Epidemiology and economic impact of moderate and severe neurotrophic keratopathy in Italy

Sanja Stanisic¹, Alessia Marocco¹, Anna Gallo¹, Paolo Rama², Marta Sacchetti³, Maurizio Rolando⁴, Augusto Pocobelli⁵, Roberto Ceccuzzi⁶, Andrea Leonardi⁷, Rita Mencucci⁸, Emilio Pedrotti⁹, Elisa Postorino¹⁰, Maurizio Mascia¹¹, Lucia R Mazzamuto¹¹, Luisanna Prisco¹¹, Floortje Van Nooten¹¹ and Patrizia Berto¹

Abstract

Neurotrophic keratopathy is a rare corneal disease caused by impaired corneal innervation. There is a paucity of published evidence on neurotrophic keratopathy with no published studies on the economics of neurotrophic keratopathy in the Italian or international literature. This cost analysis aimed at assessing the economic impact of moderate (persistent epithelial defect) and severe (corneal ulcer without perforation) neurotrophic keratopathy from the perspective of the National Health Service and patients in Italy. Treatment algorithm and health resource use information were collected from a panel of nine experts from Italian centres specialized in ocular/corneal conditions. National ambulatory and inpatient hospital tariffs were applied to units of service, and Agenzia Italiana del Farmaco (AIFA) published prices to pharmaceuticals. Mean annual per patient cost was derived as an average cost weighted by the proportion of patients on each respective treatment and length of the treatment. The National Health Service patient perspective additionally included patients’ out-of-pocket expenses. The mean annual estimated National Health Service cost of treatment was €5,167 (persistent epithelial defect) and €10,885 (corneal ulcer without perforation) per patient. Costs were largely driven by ambulatory visits and hospital interventions. The mean annual estimated National Health Service + patient cost was €5,731 (persistent epithelial defect) and €11,478 (corneal ulcer without perforation) per patient, including cost of out-of-pocket expenses for pharmaceuticals and therapeutic contact lenses. Mean annual cost of neurotrophic keratopathy in Italy doubles with disease severity. Further research is warranted to provide more insight especially into societal costs.

Keywords

Neurotrophic keratopathy, corneal diseases, corneal sensitivity, cornea/innervation, keratitis/therapy, cost analysis

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¹Analytica LASER, Milano, Italy
²San Raffaele Hospital, Milan, Italy
³Department of Sense Organs, Sapienza University of Rome, Rome, Italy
⁴Ocular Surface Centre, Ispre Ophthalmics Genoa, Genoa, Italy
⁵San Giovanni Addolorata Hospital, Rome, Italy
⁶Department of Ophthalmology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
⁷Department of Neuroscience, Ophthalmology Unit, University of Padua, Padua, Italy
⁸Careggi University Hospital, Florence, Italy
⁹Borgo Trento Hospital, Verona, Italy
¹⁰Messina University Hospital, Messina, Italy
¹¹Dompé Farmaceutici S.p.A., Milan, Italy

Corresponding author:
Sanja Stanisic, Analytica LASER, Via Giovanni Battista Pirelli 27, Milano 20124, Italy.
Email: s.stanisic@analytica-laser.com

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Neurotrophic keratopathy (NK), also known as neuroparalytic keratitis or neurotrophic keratitis, is a rare corneal disease which can originate from ocular, iatrogenic, systemic and/or congenital disorders.\(^1\) It is caused by damage to the ophthalmic branch of the trigeminal nerve which plays a key role in eye homeostasis.\(^{1,2}\) Impaired trigeminal innervation has a negative impact on anatomic integrity and function of the cornea and its epithelium in particular, leading to epithelial lesions, reduced corneal healing, and development of ulcerations, melting, corneal perforation and in the most severe cases functional eye loss. The primary physical symptom of NK is a decrease or absence of corneal sensation.\(^3\)

Various underlying diseases, including ophthalmic and systemic conditions, may induce trigeminal nerve impairment and hence cause NK development. Mastropasqua et al.\(^2\) provided an overview of the current understanding on the causes of the trigeminal nerve damage that may lead to NK development (Figure 1). The most frequent are recurrent viral conditions such as herpes simplex keratitis and herpes zoster keratoconjunctivitis\(^1\) and corneal hypoesthesia and/or anaesthesia as sequelae of diabetes mellitus or multiple sclerosis. Other frequent causes are of iatrogenic nature and include surgical interventions, excessive use of topical anaesthetics and chronic glaucoma therapy.\(^1\)

Clinical staging is based on disease severity and includes the following categories, according to Mackie\(^4,5\):

- **Stage I (mild).** Punctate keratopathy and/or corneal epithelial hyperplasia and irregularity, which may be associated with superficial neovascularization and stromal scarring. Disease onset is usually unnoticed by patients due to reduced corneal sensitivity.\(^6\) Dry eye signs may be observed, including vital dye (such as fluorescein or lissamine green) staining of the inferior palpebral conjunctiva and decreased tear film break-up time. If left untreated, stage I may evolve to persistent epithelial defects (PEDs).
- **Stage II (moderate).** PED, defined as the loss of epithelial integrity, caused by an injury or disease, which does not heal within the expected time course (2 weeks) in the absence of microbial keratitis, and

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**Figure 1.** Causes of trigeminal nerve damage leading to NK development (Mastropasqua).\(^2\)

NK: neurotrophic keratopathy.
despite the use of topical lubricants,\(^7\)\(^-\)\(^9\) is typically oval or circular in shape, with smooth and rolled edges. Usually, there is an area of poorly adherent opaque and oedematous epithelium around the epithelial defect, which can spontaneously detach leading to PED enlargement. A drop in visual acuity may be reported.\(^9\)

- **Stage III (severe).** Often ensues if stages I and II are not treated appropriately. This stage is characterized by stromal involvement with corneal ulcer (CU), defined as epithelial defects with coexisting stromal loss with or without secondary infections,\(^1\)\(^,\)\(^6\)\(^,\)\(^10\) which may progress to perforation and/or stroma melting. CU with secondary infection (bacterial, viral, fungal) are usually resolved with antimicrobial therapy while the non-infectious (neurotrophic, chemical, immune-mediated, toxic) ones present significant diagnostic and therapeutic challenges.

The course of NK progression may vary depending on the trigeminal damage duration and the presence of concomitant ocular surface diseases such as dry eye, exposure keratitis and limbal stem cell deficiency.\(^3\) Due to reduced innervation and thus reduced sensitivity, progression is frequently asymptomatic. NK patients will frequently report blurred vision but rarely report ocular discomfort.\(^3\) NK prognosis depends on multiple factors including the underlying cause of disease, level of corneal impairment and potential association with other eye conditions. If not appropriately treated, NK may lead to corneal melting, perforation and ultimately functional eye loss.\(^1\)

NK is an orphan disease with an estimated prevalence across EU of less than 5 in 10,000 individuals (www. orpha.net). Due to its rarity, there is also general paucity of evidence on NK: the only published data available are reported by the Italian authors Sacchetti and Lambiase,\(^3\) suggesting an incidence and prevalence below 1.6/10,000. The estimate was derived by combining the prevalence rate of underlying NK disease or surgical procedure, in the general population, with the percentage of NK patients affected by the respective disease/procedure: estimated prevalence of NK due to herpetic keratitis was 1.22/10,000 (based on the incidence of NK (6%) in herpetic keratitis (prevalence of herpetic keratitis in general population 149/10,000)), and for NK as a consequence of surgical conditions was 0.02/10,000 (based on the occurrence of NK as a consequence of trigeminal neuralgia interventions 2.8%).\(^3\) Notably, all the reported estimates fall quite below the threshold for orphan diseases.\(^3\)

There is no international consensus on treatment and management of NK. A few publications discuss possible management options in treating patients with PED, CU or NK as a whole,\(^1\)\(^,\)\(^3\)\(^,\)\(^10\)\(^-\)\(^12\) while only Sacchetti and Lambiase\(^3\) provided indications on a stepwise approach to disease management. The main treatment goals are preserving epithelial integrity, promoting epithelial healing and preventing corneal damage progression.\(^1\) Early diagnosis, severity-based treatment and frequent monitoring are key for achieving this.\(^1\)\(^,\)\(^3\) Treatment is commonly sequential in nature: it is initiated with the use of less invasive, pharmacological options, for example, lubricant eye drops to provide eye lubrication, topical antibiotics to prevent super-infections and eye drops or gels to promote healing and preserve epithelial integrity. In refractory patients, or those with already progressed disease at diagnosis, the use of therapeutic contact lenses or more invasive, non-pharmacological, treatment alternatives is required. These include amniotic membrane transplantation (AMT), tarsorrhaphy (permanent or temporary) or conjunctival flap. The use of supportive therapies with the aim to preserve humidity and protect eye surface (e.g. artificial tears) is chronic and often lifelong.\(^1\)\(^,\)\(^3\) Nonetheless, all treatments are palliative and none addresses the underlying cause of the disease, that is, the impairment of corneal innervation and decrease of corneal sensitivity due to neurotrophic defect.\(^1\)\(^,\)\(^3\) In addition, none is specifically developed for NK population and only few studied systematically in prospective, controlled, randomized trials of NK patients.\(^1\)\(^,\)\(^3\) Indeed, considerable variability in treatment approaches could be likely explained by their palliative nature. As a matter of fact, the NK management is tailored to individual needs and in practice many treatments are used sequentially and/or concurrently. Even if complete corneal healing is achieved, patients remain at risk of relapse and need to be followed up at regular time intervals.

While there are no studies on the economics associated with NK, it is anticipated that frequent monitoring, chronic use of topical therapies, surgical interventions in mild and severe stages, as well as absenteeism due to recurrent medical examinations may lead to substantial costs for the National Health Service (NHS), for individual patients and for the society as a whole.

The aim of the present cost analysis is to assess the economic impact of moderate (PED) and severe (corneal ulcer without perforation, CU-wp) NK, from the NHS and patient perspectives in Italy.

**Methods**

**Expert panel**

Given the lack of published data, information on the distribution of NK patients by severity, treatment approach, including estimated percentage of use for each individual treatment/therapy, as well as the use of healthcare resources were collected from a panel of nine experts from Italian centres specialized in ocular/corneal conditions.\(^14\) Italian experts were selected by geographic distribution,
representativeness of their centre in treating NK and duration of practicing medicine. The expert panel was conducted in March 2017. Participants were asked to report estimates based on their own experience and judgement, by means of a semi-structured questionnaire, which was administered during 1- to 1.5-hour telephone interviews. The questionnaire included sections on: (a) estimated average distribution of NK patients they annually follow-up by stage, (b) treatment approach and (c) healthcare resources use (physician and nurse ambulatory visits, examinations, treatments, hospital admissions) in the course of NK management. Data were reported by disease stage.

In addition, experts were also asked to react to the concept of complete healing in their practice defined as: ‘lesion smaller than 0.5 mm in its longer diameter, assessed in front of the slit lamp after fluorescein staining’. A rather broad definition was offered to acknowledge potential variability in the clinical practice and variability in fluorescein staining in patients with healthy cornea reported in the literature.15,16

Cost analysis

This cost analysis was developed in line with principles of good practice for conducting economic evaluations of the healthcare programmes.17 The cost analysis from the NHS’ perspective included medical costs of health resources (cost of pharmaceuticals, ambulatory and inpatient hospital procedures and ambulatory follow-up visits) funded through the NHS calculated based on consumption estimates reported by the experts and unit costs applied from the published Italian NHS’ sources (see Supplementary Material).18–21

The cost of pharmaceuticals was derived from official 2017 drug list prices.20 For ambulatory and inpatient hospital procedures (such as AMT, tarsorrhaphy and scleral lens implants), procedure codes were identified using the ICD-9-CM classification of diseases and procedures and their unit costs were retrieved from published official Tariff Lists.18

The cost of each treatment was derived by multiplying unit cost by treatment frequency; the mean annual per patient cost was derived as an average cost weighted by the proportion of patients on each respective treatment and length of treatment.

The analysis from the NHS + patient perspective included medical costs incurred by the Italian NHS and those incurred by the patients for non-reimbursed treatments and technologies (i.e. out-of-pocket expenses). Out-of-pocket expenses for medical costs were based on expert-reported consumption estimates and official market prices or tariffs.

Results

According to the experts, patients affected by PED and CU-wp, respectively, represent 34% and 21%, of all NK patients, in Italy. This estimate included newly diagnosed patients, patients on regular follow-up at ophthalmology centres, as well as patients referred by other centres or by general practitioners.

Half of the respondents (50%) confirmed they use the definition presented in the discussion in their daily practice ‘lesion smaller than 0.5 mm in its longer diameter, assessed in front of the slit lamp after fluorescein staining’, whereas 50% considered patients as completely healed only in ‘complete absence of eye lesion’, that is, lesion size = 0 mm.

Current approaches in NK management

Eight out of nine experts reported the use of a defined treatment approach in NK management. Respondents were highly consistent on the type of treatments used, while the sequences varied based on their opinions, patients’ preferences and access to therapy. The typical treatment approach by disease stage is provided in Table 1.

The experts reported that 100% of their patients presenting PED and in 95% of their patients with CU-wp use artificial tears during the whole disease course. The use of contact lenses (both therapeutic and scleral) was reported for approximately 60% of their patients for an average duration of 2 months; depending on treatment outcomes, contact lenses may be used as short as 2 weeks if there is no improvement, for up to several months if shown beneficial; only one of nine respondents indicated some patients keep using contact lenses for their lifetime. Contact lens use was often associated with prophylactic use of antibiotics (in 56% patients). The use of AMT was reported for approximately 11.3% of patients and conjunctival flap for a much smaller group and typically after ‘failure of all other therapies’ (in 2.2% subjects with PED). The use of contact lenses was reported for over 60% of patients with CU-wp. Approximately 47% of CU-wp patients undergo AMT. 25.6% temporary tarsorrhaphy (medical and surgical), 23.9% are treated with autologous serum drops, 7.5% undergo conjunctival flap intervention, 2.2% permanent tarsorrhaphy and 2.0% corneal transplant.

Resource use and cost of NK management in patients with PED and CU-wp

Respondents uniformly confirmed that only ophthalmology specialists, in particular cornea specialists, are involved in the NK patient management. Reported frequency of visits was largely dependent on disease stage and progression.

The mean annual number of visits per patient is reported in Table 2. The mean monthly frequency of visits for PED stage ranged from 1 to 8 for patients with stable and 2 to 16 for patients with worsening symptoms. In CU-wp patients, reported frequency ranged from 2 to 16 in patients with stable and 6 to 16 in patients with worsening conditioning. The reported mean frequency of annual visits, in patients considered completely healed, was reduced to 9 in PED and 15 in CU-wp patients.
Calculated estimated average annual number of physician visits for patients without complete healing (either stable or worsening) was 64 visits per year for patients with PED and 105 for patients with CU-wp.

The estimated total mean annual medical cost of NK management for the Italian NHS was €5167 and €10,885 per NK PED and NK CU-wp patient, respectively (Tables 3 and 4 and Figure 2). The costs were largely driven by the cost of follow-up specialist visits (>80% and >60% of the total annual cost in the management of PED and CU-wp patients, respectively), while the cost of surgical interventions represented from 10% to 30% of the total disease management costs in these patients.

The total estimated mean annual cost from the NHS+patient perspective was €5731 and €11,478 for NK PED and NK CU-wp patients, respectively. The additional cost is associated with out-of-pocket expenses for pharmaceuticals such as artificial tears, topical antibiotics and corticosteroid drops, ophthalmic solutions based on the Regenerating Agents (RGTA®) Technology and therapeutic contact lenses not reimbursed by the Italian NHS (Tables 3 and 4 and Figure 2).

**Table 1.** Current approaches to management of NK patients with PED and CU without perforation (provided in the order from conservative to more invasive, that is, surgical approaches).

| NK management approach                      | Proportion of patients treated (%) by stage |
|---------------------------------------------|--------------------------------------------|
|                                            | PED                          | CU-wp             |
| Artificial tears                           | 100%                         | 95.6%             |
| Contact lens                               | 61.1%                        | 63.3%             |
| Therapeutic                                | 48.9%                        | Therapeutic 63.3% |
| Scleral                                    | 12.2%                        | Scleral           |
| Autologous serum eye drops                 | 20.6%                        | 23.9%             |
| Use of other topical treatments to promote healing | 17.8%                        | 17.8%             |
| AMT                                         | 11.3%                        | 47.2%             |
| Temporary tarsorrhaphy                     | 3.3%                         | 25.6%             |
| Conjunctival flap                          | 2.2%                         | 7.5%              |
| Permanent tarsorrhaphy                     | –                            | 2.2%              |
| Corneal transplant (lamellar)              | –                            | 2.0%              |

AMT: amniotic membrane transplant; PED: persistent epithelial defect; NK: neurotrophic keratopathy; CU: corneal ulcer.

*RGTA® Technology–based ophthalmic solution.

**Table 2.** Estimated number of specialist visit per stage and disease progression (per patient per year).

| NK stage/disease status                  | PED | Range (mean number of visits per patient per month) | CU-wp | Range (mean number of visits per patient per month) |
|------------------------------------------|-----|-----------------------------------------------------|-------|-----------------------------------------------------|
| Not completely healed but remaining stable | 36.9 | 1–8                                                 | 78.7  | 1–12                                                 |
| Not completely healed but worsening      | 90.8 | 2–16                                                | 132   | 6–16                                                 |
| Completely healed                        | 9.0  | 0.2–2                                               | 15.6  | 0.2–4                                               |

CU-wp: corneal ulcer without progression; NK: neurotrophic keratopathy; PED: persistent epithelial defect.

**Discussion**

Despite its complexity, a key challenge in NK management is the asymptomatic nature of this disease. Appropriate management is possible only with timely diagnosis and very frequent monitoring (e.g. up to every 36 hours in patients with CU-wp). NK poses a significant burden to the Italian NHS and to the patients with the mean annual per patient costs of €5731 and €11,478 in patients with PED and CU-wp, respectively. Considering reported distribution of PED and CU-wp patients (34% and 21%), weighted annual NHS + patient costs could be estimated at €7955 per patient. Reported costs may be substantially reduced in patients with punctate keratopathy as these patients require fewer monitoring visits and the use of invasive interventions is anticipated in very few patients. In contrast, severe patients with CU perforation or melting may need hospitalization for the initial surveillance (as reported by the panelists) or ambulatory monitoring on daily basis. In addition, distribution of treatments in this group is highly skewed towards surgical interventions.
Costs of NK are largely driven by the frequency of specialist visits. Given the estimated number of follow-up visits in patients with healed condition, from 1 to 2 per month in the first year and up to 1 visit annually in the subsequent years, it is anticipated that burden to the NHS could be substantially reduced if patients are managed timely and appropriately. Panellists showed unequivocal consensus on the importance of timely disease management.

Current treatment approaches reported by survey experts, although broadly consistent in the treatment type, varied in the proposed sequence depending on physicians’ and patients’ preferences. For example, it is widely

### Table 3. Estimated mean annual per patient cost of NK-PED, 2017.

| Description                              | Unit cost (€) | Mean frequency per patient/year | Mean treatment duration | Probability | Total cost per patient/year (€) |
|------------------------------------------|---------------|---------------------------------|-------------------------|-------------|---------------------------------|
| Specialist visit                         | 52            | 1 at treatment initiation       |                         | 100%        | 52                              |
| Specialist visit (follow-up)             | 71            | 64 per year                     |                         | 100%        | 4557                            |
| Autologous serum drops                   | 152           | 1                               | 2 months                | 21%         | 62                              |
| Permanent tarsorrhaphy                   | 1167          | 1                               |                         | 0%          | 0                               |
| Temporary tarsorrhaphy                   | 1167          | 3                               |                         | 3%          | 117                             |
| AMT                                      | 1522          | 2                               |                         | 11%         | 345                             |
| Conjunctival flap                        | 1522          | 1                               |                         | 2%          | 34                              |
| NHS cost per patient/year                |               |                                 |                         |             | €5,167                          |
| Artificial tears                         | 15            | Preservative free two bottles per month | 12 months              | 100%        | 360                             |
| Contact lens                             | 23            | 2 per month                     | 3 months                | 49%         | 68                              |
| Topic antibiotics                        | 17            | 3 bottles per month             | 3 months (assumed used during the course of contact lens use) | 56%         | 83                              |
| Topic corticosteroids                    | 13            | 3 bottles per month             | 1 months                | 19%         | 8                               |
| RGTA® Technology–based ophthalmic solution | 58          | 2.5 per year                   | Estimated 1.78         | 18%         | 46                              |
| NHS + patient cost per patient/year      |               |                                 |                         |             | €5,731                          |

AMT: amniotic transplant; NHS: National Health Service; NK: neurotrophic keratopathy; PED: persistent epithelial defect.

### Table 4. Estimated mean annual per patient cost of NK-CU-wp, 2017.

| Description                              | Unit cost (€) | Mean frequency per patient/year | Mean treatment duration | Probability | Total cost per patient/year (€) |
|------------------------------------------|---------------|---------------------------------|-------------------------|-------------|---------------------------------|
| Specialist visit                         | 52            | 1 at treatment initiation       |                         | 100%        | 52                              |
| Specialist visit (follow-up)             | 71            | 105 per year                    |                         | 100%        | 7,519                           |
| Autologous serum drops                   | 152           | 1                               | 2.5 months              | 24%         | 91                              |
| Permanent tarsorrhaphy                   | 1167          | 1                               |                         | 2%          | 26                              |
| Temporary tarsorrhaphy                   | 1167          | 3                               |                         | 26%         | 894                             |
| AMT                                      | 1522          | 3                               |                         | 47%         | 2,156                           |
| Conjunctival flap                        | 1522          | 1                               |                         | 8%          | 114                             |
| Corneal transplant                       | 1641          | 1                               |                         | 2%          | 33                              |
| NHS cost per patient/year                |               |                                 |                         |             | €10,885                          |
| Artificial tears                         | 15            | Preservative free two bottles per month | 12 months              | 96%         | 344                             |
| Contact lens                             | 23            | 2 lenses per month              | 3 months                | 63%         | 88                              |
| Topic antibiotics                        | 17            | 3 bottles per month             | 3 months (assumed used during the course of contact lens use) | 77%         | 115                             |
| Topic corticosteroids                    | 13            |                                 |                         |             |                                  |
| RGTA® Technology–based ophthalmic solution | 58          | 2.5 per year                   | Estimated 1.78         | 18%         | 46                              |
| NHS + patients cost per patient/year     |               |                                 |                         |             | €11,478                          |

AMT: amniotic transplant; CU-wp: corneal ulcer without progression; NHS: National Health Service; NK: neurotrophic keratopathy.
recognized that tarsorrhaphy impacts individual quality of life (discomfort, avoiding social activities given mechanical lid closure) as compared to the conjunctival flap where the impact on quality of life is associated with limited eye acuity (since the intervention preserves the eye, but visual function is disabled).

Another example of the difficulties and problems that impact the treatment approach and sequence, as well as access to treatment, are out-of-pocket expenses associated with chronic use of topical eye gels and drops (e.g. RGTA® Technology–based solutions) and challenges with autologous serum drops production. In particular, production of autologous serum drops in Italy is reserved only in specialized healthcare centres (not uniformly distributed across the country) and these logistical challenges pose hurdles to patient access to treatment.

Since the present analysis is the first to describe the economics and treatment patterns of NK, these results cannot be put into context of other literature. Even so, there are some limitations to the current analysis which should be regarded in the context of the remarkable paucity of evidence for this particular condition. There are only a very few studies focused on NK as to epidemiology, treatment sequences, effect of the various treatments, technologies or sequences in terms of their clinical and no published studies reporting HRQoL and cost outcomes. There are no studies to inform the rate of recurrence in these patients. There is no specific ambulatory tariff or DRG code designated for interventions in the management of NK which indeed poses a challenge in identifying reliable administrative data on hospital admissions and procedures associated with the condition. In addition, due to limited information, some costs were not included in the analysis from the NHS + patient perspective: use of scleral contact lenses was reported only as a resource but not accounted for as a cost, due to the challenges of estimating cost of scleral lenses (there is no official national reference related to the unit cost). Limited information was available to account for societal perspective and account for productivity losses associated with absence from work, due to the frequent monitoring required by the condition.

For a comprehensive assessment of disease burden, it would be necessary to estimate the population size as well as all the healthcare and social resources utilized. Presently, there are no national or international registries of NK patients, which pose important challenges in estimating the number of NK patients in Italy. Based on the panellists’ experience, patients may circulate across referral centres due to disease recurrence and care-seeking needs. Considering the prevalence estimate (1.6/10,000) proposed by Sacchetti and Lambiase, it is estimated that approximately there are 9700 NK patients in Italy (based on the national population of 60,665,551 – Italian national census data, 2016). However, there are no official

Figure 2. Mean annual per patient cost of NK, 2017 – cost to the NHS and patients.
CU-wp: corneal ulcer without perforation; NHS: National Health Service; NK: neurotrophic keratopathy; PED: persistent epithelial defect.
registry to confirm the number of diagnosed patients in the country. While timely diagnosis plays an important role in the management of NK, this condition is underdiagnosed and patients are often referred to specialized centres when already at advanced stage. In contrast, some mild patients may never reach specialized centre and circulate between referrals without an appropriate treatment and monitoring. Thus, there is a clear need for structured collection of patient data and follow-up. Moreover, there is an impelling need for higher awareness about the condition to allow for early and appropriate diagnosis when patients are still in stage I or they report only initial epithelial defect.

Given there are no international and national guidelines with recommendations on the management of NK and no published studies that focused on economic implications of this condition, this research offers insight into the current approaches in daily management of NK patients with PED and CU-wp in Italy and provides an estimate on the associated economic implications.

The mean per patient annual cost of neurotrophic keratitis in the Italian healthcare setting is substantial and doubles with disease severity. Further research is warranted to enhance understanding of the overall NK burden, including economic impact of societal costs as well as HRQoL burden in this patient group.

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References
1. Bonini S, Rama P, Olzi D, et al. Neurotrophic keratitis. Eye (Lond) 2003; 17(8): 989–995.
2. Mastropasqua L, Massaro-Giordano G, Nubile M, et al. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol 2017; 232(4): 717–724.
3. Sacchetti M and Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol 2014; 8: 571–579.
4. Groos JJ. Neurotrophic keratitis. In: Krachmer J, Mannis M and Holland E (eds) Cornea: clinical diagnosis and management. St Louis, MI: Mosby, 1997, p. 1340.
5. Mackie I. Neuroparalytic keratitis. In: Roy F and Mitchell P (eds) Current ocular therapy. Philadelphia, PA: W.B. Saunders, 1995, pp. 452–454.
6. Pushker N, Dada T, Vajpayee RB, et al. Neurotrophic keratopathy. CLAO J 2001; 27(2): 100–107.
7. Geerling G and Hartwig D. Autologous serum eyedrops for ocular surface disorders. In: Reinhard T and Larkins F (eds) Cornea and external eye disease, Switzerland: Springer, 2006, pp. 2–20.
8. McCulley JP, Horowitz B, Hussein ZM, et al. Topical fibroenectin therapy of persistent corneal epithelial defects. Fibronectin Study Group. Trans Am Ophthalmol Soc 1993; 91: 367–386.
9. Roy F, Fraunfelder F and Mackie I. Roy and Fraunfelder’s current ocular therapy. Philadelphia, PA: Elsevier; W.B. Saunders, 2008, pp. 383–386.
10. Tuli SS, Schultz GS and Downer DM. Science and strategy for preventing and managing corneal ulceration. Ocul Surf 2007; 5(1): 23–39.
11. Katzman LR and Jeng BH. Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol 2014; 28(3): 168–172.
12. Mantelli F, Nardella C, Tiberi E, et al. Congenital corneal anesthesia and neurotrophic keratitis: diagnosis and management. Biomed Res Int 2015; 2015: 805876.
13. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. Cornea 2005; 24(6): 654–660.
14. The Belgian Health Care Knowledge Centre (KCE). Belgian guidelines for economic evaluation and budget impact analysis (No. KCE Report 183C). 2nd ed. Brussels: The Belgian Health Care Knowledge Centre, 2012.
15. Dundas M, Walker A and Woods RL. Clinical grading of corneal staining of non-contact lens wearers. Ophthalmic Physiol Physiol 2001; 21(1): 30–35.
16. Schwallie JD, Mckenney CD, Long WD, et al. Corneal staining patterns in normal non-contact lens wearers. Optom Vis Sci 1997; 74(2): 92–98.
17. Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press, 2015.
18. Gazzetta Ufficiale n. 23 del 28 gennaio 2013: Tariffe delle Prestazioni di Assistenza Ospedaliera per Acuti e Prestazioni di Assistenza Specialistica Ambulatoriale, 2013.
19. Regione Lombardia Deliberazione N X/5235 del 31-05-2016 Tariffe di Cessione degli Emocomponenti e degli Emoderivati, 2016.
20. Informatore Farmaceutico, 2017, www.codifa.it (accessed 2 May 2017).
21. RER Delibera 2016-06-22 Linee di Indirizzo Regionali per la Produzione e L’utilizzo di Emocomponenti per Uso Non Trasfusionale e per le relazioni tra strutture pubbliche e private interessate al loro impiego (Allegato B. Tariffe Non Trasfusionale e per le relazioni tra strutture pubbliche per la Produzione e L’utilizzo di Emocomponenti per Uso Non Trasfusionale).
22. ISTAT. Popolazione residente al 1° gennaio 2016, 2017 http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1# (accessed 2 May 2017).