osteosarcoma, myosarcoma, and melanoma (Fletcher et al., 2004). Approximately 90-92% of patients with bilateral retinoblastoma have a detectable germline mutation in the RB1 gene, whereas approximately 13-14% of patients with unilateral retinoblastoma harbor a germline mutation (Rushlow et al., 2009).

To date over 900 distinct mutations have been reported (Ali et al., 2010) in patients with both unilateral and bilateral retinoblastoma including single base mutations, whole gene deletions, partial deletions and rarely, partial duplications. However the majority of mutations reported in retinoblastoma are somatic point mutations such as single-base substitutions, shorter length alterations, and complex mutations (Albrecht et al., 2005). The manifestation and inheritance of retinoblastoma depend in part on the nature of such causative mutations, somatic versus germline mutation development, and whether germline mosaicism is present (Lohmann et al., 1997). Although retinoblastoma is typically inherited in an autosomal dominant manner, some families
show a low-penetrance phenotype with reduced expressivity and incomplete penetrance of *RB1* mutations (Serrano et al., 2011). Yet another possible presentation of retinoblastoma is when deletions encompassing *RB1* and surrounding genes are present. Patients with a 13q14 deletion syndrome may present with retinoblastoma and variable clinical features such as characteristic facial features and developmental delay (Motegi et al., 1983). Given the extreme heterogeneity of *RB1* mutations and germline versus somatic acquisition of mutations, it is standard practice to employ multiple techniques of mutational analysis to ensure the highest probability of detecting a mutation in any single patient. For instance, sequencing methodology alone may miss deletions or duplication in the *RB1* gene. Genetic tests may be performed on either tumor or peripheral blood samples or both to identify mutations in patients with retinoblastoma.

Individuals with retinoblastoma who receive genetic testing and their family members have been shown to have improved clinical outcomes when compared to patients who do not receive genetic testing. In families where a proband received genetic testing and a germline molecular mutation was found, tumors were diagnosed earlier in offspring of the proband and therapy outcomes were improved when compared to the probands (Kobylarz, Dudzik, Kubicka-Trzaska, Debicka-Kumela, & Romanowska-Dixon, 2013). When genetic evaluation was incorporated into the management plans of patients with retinoblastoma, risk prediction was improved in patients and at-risk family members (Dhar et al., 2011).

In a case series of 52 families who had undergone *RB1* genetic testing 3-10 years following enrollment in the study, most families remained satisfied with their decision to receive genetic testing and families reported that the genetic testing process improved their understanding of retinoblastoma genetics and risks for future cancer development, reduced distress, and increased the families’ sense of empowerment when planning for the future (Cohen, Dryja, Davis, Diller,
There is extensive evidence that all patients with retinoblastoma should receive genetic evaluation and testing in order to maximize clinical and psychosocial outcomes for patients and families.

Genetic testing and counseling are frequently included in best-practice care for patients with retinoblastoma (Pradhan et al., 2010). Currently, the National Society of Genetic Counselors (NSGC), National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO) do not offer any specific guidelines for optimal genetic testing or genetic counseling for patients with retinoblastoma. Practice guidelines published by NSGC in 2012 state that genetic testing should be offered when an individual has a personal or family history suggestive of any inherited cancer syndrome (Riley et al., 2012). The genetic test must be adequately interpreted and should have the potential to influence medical management of the patient or other relatives. The American Society of Clinical Oncology (ASCO) recommends that genetic testing be offered when 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at risk of developing cancer. ASCO recommends that genetic testing only be done in the setting of pre- and post-test genetic counseling, which should include discussion of possible risks and benefits of early cancer detection and prevention (American Society of Clinical Oncology, 1996). According to these practice guidelines, all patients with retinoblastoma, regardless of disease presentation, should receive genetic testing and counseling.

Genetic counseling is a critical intervention for patients with germline RB1 mutations and their families in order to help them understand the risk of future ocular and extraocular tumors. Genetic counseling for hereditary cancer syndromes has been shown to increase knowledge of
cancer without having an adverse effect on patient anxiety (Emery, Braithwaite, Walter, Prevost, & Sutton, 2003). It has been shown in other hereditary cancer syndromes that genetic counseling improves the patient experience by providing education, thereby decreasing decisional conflict, increasing patient screening uptake and compliance, and decreasing cancer related stress (Christie et al., 2012). The complexity of the genetic counseling process necessitates the involvement of an experienced cancer genetic service provider. The Commission on Cancer (CoC) defined such a provider in the 2012 Cancer Program Standards as “an individual who has extensive experience and educational background in genetics, cancer genetics, counseling, and hereditary cancer syndromes to provide accurate risk assessment and empathetic genetic counseling to patients with cancer and their families” (Commision on Cancer, 2012).

At this time, it is unclear if all patients with retinoblastoma receive genetic testing and genetic counseling. Although generalized recommendations for hereditary cancer syndromes would suggest that all patients with retinoblastoma receive genetic testing and counseling, there are no specific practice guidelines regarding patients with retinoblastoma. This lack of specificity could allow for varied interpretation and implementation of these recommendations by health care providers, leading to diverse methods of clinical practice regarding genetic testing and counseling. The purpose of this study was to describe the frequency of genetic testing and genetic counseling services received by a large population of patients with retinoblastoma seen at a large pediatric institution.
Methods

This study was reviewed and approved by the Institutional Review Board at Cincinnati Children’s Hospital Medical Center (IRB# 2014-3639).

Participants

Seventy-four patients who were diagnosed with retinoblastoma and were seen at CCHMC from January 1, 2000 to August 1st, 2014 were selected for participation in this study. Selected patients were diagnosed over a twenty year span from 1994-2014. The CCHMC arm of i2b2 (Informatics for Integrating Biology and the Bedside), an NIH-funded National Center for Biomedical Computing based at Partners HealthCare System, performed a preliminary electronic medical records query for all patients with retinoblastoma in their diagnosis/problem list, billing codes, or encounter codes who were seen at CCHMC from January 1, 2000 – August 1, 2014. This preliminary search returned 190 patient names. This list was then reviewed to assure the patient had been diagnosed with retinoblastoma. Of these 190, 114 were found to have a diagnosis of retinoblastoma. Any patient who was seen exclusively for surgery or outpatient consultation was also removed from the patient list due to limited documentation in the medical record. One patient with trilateral disease was removed from any analysis based on tumor laterality, and two patients were excluded as they were diagnosed before 1980 and no clinical information was available regarding their diagnosis, treatment, or genetics involvement. Thus, the finalized list was narrowed to 74 patients with retinoblastoma who received comprehensive care at CCHMC.
Procedures

This retrospective chart review was performed in which one author (SF) reviewed the electronic medical record for each of the 74 patients in order to extract the needed information using the Data Abstraction Tool (Appendix 1). Generalized information abstracted included demographics, date of diagnosis, presenting clinical features, and involvement of a genetics provider in the care of the patient. The retinoblastoma patient population was also characterized in regards to which patients received genetic testing, what genetic testing methodology was performed, what type of genetic testing sample was used, and whether patients were seen by a genetics provider. This study also assessed which patients with retinoblastoma seen at CCHMC received genetic counseling and if pre- and post-test counseling was optimal. For this study, optimal genetic counseling practices among providers for patients with retinoblastoma was defined as the inclusion of five of the six essential elements of genetic counseling for cancer risk assessment as stated by NSGC. These six elements include (i) obtaining a three-four generation pedigree, (ii) obtaining familial and personal medical history, (iii) explanation of genetic testing options, (iv) informed consent, (v) result disclosure, and (vi) psychosocial assessment (Riley et al., 2012). According to the NSGC, “these recommendations are considered essential for enhancing the quality of patient care.” Of the patients seen by a genetics provider, the presence or absence of documentation of the 6 essential elements of genetic counseling was recorded (Riley et al., 2012). Previous studies have shown that providers may sometimes omit information regarding psychosocial assessment and counseling from the medical record due to concerns of patient privacy (Stahl, Granlund, Gare-Andersson, & Enskar, 2011b). Therefore, optimal genetic counseling was defined as only five of the six essential elements. of genetic counseling for
cancer risk assessment due to the assumption that documentation of psychosocial assessment and counseling would frequently not be present in the medical record.

To evaluate changes over time in genetic testing and counseling practice, patients were divided into two groups based on the year of diagnosis; 2007 and previous, and after 2007. Beginning in the year 2007, the CCHMC Division of Human Genetics initiated a partnership between the Hereditary Cancer Program and the Division of Oncology. At this time, a genetic counselor was dedicated to seeing patients with retinoblastoma on a consult basis when needed in Oncology. The primary referral point for genetic evaluation occurred in the pediatric oncology clinic.

All data collected was deposited into a database created using Research Electronic Database Capture (REDCap\textsuperscript{TM}). REDCap\textsuperscript{TM} is a secure, web-based database that includes an interface for data entry as well as the ability to track changes made to the data, export procedures to common statistical software, and import data into the database. Data collected from the patient charts was recorded using a paper data extraction sheet and stored in REDCap\textsuperscript{TM} hosted at CCHMC.

*Data Analysis:*

Statistical analyses were performed using Statistical Analysis Software (SAS), version 9.3 (SAS Institute Inc., Cary, NC).

Prior to the analyses, quality and distribution of data were checked. Demographics and clinical manifestations were compared between bilateral and unilateral patients using Wilcoxon rank sum tests or Fisher’s exact tests. Two primary outcome variables were examined: (1) whether patient received genetic testing and (2) whether genetics providers were involved. Within patients who were seen by genetics providers, we also examined whether optimal genetic counseling was documented. To test the association of outcomes with age, we performed Wilcoxon rank sum
tests. To test the association with tumor laterality, year of diagnosis, and race, we used Fisher’s exact tests. To test the association with stage of the tumor at diagnosis, we performed both Spearman correlation and Fisher’s exact tests. Besides the univariate association tests, we also performed multivariable logistic regression in which all the factors were included and tested in the same model. In this study, multiple hypotheses were tested. A p value adjustment is usually needed to control the family-wise error rate. However, given the exploratory nature of the study, we opt to use 0.05 as the threshold for statistical significance.

Results

Demographics

A total of 74 patients with retinoblastoma were included in analyses, of which 44 were unilateral, 29 were bilateral, and one was trilateral. The only trilateral patient was white male diagnosed at 3 months of age with bilateral retinoblastoma and found to have tumor involvement of the pineal gland. The demographics and clinical manifestations for the bilateral and unilateral cases are summarized in Table 1. No significant differences were observed in gender, race or ethnicity. As expected, bilateral tumors presented at a younger age and were associated more often with multifocal tumors. The most common reasons for referral prior to diagnosis included leukocoria (43.7%), detached retina (28.1%), and strabismus (25%). Three patients (75%) with full or partial 13q.14 deletions presented with extraocular phenotypes including developmental delay, microcephaly, hypotonia, hearing loss, and epilepsy. One patient with a germline missense mutation presented with retinoblastoma and Chiari I malformation. A full summary of phenotypic presentations for patients with genetic findings can be seen in Appendix 1.
Genetic Testing

To assess whether the likelihood of genetic testing can be influenced by age, race, tumor laterality, stage of tumor or year of the diagnosis, we first performed univariate association tests. As shown in Table 2, 49 out of 74 patients (66%) received genetic testing for retinoblastoma. Age, race, and stage of the tumor did not show significant impact. However, patients with unilateral disease received genetic testing more frequently than patients with bilateral disease (77% vs. 48%, p=0.013), and patients diagnosed after 2007 were more likely to receive genetic testing (82% vs. 33%, p<0.001). A multivariable logistic regression was also conducted, in which only year of diagnosis and tumor laterality were identified to be significantly associated with the likelihood of genetic testing (data not shown).

We examined how frequently patients with retinoblastoma received genetic testing by reviewing laboratory reports or notation in the patient chart. Of the bilateral patients who received genetic testing, all 14 (100%) received germline testing through submission of a blood sample. Two bilateral patients (15%) underwent enucleation procedures for disease progression and received genetic testing on tumor samples. All 14 bilateral patients (100%) were found to have a germline molecular mutation or cytogenetic abnormality. Of the unilateral patients who received genetic testing, 32 (97%) received germline testing through submission of a blood sample. Fifteen unilateral patients (50%) underwent enucleation procedures for disease progression and received genetic testing on tumor samples. Seven unilateral patients (23%) were found to have a germline molecular mutation or cytogenetic abnormality. Please see Appendix 1 for a summary of molecular and cytogenetic findings for all patients.
Fifteen patients with bilateral disease did not receive genetic testing. Of these 15 patients who did not receive genetic testing, 9 were referred for second-line therapy only while 6 received first-line therapy and confirmed diagnosis at CCHMC.

**Involvement of Genetics Provider**

Out of the 74 patients in our study, 36 (48.6%) patients with retinoblastoma were seen by genetics providers during their care at CCHMC, including 25 (33.8%) seen by a genetic counselor only, 4 (5.4%) seen by a geneticist only, and 7 (9.5%) seen by both a geneticist and a genetic counselor. Thirty-eight (51.4%) patients did not have genetics involved in their care. The involvement of a genetics provider was highly associated with an increased probability of receiving genetic testing (92% vs. 42%, \( p<.0001 \)). While this did not reach statistical significance, year of diagnosis and stage of disease tended to be associated with the involvement of genetics providers (Table 3). Genetics providers were involved more after 2007 (56%) compared to before (33%). In contrast, age of diagnosis, tumor laterality, or race did not show significant impact on the involvement of genetic professional.

After 2007 when a partnership between the Divisions of Human Genetics and Oncology was initiated at CCHMC, there was a 45% increase in the number of patients who were seen by a genetics provider from 8 patients (10.8%) prior to 2007 and 28 patients (56%) in the years 2008-2014. Genetic testing was received by only 8 patients (33.3%) diagnosed prior to 2007 and by 41 (82%) patients in the years 2008-2014. Of all patients seen by a genetics provider (N=36), 3 (8.3%) declined genetic testing.
**Documentation of Optimal Genetic Counseling**

In our study, 30 patients were seen by a genetics provider and had documentation of their genetic counseling. Among these 30, 10 patients (33.3%) had documentation of optimal genetic counseling, while 20 did not. Factors were examined to identify their potential influence on the optimization of genetic counseling. As shown in table 4, none of the factors we tested were significantly associated with the optimal genetic counseling. While not statistically significant, the proportion of optimal genetic counseling tended to be higher in bilateral compared to unilateral patients (40% vs. 30%), and after 2007 compared to 2007 and prior (38% vs. 17%).

A complete description of the frequencies for which each element of genetic counseling cancer risk assessment was documented in the electronic medical record for the 30 patients who were seen by a genetics provider and for whom documentation was present in the electronic medical records from 1994-2014 can be found in Figure 1. Of note, documentation of psychosocial assessment and counseling was not present for any patient diagnosed from 1994-2014.

Explanation of genetic testing was documented most frequently followed by personal medical history intake and informed consent.

**Discussion**

**Involvement of Genetics Provider and Genetic Testing**

Although genetic testing for retinoblastoma is considered standard of care, of the 74 patients enrolled in this study, only 49 (66.2%) received genetic testing. Involvement of genetics provider was shown by this study to be associated with receiving genetic testing for retinoblastoma. Of the 29 patients with bilateral retinoblastoma enrolled in this study, only 14 (48.3%) received
germline genetic testing. Of the 15 bilateral patients who did not receive testing, only two were seen by genetics provider.

One potential reason why these patients with bilateral disease were not seen by a genetics provider is a lack of referral to genetics due to the assumption that all bilateral retinoblastoma is hereditary and therefore there is no need to refer to genetics. In the case of one patient with bilateral disease who was seen by genetics and declined testing, the mother stated that she never pursued genetic testing for her teenage son as she had been told his disease was bilateral and therefore hereditary and did not need genetic testing. Distance could also have played a role in why genetics was not involved in the care of these 13 individuals as many lived out of state. CCHMC is a large referral center for the Midwest and Midsouth regions of the United States. Patients and their families coming from farther away for treatment may have been less likely to have time to see genetics. Another possibility for lack of genetics involvement during care is that many patients with retinoblastoma are referred to CCHMC for second-line therapies and consultation for treatment options following initial diagnosis and treatment at a different location. Insurance coverage may have also played a role in whether families elected to proceed with genetic testing. Although many retinoblastoma patients meet criteria for insurance coverage for RB1 sequencing and deletion/duplication analysis (Capasso, 2014), some patients who do not qualify for coverage may be deterred from receiving genetic testing due to cost barriers. However, insurance coverage was not assessed in this study.

*Improvement in Genetics Involvement and Increased Genetic Testing Screening*

Involvement of a genetics provider was shown by this study to be associated with receiving genetic testing for retinoblastoma. After collaboration between the Divisions of Human Genetics
and Oncology was initiated in 2007, increases in both the number of patients seen by a genetics
provider and the number of patients receiving genetic testing were observed. Other studies have
also shown that the likelihood of completion of genetic evaluation, including genetic testing,
increased with the presence of genetics providers (Dhar et al., 2011) (Pradhan et al., 2010).
Multidisciplinary care can also affect the usefulness of genetic evaluation as results of genetic
testing may inform follow-up and screening recommendations for patients and at-risk family
members that would be made by the oncology provider. Future studies should evaluate the
cost/benefit ratio of genetic testing for at-risk family members of patients with retinoblastoma to
analyze whether genetic testing is more cost-effective than clinical screening. Continued
partnership between the Divisions of Human Genetics and Oncology ensures that most patients
are receiving comprehensive evaluation from both oncology and genetics providers.

*Universal Genetic Screening for Patients with Retinoblastoma*

Further justification for universal genetic testing for patients with retinoblastoma includes the
variable expressivity of the disease. Historically, 100% of bilateral retinoblastoma was expected
to be hereditary while unilateral retinoblastoma was presumed to be hereditary in approximately
10-15% of cases (Aerts et al., 2006). Of the 29 bilateral patients enrolled in this study, 14
(48.3%) received genetic testing and of those all 14 were found to have a germline mutation or
cytogenetic aberration. Of the 44 unilateral patients enrolled in this study, 34 (77%) received
genetic testing and of those 7 (23%) were found to have a germline mutation or cytogenetic
aberration.

The variable presentation of hereditary retinoblastoma further validates the necessity of genetic
testing for all patients with retinoblastoma. Patients with 13q14 deletions may present with
unilateral or bilateral presentation. Studies have shown that the proportion of individuals who carry a 13q14 deletion and present with unilateral disease is higher compared to patients with intragenic point mutations (Albrecht et al., 2005). Four patients in this study were found to have partial or complete deletions of the 13q14 region. Three patients (75%) presented with unilateral disease and one (25%) presented with bilateral disease.

There have also been reports of patients found to have germline mosaicism who are diagnosed at later ages and with unilateral presentation (Rushlow et al., 2009). Two patients within this study presented with a low-penetrance germline mutation. One patient presented with a family history of a paternal great-uncle and two paternal second cousins with retinoblastoma. This patient was diagnosed with unilateral, unifocal disease at 29.6 months of age. The patient’s mother had no history of cancer development and the patient’s father had been diagnosed with acute lymphoblastic leukemia at the age of 28 but had no history of retinoblastoma. Upon genetic testing, the patient was found to have a well-described, low-penetrance mutation (p.Arg661Trp) in exon 20 of RB1 (Otterson, Chen, Coxon, Khleif, & Kaye, 1997). Another patient with unilateral disease was found to have the same missense mutation (p.Arg661Trp) with no family history of retinoblastoma development. Low penetrance mutations differ from the majority of RB1 alterations as they do not result in total loss-of-function for that allele. The reduced penetrance of retinoblastoma is the result of residual function of these alleles in retinoblastoma precursor cells (Lohmann, Brandt, Hopping, Passarge, & Horsthemke, 1994). Families with detected RB1 germline mutations that exhibit incomplete penetrance increase the difficulty of providing screening and follow-up recommendations to patients and at-risk family members, as there is no standard follow-up protocol for adults with hereditary retinoblastoma (Serrano et al., 2011).
Documentation and Implementation of Optimal Genetic Counseling

Of the 30 patients enrolled in this study who were seen by a genetics provider and documentation of genetic counseling elements were present in the EMR, only 10 (33.3%) received optimal genetic counseling. Bilateral patients were slightly more likely to receive optimal genetic counseling than unilateral patients with 40% of bilateral patients and 30% of unilateral patients receiving optimal genetic counseling. As mentioned, documentation of the elements of genetic counseling cancer risk assessment was not equally distributed across elements. Documentation of psychosocial assessment was not present in the EMR for any of the 30 patients seen by a genetics provider who documented the elements of genetic counseling cancer risk assessment. Documentation of explanation of genetic testing was most frequently documented, followed by intake of personal and family medical history. This data could reflect a possible prioritization of certain elements of the genetic counseling cancer risk assessment by genetics providers. This prioritization could indicate that genetics providers feel that education regarding genetic testing options and the intake of the personal and family medical history are the most crucial elements to the genetic counseling cancer risk assessment for patients with retinoblastoma.

While the implementation of the electronic medical record (EMR) has revolutionized and streamlined the application of health care services in the United States, at this point in time, the EMR is by no means a complete communication tool. Providers mainly view the EMR as a medical tool in which to record health from a biometric viewpoint. This approach leaves gaps in the EMR and is not sufficient in documenting psychosocial issues (Stahl, Granlund, Gare-Andersson, & Enskar, 2011a). Studies have suggested that although providers may feel psychosocial assessment and counseling are important, these elements are omitted from
documentation in an effort to protect patient privacy (Stahl, Granlund, Gare-Andersson, & Enskar, 2011b).

These concepts are important to consider when analyzing data to determine if patients with retinoblastoma receive optimal genetic counseling, particularly when evaluating psychosocial assessment. Providers may offer psychosocial assessment and counseling to families more often than what they are documenting in the EMR. Differences in the number of elements of genetic counseling cancer risk assessment that were recorded may not fully represent whether there is a difference in the quality of the provider–patient relationship. Genetic counseling services also may not be exclusively delivered by a genetics provider. In the setting of a pediatric oncology clinic, patients may be receiving genetic counseling from oncology providers as well. For the purpose of this study, genetic counseling services documented were only recorded for patients seen by a genetics provider. Continued partnership between genetics and oncology will ensure that patients are receiving the most comprehensive care and are being educated on oncology and genetics concepts.

Alternative research models such as audio or video recording of the genetic counseling session may prove to be more useful in documenting all psychosocial assessment and counseling concepts provided by the health care provider. However, if patients with retinoblastoma are truly not receiving psychosocial assessment and counseling, providers are not only falling short of the national standards for genetic counseling cancer risk assessment, they are potentially underserving their patients and families of their patients as psychosocial assessment and counseling in the medical setting has been shown to reduce emotional distress while improving quality of life, patient satisfaction and patient-provider communication.
Another consideration for this study when evaluating the frequency with which patients received optimal genetic counseling is that not all patients who were seen by genetics provider elected to pursue genetic testing. Of all patients seen by a genetics provider (N=36), 3 (8.3%) declined genetic testing. Patients who declined genetic testing would not have been counseled on informed consent and would not have received result disclosure.

Another gap in the EMR included lack of documentation of the specific genetic testing results for patients with retinoblastoma. Seven patients in this study had documentation in the EMR that genetic testing was completed and a germline molecular mutation or cytogenetic abnormality had been found. However, there were no original laboratory reports available to verify if this documentation was correct. Verification of the specific mutation found in the proband is important for the testing of at-risk family members. If the mutation found in the proband is verified, family members can opt to have site-specific analysis as opposed to whole gene sequencing and deletion/duplication analysis of the entire RB1 gene. This option is significantly less expensive and typically offers a faster return of results.

*Improvement in Genetic Counseling Services over Time*

Genetic counseling practices for patients with retinoblastoma seen at CCHMC have improved since 2007, when a partnership between the Divisions of Human Genetics and Oncology was initiated. Prior to 2007, only 1 patient chart (16.7%) had documentation of optimal genetic counseling, while 9 patient charts (37.5%) diagnosed from 2008-2014 had documentation of optimal genetic counseling. While this is a marginally significant improvement, reasons for why over half (62.5%) of patients with retinoblastoma continue to receive suboptimal genetic counseling must be explored. Barring that genetics providers may simply not be fully
documenting the genetic counseling encounter in the EMR, other possibilities must be considered for this suboptimal outcome. Reasons for this outcome are speculative but may include lack of dedicated time with patient and families for genetic counseling as well as prioritization of certain elements of the genetic counseling cancer risk assessment.

Typically, retinoblastoma patients are seen by genetics at CCHMC on a consult basis and are seen in the physical location of the Pediatric Oncology department. In this setting, the genetics provider may only have a limited amount of time in-between the patient’s other appointments such as scheduled treatment and therapy procedures. This may influence the genetics provider to obtain what he or she perceives to be the most critical aspects of health and family history information and educate solely on genetic testing rather than other aspects of the genetic counseling cancer risk assessment. Referral to genetics and the ability for the genetics provider to see patients and families in a dedicated outpatient clinic setting may improve these outcomes.

Conclusions

Retinoblastoma is a hereditary cancer syndrome for which genetic testing is considered standard of care for patients and at-risk family members (Robson et al., 2010). Despite this recommendation, our study has shown that not all patients with retinoblastoma at one large pediatric hospital are receiving genetic testing in clinical practice. Genetic testing for retinoblastoma results in streamlined long-term care for patients and identified at-risk relatives (Dhar et al., 2011). Genetic testing for retinoblastoma has also been shown to be associated with a significant reduction in health care expenditures by reducing the number of unnecessary anesthetized examinations and screening visits for patients and family members who do not have hereditary retinoblastoma (Joseph, Shanmugam, Srinivasan, & Kumaramanickavel, 2004).
Although genetics providers seem to prioritize documentation of genetic testing options and intake of personal and family medical history, this study has shown that involvement of a genetics provider (geneticist and/or genetic counselor) increases the likelihood that patients will receive genetic testing for retinoblastoma. This prioritization may be influenced by limited time, lack of clinic space or other unknown factors. The lack of documentation of specific elements of the genetic counseling cancer risk assessment may or may not be reflective of the care received by the patient. Genetics providers are uniquely trained to educate patients on the genetics of hereditary cancer syndromes as well as provide information about genetic testing options. Presentation of this information from a genetics provider may be influential for families when deciding to pursue genetic testing for retinoblastoma.

**Limitations and Future Directions**

Limitations of this study include the concerns for generalizability as well as the inability to fully capture the genetic counseling cancer risk assessment through retrospective evaluation of documentation alone. As this cohort was limited to one large referral center, the outcomes of this population may not full represent the clinical practice of all patients with retinoblastoma. Future studies could expand the findings of this study and include the evaluation of genetic testing and counseling practices for patients with retinoblastoma from multiple sites offering comprehensive care for patients with retinoblastoma. Our study only reports the number of specific elements of the genetic counseling cancer risk assessment that were documented in the patient chart. We had no way to assess the length of time spent discussing each element or the depth of this discussion. As previously mentioned, the genetics provider is not likely to document the psychosocial assessment of the patient and family or the use of specific counseling skills. The number of
genetic counseling risk assessment elements recorded may not fully represent the quality of the provider–patient relationship and therefore may not represent whether patients truly received optimal or sub-optimal genetic counseling services. Evaluations of the genetic counseling cancer risk assessment may be best performed with a different research model. Prospective studies such as audio- or video-recorded sessions may serve as better research methods to capture elements discussed and psychosocial counseling methods demonstrated by the genetics provider.

Despite its limitations, this current study has provided a platform for promoting the involvement of genetic testing and counseling for patients with retinoblastoma. Larger, prospective studies will be able to more accurately determine the differences between clinical practice and documentation in the medical record. Incorporation of genetic testing as well as the inclusion of all essential elements of cancer risk assessment and counseling by genetics providers will help to ensure that patients with retinoblastoma and their families receive the most benefit from the unique medical and psychosocial components of genetic medicine.
References


Commision on Cancer. (2012). Cancer Program Standards: ensuring patient-centered care *VI.1*


### Table 1. Demographics and Disease characteristics

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<th></th>
<th>Bilateral</th>
<th>Unilateral</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (month)</strong></td>
<td>6.2 (1.9, 18.3)</td>
<td>19.3 (9.3, 29.1)</td>
<td>0.001</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>15 (52%)</td>
<td>23 (52%)</td>
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</tr>
<tr>
<td>Male</td>
<td>14 (48%)</td>
<td>21 (48%)</td>
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</tr>
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<td><strong>Ethnicity</strong></td>
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<td></td>
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<tr>
<td>Hispanic/Latino</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>27 (100%)</td>
<td>43 (98%)</td>
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<td><strong>Race</strong></td>
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<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>6 (22%)</td>
<td>11 (26%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21 (78%)</td>
<td>32 (74%)</td>
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</tr>
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<td><strong>Stage disease at diagnosis</strong></td>
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<td>3 (19%)</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0 (0%)</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>7 (44%)</td>
<td>13 (42%)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>6 (38%)</td>
<td>10 (32%)</td>
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</tr>
<tr>
<td><strong>Focality of tumors</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unifocal</td>
<td>0 (0%)</td>
<td>38 (86%)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>29 (100%)</td>
<td>6 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>2008-2014</td>
<td>17 (59%)</td>
<td>32 (73%)</td>
<td></td>
</tr>
<tr>
<td>1994-2007</td>
<td>12 (41%)</td>
<td>12 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

Age was shown as median (IQR) and compared using Wilcoxon rank sum test; other variables were shown as frequency (%) and tested using Fisher’s exact tests.
Table 2. Genetic Testing for Patients with Retinoblastoma

<table>
<thead>
<tr>
<th>Did patient receive genetic testing?</th>
<th>No (N=25)</th>
<th>Yes (N=49)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (month)</td>
<td>15.2 (2.0, 26.3)</td>
<td>12.0 (5.4, 23.4)</td>
<td>0.87</td>
</tr>
<tr>
<td>Tumor laterality</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Bilateral</td>
<td>15 (52%)</td>
<td>14 (48%)</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>10 (23%)</td>
<td>34 (77%)</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2008-2014</td>
<td>9 (18%)</td>
<td>41 (82%)</td>
<td></td>
</tr>
<tr>
<td>1994-2007</td>
<td>16 (67%)</td>
<td>8 (33%)</td>
<td></td>
</tr>
<tr>
<td>Stage disease at diagnosis</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>B</td>
<td>1 (14%)</td>
<td>6 (86%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0 (0%)</td>
<td>4 (100%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3 (15%)</td>
<td>17 (85%)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>3 (19%)</td>
<td>13 (81%)</td>
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</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>6 (35%)</td>
<td>11 (65%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (33%)</td>
<td>36 (67%)</td>
<td></td>
</tr>
</tbody>
</table>

Age was shown as median (IQR) and compared using Wilcoxon rank sum test; other variables were shown as frequency (%) and tested using Fisher’s exact tests.
Table 3. Involvement of a Genetics Provider in the Care of Patients with Retinoblastoma

<table>
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<tr>
<th></th>
<th>No (N=38)</th>
<th>Yes (N=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (month)</td>
<td>10.2 (4.5, 24.6)</td>
<td>13.0 (4.1, 28.5)</td>
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<td>Tumor Laterality</td>
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<td>0.63</td>
</tr>
<tr>
<td>Bilateral</td>
<td>16 (55%)</td>
<td>13 (45%)</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>21 (48%)</td>
<td>23 (52%)</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>2008-2014</td>
<td>22 (44%)</td>
<td>28 (56%)</td>
<td></td>
</tr>
<tr>
<td>1994-2007</td>
<td>16 (67%)</td>
<td>8 (33%)</td>
<td></td>
</tr>
<tr>
<td>Stage disease at diagnosis</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>B</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3 (15%)</td>
<td>17 (85%)</td>
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<tr>
<td>E</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
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</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Black</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27 (50%)</td>
<td>27 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Age was shown as median (IQR) and compared using Wilcoxon rank sum test; other variables were shown as frequency (%) and tested using Fisher’s exact tests.
## Table 4. Optimal Genetic Counseling for Patients with Retinoblastoma

<table>
<thead>
<tr>
<th>Was optimal genetic counseling documented in the patient chart?</th>
<th>No (N=20)</th>
<th>Yes (N=10)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>12.2 (2.8, 26.0)</td>
<td>18.5 (6.2, 34.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Tumor laterality</td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
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</tr>
<tr>
<td>Unilateral</td>
<td>14 (70%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>2008-2014</td>
<td>15 (63%)</td>
<td>9 (38%)</td>
<td></td>
</tr>
<tr>
<td>1994-2007</td>
<td>5 (83%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Stage disease at diagnosis</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>B</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>9 (60%)</td>
<td>6 (40%)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>4 (67%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (65%)</td>
<td>8 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

Age was shown as median (IQR) and compared using Wilcoxon rank sum test; other variables were shown as frequency (%) and tested using Fisher’s exact tests.
Figures

Figure 1. Documentation of the Essential Elements of Genetic Counseling Cancer Risk Assessment

![Diagram showing the documentation of essential elements in genetic counseling cancer risk assessment](chart.png)

- Number of times element documented in patient charts (N=30)
## Appendices

### Appendix 1: Phenotype and Genotype of Patients with Molecular and/or Cytogenic Abberations

<table>
<thead>
<tr>
<th>Pt. ID</th>
<th>Laterality of Tumors</th>
<th>Age at Diagnosis (months)</th>
<th>Ocular Phenotype</th>
<th>Extraocular phenotype</th>
<th>Germline Phenotype</th>
<th>Tumor Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB002</td>
<td>unilateral</td>
<td>12.0</td>
<td>abnormal red reflex, strabismus, detached retina</td>
<td>none</td>
<td>unavailable</td>
<td>hypermethylation of RB1 promoter region on both alleles</td>
</tr>
<tr>
<td>RB006</td>
<td>unilateral</td>
<td>2.3</td>
<td>unavailable</td>
<td>none</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB010</td>
<td>unilateral</td>
<td>28.6</td>
<td>strabismus</td>
<td>unavailable</td>
<td>unavailable</td>
<td>c.1285A&gt;T(Tp.Lys429X) / c.2490-1G&gt;A</td>
</tr>
<tr>
<td>RB015</td>
<td>unilateral</td>
<td>13.6</td>
<td>leukocoria, detached retina</td>
<td>none</td>
<td>unavailable</td>
<td>del RB1 exons 18-27 del P-exon 2</td>
</tr>
<tr>
<td>RB023</td>
<td>unilateral</td>
<td>9.8</td>
<td>unavailable</td>
<td>none</td>
<td>unavailable</td>
<td>a.1735C&gt;T(Tp.Arg579X) / g.38923-3990del28</td>
</tr>
<tr>
<td>RB026</td>
<td>unilateral</td>
<td>36.7</td>
<td>detached retina</td>
<td>none</td>
<td>unavailable</td>
<td>deletion exons 18-27 RB1 gene / deletion exons 18-27</td>
</tr>
<tr>
<td>RB027</td>
<td>unilateral</td>
<td>44.4</td>
<td>leukocoria, detached retina, loss visual acuity</td>
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<td>unavailable</td>
<td>c.763C&gt;T(p.Arg255X) / del P-exon 27</td>
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<tr>
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<td>1.4</td>
<td>unavailable</td>
<td>normal</td>
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</tr>
<tr>
<td>RB030</td>
<td>unilateral</td>
<td>44.2</td>
<td>detached retina</td>
<td>normal</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB041</td>
<td>unilateral</td>
<td>10.9</td>
<td>leukocoria</td>
<td>unavailable</td>
<td>unavailable</td>
<td>c.234G&gt;A(Tp.W78X) / c.234G&gt;T(Tp.W78X)</td>
</tr>
<tr>
<td>RB042</td>
<td>bilateral</td>
<td>6.2</td>
<td>unavailable</td>
<td>leukocoria, detached retina</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
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<td>6.2</td>
<td>leukocoria</td>
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<td>unavailable</td>
</tr>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
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<td>RB045</td>
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<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
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<tr>
<td>RB046</td>
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<td>leukocoria</td>
<td>detachment</td>
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</tr>
<tr>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
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<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB049</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB050</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
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<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB052</td>
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<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
</tr>
<tr>
<td>RB053</td>
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<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB054</td>
<td>bilateral</td>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB055</td>
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<td>leukocoria</td>
<td>detachment</td>
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<tr>
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</tr>
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<td>leukocoria</td>
<td>detachment</td>
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</tr>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB059</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB060</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB061</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
</tr>
<tr>
<td>RB062</td>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
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<tr>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
</tr>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
</tr>
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<td>leukocoria</td>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
</tr>
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<td>leukocoria</td>
<td>detachment</td>
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<td>leukocoria</td>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
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<td>bilateral</td>
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<td>leukocoria</td>
<td>detachment</td>
<td>unavailable</td>
<td>unavailable</td>
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<td>leukocoria</td>
<td>detachment</td>
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<td>unavailable</td>
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<tr>
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<td>6.2</td>
<td>leukocoria</td>
<td>detached retina</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
<tr>
<td>RB077</td>
<td>bilateral</td>
<td>6.2</td>
<td>leukocoria</td>
<td>detached retina</td>
<td>unavailable</td>
<td>unavailable</td>
</tr>
</tbody>
</table>
Appendix 2: Data Abstraction Form

Demographic Information

ID number ___________________________         Sex _________________________________
Ethnicity ______________________________          DOB ______________________________

Data Collection

1. Presentation of Retinoblastoma Tumor(s)

   I. Age at diagnosis of retinoblastoma: ________ months (nearest whole month)

   II. Date of diagnosis of retinoblastoma: ___/___/__________

   III. Stage of tumor at diagnosis: Stage__________ (A-E; based on International Classification Intraocular Retinoblastoma)

IV. Laterality of Tumor(s)
   □ A. unilateral
   □ B. bilateral
   □ C. trilateral

V. Focality of Tumor(s)
   □ A. unifocal
   □ B. multifocal

VI. Location of Tumor(s)
   □ A. Intraocular
   □ B. Extraocular

VII. Recurrence of Retinal Tumor(s)
   1. Did the patient develop new primary retinal tumors at any point after initial diagnosis?
      □ A. Yes
          Specify______________________________________________________

      □ B. No

   2. Did the patient develop new primary non-retinal tumors at any point after initial diagnosis?
      □ A. Yes
          Specify______________________________________________________
2. Treatment

What type(s) of treatment did the patient receive? (check all that apply and include first date of treatment)

☐ Enucleation: ___/___/________
☐ Radiation Therapy: ___/___/________
☐ Local Treatment (chryo/thermotherapy): ___/___/________
☐ Systemic Chemotherapy: ___/___/________
☐ Ophthalmic Artery Infusion of Chemotherapy: ___/___/________
☐ Intravitreal Chemotherapy: ___/___/________
☐ Subtenon Chemotherapy: ___/___/________
☐ Other: ___/___/________
   Specify________________________________________

3. Presenting features other than retinoblastoma

☐ Developmental Delay
☐ Intellectual/ Cognitive Disability
☐ Autism/ Autistic Like Features
☐ Cardiovascular Anomalies Specify_____________________
☐ Respiratory Problems Specify_____________________
☐ Gastrointestinal Problems Specify_____________________
☐ Psychological Problems Specify_____________________
☐ GU Problems Specify_____________________
☐ Endocrine Problems Specify_____________________
☐ Orthopedic Problems Specify_____________________
☐ Rheumatology (Joint) Problems Specify_____________________
☐ Ophthalmology Problems Specify_____________________
☐ Growth Problems Specify_____________________
☐ Prematurity Specify_____________________
☐ Neurological Disorders Specify_____________________

4. Genetics Evaluation

1. Did patient see a genetics provider for evaluation at CCHMC at any point from January 1, 2000 to present?

☐ A. Yes (check all that apply)
   ☐ Geneticist-MD
2. Presence of the 6 elements of optimal genetic counseling (check all where documentation is present in the medical record)

☐ Three to four generation family history (pedigree)
☐ Intake of personal and family medical history
☐ Explanation of genetic testing
☐ Informed consent for genetic testing
☐ Disclosure of test results
☐ Psychosocial assessment

5. Genetic Testing

1. Did patient receive genetic testing from January 1, 2000 to present?

☐ A. Yes
  ☐ Test Sample Type (check all that apply)
    ☐ Tumor Sample
      Genetic Test Type (check all that apply)
      ☐ FISH
      ☐ RB1 Gene Sequencing
      ☐ Gross Deletion/Duplication Sequencing
      ☐ Hypermethylation
      ☐ Microarray
      ☐ Other ______________________
    ☐ Peripheral Blood Sample
      Genetic Test Type (check all that apply)
      ☐ FISH
      ☐ RB1 Gene Sequencing
      ☐ Gross Deletion/Duplication Sequencing
      ☐ Hypermethylation
      ☐ Microarray
      ☐ Other ______________________

☐ B. No

2. Date of Genetic Testing on Report: _____/___________/___________
5. *Genotype of RB1 gene mutations*

I. Exact mutations of the RB1 gene as reported in lab report:
   (Specify if not mutation was found and specify if tumor or blood)

   ___________________________________________________________ Tumor or Blood
   ___________________________________________________________ Tumor or Blood

II. Mutation Type (Blood)
   - Single Base Substitution
   - Exonic deletion or duplication (in frame)
   - Exonic deletion or duplication (frameshift)
   - Splice site mutation
   - Multi-Exonic deletion or duplication
   - Whole gene deletion
   - Submicroscopic deletion
   - Translocation
   - Hypermethylation of the promoter region of RB1
   - Other
     Specify ________________

Mutation Type (Tumor)
   - Single Base Substitution
   - Exonic deletion or duplication (in frame)
   - Exonic deletion or duplication (frameshift)
   - Splice site mutation
   - Multi-Exonic deletion or duplication
   - Whole gene deletion
   - Submicroscopic deletion
   - Translocation
   - Hypermethylation
   - Other
     Specify ________________

6. *Family History*

I. Does the patient have a family history of retinoblastoma?
   - □ A. Yes
     Specify relatives (list all that apply):
     ______________________________
     ______________________________

   - □ B. No
Appendix 3: Codebook

Demographic Information

**Gender**
Variable: **Gen**
- 01 Male
- 02 Female

**Ethnicity**
Variable: **Ethn**
- 01 White
- 02 Black or African American
- 03 Asian
- 04 American Indian or Alaskan Native
- 05 Native Hawaiian or other Pacific Islander
- 06 Hispanic/Latino
- 07 Other

Presentation

**Age at diagnosis of retinoblastoma**
Variable: **Age1**
Format: rounded to nearest whole month(s)

**Date at diagnosis of retinoblastoma**
Variable: **DatDx**
Format: dd/mo/yyyy

**Stage of tumor(s) at diagnosis (based on ICIR)**
Variable: **Stage**
- 01 A
- 02 B
- 03 C
- 04 D
- 05 E

**Laterality of tumor(s)**
Variable: **Lat**
- 01 Unilateral
- 02 Bilateral
- 03 Trilateral

**Focality of Tumor(s)**
Variable: **Foc**
- 01 Unifocal
02 Multifocal

Location of Tumor(s)
Variable: Loc
  01 Intraocular
  02 Extraocular

Development of new primary retinal tumors
Variable: RetRec
  01 Yes
  02 No

Development of new primary non-retinal tumors
Variable: NonRetRec
  01 Yes
  02 No

Specification of development new primary non-retinal tumor
Variable: SpecRec
  01 Brain
  02 Pineal gland
  03 Bone
  04 Soft Tissue
  05 Blood
  06 Lymph/lymph nodes
  06 Other

Genetic Testing

Receive Genetic Testing
Variable: GenTest
  01 Yes
  02 No

Date of Genetic Testing Results
Variable: DateGT
Format: dd/mo/yyyy

Blood Testing
Variable: Blood
  01 Yes
  02 No

Type(s) of Genetic Testing Received on Blood Sample
Variable: TestTypeBld
  01 FISH
02 RB1 Gene Sequencing
03 Gross Deletion/Duplication Sequencing
04 Hypermethylation
05 Microarray
06 Other

*Exact Mutation Blood*
Variable: **MutBlood**

*Mutation Type Blood*
Variable: **MutTypBld**
01 Single base substitution, small intragenic deletion or insertion
02 Deep intronic splice mutation, gross rearrangement
03 Exonic, multi-exonic and whole gene deletions, large insertion or rearrangement
04 Submicroscopic deletion or translocation
05 Hypermethylation of the promoter region of *RB1*
06 Other

*Tumor Testing*
Variable: **Tumor**
01 Yes
02 No

*Type(s) of Genetic Testing Received on Blood Sample*
Variable: **TestTypeTum**
01 FISH
02 RB1 Gene Sequencing
03 Gross Deletion/Duplication Sequencing
04 Hypermethylation
05 Microarray
06 Other

*Exact Mutation Tumor*
Variable: **ExMut**

*Mutation Type*
Variable: **MutTypTum**
01 Single base substitution, small intragenic deletion or insertion
02 Deep intronic splice mutation, gross rearrangement
03 Exonic, multi-exonic and whole gene deletions, large insertion or rearrangement
04 Submicroscopic deletion or translocation
05 Hypermethylation of the promoter region of *RB1*
06 Other
Presence of Optimal Genetic Counseling Elements:

*Three to four generation family history (pedigree)*
Variable: **Ped**
  01 Yes
  02 No

*Intake of personal and family medical history*
Variable: **MedHx**
  01 Yes
  02 No

*Explanation of genetic testing*
Variable: **GenTest**
  01 Yes
  02 No

*Informed consent for genetic testing*
Variable: **InfCon**
  01 Yes
  02 No

*Disclosure of test results*
Variable: **DisTest**
  01 Yes
  02 No

*Psychosocial assessment*
Variable: **Psych**
  01 Yes
  02 No

*Adherence to Medical Management Screening*
Variable: **Screen**
  01 Yes
  02 No

*Follow up Visits*
Variable: **FUV**
  01 Yes
  02 No

*Testing*
Variable: **Test**
  01 Yes
02 No

Family History of Retinoblastoma

Family History
Variable: FamHX
  01 Yes
  02 No

Family Members Affected by Retinoblastoma
Variable: FamAff
  01 Mother
  02 Father
  03 Sister
  04 Brother
  05 Maternal (other)
  06 Paternal (other)

Type of treatment(s) received
Variable: Treat
  01 Enucleation
  02 Radiation Therapy
  03 Local Treatment
  04 Systemic Chemotherapy
  05 Ophthalmic Artery Infusion
  06 Intravitreal chemotherapy
  07 Subtenon Chemotherapy
  08 Other

Presenting feature(s) other than Retinoblastoma
Variable: OtherFx
  01 Developmental Delay
  02 Intellectual/ Cognitive Disability
  03 Autism/ Autistic Like Features
  04 Renal Anomalies
  05 Cardiovascular Anomalies
  06 Respiratory Problems
  07 Gastrointestinal Problems
  08 Psychological Problems
  09 Cardiovascular Problems
  10 Endocrine Problems
  11 Orthopedic Problems
  12 Rheumatology (Joint) Problems
  13 Neurological Problems