# Extrapolation Limitations:
## *Where are the Gaps?*

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# Children Aren't Just Little Adults

## What's different about children?

1) Differences in drug metabolism (PK) → Needed, esp. for youngest
2) Differences in medication intake
   - Young children can't swallow tablets
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   - Adherence rates are not extrapolatable

   → Liquid +/- small/ crushable tabs, partial SQ doses
3) Children are still receiving vaccines

*1980s advertisement for Minnesota Children's Hospital*

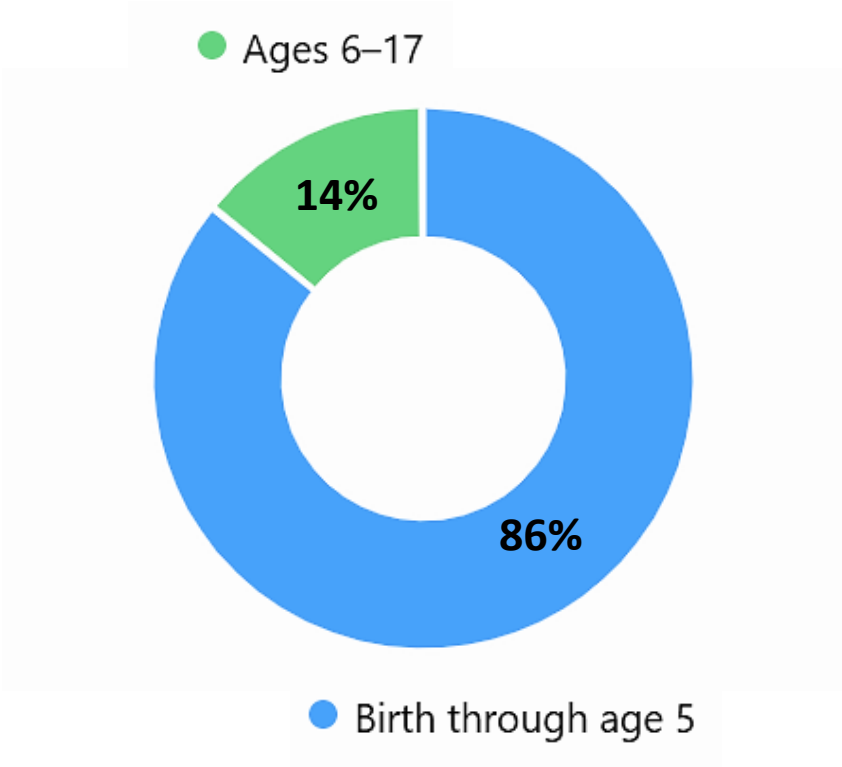
# Childhood Vaccines

**Routine vaccines completed by age 5y: 28 doses**

- Hepatitis B (3 doses)
- Rotavirus (2–3 doses, depending on product)
- DTaP (5 doses)
- Hib (3–4 doses, depending on product)
- Pneumococcal conjugate (4 doses)
- Polio (4 doses)
- MMR (2 doses)
- Varicella (2 doses)
- Hepatitis A (2 doses)

**Routine vaccines after age 5y: 5 doses**

- Tdap (1 dose)
- HPV (2 doses if started before age 15)
- Meningococcal ACWY (2 doses)



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4) Monogenic lupus cases

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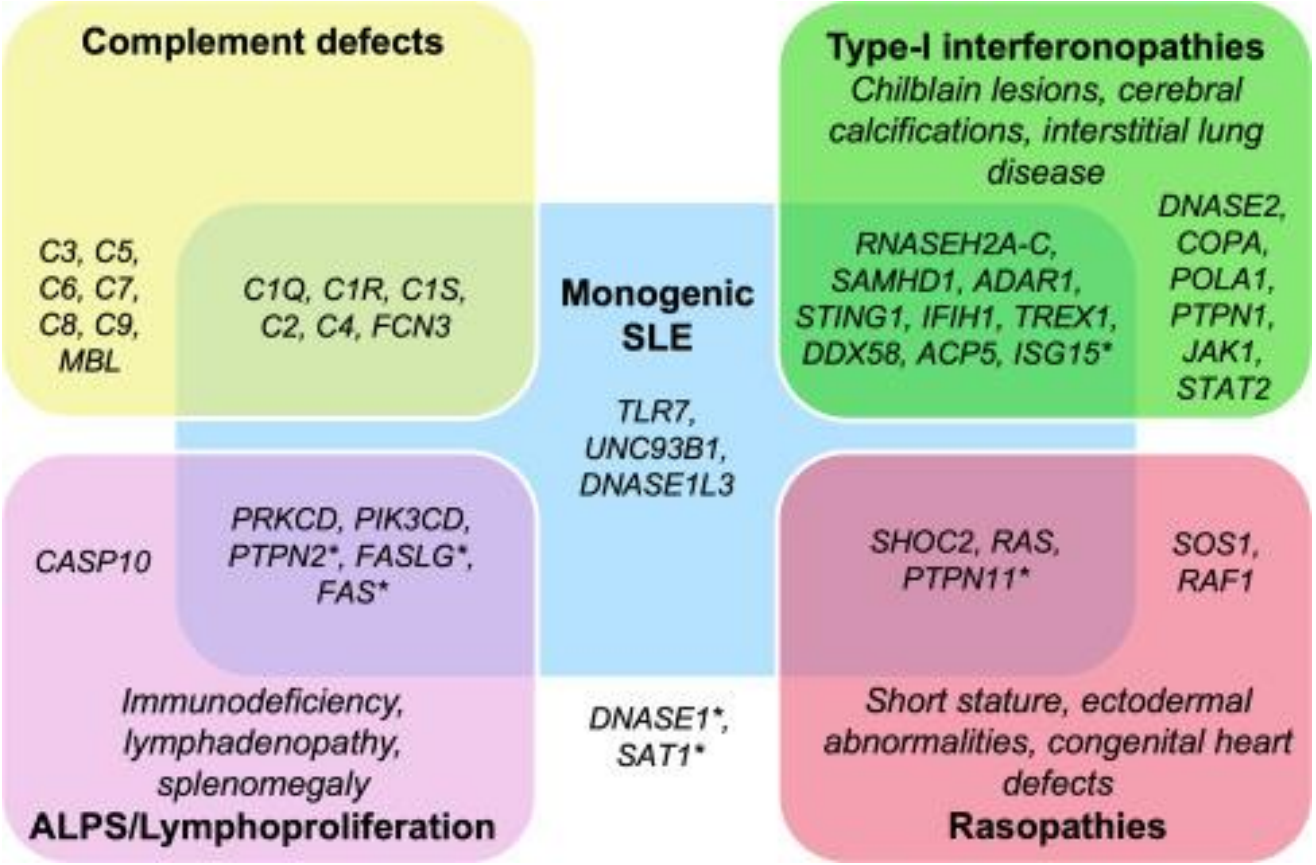
# Monogenic Lupus

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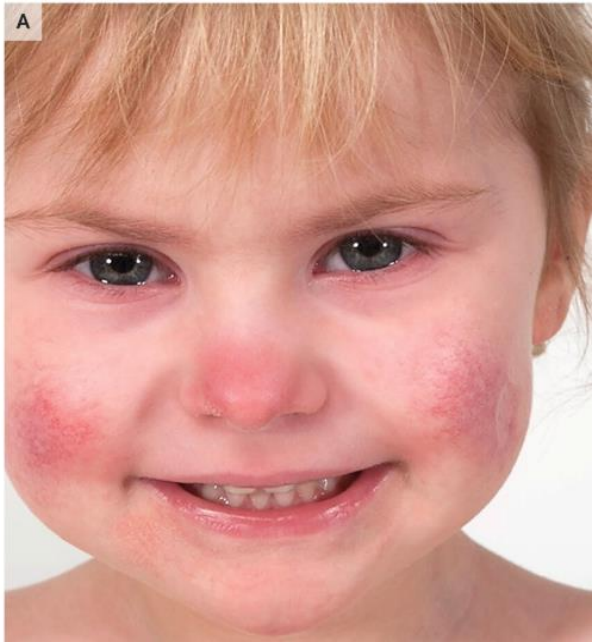
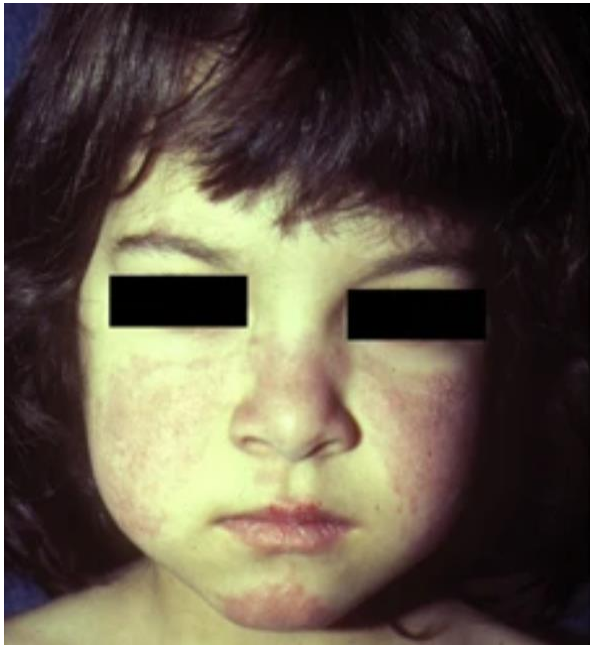



**SAVI**

"Interferonopathy"

*Tx target: anifrolumab*



**C4 deficiency**

Normal interferon levels

*Anifrolumab unlikely to work*

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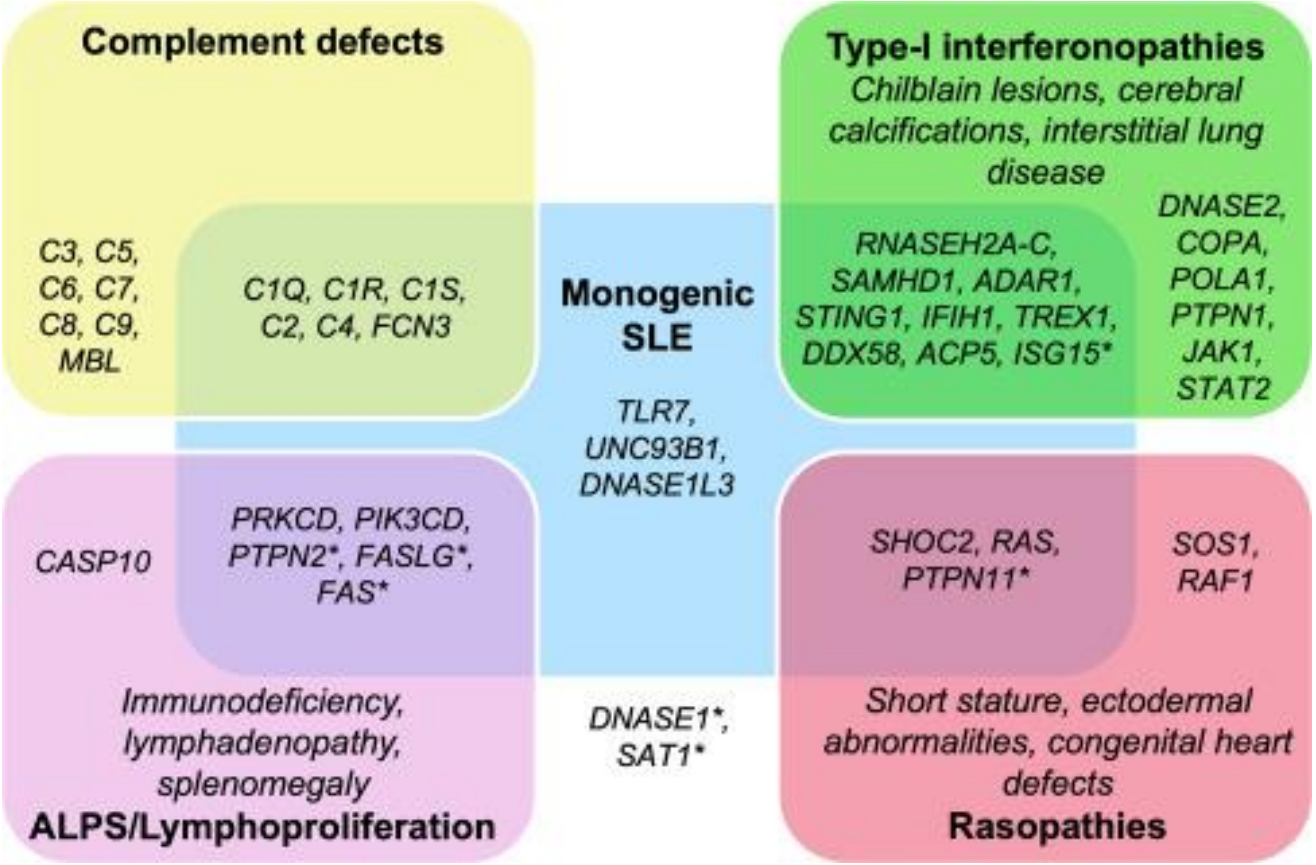


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   - Differences in efficacy (PD) → Not a concern in non-monogenic dz
   - Impacts on growth and/or development (safety)

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# Impacts on Growth / Development

| Dimensions | Impact of Steroids | Impact of Other Rheum Meds |
|---|---|---|
| **Linear growth (height)** | Short stature | JAKi? … no |
| **Metabolic syndrome** | Dyslipidemia/weight gain | JAKi: dyslipidemia/weight gain |
| **Bone development** | ↑ Rate of avascular necrosis | |
| **Puberty** | Can delay onset | Cytoxan: $1^{o}/2^{o}$ ovarian failure |
| **Brain development** | Alter brain plasticity<br>↓ White matter integrity<br>Impair growth of hippocampus<br>→ Difficulty w/ memory, mood, and attention | |
| **Immune system** | Largely reversible upon discontinuation | Cytoxan: longstanding impacts on lymphocyte # and subset ratios |

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   → Preclinical animal studies & **post-marketing safety**

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# Key Points

- Significant caution should be used when extrapolating from adult studies to children under age 5
- For children age 5+, we still need:
  - PK/dosing studies
  - Attention to growth/development perturbation signals in preclinical animal studies (could warrant further safety studies)
  - Emphasis on post-marketing drug safety (impacts on growth & development aren't apparent for years)
  - Every opportunity to get sick children with bad lupus off of high-dose corticosteroids and chemotherapy agents