



## Photo-Prevention and Surgical Interventions in Xeroderma Pigmentosum

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### Abstract

Xeroderma pigmentosum (XP) is a genodermatosis that results in increased sensitivity to UV radiation, resulting in early onset of photodamage and skin cancers. There are eight XP subtypes, seven due to variable defects in the nucleotide excision repair pathway and one due to a defect in translesion synthesis. Patients with XP have mucocutaneous, ocular, and sometimes neurologic manifestations. Prevention is key for these patients. In this article, we discuss the background, subtypes, clinical manifestations, and diagnosis of XP. Photo-preventative measures for patients with XP are discussed as well as pharmacological and surgical treatments of the cutaneous manifestations of the disease.

### Keywords

Xeroderma pigmentosum, Non-melanoma skin cancer, Melanoma, UV radiation, Sunscreen

### Abbreviations

5-fu: 5-fluorouracil; 6-4PPs: 6-4 photoproducts; AKs: actinic keratoses; BCC: basal cell carcinoma; CPDs: cyclobutane-pyrimidine dimers; NER: nucleotide excision repair; PDT: photodynamic therapy; NMSCs: non-melanoma skin cancers; SCC: squamous cell carcinoma; SPF: sun protective factor; UV: ultraviolet; XP: xeroderma pigmentosum

### Introduction

Xeroderma Pigmentosum (XP) is a rare, autosomal recessive genodermatosis affecting the nucleotide excision repair (NER) pathway or translesion synthesis that dramatically increases susceptibility to ultraviolet (UV)-induced cutaneous malignancy. The disease prevalence of XP varies geographically with 1 in 1,000,000 affected in the United States, 2.3 in 1,000,000 affected in Western Europe, and 45 in 1,000,000 affected in Japan [1]. XP was first described by Moritz Kaposi in 1870, and the mechanism of disease was elucidated by James Cleaver in 1968 [2,3]. Despite years of research, the rarity of the disease and complexity of the pathogenesis contribute to diagnostic and therapeutic challenges. This review outlines the current understanding of XP with particular emphasis on recent developments in diagnosis and management.

### Pathogenesis and clinical manifestations

Exposure to UV radiation contributes to DNA alterations between adjacent pyrimidine nucleotides in-

cluding cyclobutane-pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs) [4]. Under normal circumstances, CPDs and 6-4PPs are corrected via the NER pathway, a genomic correction mechanism involving over 30 proteins. The roles of the seven proteins implicated in the pathogenesis of XP subtypes associated with the NER pathway are as follows. XPE and XPC recognize damaged DNA, triggering global genome repair. Then, a protein complex incorporating XPB and XPD mediates unwinding of the DNA helix. XPA activity allows endonucleases XPF and XPG to cleave the damaged DNA

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segment. Finally, DNA polymerase replaces the segment with complementary nucleotides sealed by DNA ligase. The final XP subtype is due to a mutation in DNA polymerase  $\eta$ , a DNA polymerase that performs DNA replication involving a damaged template in a process known as translesion synthesis [5-7].

The accumulation of CPDs and 6-4PPs has significant consequences ranging from the obstruction of DNA replication and transcription to mutations transmitted to all cellular lineage [4]. The resultant clinical manifestations are discussed below.

**Mucocutaneous:** The mucocutaneous manifestations of XP are often the most salient disease feature. Approximately 60% of XP patients will exhibit a dramatic sunburn reaction requiring days or weeks to achieve full recovery. Macular lentiginosities and dyschromatosis usually manifest in sun-exposed areas by two years of age, and continued UV exposure contributes to characteristically atrophic, xerotic skin with a poikilodermic appearance [1,6-8]. Cutaneous manifestations have been shown to be delayed until after the age of 14 in 5% of patients [9]. Interestingly, patients with XP who present with a dramatic sunburn reaction often experience less cutaneous malignancy associated morbidity and mortality ostensibly due to increased UV-protective efforts [8].

The inability to correct UV-induced DNA photodamage contributes to a significantly increased risk of cutaneous malignancy, and this tumor burden is the major source of morbidity and mortality for patients with XP [6]. Specifically, patients with XP have a nearly 10,000 fold increase in the risk of non-melanoma skin cancers (NMSCs) such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) paired with a greater than 2,000 fold increase in the risk of melanoma than the general population [5]. The heavy tumor burden afflicts XP patients at a young age. Patients with XP typically ex-

perience their first cutaneous malignancy five years after diagnosis at a median age of 8, and the tumor burden increases with age [8,9]. Studies conflict on whether XP results in a larger BCC or SCC NMSC burden [9-12]. Other NMSCs can be seen with increased frequency as well. An unusual presentation of an UV-associated tumor was also described in a case report with an atypical fibroxanthoma, commonly associated with sun-exposed regions in elderly adults, discovered on the digit of a 13-year-old with XP [13].

Additionally, approximately 4% of patients with XP have oral manifestations that include leukoplakia, actinic cheilitis and squamous cell carcinoma on the tongue apex from presumed UV exposure [7,8]. In fact, patients with XP exhibit higher rates of cutaneous malignancy as well as ocular, oral, and central nervous system malignancies which are discussed below [14-16]. The incidence and number of observed/expected cases of XP-associated malignancies are provided in Table 1.

**Ocular:** Ocular complications affecting the UV-exposed structures of the anterior eye are evident in approximately 40% of patients with XP. Patients often exhibit photophobia and keratitis that contributes to corneal opacification, neovascularization, and malignancy with repeated UV insult [6-8]. Scarring of immediately adjacent skin can also result in ectropion and symblepharon with vision-threatening consequences [8]. Blindness will result if the UV-induced changes are not adequately prevented and treated.

**Neurological:** Neurological complications affect between 20-30% of patients with XP with high-frequency hearing loss being the most common complication. However, regression characterized by gradual loss of deep tendon reflexes, ataxia, aphasia, and dysphagia have also been noted [2,7,8,17]. Additionally, patients with XP have greater than ten times the risk of developing cen-

**Table 1:** Incidence and observed/expected ratio of Xeroderma Pigmentosum-associated malignancies [14-16].

Malignancy		Incidence (all ages)	Observed/Expected (age < 20)	Observed/Expected (all ages)
Cutaneous	NMSC	58-60%	4900-9757	327
	Melanoma	22-32%	1879-8000	193-700
Non-Cutaneous	Ocular <sup>^</sup>	9-26%	1000	1700
	Oral <sup>*</sup>	2%	100,000	800
	Central Nervous System <sup>#</sup>	2%	50	33

<sup>^</sup>Reported ocular malignancies include SCC, epithelioma/BCC, melanoma.

<sup>\*</sup>Reported oral malignancies include SCC of the tongue apex, gingiva, and palate.

<sup>#</sup>Reported central nervous system malignancies include brain sarcoma and spinal cord astrocytoma.

**Table 2:** Generalized findings associated with XP subtypes [2,6].

XP Subtype	United States Prevalence	Cutaneous Manifestation Severity	Mean Age of BCC	Neurologic Regression Severity
XPA	9%	Severe	9.7	Mild to Severe
XPB	1%	Moderate	-	None to Severe
XPC	43%	Moderate	14.0	Absent
XPD	28%	Moderate	38.0	None to Severe
XPE	3%	Mild	38.3	Absent
XPF	0%	Mild	43.7	None or Severe
XPG	3%	Moderate	32.0	None or Severe
XPV	7%	Mild	41.5	Absent

tral nervous system-related malignancies than the general population [8]. The neurologic complications of XP are an additional source of morbidity and mortality, as evidenced by the fact the average life expectancy for a patient with XP is 37 years of age if neurologic complications are absent and 29 years of age if neurologic complications are present [6].

### Classification

The milieu of clinical manifestations a patient with XP will experience depends on the patient's XP subtype, which is differentiated by the protein implicated in disease pathogenesis. Subtype XPA, for instance, is associated with mutations in the NER protein XPA, while subtype XPB is associated with mutations in the NER protein XPB. XPV, the variant subtype, is an exception to this general rule and is caused by a mutation in the error-prone DNA polymerase  $\eta$  [1,5]. Generalized findings associated with each XP subtypes are provided in Table 2. Notably, the specific phenotypic expression is also dependent on the mutation's location and type with implications ranging from equivocal alterations in protein levels to the devastating effects of complete protein absence [18].

### Diagnosis

The diagnosis of XP is suspected with the development of the disease's characteristic cutaneous manifestations and verified with laboratory assessment [18]. UV cell survival is one of the simplest diagnostic assessments. Fibroblasts isolated from a small skin biopsy or lymphoid cells isolated from a blood draw are exposed to UV radiation. Cells from patients with XP succumb with lower UV exposure due to the defective NER pathway [2,5,7,18,19]. Cells from patients with XPV are unique in that this effect is only observed after sensitization with caffeine, an effect partially attributed to caffeine's activity as a kinase inhibitor [7,18]. This technique is sufficient to confirm the diagnosis of XP in the majority of cases [5,18]. In 2008, Cleaver proposed implementing immunohistochemistry to efficiently diagnose XP. Immunohistochemistry can be utilized to evaluate the level of expression for XP proteins in fixed tissue. Since the ma-

jority of recognized XP causative mutations (specifically for XPA, XPC, XPF, XPG, and XPV) result in reduced protein levels, an aberrantly low immunohistochemistry signal would indicate disease [18].

More recently, next-generation sequencing has simplified the diagnosis of XP. The sequence of DNA composing the eight causative XP proteins can be constructed from saliva samples or blood samples and compared to a human reference genome to detect mutations. This process can be performed rapidly, eliminates the necessity of skin biopsies, and has been readily employed to diagnose XP [20-22].

Subtype frequency varies with geography due to a presumed founder effect [2,6]. Over 50% of Japanese patients with XP are afflicted with XPA, and roughly 80% of those patients exhibit an identical homozygous IVS3-1G>C mutation [2]. 94% of patients with suspected XPC were found to have an identical c.1643\_1644delTG mutation in a Tunisian study [23], while Munford et al. reported that a community in the Brazilian state of Goias had 17 of its approximately 1000 inhabitants affected by XP. Genomic analysis demonstrated that all of the affected individuals were homozygous for c.764 + 1 G > A in intron 6 of DNA polymerase  $\eta$ , homozygous for c.907 C > T in intron 8 of DNA polymerase  $\eta$ , or a compound heterozygote of these two mutations [24]. Similarly, Yulmacap is a small, isolated mountain town in Guatemala with a population of several hundred. Over 12 individuals from Yulmacap are afflicted with XPC [25].

These examples, and many others, demonstrate the geographically based uniformity of XP mutations and the profound impact that XP can have on isolated communities where the prevalence rate can significantly exceed established international rates due to factors that can include consanguinity [2,7,9,11,24,26]. Kraemer's 1987 review article on 830 patients with XP revealed that 31% of patients' parents were in consanguineous relationships [9], while a more recent study by Khatri et al. on XP trends in Libya demonstrated that 39 of the 42 patients studied had parents in consanguineous relationships [11].

Early diagnosis is critical. Patients with XP subtypes without neurological involvement can achieve normal life expectancy if the disease is diagnosed early and stringent UV-protective measures are implemented to preclude carcinogenesis. However, UV damage sustained prior to diagnosis may manifest as disease complications years after the inciting event [7].

### Differential diagnosis

Several alternative conditions can present with cutaneous manifestations similar to XP at an early age including freckles, dyschromatosis symmetrica hereditaria, and erythropoietic protoporphyria [2]. Freckles are typically limited to the face and present without symptoms of photosensitivity. Dyschromatosis symmetrica hereditaria is an autosomal dominant condition that manifests with mottled hyperpigmented and hypopigmented macules located on the dorsal surfaces of the extremities. It may also manifest with macules that resemble freckles on the face [2,27]. Erythropoietic protoporphyria is the most frequent porphyria present in childhood and is due to loss of function in the protein ferrochelatase. Patients with erythropoietic protoporphyria experience pain with exposure to sunlight and swelling with prolonged sunlight exposure. This condition is often diagnosed by a combination of the patient’s symptoms paired with an elevated free erythrocyte protoporphyrin level [2,28].

Additional photodermatoses can affect the NER pathway and present with photosensitivity. Cockayne syndrome, for instance, presents with progressive neurological symptoms, intellectual deficiency, kyphosis, osteoporosis, thin hair, dwarfism, and sun sensitivity manifesting as an erythematous rash [6,7,21]. Trichothiodystrophy presents with progressive neurological symptoms, intellectual deficiency, microcephaly, protruding ears, micrognathia, and a characteristic brittle hair with “tiger” appearance under polarizing microscopy due to a sulfur deficiency [6,21,29]. While photosensitivity is common to both conditions, there is no association with elevated skin cancer risk [21].

## Body

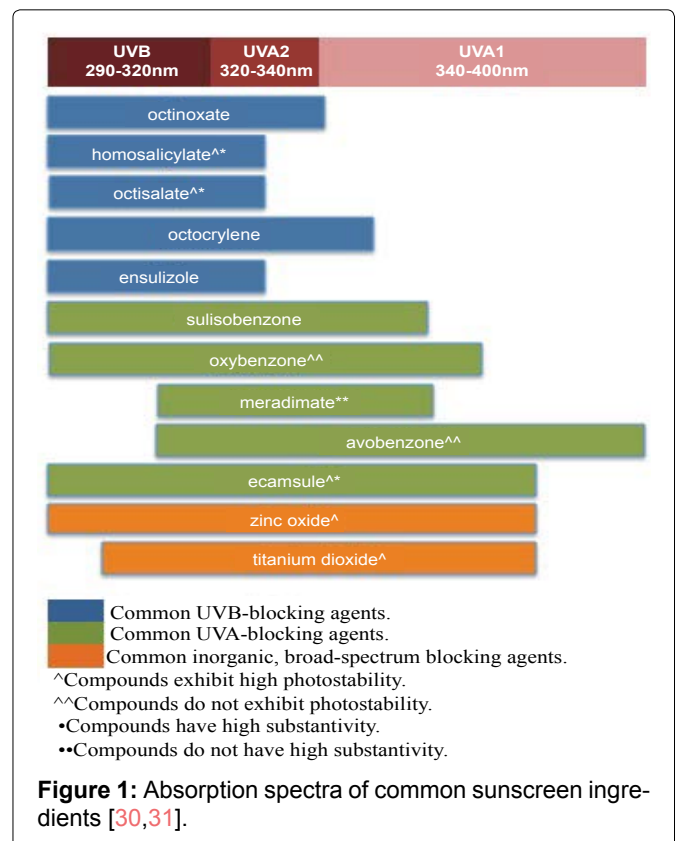
### Prevention of cutaneous and ocular manifestations

No cure presently exists for XP, but the morbidity and mortality associated with XP’s cutaneous manifestations can be controlled with stringent sun protection [7]. In 2007, the Japanese Ministry of Health, Labor, and Welfare classified XP as a neurocutaneous syndrome and subsequently outlined management guidelines proposing multiple specific UV-protective measures that include applying a broad spectrum sunscreen with high sun protective factor (SPF) to all exposed skin prior to sun exposure, wearing UV-protective clothing that cov-

ers the extremities, and wearing UV-protective glasses for ocular protection [2].

Sunscreens preclude UV-related cutaneous alterations including erythema, pigment darkening, epidermal hyperplasia, free radical formation, and carcinogenesis [18]. UVA and UVB are the only UV-spectrum components of physiologic importance because the ozone layer absorbs the entirety of UVC [30,31]. UVA radiation is minimally absorbed by DNA and its dominant contribution to carcinogenesis includes the creation of reactive oxygen species that yield DNA base transversions and strand breaks. UVB radiation is a more potent creator of CPDs and 6-4PPs because it is more readily absorbed by DNA [29,31,32]. A sunscreen’s effectiveness at protecting against UVB radiation is provided by the SPF rating, which measures the multiplicative prolongation that the sunscreen’s application has on erythema development with UV exposure. Sunscreens that combine organic and inorganic compounds to absorb and/or reflect UV radiation into the UVA range can claim to offer broad-spectrum protection [30,31]. The UV-spectrum protection offered by common sunscreen ingredients is demonstrated in Figure 1. In addition to offering broad-spectrum protection, the ideal sunscreen is photostable (contents are not degraded by UV radiation) and highly substantive (contents maintain effectiveness with exposure to water) [30,31].

Modern sunscreens also integrate vitamin C, lipophilic vitamin E, and/or green tea polyphenols that pro-



protect against the activity of reactive oxygen species upon light penetration [31]. Tamura, et al. specify that sunscreen should have an SPF 30 or greater and be applied every 2-3 hours [26]. Other sources indicate sunscreen with high or the highest available radiation protection should be employed in patients with XP [2,33]. UV-resistant face masks, broad-brimmed hats offering neck coverage, and lip balm with SPF are additional protective equipment recommendations [6,7].

Commonly encountered environments should also be augmented in order to minimize UV exposure. Home, school, and car windows of patients with XP should be lined with UV-protective film or sunshades [2,7]. Additionally, light sources should be investigated for UV emissions with a light meter [34]. Halogen lights, metal halide lights, mercury arc lights, and some fluorescent lights produce disease-aggravating UV radiation [6,17,34]. These light sources should be replaced with suitable alternatives.

One complication of eliminating UV exposure is vitamin D deficiency, a condition associated with bone demineralization, fractures, hypertension, and depression. Vitamin D levels should be routinely measured and dietary supplementation should be initiated for patients with XP exhibiting low vitamin D serum concentration levels [1,5-7].

Patients with XP should undergo routine comprehensive skin examinations by a dermatologist, but frequency recommendations vary from every 3 months to once yearly based on disease severity [1,2,5-7,34]. Prudent clinical judgment regarding skin examination frequency should be employed, and regular skin examinations by family members is highly recommended [6]. Disease education is critical to ensure compliance with preventative measures [21].

Systemic retinoids, such as isotretinoin and acitretin, are well-studied chemopreventive agents that induce apoptosis through their action on nuclear receptors [5,17]. In a seminal study from 1988, Kraemer et al. demonstrated that 2 mg/kg daily of oral isotretinoin resulted in a statistically significant 63% reduction in skin cancer incidence during the two year drug administration period when compared to the skin cancer incidence prior to isotretinoin administration in five patients with XP [35]. The utility of retinoids may, however, be limited by their known side effects that include xerosis, cheilitis, triglyceride elevation, liver function abnormalities, skeletal abnormalities, and teratogenicity as well as the known flare in tumor burden that occurs upon retinoid discontinuation [17,35]. The xerosis and cheilitis, in particular, may be difficult to manage in XP, a condition characterized by xerotic skin. Nonetheless, the European Dermatology Forum recommends retinoids when toler-

able to manage the skin cancer burden in patients with XP [33].

Of note, chemical peels and ablative resurfacing laser have been used in clinical practice to successfully treat the severe actinic damage in XP patients. Different chemical peels have been utilized to treat premalignant lesions, including phenol peel and trichloroacetic acid (TCA) 30% peel, with good results [36,37].

Finally, T4 endonuclease V is a protein originating from the T4 bacteriophage that selectively cleaves CPDs and can be packaged in liposomes for topical administration [38]. A study performed by Yarosh et al. in 2001 demonstrated that the 20 patients with XP randomized to administer the experimental liposomal lotion containing 1 mg/L of T4 endonuclease V experienced a 70% decrease in the number of precancerous, actinic keratoses (AKs) lesions and a 30% decrease in the number of BCCs [39]. The FDA has yet to approve its use [6].

### **Pharmacologic treatment of cutaneous manifestations**

5-fluorouracil (5-fu) and imiquimod are pharmacologic therapies proven to treat precancerous and cancerous lesions in patients with XP. 5-fu is a thymidylate synthase inhibitor whose activity results in cell death through apoptosis and is proven to treat AKs and superficial carcinomas [5]. Imiquimod is an immunomodulatory agent that activates specific cutaneous toll-like receptors, increasing the immune system's clearance of AKs and BCCs [2,17]. For patients with XP, Lambert and Lambert recommend a three-week treatment with either agent every 3-6 months once the disease's cutaneous stigmata materialize [17]. Complications of treatment include punctate erythema, pain, and irritation. Analgesics other than non-steroidal anti-inflammatories should be pursued to manage pain since inflammation is a vital component of both agents' therapeutic effects [17]. Notably, a newly FDA approved medication for the treatment of actinic keratoses (AKs) ingenol mebutate, would be a reasonable alternative to 5-fu and imiquimod for XP patients. However, to our knowledge there are no case reports of its use in children with XP. A recent case report demonstrates that imiquimod is an effective therapy for multiple superficial BCCs recurring after surgical excision in a patient with XP [40].

Photodynamic therapy (PDT) is a dubious intervention to treat field, superficial malignancies in patients with XP. PDT incorporates aminolevulinic acid, which produces apoptosis-inducing reactive oxygen species when activated by specific wavelengths of blue or red light [5]. This therapy is controversial in patients with XP due to its dependence on light activation.

Lastly, several case reports show promising results from novel chemotherapeutic agents to treat cutaneous manifestations in patients with XP. Four months of 150 mg/day oral vismodegib, a Hedgehog pathway inhibitor, was administered to treat a nodular BCC located on the nasal tip of an 8-year-old with XP. The patient's tumor regressed without reoccurrence within the 21-month follow-up period [41]. Of note, this use of vismodegib is off-label as it is not FDA-approved for treatment of resectable BCCs in children. 3 mg/kg of nivolumab, an anti-programmed cell death protein 1 therapy, was administered every 2 weeks to treat a non-operable sarcomatoid carcinoma of the scalp in a 6-year-old with XP. The sarcomatoid carcinoma regressed with treatment; however, the patient developed two melanomas and several NMSCs during the treatment period [42]. Collectively, these case reports demonstrate the potential of novel chemotherapeutic agents to treat challenging or inoperable cutaneous malignancies in patients with XP. Additional studies are necessary to verify effects on a larger scale.

### **Surgical treatment of cutaneous manifestations**

Interventions in patients with XP to treat precancerous or cancerous lesions are similar to those for the general population. Freezing with liquid nitrogen is an option to treat AKs, while electrodesiccation and curettage or surgical excisions are viable treatment modalities for cutaneous malignancies [6]. Surgical excision in patients with XP requires special consideration. UV-protective films should be employed to minimize exposure to any sources of natural light and operating lights should be evaluated for UV exposure [43]. Anesthetic agents known to damage DNA including halothane should be avoided [2,43]. Patients with XP are known to exhibit prolonged awakening from anesthesia [2].

Additionally, cutaneous malignancies are typically removed with a wide surgical margin to minimize recurrence risk. This strategy proves challenging in patients with XP due to their high tumor burden, often afflicted by multiple cancerous lesions whose removal with wide surgical margins may not reduce the risk of adjacent malignancy. Excisions should aim to remove the entire tumor while simultaneously preserving adjacent tissue in patients with XP [3,17]. Mohs micrographic surgery should be considered for the treatment of recurrent tumors or for the treatment of tumors located in regions predisposed to recurrence when available [3,6].

Cryosurgery has also been implemented to treat facial BCCs in patients with XP. A retrospective study performed by Zghal et al. on the treatment of 45 facial BCCs reported adequate response to treatment with only a single tumor recurring during the 16 to 60 month follow-up period [44].

### **Management of extracutaneous manifestations**

The neurological complications associated with 20-30% of XP cases are poorly understood and presently cannot be prevented. Patients with XP should receive regular audiometry examinations as well as gait and deep-tendon reflex assessments to screen for neurologic involvement [7]. Management of complications involves hearing aids in response to sensorineural hearing loss, speech therapy in response to dysarthria, physical therapy in response to ataxia, and occupational therapy in response to dysphagia [2,7].

Additionally, special care should be taken in patients with XP to avoid carcinogen exposure. Patients with XP are particularly susceptible to compounds normally eliminated by the NER pathway such as benzo[a]pyrene in cigarette smoke, aflatoxins, photoactivated psoralens, and cis-platinum [6,8,17,18]. Patients with XP who smoke cigarettes have been shown to develop early-onset lung cancers [6]. A case report also demonstrates severe adverse events including multi-organ failure occurring in two patients with XP exposed to cisplatin [45]. This set of adverse events should be explored due to the implications for chemotherapy.

### **Conclusion**

XP remains a difficult disease to diagnose and treat nearly 50 years after its mechanism of disease was elucidated by James Cleaver [2]. Experiments involving gene transfer through retroviruses have shown promising results both *in vitro* and in skin humanized murine models. Warrick et al. used retroviruses to transduce the wild type XPC gene into human keratinocytes and demonstrated a fully functional NER pathway capacity [46]. Dupuy et al. demonstrated that more targeted therapies involving engineered meganucleases and TALE-nucleases are also efficacious despite complications associated with DNA demethylation [47]. CRISPR technique may soon be applied to XP [5]. Nonetheless, any curative attempts must have proven safety and the capability of broadly correcting deficiencies in all skin cells- an imposing set of challenges [5].

Management and prevention of complications in order to minimize disease associated morbidity and mortality is paramount at this point. As previously mentioned, stringent sun protection can contribute to normal life expectancies in patients with XP subtypes devoid of neurological involvement, making early diagnosis and intervention critical [5,7,48]. Tamura et al. as well as Bensenouci et al. suggest prenatal diagnosis or newborn screening in communities with high disease prevalence and known common founder mutations [21,48]. Early diagnosis grants the opportunity to engage in sun pro-

tective behaviors early on to preclude UV-induced cutaneous and ocular manifestations, including malignancy.

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