Scratching Beyond the Surface:
A Dermatology Therapeutic Revolution for Patients with Down Syndrome

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Justin Ko, MD MBA

Clinical Professor, Stanford Medicine
Associate Chair and Chief, Dermatology
Associate Chief Quality Officer, Patient Experience and Ambulatory Access

Our Journey for the Talk

The Skin We're In

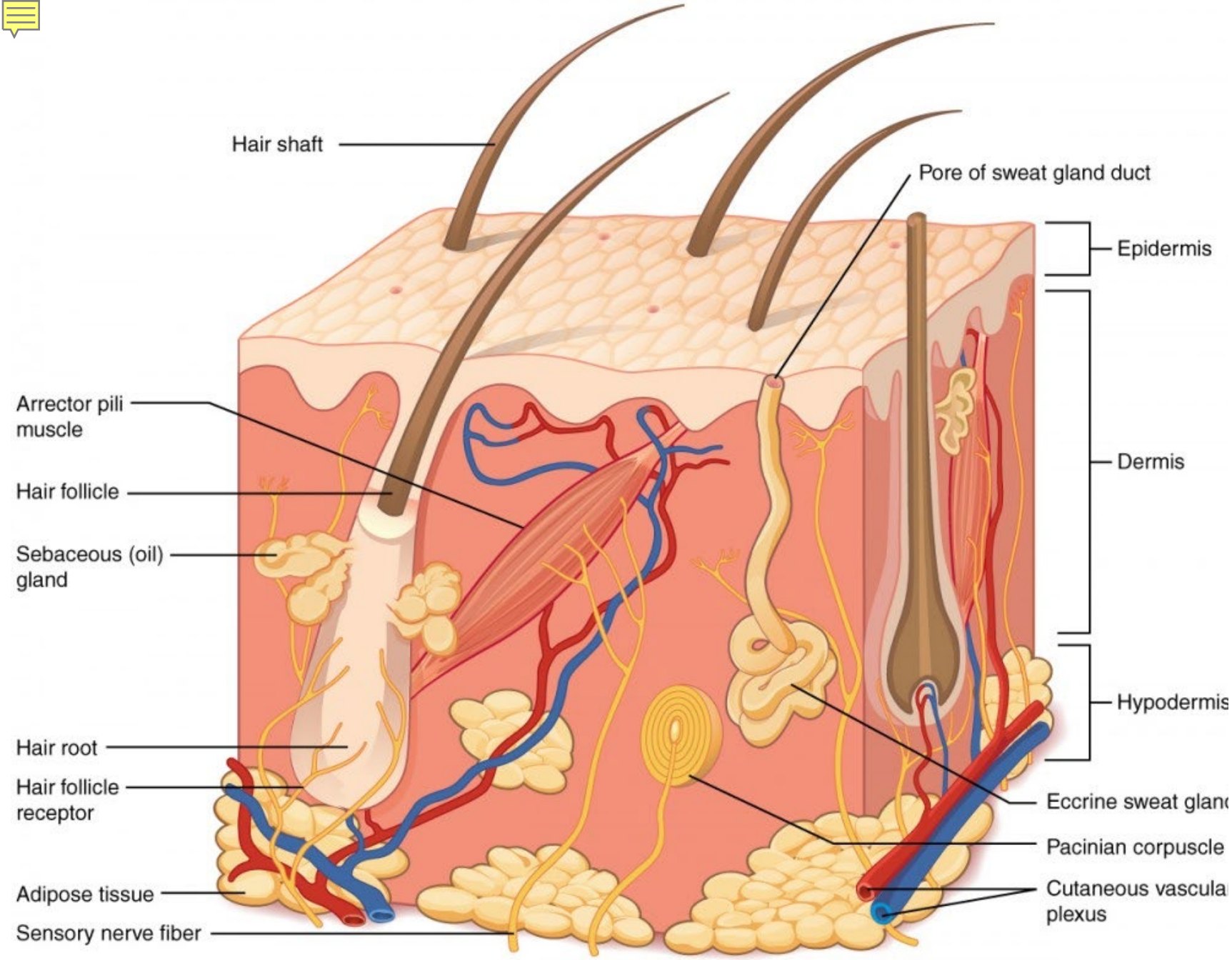
The Core Pathophysiology: The genetic basis and the "Interferonopathy Hypothesis."

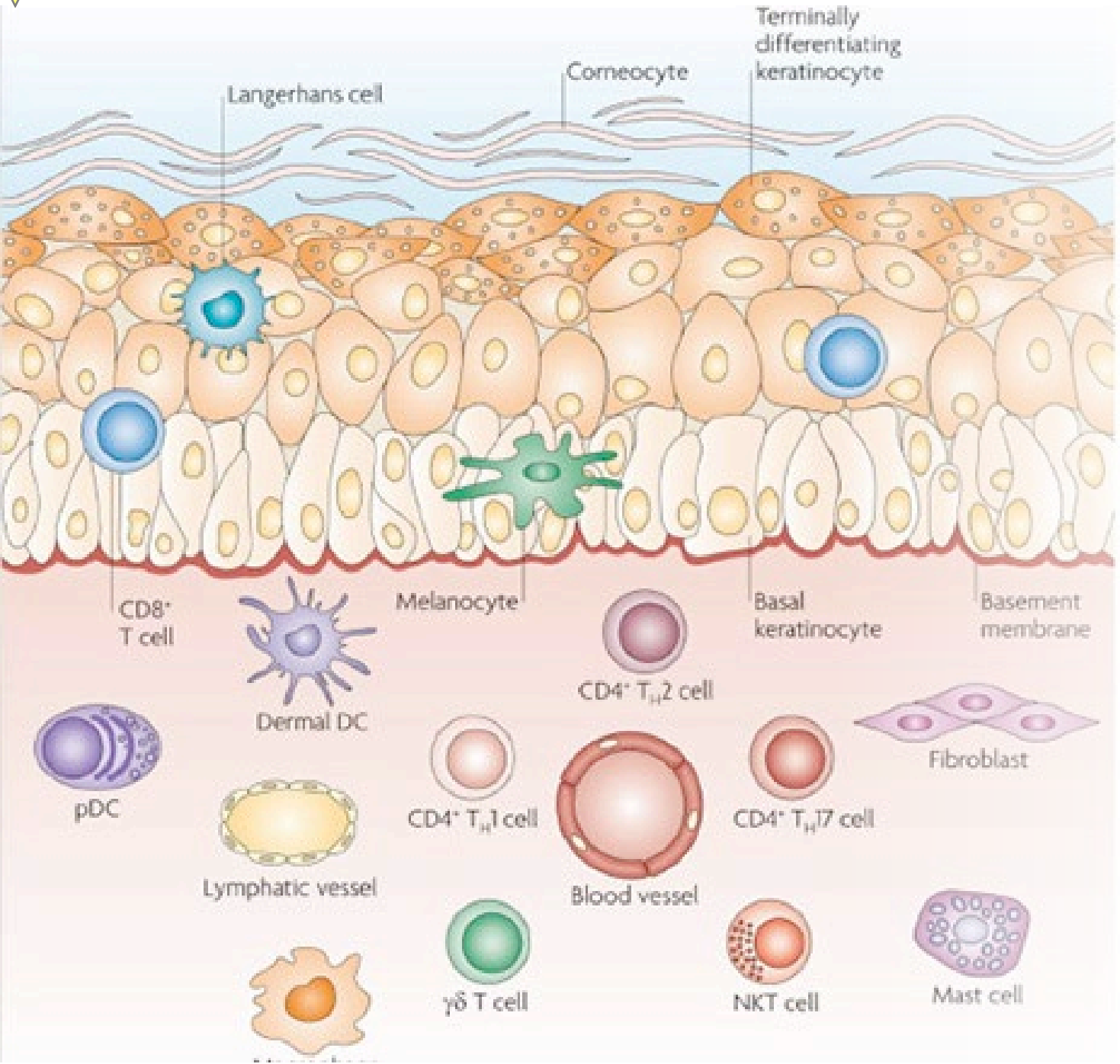
The Clinical Spectrum: A deeper dive into the specific diseases we see.

The Therapeutic Revolution: From conventional failures to targeted successes.

The Future: Where we go from here in research and clinical care.

The Skin We're In





A Sophisticated Immune Ecosystem

- Elements of both arms of the immune system (innate and adaptive)
- Continuous trafficking of immune cells between skin, lymph nodes, and blood
- The skin also has “resident” immune cells that live in the skin

The Impact, Burden and Toll of Skin Disease is Immense

A

B

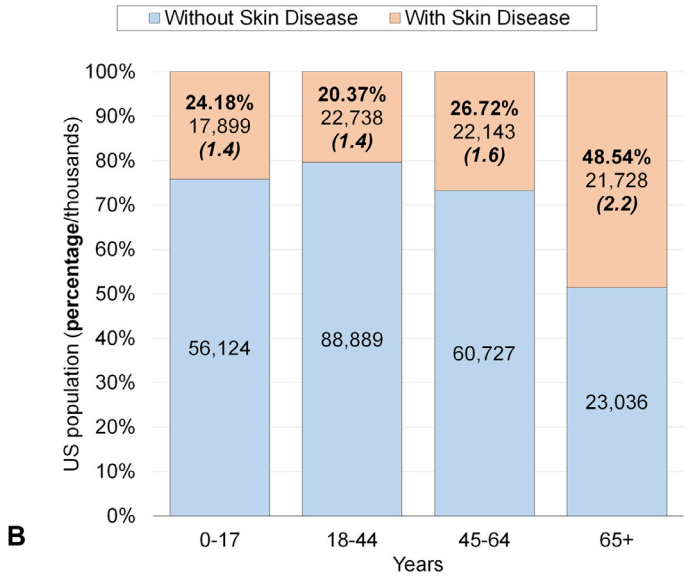


Table 1. DALY ranks when considering skin conditions collectively

Cause	Global DALYs	DALY rank
Ischemic heart disease	129,800,000	1
Lower respiratory infections	115,200,000	2
Cerebrovascular disease	102,200,000	3
Diarrheal diseases	89,523,909	4
Malaria	82,688,806	5
HIV/AIDS	81,549,177	6
Low back pain	80,666,896	7
Preterm birth complications	76,979,669	8
Chronic obstructive pulmonary disease	76,778,819	9
Road injury	75,487,102	10
Major depressive disorder	63,239,334	11
Neonatal encephalopathy (birth asphyxia and birth trauma)	50,162,510	12
Tuberculosis	49,399,351	13
Diabetes mellitus	46,857,136	14
Iron-deficiency anemia	45,349,897	15
Sepsis and other infectious disorders of the newborn baby	44,236,488	16
Congenital anomalies	38,890,019	17
Skin conditions	**36,921,995**	**18**
Self-harm	36,654,590	19
Falls	35,405,935	20

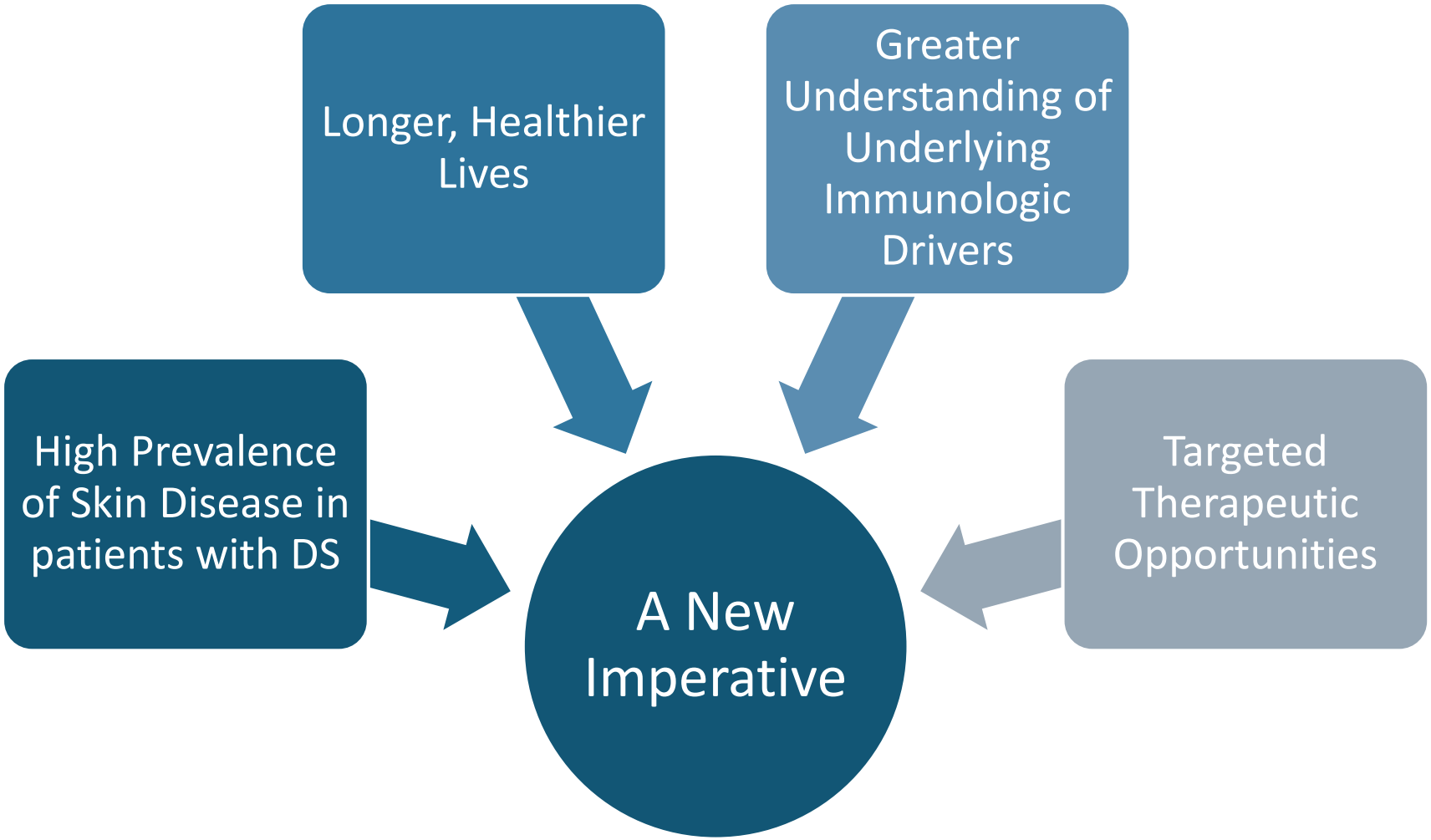
Abbreviation: DALY, disability-adjusted life year.
Bold values indicate the skin data.

Table 2. YLD ranks when considering skin conditions collectively

Cause	Global YLDs	YLD rank
Low back pain	80,666,896	1
Major depressive disorder	63,239,334	2
Iron-deficiency anemia	42,505,250	3
Skin conditions	**33,717,725**	**4**
Neck pain	32,650,797	5
Chronic obstructive pulmonary disease	29,420,262	6
Other musculoskeletal disorders	28,247,230	7
Anxiety disorders	26,847,326	8
Migraine	22,362,507	9
Diabetes mellitus	20,791,397	10
Falls	19,479,581	11
Osteoarthritis	17,148,545	12
Drug use disorders	16,434,052	13
Other hearing loss	15,824,531	14
Asthma	13,843,163	15
Alcohol use disorders	13,838,157	16
Road injury	13,489,949	17
Schizophrenia	12,975,089	18
Bipolar affective disorder	12,878,832	19
Dysthymia	11,091,105	20

Abbreviation: YLD, years lost due to disability.
Bold values indicate the skin data.

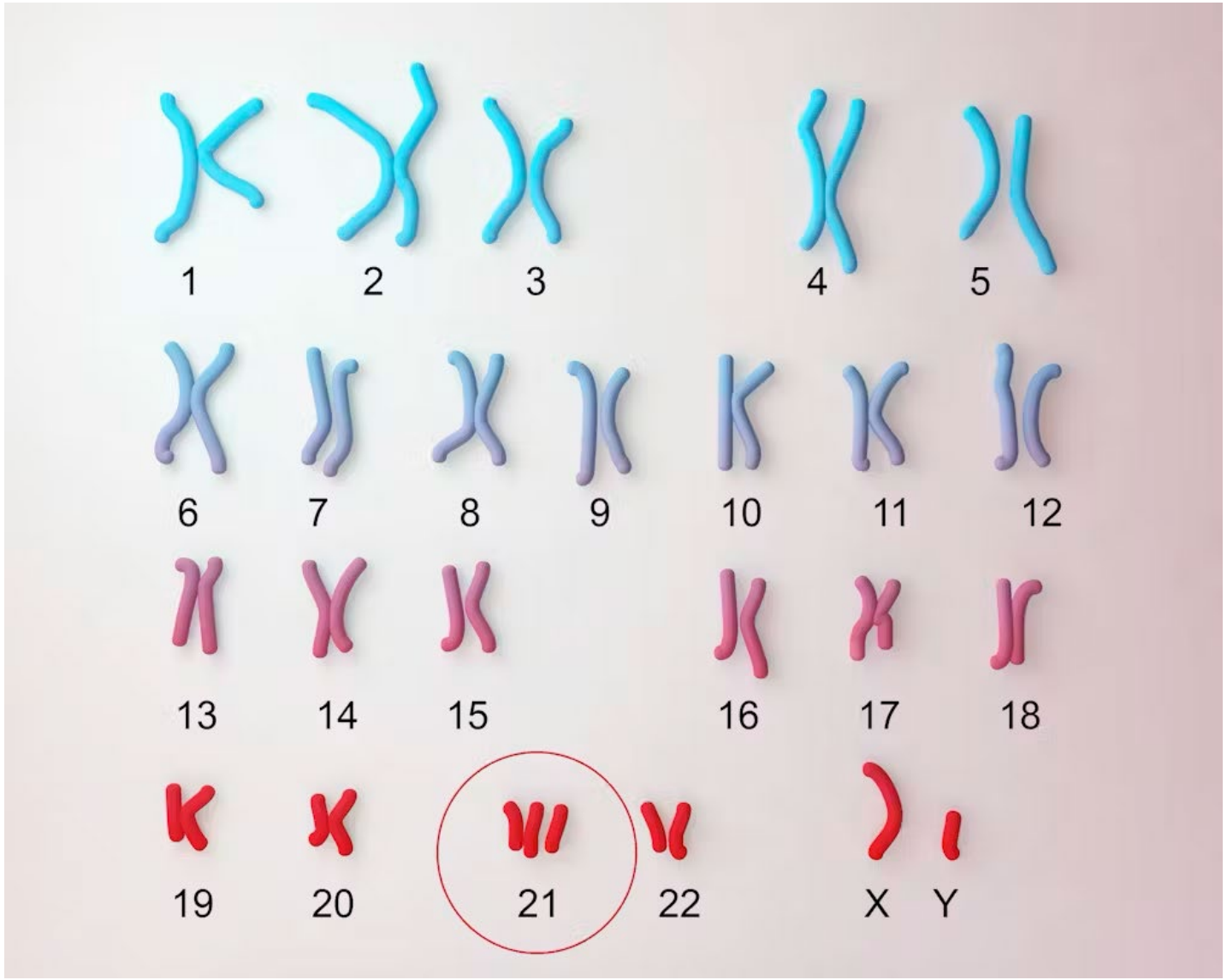
A Confluence of Factors Presents a Focus on Skin in Patients with DS

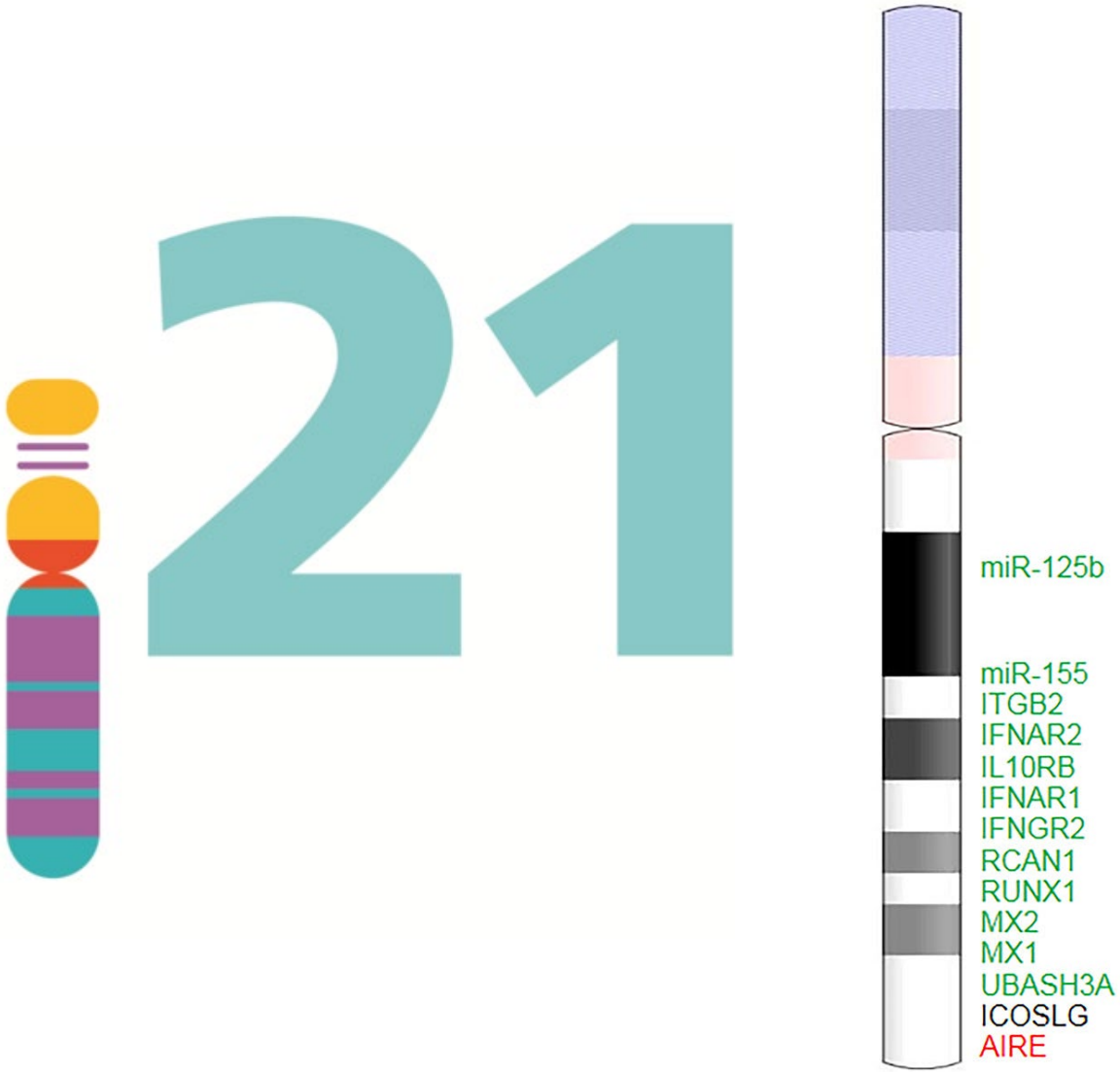


Paradigm shift

The Old	The New
DS is associated with a random list of skin issues.	Skin disease is a core feature of DS.
Conditions are treated as isolated problems.	Seemingly unrelated conditions share a common root cause.
Treatment is reactive and symptom-based.	Treatment is proactive and mechanism-based.
Focus: The Skin	**Focus: The Systemic Immune Dysregulation**

The Genetic Foundation





Key Immune Genes Reside on Chromosome 21

The Interferonopathy Hypothesis: The Overly Sensitive Alarm

Cellular Hypersensitivity: Due to the extra receptors, cells in individuals with DS are **3 to 7 times more sensitive** to interferons.

+

Chronic "Antiviral Alert": This creates a constant, low-grade activation of the body's primary antiviral defense pathway, leading to chronic inflammation.

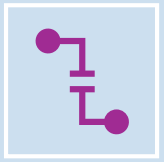
→

Down Syndrome as a Chronic Interferonopathy

The Immune Paradox

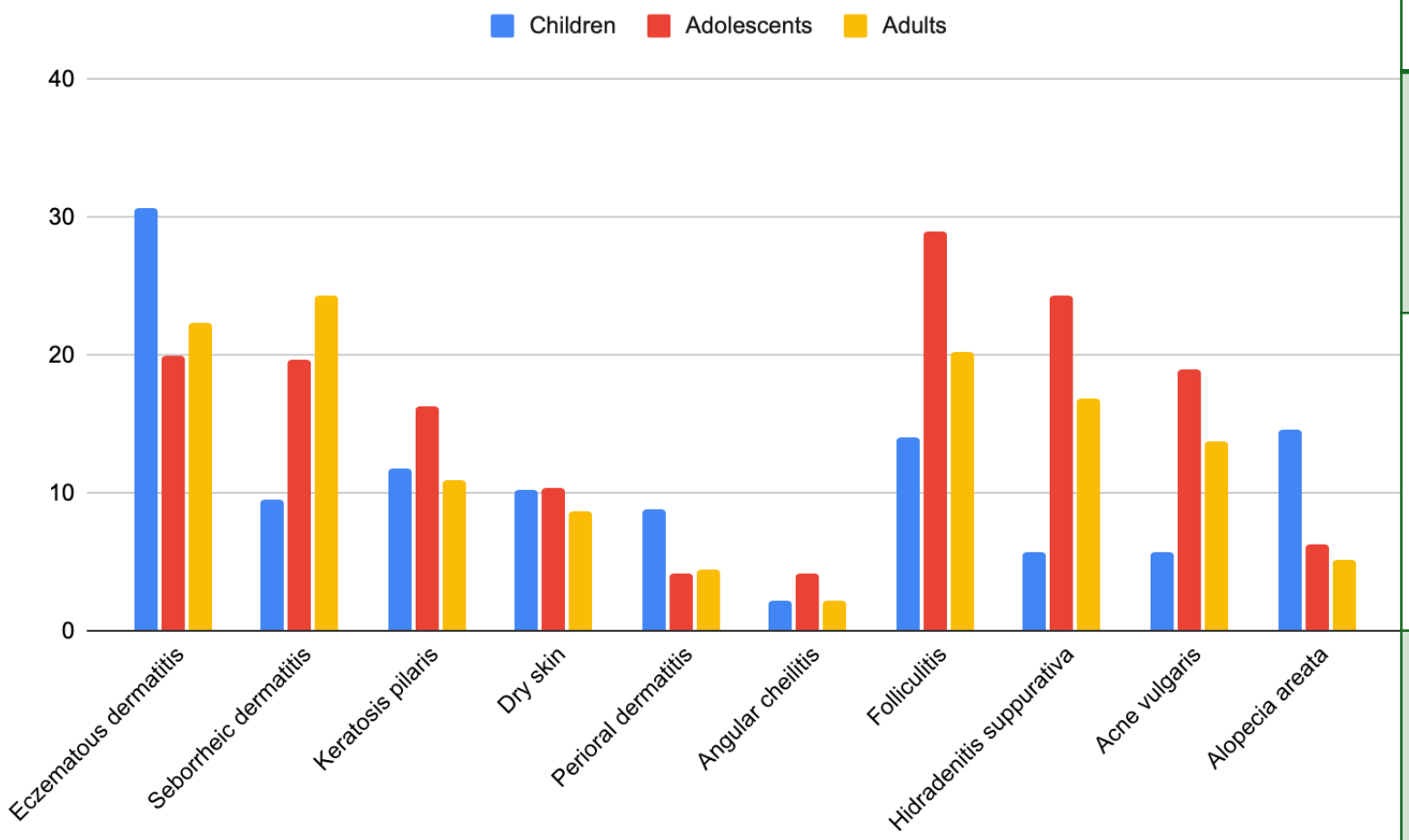
The constant interferon signaling creates a paradoxical state:

Over-response: The system is primed to attack, leading to **autoimmunity** where it targets the body's own cells (hair follicles, melanocytes).



Dysregulated Response: The constant signaling leads to T-cell exhaustion and an impaired ability to mount a coordinated, effective response to **certain real pathogens**.

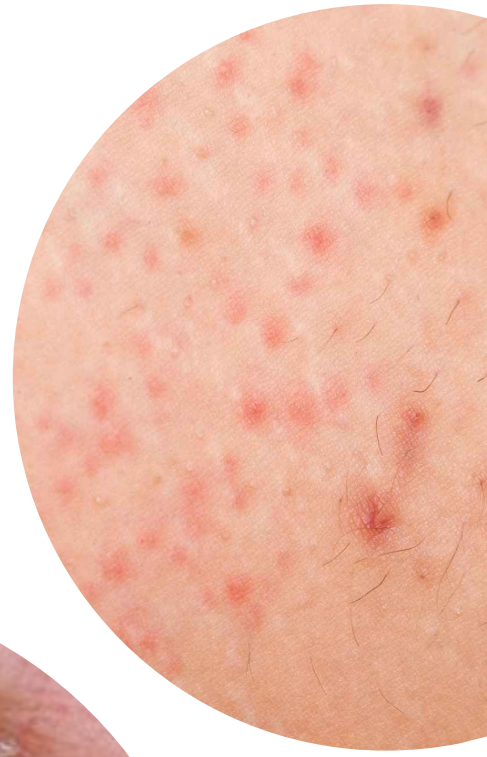
The Clinical Spectrum: A Dermatologic Progression?

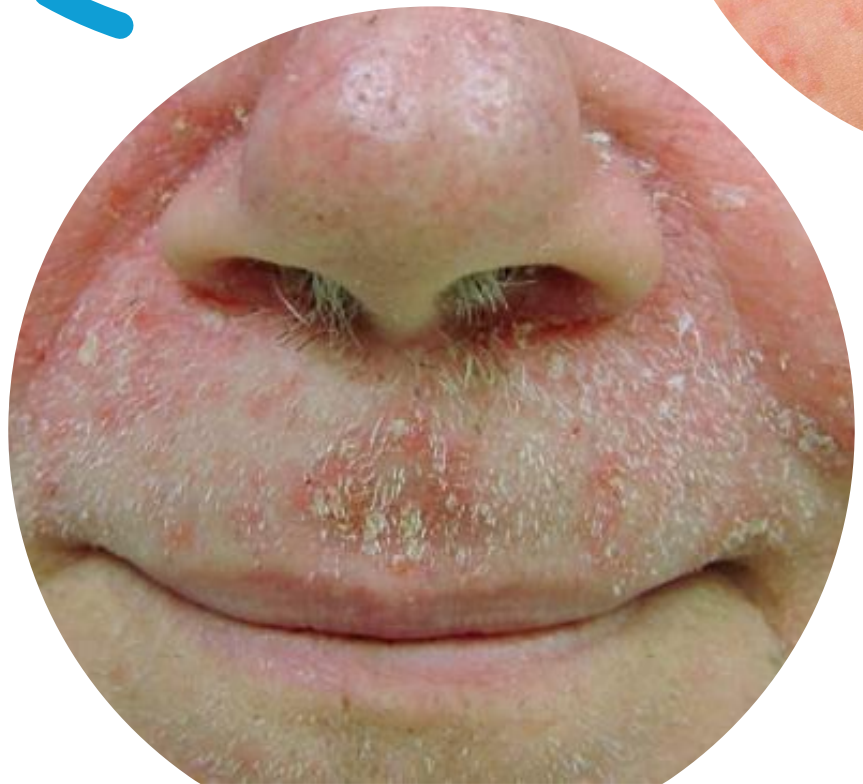


Age Group	Top 3 Most Prevalent Conditions	Primary Driver
Children (0-12)	1. Eczematous Dermatitis 2. Alopecia Areata 3. Folliculitis	Barrier Dysfunction & Early Autoimmunity
Adolescents (13-17)	1. Folliculitis 2. Hidradenitis Suppurativa 3. Eczematous Dermatitis	Hormonal Changes & Inflammation
Adults (≥18)	1. Seborrheic Dermatitis 2. Eczematous Dermatitis 3. Folliculitis	Chronic Inflammation & Cumulative Effects

Deep Dive: Inflammatory & Barrier-Related Conditions

- **Eczematous Dermatitis:** Very common. Caused by a combination of impaired skin barrier function (reduced filaggrin, increased water loss) and immune-driven inflammation.
- **Seborrheic Dermatitis:** The most common diagnosis in adults. A chronic inflammatory reaction, often related to *Malassezia* yeast, which thrives on skin with altered sebum production.
- **Folliculitis:** Inflammation of hair follicles, often presenting as persistent pimples or pustules. Can be bacterial but is often driven by sterile inflammation.





Deep Dive: Autoimmune - Alopecia Areata

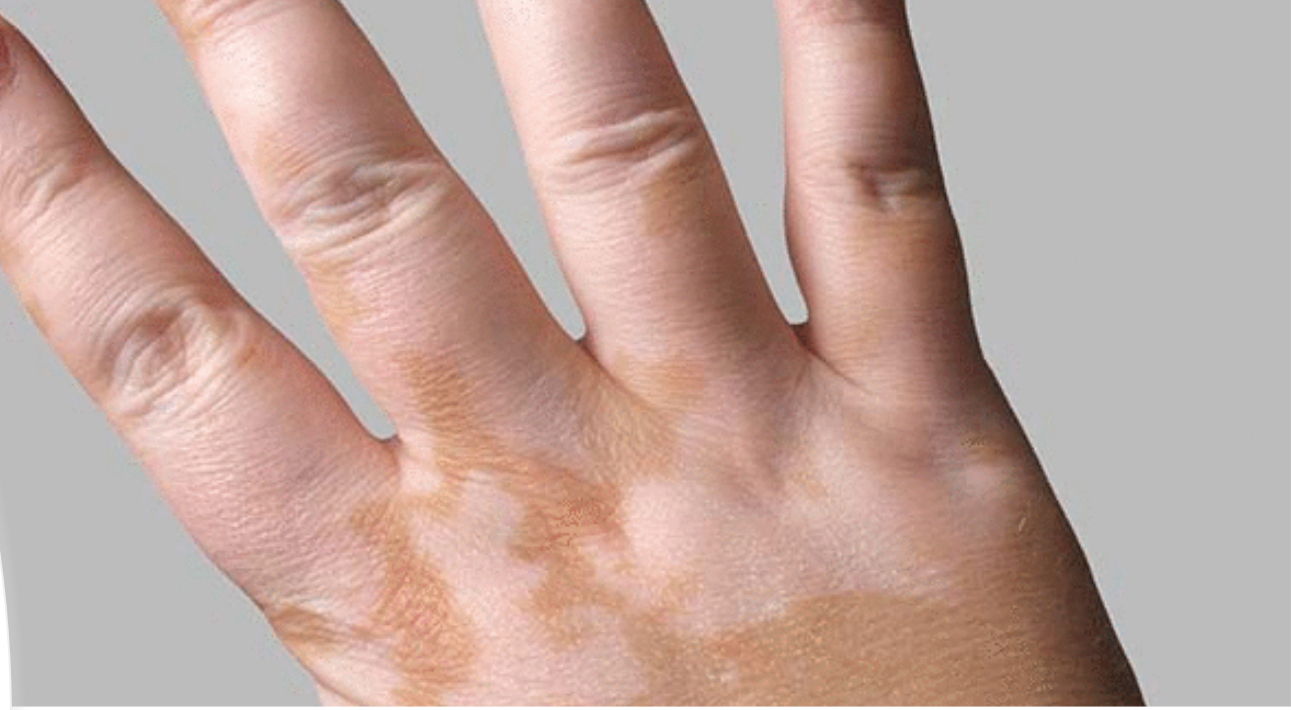
The Hallmark Autoimmune Association

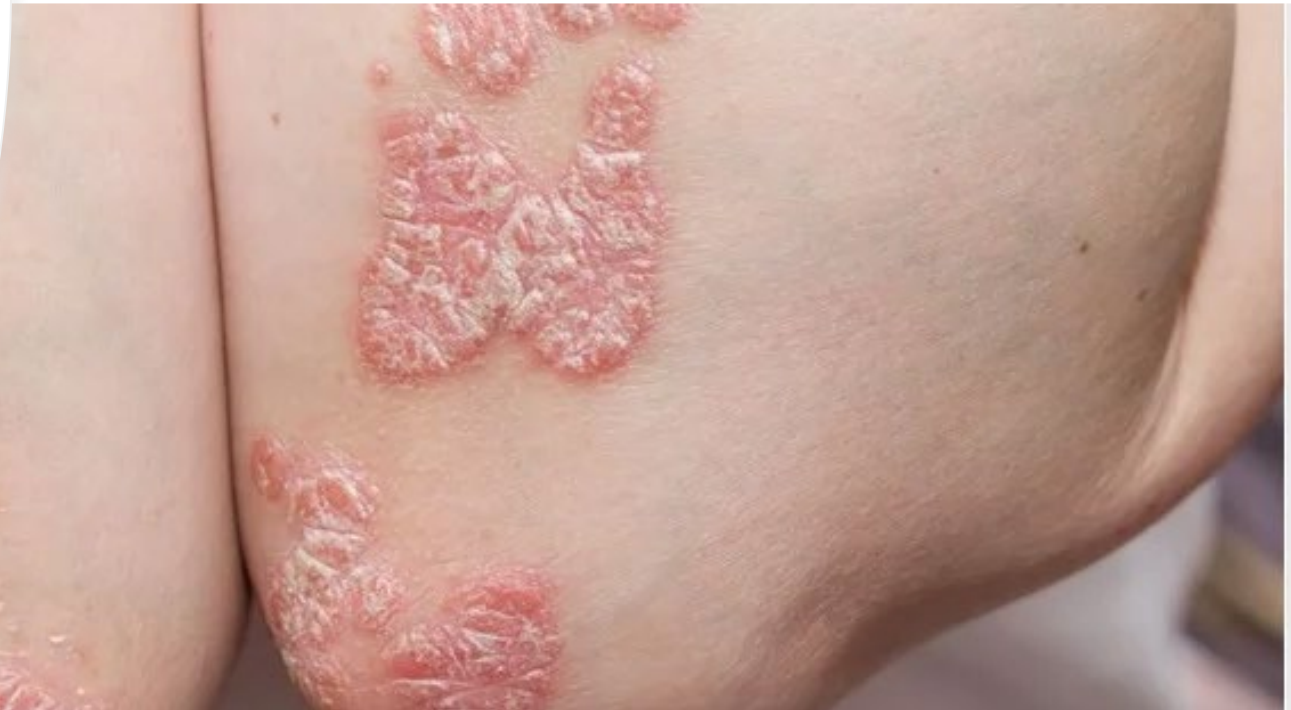
- **Prevalence:** Up to **11.6%** in DS vs. ~2% lifetime risk in the general population. A >5-fold increase.
- **Severity & Course:**
  - Earlier age of onset (mean age of 7).
  - Often more extensive, rapidly progressing to total scalp (totalis) or full body (universalis) hair loss.
  - Historically, very poor response to conventional treatments like corticosteroids.

Deep Dive: Autoimmune - Vitiligo & Psoriasis

- **Vitiligo:** Autoimmune destruction of melanocytes, causing patches of white skin. Prevalence is significantly increased in the DS population. The interferon pathway is a known key driver of vitiligo pathogenesis

- **Psoriasis:** While less common than eczema, it still occurs at a higher rate. It serves as a crucial model for understanding targeted therapy

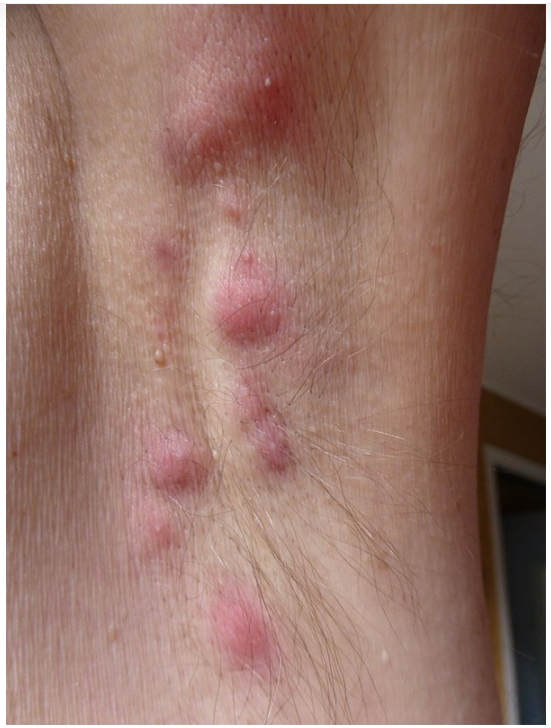


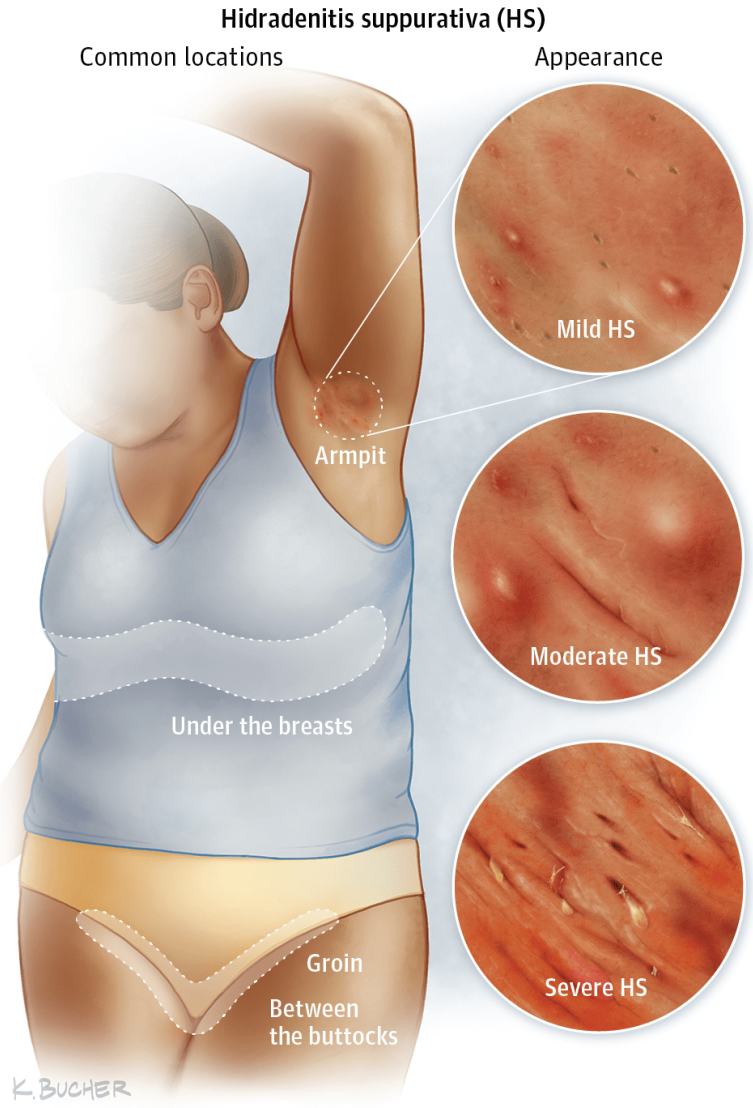


Deep Dive: Hidradenitis Suppurativa (HS)

A Painful and Under-recognized Condition

- **What is it?** A chronic, inflammatory follicular occlusion disorder causing painful nodules, abscesses, and scarring in skin folds (axillae, groin).
- **The DS Connection:** Prevalence is elevated, especially in post-pubertal adolescents and young adults.
- **Pathogenesis:** Driven by a combination of follicular plugging, bacterial dysbiosis, and a profound, hyper-inflammatory response—a perfect storm in the context of DS immune dysregulation.





Conventional Therapies: A History of Limited Success

Treating Smoke, Not Fire

- **Topical Steroids/Calcineurin Inhibitors:** Useful for mild eczema, but often insufficient for moderate-to-severe or widespread disease. High potential for skin atrophy with long-term use.

- **Intralesional Steroids:** Can be painful and traumatic. Low success rate for the aggressive alopecia seen in DS.

- **Systemic Immunosuppressants (e.g., Methotrexate, Cyclosporine):** Broad immunosuppression carries a high risk of infection and organ toxicity in a population already prone to both.

- **Phototherapy:** Logistical challenges (frequent visits, standing still) can make this modality difficult for many patients.

A Lesson in Targeted Therapy: Psoriasis Biologics

Imprecise Target: Early biologics, like TNF-α inhibitors, were tried for severe psoriasis for patients with DS. They showed a **~90% failure rate**.

The Right Target: Newer biologics targeting the **IL-23/Th17 axis** have shown excellent success rates.

Agents: Ustekinumab (IL-12/23), Risankizumab (IL-23), Guselkumab (IL-23).

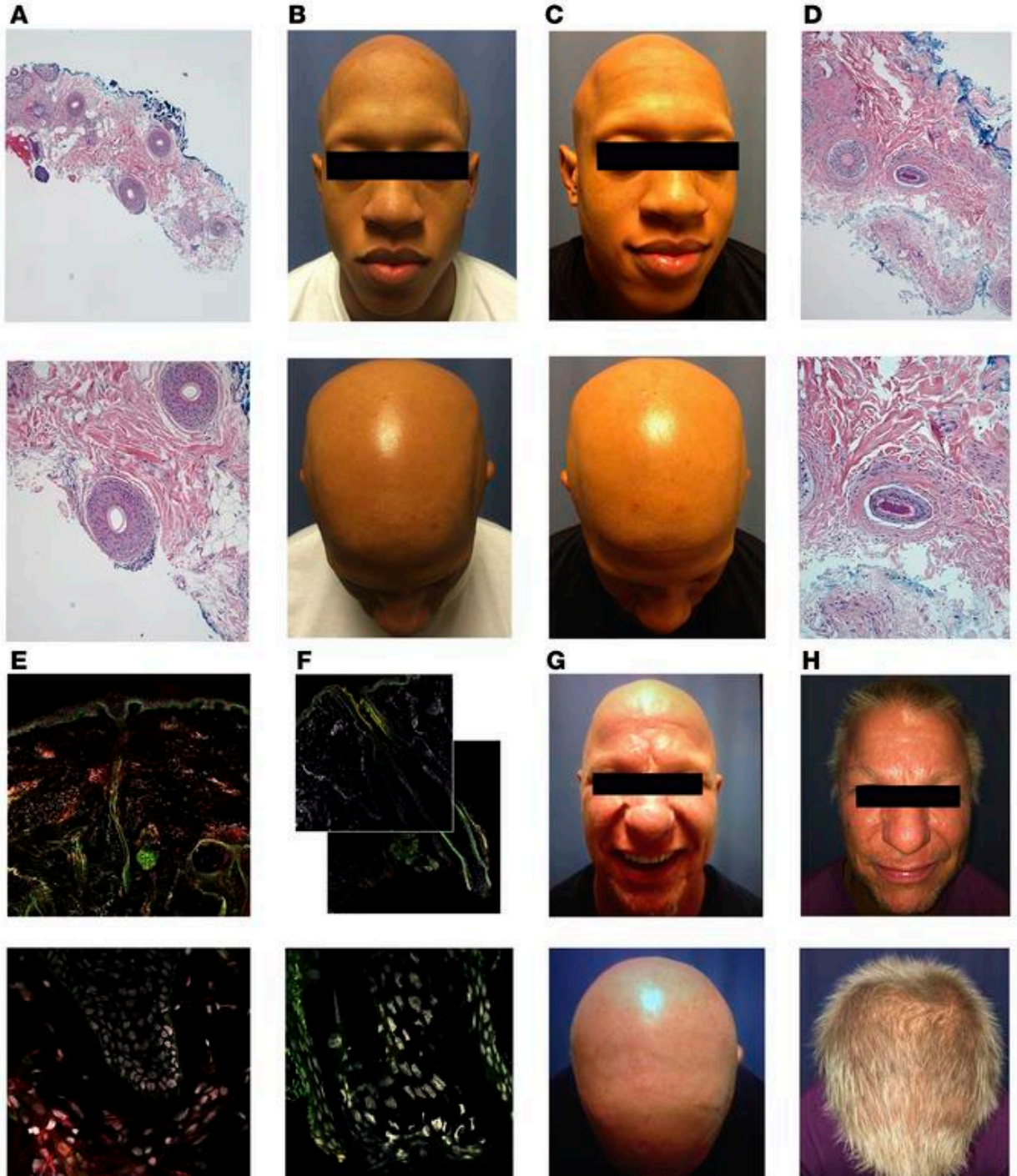
The Rationale: This demonstrated that simply blocking inflammation isn't enough. We must block the *specific pathway* being driven by the underlying interferonopathy—the more we understand, the better we can find the right therapies to fit.

The Game Changer: JAK Inhibitors

Mechanism: Janus Kinase (JAK) enzymes are intracellular messengers that are essential for transmitting the signal from the interferon receptor to the cell's nucleus.

The "Off Switch": JAK inhibitors act as a circuit breaker, directly blocking this hypersensitive signaling pathway at its source.

A "Trisomy 21 Immunomodulator": Because they target the foundational problem, they are effective for a whole range of interferon-driven autoimmune conditions.



Proof of concept of Jak-Stat inhibition in treatment of Alopecia Areata

A Clinical Trial for JAK inhibition in Down Syndrome Patients

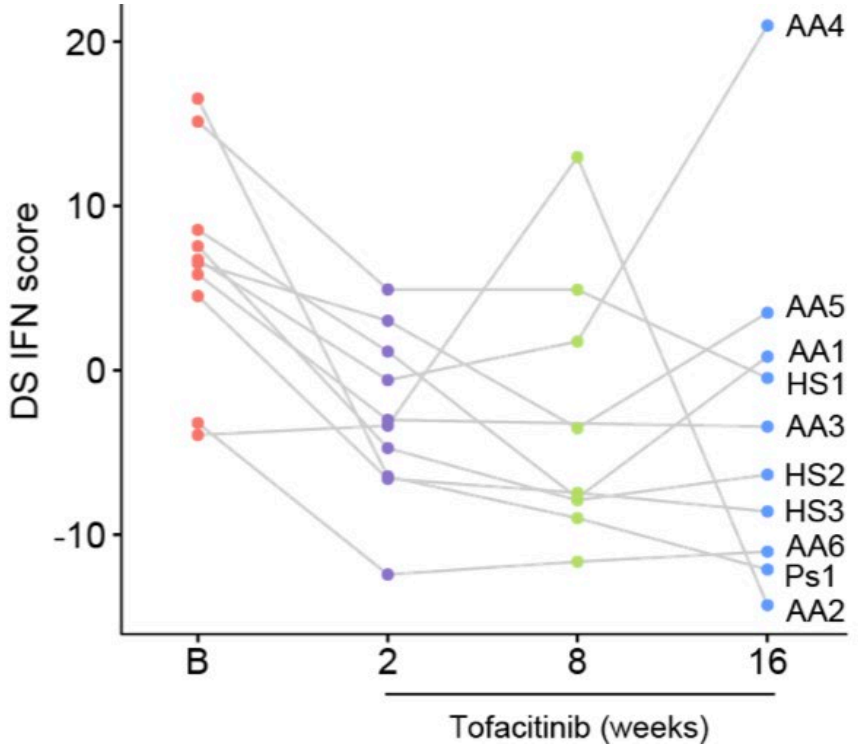
Landmark Study (Dutkiewicz et al.)

Design: Open-label trial of the JAK inhibitor Tofacitinib in adults with DS and severe dermatologic disease (AA, vitiligo, psoriasis, AD).

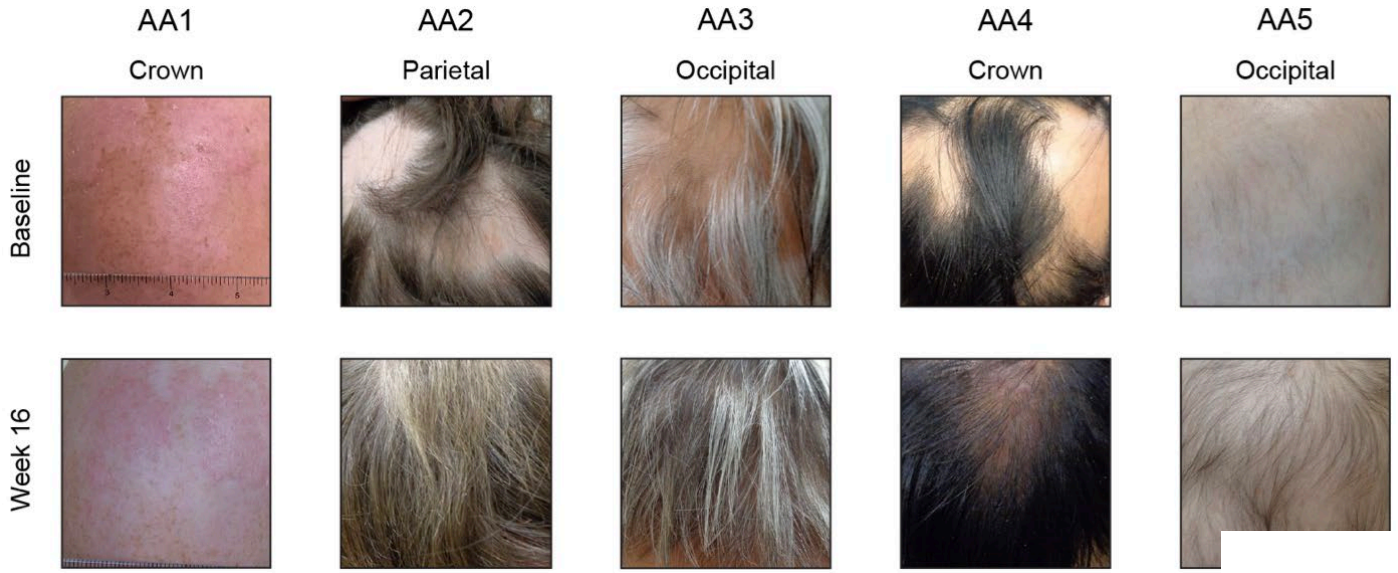
Primary Outcome: Showed significant, clinically meaningful improvements in skin disease scores across all cohorts.

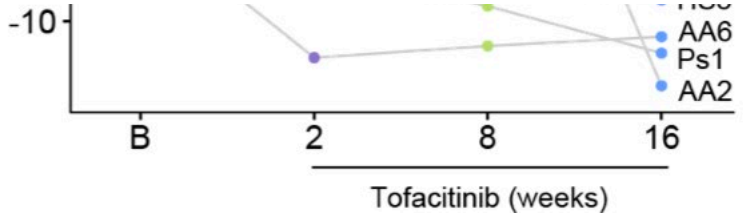
Biomarker Confirmation: Crucially, treatment led to a **statistically significant reduction in systemic interferon scores** in the blood.

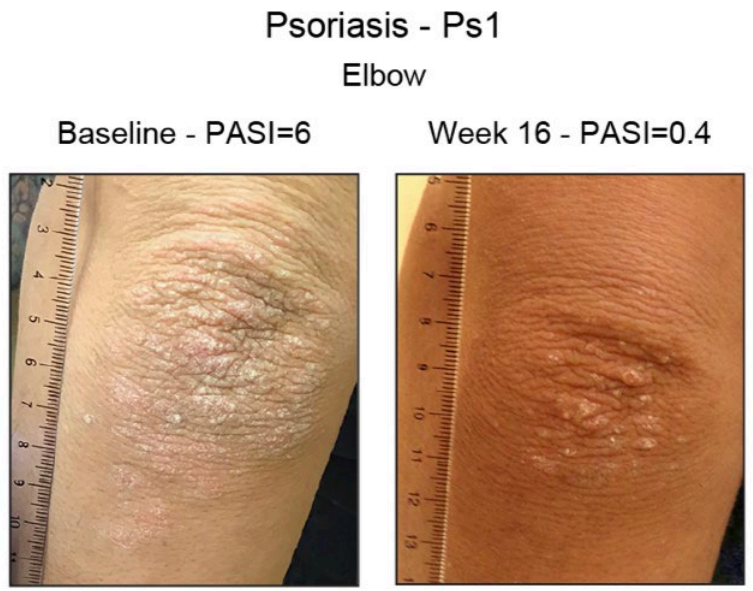
Safety: The drug was well-tolerated with no serious adverse events reported during the study period.

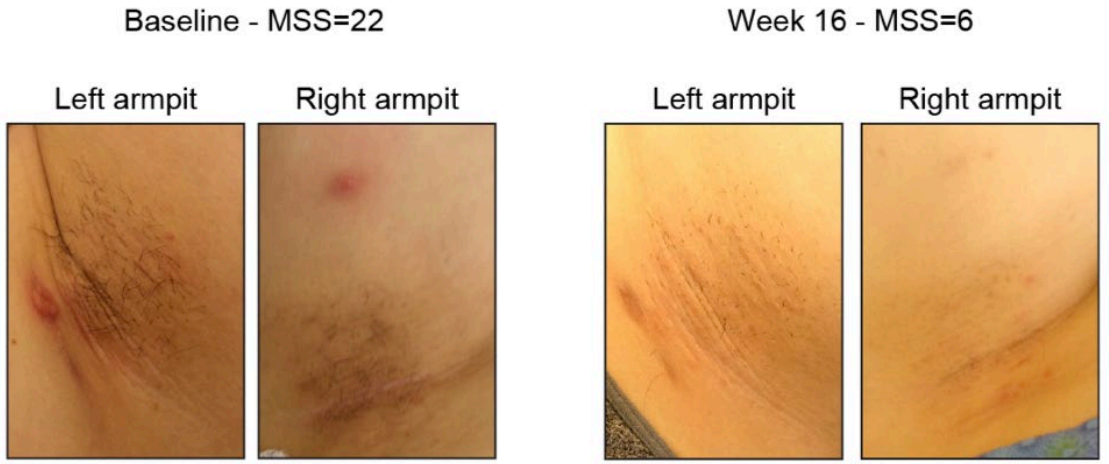


Improvement of Diverse Skin Conditions









Safety considerations

Black Box Warning: The JAK inhibitor class carries a warning regarding risk of serious infections, malignancy, cardiac events, and thrombosis.

Context is Key: These risks were identified in older, rheumatoid arthritis populations with existing comorbidities. The risk profile in a younger, healthier DS population is still being studied but appears favorable so far.

Active Monitoring: Requires careful patient selection and laboratory monitoring (blood counts, lipids).

Ongoing Research: A new $4M NIH-funded trial is now studying next-generation JAK inhibitors (Abrocitinib, Ritlecitinib) over a longer term (60 weeks) to gather more safety data.

A Path Forward

- **Clinical Practice:**
  - Develop age-stratified screening guidelines
  - Establish evidence-based treatment algorithms (e.g., Use IL-23 inhibitors first-line for psoriasis; consider JAK inhibitors for severe AA) specific for DS patients
- **Research:**
  - Conduct long-term safety and efficacy studies
  - Identify biomarkers to predict treatment response
  - Explore the role of interferonopathy in other DS comorbidities (e.g., autoimmune thyroid disease, celiac disease), neuroinflammation?
  - Explore concept and promise of early intervention
- **Care Models:**
  - Promote multidisciplinary DS clinics that integrate dermatology
  - Create patient-friendly educational resources for families

Key Takeaways

Dermatologic disease is a **core, systemic feature** of Down syndrome, not an incidental finding.

The unifying cause is a genetically driven **chronic interferonopathy**.

This understanding has enabled a therapeutic pivot from broad immunosuppression to **highly specific, mechanism-based treatments**.

JAK inhibitors represent a revolutionary tool, acting as a "Trisomy 21 immunomodulator" with the power to transform patient outcomes across multiple diseases.

The future is bright, and requires a concerted effort to translate these scientific gains into a new, evidence-based **standard of care**.