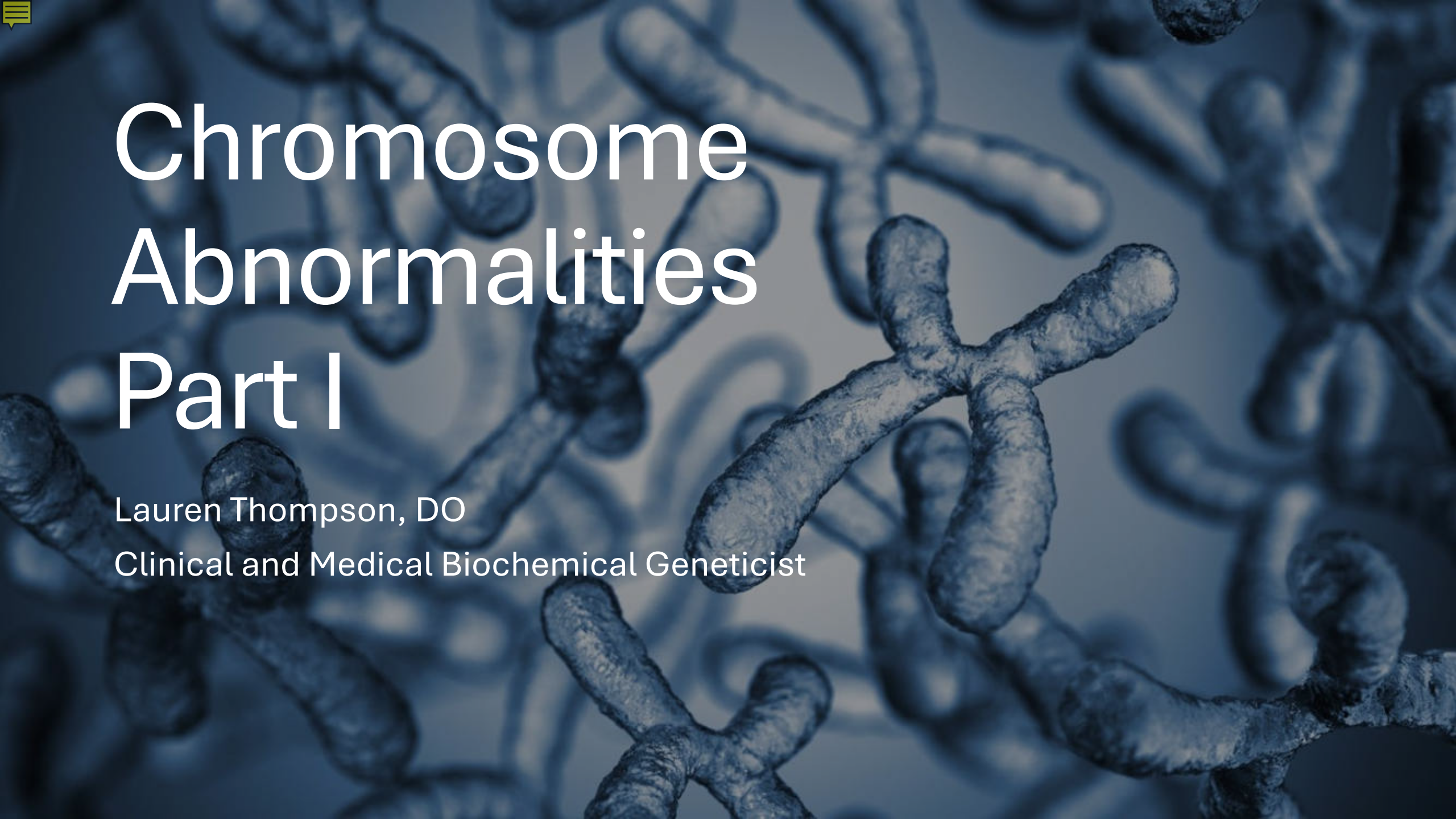


Chromosome Abnormalities Part I

Lauren Thompson, DO

Clinical and Medical Biochemical Geneticist

POPULATION CYTOGENETICS

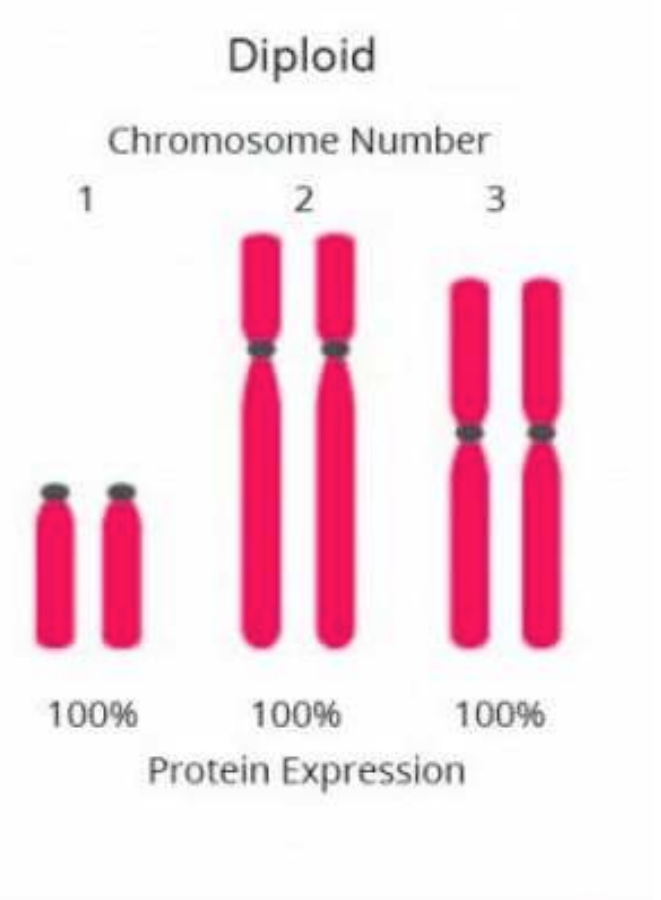
- Risk for chromosome abnormalities ~ 1 in 150 live births.
- Prevalence of spontaneous abortions is higher if an offspring has a chromosomal aberration.

Detection of Chromosomal Aberrations Based Upon Ascertainment

Spontaneous Abortion	Up to 24 weeks	~ 50%
Stillbirth	24 - 28 weeks	~ 4% - 13%
Neonatal death	0 - 30 days after birth	~ 5%
Liveborn		~ 0.6%

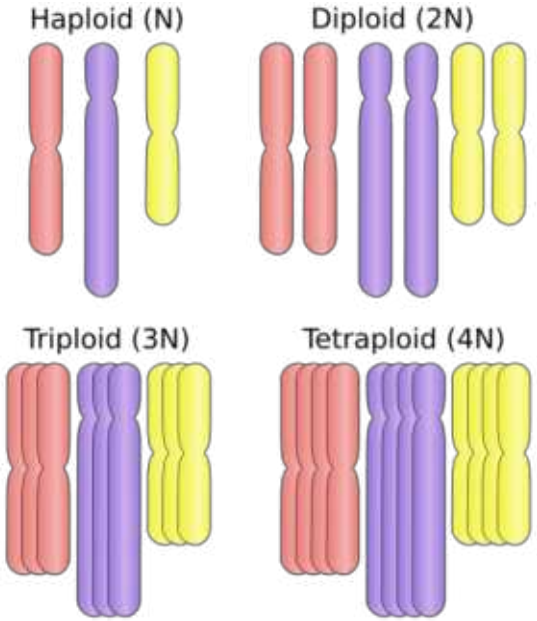
CHROMOSOME ABNORMALITIES: TERMS TO KNOW

- **Euploid**: Chromosome number that is a multiple of the base haploid number for a species, meaning it's a <u>normal</u> number of chromosomes
  - Disomy (2n): Normal state in which an organism or (body) cell has two copies of a particular chromosome



CHROMOSOME ABNORMALITIES: TERMS TO KNOW

- Variations in euploidy involve changes in the total number of **chromosome sets** in a cell or individual
  - **Haploid** (n).
    - One chromosome set (i.e., one copy of every chromosome). Normal state for gamete (sex) cells and some eukaryotic organisms.
      - 23 total chromosomes
  - **Diploid** (2n)
    - Two chromosome sets. One chromosome set is inherited from each parent. Normal state for many eukaryotic organisms and for most of the cells in the human body.
      - 23 pairs of chromosomes = 46 total chromosomes
  - **Polyploid**. More than two <u>whole sets</u> of chromosomes
    - **Triploidy** (3n): Three chromosome sets (69 chromosomes)
      - Dyspermy and Dygyny – *detailed next slide*
    - **Tetraploidy** (4n): Four chromosome sets (92 chromosomes)
      - Doubling of the normal 46 chromosomes
      - Failure of zygote to complete first division (post-zygotic, post-fertilization)



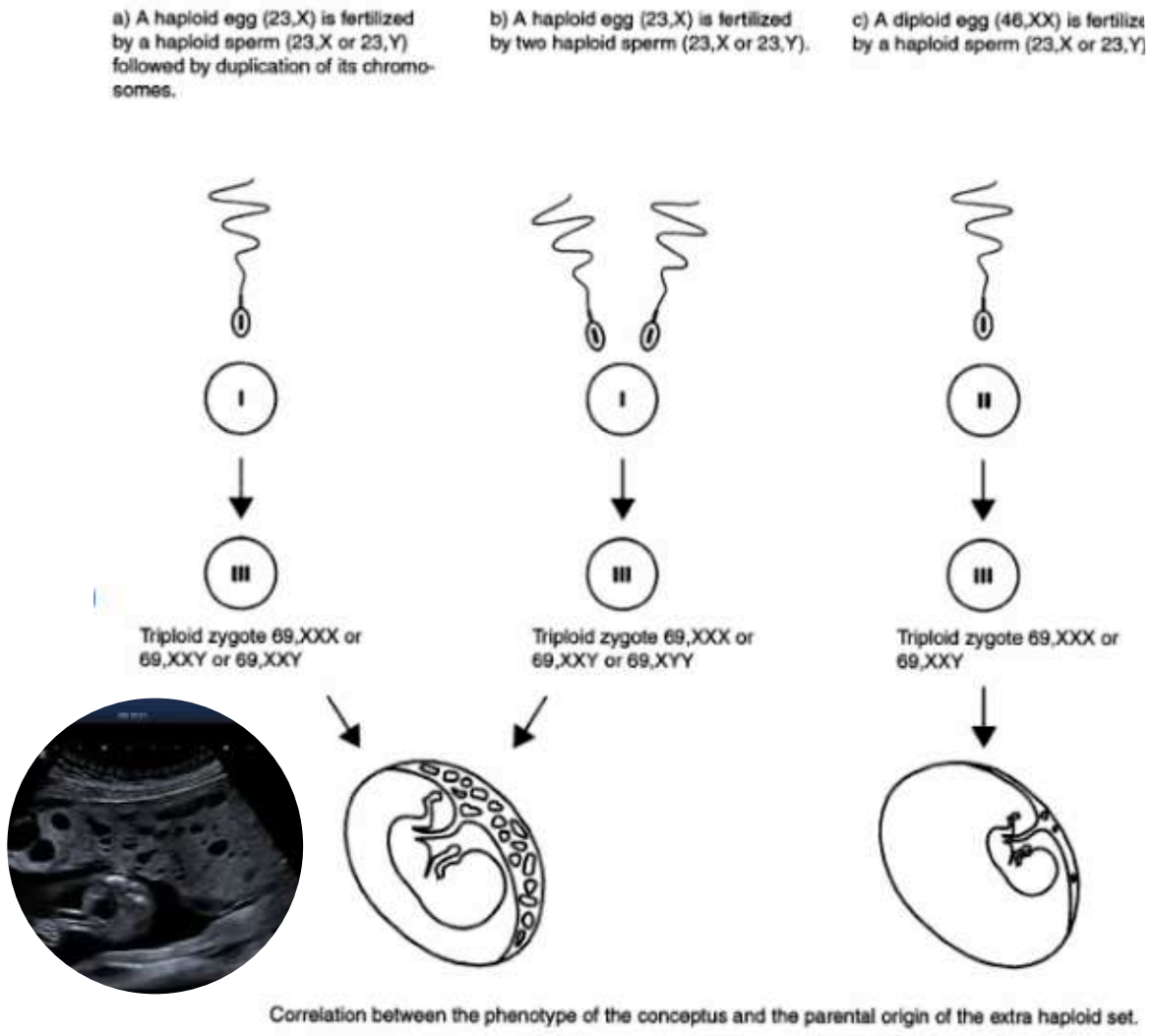
https://books.byui.edu/genetics_and_molecul/14___chromosome_vari

n = the number of chromosomes within a set

CHROMOSOME ABNORMALITIES: POLYPLOIDY

Polyploidy occurs in 2-3% of pregnancies

- <1% liveborn. Most result in spontaneous abortions and/or stillbirths
- **Triploid** (3n) can result in:
  - **1. Diandry/Dispermy;** extra chromosomes of paternal origin
    - Two spermatozoa fertilize a single ovum
    - Most common cause of triploidy (2/3 of cases)
    - Presentation:
      - **Partial hydatidiform mole**
        - Large placenta with hydropic changes ("bundles of grape appearance")
  - **2. Digyny**: extra chromosome of maternal origin
    - A spermatozoon fertilize a diploid ovum
    - Presentation:
      - Small placenta without hydropic changes



https://www.researchgate.net/figure/Mechanisms-of-formation-of-triploidy_fig4_10914524

CHROMOSOME ABNORMALITIES

Numerical Abnormalities:

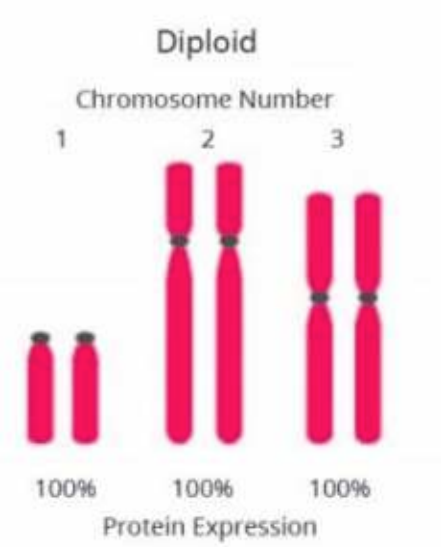
Aneuploidies

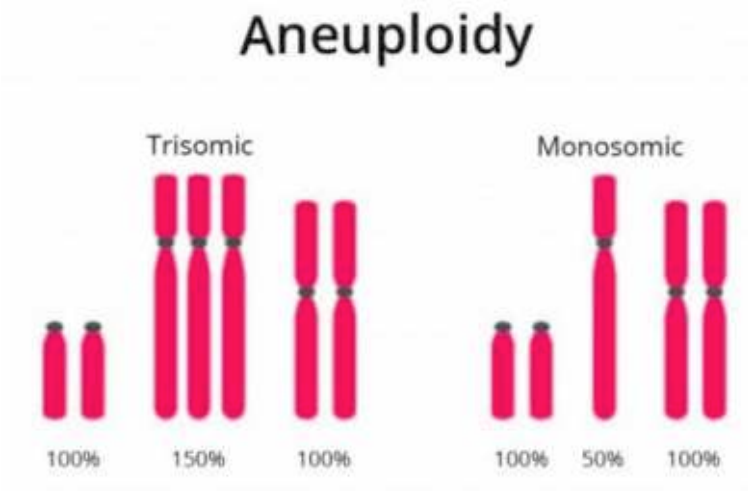
Structural Abnormalities:

Translocations, inversions, deletions, duplications

CHROMOSOME ABNORMALITIES: ANEUPLOIDY

- **Aneuploidy**:
  - Changes to the number of chromosomes within a chromosome set (not an exact multiple of the usual haploid number).
    - **Monosomy** (2n-1): 1 missing copy of a particular chromosome
      - Ex: 45, X (Turner syndrome)
    - **Trisomy** (2n+1): 1 extra copy of a particular chromosome
      - Ex: 47, XX, +21 (Trisomy 21)
    - **Nullisomy** (2n-2): Missing both copies of the chromosomes that constitute a homologous chromosome pair.
      - Ex: 44, XX, -7, -7 (no chromosome 7)

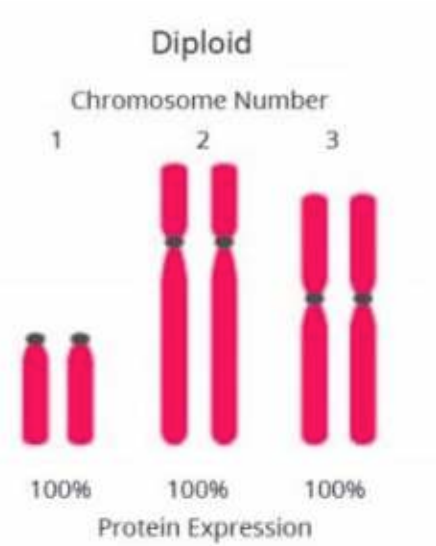


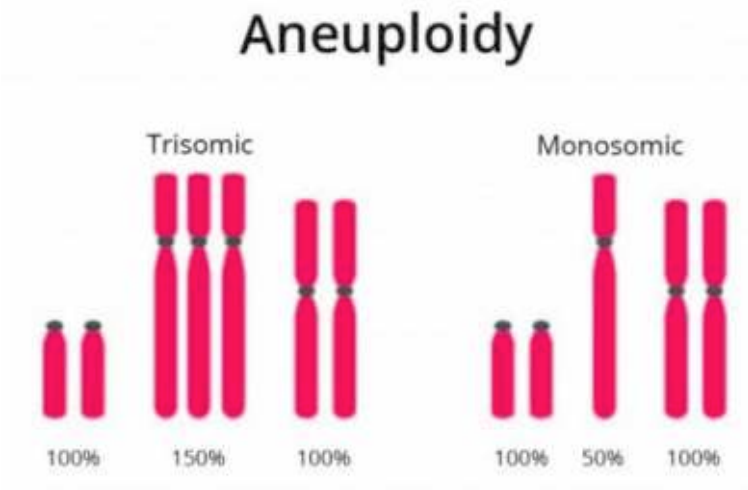


https://books.byui.edu/genetics_and_molecul/14__chromosome_vari

CHROMOSOME ABNORMALITIES: ANEUPLOIDY

- **Aneuploidy**:
  - Most common cause of clinically significant chromosome abnormalities
  - Aneuploidy of the sex chromosomes is usually better tolerated than aneuploidy of the autosomes (non-sex chromosomes)
  - Most common cause of aneuploidy is nondisjunction from maternal meiosis I





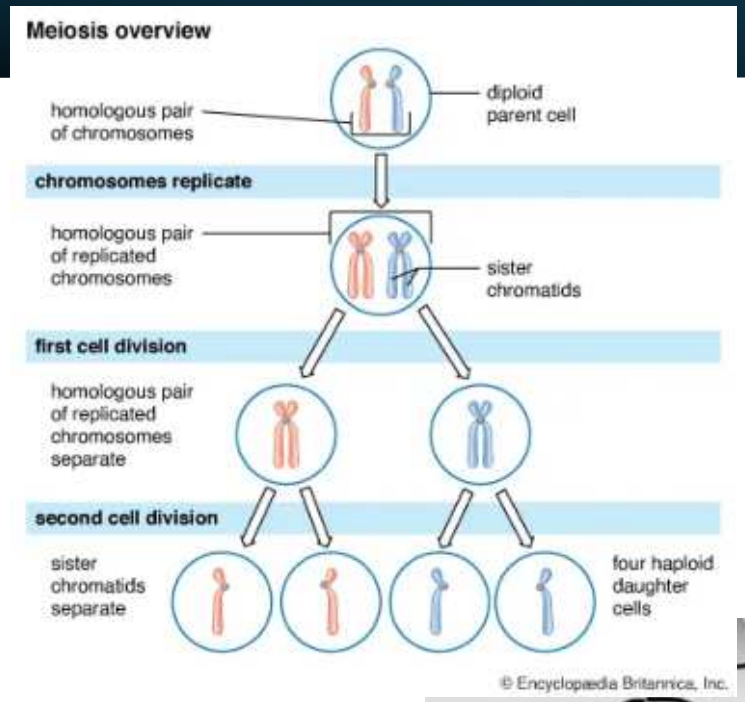
https://books.byui.edu/genetics_and_molecul/14___chromosome_vari

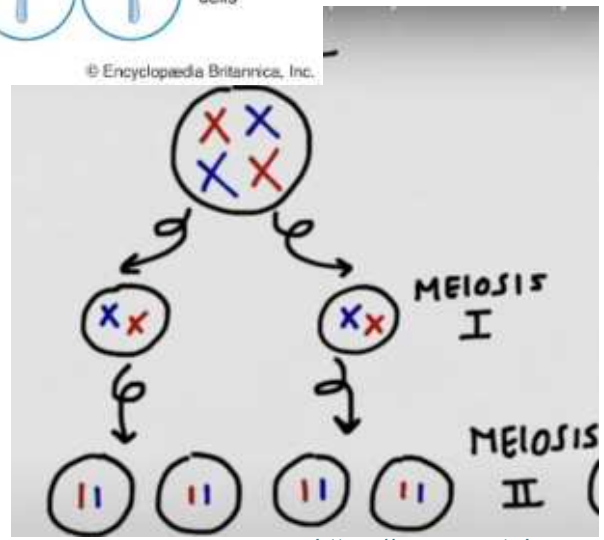
NONDISJUNCTION

- Abnormal chromosome segregation
  - Meaning you end up with too few or too many chromosome in one or more daughter cells.

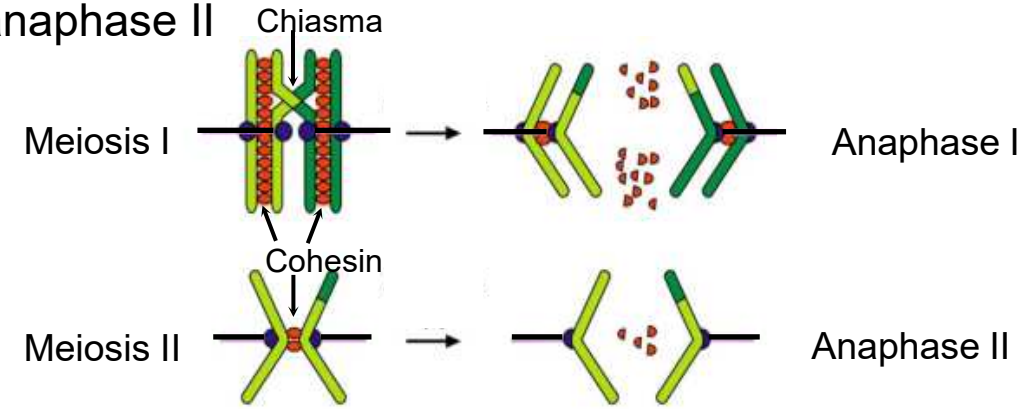
- Can occur in meiosis I or II

Meiosis



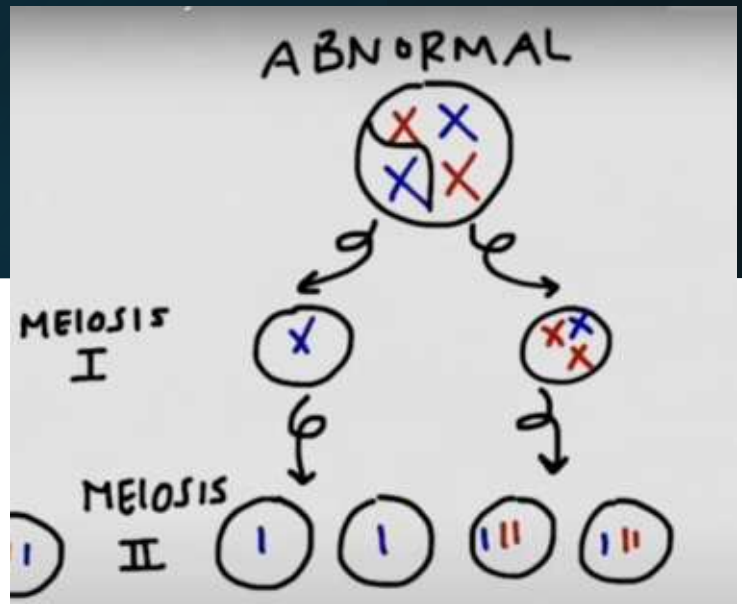


- Meiosis you go through two rounds of division:
  - Meiosis I
    - Homologous chromosomes remain attached during diplotene arrest via chiasmata.
    - Cohesions hold the sister chromatids together and helps to keep chiasmata in place during prophase I until each pair of homologous chromosomes separates and move to opposite poles during anaphase I.
  - Meiosis II:
    - Cohesins are utilized to attach sister chromatids at their centromeres
    - Cohesions are released as sister chromatids move to opposite poles during anaphase II



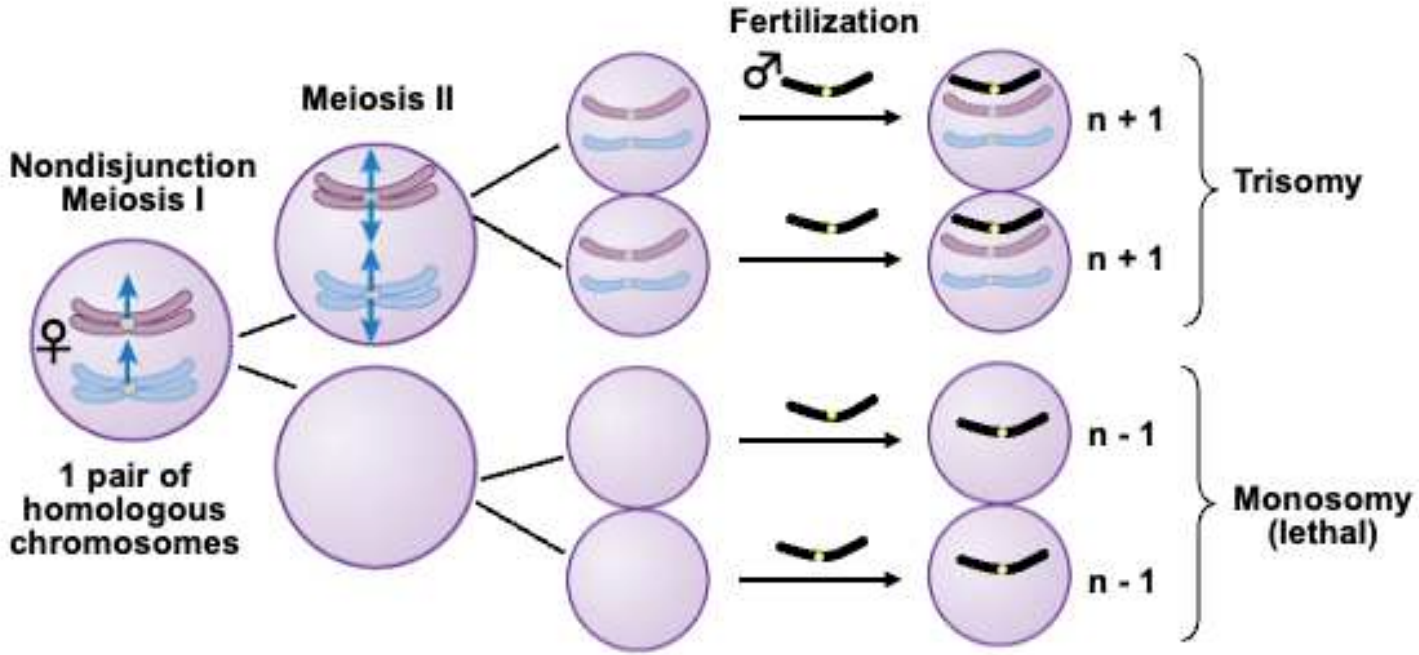
https://www.youtube.com/watch?v=sg7xe8C9DmQ

NONDISJUNCTION

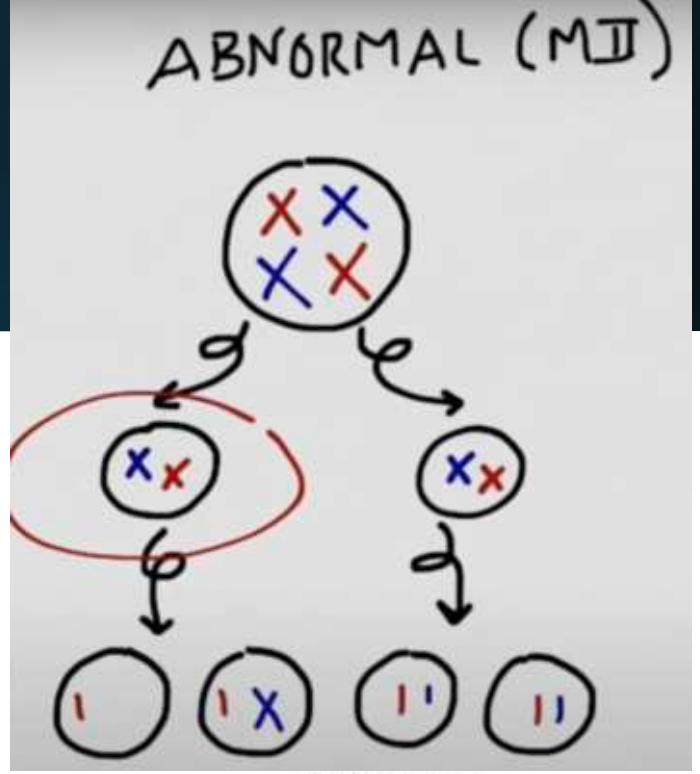


https://www.youtube.com/watch?v=sg7xe8C9DmQ

- **Meiosis I:** failure to separate pair of homologous chromosomes
  - Causes for nondisjunction during meiosis I:
    - 1. Achiasmate: chiasmata not formed
    - 2. Premature loss of cohesion
      - Occurs with increasing age
  - Will always result in an aneuploid offspring (either monosomy or trisomy)
  - All three chromosomes are unique

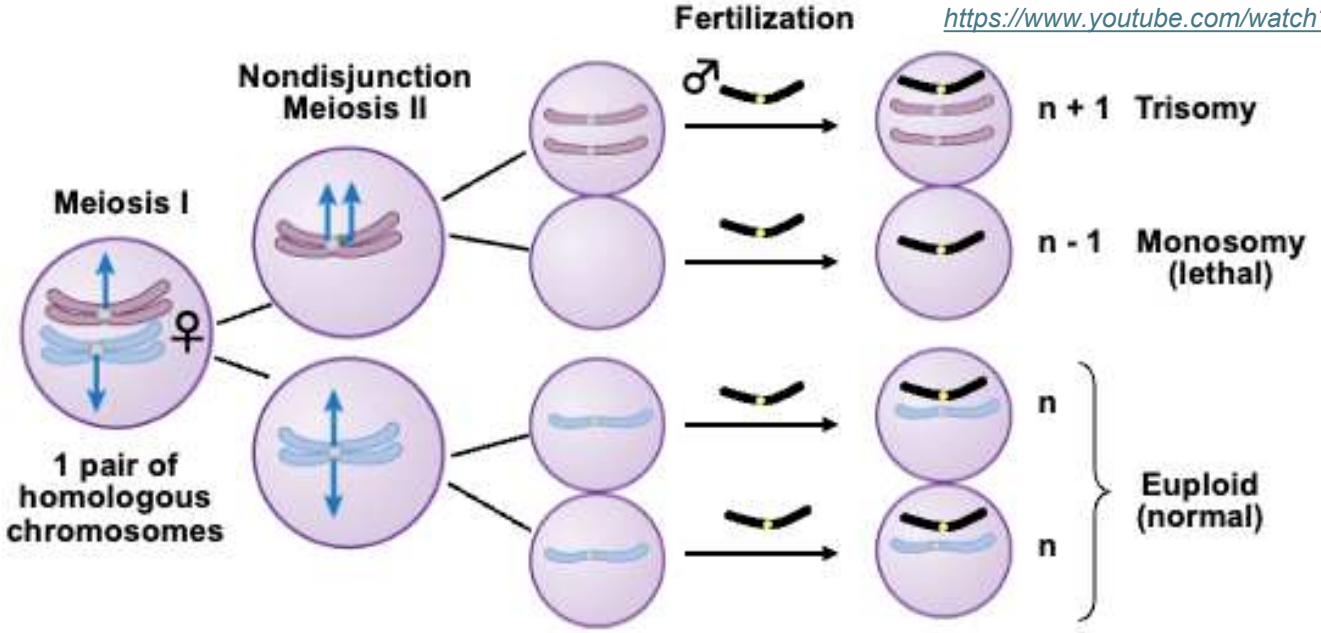


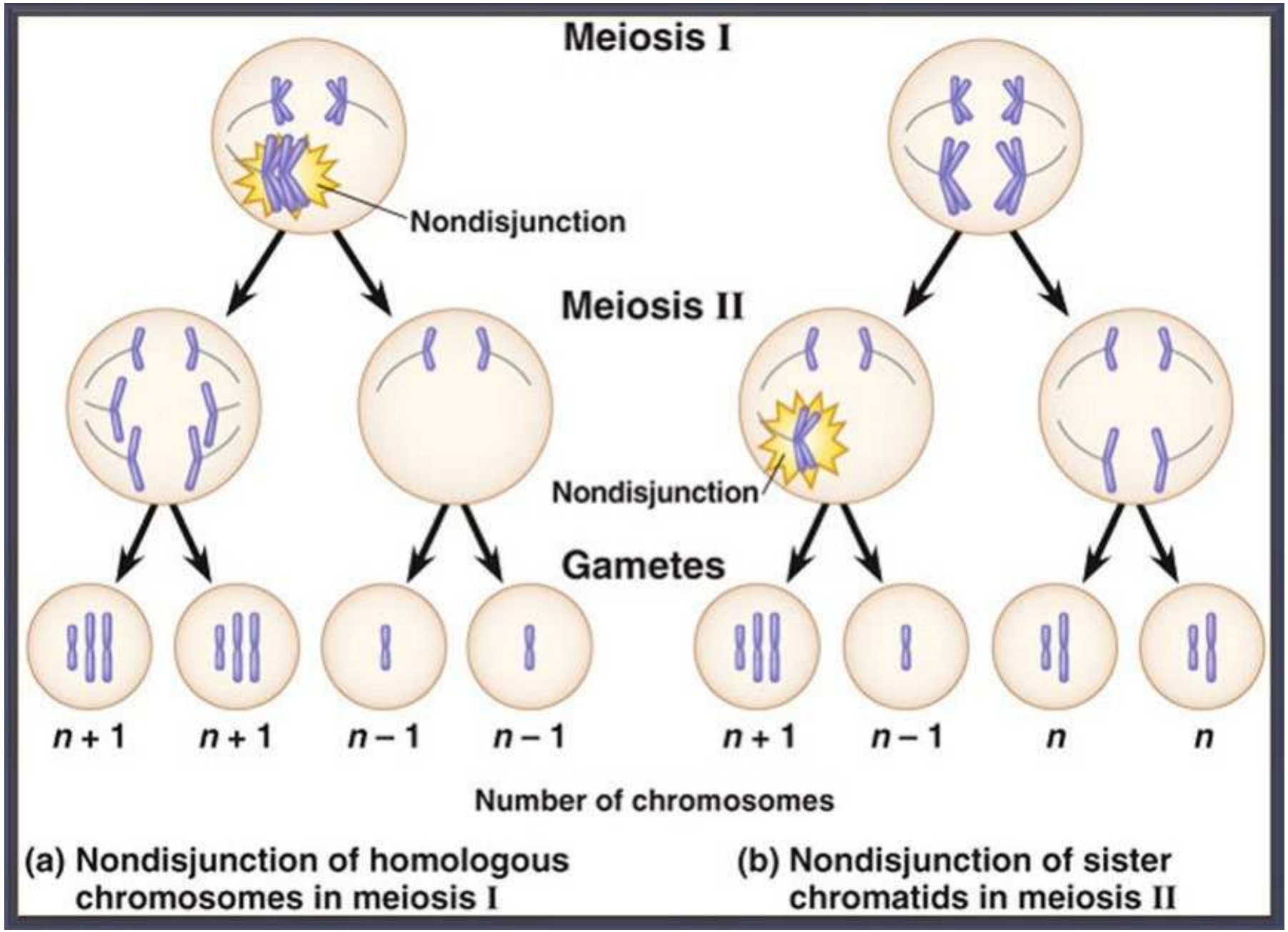
NONDISJUNCTION



- **Meiosis II:** failure to separate sister chromatids
  - Causes for nondisjunction during meiosis II:
    - Premature loss of cohesion function
      - Occurs with increasing age
  - Half the offspring will be aneuploid (monosomy or trisomy) while the other half will be euploid (normal number)
  - Extra chromosome is identical
    - Because the sister chromatids are identical, the resulting gametes will be genetically identical for that specific chromosome.

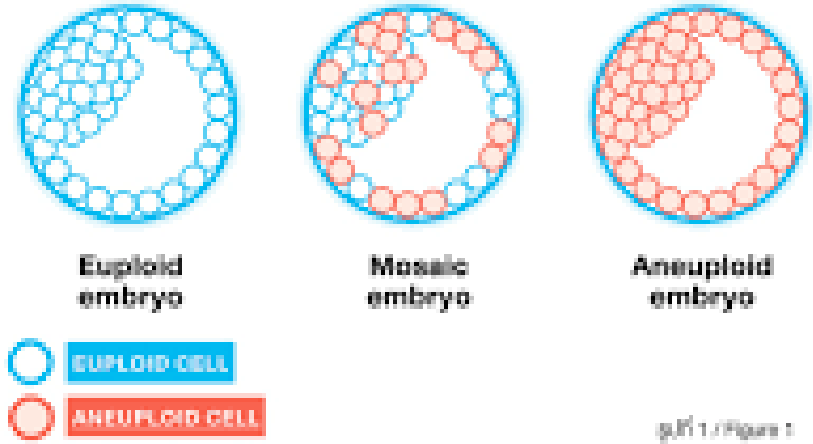
https://www.youtube.com/watch?v=sg7xe8C9D

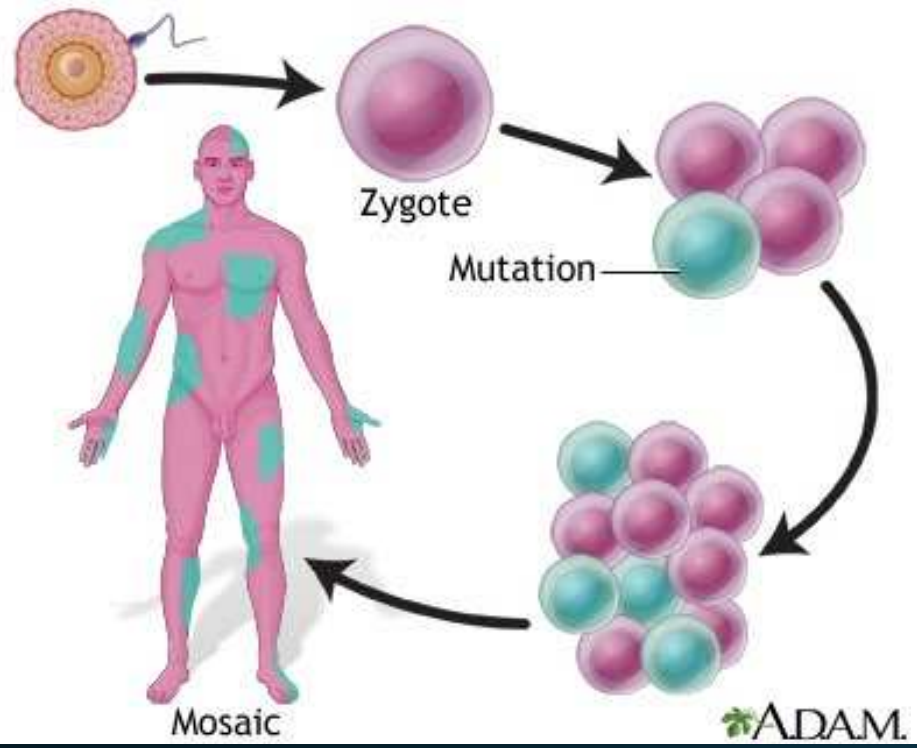



Meiosis I
Nondisjunction
Meiosis II
Nondisjunction
Gametes
n + 1
n + 1
n – 1
n – 1
n + 1
n – 1
n
n
Number of chromosomes
(a) Nondisjunction of homologous chromosomes in meiosis I
(b) Nondisjunction of sister chromatids in meiosis II

CHROMOSOME ABNORMALITIES: TERMS TO KNOW

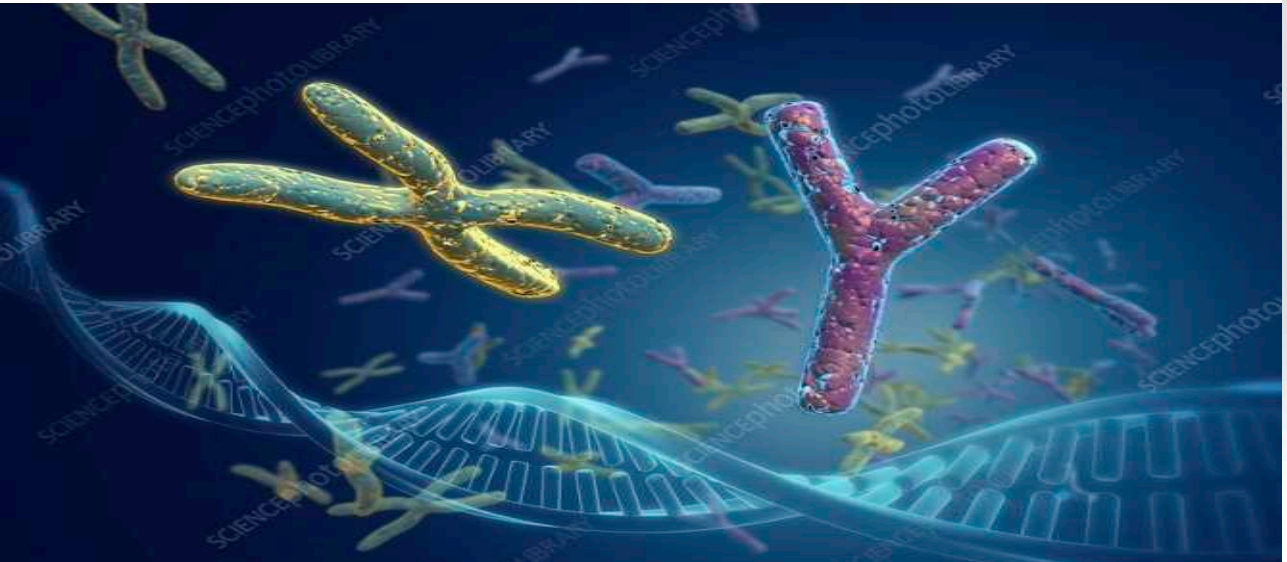
- **Mosaicism**
  - Two or more cell lines derived from a single zygote, always post fertilization/post zygotic
    - Mitotic errors are more commonly associated with mosaicism, particularly in embryos
  - Karyotype will have one normal cell line and one aneuploid cell line
    - Ex: 46, XY [16]/ 47, XXY[4] = means that 4 cells have XXY while the other 16 cells are euploid
  - Clinically, this can present with a less severe phenotype than the full aneuploid phenotype or could be asymptomatic depending on the percentage of mosaicism





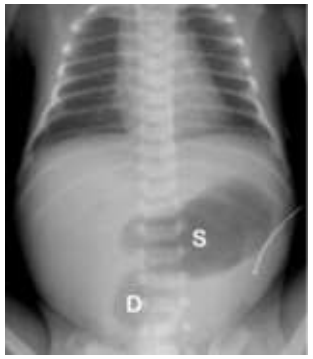
ABNORMALITIES IN CHROMOSOME NUMBER

- Viable aneuploidies are those that include chromosomes:
  - 13, 18, 21, X and Y



Type	Chromosome #	Nomenclature	Phenotype
Monosomy:			
Autosomal	46 - 1	NA	Embryonic lethal
Sex Chromosomal	46 - 1	45,X	Turner Syndrome
Trisomy:			
Autosomal	46 + 1	47,XX,+21	Down Syndrome
Sex Chromosomal	46 + 1	47,XXY	Klinefelter Syndrome
Triploidy	46 + 23	69,XXX	1-3% of conceptuses, 15% of miscarriages
Tetraploidy	46 + 46	92, XXXX	5% of chromosomally abnormal spontaneous abortions
Mosaicism:			
Autosomal	46/46 + 1	46,XY/47,XY,+21	Down Syndrome (5%)
Sex Chromosomal	46/46 + 1	46,XY/47,XXY	Klinefelter Syndrome

TRISOMY 21
DOWN SYNDROME

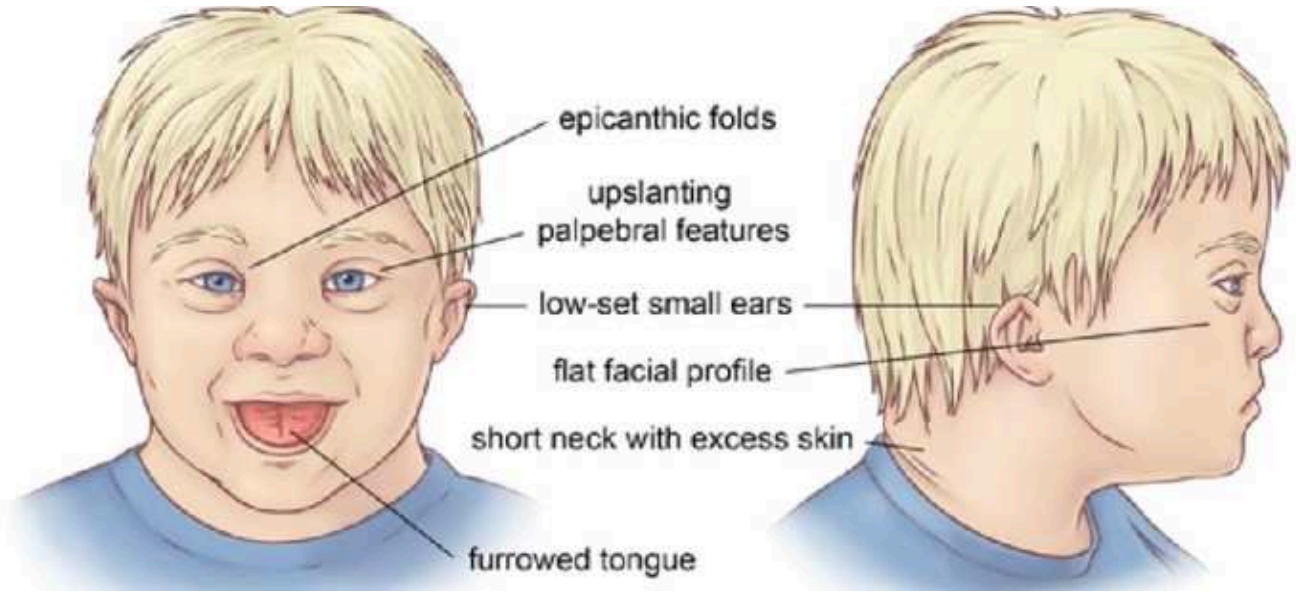


Common Features / Buzzwords
Congenital heart defects **(AV canal)**
Single palmar crease Wide sandal gap Short, broad hands and feet
Characteristic facial features (next slide)
Atlanto-occipital instability
Intellectual disability
GI anomalies (Hirschsprung, duodenal atresia)
Autoimmune (thyroid, celiac)
Brushfield spots
Hypotonia
Risk for leukemia and Alzheimers

TRISOMY 21
DOWN SYNDROME

Facial Features:

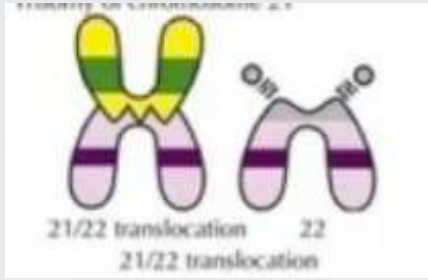
- Flattened face
- Flattened occiput
- Epicanthal fold
- Up slanting palpebral fissures
- Small mouth with prominent tongue
- Short, upturned nose
- Small, posterior-rotated ears
- Short neck with excess nuchal skin



Nejm.com
Radiopaedia.com

TRISOMY 21
DOWN SYNDROME

- Chromosome 21 is the smallest chromosome in the human genome
- Etiology
  - 95% nondisjunction during meiosis I
    - Of these, majority are maternal with <10% being paternal
  - 3-4% translocations
    - Majority involve chromosome 14 and 22 (others include chromosome 13,15)
  - 1-2% mosaic

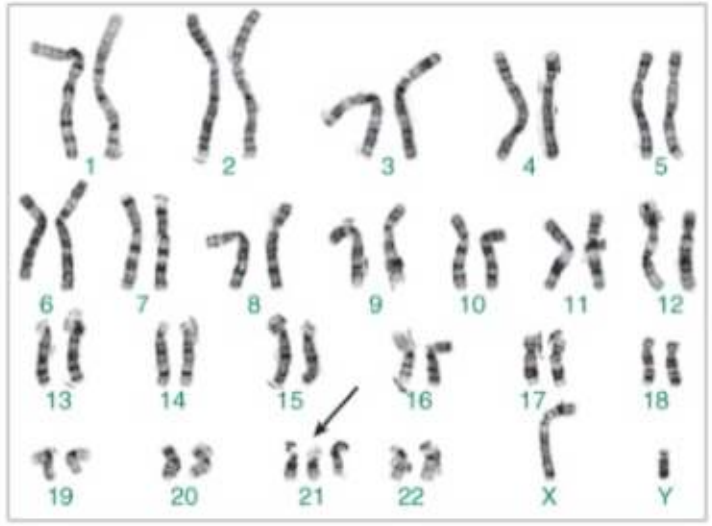


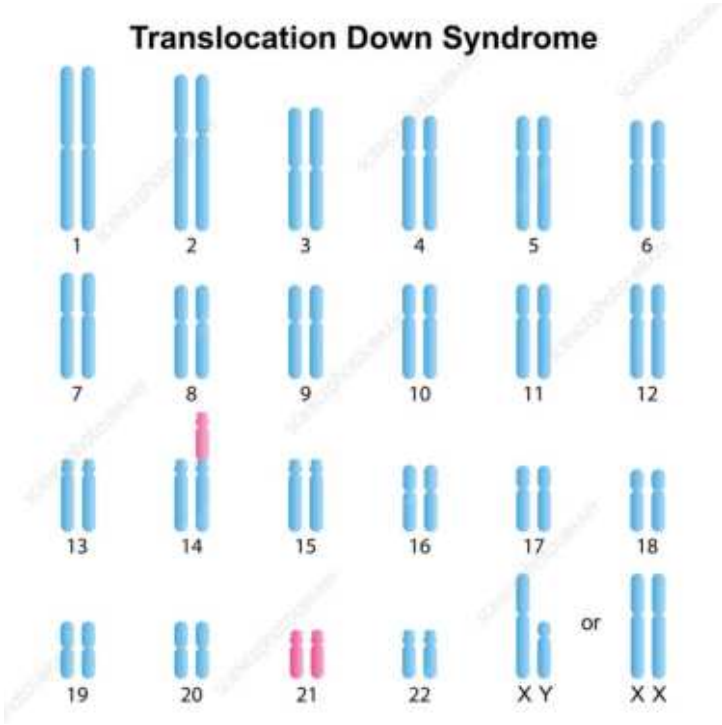
https://www.labtestsguide.com/down-syndrome

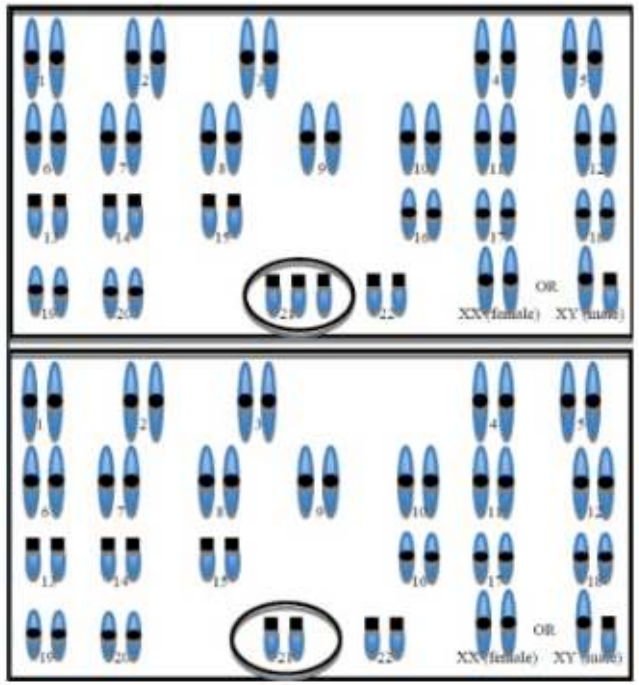
TRISOMY 21
DOWN SYNDROME

Karyotypes

Aneuploidy	Translocation	Mosaic
47,XX,+21 or 47,XY,+21	46, XX, der(14;21) (q10;q10), + 21	47,XY,+21[13]/46,XY[7]

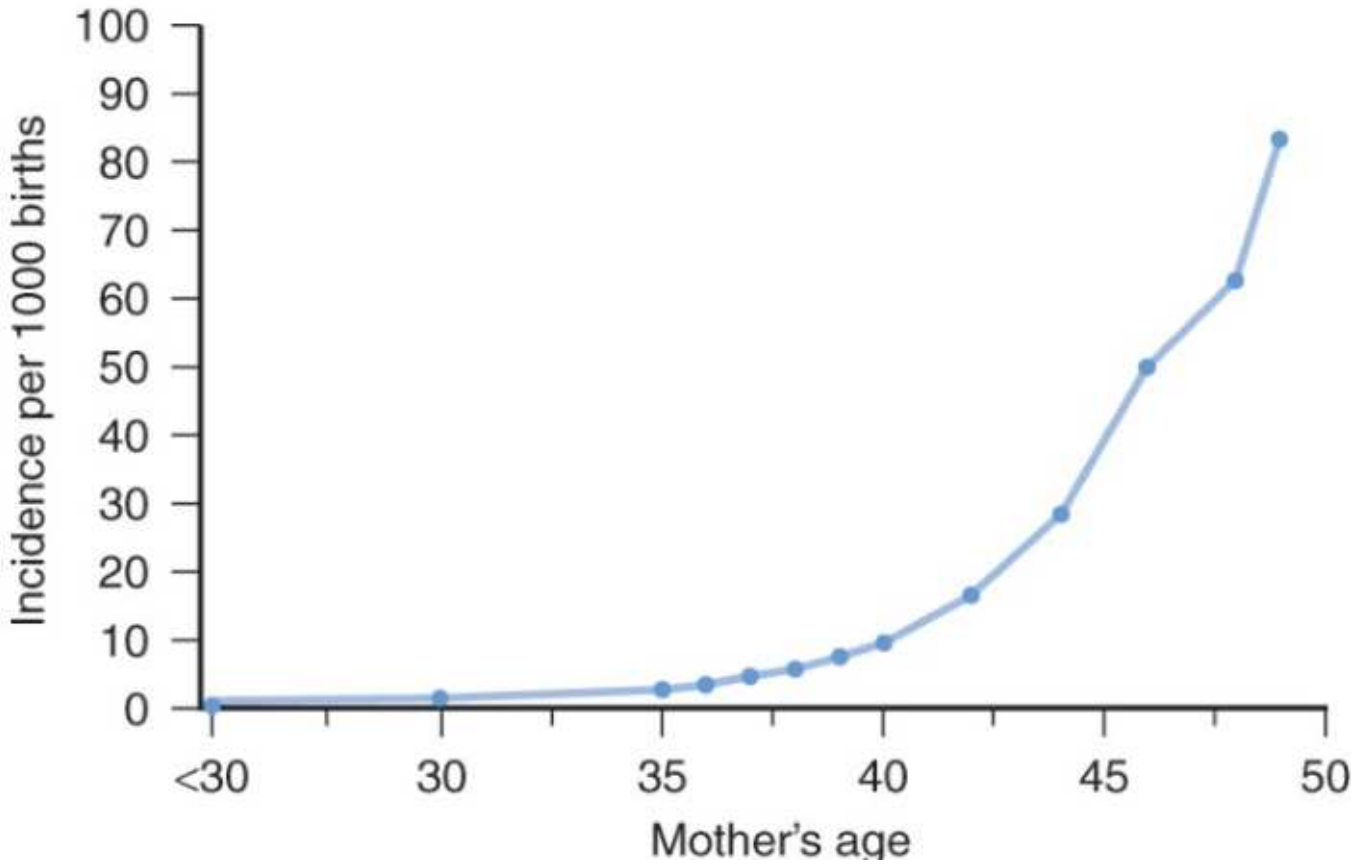






TRISOMY 21
DOWN SYNDROME

- Incidence:
  - 1 in 800-1000 livebirths in general population
- Many affected pregnancies spontaneously abort
- Major risk factor for nondisjunction subtype: Maternal age
  - 35 years: 1 in 365
  - 40 years: 1 in 100
  - 45 years; 1 in 35
- *Maternal age is not a risk factor for translocation subtype, which occurs de novo or due to a parent with a balanced translocation*



TRISOMY 21
DOWN SYNDROME

- Recurrence risk
  - De novo nondisjunction event: 1% or age related risk
  - Translocation
    - De novo: <1%
    - Paternal: 1-2%
    - Maternal: 10-15%
    - *Exception*: Translocation 21:21
      - De novo is still <1%
      - If inherited from a parent recurrence is 100%
        - Would either be trisomy (viable) or monosomy (non-viable)
  - Mosaic
    - 1% or age related risk

TRISOMY 13
PATAU SYNDROME

Common Features / Buzzwords
Cleft lip, palate
Holoproscencephaly, microcephaly
Micropthalmia
Cardiac defects (ASD/VSD)
Post-axial polydactyly
Cutis aplasia
Renal/GU abnormalities
Omphalocele
Intellectual Disability

Semanticscholar.org

TRISOMY 13
PATAU SYNDROME

- 47,XX,+13 or 47,XY,+13
- Etiology
  - 80% nondisjunction during maternal meiosis
  - 20% by translocation
    - Most common with chromosome 14
  - <5% are mosaic
- Incidence: <1 in 20,000 live births
  - >90% die within the first year of life
- >95% of cases are aborted spontaneously

TRISOMY 13
PATAU SYNDROME

- Recurrence risk:
  - De novo nondisjunction event: 1% or age related risk
  - Translocation
    - De novo: <1%
    - Paternal: <<1%
    - Maternal: <1%
  - *Exception*: Translocation 13:13
    - De novo is still <1%
    - If inherited from a parent recurrence is 100%
      - Would either be trisomy (viable) or monosomy (non-viable)
  - Mosaic : 1% or age related risk

TRISOMY 18
EDWARDS SYNDROME

Common Features / Buzzwords
Cardiac defects (ASD/VSD)
Rocker bottom feet
Clenched hands, nail hypoplasia Overriding fingers (2 over 3, 5 over 4)
Microcephaly, prominent occiput, micrognathia
Intrauterine growth restriction (prenatal growth failure)
Short sternum
Feeding difficulties, failure to thrive
GU abnormalities
Severe intellectual Disability
Low subcutaneous fat, underdeveloped muscles

TRISOMY 18
EDWARDS SYNDROME

- 47,XX,+18 or 47,XY,+18
- Etiology
  - ~80-95% nondisjunction maternal meiosis
  - 10% translocation
  - 5% mosaic
- Incidence: 1 in 6000 live births
  - >90% die within the first year of life
- >95% of cases aborted spontaneously

TRISOMY 18
EDWARDS SYNDROME

- Recurrence risk:
  - De novo nondisjunction event: 1% or age related risk
  - Translocation
    - De novo: <1%
    - From a balanced translocation carrier parent: recurrence specific to rearrangement
  - Mosaic
    - 1% or age related risk

SEX CHROMOSOME ANEUPLOIDIES

- Incidence around 1 in 400
- Numerical or structural
- All cells vs. mosaic
- Phenotypes typically less severe due to:
  - X-inactivation in females
  - Low gene content of Y chromosome
- Most (with exception of Turner syndrome) are not recognized clinically until puberty

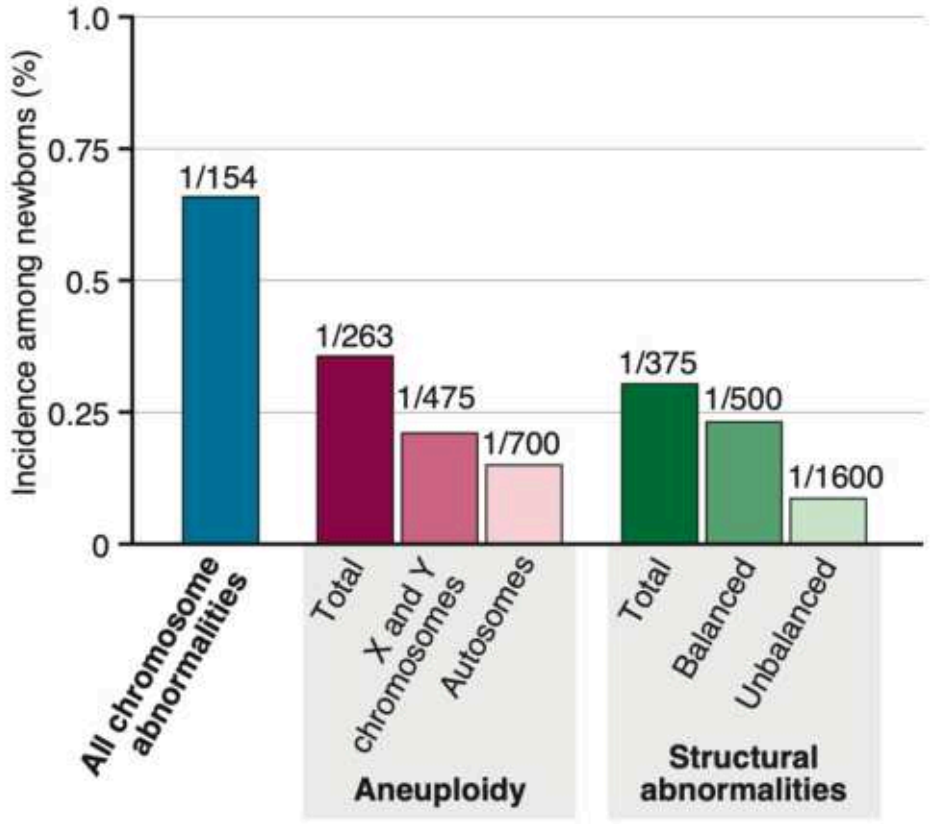
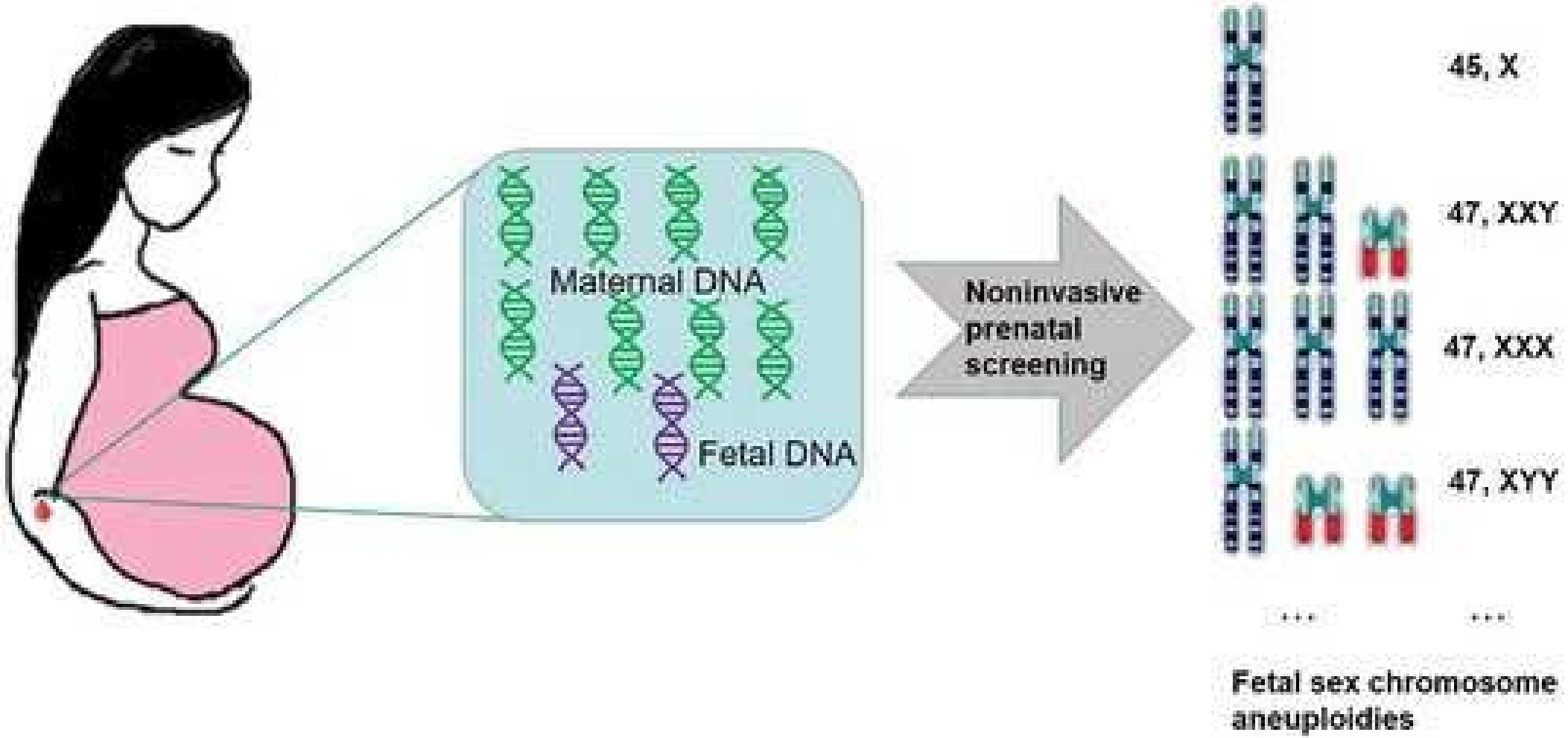


Figure 5-8 Incidence of chromosome abnormalities in newborn surveys, based on chromosome analysis of over 68,000 newborns.



Noninvasive prenatal cell-free DNA screening increasing detection of sex chromosome aneuploidies

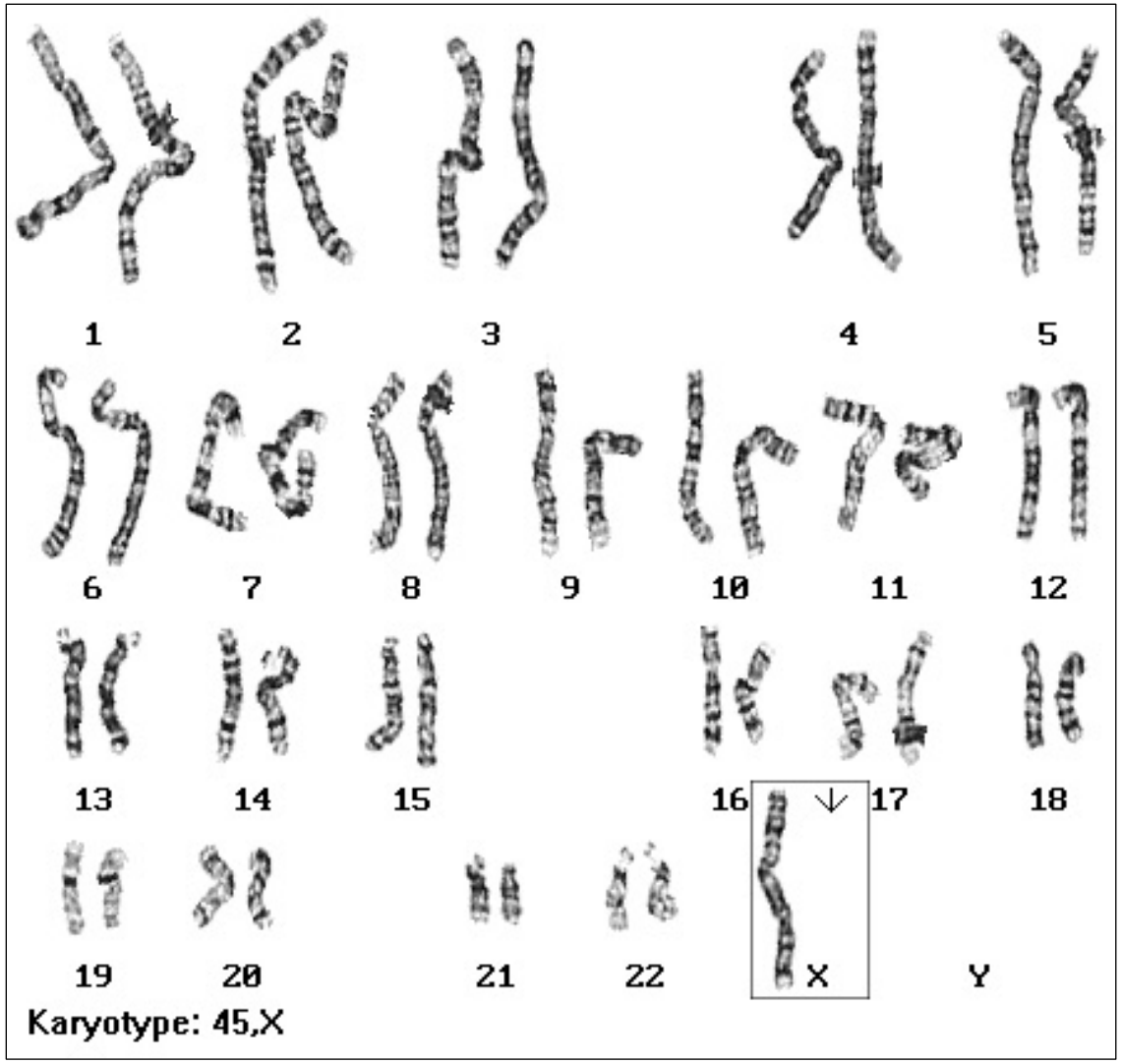
MONOSOMY X
TURNER SYNDROME

Common Clinical Features
Webbed neck
Cardiac defects (bicuspid, aortic valve stenosis, or coarctation)
Widely spaced nipples (shield chest)
Horseshoe kidney / kidney defects
Streak ovaries / ovarian dysgenesis
Lymphedema of hands and feet
Short stature
Risk of gonadoblastoma in 45X/46XY mosaic
Normal intelligence
Increased elbow carrying angle

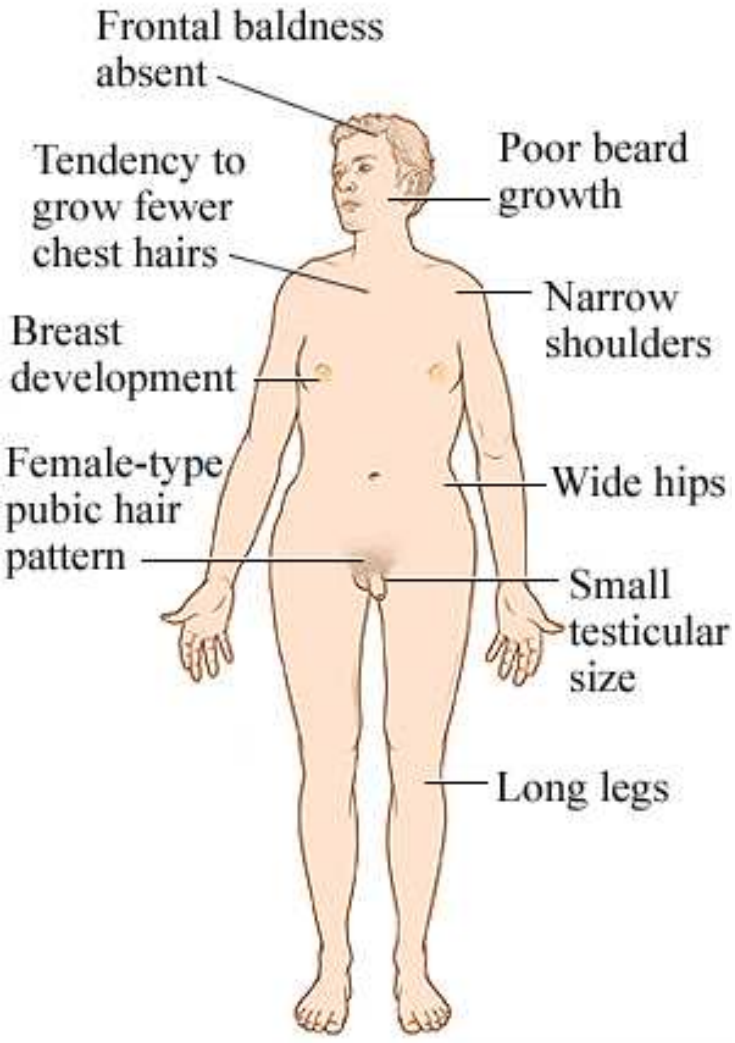
Medlineplus.gov

MONOSOMY X
TURNER SYNDROME

- Monosomy X = karyotype 45,X
- Only 1% cases result in live births
  - 99% spontaneously abort
    - 20% result in first trimester loss
- Incidence ~1 in 4,000 live births
  - **45,X**: 50% of cases
  - **Isochromosome (Xq):** 20% of cases
  - **Xp or Xq deletion**: 6% of cases
  - **Mosaic**: 30% of cases (typically 45X/46XX or 46,XY)
    - Can include marker and ring chromosomes



XXY
KLINEFELTER SYNDROME



Common Clinical Features
Infertility
Hypogonadism (less testosterone)
Gynecomastia With increased risk for breast cancer
Motor and speech delays Behavior issues
Hypotonia
Tall, long limbs “Marfanoid habitus”
Sparse facial, axillary, pubic and/or body hair
Feminine distribution of adipose tissue

XXY
KLINEFELTER SYNDROME

- Karyotype 47,XXY
- Etiology:
  - Non-disjunction in meiosis I
    - 50% paternal; 50% maternal meiosis
- Incidence ~1 in 600
  - 15% are mosaic (most commonly 46,XY/47,XXY)
  - Other variants: 48, XXXY and 49, XXXXY

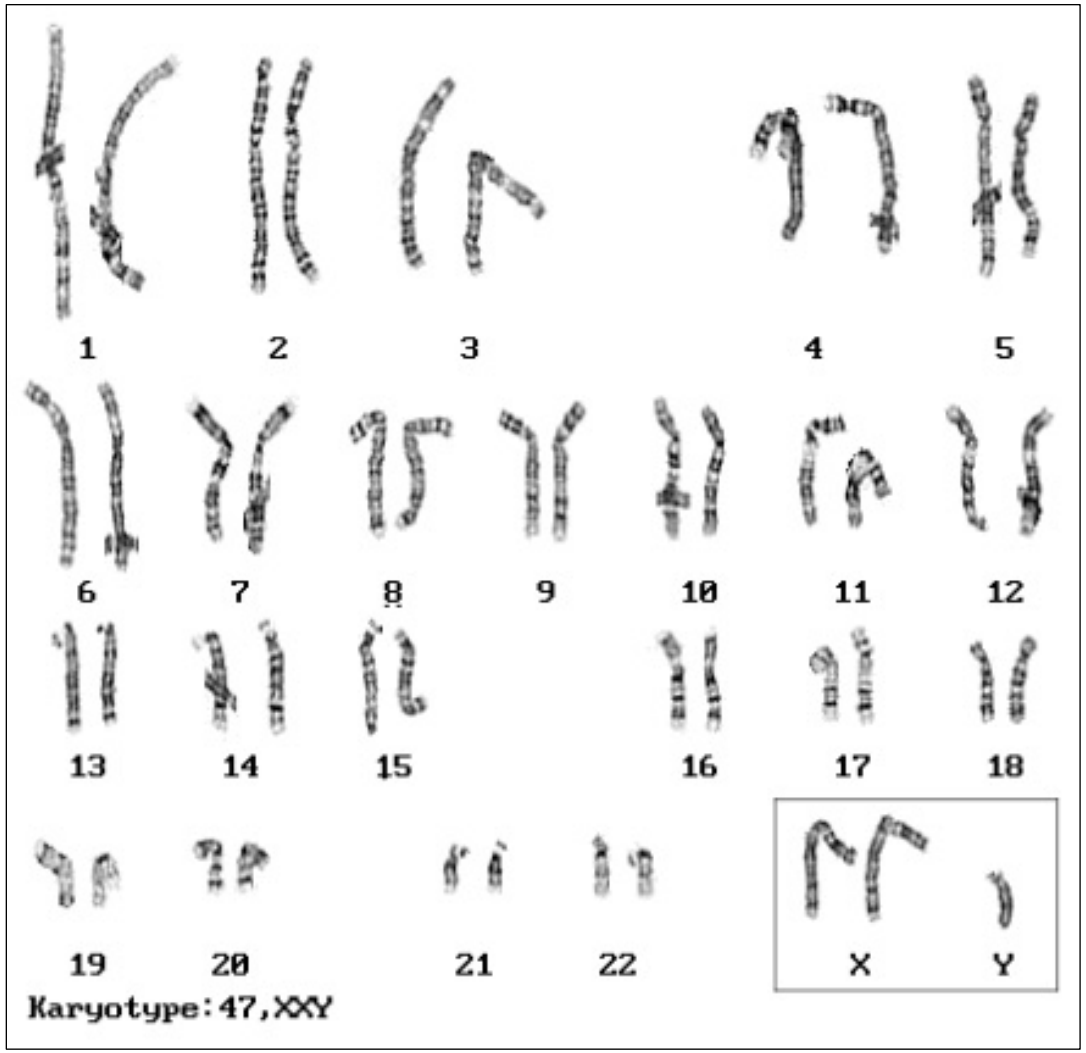
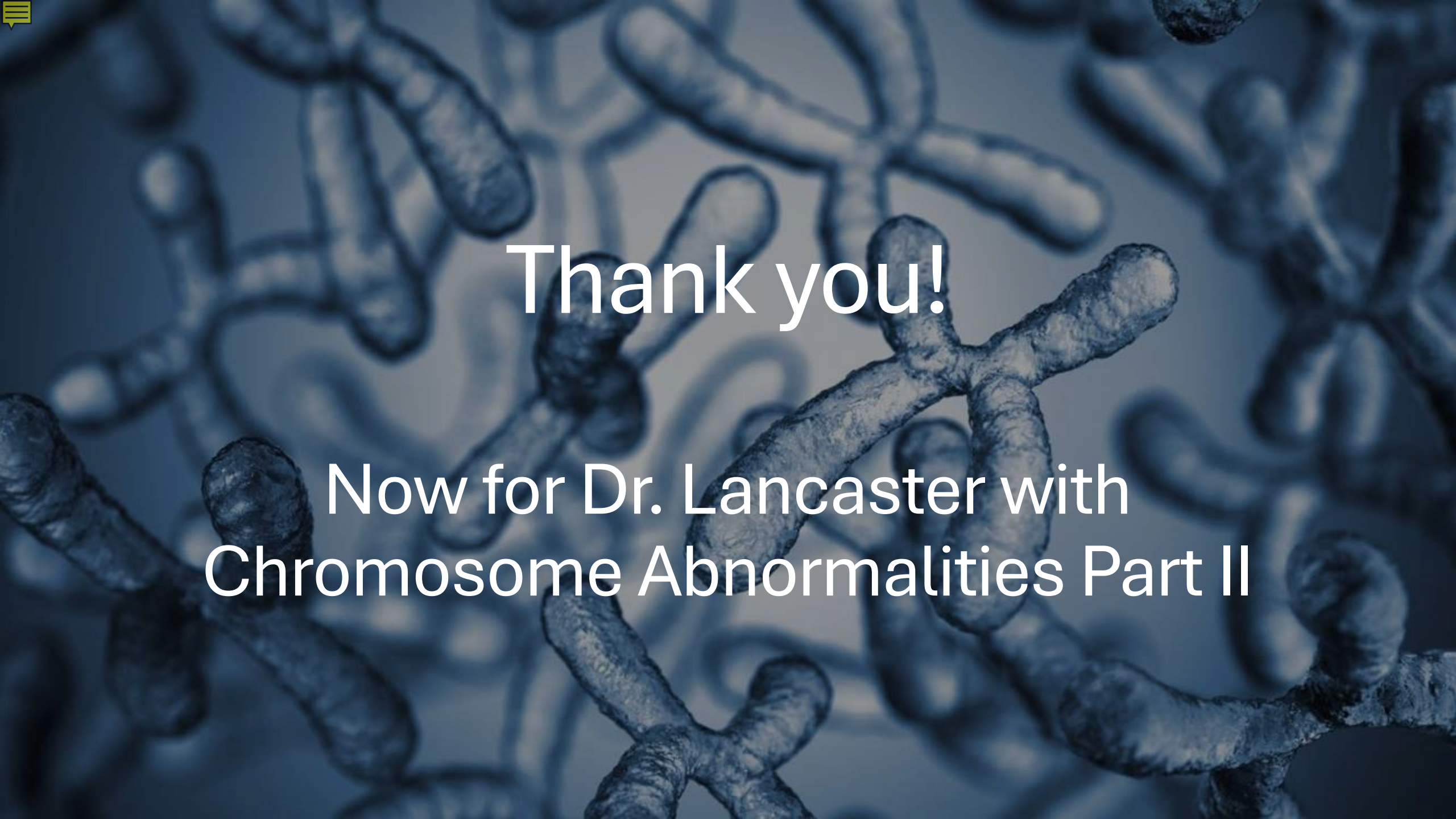


TABLE 6-7 Features of Sex Chromosome Aneuploidy Conditions

Feature	47,XXY Klinefelter Syndrome	47,XYY	47,XXX Trisomy X	45,X Turner Syndrome
Prevalence	1 in 600 male births	1 in 1000 male births	1 in 1000 female births	1 in 2500 to 4000 female births
Clinical phenotype	Tall male; see Figure 6-15 and text	Tall, but otherwise typical male appearance	Hypotonia, delayed milestones; language and learning difficulties; tend to be taller than average	Short stature, webbed neck, lymphedema; risk for cardiac abnormalities
Cognition/intelligence	Verbal IQ reduced to low-normal range; educational difficulties	Verbal IQ reduced to low-normal range; language delay; reading difficulties	Normal to low-normal range (both verbal and performance IQ decreased)	Typically normal, but performance IQ lower than verbal IQ
Behavioral phenotype	No major disorders; tendency to poor social adjustments, but normal adult relationships	Subset with specific behavioral problems likely associated with lower IQ	Typically, no behavioral problems; some anxiety and low self-esteem; reduced social skills	Typically normal, but impaired social adjustment
Sex development/fertility	Hypogonadism, azoospermia, infertility	Normal	?Reduced fertility in some ?Premature ovarian failure	Gonadal dysgenesis, delayed maturation, infertility
Variant karyotypes	See Table 6-6		48,XXXX; 49,XXXXX Increased severity with additional X's	46,Xi(Xq); 45,X/46,XX mosaics; other mosaics

Summarized from Ross JL, Roeltgen DP, Kushner H, et al: Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. *Pediatrics* 129:769-778, 2012; Pinsker JE: Turner syndrome: updating the paradigm of clinical care. *J Clin Endocrinol Metab* 97:E994-E1003, 2012; and AXYS, http: www.genetic.org.

XYY: Due to nondisjunction paternal meiosis II


Thank you!
Now for Dr. Lancaster with
Chromosome Abnormalities Part II