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Guidelines

Management of congenital ichthyoses: guidelines of care: Part one: 2024 update

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Abstract

In 2019, a group of experts published the first European guidelines for the management of congenital ichthyoses after a multidisciplinary expert meeting held in 2016. An update of these guidelines and literature search was planned every 5 years, given the clinical, molecular and therapeutic advances, including the use of biologic therapies. We present here updated guidelines that have been developed by a reorganized multidisciplinary group of international experts. The evidence is based on a systematic review of recent literature, discussions and consensus reached at an expert conference held in June 2023. The guidelines provide summarized evidence and expert-based recommendations that aim to guide clinicians in the management of these rare and often complex diseases. These guidelines consist of two sections. This Part one covers topical and systemic therapies (including oral retinoids, biologics and Janus kinase inhibitors), future therapeutic approaches, psychosocial management, telemedicine, communicating the diagnosis and genetic counselling, prenatal diagnosis and preimplantation genetic testing.

Lay summary

Congenital ichthyoses are a group of rare skin diseases. In 2019, clinical experts released guidelines for treating them. The team of experts updates these guidelines every 5 years. This ensures they include advancements in treatments and understanding of the diseases.

An international team of experts carried out the latest update in 2023, in two parts. In this Part one, we focus on providing recommendations for different treatments options. These treatments include both oral and injected medications. The team reports Part two separately.

Part one also covers future treatment options. These include managing the psychological and social impacts of living with a rare skin disease. This part also covers telemedicine, and how to communicate diagnoses and genetic information. Finally, this part addresses genetic testing before birth and before implantation.

What is already known about this topic?

- In 2019, a group of experts published the first European guidelines for the management of congenital ichthyoses.
- Clinical, molecular and therapeutic advances have been made recently, justifying an update of these guidelines.

What does this study add?

- These updated 2024 guidelines for the management of congenital ichthyosis are now international and may help to improve outcomes and quality of life for patients.

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Congenital ichthyoses (CIs) are a heterogeneous group of genetic diseases that typically appear at birth or early in life. They affect the entire skin and are characterized by hyperkeratosis, scaling and often skin inflammation and fragility. The CIs are primarily monogenic, with defects in around 75 genes identified so far, all leading to a defective skin barrier.[1] Classification is based on clinical presentation, distinguishing between nonsyndromic ichthyoses and syndromic ichthyoses (associated with nonskin anomalies).[2] CIs significantly impact quality of life and require lifelong treatment.

In 2019, we published the first European CI management guidelines, with updates planned every 5 years. This update is prompted by new therapeutic options.[3,4] Developed by a reorganized multidisciplinary team of international experts, the updated guidelines are based on systematic literature review, discussions and consensus reached at an expert conference. The recommendations are split into two sections. Part one addresses therapies (topical and systemic), psychosocial management, education, telemedicine and genetics. Part two covers complications and specific features of certain forms of CI.

Methods

The methodology for this update is detailed in Appendix S1 (see Supporting Information). Briefly, it followed the 'CheckUp' process.[5] A group of international experts and patient support group representatives attended a consensus meeting in June 2023, following a literature review. Evidence levels and recommendation grades were assessed using the Scottish Intercollegiate Guidelines Network (Appendix S2; see Supporting Information).

As only a few double-blind randomized controlled trials (DBRCTs) were found, most evidence came from small series or case reports, resulting in evidence level 3 or 4 (expert

Table 1 Use of topical therapies: recommendations with level of evidence and grade

Recommendations	Level of evidence	Grade	Type of recommendation
Topical therapy			
• The choice of the topical agent is based on several parameters: severity and form of ichthyosis, location of the lesions, availability in the country, formulation and texture, reimbursement and cost, personal experience of the clinician and patient preferences	4	D	UR
Emollients			
• Emollients should be used in all types of ichthyosis, alone or in combination with other therapies	1	B	UR
• Emollients should be applied at least twice daily and ideally after bathing	3	D	UR
• Occlusive moisturizers should be used with caution in hot climates	4	D	UR
Keratolytics			
• Thickened or hyperkeratotic skin may require keratolytics	1	B	UR
• Keratolytics may be applied once or twice daily and can be tapered depending on the response and side-effects	1	B	UR
• Keratolytics should be avoided in cases of inflamed or eroded skin, and on the flexures and face	1	B	UR
• Keratolytics are relatively contraindicated during the first 6–12 months of life	3	D	UR
• Urea must be used with caution in the neonatal period, except in very limited areas such as palms and soles	3	D	**MR**
• Salicylic acid is strictly contraindicated in children under the age of 2 years	3	D	UR
• Calcipotriol may be worth trying in some patients	3	B	UR
Topical retinoids			
• Topical retinoids are contraindicated during pregnancy	1	D	UR
• We recommend tazarotene as a first-line option to reduce scaling or skin thickening and avoid systemic therapy	3	B	**NR**
N-Acetylcysteine			
N-Acetylcysteine is not recommended (due to the sulfuric smell, irritation and cost)	3	D	UR
Targeted topical therapy			
• The combination of topical cholesterol with a topical statin is recommended in CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)	3	B	**NR**
Bathing			
• Bathing once or twice a day with mild soap is recommended	4	D	UR
• Additives and mechanical removal of scales may be used	4	D	UR
• Routine use of antiseptics is not recommended	4	D	UR
• Thermal therapy may be useful	2+	C	UR
Scalp			
• In case of thick scales, apply emollient or keratolytic (washable preparation) before shampooing then gently remove scales. Variable weekly periodicity. Caution in children	4	D	UR
Palmoplantar keratoderma			
• In case of disabling lesions in adults: manual removal of excess callus after application for a limited period, under a plastic film, of high concentrations of keratolytics in ointment formulations after protection of fissures and surrounding skin	4	D	UR

Adapted from the SIGN50 Guideline Developer's Handbook, NHS Scottish Intercollegiate Guidelines Network, revised edition 2019 (https://www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook). MR, modified recommendation; NR, new recommendation; UR, unchanged recommendation.

opinion). Recommendations for Part one are outlined in the text and are summarized in Tables 1–3, where they are categorized as new, modified, unchanged or deleted, along with detailed explanations. A summary of the actions for each section is provided in Table S1 (see Supporting Information).

Topical and systemic therapies

Treatment choice depends on morphology (scaling, skin thickening), distribution, presence of inflammation or erosions, severity, impact on quality of life and patients' age.

Table 2 Use of systemic therapies: recommendations with level of evidence and grade

Recommendations	Level of evidence	Grade	Type of recommendation
Systemic therapy			
• Systemic therapy may be considered in addition to topicals if insufficiently effective, or in lieu of topicals if patients need respite from constraining skincare	2	D	UR
Oral retinoids			
• Initial prescription and treatment initiation must be supervised by or at least discussed with a dermatologist experienced in ichthyosis management	2	D	UR
• The choice of the oral retinoid depends on the country. Acitretin, if available and licensed, is the best option (efficacy and safety profile). Alitretinoin and isotretinoin are preferred for female patients considering a future pregnancy (shorter half-life)	2	D	**MR**
• The optimal dosage of acitretin varies between patients and depends on the type of ichthyosis. Most patients do not require > 0.5 mg kg^{-1} per day. The optimal dose is the lowest dose that will achieve and maintain the desired therapeutic effect with acceptable side-effects. Patients with marked erythroderma and/or skin fragility should be treated with caution using a low dose	2	D	UR
• Precautions and regular monitoring are mandatory	2	D	UR
• The pregnancy prevention programme must be performed carefully in women of childbearing potential	2	D	UR
• Treatment for children should be prescribed in collaboration with an expert in paediatric dermatology	2	D	UR
• Patients with syndromic ichthyosis may be candidates for oral retinoids if side-effects are monitored more closely	2	D	UR
Biologics and small molecules			
• Biologics (at standard doses used for atopic dermatitis or psoriasis) are worth trying in the severe erythrodermic form of ichthyosis. Oral retinoids may be given in parallel to reduce scaling	3	D	**NR**
• Janus kinase inhibitors cannot be recommended (not enough data)	3	D	**NR**

Adapted from the SIGN50 Guideline Developer's Handbook, NHS Scottish Intercollegiate Guidelines Network, revised edition 2019 (https://www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook). MR, modified recommendation; NR, new recommendation; UR, unchanged recommendation.

Table 3 Use of psychosocial management, telemedicine, communicating the diagnosis and genetic counselling, prenatal diagnosis and preimplantation genetic testing: recommendations with level of evidence and grade

Recommendations	Level of evidence	Grade	Type of recommendation
Psychosocial management, educational therapy, telemedicine, communicating the diagnosis, genetic counselling, prenatal diagnosis and preimplantation genetic testing			
• Families must be informed about patient support groups	4	D	UR
• Quality of life and burden must be assessed	3	D	UR
• Mental health must be assessed	2	D	**NR**
• Psychosocial management should be offered as soon as possible and throughout life. It should be adapted to the patient's age, sociocultural level, needs and expectations	4	D	UR
• During the neonatal period, close physical contact between the baby and the parents is essential	4	D	UR
• Families must be informed about the opportunities related to reimbursement, school facilities and professional help, ideally with the aid of a social worker and patient association	4	D	UR
• If available, educational interventions may be very useful	3	D	UR
• Telemedicine can be a useful option to minimize travel times and cost, but cannot replace a face-to-face visit	4	D	**NR**
• Communication of the diagnosis to the family should be offered as soon as possible, ideally during a multidisciplinary consultation involving a clinical geneticist, psychologist and dermatologist	4	D	UR
• Molecular diagnosis should be performed as early as possible	4	D	UR
• Genetic counselling must be offered to the family and patient	4	D	UR
• Prenatal diagnosis and preimplantation genetic testing can be offered to families if available	4	D	UR

Adapted from the SIGN50 Guideline Developer's Handbook, NHS Scottish Intercollegiate Guidelines Network, revised edition 2019 (https://www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook). NR, new recommendation; UR, unchanged recommendation.

Topical therapy

A summary of topical agents used in CIs is provided in Table S2 (see Supporting Information).

Emollients (no update, revision of the references)

Emollients are summarized in Appendix S3 (see Supporting Information).

Keratolytics (update)

Several studies, including DBRCTs, have shown that keratolytics like urea, alpha-hydroxyacids, propylene glycol and salicylic acid are more effective in reducing scaling and skin thickening than emollients alone.[6–13] No specific keratolytic agent has proven superior, but urea is most common (requiring ≥ 10% for keratolysis and up to 40% for localized thickening, e.g. joints or palmoplantar keratoderma).

Keratolytics can be applied once or twice daily and tapered as needed. They may cause irritation, especially on sensitive areas like the face or flexures. Keratolytics are relatively contraindicated in the first 6–12 months due to epidermal barrier defects in CI, immature stratum corneum, and higher body-surface-to-mass ratio,[14] increasing systemic absorption and toxicity risk.[15–20] For example, salicylic acid has caused life-threatening toxicity in young children,[15,16,18–20] while poisoning was reported using lactic acid[17] and propylene glycol.[17,21] There are no reports of toxicity from urea in children, but high blood urea concentrations after cutaneous application of 10% urea (plus 5% lactic acid) have been reported in collodion babies and infants with lamellar ichthyosis (LI).[22,23]

Therefore, salicylic acid and lactic acid are strictly contraindicated in children under the age of 2 years, and urea should not be used in the neonatal period, except on very limited areas such as the palms and soles.

Calcipotriol, a vitamin D derivative, used in amounts up to about 100 g per week, was demonstrated to be moderately efficacious, well tolerated and safe in short-term treatment of adults (DBRCT of 67 patients with various disorders of keratinization, including CI).[24] In children, it should be used with caution because of a lack of data, especially on safety.

Topical retinoids (update)

A DBRCT of topical trifarotene (0.01% or 0.02%) was recently withdrawn due to lack of efficacy.

Another DBRCT on CI (seven patients with LI, seven with X-linked recessive ichthyosis) showed topical isotretinoin (0.05% or 0.1% on < 12% body surface) to be effective, with mild side-effects and no major safety concerns or systemic exposure.[25] A trial with topical isotretinoin 0.05% is currently ongoing. Clinical results are pending, with no clinically significant changes observed in laboratory values so far.[26]

Tazarotene has shown efficacy in various forms of CI, including an open study of 12 patients,[27] small series and case reports.[28–38] Tazarotene (0.05–0.1%) is recommended as a first-line option to reduce scaling or skin thickening and avoid systemic therapy, although availability may be limited due to cost, insurance and off-label use. Concerns remain about systemic exposure, although an open-label study including children found no detectable plasma levels in most patients using it long term on large body areas.[39]

While adapalene was used in one case of epidermolytic ichthyosis,[40] weaker topical retinoids for acne have not been sufficiently studied to issue recommendations.

Regarding teratogenesis, a meta-analysis of pregnant women exposed to topical retinoids suggests they are safe, and repeated use on limited areas is unlikely to cause systemic effects.[41,42] However, due to the risks of systemic retinoids in fetal development, topical retinoids remain contraindicated during pregnancy or if pregnancy is planned.

N-Acetylcysteine (no update, new references)

N-Acetylcysteine is discussed in Appendix S4 (see Supporting Information).

Targeted topical therapy (update)

In CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects), combining topical cholesterol with a statin has led to remission in several case reports.[43–45] The most commonly used concentration is 2% statin (lovastatin or simvastatin) with 2% cholesterol, although other concentrations are being tested.[46,47] Using statins without cholesterol or evidence for statin or cholesterol in autosomal recessive CI is very limited.[46,48] While these preparations are easy to make, access to components and reimbursement could be limiting factors, despite the low ingredient cost.

Bathing (no update, no new references)

Bathing is covered in Appendix S5 (see Supporting Information).

Treatment of the scalp (no update, no new references)

Treatment of the scalp is discussed in Appendix S6 (see Supporting Information).

Treatment of palmoplantar keratoderma (no update, no new references)

Palmoplantar keratoderma is described in Appendix S7 (see Supporting Information).

Systemic therapy

Systemic therapy can be considered alongside or instead of topical treatments when efficacy is insufficient or patients need a break from intensive skincare.[49,50]

The standard treatment is oral retinoids, which help correct abnormal epidermal differentiation.[51]

Oral retinoids (update)

Four systemic retinoids are used: acitretin, alitretinoin, isotretinoin and etretinate (no longer available in most countries except Japan and Taiwan; Table 4).[51–53] Evidence of retinoid efficacy dates back to the late 1970s, initially with isotretinoin and etretinate.[54] Oral retinoids have revolutionized the lives of many patients with severe CI, particularly harlequin ichthyosis (HI) and LI. For Netherton syndrome or CI with severe erythroderma and skin fragility, retinoids may increase skin fragility.[55] Oral retinoids should be reserved for those with a severe phenotype and functional impairment.

Acitretin

Efficacy

The efficacy of acitretin has been demonstrated in a few pilot studies and case series. It is registered for keratinization

Table 4 Which retinoids should be recommended?

- Europe
  - First choice: acitretin. This is the only oral retinoid approved by the European Medicines Agency for congenital ichthyoses. It is more effective at reducing scaling and skin thickening, with more data supporting long-term skeletal safety
  - Women of childbearing age: alitretinoin and isotretinoin due to their faster clearance
- USA
  - No licensed retinoids
  - Isotretinoin is often prescribed to children and adolescents because of its rapid clearance, despite the burdensome iPledge monitoring system
- Asia
  - Acitretin when available
  - Etretinate in Japan

disorders in Europe by the European Medicines Agency.[56–65] Acitretin reduces scaling and skin thickening, with variable effects on erythema. Other reported benefits include improved hypohidrosis,[66] reduction of ectropion and eclabion, improved hearing (by reducing ear canal scaling) and less time on skincare.[49,50,67,68] Acitretin is particularly useful for patients with thick scaling and thickening, but also for milder forms.[69] In epidermolytic ichthyosis, the results are much better for patients with variant *KRT10* (encoding keratin 10) than those with a variant in *KRT1* (encoding keratin 1), who may worsen on retinoids.[28]

The efficacy of acitretin in children has been documented in a few small case series of various inherited epidermal differentiation disorders (EDDs), especially LI, congenital ichthyosiform erythroderma and HI.[56,62–65,70–77]

Dosage

The dosage of acitretin in adults and children is detailed in Appendix S8 (see Supporting Information).

Contraindications

Contraindications of acitretin are described in Appendix S9 (see Supporting Information). The main issue is the teratogenicity,[78–80] necessitating a strict pregnancy prevention programme.

Adverse effects of acitretin and monitoring

Common reversible effects include dryness, lipid or hepatic blood abnormalities, benign intracranial hypertension and hair loss (Table S3; see Supporting Information). The relationship between use of systemic retinoids and development of depression is controversial.[81]

Long-term musculoskeletal adverse effects are a significant source of concern, and monitoring is mandatory (Table S3). In adults, spinal and extraspinal hyperostosis and calcifications of tendons and ligaments have been reported, although these changes may overlap with age-related bone changes.[82] Most affected patients were on long-term retinoid therapy or had previously used etretinate.[83–90] Risk factors include high cumulative retinoid dose, prior etretinate use and older age. The link between retinoids and osteoporosis is debated, although some cases were reported with long-term etretinate.[91–93] A short-term prospective study with acitretin and a 25-year retrospective study of 23 patients with various EDDs on acitretin or etretinate found no increased risk.[57] Osteoporosis in patients with CI may instead relate to vitamin D deficiency (see Part two).[94,95]

In children, no bone changes have been reported with acitretin or in long-term studies (up to 25 years) of etretinate, or with both etretinate and acitretin.[56,64,96,97] Severely affected children with growth failure due to chronic disease showed improved growth after starting retinoids.[98]

Other retinoids (alitretinoin and isotretinoin)

Alitretinoin is available in most European countries but not licensed for CI. Even if it is covered by insurance it is rather expensive. It is unavailable in the USA and most of Asia, except Korea.

Significant improvements have been reported in patients with CI taking daily doses of alitretinoin 10–30 mg in seven case studies.[99–102]

Alitretinoin offers a key advantage over acitretin in terms of teratogenic risk as it has a faster clearance rate, requiring contraception for only 1 month after stopping treatment. This makes alitretinoin a preferable option for patients considering future pregnancy, although availability and cost may be limiting factors. In terms of safety, alitretinoin has similar side-effects to acitretin, with less dryness of skin and mucosa and with an added risk of central hypothyroidism and more frequent headaches.

Isotretinoin (0.5–1 mg kg^{-1} per day) is available in most countries, but only licensed for acne. It has demonstrated efficacy in CI in an large open-label study and several case reports.[103–105]

Isotretinoin has the same rapid clearance and contraception requirements as alitretinoin, making it another suitable alternative for patients planning pregnancies. The risk of depression with isotretinoin in CI has not been studied, with most research focused on patients with acne.

The safety profile of isotretinoin appears comparable with that of acitretin, showing less hair loss but raising concerns about skeletal toxicity. Hyperostosis, often affecting the spine with or without symptoms, has been reported in several studies and case reports of patients with EDD.[106–108]

A recent retrospective review of 127 adults with EDD found that only three young women developed hyperostosis, ligamentous ossification and joint stiffness after high doses of isotretinoin.[109]

Hyperostotic bone changes are common in the general population and tend to increase with age, even without retinoid exposure. This makes it unclear whether the observed toxicity is due to the drug, disease severity, treatment regimen or therapy duration.[82]

In children, premature closure of the epiphyses and growth plate deformities have been reported in case reports involving isotretinoin (or etretinate), and seem to be linked to high doses of isotretinoin (up to 3.5 mg kg^{-1}) for the duration of months to years.[98,110–114] Therefore, monitoring for musculoskeletal issues is essential. International recommendations for retinoids are described in Table 4.

The specific situation of syndromic ichthyosis

Patients with syndromic ichthyosis may be candidates for oral retinoids, even with ocular symptoms or liver involvement.[115–121] A retrospective series of 15 patients with Chanarin–Dorfman syndrome followed long term did not show liver toxicity.[122] However, these patients should be monitored more closely.

Other systemic therapies

Immunosuppressants

Ciclosporin was ineffective in an open trial of five patients with LI and therefore cannot be recommended.[123]

Biologics and Janus kinase inhibitors (new section)

Biologics

Recent findings highlight the predominance of the T helper 17 pathway in CI, along with the expanding range of biologics for common skin disorders, creating opportunities to repurpose existing biologics.[124,125]

A literature review on biologics for CI revealed numerous case reports and series showing successful treatments.[126] However, only one DBRCT was found. This involved 20 patients and reported unsuccessful results with secukinumab, an interleukin (IL)-17A inhibitor.[127]

A large retrospective international study of 98 patients with long-term follow-up showed that less than half of patients with CI responded to biologics, with only 18 showing significant improvement: patients with Netherton syndrome, congenital ichthyosiform erythroderma, HI and SAM syndrome (severe dermatitis–multiple allergies–metabolic wasting). In some cases, patients experienced worsening or only transient effects. While no safety issues were identified, cost and lack of licensing remain concerns.[126]

Therefore, we conclude that biologics at standard doses used for atopic dermatitis or psoriasis are worth considering mostly in the severe erythrodermic form of CI. Oral retinoids may be given in parallel to reduce scaling. Patients using biologics should follow their country's medication-specific recommendations, including live vaccines.

Janus kinase inhibitors

Three recent case reports describe the short-term and sometimes transient effect of Janus kinase inhibitors in CI.[128–130] There are not enough data to give any recommendations.

Future therapeutic perspectives (new section)

Due to a better understanding of the mechanisms of CI, new pathogenesis-based interventions should be considered.[131] Clinical trials are exploring topical herpes virus delivery of *TGM1* (encoding transglutaminase 1) in LI,[132] genetically engineered autologous epidermal sheets for Netherton syndrome,[133] and intravenous delivery of *SPINK5* using adeno-associated virus.[134,135] Additional research is progressing both *in vitro* and *in vivo* with gene delivery systems such as *ABCA12* (ATP binding cassette subfamily A member 12) for harlequin ichthyosis and mRNA degradation targeting mutant keratin in epidermolytic ichthyosis. *TGM1* prime editing in embryos highlights the potential of germline gene therapy for pre-emptive treatment.[136–138]

Other targeted therapies include protein replacement for LI and peeling skin syndrome, which improves skin barrier function in preclinical models,[139–141] and inhibitors targeting proteins and pathways downstream of genetic variants, such as anti-IL-36 receptor or kallikrein inhibitors.[142–144] Another approach is repurposing psoriasis biologics for CI (see 'Biologics and Janus kinase inhibitors'), epidermal growth factor receptor inhibitors for palmoplantar keratoderma and epidermolytic ichthyosis, and IL-31 receptor A antibodies for prurigo nodularis and CI.[145,146]

Gentamicin has been shown to induce readthrough of premature termination *in vitro* and in *in vivo* models of disorders caused by nonsense mutations like junctional epidermolysis bullosa.[147–149] It may therefore be useful for treatment of CI, as approximately 15% of patients carry nonsense mutations.[150–152]

Psychosocial management (update)

CI may have profound lifelong psychological implications in terms of daily life experiences, emotional state, self-perception, self-esteem and quality of life for the patient and family.[153–162]

Identified factors influencing quality of life include physical health, daily life, mental health and relationships with others or oneself.[154] Cutaneous pain is the most significant factor affecting quality of life.[158] Skin odour and facial lesions are also an issue.[163]

Disease burden is multifactorial, encompassing issues in domestic life (skincare, extra house chores, additional washing and choosing skin-friendly clothing), education and work (rejection, bullying, discrimination and absenteeism) and limitations in leisure and sports activities.[161,164–166] The burden is further exacerbated by lack of education or knowledge, which may lead to underestimation of its impact by healthcare professionals, health insurance companies and supplementary health coverage.[167,168] An increased risk for depression and anxiety has also been reported in children or adults, and occurs in up to one-third of patients.[169,170]

The recommendations for the psychosocial evaluation of patients are detailed in Appendix S10 (see Supporting Information).

While the effects of psychosocial interventions on ichthyosis outcomes have not been tested, we believe they prevent and alleviate psychological trauma. We recommend psychological support, with the psychologist in the lead involving other healthcare providers, as a crucial part of care for all patients. Care should start early and continue throughout life, including for family members. During the neonatal period, maternal– and paternal–infant attachment is essential, including facilitating close physical contact between the baby and parents.[171–173] Later on, sensitive topics such as intercourse and sexuality should also be addressed.

The social impact of CI can constrain the economic resources of patients or their families due to care costs. Coverage for these expenses varies across European countries and depends on insurance in the USA and elsewhere, with moisturizing creams often being the primary expense.[164,166] It is essential to inform families about reimbursement opportunities, ideally via the help of a social worker and a patient association representative. Given the impact of CI on professional lives, physicians and social workers should advise patients on suitable career paths.

Educational therapy (no update, no new references)

Educational therapy is discussed in Appendix S11 (see Supporting Information).

Telemedicine (new section)

Telemedicine can help minimize travel time and costs, but local regulations must be followed, including obtaining the patient's informed consent, and insurance coverage. High-quality skin photographs are essential for evaluating ichthyotic skin. Telemedicine is particularly useful for follow-up with patients living far from expert centres.[174] However, it should not replace the initial visit, which must include a thorough physical examination, personal and family history and psychosocial and quality-of-life assessments, ideally conducted face-to-face.[175]

Communicating the diagnosis and genetic counselling (update)

Communicating the diagnosis and genetic counselling are discussed in Appendix S12 (see Supporting Information).

Prenatal diagnosis and preimplantation genetic testing (new section)

Prenatal diagnosis (PND) and preimplantation genetic testing (PGT) have been available in some countries for many years, allowing early detection of genetic defects and the prevention of severe diseases in newborns, including EDD.[176–178] PND involves medical tests during pregnancy to assess the health and development of the fetus. These include noninvasive prenatal tests such as ultrasound and maternal blood tests, and invasive procedures such as chorionic villus sampling and amniocentesis. CI has also been diagnosed by ultrasound, particularly in reports of harlequin ichthyosis and ichthyosis prematurity syndrome.[179–183]

PGT is an advanced reproductive option that involves genetic testing of blastomeres or blastocysts (trophectoderm) conceived by assisted reproductive technology (ART), for example *in vitro* fertilization or intracytoplasmic sperm injection. It is then possible to select those that are not affected by a monogenic disorder before implantation. It is important to note that the pregnancy success rate after PGT for monogenic disorders is approximately 25%, but it depends on many factors (e.g. age of the mother). PGT is associated with the potential complications of assisted reproductive technology, such as ovarian hyperstimulation syndrome and increased risk of pregnancy complications.

Currently, there are no international guidelines on when to discuss PND and PGT with families. Regulations and the availability of PND and PGT techniques also vary between countries. Therefore, it is important to offer genetic counselling to affected individuals or parents of affected children prior to planning a pregnancy.

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Conflicts of interest

JMH has been an investigator for the last 5 years for companies relevant to ichthyosis: LEO Pharma, Lilly, Mayne, Sanofi and Timber Pharmaceuticals. **ASP** is an investigator for Biomendics, Janssen, Regeneron and Timber, and a consultant for BioCryst, Boehringer Ingelheim, LEO and Regeneron/Sanofi relevant to ichthyosis. **ES** is a consultant for Kamari, BiomX, Bayer, Amryt, Medison, SolGel, Krystal, BiondVax, Galmed, Laser Team, IDERM and PINCELL. **AD** has been a consultant for Amryt Pharma/Chiesi (not related with ichthyosis) and Novartis (not directly related with ichthyosis). **MEH** is a consultant for Chiesi and Novartis, not related to ichthyosis. **AM** has done consultancy work with Krystal Bio and Amryt Pharma. **KS** is medical advisor for Nia Health GmbH, has received a fund for 'Innovative Medical Research' from the University of Münster Medical School, has received a clinician scientist program grant from the Deutsche Dermatologische Gesellschaft (DDG) and Arbeitsgemeinschaft Dermatologische Forschung (ADF), has received honoraria for presentations for Julius Zorn GmbH (Juzo) and Sanofi and is a member of the DDG, ADF and Arbeitsgemeinschaft Pädiatrische Dermatologie. **AHM** is a consultant for Sanofi but has no conflicts of interest relevant to ichthyosis. The other authors have no conflicts of interest to declare.

Data availability

No data generated.

Ethics statement

Not applicable.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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