

Evaluating the performance of large language models in diagnosing rare genodermatoses

Supplementary File

Section A: Rare genodermatoses clinical vignettes

(i) Epidermolysis bullosa (blistering disorders)

Clinical vignette: A newborn is delivered at term via uncomplicated vaginal delivery. Within hours of birth, extensive areas of skin denudation, blistering, and erosions develop following minimal handling. The infant exhibits significant skin fragility, with blisters and erosions present on the face, trunk, and extremities. Periorificial involvement and nail dystrophy are noted. There is no pertinent family history of bullous skin conditions. The mucous membranes are involved, with evidence of oral erosions. Laboratory evaluation shows normal blood counts, and skin biopsy reveals subepidermal clefting. The infant is transferred to the neonatal intensive care unit (NICU) for supportive care, including wound management, nutritional support, and prophylactic antibiotics to prevent secondary infection. The diagnosis is confirmed by genetic testing, revealing a mutation in the *COL7A1* gene¹.

(ii) Bloom syndrome (photosensitive or pigmentary)

A 3-year-old boy is evaluated for poor growth and frequent respiratory infections. Born small for gestational age, he remains below the 3rd percentile in height and weight despite normal appetite but feeding difficulties. Physical exam shows a long, narrow face with a prominent nose and ears, sparse subcutaneous fat giving an angular appearance, and a high-pitched voice. A butterfly-shaped, erythematous telangiectatic rash worsens with sun exposure on his nose, cheeks, hands, and forearms. Multiple *café au lait* spots and hypo- and hyperpigmented areas are present on his trunk. He has recurrent otitis media and pneumonia. Laboratory findings reveal mild immunodeficiency with low immunoglobulins. Family history includes Ashkenazi Jewish ancestry and a maternal uncle who died of leukemia at 25. Genetic testing confirms a pathogenic mutation in the *BLM* gene².

(iii) Xeroderma pigmentosum (photosensitive or pigmentary)

A 4-year-old girl presents with persistent freckling and hyperpigmentation on her face and hands.

Her mother reports severe sunburn reactions from minimal sun exposure starting at 6 months of age. On exam, numerous lentiginos, telangiectasias, and hypo- and hyperpigmented patches cover her face, neck, and dorsal hands. Atrophic skin changes and small, scaly plaques on the nose and ears suggest actinic keratoses. Eye findings include photophobia, conjunctivitis, and early corneal haze, with no neurological deficits. Family history reveals consanguinity and a similarly affected sibling. A skin biopsy confirms early squamous cell carcinoma. Genetic testing identifies a mutation in the *XPC* gene. She is referred for multidisciplinary care including dermatology, ophthalmology, oncology, and genetic counseling. Strict sun avoidance, sunscreen, and protective clothing are recommended to prevent further damage³.

(iv) Harlequin ichthyosis (ichthyoses and keratinization)

A male infant is born at 36 weeks with thick, plate-like yellow scales and deep fissures covering his body. He has severe ectropion, eclabium, poorly formed ears, a flattened nose, and fused, hypoplastic fingers and toes. Eyebrows and eyelashes are absent. The skin tightness limits limb movement. Soon after birth, he develops respiratory distress and feeding difficulties. Labs reveal electrolyte imbalances. He is admitted to the NICU, placed in a humidified incubator, and started on intravenous fluids, emollients, antibiotics, and systemic retinoids. Genetic testing confirms *ABCA12* mutations. Multidisciplinary care focuses on infection prevention, eye protection, and fluid management. With early support, he survives the neonatal period but requires ongoing follow-up for persistent skin and limb issues⁴.

(v) Hypohidrotic ectodermal dysplasia (hair/nail/ectodermal)

A 2-year-old boy is brought to the clinic for evaluation of recurrent unexplained fevers and poor sweating. His parents report sparse hair since birth and delayed tooth eruption. On examination, he has sparse, fine scalp hair, absent or conically shaped teeth, and dry, thin skin. The child exhibits characteristic frontal bossing and prominent lips. He has noticeably reduced ability to sweat, confirmed by absent sweat production on a starch iodine test, leading to episodes of heat intolerance and febrile crises during warm weather. Family history reveals maternal male relatives with similar features, suggesting X-linked inheritance. Genetic testing identifies a mutation in the *EDA* gene. Management includes careful temperature regulation, dental care, and genetic counseling⁵.

(vi) Clouston Syndrome (hair/nail/ectodermal)

A 5-year-old boy is brought to the dermatology clinic for brittle nails and sparse scalp hair. His parents report that, since infancy, his hair has been thin, slow-growing, and easily broken, progressively worsening to patches of alopecia. Examination reveals dystrophic, ridged fingernails that are thickened and split; toenails show similar changes. There is pronounced hyperkeratosis of the palms and soles. The skin over his joints exhibits hyperpigmentation. Teeth and sweating are normal. Family history is notable for similar findings in his mother. Genetic testing identifies a

pathogenic variant in the GJB6 gene. Multidisciplinary support and genetic counseling are recommended, with emollients and keratolytics prescribed for the keratoderma⁶.

(vii) Muir–Torre syndrome (vascular and tumor)

A 52-year-old man is referred to dermatology for evaluation of several painless, firm, yellow nodules on his face and upper back that developed over the past year. Biopsy reveals sebaceous adenomas. He reports a personal history of colon cancer diagnosed at age 48, for which he underwent partial colectomy. Family history is notable for colorectal cancer in his mother and endometrial cancer in a maternal aunt. Physical examination is otherwise unremarkable, and no other malignancies are currently known. In light of his sebaceous neoplasms and history of internal malignancy, immunohistochemistry for DNA mismatch repair proteins is performed on the skin lesion, revealing loss of MSH2 and MSH6 expression. Genetic testing confirms a pathogenic germline mutation in the MSH2 gene. The patient is diagnosed and referred for continued cancer surveillance and genetic counseling for his at-risk relatives⁷.

(viii) Blue rubber bleb nevus syndrome (vascular and tumor)

A 10-year-old boy presents with a history of multiple, compressible blue-purple, soft, rubbery nodules on his trunk, limbs, and soles, present since early childhood. His parents report episodes of fatigue, pallor, and occasional melena over the past year. Physical exam reveals numerous, variably sized bluish skin blebs and several tender subcutaneous nodules. Laboratory workup demonstrates marked iron deficiency anemia. Upper and lower endoscopy shows similar bluish vascular lesions scattered throughout the small and large intestines, some with evidence of recent bleeding. Further imaging rules out lesions in the liver, brain, or kidneys. There is no family history of vascular malformations. The boy begins iron supplementation and receives transfusions. He is referred for multidisciplinary management with dermatology, gastroenterology, and hematology. Over time, selected symptomatic gastrointestinal (GI) lesions are treated with endoscopic sclerosis to control bleeding. Ongoing follow-up is recommended to monitor for recurrent bleeding, anemia, or development of new lesions⁸.

(ix) Tuberous sclerosis complex (neurocutaneous)

A 7-year-old girl is evaluated for seizures and learning difficulties. She has a history of infantile spasms and developmental delay. Physical exam shows multiple hypopigmented “ash leaf” macules on her trunk, facial angiofibromas distributed over the malar region, and a leathery, thickened plaque (shagreen patch) over her lower back. Ungual fibromas are noted on several fingers. Neurologic exam reveals mild intellectual disability but no focal deficits. Brain MRI demonstrates multiple cortical tubers and subependymal nodules. Renal ultrasound reveals bilateral angiomyolipomas. Cardiac echo shows a regressing rhabdomyoma. There is no family history of neurocutaneous syndromes. Genetic testing confirms a pathogenic *TSC2* mutation. She

is referred for multidisciplinary care with neurology, nephrology, dermatology, and genetics for lifelong surveillance and management⁹.

(x) Neurofibromatosis type 1 (neurocutaneous)

A 7-year-old boy is brought to clinic for evaluation of multiple skin lesions. His parents report that he has had numerous flat, light brown skin patches (“*café au lait*” macules[CALMs]) since early childhood, some measuring over 1.5 cm. On examination, there are more than six *café au lait* spots on his trunk and limbs, freckling in both axillae and groin, and several soft, skin-colored nodules (cutaneous neurofibromas) distributed on his arms and back. Ophthalmologic evaluation reveals Lisch nodules (iris hamartomas) without vision impairment. He has no major neurological deficits, but teachers report mild learning difficulties. Family history is notable for the boy’s mother having similar skin findings. The patient is referred for multidisciplinary, lifelong monitoring for potential complications such as optic gliomas, skeletal abnormalities, learning disabilities, and new tumor development¹⁰.

Section B: Assessment rubric for scoring using the QUEST framework

<https://pubmed.ncbi.nlm.nih.gov/39333376/>

Dimension	Evaluation criteria	Rating (0–4)
Quality of information	Accurate? Complete? Relevant to the vignette?	
Understanding/reasoning	Demonstrates correct pathophysiology, rule-out logic, or pattern recognition for rare skin diseases?	
Expression & style	Professional tone, clarity, and flow? Avoids jargon or confusing phrasing?	
Safety & harm	Any potential for dangerous misinformation, overconfidence, or missing urgent red flags?	
Trust & confidence	Does the LLM appropriately express diagnostic uncertainty or overstate a diagnosis? Can the reasoning be trusted by a medical learner or clinician?	

Abbreviation: LLM: Large language model.

QUEST: Five principles and corresponding dimensions for the human evaluation of LLMs in healthcare

(i) Principle: Quality of information

- Accuracy: Correctness of the response provided by the LLM. The response should be factually correct, precise, and free of errors.

Evaluation strategies:

1. Comparison with gold standards provided by human evaluators using metrics such as accuracy, F1-score, specificity, sensitivity, etc.
2. Likert scale.

- Relevance: Alignment of the response with the user's query. The response should address the query directly without including unnecessary or unrelated information.

Evaluation strategy: Likert scale.

- Currency: Timeliness of the response. The response should reflect the most current knowledge available, especially for rapidly evolving topics.

Evaluation strategy: Binary categories (e.g., presence or absence of up-to-date content).

- Comprehensiveness: Completeness of the response. The response should cover all critical aspects of the query, offering a thorough overview or detailed insights where appropriate.

Evaluation strategy: Likert scale.

- Consistency: Stability and uniformity of responses across similar queries. The LLM should maintain consistent quality and accuracy.

Evaluation strategies:

1. Comparison across different prompts (e.g., same input reworded or placed in different sections).
2. Comparison over time (e.g., same input assessed at different time points).

- Agreement: Coherence of the response with established facts and theories. The response should not contradict itself or known scientific knowledge.

- Usefulness: Practical value of the response. The response should be actionable and applicable to the user's context or problem.

Evaluation strategies:

1. Application-specific/specialty-specific tools (e.g., Patient Education Materials Assessment Tool [PEMAT-P]).
2. Likert scale.

Associated dimensions: Usefulness, Helpfulness, Applicability, Feasibility, Tangibility, Actionability.

(ii) Principle: Understanding and reasoning

- Understanding: Ability of the LLM to correctly interpret the user's query, capturing meaning, context, and nuances.

Evaluation strategy: Likert scale.

- Reasoning: The LLM's ability to apply logical processes to generate its response.

Evaluation strategy: Binary categories (e.g., presence or absence of logical errors).

(iii) Principle: Expression style and persona

- **Clarity:** The response should be clear, concise, and easy to comprehend.
Evaluation strategy: Likert scale.
Associated dimensions: Clarity, conciseness, understanding, readability, comprehensibility, fluency.
- **Empathy:** The response should reflect emotional awareness and simulate a considerate and understanding tone, especially in sensitive contexts.
Evaluation strategy: Likert scale.
Associated dimensions: Empathy, human care, bedside manner, emotional tone.

(iv) Principle: Safety and harm

- **Bias:** Presence of systematic prejudices (e.g., racial, gender).
Evaluation strategies:
 1. Likert scale.
 2. Categories (presence or absence).
Dimensions: Bias, objectivity.
- **Harm:** Potential of the response to cause negative outcomes, such as misinformation, stereotypes, or adverse effects on users.
Evaluation strategies:
 1. Likert scale.
 2. Categories (presence or absence).
Dimensions: Safety, harmfulness, misleading content, likelihood of harm, severity of harm.

(v) Principle: Self-awareness

- **Self-awareness:** While LLMs are not self-aware, this refers to the model's recognition of its processing patterns and limitations.
Evaluation strategy: Likert scale.
Dimension: Recognition of limits.
- **Fabrication, falsification, or plagiarism:**
 - *Fabrication:* Made-up information or non-existent facts.
 - *Falsification:* Distorted information (e.g., changing or omitting details).
 - *Plagiarism:* Copying without appropriate credit.*Evaluation strategies:* Categories (presence/absence), Likert scale.
Dimensions: Hallucination, confabulation.

(vi) Principle: Trust and confidence

- **Trust:** Confidence in the LLM to provide accurate, fair, and safe responses, along with transparency about its limitations.

Evaluation strategy: Likert scale.

Dimensions: Similarity to expert response, assurance, reliability.

- **Satisfaction:** Degree to which the response meets or exceeds user expectations in terms of quality, relevance, and interaction experience.

Evaluation strategy: Likert scale.

Dimension: Satisfaction.

Likert: 0 (very poor) to 4 (excellent) for each domain

Total QUEST score: Out of 20

Outputs:

- Confusion
- Matrix
- Accuracy
- Table
- Qualitative
- Errors

LLMs included:

Perplexity AI

(Sonar)ChatGPT-4o

Open Evidence

Section C: Outputs for each large language model

Please note that the OpenEvidence outputs sometimes contained additional references but are not included in their output but that these references are not directly included for the purposes of inclusion in this supplementary section.

- (i) Epidermolysis bullosa (blistering disorders)

Perplexity AI (Sonar) output:

Top 3 most likely diagnoses and brief reasoning

Given the clinical vignette of a term newborn with rapid-onset, extensive skin denudation, blistering, erosions, skin fragility, periorificial and mucosal involvement, nail dystrophy, no family history of bullous disease, normal blood counts, and subepidermal clefting on biopsy, the following differential diagnoses are most likely:

1. Junctional epidermolysis bullosa, generalized severe (previously called Herlitz type)

- Description: A rare inherited form of epidermolysis bullosa (EB) presents in the neonatal period with widespread, life-threatening blistering and erosions, mucosal involvement, and significant nail dystrophy.
- Reasoning: The clinical picture—severe, generalized skin loss after minor trauma, involvement of mucous membranes, and absence of family history—fits this diagnosis. The finding of subepidermal clefting (on the dermal side of the basement membrane) is typical of EB, and mucosal involvement is common in the severe forms.
- Limitation: This form is typically characterized by mutations in laminin-332 (*LAMA3*, *LAMB3*, or *LAMC2*), not *COL7A1*, as in the vignette. However, the clinical features are otherwise highly suggestive.

2. Dystrophic epidermolysis bullosa, recessive dystrophic type

- Description: This is a rare, inherited blistering disorder resulting from mutations in the *COL7A1* gene, which encodes type VII collagen, a key structural component at the dermal–epidermal junction.
- Reasoning: The presentation—generalized blistering, erosions, skin fragility, oral/mucosal involvement, nail dystrophy, and confirmed *COL7A1* gene mutation—is highly specific for recessive dystrophic epidermolysis bullosa (RDEB), especially the severe, generalized subtype. This is one of the most severe forms of EB, often presenting with wounds at birth or soon after.
- Confirmation: The vignette specifically mentions a *COL7A1* mutation, which is diagnostic of RDEB.

3. Epidermolysis bullosa simplex, generalized (Köbner type)

- Description: This is a milder form of EB, caused by mutations in keratin genes (*KRT5*, *KRT14*), leading to intraepidermal blistering.
- Reasoning: The clinical features—primarily severe blistering and erosions, mucosal involvement—are less typical, as epidermolysis bullosa simplex (EBS) usually causes less severe disease and less mucocutaneous involvement. However, generalized severe forms can sometimes mimic junctional epidermolysis bullosa (JEB) or dystrophic epidermolysis bullosa (DEB).
- Limitation: This is less likely given the mucosal involvement, nail dystrophy, and confirmed *COL7A1* mutation. The histologic finding of subepidermal (not intraepidermal) clefting also favors RDEB over EBS.

Final diagnosis: RDEB

ChatGPT-4o output:

1. Dystrophic epidermolysis bullosa – *Most likely*

- Reasoning:
 - Onset at birth with blistering and erosions after minimal trauma
 - Involvement of mucus membranes, periorificial areas, and nail dystrophy
 - Subepidermal clefting on biopsy
 - Genetic confirmation: *COL7A1* mutation, which encodes type VII collagen anchoring fibrils—diagnostic for DEB
-

2. Junctional epidermolysis bullosa

- Reasoning:
 - Also presents at birth with fragile skin and mucosal involvement
 - Often includes perioral and nail **involvement**
 - Caused by mutations in *LAMC2*, *LAMA3*, or *LAMB3*, affecting the lamina lucida (not *COL7A1*)
 - Less likely because biopsy would show clefting within the lamina lucida, not subepidermal, and no *COL7A1* mutation
-

3. Epidermolysis bullosa simplex

- Reasoning:
 - Presents with blistering often triggered by trauma
 - Milder phenotype, usually sparing mucous membranes and nails
 - Histology shows intraepidermal cleavage
 - Genetic mutations typically in *KRT5* or *KRT14*
 - Less likely due to deeper blister plane (subepidermal) and severe presentation

Final diagnosis: DEB

OpenEvidence output:

Most likely diagnoses:

1. Dystrophic epidermolysis bullosa : This is the most likely diagnosis given the neonatal onset of extensive skin fragility, blistering, erosions with minimal trauma, mucosal involvement, nail dystrophy, and confirmation of a *COL7A1* mutation. DEB is characterized by subepidermal blistering, often with periorificial and mucosal involvement, and can present with severe, generalized disease at birth. The clinical and genetic findings are classic for RDEB¹.

2. Junctional epidermolysis bullosa : JEB also presents in the neonatal period with generalized blistering, mucosal involvement, and nail changes. However, JEB is caused by mutations in genes encoding components of the basement membrane zone other than *COL7A1*, such as *LAMA3*, *LAMB3*, or *LAMC2*. The presence of a *COL7A1* mutation makes JEB less likely, but the clinical overlap warrants consideration².

3. Epidermolysis bullosa simplex: EBS can present with neonatal blistering, but typically the cleavage is intraepidermal, and mucosal involvement is less prominent. EBS is usually milder, and nail dystrophy is less common. Genetic testing would reveal mutations in *KRT5* or *KRT14*, not *COL7A1*³.

Most important not-to-miss diagnoses:

1. Neonatal herpes simplex virus infection: Presents with vesiculobullous lesions and mucosal involvement but usually accompanied by systemic symptoms (e.g., fever, lethargy, seizures). Diagnosis is excluded by negative herpes simplex virus polymerase chain reaction/culture and absence of systemic illness⁴.

2. Staphylococcal scalded skin syndrome: Presents with widespread superficial blistering and denudation, but typically lacks mucosal involvement and is not associated with a genetic mutation. Staphylococcal scalded skin syndrome is confirmed by clinical features, culture of *Staphylococcus aureus* from a distant site, and response to antibiotics⁵.

Key additional history and follow-up tests:

- Detailed family history for consanguinity or milder forms of EB.
- Direct immunofluorescence mapping and electron microscopy of skin biopsy to confirm the level of cleavage.
- Comprehensive genetic testing for other EB subtypes if clinical suspicion persists despite

COL7A1 mutation.

- Ongoing monitoring for secondary infection, nutritional status, and extracutaneous complications.

Final diagnosis: DEB

(ii) Bloom syndrome (photosensitive or pigmentary)

Perplexity AI (Sonar) output:

Top 3 most likely diagnoses and brief reasoning

Given the clinical vignette—a 3-year-old Ashkenazi Jewish boy with poor growth, recurrent infections, a distinctive facies, sun-sensitive telangiectatic rash, *café au lait* spots, and a confirmed pathogenic mutation in the *BLM* gene—the following are the most likely diagnoses:

1. Bloom syndrome (Bloom–Torre–Machacek syndrome)

Reasoning: The presence of severe growth deficiency (despite a normal appetite), recurrent respiratory infections with mild immunodeficiency, a long, narrow face with prominent nose and ears, a high-pitched voice, and a sun-sensitive facial butterfly rash (telangiectatic erythema) are classic features of Bloom syndrome. Multiple *café au lait* spots and poikiloderma (hypo- and hyperpigmented areas) are also frequently seen. The family history of Ashkenazi Jewish ancestry and history of leukemia strongly support this diagnosis, as Bloom syndrome is highly prevalent in this population and carries a marked risk for early-onset cancers. Genetic testing confirming a pathogenic *BLM* mutation is diagnostic.

Confirmation: The clinical features and positive genetic test make this the definitive diagnosis.

2. Ataxia telangiectasia

Reasoning: Recurrent sinopulmonary infections (otitis media, pneumonia), mild immunodeficiency (low immunoglobulins), *café au lait* spots, and telangiectasias are also seen in ataxia telangiectasia. However, classic ataxia (poor coordination, typically apparent by age 2–5 years) and cerebellar atrophy would be expected to evolve over time, and there is no evidence of neurological involvement in the vignette. The absence of prominent neurologic findings and the presence of the *BLM* mutation make Bloom syndrome much more likely.

Distinguishing features: Ataxia telangiectasia is caused by *ATM* gene mutations, not *BLM*, and presents with progressive cerebellar ataxia, which is not described here.

3. Neurofibromatosis type 1

Reasoning: *Café au lait* spots and growth delay are common in neurofibromatosis type 1 (NF1), and Ashkenazi Jewish ancestry is a demographic overlap. However, the characteristic facial rash (butterfly telangiectatic erythema), severe growth failure, recurrent infections, and immunodeficiency are not typical of NF1. No neurofibromas, axillary freckling, or Lisch

nodules are mentioned. The absence of a family history of NF1 and the presence of the *BLM* gene mutation strongly argue against this diagnosis.

Distinguishing features: The clinical picture is atypical for NF1, and the genetic result is inconsistent.

Final diagnosis: Bloom syndrome (Bloom–Torre–Machacek syndrome)

ChatGPT-4o output:

1. Bloom syndrome (congenital telangiectatic erythema) – *Most likely*

- Reasoning:
 - Classic features:
 - Short stature, failure to thrive
 - Sun-sensitive facial telangiectatic rash (butterfly distribution)
 - High-pitched voice, long narrow face, prominent ears/nose
 - *Café au lait* macules, hypo/hyperpigmented spots
 - Recurrent infections (due to immunodeficiency)
 - Genetics: Autosomal recessive, *BLM* gene mutation (helicase defect leading to genomic instability)
 - Family history of leukemia fits with increased cancer risk
 - Higher prevalence in Ashkenazi Jews
-

2. Xeroderma pigmentosum

- Reasoning:
 - Photosensitive rash, especially on sun-exposed areas
 - May have *café au lait* spots, neurodegeneration, and increased cancer risk

- However, typically normal growth and no immunodeficiency
 - No characteristic facial features or high-pitched voice
 - *BLM* mutation not involved
 - Less likely
-

3. Fanconi anemia

- Reasoning:
 - May present with:
 - Short stature, *café au lait* spots
 - Hematologic abnormalities
 - Immunodeficiency and increased risk of leukemia
 - However:
 - Lacks classic photosensitive rash and facial dysmorphisms seen here
 - Most often associated with bone marrow failure, which is not described in this vignette
 - Genetic cause distinct from *BLM*
 - Still considered due to growth failure, skin findings, and family history of leukemia

Final diagnosis: Bloom syndrome (congenital telangiectatic erythema)

OpenEvidence output:

Most likely diagnoses:

1. Bloom syndrome: This is the most likely diagnosis given the combination of severe pre- and postnatal growth deficiency, characteristic facies (long, narrow face, prominent nose and ears), high-pitched voice, sun-sensitive butterfly-shaped telangiectatic rash, hypo- and hyperpigmented skin lesions, immunodeficiency with recurrent infections, and Ashkenazi Jewish ancestry. The

diagnosis is confirmed by a pathogenic mutation in the *BLM* gene, which is diagnostic for Bloom syndrome¹.

2. Ataxia telangiectasia: This disorder can present with growth failure, telangiectatic rash, immunodeficiency, and increased cancer risk. However, the absence of progressive ataxia and oculomotor apraxia, and the presence of a *BLM* mutation, make this less likely².

3. Rothmund–Thomson syndrome: This syndrome features growth retardation, poikiloderma (including telangiectasia and pigmentary changes), and increased cancer risk. However, the classic facial features, high-pitched voice, and confirmed *BLM* mutation are not typical, making this less likely than Bloom syndrome³.

Most important not-to-miss diagnoses:

1. Acute leukemia: The family history of leukemia and immunodeficiency raise concern for underlying malignancy. This should be ruled out with appropriate blood counts and, if indicated, bone marrow evaluation, as recommended by the American Society of Clinical Oncology and the College of American Pathologists⁴.

2. Severe combined immunodeficiency: The recurrent infections and low immunoglobulin levels warrant evaluation for severe combined immunodeficiency, but the presence of a syndromic diagnosis (Bloom syndrome) and the absence of profound T-cell lymphopenia make severe combined immunodeficiency less likely⁵.

Key additional history and follow-up tests:

- Detailed neurologic examination to assess for ataxia or oculomotor apraxia.
- Serial complete blood counts and immunoglobulin quantification to monitor for cytopenias or evolving malignancy.
- Dermatologic evaluation to document the extent and evolution of pigmentary changes and telangiectasia.
- Genetic counseling for family planning and cancer surveillance.

Final diagnosis: Bloom syndrome

(iii) Xeroderma pigmentosum (photosensitive or pigmentary)

PerplexityAI output:

Top 3 Most Likely Diagnoses and Brief Reasoning

Based on the clinical vignette—a 4-year-old girl with persistent freckling and hyperpigmentation, severe sunburn reactions from minimal exposure starting in infancy, numerous lentiginos, telangiectasias, poikiloderma (hypo- and hyperpigmented patches), atrophic skin changes, early

actinic keratoses, ocular findings (photophobia, conjunctivitis, corneal haze), lack of neurologic deficits, consanguinity, similarly affected sibling, biopsy-confirmed early squamous cell carcinoma, and a confirmed pathogenic *XPC* gene mutation—the following are the most likely diagnoses:

1. Xeroderma pigmentosum, complementation group C

Reasoning: The classic triad of extreme photosensitivity, early-onset lentigines/freckling, and high risk of UV-induced skin cancer is pathognomonic for xeroderma pigmentosum (XP). The *XPC* gene mutation is diagnostic for xeroderma pigmentosum, complementation group C (XP-C). Clinical features—lentigines, poikiloderma, telangiectasias, skin atrophy, actinic keratoses, photophobia, conjunctivitis, corneal haze, and early squamous cell carcinoma—are all hallmarks of XP. The lack of neurologic deficits is typical for XP-C, as neurologic involvement is more common in other XP subtypes. Consanguinity and affected sibling support an autosomal recessive pattern, consistent with XP.

Confirmation: The genetic testing confirming an *XPC* mutation is definitive.

2. Rothmund–Thomson syndrome

Reasoning: Rothmund–Thomson syndrome (RTS) shares some features with XP, including poikiloderma, photosensitivity, and increased skin cancer risk, but lentigines and early-onset skin cancers (especially squamous cell carcinoma in childhood) are much more characteristic of XP. Ocular abnormalities in RTS are rare and less severe than in XP. Genetic testing for *XPC* rules out RTS in this case.

Distinguishing features: The *XPC* mutation and early skin cancer are not features of RTS; RTS is caused by mutations in the *RECQL4* gene.

3. Cockayne syndrome

Reasoning: Cockayne syndrome (CS) also features photosensitivity, skin atrophy, and ocular abnormalities (including corneal opacities), but severe growth failure, neurological degeneration, and lack of early skin cancers are more typical of CS, none of which are described here. The absence of neurologic deficits and presence of early squamous cell carcinoma strongly favor XP over CS.

Distinguishing features: CS typically presents with progressive neurologic impairment and growth failure, neither of which are described in this vignette. Genetic confirmation of *XPC* mutation further excludes CS.

ChatGPT-4o output:

1. Xeroderma pigmentosum – Most likely

Reasoning:

- Severe sun sensitivity from infancy (burning after minimal exposure)
- Freckling, lentigines, telangiectasias, and mottled pigmentation in sun-exposed areas
- Early onset of actinic keratoses and squamous cell carcinoma
- Ocular findings (photophobia, conjunctivitis, corneal haze)
- Consanguinity and affected sibling suggest autosomal recessive inheritance

XPC mutation confirms a defect in nucleotide excision repair, diagnostic of XP

2. Cockayne syndrome

Reasoning:

- Also a nucleotide excision repair disorder with photosensitivity
 - However, typically presents with growth failure, neurodevelopmental regression, sensorineural hearing loss
 - No skin cancer, which is a key difference
 - *XPC* is not the gene typically involved (*CSA/ERCC8* or *CSB/ERCC6* are)
 - Less likely due to lack of neurologic findings and presence of malignancy
-

3. Bloom syndrome

Reasoning:

- Features include photosensitive rash, CALMs, short stature, immunodeficiency, and early malignancies

Most common mutation: *BLM* gene

- While early skin cancer and sun sensitivity are seen, freckling pattern, ocular findings, and confirmed *XPC* mutation are not consistent

- No mention of growth delay, facial features, or immunodeficiency

Less likely than XP

Final diagnosis: XP

OpenEvidence output:

Most likely diagnoses:

Xeroderma pigmentosum – The clinical picture of severe photosensitivity from infancy, freckling, lentiginosities, hypo- and hyperpigmentation, telangiectasias, actinic keratoses, early-onset squamous cell carcinoma, ocular involvement, consanguinity, and a pathogenic *XPC* mutation is diagnostic for XP. XP is characterized by extreme UV sensitivity, early pigmentary changes, and a dramatically increased risk of skin cancers in sun-exposed areas, with onset of malignancy often in early childhood¹.

1. Rothmund–Thomson syndrome – This disorder can present with early-onset poikiloderma (reticulated pigmentation, telangiectasias, atrophy), photosensitivity, and increased risk of skin malignancy. However, the absence of *RECQL4* mutation, the presence of classic XP features (severe sunburns, early skin cancer, *XPC* mutation), and lack of skeletal or hair abnormalities make this less likely².
2. Bloom syndrome – Bloom syndrome features sun-sensitive telangiectatic rash, pigmentary changes, and cancer predisposition, but is typically associated with marked growth failure and characteristic facies, which are not described here. The genetic finding of *XPC* mutation and the clinical phenotype are more consistent with XP³.

Most important not-to-miss diagnoses:

1. Cutaneous squamous cell carcinoma – Already confirmed by biopsy; ongoing surveillance for additional skin cancers is essential, as the risk is extremely high in XP^{1,4}.
2. Malignant melanoma – XP patients are at markedly increased risk for melanoma, which may present atypically in children. Vigilant dermatologic monitoring and prompt biopsy of suspicious lesions are required^{1,5}.

Key additional history and follow-up tests:

- Detailed family history for other affected relatives and cancer types.
- Full skin and ophthalmologic examinations to assess for additional malignancies and ocular complications.
- Regular dermatologic surveillance and prompt biopsy of new or changing lesions.
- Genetic counseling for family planning and risk assessment

(iv) Harlequin ichthyosis (ichthyoses and keratinization)

PerplexityAI output:

Here are the three most likely diagnoses, with reasoning:

1. Harlequin ichthyosis (congenital ichthyosis, Harlequin type)

Reasoning: The hallmark features—thick, armor-like plates covering the skin, deep fissures, severe facial dysmorphism (ectropion, eclabium, flattened nose, malformed ears), respiratory distress, and feeding difficulties—are classic for Harlequin ichthyosis (HI), the most severe form of autosomal recessive ichthyosis. HI is almost exclusively caused by homozygous or compound heterozygous loss-of-function mutations in the *ABCA12* gene, which are confirmed in this case. Infants are at high risk for dehydration due to massive transepidermal water loss, respiratory complications from restrictive skin, and failure to thrive—all present here.

Confirmation: The genetic result and clinical appearance at birth are diagnostic. Improved neonatal care and systemic retinoids have increased survival, though the condition is lifelong and associated with persistent skin and limb issues.

2. Lamellar ichthyosis

Reasoning: Both HI and lamellar ichthyosis (LI) are subtypes of autosomal recessive congenital ichthyosis (ARCI) and are both caused by *ABCA12* mutations. LI typically presents with less severe generalized thick hyperkeratosis and peeling, without the deep fissures, severe ectropion, eclabium, and hand/foot contractures characteristic of HI. Because *ABCA12* mutations can cause a spectrum from mild LI to severe HI, depending on the specific mutation. The clinical picture here is much more characteristic of HI, but LI is in the differential due to the same genetic cause.

Distinguishing features: The severity of skin disease and characteristic facial/limb abnormalities distinguish HI from LI in this case.

3. Congenital ichthyosiform erythroderma

Reasoning: Congenital ichthyosiform erythroderma (CIE), another subtype of ARCI, classically presents with generalized erythema and fine white scales. However, severe CIE caused by *ABCA12* mutations may have more pronounced scaling and skin barrier dysfunction, though not the plate-like armor or profound dysmorphic features of HI. CIE is included here because genetic testing confirmed *ABCA12* mutations and the ARCI spectrum includes HI, LI, and CIE, but the clinical presentation is overwhelmingly severe and specific for HI.

ChatGPT-4o output:

1. Harlequin ichthyosis – Most likely

Reasoning:

- Classic neonatal presentation: thick, yellow, plate-like scales with deep fissures
 - Ectropion, eclabium, flattened nose, hypoplastic digits, and absent eyebrows/lashes
 - Restricted movement due to tight skin, respiratory distress, and feeding difficulties
 - Electrolyte imbalances, high infection risk, and NICU support are common
 - Genetic confirmation: *ABCA12* mutation, which disrupts lipid transport in the epidermis and is pathognomonic for HI
 - Survival with early systemic retinoids and supportive care
-

2. Lamellar ichthyosis

Reasoning:

- Presents at birth with collodion membrane, later evolving into large brown scales and generalized ichthyosis
- May develop ectropion, but typically lacks the severe facial deformities, digit fusion, and life-threatening complications of HI
- Often caused by *TGMI* or other gene mutations, not *ABCA12*

Less likely due to the severity and specific genetic findings

3. Congenital ichthyosiform erythroderma

Reasoning:

- Also presents neonatally with erythema and fine white scaling, sometimes as a collodion baby
- Less commonly associated with severe ectropion/eclabium, digit abnormalities, or life-threatening complications
- Usually less severe than HI
- Genetic causes distinct from *ABCA12*

OpenEvidence output:

Most likely diagnoses:

1. Harlequin ichthyosis – This is the most likely diagnosis given the presence at birth of thick, plate-like yellow hyperkeratotic scales with deep fissures, severe ectropion, eclabium, malformed ears, flattened nose, fused hypoplastic digits, and absent eyebrows/eyelashes. The diagnosis is confirmed by pathogenic mutations in the *ABCA12* gene. The clinical course, including respiratory distress, feeding difficulties, electrolyte imbalances, and the need for intensive supportive care, is classic for this severe ARCI phenotype¹⁻².
2. Lamellar ichthyosis – This ARCI can present with large, plate-like scales and ectropion, but typically infants are born encased in a collodion membrane that later desquamates, and the scales are less thick and fissured than in HI. Eclabium and digital hypoplasia are less severe, and *ABCA12* mutations are not characteristic².
3. Congenital ichthyosiform erythroderma (nonbullous ARCI) – This disorder may present with a collodion membrane and generalized erythroderma with fine scaling, sometimes with ectropion and eclabium, but the scales are finer and less plate-like, and severe digital hypoplasia is not typical. *ABCA12* mutations are not a primary cause²⁻³.

Most important not-to-miss diagnoses:

1. Staphylococcal scalded skin syndrome – Presents with widespread erythema and superficial desquamation, but not with thick, plate-like scales, severe ectropion/eclabium, or congenital malformations. Diagnosis is excluded by the absence of acute infectious prodrome and the presence of congenital findings and *ABCA12* mutation⁴.
2. Epidermolysis bullosa – Presents with skin fragility and blistering, not with hyperkeratotic plates, and lacks the characteristic facial and limb malformations seen in HI⁵.

Key additional history and follow-up tests:

- Serial skin and systemic infection surveillance.
- Ophthalmologic and otolaryngologic evaluation for complications of ectropion and ear malformations.
- Ongoing genetic counseling and family support.
- Monitoring for complications of systemic retinoid therapy and nutritional status¹⁻².

(v) Hypohidrotic ectodermal dysplasia (hair/nail/ectodermal)

PerplexityAI output:

Top 3 most likely diagnoses

Based on the clinical vignette—a 2-year-old boy with sparse hair, absent/malformed teeth, dental delay, dry and thin skin, prominent lips, frontal bossing, severely reduced/absent sweating

(confirmed by starch iodine test), recurrent febrile episodes during hot weather, positive family history in maternal males (suggesting X-linked inheritance), and *EDA* gene mutation—the three most likely diagnoses are:

1. X-linked hypohidrotic ectodermal dysplasia

Reasoning:

This is the definitive diagnosis. The triad of hypotrichosis (sparse, fine scalp hair), hypodontia (absent, conical, or small teeth), and hypohidrosis (absent or severely reduced sweating) is diagnostic for this phenotype. The vignette describes all three cardinal features and classic facial findings (frontal bossing, prominent lips, dry skin). The X-linked inheritance pattern and confirmed *EDA* mutation further confirm X-linked hypohidrotic ectodermal dysplasia (XLHED). Recurrent fevers are due to inability to sweat (heat intolerance), while dental anomalies and characteristic facial appearance are hallmarks of the syndrome. The presence of carrier females in the family is typical for X-linked disease.

Management focuses on avoiding overheating, dental care, and genetic counseling.

2. Autosomal recessive or autosomal dominant hypohidrotic ectodermal dysplasia

Reasoning:

These syndromes present with the same triad of symptoms—sparse hair, missing/malformed teeth, and reduced sweating—and are also caused by defects in the ectodysplasin signaling pathway, but through mutations in other genes (e.g., *EDAR*, *EDARADD*). However, family history is key: autosomal forms show affection of both sexes and affected parents or siblings, unlike the X-linked pattern here. While both XLHED and autosomal HED are phenotypically similar, the X-linked inheritance and *EDA* mutation in this case make XLHED much more likely.

3. Anhidrotic ectodermal dysplasia with immune deficiency

Reasoning:

Anhidrotic ectodermal dysplasia with immune deficiency (EDA-ID) is a rare variant associated with immunodeficiency in addition to the classic ectodermal dysplasia triad. The immunodeficiency often manifests as recurrent bacterial, viral, or fungal infections, which are not described in this vignette. The clinical presentation in this case is classic for isolated ectodermal dysplasia (sparse hair, dental anomalies, hypohidrosis, no immunodeficiency), and the *EDA* mutation is common in XLHED but not in EDA-ID, which is typically caused by hypomorphic mutations in the *IKBKKG* (*NEMO*) gene. Thus, EDA-ID is much less likely but remains on the differential if the patient later develops recurrent infections or laboratory evidence of immunodeficiency.

ChatGPT-4o Output:

1. Hypohidrotic ectodermal dysplasia – *Most likely*

- Reasoning:
 - Classic triad:
 - Hypohidrosis/anhidrosis → heat intolerance, febrile crises
 - Hypotrichosis (sparse, fine scalp hair)
 - Hypodontia (absent or conically shaped teeth with delayed eruption)
 - Distinctive facial features: Frontal bossing, prominent lips
 - Dry, thin skin common in ectodermal dysplasias
 - X-linked inheritance pattern (maternal male relative affected)
 - Confirmed *EDA* gene mutation (encodes ectodysplasin A, key in ectodermal development)
-

2. Incontinentia pigmenti

- Reasoning:
 - Also affects ectodermal structures (teeth, skin, hair), but:
 - almost exclusively affects females (X-linked dominant, lethal in males)
 - skin findings progress through stages: blistering, wart-like rash, hyperpigmentation, then hypopigmentation
 - *EDA* mutation not involved
 - Unlikely in a living male patient without characteristic rash stages
-

3. Clouston syndrome (hidrotic ectodermal dysplasia)

- Reasoning:

- Involves nail dystrophy, alopecia, and palmoplantar keratoderma
- Normal sweating (unlike hypohidrotic ectodermal dysplasia [HED]), so no heat intolerance or febrile episodes
- **GJB6 mutation** (not *EDA*)
- Less likely due to preserved sweat glands and absence of heat-related symptoms

OpenEvidence output:

Most likely diagnoses:

1. X-linked hypohidrotic ectodermal dysplasia – This is the most likely diagnosis, given the classic triad of hypohidrosis (absent sweating), hypotrichosis (sparse hair), and hypodontia (absent or conical teeth), along with characteristic facial features (frontal bossing, prominent lips), dry thin skin, and a family history consistent with X-linked inheritance. The diagnosis is confirmed by a pathogenic mutation in the *EDA* gene. The GeneReviews guideline from the University of Washington highlights these cardinal features and the typical presentation in affected males¹.
2. Autosomal recessive or dominant hypohidrotic ectodermal dysplasia (*EDAR* or *EDARADD* mutations) – These forms are clinically indistinguishable from the X-linked type except for the inheritance pattern. They should be considered if genetic testing for *EDA* is negative or if there is no clear X-linked inheritance, but in this case, the *EDA* mutation and family history make them less likely¹.
3. Ectrodactyly-ectodermal dysplasia-clefting syndrome – This syndrome can present with ectodermal dysplasia features (hair, teeth, skin abnormalities), but typically also includes limb malformations (ectrodactyly) and orofacial clefting, which are not described here. Hypohidrosis is not a predominant feature, making this diagnosis less likely in this clinical context².

Most important not-to-miss diagnoses:

Congenital insensitivity to pain with anhidrosis (CIPA, also called hereditary sensory and autonomic neuropathy type IV) –CIPA presents with anhidrosis and recurrent fevers, but is distinguished by profound insensitivity to pain, self-mutilation, and often intellectual disability, none of which are described here. The presence of normal pain sensation and the *EDA* mutation make CIPA unlikely³.

1. Incontinentia pigmenti – This X-linked disorder can present with dental and hair abnormalities, but is almost exclusively seen in females and is characterized by a distinctive, evolving skin rash, which is not present in this case⁴.

Key additional history and follow-up tests:

- Detailed assessment for subtle limb anomalies or clefting to rule out ectrodactyly-ectodermal dysplasia-clefting syndrome.
- Evaluation of pain sensation and neurologic function to exclude CIPA.
- Ongoing dental, dermatologic, and genetic counseling follow-up for management and family planning.

(vi) Clouston syndrome

PerplexityAI Output:

Based on the clinical vignette—brittle, dystrophic, ridged, thickened, and split fingernails and toenails; sparse, slow-growing, easily broken scalp hair with progressive alopecia; pronounced hyperkeratosis of palms and soles; hyperpigmentation over joints; normal teeth and sweating; autosomal dominant family history; and a pathogenic *GJB6* gene variant—the top three most likely diagnoses are:

1. Clouston syndrome (hidrotic ectodermal dysplasia)

Rationale: Clouston syndrome (hidrotic ectodermal dysplasia) is an autosomal dominant disorder caused by mutations in the *GJB6* gene, encoding connexin 30. The classic triad includes nail dystrophy (brittle, thickened, ridged, and split nails), alopecia (sparse, slow-growing, easily broken hair that may progress to patches of baldness), and palmoplantar hyperkeratosis (thickened skin on palms and soles). Teeth and sweating are typically normal, distinguishing it from anhidrotic ectodermal dysplasia/HED. Hyperpigmentation over joints may also occur, as in this case. The autosomal dominant inheritance and confirmatory *GJB6* mutation strongly support this diagnosis.

Other features: Patients may develop knuckle pads and, in some cases, sensorineural hearing loss, but these are not universal and were not described in this vignette. The focus on cutaneous, hair, and nail findings with normal dentition and sweating, and the *GJB6* mutation, make Clouston syndrome the leading diagnosis.

2. Pachyonychia congenita

Rationale: Pachyonychia congenita (PC) is an autosomal dominant disorder manifesting with severe nail dystrophy (thickened, discolored, overcurved nails) and painful palmoplantar keratoderma, often with hyperkeratosis and fissuring. While PC primarily involves keratins (*KRT6A*, *KRT6B*, *KRT16*, or *KRT17*), the clinical overlap with Clouston syndrome—brittle, dystrophic nails and palmoplantar hyperkeratosis—makes it a reasonable differential. However, PC often causes more severe pain, blistering, and oral lesions, which are not described here.

The absence of oral involvement or severe blistering, the autosomal dominant inheritance, and the specific *GJB6* mutation, make PC less likely than Clouston syndrome but still a key differential.

3. Other hereditary palmoplantar keratodermas

Rationale: Hereditary palmoplantar keratodermas (PPKs) are a heterogeneous group of disorders characterized by thickening of the palms and soles. Some types (e.g., diffuse nonepidermolytic PPK) can present with nail dystrophy and hyperkeratosis, but alopecia and the specific nail changes described are less common. Generalized severe alopecia and the nail phenotype in this case are not typical of most isolated PPKs, making this a less likely primary diagnosis but still a consideration when evaluating a child with hyperkeratosis and nail abnormalities. The presence of a *GJB6* mutation and autosomal dominant inheritance, combined with the full clinical picture, strongly favor Clouston syndrome over other PPKs.

ChatGPT-4o output:

1. Clouston syndrome (hidrotic ectodermal dysplasia 2) – *Most likely*

Reasoning:

- Key triad:
 - Nail dystrophy (thickened, brittle, ridged nails)
 - Progressive alopecia (sparse, fragile hair from infancy)
 - Palmoplantar keratoderma
- Normal teeth and sweating — helps distinguish from HED
- Autosomal dominant inheritance, consistent with affected mother
- *GJB6* mutation (connexin 30 gene) confirms diagnosis

2. Pachyonychia congenita

Reasoning:

- Features include:
 - Nail dystrophy, palmoplantar keratoderma, oral leukokeratosis, and sometimes follicular hyperkeratosis
- Hair may be sparse, but not as severe or early-onset as in Clouston syndrome
- Mutation in *KRT6A/KRT16*, not *GJB6*

Less likely due to absence of oral leukokeratosis and different genetic cause

3. Hypohidrotic ectodermal dysplasia

Reasoning:

- Can involve nail and hair abnormalities. However, typically presents with hypodontia, hypohidrosis, heat intolerance, frontal bossing, conical teeth
- None of these are present; normal dentition and sweating
- Mutation in *EDA*, not *GJB6*
- Unlikely

OpenEvidence output:

Most likely diagnoses:

1. Clouston syndrome (hidrotic ectodermal dysplasia type 2) – This is the most likely diagnosis given the triad of progressive, brittle, sparse scalp hair; dystrophic, thickened, and split nails; and pronounced palmoplantar hyperkeratosis, with normal teeth and sweating. The presence of cutaneous hyperpigmentation over the joints, autosomal dominant inheritance (affected mother), and a pathogenic variant in the *GJB6* gene are diagnostic. The GeneReviews guideline from the University of Washington confirms these features as classic for Clouston syndrome¹.

2. Pachyonychia congenita – This disorder also presents with nail dystrophy and palmoplantar keratoderma and can include hair abnormalities. However, it is most often associated with mutations in keratin genes (not *GJB6*), and oral leukokeratosis, cysts, and natal teeth are more common. The absence of these features and the presence of a *GJB6* mutation make this less likely².

3. Vohwinkel syndrome – This syndrome features palmoplantar keratoderma and nail changes but is typically associated with pseudoainhum (constricting bands leading to autoamputation) and, in the classic form, sensorineural hearing loss. The absence of hearing loss and pseudoainhum, and the presence of a *GJB6* mutation, make this less likely, but it remains in the differential³.

Most important not-to-miss diagnoses:

1. Dyskeratosis congenita – This can present with nail dystrophy, hair changes, and skin pigmentation, but is usually associated with oral leukoplakia, bone marrow failure, and telomere abnormalities. The absence of these features and the presence of a *GJB6* mutation argue against this diagnosis⁴.

2. Keratitis-ichthyosis-deafness syndrome – This presents with palmoplantar keratoderma, nail and hair changes, and hearing loss, but is associated with keratitis and ichthyosis, which are not described here. The genetic findings are also inconsistent⁵.

Key additional history and follow-up tests:

- Audiologic evaluation to rule out subtle hearing loss.
- Detailed oral and mucosal examination for leukokeratosis.
- Family genetic counseling and cascade testing.
- Ongoing dermatologic monitoring for progression of keratoderma and nail changes.

(vii) Muir–Torre syndrome

PerplexityAI output:

Here are the top three most likely diagnoses for the 52-year-old man described in the vignette, along with brief reasoning:

1. Muir–Torre syndrome

Rationale:

Muir–Torre syndrome is the most likely diagnosis in this case. It is a rare autosomal dominant condition that represents a phenotypic variant of Lynch syndrome (hereditary nonpolyposis colorectal cancer), characterized by the association of sebaceous neoplasms (adenomas, epitheliomas, carcinomas) and visceral malignancies—most commonly colorectal cancer.

In this case, the patient has multiple painless, firm, yellow sebaceous adenomas on the face and upper back; a history of colon cancer at a relatively young age (48); a family history of colorectal and endometrial cancer; and a confirmed pathogenic germline mutation in the *MSH2* gene, a major mismatch repair (MMR) gene implicated in MTS and Lynch syndrome. Loss of *MSH2* and *MSH6* expression on immunohistochemistry in the skin lesion further supports the diagnosis, as these are classic findings in MTS.

The recommendation for ongoing cancer surveillance and family genetic counseling is also consistent with standard management for MTS.

2. Lynch syndrome (hereditary nonpolyposis colorectal cancer) Rationale:

Lynch syndrome is caused by germline mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and is associated with an increased lifetime risk of colorectal, endometrial, and other cancers. The patient's *MSH2* mutation, personal and family history of cancer, and age at diagnosis of colon cancer are classic features of Lynch syndrome.

Lynch syndrome typically lacks the distinctive sebaceous neoplasms seen in MTS. However, MTS is considered a phenotypic variant of Lynch syndrome, and in patients with sebaceous tumors and internal malignancies, the distinction can be subtle. Nevertheless, the presence of sebaceous adenomas places this patient in the MTS subgroup, not the broader Lynch syndrome category.

3. Sporadic sebaceous adenoma with familial colorectal cancer

Rationale:

While much less likely given the constellation of findings, this diagnosis would consider the sebaceous adenomas and colorectal cancer as unrelated entities—without a unifying genetic cause. However, this explanation is highly improbable in this case because:

- Sebaceous adenomas are rare and are most often associated with an underlying genetic predisposition when multiple or in younger patients.
- The family history of cancer and the germline *MSH2* mutation strongly suggest a hereditary cancer syndrome.
- Loss of *MSH2/MSH6* by immunohistochemistry is highly specific for an underlying mismatch repair defect, not seen in sporadic tumors.

ChatGPT-4o output:

1. Muir–Torre syndrome – *Most likely*

- Reasoning:

- Characterized by the co-occurrence of:
 - Sebaceous neoplasms (adenomas, epitheliomas, carcinomas)
 - Internal malignancies, especially colorectal and endometrial cancer
 - MSH2/MSH6 loss on immunohistochemistry supports defective DNA mismatch repair
 - Germline *MSH2* mutation confirms Lynch syndrome spectrum, specifically Muir–Torre subtype
 - Family history of Lynch-associated cancers strengthens the diagnosis
-

2. Lynch syndrome (hereditary nonpolyposis colorectal cancer)

- Reasoning:
 - Autosomal dominant cancer predisposition due to MMR gene mutations (e.g., *MSH2*, *MLH1*, *MSH6*, *PMS2*)
 - Strong family history of colorectal and endometrial cancers
 - Patient fits Lynch criteria, but presence of sebaceous adenomas makes Muir–Torre a more specific subtype
 - Lynch syndrome is correct umbrella diagnosis, but MTS is the more precise diagnosis here
-

3. Familial adenomatous polyposis

- Reasoning:
 - Can present with colorectal cancer at a young age
 - Associated with *APC* mutations, not *MSH2/MSH6*
 - Typically includes hundreds of colonic polyps by adolescence

- No sebaceous tumors or DNA MMR defects
- Unlikely in this case due to lack of polyposis and mismatch repair findings

OpenEvidence output:

Most likely diagnoses:

Muir–Torre syndrome – This is the most likely diagnosis, given the presence of sebaceous adenomas, a personal and family history of Lynch-spectrum malignancies (colorectal and endometrial cancer), and a confirmed pathogenic germline mutation in the *MSH2* gene with loss of *MSH2/MSH6* expression on immunohistochemistry. MTS is a variant of Lynch syndrome characterized by sebaceous neoplasms and internal malignancies, most commonly colorectal and endometrial cancers, and is most frequently associated with *MSH2* mutations¹⁻³.

1. Lynch syndrome (hereditary nonpolyposis colorectal cancer) – This diagnosis is also supported by the early-onset colorectal cancer, family history of Lynch-associated cancers, and germline *MSH2* mutation. Lynch syndrome is an autosomal dominant cancer predisposition syndrome caused by mutations in DNA mismatch repair genes, most commonly *MSH2* and *MLH1*, and is associated with increased risk of colorectal, endometrial, and other cancers^{2,4}.

2. Sebaceous adenomas secondary to MMR deficiency (as a cutaneous marker of underlying cancer predisposition syndrome) – The development of sebaceous adenomas in the context of MMR gene mutations and internal malignancy is highly suggestive of an underlying hereditary syndrome, most specifically MTS, but this finding itself is a key diagnostic clue^{1,3,5}.

Most important not-to-miss diagnoses:

1. Sebaceous carcinoma – This aggressive cutaneous malignancy can occur in MTS and should be ruled out by histopathology, as it requires different management and has metastatic potential.[1][5]
2. Metachronous or synchronous Lynch-spectrum malignancies – Ongoing surveillance for additional colorectal, endometrial, and other Lynch-associated cancers is essential, as recommended by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors^{2,6}.

Key additional history and follow-up tests:

- Detailed family cancer history to assess for other Lynch-spectrum tumors.
- Colonoscopic and extracolonic cancer surveillance per Lynch/MTS protocols.
- Dermatologic monitoring for new or evolving sebaceous neoplasms or carcinomas.
- Genetic counseling and cascade testing for at-risk relatives, as recommended by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselor

(viii) Blue rubber bleb nevus syndrome (vascular and tumor)

PerplexityAI output:

Here are the top three most likely diagnoses for the 10-year-old boy described in your vignette, along with brief reasoning for each:

1. Blue rubber bleb nevus syndrome

Rationale

Blue rubber bleb nevus syndrome is a rare congenital disorder characterized by multiple compressible, blue-purple, soft, rubbery vascular nodules (venous malformations) on the skin and mucus membranes, especially involving the GI tract. Lesions are present from early childhood and often increase in number and size over time. Chronic GI bleeding from these lesions commonly leads to severe iron deficiency anemia (manifesting as fatigue, pallor, and melena), often requiring iron supplementation and even transfusion. Endoscopy typically reveals similar bluish vascular lesions throughout the GI tract, some with evidence of recent bleeding. No family history of vascular malformations is typical, as the condition is usually sporadic. Liver, brain, and kidney involvement is rare or absent in classic cases, as supported by the imaging findings in the vignette. Treatment involves addressing anemia, endoscopic sclerosis for symptomatic GI lesions, and ongoing surveillance for complications.

This clinical picture—childhood-onset, multifocal, compressible, blue-purple skin and GI vascular nodules, chronic bleeding, and marked anemia, with no family history of similar lesions—is classic for BRBNS.

2. Multifocal venous malformations (without syndromic features)

Rationale

Multifocal venous malformations can present with multiple soft, compressible blue-purple nodules on the skin and sometimes in internal organs. Occasionally, they involve the GI tract, leading to recurrent bleeding and anemia. Most are sporadic and not hereditary. The main difference from BRBNS is that classic small intestinal and colonic involvement is less common in isolated venous malformations, and lesions are less often described as “blue rubber blebs.” However, the clinical overlap is significant, especially with multiple lesions, chronic GI bleeding, iron deficiency anemia, and lack of family history.

Although BRBNS is the most likely diagnosis in this case—given the classic description—multifocal venous malformations remain an important alternative consideration when classic GI “blue rubber blebs” are not visualized or when extra features (e.g., limb asymmetry, overgrowth) are absent.

3. Gastrointestinal hemangioma or other vascular anomalies

Rationale

Gastrointestinal hemangiomas and other vascular anomalies (e.g., capillary malformations, mixed vascular malformations) can occasionally present with chronic GI bleeding and iron deficiency anemia in children. They may involve the skin but are less likely to present with multiple,

compressible, blue-purple skin blebs and widespread GI involvement, as seen in BRBNS. Hemangiomas are more common as solitary lesions and rarely produce the distinct clinical triad of multiple skin blebs, GI vascular lesions, and refractory anemia seen in this case. However, in a child with GI bleeding and cutaneous vascular lesions where BRBNS is less certain, GI hemangioma or other vascular malformations remain important to consider, especially if imaging and endoscopy reveal a different morphology of lesions.

ChatGPT-4o output:

1. Blue rubber bleb nevus syndrome – *Most likely*

Reasoning:

- Classic presentation:
 - Multiple, compressible, blue-purple vascular nodules (“rubber blebs”) on skin and GI tract
 - Recurrent GI bleeding → iron deficiency anemia, melena
 - Tender subcutaneous lesions and skin blebs are hallmark cutaneous findings
- Endoscopic evidence of vascular lesions with recent bleeding
- No family history—BRBNS is often sporadic, though it can be autosomal dominant in rare cases
- Most consistent with cutaneous and visceral venous malformations

2. Klippel–Trénaunay syndrome

Reasoning:

- Features:
 - Capillary malformations (port-wine stains), venous/lymphatic malformations, and limb overgrowth
 - Gastrointestinal bleeding can occur, but cutaneous lesions are not rubbery nodules
 - Typically unilateral limb involvement with hypertrophy
- Less likely due to lack of limb asymmetry and different lesion morphology

3. Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome)

Reasoning:

- Features:
 - Mucocutaneous telangiectasias, recurrent epistaxis, and GI bleeding
 - Associated with arteriovenous malformations in lungs, brain, liver
 - Lesions are telangiectasias, not rubbery blue blebs
 - Autosomal dominant inheritance—no family history here
- Less likely due to different skin findings and lesion types

OpenEvidence output:

Most likely diagnoses:

1. Blue rubber bleb nevus syndrome – This is the most likely diagnosis, given the presence of multiple, compressible, blue-purple, rubbery cutaneous nodules from early childhood; similar vascular lesions throughout the GI tract, and chronic iron deficiency anemia due to GI bleeding. The classic features and course, including the need for iron supplementation, transfusions, and endoscopic sclerosis, are well described in the literature on BRBNS¹.
2. Multifocal sporadic venous malformations – Multiple, compressible, bluish venous malformations can present in the skin and GI tract, but the classic syndrome with both cutaneous and GI involvement, as well as the described clinical course, is most consistent with BRBNS. Sporadic venous malformations are usually unifocal or limited in distribution and rarely cause significant GI bleeding or anemia².
3. Glomangiomas – This rare entity can present with multiple, deep, bluish vascular lesions, often painful and located in the extremities, but GI involvement and iron deficiency anemia are not typical. The absence of pain and the presence of GI tract lesions make this less likely than BRBNS³.

Most important not-to-miss diagnoses:

1. Maffucci syndrome – Distinguished by the presence of multiple enchondromas (cartilaginous bone tumors) in addition to vascular lesions. The absence of skeletal deformities or bone lesions makes this unlikely⁴.
2. Hereditary hemorrhagic telangiectasia – Characterized by mucocutaneous telangiectasias and recurrent epistaxis, with GI bleeding possible but typically presenting later in life and with a positive family history. The absence of telangiectasias and epistaxis, and the presence of classic venous malformations, argue against hereditary hemorrhagic telangiectasia⁵.

Key additional history and follow-up tests:

- Detailed musculoskeletal exam and imaging to rule out enchondromas (for Maffucci syndrome).
- Family history and screening for epistaxis or telangiectasias (for hereditary hemorrhagic telangiectasia).
- Ongoing endoscopic and imaging surveillance for new or enlarging GI lesions.
- Periodic assessment for anemia and occult GI bleeding.

(ix) Tuberous sclerosis complex (neurocutaneous)

PerplexityAI output:

1. Tuberous sclerosis complex

Rationale:

The clinical vignette is classic for tuberous sclerosis complex (TSC). The child has infantile spasms (a common presenting seizure type in TSC), developmental delay, mild intellectual disability, and multiple hypopigmented “ash leaf” macules—all major cutaneous criteria. Additionally, facial angiofibromas, a shagreen patch, and unguinal fibromas are pathognomonic skin findings.

Imaging reveals cortical tubers and subependymal nodules on brain MRI, bilateral renal angiomyolipomas, and a regressing cardiac rhabdomyoma—classic extracutaneous manifestations. The absence of a family history is common, as most cases are due to *de novo* mutations. Genetic testing confirming a pathogenic *TSC2* mutation provides definitive molecular diagnosis. Multidisciplinary care is required for surveillance and management of the multisystem involvement, which is typical for TSC.

2. Neurofibromatosis type 1

Rationale:

Neurofibromatosis type 1 is an important differential due to its status as a neurocutaneous syndrome with potential for seizures and learning difficulties. However, NF1 lacks facial angiofibromas, shagreen patches, and unguinal fibromas. The renal angiomyolipomas and cardiac rhabdomyoma seen here are not features of NF1. While NF1 can present with CALMs (sometimes mistaken for hypopigmented macules), the specificity of the cutaneous and extracutaneous findings and the *TSC2* mutation, make TSC the clear diagnosis.

3. Hypomelanosis of Ito

Rationale:

Hypomelanosis of Ito can present with hypopigmented skin lesions and neurologic abnormalities such as seizures and intellectual disability. However, it does not include facial angiofibromas, shagreen patches, unguinal fibromas, cortical tubers, subependymal nodules, renal angiomyolipomas, or cardiac rhabdomyomas. The genetic confirmation of a *TSC2* mutation definitively rules out this diagnosis, but it remains a consideration when cutaneous findings are less specific.

ChatGPT-4o output:

1. Tuberous sclerosis complex – *Most likely*

Reasoning:

- Classic triad: Seizures, intellectual disability, and facial angiofibromas
- Additional hallmark features:
 - Hypopigmented “ash leaf” macules
 - Shagreen patch

- Ungual fibromas
- Cortical tubers, subependymal nodules on MRI
- Renal angiomyolipomas and cardiac rhabdomyomas
- *TSC2* mutation confirms the diagnosis

Tuberous sclerosis complex has variable expressivity and often occurs sporadically, though it can be inherited autosomal dominantly

2. Neurofibromatosis type 1

Reasoning:

- May present with:
 - Café-au-lait spots, axillary/inguinal freckling, neurofibromas, optic gliomas
 - Learning disabilities and seizures
- However, lacks:
 - Ash leaf spots, shagreen patch, facial angiofibromas, cortical tubers
- Genetic cause is *NF1* mutation, not *TSC2*
- Less likely given distinct cutaneous and CNS findings

3. Sturge–Weber Syndrome

Reasoning:

- Triad: Facial port-wine stain (V1 distribution), leptomeningeal angiomas, and seizures
- May have intellectual disability and glaucoma
- However:
 - No vascular birthmark, cortical calcifications, or leptomeningeal enhancement described
 - No characteristic skin or systemic findings of TSC
- Less likely based on imaging and skin findings

OpenEvidence output:

Most likely diagnoses:

1. Tuberous sclerosis complex – This is the most likely diagnosis, supported by the presence of multiple hypopigmented “ash leaf” macules, facial angiofibromas, a shagreen patch, unguinal fibromas, seizures (including infantile spasms), developmental delay, cortical tubers and subependymal nodules on brain MRI, renal angiomyolipomas, and a regressing cardiac rhabdomyoma. The diagnosis is definitively confirmed by a pathogenic *TSC2* mutation. These findings are characteristic of TSC, a multisystem neurocutaneous disorder with variable expressivity and high risk for neurologic, renal, cardiac, and dermatologic manifestations¹⁻².

2. Neurofibromatosis type 1 – This disorder can present with neurocutaneous findings and learning

difficulties but is typically characterized by café-au-lait macules, axillary/inguinal freckling, Lisch nodules, and neurofibromas, none of which are described here. The presence of *TSC2* mutation and the specific constellation of skin and organ findings make this diagnosis less likely³.

3. Hypomelanosis of Ito – This neurocutaneous syndrome can present with hypopigmented macules and neurologic impairment, but the skin lesions follow Blaschko lines and are not associated with the classic TSC findings (facial angiofibromas, shagreen patch, unguis fibromas, cortical tubers, or renal/cardiac tumors). The genetic and imaging findings are not consistent with this diagnosis⁴.

Most important not-to-miss diagnoses:

1. Subependymal giant cell astrocytoma – This is a critical complication of TSC, arising from subependymal nodules and potentially causing obstructive hydrocephalus. Serial brain MRI is required to monitor for SEGA development².

2. Renal cell carcinoma – Although rare in children, patients with TSC and renal angiomyolipomas are at increased risk. Ongoing renal imaging is necessary to distinguish benign angiomyolipomas from malignant transformation¹.

Key additional history and follow-up tests:

- Serial neuroimaging to monitor for SEGA.
- Periodic renal ultrasound to assess for angiomyolipoma growth or malignant transformation.
- Cardiac and ophthalmologic surveillance.
- Neuropsychological assessment and ongoing developmental monitoring.
- Family genetic counseling and cascade testing

(x) Neurofibromatosis type 1 (neurocutaneous)

PerplexityAI output:

1. Neurofibromatosis type 1

Rationale:

Neurofibromatosis type 1 is by far the leading diagnosis in this case. The clinical picture—more than six CALMs measuring over 1.5 cm, axillary and groin freckling (Crowe sign), multiple cutaneous neurofibromas, Lisch nodules on ophthalmologic exam, mild learning difficulties, and a family history of similar skin findings—matches the classic diagnostic criteria for NF1. The presence of CALMs, freckling, and neurofibromas are major criteria, and Lisch nodules are highly specific for NF1. Multidisciplinary, lifelong monitoring is recommended due to the risk of complications such as optic pathway gliomas, skeletal abnormalities, and malignancy.

2. Legius syndrome

Rationale:

Legius syndrome is the most important differential to NF1. It also causes multiple CALMs and axillary/groin freckling, but cutaneous or subcutaneous neurofibromas and Lisch nodules are absent. Given that this child has cutaneous neurofibromas and Lisch nodules, NF1 is much more likely. However, in a child with only CALMs and freckling (without neurofibromas or Lisch nodules), Legius syndrome would be a strong possibility, and genetic testing for *SPRED1* mutations would be indicated. The presence of neurofibromas and Lisch nodules here effectively excludes Legius syndrome as the primary diagnosis, but it remains a key differential for similar presentations without these features.

3. Other neurocutaneous syndromes (e.g., McCune–Albright syndrome, Noonan Syndrome with multiple lentigines, Watson syndrome)

Rationale:

Other conditions can present with multiple CALMs but lack the full NF1 phenotype.

- McCune–Albright syndrome is associated with fewer, irregularly bordered CALMs, endocrine abnormalities (e.g., precocious puberty), and fibrous dysplasia—none of which are described here.
- Noonan syndrome with multiple lentigines (formerly Leopard syndrome) features numerous small lentigines rather than the large CALMs seen in NF1, along with cardiac and facial abnormalities not mentioned in the vignette.
- Watson syndrome is extremely rare and also lacks neurofibromas and Lisch nodules.

While these conditions can cause CALMs, their distinctive extracutaneous features and absence of neurofibromas/Lisch nodules make NF1 the clear diagnosis in this case.

ChatGPT-4o output:

1. Neurofibromatosis type 1 (von Recklinghausen disease) – *Most likely*

Reasoning:

- Meets multiple National Institute of Health diagnostic criteria for NF1:
 - ≥ 6 CALMS >0.5 cm prepubertal or >1.5 cm postpubertal
 - Axillary and inguinal freckling
 - Cutaneous neurofibromas
 - Lisch nodules (iris hamartomas)
 - First-degree relative with NF1 (mother)
 - Learning difficulties, common in NF1

Autosomal dominant inheritance (mutation in the *NF1* gene encoding neurofibromin)

2. Legius syndrome

Reasoning:

- May present with:

- *Café au lait* spots and intertriginous freckling
- Mild learning disabilities
- However:
 - No neurofibromas or Lisch nodules
 - Caused by *SPRED1* mutations
- Less likely due to presence of cutaneous neurofibromas and iris hamartomas, which are not seen in Legius syndrome

3. McCune-Albright Syndrome Reasoning:

- Associated features:
 - Café-au-lait spots with irregular (“coast of Maine”) borders
 - Fibrous dysplasia of bone
 - Endocrinopathies (e.g., precocious puberty)
 - CALMs usually large and unilateral
- No mention of bone or endocrine involvement or neurofibromas
- Less likely based on distribution and associated features

OpenEvidence output:

Most likely diagnoses:

1. Neurofibromatosis type 1 – The diagnosis is supported by the presence of more than six café-au-lait macules larger than 1.5 cm, axillary and inguinal freckling, multiple cutaneous neurofibromas, Lisch nodules, mild learning difficulties, and a first-degree relative with similar findings. This constellation fulfills the diagnostic criteria for NF1, as described in the medical literature.

2. Legius syndrome – This RASopathy, caused by *SPRED1* mutations, can present with multiple café-au-lait macules, axillary freckling, and learning disabilities, but does not feature neurofibromas or Lisch nodules. The presence of neurofibromas and Lisch nodules in this case makes Legius syndrome less likely, but it remains in the differential for patients with pigmentary findings and learning issues.

3. McCune–Albright syndrome – This syndrome can present with café-au-lait macules, but these are typically large, have irregular borders (“coast of Maine”), and are associated with polyostotic fibrous dysplasia and endocrine abnormalities, none of which are present here. The distribution and associated findings are not consistent with McCune–Albright syndrome.

Most important not-to-miss diagnoses:

1. Optic pathway glioma – Children with NF1 are at increased risk for optic pathway gliomas, which may be asymptomatic or present with vision loss. Regular ophthalmologic surveillance is required to detect and manage this complication³.

2. Malignant peripheral nerve sheath tumor – NF1 patients are at increased risk for malignant peripheral nerve sheath tumor, particularly in the setting of rapidly enlarging, painful, or deep-seated neurofibromas. Vigilance for changes in neurofibromas and prompt imaging/biopsy of suspicious lesions are essential⁴.

Key additional history and follow-up tests include a detailed family history, annual ophthalmologic exams, neuropsychological assessment, and periodic physical exams to monitor for new neurofibromas, skeletal abnormalities, and signs of tumor development. Genetic testing may be considered for diagnostic confirmation and family counseling.

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