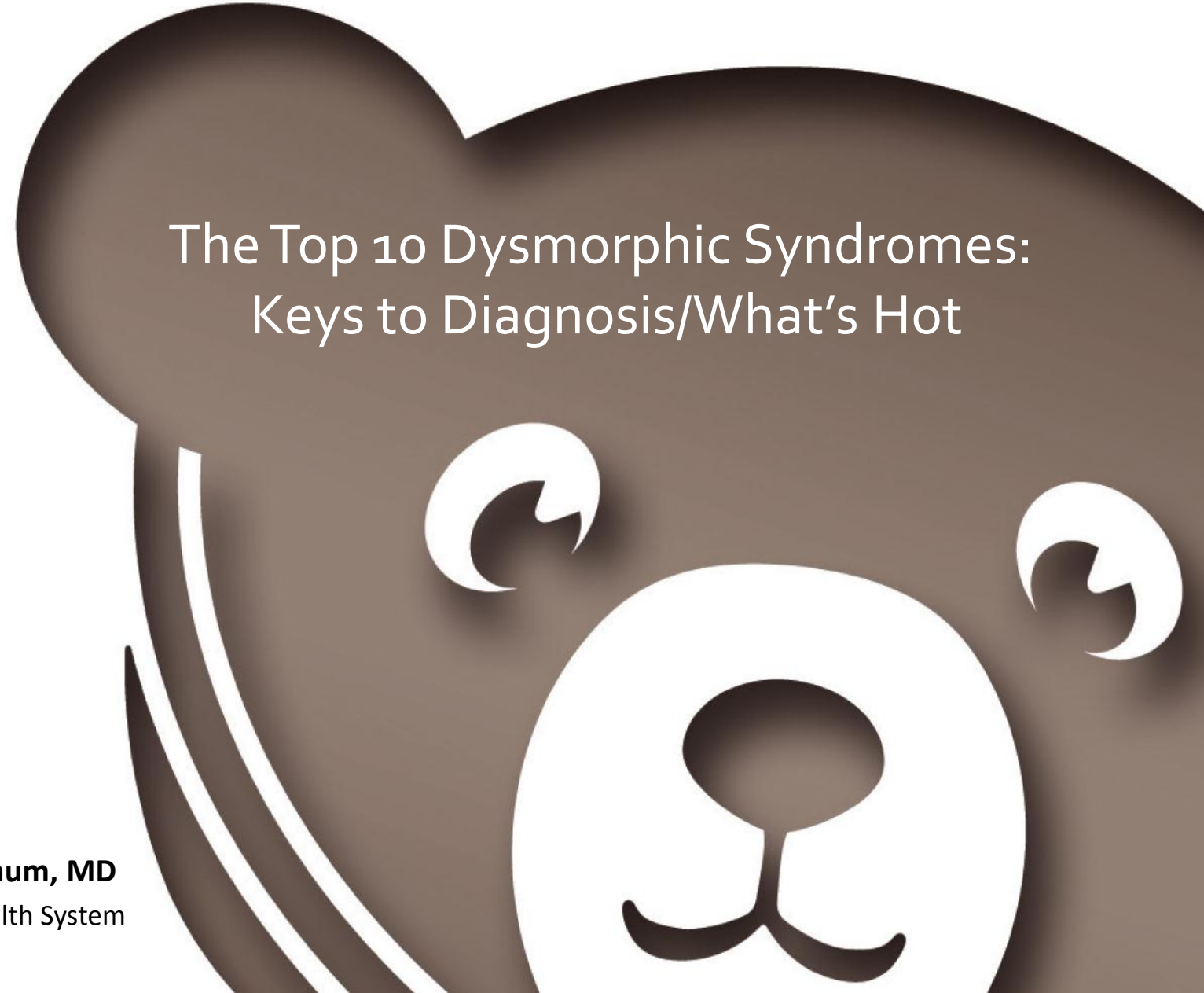
The Top 10 Dysmorphic Syndromes: Keys to Diagnosis/What's Hot



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Conflict of Interest Disclosure

Dr. Rosenbaum has no financial interests, arrangements, affiliations, or any bias with any of the corporate organizations offering financial support or educational grants for this program.

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Top 10 Dysmorphic Syndromes

- Keys to diagnosis/important clues
  - Expect variability in presentation
  - Be aware of heterogeneity
  - Low threshold for diagnosis
- Management of expected issues
- New advances/what's hot

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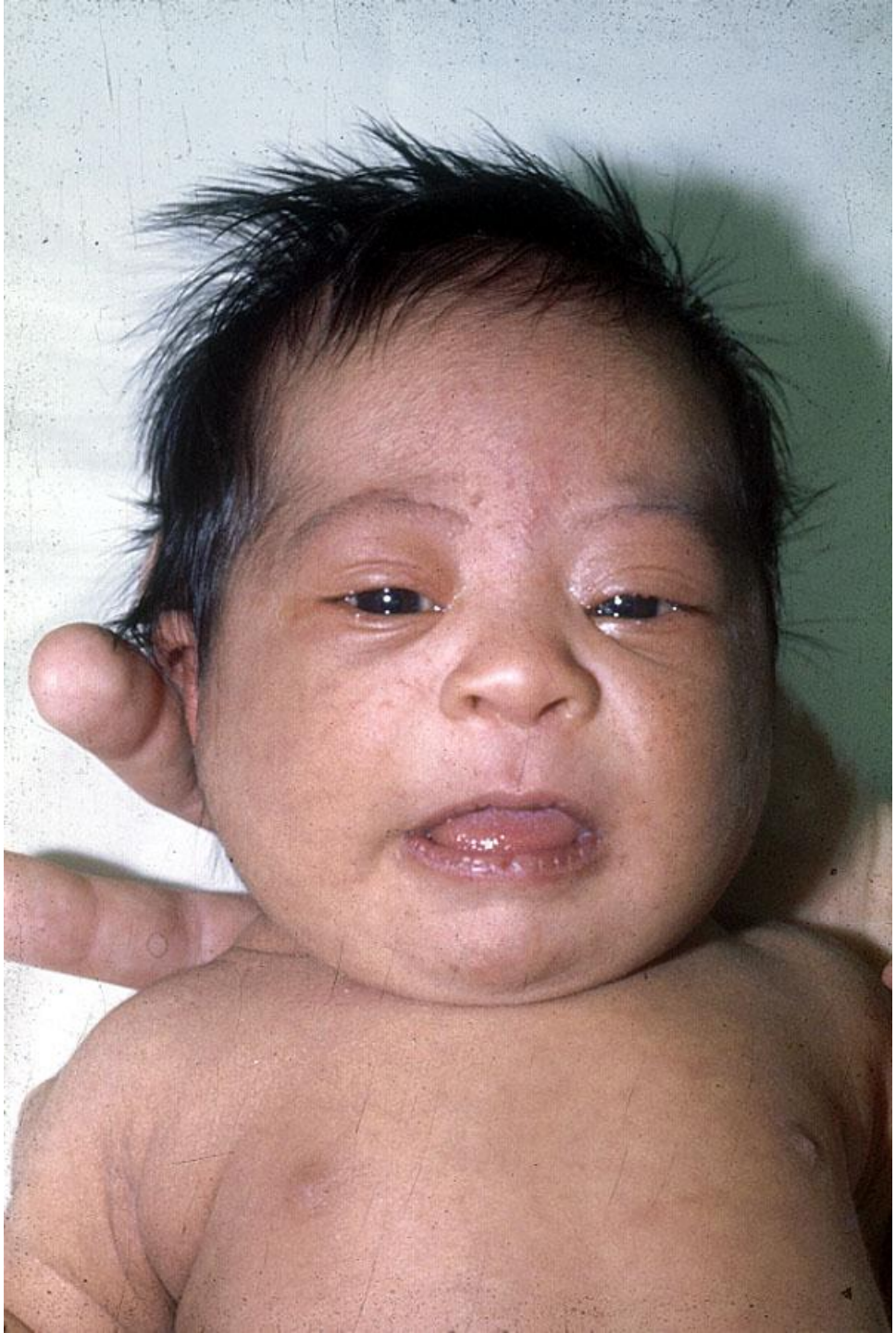
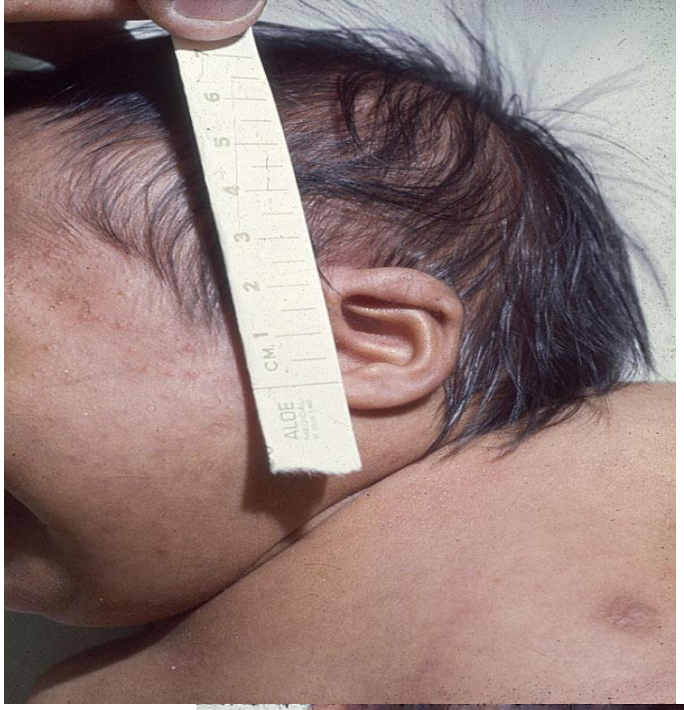
Down Syndrome

- Incidence 1/650 births; 1/270 mid-trimester
- Diagnosis based on number of minor variations; use available systems (Hall)
- Important to be comfortable with clinical diagnosis prior to cytogenetics

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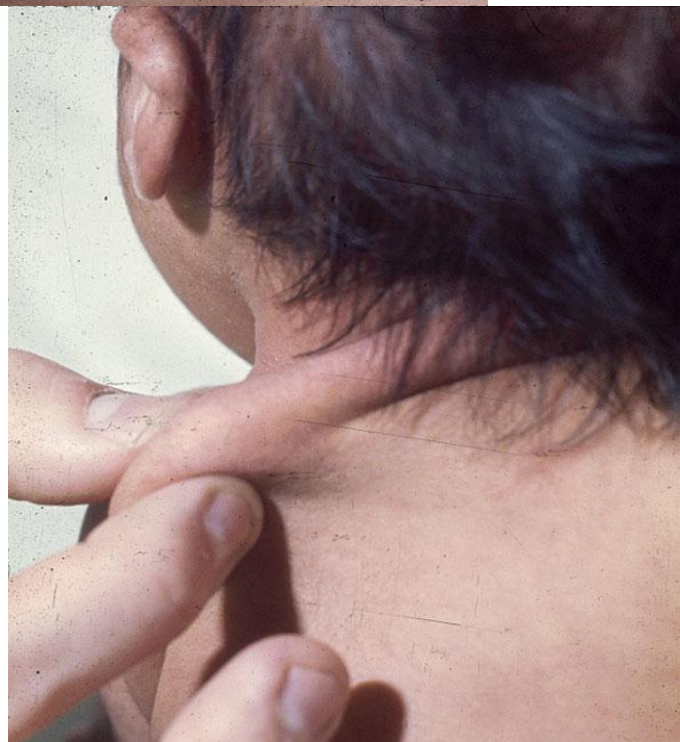

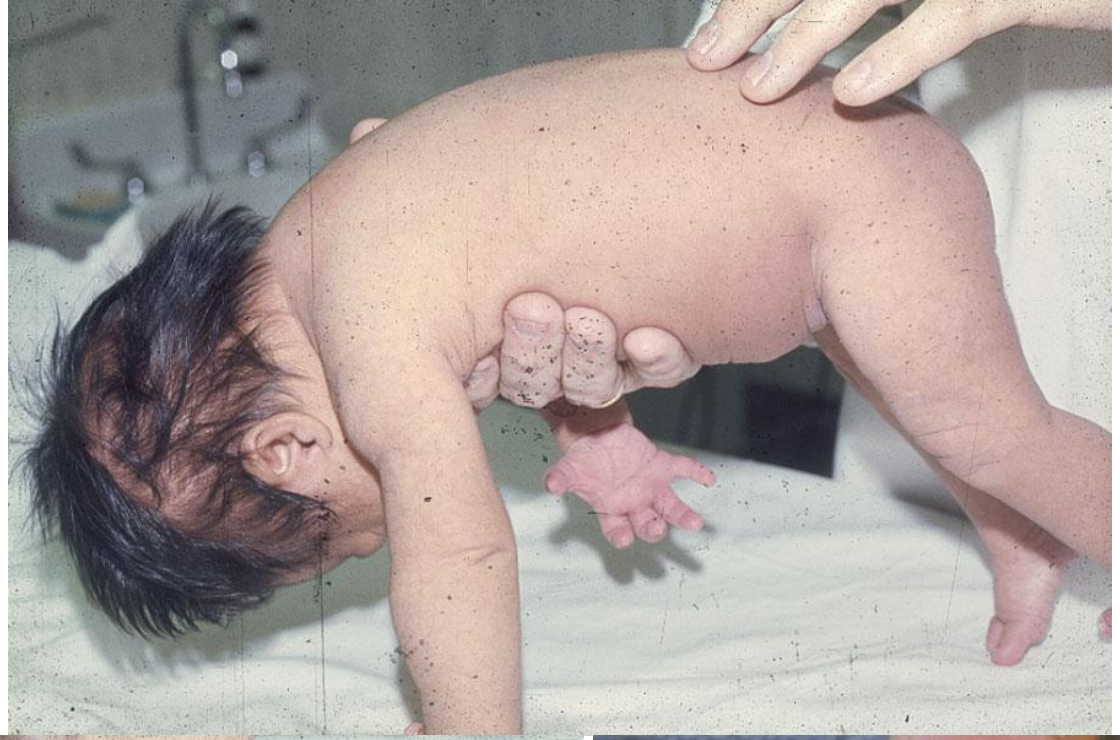

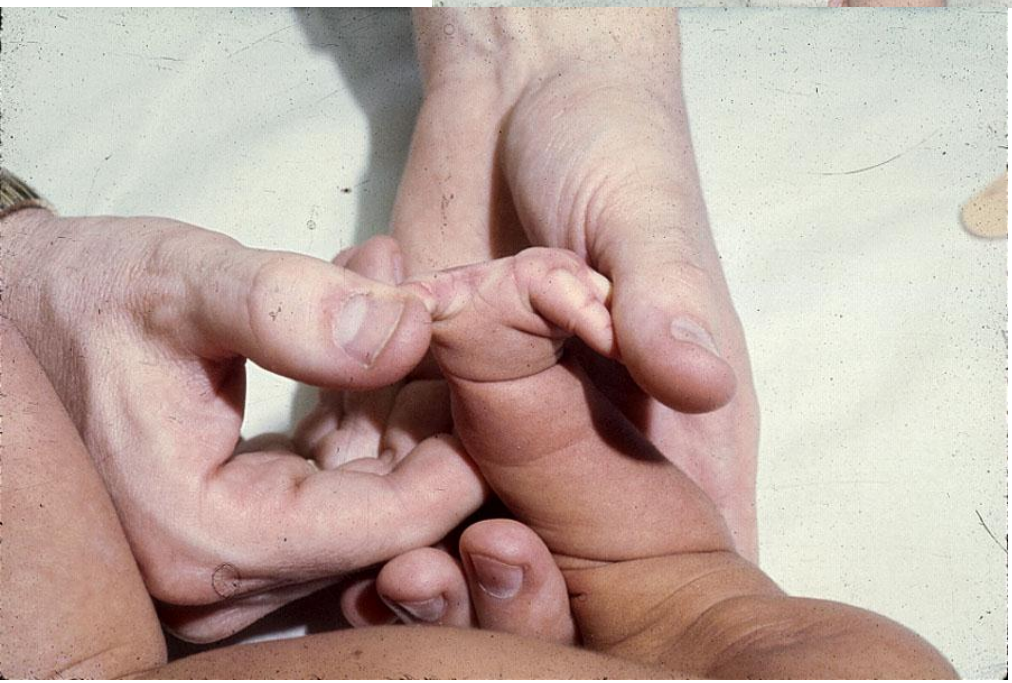

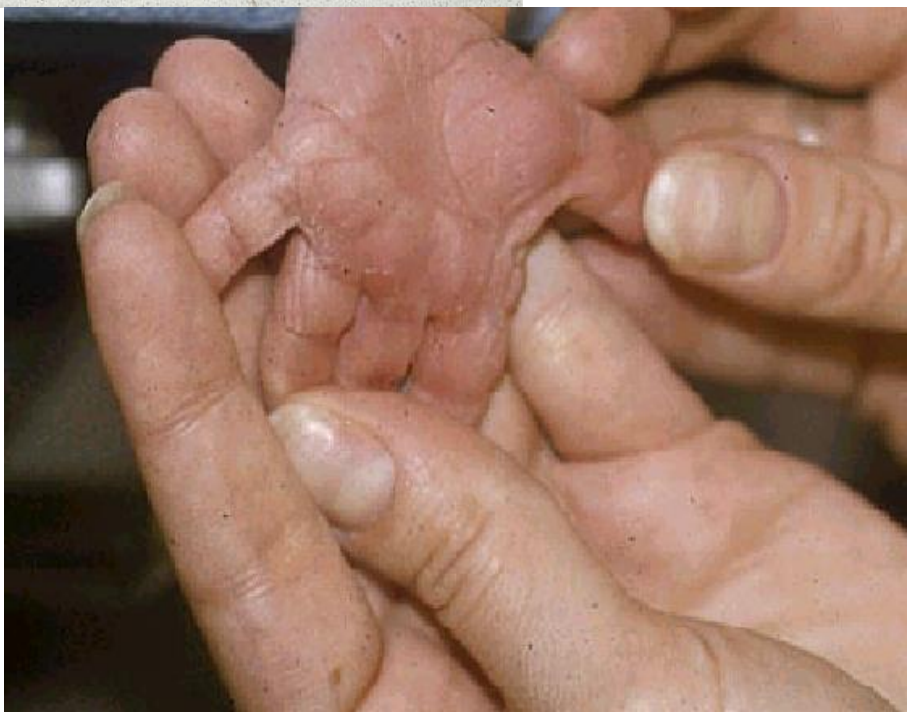

Down Syndrome-Management

- Chromosomes (rapid FISH)
- ECHO
- CBC, thyroid function
- Auditory screening
- Specialty involvement
- Intervention referral, support groups
- AAP Health Supervision for Children with Down Syndrome, 2011

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Down Syndrome-Advances

- Rapid diagnosis
- Improved outcomes?
- Pharmaceutical trials?
- Silent issues (thyroid, celiac, OSA)
- Significant risk for dyspraxia, attention deficit, autistic spectrum disorder

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Down Syndrome-Advances

- Maryland Senate bill 654: authorizing provision of information
- Non-invasive prenatal testing
  - Maternal cell-free DNA;1st trimester
  - Aneuploidy screen
  - ~99% detection rate for Down syndrome
- Digital remote diagnosis

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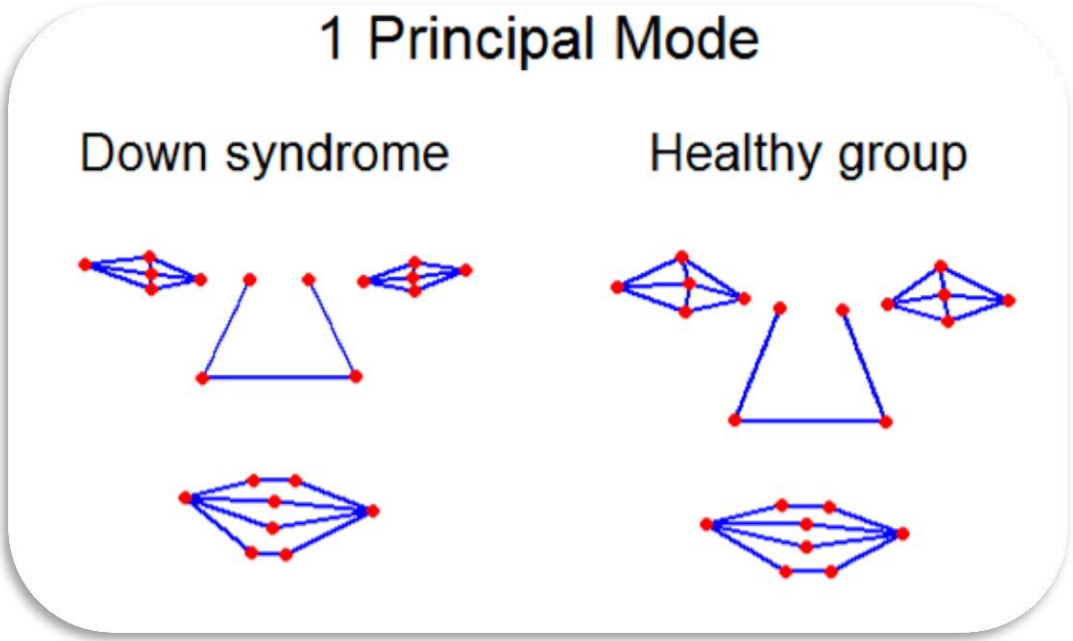
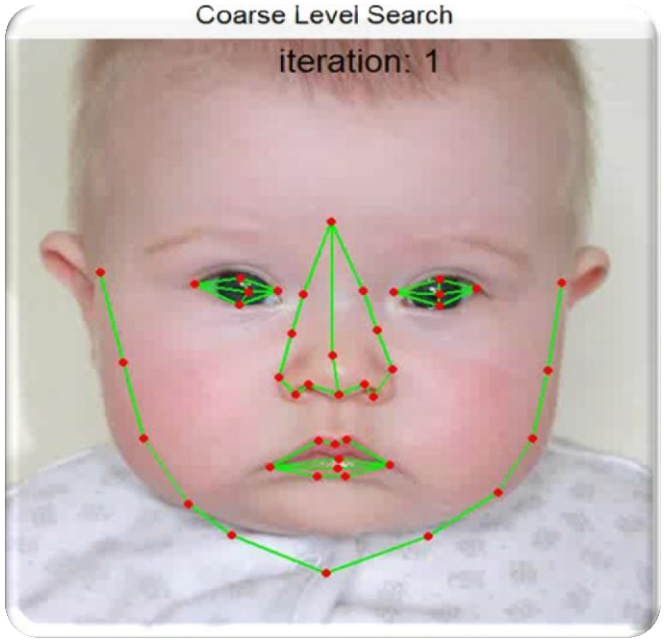
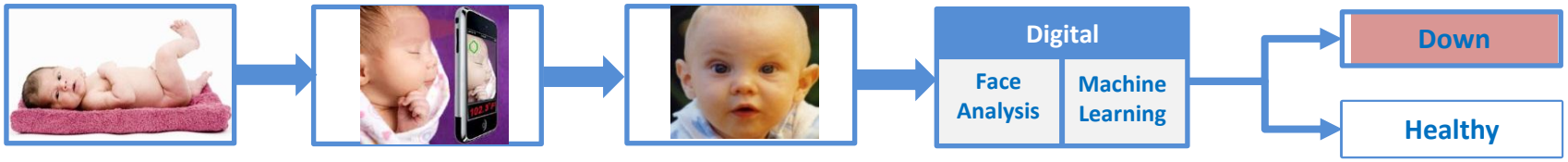
Digital Dysmorphology







Automatic Facial Analysis and Diagnosis from Photography

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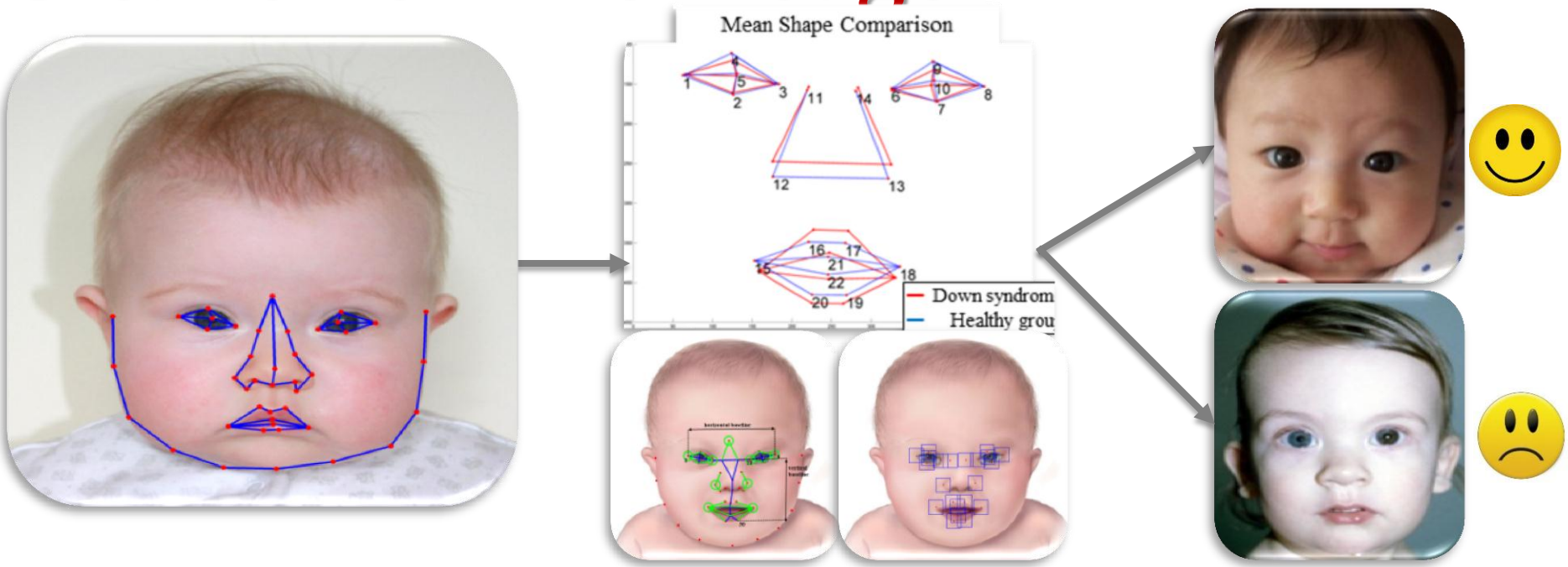
Creation of Knowledge



- Photography analysis for genetic screening
- Simple, non-invasive, accurate, affordable and instant
- Remote diagnosis (97% accuracy) – as dysmorphologists
- Various syndromes

Sex Chromosome Abnormalities

- Common, share similar frequency (1/1000)
- 47,XXY;47,XYY;47,XXX
- Prenatal diagnosis group large proportion
- Not dysmorphic
- Normal, but slightly decreased cognition
- Expressive language delay fairly universal

Sex Chromosomes-Advances

- Klinefelter syndrome
  - Early testosterone loading?
  - At-risk for academic difficulties
  - Increased risk for breast cancer
  - Risk for offspring with sex chromosome aneuploidy

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Turner Syndrome

- Incidence 1/2500 females
- High fetal lethality (~99% of conceptuses)
- Highly variable phenotype (1/3 nursery, 1/3 childhood, 1/3 adolescent)
- Diagnostic keys
  - Edema
  - Cardiac (BAV, coarctation)
- Normal cognition
- Abstract math reasoning

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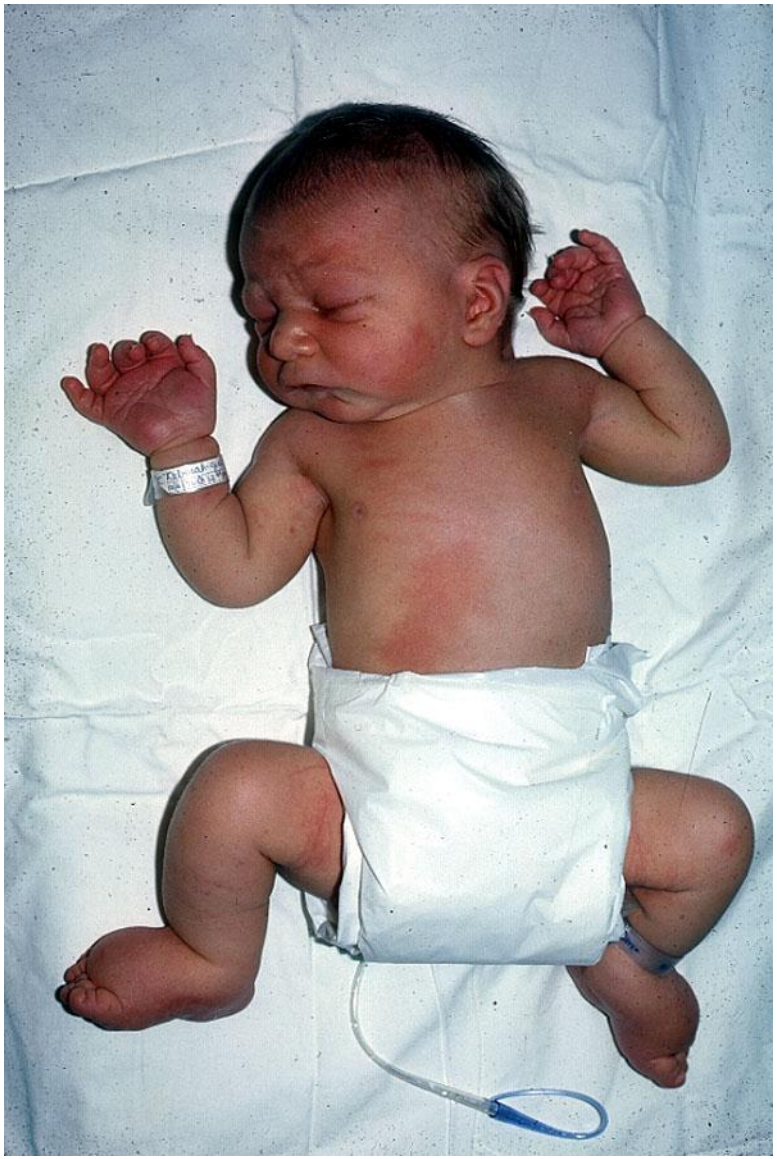

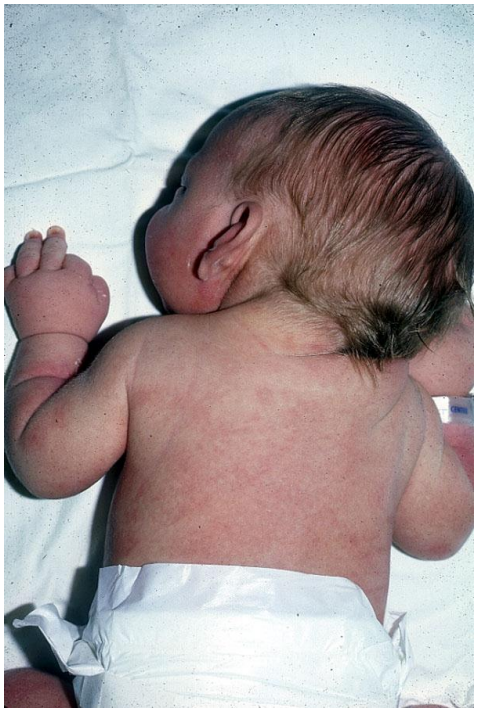

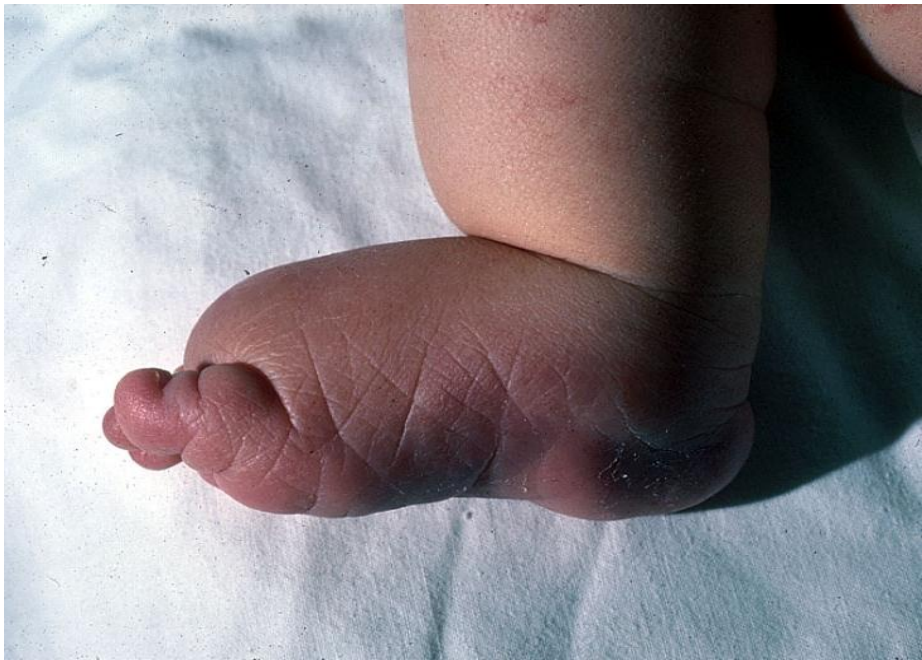

Turner Syndrome-Management

- Chromosomes (rapid FISH)
- Evaluation for additional malformations
  - ECHO, renal sono
- Thyroid function
- Specialty consultation

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Turner Syndrome-Advances

- Increased risk for auto-immune disorders (thyroid, diabetes, GI)
- Later-onset risk for aortic dilatation
- Growth hormone supplementation
  - Timing?
- Fertility
  - Assisted reproductive technologies

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Fragile X Syndrome

- Most common inherited cause of intellectual disability (1/2500 males, 1/5000 females)
- Secondary to expansion of CGG repeats
  - Full mutation >200; premutation 55-200
- Females more mildly affected
- Long face, prominent forehead & ears, large testes
- Behavioral phenotype (gaze aversion)

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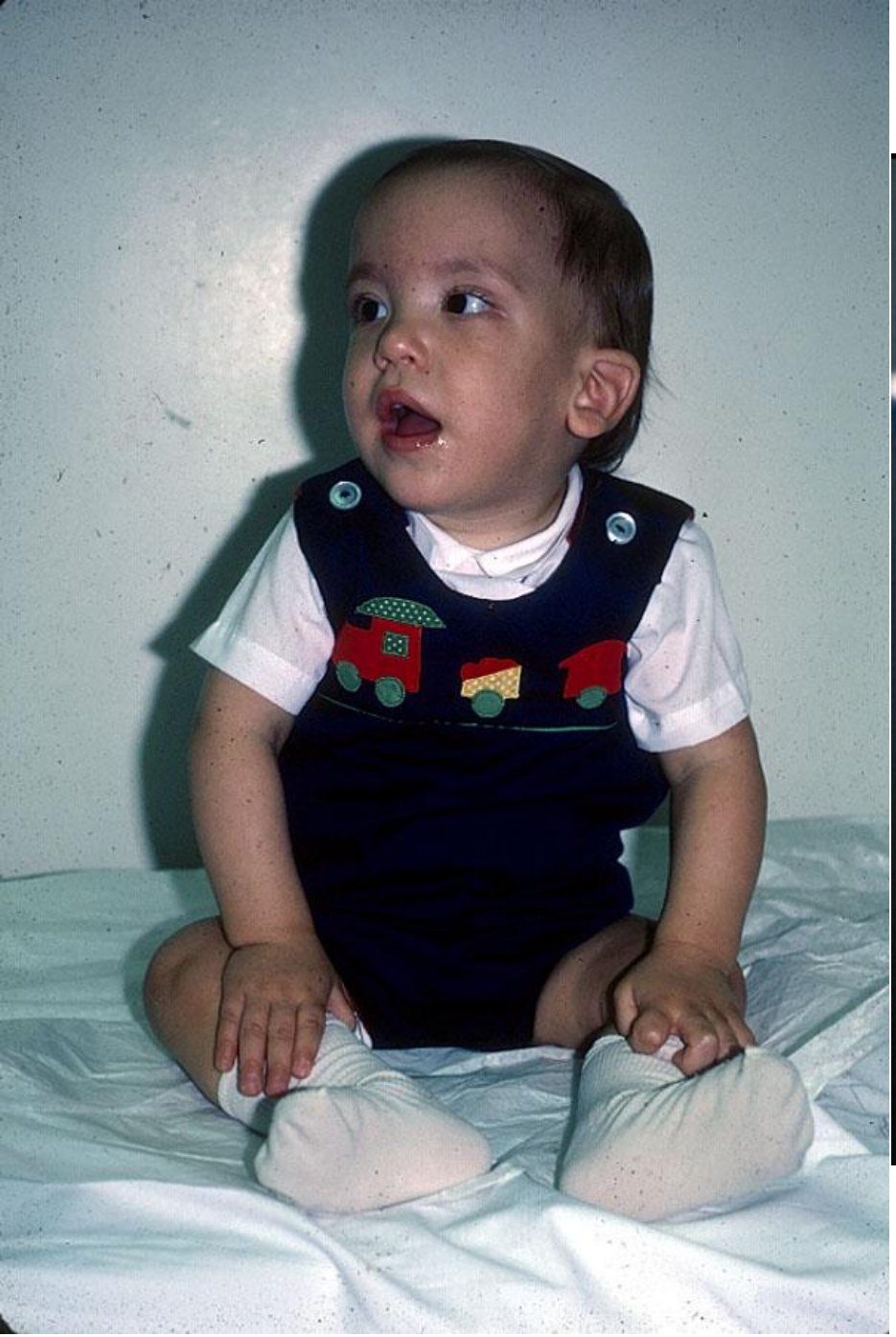

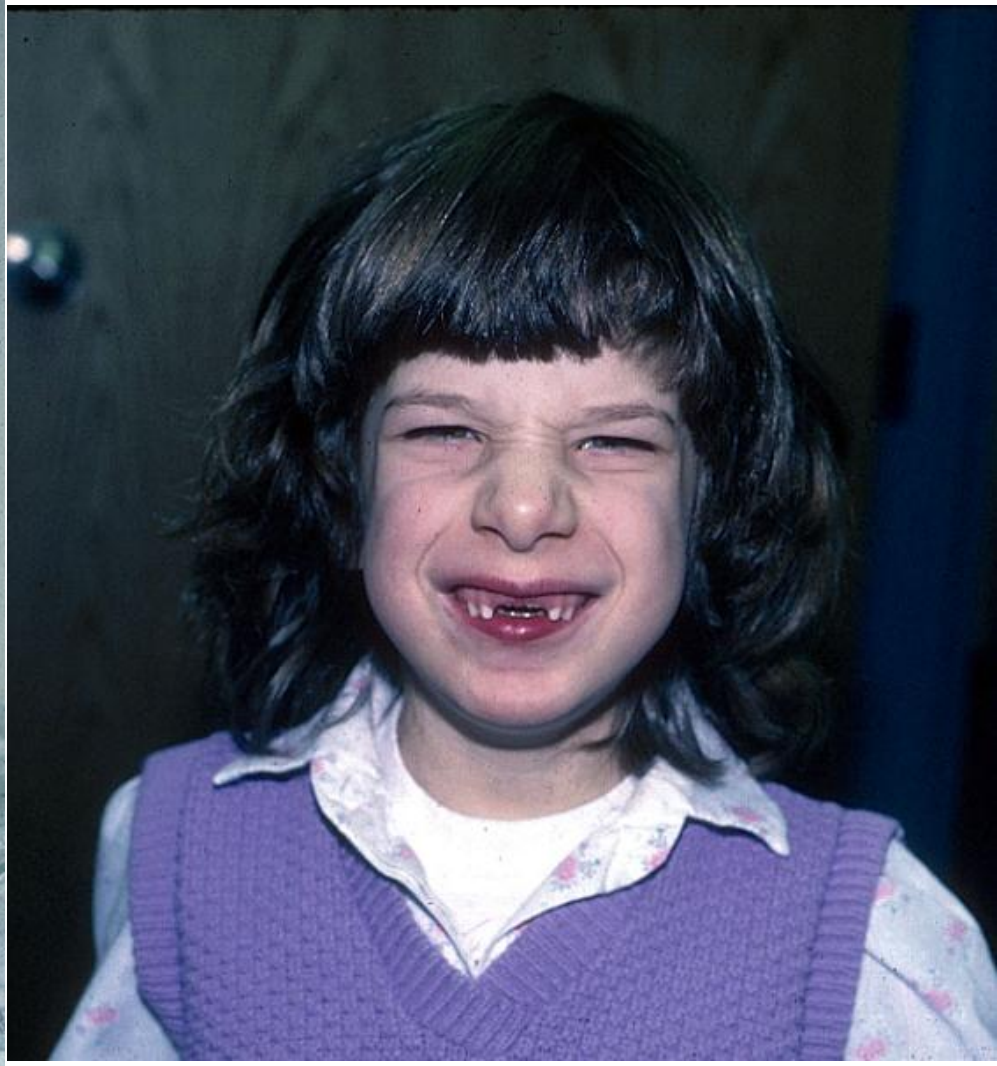

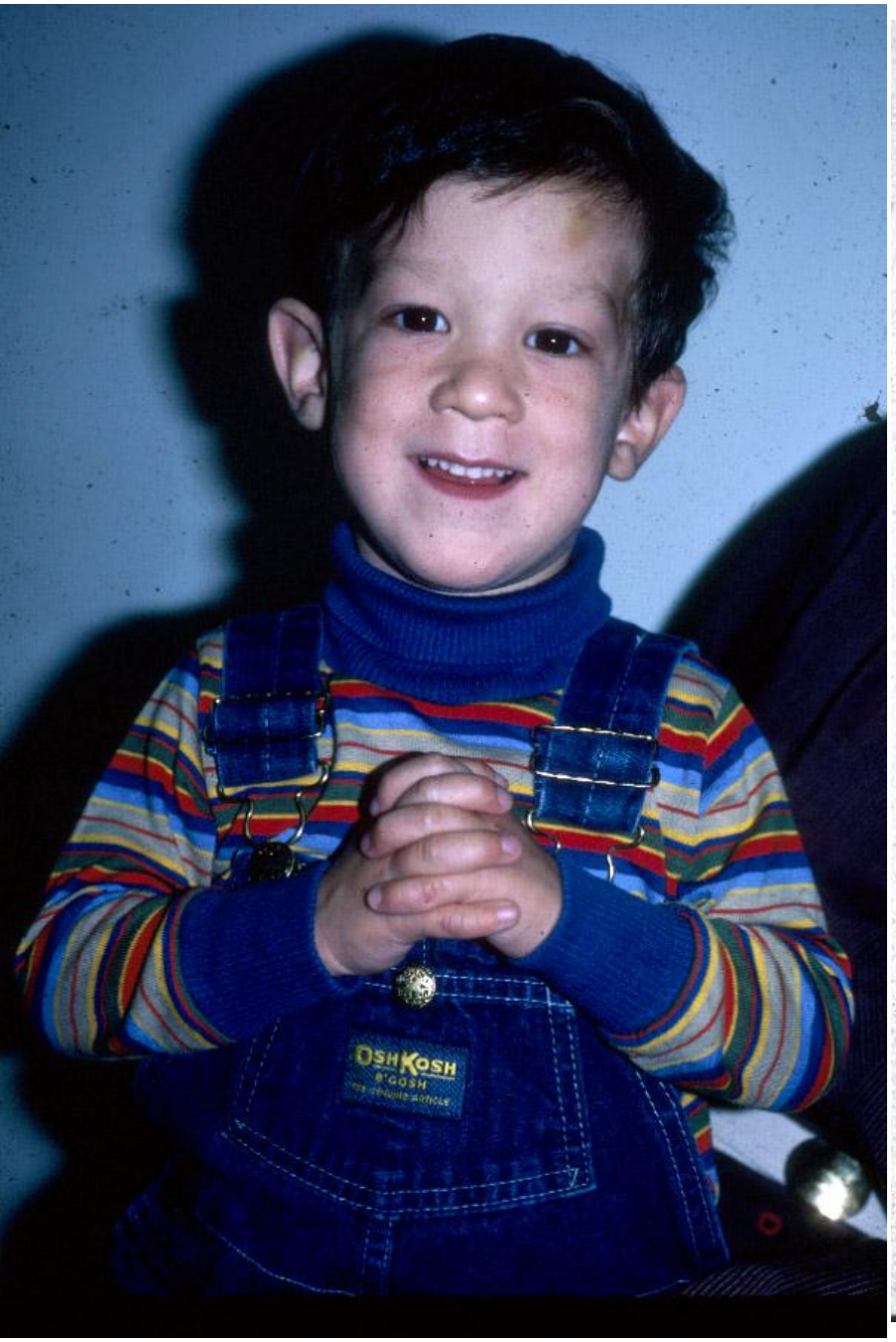
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Fragile X Syndrome-Advances

- Awareness of gray zone alleles (45-54)
- Refinement of risk for expansion/AGG interruptions
- Risks for premutation carriers
  - Premature ovarian failure
  - Fragile X tremor ataxia syndrome (FXTAS)
- Treatment protocols (minocycline)

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Fetal Alcohol Spectrum Disorder

- Alcohol-related birth defects (ARBD)
- Wide spectrum; evolves over time
- Most common preventable cause of birth defects
- 2-3/1000 births
- Classic FAS (microcephaly, ptosis, short palpebral fissures, washed-out philtrum)

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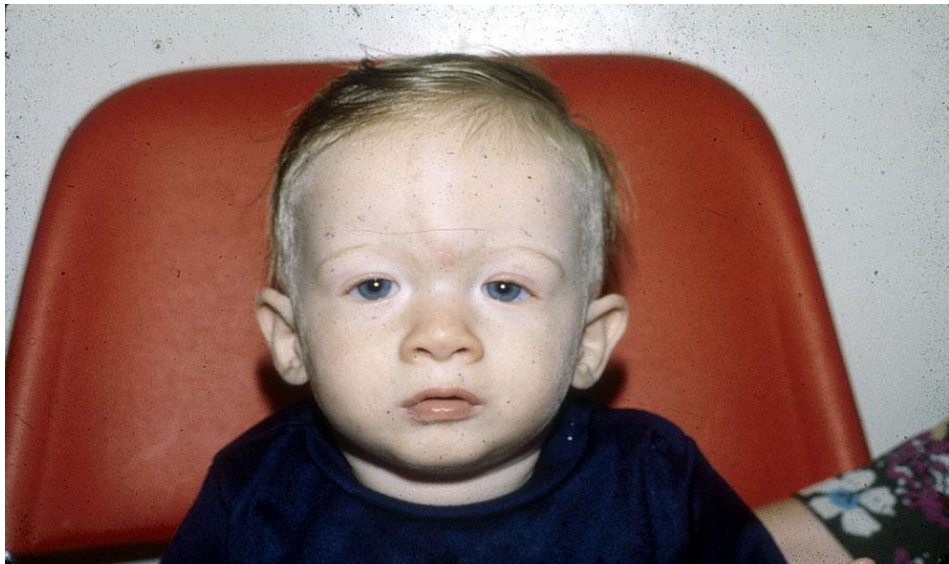

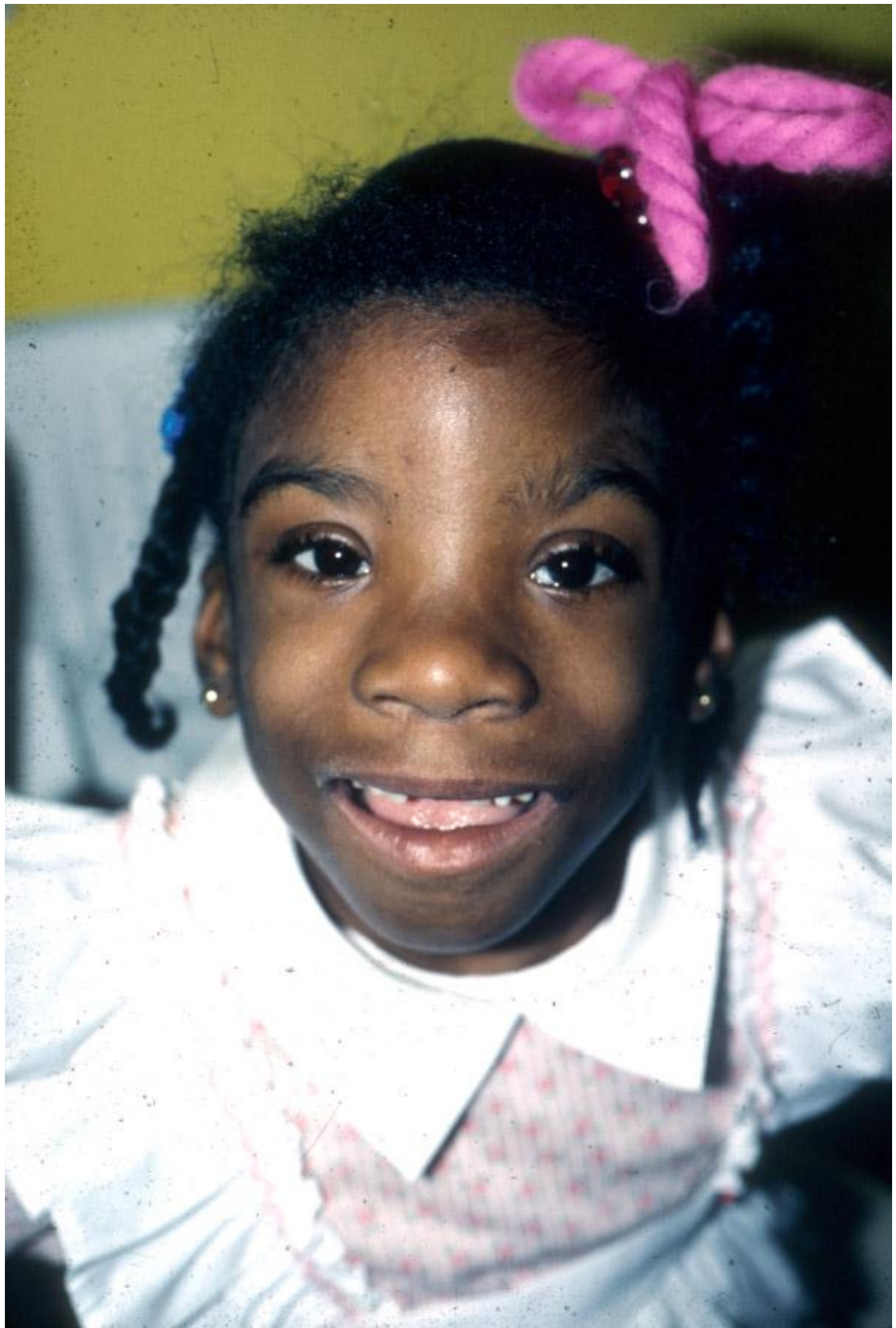

FASD-Advances

- Spectrum encompasses infants with exposure, minimal variations (IOM)
- Epidemic in some international areas
- MD ARBD legislation

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Neurofibromatosis

- 1/3000 births; 50% new; 70% mild
- Member of RAS/MAPK family
- NIH consensus criteria misleading <3 yrs
  - 6 or more CALS >0.5 cm
  - Axillary, inguinal freckling
  - Bony dysplasia
  - Positive family history
- Neurodevelopmental differences common

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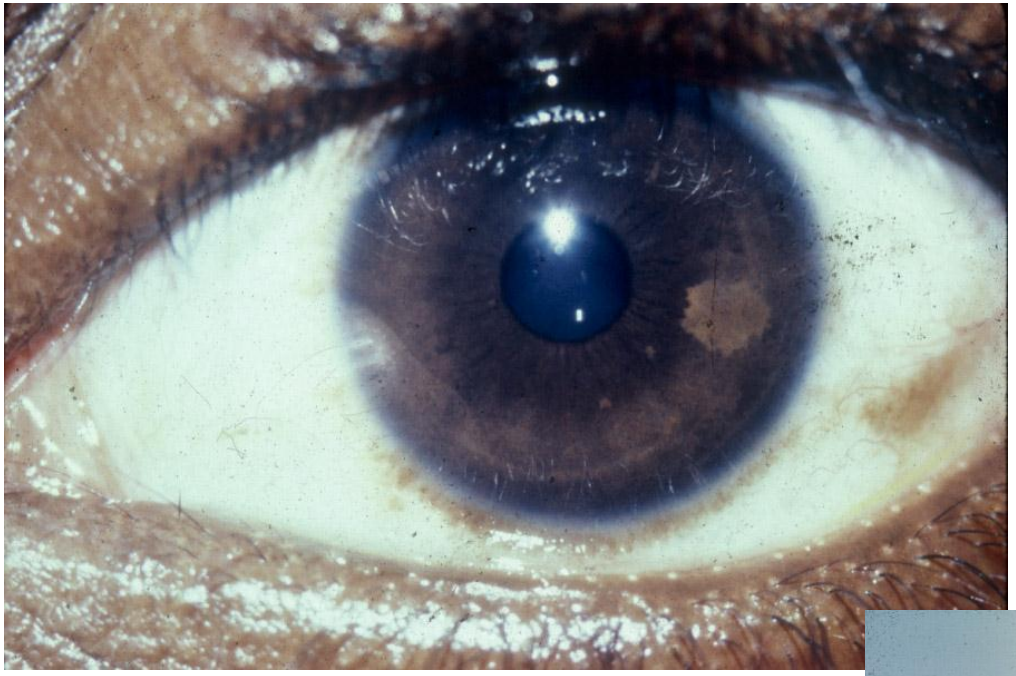

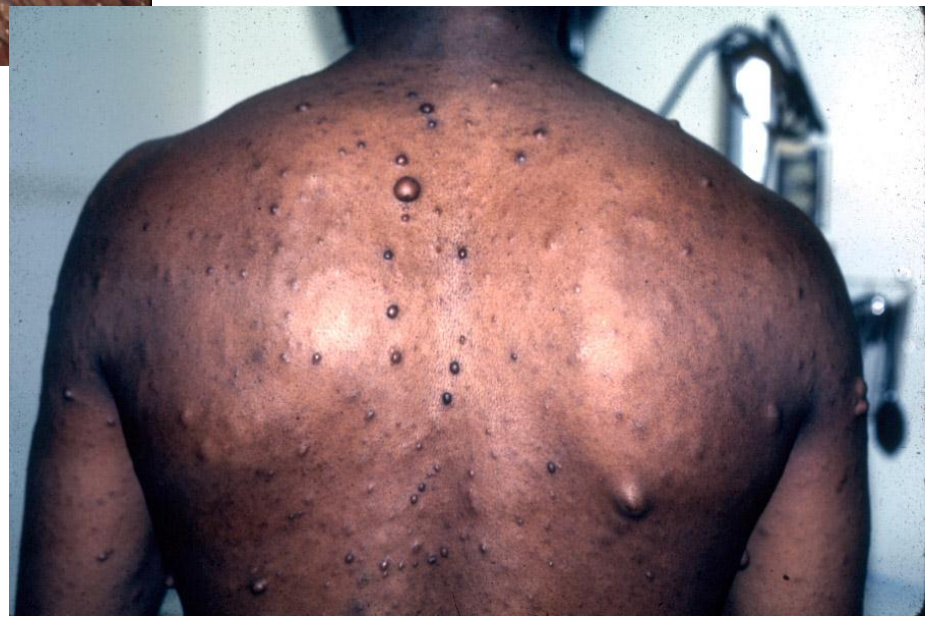

Neurofibromatosis-Advances

- 1/3 of patients with “Noonan” phenotype
- SPRED1/Legius syndrome (spots only)
- Controversies?
  - Baseline MRI (23% with optic pathway lesions)
  - Treatment options

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RAS/MAPK Syndromes

- Includes Noonan syndrome, CFC syndrome, Costello syndrome (11 genes in pathway)
- Incidence 1/5000 births
- Variable/overlapping phenotype
- Diagnostic keys
  - Macrocephaly/LGA
  - Pale irises, ptosis
  - Redundant nuchal skin
  - Congenital heart disease (pulmonary stenosis, cardiomyopathy)

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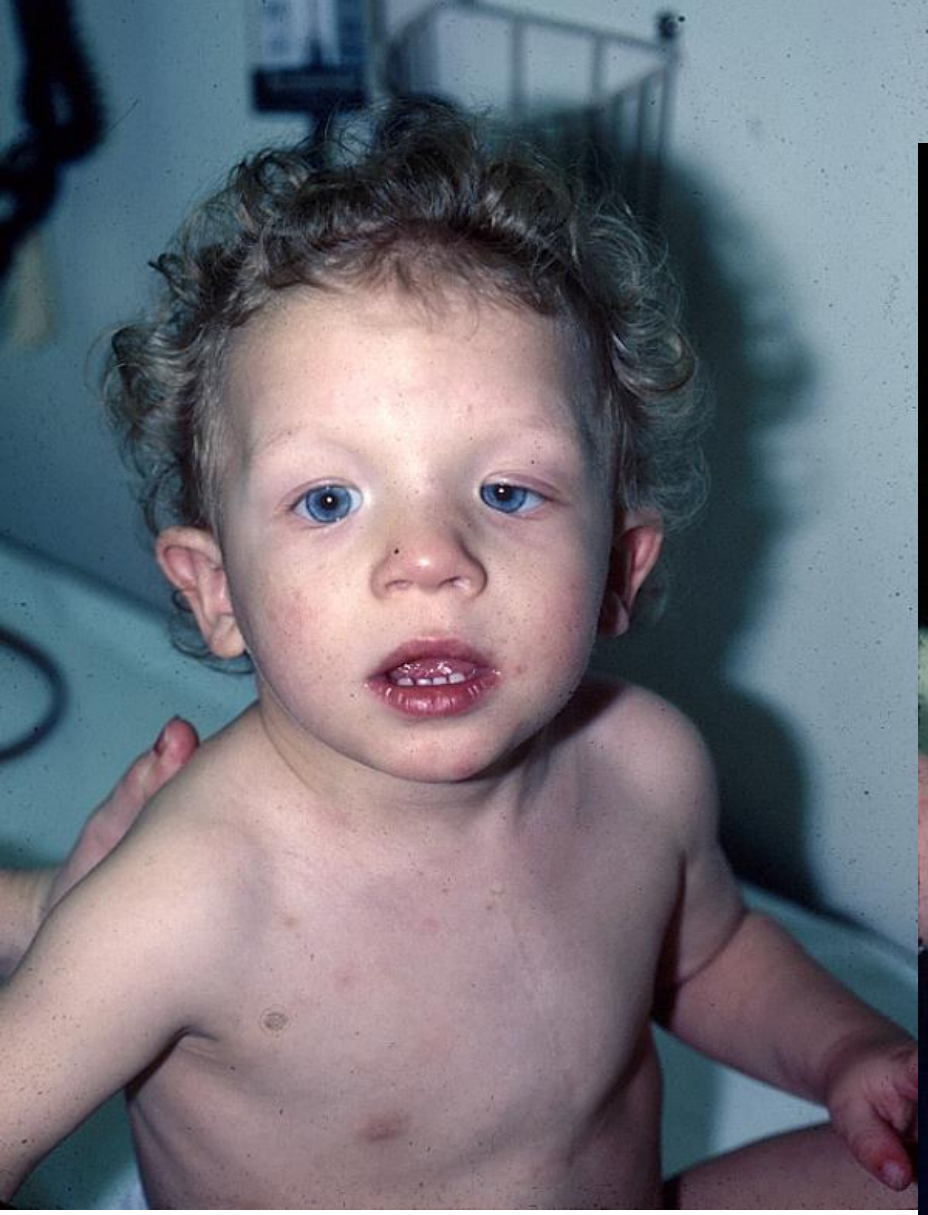

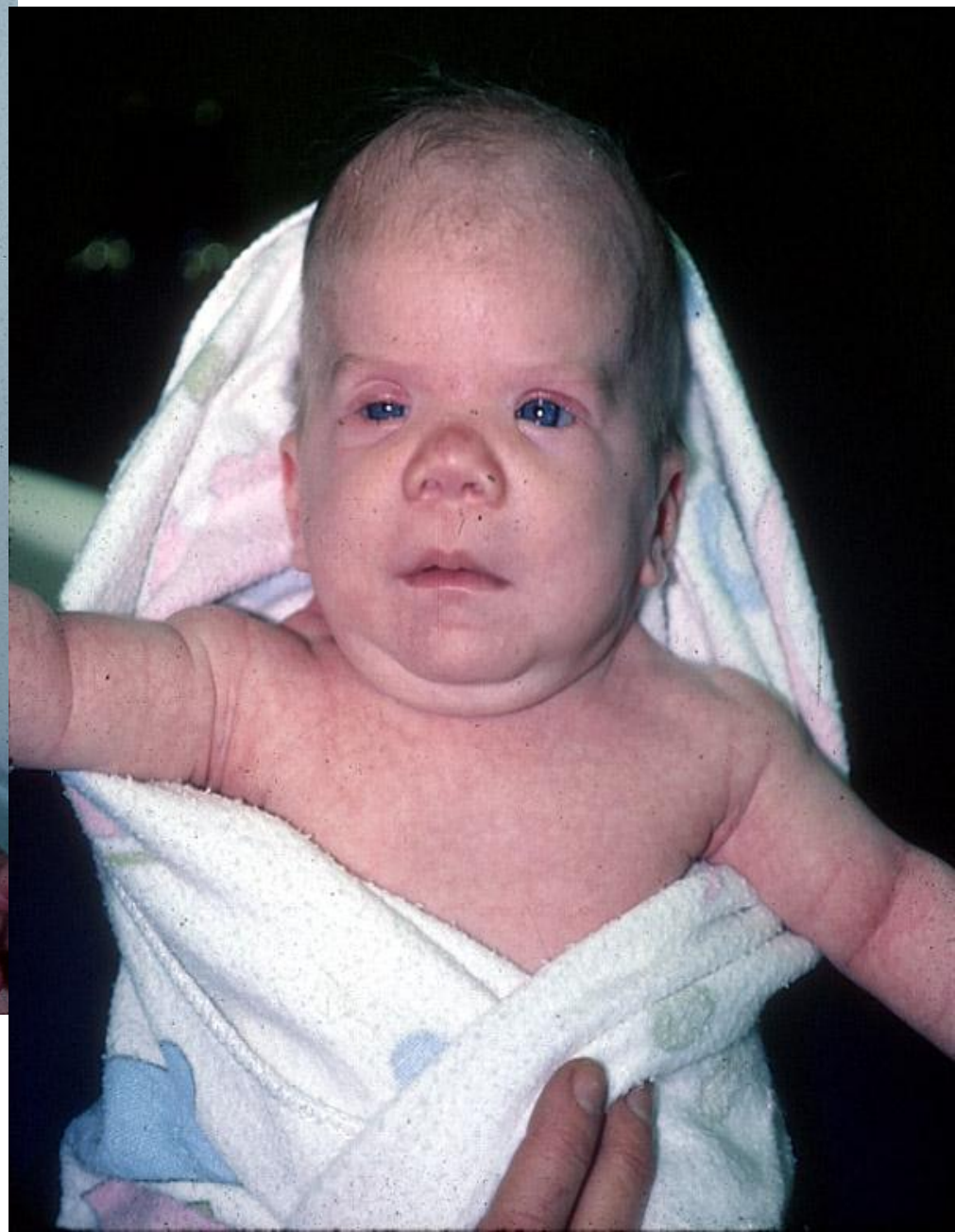

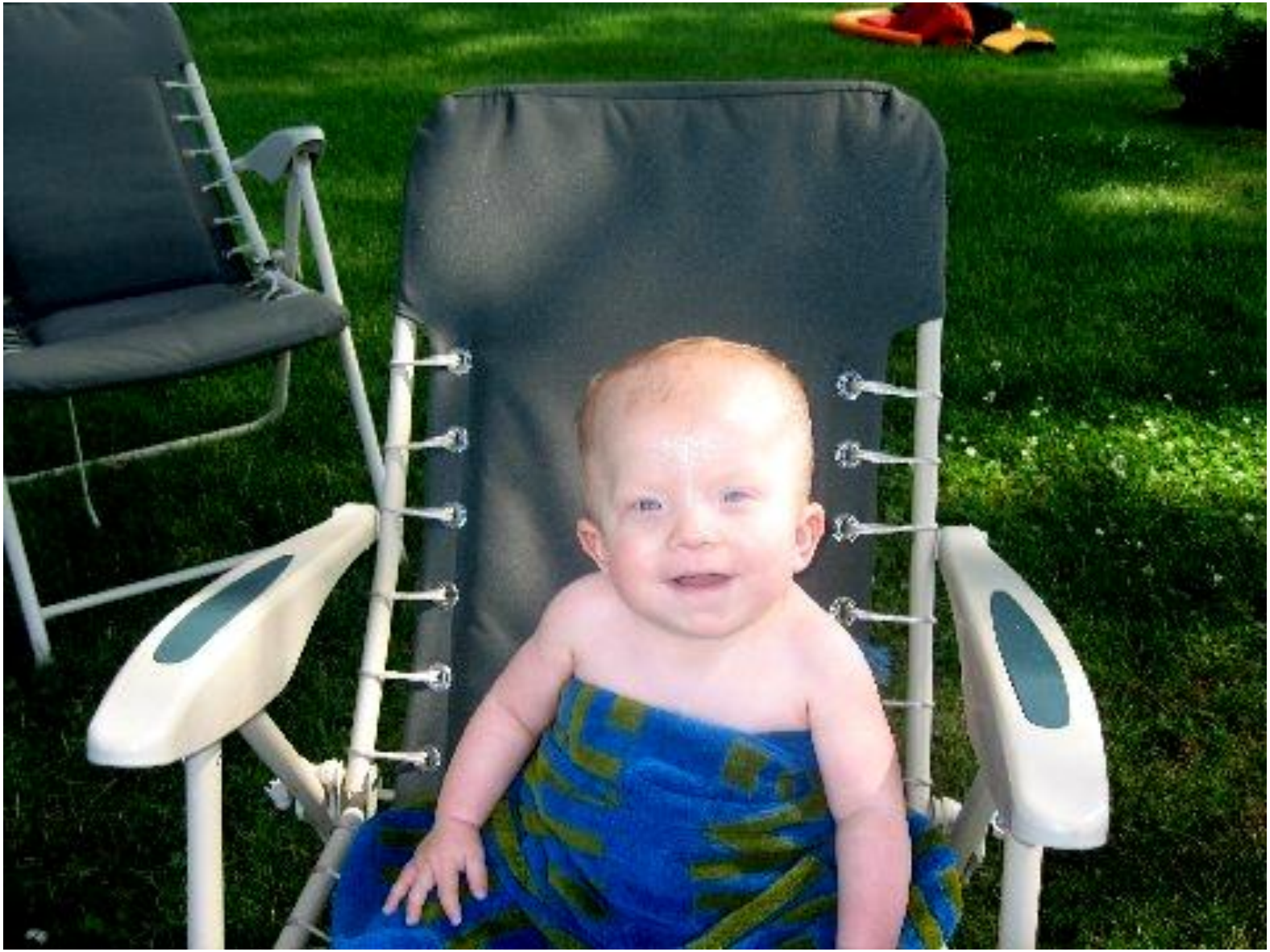

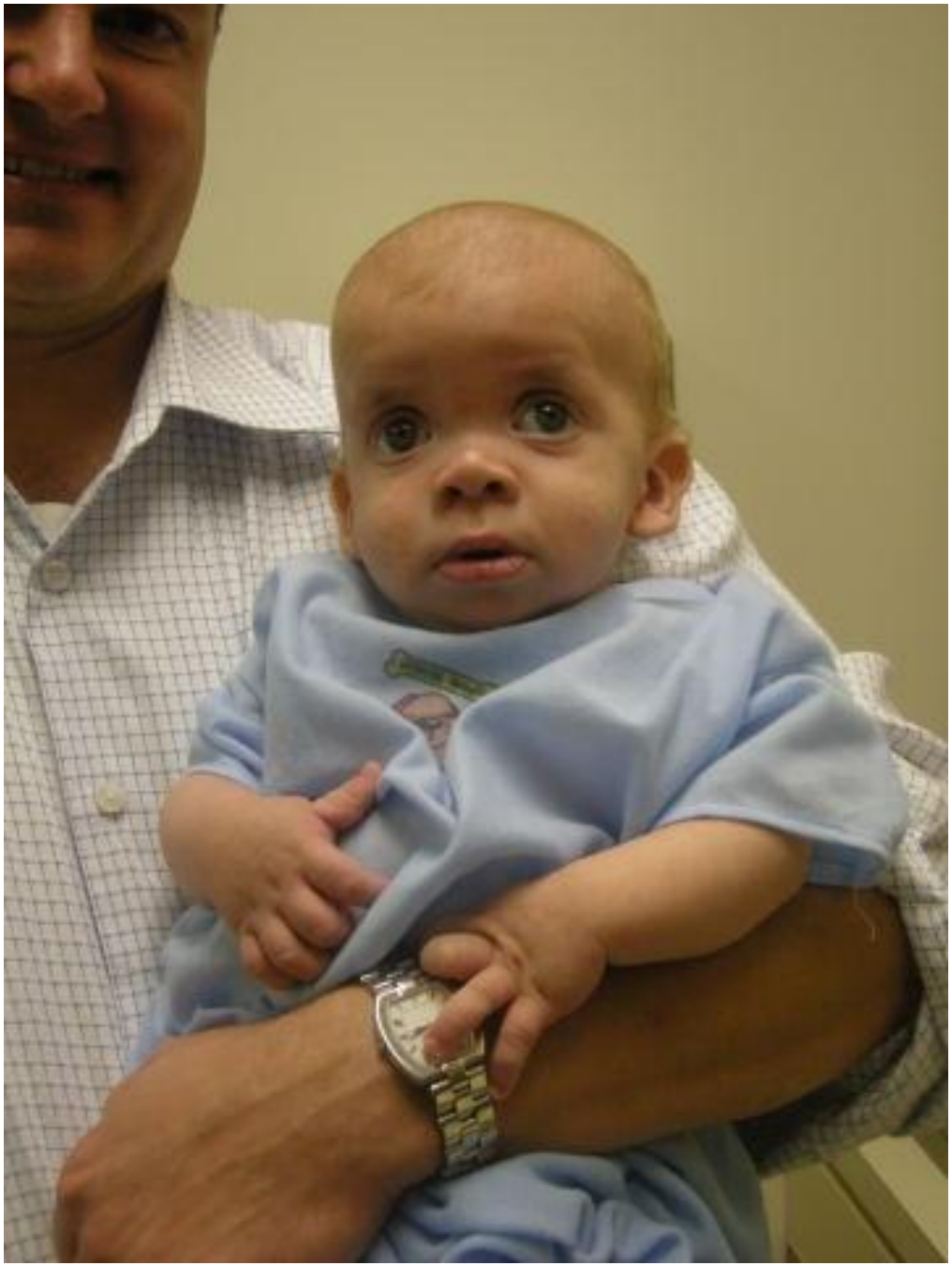

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Noonan Syndrome-Management/Advances

- MAPK chip array
- ECHO
- CBC
- Renal sono
- Increased awareness bone marrow dysfunction, pediatric tumors (HRAS)
- Growth hormone supplementation

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Marfan Syndrome

- Pediatric disorder; easily overlooked
- Incidence 1/15,000 births; 50% new
- Life-changing diagnosis
- Myopia, dolichostenomelia, arachnodactyly, mitral valve prolapse
- Differential: mitral valve prolapse-Marfanoid habitus syndrome, homocystinuria

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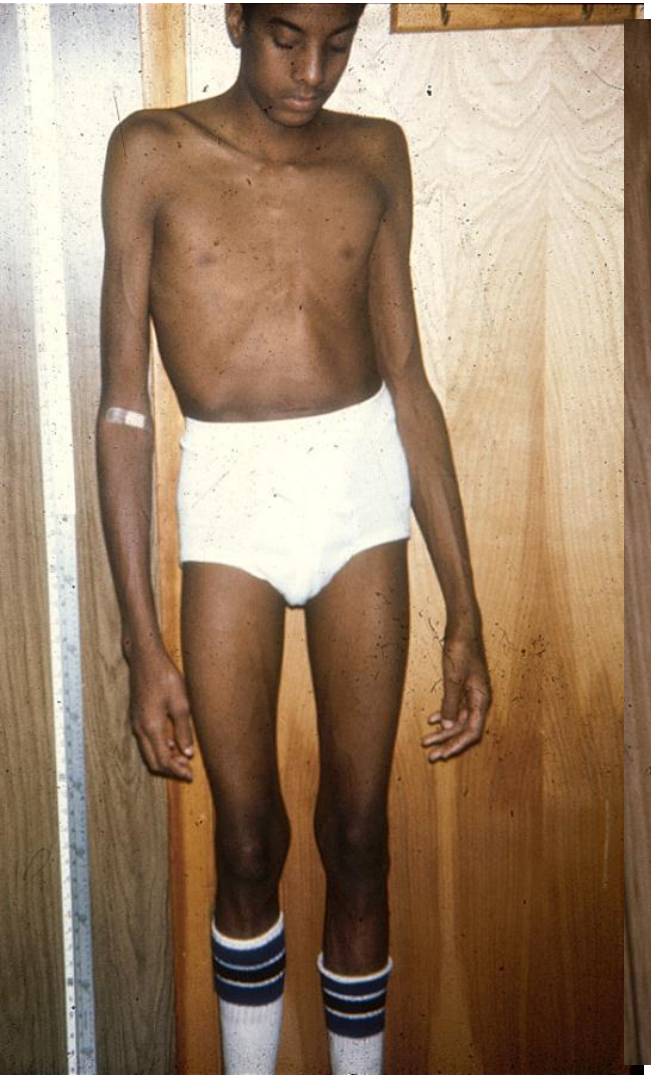

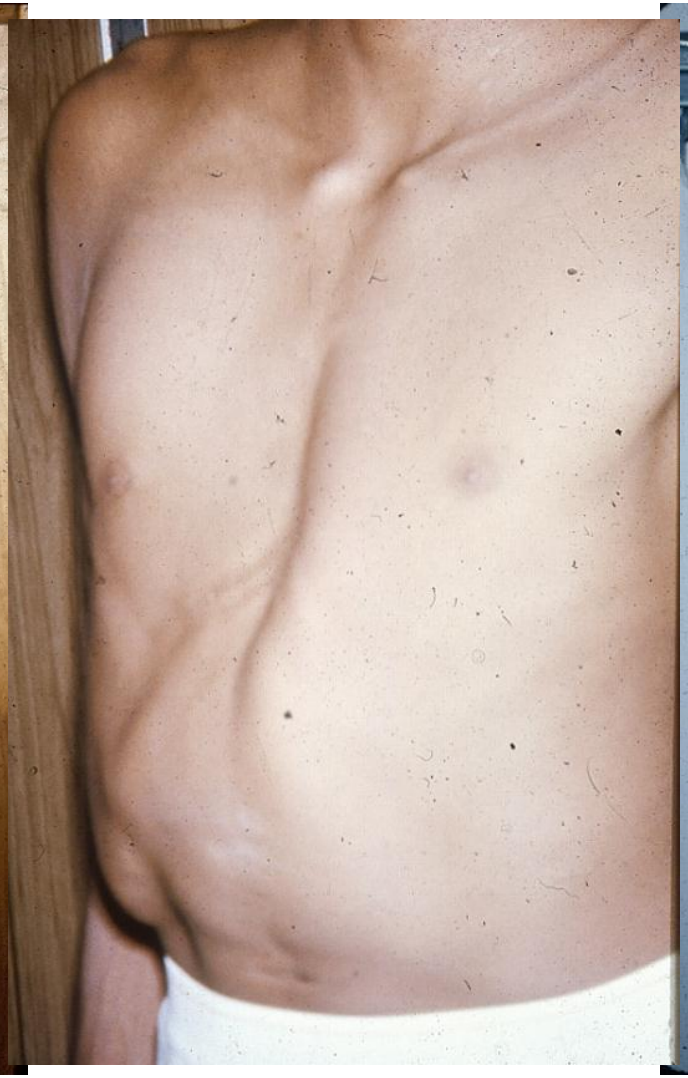

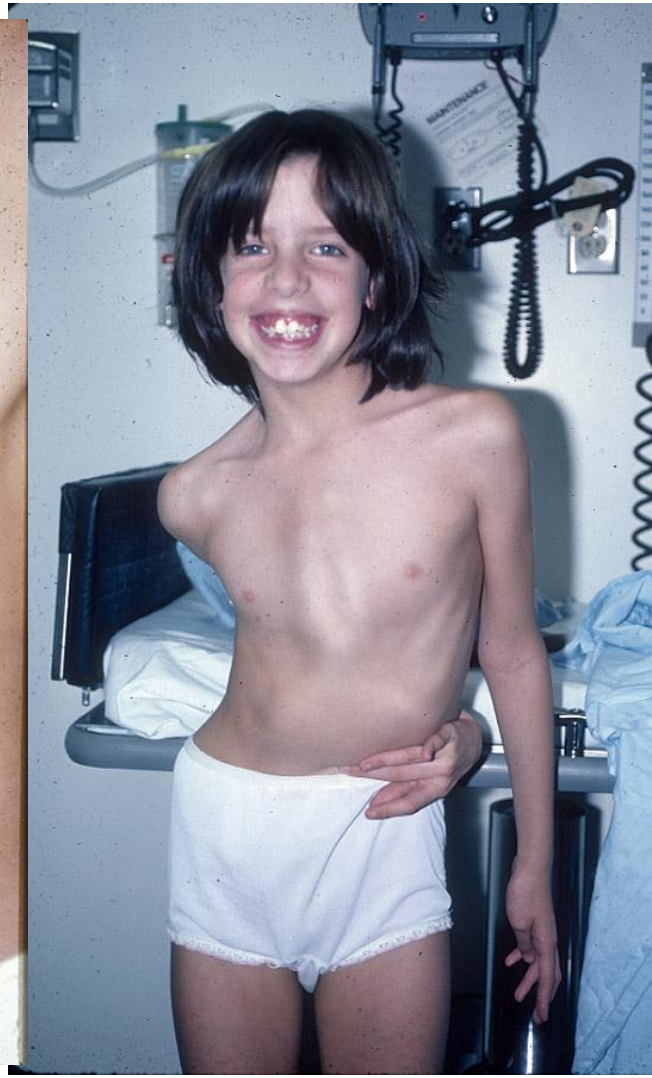

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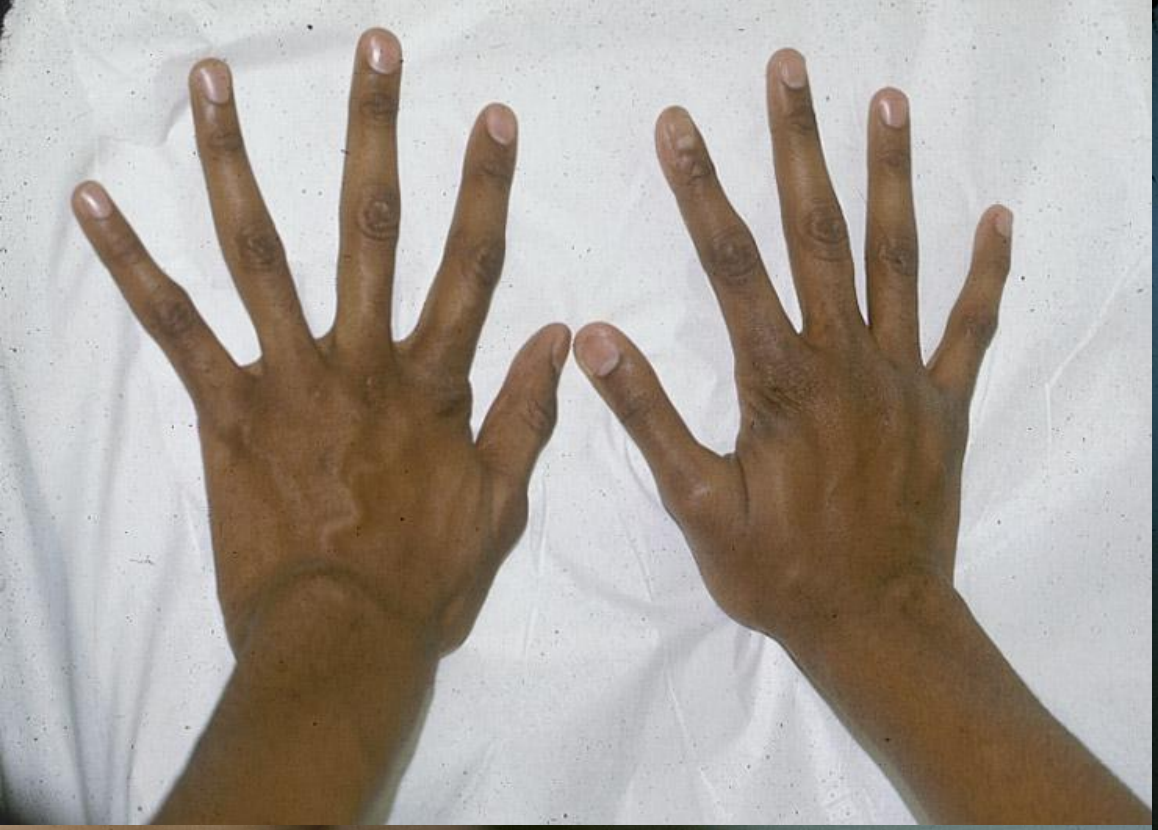

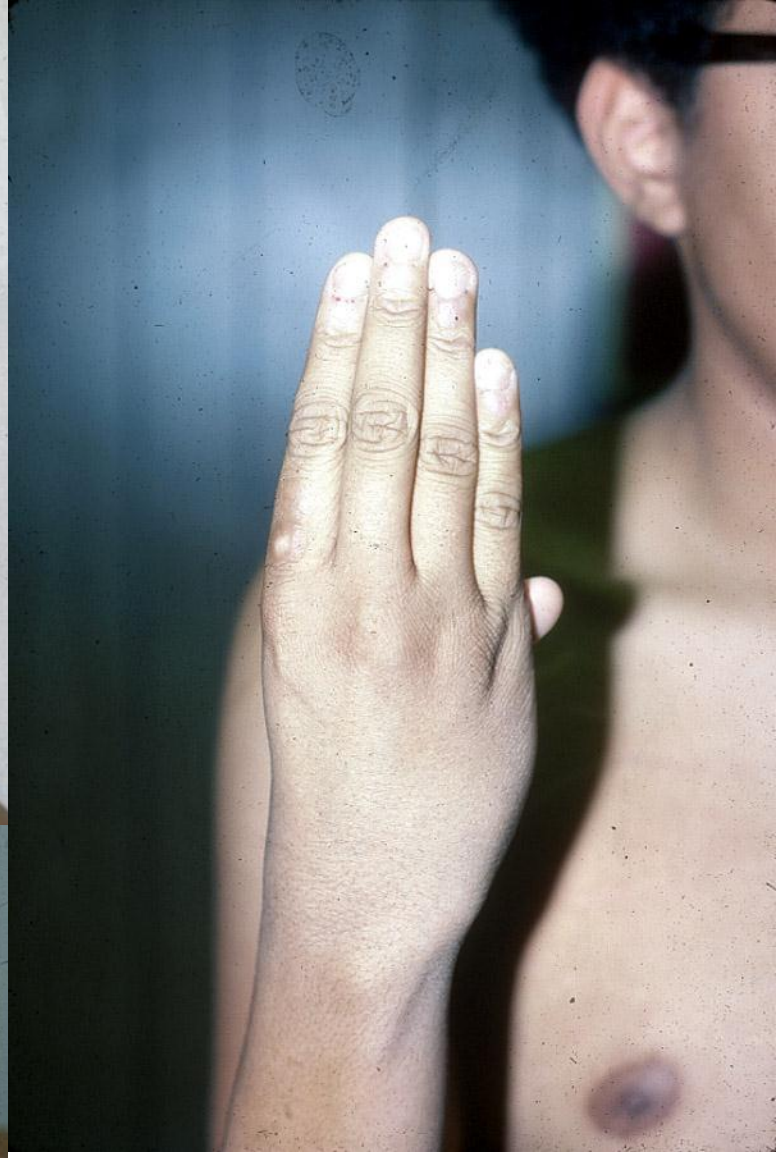

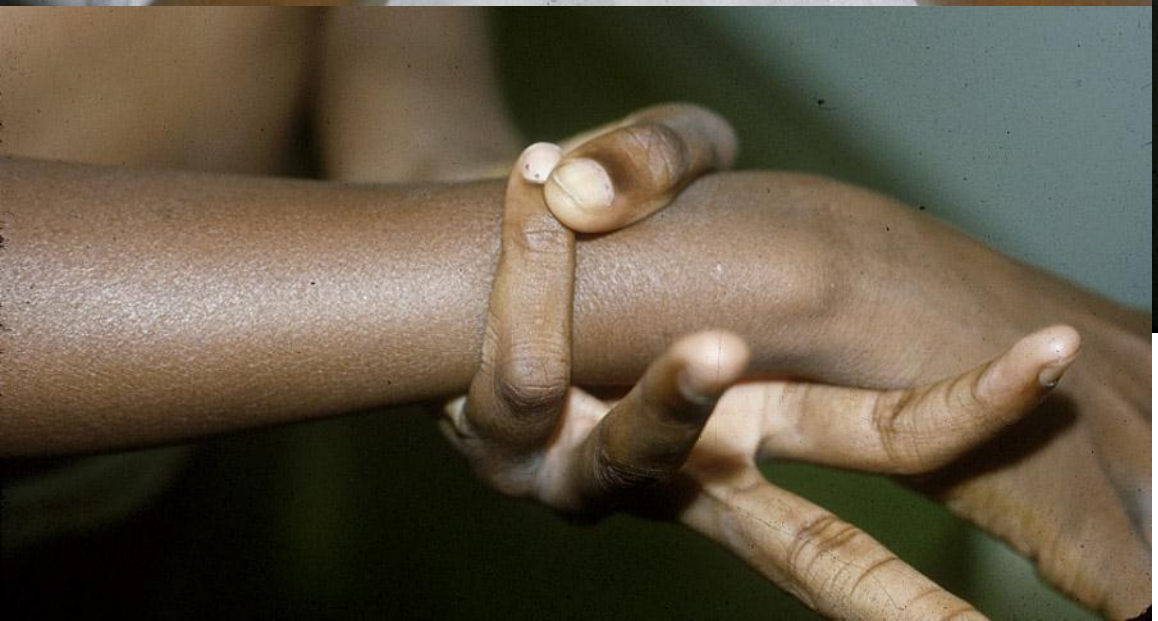

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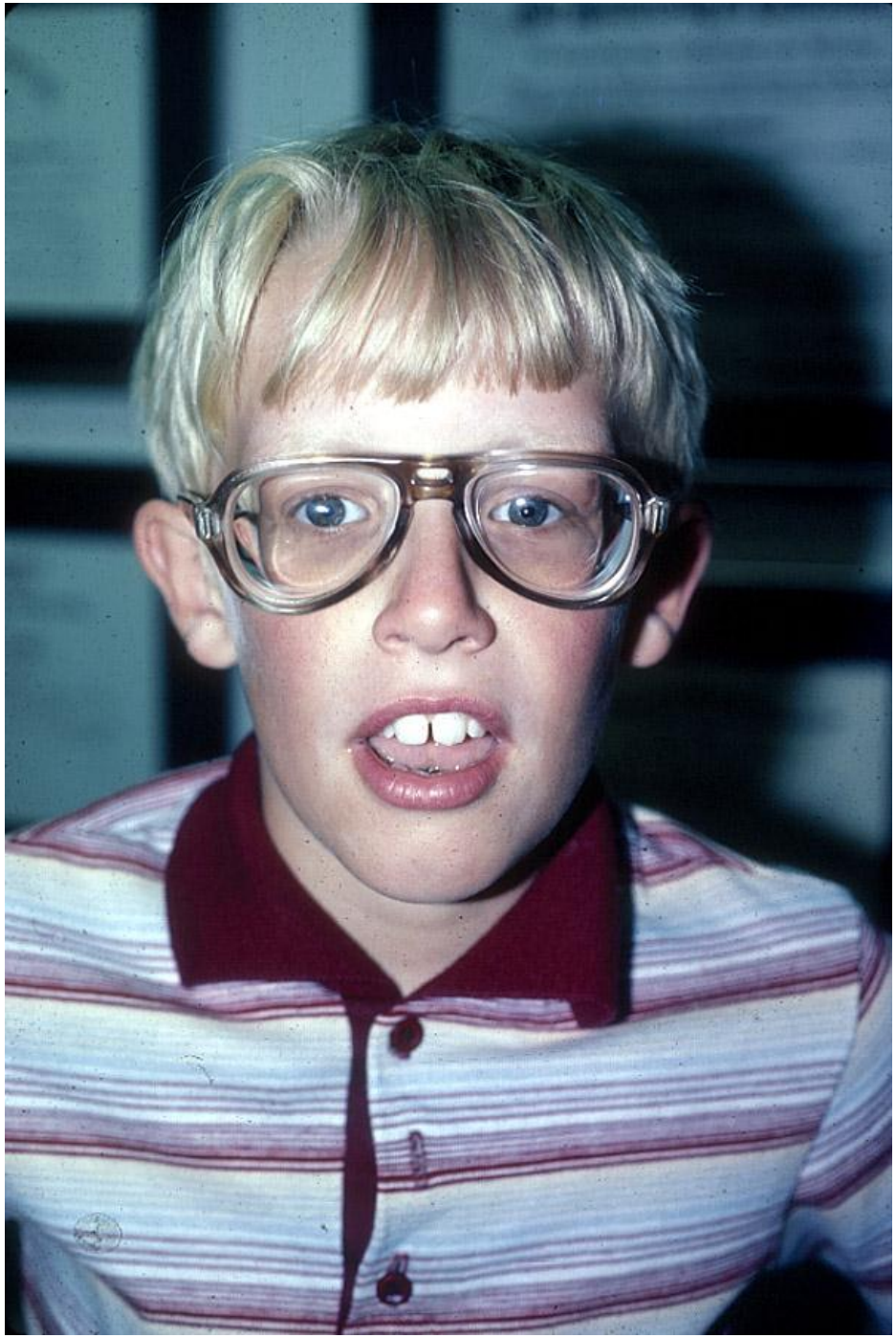

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Marfan Syndrome-Advances

- Cardiology consultation
- Molecular testing for fibrillin 1
- Loeys-Dietz syndrome (TGFBR1 and 2)
- Losartan for mutation positive patients
- Exercise restrictions

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Achondroplasia

- Incidence 1/10,000 births
- Autosomal dominant (most new)
- Secondary to alteration in FGFR3
- Diagnostic keys
  - Short stature, macrocephaly, rhizomelic shortening
  - Trident hand
  - Characteristic radiologic findings

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Achondroplasia-Management

- Exclude lethal disorder (thanatophoric dysplasia)
- Skeletal survey, molecular testing
- Evaluate chest
- MRI for foramen magnum size

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Achondroplasia-Advances

- Potential need for surgery
  - Foramen magnum, hydrocephalus
  - Orthopedic
- Role for limb lengthening procedures
- National support groups

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Osteogenesis Imperfecta

- Classic types (I-IV)
- Often diagnosed prenatally
- New types (V-XI)
- Use of bisphosphonate therapy

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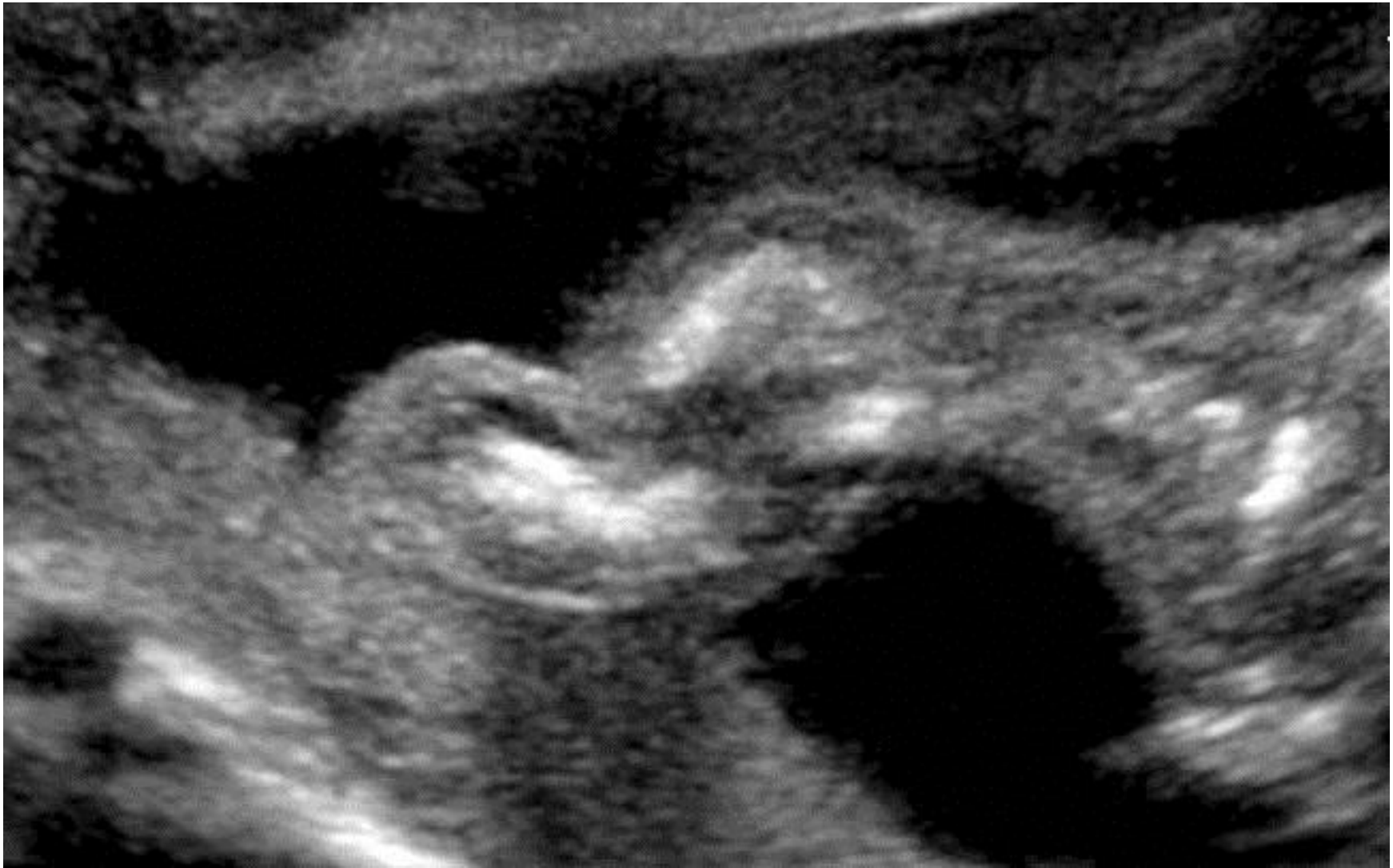

Prader-Willi Syndrome

- Incidence 1/15,000 births
- Most common syndromic cause of unexplained hypotonia
- Deletion of paternal 15q11.2 (70-80%)
- 20-30% maternal uniparental disomy (UPD)
- Childhood onset obesity

Prader-Willi Syndrome

- Diagnostic keys
  - Hypotonia
  - Bitemporal constriction
  - Tapered fingers
  - Undescended testes
  - Feeding inability

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Prader-Willi Syndrome-Management

- Neurologic evaluation for hypotonia
  - CPK, electrodiagnostics?
- Feeding evaluation
- Rapid FISH or methylation studies
- Potential for sudden death

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Prader-Willi Syndrome-Advances

- Aggressive GI/nutrition management
- Growth hormone supplementation
- Potential for pharmacologic intervention
- Increased risk for childhood/adolescent psychiatric disorders

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Deletion 22q11.2

- Incidence 1/5000 births
- DiGeorge sequence/velocardiofacial syndrome
- Accounts for 1/3 of isolated conotruncal malformations
- 5-7% inherited
- Highly variable

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Deletion 22q11.2

- Diagnostic keys
  - Prominent square nasal bridge
  - Small alae nasi
  - Long, tapered fingers
  - Cleft palate
  - Congenital heart disease (Tetralogy of Fallot, truncus arteriosus, VSD)

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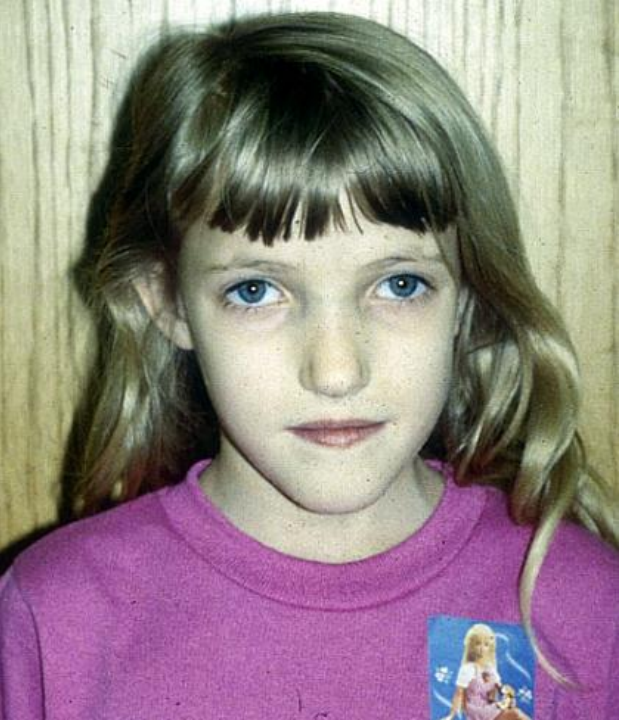

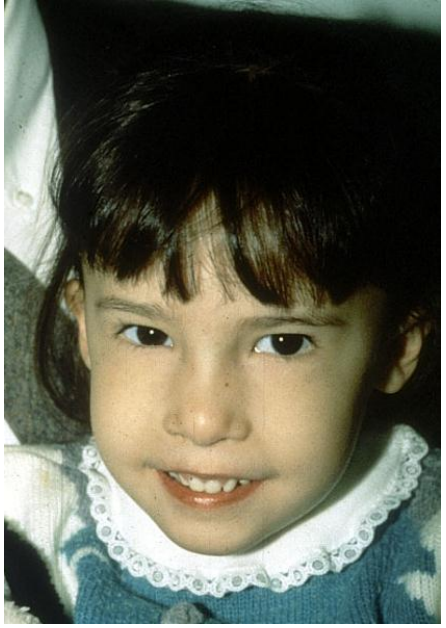

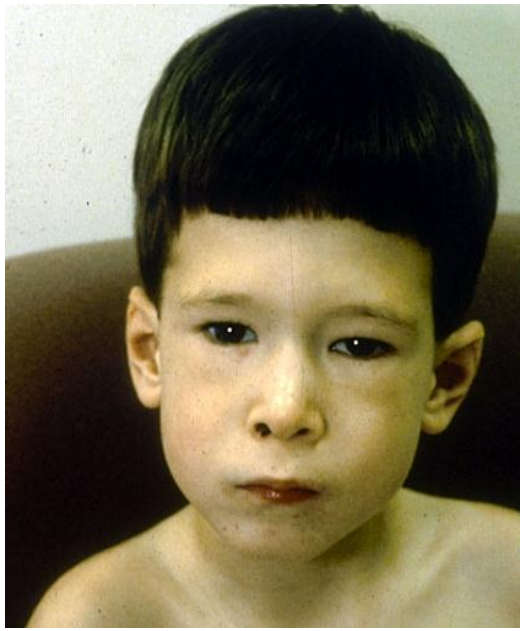

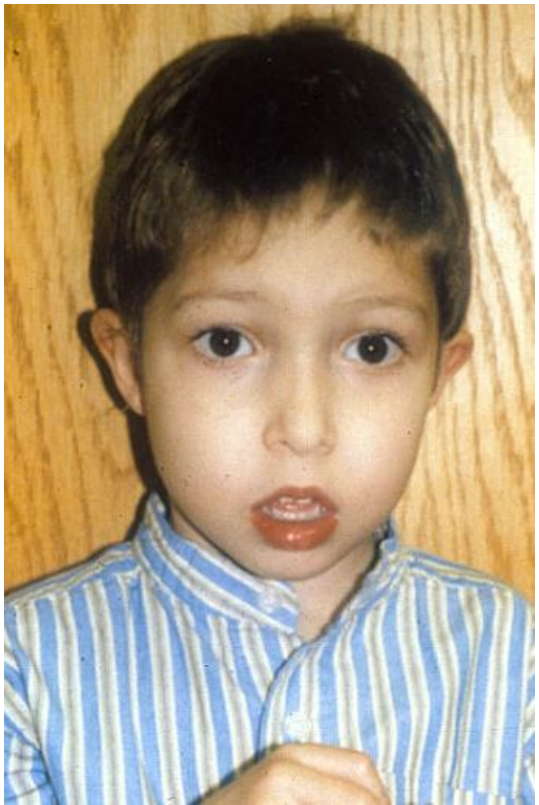

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Deletion 22q11.2-Management

- FISH or microarray
- Evaluation for additional malformations
  - Cardiac, renal
- Immunologic workup, calcium metabolism
- Defer immunizations?
- Specialty consultation (Plastics)

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Deletion 22q11.2-Advances

- Increased awareness of clinical spectrum/Low threshold for diagnosis
- Psychiatric disorders common, often difficult to manage
- National support groups

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The Rest of the Best

- CHARGE syndrome
- Beckwith-Wiedemann syndrome
- Williams syndrome
- Kabuki syndrome
- de Lange syndrome

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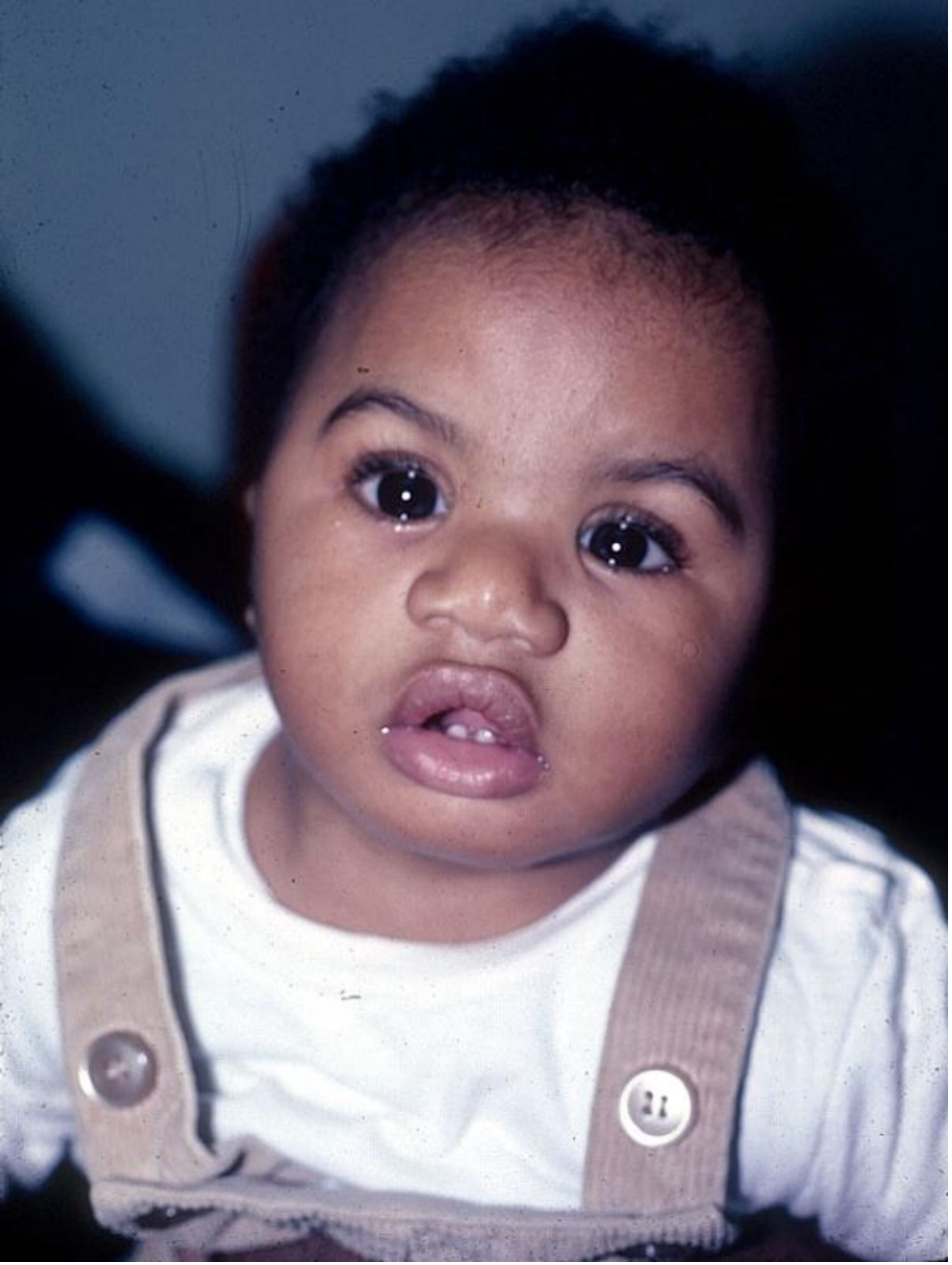
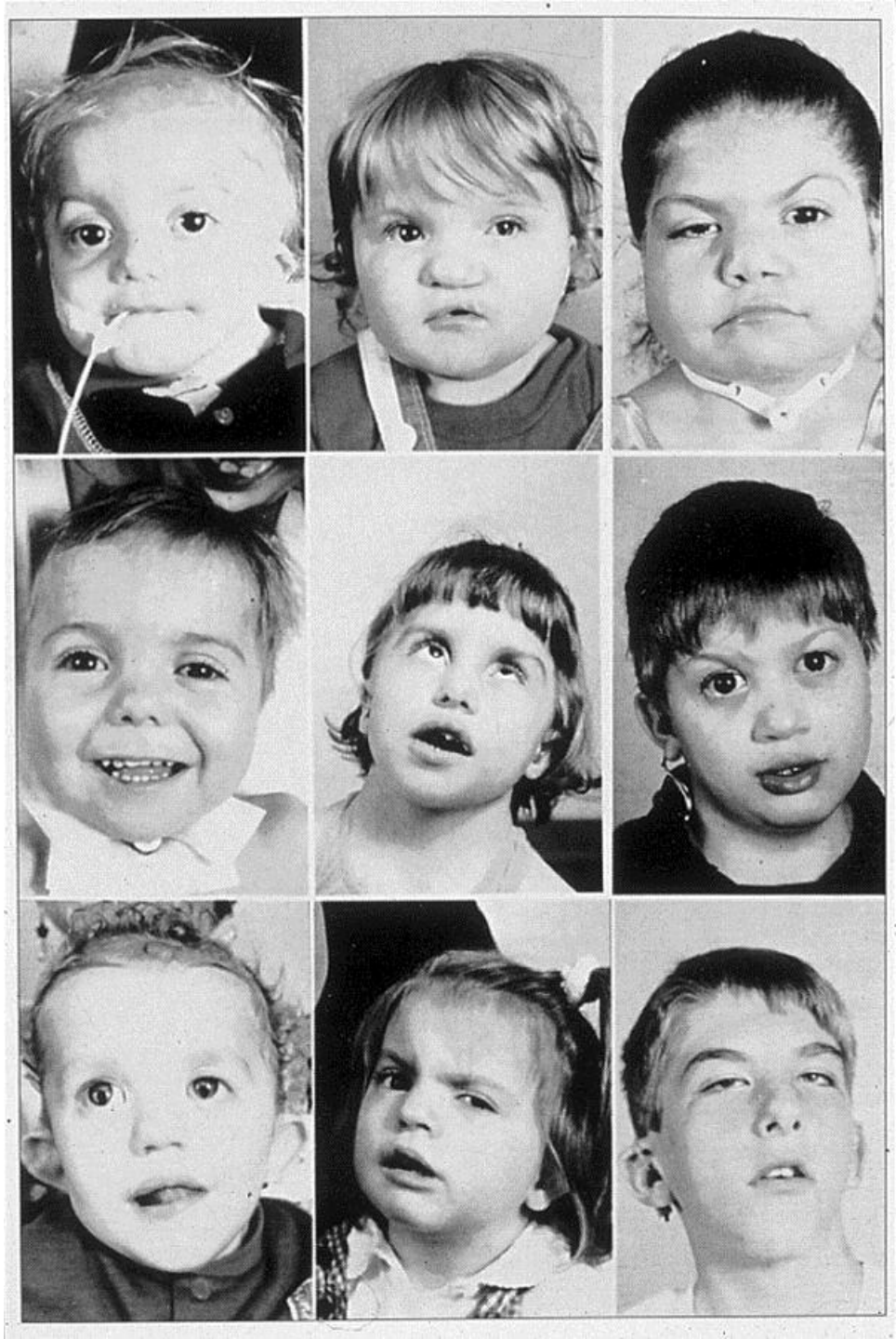
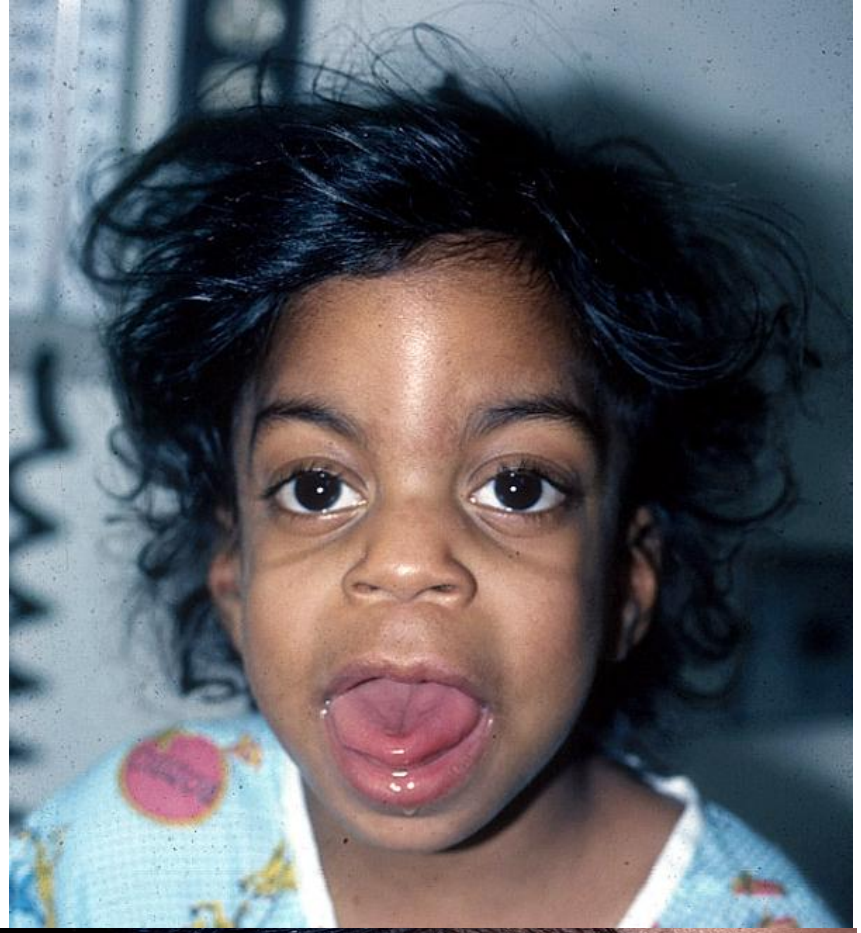
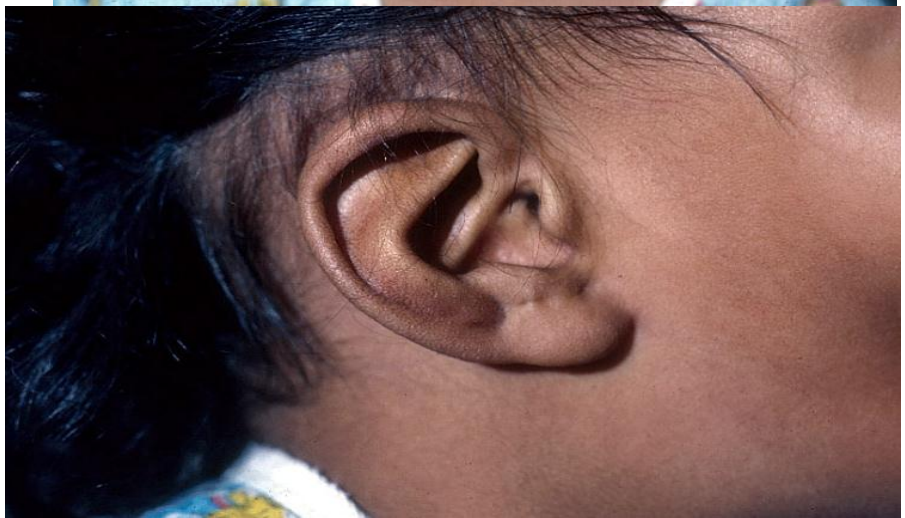
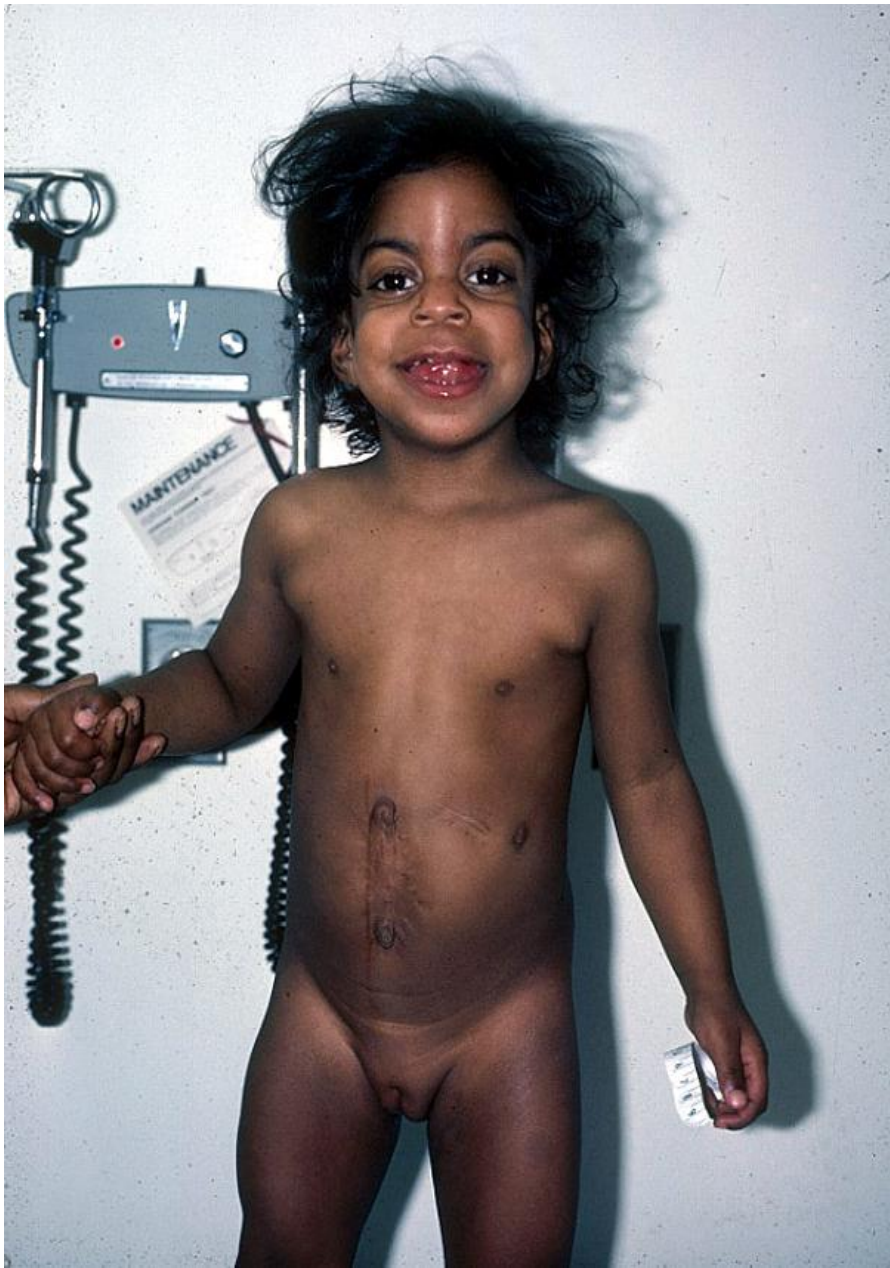
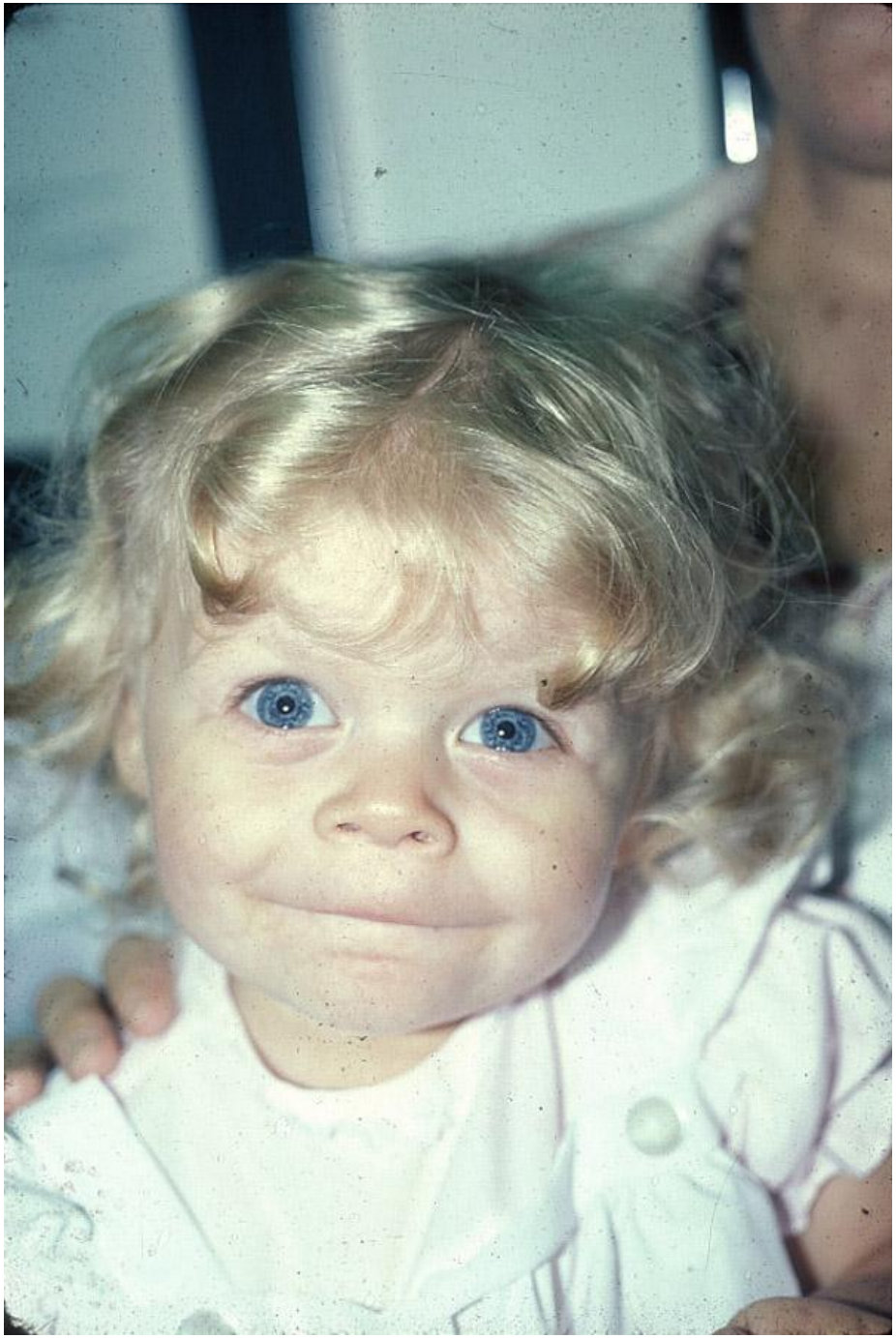









MAINTENANCE



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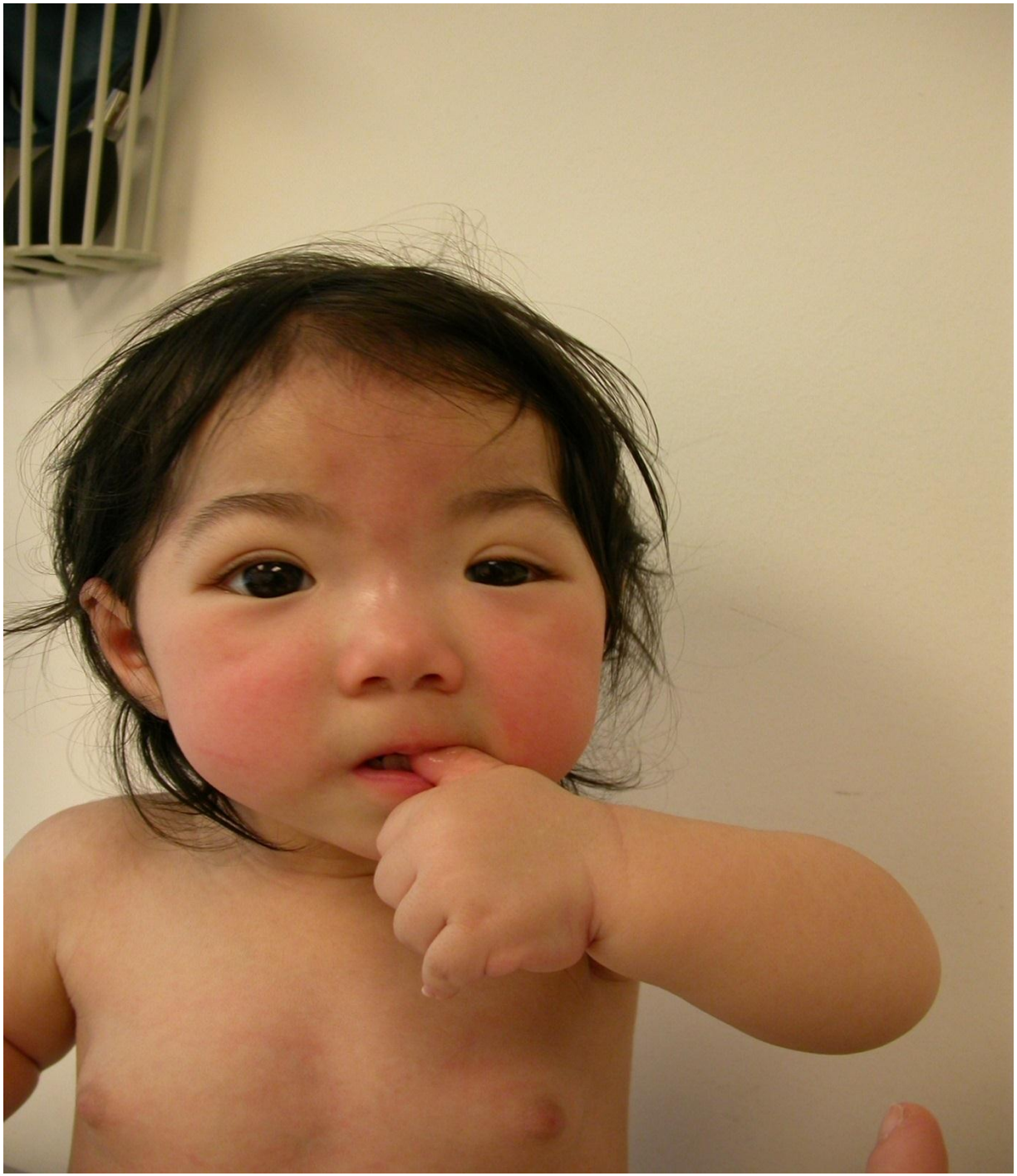
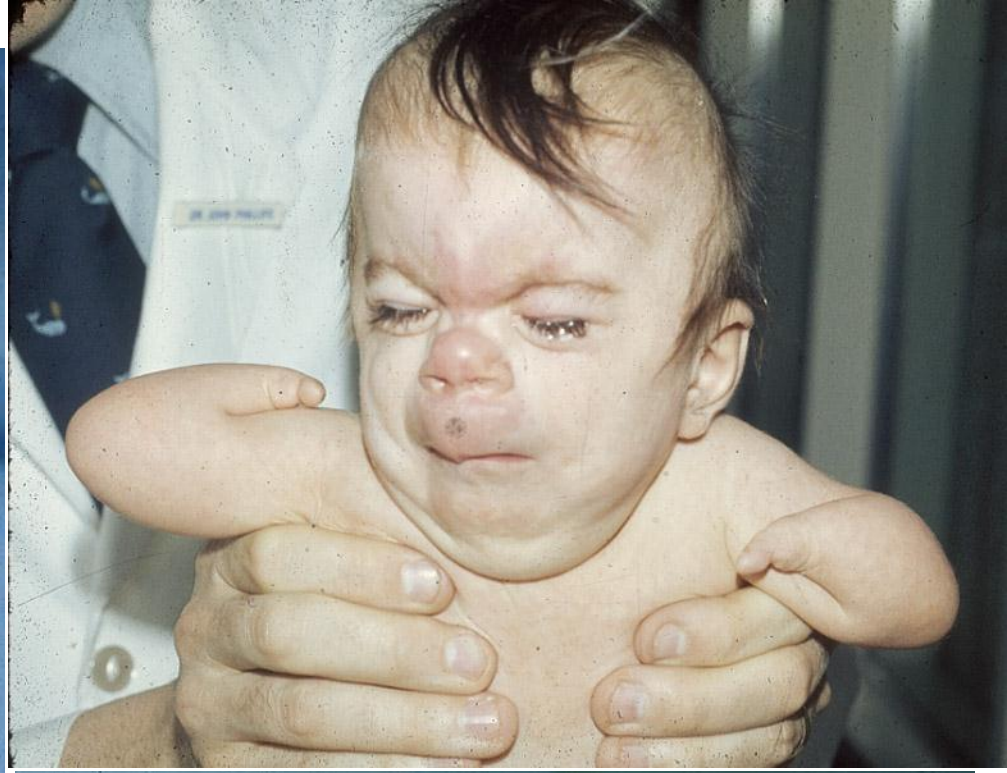
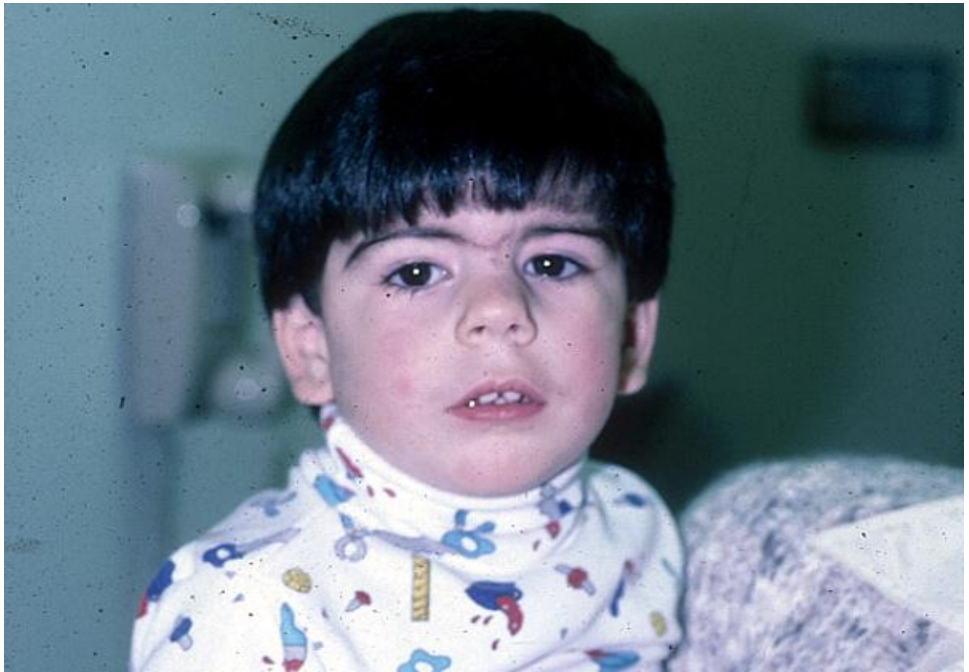


Children's National™





Resources

- www.genereviews.org
- www.clinicaltrials.gov
- www.geneticalliance.org
- Unique rare chromosome disorders support group
- NORD
- AAP Clinical Report for Practitioners: Health Supervision Guidelines for Individuals with Down Syndrome, 2011

Children's National