Eye (2005) 19, 243–252

www.nature.com/eye

REVIEW

A review of trabeculectomy in East Asian people—the influence of race

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Abstract

Glaucoma is the leading cause of irreversible blindness worldwide. East Asians account for approximately half of all glaucoma sufferers. It is likely that trabeculectomy will be needed for many of these people as the intraocular pressure is to be maintained at a satisfactorily low level. The eyes of East Asian people differ in some aspects from those of other races. This review describes the natural history of the eye after trabeculectomy in East Asians.
Eye (2005) **19,** 243–252. doi:10.1038/sj.eye.6701477
Published online 23 July 2004

Keywords: glaucoma; trabeculectomy; race; Asian; Chinese

Introduction

Glaucoma affects around 70 million people and is the second most common cause of blindness worldwide. Furthermore, it is the leading cause of irreversible blindness with estimates of blindness in around 10% of those affected. East Asians account for approximately half of all glaucoma sufferers.[1] The World Health Organisation estimates that Asia is home to 3585 million people and that this is set to rise to 5268 million by 2050. In order to avoid blindness in over 3 million people, the management of glaucoma in East Asia has become a pressing issue.

The publication of large prospective surveys such as the Ocular Hypertension Treatment Study (OHTS),[2] Collaborative Normal Tension Glaucoma Study (CNTGS),[3] and the Early Manifest Glaucoma Treatment Study (EMGTS)[4] have emphasized once more the important role that lowering intraocular pressure (IOP) plays in preventing the progression of glaucoma. Trabeculectomy remains the most effective weapon in the ophthalmologist's armoury with which we can achieve a satisfactory low IOP. Despite the introduction in recent years of new powerful medications, trabeculectomy has usually outperformed both medical and laser treatment in this regard.[5,6] This has led to a renewed interest in the natural history of the eye after trabeculectomy and how we can modify the operation to produce the most desirable result.

Cairns was the first to describe the partial thickness trabeculectomy that we know today, and the procedure remains much the same now as when he described it in 1967.[7] Modifications introduced since then such as the introduction of antimetabolites have improved success rates.[8–15] This has been of particular benefit to those patients who were identified as having a higher risk for failure such as those who had had previous surgery, secondary glaucomas, young people, and non-Caucasian populations. It was established early on in its history that trabeculectomy in black subjects failed earlier compared to white subjects, presumably due to a more vigorous fibrotic response in the subconjunctival space.[16–22] The reason black populations were studied in preference to the East Asian populations, for example, was probably because comparatively large communities of African-American blacks in the USA and Afro-Caribbean blacks in the UK provided a ready population to study in the countries where most of the academic literature was arising from.

Quigley's estimation that half of all the world's glaucoma sufferers are of East Asian origin has put this into perspective and, as a result, there has been a growing emphasis in the medical literature on this population. East Asian eyes have been shown to differ in many ways from the eyes of other racial groups and the

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Published online: 23 July 2004

assumption that these eyes will respond to trabeculectomy in the same manner as others cannot be taken as granted. An understanding of the natural history of the eyes both in terms of the glaucomatous progression and the response to standard treatments has become of prime importance in order for the burden of world preventable blindness to be lessened. Much of the populace in this region have inadequate access to health care services and this raises problems with screening and identifying at risk or affected individuals, before the treatment stage even begins. 'One stop' eye camps whereby trabeculectomies are performed have been proposed in those areas where follow-up would prove very difficult or access to medication is not available.[23] The dictum of 'primum non nocere', that is, first do no harm means that the natural history of trabeculectomy in this distinct population needs to be addressed as the impact in terms of number of people treated is likely to be huge.

For the purposes of this review, East Asian is taken as meaning those peoples from China, Japan, and South-east Asia, excluding the Indian subcontinent. East Asian peoples in this context share a common racial heritage (ie Mongoloid), although heterogeneity within this group itself undoubtedly exists. Generally, as migration, genetic, and linguistics studies have shown, Northern Chinese, Korean, and Japanese form one subgroup, Southern Chinese (including Chinese Singaporeans) form another, and Malays, Indonesians, Thais, and Philippinos form yet another subgroup.[24]

Trabeculectomy in Whites, Hispanics, Blacks, and Indians

The natural history of trabeculectomy in white Caucasians has been studied in great detail. A national survey of the current practice of UK Ophthalmologists provided data for the first time on how individual surgeons in the UK differ in their surgical technique and subsequent management.[25–27] Despite a wide variation in surgical technique, the success rate in this group of mainly unaugmented trabeculectomies was an impressive 84% at 1 year. The complication rate, however, was between 42 and 47% and more emphasis is now being placed on how best to modify Cairn's technique further to reduce this rate to acceptable levels, resulting a 'tailor-made' approach to patients, particularly with regard to augmentation with antimetabolite.

There have been a number of long-term studies. In a study of 150 eyes which had undergone unaugmented trabeculectomy with 9-year follow-up (predominantly white patients), 90% were controlled (IOP $<$ 20 mmHg no medication) at the last visit.[28] Chen *et al*[29] retrospectively reported a series of patients with various glaucoma diagnoses from a mixed white and black population, who underwent unaugmented primary trabeculectomies. In all, 40 patients were identified who had successful IOP control at 1 year (IOP $<$ 21 mmHg or 33% reduction). After 10 years follow-up, 27 subjects (67%) were able to maintain successful IOP control, although many of these required topical medications. Separate analysis by race was not performed. Suzuki *et al*[30] performed a similar study of 87 eyes looking at trabeculectomies augmented with postoperative 5-fluorouracil (5-FU) injections and which were successful (IOP $<$ 21 mmHg or 33% reduction) at 1 year, but by year 10 the success rate had dropped to 44%. This poor rate could be attributed to the fact that the patients were deemed at 'high risk' for failure. Comparisons between studies are notoriously difficult due to differences in surgical technique, postoperative management, and patient demographics.

There are few prospective data from large studies. However, one such landmark study from the Fluorouracil Filtering Surgery Study Group (FFSSG) found that there was no significant difference in time to failure (IOP criteria) between blacks and whites. This was evident in both the treatment group (postoperative subconjunctival 5-FU injections) and the control group. There was, however, a significant difference between time to failure between Hispanics and whites, with Hispanics failing much earlier. Interestingly, the time to failure for Hispanics was much the same whether they received 5-FU or not, in marked contrast to the non-Hispanics, suggesting that the benefits of 5-FU to the white population may not be reflected in the Hispanic population.[9]

The FFSSG based its criteria for failure on IOP levels. The Advanced Glaucoma Intervention Study (AGIS) investigators found that although initial (mainly unaugmented) trabeculectomy lowered IOP significantly in blacks, if outcome criteria based on visual acuity and visual fields were utilised, initial treatment with argon laser trabeculoplasty (ALT) was preferable in blacks as opposed to whites.[31] Longer term follow-up is required since these trends appear to be decreasing, but these differences have led some to suggest that primary open-angle glaucoma (POAG) in blacks may be a different disease than that in whites,[32,33] with more non-pressure-related factors being involved. The fact that glaucoma is more prevalent and occurs at a younger age in blacks lends some credence to this theory.[34–37] The AGIS investigators conclusions were that 'planning and analysis of further studies of glaucoma treatment should take race into account'.[38] The assumption that blacks from the Caribbean, Europe, America, and Africa all have the same disease process and reaction to surgery because of a shared ancestry is likely to be incorrect.

Heterogeneity in these populations is marked and, even within Africa, different glaucoma epidemiological data are evident.[21] It should be noted that almost all studies of trabeculectomy in black Africans have used IOP as an outcome measure of success—the AGIS results have highlighted the need for a broader definition of outcome.

The mounting evidence that blacks produce more conjunctival scarring after trabeculectomy leading to earlier failure rates[20,22,39] led some to promote the use of antimetabolites in this group. Indeed many studies did show benefits of this in terms of lowered IOP,[17,40–42] although there was some evidence to the contrary.[43] However, the consensus of opinion is that use of antimetabolites in blacks has now become the norm, particularly as complications such as hypotony seem to be lower in blacks than in whites.[44,45] Intraoperative antimetabolites are now used by the majority of practitioners in the American and Japanese glaucoma societies.[46] Their use has improved the success rate, with 92.6 and 98.1% achieving IOP <22 mmHg for 5-FU and mitomycin-C (MMC), respectively, at 1 year in a recent randomised control trial of a racially mixed group.[47] Results with long-term follow-up (>10 years) are yet to be published, as the routine use of intraoperative antimetabolites only became popular in the early 1990s.[48]

The Indian subcontinent consists of a heterogeneous group of people with the north consisting of predominantly Caucasian race and the south Dravidian. However, intermarrying and migration has meant that divisions along these lines have become impossible for a large portion of the population.

In a study from New Delhi, 33 patients were randomly assigned to undergo unaugmented trabeculectomy, trabeculectomy with intraoperative 5-FU or trabeculectomy with post-operative 5-FU injections.[49] The success rates (IOP <22 mmHg, no medications) at 3 months were 67%, 90%, and 80%, respectively. There was a significant difference in the IOP between the groups receiving 5-FU and the control, although the former groups also had higher complication rates. Another study from Southern India examined trabeculectomy in 76 patients augmented with 0.4 mg/ml of MMC and found 93.4% success rate (IOP <21 mmHg, no medication) at 18 weeks.[50] The main complications were choroidal detachment in 14% and cataract formation in 13%. These data seem to suggest that MMC-augmented trabeculectomy is the preferred option in this group of patients although larger comparative studies with longer follow-up are required.

Trabeculectomies in an East Asian population

The idea that fibrosis of the conjunctival space occurs more in darker skinned people may suggest that people of East Asian origin would be expected to have a fibrotic response similar to whites or perhaps in between whites and Indians.

However, a study from Singapore in 1996 reported that in a series of 51 eyes of mainly ethnic Chinese (76.5%) who underwent unaugmented trabeculectomy, success rate (IOP <21 mmHg) was achieved in only 48.7% of primary glaucomas at 2 years.[51] This was a poorer success rate than any of the studies performed on black patients. Poor success rates were also reported in Malaysia where a study performed on 61 eyes of adult patients, mainly Chinese and Malay ethnicity, examined the results of unaugmented trabeculectomy at 2-year follow-up.[52] They found 62% success (IOP <21 mmHg, no medications) for POAG and around 45% for primary angle closure glaucoma (PACG). Serious complications were low with only one eye having choroidal detachment.

Augmentation with intraoperative 5-FU has produced conflicting results in a similar population. In 1998, two studies were published from Singapore comparing unaugmented trabeculectomy to trabeculectomy augmented with intraoperative 5-FU. In the first, a retrospective review of 89 patients with a follow-up of around 36 months, it was found that IOP <22 mmHg without medication was achieved in 36.4% in the control group and 65.8% in the 5-FU group, which was significant.[53] Conversely, Wong and Seah[54] found in a series of 135 eyes, 27 of which had 5-FU-augmented trabeculectomies and 108 controls, that success (IOP <22 mmHg, no medications) at 1 year was 75.9% in the control group and 63% in the 5-FU group. This unusual result may be explained by the 5-FU group having a higher proportion of high-risk cases compared to the control group. Both studies had a similar racial distribution (mainly ethnic Chinese) and both had patients with POAG and PACG.

The relatively poor results even with 5-FU prompted some to see if MMC gave better results. A study from China in 1992 randomly assigned 40 eyes of 30 patients to receive unaugmented trabeculectomy or trabeculectomy augmented with 0.4 mg/ml MMC.[55] Most of the eyes were at high risk of failure including uveitics, neovascular glaucomas, etc. The MMC group had a 67% drop in IOP at 1 year compared to 33% drop in the control group. Complications were minimal, with macular oedema being the most common (14% in the MMC group). A larger series from Hong Kong[56] looked at 48 eyes, which underwent trabeculectomy augmented with 0.4 mg/ml MMC and had a follow-up of 21.8 months, found that 47.9% had IOP <22 mmHg (no medications). In all, 4% developed hypotony maculopathy and 2% required resuturing of a leaking conjunctival wound.

The data from Japan are more substantial. In a retrospectively analysed series of 427 eyes which underwent unaugmented trabeculectomy (mixed diagnoses and follow-up of 3 months to 5 years), the success rate was only 25% (IOP < 21 mmHg, no medications).[57] Complication rates were not reported. Two studies comparing trabeculectomy with postoperative subconjunctival injections of 5-FU *vs* control showed a much higher success rate with 5-FU.[58,59] Trabeculectomy augmented with MMC also had good results in one series of 59 eyes with 90% having IOP < 21 mmHg at 2 years. A prospective comparative study between trabeculectomy with intraoperative MMC *vs* subconjunctival injections of 5-FU found MMC to be superior with success rates (IOP < 21 mmHg without medications) of 88% *vs* 47% and no significant differences in complications.[60]

On the whole, complications in Japanese eyes seem to be more common than those in white Caucasian eyes. One large study of 211 eyes showed an incidence rate of 10% of flat anterior chamber after unaugmented trabeculectomies.[58] This compares to a rate of only 0.2% in the UK survey. Furthermore, the rate of choroidal detachments has been reported as 31% for unaugmented trabeculectomies[59] and as high as 47% for trabeculectomies with postoperative 5-FU injections[60]—this compares to 14% in the UK survey. Table 1 summarises the data from East Asia.

Characteristics of East Asian Eyes

The above statistics reveal a general trend of poorer success rates of both augmented and unaugmented trabeculectomy for East Asians in comparison with other races, including blacks, and arguably higher complication rates. There are a number of characteristics of East Asian eyes that could potentially account for this.

People of East Asian descent have a higher rate of PACG than those of European descent,[1] with approximately 50–75% of East Asian glaucoma patients suffering from PACG.[61–63] In Mongolia, the prevalence of PACG is 1.4%,[64] while in the Inuit of Greenland, which share a common ancestry with the Sino-Mongoloid races of North-east Asia, this rises to 5%.[65] Indeed, the preponderance of PACG over POAG is evident over much of East Asia.[64,66–68] A number of biometric features associated with the development of PACG have been identified, including shallow anterior chamber,[69,70] anterior lens position,[70,71] thick lens,[72,73] smaller corneal diameter,[74,75] and short axial length.[76,77] One can imagine that trabeculectomy in eyes that have the biometric features described above are at greater risk of lenticulo-corneal touch, as the anterior chamber has been shown to shallow after trabeculectomy.[78–80] Cataract formation after trabeculectomy would be one of the expected consequences, but comparative data between East Asians and others are not yet available in this regard. There is conflicting evidence that East Asian eyes not known to have PACG may also have shallower and/or more crowded anterior chambers than Caucasians, and therefore have the same risk factors for post-trabeculectomy complications.[74,81]

The main cause for failure of trabeculectomy remains excessive fibrosis at the conjunctival–scleral interface.[82–85] The differences in conjunctival cell profile between blacks and whites have already been investigated.[86,87] It was shown that blacks have a greater number of fibroblasts and macrophages in their conjunctiva compared to whites, and it has been postulated that this may be why black patients fail more than whites. Such comparative studies have not been performed on East Asian eyes. The skin of East Asians has been found to differ in structural and functional ways compared to the skin of whites.[88] A study analysing the response to skin trauma found that the Chinese produced more keloid scarring than the darker skinned Malays.[89] Such differences in the skin response to trauma may indicate similar differences in the response to trauma at the conjunctival–scleral interface, since the healing mechanism in skin and conjunctiva is thought to be similar.[90]

Another issue frequently overlooked in studies examining trabeculectomy success rates is the use of preoperative medications. A study comparing the success rates of trabeculectomy between patients on beta-blockers and pilocarpine *vs* those on beta-blockers alone found that the former group had a significantly higher failure rate.[91] The conjunctival cell profile of those patients receiving pilocarpine and who failed contained significantly more fibroblasts and macrophages than those who did not. The same investigators also found that stopping of the antiglaucoma medication and prescribing 1 month course of topical steroid reversed these conjunctival changes.[92] The preponderance of PACG in the East Asian population as well as for economic reasons means that the use of pilocarpine is likely to be much more prevalent among those glaucoma sufferers who undergo trabeculectomy. In an ongoing trial in Singapore, 61% of glaucoma patients assessed for primary trabeculectomy had used pilocarpine for more than 6 months (unpublished data, Husain *et al*). An examination of the conjunctival cell profile in this population, with perhaps a comparison between those that are taking pilocarpine and those that are not, is warranted.

The incidence of hypotony in different racial populations is difficult to determine, although a trend towards a greater incidence in whites and East Asians

Table 1 Summary of studies on the efficacy of trabeculectomy in East Asians

Authors	*Study population*	*No. of eyes*	*Diagnosis*	*Study design*	*Follow-up*	*Procedure*	*Definition of success*	*Success rate*
Ng *et al* (1999)[117]	Mainly Chinese Hong Kong	48	POAG	Retrospective interventional case series	22 months	Trabeculectomy + MMC[a]	IOP < 22 mmHg, no meds.	48%
			PACG					
			Other					
Jun *et al* (1998)[53]	Mainly	89	POAG	Retrospective comparative trial	36 months	Trabeculectomy	IOP < 21 mmHg, no meds.	36
	Chinese Singaporean		PACG Other			Trabeculectomy + 5-FU[b]		66%
Wong *et al* (1998)[54]	Mainly	135	POAG	Retrospective comparative trial	12 months	Trabeculectomy	IOP < 22 mmHg, no meds.	76%
	Chinese Singaporean		CACG AACG			Trabeculectomy + 5-FU[b]		63%
Sharif *et al* (1997)[52]	Malay,	61	POAG	Retrospective interventional case series	24 months	Trabeculectomy	IOP < 20 mmHg, no meds.	52%
	Chinese & Indian		PACG CACG					
Tan *et al* (1996)[118]	Mainly	51	POAG	Retrospective interventional case series	29 months	Trabeculectomy	IOP < 21 mmHg, no meds.	43%
	Chinese Singaporean		CACG Other					
Wong *et al* (1995)[119]	Mainly	23	POAG	Retrospective interventional case series	3–9 months	Trabeculectomy + 5-FU[c]	IOP < 22 mmHg, no meds.	65%
	Chinese Singaporean		CACG Other					
Uchida *et al* (2001)[120]	Japanese	117	POAG	Retrospective interventional case series	12 years	Trabeculectomy + 5FU[d]	IOP < 21 mmHg, no meds + ≥30% reduction in IOP	38%
Araie *et al* (1992)[58]	Japanese	211	POAG	Retrospective comparative trial	5 years	Trabeculectomy	IOP < 21 mmHg, no meds.	40%
						Trabeculectomy + 5FU[e]		92%
Kitazawa *et al* (1991)[60]	Japanese	32	POAG	Prospective randomised comparative trial	12 months	Trabeculectomy + 5-FU[e]	IOP < 21 mmHg, no meds.	47%
			Other			Trabeculectomy + MMC[f]		88%
Nakano *et al* (1989)[59]	Japanese	82	POAG	Prospective comparative trial	3 years	Trabeculectomy	IOP < 21 mmHg, no meds.	11%
						Trabeculectomy + 5-FU[e]		77%

Table 1 (*Continued*)

Authors	*Study population*	*No. of eyes*	*Diagnosis*	*Study design*	*Follow-up*	*Procedure*	*Definition of success*	*Success rate*
Inaba (1982)[57]	Japanese	427	POAG	Retrospective interventional case series	3 months—5 years	Trabeculectomy	IOP <21 mmHg, no meds.	25%
			PACG					
			Other					
Oh *et al* (1994)[121]	South Korean	55	POAG	Prospective Comparative trial	6 months	Trabeculectomy + 5-FU[d]	IOP <22 mmHg, no meds.	77%
			CACG			Trabeculectomy + MMC[f]		90%

[a]Intraoperative MMC (0.4 mg/ml) for 3–5 min
[b]Intraoperative 5-FU (25 or 50 mg/ml) for 5 min
[c]Intraoperative 5-FU (25 mg/ml) for 5 min
[d]Intraoperative 5-FU (50 mg/ml) for 5 min
[e]Postoperative subconjunctival injections of 5% 5-FU solution post-trabeculectomy (mean total 35–50 mg).
[f]Intraoperative MMC (0.2 mg/ml) for 5 min

populations is evident. Hypotony rates have been reported between 10 and 33% in these populations.[44,93–96] Blacks and Indians appear to have less incidence of hypotony or hypotony-related complications. In a study of 5-FU- and MMC-augmented trabeculectomy in a West African population, Singh *et al*[45] found no cases of hypotony maculopathy or choroidal detachment and only three cases of flat anterior chamber in 101 eyes. A report by Ramakrishnan *et al*[97] reported an incidence of only 0.7% of hypotony maculopathy in 778 Indian eyes which had had trabeculectomy augmented with MMC. Hypotony occurs with antimetabolite use due to overfiltration at the bleb site or underproduction of aqueous by the effect of antimetabolites on the ciliary body, or both.[98,99] It has been suggested that a thin sclera predisposes an eye to postoperative hypotony.[100–102] The high prevalence of myopia (and hence thinner sclera) in the Chinese population may be relevant in this respect.[103] The thickness of the sclera at the point of exposure to antimetabolite and subsequent damage to the ciliary body also needs to be considered. The racial variation of scleral thickness has not been examined before, but is likely to have relevance in this scenario.

One would expect higher rates of malignant glaucoma in Asian eyes due to their biometric features described above. Surprisingly, this has rarely been reported, although it is unclear whether this is due to low incidence or deficiencies in reporting.

Glaucoma in East Asians, both POAG and PACG, has similarities and differences with the disease profile in other races. It is still very much a disease of old age, with the median age for POAG and PACG being over 70 years in the Chinese Singaporean population,[104] although one population-based study of 10 414 subjects from China found POAG to be far more prevalent in those aged under 40 years (methodological issues may account for this unusual result).[105] The association between high intraocular pressures and glaucoma has been observed in most studies on East Asian peoples, the notable exception being the high prevalence of normal pressure glaucoma (NTG) in the Japanese population. This has been consistently reported and merits further investigation into the possibility of a different pathogenesis of glaucoma in this distinct population. It may be of relevance that the mean IOP in East Asian populations tends to be lower than that in Europeans[68,106] and therefore a re-classification of what constitutes 'high' and 'normal' pressures may result in a lower prevalence of NTG. The speed of progression of glaucoma also has an important role in management of the disease. Blacks are thought to have a more rapid disease progression than whites;[107] the corresponding longitudinal data on East Asians are lacking and much needed.

Reports from Singapore,[103] Taiwan,[108] Hong Kong,[109] and Japan[110] have suggested that the prevalence of myopia is higher in East Asians than in European-derived populations. This has led to much debate on the aetiology of myopia and the role of genetic and environmental factors. The association between myopia and POAG have been reported previously,[111,112] as have the challenges of filtration surgery on the highly myopic eye.[101] More recently, interest has focused on the associations between myopia, ocular dimensions, and PACG. PACG occurs more often in eyes with shallow anterior chambers and short axial lengths.[69,76] Myopia, which tends to be more prevalent in societies with high educational standards,[113] is associated with deeper anterior chambers and longer eyes.[114] The economic boom evident in much of East Asia has been accompanied by higher standards of living and higher prevalence of myopia.[103,108,115,116] This is particularly evident in Singapore where increasing prosperity since the 1970s has led to a highly educated young population which has a higher rate of myopia than the older population.[103] If this really is due to a cohort effect rather than reflecting an actual change in refractive status of the eye with age, this will have profound implications for glaucoma screening and management, due to a likely shift in the balance between POAG and PACG incidence as the population ages.

Summary

The race of a person has been shown to affect the outcome of trabeculectomy. East Asian eyes have characteristics which make it likely that the natural history of trabeculectomy in these patients would differ from that in whites and blacks in whom most of the data are available. Glaucoma is the world's leading cause of irremediable blindness and half the world's 67 million glaucoma sufferers are of East Asian origin.[1] It is likely that trabeculectomy is needed in many of these cases if the IOP is to be lowered to the target levels recently found to have the best chance of preventing glaucomatous progression. It is therefore of utmost importance to study the natural history of the eyes after trabeculectomy and in particular examine the effects of antimetabolites, preoperative topical medication use, scleral thickness, and postoperative complications such as hypotony and cataract formation.

At present, a prospective, randomised, placebo-controlled trial of the use of intraoperative 5-FU in glaucoma-filtering surgery is underway in Singapore. The trial will end in 2004 when all patients will have reached at least 3 years follow-up and it is hoped that analysis of the results will provide, for the first time, much needed data on the natural history of trabeculectomy in East Asia, and in particular, the effect of intraoperative 5-FU. It is hoped that this will enable ophthalmologists to modify filtration procedures such that the ocular morbidity due to glaucoma is reduced.

Acknowledgements

This study is supported in part by the Singapore National Eye Centre, Singapore Eye Research Institute, Singapore National Medical Research Council (grant NMRC/0044/1994), United Kingdom Medical Research Council (grant MRCG9330070), Moorfields Trustees, and the Michael and Ilse Katz Foundation.

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