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Review Article

Limbal Stem Cell Deficiency: Diagnostic Criteria and Transplantation Outcomes

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Abstract

Background: Limbal stem cell deficiency destroys the corneal epithelial progenitor population. A 2019 global consensus fixed staging by the central 5 mm zone and the arc of limbal involvement, but postdates almost every outcome series.

Objective: To set out the diagnostic criteria as they now stand and ask what the comparative transplantation outcome literature can legitimately support.

Methods: Narrative review of cytology and imaging studies, consensus statements, surgical cohorts, meta-analyses and one phase I/II trial.

Findings: Reported success ranges from 64.7% to 83.8% across techniques whose endpoints and follow-up differ. Cultivated autologous grafts restored the epithelium permanently in 76.6% of eyes in a 112-patient series; within it, grafts with more than 3% p63-bright cells succeeded in 78% of patients against 11% where p63-bright cells were 3% or less.

Conclusions: The evidence supports staged diagnosis and graft potency as a predictor of outcome, but not ranking surgical techniques by their headline success rates.

Keywords: Limbal stem cell deficiency; Corneal epithelium; Limbal transplantation; Diagnostic staging; Graft potency

Introduction

Limbal stem cell deficiency (LSCD) is the failure of the corneal epithelial progenitor population at the corneoscleral junction. When that population is destroyed or its niche damaged, conjunctival epithelium resurfaces the cornea, producing a vascularised, unstable, chronically painful surface that no lamellar or penetrating graft alone can rescue. The condition is the end point of chemical and thermal burns, Stevens-Johnson syndrome, ocular mucous membrane pemphigoid, congenital aniridia and chronic contact lens wear, each with a different tempo and distribution of limbal loss [1,2].

Two literatures have developed around this disease, and have not converged. One is diagnostic: a forty-year effort to move from clinical signs to a reproducible, staged, quantitative definition of who has LSCD and how much. The other is surgical: increasingly ingenious transplantation techniques, each reported with a headline success rate. Ranking those rates, the routine summary, is not interpretable, because the series do not share an endpoint. This review sets out the diagnostic criteria as they stand, argues that the comparative outcome literature must be read through its definitions before its percentages, and identifies the one graft attribute shown to predict outcome within a single, internally consistent series.

Cellular Basis and the Search for a Marker

Schermer and colleagues showed that the 64K corneal keratin is expressed by suprabasal and central corneal cells but not by limbal basal cells, placing the least differentiated compartment at the limbus [3]. Cotsarelis and colleagues then showed that limbal basal cells are slow-cycling label-retaining cells recruitable into proliferation, meeting the kinetic definition of a stem cell [4]. Together these established the limbus as the reservoir whose loss defines the disease, and explain why the deficiency state is progressive rather than static: the

surface is then maintained by whichever epithelium can migrate onto it, and conjunctival epithelium brings its own vasculature and goblet cells [5].

The search for a positive marker has been less decisive. p63 identifies keratinocyte stem cells and holds up as a proliferative-potential marker in cultured epithelium [6], and the DeltaNp63 isoform pattern tracks the migratory and regenerative behaviour of limbal cells during corneal regeneration [7]. No marker is used at the slit lamp; p63's practical use has been on the manufacturing side, as a release assay for cultured grafts. The diagnostic and manufacturing literatures have drawn different conclusions from the same molecule: to the clinician p63 is a research marker, to the tissue engineer a specification.

Diagnostic Criteria: From Cytology to Consensus Staging

The first operational test was cytological. Puangsricharern and Tseng showed that impression cytology could demonstrate goblet cells and conjunctival-phenotype epithelium on the cornea, converting a clinical impression into tissue evidence [8]. It remains confirmatory, but its sensitivity depends on sampling and on the extent of conjunctivalisation, and it does not grade severity.

In vivo confocal microscopy supplied the first quantitative criterion. Chan and colleagues, studying 43 eyes of 30 patients with LSCD against 10 normal subjects, found mean basal cell density in normal eyes of 9264 +/- 598 cells/mm² centrally and 7120 +/- 362 cells/mm² at the limbus; in LSCD eyes central density fell by 31.0% to 6389 +/- 1820 cells/mm² and limbal density by 23.6% to 5440 +/- 1123 cells/mm², both $P < .001$, with further decline in more advanced disease [9]. That is a stageable variable, not a binary sign. Confocal microscopy and anterior segment optical coherence tomography have since developed as complementary structural tools [10], and the literature has been synthesised into an algorithm combining clinical signs, cytology and imaging [11]. Table

1 sets each modality against what it demonstrates and the limitation stated for it.

Table 1: Diagnostic modalities in limbal stem cell deficiency, what each demonstrates and the limitation stated for it [8,9,10,11,12,6].		
Modality	What it demonstrates	Stated limitation
Impression cytology	Goblet cells and conjunctival epithelium on the cornea	Confirmatory only; sampling-dependent, does not grade severity
In vivo confocal microscopy	Basal cell density down 31.0% centrally and 23.6% at the limbus in LSCD, both $P < .001$ (43 eyes of 30 patients)	Normal reference drawn from 10 control subjects
Anterior segment OCT	Structural change at the limbus and corneal epithelium	Complementary to confocal microscopy rather than standalone
Combined diagnostic algorithm	Clinical signs, cytology and imaging read together	Synthesis of existing tests; adds no new measurement
Consensus staging (2019)	Stages I to III by central 5 mm zone and arc of limbal involvement	Postdates almost every outcome series, so cohorts were not staged by it
Molecular markers (p63)	Proliferative potential of cultured limbal epithelium	Not used at the slit lamp; serves as a graft release assay

The 2019 global consensus fixed the vocabulary. Staging is defined by the central 5 mm zone and the arc of limbal involvement: stage I is a normal corneal epithelium within the central 5 mm zone, subdivided as IA with less than 50% limbal involvement, IB with 50% or more but less than 100%, and IC with 100%; stage II has the central 5 mm zone affected, subdivided as IIA with less than 50% limbal involvement and IIB with 50% or more but less than 100%; stage III is involvement of the entire corneal surface [12]. A companion consensus addressed management [13]. This staging system is the field's most important development in a decade, and it postdates almost every outcome series below. None of those cohorts was assembled under it, so each series' severity distribution must be inferred from its inclusion criteria rather than read off a common scale. Two series reporting the same percentage may have operated on populations a full stage apart.

The Definition of Success Is Not Shared

Before any technique is compared with another, the reader needs to know what the series counted. They did not count the same thing. Rama and colleagues defined success as permanent restoration of a transparent, renewing corneal epithelium [14]. Sangwan and colleagues, and later Basu and colleagues, required a completely epithelialised, avascular and stable corneal surface [15,16]. The allogeneic cultivated series required complete epithelialisation without an explicit avascularity criterion [17]. The multicentre simple limbal epithelial transplantation (SLET) study required complete epithelialisation with an avascular corneal surface [18]. Cheung and colleagues counted a stable ocular surface [19]. The longest-follow-up SLET series required a normal corneal epithelial phenotype confirmed jointly by slit lamp examination, in vivo confocal microscopy and impression cytology, the most demanding criterion in the literature [20]. The CALEC trial reported a composite of complete or partial success [21].

These are not equivalent endpoints. A composite admitting partial success and a phenotypic endpoint requiring three concordant modalities sit at opposite ends of a stringency range; a percentage from one cannot be set beside one from the other. Follow-up compounds the problem: the series span six months [22] to twelve years [20], and because failures cluster early — every failure in the Rama cohort occurred within the first postoperative year [14] — short series are biased upward by construction. Case mix differs again: partial versus total deficiency, unilateral versus bilateral disease, and whether keratoplasty was simultaneous, an independent risk factor for failure in the multicentre SLET data [18]. The numbers that follow measure different quantities that happen to share a name. This is not a caveat to be appended after a comparison; it is a constraint on what comparisons are permissible at all.

Table 2: Technique, cohort size, follow-up and the success definition actually used in each series, showing that the reported percentages measure different endpoints [14,15,17,16,18,20,19,21].			
Series	N	Follow-up	Success definition
CLET, Rama 2010	112	mean 2.9 y	Transparent renewing epithelium
CLET, Sangwan 2011	200	mean 3 y	Epithelialised, avascular, stable
CLET allo, Basu 2012	28	mean 4.8 y	Epithelialised surface only
SLET, Basu 2016	125	median 1.5 y	Epithelialised, avascular, stable
SLET, Vazirani 2016	68	median 12 mo	Epithelialised and avascular
SLET, Shanbhag 2025	47	5-12 y	Slit lamp, IVCN and cytology
KLAL, Cheung 2020	224	mean 7.2 y	Stable ocular surface
CALEC, Jurkunas 2025	14	18 mo	Complete OR partial success

Autologous Transplantation: Tissue, Culture and Fragment

Autologous transplantation began with direct transfer of limbal tissue from the fellow eye [23]. Cultivation followed, first as autologous cultivated corneal epithelium restoring damaged surfaces long term [24], then as cultivated autologous limbal epithelial cells [25].

The reference cultivated limbal epithelial transplantation (CLET) series is Rama and colleagues: 112 patients, fibrin-carrier autologous grafts, mean follow-up 2.91 +/- 1.99 years, median 1.93 years, maximum 10 years, and permanent restoration of a transparent, renewing corneal epithelium in 76.6% of eyes [14]. A xeno-free explant-on-amniotic-membrane protocol in 200 eyes, mean follow-up 3 +/- 1.6 years, range 1 to 7.6 years, produced a completely epithelialised, avascular, stable surface in 142 of 200 eyes (71%), with a two-line best corrected acuity gain without further surgery in 60.5% [15].

SLET replaced culture with direct fixation of minced limbal fragments onto amniotic membrane at surgery, removing the laboratory [26,27]. A single-centre

prospective cohort of 125 eyes, 65 adults and 60 children, reported success in 95 eyes (76%, 95% CI 68.5-83.5) at a median follow-up of 1.5 years, range 1 to 4 years, a two-line acuity gain in 75.2%, and progressive conjunctivalisation in 18.4% [16]. An eight-centre retrospective series of 68 eyes reported success in 57 (83.8%), acuity of 20/200 or better in 65%, a gain of two or more Snellen lines in 64.7%, at a median follow-up of 12 months [18]. The longest follow-up available, 5 to 12 years postoperatively, gave a normal corneal epithelial phenotype in 32 of 47 eyes (68%), with failure in 15 [20]. The apparent decline from 83.8% to 68% across those three series is at least as much a change of endpoint and follow-up as of biology. A glueless variant reported clinical success in 9 of 11 cases (81.8%) with partial success in a further 2 at a six-month interim endpoint, too small and too short to weigh against the others [22]. A randomised comparison of SLET against conjunctival limbal autograft in 20 patients with more than 270 degrees of limbal involvement, 10 per arm and 6 months of follow-up, reported mean symblepharon score falling from 1.80 +/- 1.14 to 0.30 +/- 0.63 with SLET and from 1.70 +/- 1.06 to 0.15 +/- 0.24 with autograft [28]. A head-to-head comparison of SLET against CLET in ocular burns has since been published; its outcome figures are the most relevant missing datum here [29].

Allogeneic Grafts and the Limits of Pooling

Bilateral disease removes the autologous option. Xeno-free allogeneic CLET in 28 eyes maintained a completely epithelialised surface in 20 (71.4%) at mean follow-up 4.8 +/- 2.8 years; 13 eyes (46.4%) proceeded to penetrating keratoplasty, with Kaplan-Meier allograft survival of 76.9 +/- 11.7% at one year and median survival 3.3 years, and 19 eyes (67.8%) reached 20/60 or better [17]. In a single high-volume centre with mean follow-up 7.2 years (range 1.0-16.0), 82.5% of 63 living-related conjunctival limbal allograft eyes maintained a stable ocular surface against 64.7% of 224 keratolimbal allograft

eyes; acute rejection occurred in 30.2% and 43.3%, of which 79.0% and 53.6% resolved with treatment [19].

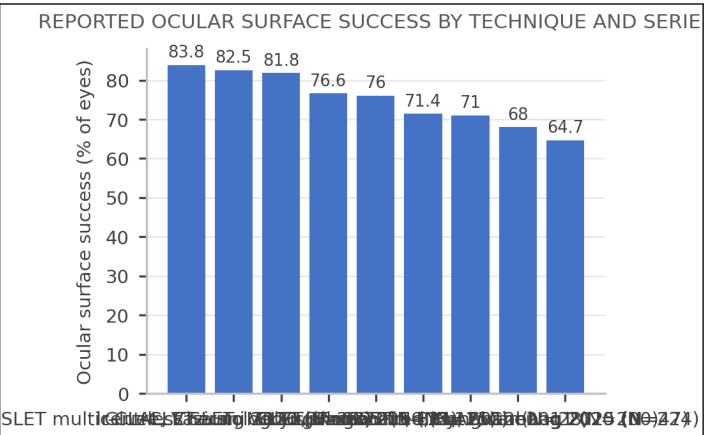


Figure 1: Reported ocular surface success in nine transplantation series (N = 11 to 224 eyes or patients per series), plotted only after noting that the success definitions and follow-up durations differ across series and that the values are therefore not directly comparable [18,19,22,14,16,17,15,20].

Meta-analysis pools 40 studies and 2202 eyes, mean follow-up 31.3 (SD 20.9) months: ocular surface improvement in 85.7% (95% CI 79.5-90.3) of 505 autologous limbal transplantation eyes, 84.7% (77.2-90.0) of 771 cultivated autologous eyes, 63.2% (49.3-75.2) of 184 cultivated allogeneic eyes and 57.8% (49.0-66.1) of 742 allogeneic eyes, and 74.5% overall; acuity improvement followed the same ordering at 76%, 56.4%, 52.3% and 43.3% (P < .001) [30]. A synthesis of 18 studies covering 572 eyes of 562 patients reported two pooled proportions, 67% (95% CI 0.59-0.75) and 62% (0.57-0.66), for overall success and two-line acuity gain, though which value belongs to which endpoint cannot be settled from the abstract [31]. A third, of 30 studies and 1306 eyes of 1288 patients, 982 autograft and 324 allograft, found pooled odds ratios favouring autograft of 1.82 (95% CI 0.80-4.11) for success and 1.20 (0.54-2.65) for acuity gain, neither significant [32]. Pooling inherits every definitional inconsistency above and adds between-study variance; these estimates describe the literature, not the operation. Their value is the ordering they recover — autologous above allogeneic on both endpoints, with wide and overlapping confidence

intervals — not any individual pooled percentage.

Graft Potency Predicts Outcome

One result escapes the definitional critique, because it compares outcomes within a single cohort under a single endpoint. In the 112-patient CLET series, grafts in which p63-bright cells constituted more than 3% of total clonogenic cells succeeded in 78% of patients, while grafts with 3% or less succeeded in 11% [14]. A sevenfold difference tracked with a measurable property of the tissue before implantation. That is a stronger claim than any inter-series comparison here can support, and it converts graft manufacture from a craft into something with a testable release specification. The regulatory dossier that carried Holoclar to European market authorisation rests on this logic [33].

Recent manufacturing follows it. The CALEC phase I/II trial produced grafts meeting release criteria in 14 of 15 participants (93%), transplanted 14, and reported complete or partial success in 86%, 93% and 92% of grafts at 3, 12 and 18 months; intracellular ATP correlated with colony-forming efficiency at r = 0.65 (95% CI 0.04-0.89) [21]. The composite endpoint means those percentages cannot be ranked against the binary anatomical results elsewhere, but the potency correlation is the point of interest, continuous with the p63 finding.

Conclusion

The diagnostic side has converged on a staged, partly quantitative definition anchored by the central 5 mm zone and the arc of limbal involvement, supported by confocal cell-density measurement and cytology. The outcome side has not converged at all. Reported success ranges from 64.7% to 83.8% across techniques, but the range is generated as much by endpoint stringency, follow-up length and case mix as by surgical method, and no honest ranking can be extracted from it. The remedy is procedural rather than surgical: report outcomes staged by the 2019 criteria, at a fixed minimum follow-up beyond the first

postoperative year where failures concentrate, against a single prespecified anatomical endpoint. Until then, the most useful predictor available remains an attribute of the graft rather than a feature of the operation.

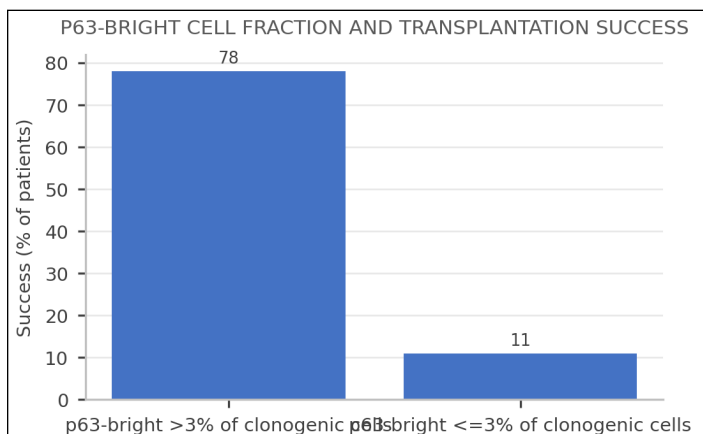


Figure 2: Transplantation success by p63-bright colony-forming cell fraction in a single cultivated autologous limbal epithelial transplantation cohort of N = 112 patients; the per-category denominators are not stated in the source abstract and were not confirmed [14].

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