Corneal transplantation or keratoplasty has developed rapidly in the past 10 years. Penetrating keratoplasty, a procedure consisting of full-thickness replacement of the cornea, has been the dominant procedure for more than half a century, and successfully caters to most causes of corneal blindness. The adoption by specialist surgeons of newer forms of lamellar transplantation surgery, which selectively replace only diseased layers of the cornea, has been a fundamental change in recent years. Deep anterior lamellar keratoplasty is replacing penetrating keratoplasty for disorders affecting the corneal stromal layers, while eliminating the risk of endothelial rejection. Endothelial keratoplasty, which selectively replaces the [A: ok?] corneal endothelium in patients with endothelial disease, has resulted in more rapid and predictable visual outcomes. Other emerging therapies are ocular surface reconstruction and artificial cornea (keratoprosthesis) surgery, which have become more widely available because of rapid advances in these techniques. Collectively, these advances have resulted in improved outcomes, and have expanded the number of cases of corneal blindness, which can now be treated successfully. Femtosecond-laser-assisted surgery, bioengineered corneas, and medical treatment for endothelial disease are also likely to play a part in the future.

Introduction
Blindness due to corneal disease results both from numerous degenerative, dystrophic, infectious, and inflammatory corneal disorders and from corneal damage secondary to ocular surface disease. The epidemiology of corneal blindness is varied and complex, with infectious and nutritional corneal diseases, such as trachoma, onchocerciasis (river blindness), and vitamin A deficiency (xerophthalmia), second only to cataract as a cause of blindness worldwide. These disorders are common in developing countries in Asia and Africa, and amenable to prevention through public health measures, whereas corneal scarring is the most important cause of reversible blindness in children. Corneal transplantation remains the main method for visual rehabilitation once disease has affected corneal clarity, but is dependent on the availability of corneal donor tissue, which is the major limiting factor in developing countries. By contrast, developed countries in the west have more inherited, degenerative, or iatrogenic disorders, such as Fuchs’ corneal endothelial dystrophy, keratoconus, and postcataract surgery corneal decompensation, which have better prognoses.

Corneas are the most commonly transplanted tissue worldwide, and the indications for transplantation cover a wide range of diseases (tables 1 and 2). In the USA, 42,642 corneal transplantations were done in 2010, compared with 12,623 solid-organ transplantations in 2008, including kidney, liver, lung, pancreas, heart, and intestine. In the UK in 2010 and 2011, there were 3,565 corneal, 2,671 kidney, and 689 liver transplantations. Eye banks cannot match demand worldwide, however, resulting in long waiting lists for corneal transplantation in most developing countries.

This review provides a clinical perspective of the rapidly changing techniques and indications for corneal transplantation, which has led to significant improvement in graft survival and outcomes, for a widening range of indications. It covers four key aspects: the success and complications of penetrating keratoplasty as the major surgical procedure over the last half century, the recent transformation to newer selective techniques for lamellar keratoplasty and adoption of keratoprosthesis surgery, the development of adjunctive treatments such as ocular surface and stem-cell transplantation, and future developments in this fast evolving specialty.

History of corneal transplantation
The history of corneal transplantation dates back to more than two centuries with experiments using allografts and xenografts. Techniques for anterior lamellar keratoplasty were established during the 1800s, but it was Eduard Zirm who did the first successful full-thickness penetrating keratoplasty in 1905. However, poor graft survival for penetrating keratoplasty resulted in renewed interest in anterior lamellar keratoplasty surgery, which eliminated endothelial failure. By the mid 1950s, the introduction of topical steroids and surgical improvements resulted in the modern era of penetrating keratoplasty, which became the mainstay of corneal transplantation surgery until recently. In the past 10 years however, the notion of selective lamellar
keratoplasty has emerged, leading to fundamental changes in keratoplasty.

All surgery of corneal transplantation demands meticulous preparation of the ocular environment to maximise success. This preparation includes optimisation of the state of the ocular surface by use of measures to minimise the adverse effects of ocular surface diseases; these include the surgical correction of corneal exposure and lid malposition and medical treatment of dry eye and inflammatory diseases. Treatment of inflammatory diseases can include both local and systemic therapies (as for severe atopic disease and rheumatoid arthritis). Preoperative control of glaucoma, either medically or surgically, is also crucial for successful outcomes.

**Lamellar corneal transplantation**

Selective lamellar keratoplasty describes procedures that selectively replace only diseased layers of the cornea while retaining healthy layers, resulting in improved visual outcomes and reduced complications (tables 1–3). The cornea consists of five main layers (figure 1). Corneal endothelial cells have poor capacity for regeneration.

### Table 1: Keratoplasty techniques, indications, and technique selection

<table>
<thead>
<tr>
<th>PK</th>
<th>Selective LK</th>
<th>Ocular surface reconstruction</th>
<th>Boston type 1 keratoprostheses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Replaces all five corneal layers (figure 1)</td>
<td>Replaces only the epithelium and stroma with donor Bowman’s membrane and stroma; DALK describes the removal of almost all the host stroma</td>
<td>replaces the epithelial layer with donor tissue which includes donor limbus (stroma and epithelium)</td>
</tr>
<tr>
<td>EK</td>
<td>Replaces only Descemet’s membrane and the endothelium (removed by stripping) with donor endothelium and Descemet’s membrane, with or without stromal carrier</td>
<td>Replaces only the epithelial layer with ex-vivo cultivated epithelium (usually on a carrier of amniotic membrane)</td>
<td>replaces all five layers by a Perspex optical device fixated within a conventional allogeneic donor PK</td>
</tr>
</tbody>
</table>

### Variations in technique

The donor may be cut manually or with a mechanical trephine or with a femtosecond laser known as FLAK.

**Two variations in DALK technique are used:**

- Pre-Descemetic DALK (DALK decribes the removal of almost all the host stroma)
- Descemetic DALK (Descemet’s stripping automated endothelial keratoplasty; DSAEK, see figure 1).

The donor epithelium can be a conjunctival limbal autograft; allografts can be from living related donors (lr-CLAL) or from a cadaveric donor (KLAL).

The donor limbus can be of limbal origin (CLET) or mucosal origin (COMET).

The donor epithelium can be of limbal origin (CLET) or mucosal origin (COMET).

Replaces only the epithelial layer with donor tissue and with amenotic membrane transplantation as adjunctive treatment.

### Indications for corneal transplantation and for technique selection

| Ocular surface disorders || NA | NA | NA | Yes |
| Corneal ectasias*** || Yes | Yes | NA | NA |
| Primary and acquired stromal disorders†† || Yes | Yes | NA | Combined with PK or DALK when there is limbal stem cell deficiency (eg, after chemical burns or in aniridia) |
| Endothelial disorders†† || Yes | NA | Yes | NA |
| Late endothelial failure§§ || Yes | NA | Yes | NA |
| Immunological disorders¶¶ || Yes (when central and associated with corneal perforation) | Yes | NA | NA |
| Therapeutic (usually carried out to treat infection) || Yes | Yes | NA | NA |

None of these procedures are effective in severely dry eyes. PK=penetrating keratoplasty. LK=lamellar keratoplasty. ALK=anterior lamellar keratoplasty. EK=endothelial keratoplasty. DALK=deep anterior lamellar keratoplasty. FLAK=femtosecond laser-assisted keratoplasty. MCLAL=lying related conjunctival limbal allograft. KLAL=cadaver-donor keratolimbal allograft. CLET=cultivated limbal epithelial transplantation. COMET=cultivated oral mucosal epithelial transplantation. NA=not appropriate. **Femtosecond laser-assisted keratoplasty. ††Pre-Descemetic DALK; more than 75% of the stroma is removed; in descemetic DALK, all the stroma is removed. §§Descemet’s stripping automated endothelial keratoplasty. ¶¶Corneal ectasias: commonly keratoconus, post-lasik corneal ectasia, keratoglobus, and pellucid marginal degeneration. ††Primary and acquired stromal disorders: corneal stromal dystrophies (eg, lattice, granular and macular), post-infectious scars (after herpes simplex virus, bacterial, fungal, and Acanthamoeba keratitis), post-traumatic scars. ††Endothelial disorders: commonly Fuch’s corneal dystrophy, pseudophakic and aphakic bullous keratopathy. §§Late endothelial failure follows acute or recurrent transplant rejection episodes or endothelial cell loss unrelated to rejection. ¶¶Immunological disorders: commonly associated with rheumatoid arthritis and Mooren’s ulcer.

![Table 1: Keratoplasty techniques, indications, and technique selection](http://www.thelancet.com)
when lost because of trauma or disease. When cell numbers fall below the critical level needed to maintain normal corneal hydration corneal oedema can occur. In penetrating keratoplasty, all five layers of the cornea are transplanted, whereas in anterior lamellar keratoplasty, varying amounts of the stroma are replaced, retaining Descemet’s membrane and the endothelium (figure 1). Endothelial keratoplasty replace the endothelium (table 1, figure 1) for disorders with endothelial cell dysfunction, of which Descemet’s stripping automated endothelial keratoplasty (DSEA)K is the most widely used (figures 1 and 2). The growth of endothelial keratoplasty in the USA has been exponential: in 2010, 44.9% of corneal transplantations were endothelial keratoplasties compared with only 4.5% in 2005. The frequency of anterior lamellar keratoplasty, however, is still considerably lower than that of penetrating keratoplasty, especially in USA. In the UK, selective lamellar keratoplasty (either endothelial keratoplasty or anterior lamellar keratoplasty) is now the procedure of choice by specialist surgeons for the most common UK optical indications for keratoplasty: keratoconus, Fuchs’ endothelial dystrophy, aphakic, and pseudophakic bullous keratopathy.

Penetrating keratoplasty

The development of new anterior lamellar keratoplasty and endothelial keratoplasty techniques has delivered visual outcomes that are equivalent, or better, than those for penetrating keratoplasty, usually with reduced risks of complications for both anterior lamellar keratoplasty and endothelial keratoplasty (table 3). This has resulted in the rapid uptake of lamellar keratoplasty techniques as described above. Despite the rapid adoption of these newer procedures, however, penetrating keratoplasty (figure 2A) is probably still the most common keratoplasty procedure worldwide.

In specialist centres, penetrating keratoplasty is limited to use in diseases where the benefit, compared with lamellar keratoplasty, of replacing all the diseased tissue, will provide the best optical or therapeutic result. Tables 1–3 compare penetrating keratoplasty with anterior lamellar keratoplasty and endothelial keratoplasty for common indications, advantages and disadvantages, and complications. For the treatment of deep stromal scars in the absence of inflammation (eg, after corneal hydrops in keratoconus, trauma, and severe infection), penetrating keratoplasty can provide good outcomes. Penetrating keratoplasty remains the dominant technique for the management of deep-seated corneal infection such as fungal keratitis unresponsive to medical therapy. However, deep anterior lamellar keratoplasty (DALK) can be used in selected cases having the benefit of a reduced risk of rejection compared with penetrating keratoplasty.

Transplant survival and corneal transplant registries

Data of corneal transplant survival, the identification of preoperative and postoperative risk factors, and the effect of transplantation techniques on survival, have been derived largely from corneal transplantation registries and pertain mainly to penetrating keratoplasty surgery because of the short follow-up available with selective lamellar keratoplasty techniques to date. Large single-centre case series also have value in that they can give more detail than it is practical for registries to collect. Registry data have shown us that penetrating keratoplasty surgery outcomes are dependent on the indication for surgery, and are best for keratoconus. 10-year graft survival is 89% for keratoconus, 73% for Fuchs’ corneal dystrophy, 70% for non-herpetic corneal scars, 60% for herpetic corneal scars, 40% for pseudophakic and aphakic corneal oedema, and 37% for regrafts.

These studies have shown us that penetrating keratoplasty survival depends on various factors, many of which are not fully understood, which affect donor endothelial cell survival, with donor corneal endothelial cell loss being the most common cause of transplant failure (table 3). Additionally to endothelial failure due to immune rejection, donor corneal endothelial cell loss is progressive for 10 years after penetrating keratoplasty surgery, in the absence of rejection, and this is an

<table>
<thead>
<tr>
<th>PK</th>
<th>ALK compared with PK</th>
<th>EK compared with PK</th>
<th>Boston keratoprosthesis compared with PK, ALK, and EK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Can be used for any indication (stromal and or endothelial disease) instead of DALK or PK. Potentially the best optical result since no lamellar corneal interface problems exist. Relatively undemanding technique.</td>
<td>Extraocular procedure resulting in a low risk of many complications, including transplant rejection and failure (table 3). Less topical steroid use than PK or EK. Early suture removal safe.</td>
<td>Can be used for any indication. No induced astigmatism resulting in early visual recovery and better visual outcomes. Fewer suture and wound related complications. Lower risk of other complications (table 3).</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Increased risks of many complications compared with lamellar techniques (table 3). Regular and irregular astigmatism common.</td>
<td>Usually more technically demanding than PK. Fails unless host endothelium is healthy. Regular and irregular astigmatism the same as for PK.</td>
<td>The highest risk procedure of all. Retroprosthetic membrane, glaucoma, device dehiscence, corneal melt, endophthalmitis, and retinal detachment all relatively common. More intensive lifelong therapy required than for other procedures.</td>
</tr>
</tbody>
</table>

Table 2: Comparison of the advantages and disadvantages of the different keratoplasty techniques.
additional and common cause of late failure such that after 20 years follow-up, the failure rate for keratoconus increases to more than 50%, similar to that for all other indications for penetrating keratoplasty. This has been one of the findings driving the transition from penetrating keratoplasty to anterior lamellar keratoplasty for stromal disease; because in anterior lamellar keratoplasty, host endothelial cells are retained and relatively unaffected in both the short-term and long-term after the procedure (table 3), leading to the expectation that future registry studies will show much lower rates of late endothelial failure than are currently seen after penetrating keratoplasty. The other major cause of transplant failure is recurrence of the original disease in the transplant, which occurs commonly in patients who have corneal transplantations in the setting of ocular surface diseases, or for the management of infection such as herpes and fungal keratitis. It occurs in

<table>
<thead>
<tr>
<th>Complications</th>
<th>PK</th>
<th>ALK</th>
<th>EK</th>
<th>Ocular surface reconstruction</th>
<th>Boston keratoprosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial failure, retroprosthetic, and retrocorneal corneal membranes</td>
<td>The major cause of transplant failure. Multifactorial with principal determinants being the loss of 30–40% of donor endothelial cells at the time of surgery, followed by progressive loss of donor endothelial cells for 10 years after surgery. Exacerbated by glaucoma and transplant rejection. Up to half of cases of endothelial failure have fibrous retrocorneal membranes</td>
<td>Rarely a problem because loss of host endothelial cells is limited to 8–15% during surgery, and probably no further postoperative accelerated cell loss occurs</td>
<td>As for PK, the major cause of transplant failure. Endothelial cell loss probably higher than for PK at the time of surgery, but similar to PK by 12 months after surgery in most studies. Long-term endothelial cell loss rates and failure rates are yet to be established for EK, but could be reduced compared with PK. Exacerbated by transplant rejection as for PK. Probably exacerbated by glaucoma. Fibrous retrocorneal membranes are reported in failed grafts as for PK</td>
<td>NA</td>
<td>Endothelial failure cannot occur but retroprosthetic membranes are reported in 25–65% of case series, can substantially impair vision, and may be difficult to treat. Whereas in PK and EK retrocorneal membranes are associated with endothelial failure but probably do not cause it</td>
</tr>
<tr>
<td>Transplant rejection</td>
<td>Acute endothelial rejection: 20% by 5 years. Epithelial rejection functionally insignificant and stromal rejection difficult to identify as a separate entity from endothelial rejection</td>
<td>No risk of endothelial rejection. Stromal rejection in 1–2% usually functionally insignificant</td>
<td>Endothelial rejection rates probably similar to PK rates</td>
<td>A major problem for limbal stem-cell allografts (lr-CLAL and KLAL) as well as CLET such that systemic immunosuppression is recommended by all authors although the regimens do not have a firm evidence base</td>
<td>The donor might reject but this is rarely a clinical problem</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>PK and ALK astigmatism similar. Mean regular astigmatism 4-5 D about 10% of cases requires surgery. Irregular astigmatism occurs in 15–50% of keratoconus patients can be corrected by rigid contact lenses but not spectacles</td>
<td>PK and ALK astigmatism similar. Mean regular astigmatism 4-5 D about 10% of cases requires surgery. Irregular astigmatism occurs in 15–50% of keratoconus patients can be corrected by rigid contact lenses but not spectacles</td>
<td>Surgically induced regular and irregular astigmatism insignificant</td>
<td>A problem related to the shape of the underlying stroma, but not procedure related</td>
<td>Eliminated by the prosthesis</td>
</tr>
<tr>
<td>Surgical complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choroidal haemorrhage</td>
<td>About 1:200 or less per-operatively and occurs late as the result of minor trauma. Blindness commonly results</td>
<td>Unreported during surgery and possibly reduced late risks compared with PK</td>
<td>One reported per-operative case only. Unlikely occur late because of small incision size</td>
<td>Unreported and unlikely to occur</td>
<td>Unreported but potentially a problem</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>1:500</td>
<td>Rare</td>
<td>Rates currently unreported but likely to be similar to those for other small incision intraocular procedures (eg, cataract surgical rates at about 1:1200)</td>
<td>Unreported and unlikely to occur</td>
<td>Late endophthalmitis a problem in 0–12.5% of cases</td>
</tr>
<tr>
<td>Epithelial downgrowth</td>
<td>Rare</td>
<td>Very unlikely to occur</td>
<td>Unlikely to occur</td>
<td>NA</td>
<td>A few retroprosthetic membranes have been of epithelial origin</td>
</tr>
<tr>
<td>Wound leaks</td>
<td>Can occur</td>
<td>Rare</td>
<td>Associated with pupil block following air tamponade</td>
<td>Uncommon</td>
<td>Can occur</td>
</tr>
<tr>
<td>Urrets-Zavalia syndrome*</td>
<td>Can occur</td>
<td>Can occur</td>
<td>Associated with pupil block following air tamponade</td>
<td>NA</td>
<td>Can occur</td>
</tr>
<tr>
<td>Transplant dehiscence or detachment</td>
<td>1–2%. Can require resuturing</td>
<td>1–2%. Can require resuturing</td>
<td>Detachment of the posterior lamellar in 5–30% of cases. Most reports are less than 10%. Can be re-attached by re-injecting air</td>
<td>Can occur</td>
<td>Can occur</td>
</tr>
</tbody>
</table>

(Continues on next page)
about 5% of keratoconus cases, is relatively common in the stromal dystrophies, but does not occur in Fuchs' corneal endothelial dystrophy.

**Anterior lamellar keratoplasty**

The major advantage of anterior lamellar keratoplasty surgery results from the retention of unaffected healthy endothelium while replacing epithelium and corneal stroma (table 1), thereby eliminating endothelial allograft rejection, the major cause of graft failure affecting penetrating keratoplasty (table 3). The surgical challenge of anterior lamellar keratoplasty surgery is the technical difficulty inherent in separating the anterior stromal layers from Descemet's membrane and endothelium: currently the techniques are manual, and difficult to do, which has limited their widespread adoption. Descemet's corneal replacement (figure 1D) removes the entire corneal stroma with little damage to the host

![Table 3: Complications of keratoplasty techniques](image-url)
endothelium, avoids the stroma-to-stroma interface, which might reduce the vision in both traditional anterior lamellar keratoplasty and predescemetic DALK (figure 1C, table 1), and is most widely done with Anwar’s “Big Bubble” technique, in which a deep stromal air injection separates Descemet’s membrane from the stroma by the formation of a big air bubble between the two layers.

Complications of anterior lamellar keratoplasty compared with penetrating keratoplasty

Tables 2 and 3 summarise the advantages, disadvantages, and complications, of penetrating keratoplasty compared with anterior lamellar keratoplasty; among the most important advantages is the fact that the late corneal failure, due to endothelial cell loss, which is common after penetrating keratoplasty, is not anticipated after anterior lamellar keratoplasty.7

Complications unique to DALK surgery

These complications are related to the inherent difficulty in separating Descemet’s membrane from the stroma. Complications include microperforations of Descemet’s membrane (in which the DALK can still be done), macroperforations or larger splits in Descemet’s membrane (in which conversion to penetrating keratoplasty is usually necessary), a double anterior chamber postoperatively due to separation of the donor from host Descemet’s membrane, and interface irregularities (if total stromal removal is not achieved [as in predescemetic DALK]). Intraoperative perforation rates vary from 4% to 39% in five series, whereas conversion rates to penetrating keratoplasty have been reported to range from 0% to 14% in four series.7

Endothelial keratoplasty

Endothelial keratoplasty (figures 1 and 2) has replaced penetrating keratoplasty as the preferred technique for treating endothelial disease. Modern endothelial keratoplasty techniques involve stripping Descemet’s membrane and endothelium from the recipient stroma, and the donor tissue is then attached without sutures by use of air tamponade. These procedures are described in table 1 and are known as Descemet’s stripping with endothelial keratoplasty (DSEK and DSAEK) (figures 1 and 2). Newer variations to endothelial keratoplasty surgery include Descemet’s membrane endothelial keratoplasty (DMEK) and Descemet’s membrane automated endothelial keratoplasty (DMAEK; table 1, figure 1), where only Descemet’s membrane and endothelium are transplanted, compared with the additional thin strip of stroma in DSAEK or DSEK.

Comparisons between endothelial keratoplasty and penetrating keratoplasty

Tables 2 and 3 summarise the advantages and disadvantages of the two techniques. For most surgeons the predictability and rapidity of visual rehabilitation with endothelial keratoplasty is what has driven the rapid uptake of this technique. This faster visual rehabilitation is due to the elimination of astigmatism after penetrating keratoplasty, which accounts for the extended rehabilitation time after penetrating keratoplasty. By contrast, the most common endothelial keratoplasty complications, which include graft dislocations requiring rebubbling, endothelial graft rejection, primary graft failure, and
iatrogenic glaucoma, do not impede patients’ vision recovery.6,23 The main complication of endothelial keratoplasty surgery is the unpredictability of donor lamellar adhesion resulting in variable rates of dislocation, ranging from up to 50% in the earliest cases of endothelial keratoplasty surgery, to as low as 4% after modifications to insertion technique and overcoming the initial learning curve.24 The benchmark for experienced surgeons should be a dislocation rate of less than 10% and a primary graft failure rate of less than 1%.24 From an economic standpoint, cost-utility analysis has shown endothelial keratoplasty to be less costly than penetrating keratoplasty.25

**Challenges and future trends in endothelial keratoplasty surgery**

Further development of endothelial keratoplasty surgery is driven by the desire for better visual results. Limitations to achieving 20/20 vision after DSAEK include induced astigmatism from the incision, subepithelial haze,26 hyperopic shift caused by transplanted stroma,27 and any mismatch between the donor and host corneal curvatures, which can be accentuated when thicker grafts are transplanted. Advocates of DMEK and DMAEK claim that more patients achieve vision in the 20/15 to 20/25 range with these procedures than with DSAEK.28 However, donor preparation is time consuming and challenging, and unfolding the extremely thin tissue into the right orientation is difficult leading to higher rates of graft dislocation, with one prospective study by experienced surgeons reporting a reattachment rate of 25%.29 As an alternative, some surgeons advocate cutting thinner DSAEK grafts that might achieve similar visual outcomes to DMEK but with the benefits of greater ease of preparation and handling, and a lower rate of dislocation.30

Endothelial cell loss is an issue in both endothelial keratoplasty and penetrating keratoplasty. Endothelial keratoplasty cell loss is greater than for penetrating keratoplasty during the first 6 months, but subsequent cell loss is similar.31 At 5 years, endothelial cell loss is better after endothelial keratoplasty versus penetrating keratoplasty (53% vs 70%).32 Minimising trauma to the donor endothelial cells during tissue insertion through the small incision improves endothelial cell survival. Rather than using forceps to fold and insert the donor cornea tissue, various insertion devices are being studied. Early reports indicate that these inserter might result in lower rates of endothelial cell loss.33

Currently, DSAEK is the predominant form of endothelial keratoplasty. However, if the problems of donor preparation and manipulation with DMEK and DMAEK are solved, these techniques could supplant DSAEK, as the preferred endothelial keratoplasty technique, providing the visual outcomes are confirmed to be better. In the USA, the increased demand for endothelial keratoplasty tissue could lead to future tissue supply problems, which might be alleviated if future developments in tissue technology allow the culture of endothelial cells on a Descemet’s membrane-like substrate.

**Ocular surface transplantation**

The ocular surface consists of two distinct mucosal epithelia—corneal and conjunctival. The presence of corneal epithelial stem cells is very important for maintaining healthy corneal epithelium. Complete destruction of those cells can result from an acute injury such as a chemical burn or Stevens-Johnson syndrome, from chronic damage in ocular cicatricial pemphigoid, or in congenital defects like aniridia.32,33 In such cases, the
corneal surface is covered by the adjacent inflamed conjunctival epithelium with vascularisation and subepithelial fibrosis, resulting in severe visual impairment. In cases in which corneal epithelial stem cells are depleted, surgical reconstruction of the ocular surface is now possible.

The corneal epithelial stem-cell concept
Following the discovery of the centripetal movement of corneal epithelium and the important role of limbal epithelium, the corneal epithelial stem-cell concept was established proving that corneal epithelial stem cells are preferentially located in the limbal basal layer and limbal crypts, yet might also be located in the central cornea.

Evolution of ocular surface rehabilitation
Ocular surface reconstruction procedures, such as autologous conjunctival transplantation for unilateral chemical injury and allogeneic corneal epithelial transplantation (keratoepithelioplasty), were first introduced 30 years ago. Since the development of the corneal epithelial stem cell concept, autologous or allogeneic limbal transplantation has been used for reconstructing damaged ocular surfaces. More recently, ex-vivo cultivated mucosal epithelial transplantation has been described, using both allogeneic and autologous limbal epithelium and autologous oral mucosal epithelium.

Successful ocular surface transplantation depends upon postoperative management of biological and immunological aspects, especially in allogeneic transplantation cases in which the immunological response differs from that of penetrating keratoplasty and lamellar keratoplasty. Nomenclature for the various ocular surface transplantation procedures uses the anatomic source of the transplanted tissue, the donor cell source (autologous or allogeneic), and the cell culture technique. Tables 1 and 3 summarise the different techniques, indications, and complications.

Amniotic membrane transplantation
Kim and Tseng reported the benefit of human amniotic membrane transplantation for ocular surface repair with minimal postoperative fibrosis and inflammation in rabbits. Amniotic membrane transplantation has been used for reconstructing subepithelial extracellular matrices, including the stem cell niche, in patients with recurrent pterygium and severe ocular surface diseases, and as an epithelial carrier for ex-vivo cultivated mucosal epithelial transplantation.

Limbal transplantation
In patients with unilateral limbal stem-cell deficiency, conjunctival limbal autograft (CLAU) from the healthy contralateral eye is the optimum procedure. Outcomes are excellent since rejection is not an issue. In severe bilateral ocular surface disease, allogeneic tissue can come from either a living-related conjunctival limbal allograft (lr-CLAL) or a cadaver-donor keratolimbal allograft (KLAL). In allogeneic transplantations, oral immunosuppression protocols similar to those used in solid-organ transplantation are essential to prevent rejection. Systemic immunosuppression has been shown to be safe with minimum side-effects in such cases. Reported rates of success for ocular stability vary from as low as 33·3% with inadequate immunosuppression to as high as 77·2% with appropriate immunosuppression protocols. In a review of surgical interventions for limbal stem cell deficiency, the most common procedure done for unilateral limbal stem cell deficiency (LSCD) was CLAU, and that for bilateral LSCD was KLAL.

Cultivated mucosal epithelial transplantation
The efficacy of cultivated limbal epithelial transplantation using ex-vivo expansion of autologous corneal epithelial stem cells has been reported in unilateral disease cases. In this procedure, fibrin glue, amniotic membrane, or a contact lens are used as an epithelial carrier to transplant an epithelial sheet. In bilateral cases, where no source of healthy limbus is available, an allogeneic source from fresh donor corneoscleral tissue can be used. However, allogeneic cultivated limbal epithelial transplantation results vary substantially because of acute and chronic allogeneic rejection, and intensive immunosuppressive therapy is essential. An alternative procedure for bilateral cases is autologous cultivated oral mucosal epithelial transplantation. Although long-term results of cultivated oral mucosal epithelial transplantation show significant inhibition of postoperative conjunctivalisation and symblepharon, varying degrees of corneal neovascularisation occur postoperatively. Further advances in this area will hopefully yield better long-term results.

High-risk keratoplasty
Some corneal transplantations are at high risk of failure because of loss of clarity, loss of refractive quality, failure to epithelialise leading to ulceration and loss of stromal tissue, and tissue degradation secondary to severe inflammation. These events result either from the adverse effects of the underlying disease or from immunological rejection. Risks are increased in patients with surface disease or having transplants for therapeutic (for corneal disease that is not optical) and tectonic (for corneal perforations or thinning) indications. Common therapeutic indications are for infection unresponsive to medical therapy, typically fungal keratitis, pain relief in patients with bullous keratopathy, and to heal ulcers. Tectonic transplantations are used to repair perforated globes in inflammatory disease (such as rheumatoid arthritis and Mooren’s ulcer), for perforations following infections and trauma, and for corneal thinning disorders such as Terrien’s marginal degeneration. These situations are often associated with severe corneal and ocular
surface inflammation, dry eye, and lid position disorders, all of which have to be corrected or carefully managed to achieve a successful outcome; any improvement in vision is a secondary outcome and late optical keratoplasty is often needed.

**Transplant failure due to adverse effects of the underlying disease**

Causes are many and include recurrence of infection in therapeutic transplants (typically for fungal and herpes simplex virus keratitis), failure to heal in anaesthetic corneas (most commonly after herpes zoster ophthalmicus) and in eyes with corneal epithelial stem-cell failure (eg, chemical injuries). Epithelial defects and secondary ulceration, often complicated by infection, are common in transplantations in the setting of allergic eye disease, dry eye, rheumatoid arthritis, Stevens-Johnson syndrome, and ocular pemphigoid.

**Immunological rejection**

Corneal immunological privilege allows corneal transplantations to remain rejection free, with the use of prophylaxis, in about 80% of low-risk transplantations such as those for keratoconus. Corneal transplant rejection can affect the corneal epithelium and stroma, at which sites there are usually minor consequences for vision, because rejection is invariably reversible with topical steroids. However, acute corneal endothelial rejection results in rapid and permanent loss of endothelial cells and precipitates either immediate, or earlier than usual, corneal transplant failure. This occurs because of loss of corneal endothelial pump function. This function is dependent on having adequate numbers of corneal endothelial cells (usually about 2500 per mm²). These cells are terminally differentiated and unable to replicate such that loss of these, to levels of about 500 per mm², results in graft oedema and resultant loss of graft clarity.

**Clinical situations increasing the risk of endothelial rejection**

Registry data has shown that this occurs when transplantations including donor endothelium are done in presence of recent corneal inflammation, when the host corneal stromal is vascularised, and when there has been a history of previously rejected corneal transplant. These situations increase the risk of rejection to about 50% at 5 years.

**Corneal transplant rejection prophylaxis**

The value of tissue matching in the prophylaxis of corneal transplant rejection remains controversial and its role is uncertain. Topical steroids have been the mainstay of rejection prophylaxis and the common side-effects of cataract and glaucoma can generally be effectively managed by cataract surgery and glaucoma treatment; recently, extended use of topical steroids has been shown to reduce rejection risk and improve outcomes. Topical ciclosporin, added to topical steroid, has been ineffective in rejection prophylaxis regimens in several studies including randomised clinical trials. When topical steroids have been shown to be inadequate in rejection prophylaxis, systemic immunosuppressive therapy has been used. Systemic ciclosporin, successful in an early study, has now been shown to be ineffective in several subsequent studies including a randomised controlled trial. Success with tacrolimus monotherapy and sirolimus and mycophenolate combination therapy has been reported in small case series. One randomised trial of mycophenolate monotherapy has shown an effect. However, there is little high quality evidence supporting the use of any systemic immunosuppressive regimen and no consensus regarding either the value of systemic immunosuppression, or the optimum therapy for this.

**Artificial cornea (keratoprosthesis) as an alternative to corneal transplantation**

**Keratoprosthesis designs**

In cases of multiple failed corneal transplants or ocular surface disease for which corneal transplants are likely to fail, artificial corneas or keratoprostheses have an important role. Several keratoprosthesis devices have been described such as the osteo-odonto keratoprosthesis (OOKP), the AlphaCor, the Boston keratoprosthesis. The Boston type 1 keratoprosthesis (both aphakic and pseudophakic versions) consists of front and back plastic (polymethylmethacrylate) plates supported by a donor corneal transplant. The Boston type 2 keratoprosthesis is similar to the type 1 with the addition of a 2-mm anterior nub, which penetrates through a closed eyelid. The OOKP is done only at a few centres worldwide and consists of complex multistep surgeries using the patient’s tooth to carry an optical cylinder. Both the OOKP and Boston type 2 keratoprosthesis are used as last resort options for patients with endstage ocular surface disease in whom conventional corneal surgery is known to fail. The AlphaCor is now rarely used because of complications. The following discussion will focus on the Boston type 1 keratoprosthesis, which is the most widely used and viable alternative to conventional corneal transplantation.

**Indications**

Indications for keratoprosthesis implantation can be divided into three categories: corneas at high risk for immunological rejection after penetrating keratoplasty; corneas with factors that might predispose them to endothelial failure after penetrating keratoplasty such as a tube shunt or hypotony, and eyes with ocular surface failure and limbal stem-cell deficiency. Use of the Boston type 1 keratoprosthesis has been reported for many indications including: corneal scarring after herpes zoster or herpes simplex keratitis, paediatric corneal opacities, ocular trauma, aniridia, and failed penetrating keratoplasty in eyes with pseudophakic bullous keratopathy,
iridocorneal endothelial syndrome, keratoconus, corneal dystrophies, trauma, toxic effects of medication [A: ok?], atopic keratoconjunctivitis, and tumour. Patients with autoimmune ocular disorders (eg, Stevens-Johnson syndrome, ocular cicatricial pemphigoid) are poor candidates for penetrating keratoplasty because of continuous ocular surface inflammation and limbal stem-cell deficiency but also have the least favourable prognosis with keratoprosthesis surgery because of a high incidence of tissue melt.

Outcomes
Although rapid visual recovery can be achieved after implantation of Boston type 1 keratoprosthesis, long-term visual prognosis is limited by glaucoma and other complications. The appendix lists reported retention rates and complications. The use of postoperative topical vancomycin and a fluoroquinolone has substantially reduced the rates of endophthalmitis, although gram-negative and fungal infections are becoming a concern.

Keratoprosthesis surgery is a viable option, with good short-term visual outcomes, for salvaging vision in eyes at a high risk of graft failure. Good medium-term outcomes are achievable in patients with life-long close follow-up with a multidisciplinary team of glaucoma, retina, and corneal surgeons to manage the various complications that might arise.

Future developments
Three developments that have the potential to result in major changes in surgery for corneal disease are the use of the surgical femtosecond laser, the artificial or bioengineered cornea, and the manipulation of corneal endothelial cells as an alternative to transplantation.

Femtosecond lasers for corneal transplantation surgery
Ophthalmic femtosecond lasers are currently used to do surgical corneal flap dissections in laser-assisted in-situ keratomileusis (LASIK) surgery for the correction of refractive errors. These femtosecond surgical lasers are able to create precise vertical, horizontal, and oblique cuts in the cornea with minimum damage to adjacent corneal tissues and are being used to do precise corneal trephination for donor and recipients. These techniques have been termed femtosecond-laser-assisted keratoplasty (FLAK). It is possible that femtosecond lasers will eventually replace the manual and semi-automated corneal cutting that is required for corneal transplantation surgery resulting in better visual and tectonic outcomes.

Bioengineered corneas
Biosynthetic corneas have recently been used as an anterior lamellar corneal transplant. In the future, bioengineered corneas could ultimately prove to be substitutes for the plastic artificial corneas currently used in keratoprosthesis surgery.

Cultured human corneal endothelial cells for corneal endothelial repair
Because of our inability to medically propagate corneal endothelial cells and increase cell density, corneal transplantation procedures (penetrating keratoplasty and endothelial keratoplasty) are currently the only treatment for corneal endothelial damage or dysfunction. Spurred by a worldwide shortage of donor corneas, coupled with improved understanding of the cell-cycle activation pathways of endothelial cells in vitro, some progress has been made in human corneal endothelial cell culture and cultured corneal endothelial cells have been transplanted with some success in experimental settings. Thus, the use of these cultured cells, either as a monolayer or by injection of the cells into the anterior chamber, is likely to become a reality for clinical applications in the near future.
Gene therapy for corneal endothelial regeneration

Gene transfer into corneal endothelial cells, with adenoviral or lentiviral vectors, either to decrease allogeneic endothelial rejection, or to extend donor corneal storage periods, has had some success in animal experiments.17,18 The success of future clinical trials will also depend on clinical safety and ethics issues.

Medical treatments for corneal endothelial dysfunction

The topical application of various agents has been investigated as treatments for corneal endothelial cell dysfunction, by the promotion of corneal endothelial cell proliferation and migration, in experimental models of the disorder. These treatments have included release of cell-cell contact inhibition with EDTA,19 knockdown of connexin43 by siRNA, and inhibition of Rho-associated protein kinase (ROCK) with Y-27632.20 Of these, ROCK-inhibitor eye-drop treatment seems to be the most promising and is currently used in human clinical trials.

These developments promise medical treatment for what have previously been conditions that could only be treated by surgery.

Conclusion

In the field of corneal transplantation, conventional penetrating keratoplasty procedures are being rapidly replaced by newer forms of selective lamellar keratoplasty, such as endothelial keratoplasty and deep anterior lamellar keratoplasty, which provide improved visual outcomes, higher graft survival rates, and less postoperative complications. Further developments in artificial cornea technology, stem-cell transplants, and corneal endothelial therapies are on the horizon in this rapidly evolving ophthalmic subspecialty.

Contributors

DT devised the overall design and concept of the article, wrote the introduction and anterior lamellar keratoplasty sections, provided figure 1, and edited all other contributors’ sections and the overall manuscript. ED contributed to the endothelial keratoplasty and artificial cornea sections, and provided all other images. SK contributed to the ocular surface transplantation and future developments sections.

Conflicts of interest

JKGD, EJH, and SK declare that they have no conflicts of interest with regards to this manuscript. DHT has filed a patent for the Tan EndoClide device for use in Descemets Stripping Automated Endothelial Keratoplasty and receives royalty payments from Network Medical Products, North Yorkshire, UK. The other authors declare that they have no conflicts of interest.

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Age-related macular degeneration is a major cause of blindness worldwide. With ageing populations in many countries, more than 20% might have the disorder. Advanced age-related macular degeneration, including neovascular age-related macular degeneration (wet) and geographic atrophy (late dry), is associated with substantial, progressive visual impairment. Major risk factors include cigarette smoking, nutritional factors, cardiovascular diseases, and genetic markers, including genes regulating complement, lipid, angiogenic, and extracellular matrix pathways. Some studies have suggested a declining prevalence of age-related macular degeneration, perhaps due to reduced exposure to modifiable risk factors. Accurate diagnosis combines clinical examination and investigations, including retinal photography, angiography, and optical coherence tomography. Dietary anti-oxidant supplementation slows progression of the disease. Treatment for neovascular age-related macular degeneration incorporates intraocular injections of anti-VEGF agents, occasionally combined with other modalities. Evidence suggests that two commonly used anti-VEGF therapies, ranibizumab and bevacizumab, have similar efficacy, but possible differences in systemic safety are difficult to assess. Future treatments include inhibition of other angiogenic factors, and regenerative and topical therapies.

Introduction

Age-related macular degeneration is a progressive chronic disease of the central retina and a leading cause of vision loss worldwide. Most visual loss occurs in the late stages of the disease due to one of two processes: neovascular (“wet”) age-related macular degeneration and geographic atrophy (“late dry”). In neovascular age-related macular degeneration, choroidal neovascularisation breaks through to the neural retina, leaking fluid, lipids, and blood, and leading to fibrous scarring. In geographic atrophy, progressive atrophy of the retinal pigment epithelium, choriocapillaris, and photoreceptors occurs. Most severe visual loss from age-related macular degeneration is caused by the these advanced forms of the disease.

A decade ago, age-related macular degeneration was largely untreatable. However, new pharmaceuticals based on suppression of vascular endothelial growth factor (VEGF) have substantially changed the management of the disease. In 2006, landmark clinical trials showed that monthly intravitreal injections of ranibizumab (Lucentis, Genentech/Novartis) prevented vision loss in nearly 95% of patients, and significantly improved vision in 40%. Recent population-based data have shown that legal blindness attributable to age-related macular degeneration has been reduced by 50% in some countries since the introduction of VEGF antagonists. Another drug, bevacizumab (Avastin, Genentech), originally developed for systemic treatment of colon cancer and related to the parent ranibizumab molecule, is now widely used as an off-label alternative. Intravitreal bevacizumab is popular because its efficacy seems to be similar to that of ranibizumab but is substantially cheaper. In 2011, an important head-to-head trial showed that bevacizumab and ranibizumab have equivalent efficacy over a 1-year period. In addition to treatment, major advances have been made in understanding the epidemiology, risk factors, and genetics of age-related macular degeneration.

Epidemiology, risk factors, and natural history

Prevalence and incidence

There have been many epidemiological studies on age-related macular degeneration in the past 30 years. In a meta-analysis of population-based studies in white people aged 40 years and older, the prevalence of early age-related macular degeneration was estimated to be 2.0% and late age-related macular degeneration 1.5%.

Epidemiological data in other ethnic groups have been reported. Results from the Baltimore Eye Study showed that late age-related macular degeneration was nine to ten times more prevalent in white participants than in black ones. However, an Asian meta-analysis showed that the age-specific prevalence of late age-related macular degeneration in Asians was largely similar to that in white people.

There is emerging evidence that many Asian patients with neovascular age-related macular degeneration have polypoidal dilatation of the choroidal vasculature, a
variant termed polypoidal choroidal vasculopathy. Polypoidal choroidal vasculopathy can account for 50% of neovascular age-related macular degeneration cases in Asians, but only 8–13% in white people.8 Another variant of age-related macular degeneration is retinal angiomatosus proliferation, which accounts for 12–15% of neovascular age-related macular degeneration.9 These variants might not respond as well to standard management of neovascular age-related macular degeneration (see below).

There are few incidence studies on age-related macular degeneration. The US Beaver Dam Eye Study in the USA reported a 14-3% 15-year cumulative incidence for early age-related macular degeneration and 3-1% for late age-related macular degeneration in adults aged 43–86 years.11 Similar findings were seen from an Australian study in adults aged 49 years or older.12 The Los Angeles Latino Eye Study13 reported a 4-year incidence of age-related macular degeneration of 2.5% in Hispanics aged 40 years and older.14 In Asia, a Japanese study,15 also in adults aged 40 years and older, reported 9-year cumulative incidence of 10.0% for early age-related macular degeneration and 1.4% for late age-related macular degeneration.

Risk factors
Panel 1 summarises the risk factors for age-related macular degeneration. Older age is the major risk factor for age-related macular degeneration, with more than 10% of people older than 80 years having late age-related macular degeneration.4 Female sex has been consistently reported as a risk factor as well.6

Ocular risk factors for age-related macular degeneration include darker iris pigmentation,7 previous cataract surgery,8 and hyperopic refraction.7 A meta-analysis9 suggested previous cataract surgery was a strong risk factor for age-related macular degeneration,10 but this association was not shown in a randomised clinical trial.10

Systemic risk factors include cigarette smoking,10 obesity,10 sunlight exposure,21 and cardiovascular diseases. Cigarette smoking in particular is a strong and consistent risk factor for age-related macular degeneration.15 Cardiovascular risk factors (eg, hypertension) have been linked with the disorder.15,12,22,23 People with age-related macular degeneration are also at increased risk of cardiovascular disease and stroke.15

Natural history and economic impact
Over 5 years, up to 5% of patients with early age-related macular degeneration can progress to late age-related macular degeneration, increasing to nearly 15% over 15 years.10,16 In untreated neovascular age-related macular degeneration, visual loss is progressive, with 1–3 lines of visual acuity lost on the LogMAR chart (similar to the Snellen chart but more precise at lower visual acuity levels) at 3 months and 3–4 lines by 1 year.17 A 3-line loss of acuity corresponds to halving of the eye’s angular resolution, which means a symbol would need to be twice as large to be read. The Verteporfin in Photodynamic Therapy (VIP) trial24 reported a mean loss of 5 LogMAR lines by 24 months in its control group. Visual impairment from late age-related macular degeneration can also lead to significant functional loss, reduced quality of life, and depression, which are often underestimated. By contrast, early age-related macular degeneration has less impact,7 emphasising the need for early detection and prevention.

The economic costs associated with visual impairment are substantial. Analyses of US medical claims data have estimated the total annual direct cost of age-related macular degeneration to be US$575–733 million.28

Genetics and pathogenesis
Genetics
For several years there has been strong evidence for genetic influences on the development of age-related macular degeneration, supported by familial aggregation, segregation, linkage, and twin studies (appendix). Since 2005, several genetic loci have been associated with age-related macular degeneration, including two major loci in the complement factor H (CFH) gene on 1q32 and the ARMS2/HTRA1 locus on the 10q26 gene cluster (see appendix). Other confirmed genes in the complement pathway include C2, CFB, C3 and CFI.29–31

Panel 1: Risk factors for age-related macular degeneration

<table>
<thead>
<tr>
<th>Environmental and behavioural factors</th>
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<tr>
<td>• Cigarette smoking</td>
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<td>• Obesity</td>
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<td>• Low dietary intake of vitamins A, C, and E, and zinc</td>
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<tr>
<td>• Low dietary intake of lutein and omega-3 fatty acids</td>
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<tr>
<td>• Unhealthy lifestyle related to cardiovascular risk factors</td>
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<table>
<thead>
<tr>
<th>Genetic</th>
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<tbody>
<tr>
<td>• CFH (complement factor H; chr 1)</td>
</tr>
<tr>
<td>• ABCA4 (ATP-binding cassette transporter; chr 1)</td>
</tr>
<tr>
<td>• COLB1A1 (collagen type B alpha 1 subunit; chr 3)</td>
</tr>
<tr>
<td>• CF1 (complement factor 1; chr 4)</td>
</tr>
<tr>
<td>• VEGFA (vascular endothelial growth factor A; chr 6)</td>
</tr>
<tr>
<td>• FRK/COL10A1 (fyn-related kinase/alpha chain of type X collagen; chr 6)</td>
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<tr>
<td>• CFB (complement factor B [properdin]; chr 6)</td>
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<tr>
<td>• C2 (complement component 2; chr 6)</td>
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<tr>
<td>• ARMS2/HTRA1 (HtrA-serinepeptidase1; chr 10)</td>
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<td>• LIPC (hepatic lipase; chr 15)</td>
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<td>• CETP (cholesterylester transfer protein; chr 16)</td>
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<td>• APOE (apolipoprotein E; chr 19)</td>
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<td>• C3 (complement component 3; chr 19)</td>
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<td>• TIMP3 (tissue inhibitor of metalloproteinase 3; chr 22)</td>
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<td>• TNFRSF10A (tumour necrosis factor receptor superfamily 10a; chr 8)</td>
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<tr>
<th>Other</th>
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<td>• Hyperopic refraction</td>
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See Online for appendix
In summary, genes influencing several biological pathways are related to age-related macular degeneration. Complement and immune processes, HDL cholesterol, and mechanisms involving collagen, extra-cellular matrix, and angiogenesis pathways are associated with the onset, progression, and bilateral involvement of early, intermediate, and advanced states of age-related macular degeneration. Genetic susceptibility can be modified by environmental factors and together these factors are highly predictive of onset and progression. Genetic variations can also influence differential responses to treatments for age-related macular degeneration, an emerging research area.

Pathogenesis

Several biological pathways have been implicated in the pathogenesis of age-related macular degeneration. These include senescence, shown by lipofuscin accumulation in retinal pigment epithelium cells, choroidal ischaemia, and oxidative damage. More recently, attention has been focused on the function of VEGF in light of its role as a therapeutic target. VEGF is a key regulator of angiogenesis, and withdrawal or interference with its function leads to cessation of vascular growth and neovascular regression. VEGF expression has been shown in experimental choroidal neovascularisation, and shown to induce choroidal neovascularisation growth in animals. In man, VEGF exists as four isoforms: VEGF-121, VEGF-165, VEGF-189, and VEGF-206. VEGF-121 has been shown to persist for at least 14 days, whereas VEGF-165 is short-lived. This might explain why pegaptanib, a drug specifically targeting VEGF-165, has been less successful in treating choroidal neovascularisation than ranibizumab or bevacizumab, which target all isoforms. Other candidate molecules have been identified, among which matrix metalloproteinases, endostatin, and pigment epithelium-derived factor, in particular, seem to contribute the most.

The role of VEGF in the pathogenesis of polypoidal choroidal vasculopathy is believed to be substantially less important than in choroidal neovascularisation. VEGF staining is weak in the vascular endothelial cells of polypoidal choroidal vasculopathy, and aqueous VEGF concentrations in patients with polypoidal choroidal vasculopathy might also be lower than those with choroidal neovascularisation. Retinal angiomatous proliferation differs from choroidal neovascularisation in that the vaso-proliferative process is started in the retinal capillaries with intraretinal neovascularisation. In later stages, subretinal neovascularisation occurs and eventually anastomoses with the intraretinal proliferation. Unlike polypoidal choroidal vasculopathy, VEGF is believed to have a key role in the development of retinal angiomatous proliferation.

Clinical features and classification

Patients with early age-related macular degeneration are usually asymptomatic, and present clinically with...
yellowish drusen seen underneath the retinal pigment epithelium, with areas of mottled retinal pigment epithelium hyperpigmentation and hypopigmentation.

Patients usually develop rapid visual loss when neovascular age-related macular degeneration occurs. Typically, patients describe sudden worsening of central vision with distortion of straight lines (metamorphopsia) or a dark patch in their central vision (scotoma), or both. In geographic atrophy, there is slower progressive loss of vision over many years. Clinically, there is a sharply demarcated area of depigmentation showing retinal pigment epithelium atrophy (figure 1). Neovascular age-related macular degeneration is characterised by subretinal or intraretinal fluid and haemorrhage; occasionally, the choroidal neovascularisation complex can be seen clinically (figure 1).

Various age-related macular degeneration classification schemes have been developed. Some of these systems have been shown to be useful for both research and clinical practice. The Age-Related Eye Disease Study (AREDS) classified age-related macular degeneration into four categories (panel 2).

In the AREDS, the 5-year risk of developing advanced age-related macular degeneration in at least one eye in control participants was 1.3% in eyes in category 2, 18.3% in those in category 3, and 43.9% in those in category 4.

Polypoidal choroidal vasculopathy is difficult to distinguish clinically from choroidal neovascularisation. Occasionally, orange, bulging dilatations might be visible under the retina. However, polypoidal choroidal vasculopathy more commonly presents with recurrent serous and haemorrhagic retinal pigment epithelium detachments (figure 2). Retinal angiomatous proliferation is characterised clinically by signs of haemorrhage, oedema, and exudates within the retinal layers in addition to other typical signs of choroidal neovascularisation. In some cases, the anastomosis between the retinal and subretinal new vessels might be visible.

Retinal imaging

Major advances have occurred in retinal imaging for the management of age-related macular degeneration. Traditionally, fundus fluorescein angiography (FFA) is done. It is an invasive investigation in which a yellow dye (fluorescein) is intravenously injected with sequential photographs taken to assess choroidal and retinal blood flow. In neovascular age-related macular degeneration, leakage of dye (hyperfluorescence) into the retinal tissues is noted. This leakage is classified by location (subfoveal, juxtafoveal, or extrafoveal), and by type (classic, occult, or mixed). Classic choroidal neovascularisation represents a lesion that has penetrated the retinal pigment epithelium and thus lies in front of the retinal pigment epithelium, whereas occult choroidal neovascularisation is a neovascular lesion lying under the retinal pigment epithelium. These patterns have implications for both prognosis and treatment, with classic lesions progressing more rapidly with greater vision loss than occult lesions, but responding better to laser and photodynamic therapy. However, with current anti-VEGF therapies, this classification is less useful in the determination of treatment response.

Panel 2: Age-Related Eye Disease Study (AREDS) classification of signs of age-related macular degeneration

- Category 1: none or a few small drusen (<63 μm in diameter).
- Category 2: any or all of the following: multiple small drusen, few intermediate drusen (63–124 μm in diameter), or retinal pigment epithelium abnormalities.
- Category 3: any or all of the following: extensive intermediate drusen, and at least one large drusen (≥125 μm in diameter, roughly equivalent to the size of the retinal vein at the rim of the optic disc), and geographic atrophy not involving the fovea.
- Category 4: geographic atrophy involving the fovea or any of the features of neovascular age-related macular degeneration, and visual loss presumed to be due to age-related macular degeneration. Although not part of this classification, advanced age-related macular degeneration might also include the involutional, atrophic stage of neovascular age-related macular degeneration that is not amenable to further treatment.
Indocyanine green angiography uses an intravenous dye with different characteristics from fluorescein (eg, less melanin absorbance). It improves identification and characterisation of neovascular variants of age-related macular degeneration such as polypoidal choroidal vasculopathy.

Optical coherence tomography (OCT) is a newer non-invasive optical imaging method using near-infrared light and an interferometric analysis. It enables high-resolution in-vivo cross-sectional or volumetric tomographic visualisation of the retinal microarchitecture. OCT allows visualisation of the cross-sectional outline of the neovascular choroidal neovascularisation complex, but its internal structure cannot be resolved and the neovascular components cannot be definitively distinguished from its fibrous components, haemorrhage, fibrous, or dense exudates. With anti-VEGF therapy, OCT imaging is now widely used for early diagnosis and to guide management, particularly the need for retreatment (figure 3). In early age-related macular degeneration, newer spectral domain OCTs can show various morphological features of drusen that allow for refined disease phenotyping. OCT is also useful in substantiating a diagnosis of retinal angiomatous proliferation by showing intra-retinal exudation.

Fundus autofluorescence imaging is another new non-invasive method for mapping of naturally or pathologically occurring fluorophores (mainly lipofuscin) in the retina. Lipofuscin accumulation is a hallmark of ageing produced by phagocytosis of shed photoreceptor outer segments. Fundus autofluorescence imaging is now increasingly used clinically for characterisation of geographic atrophy, which is marked by areas of decreased autofluorescence signal intensity. Importantly, these changes can be assessed sequentially (figure 3).

Prevention

One strategy for prevention of age-related macular degeneration is based on modification of nutrient intake. Studies show increased intake of the macular carotenoids lutein and zeaxanthin and foods rich in these nutrients (eg, spinach and collard greens) are associated with a decreased risk of neovascular age-related macular degeneration. Dietary analyses of the observational component of the AREDS study also showed that lutein and zeaxanthin reduced age-related macular degeneration risk.

In the AREDS, dietary supplements containing high dose antioxidants and minerals (vitamins C and E, β-carotene, and zinc) delayed the progression of age-related macular degeneration from intermediate to advanced stages. AREDS-2 is now evaluating a modification of the supplement formula without β-carotene, with reduced zinc content, and adding lutein and zeaxanthin supplements.
Omega-3 fatty acids, found in photoreceptor outer-segment membranes and derived mainly from fish sources, represent another potentially important nutrient. Observational studies and a meta-analysis now support their beneficial effects on age-related macular degeneration.\textsuperscript{56–58} Omega-3 fatty acid supplements are also being evaluated in AREDS-2.

Lifestyle factors associated with age-related macular degeneration include cigarette smoking,\textsuperscript{19} obesity, and lack of physical exercise.\textsuperscript{20} Modification of these risk factors should therefore be recommended for reduction of age-related macular degeneration risk. Sunlight exposure might also be related to age-related macular degeneration but the evidence is weaker.\textsuperscript{21}

Treatment

Laser photocoagulation

In the 1980s, the Macular Photocoagulation Study\textsuperscript{46,47} reported favourable outcomes for direct laser photocoagulation in a proportion (about 20%) of eyes with small classic extrafoveal and juxtafoveal choroidal neovascularisation lesions, but poorer visual outcomes for subfoveal choroidal neovascularisation lesions.\textsuperscript{46–48} Treatment with laser in these selected patients was effective in reducing long-term severe visual loss, but was limited by lack of vision gain and high recurrence rates (50%), and a risk of immediate moderate visual loss (41%). Treatment with direct laser is now much less used, except in cases with discrete small extrafoveal choroidal neovascularisation lesions distant from the fovea, or for extrafoveal polypoidal choroidal vasculopathy.\textsuperscript{9}

Photodynamic therapy

Photodynamic therapy with verteporfin was introduced in the late 1990s and is now rarely used for age-related macular degeneration. It consists of a two-stage process involving intravenous infusion of verteporfin, a green photosensitising dye that accumulates preferentially in neovascular membranes, followed by dye activation with infrared light. This process generates oxygen-free radicals that damage the endothelium, promoting closure of newly formed vessels. Successful clinical trials with photodynamic therapy expanded the therapeutic options for patients with subfoveal classic choroidal neovascularisation lesions.\textsuperscript{26,59,60} In one trial, over two years, 53% of subjects with classic choroidal neovascularisation treated with photodynamic therapy had “visual stabilisation” (defined in most age-related macular degeneration trials as loss of <3 LogMAR vision lines), compared with 38% in untreated controls. However, the mean visual change was still an average 13-letter loss for photodynamic therapy, compared with an average 19-letter loss for untreated controls. In the poorly-defined (“occult”) choroidal neovascularisation subgroups, treatment benefits were generally less. Adverse events with photodynamic therapy include photosensitivity, headaches, back pain, and acute severe visual loss in 4% of individuals. Chorioretinal atrophy can also develop, leading to gradual visual deterioration.

Anti-VEGF therapy

The recognition of the key role that VEGF has in choroidal neovascularisation pathogenesis led to the development of VEGF inhibitors, a class of drugs that has since become firmly established as the standard of care. Anti-VEGF drugs are typically given via an intravitreal injection (webvideo, figure 4).

Pegaptanib (Macugen, Pfizer), a small oligonucleic acid molecule that specifically binds the VEGF-165 isoform, was the first drug to obtain US Food and Drug Administration (FDA) approval for age-related macular degeneration treatment in 2004,\textsuperscript{4} with more patients with visual stabilisation than placebo.

The second anti-VEGF drug approved by the FDA was ranibizumab (Lucentis, Genentech/Novartis), an antibody fragment that binds all VEGF isoforms. Landmark clinical trials\textsuperscript{1,2} using ranibizumab showed not only visual stabilisation but, for the first time, substantial visual gains as well. The ANCHOR\textsuperscript{1} trial compared 0.3 mg or 0.5 mg of ranibizumab monthly, against photodynamic therapy for predominantly classic choroidal neovascularisation. Participants received injections every month for 24 months, whereas photodynamic therapy was done when indicated every 3 months. 89.9% of the 0.5 mg ranibizumab group achieved visual stabilisation over two years compared with 65.7% of the photodynamic therapy group. Patients receiving 0.5 mg ranibizumab achieved a median gain of about 2 lines of vision (10 letters), compared with almost 2 lines of vision lost with photodynamic therapy. These results were mirrored in the MARINA\textsuperscript{1} trial, which compared the same ranibizumab dosage regimens against placebo for minimally classic or purely occult choroidal

Figure 4: Intravitreal injection of an anti-VEGF agent
neovascularisation. Over 2 years, 90% of the 0·5 mg group had visual stabilisation, compared with 53% of the placebo group. The median vision change was a gain of slightly more than 1 line of vision with ranibizumab, compared with 3 lines lost with placebo. Serious adverse events, notably endophthalmitis, were rare.

A third anti-VEGF drug, bevacizumab (Avastin, Genentech), is commonly used as an alternative off-label treatment. Bevacizumab is a full-length antibody that binds all VEGF isoforms, and was originally developed and now approved for systemic malignancies. Despite the availability of ranibizumab, bevacizumab is the most commonly used anti-VEGF drug in the USA, accounting for 58% of all injections in 2008. This phenomenon, together with incentives for uninsured or only partly insured patients to accept the cheaper unapproved alternative, is attributable to apparently similar efficacy but large price differential between ranibizumab (US$1593 per injection) and bevacizumab ($42). Results from the CATT trial showed that bevacizumab and ranibizumab had equivalent efficacy, with few differences in visual outcomes with monthly injection (bevacizumab given monthly was non-inferior to ranibizumab given monthly, with mean 8·0 letters gained in 1 year for bevacizumab and 8·5 letters gained with ranibizumab) or treatment on an as needed basis.

A fourth anti-VEGF drug, aflibercept (VEGF Trap-Eye, Regeneron/Bayer), an engineered protein that binds VEGF, has recently received FDA approval for neovascular age-related macular degeneration treatment. Initial results from trials showed aflibercept 2 mg given every 2 months after an initial loading phase in which it was given every 4 weeks showed similar efficacy to monthly ranibizumab, gaining 6·8 letters and 8·5 letters, respectively. However, the comparison between bevacizumab as needed and monthly bevacizumab or ranibizumab was inconclusive.

The second important issue is one of safety, particularly systemic safety. Both ranibizumab and bevacizumab enter the systemic circulation substantially after ocular injection. Prolonged suppression of plasma VEGF levels for at least 28 days after injection has been shown with bevacizumab but not ranibizumab, and their systemic half-lives are about 6 days and 0·5 days respectively. In theory, systemic inhibition of VEGF levels might lead to a higher risk of systemic vascular events. However, clinical data on the systemic safety of both bevacizumab and ranibizumab have been sparse, with studies to date of inadequate size to address safety concerns. Although results from individual ranibizumab trials did not show a significant increase in mortality or stroke risk, other studies suggest that patients with a history of previous stroke might be at higher risk, with one reporting that 10% of patients with previous stroke suffered another stroke within 1 year. A meta-analysis of anti-VEGF therapy trials for age-related macular degeneration also showed that ranibizumab was linked to increased non-ocular haemorrhage. In the CATT, arterio-thrombotic and veno-thrombotic events did not differ significantly between bevacizumab and ranibizumab. However, in an analysis of US Medicare/Medicaid claims in 2004–07, patients treated with bevacizumab had significantly higher stroke and mortality rates than did those treated with ranibizumab. Such data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Duration of follow-up (years)</th>
<th>Mean change in visual acuity in treatment group (letters)</th>
<th>Mean change in visual acuity in control group (letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS (extrafoveal)</td>
<td>Laser</td>
<td>Placebo</td>
<td>5</td>
<td>-25</td>
</tr>
<tr>
<td>MPS (juxtafoveal)</td>
<td>Laser</td>
<td>Placebo</td>
<td>5</td>
<td>-25</td>
</tr>
<tr>
<td>MPS (subfoveal)</td>
<td>Laser</td>
<td>Placebo</td>
<td>4</td>
<td>-20</td>
</tr>
<tr>
<td>TAP</td>
<td>Photodynamic therapy</td>
<td>Placebo</td>
<td>2</td>
<td>-13</td>
</tr>
<tr>
<td>VIM</td>
<td>Photodynamic therapy</td>
<td>Placebo</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>VIP</td>
<td>Photodynamic therapy</td>
<td>Placebo</td>
<td>2</td>
<td>-19</td>
</tr>
<tr>
<td>ANCHOR</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>Photodynamic therapy</td>
<td>2</td>
<td>+7</td>
</tr>
<tr>
<td>MARINA</td>
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<td>Placebo</td>
<td>2</td>
<td>+11</td>
</tr>
<tr>
<td>PRONTO</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
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<td>2</td>
<td>+10.7</td>
</tr>
<tr>
<td>SUSTAIN</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
<td>NA</td>
<td>1</td>
<td>+6.7</td>
</tr>
<tr>
<td>SAILOR</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
<td>NA</td>
<td>1</td>
<td>+2.3</td>
</tr>
<tr>
<td>CATT</td>
<td>Bevacizumab 1·25 mg monthly</td>
<td>Ranibizumab 0·5 mg monthly</td>
<td>1</td>
<td>+8</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>Aflibercept 2 mg two-monthly</td>
<td>Ranibizumab 0·5 mg monthly</td>
<td>1</td>
<td>+7.9</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>Aflibercept 2 mg two-monthly</td>
<td>Ranibizumab 0·5 mg monthly</td>
<td>1</td>
<td>+8.9</td>
</tr>
</tbody>
</table>

Table: Visual outcomes in major treatment trials of age-related macular degeneration.
are however prone to confounding that is difficult to adequately adjust for.

It is worth repeating that patients with age-related macular degeneration might already be at increased risk of cardiovascular disease, particularly haemorrhagic stroke. Thus, until further data become available, ophthalmologists and physicians should have a heightened appreciation of the systemic cardiovascular risks involved in the prescription of anti-VEGF drugs, particularly bevacizumab, to patients with age-related macular degeneration.

Visual rehabilitation

Visual rehabilitation for people with severe central visual loss from advanced age-related macular degeneration is useful. Visual aids focus on improving both reading ability and mobility, and are based on principles of either facilitating a closer reading distance or by magnifying a distant image. In a systematic review, standard low-vision rehabilitation programmes, conventional in-clinic assessments, and optical devices were effective ways of managing vision loss from age-related macular degeneration, although the most effective programmes are still unclear.

New research

Progress has been made in the improvement of screening methods to detect age-related macular degeneration. Recently, a system for automated detection of early age-related macular degeneration signs from retinal photographs has been described, with sensitivity and specificity rates of 75%. Further development of such systems might facilitate community screening.

Much research has focused on improved anti-VEGF treatment protocols that reduce the burden of monthly intravitreal injections, including combining anti-VEGF agents with photodynamic therapy and corticosteroids.

In theory, combination therapy targets the multiple pathogenic pathways of age-related macular degeneration. However, in a series of large trials, the combination of photodynamic therapy with ranibizumab resulted in only minor visual improvements. Several larger studies are still unreported, including trials comparing combinations of photodynamic therapy, ranibizumab, and dexamethasone.

The best treatment for polypoidal choroidal vasculopathy is currently unclear. For juxtapfoveal and subfoveal lesions, the diminished role of VEGF in polypoidal choroidal vasculopathy pathogenesis has been reflected in poor responses to anti-VEGF therapies. By contrast, photodynamic therapy has been shown to be effective. In a small randomised trial (n=60), combination therapy of photodynamic therapy and ranibizumab led to a greater proportion of complete polyp regression at 6 months (77.8%) than ranibizumab monotherapy (28-6%). Thus, active polypoidal choroidal vasculopathy should be treated with photodynamic therapy (monotherapy or combination therapy). Given the growing number of Asian age-related macular degeneration patients, larger and longer studies of polypoidal choroidal vasculopathy treatment are clearly needed.

Similarly, the best treatment of retinal angiomatous proliferation has not been identified, since no randomised clinical trials have yet been reported. Combinations of anti-VEGF agents, focal laser, and photodynamic treatment have all found to have some benefit for retinal angiomatous proliferation in case series.

A broad range of investigational treatments is being developed for both neovascular age-related macular degeneration and geographic atrophy. Drugs that can potentially treat geographic atrophy target inflammatory pathways, complement inhibition, trophic factor supplementation, oxidative stress, and retinal toxins. Sirolimus, an anti-fungal agent with anti-inflammatory activities, is being investigated as treatment for geographic atrophy in a phase 1/2 study. Geographic atrophy lesions stain strongly for complement 5a, and intravitreal complement inhibitors, such as ARC-190, are undergoing assessment. Ciliary neurotrophic factor supplementation in the form of an encapsulated cell implant is another approach that has produced visual stabilisation in a phase 2 trial.

Another goal is to develop a topical therapy. Pazopanib is a small molecule tyrosine kinsase inhibitor that targets VEGF receptors, and is currently in use as an anti-angiogenic oral drug for renal cell cancer. Phase 2 trials of topical pazopanib for neovascular age-related macular degeneration have reported improvement in visual acuity after 29 days. OT-551 is another topical agent that targets the NF-kB pathway to suppress angiogenesis, with phase 2 trials for geographic atrophy demonstrating a modest benefit in visual stabilisation.

Radiation therapy has also been investigated. Low-dose radiation targets the rapidly dividing cells of the vascular endothelium in the choroidal neovascular complex. Radiotherapy was first attempted using external photon beam therapy, with variable success. The most significant limitation was radiation retinopathy, a potentially blinding microangiopathy. By contrast, brachytherapy allows for a higher dose of radiation with lower radiation retinopathy risk. Recently, intraocular approaches have been explored. An epiretinal strontium-90 source introduced surgically was evaluated in 19 patients with choroidal neovascularisation. In 36 months, no adverse radiation related events were reported. 90% of patients had visual stabilisation, with a mean gain of 4 letters. Two large trials are currently investigating this treatment.

Genetic approaches to age-related macular degeneration treatment have progressed along various lines. Genetic polymorphisms have been used to classify the expected responses to treatment. For example, factor XIII-A G185T polymorphisms have been used to classify the expected treatment have progressed along various lines. Genetic pathways, complement inhibition, trophic factor supplementation, oxidative stress, and retinal toxins. Sirolimus, an anti-fungal agent with anti-inflammatory activities, is being investigated as treatment for Geographic atrophy lesions stain strongly for complement 5a, and intravitreal complement inhibitors, such as ARC-190, are undergoing assessment. Ciliary neurotrophic factor supplementation in the form of an encapsulated cell implant is another approach that has produced visual stabilisation in a phase 2 trial.72

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Genetic approaches to age-related macular degeneration treatment have progressed along various lines. Genetic polymorphisms have been used to classify the expected responses to treatment. For example, factor XIII-A G185T substitution (rs5985), an anti-thrombophilic genetic variant in white people, was associated with a reduced choroidal neovascularisation responsiveness to photodynamic therapy.76 Presence of the APOE ε4 allele conferred slightly better visual outcomes after anti-VEGF
therapy. Pharmacogenomics could thus potentially help to individualise treatment approaches.

Attempts at gene therapy are in their infancy but have been reported. Theoretically, the eye represents an optimum target for gene therapy as it is readily accessible, compartmentalised, and immune-privileged. Intraretinal and subretinal adeno-associated viral (AAV) vector-PEDF has been shown to treat laser-induced experimental choroidal neovascularisation in mice. Phase 1 clinical trials have been done with an AAV-PEDF vector (GenVec), with no toxic effects reported and stabilisation of choroidal neovascularisation lesion size for several months.

Stem-cell therapy is being explored to regenerate damaged retinal cells. Stem cells can potentially provide a continuous intraocular source of neurotrophic factors to slow photoreceptor cell loss. For patients with advanced age-related macular degeneration, intraocular transplantation of stem cells with subsequent differentiation into photoreceptors, offers hope for restoration of vision. Visual recovery in a rodent model of retinal degeneration has been shown with embryonic stem cells differentiated into photoreceptors before transplantation. Recently, human embryonic stem-cell derived retinal pigment epithelium cells have been transplanted in a patient with dry AMD. Initial results suggest some visual improvement with no rejection or adverse outcomes after 4 months.

Retinal prostheses (or the bionic eye) constitute an exciting research specialty that has received important public interest. Retinal prostheses require intact retinal ganglion cells to convey signals to the visual cortex and preserve the retinotopic cortical mapping, and could thus be successfully applied to age-related macular degeneration. One group has developed a microphotodiode array that is implanted in the subretinal space, and in a trial including six patients, two reported phosphenes. Another system consists of a glass-mounted camera and an external image processor connected through a telemetry link to an intraocular electrode array. Tests on six individuals with advanced retinitis pigmentosa showed that the implant restored the ability to detect motion and to discriminate common household objects. Several other devices are currently in development.

Conclusion
Age-related macular degeneration is a major cause of visual impairment in older adults. No effective preventive drug therapies exist although nutritional and behavioural modifications can reduce progression to advanced age-related macular degeneration. This disorder is heritable and up to 20 genes are associated with age-related macular degeneration. However, the disease is complex and environmental factors also have a role. Advances have been made in disease detection allowing for earlier intervention. Anti-VEGF therapies have proven to be effective in reducing and, in some cases, reversing visual loss in those with neovascular age-related macular degeneration, although the monthly or bi-monthly treatment burden is high and the systemic long-term safety of these drugs remains unclear. A host of novel treatment modalities, including inhibition of other angiogenic factors, new preventive approaches, regenerative therapy, and visual prostheses, are on the horizon. These hold the promise of even better outcomes in the near future.

Contributors
LSL and TYW did the literature search, data interpretation, formatting of the figures and tables, and writing of the initial and final version of the report. PM, JMS, and FGH provided specific input on different sections, as well as critical revision of the initial and final report.

Conflicts of interest
LSL has received travel support from Novartis. PM is on advisory boards for Allergan, Bayer, Novartis, Pfizer, and Solvay, and has received travel, honorarium and research support from these companies. JMS has received grant support from Genentech; Tufts Medical Center has filed patent applications regarding some of her research. FGH is on advisory boards for Acucela, Alcon, Allergan, Bayer, GlaxoSmithKline, Genentech, Heidelberg Engineering, Optos, Novartis, and Pfizer and has received travel, honorarium, and research support from these companies. TYW is on advisory boards for Allergan, Bayer, Novartis, Pfizer, and Solvay, and has received travel, honorarium, and research support from these companies. None of the authors have stocks, equity, contract of employment or named position on company boards.

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