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THE ECONOMICS OF INNOVATION IN RARE EYE DISEASE:

Lessons from Epithelium-On Corneal Cross-Linking

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1. INTRODUCTION: PATIENT-CENTRIC INNOVATION IN RARE CHRONIC EYE DISEASES

1.1. What is keratoconus?

Some of the greatest challenges in medicine don't involve common diseases–they involve rare illnesses that affect smaller, often overlooked groups of patients. Keratoconus is a clear example. It's a progressive eye condition in which the cornea (the transparent outer layer of the eye) gradually thins and bulges outward into a cone shape. This structural change distorts vision and may result in severe visual impairment.[1,2]

Keratoconus is considered a rare disease.[3] In one commonly-cited clinical and epidemiologic study, the prevalence was 54.5 per 100,000 population.[4] Among those afflicted, its impact on daily life can be enormous. It most commonly emerges in teenagers or young adults–just as they're preparing for independence and early adulthood. Picture a 19-year-old art student whose world starts to blur. The diagnosis: keratoconus. Suddenly, their future (from reading to driving to finishing college) feels uncertain.

1.2. Limited treatment options until recently

For years, managing keratoconus meant symptomatically managing vision loss with glasses or rigid contact lenses while the underlying disease continued to progress.[1,2] But once the disease advanced, the main path to visual rehabilitation was a corneal transplant–a major surgery associated with risks such as graft rejection, cataracts, and long-term complications like glaucoma,[5] as well as the likely need to receive multiple regrafts over a lifetime. For many patients, the path forward was uncertain, and the outcomes weren't guaranteed.

1.3. A new direction: corneal cross-linking technology

Things began to change around 2010 with the arrival of corneal collagen cross-linking. This procedure uses a specific formulation of riboflavin (vitamin B2) activated by UV-A light to strengthen the cornea by creating new molecular bonds in the tissue.[6] The standard method, called epithelium-off cross-linking, works by surgically removing the top layer of the cornea (the epithelium) so the riboflavin can penetrate the underlying layers. It's effective, but not without downsides. Patients often experience significant pain after the procedure, prolonged recovery time with disruptions to the activities of daily living (school, work) and there's a risk of infection and corneal haze, which may be permanent in rare situations.

That's what led researchers to look for a less invasive alternative: epithelium-on oxygen-enriched cross-linking. This newer approach leaves the protective surface of the eye intact. As a result, patients tend to have less pain,[7] a lower risk of corneal haze,[8] and a faster recovery.[9] Additionally, early animal studies suggest that keeping the epithelium in place may reduce the risk of infection by preventing bacterial adhesion to the deeper layers of the cornea.[10,11] A 2025 review of epithelium-on cross-linking in humans concluded that "[t]he preservation of the epithelial layer likely contributes to offer a natural barrier against infection."[12]

Epithelium-on oxygen-enriched cross-linking (Epioxa®, Glaukos Corporation, Aliso Viejo, CA, USA), recently approved by the FDA, uses a new proprietary topical formulation which is catalyzed by oxygen and a UV light source; it has been shown to halt keratoconus progression in a single administration without undergoing an invasive or painful procedure. In addition, unlike epithelium-off cross-linking, Epioxa does not require that disease progression be shown prior to treatment, thereby facilitating earlier intervention. Getting riboflavin through the intact epithelium without surgically debriding the cornea was a significant challenge. It took years of advances in drug formulation and delivery techniques, however the effort is paying off. Today's epithelium-on oxygen-enriched method is showing efficacy comparable to the traditional epithelium-off approach[12,13]–with fewer tradeoffs for patients.

2. FROM CONCEPT TO CLINIC: HOW CROSS-LINKING REACHED PATIENTS

Turning a promising idea into an approved therapy–especially for a rare disease like keratoconus–is rarely straightforward. The process is long, expensive, and often unpredictable. Scientific setbacks, financial risks, and regulatory red tape can all slow progress. Analogous to the corneal epithelium itself, each phase of development presents its own tough-to-penetrate barrier (e.g., scientific idea, pre-clinical testing, clinical development, regulatory hurdles, etc.) as the technology progresses from concept to clinic.

2.1. Science alone is not enough

Cross-linking didn't start as a commercial project. It came out of basic science–careful lab work done in the 1990s at the University of Dresden.[14-16] Researchers were curious: could UV light and riboflavin stiffen the cornea enough to stop keratoconus from progressing? Their early studies showed it was possible, however proving it works in a lab is a far cry from delivering a new treatment to patients.

That next step–getting cross-linking into clinics–required substantially more money: not just for the successful version, but to pay for all the dead-ends along the way. Without the promise of patent protection and the chance to eventually recoup their costs, private investors wouldn't have gotten involved. Like many rare disease breakthroughs, the science alone wasn't enough. It took robust commercial backing to bring cross-linking to patients.[17,18]

2.2. The roadblock before trials: preclinical testing

Once investors were on board, the next hurdle was proving the treatment was safe and effective–at least in the lab. That meant figuring out the precise UV-A intensity and frequency, how much riboflavin to use, and how long to expose the cornea to light. For the original epithelium-off

method, this became known as the Dresden protocol, and it was carefully calibrated to stiffen the cornea without damaging deeper layers.[19]

However, epithelium-on cross-linking–using topical drops without epithelial removal–brought a tougher challenge. The corneal epithelium is naturally good at keeping things out, including riboflavin. Getting the drug to reach the right layer without removing the surface required new formulations, special additives, and lots of trial and error.[20-23] And because cross-linking involves the eye–a delicate organ–researchers had to go further, testing for things like endothelial cell density (a key measure of corneal health)[24-26] that aren't even considered in most systemic drug development.

Another complication: keratoconus does not naturally occur in animals.[27] That made it harder to run realistic animal studies and slowed down the transition to human trials.

2.3. Conducting clinical trials for a rare eye disease is difficult

Once a therapy is ready for testing in people, the next challenge is running the clinical trials. For keratoconus, these challenges are substantial, possibly even more challenging than those encountered in the pre-clinical phase.

It is hard to find patients. The disease is rare, and people who have it are scattered geographically.[28,29] That often means trials must recruit from many different sites, which adds cost and complexity.[30,31]

New therapies must prove they meet a sufficiently high bar of efficacy. With epithelium-off cross-linking already in use, epithelium-on trials couldn't simply show that the treatment worked–they had to show it had significantly higher efficacy than the sham comparator–just as the original epithelium-off trial had done.[32]

Outcomes and disease progression may be unpredictable. Keratoconus progression is variable, with younger patients often progressing faster than older patients. This variability may impede standardized clinical trial protocols.

The results aren't easy to measure. Researchers need specialized tools to track changes in maximum keratometry (Kmax) and other indicators of disease progression.[33] Not every clinic has that equipment or expertise, especially outside of major academic or surgical centers.

Standard outcomes don't always apply. Unlike common diseases like hypertension–where blood pressure is an easy, well-understood metric[34]–ophthalmologic diseases do not always have universally accepted endpoints. Researchers may have to create and validate new endpoints. For example, the FDA approved Luxturna, a gene therapy for a rare retinal disease, based in part on a novel test called the multi-luminance mobility test (MLMT), which assessed how well patients navigated obstacles under different lighting conditions.[34,35]

2.4. Navigating the regulatory maze

Even once the science and trials are in place, there's still the challenge of regulation. In the U.S., the Orphan Drug Act provides valuable support such as tax breaks, waived fees, and market exclusivity for developers of rare disease treatments.[35,36] But that doesn't mean approval is easy. Because cross-linking is a drug-device combination, it receives extra scrutiny. The FDA expects companies to work closely with it to agree on trial design, outcome measures, and safety standards. In essence, companies have to build the road as they walk it, working hand-in-hand with regulators to define how the treatment should be tested and judged.[37,38]

3. THE UNFORGIVING ECONOMICS OF RARE DISEASE THERAPY DEVELOPMENT

Bringing any new therapy to market is both risky and expensive, but when it comes to rare diseases, the financial risks increase dramatically.[28]

3.1. Why small patient populations make costs harder to bear

Developing a new treatment means committing substantial money to research, clinical trials, manufacturing validation, and navigating the regulatory system.[39,40] That's true whether you're treating millions of people with high blood pressure or just a few thousand with a rare condition, such as keratoconus. But here's the difference: in common diseases, those costs are spread out across huge patient populations. In rare diseases, they're not. With far fewer patients to treat, the cost per person goes way up. The science might be equally promising, but the math behind it is far less forgiving.

3.2. How to make a return when there are so few patients?

At the heart of the problem is a simple return on investment equation: ROI=(Total revenue-Total costs)/(Total costs).

The "total costs" part can easily run into the hundreds of millions of dollars.[41] But for rare diseases, the "total revenue" side of the equation is capped by the small number of people who will ever receive the therapy.

To make the numbers work, the price per treatment has to be high–sometimes uncomfortably high. That puts developers in a tough spot. On one hand, they need to charge enough to recoup their investment and attract future funding. On the other hand, payers and the public are rightly concerned about the rising costs of health care. It's a real tension–one that industry can't ignore and tries its best to navigate.[28]

The investment landscape adds another layer of complexity. While some venture capital firms are willing to back rare disease programs, they typically do so only when key conditions are met: strong patent protection, regulatory incentives, and a clear reimbursement path.[42] If those pieces are missing, it becomes much harder to raise money. Even great science can stall if there's no clear way to pay for it. This fact is particularly relevant given the continually changing dynamics of government grants, assistance from private foundations, and the groundwork role of academic institutions, all of whose support is often not able to be secured by medical technology companies.[43]

4. JUSTIFYING THE PRICE TAG

4.1. Why pricing isn't just about covering manufacturing costs

When it comes to new therapies–especially for rare diseases–the price tag covers much more than the cost of making the drug. Companies need to cover what they've spent on research, development, and all the failed attempts that came before the one that worked.[44] For a rare disease therapy, they also need to provide technical training for staff and healthcare providers; technical support; inventory management; continuous product maintenance; next-generation innovation; and financial access programs. Even with incentives like market exclusivity, the math doesn't always work out. More and more, payers want to see proof that a therapy delivers real, lasting results–not just in the clinic, but in the long run–before they commit to coverage.[45]

4.2. Value-based pricing: paying for what matters

That's why there's growing interest in value-based pricing–a model that ties the cost of a treatment to the real-world benefits it delivers, not simply to how much it costs to produce a new treatment.[46,47] For a procedure like cross-linking, the value goes well beyond clinical success. It means helping people avoid surgery, stay independent, and live fuller, more productive lives. It also means added value to the provider, healthcare system, and/or payer in terms of efficiency, fewer postoperative visits, and fewer interventions or devices for visual rehabilitation (e.g., glasses and contact lenses).

Organizations like the Institute for Clinical and Economic Review (ICER) have pointed out that traditional pricing

models often undervalue treatments for rare diseases, especially when those models overlook things like disease severity, lack of alternatives, or broader societal impact.[48] Payers seem to agree. A 2020 survey of U.S. insurers found that they were more open to higher prices for treatments that target rare or pediatric conditions, especially when the therapy offers a real advantage over what is already available.[49]

In that light, epithelium-on oxygen-enriched cross-linking makes a strong case. Yes, epithelium-off cross-linking is the existing gold standard, but epithelium-on oxygen-enriched cross-linking offers real benefits: less pain, lower risk of corneal haze, faster recovery, more rapid return to daily activities, less time away from work and school, ability to treat patients with thinner corneas, and a greater propensity of cross-linking-treated patients electing this treatment for their second eye in addition to their first. These are more than clinical conveniences; they're patient-centered advantages that matter in a value-based system. And because keratoconus often hits people in their teens or twenties, a treatment that's both effective and easy to tolerate can offer lifelong returns in education, employment, and independence.

4.3. Outcomes-based pricing

Some insurers are experimenting with outcomes-based contracts (also known as value-based drug pricing agreements)–arrangements where payment depends on how well the therapy performs over time.[50] It's a promising model, but it's tricky in cases like keratoconus, where the most meaningful results–like avoiding a transplant–may take years to show up. For conditions that have variable rates of progression, measuring impact in a timeframe that satisfies payers is a challenge.

4.4. Why preserving vision saves more than just eyesight

Losing vision doesn't just limit what people can see. It limits what they can do. The costs stack up quickly: doctor visits, assistive technology, home modifications, caregiving, and indirect costs such as lost productivity. One study estimated that vision loss costs the U.S. more than $134 billion a year–and the more severe the impairment, the more those costs rise.[51]

But there's an even deeper impact. People who lose their sight may stop driving, working, or even recognizing loved ones' faces.[52] Depression, anxiety, and isolation are common.[53,54] For working-age adults, it can mean early retirement. For teens or young adults, it might mean putting education or independence on hold, or pursuing a non-preferred career path.[55] In other words, saving vision isn't just about eyesight–it's about helping people stay active, connected, and self-sufficient.

That's where cross-linking comes in. By stopping keratoconus from getting worse, it helps many patients avoid corneal transplants, which can cost $13,000 to $27,000 per eye[56] and often come with long-term complications (e.g. graft rejection, vision loss) and follow-up. The earlier cross-linking is performed, the better the odds of maintaining good vision through some of the most formative stages of life.

Epithelium-on oxygen-enriched cross-linking takes that value further. It's more comfortable, has fewer complications, and works for patients who aren't good candidates for epithelium-off cross-linking. That makes early treatment more accessible and more acceptable. And when patients can be treated earlier, with fewer tradeoffs, the long-term benefits ripple outward for families, health care systems, and society.

4.5. Turning value into access: codes, coverage, and communication

Even a therapy with strong clinical results and a fair price won't succeed unless it gets reimbursed. That starts with the basics: billing codes, the language of payers. The drug component needs its own J-code (like J2787 for Photrexa), and the procedure itself needs a Current Procedural Terminology (CPT) code that reflects the time, skill, and complexity involved.

Once the codes are in place, developers approach payers with a clear, well-supported case. For epithelium-on oxygen-enriched cross-linking, that means showing not just that it works, but how it compares to what's already covered. The unique value here is its safety and comfort profile, especially for patients with thinner corneas. To back that up, health economic models are used to calculate the cost per quality-adjusted life year (QALY) and to project long-term cost-effectiveness.

Studies from the United States, United Kingdom, Brazil, the Netherlands, and Canada have found that epithelium-off cross-linking is cost-effective.[57-61] The U.S. study found cross-linking was dominant (cost saving) relative to conventional care, owing to fewer penetrating keratoplasties and increased quality of life years (QALYs).[57] The U.K. study concluded that cross-linking is "very likely to be cost effective, compared with standard management."[58] The Brazilian study concluded that "corneal cross-linking is a highly cost-effective intervention."[59] The Dutch study concluded that crosslinking is cost effective at a willingness-to-pay threshold of 3 times the current gross domestic product (GDP) per capita."[60] The Canadian study concluded that "cross-linking is cost-effective compared with conventional management with PKP [penetrating keratoplasty]."[61] A similar model for epithelium-on oxygen-enriched cross-linking may need to be developed–one that could help unlock payer coverage and bring this newer technology to more patients who need it.

4.6. It's not just about the U.S.A.

Getting FDA approval is a huge milestone–but it's just one piece of the puzzle. Around the world, reimbursement decisions are made by different agencies, using different criteria. In the U.K., the National Institute for Health and Care Excellence NICE looks at cost-per-QALY thresholds.[62] In Germany, the G-BA evaluates how much better a new therapy is compared to what's already on the market–and that rating helps determine the price.[63]

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) applies a unique regulatory approach that emphasizes both clinical efficacy and post-marketing surveillance obligations. Therapies approved under Japan's conditional early approval system may face additional scrutiny before full reimbursement is granted by the Central Social Insurance Medical Council (Chuikyo), which also negotiates pricing.[64]

In France, the Haute Autorité de Santé (HAS) conducts a two-tiered evaluation: clinical benefit (SMR) and clinical added value (ASMR). These ratings directly impact both access and pricing, with lower ASMR scores limiting reimbursement rates–even if the product is approved for use.[65,66]

These systems are designed to keep spending in check, but they can make things especially hard for rare disease therapies. With smaller patient populations and less clinical data, it's harder to meet the usual thresholds. That means companies have to build customized market access plans for each country–creating evidence packages, value stories, and pricing strategies that match each system's rules and expectations, and also that align with the desire to have novel treatments available to all (rather than just higher-income) segments of society.

5. EPITHELIUM-ON CROSS-LINKING'S DEVELOPMENT JOURNEY

5.1. The epithelial fortress

One of the biggest scientific challenges with epithelium-on cross-linking has always been the corneal epithelium itself. It's like a tightly sealed barrier–designed to keep harmful substances out. That's great for protecting the eye, but not as helpful when you're trying to get the photosensitizing agent deep enough into the cornea to perform cross-linking.

To get around this, researchers had to build a sophisticated delivery system. That meant creating a specialized riboflavin formula packed with permeation enhancers–compounds that temporarily loosen the cell junctions and allow deeper drug penetration into tissue–without causing damage. The UV-A light source also had to be precisely tuned to ensure the drug was activated at the right depth, without harming the eye's delicate inner layers.[67,68] Getting all of that right took years of experimentation and iteration in both chemistry and optics.

5.2. Regulatory hurdles

Even once the science was in place, epithelium-on oxygen-enriched cross-linking still had to clear a long list of regulatory hurdles. Glaukos, the company leading development, ran two large, randomized Phase 3 trials at multiple sites. They weren't just trying to prove that epithelium-on cross-linking worked–they had to prove it had sufficiently greater effect than its sham comparator.

To get everyone aligned early, Glaukos negotiated a Special Protocol Assessment (SPA) with the FDA. This is a formal agreement confirming that the trial design is strong enough to support an eventual approval application. These Phase 3 trials were designed as superiority studies; thus even if epithelium-on cross-linking offered better comfort and safety than the alternative, it still had to surpass the clinical bar of having significantly higher efficacy than the comparator.

Once the trials showed success, the next step was pulling together the New Drug Application (NDA)–a huge and complex regulatory filing requiring over 40,000 pages of supportive evidence. That effort happens in parallel with building a commercial strategy: scaling up manufacturing, educating doctors and insurers, and laying the groundwork for launch.

5.3. What it cost to get here

Determining the precise cost of developing epithelium-on oxygen-enriched cross-linking is challenging. However, by examining other rare disease drugs, it's estimated that the entire process–from initial preclinical studies through Phase 3 trials to launch preparation–can range from several hundred million to several billion dollars.[44,69,70] This encompasses a variety of expenses, including preclinical testing (which often costs tens of millions of dollars),[71] Phase 3 trials (which average hundreds of millions of dollars for rare diseases),[72] the creation of specialized formulations and devices, scaling up manufacturing for a drug-device combination, and the economic modeling necessary to showcase value to global payers. Additionally, these figures do not cover costs associated with acquiring or licensing technologies that will undergo further research and development to prove their safety and efficacy to meet FDA standards for commercial approval. Once a product is approved, companies also face costs related to launching the product which requires building a commercial infrastructure designed to support the patient journey, including educational initiatives aimed at increasing awareness among patients and healthcare providers to support identification, diagnosis, and treatment of the disease.

These extrapolated figures reflect the broader economics of rare disease therapy development and help frame the commercial risk involved. Epithelium-on oxygen-enriched cross-linking shares key characteristics with these other high-investment rare disease programs.

There is no guarantee that the hefty investment will pay off. But it's the kind of high-stakes investment required to bring a safer, more accessible therapy like epithelium-on oxygen-enriched cross-linking to market to advance patient care. The result is a treatment that matches the performance of its predecessor while removing many of the barriers that have kept patients from getting treated earlier and more comfortably.

6. FINDING THE BALANCE: INNOVATION, ACCESS, AND ECONOMIC REALITY

The story of epithelium-on oxygen-enriched corneal cross-linking highlights one of the biggest questions in modern medicine: How do we support innovation without leaving patients behind? On one side, we need to keep developing better, safer, more effective treatments. On the other hand, we need to make sure those treatments are accessible to the people who need them irrespective of drug price.

6.1. The price of hope

It's easy to look at the price of a new treatment and wonder why it's so high in the current research structure environment. But behind every approved therapy is a long, expensive, and risky journey. For early-stage biotechnology startups, the chance to earn a return is what gets investors to take a leap of faith in the first place. For larger pharmaceutical companies, revenue from one success helps pay for the dozens of programs that don't make it.

Either way, pricing isn't just a number on a chart; it's part of a system that keeps innovation going. If there's no potential reward, the engine that drives progress slows down. That's why pricing can't be looked at in a vacuum. It's not just about what something costs; it's about what that cost enables.

6.2. Everyone has a role to play

Making therapies like epithelium-on oxygen-enriched cross-linking viable isn't up to just one group. It takes real cooperation between industry, payers, providers, regulators, patients, and society at large. Each one plays a key part in making the system work.[28,47]

Industry needs to run strong clinical trials and build valid health economic models that show why a therapy is worth paying for. If a company wants premium pricing, it has to show premium value–and be open about the data behind it.

Payers can't just focus on short-term budgets.[28,36] For a disease like keratoconus, where the benefits of early treatment may take years to fully manifest, value- or outcomes-based models may make more sense. These let payers support innovation while still protecting their bottom line.

Providers are the ones on the front lines. They need to catch keratoconus early and refer patients before the damage is done. That means staying up to date on emerging treatments and adopting screening strategies that can catch cases sooner.[73]

Regulators and policymakers have a balancing act too–encouraging innovation without compromising safety. Adaptive frameworks can help–especially for complex products like drug-device combinations. So can making orphan drug incentives stronger and more predictable, particularly across international markets.

Patients and families aren't just passive recipients. They can be powerful advocates and partners.[18] By helping define what outcomes matter and by participating in research, they bring urgency and focus to clinical development.

And as a society, we have to be willing to invest in the early stages of discovery–especially when the market alone can't carry the risk. Public-private partnerships, basic research funding, and global coordination all may play a part in turning scientific breakthroughs into real-world treatments.[36]

6.3. Access can't be an afterthought

Innovation only matters if people can benefit from it. A therapy like epithelium-on oxygen-enriched cross-linking can transform lives–but not if it's out of reach for the people who need it most.

Equity matters. That means recognizing that people with fewer resources should still have access to care that preserves their sight and independence. Without insurance coverage, patient assistance programs, or strong public reimbursement systems, high-cost therapies often go to those who are already well-insured–leaving others

behind.[28] We have already seen these factors in play in keratoconus treatment, where race, insurance status, and neighborhood have been shown to impact whether patients undergo cross-linking.[74]

When inequity happens, it's not just a personal loss. It's a failure of the system. Ensuring that new treatments reach all patients–regardless of income, insurance status, or geography is the real measure of whether innovation is working for the people it's supposed to help.

7. FINAL THOUGHTS

The story of epithelium-on corneal cross-linking is about more than just a new treatment for keratoconus. It's a window into the bigger challenge facing modern medicine: how to keep innovation moving forward while making sure the people who need it can actually afford and access it.

Bringing epithelium-on oxygen-enriched cross-linking from the lab to the clinic took years of work and investment–across chemistry, clinical trials, regulatory navigation, and business strategy. That journey reflects the hard reality of rare disease development: it's expensive, risky, and complex. And that work continues to produce new advancements in keratoconus treatments. But it also shows what's possible when science is matched with persistence and purpose.

Now, the focus shifts to the broader healthcare system. Will payers recognize the long-term value of a safer, more accessible vision-preserving treatment? Will regulators continue to support flexible frameworks for complex therapies? Will investors stay engaged if pricing remains uncertain?

The way epithelium-on oxygen-enriched cross-linking is handled–by insurers, by public programs, and by the market–could influence what comes next. If this therapy succeeds not just clinically, but economically and equitably, it may encourage the next wave of innovation for other rare conditions that are still waiting for solutions.

Ultimately, this is about more than just one product. It's about whether we can build a health care system that rewards real breakthroughs without leaving patients behind. If we get that balance right, therapies like epithelium-on oxygen-enriched cross-linking won't just preserve vision–they'll help define the future of rare disease care. ■

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