The Top 10 Retinoblastoma Research Priorities in Canada as Determined by Patients, Clinicians and Researchers

Running Title: Top 10 Retinoblastoma Research Priorities

Authors: Kaitlyn Flegg, MSc,[a] Maxwell J. Gelkopf, BSc,[a] Sarah A. Johnson, PhD,[b] Helen Dimaras, PhD,[a,c,d,e,f] on behalf of the Canadian Retinoblastoma Research Advisory Board Priority Setting Steering Committee

Affiliations: [a]Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, Canada; [b]Department of Neuroscience, Evelyn F. and William L. McKnight Brain Institute, University of Florida, Gainesville, Florida, [c]Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada; [d]Division of Clinical Public Health, Dalla Lana School of Public Health, The University of Toronto, Toronto, Canada; [e]Child Health Evaluative Sciences Program, SickKids Research Institute, Toronto, Canada; [f]Centre for Global Child Health, SickKids Research Institute, Toronto, Canada

Corresponding Author: Dr. Helen Dimaras, Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, 555 University Ave, Toronto, ON, M5G 1X8, Canada. helen.dimaras@sickkids.ca, +1-416-813-7654 ext: 201876

Funding: This work was funded by a Meeting, Planning and Dissemination grant from the Canadian Institutes of Health Research (CIHR), Institute for Cancer Research.

Conflict of Interest: The authors declare they have no conflicts of interest to disclose.

Authors' contributions: Ms. Flegg contributed to conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration and writing – original draft. Mr. Gelkopf contributed to conceptualization, data curation, formal analysis, methodology, project administration and writing – review and editing. Dr. Johnson contributed to conceptualization, data curation, formal analysis and writing – review and editing. Dr. Dimaras contributed to conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration and writing – review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements: The authors acknowledge the WG, SC and priority setting workshop participants: Arvinder Aulakh, Mignonne Baddeliyanage, Richelle Baddeliyanage, Karen Born (Chair), Rod Bremner, Ella Bowles, Rob Downie, Brenda Gallie, Hannah Girdler, Stephanie Hoang, Jaime Jessen, Heather Karasch, Stephanie Kletke, Morgan Livingstone, Marg MacFarlane, Leslie MacKeen, Richard Mackette, Catherine Moses, Katherine Paton, Catharine Ramsey, Ivana Ristevski, Jill Robert, Carlos Solarte, Sameh Soliman, Jennifer Steeves, Caron Strahlendorf and Kim Zink.

Lay Summary: A national cross-sectional study of retinoblastoma (childhood eye cancer) patients (including survivors, parents and caregivers), healthcare personnel and researchers was undertaken in Canada to answer the question "What are the top 10 retinoblastoma research priorities in Canada?". The method used was an adaptation of the James Lind Alliance Priority Setting method, commonly used in such joint priority setting initiatives. The top priority identified was related to early diagnosis of retinoblastoma. Advocacy groups, research teams and

funding agencies are encouraged to align their practices with the identified retinoblastoma research priorities.

Abstract

Background: Retinoblastoma is a childhood cancer of the eye that can have lifelong effects on patients and families. The purpose of this study was for retinoblastoma patients (including caregivers), clinicians and researchers to jointly determine the top 10 retinoblastoma research priorities in Canada.

Methods: An adaptation of the James Lind Alliance Priority Setting Partnership methodology was employed. In an online survey, retinoblastoma patients, clinicians and researchers were asked, "what questions about retinoblastoma would you like to see answered by research?". A national Priority Setting Steering Committee was assembled to review and refine the list of survey responses. A final list of 30 retinoblastoma research questions were ranked, using the nominal group technique, by a group of patients, clinicians and researchers, during an in-person priority setting workshop. This resulted in consensus on the 10 retinoblastoma research priorities.

Results: A total of 175 retinoblastoma research questions were suggested by 59 survey participants. The top 10 questions fell into seven categories: Second Cancer (n = 2), Follow Up (n = 2), Psychosocial (n = 2), Treatment (n = 1), Diagnosis (n = 1), Miscellaneous (n = 1) and Global Health (n = 1). The early diagnosis of retinoblastoma was identified as the top retinoblastoma research priority in Canada.

Conclusions: The list of priorities will serve as a resource for advocacy groups, research teams and funding agencies which focus on retinoblastoma. The inclusion of researchers as participants was a novel and valuable element in identifying research priorities valued also by clinicians and patients.

Keywords: Priority setting, patient engagement, patient partnership, retinoblastoma, cancer, research.

Manuscript text pages: 25 pages (manuscript word count: 2,983; abstract word count: 249)

Manuscript tables: 3

Manuscript figures: 2

Supplementary files: 4

List of abbreviations:

- CRRAB: Canadian Retinoblastoma Research Advisory Board
- GRIPP2: Guidance for Reporting Involvement of Patient and the Public
- JLA: James Lind Alliance
- PICO: patient or population, intervention, comparator or control and outcome
- PPI: Patient and Public Involvement
- PSP: Priority Setting Partnerships
- SC: Priority Setting Steering Committee
- WG: Working Group

Introduction

The role of patients in health research is shifting from serving as study subjects to participating as authentic partners. Referred to as patient engagement, this partnership occurs when patients meaningfully and actively collaborate in the governance, priority setting and conduct of research, as well as in summarizing, distributing, sharing and applying its resulting knowledge. (1, 2) In this context, 'patient' refers to individuals with personal experience of a health issue and their informal caregivers, including family and friends.(2)

Research priority setting is an important element of patient engagement. A form of advocacy, priority setting identifies the research most relevant to, and valued by, patients and clinicians. This is necessary given that most funded research does not reflect the priorities of patients and clinicians, potentially reducing its impact.(3, 4) There are several established methods for research priority setting; the James Lind Alliance (JLA) Priority Setting Partnerships (PSP) method is arguably the most popular. The JLA PSP method involves patients and clinicians equally in setting a top 10 list of research priorities.(5)

Retinoblastoma is a cancer of the infant retina usually caused by a biallelic *RB1* gene mutation.(6) About 45% of retinoblastoma patients have the heritable form, meaning they carry a constitutional *RB1* mutation that confers risk of second cancers later in life, and can be passed on to offspring. Each year 8,000 children newly diagnosed with retinoblastoma globally, approximately 24 of which are in Canada.(6) The retinoblastoma research community in Canada practices patient engagement. For example, patients were key contributors to the first clinical retinoblastoma guidelines, published in 2009.(7) Although clinicians and researchers appreciate

the value of authentic partnerships with retinoblastoma patients, a formal process to ensure equitable, diverse and sustainable inclusion has only recently been established.

A National Retinoblastoma Patient Engagement Strategy was formed in Canada in 2016, aiming to; i) include a large diverse group of people affected by retinoblastoma in research; ii) share research results with people affected by retinoblastoma; and iii) promote research that is created and led by people affected by retinoblastoma. The Canadian Retinoblastoma Research Advisory Board (CRRAB), a national multidisciplinary group, leads the strategy. CRRAB collectively agreed that an early objective of the strategy was to identify the top 10 retinoblastoma research priorities in Canada.

Methods

Study Purpose

The purpose of this study was for retinoblastoma patients, clinicians and researchers to jointly determine the top 10 retinoblastoma research priorities in Canada using an adaptation of the JLA PSP method. The study was approved by The Hospital for Sick Children Research Ethics Board (#1000057519).

Working Group and Steering Committee

A multidisciplinary CRRAB Working Group (WG) led study design from December 2016 to October 2017. The WG recruited additional members and evolved into a national Steering Committee (SC) in October 2017 (Additional File 1).

Study Participants

Retinoblastoma patients, clinicians and researchers in Canada were eligible to participate in any stage of the priority setting process. The inclusion of researchers is a noteworthy change to the customary JLA PSP method, which traditionally only uncovers research priorities of patients and clinicians.(8) Non-clinician researchers are excluded from the priority setting process, although they may sit on the SC.(5) We too are committed to the inclusion of patients and clinicians in setting research priorities, and advocate that this should be carefully conducted alongside researchers. Researchers have unique expertise in new research directions, study design and implementation. We also anticipated that having researchers present would result in accelerated uptake of the identified research priorities.(9) With this in mind, we set out to establish an equitable process with a 1:1 ratio of patients and non-patients (clinicians and researchers).

Study Design

The study design was adapted from the 3-phased JLA PSP method (Figure 1). The study adhered to GRIPP2 reporting guidelines (Additional File 2).(10) The study consisted of an online survey (Phase 1), an interim ranking exercise (Phase 2) and an in-person priority setting workshop (Phase 3). Further information about the methods employed during each study phase are documented in Additional File 3.

One deviation from the JLA PSP method was that, as part of Phase 1, research questions were not identified by a literature search. Given the relatively small body of retinoblastoma literature, and that SC members have been involved in writing seminal retinoblastoma reviews(6, 11-13) and clinical care guidelines(7, 14), participation of SC members as respondents in Phase 1 ensured questions identified in current retinoblastoma literature were put forward for

consideration in Phase 2. In addition, while Phase 2 is often completed by Phase 1 participants (or general patient and clinician communities), SC members completed this interim ranking.

Phase 1: Online Survey

An online survey was developed by the WG and made available for 41 days using REDCap electronic data capture tools hosted at The Hospital for Sick Children (Toronto, Ontario).(15) The survey asked, "what questions about retinoblastoma would you like to see answered by research?". Submissions were categorized per a coding taxonomy (Additional File 4). Submissions were separated into more than one question and then reworded – with narrative text removed (if applicable) – to result in concise questions. Duplicate questions were combined. Questions that were out-of-scope were removed. Questions known to be answered by existing systematic reviews, clinical care guidelines or individual studies were identified and removed.

Phase 2: Steering Committee Interim Ranking

The SC reviewed Phase 1 results and completed a second round of processing to produce a refined list of questions. The SC conducted an interim ranking of this refined list of questions. By consensus, the SC reached a list of 30 questions to be ranked at the priority setting workshop.

Phase 3: Priority Setting Workshop

The workshop followed the established process.(5) An experienced Chair was hired to lead the priority setting workshop with 2 facilitators (KH, MG). The SC was committed to an equitable workshop, employing the Nominal Group Technique, that included diverse perspectives, with a 1:1 ratio of patients to non-patients.

Results

Phase 1: Online Survey

Online survey respondents included 38 patients (64%) and 21 non-patients (36%) (Table 1). Respondents were primarily female (50/59, 85%) and Ontario residents (34/59, 58%). Patients were 38 ± 8 years of age and primarily parents (28/38, 74%) and survivors (10/38, 26%). Most patients (26/38, 68%) were affected by bilateral (both eyes) retinoblastoma. Non-patients were clinicians (16/21; 76%), clinician scientists (3/21; 14%) or researchers (2/21; 10%).

In total, 175 questions were suggested (Table 2). The categories with the greatest number of questions were genetics and molecular, second cancer and psychosocial, representing 26%, 17%, and 15% of all suggested questions, respectively. Patients most commonly suggested genetics and molecular (31/114, 27%), second cancer (22/114, 19%) and psychosocial (15/114, 13%) questions. Non-patients most commonly suggested treatment (15/61, 25%), genetics and molecular (14/61, 23%) and psychosocial (12/61, 20%) questions. All of the awareness and vision questions were suggested by patients, whereas all of the global health and the majority of treatment (15/21, 71%) questions were suggested by non-patients. After survey responses were processed, 46 of the questions were removed (Figure 2) resulting in 129 questions that were presented to the SC across all 12 categories.

Phase 2: Steering Committee Interim Ranking

The SC generated a refined list of 96 questions subject to SC ranking (Figure 2). The top 30 questions from the SC ranking and 9 additional questions that fell outside of the top 30 but were suggested by more than one of the survey respondents were further considered by the SC for the

workshop. A final list of 30 questions was agreed upon by the SC for consideration in Phase 3. Questions from all categories, except trilateral retinoblastoma, were included in the final list.

Phase 3: Priority Setting Workshop

Ten patients (3 survivors, 5 unaffected parents, 1 parent who carried an *RB1* mutation and 1 survivor who is a grandparent of a child with retinoblastoma), and 10 non-patients (4 clinicians, 2 clinician scientists and 4 researchers) participated in the workshop. All patients were affected by heritable retinoblastoma. Parents included those with young children currently undergoing retinoblastoma treatment and parents of adult survivors.

There were similarities in the first and second aggregate rankings (Table 3). Six of the top 10 questions in the second aggregate ranking were also in the top 10 in the first aggregate ranking. Similarly, 6 of the bottom 10 questions in the second aggregate ranking were also in the bottom 10 of the first aggregate ranking. For the final ranking, 4 ties in the second aggregate ranking were decided by vote. Four additional questions were reorganized in response to suggestions of the group.

The final ranked list appears in Table 3. The top question was, "how to increase early diagnosis of retinoblastoma?". The top 10 questions covered 7 of the 12 categories, namely diagnosis (n = 1), second cancer (n = 2), psychosocial (n = 2), follow-up (n = 2), treatment (n = 1), miscellaneous (n = 1) and global health (n = 1). No question from the awareness, family planning, genetics or molecular or vision categories ranked among the top 10.

Discussion

This study brought together retinoblastoma patients, clinicians and researchers to jointly identify the top 10 retinoblastoma research priorities in Canada. As determined by this study, the most highly prioritized area of retinoblastoma research in Canada is early diagnosis.

To our knowledge, this is the first project to determine research priorities for retinoblastoma. The only other research priority setting exercise that mentions retinoblastoma is the UK Sight Loss JLA PSP.(16)

Our sample size in Phase 1 (n = 59) was lower than other JLA PSPs but expected given the rarity of retinoblastoma.(5) Survey respondents provided a wide-range of patient and non-patient perspectives. However, participation of males was limited, and only 5/13 Canadian provinces and territories were represented. Participation may be proportional to retinoblastoma burden as the 3 provinces expected to have the highest retinoblastoma prevalence based on birth rate (Ontario, Quebec and Alberta) were represented.(17) There was underrepresentation of certain non-patient groups including nurses. Lastly, only 29% of the patient survey respondents (11/38) were affected by unilateral retinoblastoma. Those affected by unilateral retinoblastoma, which is mostly non-heritable, may not be as motivated to participate in research.

Genetics and molecular questions were suggested in the survey more often than any other category. Despite this, the top 10 research priorities identified in Phase 3 did not include a question from the genetics and molecular category. We propose 3 possible explanations for this apparent mismatch. First, the equal distribution of patients and non-patients in the workshop may have corrected for a disproportionate propensity among patients to suggest questions in the genetics and molecular category; this was the most popular category among patients whereas treatment was the most popular category among non-patients. Next, the proportion of genetics

and molecular questions suggested in the survey might not reflect their relative importance. Rather, genetics and molecular questions may be more common. Our research has demonstrated that patients have challenges accessing information about and understanding retinoblastoma genetics, and in turn, might have developed more questions in this domain.(18) Lastly, given that nearly half of the genetics and molecular questions suggested in the survey addressed second cancers, and 2 questions from the second cancer category were in the top 10, it is possible that the genetics and molecular questions were ranked lower to ensure a diverse list of research priorities. It could also be argued that the second cancer questions within the top 10 priorities (i.e., questions 2 and 7) might precede some of the genetics and molecular questions relevant to second cancer (i.e., questions 12, 24 and 26).

The top research priority identified by this study was, how to increase early diagnosis of retinoblastoma. Yet, the category of diagnosis only accounted for 7% (13/175) of the questions from the survey. Early diagnosis of retinoblastoma increases the possibility of favorable outcomes (vision and survival).(7) For children with a family history of retinoblastoma (10% of all patients), early diagnosis can be achieved with comprehensive genetic counseling and genetic testing.(6, 19) Prenatal genetic testing together with early term delivery is linked to lower treatment burden and excellent visual outcomes.(20) However, for the vast majority of patients who are the first in their family to develop retinoblastoma, early diagnosis becomes more challenging. Current vision screening guidelines recommend dilated eye examinations for children, including inspection of the red reflex, when (newborn to 3 months of age and) 6 to 12 months of age, and instruct clinicians to urgently refer patients with abnormalities to an ophthalmologist.(21) Yet, the mean age of retinoblastoma diagnosis in Canada – while significantly better than less developed countries – is 27 months for unilateral retinoblastoma and

15 months for bilateral retinoblastoma.(11) This suggests that there may be poor adherence to current vision screening recommendations, or more likely, the recommended screening guidelines will not detect all retinoblastoma patients, owing to variable timing and topography of tumor development in the infant retina. The prioritization of an early diagnosis question sends a strong message that, in spite of excellent survival rates and younger age at diagnosis in comparison to other settings, the Canadian retinoblastoma community would like to reduce the age at retinoblastoma diagnosis even further, knowing that earlier detection leads to better outcomes.

Four of the research priorities (questions 2, 4, 7 and 9) address second cancer or follow-up. Studies estimate that heritable retinoblastoma survivors have a 50% risk of developing a second cancer by the age of 50 if they received electron beam radiation therapy.(6, 22) There is a paucity of reliable information about second cancer risk for the more recent cohort of heritable retinoblastoma survivors who have received new types of first-line therapy including intra-arterial chemotherapy.(23) Consequentially, no standardized plan exists for adult follow-up of heritable retinoblastoma survivors.

Two of the research priorities (question 3 and 6) address psychosocial considerations. Psychosocial was the third most popular category among patient (15/114, 13%) and non-patient (12/61, 20%) survey respondents. Children diagnosed with cancer, and their families, have increased risk of psychosocial effects.(24) Examination of psychosocial outcomes among retinoblastoma patients shows some discrepant findings and these outcomes have yet to be examined in Canada.(25-29) Even without empirical data to characterize the psychosocial outcomes of Canadians affected by retinoblastoma, given the lived experience of those involved

in this study, determining how to provide psychological support to survivors, parents and families was highly prioritized.

Only one of the research priorities (question 5) specifically addressed acute treatment of the disease (aside from follow-up and second cancers). In the survey, treatment was the most popular category among non-patients (15/61, 25%), but far less popular among patients (6/114, 5%). Question 5 is very broad and could theoretically encompass the treatment questions that fell outside of the top 10 retinoblastoma research priorities. Other Canadian cancer research prioritization exercises have had more treatment questions in their top 10, albeit this may be partly due to different survey wording.(30, 31) The de-emphasis of treatment in the final research priorities is likely because > 95% of children affected by retinoblastoma in Canada survive with favorable outcomes. We might expect a very different list of top 10 retinoblastoma research priorities in settings where survival is < 30%.(6) The issue of international research prioritization has been raised by others and requires further consideration.(9)

The research priorities ranked 9 and 10 fall within the miscellaneous and global health categories, respectively, and are both related to care provision. Priority 9 is how to provide a detailed pathway of care to retinoblastoma patients and families. Research that examines how to effectively educate patients to become fully informed decision makers has been part of other lists of top 10 research priorities.(30, 31) This aligns with growing evidence that supports patient centered care and providing patients with access to electronic medical records.(32) DEPICT HEALTH, a point-of-care retinoblastoma database, has been shown to improve parental understanding of treatment and follow-up plans.(33, 34) This priority might have been partly motivated by plans to deploy DEPICT HEALTH globally.(35) Priority 10 asks, how optimal retinoblastoma care can be delivered in low-resource settings. This question, as discussed at the

workshop, also applied to rural and remote communities in Canada. The importance of focusing on global efforts to reduce the disparity in retinoblastoma outcomes between high and low-income settings has been discussed previously.(6) This is the only question in the top 10 suggested by a researcher alone. Given that this question was then later prioritized by the group, it supports our assertion that there is value including researchers in research prioritization exercises.

There are limitations in this study that warrant consideration. The majority of patient participants in the workshop (and to a lesser extent, the survey) were affected by heritable retinoblastoma. Given the lifelong implications of the disease, it is not surprising that those affected by heritable retinoblastoma are particularly incentivized to participate in research. This imbalance may have biased the study results towards survivorship and long-term effects of retinoblastoma. Two additional deviations from the customary JLA PSP method are important to note. First, in Phase 1 we were precluded from only using systematic reviews and guidelines to verify the questions were unanswered, given that retinoblastoma systematic reviews and guidelines are rare. However, given the expertise of the SC, we are confident that novelty of suggested questions was accurately evaluated. Then, in rewording the questions, PICO (patient or population, intervention, comparator or control and outcome) structure was not consistently adopted. To this end, feedback from the workshop suggest that participants would have valued the opportunity to participate in the question wording or have an orientation to each question with an outline of the meaning and relevant background.

Conclusions

We achieved consensus on the top 10 research priorities in Canada using an adaptation of the JLA PSP method. Our novel modification, to include researchers as participants, was a valuable element in identifying a research priority that was subsequently ranked in the top 10 by all participants. By sharing the final research priorities broadly, we expect that the top 10 list will serve as a resource for advocacy groups, research teams and funding agencies which focus on retinoblastoma.

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TABLES

Table 1. Demographics of Online Survey Respondents

	Variable		Mean ± SD	n (%)
Patients (*n* = 38, 64%)	**Age**		38 ± 8	
	Sex	Female		34 (89)
		Male		4 (11)
	Category	Parent		24 (63)
		Parent and survivor		2 (5)
		Survivor		8 (21)
		Parent and spouse of a survivor		2 (5)
		Family		1 (3)
		Unaffected *RB1* mutation carrier and parent		1 (3)
	Laterality	Bilateral		26 (68)
		Unilateral		11 (29)
		Information not provided		1 (3)
	Place of Residence	Ontario		22 (58)
		Alberta		11 (29)
		New Brunswick		1 (3)
		Quebec		1 (3)
		Information not provided		3 (8)
Non-Patients (*n* = 21, 36%)	**Age***		46 ± 9	
	Sex	Female		16 (76)
		Male		5 (24)
	Category	Clinician		16 (76)
		Ophthalmologist		5
		Oncologist		4
		Genetic Counsellor		3
		Child Life Specialist		2
		Molecular Geneticist		1
		Social Worker		1
		Clinician Scientist		3 (14)
		Ophthalmologist		2
		Medical Genetics		1
		Researcher		2 (10)
	Place of Residence	Ontario		12 (57)
		Quebec		3 (14)
		Alberta		2 (10)
		Nova Scotia		2 (10)
		Information not provided		2 (10)

*$n = 20$

Table 2. Phase 1 Online Survey Responses

Category	Online Survey Responses						Questions Removed			Total Questions Presented to SC n (%)
	Questions Suggested by Patients n (%)	Questions Suggested by Non-Patients				Total n (%)	Out-of-Scope	Already Answered by Research	Duplicates	
		Clinician	Clinician Scientist	Researcher	Non-Patient Total n (%)					
Awareness	4 (4)	0	0	0	0	4 (2)	1	0	0	3 (2)
Diagnosis	9 (8)	4	0	0	4 (7)	13 (7)	0	0	4	9 (7)
Family Planning	7 (6)	1	0	0	1 (2)	8 (5)	1	2	0	5 (4)
Follow-Up	9 (8)	1	1	0	2 (3)	11 (6)	0	0	0	11 (9)
Genetics and Molecular	31 (27)	3	4	7	14 (23)	45 (26)	6	3	8	28 (22)
Global Health	0	2	0	1	3 (5)	3 (2)	0	0	0	3 (2)
Miscellaneous	2 (2)	2	0		2 (3)	4 (2)	0	0	0	4 (3)
Psychosocial	15 (13)	11	0	1	12 (20)	27 (15)	0	0	3	24 (19)
Second Cancer	22 (19)	6	1	0	7 (11)	29 (17)	0	1	9	19 (15)
Treatment	6 (5)	14	1	0	15 (25)	21 (12)	3	0	4	14 (11)
Trilateral	2 (2)	1	0	0	1 (2)	3 (2)	0	1	0	2 (2)
Vision	7 (6)	0	0	0	0	7 (4)	0	0	0	7 (5)
Total	**114 (65)**	**45**	**7**	**9**	**61 (35)**	**175**	**11**	**7**	**28**	**129**

Table 3. Top 30 Retinoblastoma Research Priorities

Final Rank	Question	Category	Aggregate Rankings	
			First	Second
1	How to increase early diagnosis of retinoblastoma (i.e., decrease age or stage at diagnosis)?	Diagnosis	7	1
2	What second cancer screening is optimal for heritable retinoblastoma survivors (including whole body magnetic resonance imaging)?	Second Cancer	1	1
3	How to provide culturally competent social, emotional and psychological support to retinoblastoma patients, survivors, parents and families (at diagnosis and beyond)?	Psychosocial	2	2
4	What is the optimal follow-up (including ophthalmological and oncological) for heritable retinoblastoma patients and survivors (by diagnosis and treatment) and how can we ensure this is provided to all?	Follow-Up	9	3
5	Prospective retinoblastoma treatment studies with long-term follow-up.	Treatment	5	4
6	What is the effect of enucleation and vision loss on retinoblastoma survivors?	Psychosocial	11	5
7	What are the risk factors for second cancers in heritable retinoblastoma survivors and, in turn, what do heritable retinoblastoma survivors need to know about living well and minimizing risk of second cancers?	Second Cancer	7	6
8	How to improve collaboration across the different top centers caring for Retinoblastoma: forming an international consortium, a unified registry, and combined trials, instead of the current air of competition?	Miscellaneous	17	10
9	How to provide a detailed pathway of care or plan, outlining treatment and follow-up, to retinoblastoma patients and families?	Follow-Up	13	8
10	How can optimal retinoblastoma care be delivered in low-resource settings (including rural and remote communities)?	Global Health	4	9
11	Clinical trials of; i) novel agents; ii) targeted agents added to backbone chemotherapy; or iii) IAC to improve eye salvage rates.	Treatment	3	9
12	What genetic mechanism result in second cancers in heritable	Genetics and	10	7

	retinoblastoma survivors?	Molecular		
13	Better identification of who needs chemotherapy after high risk pathology.	Treatment	12	10
14	What new technology could be used to diagnose retinoblastoma earlier, including non-invasive in utero testing?	Diagnosis	6	11
15	How to increase family doctor/ pediatrician; i) awareness of retinoblastoma (i.e., signs and symptoms and the importance of early diagnosis); and ii) screening and diagnosis of retinoblastoma?	Awareness	6	12
16	How can we help families cope better during diagnosis and critical stages (including enucleation)?	Psychosocial	8	13
17	What are the risks of second cancers for mosaic RB1 mutation carriers (i.e., those where *RB1* mutation is present in some, but not all cells in their body)?	Second Cancer	18	14
18	How to reduce side effects from retinoblastoma treatments?	Treatment	12	15
19	Can we identify the key molecular event that distinguishes retinoma (benign retinoblastoma precursor) from retinoblastoma?	Genetics and Molecular	16	16
20	Can a known *RB1* gene mutation be corrected?	Genetics and Molecular	15	18
21	How to improve the sensitivity of minimal residual disease (i.e., metastasized cancer cells that cannot be detected by routine tests) diagnostics in retinoblastoma?	Follow-Up	20	17
22	How to communicate with and educate patients, survivors and parents about retinoblastoma genetics and their specific retinoblastoma genetic testing results (including new tools, techniques and innovations)?	Genetics and Molecular	16	19
23	What is the best way to support and educate heritable retinoblastoma survivors; i) before they have their own children; and ii) to ensure their children have optimal perinatal care?	Family Planning	14	20
24	How can second cancers be prevented in heritable retinoblastoma survivors?	Genetics and Molecular	13	21
25	What is the second cancer incidence among heritable retinoblastoma survivors?	Second Cancer	18	22
26	How can we reduce the risk of second cancers in heritable retinoblastoma survivors?	Genetics and Molecular	19	22
27	What social, emotional and psychological support services are available	Psychosocial	21	23

	across Canada for retinoblastoma patients, survivors and parents (i.e., comparisons nationally)?			
28	What is the impact - on mental health, finances, employment, siblings and family life - when one must travel long distance for retinoblastoma care?	Psychosocial	22	24
29	How can scar tissue/ calcium in the eye from retinoblastoma treatment be removed to give better vision?	Vision	23	25
30	What causes heritable (germline) and non-heritable (somatic) retinoblastoma mutations?	Genetics and Molecular	24	26

6

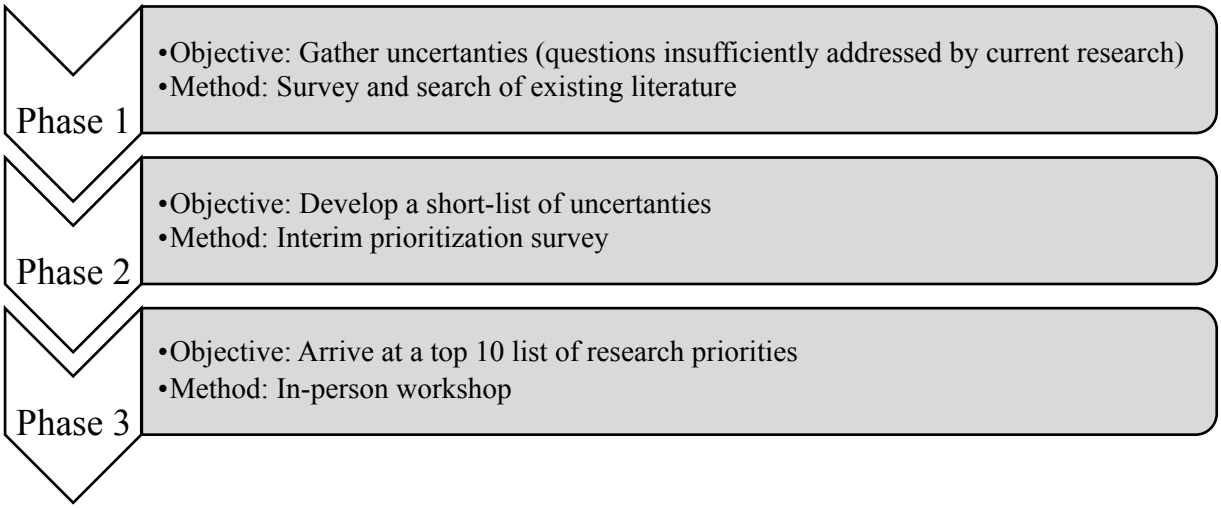
FIGURE LEGENDS

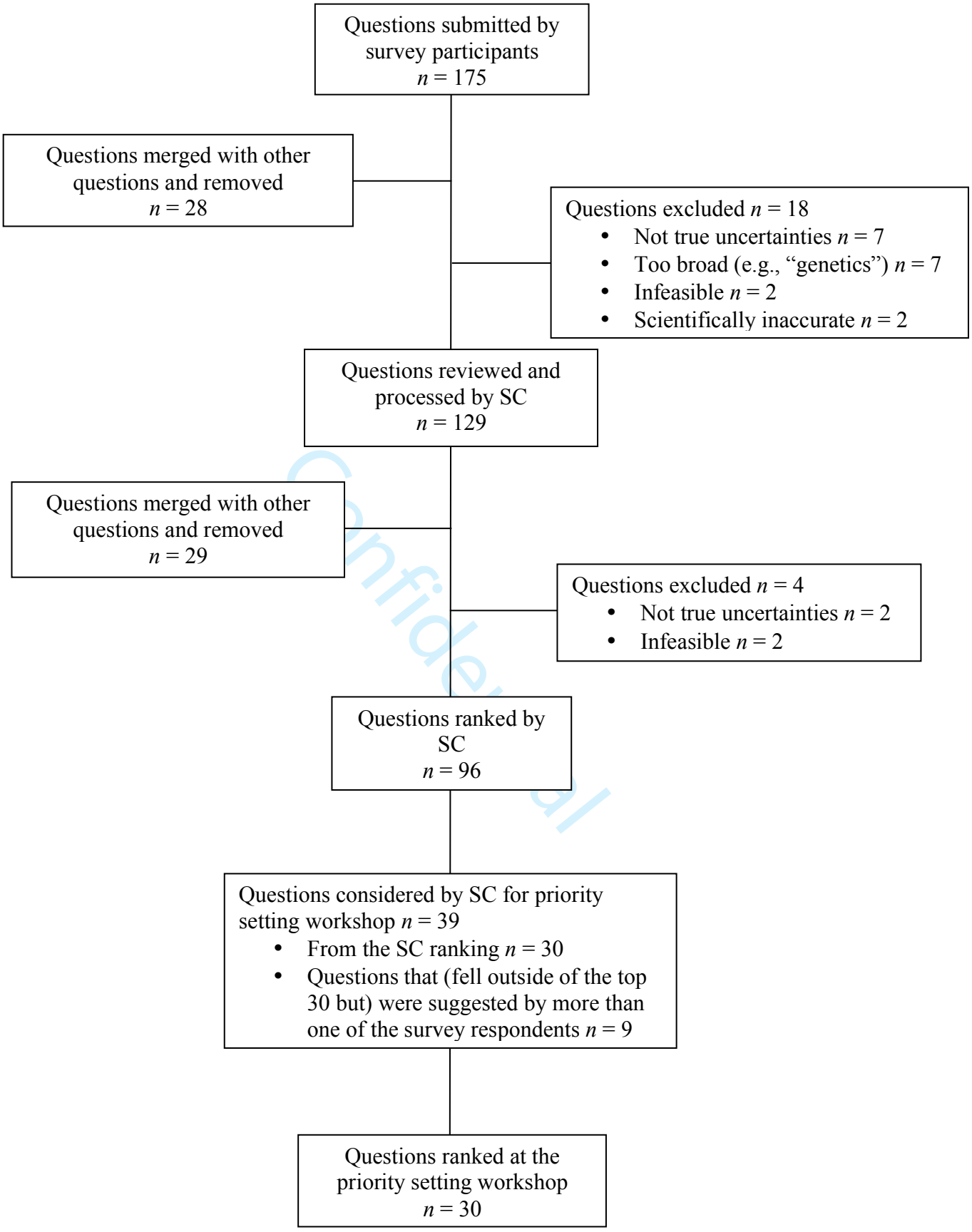
Figure 1. James Lind Alliance Priority Setting Process Method Overview

The study design was adapted from the 3-phased James Lind Alliance Priority Setting Process method. Generally Phase 1 involved gathering a broad range of research questions (uncertainties) from the retinoblastoma community; Phase 2 involved ranking all the uncertainties, by a steering committee, to develop a short list; and Phase 3 identified the top 10 uncertainties through an in-person workshop involving patients, clinicians and researchers.

Figure 2. Retinoblastoma Research Priority Setting Process

Phase 1 generated 175 research questions (uncertainties). During Phase 2, these 175 questions were processed and discussed by the steering committee to arrive at 96 final questions for ranking. The Top 30 questions from Phase 2 where then considered and ranked during the Phase 3 in-person workshop, at which consensus were reached on the top 10.





Additional File 1: CRRAB WG and SC Composition

	WG	SC
Parent	0	2
Survivor	1	2
Genetic Counsellor	2	2
Child Life Specialist	0	2
Clinician Scientist	0	3
Ophthalmologist	0	2
Oncologist	1	1
Researcher	1	2
Ophthalmic Imaging Specialist	1	0
Trainee	4	2
Total	10	15

Additional File 2: GRIPP2 Short Form

Section and Topic	Item	Reported on Page Number
1: Aim	Report the aim of patient and public involvement (PPI) in the study	6-7
2: Methods	Provide a clear description of the methods used for PPI in the study	8-9; 30
3: Study results	Outcomes - Report the results of PPI in the study, including both positive and negative outcomes	10-11
4: Discussion and conclusions	Outcomes - Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	12-17
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	12, 16

Additional File 3: Detailed Phase 1-3 Methods

Phase 1: Online Survey	• The survey included sample questions and explained that, "questions can be about any aspect of retinoblastoma including (but not limited to); diagnosis, treatment, genetics, side effects and mental health". • Demographic information about respondents was collected. • The survey was advertised in eye clinics, on social media and using existing networks including the Canadian Retinoblastoma Research Registry, CRRAB, the Canadian National Retinoblastoma Tumor Board and the Canadian Association of Genetic Counsellors.
Phase 2: SC Interim Ranking	• Since the SC had an imbalance of patient to non-patient members (4:11, respectively), to ensure fair weighting, an SC patient rank and SC non-patient rank were individually calculated and then combined to produce an adjusted SC interim ranking. • When determining the final list of 30 questions to be ranked at the priority setting workshop, the SC considered the top 30 questions from the adjusted SC interim ranking and all questions that fell outside of the top 30 but were suggested by more than one survey respondent.
Phase 3: Priority Setting Workshop	• Prior to the workshop, participants were sent the list of 30 questions. • Each participant arrived at the workshop having independently ranked the questions. • After an introduction by the Chair, participants were separated into 3 facilitator-led groups with representation from patients and non-patients. • Groups had a set of 30 cards displaying a question and contextual information from the online survey (e.g., frequency, quotes etc.). • In succession, participants shared their highest and lowest ranked questions, and the cards were then organized into; highest priority, lowest priority and undecided. • Using the cards, each group organized the questions from highest to lowest priority. • The ranking of all questions was noted. • An aggregate ranking was computed by the Chair and facilitators, using the individual group rankings, and presented to all participants. Ties were noted, but not addressed. • Participants were then assigned to 3 new groups, again led by a facilitator with representation from patients and non-patients. • The first aggregate ranking was reviewed and revised by each group. • Groups noted their revised ranking of all questions and this was used to compute a second aggregate ranking. • The Chair led all participants in a review of the second aggregate ranking. Ties and suggested refinements were discussed and agreed upon by a vote.

Additional File 4. Study Developed Retinoblastoma Research Question Taxonomy

Awareness
Diagnosis
Family Planning
Follow-Up
Genetics and Molecular
Global Health
Miscellaneous
Psychosocial
Second Cancer
Treatment
Trilateral
Vision