

# Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43 African countries and 518 patients from 40 European countries

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For numbered affiliations see end of article.

## Correspondence to

Ido Didi Fabian, International Centre for Eye Helath, London School of Hygiene and Tropical Medicine, London, UK and The Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Tel-Aviv University, Tel-Aviv, Israel [didi@didifabian.com](mailto:didi@didifabian.com)

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Ido Didi Fabian,<sup>1,2</sup> Andrew W Stacey,<sup>3</sup> Allen Foster,<sup>1</sup> Tero T Kivelä,<sup>4</sup> Francis L. Munier,<sup>5</sup> Naama Keren-Froim,<sup>6</sup> Nir Gomel,<sup>7</sup> Nathalie Cassoux,<sup>8</sup> Mandeep S Sagoo,<sup>9</sup> M Ashwin Reddy,<sup>10</sup> Lamis Al Harby,<sup>10</sup> Marcia Zondervan,<sup>1</sup> Covadonga Bascaran,<sup>1</sup> Elhassan Abdallah,<sup>11</sup> Shehu U Abdullahi,<sup>12</sup> Sahadatou Adamou Boubacar,<sup>13</sup> Dupe S Ademola-Popoola,<sup>14</sup> Adedayo Adio,<sup>15</sup> Ada E Aghaji,<sup>16</sup> Silvia Alarcón Portabella,<sup>17</sup> Amadou I Alfa Bio,<sup>18</sup> Amany M Ali,<sup>19</sup> Donjeta B Alia,<sup>20</sup> Charlotta All-Eriksson,<sup>21</sup> Argentino A Almeida,<sup>22</sup> Khalifa M Alsawidi,<sup>23</sup> Romanzo Antonino,<sup>24</sup> Nicholas J Astbury,<sup>1</sup> Rose Atsiaya,<sup>25</sup> Julia Balaguer,<sup>26</sup> Walentyna Balwiercz,<sup>27</sup> Honorio Barranco,<sup>26</sup> Maja Beck Popovic,<sup>28</sup> Sarra Benmiloud,<sup>29</sup> Nissrine Bennani Guebessi,<sup>30</sup> Rokia C Berete,<sup>31</sup> Shelley J Biddulph,<sup>32</sup> Eva M Biewald,<sup>33</sup> Sharon Blum,<sup>2</sup> Nadia Bobrova,<sup>34</sup> Marianna Boehme,<sup>33</sup> Norbert Bornfeld,<sup>33</sup> Gabrielle C Bouda,<sup>35</sup> Hédi Bouguila,<sup>36</sup> Amaria Boumedane,<sup>37</sup> Bénédicte G Brichard,<sup>38</sup> Michael Capra I,<sup>39</sup> Guilherme Castela,<sup>40</sup> Jaume Català-Mora,<sup>41</sup> Guillermo L Chantada,<sup>41</sup> Violeta S Chernodrinska,<sup>42</sup> Faraja S Chiwanga,<sup>43</sup> Krzysztof Cieslik,<sup>44</sup> Codruta Comsa,<sup>45</sup> Maria G Correa Llano,<sup>41</sup> Monika Csóka,<sup>46</sup> Isac V Da Gama,<sup>47</sup> Alan Davidson,<sup>48</sup> Patrick De Potter,<sup>38</sup> Laurence Desjardins,<sup>49</sup> Monica D Dragomir,<sup>45</sup> Magritha Du Bruyn,<sup>50</sup> Asmaa El Kettani,<sup>30</sup> Amal M Elbahi,<sup>23</sup> Dina Elgalaly,<sup>51</sup> Alaa M Elhaddad,<sup>51</sup> Moawia M Ali Elhassan,<sup>52</sup> Mahmoud M Elzembely,<sup>19</sup> Vera A Essuman,<sup>53</sup> Ted Grimbert A Evina,<sup>54</sup> Oluyemi Fasina,<sup>55</sup> Ana Fernández-Teijeiro,<sup>56</sup> Moira Gandiwa,<sup>57</sup> David García Aldana,<sup>58</sup> Jennifer A Geel,<sup>32,59</sup> Zelalem Gizachew,<sup>60</sup> Pernille A Gregersen,<sup>61</sup> Koffi M Guedenon,<sup>62</sup> Theodora Hadjistilianou,<sup>63</sup> Sadiq Hassan,<sup>12</sup> Stanislava Hederova,<sup>64</sup> Laila Hessissen,<sup>65</sup> Diriba F Hordofa,<sup>66</sup> Marlies Hummlen,<sup>67</sup> Kristina Husakova,<sup>64</sup> Russo Ida,<sup>24</sup> Vesna R Ilic,<sup>68</sup> Helen Jenkinson,<sup>69</sup> Theophile B Amani Kabesha,<sup>70</sup> Rolande L Kabore,<sup>35</sup> Abubakar Kalinaki,<sup>71</sup> Noa Kapelushnik,<sup>2</sup> Tamar Kardava,<sup>72</sup> Pavlin Kroumov Kemilev,<sup>42</sup> Tomas Kepak,<sup>73</sup> Zaza Khotenashvili,<sup>72</sup> Artur Klett,<sup>74</sup> Jess Elio Kosh Komba Palet,<sup>75</sup> Dalia Krivaitiene,<sup>76</sup> Mariana Kruger,<sup>77</sup> Alice Kyara,<sup>43</sup> Eva S Lachmann,<sup>78</sup> Slobodanka Latinović,<sup>79</sup> Karin Lecuona,<sup>80</sup> Robert M Lukamba,<sup>81</sup> Livia Lumbroso,<sup>49</sup> Lesia Lysytsia,<sup>82</sup> Erika Maka,<sup>46</sup> Mayuri Makan,<sup>83</sup> Chatonda Manda,<sup>57</sup> Nieves Martín Begue,<sup>17</sup> Ibrahim O Matende,<sup>25</sup> Marchelo Matua,<sup>84</sup> Ismail Mayet,<sup>32</sup> Freddy B Mbumba,<sup>85</sup> Aemero A Mengesha,<sup>86</sup> Edoardo Midená,<sup>87</sup> Furahini G Mndeme,<sup>88</sup> Ahmed A Mohamedani,<sup>89</sup> Annette C Moll,<sup>90</sup> Claude Moreira,<sup>91</sup> Mchikirwa S Msina,<sup>88</sup> Gerald Msukwa,<sup>57</sup> Kangwa I Muma,<sup>92</sup> Gabriela Murgoi,<sup>45</sup> Kareem O Musa,<sup>93</sup> Hamzah Mustak,<sup>80</sup> Okwen M Muyen,<sup>94</sup> Gita Naidu,<sup>32</sup> Larisa Naumenko,<sup>95</sup> Paule Aïda Ndoye Roth,<sup>96</sup> Vladimir Neroev,<sup>97</sup> Marina Nikitovic,<sup>68</sup> Elizabeth D Nkanga,<sup>98</sup> Henry Nkumbe,<sup>54</sup> Mutale Nyaywa,<sup>99</sup> Ghislaine Obono-Obiang,<sup>100</sup> Ngozi C Oguego,<sup>16</sup> Andrzej Olechowski,<sup>44</sup> Alexander Hugo Oscar,<sup>42</sup> Peter Osei-Bonsu,<sup>101</sup> Sally L Painter,<sup>69</sup> Vivian Paintsil,<sup>101</sup> Luisa Paiva,<sup>102</sup> Ruzanna Papyan,<sup>103</sup> Raffaele Parrozzani,<sup>87</sup> Manoj Parulekar,<sup>69</sup> Katarzyna Pawinska-Wasikowska,<sup>27</sup> Sanja Perić,<sup>104</sup> Remezo Philbert,<sup>105</sup> Pavel Pochop,<sup>106</sup>



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Vladimir G Polyakov,<sup>107,108</sup> Manca T Pompe,<sup>109</sup> Jonathan J Pons,<sup>110</sup> Léa Raobela,<sup>111</sup> Lorna A Renner,<sup>112</sup> David Reynders,<sup>113</sup> Dahiru Ribadu,<sup>114</sup> Mussagy M Riheia,<sup>115</sup> Petra Ritter-Sovinz,<sup>116</sup> Svetlana Saakyan,<sup>97</sup> Azza MA Said,<sup>117</sup> Sonsoles San Román Pacheco,<sup>118</sup> Trish A Scanlan,<sup>43</sup> Judy Schoeman,<sup>113</sup> Stefan Seregard,<sup>21</sup> Sadik T Sherief,<sup>60</sup> Sidi Sidi Cheikh,<sup>119</sup> Sónia Silva,<sup>40</sup> Tetyana Sorochnytska,<sup>34</sup> Grace Ssali,<sup>120</sup> Christina Stathopoulos,<sup>5</sup> Branka Stirn Kranjc,<sup>109</sup> David K Stones,<sup>121</sup> Karel Svojgr,<sup>122</sup> Fatoumata Sylla,<sup>123</sup> Gevorg Tamamyan,<sup>103</sup> Alketa Tandili,<sup>20</sup> Bekim Tateshi,<sup>124</sup> Tuyisabe Theophile,<sup>125</sup> Fousseyni Traoré,<sup>126</sup> Harba Tyau-Tyau,<sup>127</sup> Ali B Umar,<sup>12</sup> Steen F Urbak,<sup>128</sup> Tatiana L Ushakova,<sup>107,108</sup> Sandra Valeina,<sup>129</sup> Milo van Hoefen Wijsard,<sup>90</sup> Nevyana V Veleva-Krasteva,<sup>42</sup> Maris Viksnins,<sup>129</sup> Werner Wackernagel,<sup>130</sup> Keith Waddell,<sup>84</sup> Patricia D Wade,<sup>131</sup> Amina H Wali Nigeria,<sup>132</sup> Amelia DC Wime,<sup>102</sup> Charlotte Wolley Dod,<sup>17</sup> Jenny M Yanga,<sup>133</sup> Vera A Yarovaya,<sup>134</sup> Andrey A Yarovoy,<sup>134</sup> Ekhtelbenina Zein,<sup>135</sup> Shirley Sharabi,<sup>136</sup> Katsiaryna Zhilyaeva,<sup>95</sup> Othman AO Ziko,<sup>117</sup> Richard Bowman<sup>137</sup>

## ABSTRACT

**Background** The travel distance from home to a treatment centre, which may impact the stage at diagnosis, has not been investigated for retinoblastoma, the most common childhood eye cancer. We aimed to investigate the travel burden and its impact on clinical presentation in a large sample of patients with retinoblastoma from Africa and Europe.

**Methods** A cross-sectional analysis including 518 treatment-naïve patients with retinoblastoma residing in 40 European countries and 1024 treatment-naïve patients with retinoblastoma residing in 43 African countries.

**Results** Capture rate was 42.2% of expected patients from Africa and 108.8% from Europe. African patients were older (95% CI –12.4 to –5.4,  $p < 0.001$ ), had fewer cases of familial retinoblastoma (95% CI 2.0 to 5.3,  $p < 0.001$ ) and presented with more advanced disease (95% CI 6.0 to 9.8,  $p < 0.001$ ); 43.4% and 15.4% of Africans had extraocular retinoblastoma and distant metastasis at the time of diagnosis, respectively, compared to 2.9% and 1.0% of the Europeans. To reach a retinoblastoma centre, European patients travelled 421.8 km compared to Africans who travelled 185.7 km ( $p < 0.001$ ). On regression analysis, lower-national income level, African residence and older age ( $p < 0.001$ ), but not travel distance ( $p = 0.19$ ), were risk factors for advanced disease.

**Conclusions** Fewer than half the expected number of patients with retinoblastoma presented to African referral centres in 2017, suggesting poor awareness or other barriers to access. Despite the relatively shorter distance travelled by African patients, they presented with later-stage disease. Health education about retinoblastoma is needed for carers and health workers in Africa in order to increase capture rate and promote early referral.

## INTRODUCTION

Rare cancers, defined as having an incidence of less than six cases per 100 000 population per year,<sup>1</sup> pose a particular burden on patients and professionals alike because of the need for specialist care, frequent lack of standardised treatments and lack of funding for research.<sup>2,3</sup> It is not uncommon to have only one or two specialised referral centres in a country for a given type of rare cancer, to which most cases are referred. Such a policy of centralised tertiary centres may result in reduced access and a high travel burden on patients, which can lead to poorer quality of life, advanced disease at diagnosis, late treatment and worse prognosis.<sup>4,5</sup>

Retinoblastoma is a rare, potentially deadly, childhood cancer. Its incidence is believed to be constant across populations, ranging from 1:16 000 to 18 000 live births.<sup>6</sup> In most countries, only

few specialised retinoblastoma centres exist. In Europe, for example, there is a single centre in France, two in the UK and three in Russia, all in Moscow. Travel burden associated with retinoblastoma, to the best of our knowledge, has not been explored. This information, which also reflects on the accessibility to tertiary centres and their catchment area, is important for healthcare planning.

Prognosis of patients with retinoblastoma has improved significantly over the past 50 years to reach over 90% 5-year survival in Europe.<sup>7–9</sup> These improvements are attributed to several factors, including the implementation of national strategies associated with retinoblastoma referral pathways, and the introduction of novel and improved treatment modalities, several of which were developed in European specialised referral centres.<sup>10–13</sup> Indeed, in the field of retinoblastoma, Europe serves as a potential model for under-resourced regions of the world. In Africa, where birth rate is higher, resulting in higher retinoblastoma prevalence, these improvements in survival have not been observed. Reports on retinoblastoma from Africa are scarce, and anecdotal evidence suggests that survival rates are as low as 50%,<sup>14,15</sup> and in some regions of sub-Saharan Africa are even less than 30%.<sup>16</sup>

We have recently reported the stage at presentation of more than 4000 newly diagnosed patients with retinoblastoma from over 150 countries analysed by national-income level.<sup>17</sup> The aim of the present study is to use the data from all countries in Africa and Europe to (1) investigate and compare the travel burden experienced by patients, (2) compare the stage at the time of diagnosis and (3) investigate risk factors for advanced disease at the time of diagnosis. Such information is important to better understand the current gaps in retinoblastoma service provision and to inform policymakers at national and international levels.

## METHODS

The study methodology, data collection and quality assurance process have been described in detail previously.<sup>17</sup> Briefly, the data were collected through a 1-year cross-sectional analysis of treatment-naïve patients with retinoblastoma who presented to retinoblastoma referral centres across the world from 1 January 2017 to 31 December 2017. Data on country of residence, sex and laterality of retinoblastoma were considered essential minimum criteria for inclusion. In the present analysis, patients that resided in African and European countries were included. The study was approved by the Institutional Review

Board of the London School of Hygiene & Tropical Medicine (reference number 14574) in accordance with the tenets of the Declaration of Helsinki. Participating centres, according to local institutional and national guidelines, applied to and received ethics clearance in their countries.

Data collected from medical charts included patient country of residence, initial clinical sign leading to referral, distance travelled from home to retinoblastoma centre, sex, family history of retinoblastoma, age at the time of diagnosis at retinoblastoma centre, tumour laterality, and stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) clinical Tumor, Node, Metastasis, Hereditary (cTNMH) scheme<sup>18</sup> and the International Retinoblastoma Staging System.<sup>19</sup> For travel distance calculation, a Google-based map was used and the orthodromic distance (ie, 'as the crow flies') between home and the retinoblastoma centre was measured. In case both were in the same city or site, the distance was considered to be zero, unless mentioned otherwise by the retinoblastoma centre that submitted the data. Data on national-income level, crude birth rate, country surface area and population size were retrieved from the United Nations World Population Prospects.<sup>20</sup>

### Statistical analysis

Analyses were performed using R software<sup>21</sup> and IBM SPSS statistics v25.0 (IBM Corp, Chicago, IL, USA). The predicted number of new patients with retinoblastoma per country was calculated as follows: country population × crude birth rate / 1000 / 17 000.<sup>22</sup> The predicted number does not take into account deviations from the average percentage with familial retinoblastoma, in which the risk of the offspring is ~1/2 rather than 1/17 000. The predicted number per continent was the sum for all countries in that continent. Fisher's exact test and Student's t-test was used to compare categorical and continuous variables between groups. A one-way analysis of variance was used to test differences in the age at the time of diagnosis between the continents and the Kruskal-Wallis test to test for differences in travel distance between the continents. Binomial logistic regression was used to model the effect of income level, continent, travel distance from home to retinoblastoma centre, age at diagnosis, family history of retinoblastoma and tumour laterality on the likelihood of children having advanced disease at presentation (cT4). A value of  $p < 0.05$  was considered significant, and data throughout the manuscript are presented as mean (SD) with 95% CI.

### RESULTS

The analytic sample included 1542 newly diagnosed patients with retinoblastoma. Of these, 518 (33.6%) resided in 40 European countries and 1024 (66.4%) in 43 African countries. Using an average incidence figure of 1/17 000 live births,<sup>6</sup> the observed capture rates were 42.2% and 108.8% of expected patients from Africa and Europe, respectively.

Clinical data were available for both the African and European subcohorts for over 90% of the patients, with the exception of travel distance, which was available for 81.5% and 84.6% of the patients, respectively. Table 1 shows the clinical data of the study patients by continent.

#### Travel burden and retinoblastoma centre catchment area

Overall, the mean travel distance from home to a retinoblastoma centre was 233.3 km (SD 468.78, 95% CI 207.0 to 259.0). To

reach a retinoblastoma centre within the country of residence, patients from European countries travelled on average more than twice the distance compared to patients from African countries: 421.8 km (SD 814.6, 95% CI 328.6 to 537.5) and 185.7 km (SD 201.0, 95% CI 168.0 to 205.2), respectively ( $p < 0.001$ , online supplemental table 1 in the appendix). Figure 1 shows the number of retinoblastoma centres by country and continent (see online supplemental figure 1 in the appendix for geographical location of the centres). No significant differences were found in the mean number of retinoblastoma centres per country in Africa and Europe: 1.8 (SD 1.8, 95% CI 1.2 to 2.4) and 1.4 (SD 0.9, 95% CI 1.1 to 1.7), respectively ( $p = 0.22$ ). Similarly, on analysis of the mean country population size and country surface area, differences between African and European countries were non-significant ( $p = 0.32$  and  $p = 0.89$ , respectively). The catchment area of each retinoblastoma centre in Africa and Europe is represented in figure 2 by the mean travel distance  $\pm$  SD. While the distribution of retinoblastoma centres in Europe covers the entire continent, in many African countries, large parts remain underserved.

#### Presentation to retinoblastoma centre

##### Age at the time of diagnosis

For the entire sample, the mean age at the time of diagnosis at a retinoblastoma centre was 27.9 months (95% CI 26.7 to 29.0): 22.0 months (SD 27.6; 95% CI 19.7 to 24.4) for European patients compared to 30.9 months (SD 21.0; 28.7 to 32.8) for those from Africa (diff = (-8.9), 95% CI -12.4 to -5.4,  $p < 0.001$ ).

##### Bilateral and familial retinoblastoma

Overall, 28.1% of the patients presented with bilateral disease, and 4.5% had a family history of retinoblastoma. Of the African patients, 26.7% had bilateral disease at the time of diagnosis compared to 31.1% of the European patients (OR 0.8, 95% CI 0.6 to 1.0,  $p = 0.07$ ). A positive family history was reported for 2.8% vs 8.4% of the African and European patients, respectively (OR 3.2, 95% CI 2.0 to 5.3,  $p < 0.001$ ).

Referral to a retinoblastoma centre for screening in case of positive family history of retinoblastoma was uncommon in Africa as compared to Europe: 3/26 (11.5%) of the familial cases in Africa vs 31/42 (73.8%) in Europe (OR 20, 95% CI 5.3 to 100.0,  $p < 0.001$ ). All three screened African patients were staged cT1 at the time of diagnosis. Of the African familial cases, 57.7% had advanced intraocular (cT3) or extraocular retinoblastoma (cT4) at the time of diagnosis. In comparison, of the European familial cases, 64.3%, 31.0% and 4.8% were staged cT1, cT2 and cT3, respectively.

##### Tumour staging

Overall, the most common cTNM stages were cT3 (44.7%), N0 (74.3%) and M0 (89.6%). Significantly more patients from African countries as compared to European countries had at the time of diagnosis advanced retinoblastoma (ie,  $>cT2$ ; OR 7.7, 95% CI 6.0 to 9.8,  $p < 0.001$ ), extraocular retinoblastoma (OR 25.7, 95% CI 15.1 to 43.6,  $p < 0.001$ ), lymph node involvement (OR 65.2, 95% CI 9.0 to 469.7,  $p < 0.001$ ) and metastasis (OR 18.7, 95% CI 7.6 to 45.8,  $p < 0.001$ ). Overall, 43.4% and 15.4% of the African patients had at the time of diagnosis extraocular retinoblastoma and distant metastasis, respectively, compared to 2.9% and 1.0% of the European patients, respectively.

**Table 1** Clinical data of 518 European and 1024 African patients with retinoblastoma

Parameter	European sample, n (%)	African sample, n (%)	Significance
Travel distance from home to retinoblastoma centre*			p<0.001
Mean distance in km (SD, 95% CI)	421.8 (814.6, 328.6 to 537.5)	185.7 (201.0, 168.0 to 205.2)	
Reported cases	396/468 (84.6)	736/903 (81.5)	
Age at diagnosis			p<0.001
Mean age in months (SD, 95% CI)	22.0 (27.6, 19.7 to 24.4)	30.9 (21.0, 28.7 to 32.8)	
Reported cases	514/518 (99.2)	1015 (99.1)	
Sex			p=0.75
Male	280 (54.0)	544 (53.1)	
Female	238 (46.0)	480 (46.9)	
Reported cases	518/518 (100)	1024/1024 (100)	
Laterality			p=0.07
Unilateral	357 (68.9)	751 (73.3)	
Bilateral	161 (31.1)	273 (26.7)	
Reported cases	518/518 (100)	1024/1024 (100)	
Familial retinoblastoma			p<0.001
No	468 (91.6)	910 (97.2)	
Yes	43 (8.4)	26 (2.8)	
Reported cases	511/518 (98.6)	936/1024 (91.4)	
Primary tumor (T)			p<0.001
cT1	76 (14.9)	32 (3.3)	≤cT2 versus >cT2
cT2	237 (46.6)	134 (13.9)	
cT3	192 (37.7)	465 (48.3)	
cT4	4 (0.8)	331 (34.4)	
Reported cases	509/518 (98.3)	962/1024 (93.9)	
Regional lymph node (N)			p<0.001
NX	34 (6.6)	265 (26.8)	N0 versus N1
N0	482 (93.2)	636 (64.4)	
N1	1 (0.2)	86 (8.7)	
Reported cases	517/518 (99.8)	987/1024 (96.4)	
Distant metastasis (M)			p<0.001
M0	513 (99.0)	830 (84.6)	M0 versus M1 †
cM1	1 (0.2)	110 (11.2)	
pM1	4 (0.8)	41 (4.2)	
Reported cases	518/518 (100)	981/1024 (95.8)	
Extraocular retinoblastoma			p<0.001
No	503 (97.1)	561 (56.6)	
Yes‡	15 (2.9)	430 (43.4)	
Reported cases	518/518 (100)	991/1024 (96.8)	

\*50/518 (9.7%) European and 121/1024 (11.8%) African patients with retinoblastoma travelled across borders for diagnosis and primary treatment (not included in the analysis).

†M1=cM1+pM1.

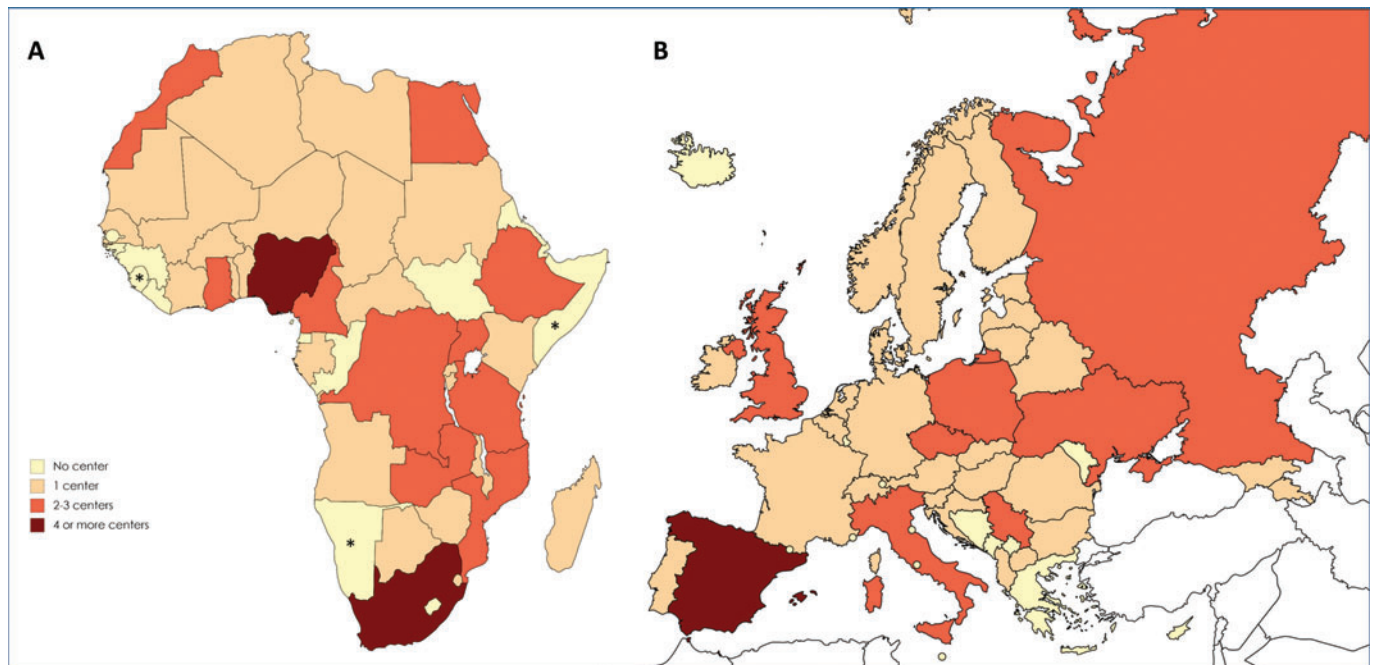
‡Based on the International Retinoblastoma Staging System.<sup>19</sup>

### Risk factors for advanced disease at the time of diagnosis

Lower-national-income level, African continent, older age at presentation, familial retinoblastoma and bilateral retinoblastoma ( $p \leq 0.010$ ), but not distance from home to retinoblastoma centre ( $p = 0.19$ ), were found to be significant factors for the prediction of cT4 category (ie, extraocular disease). On logistic regression, national-income level, continent and age at presentation were found to be independent, significant predictors for cT4 category (table 2). On further analysis by continent, no predictors were found for the European subgroup, whereas for the African subgroup, older age and lower-income level ( $p < 0.001$ ) were found to be significant predictors of cT4 category (online supplemental table 2 in the appendix).

### DISCUSSION

Our findings confirm a large disparity in the presentation patterns of retinoblastoma between patients from African and European countries. Patients from Africa were significantly older, nearly half of them had extraocular spread at the time of diagnosis, and nearly one-fifth had distant metastasis. Of the European patients, less than 3% had extraocular tumour spread and only 1% had metastatic spread at the time of diagnosis. Patients from lower-income level countries, those from the African continent and older patients at the time of diagnosis were at increased risk to have advanced retinoblastoma. Interestingly, distance patients travelled in order to reach a retinoblastoma referral centre did not play a role in this risk. These results are in contrast to previous analyses of other



**Figure 1** Number of retinoblastoma centres in (A) Africa and (B) Europe. \*Centers in Namibia (n=1), Sierra Leone (n=1) and Somalia (n=1) that were contacted did not join the study; hence, no information was available from these centres. Of the two known Kenyan centres and two known Algerian centres that were contacted, only one from each country has joined in the study.

forms of cancer, including breast, colon, lung and skin melanoma,<sup>23–26</sup> as well as rare cancers such as Merkel cell carcinoma,<sup>27</sup> in which high travel burden correlated with advanced-disease stage. Noteworthy, all of the above-referenced studies were single-centre rather than multicentre multinational studies, as the present one.

Analysis of the travel burden, however, in conjunction with data on the number of retinoblastoma centres in African and European countries, and demographic data, including country population and surface area, suggests a more complex picture. Patients from African countries travelled less than half the distance compared to European patients in order to reach a specialised retinoblastoma treatment centre. Assuming that nearly all retinoblastoma centres in the participating African countries were contacted and recruited, our findings suggest that these centres serve mainly patients that reside in close vicinity.

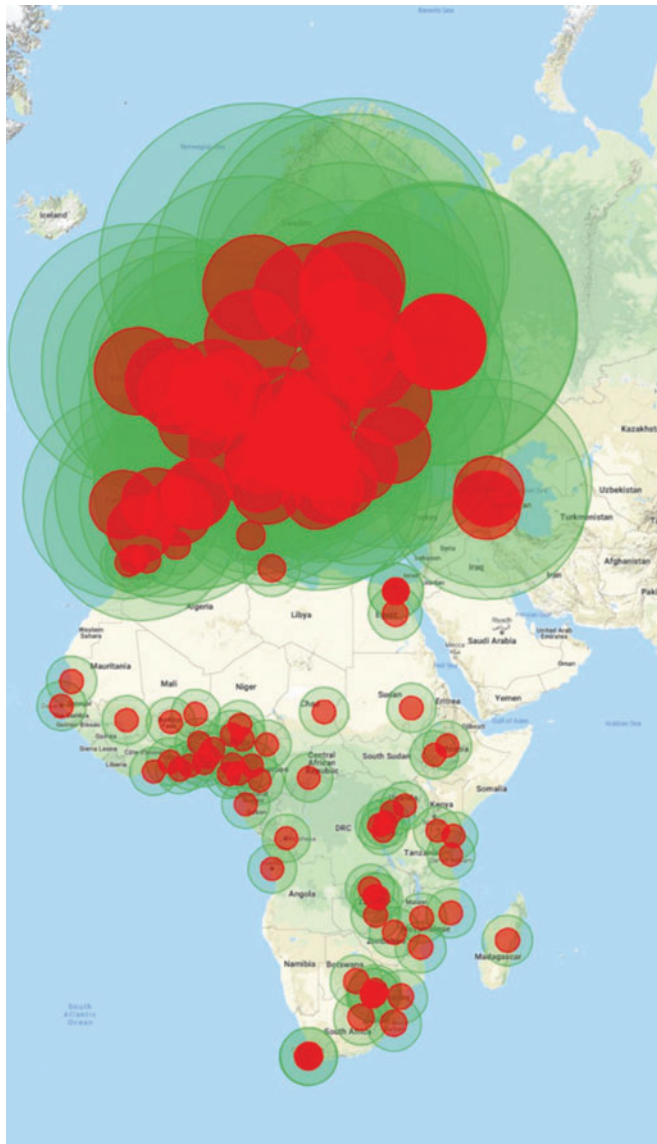
Taking into account the low capture rate in Africa, underlying causes for the findings of this study are multifactorial; they include poor awareness by carers and health workers, lack of knowledge about clinical presentation by health workers, travel distance and cost to reach a specialised retinoblastoma treatment centre, and probably the absence of specialised retinoblastoma treatment centres in some parts of Africa.

It is well documented that poor awareness of retinoblastoma both by the public and health workers can lead to delays in diagnosis.<sup>28–31</sup> Delayed retinoblastoma diagnosis, in turn, leads to poor outcome.<sup>32–34</sup> Poor awareness and health education is likely to be the main factor for those cases that reside in proximity to a treatment centre, yet presented late. Initiatives are addressing this need by creating twinning programmes that link centres from higher- and lower-resource countries, as well as interventions such as public awareness campaigns, and health worker

education.<sup>29 31 35–39</sup> There is a pressing need, to promote this action at national and global level. In a rare curable cancer such as retinoblastoma, with a finite number of patients worldwide, such action is feasible.

Barriers to healthcare in Africa have been reported in relation to several medical fields, including oncology,<sup>40 41</sup> ophthalmology<sup>42–46</sup> and paediatrics.<sup>42 44 47</sup> Most barriers, whether financial, structural (ie, accessibility), lack of transport, poor roads, were also found relevant in the context of retinoblastoma in Africa.<sup>33 48 49</sup> Possible solutions should be inclusive and account for all factors; most are not in the scope of the present study. Number and distribution, however, of retinoblastoma centres in a country is a matter that warrants further discussion. The need for and number of retinoblastoma centres derive first and foremost from the number of new retinoblastoma cases in a country. There should be enough centres with an appropriate distribution to serve all patients within a country. On the other hand, there should not be too many, as expert centres need to remain ‘vivid’, an ability that relates directly to the number of cases managed, as was shown in other rare malignancies.<sup>50</sup> In this sense, European and African countries face different challenges. In Europe, with a low birth rate and therefore low prevalence of retinoblastoma, the need for a treatment centre in countries with 1–2 new cases per year is questionable. In Africa, with a high birth rate and increasing population, the situation is more complex. New retinoblastoma centres will be needed where there is a large population (10 million population and 20–30 new retinoblastoma cases/year) with no available centre. The number and distribution of retinoblastoma treatment centres need to be tailored to the country’s requirements.

Familial retinoblastoma was significantly more common in European than in African countries. A possible explanation is the high survival rate of hereditary cases in Europe due to early diagnosis and efficient treatments. This possibly could



**Figure 2** Retinoblastoma centre catchment area in Africa and Europe. The red circles represent the mean patient travel distance and green circles, the travel distance SD. Patients in European countries travelled in average significantly longer distances ( $421.8 \text{ km} \pm 814.6$ ) compared to patients from African countries ( $185.7 \text{ km} \pm 201.0$ ) in order to reach a retinoblastoma centre ( $p < 0.001$ ). Superimposing the red and green circles on the map, retinoblastoma centres in European countries cover the whole continent, whereas in Africa, large parts in many African countries remain uncovered.

explain the high capture rate of retinoblastoma in Europe too, higher than the predicted annual number. Further studies are warranted to better understand the trends in retinoblastoma incidence in Europe. Three-quarters of the European familial cases were screened for retinoblastoma (ie, examined before clinical signs were evident) and most were diagnosed with early disease stage. In Africa, screening rate was as low as 11.5% of the familial cases, lower than previously reported in ‘developing countries’ outside Africa.<sup>51</sup> Screening may result in less invasive treatments being needed, resulting in higher chances for eye salvage and better vision.<sup>52 53</sup> Patients with retinoblastoma from both continents should receive

future counselling regarding the need for screening of their offspring, especially the  $\sim 30\%$  that presented with bilateral disease whose children have a nearly 50% chance of developing retinoblastoma. Interestingly, the rates of bilateral cases were similar between Africa and Europe. Most of them are known to result from sporadic germline mutations. The proportion of cases with familial retinoblastoma who presented with bilateral disease was also similar. Given the risk factor analysis, which showed that lower-income level and African continent were independently associated with advanced disease, it is possible that other, unrecorded variables are responsible for disease progression before diagnosis is made in Africa, as well as for tendency to present with bilateral retinoblastoma. Further studies should explore these possibilities.

Our study has limitations. First, the orthodromic distance was used as a surrogate for the travel burden, whereas other related factors that may play a role were not taken into account, especially travel costs, time costs, loss of parental income, availability and mode of transportation, road conditions, availability of transport and the actual distance travelled from home to a specialised referral retinoblastoma centre. Second, our study was cross-sectional by design and some of the data were collected in a retrospective manner (centres that were recruited after January 2017), with the inherent limitations of such a design. Nevertheless, we were able to collect data from an unprecedented number of retinoblastoma centres and countries, and to perform a quality and assurance process to make sure that the data are accurate. Third, our sample was a convenience sample, and although repeated attempts were made to reach every retinoblastoma treatment centre in Africa and Europe, it is possible that some were missed. Notably, centres in Namibia ( $n=1$ ), Sierra Leone ( $n=1$ ) and Somalia ( $n=1$ ) that were contacted did not join in the study; hence, no information on these centres was available. In addition, only 1 out of 2 centres in Kenya, and 1 out of 2 in Algeria, joined in the study, and similarly, no information was available on those centres that did not join in.

In summary, our findings show that in European countries, travel distance from home to retinoblastoma centre is not a barrier to early disease diagnosis. European patients travel on average more than 400 km and  $>60\%$  present at stage cT2 or earlier. In Africa, the picture is more complex —patients travel on average less than 200 km, yet  $>80\%$  present at stage cT3 or worse, suggesting that factors other than geographic distance to retinoblastoma centre play a role in late disease diagnosis. Poor awareness and education by both caregivers and health workers, other barriers to access, and possibly, number and distribution of specialist retinoblastoma treatment centres in those African countries in which the population is underserved, are key factors that warrant intervention on national and international levels. Familial retinoblastoma is more common in Europe than in Africa, most probably due to death related to late disease presentation, and screening of patients at risk of developing retinoblastoma is more common in Europe. Comprehensive counselling of families and patients with germline disease (ie, bilateral retinoblastoma and/or positive family history) may be found useful in order to detect the disease at early stage to increase survival rates in this highly curable malignancy.

**Table 2** Predictors of advanced retinoblastoma disease at presentation (cT4): univariate and multivariate analyses

Variable	Category	B	SE	Corrected pvalue	OR	95% CI for OR	
						Lower	Upper
Univariate analysis							
Income level	Low versus lower-middle	1.04	0.14	<0.001	2.82	2.13	3.74
	Low versus upper-middle	1.25	0.15	<0.001	3.50	2.60	4.70
	Low versus high	1.89	0.34	<0.001	6.64	3.44	12.82
	Lower-middle versus upper-middle	1.47	0.31	<0.001	4.33	2.38	7.90
	Lower-middle versus high	2.32	0.50	<0.001	10.19	3.80	27.35
	Upper-middle versus high	3.18	1.04	<0.001	23.96	3.11	184.62
Continent	Africa versus Europe	0.84	0.10	<0.001	2.32	1.90	2.82
Familial retinoblastoma	Yes versus no	1.51	0.52	0.001	4.54	1.64	12.57
Bilaterality	Yes versus no	0.38	0.15	0.010	1.46	1.10	1.94
Distance from home to Rb centre*				0.19			
Age at diagnosis*				<0.001			
Multivariate analysis (binomial logistic regression)							
Income level	Lower-middle	0.90	0.15	<0.001	2.45	1.83	3.30
	Upper-middle	1.48	0.34	<0.001	4.38	2.26	8.47
	High	3.08	1.18	0.001	21.74	2.14	220.82
Continent	Europe	2.34	0.62	<0.001	10.37	3.07	35.01
Age at diagnosis†	≥24 months	-1.33	0.16	<0.001	0.27	0.19	0.37
Constant		1.07	0.16	<0.001	0.34		

\*t-Test for numerical variables.

†Median age=24.2 months (categorical variable).

**Author affiliations**<sup>1</sup>International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, UK<sup>2</sup>The Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Tel-Aviv University, Tel-Aviv, Israel<sup>3</sup>Department of Ophthalmology, University of Washington, Seattle, WA, US<sup>4</sup>Ocular Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland<sup>5</sup>Jules-Gonin Eye Hospital, Fondation Asile de Aveugles, University of Lausanne, Lausanne, Switzerland<sup>6</sup>Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel<sup>7</sup>Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel<sup>8</sup>Institut curie, université de Paris médecine Paris V Descartes, Paris, France<sup>9</sup>NIHR Biomedical Research Center for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology and London Retinoblastoma Service, Royal London Hospital, London, UK<sup>10</sup>The Royal London Hospital, Barts Health NHS Trust, and Moorfields Eye Hospital NHS Foundation Trust, London, UK<sup>11</sup>Ophthalmology Department of Rabat, Mohammed V university, Rabat, Morocco<sup>12</sup>Bayero University, Aminu Kano Teaching Hospital, Kano, Nigeria<sup>13</sup>National Hospital of Niamey, Niamey, Niger<sup>14</sup>University of Ilorin and University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria<sup>15</sup>Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria<sup>16</sup>Department of Ophthalmology, College of Medicine, University of Nigeria, Enugu, Nigeria<sup>17</sup>Department of Pediatric Ophthalmology, Hospital Vall d'Hebron, Barcelona, Spain<sup>18</sup>University of Parakou, Parakou, Benin<sup>19</sup>Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt<sup>20</sup>University Hospital Center 'Mother Theresa', Tirana, Albania<sup>21</sup>St Erik Eye Hospital, Stockholm, Sweden<sup>22</sup>Beira Central Hospital, Beira, Mozambique<sup>23</sup>Tripoli Eye Hospital, Tripoli University, Tripoli, Libya<sup>24</sup>Bambino Gesù IRCCS Children's Hospital, Rome, Italy<sup>25</sup>Light House For Christ Eye Center, Mombasa, Kenya<sup>26</sup>Pediatric Oncology Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain<sup>27</sup>Institute of Pediatrics, Jagiellonian University Medical College, Childrens University Hospital of Krakow, Krakow, Poland<sup>28</sup>Unit of Pediatric Hematology-Oncology, University Hospital CHUV, Lausanne, Switzerland<sup>29</sup>Department of Pediatric Oncology, University Hassan II Fès, Fez, Morocco<sup>30</sup>Center Hospitalier et Universitaire Ibn Rochd, Casablanca, Morocco<sup>31</sup>Ophthalmologic Department of the Teaching Hospital of Treichville, Abidjan, Côte d'Ivoire<sup>32</sup>University of the Witwatersrand, Johannesburg, South Africa<sup>33</sup>University Hospital Essen, Department of Ophthalmology, University Duisburg-Essen, Essen, Germany<sup>34</sup>The Filatov Institute of Eye diseases and Tissue Therapy, Odessa, Ukraine<sup>35</sup>Center Hospitalier Universitaire Yalgado Ouédraogo de Ouagadougou, Ouagadougou, Burkina Faso<sup>36</sup>Institut Hédi-Rais d'Ophthalmologie de Tunis, Faculté de Médecine de Tunis, Université Tunis El Manar, Tunis, Tunisia<sup>37</sup>Établissement Hospitalière Spécialise Emir Abdelkader CEA Service d'Oncologie Pédiatrique, Oran, Algeria<sup>38</sup>Cliniques Universitaires Saint-Luc, Brussel, Belgium<sup>39</sup>Our Lady's Children's Hospital, Dublin, Ireland<sup>40</sup>Centro Hospital Universitário de Coimbra, University of Coimbra, Coimbra, Portugal<sup>41</sup>Hospital Sant Joan de Déu, Barcelona, Spain<sup>42</sup>Eye Clinic, University Hospital 'Alexandrovska', Department of Ophthalmology, Medical University, Sofia, Bulgaria<sup>43</sup>Muhimbili National Hospital, Dar es Salaam, Tanzania<sup>44</sup>Department of Ophthalmology, The Children's Memorial Health Institute, Warsaw, Poland<sup>45</sup>Oncology Institute 'Prof. Dr. Al. Trestioreanu' Bucharest, Romania<sup>46</sup>Semmelweis University Budapest, Budapest, Hungary<sup>47</sup>Quelimane central Hospital, Quelimane, Mozambique<sup>48</sup>Red Cross Children's War Memorial Hospital and the University of Cape Town, Cape Town, South Africa<sup>49</sup>Institut curie, Paris, France<sup>50</sup>University of KwaZulu-Natal, Durban, South Africa<sup>51</sup>Children's Cancer Hospital Egypt 57357, Cairo, Egypt<sup>52</sup>Oncology Department, National Cancer Institute, University of Gezira, Wadi Madani, Sudan<sup>53</sup>Ophthalmology Unit, Department of Surgery, School of Medicine and Dentistry, University of Ghana, Accra, Ghana<sup>54</sup>Magrabi ICO Cameroon Eye Institute, Yaounde, Cameroon<sup>55</sup>Department of Ophthalmology, University College Hospital/University of Ibadan, Ibadan, Oyo State, Nigeria<sup>56</sup>Hospital Universitario Virgen Macarena, Sevilla, Spain

- <sup>57</sup>Lions Sight First Eye Hospital, Queen Elizabeth Central Hospital, Blantyre, Malawi  
<sup>58</sup>Servicio Andaluz de Salud (SAS), Sevilla, Spain  
<sup>59</sup>Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa  
<sup>60</sup>Addis Ababa University, School of Medicine, Department of Ophthalmology, Addis Ababa, Ethiopia  
<sup>61</sup>Department of Clinical Genetics, and Center for Rare Disorders, Aarhus University Hospital, Aarhus, Denmark  
<sup>62</sup>Département de Pédiatrie, CHU Sylvanus Olympio, Université de Lomé, Lomé, Togo  
<sup>63</sup>Retinoblastoma referral center, University of Siena, Siena, Italy  
<sup>64</sup>University Childrens' Hospital, Bratislava, Slovakia  
<sup>65</sup>Pediatric Hematology and Oncology Department of Rabat – Mohammed V University, Rabat, Morocco  
<sup>66</sup>Department of Pediatrics and Child Health, Jimma University Medical Center, Jimma, Ethiopia  
<sup>67</sup>Department of Ophthalmology, Oslo University Hospital, Oslo, Norway  
<sup>68</sup>Institute for Oncology and Radiology, Belgrade, Serbia  
<sup>69</sup>Birmingham Children's Hospital Eye Department, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK  
<sup>70</sup>Bukavu Eye Clinic – Bukavu Official University, Bukavu, DRC  
<sup>71</sup>Makerere University College of Health Sciences, Department of Ophthalmology, Kampala, Uganda  
<sup>72</sup>Ophthalmology Department, Central Children's Hospital of Georgia, Tbilisi, Georgia  
<sup>73</sup>University Hospital Brno, Masaryk University and ICRC/St. Anna University Hospital, Brno, Czech Republic  
<sup>74</sup>East Tallinn Central Hospital, Tallinn, Estonia  
<sup>75</sup>Oncologue Pédiatre Responsable d'Unité de Bangui, Bangui, Central African Republic  
<sup>76</sup>Children's Ophthalmology Department, Children's Hospital of Vilnius, University Hospital Santaros Clinic, Vilnius, Lithuania  
<sup>77</sup>Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa  
<sup>78</sup>University Hospital Hamburg-Eppendorf, Hamburg, Germany  
<sup>79</sup>Clinical Center Of Vojvodina – University Eye Clinic, Eye Research Foundation Vidar – Latinović, Novi Sad, Serbia  
<sup>80</sup>Division of Ophthalmology, University of Cape Town, Cape Town, South Africa  
<sup>81</sup>University Clinics of Lubumbashi, University of Lubumbashi, Lubumbashi, DRC  
<sup>82</sup>The Okhmatdyt National Children's Hospital, Kiev, Ukraine  
<sup>83</sup>Sekuru Kaguvi Eye Unit, Parirenyatwa Group of Hospitals, Harare, Zimbabwe  
<sup>84</sup>Ruharo Eye Hospital, Mbarara, Uganda  
<sup>85</sup>Botswana Government – Scottish Livingstone Hospital, Molepolole, Botswana  
<sup>86</sup>Department of Ophthalmology, Jimma University, Jimma, Ethiopia  
<sup>87</sup>Department of Ophthalmology, University of Padova, Padova, Italy  
<sup>88</sup>Kilimanjaro Christian Medical Center, Moshi, Tanzania  
<sup>89</sup>Pathology Department, Faculty of Medicine, University of Gezira, Wadi Madani, Sudan  
<sup>90</sup>Department of Ophthalmology, Amsterdam UMC, Amsterdam, Netherlands  
<sup>91</sup>Service d'oncologie pédiatrique de l'hôpital Aristide le Dantec, Dakar, Senegal  
<sup>92</sup>Ministry of Health, Lusaka, Zambia  
<sup>93</sup>Department of Ophthalmology, Lagos University Teaching Hospital/College of Medicine of the University of Lagos, Lagos, Nigeria  
<sup>94</sup>Abii Specialists Hospital, Bamenda, Cameroon  
<sup>95</sup>N.N. Alexandrov National Cancer Center of Belarus, Minsk, Belarus  
<sup>96</sup>Cheikh Anta DIOP University of Dakar, Le Dantec Hospital, Dakar, Senegal  
<sup>97</sup>Moscow Helmholtz Research Institute of Eye Diseases, Moscow, Russia  
<sup>98</sup>Calabar Children's Eye Center, Department of Ophthalmology University of Calabar Teaching Hospital Calabar Cross River State, Nigeria  
<sup>99</sup>Arthur Davison Children's Hospital, Ndola, Zambia  
<sup>100</sup>Chu Angondje Cancerologie, Libreville, Gabon  
<sup>101</sup>Komfo Anokye Teaching Hospital, Kumasi, Ghana  
<sup>102</sup>National Ophthalmological Institute of Angola, Luanda, Angola  
<sup>103</sup>Yerevan State Medical University, Department of Oncology and Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after R.H. Yeolyan, Yerevan, Armenia  
<sup>104</sup>University Hospital Center Zagreb, Zagreb, Croatia  
<sup>105</sup>Center Hospitaliere Universitaire de Kamenge, Bujumbura, Burundi  
<sup>106</sup>Department of Ophthalmology for Children and Adults, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic  
<sup>107</sup>Head and Neck Tumors Department, SRI of Pediatric Oncology and Hematology of N. N. Blokhin National Medical Research Center of Oncology of Russian Federation, Moscow, Russian Federation  
<sup>108</sup>Medical Academy of Postgraduate Education, Moscow, Russia  
<sup>109</sup>Univ. Medical Center Ljubljana, Univ. Eye Hospital Ljubljana, Ljubljana, Slovenia  
<sup>110</sup>Good Shepherd Hospital, Siteki, Swaziland  
<sup>111</sup>Center Hospitalier Universitaire Joseph Ravoahangy Andrianavalona, Antananarivo, Madagascar  
<sup>112</sup>University of Ghana School of Medicine and Dentistry, Korle Bu Teaching Hospital, Accra, Ghana  
<sup>113</sup>University of Pretoria, Pretoria, South Africa  
<sup>114</sup>Federal Medical Center, Yola, Nigeria  
<sup>115</sup>Nampula central hospital, Nampula, Mozambique  
<sup>116</sup>Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Medical University of Graz, Graz, Austria  
<sup>117</sup>Ophthalmology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt  
<sup>118</sup>Pediatric Hemato-Oncology, Hospital Universitario Infantil La Paz, Madrid, Spain  
<sup>119</sup>Ophthalmology department, Nouakchott Medical University, Nouakchott, Mauritania  
<sup>120</sup>Mulago National Referral and Teaching Hospital, Kampala, Uganda  
<sup>121</sup>Department of Paediatrics and Child Health, University of the Free State, Bloemfontein, South Africa  
<sup>122</sup>Department of Pediatric Hematology and Oncology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic  
<sup>123</sup>Africa Institute of Tropical Ophthalmology, Bamako, Mali  
<sup>124</sup>University Eye Clinic, Skopje, Macedonia  
<sup>125</sup>Kabgayi Eye Unit, Gitarama, Rwanda  
<sup>126</sup>Pediatric Oncology Service, Gabriel Toure Hospital, Bamako, Mali  
<sup>127</sup>Université Adam Barka, Adam Barka, Chad  
<sup>128</sup>Department of ophthalmology, Aarhus University Hospital, Aarhus, Denmark  
<sup>129</sup>Children's Clinical University Hospital, Riga, Latvia  
<sup>130</sup>Department of Ophthalmology, Medical University Graz, Graz, Austria  
<sup>131</sup>Jos University Teaching Hospital, Jos, Nigeria  
<sup>132</sup>National Eye Center Kaduna, Kaduna, Nigeria  
<sup>133</sup>Service d'Ophthalmologie, Cliniques Universitaires de Kinshasa, Université de Kinshasa, Kinshasa, DRC  
<sup>134</sup>S.Fyodorov Eye Microsurgery Federal State Institution, Moscow, Russia  
<sup>135</sup>Assistante Hospitalo – Universitaire, Faculte de Medecine de Nouakchott Medecin Oncopédie, Center National d'Oncologie, Nouakchott, Mauritania  
<sup>136</sup>Radiology Department, Sheba Medical Center, Ramat-Gan, Israel  
<sup>137</sup>Ophthalmology Department, Great Ormond Street Children's Hospital, London, UK

**Contributors** Conception and design: IDF, AF, RB. Administrative support: CB, MZ. Collection and assembly of data: all authors. Data analysis and interpretation: IDF, NC, AF, TTK, FLM, MAR, MSS, ASS. Statistical analysis: AWS. Manuscript drafting: IDF, AF, AWS, RB. Critical revision of the manuscript for important intellectual content: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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