Management of congenital ichthyoses (epidermal differentiation disorders) :

2024 Update for patients.

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This text has been adapted from the recent guidelines published in the medical literature in 2025 by Professor Juliette Mazereeuw-Hautier et al **[1,2]**, a group of international experts (some of them being members of the ERN-Skin network) and patient support groups. These updated guidelines were prepared using the latest information from medical journals and after discussions between experts. These guidelines will be updated every 5 years, as we continue to learn new information about ichthyoses/epidermal differentiation disorders (EDD) from medical research, so that everyone has easy access to the latest information.

The guidelines aim to improve the management and treatment of patients with EDD and to make their daily lives easier. This is a simpler and shorter version for the use of patients. Technical words* are explained in the glossary.

INTRODUCTION

Congenital ichthyoses (CI) are a group of rare genetic diseases in which the protective skin barrier* no longer works properly **[3]**. A new classification for ichthyosis has been developed by an international group of experts, after the publication of earlier medical guidelines **[4]**. This new classification is used in these guidelines for Patients**.** Ichthyosis is now considered part of a broader group of skin conditions called Epidermal Differentiation Disorders (EDD). This group includes: nEDD (non-syndromic EDD): conditions where only the skin is affected, sEDD (syndromic EDD): conditions where the skin is affected along with one or more other organs, pEDD: a form mainly affecting the palms of the hands and soles of the feet. The different forms are also grouped based on the specific issue in the body that causes them, each form is named after the gene* that is affected (for example, *SPINK5*-sEDD). CI/ s or nEDD are usually present at birth or in early childhood. CI/ s or nEDD normally affect the whole skin; the skin becomes very dry and scaly* and, in some places, thick, rough and/or inflamed. CI/ s or nEDD usually have a major effect on daily life and require long-term treatment. So far, there are no known cures for CI/ s or nEDD, but various treatments exist that can reduce symptoms and help patients to feel more comfortable.

TOPICAL AND SYSTEMIC THERAPIES

Here we will describe the different treatment choices that are currently available. The choice of treatment depends on a variety of factors including the type of skin changes that patients have (e.g., scaling or skin thickening or inflammation), how important the skin changes are, where they are in the body (e.g., face, scalp, folds), the presence of blisters or wounds, the extent to which the disease affects daily life, and the age of the patient.

Topical therapy

Nearly all CI/ s or nEDD patients use topical treatments* (“creams”) as their first choice of therapy, as recommended by experts. Topical treatments help to reduce scaling, discomfort, and itching, as well as improving how the skin looks. They can be used alone or together with other treatments.

Many different creams are available. As well as the factors mentioned above, the choice of the cream may depend on how easily patients can access it, its composition and texture, how much it costs and whether or not it can be reimbursed. Patients usually don’t like creams that are very greasy or have an unpleasant smell. For the treatment to work properly, it needs to be applied correctly and regularly and this is often time-consuming.

Emollients [5–7]

Emollients are moisturizing creams that soften and smooth the skin. They work by hydrating, lubricating, and sealing the skin to create a protective barrier that traps in moisture. There are many different types of emollients available. Their properties vary according to their composition and how much oiland water they contain. The differents emollients are hydrating agents (urea (<10%), propyleneglycol (<20%), dexpanthenol , macrogol 400, glycerol (i.e. glycerine), sodium chloride (3-5%) and lubricating agents (petrolatum/vaseline, paraffin). Emollients should be applied to the skin as often as necessary, but at least twice a day and ideally after bathing to improve skin hydration. Except for short-lasting minor symptoms such as itching or a burning sensation, emollients are generally safe. Since the skin barrier* is defective in CI/ s or nEDD , the risk of an allergic reaction may be increased. Ointments seal the skin more than creams and can make skin more sensitive to heat and more vulnerable to infection, particularly in hotter climates. They should thus be used carefully. For patients with thick skin or thick scaling, it is usually necessary to add a keratolytic* agent into the cream (with caution in children, as explained below).

Topical keratolytics [8–22]

Topical keratolytics are creams that reduce the thickness of the skin by helping to remove scales*. The different types of topical keratolytics available include urea (≥10%), alpha hydroxy acids, propylene glycol, and salicylic acid. A cream can contain one keratolytic or a combination of several. Urea is the most commonly used keratolytic; a concentration of at least 10% is required in order to have an effect. Urea concentrations can be increased up to 20% or even 40% on specific areas of thick scaling or skin thickening in adults, such as over joints or on the skin of the palms and soles.

Keratolytics are initially applied once or twice daily and then less frequently if the patient's skin responds well. They may cause irritation, especially when applied to the face, skin folds (e.g. armpits, groin, beneath breasts and between the thighs), or areas of inflamed, cracked or damaged skin.

Keratolytics should NOT be used during the first 6-12 months of life, as they are much more likely to be absorbed by the body and be toxic at this time. Salicylic acid has caused life-threatening problems in young children and is strictly forbidden in children under the age of 2. Even if there are no reports of toxicity from urea in children, it must be used with caution in newborn babies and in very young children, except in very limited areas such as the palms and soles. Calcipotriol (should not be used during pregnancy), a cream containing vitamin D derivatives, has been shown to be effective, well-tolerated, and safe for short-term treatment in adults. However, in children, it must be used with caution, because of a lack of safety data, especially regarding its possible toxicity.

Topical retinoids [23–32],

Retinoids are treatments that regulate the biological processes resulting in abnormal skin. Based on recent research, experts recommend that topical retinoids (currently tazarotene (0.05-0.1%) and possibly isotretinoin (0.05-0.1%) in the future) can be used as a first-line treatment to reduce scaling or skin thickening and avoid oral retinoids. However, tazarotene is only available in some countries. Also, these creams may be relatively expensive and are not necessarily covered by patients' health insurance. Caution should be taken when applying topical retinoids to large areas of the body. It is not yet known whether these treatments can be absorbed into the bloodstream if used on large skin surfaces. Topical retinoids should NOT be used during pregnancy or when planning a pregnancy.

N-acetylcysteine[33,34]

N-acetylcysteine incorporated into a cream has been shown to be effective in small groups of adult patients with CI/ s or nEDD. However, it is relatively expensive, has an unpleasant smell, and can cause irritation. For these reasons, we do not recommend it.

Targeted topical therapy [35,36]

Topical therapies can sometimes be combined to specifically treat the underlying problem. For example, in *SDHL*-sEDD-CHILD (CHILD syndrome) a cream containing a combination of topical cholesterol and a topical statin, has been shown to reduce symptoms. Making these combined treatments is usually relatively simple and inexpensive. However, it may be more difficult for patients to be reimbursed.

Bathing [37,38]

It is very important to wash the skin, to remove scales and ointments and make the skin more comfortable. Some patients prefer taking showers but most patients prefer taking a bath (long, lukewarm baths (for 15-30 min or more), which may be better for removing scales. Mild soaps

or soap-free cleansers can be used. Scales can be removed by gently rubbing (e.g., with a sponge, microfiber cloth or pumice stone). Moisturizing additives, colloidal preparations, baking soda (6g/L) or saltwater baths can have added benefits. Antiseptics should not be used on a routine basis, except for patients with CI/ s or nEDD who have frequent skin infections (e.g., patients with epidermolytic ichthyosis (EI) (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic), keratitis-ichthyosis-deafness syndrome (GJB2-sEDD-KID), or Netherton syndrome (*SPINK5*-sEDD). These antiseptics include chlorhexidine (dilution 5/1,000-5/10000), octenidine 0.1%, polihexanide 0.1%, and potassium permanganate (dilution 1/10000)). If used, they should be rinsed afterwards. Bleach baths (0.005% to 0.01%; 1-2 ml per liter) have been shown to improve the skin barrier and reduce itching in patients with atopic dermatitis (AD). Although their safety and effectiveness have not been properly tested in patients with CI/ n or sEDD, many doctors recommend using bleach baths to reduce unpleasant odors in some forms of CI/ s or nEDD. It is not normally necessary to rinse after dilute bleach baths, unless the skin becomes very dry or irritated. Antiseptics that contain iodine are not recommended, as they may affect the thyroid gland. Balneotherapy and hydrotherapy with thermal waters have been shown to improve CI/ s or nEDD patients' symptoms in one study.

Treatment of the scalp

Most patients with CI/s or nEDD have thick scales on their scalp, that are difficult to remove. To treat these symptoms, patients often prefer foams, solutions, or shampoos rather than gels and creams. However, these do not always work as well. It may be necessary to apply a layer of emollient cream (often an oil) or keratolytic cream (washable preparation) for a few hours or overnight. Depending on the thickness of the scaling, and the response to treatment, the treatment should be applied at regular intervals ranging from once a week to daily. Covering the scalp with a plastic hat or film may help the treatment to work faster. However, care should be

taken, especially in children, as substances are absorbed more quickly into the scalp than into other areas of the body. After shampooing, scales should be gently removed with a fine comb. A steam hot helmet, if available and under nurse supervision, can be useful to help remove stubborn scales. In CI/ s or nEDD patients with fragile skin or brittle hairs (e.g., patients with Netherton syndrome (*SPINK5*-sEDD), it is better to use more gentle methods. Note that some biologic treatments can affect hair growth in patients with Netherton syndrome receiving such therapy (please see section on biologics/alternative systemic therapies) but should not be used for hair issues only.

Treatment of palmoplantar keratoderma

Some patients with CI/ n or sEDD also have palmoplantar keratoderma (PPK): that is abnormal thickening of the skin located on the palms of the hands and the soles of the feet. Their thick skin is more likely to crack and to be painful in these places. Adult patients with moderate to severe PPK, can be treated with creams containing high concentrations of keratolytics (salicylic acid (up to 25%) and urea (up to 40%) seem to be the most effective). They can be used once or twice daily after protection of skin cracks and the surrounding area (e.g., using petroleum jelly). A plastic film can be used with caution over the treated area to help the ointment to be better absorbed and to work properly. As mentioned above, keratolytics should NOT be used in babies or in young children, as they are more likely to be absorbed into the bloodstream and have greater toxicity in this age group. Topical retinoids and topical calcipotriol are not very effective on the palms or the soles. Manual removal of excess callus* is usually required and may involve grinding wheels and/or podiatrists. New targeted therapies may be used in some forms of PPK (please see section on therapeutical advances).

Systemic therapy

Systemic therapies, usually taken by mouth (orally) or by injection, work by treating the entire body. If topical therapies don't work well enough on their own or are too demanding for the patient, additional systemic therapies can be given**.**

Oral retinoids-[39–91]

The main systemic treatment given to patients with CI/ s or nEDD is oral retinoids. They work by preventing the skin from making too many scales*. There are four different types of retinoids: acitretin, alitretinoin, isotretinoin and etretinate (no longer available in Europe). Oral retinoids have greatly improved the lives of many patients with severe CI/ s or nEDD.

Acitretin

Acitretin is the only oral retinoid that is currently approved by the European Medical Agency for treating CI/ s or nEDD. This means that it is the first choice of therapy for long-term treatment of patients with CI/ s or nEDD.

Research studies have shown that acitretin improves many different symptoms in patients with CI/ s or nEDD. It reduces scaling and thickening of the skin, and shortens the time spent on daily skin care. It has also been shown to improve sweat production and hair regrowth. Acitretin helps to reduce ectropion (an outward turning of the eyelids) and eclabion (an outward turning of the lips) in patients with CI/ s or nEDD, and can improve patients' hearing by reducing scaly skin inside the ear. It is most helpful for patients who have thick scaling or skin thickening (i.e. patients with lamellar ichthyosis (SULT2B1-nEDD, ALOX12B-nEDD, ALOXE3-nEDD, CYP4F22-nEDD, LIPN-nEDD, CERS3-nEDD, PNPLA1-nEDD, SDR9C7-nEDD, NKPD1-nEDD, NIPAL4-nEDD, TGM1-nEDD, CASP14-nEDD, ASPRV1-nEDD) and harlequin ichthyosis (*ABCA12*-nEDD)), but it can also help patients with milder forms of CI/ s or nEDD. Note that, for patients with EI (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic), acitretin works best at reducing symptoms

in those who have a change in the *KRT10* gene. EI patients who have a change in the *KRT1* gene, may become worse on oral retinoids. For patients with Netherton syndrome (*SPINK5*-sEDD) or other types of CI/ s or nEDD, who have very widespread, red, scaly and weak skin, retinoids are either not used or must be tried at very low doses. This is because retinoids can irritate or weaken skin more in these patients.

When and how to take acitretin (adults patients CI/ s or nEDD)

Acitretin capsules (available at 10 and 25mg) should be taken once a day at meal times. Treatment with acitretin should be supervised by a dermatologist who has experience in CI/n or sEDD. The starting dose should not be higher than 0.5mg/kg each day. After a few weeks, the doctor should check with the patient whether the treatment is working well and whether they have any side-effects. Depending on how the patient feels and how well the treatment is working, the dose of acitretin taken may be adjusted by the doctor. This is a long-term treatment. It can be stopped for a short time during humid and hot weather conditions when symptoms naturally improve. However, stopping for a longer time will result in skin returning to its original pre-treatment condition. Note that patients with very red, inflamed and/or fragile skin, e.g. patients with Netherton syndrome (Spink5-sEDD) or EI (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic), should be treated with caution using a low retinoid dose (e.g. 0.3 mg/kg).

When and how to take acitretin (children with CI/ s or nEDD)

For children with CI/ s or nEDD, acitretin treatment must be prescribed by an expert in pediatric dermatology. There is no strict lower age limit for using retinoids (for newborn babies and young infants please see Part 2). However, oral retinoids should only be used in children who have severe symptoms or severe disability due to their illness. The daily dose of acitretin should be

kept as low as possible (less than 1 mg/kg/day and ideally close to or lower than 0.5 mg/kg/day, to limit potential side effects). A pharmacist can prepare the prescribed dose of acitretin for the child. As acitretin is sensitive to light, capsules should be opened away from daylight and added to breast milk or formula in a bottle protected by aluminum foil. For newborn babies (0 to 4 weeks), the pharmacist can prepare the correct dose of acitretin in a liquid form.

Pregnancy and women of child-bearing age

Acitretin should not be taken during pregnancy. This is because it would be very harmful to the growth of the baby in the womb. Women of childbearing age must use contraception to prevent pregnancy, when taking acitretin. Monthly pregnancy tests are mandatory. Alcohol must also be strictly avoided, when taking acitretin, and for at least 2 months after stopping treatment. This is because alcohol changes acitretin into a different type of substance (called etretinate) that can affect parts of the baby's body as they are growing, and can stop them forming properly. Etretinate can stay in the body for many months or even years. For this reason, experts recommend that women must continue to use contraception for 36 months (3 years) after stopping acitretin treatment. Patients CANNOT donate blood when taking acitretin, or during the 3 years after stopping acitretin treatment. Patients who are hypersensitive to acitretin or any other substance contained in the acitretin capsule, have severe liver or kidney failure, hypervitaminosis A or hyperlipidemia should not take acitretin. Similarly, individuals who are already taking other medicines including–tetracyclines, methotrexate, vitamin A or other retinoids should not take acitretin. Patients should ask their doctors regarding these contraindications and interactions with other drugs.

Side effects of acitretin

Side effects are well-known by doctors. The most common side effects are dryness (especially chapped lips and dry eyes), higher blood levels of cholesterol (fat), higher blood levels of enzymes* produced by the liver, headaches and hair loss.

Research studies in adults suggest that if acitretin is taken for many years, it may affect the muscles, bones and joints. Patients who are older, who are taking a higher dose of acitretin or who have previously been treated with etretinate, are thought to be more vulnerable to these long-term side-effects.

The risk of osteoporosis* is controversial. Some studies have found an increased risk of osteoporosis* in patients with CI/ s or nEDD and/or other types of skin disease, who took etretinate for many years. However, other studies found no relationship between the use of etretinate or acitretin and osteoporosis*. Osteoporosis associated with CI/ s or nEDD may also be related to vitamin D deficiency (please see Part Two).

So far, studies in children taking acitretin (and/or etretinate) over many years have found no long-term side effects on their bones. In one study, children who were severely affected by CI/ s or nEDD, even had better growth once they started taking retinoids. Nevertheless, to limit side-effects, all patients taking acitretin should be carefully checked by their doctor, at regular times.

Alternative treatments to acitretin

Two alternative treatments to acitretin are alitretinoin and isotretinoin. These treatments are available in most European countries, although they have not been specially approved for treating CI/s or nEDD and are likely to be expensive. As for acitretin, alitretinoin and isotretinoin CANNOT be used during pregnancy as they can cause fetal malformations they can stop the baby from growing properly in the womb. However, for women who want to become pregnant in the future, alitretinoin or isotretinoin are better treatment options, as they don’t stay in the body

for as long as acitretin (1 month instead of 3 years). Women taking alitretinoin or isotretinoin MUST use contraception during treatment, but they can stop taking contraception 1 month after finishing their treatment. Side effects are similar to those for acitretin, although in some patients taking alitretinoin, headaches can be more frequent and thyroid hormone levels may be decreased. Research studies have shown that isotretinoin (especially if taken at high doses for many months or years) can affect the muscles, bones and joints of both children and adults. As for acitretin, all patients taking isotretinoin or alitretinoin need to be carefully checked by their doctor, at regular times.

The psychiatric effects (depression) of isotretinoin use in CI/ s or nEDD, have not been examined. Most studies exploring these relationships evaluate patients with acne.

Which retinoids should be used?

There are no studies directly comparing acitretin, alitretinoin, and isotretinoin. Acitretin seems to be better at reducing scales and skin thickening than alitretinoin or isotretinoin. There is also more information available on the long-term safety of acitretin than the other retinoids, particularly regarding its effects on bones. As stated above, acitretin is the only oral retinoid approved by the EMA for CI/ s or nEDD treatment in Europe. For this reason, it is the first choice for long-term therapy. However, due to their more rapid clearance from the body, alitretinoin and isotretinoin should be considered in women of child-bearing age. In the US, no retinoid is specifically licensed for CI/ s or nEDD treatment.

Alternative systemic therapies [92–100]

Although oral retinoid treatments can help to reduce skin scales, they don't usually stop redness and itching and can sometimes make these symptoms worse. This means that new treatments are needed. Biological drugs, also known as 'biologics,' are currently being tested as a treatment

for CI/n or sEDD. These drugs work by targeting specific cells in the immune system (called helper T cells) and reducing inflammation.

Several reports on single patients have found promising results with biologics in CI/ s or nEDD patients, but a clinical trial and a large international series of patients found no or mild effects, often transient. Efficacy was only reported in patients with inflamed skin. At present, due to their cost and lack of licensing, biologics are only recommended as a possible treatment option for CI/ s or nEDD patients with severe redness and itching. Patients treated with biologics can continue to take oral retinoids to reduce scaling.

Other new treatments that are currently being tested are Janus kinase inhibitors (JAKI). These drugs block the effect of janus kinase, an enzyme* that plays an important role in inflammation. In this way, they help to reduce inflammation in disease. So far, a few reports have shown promising short-term effects of these inhibitors in one patient with autosomal recessive CI/ s or nEDD and in two patients with Netherton syndrome (*SPINK5*-sEDD). However, further research is needed in larger patient groups, before doctors can recommend their use.

FUTURE THERAPY OPTIONS [101–119]

As scientists learn more about the different types of CI/ s or nEDD and how they evolve, new ideas for treatments are being developed. Gene therapy is one promising option. In patients who are known to have a defect in a specific gene, strategies are being developed to either repair the faulty gene or to replace it with a gene that works properly. For example, in patients with lamellar ichthyosis (SULT2B1-nEDD, ALOX12B-nEDD, ALOXE3-nEDD, CYP4F22-nEDD, LIPN-nEDD, CERS3-nEDD, PNPLA1-nEDD, SDR9C7-nEDD, NKPD1-nEDD, NIPAL4-nEDD, TGM1-nEDD, CASP14-nEDD, ASPRV1-nEDD), who have a defect in the *TGM1* gene (*TGM1*-nEDD), clinical trials are currently underway using different gene delivery methods to replace the faulty *TGM1* gene

with a normal gene. Similarly, in patients with Netherton syndrome (*SPINK5*-sEDD), gene therapy methods are being tested to replace a faulty gene with a normal one.

Another treatment option being tested is to replace defective skin proteins with healthy ones so that the skin barrier works better. This method has been shown to improve skin barrier function in cellular and animal models of lamellar ichthyosis (SULT2B1-nEDD, ALOX12B-nEDD, ALOXE3-nEDD, CYP4F22-nEDD, LIPN-nEDD, CERS3-nEDD, PNPLA1-nEDD, SDR9C7-nEDD, NKPD1-nEDD, NIPAL4-nEDD, TGM1-nEDD, CASP14-nEDD, ASPRV1-nEDD) and peeling skin syndrome (CDSN-nEDD, FLG2-nEDD, CSTA-nEDD).

Specific drugs may also be used to block faulty signals sent by defective genes to *skin* cells. For example, in patients with Netherton syndrome (*SPINK5*-sEDD), a defect in the *SPINK5* gene causes enzymes* known as kallikreins to become overactive. Kallikreins play an important role in inflammation and skin cell peeling, and patients with this syndrome have severe skin inflammation and excessive skin peeling. Drugs that block kallikrein (known as kallikrein inhibitors) are currently being tested as a treatment for these patients.

Lastly, gentamicin, a widely used antibiotic, has been shown to help overcome faulty stop signals in genes, known as nonsense mutations*. Nonsense mutations* lead to shortened skin proteins that do not work properly. Gentamicin treatment has been shown to improve the production of normal (full-length) proteins in cellular models of skin diseases caused by nonsense mutations*, and in patients with skin diseases caused by nonsense mutations*. Approximately 15% of CI/ s or nEDD patients carry nonsense mutations* in their genes, and a clinical trial with gentamicin treatment is currently ongoing in individuals with CI/s or nEDD (NCT06362447).

Further research into these potential treatment options is needed. New therapies can only become available once their safety and efficiency in humans have been thoroughly checked.

PSYCHOSOCIAL DIFFICULTIES AND PATIENT SUPPORT [120–141]

Living with CI/n or sEDD can have a major effect on everyday life. It can affect how patients feel physically and mentally, how they see and value themselves, and how they relate to others. It can impacttheir quality of life (QOL), as well as that of their families. Symptoms often affect people differently; QOL is particularly impaired in patients who are female, patients with severe scaling and/or inflammation and those with very painful skin. Like patients with other types of skin disease, people with CI/ s or nEDD can feel rejected or excluded by others due to the appearance of their skin.

Home life can be more difficult as people with CI/ s or nEDD need to spend more time on skin care, and more time cleaning and washing their clothes. They also may choose clothes that are gentler on the skin and cover up more of the body in order to hide their skin. School life may be affected by rejection and bullying by other children, being less able to take part in certain leisure or sports activities, or being absent more frequently. Similarly, work life may be affected by unfair treatment from work colleagues or managers. Understandably, people with CI/ s or nEDD are more likely to feel anxious or depressed.

For these reasons, it is very important for patients with CI/ s or nEDD to have continued psychological and social support throughout their lives. Experts recommend psychosocial support as an essential part of care for every patient with CI/ s or nEDD, no matter how severe their symptoms. Ideally, this support should be offered to both the patient and their family as soon as possible, starting at the time of diagnosis. Support will mainly be provided by a psychologist, but should also be given by other healthcare workers including the patients' doctor (general practitioner), paediatrician, genetic counsellor, dermatologist, social worker, specialist nurse, or case manager. This support should help the patient and their family to cope better with the everyday difficulties faced when living with CI/ s or nEDD.

For newborn babies, close physical contact with the parents is essential in order to form an attachment (bond). This is also very important when a baby (or a parent) has CI/ s or nEDD. Family therapy can be helpful if parents feel uncomfortable or worried about holding their baby close. Brothers and sisters should be included in this therapy, so that they don't feel left out.

QOL and mental health should be regularly assessed in CI/ s or nEDD patients, especially using questionnaires that are specifically designed for patients with skin disease. These include the Dermatology Life Quality Index (DLQI), the Children's Dermatology Life Quality Index (CDLQI) and the Cartoon CDLQI, a picture version of the CDLQI designed for younger children. There are also questionnaires specifically designed for CI/ s or nEDD patients and their families; the IQoL-32, a 32-item CI/ s or nEDD -specific measure of QOL, and the Family Burden Ichthyosis (FBI) questionnaire, a 25-item questionnaire measuring the impact of the disease on familiesCI/ s or nEDD . Assessment of anxiety and depression is done using validated questionnaires; these include the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder Scale (GAD-7), PROMIS short forms (for depression and anxiety (www.healthmeasures.net) in adults), Screen for Child Anxiety Related Emotional Disorders (SCARED) (for children from the age of 8), and PROMIS short forms (for anxiety, depression, peer relationships, and stigma for children from the age of 8, with caregiver proxy forms validated for children from the age of 5).

Educational interventions ("CI/n or sEDD schools") may help to improve people's understanding of what the disease is, to reduce false ideas and fears, and to encourage patients to use their prescribed treatment. Nevertheless, formal and structured educational programs about CI/ s or nEDD have only been introduced in a small number of European countries so far, and few studies have measured their impact.

Caring for a person with CI/ s or nEDD can be expensive. Not all patients or families are able to pay for these costs. The extent to which a patients' health service or health insurance covers

costs will vary depending on which country they live in. Similarly, access to disability allowance and opportunities for reimbursement are different in different countries. The healthcare team should be able to advise patients on these matters.

Lastly, the family doctor or social worker can put patients in touch with their national or local patient support group. These support groups, which exist in many European countries and in the US, allow people to share individual experiences and valuable advice with other patients who have CI/ s or nEDD and their families. Please see the following websites: https://ichthyosis.info/; https://www.firstskinfoundation.org/ for further details.

VIDEO/PHONE APPOINTMENTS (TELEMEDICINE)-[142,143]

A video or phone appointment with the doctor can help patients to save time and money. However, it is not the same as a face-to-face visit and it is difficult to take good quality photos of the skin in this way. Except for in some countries where it is extremely difficult to see a specialist, a patient's first medical appointment should be face-to-face with their doctor. He or she should do a thorough physical examination, and will ask questions about personal and family history as well as daily life and psychological wellbeing. For further visits, video or phone appointments may be helpful for those patients who live far away from their medical centre.

GENETIC COUNSELING[128,129]

It is important for all patients with CI/ s or nEDD (and their parents) to see a genetic counselor. The genetic counselor can provide patients and their families with information about CI/ s or nEDD and help to explain which type of CI/ s or nEDD they have and how it is inherited. Molecular diagnosis* should be performed as early as possible. Based on this diagnosis, the genetic counselor can tell patients more about the expected effects of their disease, whether other members of their family are likely to be affected or not, and whether there is a risk of passing it

on to their children should they wish to have a family. They can also provide information about the different methods available to detect a risk of CI/ s or nEDD before planning a pregnancy, or during early pregnancy. These methods include predictive testing* and prenatal diagnostic (PND*) or preimplantation genetic testing (PGT*), if available (please see below). Molecular diagnosis* may also help to plan personalized treatments in the future (please see section on future therapy options).

In general, CI / s or nEDD can be inherited as an autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive trait (supplmentary informations in Appendix 1)

PRENATAL DIAGNOSIS AND PREIMPLANTATION GENETIC TESTING[144–148]

Prenatal diagnosis (PND) and preimplantation genetic testing (PGT) have been available in some countries for many years. These techniques allow early detection of genetic defects and the prevention of severe diseases in newborn babies. PND involves medical tests during pregnancy to assess the health and development of the fetus, including ultrasound, maternal blood tests, non-invasive prenatal testing, and invasive procedures, such as chorionic villus sampling* and amniocentesis*. CI/ s or nEDD has also been diagnosed by ultrasound, particularly in patients with harlequin ichthyosis (*ABCA12*-nEDD) and ichthyosis prematurity syndrome (SLC27A4 - nEDD).

PGT, on the other hand, is an advanced reproductive option that involves genetic testing of blastomeres or blastocysts conceived by assisted reproductive technology, e.g., *in vitro* fertilization* or intracytoplasmic sperm injection*. Blastomeres are cells formed during the initial division of a fertilized egg, one to three days following fertilization of the egg by a sperm. A blastocyst is a fertilized egg at 5-6 days following fertilization; it is a rapidly dividing ball of cells. PGT is used to select embryos that are not affected by a specific genetic disorder before implantation in the mother's womb. It is important to note that the pregnancy success rate after

PGT for specific genetic disorders is approximately 25%. This depends on many factors, including the age of the mother. PGT is associated with potential complications of assisted reproductive technology, such as ovarian hyperstimulation syndrome (swollen, painful ovaries) and an increased risk of pregnancy complications. There are currently no international guidelines on when to discuss PND and PGT in families with CI/ s or nEDD. There are also differences between countries in the regulations and the availability of PND and PGT techniques. Therefore, it is important to offer genetic counselling to affected individuals or parents of affected children before planning a pregnancy.

COMPLICATIONS OF CONGENITAL ICHTHYOSIS

The complications associated with CI/ s or nEDD, though sometimes overlooked, profoundly increase the impact of the disease on patients' quality of life (QoL). Among the most common challenges are pain, itching, ocular complications, and alopecia. Others are ear and nail anomalies, cutaneous infections, growth failure, vitamin D deficiency, reactions to hot or cold climates and physical limitations.

These manifestations, often serious, and not very well-known, necessitate special care.

Ocular Complications [149–154]

Ichthyosis/EDD can lead to several eye problems including eyelids anomalies, dry eyes, and conjunctiva and cornea anomalies. Eyelids anomalies (Scales and induration of the eyelid, loss of eyelashes and sometimes eyebrows, Eyelid retraction and ectropion*) may result in lagophthalmos*, keratitis*, photophobia* and loss of vision.

The main goal of ophthalmic care is to ensure normal visual development, protect the eye surface, and prevent corneal damage. Here are some key points for managing these complications.

Regular Eye Exams

Regular eye exams are essential to detect any visual issues early and prevent complications. These exams typically include vision assessments, an evaluation of the eye surface, and refraction tests to detect correctable vision problems. The frequency of exams depends on the severity of CI/ s or nEDD, ranging from monthly to once or twice a year.

Eye Lubrication

If patient experiences difficulty blinking (lagophthalmos), it is essential to apply eye lubricating drops to protect the eye surface. Preservative-free drops are strongly recommended for those who need long-term use.

Effective lubricants include drops such as 0.5–1% carboxymethylcellulose, sodium hyaluronate, or Vitamin A ointments. The frequency of application varies depending on the severity of the issue, ranging from twice daily to every 30 minutes in severe cases.

Managing Ectropion (Eyelid Turning Outward)

Ectropion can make the eyelid skin more vulnerable and prone to injury, so it's crucial to start with regular lubrication. Case studies suggest that vertical lid massages in combination with eyelid moisturizers can improve the condition.

Topical* treatments such as keratolytics* (urea or lactic acid) or tazarotene have shown positive results in some cases, although they may cause irritation. Tazarotene ointment can be diluted with a petrolatum-based cream to minimize this irritation.

Medical Treatments for Severe Ectropion

In more severe cases of ectropion, oral retinoids are commonly used to help reduce symptoms. However, these can sometimes worsen dry eye symptoms, so they should be used with caution.

If conservative treatments are not effective enough and the cornea remains exposed, skin grafting may be considered. Ideally, surgery should be done before the eyelid skin becomes hardened. Recurrence of the condition after surgery is the major issue.

Recent reports suggest that other procedures, such as eyelids injection using hyaluronic acid gel fillers, may help reduce the need for surgery, though more studies are needed to confirm this approach.

ENT (Ear, Nose, and Throat) Issues [155–158]

People with CI/ s or nEDD often experience ear and throat problems, which can include itching, voice changes, ear infections, pain, discharge, ear deformities, and blocked ear canals, sometimes leading to hearing loss. These issues can be particularly concerning for children, as their smaller ear canals may make blockages worse, affecting their ability to hear and speak properly.

Ear wax plug (cerumen) is common and can cause ear canal blockages. Using ear drops or simple oils can help soften and remove the wax. For more stubborn blockages, an ENT (ear, nose and throat) specialist can use safe techniques like microsuction, debridement, or curettage up to four times a year. Oral retinoids are not typically used to prevent ear canal blockages. If the patient experiences recurrent ear blockages, it’s important to have regular check-ups with an ENT specialist. For children, this should be done at least every six months, or more frequently if symptoms are uncontrolled. For adults with mild symptoms, the check-ups can be less frequent.

Obstruction in the ear canal can lead to external otitis (ear infections), causing pain, discharge, or even damage to the eardrum, which could result in permanent hearing loss. Treatment involves cleaning the ear canal and using topical* medications like antibiotic ear drops (e.g., ciprofloxacin), sometimes combined with steroids to reduce inflammation.

A few people with CI/ s or nEDD experience voice problems, such as hoarseness, which can affect speech and development **[155]**. It's important to see a speech therapist for voice therapy and an ENT specialist to assess the vocal cords, if hoarseness persists into childhood.

If the patient experiences itching, pain, ear discharge, a feeling of fullness in the ear, or hearing loss, it is necessary to visit an ENT specialist for a thorough examination and provide appropriate treatment.

Pain and Itching [133,159–162]

Itching and pain are common symptoms in CI/ s or nEDD and are often linked to skin inflammation. These symptoms significantly affect daily life but are not often thoroughly evaluated. Pain can be aggravated by skin tightness, cracks (fissures), and joint stiffness (contractures).

The first step in reducing itching and pain is to improve the condition of the skin through treatments (see Part One).

Antihistamines and antidepressants generally have little effect on itching. However, sedative antihistamines might help improve sleep for those struggling with itch-related insomnia.

Standard pain medications can be used for managing pain, following guidelines for skin-related conditions.

Part I discusses using existing biologic medications (which target the immune system) and innovative therapies for treating itching and pain in CI/ s or nEDD.

Skin infections [163]

Since CI/ s or nEDD is associated with changes in the skin's protective barrier, patients are more vulnerable to infections. These infections are caused by bacteria or fungi and are more common

in certain forms of CI/ s or nEDD, such as *ABCA12*-nEDD (harlequin ichthyosis), epidermolytic ichthyosis (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic), Netherton syndrome (*SPINK5*-sEDD), KID syndrome (*GJB2*-sEDD-KID).

Bacterial Infections:

The skin's microbiome often changes, with an increase in Staphylococcus aureus and other bacteria.

Skin infections caused by S. aureus or group A streptococcus are frequent and may cause redness, swelling, and pain.

Fungal Infections:

Patients may experience fungal infections like dermatophytosis (ringworm), often difficult to recognize since they are presenting as itching and scaling.

GJB2-sEDD-KID is associated with mucocutaneous candidiasis (yeast infections), while human papillomavirus infections are reported in *SPINK5*-sEDD.

Scabies:

Diagnosing scabies in people with CI/ s or nEDD can be challenging and usually presents with increased itching or blistering.

Monitoring and Diagnosis:

Physical examinations by a healthcare provider is crucial to detect infections early, if suspected. The healthcare provider can perform bacterial or fungal swabs to identify the bacteria or the fungus.

Treatments:

For Bacterial Infections:

Use antiseptic soaps and topical* antibiotics for non-severe infections.

For more severe infections (larger or deeper), or if other health conditions are present, oral antibiotics must be prescribed.

It is important to avoid regular use of topical* antibiotics (e.g., fusidic acid or mupirocin) to reduce the risk of bacterial resistance.

If recurrent infections occur, bacterial cultures may be taken from the nose or skin of both the patient and close contacts. If S. aureus is found, decolonization measures like antiseptic washes or specific nasal ointments might be recommended according to the country recommendations.

For Fungal Infections:

Topical* or oral antifungal treatments are used, depending on the severity.

Important considerations: Topical Treatments in Children (see part one)* Be cautious of using topical* medications, as children are more prone to absorbing these treatments through their skin, which may lead to side effects.

Vaccination [164]

While data on vaccination in patients with CI/ s or nEDD is limited, certain vaccinations are particularly important:

- Varicella (Chickenpox) Vaccine: There is a higher risk of severe chickenpox making this vaccination essential.
- Human Papillomavirus (HPV) Vaccine: It is recommended for all patients with *SPINK5*-sEDD.

- Live and killed Vaccines: They must be administered per the national vaccination schedule. For patients on immunomodulatory biologics, country-specific guidelines regarding live vaccines must be followed.

Growth Failure and Nutritional Deficiency [165–167]

Growth failure is a common challenge in children with various forms of CI/ s or nEDD, particularly those with inflammatory conditions. It results from:

- Increased metabolic demands.
- Higher rates of skin turnover.
- Chronic inflammation.
- Loss of proteins through the skin.

Children with *SPINK5*-sEDD are at high risk of severe failure to thrive due to dehydration and early onset food allergies.

Recommendations for Monitoring:

In children, annual monitoring of growth (height-for-age and weight-for-age percentiles) and nutrition, including checking for deficiencies in micronutrients like vitamin D, selenium, iron, and zinc. In severe cases, more frequent evaluations may be needed with support from pediatricians and dieticians.

In adults, nutritional assessments should be done on a case-by-case basis, especially depending on the severity of the disease.

In adolescents, delayed puberty must be monitored and may signal nutritional or growth issues.

Treatment Options:

Severe short stature linked to CI/ s or nEDD may improve with biologics in certain forms in CI/ s or nEDD (see Part one), though these treatments should not be prescribed solely for growth concerns.

Vitamin D deficiency [82,168–170]

Vitamin D is essential for bone health and overall well-being. People with CI/ s or nEDD are at risk of vitamin D deficiency, especially in case of:

- Severe forms of CI/ s or nEDD, like ARCI (Autosomal Recessive Congenital Ichthyoses, part of nEDD) or epidermolytic ichthyosis (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic).
- Darker skin tones, as melanin reduces vitamin D production in the skin.
- Especially during the winter and spring.

A severe lack of vitamin D can lead to conditions like rickets, which weaken bones. If vitamin D levels fall below 10 ng/mL, additional investigations must be done (check calcium and phosphorus imbalances. Take X-rays if bone problems are suspected.

Routine testing is recommended to check vitamin D levels once a year, or twice if risk factors. Aim for levels between 20 and 30 ng/mL.

The supplementation must follow international guidelines.

Some children with CI/ s or nEDD have seen skin improvements with high-dose vitamin D supplements, but we cannot give any conclusion and make any recommendation based on only one publication.

Hair and Nail Health in Ichthyosis [171–173]

Hair problems (Alopecia)

Hair thinning or loss can happen in CI/ s or nEDD, particularly in ARCI caused by certain genetic changes such as mutations* in the gene *TGM1 (TGM1*-nEDD*)*. Factors that may worsen hair loss include: Low levels of iron, zinc, vitamin D, or vitamin B12, thyroid issues or medications.

While there are no specific treatments for CI/ s or nEDD -related alopecia, it's important to address these factors. Wigs can also be an option, and some charitable organizations, like Locks of Love (US) or Little Princess Trust (UK), may provide funding.

Oral medications like retinoids, which are sometimes used to treat CI/ s or nEDD, may cause hair loss and curly hair.

Nail Abnormalities

Some people with CI/ s or nEDD experience changes to their nails, such as thickened or brittle nails, fungal infections (onychomycosis), or irregular growth. Retinoids may also affect nail health.

Dealing with Hot and Cold Weather [174,175]

Many people with CI/ s or nEDD struggle with heat intolerance due to reduced sweating (hypohidrosis) caused by blocked sweat ducts. In some rare cases, excessive sweating (hyperhidrosis) may occur.

Tips for reducing heat intolerance:

- Avoid extreme temperatures and stay indoors during peak heat or when the sun is too strongest.
- Use cold packs, take frequent cool showers, and wear light, breathable clothing.
- Air conditioning can be very helpful in hot climates.

Physical Limitations and Mobility [176,177]

Thickened or cracked skin, especially around the joints or on the hands and feet, can make it hard to move comfortably. This may affect posture and vision, along with causing pain, and reducing quality of life.

Ways to improve mobility:

- Physical and occupational therapy can help improve flexibility and hand function**[177]**.
- Adaptive tools, like jar openers or utensils with large handles, can make daily tasks easier.
- In rare cases, procedures like skin grafting have been reported as improving movement.

Comorbidities (Other Conditions Linked to CI/ s or nEDD) [178–184]

The fact that C/EDD is associated with inflammation has led to the hypothesis of associated comorbidities. A recent study found that people with CI/ s or nEDD may have comorbidities, like heart issues and joint inflammation. However, the study involved a younger group of people, and because these health problems were rare, the results aren't yet very strong. More research is needed to fully understand these connections.

Certain health issues may occur more frequently in people with CI/ s or nEDD. These include:

- Migraine and Depression: People with CI/ s or nEDD may be more prone to these conditions, so regular mental health check-ins are important.
- Heart Problems (*STS*-sEDD): Men with *STS*-sEDD may have a higher risk of irregular heartbeats, like atrial fibrillation. Routine heart monitoring is recommended.
- Behavioral and Psychiatric Issues (*STS*-sEDD): Children and men with *STS*-sEDD may also experience conditions like ADHD or anxiety, so early screening and support are helpful.

SPECIFIC CONSIDERATIONS OF CONGENITAL ICHTHYOSIS: NEWBORNS AND *SPINK5*-sEDD PATIENTS

Special Considerations for Newborns with CI/ s or nEDD [185,186]

At birth, babies need extra medical attention, especially those born as a collodion baby*, *ABCA12*-nEDD, severe redness or other particular form of CI/ s or nEDD (SLC27A4 -nED / Ichthyosis Prematurity Syndrome).

These babies are at risk of several complications such as dehydration from increased water loss through the skin (transepidermal water loss (TEWL, transepidermal water loss)) and infections due to fragile or damaged skin.

Managing Collodion Baby (CB) and ABCA12-nEDD [2]

At birth, babies with collodion baby or *ABCA12-nEDD* have abnormal skin. In collodion baby, the skin is covered by a tight, shiny membrane. In harlequin ichthyosis (ABCA12-nEDD), the skin is very thick, hard, and cracked, often with redness. The eyelids and lips may be turned outward, especially in harlequin ichthyosis (ABCA12-nEDD).

Because the skin barrier is damaged, these babies are at risk of dehydration, electrolyte imbalance, and difficulty controlling body temperature. Feeding problems may lead to poor weight gain, and pain can be present. The risk of infections is increased, affecting the skin or sometimes the whole body. Tight skin can reduce blood flow to the fingers or toes, and eye, ear, and breathing problems may also occur.

Close medical monitoring is therefore essential during the newborn period.

Managing Other Types of CI/ s or nEDD in Newborns

Babies with severe redness (ie *SPINK5*-sEDD, *TGM1*-nEDD) also need close monitoring in the neonatal intensive care unit (NICU). Early regognition of the cause of erythroderma leads to better prognosis.

Babies with epidermolytic ichthyosis (*KRT10* -nEDD-epidermolytic or *KRT1* -nEDD-epidermolytic) resent with blisters or peeling skin at birth, which might be confused with another condition called epidermolysis bullosa. For these babies, care includes preventing skin trauma, avoiding adhesives, and providing gentle wound care to prevent infections.

Babies with *SLC27A4*-nEDD may face challenges like breathing problems shortly after birth. Immediate suctioning of the baby's mouth and throat is often needed to prevent serious complications.

***SPINK5*-sEDD: Managing Skin and Long-Term Risks [187–189]**

For those with *SPINK5*-sEDD, managing red, inflamed skin and eczema-like lesions is crucial.

Treatments are as follows:

- Mild Steroid Creams: These can reduce inflammation and redness but cannot be used on a regular basis to avoid side effects like thinning of the skin.
- Calcineurin Inhibitors (Tacrolimus or Pimecrolimus): These creams may help, especially during flare-ups, but they are usually used for short periods and in small areas.
- Phototherapy (Light Treatment): it can improve the skin, but is not recommended for long-term use because it increases the risk of skin cancer.

Ongoing research is looking at more targeted treatments that may be available in the future, including biologic medications (See Part One).

Long-Term Risks: Skin Cancer [190–192]

People with *SPINK5*-sEDD have a higher risk of certain types of skin cancer, like squamous cell or basal cell carcinoma. Regular skin check-ups with a dermatologist are essential to catch any issues early.

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GLOSSARY

Amniocentesis: a procedure involving removal and testing of a small sample of cells from amniotic fluid, the fluid that surrounds the baby in the womb Skin barrier: outermost layer of the skin, that functions to protect the body from external threats and keeps the skin hydrated by preventing water loss.

Callus: a thickened or hardened part of the skin or soft tissue (typically on the palms of the hands or the soles of the feet).

Chorionic villus sampling: a prenatal test, wherein a tissue sample is taken from the placenta (specifically from tiny projections of placental tissue called chorionic villi that have the same genetic material as the baby). The tissue sample is then analyzed for chromosomal abnormalities and other genetic problems.

Collodion baby : a temporary condition seen at birth, not a disease itself. The newborn is covered with a tight, shiny membrane that peels off within the first weeks of life.

DNA: deoxyribonucleic acid, a molecule found in nearly all cells of the body, that carries our genetic sequence (code): a set of instructions determining how cells grow, function and reproduce.

Ectropion : a medical condition in which the lower eyelid turns outwards.

Enzyme: a protein that helps to speed up chemical reactions in the body.

Gene: a unit of heredity which is transferred from a parent to offspring and is held to determine some characteristic of the offspring

Intracytoplasmic sperm injection: an *in vitro* fertilization procedure in which a single sperm cell is injected directly into the cytoplasm of an egg.

In vitro fertilization: a procedure in which eggs removed from a woman's ovary are combined with sperm from a man, outside the body in a laboratory environment.

Keratitis : an inflammation of the cornea

Keratolytic: a substance that breaks down the outer layers of the skin and helps it to bind moisture.

Lagophthalmos: describes the incomplete or abnormal closure of the eyelids.

Osteoporosis: a condition where the amount and thickness of bone tissue is decreased, resulting in weaker, more fragile bones.

Molecular diagnosis: laboratory methods that are used to identify a disease or the risk of developing a disease, by analyzing the sequence of DNA (our unique genetic code) in cells from a tissue or fluid sample.

Mutation: a change in the genetic sequence of a cell.

Mutated gene: a genetic sequence that has been changed or modified.

Nonsense mutation: a change in the genetic sequence that stops the complete production of a protein.

Non-syndromic ichthyoses / nEDD: ichthyoses that only affect the skin.

Photophobia: refers to eyes' sensitivity to light, especially bright light, which can cause discomfort and even pain.

Predictive testing: a type of genetic test used to predict future risk of disease in patients who have no symptoms.

Pre-implantation genetic testing (PGT): a genetic screening test that can be performed on embryos created by *in vitro* fertilization, to check that they have the correct number of

chromosomes and do not have particular genetic mutations, before being implanted in the uterus.

Prenatal diagnosis (PND): using a variety of techniques to test the health and condition of a fetus or embryo before birth, checking for birth defects and abnormalities including genetic disorders.

Scaly/scales: abnormal shedding of outer skin layer with visible peeling or flaking.

Skin barrier: The skin barrier is the outermost layer of the skin. Skin consists of three layers: the epidermis, the dermis, and the hypodermis. The epidermis is the top layer of skin, and the very outermost layer of the epidermis is called the stratum corneum. The stratum corneum, also called skin barrier, functions like a brick wall around the skin and is made up of keratinocytes that are arranged like flat bricks combined to create a shield.

Syndromic ichthyoses/ sEDD: ichthyoses that affect both the skin and other organs.

Topical therapies: treatments that are applied directly to the skin.

Appendix 1: GENETIC COUNSELING

In general, CI/ s or nEDD can be inherited as an autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive trait. In human cells, there are 23 pairs of chromosomes: structures made up of DNA (containing our genes) and proteins. Half of these chromosomes are inherited from our father and the other half from our mother. Each cell has 22 numbered pairs of chromosomes and two sex chromosomes (XX in women and XY in men). In autosomal dominant CI/ s or nEDD, one copy of a mutated* gene on a numbered chromosome (inherited from either parent), is sufficient to cause the disease. In autosomal recessive CI/ s or nEDD, two copies of a mutated* gene on a pair of numbered chromosomes (one from each parent) are required to cause the disease. In X-linked dominant CI/ s or nEDD, one copy of a mutated* gene on an X chromosome (inherited from either parent) can cause the disease. This can affect either men (XY) or women (XX). In contrast, X-linked recessive CI/ s or nEDD generally affects men and very rarely women. In men (XY) one copy of a mutated* gene on an X chromosome is sufficient to cause the disease, as they have only one X chromosome. For women to have X-linked recessive CI/ s or nEDD, they need to inherit two copies of the mutated genes, one on each of their X chromosomes. Women who have one normal X chromosome are protected from this type of CI/ s or nEDD.

In rare cases, the same patient can have two genetically different sets of cells in their body: the first set are cells with a genetic mutation, and the second set are normal cells without any genetic mutation. This phenomenon is known as genetic mosaicism. In such patients, genetic tests are often negative.