Next Generation Genetic Medicine: Practical Pearls for Pediatrics

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November 9, 2021

“The most dangerous thing in the hospital is a patient without a diagnosis”

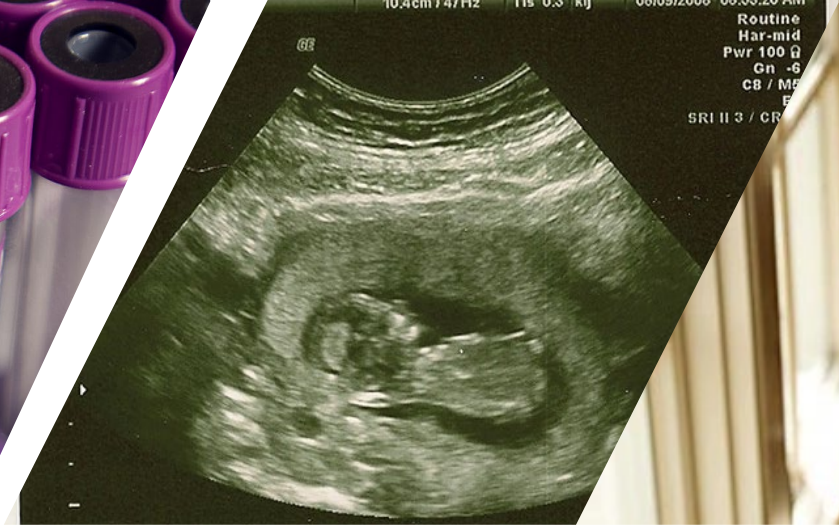
-Christopher Lentz

Outline

- Prenatal screening and diagnostic testing
- Genetic testing
- Genetic test interpretation and counseling
- Management of genetic disorders

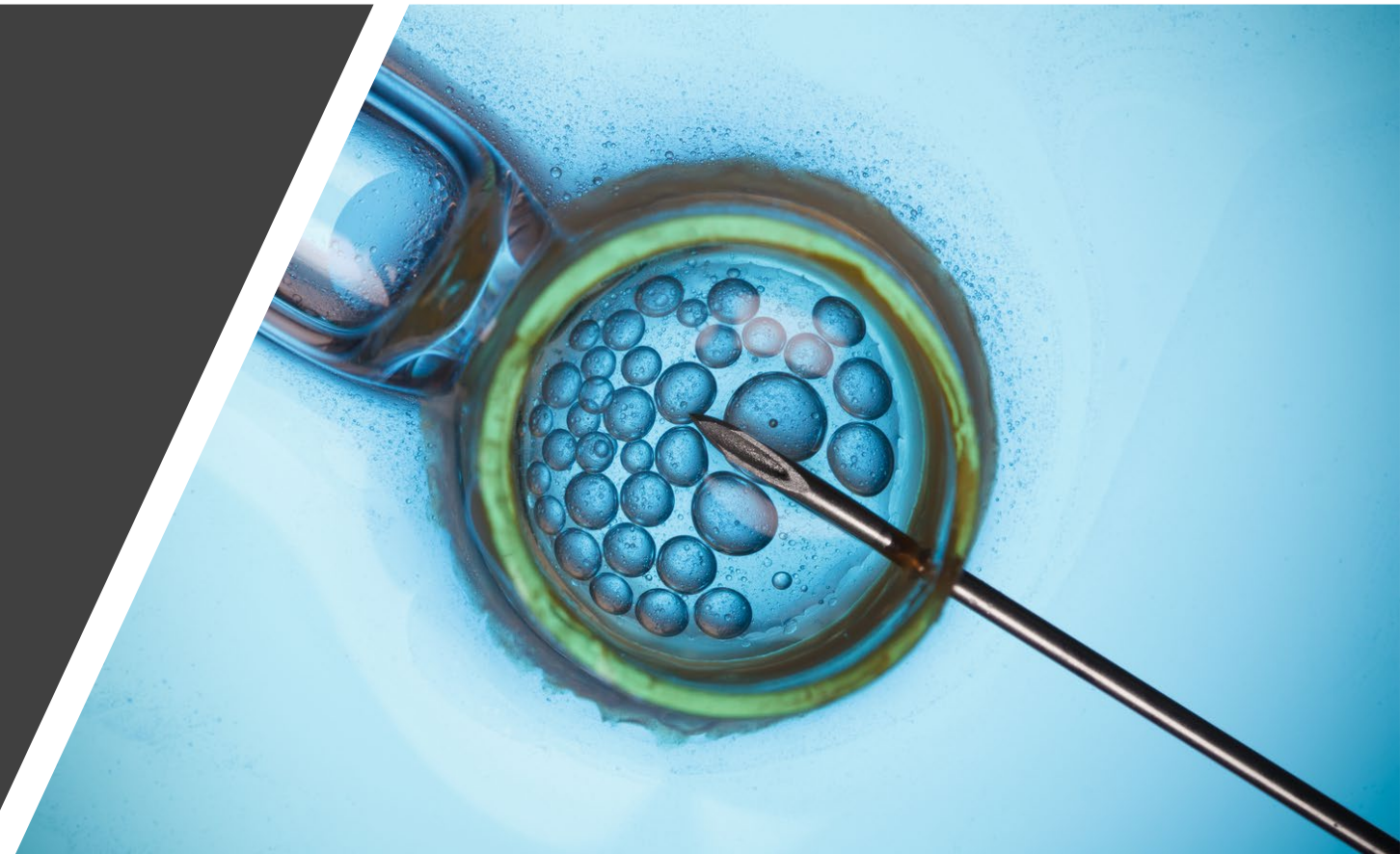
Genetics Pearl #1

Always get a copy of the test report for any genetic test

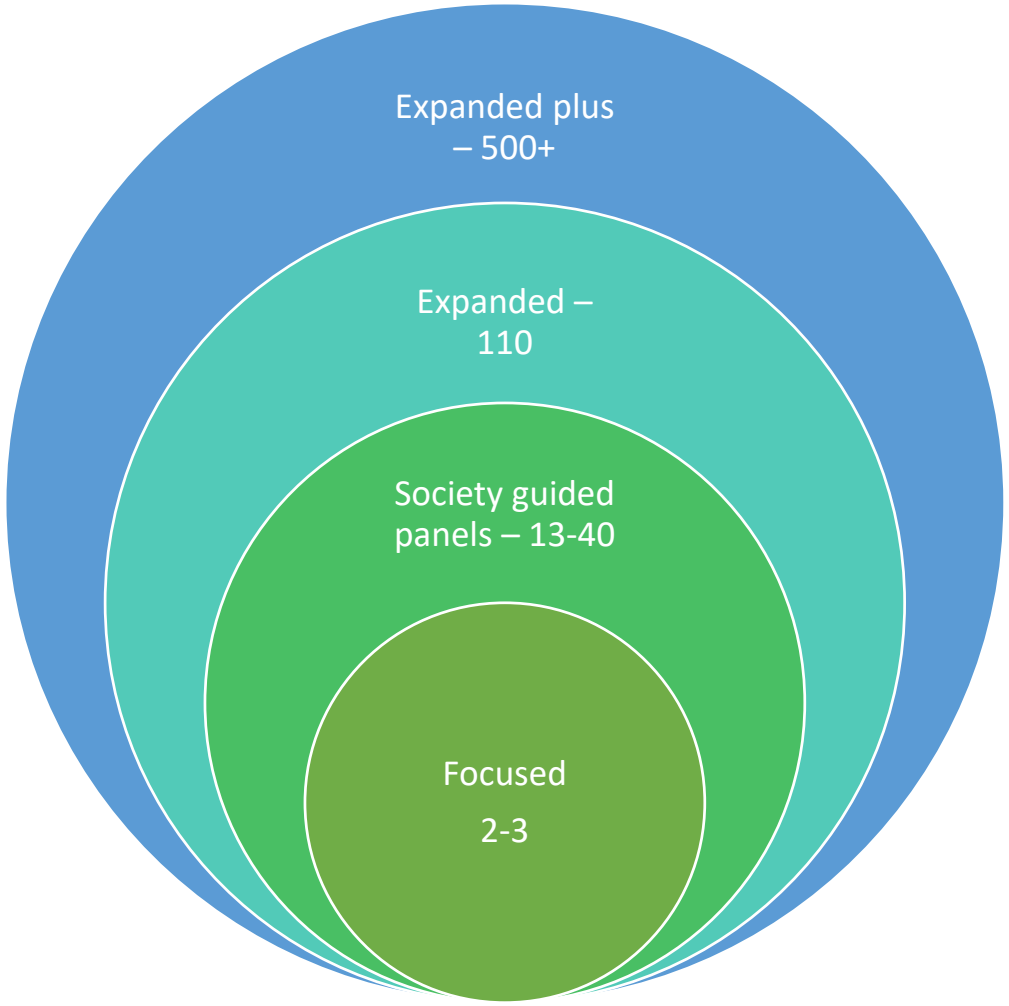


Types of prenatal genetic testing

- Preconception
- Preimplantation
- Screening
  - Blood
  - Ultrasound
- Diagnostic
  - CVS/amnio
  - Advanced fetal imaging



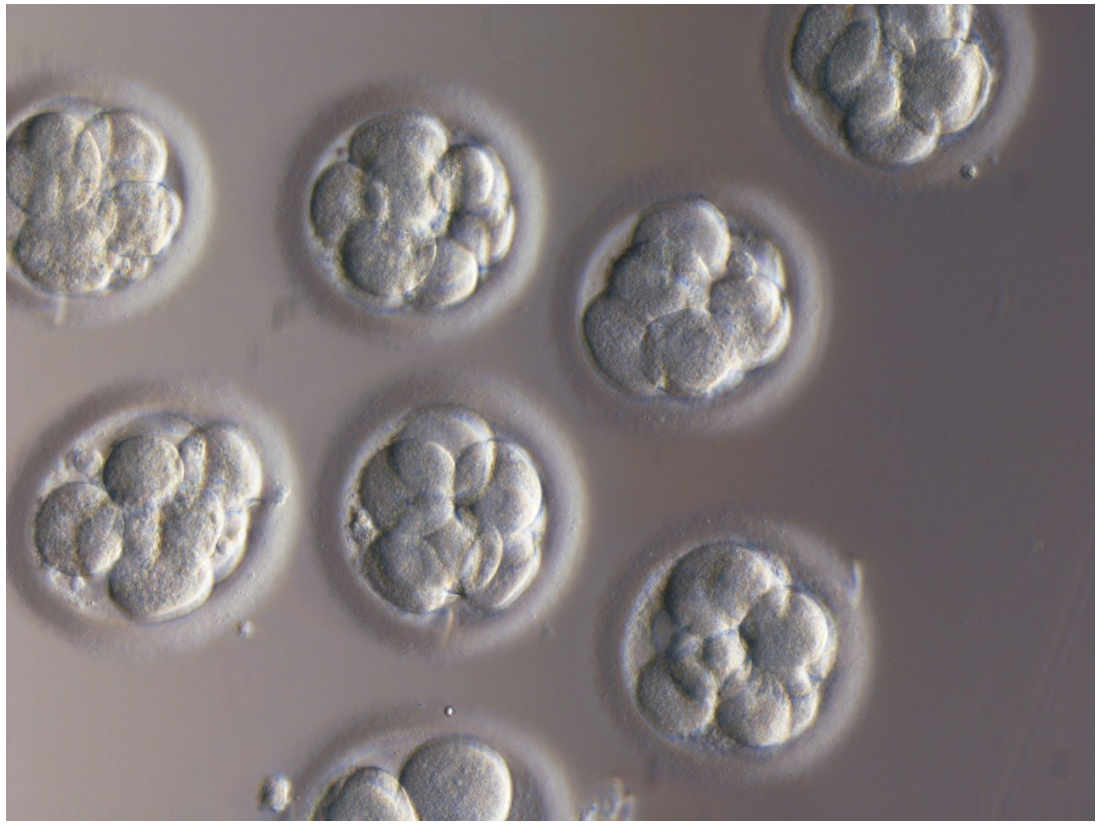
Types of carrier screening



- Recessive and X-linked conditions
- Ashkenazi panel
- ACOG panel
- Variable accuracy
  - Variant interpretation
- May not be covered by insurance

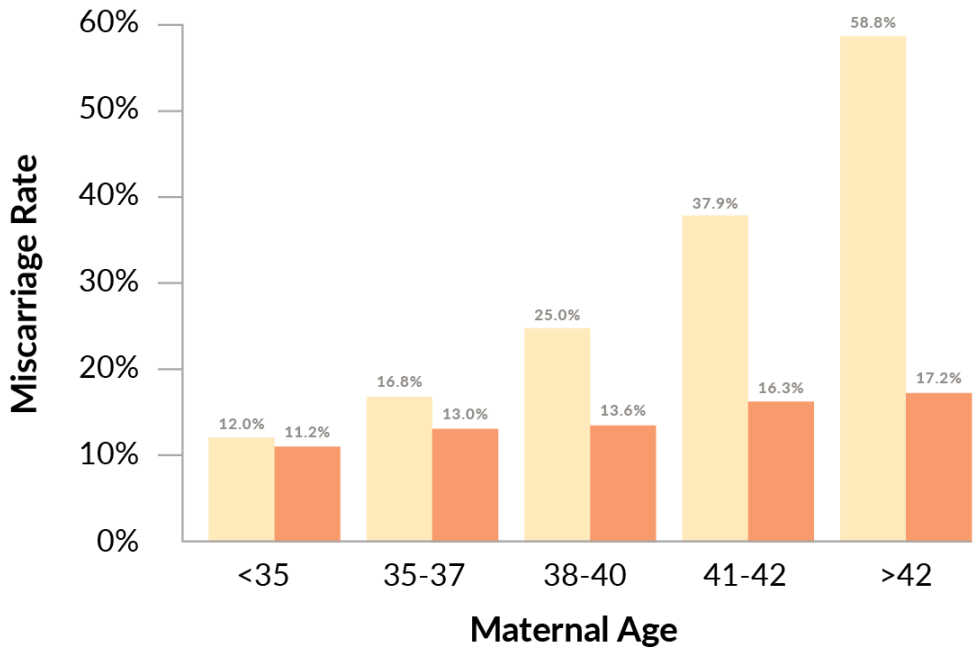
- “Carrier screening” ranges from 1 to 500+ genes
- Often done for gamete donors

Preimplantation genetic testing

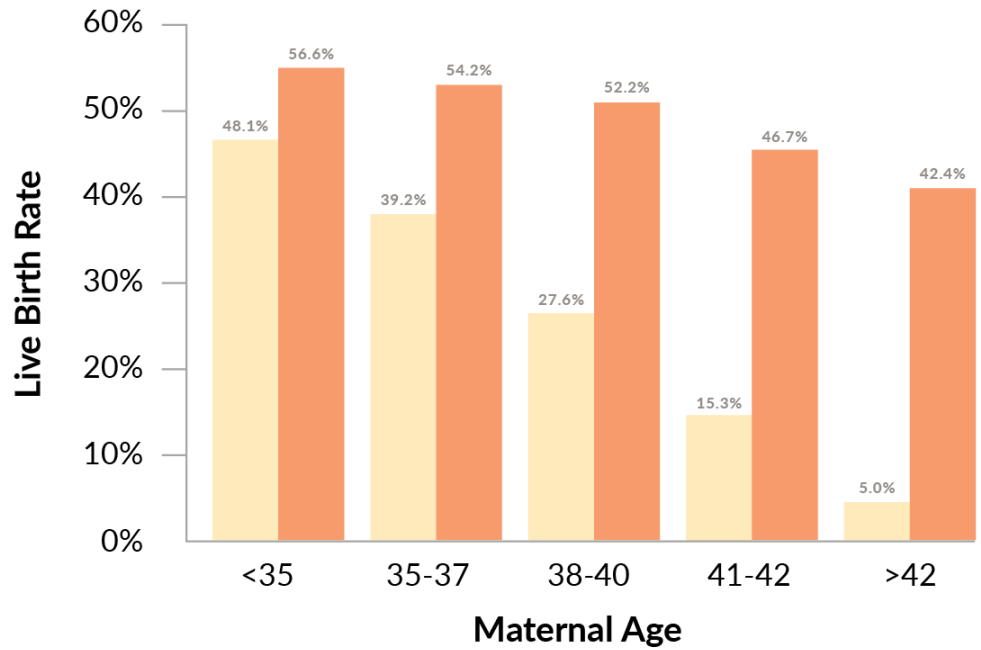


- High rate of chromosomally abnormal embryos
  - 25%-75%+ depending on age
- Lower rate of pregnancy and higher rate of miscarriage for abnormal embryos
- High financial and emotional cost of failed transfers and pregnancy losses

PGT-A Reduces Miscarriage Rates



PGT-A Increases Live Birth Rates



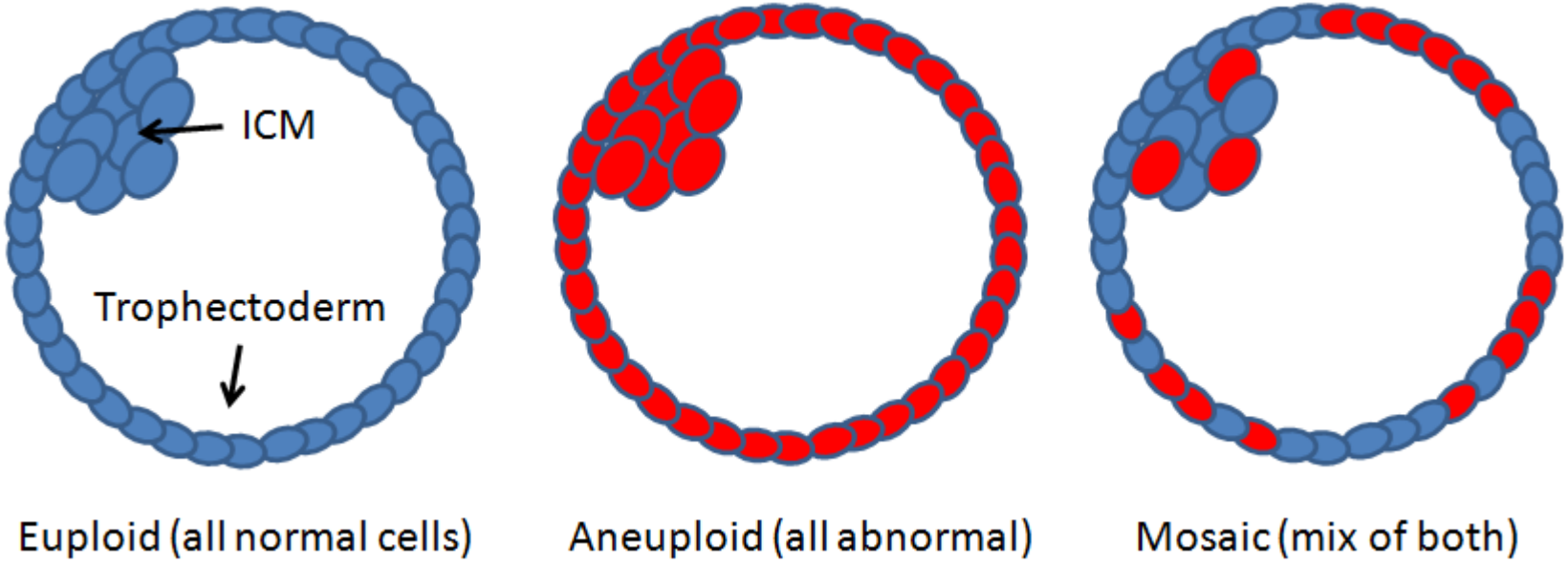
Sample Size (Number of transfers)

	<35	35-37	38-40	41-42	>42
IVF without PGT-A	29,989	13,144	10,497	4,678	3,009
IVF with PGT-A	5,326	3,366	2,941	973	243

Source: https://go.coopergenomics.com/pgs/

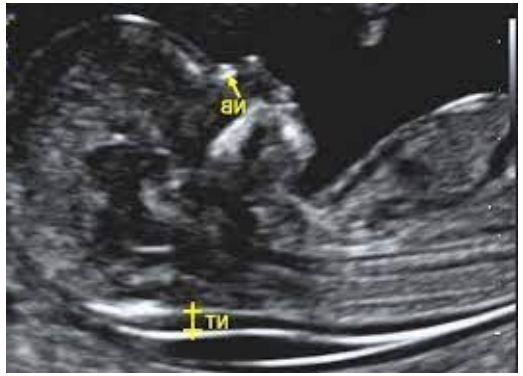
Preimplantation genetic testing

Test	Detects
PGT-A	Aneuploidy
PGT-SR	Structural rearrangements
PGT-M	Monogenic disorders



Aneuploidy screening during pregnancy

+



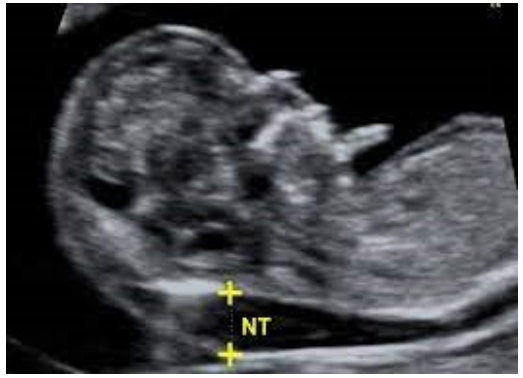
Normal nuchal translucency

+

Maternal age

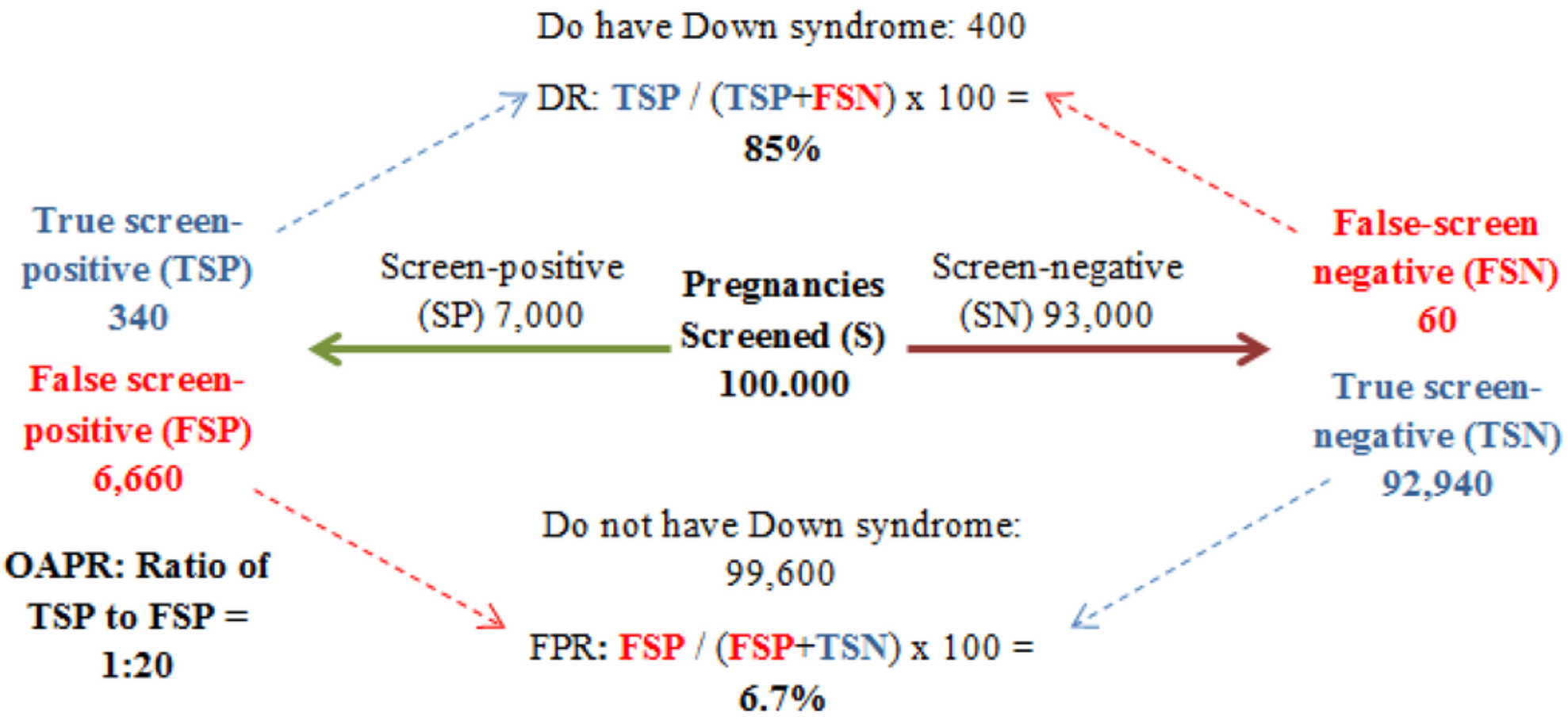
=

Risk of aneuploidy



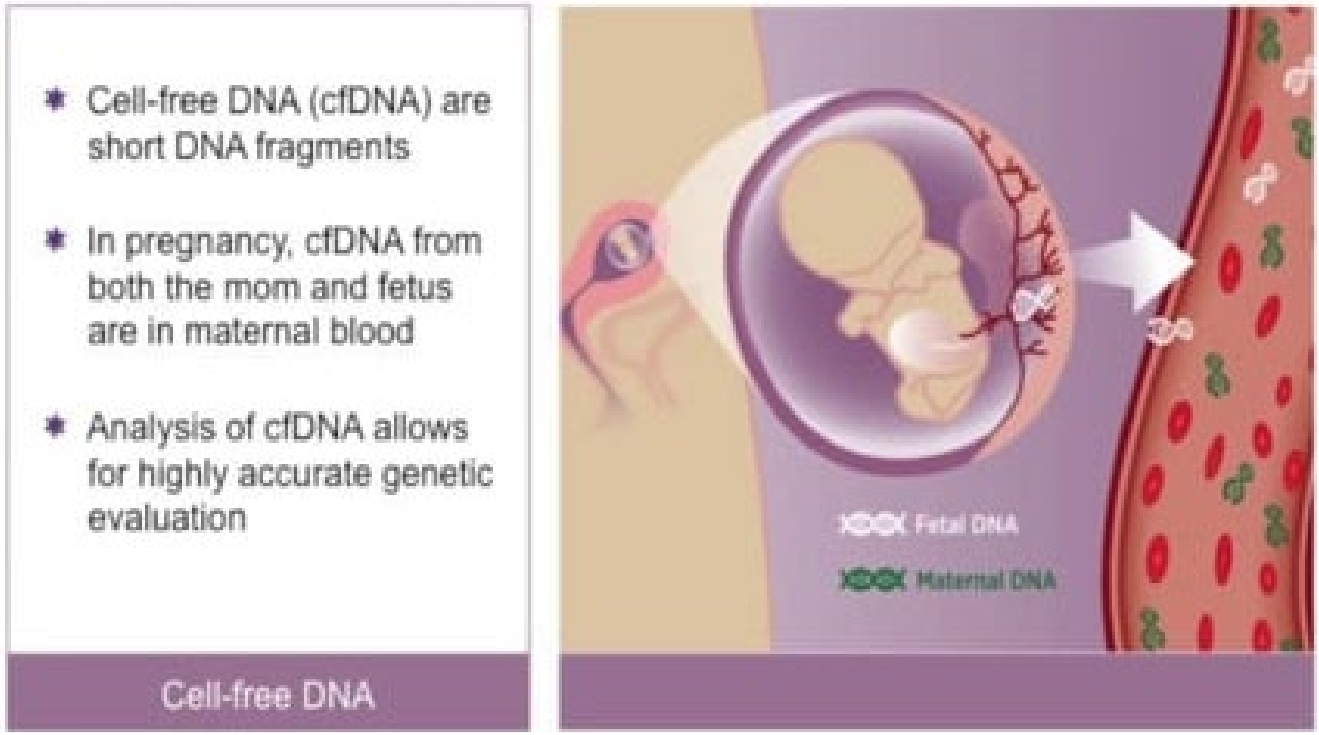
Increased nuchal translucency

Positive result in aneuploidy screening

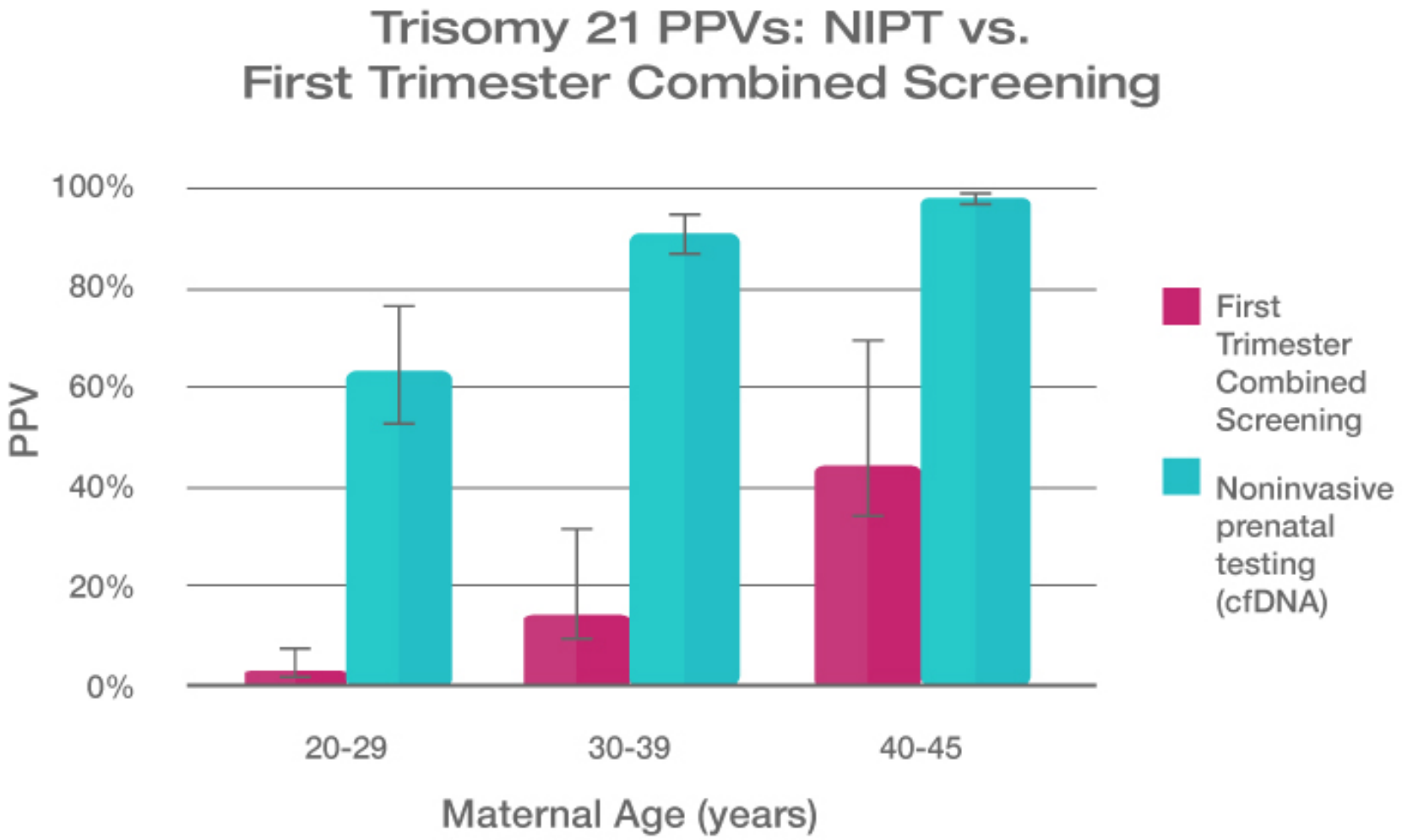


Sillence et al, 2013

Cell free placental DNA (Noninvasive prenatal screening)



Aneuploidy screening during pregnancy



https://perinatalquality.org/Vendors/NSGC/NIPT/

NIPT/Cell Free DNA Screening Predictive Value Calculator

Overview | **PPV Calculator** | NPV Calculator | Definitions | FAQs | Resources | References

Please select the chromosome condition and maternal age at the time of EDD.
Alternatively you choose to enter Prevalence directly.

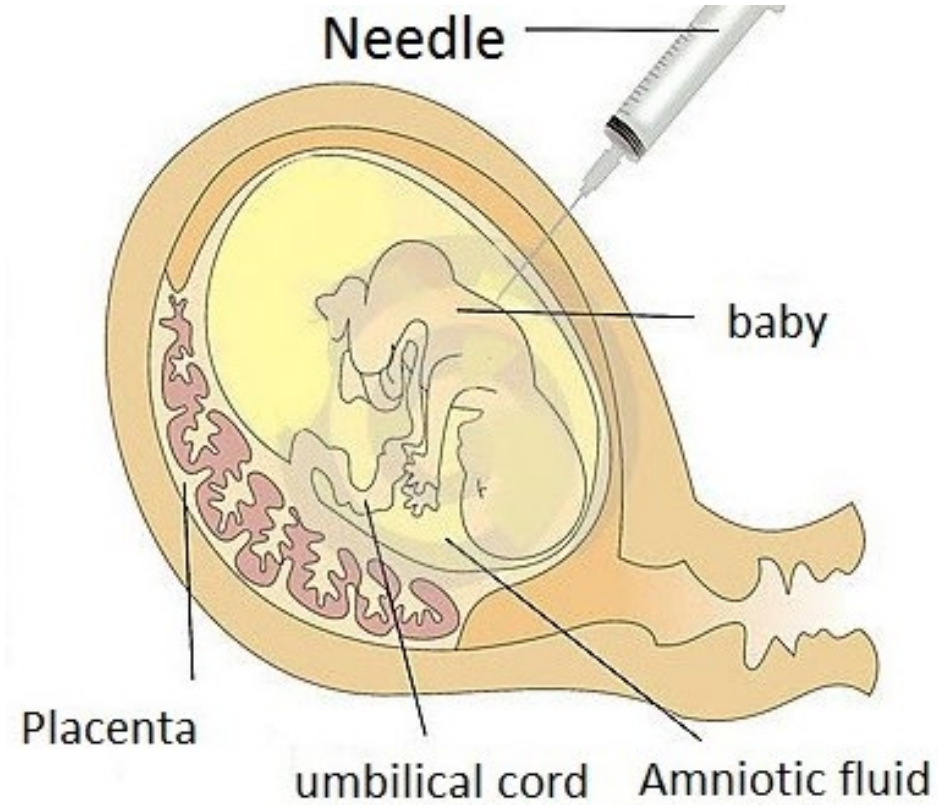
Chromosome condition

Maternal age at EDD or Enter Prevalance Directly

Possible results

	Fetus has genetic disease	Fetus does not have genetic disease
NIPS “positive” result	Accurate	Confined placental mosaicism Mosaic disorder in child Trisomy rescue Mom is affected and doesn’t know Maternal cancer Technical error
NIPS “negative” result	Mosaic disorder Technical error	Accurate

Diagnostic testing during pregnancy



- Prenatal testing – limited results
- More accurate than blood-based screening
- “Prenatal karyotype”
  - Often limited to FISH for 13, 18, 21, and sex chromosomes

Pearls for pediatrics – prenatal genetics

01

Get a copy of report

02

Screening test does not equal diagnostic test

03

“False negative” may indicate problem

04

Phone a friend

05

Look at the child and not just the report

Genetic testing

What do these patients have in common?

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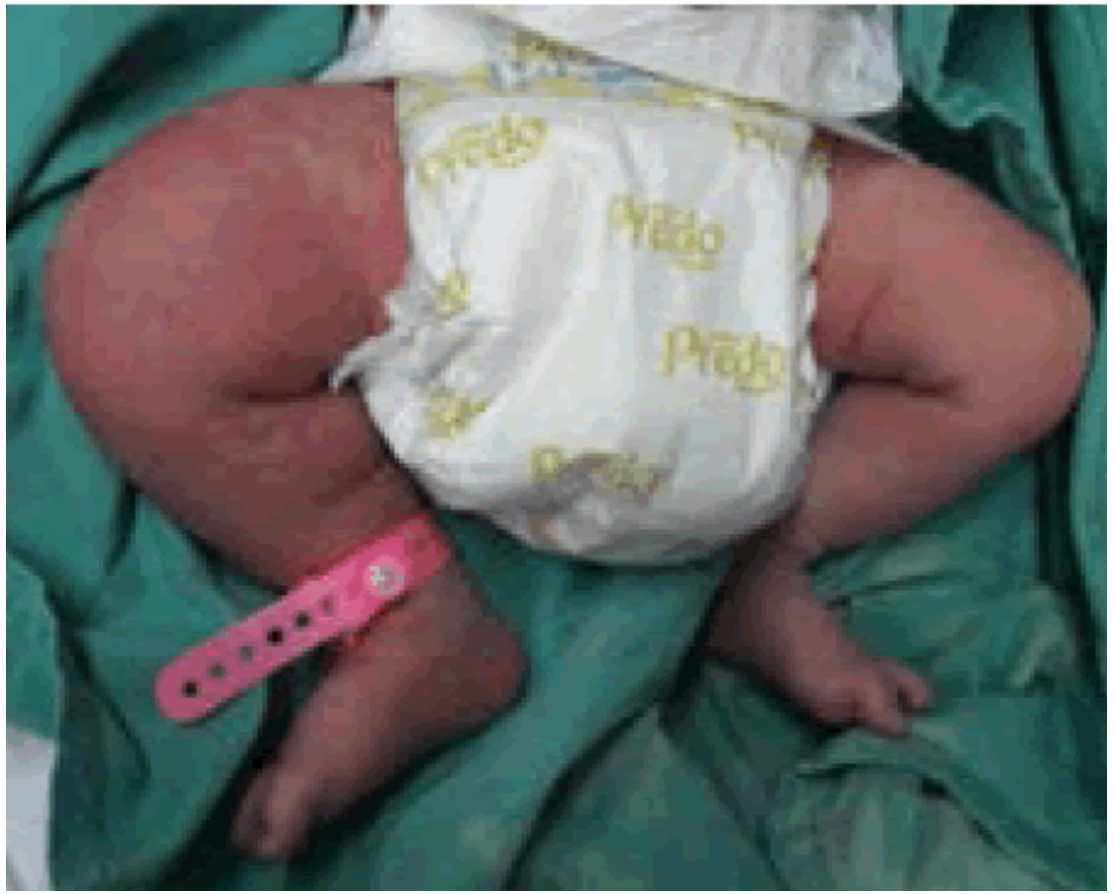

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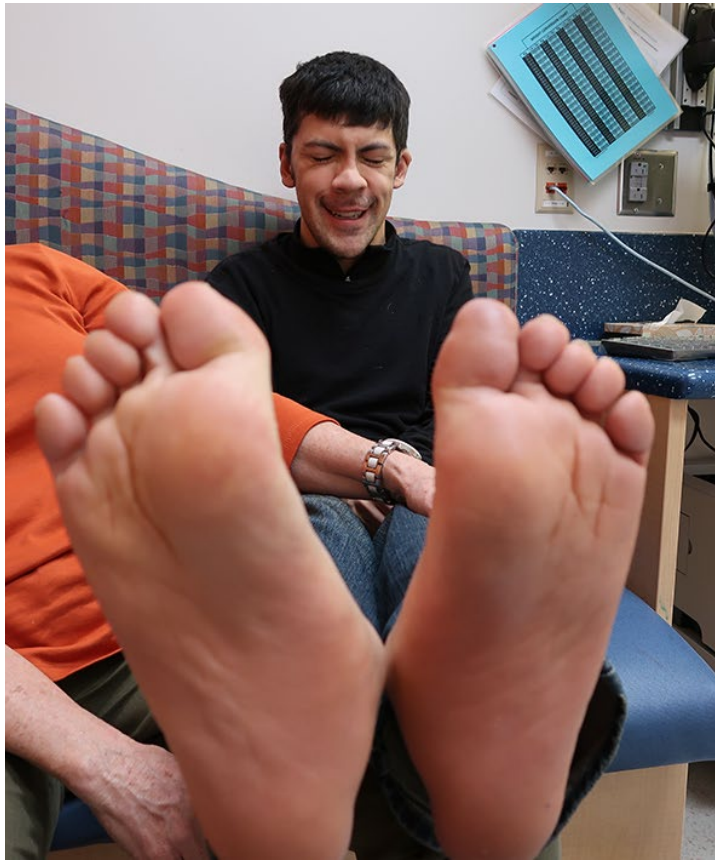

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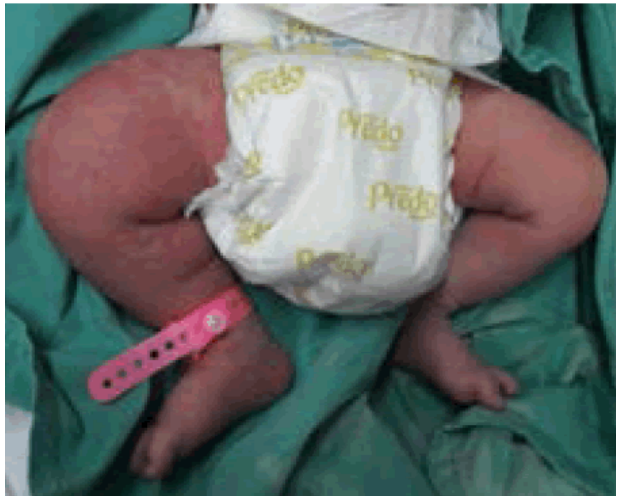
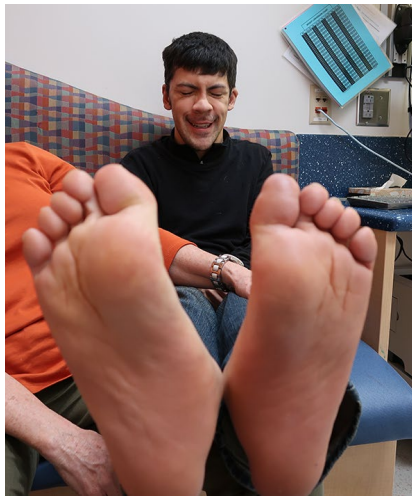
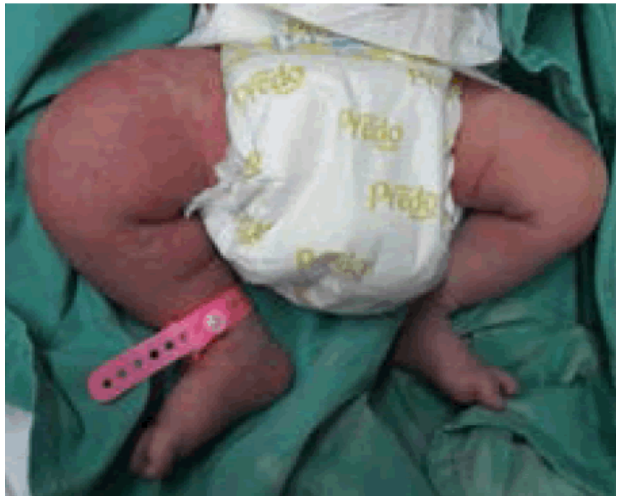


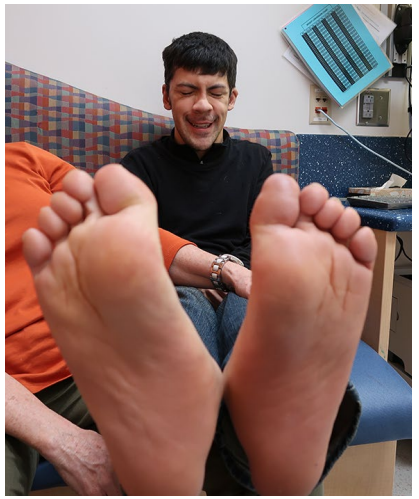


What do these patients have in common?

Beckwith-Wiedemann syndrome



Klippel-Trenaunay Weber

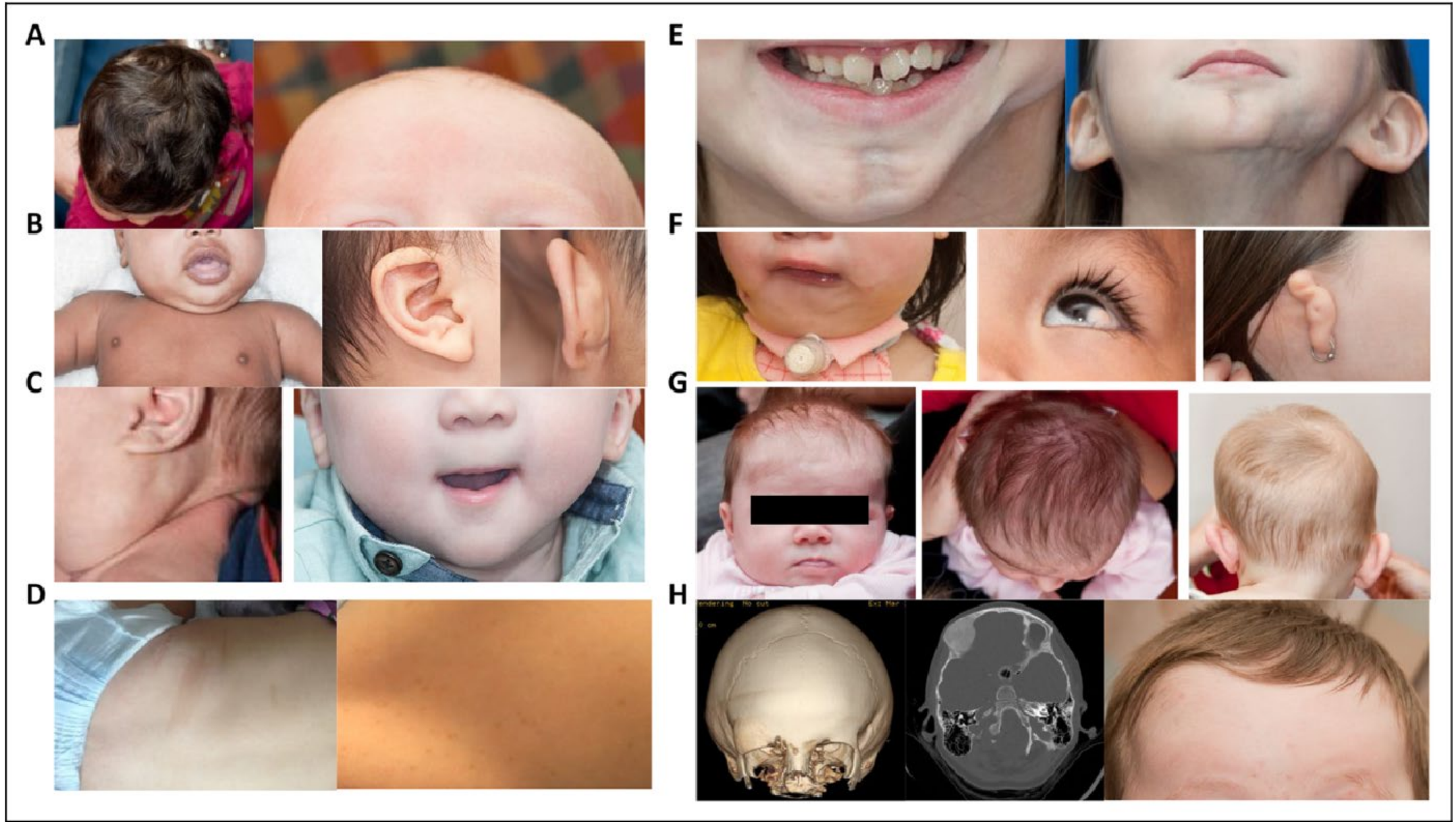


Mosaic trisomy 8

- All patients have overgrowth of a limb as part of their syndrome
- Each has a distinct syndrome
- None are detected using exome sequencing
- Very different medical management implications for each

Genetic testing pearl

- Exome sequencing does not detect every genetic condition

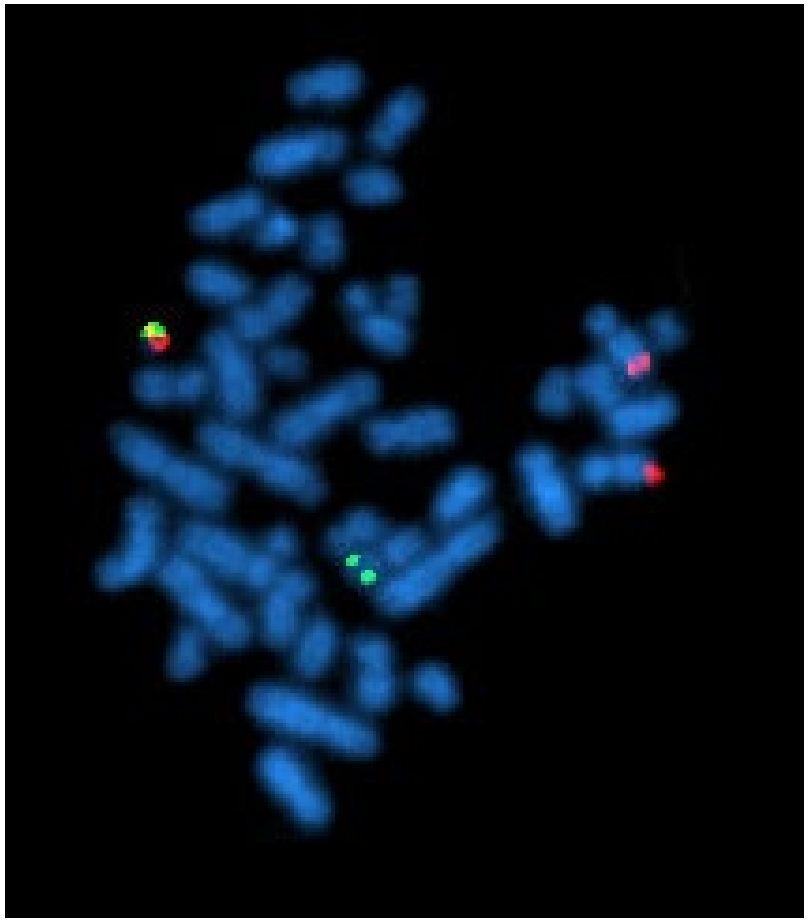


Wenger et al, 2019

Fluorescence in situ hybridization (FISH)

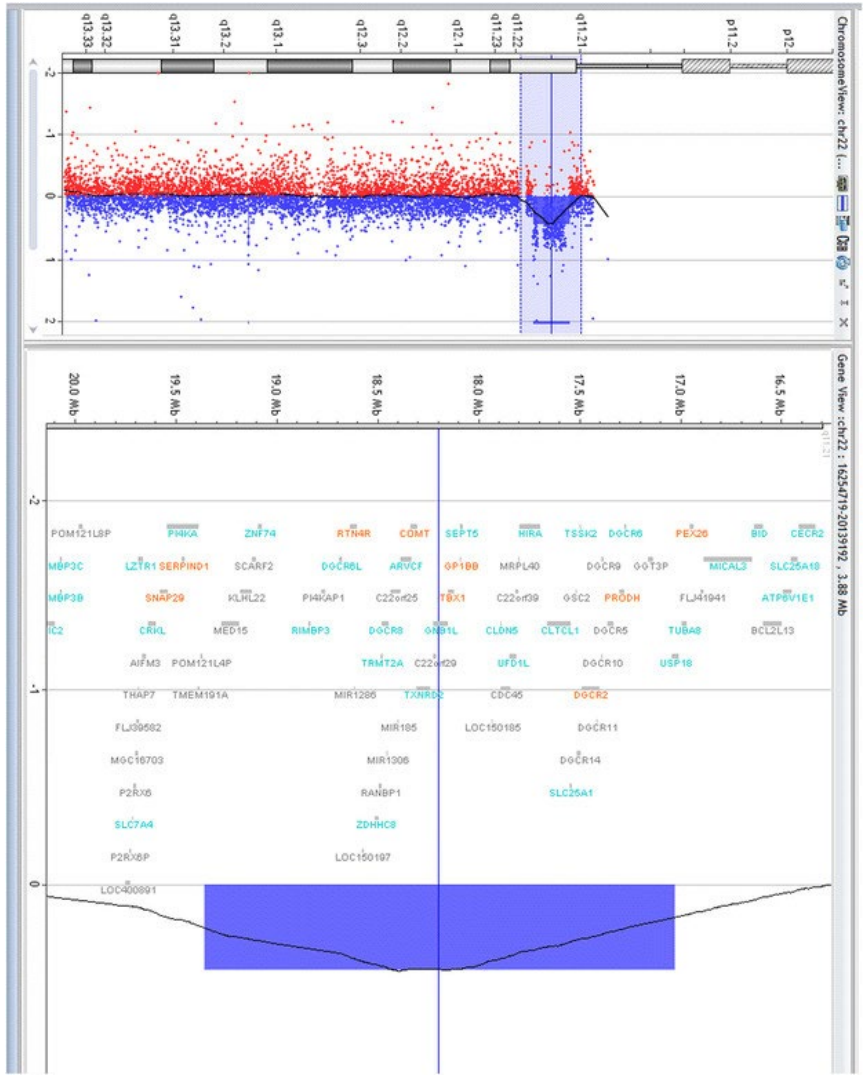
- Detects number of copies of a specific part of a chromosome

- Common uses:
  - Prenatal karyotype
  - 22q11.2 deletion (DiGeorge/VCFS)
  - Familial testing



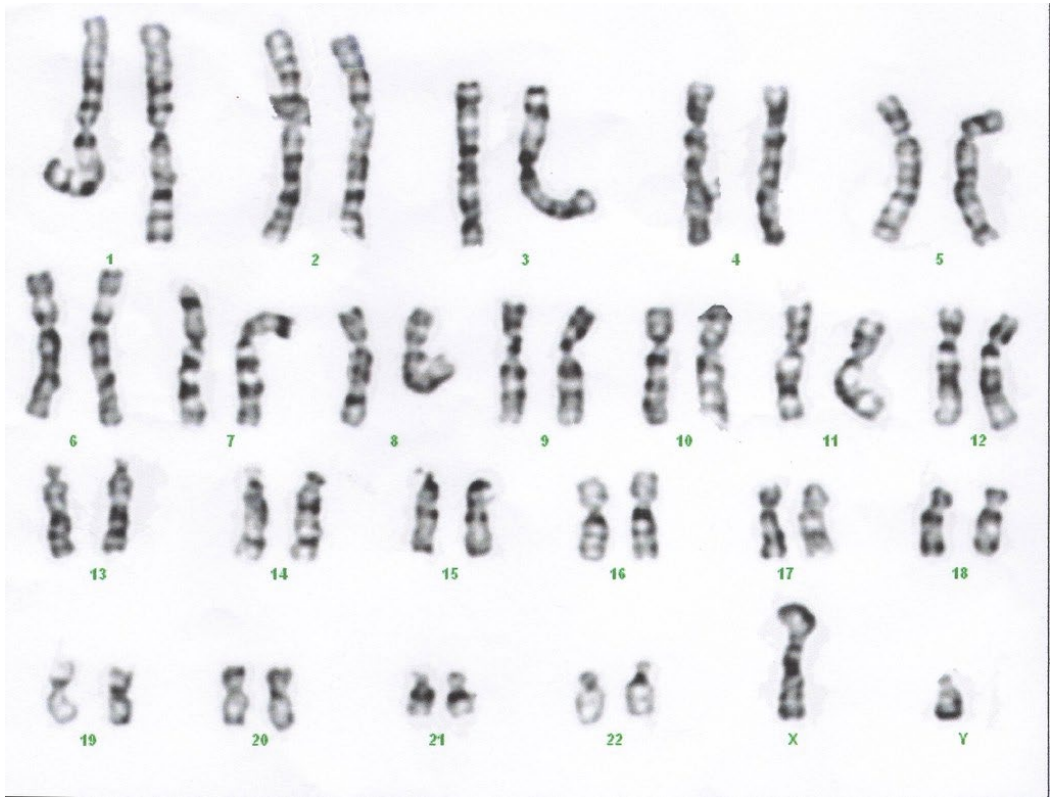
Microarray

- SNP most common
- Detects missing or extra material across all chromosomes
- Common uses:
  - Microdeletion or microduplication syndromes
  - First-line test for children with birth defects and developmental delays
- SNP array can also detect loss of heterozygosity and mosaicism
- Does not detect structural rearrangements or balanced translocations



Karyotype

- Common uses:
  - Structural rearrangements
  - Suspected trisomies
  - Disorders of sexual development, often with a FISH for *SRY*
  - Secondary test after SNP array if there is a suspected structural rearrangement



Methylation testing

- Imprinting disorders
- Sequence of genes normal, nothing missing or extra, but methylation abnormal
- Common uses
  - Suspected Beckwith-Wiedemann
  - Proportionate short stature (Russell-Silver syndrome)
  - Absent speech (Angelman)
  - Hypotonia as infant, hyperphagia as older child (Prader-Willi)

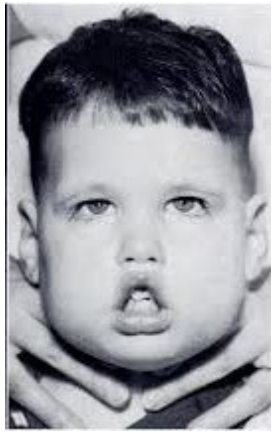
Trinucleotide repeat analysis

- Best for trinucleotide repeat disorders
- Can detect those affected and also premutation carriers

Disease	Trinucleotide repeat[a]	Repeat number			Change in gene function
		Normal	Carrier	Affected	
Fragile X syndrome	CGG 5'UTR	6–52	50–200	230 to >1000	Loss
Myotonic dytrophy	CTG 3'UTR	5–37	—	50 to >1000	mRNA stability
Spinal & bulbar muscular atrophy	CAG coding	12–34	—	40–62	Gain
Huntington's disease	CAG coding	11–36	—	42–100	Gain[b]
Spinocerebellar ataxia type 1	CAG coding	19–36	—	43–81	Gain[b]
Dentatorubral pallidoluysian atrophy	CAG coding	7–23	—	49–75	Gain[b]
FRAXE mental retardation	CCG —	6–25	116–133	200 to >800	Loss[b]

[a] All repeat are exonic with the position shown; UTR is untranslated region.
[b] Functional change is not established and is shown based upon similarity to other examples.

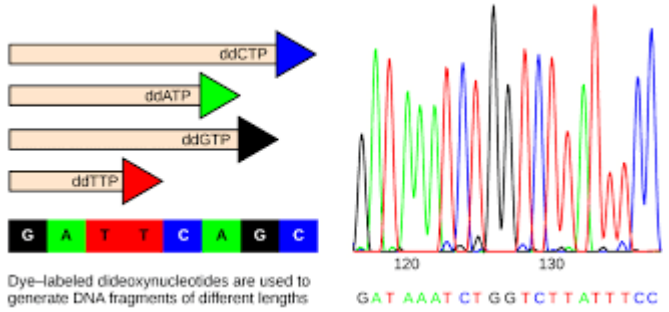
- Common uses:
  - Developmental delay (Fragile X)
  - Suspected myotonic dystrophy
  - Neurologic disorders

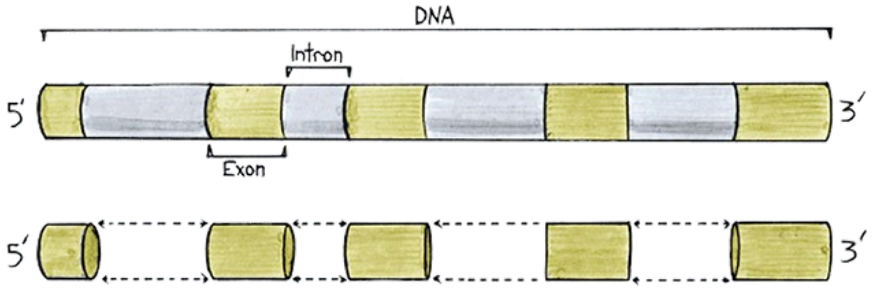


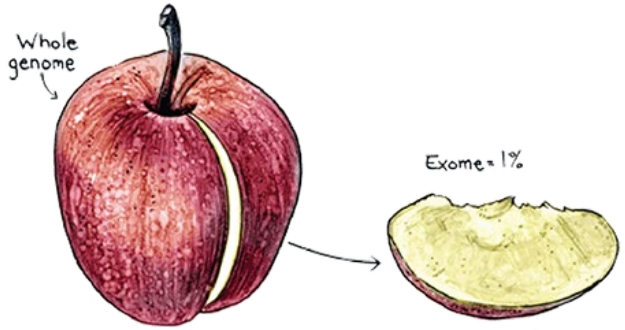
Sequencing

- Single gene sequencing
- Panels of genes
- Exome
- Genome

- Can miss deletions or duplications, structural rearrangements, trinucleotide repeat disorders, methylation defects, mosaic disorders
- Nonpaternity (when parental samples included), incidental findings

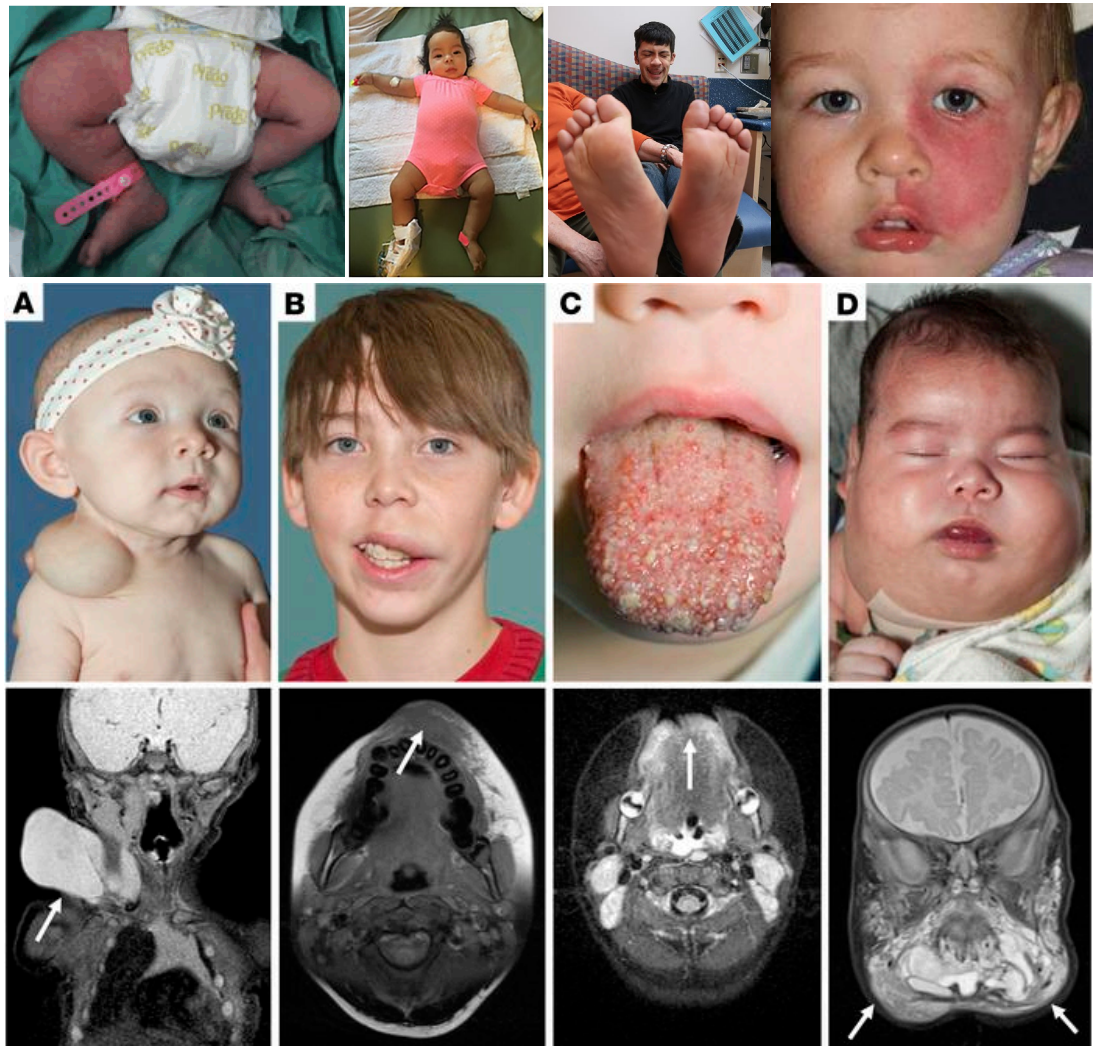






Mosaic disorders

- Affected tissues needed for analysis
- Common mosaic conditions:
  - Lymphatic malformations
  - Vascular malformations
  - Overgrowth with asymmetry
  - Mosaic trisomies
  - Hemimegalencephaly



Genetic testing pearls

01

Send the right test from the right tissue

02

SNP first for most (but not all) patients

03

Next step in testing variable

04

Phone a friend(ly geneticist)

05

Always get a copy of prior genetic testing!

ACMG variant classification

Pathogenic

Likely pathogenic

Variant of uncertain significance

Likely benign

Benign

ACMG variant classification

Pathogenic

Likely pathogenic

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ACMG variant classification

Pathogenic

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Benign

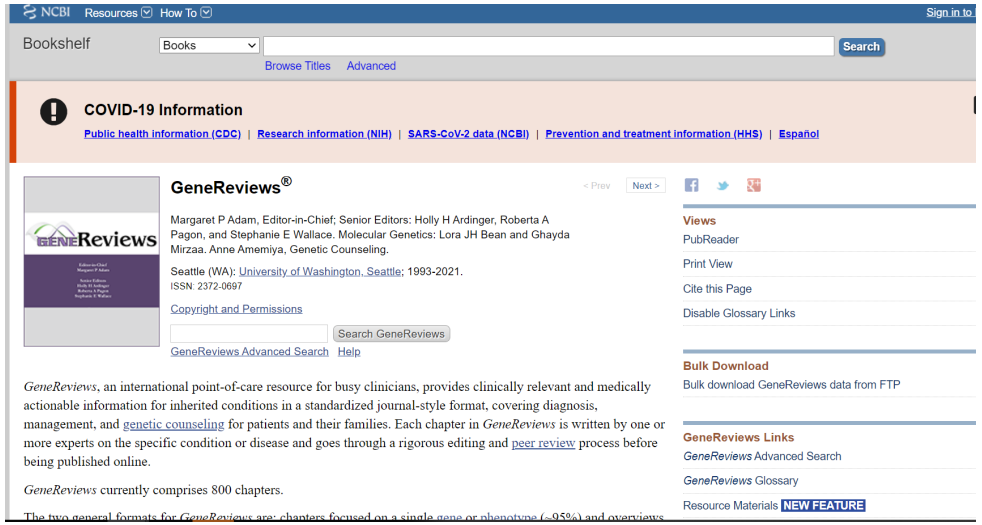
90% of the mental load

What to do with results

- Inheritance patterns match variants?
- Does condition explain the problems you know the child has?
- Does the child have problems that are not explained by the result?
- Does the condition have any manifestations you haven’t looked for yet in the child?
- Were there unexpected results?

Resources for result interpretation and counseling

- Geneticists
- Genetic counselors
- Specialists that care for condition
- Online resources
  - GeneReviews
  - OMIM
  - Unique disorder guides
  - PubMed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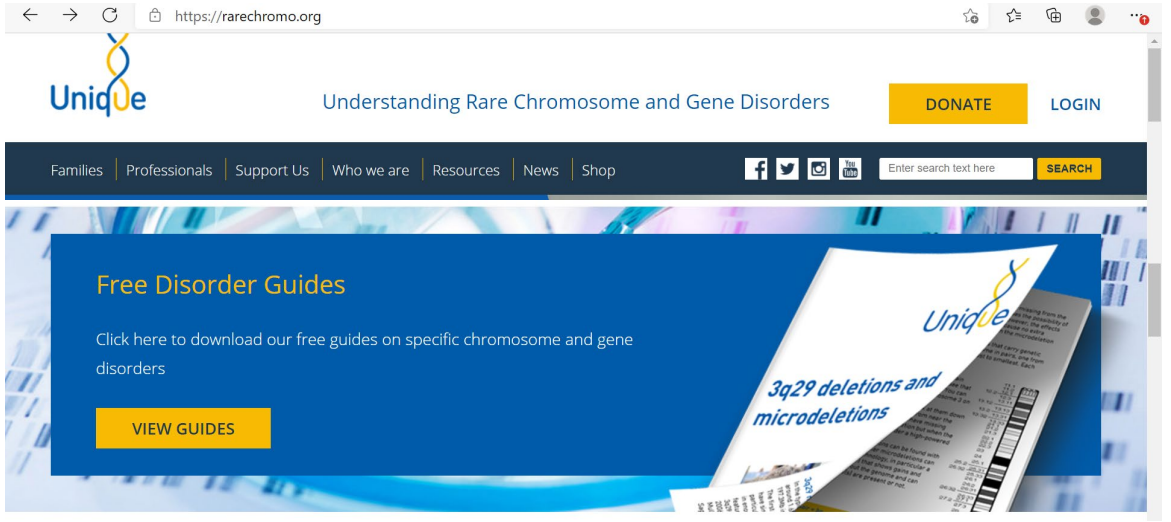
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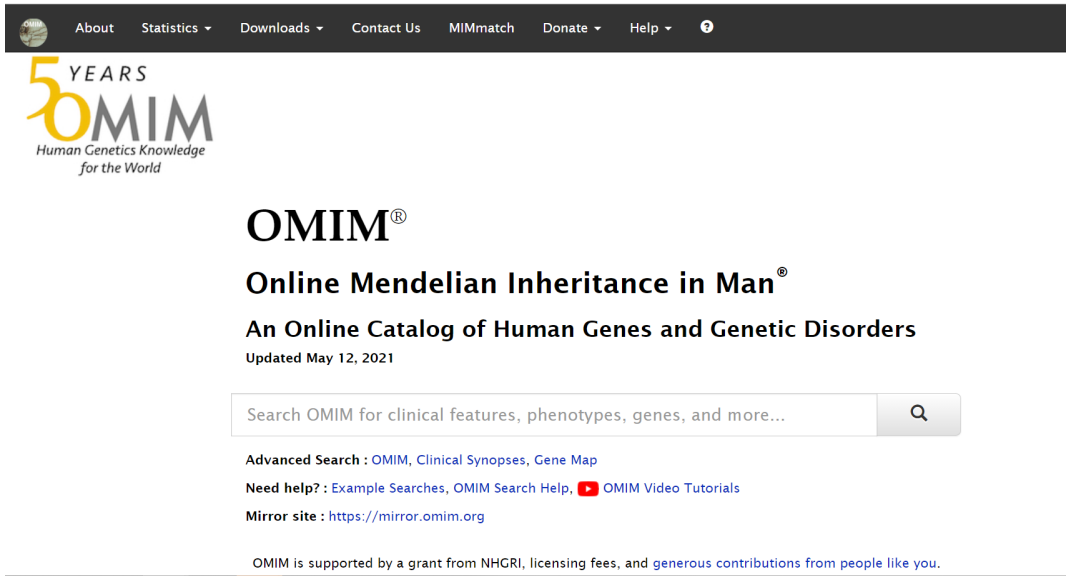
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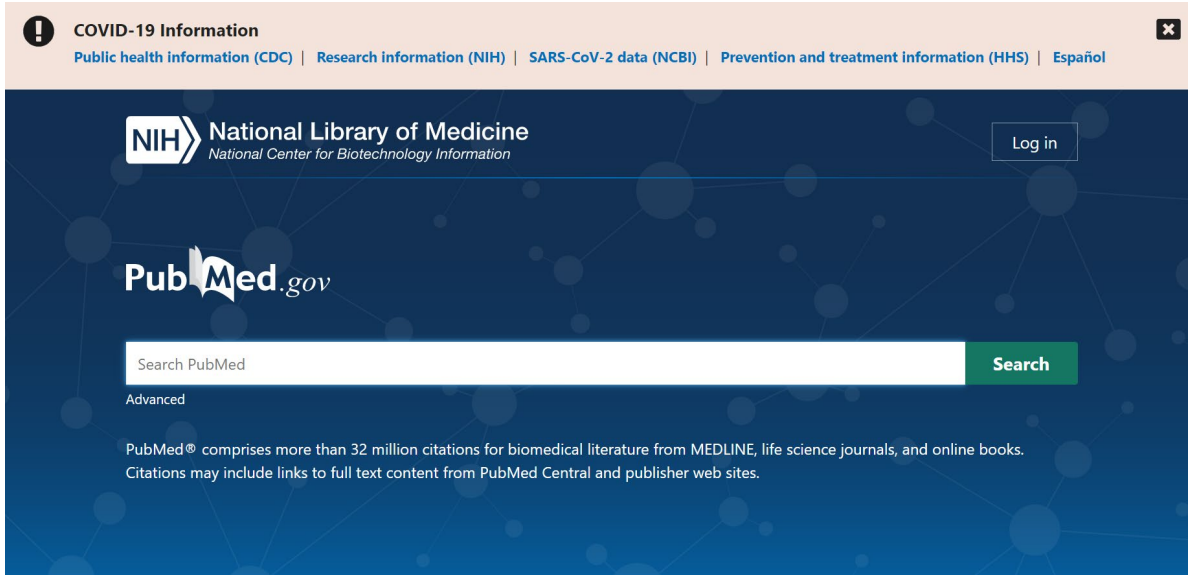
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Unexpected results

- Changes in genes unrelated to reason test was sent
- Carrier status
- Nonpaternity
- Consanguinity
- Findings that affect future life insurance, employment

Insurance authorization

- Genetic counselors provide support for family cost-containment and obtaining insurance pre-authorization
- The amount a patient will pay for a genetic test depends on:
  - Inpatient/outpatient
  - Preauthorization
  - Different labs charge different amounts
  - Different hospitals have different negotiated rates and preferred labs
  - Insurance differences: HDP, PPO, deductibles for year, Medicaid, charity care

Genetic test interpretation pearls

01

Proceed (with genetic testing) with caution

02

Targeted testing easier to interpret (and often cheaper)!

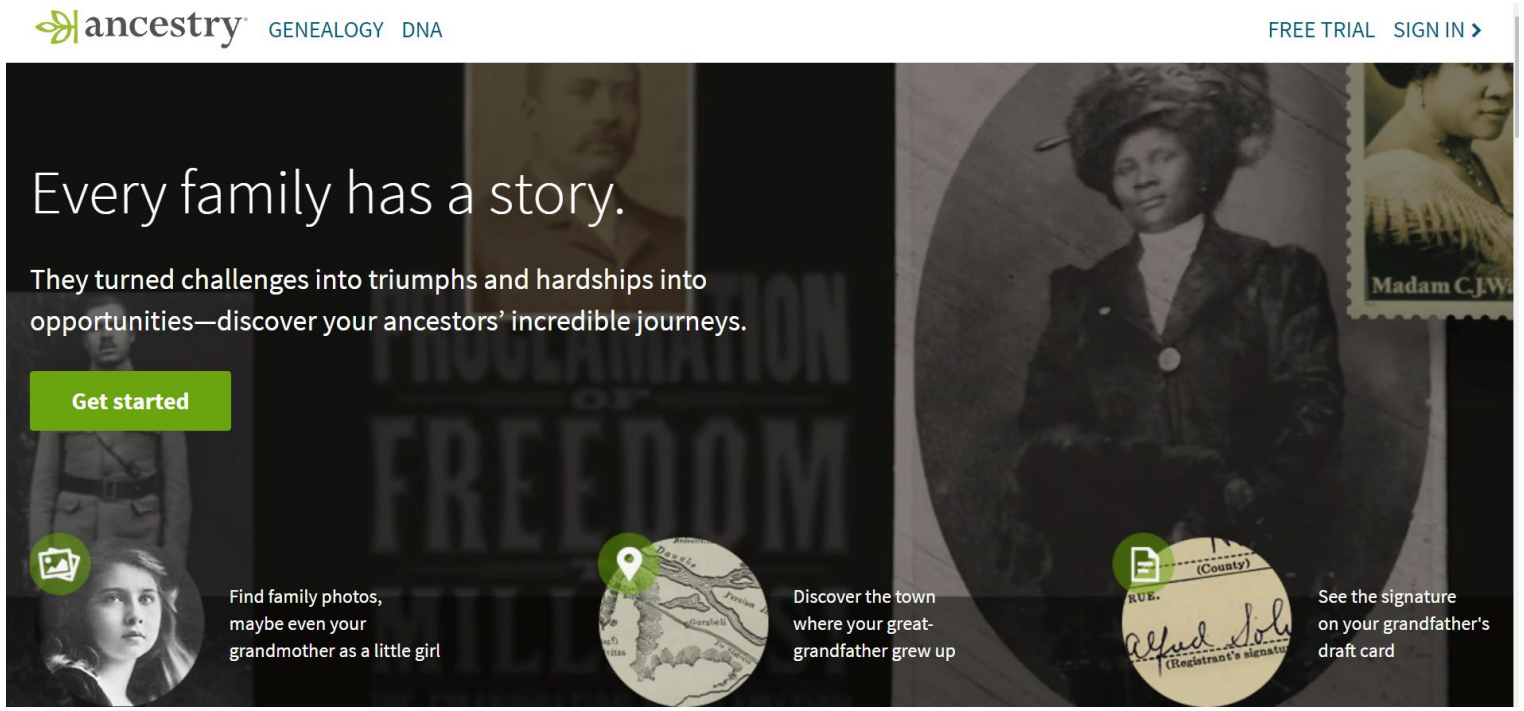
03

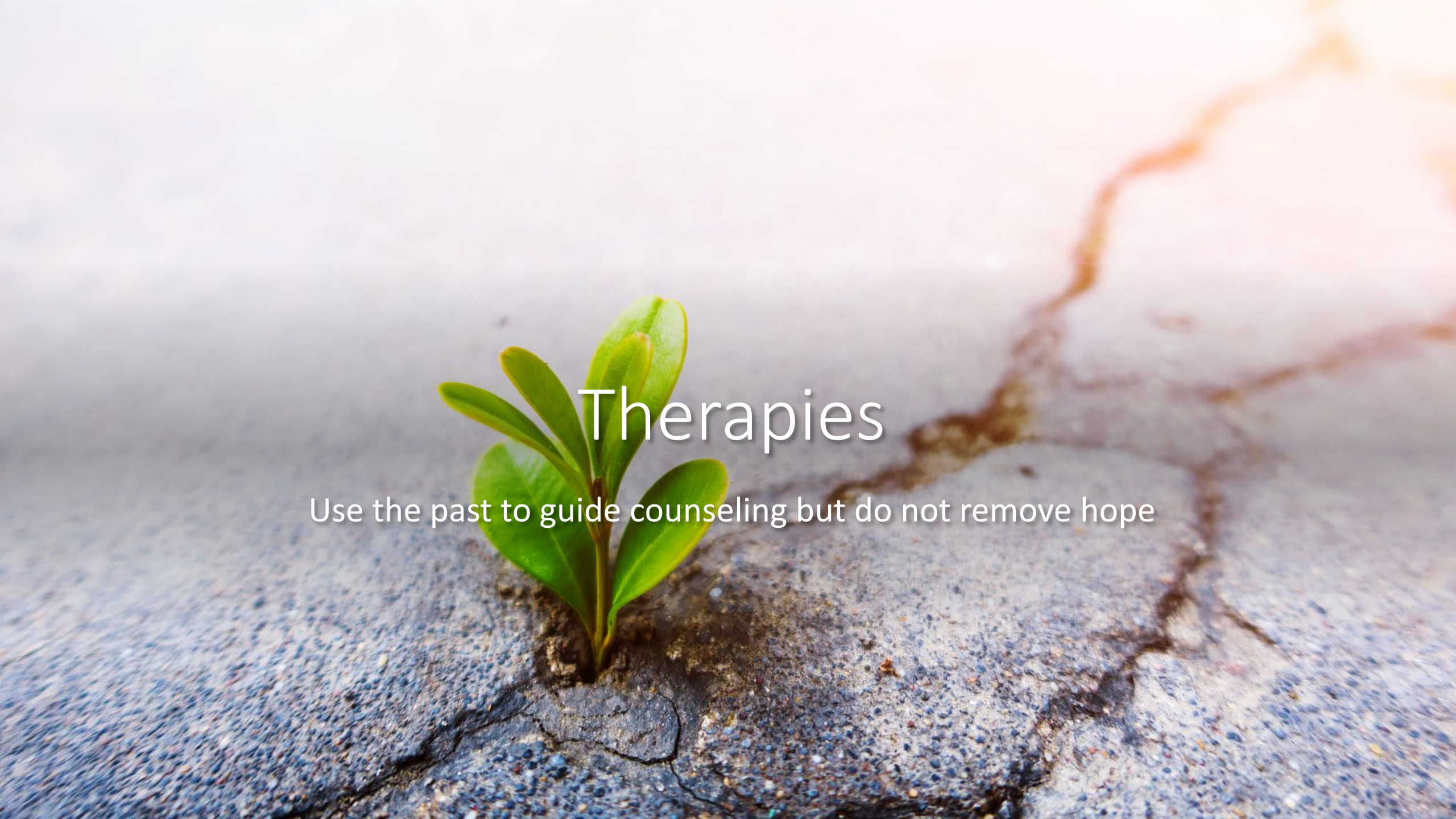
Cheapest and most effective genetic test is history and exam

04

Stay in the grey

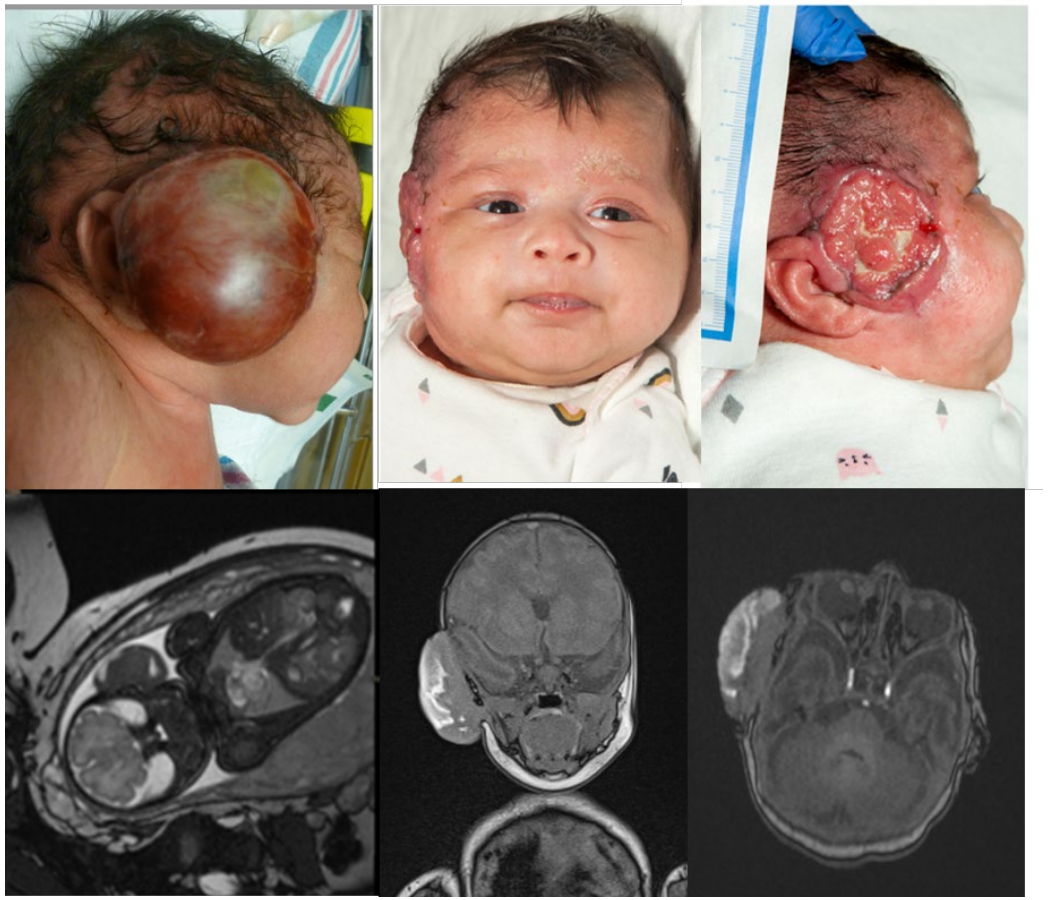
“Recreational” genetic testing




Therapies
Use the past to guide counseling but do not remove hope

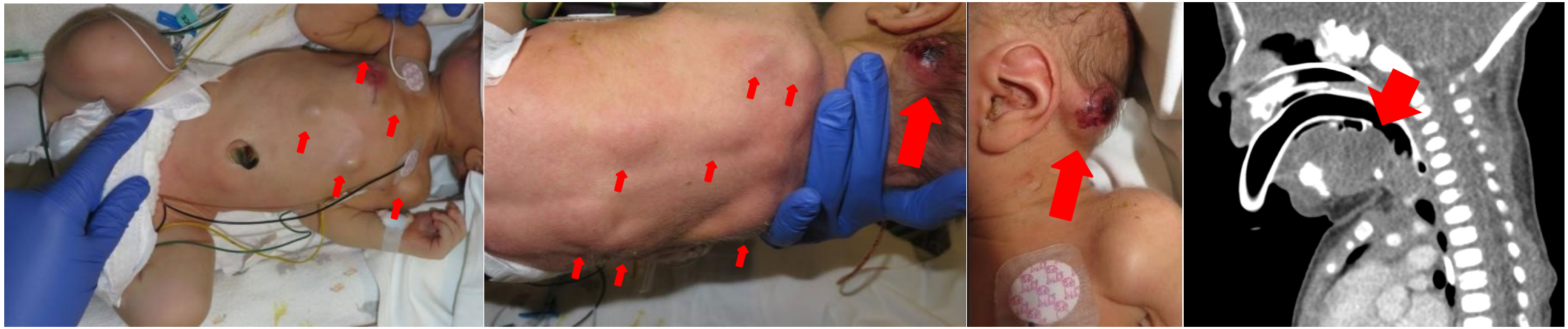
At birth

After surgical debulking



Wenger et al, 2020

At birth



Wenger et al, 2020

Infantile myofibromatosis

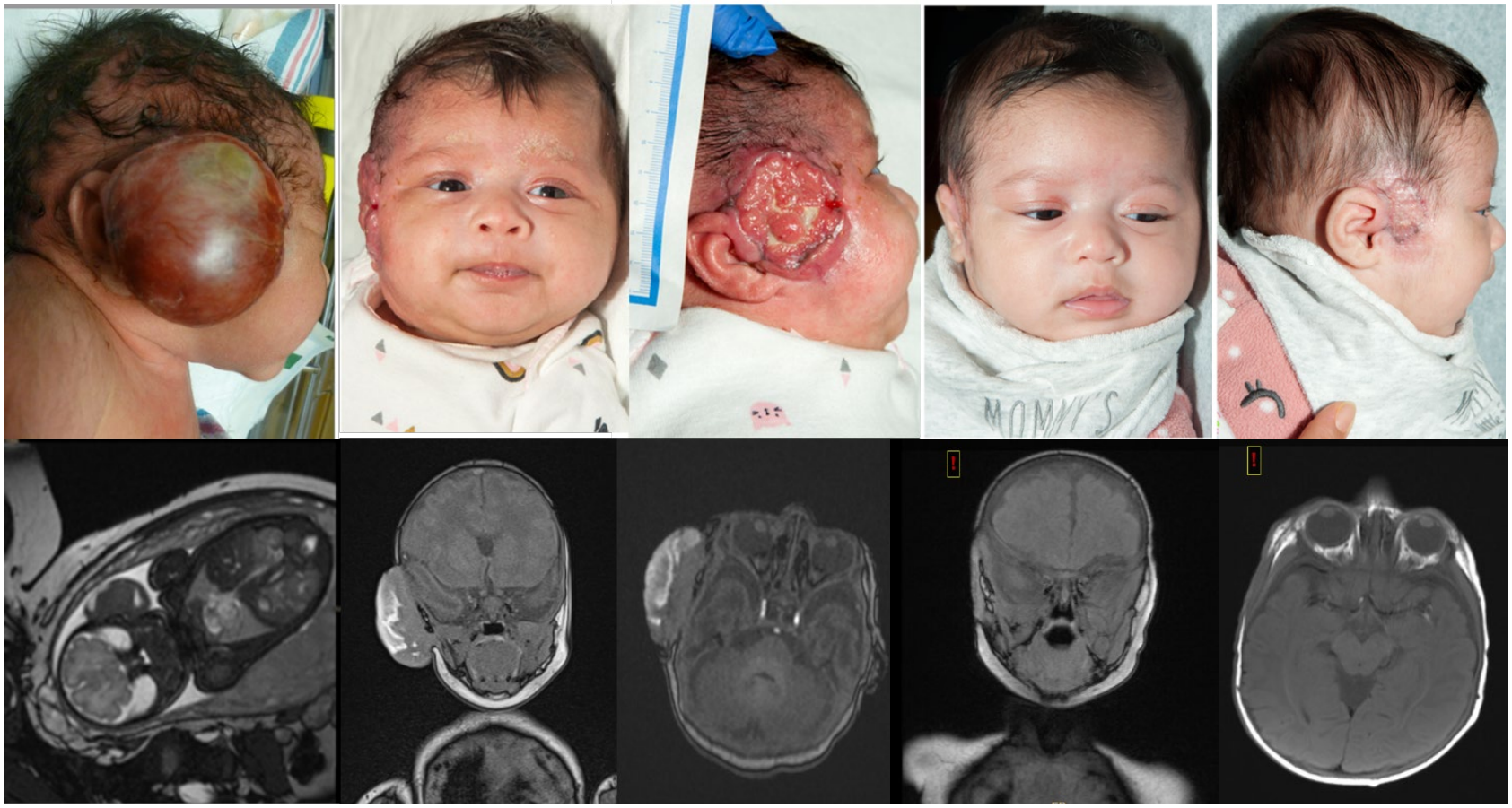
Type	Solitary (Type 1)	Multicentric type nonvisceral involvement (Type 2)	Multicentric type with singular visceral involvement (Type 3)	Multicentric type with multiple visceral involvement (Type 4)
Percent of patients	59.8%	26.7%	2.7%	10.8%
Mortality	0.6%	5.8%	0%	92.9%

Wenger et al, 2020

At birth

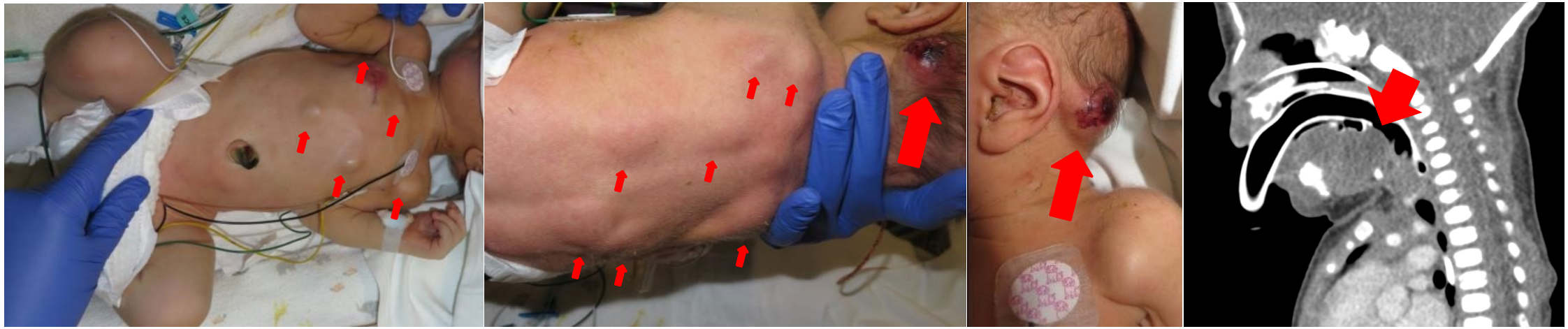
After surgical debulking

Imatinib monotherapy
3 weeks



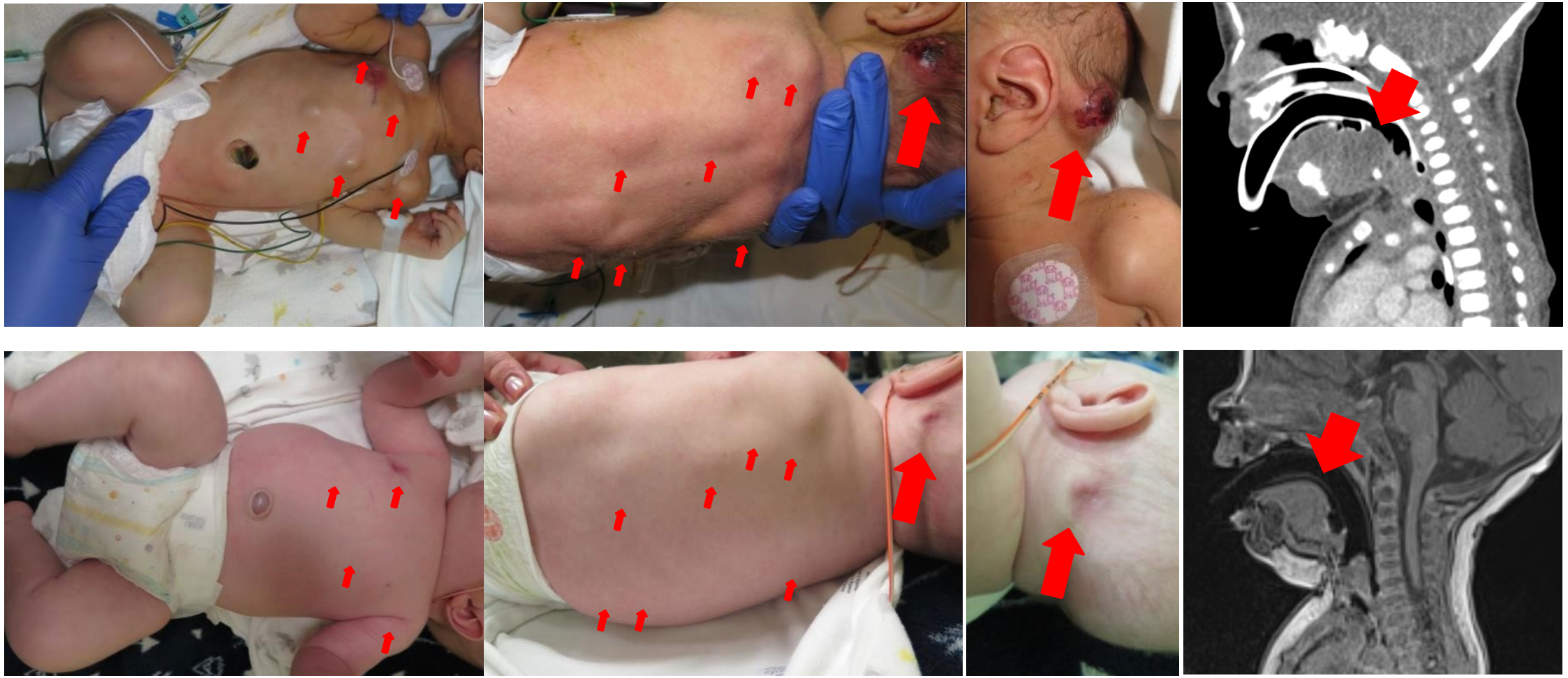
Wenger et al, 2020

At birth



Wenger et al, 2020

At birth

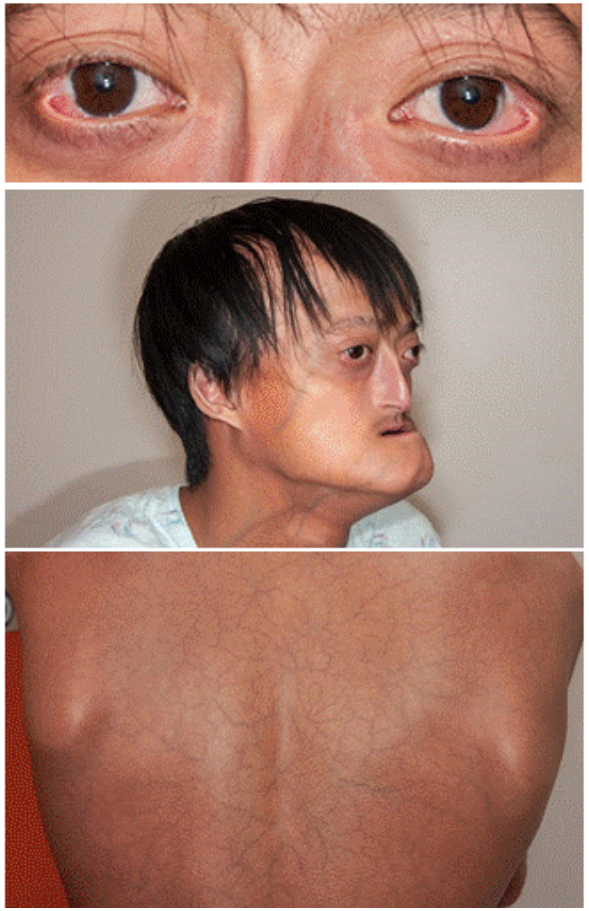


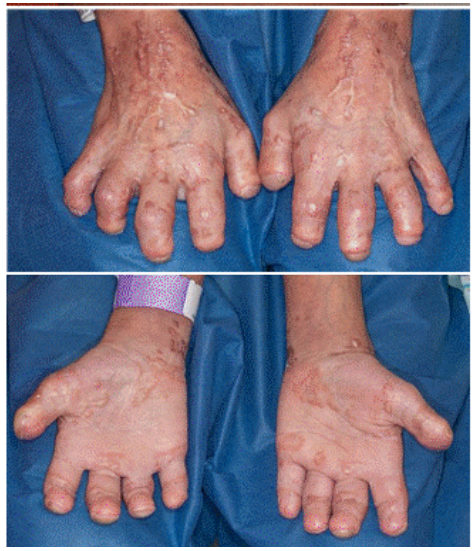
Imatinib monotherapy – 3-4 weeks

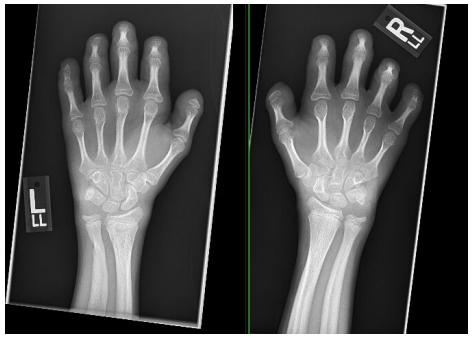
Extubation → room air by 3 weeks, discharge at 4 weeks

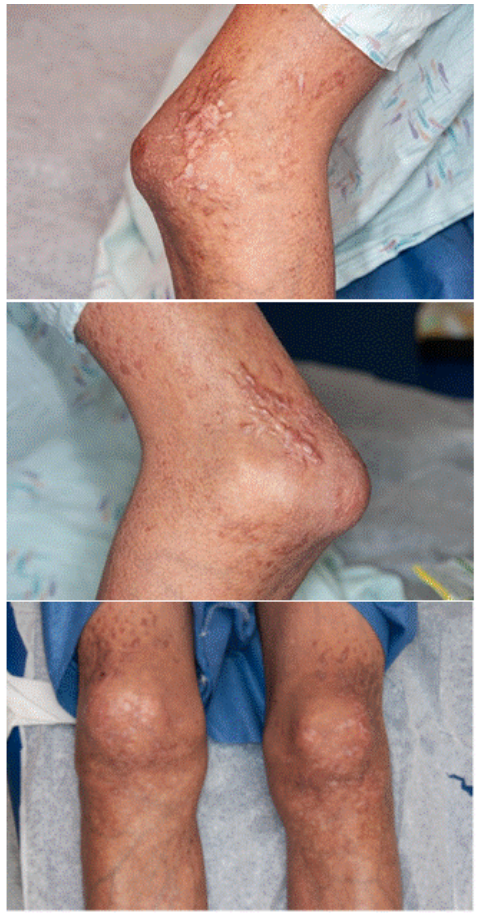
Wenger et al, 2020

Wenger et al, 2020



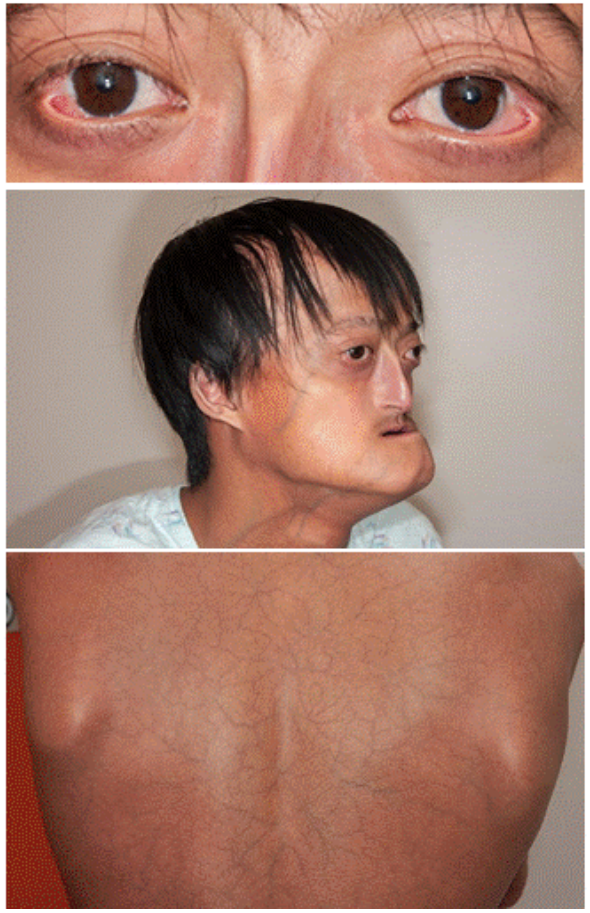




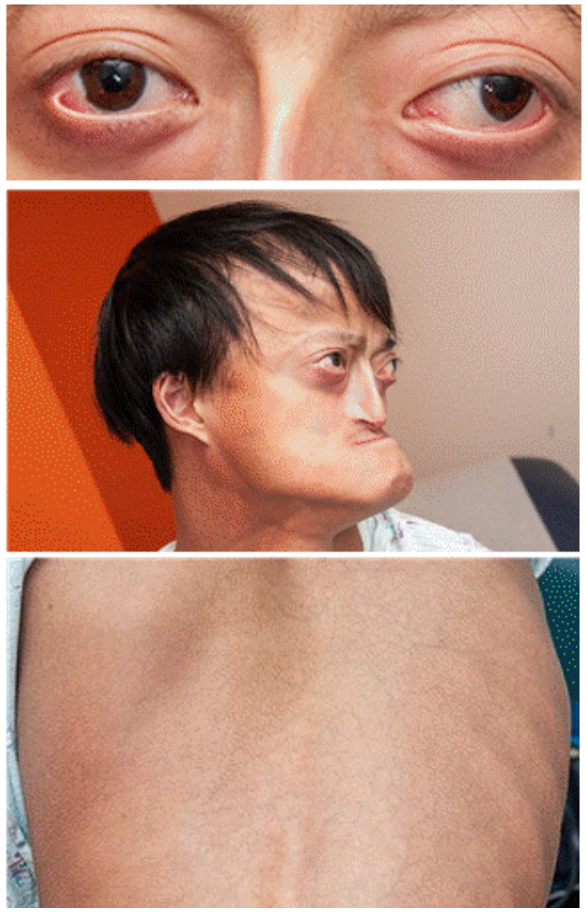


Wenger et al, 2020

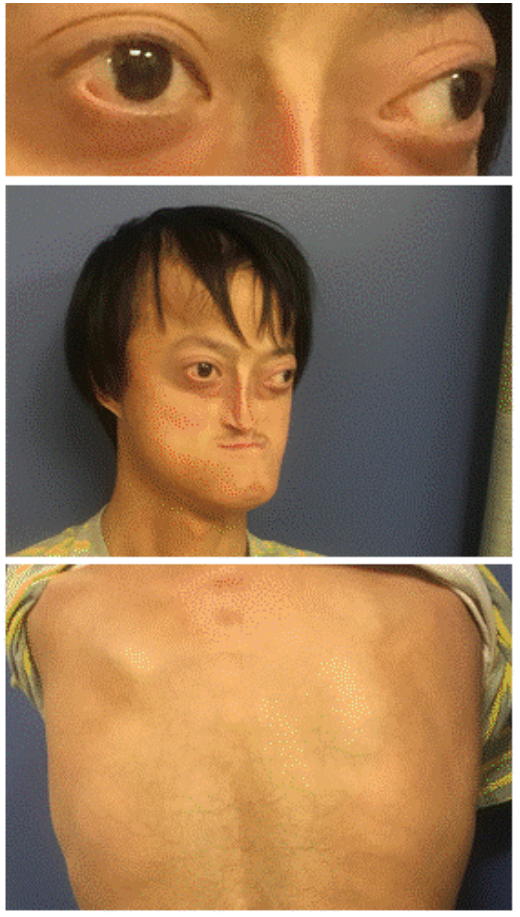
Pre-treatment



Imatinib 1-2 months



Imatinib 4 months



Wenger et al, 2020

PDGFRB associated disorders - therapy

Genetic therapy pearls

01

Rapid development of new therapies

02

ClinicalTrials.gov…. But also phone a friend

03

HOPE


Any
Questions