



European Dermatology Forum

European Dermatology Guideline for the photodermatoses

5. Genomic Instability diseases

(DNA repair deficient diseases, Helicase deficient diseases)

Conflict of interest

The authors state that they have no conflict of interest to declare.

Key words: Bloom syndrome, DNA repair, Helicase, nucleotide excision repair, xeroderma pigmentosum, Cockayne syndrome, Rothmund-Thomson trichothiodystrophy, skin cancer, premature aging

Abbreviations: BS – Bloom syndrome; CS - Cockayne syndrome; NER - nucleotide excision repair; RTS - Rothmund-Thomson syndrome; TTD - trichothiodystrophy; UDS - unscheduled DNA synthesis; UV - ultraviolet radiation; XP - xeroderma pigmentosum; XP/CS – xeroderma pigmentosum/Cockayne syndrome complex

Methodology

In the present guideline the strength of evidence for diagnostic and therapeutic recommendations is graded using the Methodology recommended by NICE and adopted by the BAD. Literature search was done using PubMed/MEDLINE and EMBASE, as far back as 1960. Studies that had no English abstract were excluded.. The overall assessment of each study is graded using a code '++', '+' or '–', based on

the extent to which the potential biases have been minimized as in the table. Studies with ‘–’ will not be included in the guideline.

Methods adopted are NICE <http://www.nice.org.uk/page.aspx?o=201982> and SIGN <http://www.sign.ac.uk/methodology/index.html> guideline websites. This takes into account recommendations from Harbour and Miller (2001) (Br Med J; 323:334-336). http://bmj.bmjournals.com/cgi/reprint/323/7308/334?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=harbour&andorexactfulltext=and&searchid=1096544973383_6825&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=323&resourcetype=1

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence ‘–’ should not be used as a basis for making a recommendation (see section 7.4)	

Level of recommendation

Class	Evidence
A	<ul style="list-style-type: none"> At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results <p>Evidence drawn from a NICE technology appraisal</p>
B	<ul style="list-style-type: none"> A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or <p>Extrapolated evidence from studies rated as 1++ or 1+</p>
C	<ul style="list-style-type: none"> A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or <p>Extrapolated evidence from studies rated as 2++</p>
D	<ul style="list-style-type: none"> Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	<ul style="list-style-type: none"> A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

INTRODUCTION

Diseases with genomic instability comprise a group of genetic disorders which show great clinical heterogeneity but also significant overlap of clinical symptoms. These symptoms include photosensitivity, pigment changes, increased incidence of skin and internal tumors, progeroid features and neurodegeneration. Based on their genetic or molecular defect they can be divided into A) DNA repair deficient and B) helicase deficient diseases.

A) DNA repair deficiency diseases

Xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD) are genodermatoses, characterized by deficiencies in DNA repair, basal transcription or translesion synthesis. They have defective nucleotide excision repair (NER), a mechanism responsible for the repair of bulky forms of DNA damage such as sunlight induced DNA photoproducts, DNA cross-links and alkylation damage. These diseases are very rare with an estimated prevalence of about $1:1 \times 10^6$ in Western countries. Typical clinical symptoms usually point to the correct diagnosis. Patients suspected of having one of these diseases can be referred to a center that specializes in their diagnosis and care. In recent years the underlying mechanisms as well as many of the genes involved have been identified. The understanding of mechanisms such as DNA repair, basal transcription and translesion synthesis have helped to form a mechanistic explanation of symptoms of XP, TTD and CS. These advances provide important insights into major physiological processes such as aging and carcinogenesis.

Ataxia telangiectasia is a disease with a deficiency in the repair mechanism double strand break repair. Although clinical symptoms do appear primarily in the face, the forearms and hands, a direct link to sun exposure is not established. Thus, ataxia telangiectasia is not discussed in this context of photodermatoses.

NUCLEOTIDE EXCISION REPAIR (NER)

Patients suffering from XP, TTD and CS are defective in the process of NER. This highly conserved mechanism repairs a multitude of DNA lesions [1-3]. The repair of damage induced by UV-radiation is one of its central functions. The most prevalent lesions induced by UV are cyclobutane pyrimidine dimers (CPD). 6-4 photoproducts (6-4PP) are less frequent but far more helix-distorting. Removal of DNA damage by NER can be carried out by two pathways which differ mainly in damage recognition. Damage present in actively transcribed genes (transcription coupled repair, TCR) Repair of DNA damage encountered by stalled RNA polymerase is very rapid. Within eight hours TCR removes about 50% of CPD from actively transcribed genes. Cells from patients with mutations in most XP genes (except XPA and DDB2(XPE)) have defects in TCR along with defects in global genome repair (GGR) as described below. Cells from CS patients are defective in TCR and have normal GGR.

Global genome repair (GGR) is a second form of repair that is carried out throughout the whole genome. GGR is slower than TCR. In this subpathway DDB2 recognizes the damage attracting a heterodimer of the XP-C protein and the human HR23B along with centrin 2. Cells from XP patients with defects in DDB2 (XPE) or XP-C are defective in GGR but not in TCR [8]. Following damage recognition both processes converge [9]. The XP-A/RPA protein complex binds to the damaged region and recruits the helicases XP-B and XP-D, which open the DNA helix. The XP-F and XP-G endonucleases incise the damaged strand of DNA on both sides of the lesion leaving a gap of about 21-29 nucleotides in length. This gap is filled in by DNA polymerases.

XERODERMA PIGMENTOSUM

Pathogenesis

Patients with XP are highly photosensitive to ultraviolet radiation due to a deficiency in NER (see above). Proteins of NER participate in DNA repair and basal transcription. For

the pathogenesis of XP it is currently believed that the defect in DNA repair is predominantly responsible for the clinical symptoms.

Clinical features

XP is a rare autosomal recessive genetic disease with an estimated prevalence of 1:10⁶ in the US and Europe and 1:10⁵ in Japan. XP is characterized by an approximately 1000-fold increased risk to develop skin cancer [1, 21]. The first symptoms of XP often manifest in early childhood. Some infants or small children with XP experience severe acute sunburn reactions after a short exposure of the skin to sunlight. This reaction can persist for several weeks. However, approximately half of the XP patients do not have this acute sun sensitivity. They tan and freckle without burning. Many of these patients are in XP complementation group C. Freckling of the face of a child less than 2 years old is unusual in normal children and is an indication that the diagnosis of XP should be considered. With continued sun exposure freckling of sun exposed skin continues to develop into the typical appearance of poikiloderma with hypo- and hyperpigmentation, atrophy and telangiectasias.

All XP patients are highly susceptible to development of sunlight induced cancers of the skin and eyes. The median age of onset of skin cancers in XP patients is less than 10 years. This is a 50 year reduction in age of onset of first skin cancer as compared to the US general population and is an indication of the importance of DNA repair in protection against skin cancer.

In some XP patients who do not have acute sun sensitivity, the early pigmentary changes might not be recognized and the presence of skin cancers may be the first indication that the child has XP. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) occur most frequently. The frequency of BCC, SCC and malignant melanoma is elevated about 1000-fold. XP patients also have an increased frequency of internal cancers including central nervous system tumors (astrocytoma of brain or spinal cord, Schwannoma of the facial nerve) and lung cancers in patients who smoke. All tissues that are exposed to sunlight may show abnormalities in XP patients. In addition to the skin, the eye and even the tip of the tongue can be involved.

XP has to be distinguished from the other DNA repair deficient photodermatoses such as CS and TTD. Other diseases with increased photosensitivity in childhood such as hydroa vacciniforme or erythropoietic porphyria (EP) have to be excluded [22]. Increased frequency of skin tumors may also point toward basal cell nevus syndrome (BCNS). Epidermodysplasia verruciformis can also show poikiloderma and is characterized by multiple Bowenoid tumors originating from verrucae vulgaris containing human papilloma virus. The rare diagnosis of dyschromatosis universalis hereditaria is particularly described to occur almost exclusively in Japanese patients. Patients with Carney syndrome or leopard syndrome have multiple pigmented lesions without sun sensitivity.

Diagnostic procedures

Early diagnosis before the development of skin tumors should be the goal. Interdisciplinary care in conjunction with dermatologists, ophthalmologists and pediatricians is necessary.

The clinical diagnosis XP can be obtained by measuring post-UV cell survival and DNA repair capacity in cellular assays (**Level of evidence 2+, Level of recommendation C**). For these assays, fibroblasts from the patient are generated from a skin biopsy and grown in the laboratory. For the survival assay cells are placed in plates and exposed to increasing doses of UVC-radiation. Cell growth is assessed for several days. The growth of most cells after UV-exposure is greatly reduced compared to normal cells. XP variant cells have normal post-UV survival but are sensitized to post-UV cell killing by addition of caffeine. Another assay is unscheduled DNA synthesis (UDS) which is reduced in most XP patients with the exception of XP-variants [8]. During the repair reaction necessary to restore the genomic integrity of the cell, radioactively labelled tritium is supplied in the medium. Radioactive incorporation into DNA as assessed by autoradiography or scintillation counting, is directly proportional to the repair capacity since in the last step of the repair reaction DNA polymerase incorporates nucleotides to fill the gap of excised damage-containing DNA. This repair reaction is reduced in fibroblasts derived from patients suffering from XP as compared to fibroblasts from normal donors. Specialized laboratories offer prenatal diagnosis for families with XP patients.

Complementation analysis revealed the presence of seven XP-subtypes (XP A to G), deficient in NER as well as a variant form with a deficiency in DNA polymerase eta [3, 25]. The genes defective in these complementation groups are cloned and designated according to the respective causative genes.

Treatment and photoprotection

Central to the care and management of patients is the strict avoidance of any exposure to ultraviolet (UV) radiation. The skin has to be protected from UV by long sleeved clothing covering the extremities to the wrists and heels. Fashionable clothing with UV-protective textiles has become available. The head and facial area should be protected by hats providing shade for nose and ears. Facial skin can additionally be protected by a visor mounted on the rim of a hat that holds a UV-protective screen providing good vision but complete filtration of UV-radiation. UV-protective films filtering at least 90% of the UV-spectrum should also cover all windows behind which XP patients live. This includes the house, kindergarten, school, work, as well as the cars in which the patients are transported (**Level of evidence 4, Level of recommendation D**).

In addition to these technical measures sunblocking lotions with highest possible UVB and UVA filters should be applied to the skin (**Level of evidence 4, Level of recommendation D**).

Effective chemoprevention of skin cancer by use of oral retinoids in XP patients has been demonstrated in a controlled study [26] however, there was considerable toxicity with the high doses used (**Level of evidence 2+, Level of recommendation C**). Local injections of interferon were shown to be effective in treating multiple melanoma in-situ lesions in one XP patient [27] (**Level of evidence 3, Level of recommendation D**).

Experimental use of DNA repair proteins from algae or bacteria applied in topical formulations containing liposomes have recently been reported. This has been shown for two different repair proteins. Photolyase, derived from the algae *ancystis nidulans*, repairs some forms of UV induced genomic DNA damage after activation by visible or

UVA-radiation. Photolyase encapsulated in liposomes has been reported to exert immunoprotective effects [28] **(Level of evidence 3, Level of recommendation D)**. The second enzyme is a DNA glycosylase/AP lyase or T4 endonuclease V (T4 endoV) that also repairs some forms of UV induced genomic DNA damage [29]. Application of T4 endoV to the skin of patients with XP significantly reduced the incidence of actinic keratoses and BCC [30, 31] **(Level of evidence 2++, Level of recommendation B)**.

The treatment of skin cancers utilizes the same methods as in people who do not have XP **(Level of evidence 4, Level of recommendation D)**. However, the increased frequency of multiple primary neoplasms often necessitates multiple excisions. These may lead to extensive scarring and removal of large amounts of skin particularly in the face. Thus, methods to adequately remove cancers while sparing tissue are preferred. Biopsy followed by surgical excision or desiccation and curettage is usually the first method of treatment. In vital areas such as near the eye or nose or with recurrent neoplasms of the face involving nerves micrographic controlled surgery of tumors is often used. Standard cryotherapy is an effective and simple method of removal (Level of evidence 4). XP patients with difficult to treat skin cancers or with internal cancers such as spinal cord or brain astrocytomas have been successfully treated with x-ray therapy. Surprisingly, in contrast to UV, the skin reaction to x-ray therapy in XP patients is usually normal [32] **(Level of evidence 3, Level of recommendation D)**.

COCKAYNE SYNDROME

Pathogenesis

There are two complementation groups in CS: CS-A and CS-B but in addition to this, mutations in XP genes from complementation groups XP-B, XP-D and XP-G can also lead to a combination of clinical symptoms of XP and CS (The XP/CS complex) [35, 36]. Cells from patients with CS are defective in transcription coupled DNA repair (TCR). For CS as well as TTD an additionally subtle defect in basal transcription of genes has been hypothesized which could be a possible reason why XP is characterized by an increased skin cancer risk but not CS or TTD [38]. However, experimental data in support of this hypothesis only exists for TTD thus far.

Clinical features

Like XP, CS is an autosomal recessive genetic disease albeit with far lower prevalence [2, 5, 33]. XP patients with neurological disease and CS patients share many of the same clinical features including marked skin sun sensitivity, microcephaly, progressive sensorineural hearing loss, short stature and progressive neurological degeneration. [34]. Their cells are also hypersensitive to killing by UV radiation and have defective DNA repair.

Characteristic features include typical bird-like face with beaked nose and deep set eyes, loss of subcutaneous fat and prematurely aged appearance. Further clinical symptoms include gait abnormalities, dental caries and often cold hands and feet with blue discoloration. Particularly the combination of growth and mental retardation with photosensitivity should lead to the clinical differential diagnosis of CS or TTD.

Neurological features of CS include dysmyelination as well as calcification of basal ganglia and other areas of the brain. Ocular changes seen in CS patients are cataracts and pigmentary retinal degeneration. Clinical forms of CS can be divided into mild, moderate and severe with reduction of life expectancy increasing from mild to severe.

Diagnostic procedures

As with XP the clinical diagnosis is secured on the cellular level. For this fibroblasts from patients are measured for their ability to recover from inhibition of RNA synthesis following UV-radiation. While in normal cells the RNA synthesis has recovered within 24 hours this is not the case in CS (**Level of evidence 2+, Level of recommendation C**). For families with CS patients, prenatal diagnosis is available in specialized centers.

Treatment and photoprotection

The care and management of patients with CS is difficult. Due to its photosensitivity strict UV avoidance is indicated and sun protection employing high protection factors in the UVA- and UVB-range (**Level of evidence 4, Level of recommendation D**).

TRICHOTHTIODYSTROPHY

Pathogenesis

There are three different complementation groups of TTD. The majority of cases reveal mutations in the *XPD* gene and in this complementation group the site at which the nucleotide is mutated determines the phenotype of the disease [42, 44, 45]. However, two patients have been reported that show the combination of TTD and XP features [49]. The second group shows mutations in the *XPB* gene and has been described in only one kindred. Mutations in a newly discovered small protein component of the TFIIH complex, TTD-A, have been found to cause TTD in a few families [46, 47]. A gene of unknown function on chromosome 7 (TTDN1) has been reported to be defective in some families with non-photosensitive TTD [48].

Clinical features

Trichothiodystrophy (TTD) is an autosomal recessive disease, termed by Price in 1980 [39, 40]. The clinical features of TTD show great variation in form, expression and severity. The clinical features include a collodion membrane at birth and marked skin sun sensitivity. The hair is brittle with thin hair shafts, breaking upon minimal trauma. Stress factors such as fever and infections can lead to effluvium represented by episodes of hair loss followed by re-growth [41]. Further clinical features are growth- and mental retardation as well as ichthyosis and other neuro-ectodermal abnormalities affecting the hair, skin, nails, nerve system and the eyes. The presence of brittle hair in combination with growth- and mental retardation under the third percentile possibly in combination with photosensitivity should lead to further diagnostic steps securing the diagnosis of TTD.

Diagnostic procedures

Most important diagnostic criterion are hair changes, caused by reduction of high sulphur matrix proteins and reduced cysteine content of the hairshaft matrix also underlying the fragility of the hair [18, 42]. As a hallmark of TTD, polarized light microscopy of TTD hair regularly reveals a pattern of light and dark areas of the hair leading to a typical “tiger tail” appearance in all hairs [43] (Level of evidence 3). Measurement of amino acid content of the hair by chromatography showing reduced content of cysteine rich matrix proteins can be used to secure the diagnosis (**Level of evidence 2+, Level of recommendation C**).

In contrast to XP, patients with TTD are not characterized by an increased risk of skin cancer although the causative mutations reside in the same gene. It has previously been demonstrated that, in addition to a repair defect, cells from XP patients also show alterations in immunosurveillance while TTD cells do not exhibit this defect [15-18]. In addition to this it is currently believed that the phenotype of TTD is also caused by subtle defects in basal transcription which would make both CS and TTD transcription deficiency syndromes [38]. Patients with TTD exhibit lower levels of β -hemoglobin than normal individuals [13]. This directly results in measurable decreases of simple clinical parameters. The mean corpuscular haemoglobin (MCH) as well as the mean cellular volume (MCV) of TTD-erythrocytes is significantly reduced (**Level of evidence 3, Level of recommendation D**). This finding facilitates diagnosis of TTD. Upon clinical suspicion of TTD MCH and MCV can be assessed in any clinical setting before more specialized tests are initiated.

Treatment and photoprotection

As with CS, care and management of TTD patients is difficult. It is restricted to stringent photoprotective measures as described above in the case of photosensitivity and supportive measures to reduce handicaps by neuro-ectodermal symptoms. Scaling induced by ichthyosis can be improved by application of urea-containing lotions (**Level of evidence 4, Level of recommendation D(GPP)**).

B) Helicase deficient diseases

BLOOM SYNDROME

Pathogenesis

Bloom syndrome is inherited autosomal-recessively but approximately $\frac{3}{4}$ of patients are male. There is an increased incidence in Ashkenazi Jews and in Japan. Cells from patients with Bloom syndrome are deficient in the RECQL3 helicase [50,51]. It helps to separate and uncoil double-stranded DNA prior to replication. The cytogenetic hallmark of Bloom syndrome is increased numbers of sister chromatid exchanges. Other defects in DNA repair are also seen and the chromosomes are easily damaged in vitro by UV radiation. Closely related helicases are involved in Werner syndrome, Rothmund-Thomson syndrome and some forms of xeroderma pigmentosum but Werner syndrome does not show photosensitivity.

Clinical features

Clinical data is summarised in a review by German et al. [52]. Patients are small at birth and later also show growth retardation. They may have small genitalia but are able to reproduce. Their intelligence is normal. The face is narrow and pointed with sunken cheeks. Occasional findings include polydactyly, dental abnormalities, and a high pitched voice. The incidence of diabetes mellitus is increased. The most prominent clinical features are telangiectases of the cheeks appearing within the first month of the patient. The patients show photosensitivity with erythema spreading with sun-exposure on nose, eyelids, forehead and, later, the extensor surfaces of the arms. The combination of the essential telangiectasia and photosensitivity leads to a poikilodermatous picture. Upon sun-exposure the patients can blister, especially on their lips. Disseminated café au lait macules can exist. Despite the photosensitivity, cutaneous malignancies are rare. Scabies has been described. Early in life, reduced immunoglobulin levels predispose to recurrent pulmonary and gastrointestinal infections, a problem that improves with time. Bloom syndrome patients have an increased incidence of leukemia, lymphoma, Wilms tumor, and gastrointestinal carcinoma, limiting life expectancy to the age of 20 or 30.

Diagnostic procedures

Characteristic clinical features point to the diagnosis. Levels of immunoglobulins have to be tested. Especially IgA and IgM are reduced. Genetic testing reveals increased sister chromatid exchanges and sequencing of the gene proves the diagnosis [53] (**Level of evidence 2+, Level of recommendation C**).

Therapy and photoprotection

Avoidance of sunlight, textile photoprotection, sunscreens with highest available filters against UVB and UVA and regular evaluation to detect internal malignancies as soon as possible are essential. Infections should be treated according to the infectious agent and standard protocols [52] (**Level of evidence 3, Level of recommendation D**).

ROTHMUND-THOMSON SYNDROME

Pathogenesis

The *RECQL4* gene encodes a DNA helicase [54]. Mutations in this gene can lead to Rothmund-Thomson syndrome both with and without cataracts. Mutations in similar helicases are found in Bloom syndrome, Xeroderma pigmentosum and Werner syndrome. Some patients are not mutated in this gene. These patients reveal cytogenetic anomalies on chromosome 8.

Clinical features and diagnostic procedures

The initial clinical features are erythema on sun-exposed skin, predominantly the cheeks [55]. Soon a reticulate pattern develops showing a livedo network. Skin symptoms begin during the first year of life, spreading to involve ears, chin, forehead, extremities and buttocks. The trunk is usually unaffected and photosensitivity is not mandatory. Patients develop acral keratoses, squamous cell carcinoma and basal cell carcinoma. Skin

appendages such as hairs, sebaceous and sweat glands may be reduced or absent. All patients show growth retardation and about half of patients have cataracts from early childhood. Other clinical features include hypogonadism, skeletal abnormalities such as bowing of the tibia, small hands and feet, hypoplastic thumbs and dental abnormalities. The intelligence is normal. There is a risk of osteosarcoma. Unless patients die from tumors, life expectancy is normal. Sequencing of the gene proves the diagnosis. **(Level of evidence 2+, Level of recommendation C)**

Therapy and photoprotection

Strict avoidance of sun-exposure, textile photoprotection and sunscreens with highest available filters against UVB and UVA are paramount. Textile photoprotection as well. Regular clinical follow-up including imaging to avoid undetected tumor formation. **(Level of evidence 4, Level of recommendation D (GPP))**

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Disease	Defect	Diagnostic procedure	Therapy and photoprotection
Xeroderma pigmentosum	NER (GGR / TCR) DNA repair	Post-UV cell survival and DNA repair capacity measurement LOE: 2+, LOR: C	Textile photoprotection UV-protective screens LOE: 4, LOR: D Sunscreens (UVB, UVA) LOE: 4, LOR: D Retinoids if tolerable LOE: 2+, LOR: C Interferon alpha s.c. LOE: 3, LOR: D Photolyase LOE: 3, LOR: D T4NV LOE: 2++, LOR: B Treatment of tumors as in normals, photodynamic therapy unclear Radiation therapy is possible LOE: 3, LOR: D
Cockayne syndrome	NER (TCR) Basal transcription	Recovery of RNA synthesis post UV LOE: 2+, LOR: C	Textile photoprotection UV-protective screens LOE: 4, LOR: D Sunscreens (UVB, UVA) LOE: 4, LOR: D
Trichothiodystrophy	NER	Measurement of cysteine content	Textile photoprotection

	Basal transcription	in hair shaft LOE: 2+, LOR: C MCH and MCV reduced LOE: 3, LOR: D	UV-protective screens LOE: 4, LOR: D Sunscreens (UVB, UVA) LOE: 4, LOR: D Urea containing lotion LOE: 4, LOR: D(GPP)
Bloom syndrome	RECQL3 helicase	Detection of immunoglobulins Increased SCE Sequencing of RECQL3 LOE: 2+, LOR: C	Avoidance of UV-exposure Textile photoprotection Sunscreens (UVB, UVA) Regular screening for tumors Treatment of infections LOE: 3, LOR: D
Rothmund-Thomson syndrome	RECQL4 helicase	Sequencing of RECQL4 LOE: 2+, LOR: C	Avoidance of UV-exposure Textile photoprotection Sunscreens (UVB, UVA) Regular screening for tumors Treatment of infections LOE: 3, LOR: D (GPP)

Table 1. Summary of Genomic instability diseases

Abbreviations: LOE – Level of evidence, LOR – Level of recommendation, MCH – median corpuscular haemoglobin, MCV – median corpuscular volume, T4NV – T4 endonuclease V