A Patient Counseling Guide for Reproductive Genetics

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Genetics overview

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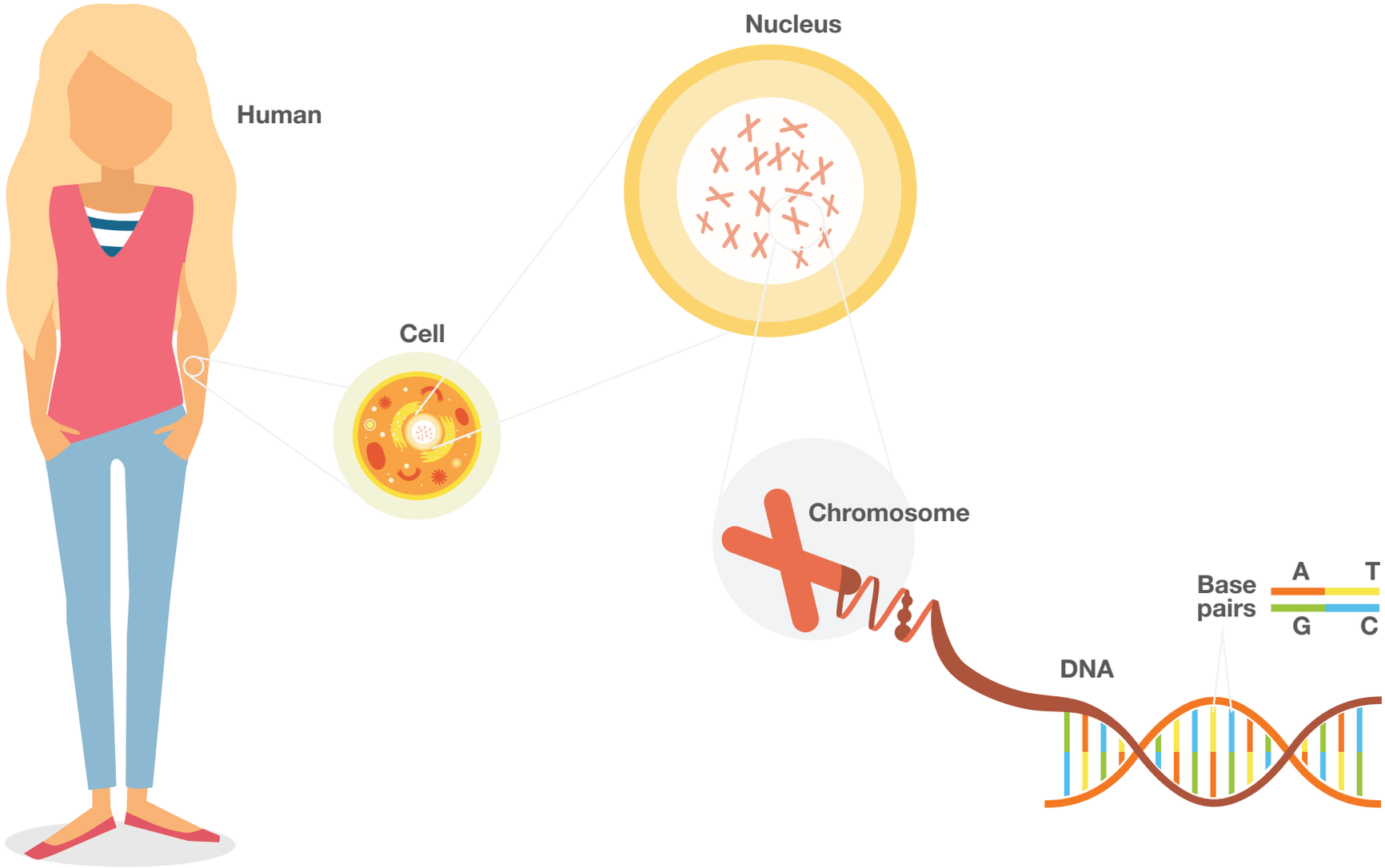
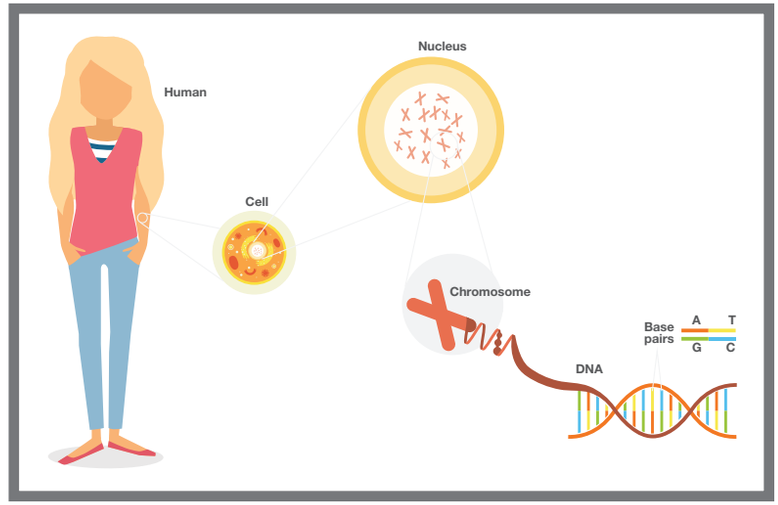
Genetics overview

Cells, chromosomes, and DNA



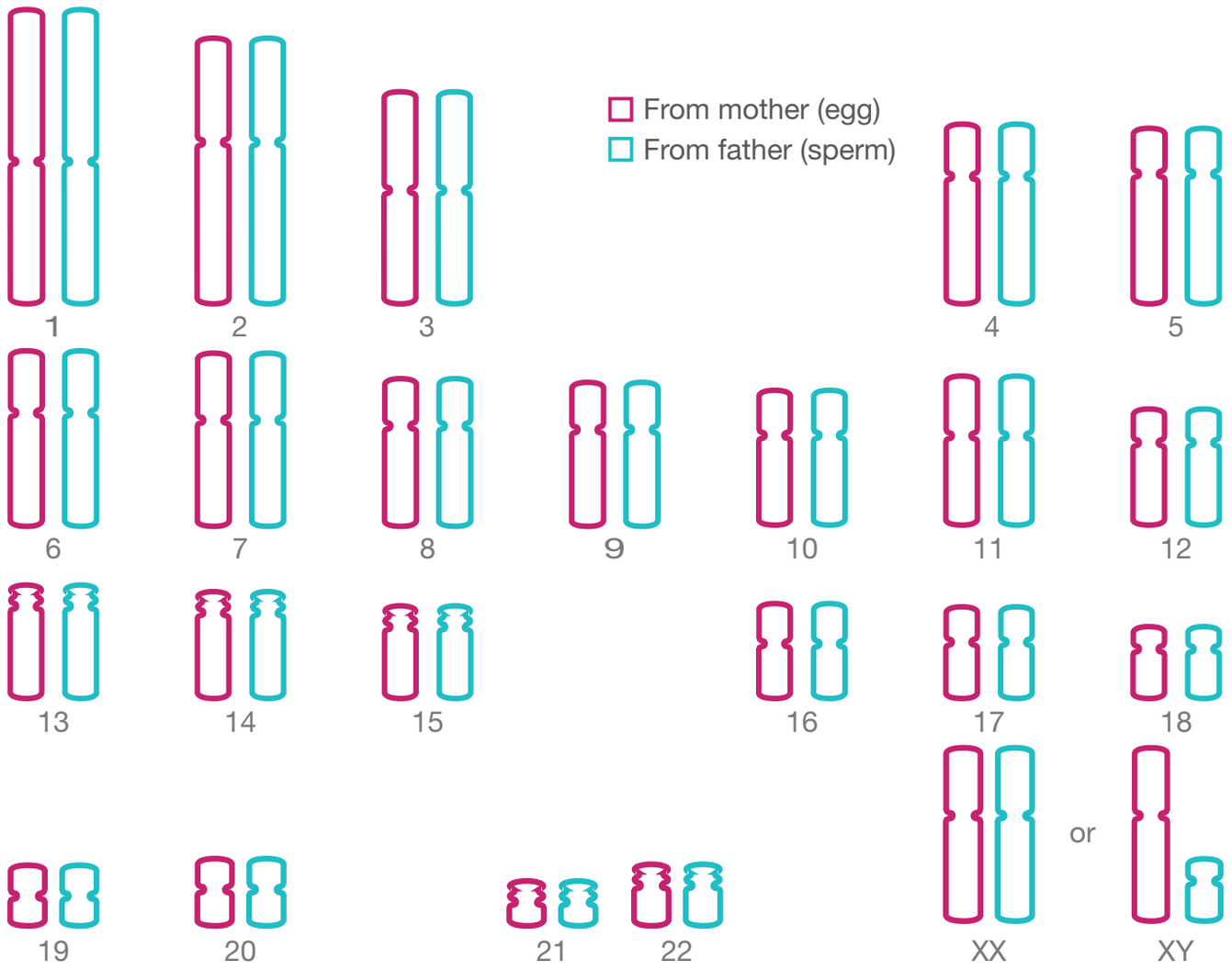
Cells, chromosomes, and DNA

- The human body is made up of trillions of cells
- Inside the nucleus of cells are structures called chromosomes. Chromosomes are made up of DNA
- DNA is made up of 4 bases (A,T,G,C). They are the building blocks of genes
  - A distinct sequence of these bases make up a gene. Humans have about 20,000 genes



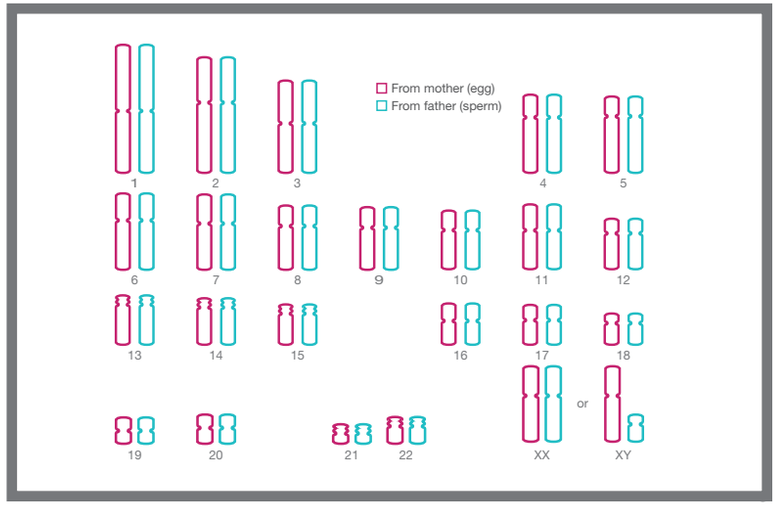
US National Library of Medicine. Help Me Understand Genetics: Cells and DNA. https://ghr.nlm.nih.gov/primer/basics.pdf. Published May 30, 2016. Accessed June 6, 2016.

Human chromosomes



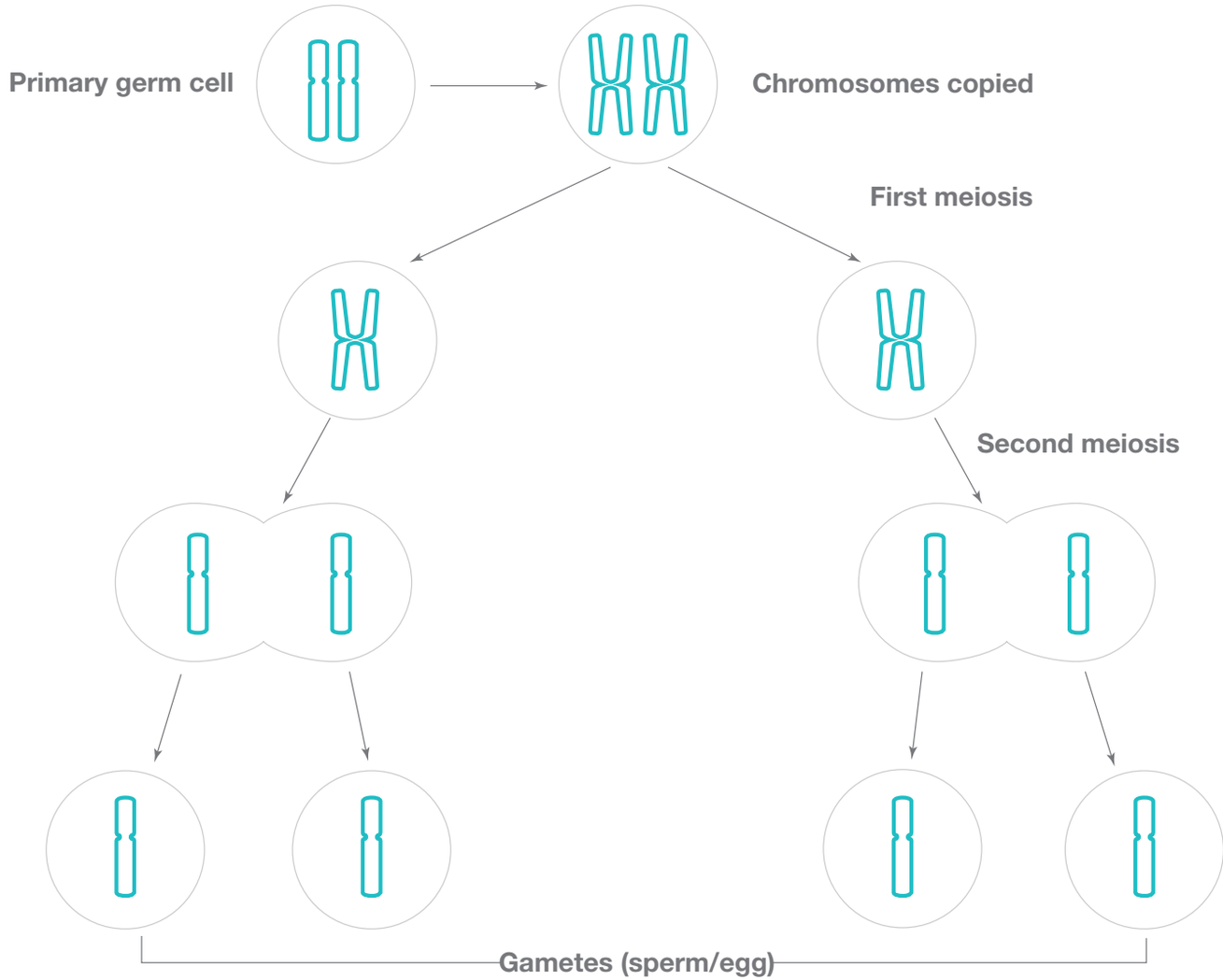
Human chromosomes

- Humans have 23 pairs of chromosomes (for a total of 46 chromosomes)
  - One copy of each chromosome comes from the mother (egg); the other copy comes from the father (sperm)
- The first 22 pairs are called autosomes, and they are same in males and females
- The 23rd pair of chromosomes is called sex chromosomes. Females have two copies of the X chromosome and males have one X and one Y chromosome



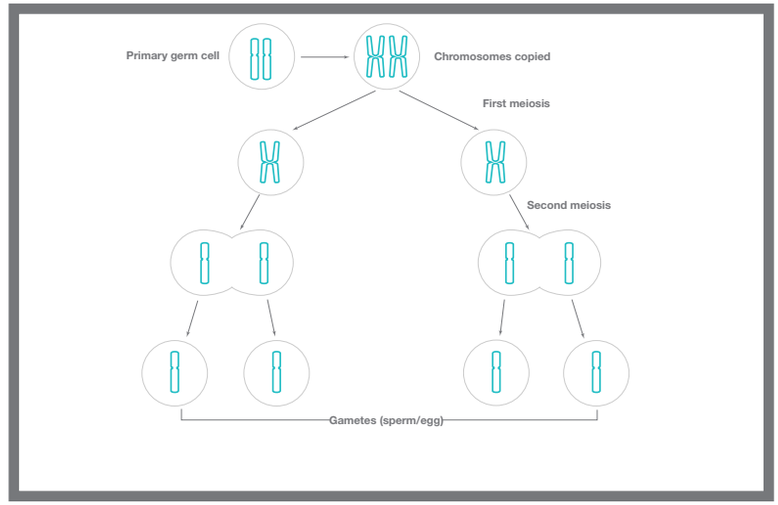
Gardner RJM, Sutherland GR, Schaffer LG. *Chromosome Abnormalities and Genetic Counseling*. 4th ed. New York, NY: Oxford University Press; 2012.

Meiosis: Sperm and egg cell production



Meiosis: Sperm and egg cell production

- Meiosis is the process in which sperm and egg cells (gametes) are produced
- During meiosis, chromosome pairs are separated so that each gamete typically has one copy of each chromosome (23 total, half the number of chromosomes found in a cell)
- At fertilization/conception, the sperm joins with the egg to form a zygote, which becomes an embryo (with 46 chromosomes)



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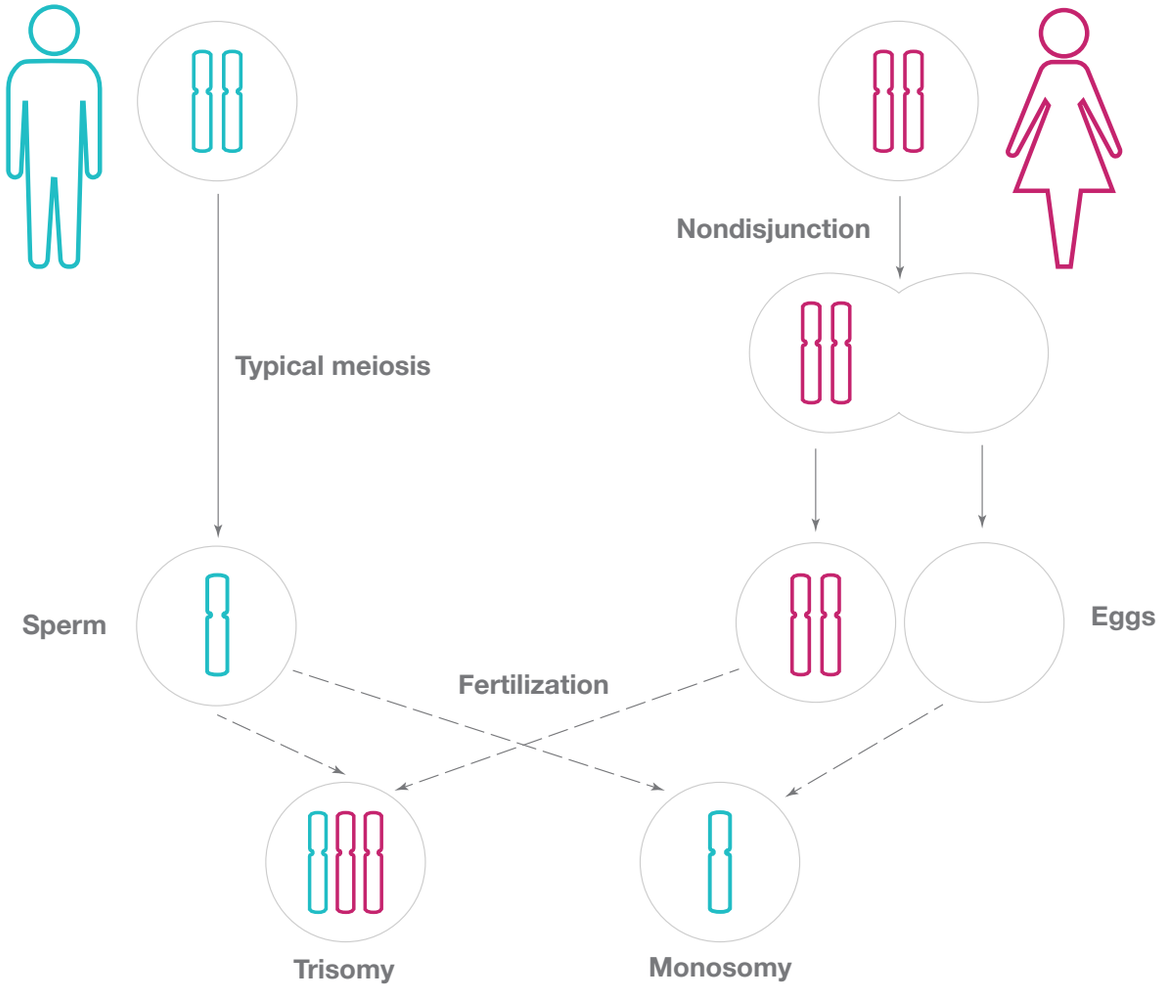
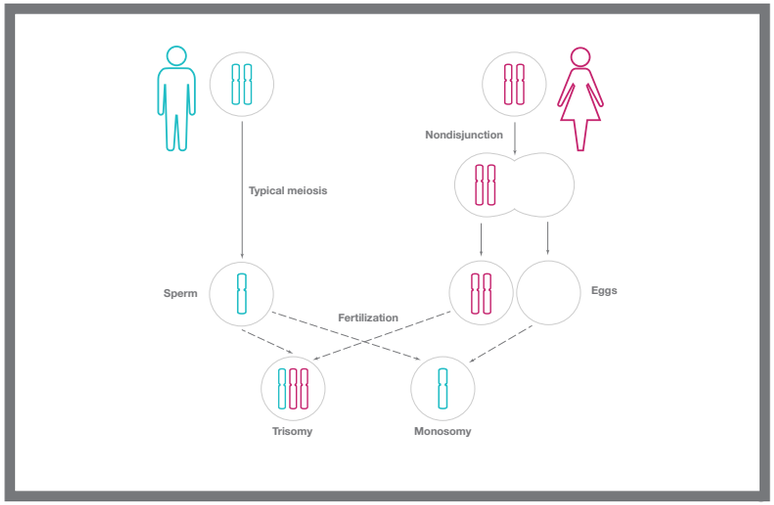
Nondisjunction in meiosis



Nondisjunction in meiosis

- Nondisjunction is the failure of homologous chromosomes to separate normally during cell division, leading to an incorrect number of chromosomes (known as aneuploidy)
  - Nondisjunction can occur in female and male meiosis
- Types of aneuploidy:
  - Trisomy: three copies of a specific chromosome
  - Monosomy: one copy of a specific chromosome
- Aneuploidy can lead to:
  - Failure of an embryo to implant
  - Pregnancy loss/miscarriage
  - Birth of a baby with a chromosome condition (eg, trisomy 21, also known as Down syndrome)



Gardner RJM, Sutherland GR, Schaffer LG. *Chromosome Abnormalities* and *Genetic Counseling*. 4th ed. New York, NY: Oxford University Press; 2012.

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Chromosomal conditions

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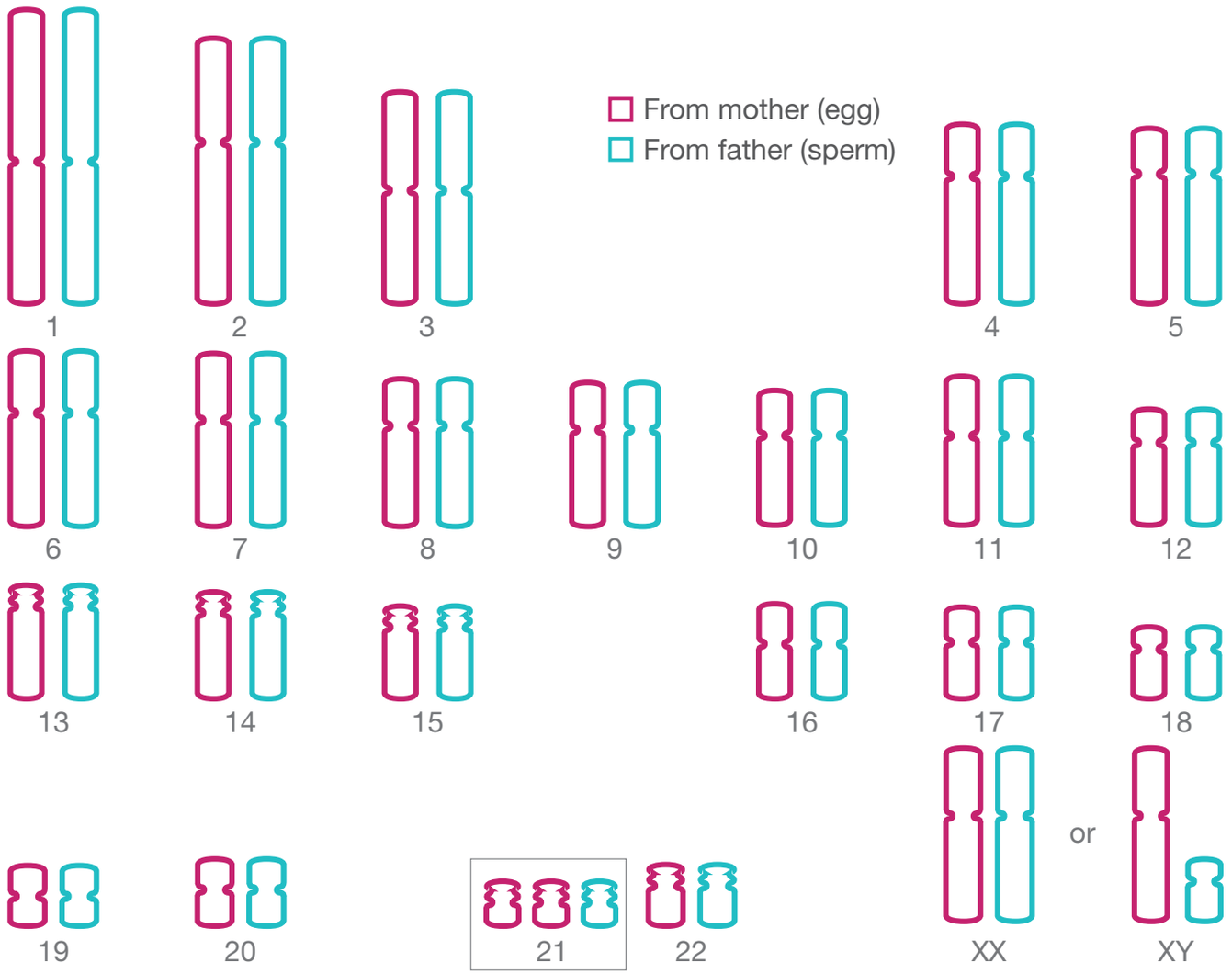
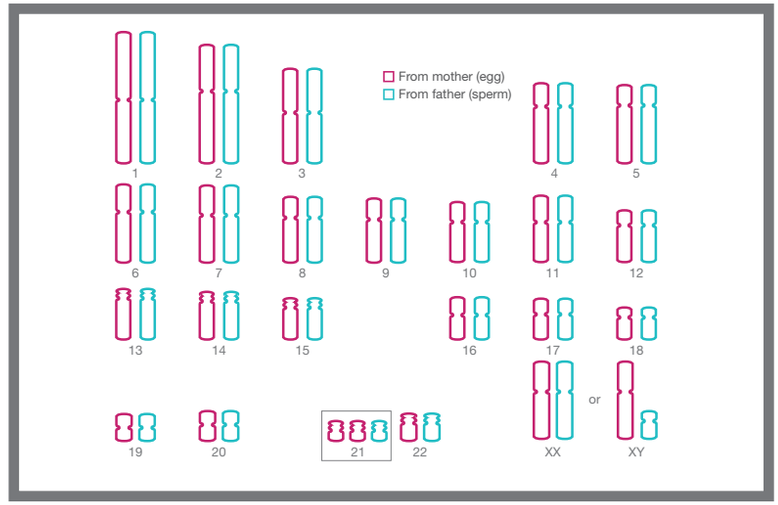
Chromosomal conditions

Trisomy 21 (Down syndrome)



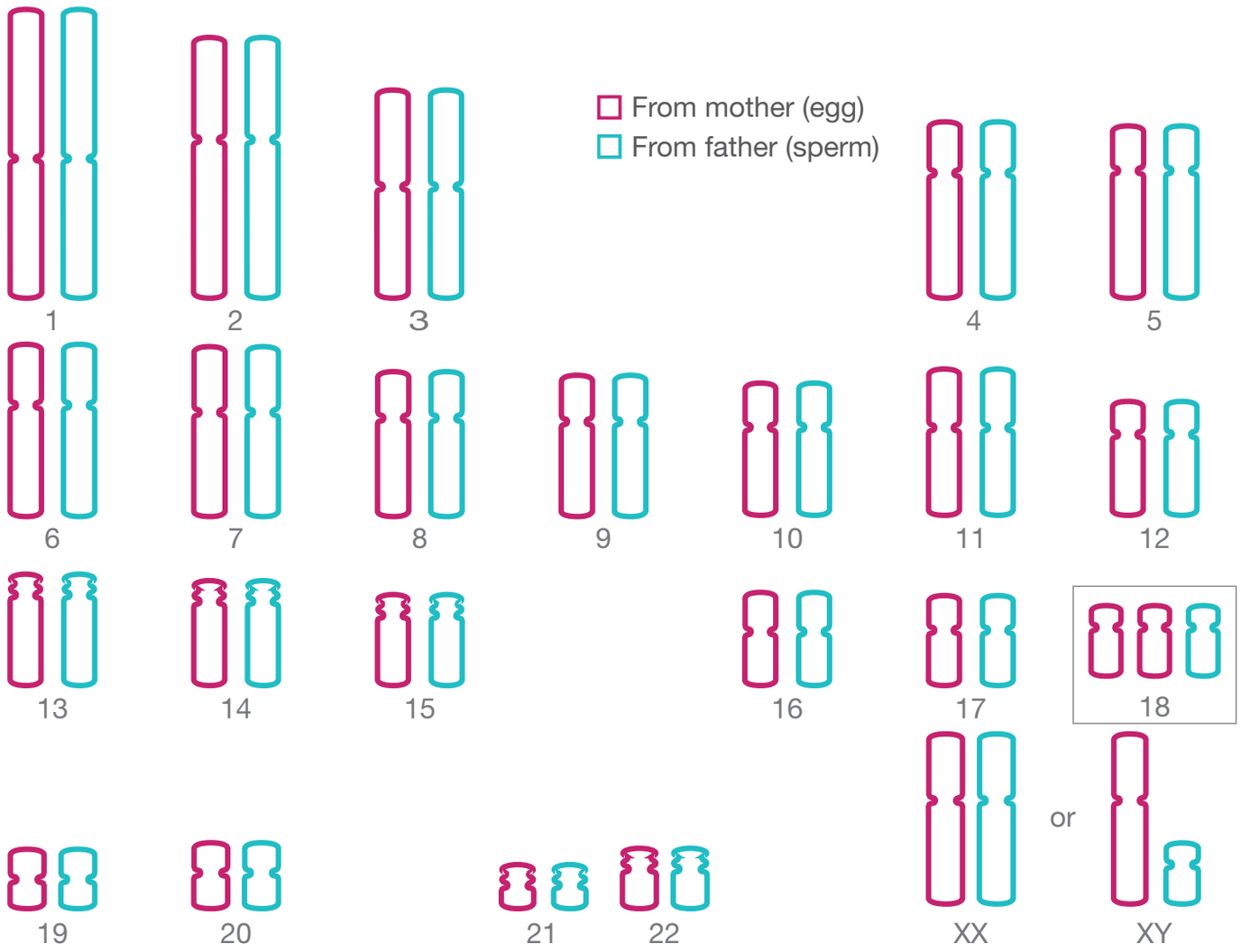
Trisomy 21 (Down syndrome)

- Trisomy 21 is the most common chromosomal condition in live born infants
- Trisomy 21 occurs in approximately 1 in every 660 live births
- Clinical presentation is variable. Common characteristics of trisomy 21 include:
  - Mild to moderate intellectual disability and developmental delay
  - Characteristic facial features
  - Structural heart anomalies
  - Low or poor muscle tone
  - Can live to adulthood



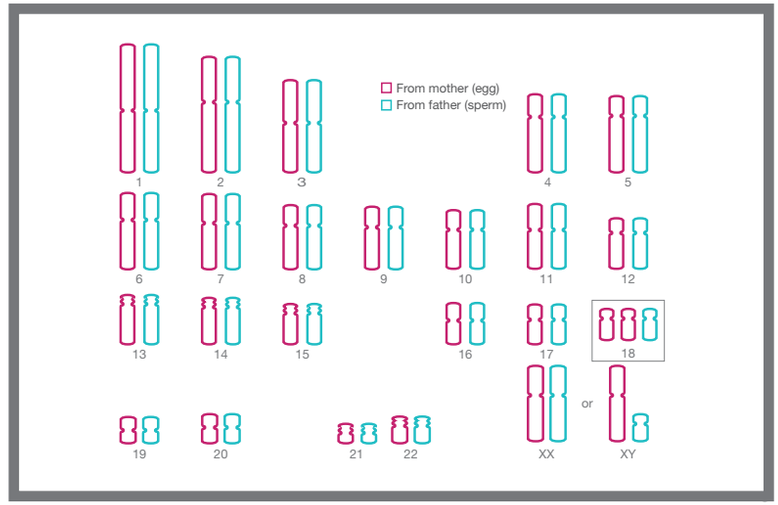
Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: Down syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/down-syndrome. Accessed April 4, 2018.

Trisomy 18 (Edwards syndrome)



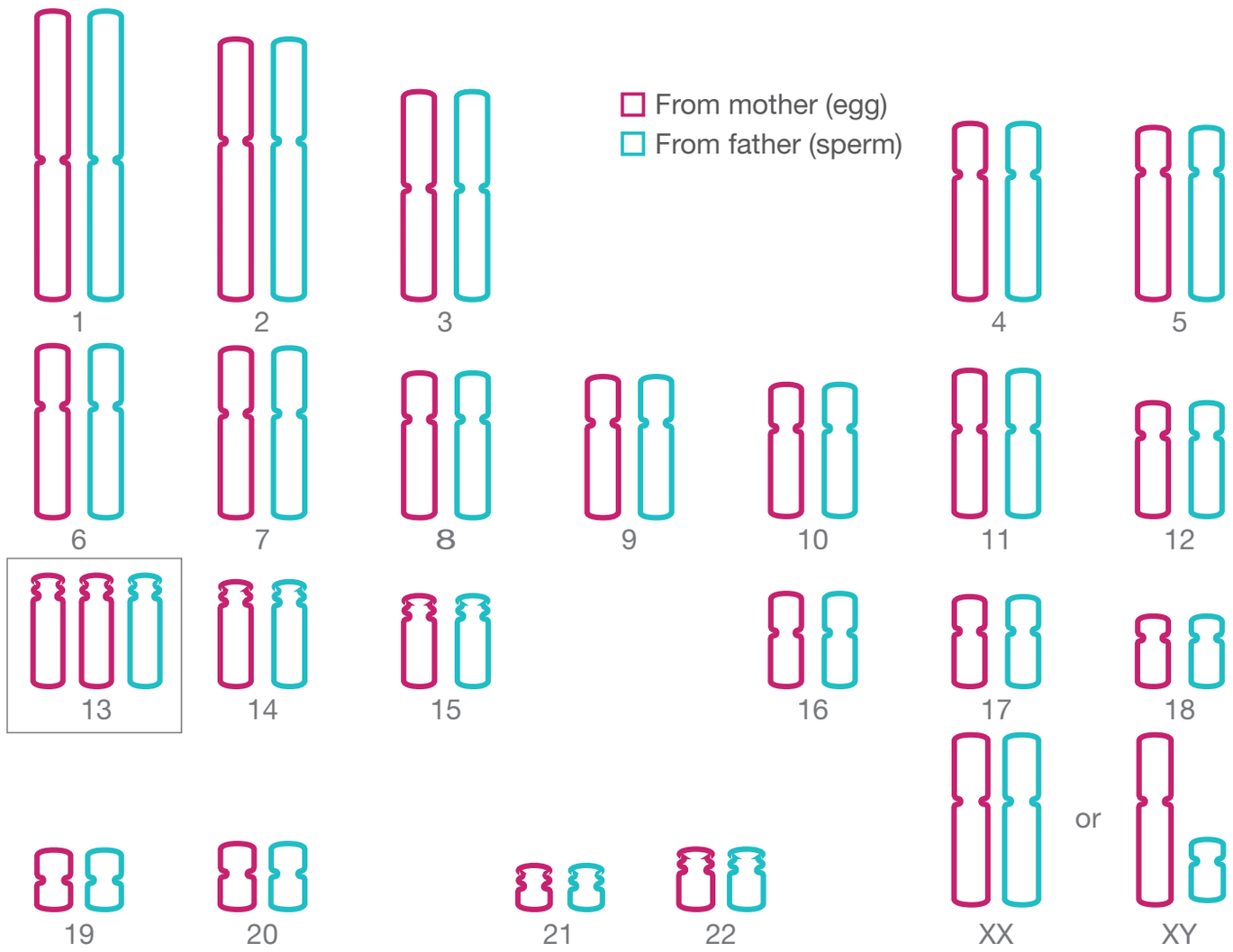
Trisomy 18 (Edwards syndrome)

- Trisomy 18 occurs in approximately 1 in every 3,333 live born infants
- Life expectancy is usually less than one year
- Clinical presentation is variable. Common characteristics of trisomy 18:
  - Intrauterine growth retardation
  - Increased muscle tone
  - Unusual positioning of the hands and/or feet
  - Heart and other organ anomalies
  - Severe developmental delay and intellectual disabilities



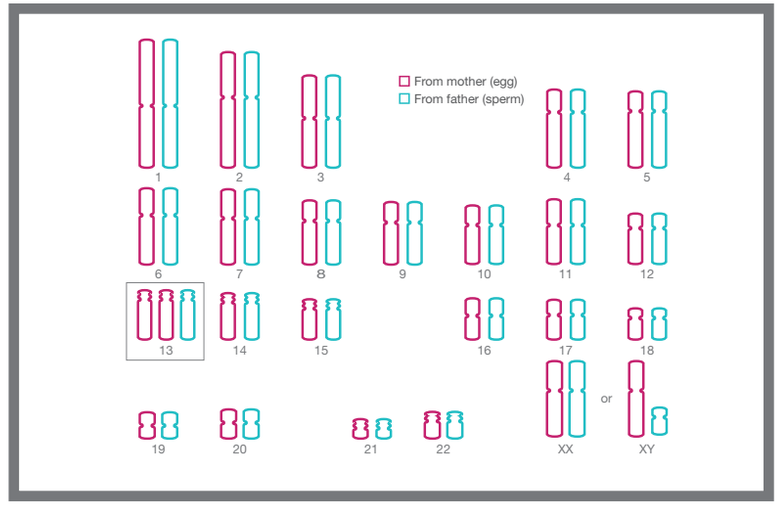
Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: Trisomy 18. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/trisomy-18. Accessed April 4, 2018.

Trisomy 13 (Patau syndrome)



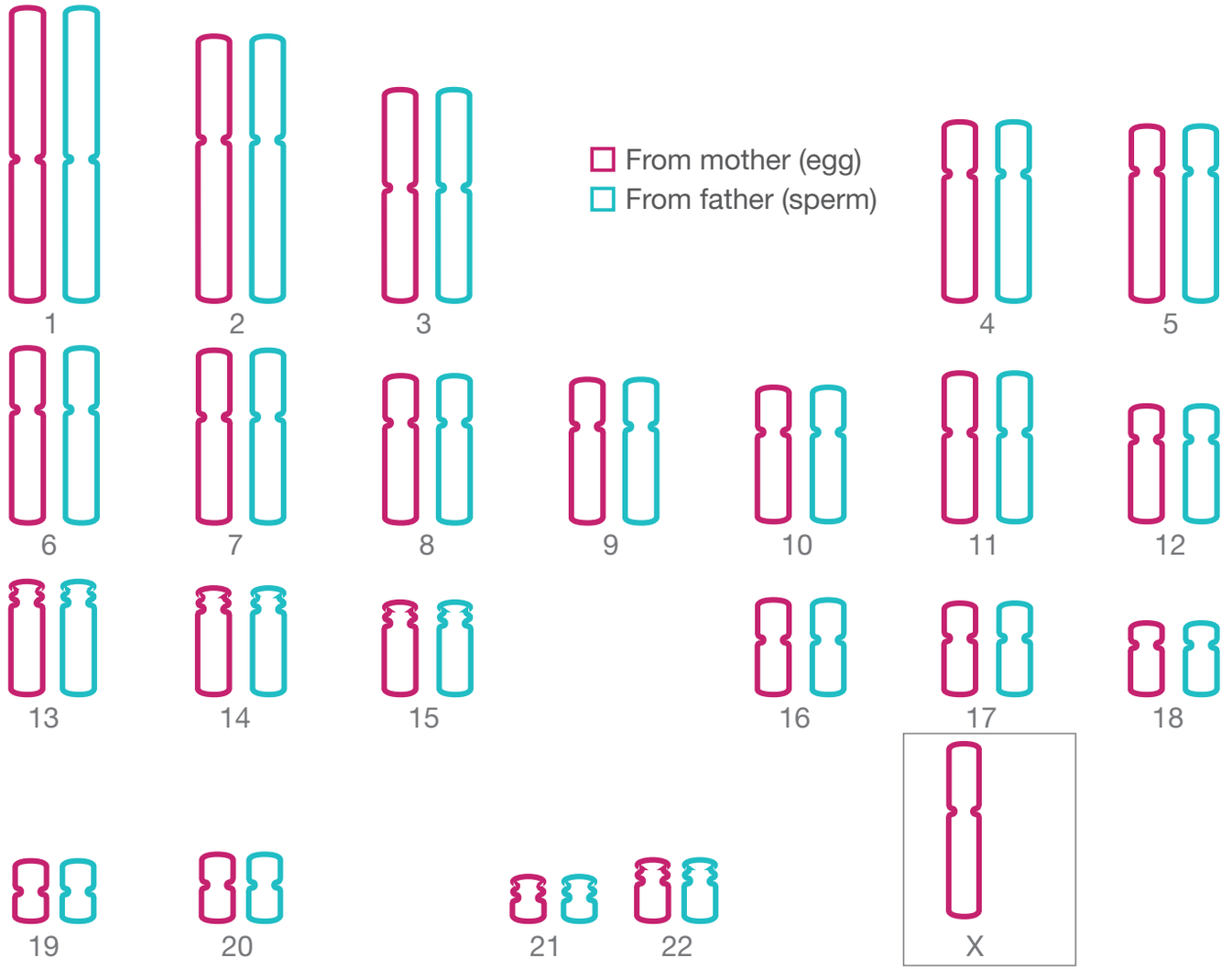
Trisomy 13 (Patau syndrome)

- Trisomy 13 occurs in approximately 1 in every 5,000 live born infants
- Life expectancy is usually less than 1 year
- Clinical presentation is variable. Common characteristics of trisomy 13 include:
  - Heart, brain, kidney abnormalities
  - Incomplete fusion of the lip and/or palate (clefting)
  - Severe developmental and intellectual disabilities



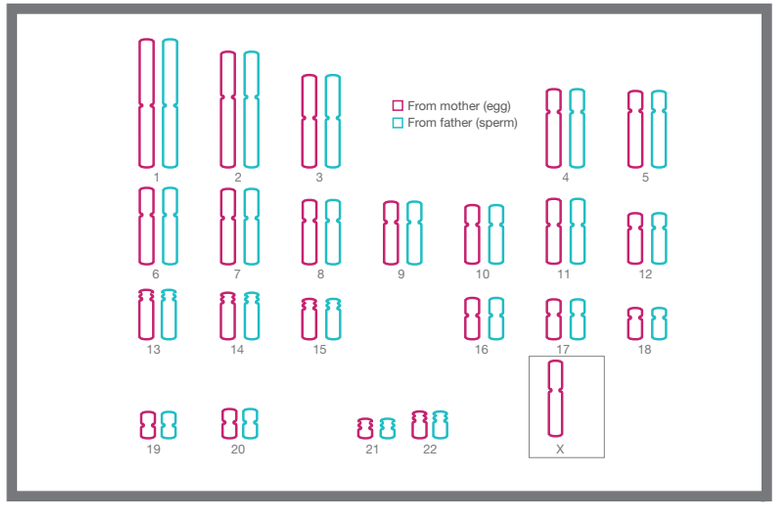
Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: Trisomy 13. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/trisomy-13. Accessed April 4, 2018.

Monosomy X (Turner syndrome)



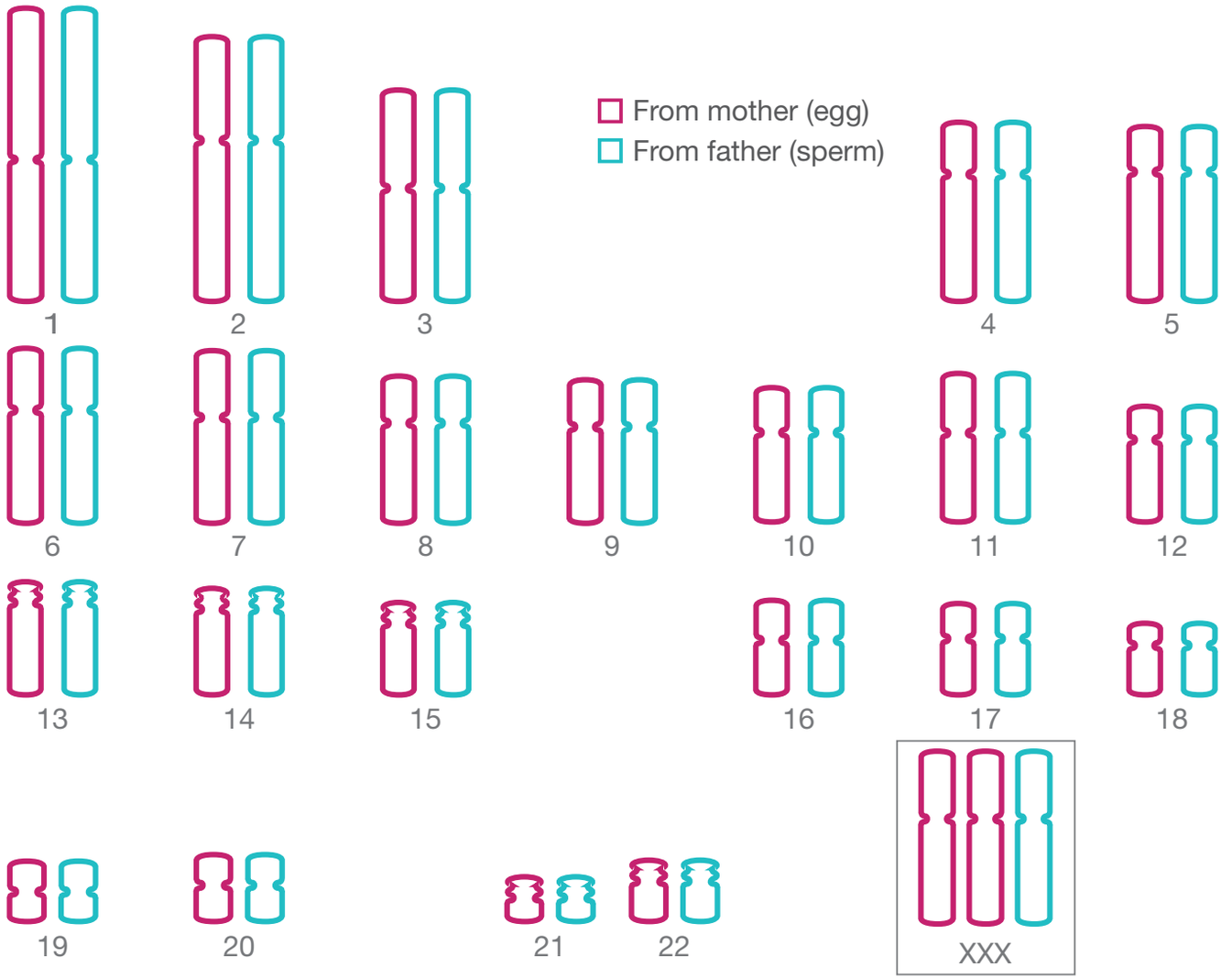
Monosomy X (Turner syndrome)

- Monosomy X occurs in approximately 1 in every 2,000 female live born infants
  - Many pregnancies with monosomy X end in miscarriage
- Clinical presentation is variable. Common characteristics of monosomy X include:
  - Structural heart anomalies
  - Short stature
  - Primary dysfunction of ovaries leading to primary amenorrhoea and infertility



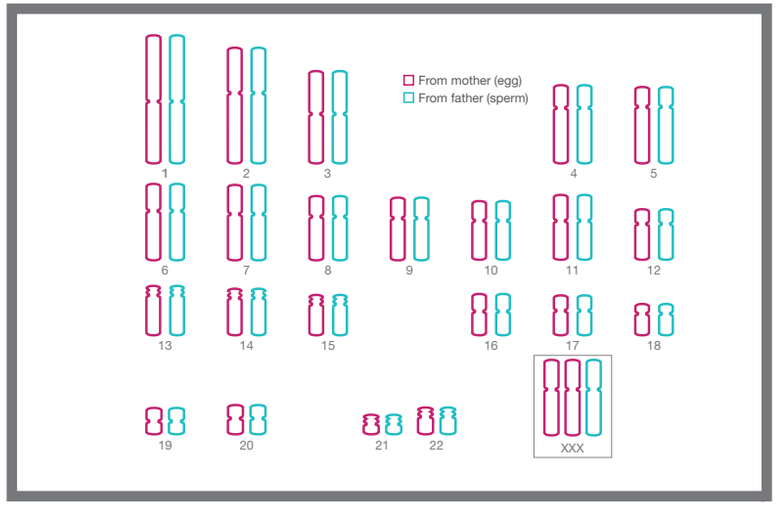
Hook EB, Warburton D. *Hum Genet.* 2014;133(4):417-424.
Jones KL, Jones MC, del Campo M. Smith's *Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: Turner syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/turner-syndrome. Accessed April 4, 2018.

47,XXX (Triple X syndrome)



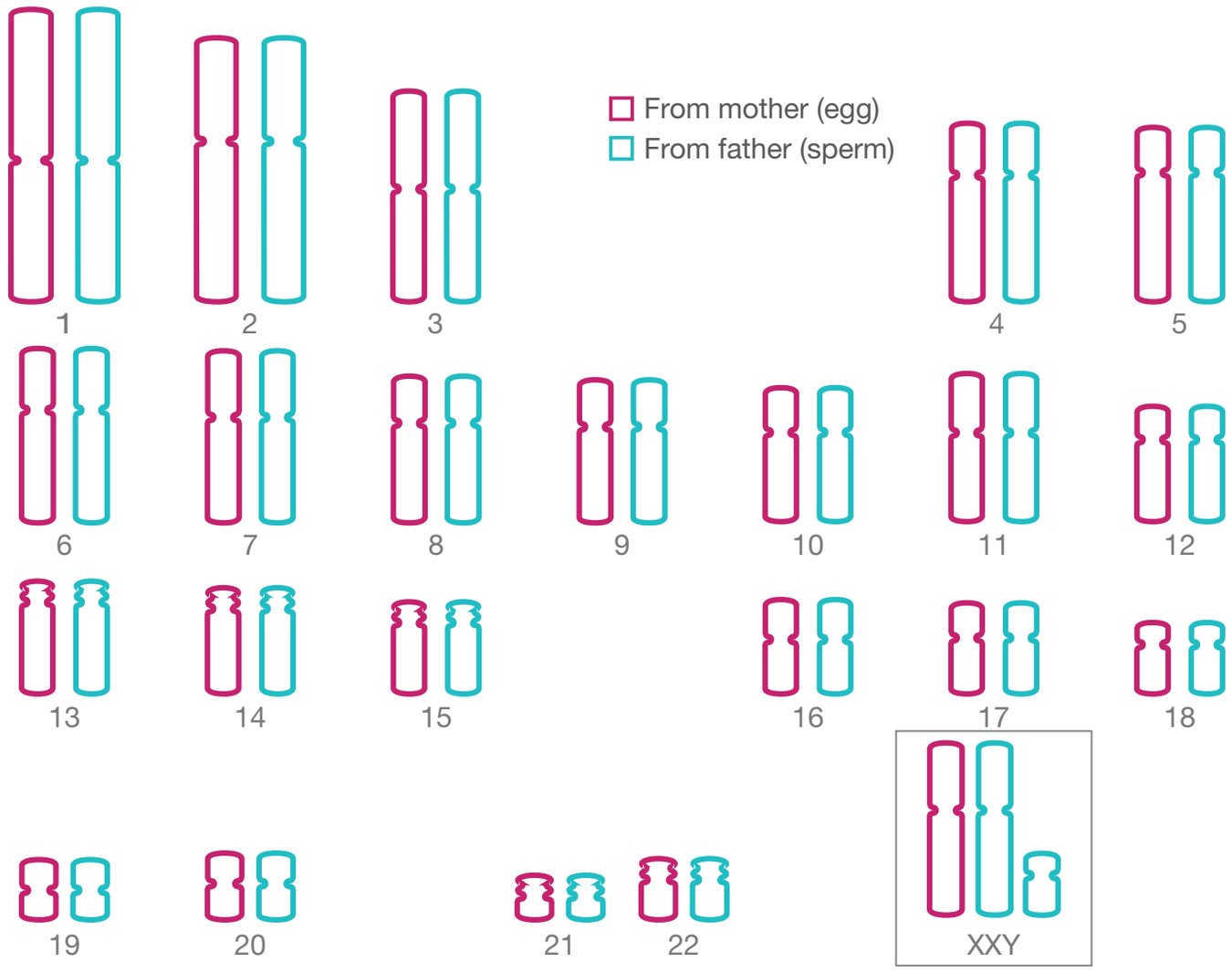
47,XXX (Triple X syndrome)

- 47,XXX occurs in approximately 1 in every 1,000 female live born infants
- Many females with 47,XXX do not have any visible characteristics
- Clinical presentation is variable. Common characteristics of Triple X syndrome include:
  - Taller than average height
  - Learning difficulties, speech, and language delays
  - Delayed development of motor skills
  - Behavioral and emotional difficulties
  - Normal fertility and sexual development



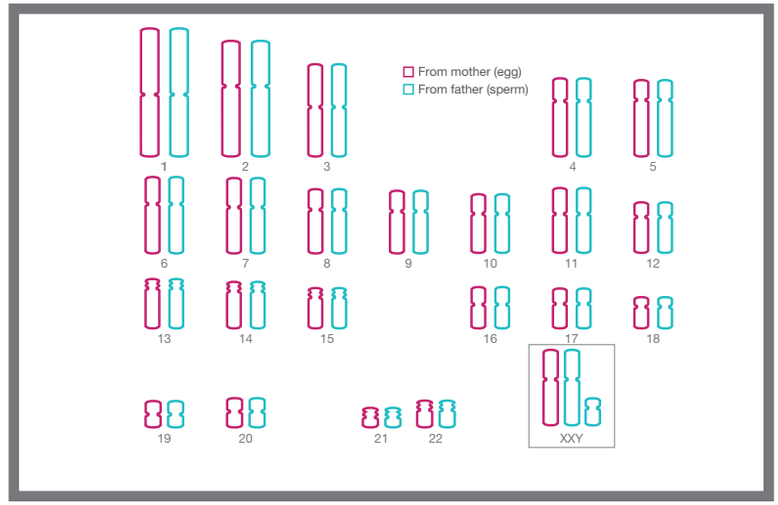
Jones KL, Jones MC, del Campo M. Smith's *Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: Triple X syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/triple-x-syndrome. Accessed April 4, 2018.

47,XXY (Klinefelter syndrome)



47,XXY (Klinefelter syndrome)

- 47,XXY occurs in approximately 1 in every 500 male live born infants
- Clinical presentation is variable. Common characteristics of Klinefelter syndrome include:
  - Learning difficulties, speech and language delays
  - Taller than average height
  - Underdeveloped testes
  - Infertility



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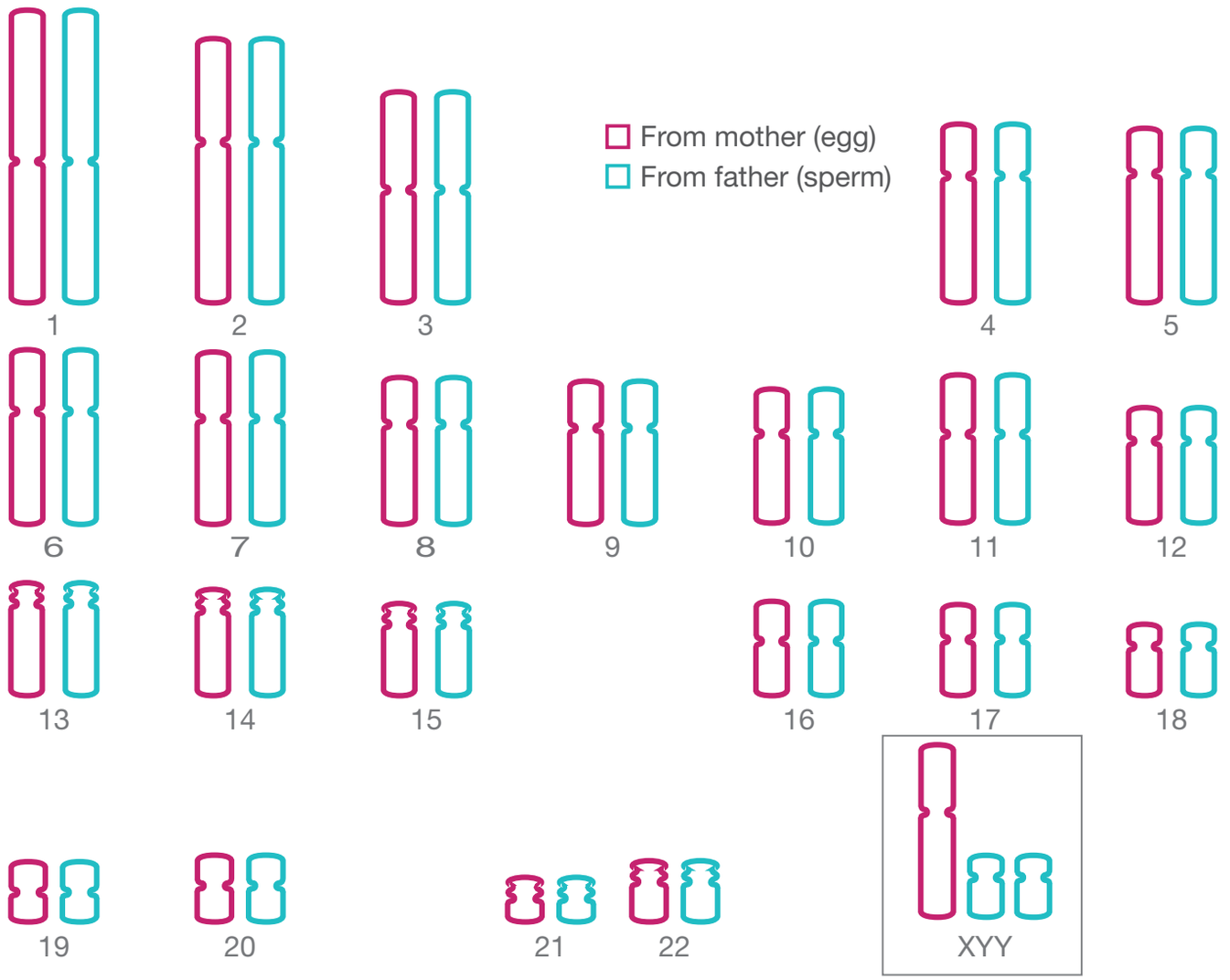
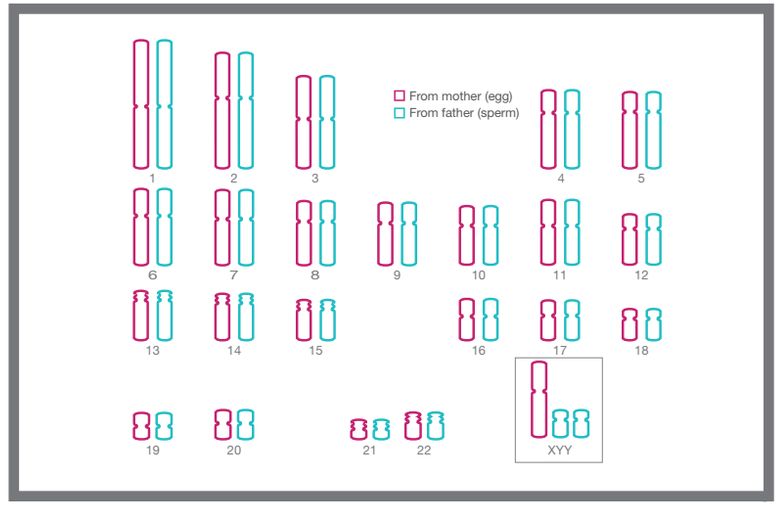
47,XYY (Jacobs syndrome)



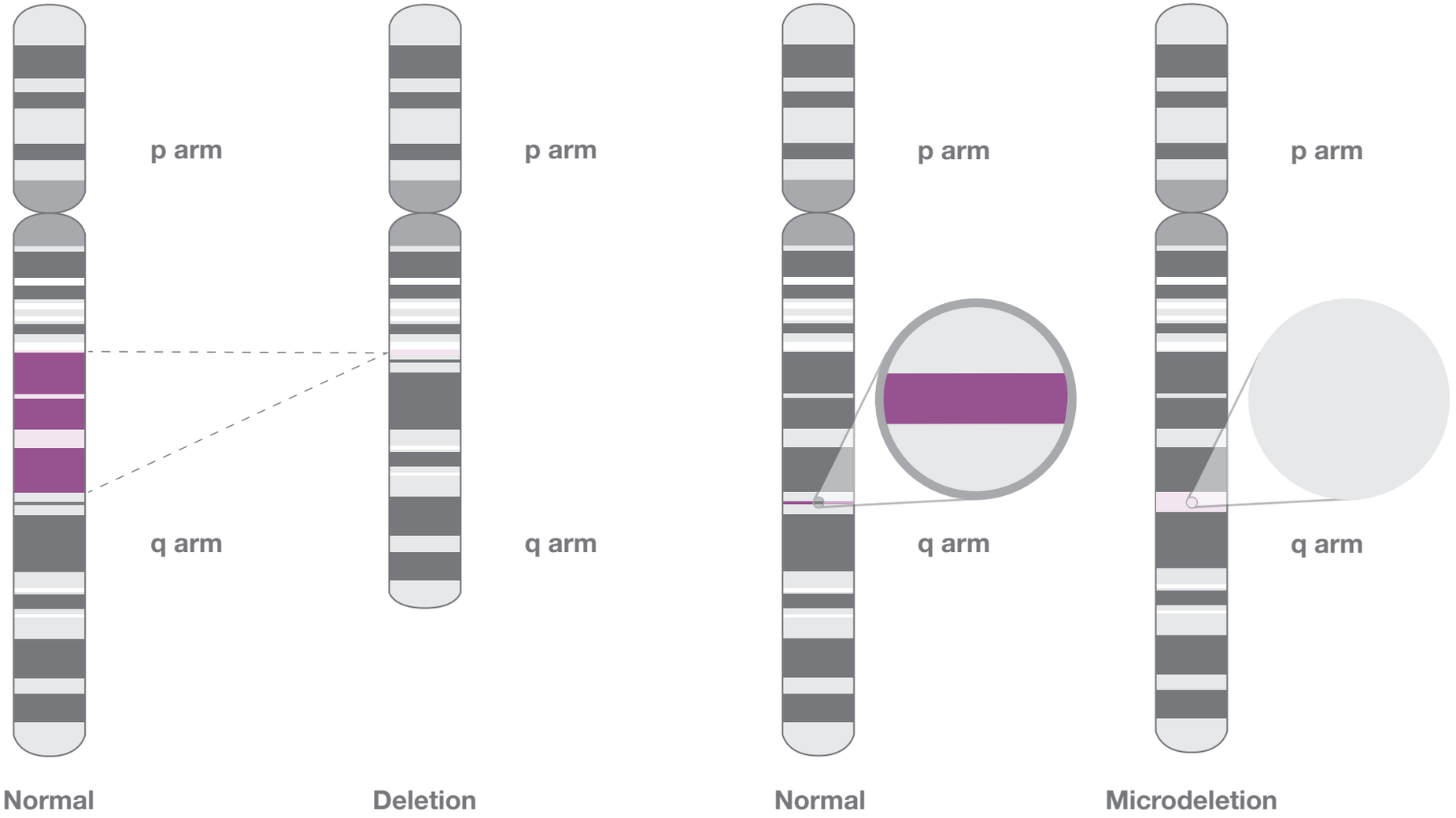
47,XYY (Jacobs syndrome)

- 47,XYY occurs in approximately 1 in every 840 male live born infants
- Clinical presentation is variable. Common characteristics of Jacobs syndrome include:
  - Learning difficulties, speech and language delays
  - Increased risk of hyperactivity and attention problems and occasionally autism spectrum disorder
  - Normal fertility



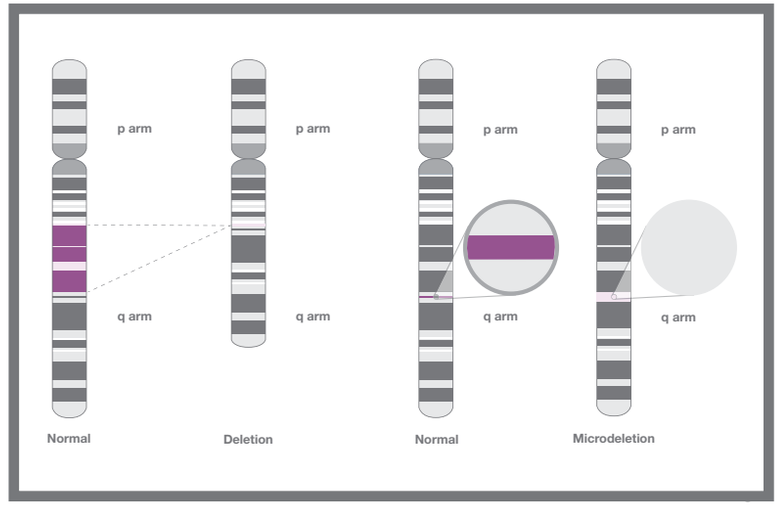
Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.
Your guide to understanding genetic conditions: 47,XYY syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/47xyy-syndrome. Accessed April 4, 2018.

Chromosome deletions and microdeletions



Chromosome deletions and microdeletions

- Deletions and microdeletions are caused by missing pieces of chromosome material
  - Microdeletions are typically too small to be seen on conventional karyotype analysis and need specialized testing for their identification
- Chromosome deletions and microdeletions may result in intellectual and developmental disabilities and congenital anomalies



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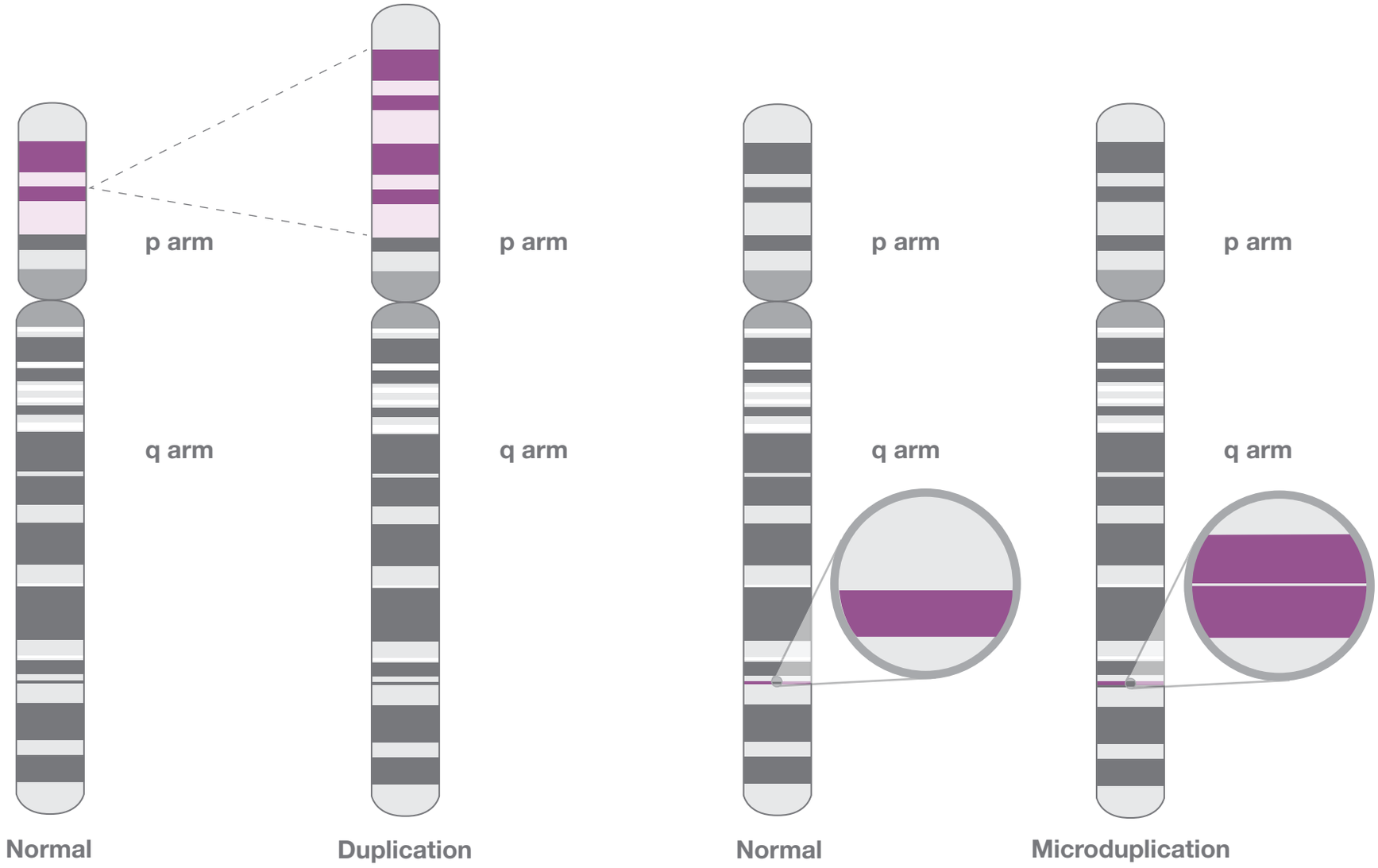
Chromosome duplications and microduplications



Chromosome duplications and microduplications

- Duplications and microduplications are caused by extra pieces of chromosome material
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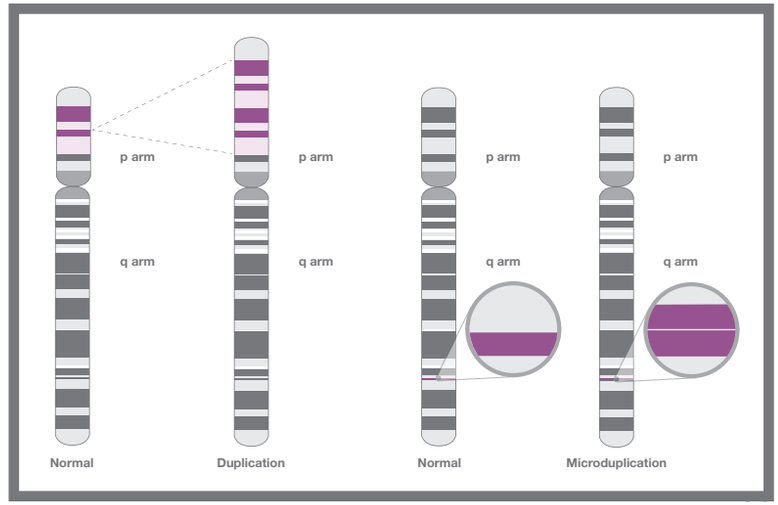
- Chromosome duplications and microduplications may result in intellectual and developmental disabilities and congenital anomalies



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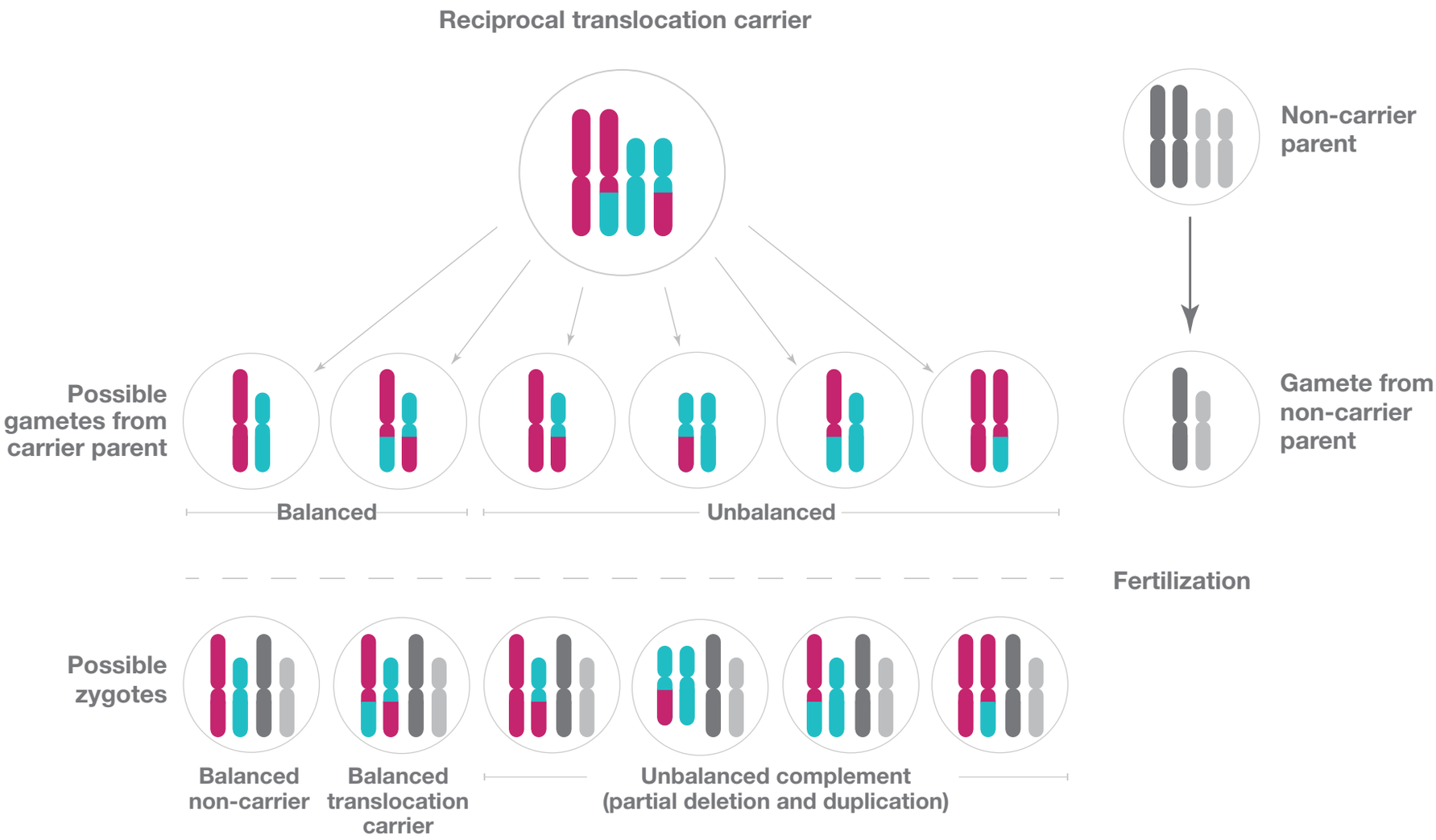
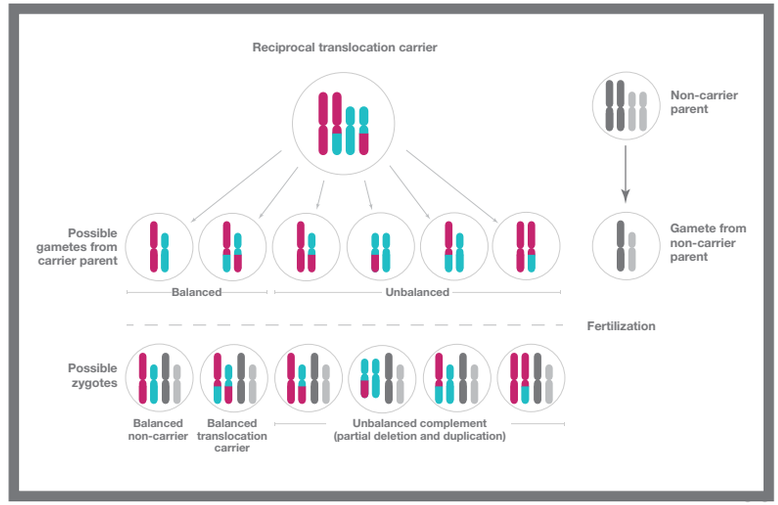
Chromosome translocation: Reciprocal



Chromosome translocation: Reciprocal

- A reciprocal translocation is the result of two different chromosomes exchanging segments
- Balanced reciprocal translocations are present in approximately 1 in 500 individuals
- Individuals who are balanced reciprocal translocation carriers usually do not have clinical features, but may be at risk for:
  - Infertility
  - Recurrent pregnancy loss
  - Birth of a baby with congenital anomalies, intellectual and developmental disability



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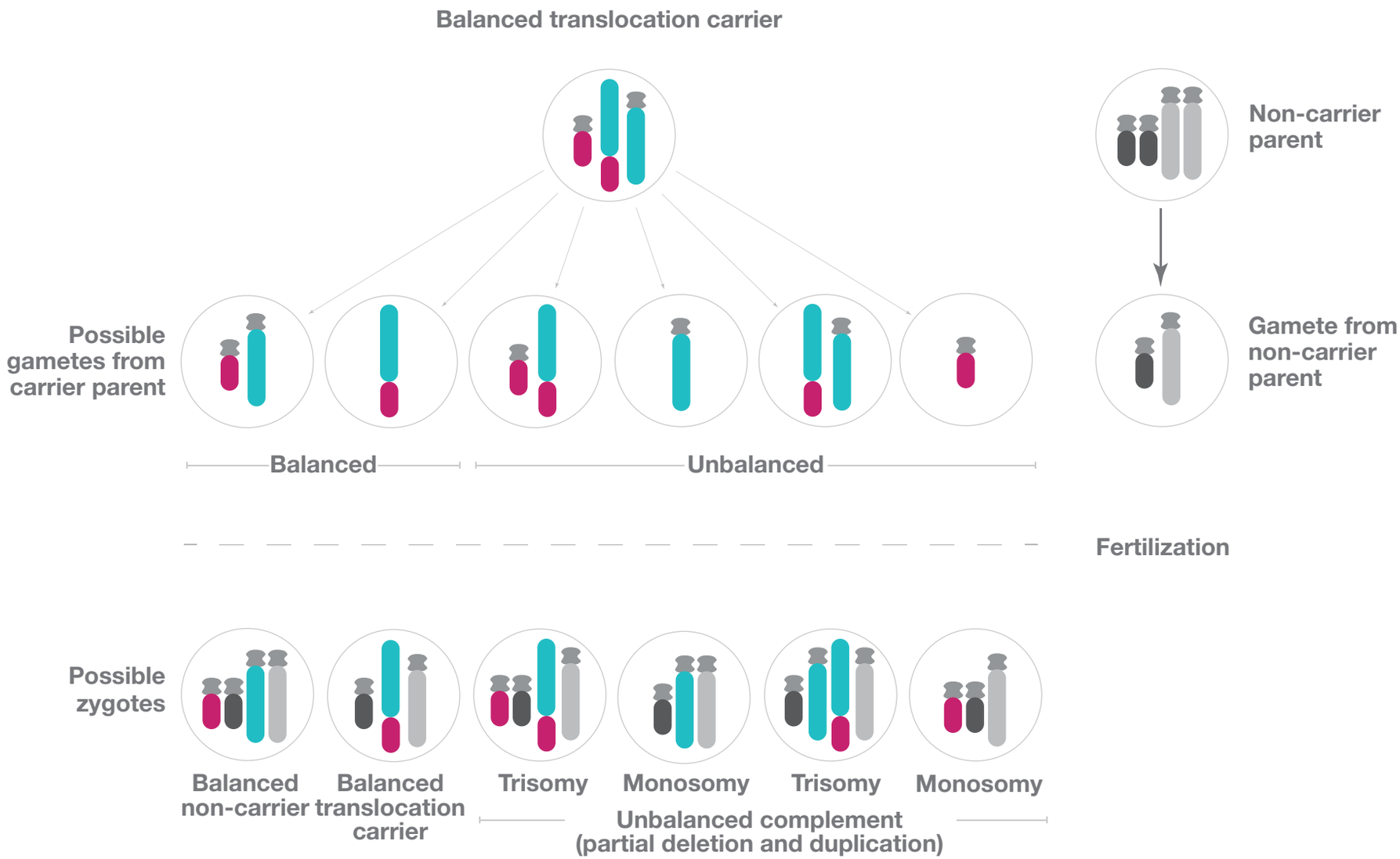
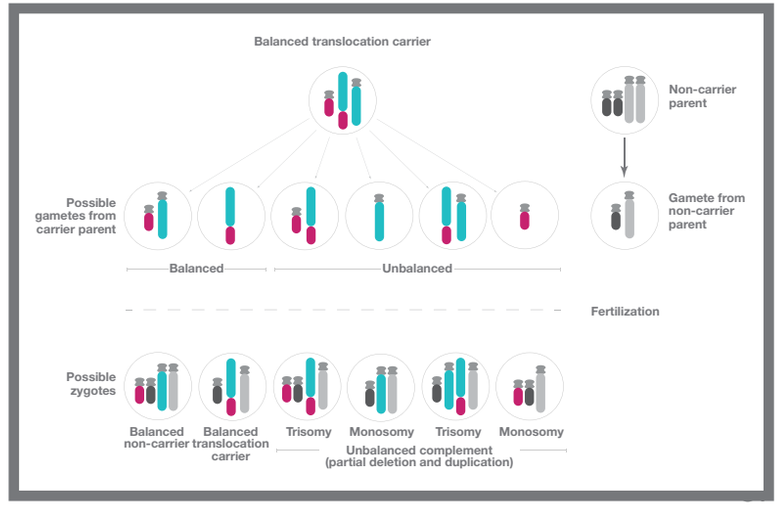
Chromosome translocation: Robertsonian



Chromosome translocation: Robertsonian

- A Robertsonian translocation occurs when two “Robertsonian” chromosomes (13, 14, 15, 21, 22) join together
- Balanced Robertsonian translocations are present in approximately 1 in every 1,000 individuals
- Individuals who are balanced Robertsonian translocation carriers usually do not have clinical features, but may be at risk for:
  - Infertility
  - Recurrent pregnancy loss
  - Birth of a baby with congenital anomalies, intellectual and developmental disability



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Prenatal screening and diagnostic options

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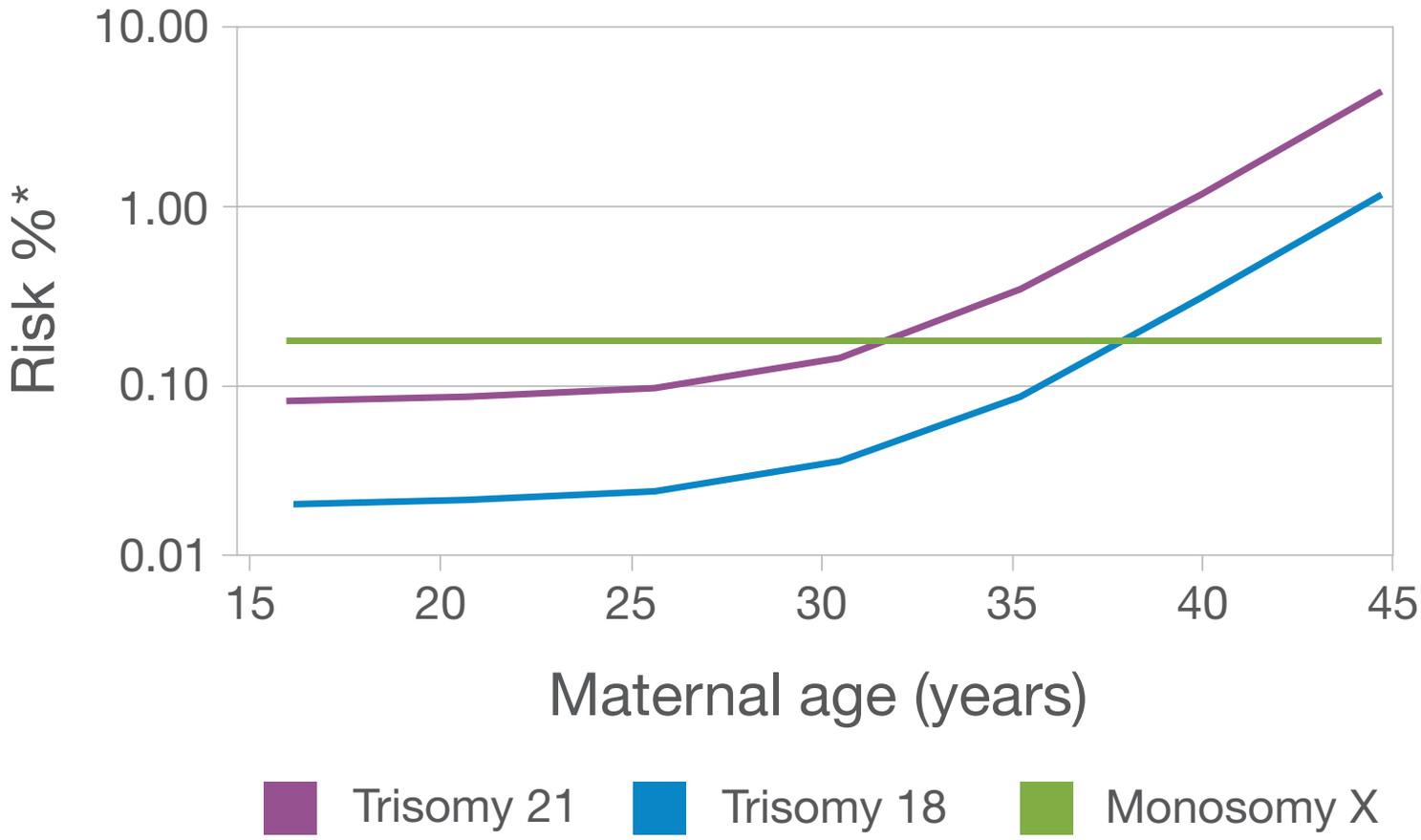
Prenatal screening and diagnostic options

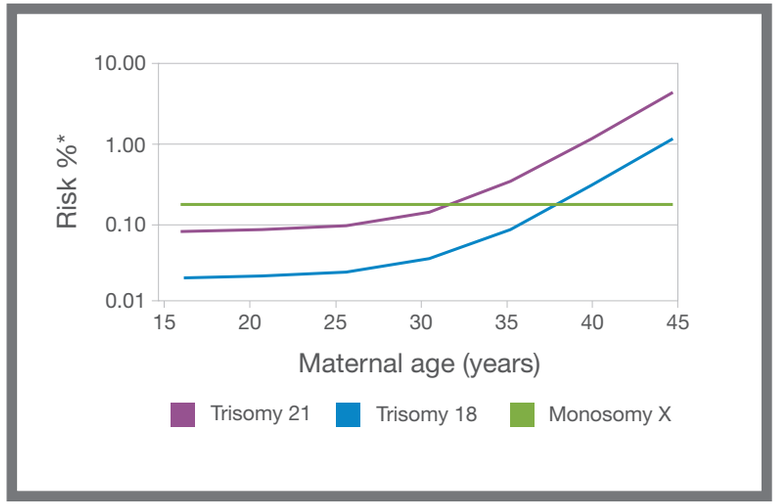
Risk of aneuploidy with maternal age



*Midtrimester risk for trisomy 21(T21), trisomy 18 (T18), Monosomy X (MX)

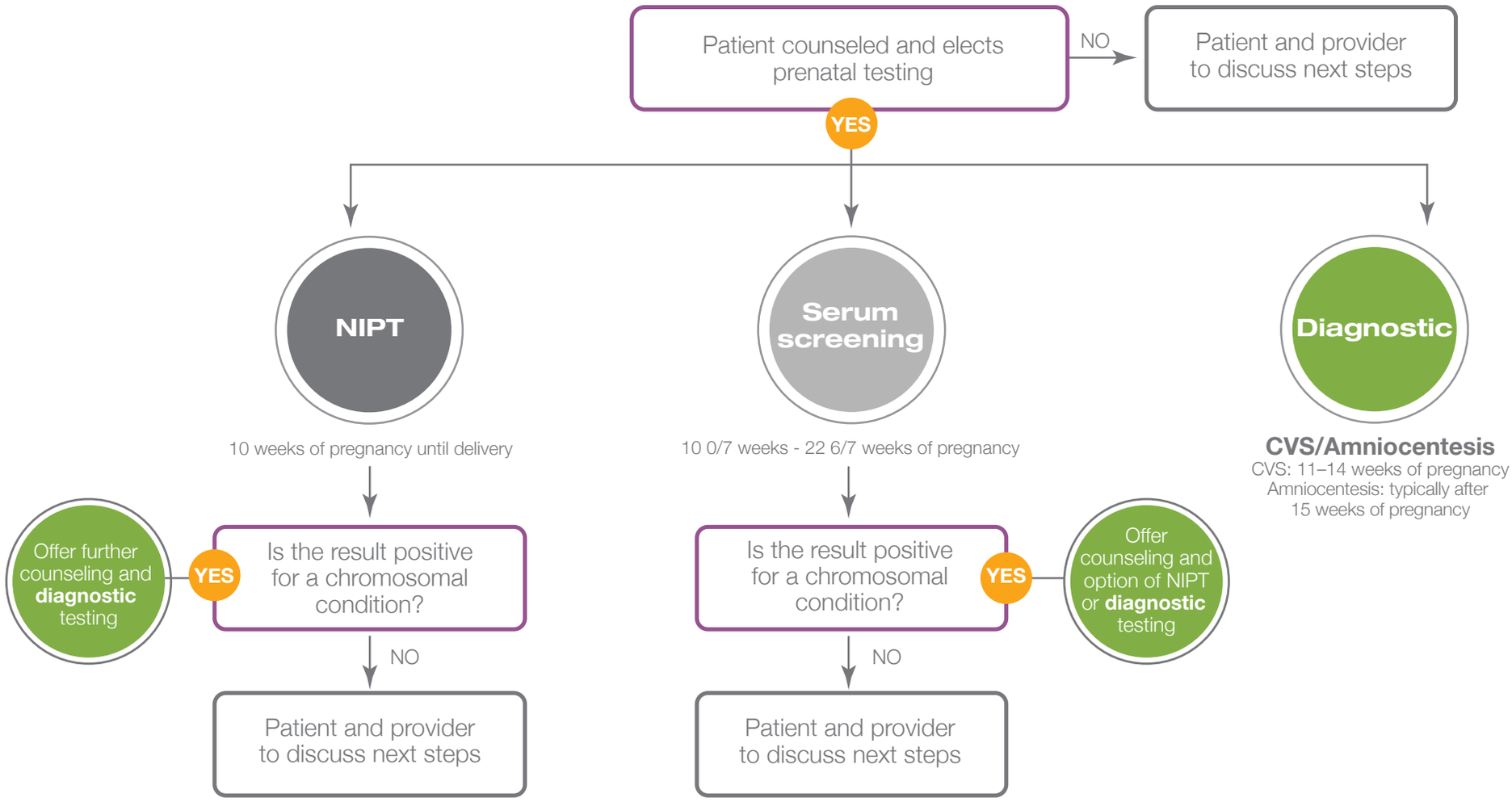
Risk of aneuploidy with maternal age

- The prevalence of certain chromosome anomalies, like trisomy 21, increases as maternal age increases. This is due to nondisjunction
- The prevalence of some chromosome anomalies, like Turner syndrome, are not impacted by maternal age



Allen EG, Freeman SB, Drschel C, Hobbs CA et al. Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects Hum Genet. 2009 Feb; 125(1): 41–52.
ACOG PB #163 Clinical Management guideline for Obstetrician-Gynecologist: Screening for fetal aneuploidies May 2016

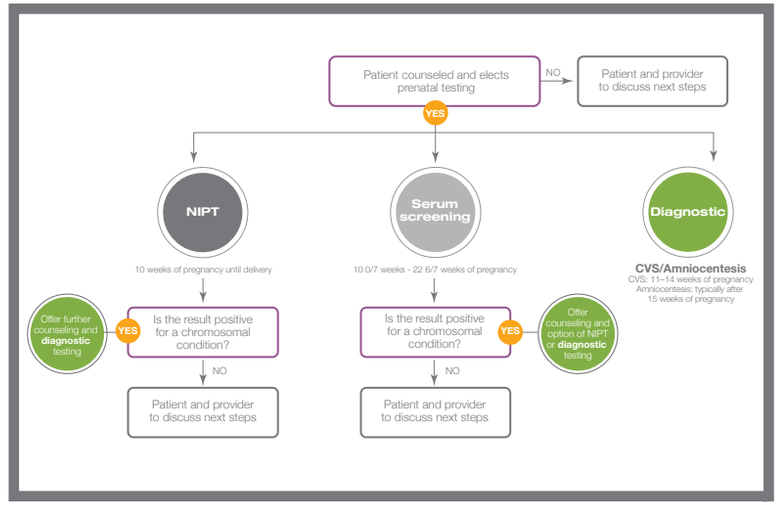
Prenatal screening and diagnostic options*



*May differ by country.

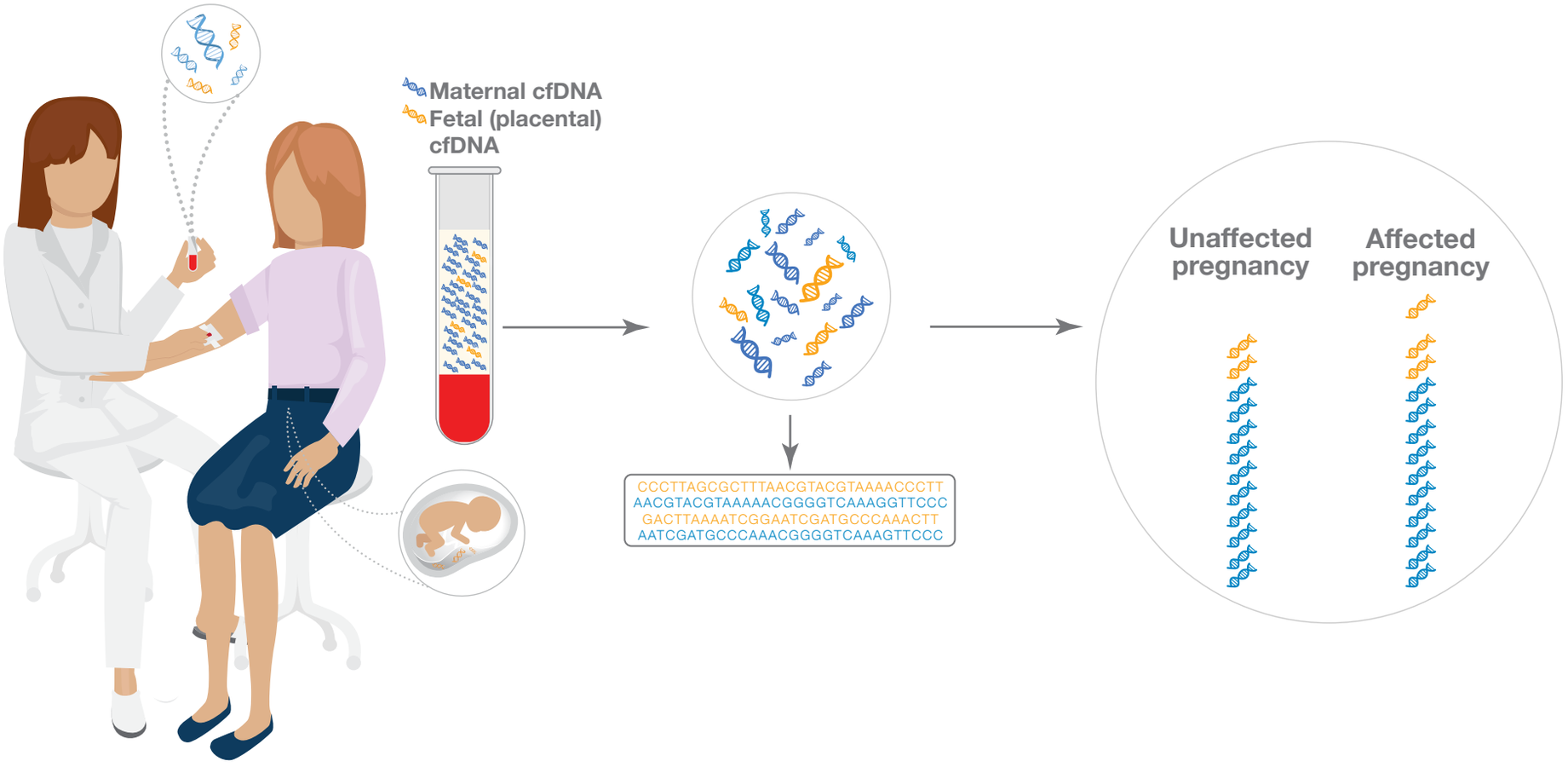
Prenatal screening and diagnostic options*

- Prenatal aneuploidy screening assesses a woman's chance of carrying a pregnancy with certain chromosomal conditions
  - Screening results are not diagnostic. If a screening result is positive, patients should receive further counseling and the option for confirmatory diagnostic testing
- Diagnostic testing can provide more definitive information about:
  - Chromosomal conditions
  - Certain genetic conditions



ACOG Practice Bulletins—Prenatal Diagnostic Testing for Genetic Disorders. *Obstet Gynecol*. 2016;127:e108–e122.
ACOG Practice Bulletins—Screening for Fetal Aneuploidy. *Obstet Gynecol.* 2016;127:e123–e137.
***Typical in USA but may differ by country.**

Noninvasive prenatal testing (NIPT) using cell-free DNA



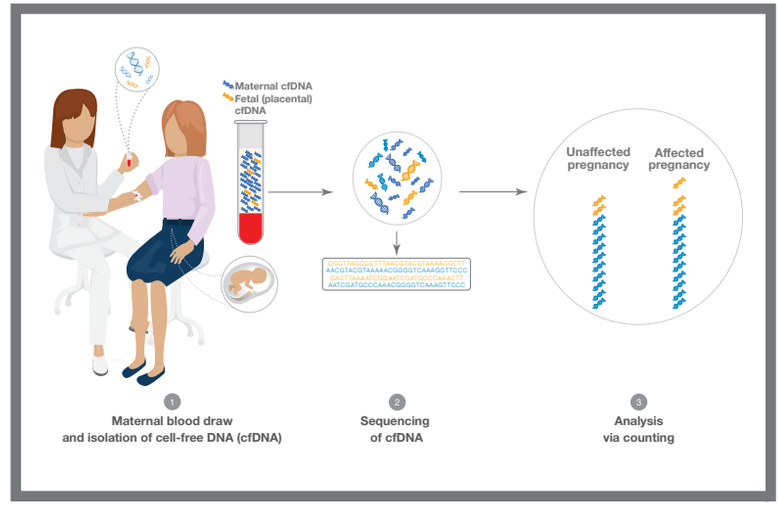
1 **Maternal blood draw and isolation of cell-free DNA (cfDNA)**

2 **Sequencing of cfDNA**

3 **Analysis via counting**

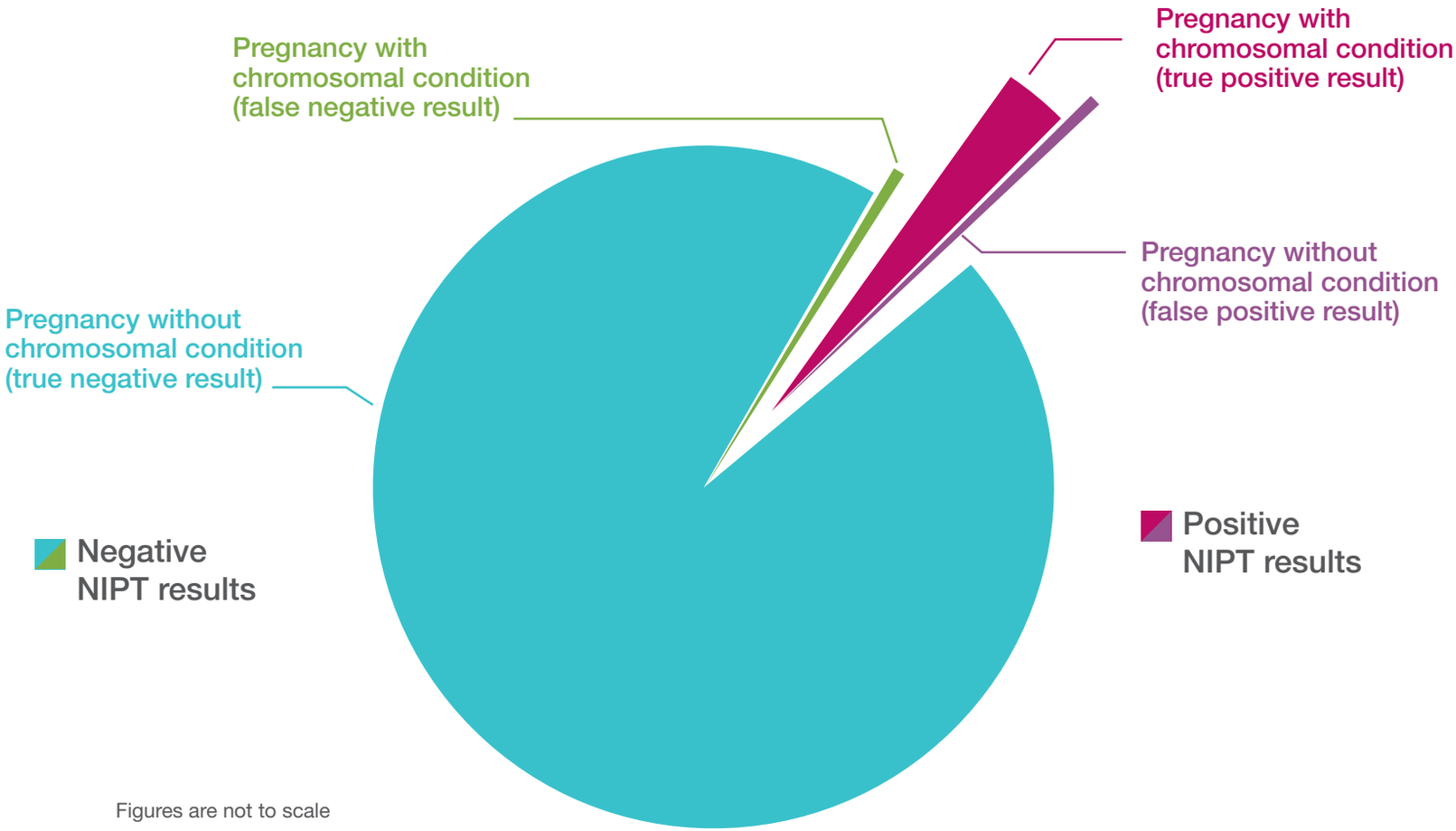
Noninvasive prenatal testing (NIPT) using cell-free DNA

- NIPT can be performed as early as 10 weeks
- A blood sample is drawn from the pregnant woman's arm. The blood sample contains maternal and placental (fetal) cfDNA
- cfDNA is sequenced and its chromosome origin is determined, then counted to screen for chromosomal conditions
- Benefits:
  - Noninvasive, with no risk of miscarriage
  - High detection rates for conditions tested
  - Very low false positive rates and low false negative rates compared with traditional serum screening
- Limitations:
  - It is not diagnostic; false positives and false negatives can occur
  - In some instances, results may represent a maternal or placental condition, rather than a fetal condition



Gil MM, et al. *Ultrasound Obstet Gynecol*. 2017; Sep;50(3):302-314.
ACOG Practice Bulletins—Screening for Fetal Aneuploidy. *Obstet Gynecol.* 2016;127:e123–e137.

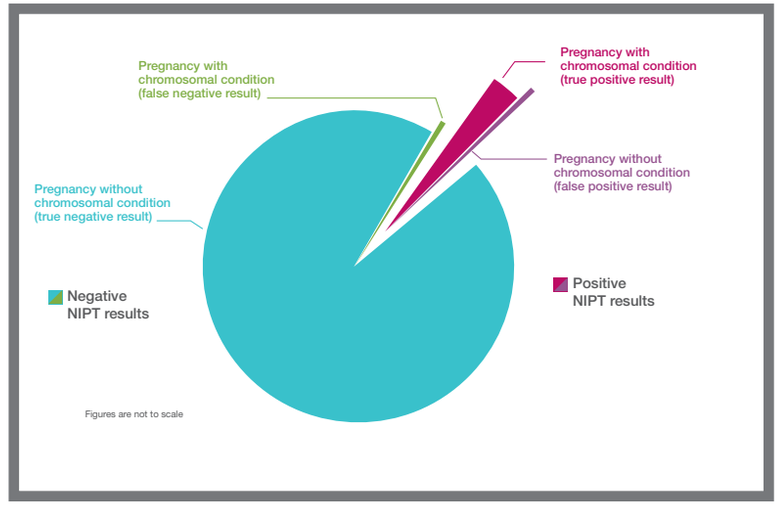
NIPT: Understanding positive and negative results



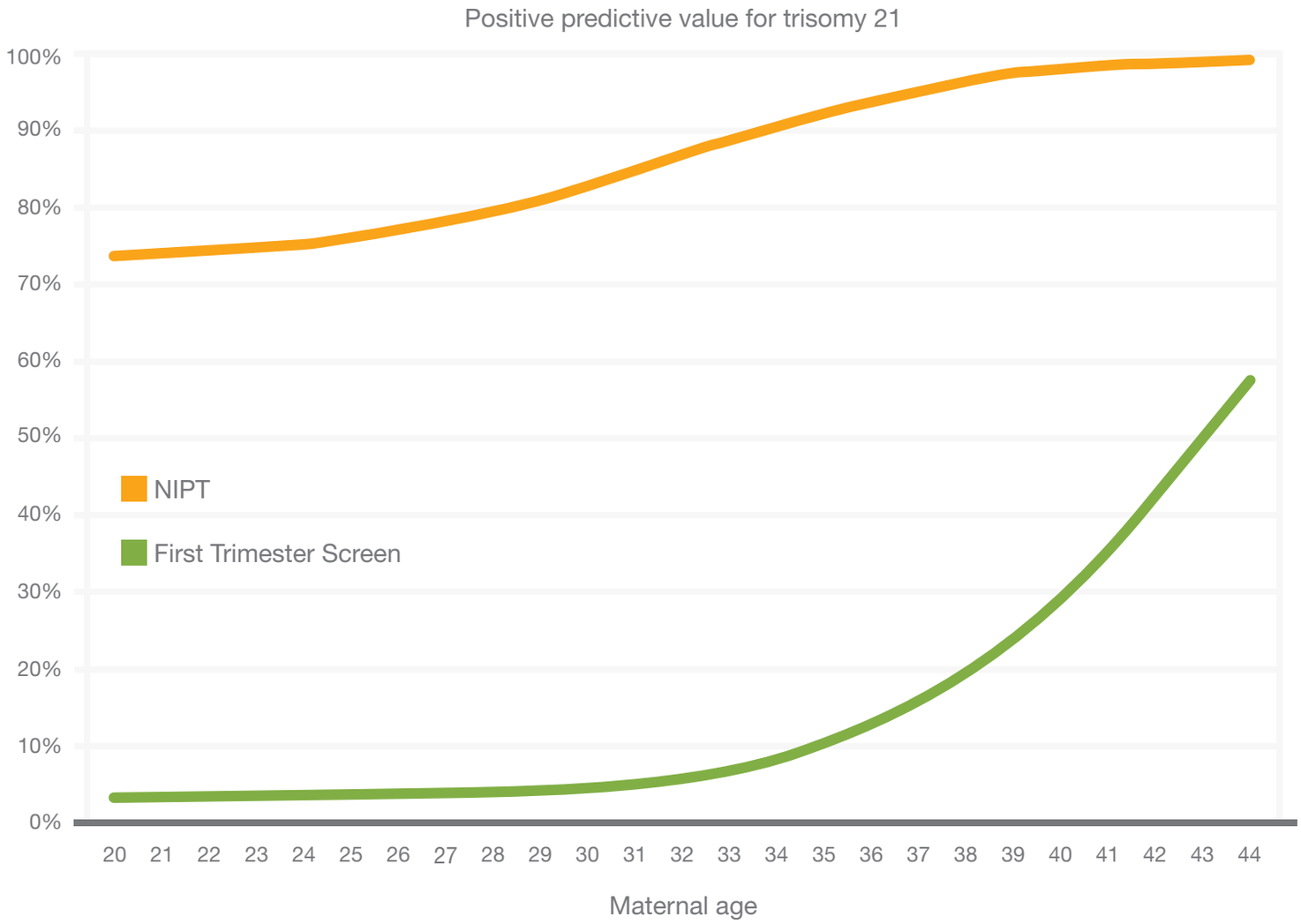
Figures are not to scale

NIPT: Understanding positive and negative results

- Results apply only to conditions tested
- A negative result means fetus has a decreased chance of having a condition
  - In most cases, the condition is truly not present (true negative result)
  - Rarely, the condition may be present (false negative result)
- A positive result means an increased chance of having the condition
  - In most cases, the condition is truly present (true positive result)
  - In some of these, the condition is not present (false positive result)
- Since NIPT is a screening test, results should be taken into context of the overall pregnancy picture and positive results should be confirmed prior to making irreversible pregnancy management decisions

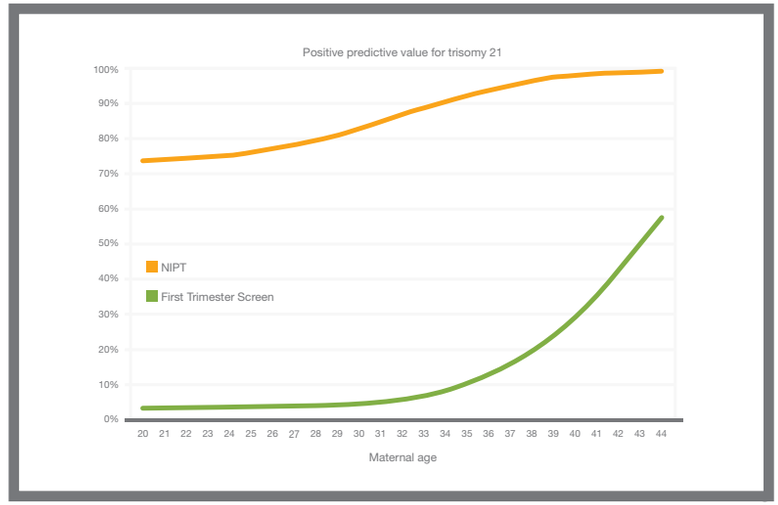


Understanding and comparisons of positive predictive value (e.g. trisomy 21)



Understanding and comparisons of positive predictive value (e.g. trisomy 21)

- Positive predictive value (PPV) refers to the chance that a pregnancy with a positive screen result truly has the condition
- PPV is influenced by the prevalence of the condition and the test performance
  - Higher prevalence results in higher PPV
  - A test with higher sensitivity and specificity leads to higher PPV
- When PPV is higher, more positive results will be true positive, and less will be false positive
- The PPV of NIPT for trisomy 21 is higher than the PPV of serum screening for trisomy 21, regardless of the maternal age



Snijders RJ, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risk for chromosomal defects. Fetal Diagn Ther. 1995;10(6):356-67.

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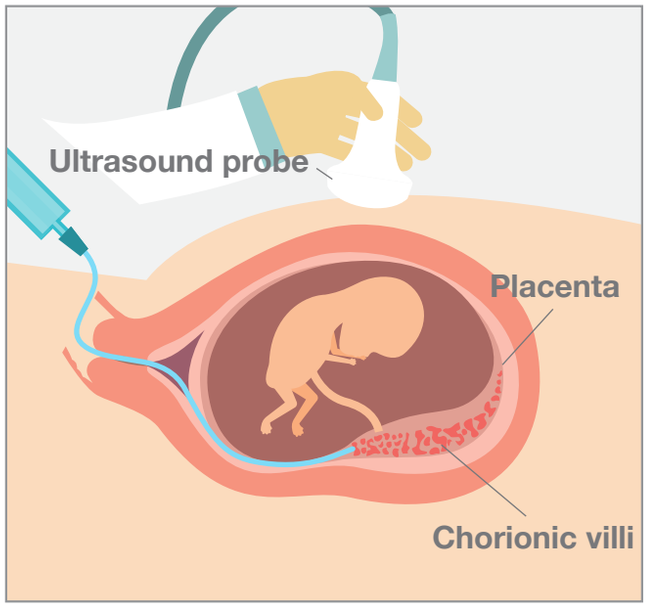
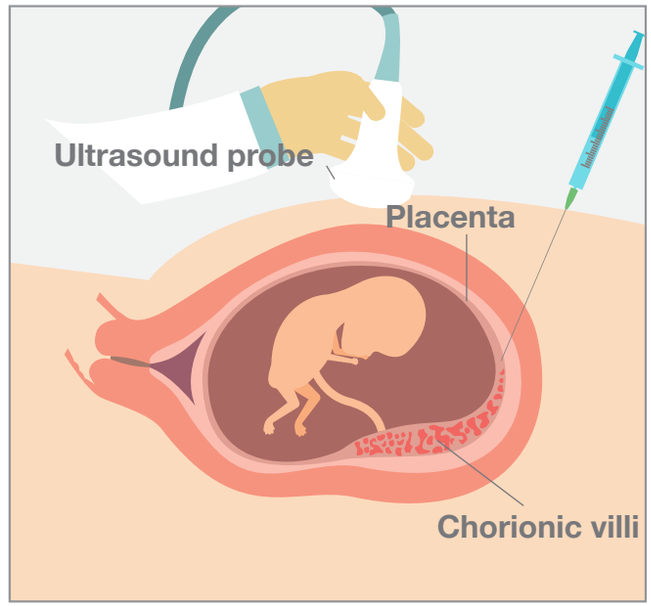
Santorum , Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol. 2017 Jun;49(6):714-720. doi: 10.1002/uog.17283.

Diagnostic testing: Chorionic villus sampling (CVS)



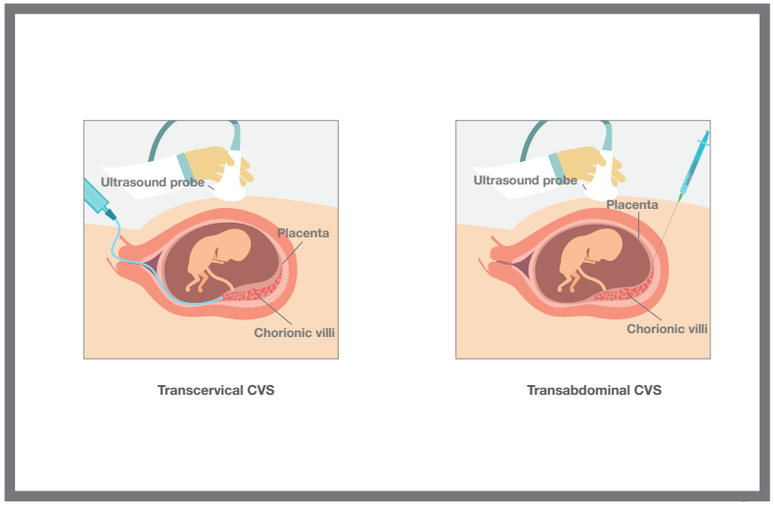
Transcervical CVS



Transabdominal CVS

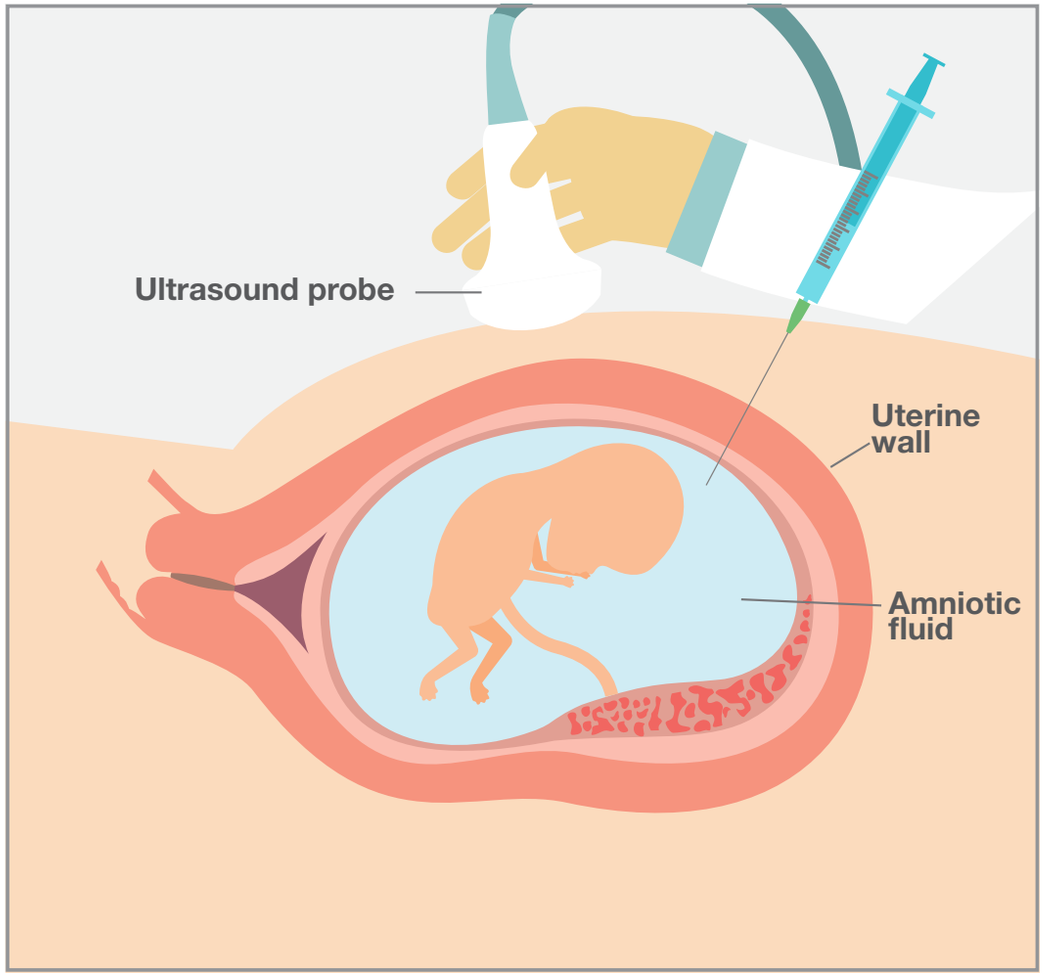
Diagnostic testing: Chorionic villus sampling (CVS)

- Can determine, with as much certainty as is possible, whether a chromosomal condition is present
  - Additional genetic testing can be performed, if indicated
- Involves testing of cells collected from the placental villi
  - Typically performed between 11 and 14 weeks of pregnancy
- Has risk of complications including miscarriage



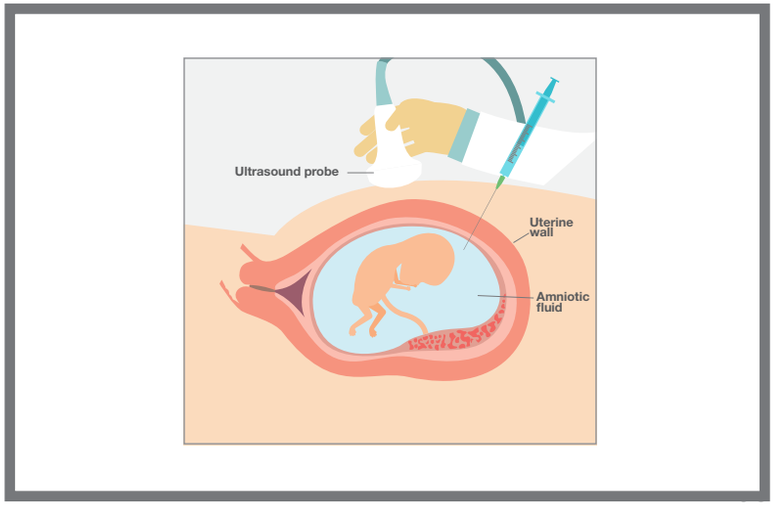
ACOG Practice Bulletins—Prenatal Diagnostic Testing for Genetic Disorders. *Obstet Gynecol*. 2016;127:e108–e122.

Diagnostic testing: Amniocentesis



Diagnostic testing: Amniocentesis

- Can determine, with as much certainty as is possible, whether a chromosomal condition is present
  - Additional genetic testing can be performed, if indicated
- Involves testing of fetal cells collected from fluid surrounding the fetus (amniotic fluid)
  - Typically performed between 15 and 20 weeks of pregnancy
  - Can be performed after 20 weeks, if indicated
- Has risk of complications, including amniotic fluid leakage and miscarriage



ACOG Practice Bulletins—Prenatal Diagnostic Testing for Genetic Disorders. *Obstet Gynecol*. 2016;127:e108–e122.

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Rare autosomal trisomies

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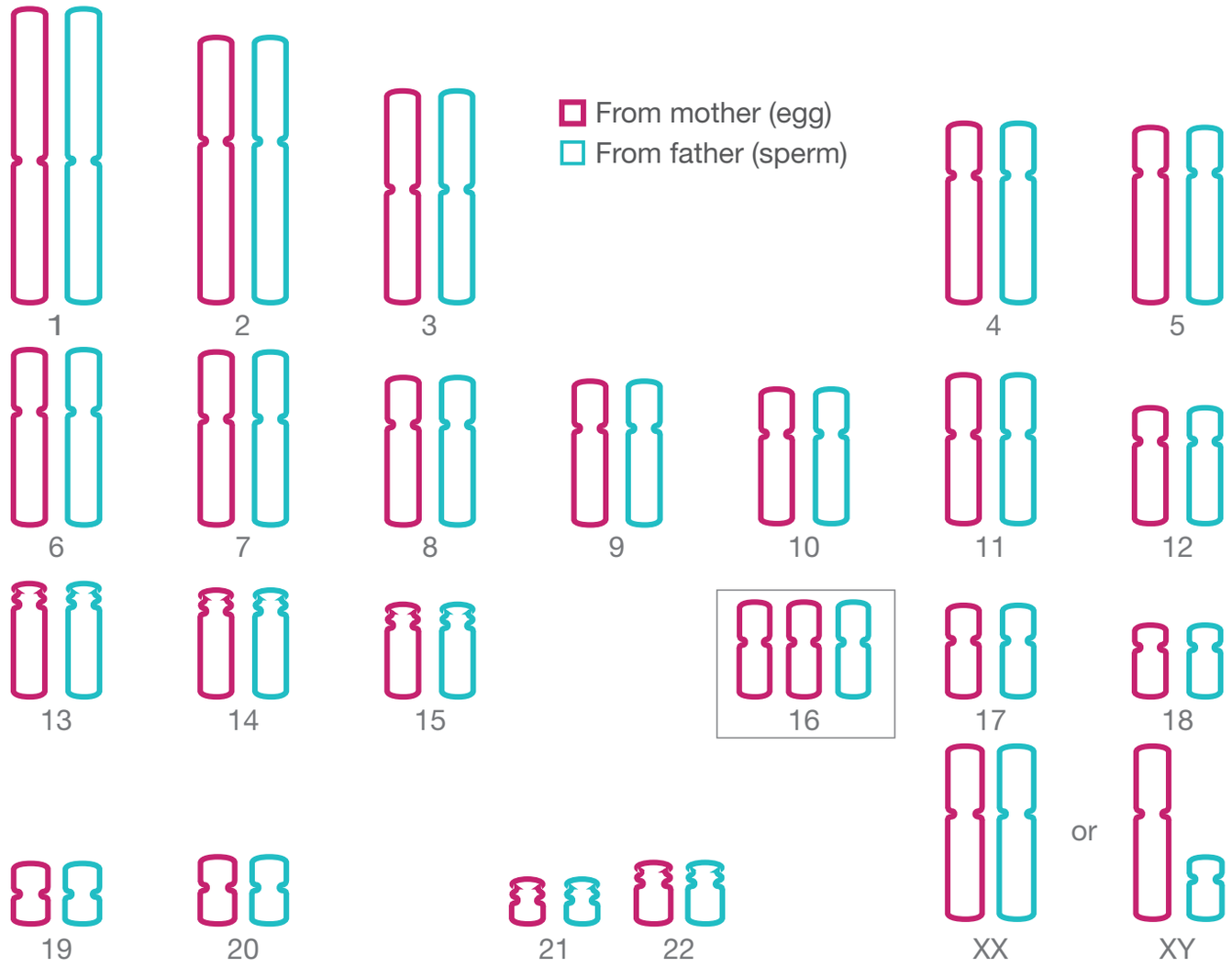
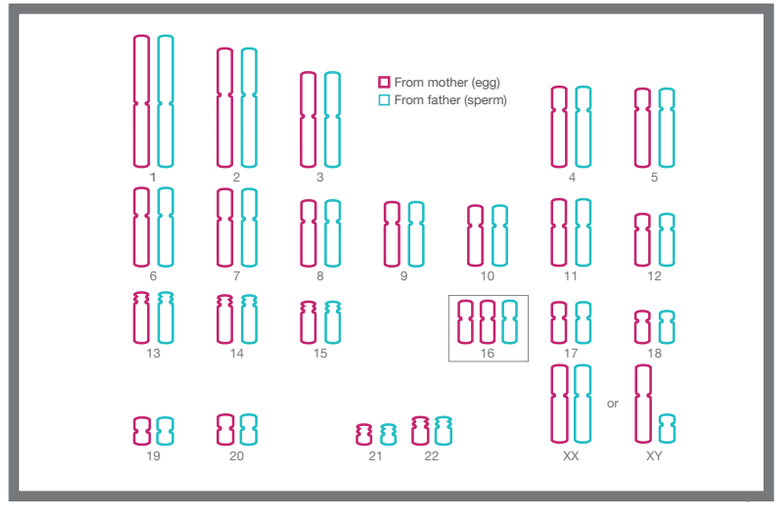
Rare autosomal trisomies

Rare autosomal trisomies (e.g. trisomy 16)



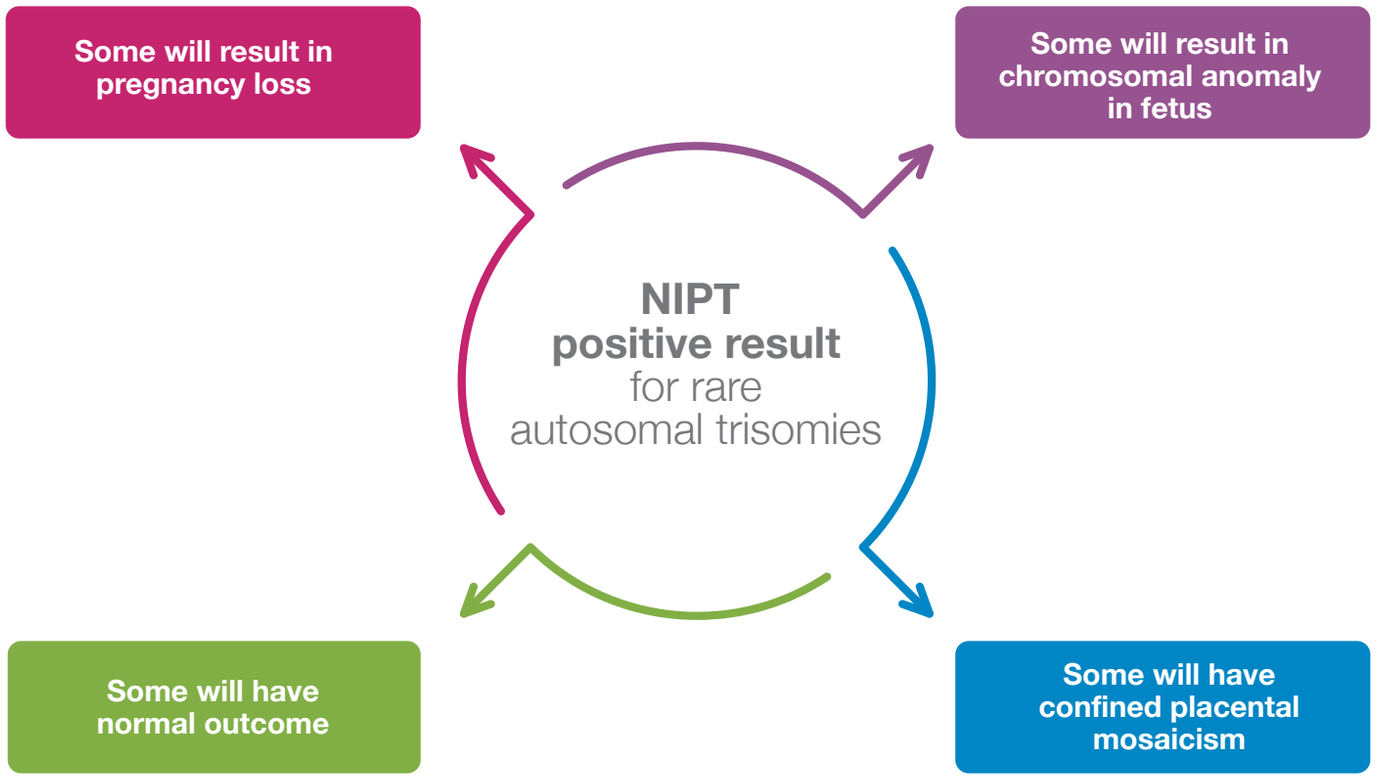
Rare autosomal trisomies (e.g. trisomy 16)

- Trisomy involving a chromosome other than 21, 18, 13, X or Y is referred to as rare autosomal trisomy
- Prevalence of rare autosomal trisomy in NIPT is 0.28-0.78%
- Clinical presentation varies and is dependent on the chromosome involved. These can include:
  - Pregnancy loss
  - Fetal demise and stillbirth
  - Confined placental mosaicism with resulting intrauterine growth restriction and uniparental disomy-related disorders
  - Intellectual and developmental disabilities and birth defects
  - In some cases, clinical phenotype may be normal



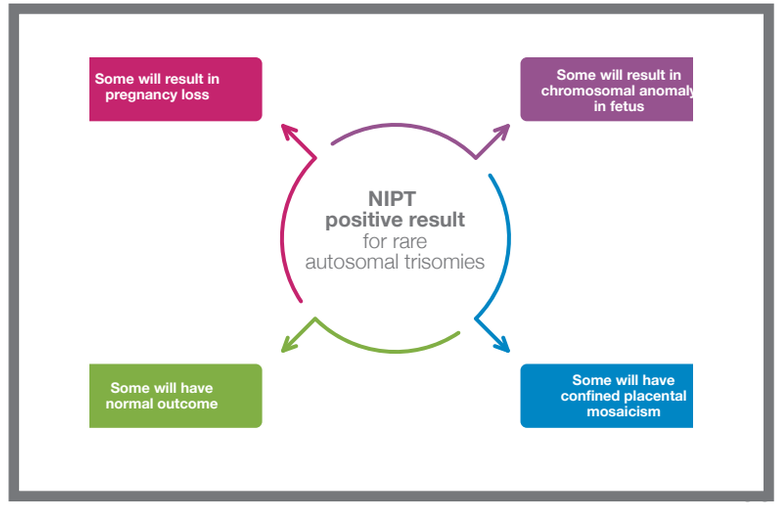
Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier Saunders; 2013.

Potential clinical outcome of rare autosomal trisomy identified by noninvasive prenatal testing (NIPT)



Potential clinical outcome of rare autosomal trisomy identified by noninvasive prenatal testing (NIPT)

- Clinical presentation after a positive NIPT result is variable, and is chromosome dependent
  - Certain chromosomal anomalies can cause pregnancy loss
  - Certain chromosomal anomalies can result in live birth with a phenotype associated with the detected chromosome anomaly
  - Certain chromosome anomalies result in confined placental mosaicism (CPM)
    - CPM can be associated with an increased risk for altered placental function, leading to intrauterine growth restriction, fetal demise and risk for uniparental disomy
  - Some cases will have no apparent clinical findings
  - False positive results can also occur
- NIPT is a screening test. Results should be confirmed by diagnostic testing (for example, CVS or amniocentesis) prior to making any pregnancy management decisions



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Kalousek DK, Barrett I. Confined placental mosaicism and stillbirth. Pediatr Pathol 1994 Jan-Feb;14(1):151-9.
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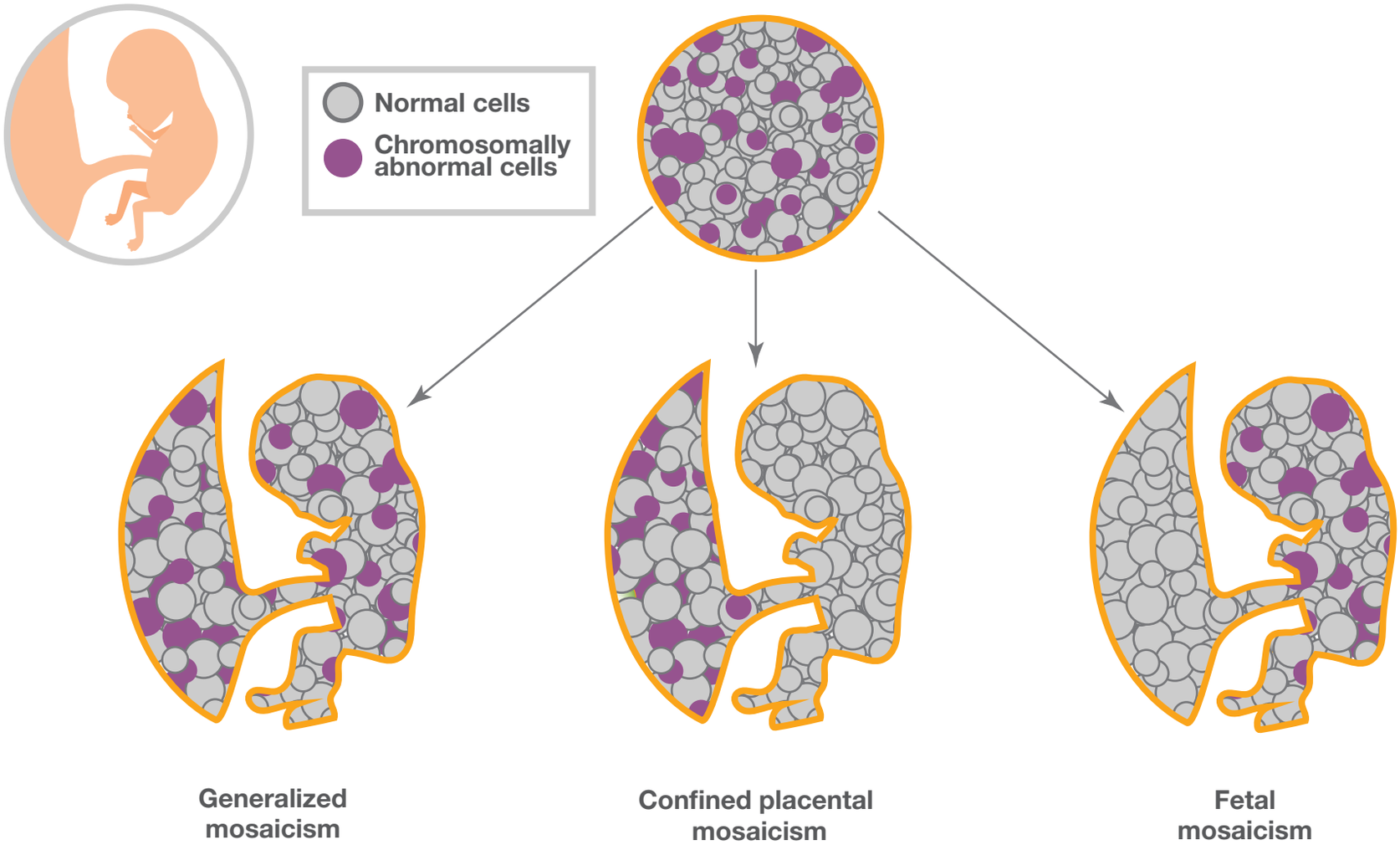
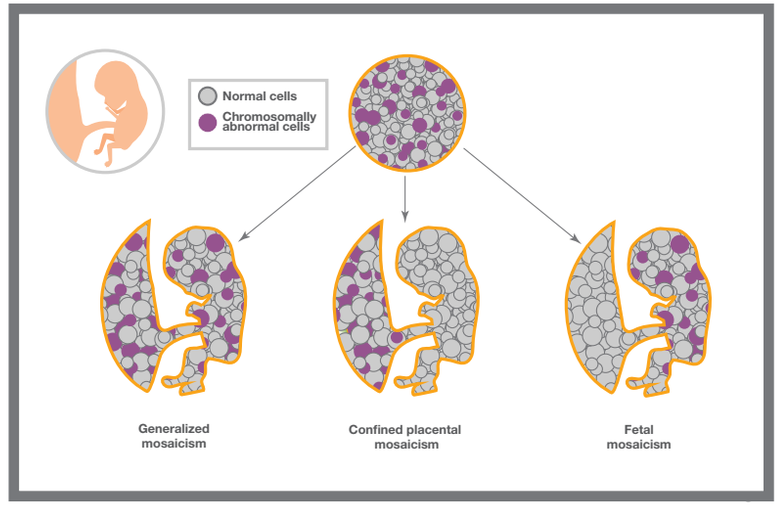
Types of chromosomal mosaicism



Types of chromosomal mosaicism

- **Generalized mosaicism**: presence of two or more chromosomally different cell lines in both the placenta and the fetus.
  - Can lead to a false negative NIPT result
- **Confined placental mosaicism**: presence of two or more chromosomally different cell lines in the placenta, but not the fetus.
  - Can lead to a false positive NIPT result
- **Fetal mosaicism**: presence of two or more chromosomally different cell lines that are present in the fetus, but not the placenta.
  - Can lead to a false negative NIPT result



Grati FR. *J Clin Med*. 2014;3(3):809-837.
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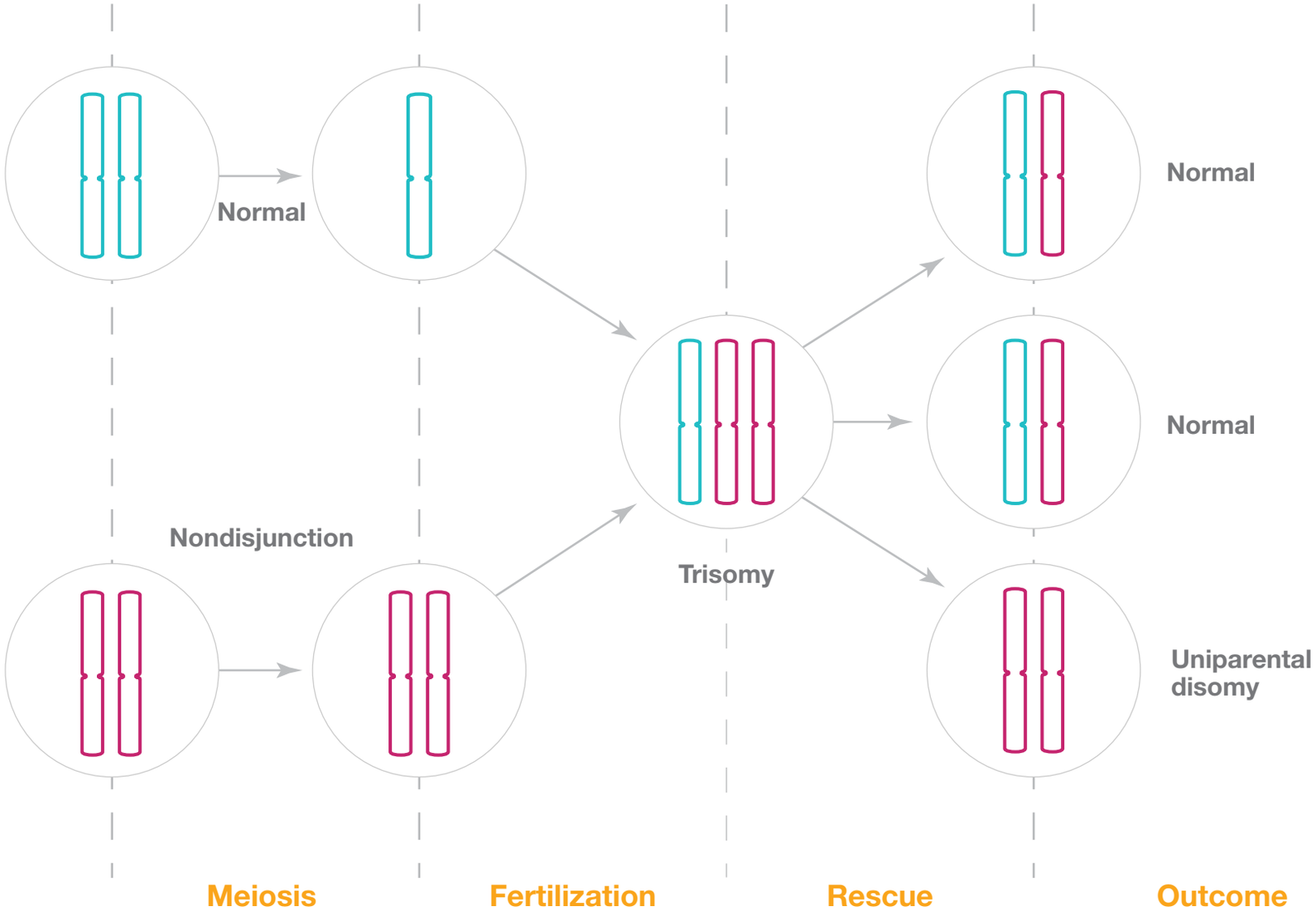
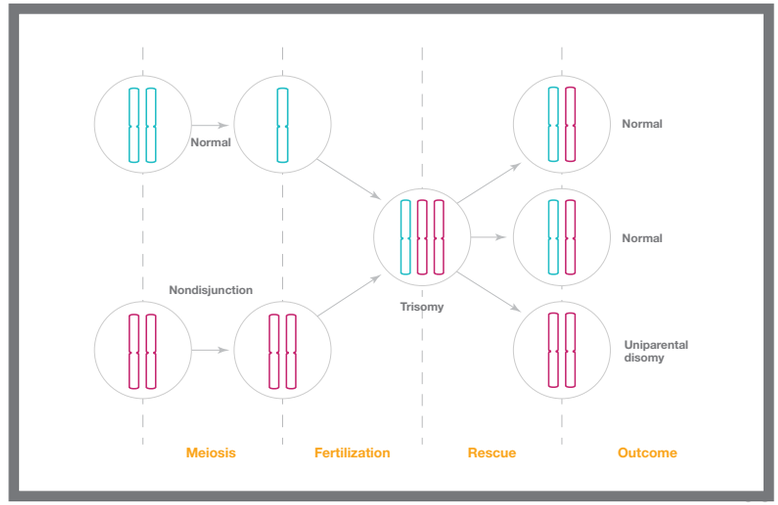
Kalousek DK. *Pediatr Pathol.* 1990;10(1-2):69-77.

Uniparental parental disomy (UPD) due to trisomic rescue



Uniparental parental disomy (UPD) due to trisomic rescue

- UPD refers to having two copies of a particular chromosome from the same parent, instead of one from each parent
  - In case of confined placental mosaicism, UPD predominantly occurs due to trisomic rescue
  - ACMG recommends UPD testing for imprinted chromosomes (6,7,11,14,15,20); clinical practice may vary
  - Additional specialized testing is required for diagnosing UPD
  - Clinical presentation is variable. UPD of certain imprinted chromosomes can cause intellectual disability and other genetic conditions
- Positive cfDNA screening for certain autosomal trisomies is associated with an increased risk of confined placental mosaicism, resulting in increased risk of uniparental disomy (UPD)



1. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. Am J Med Genet A 2005: 136: 287 – 305.
2. Shaffer LG, Agan N, Goldberg JD et al. American College of Medical Genetics statement of diagnostic testing for uniparental disomy. Genet Med 2001: 3: 206 – 211.

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Single gene inheritance

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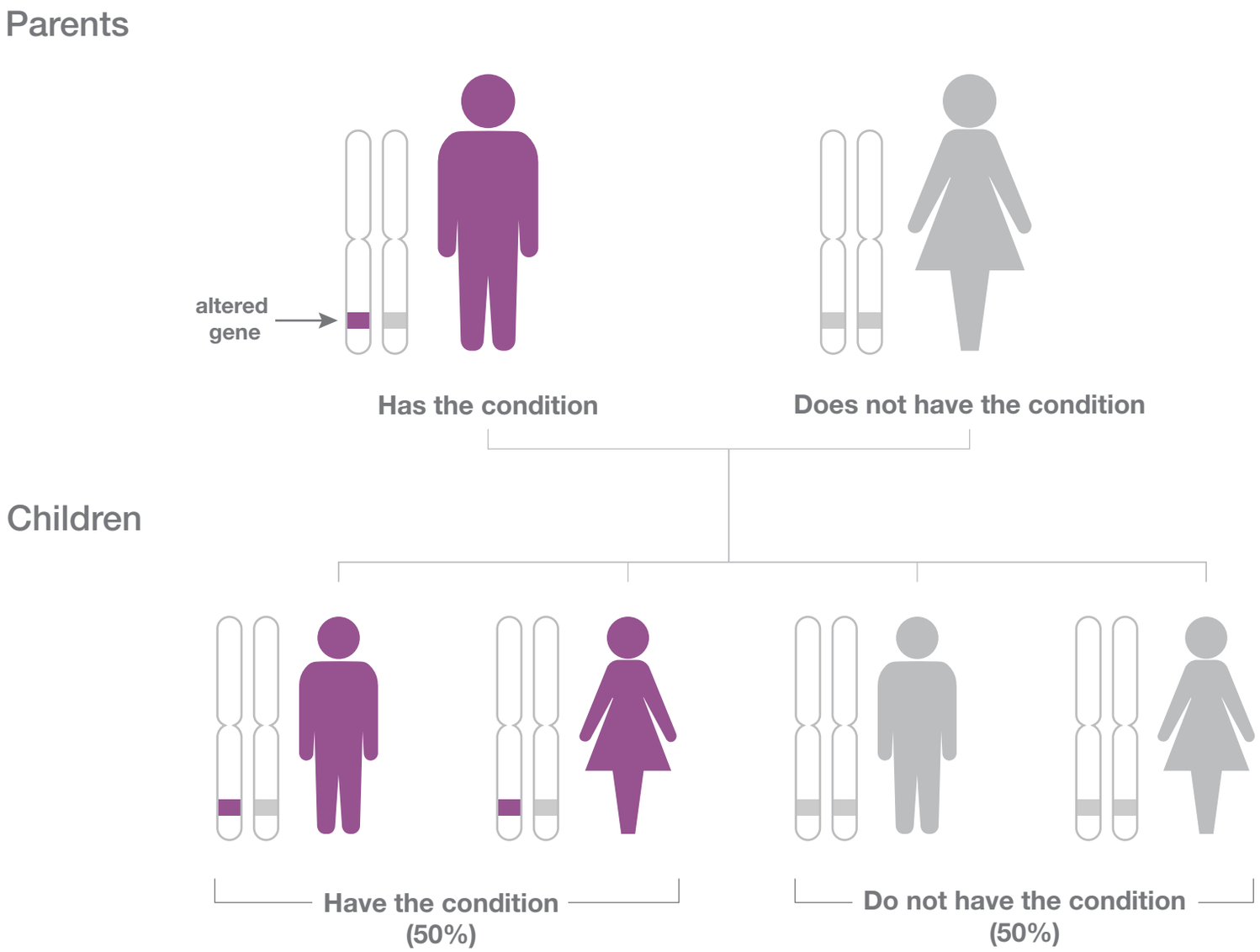
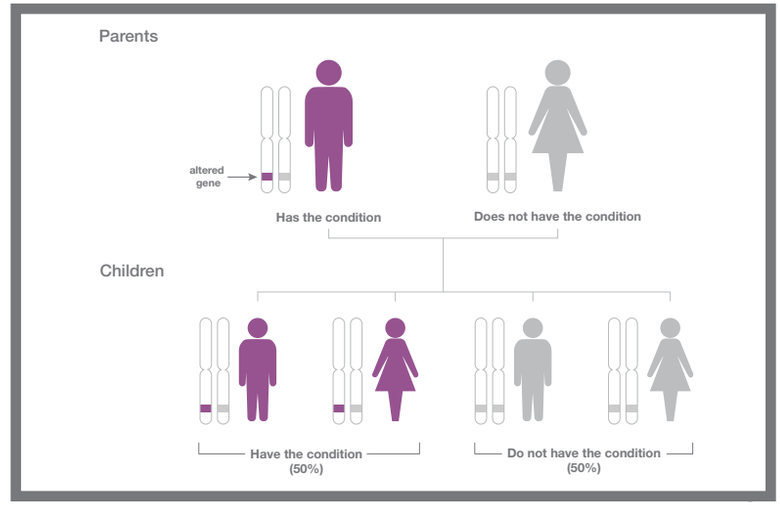
Single gene inheritance

Autosomal dominant inheritance



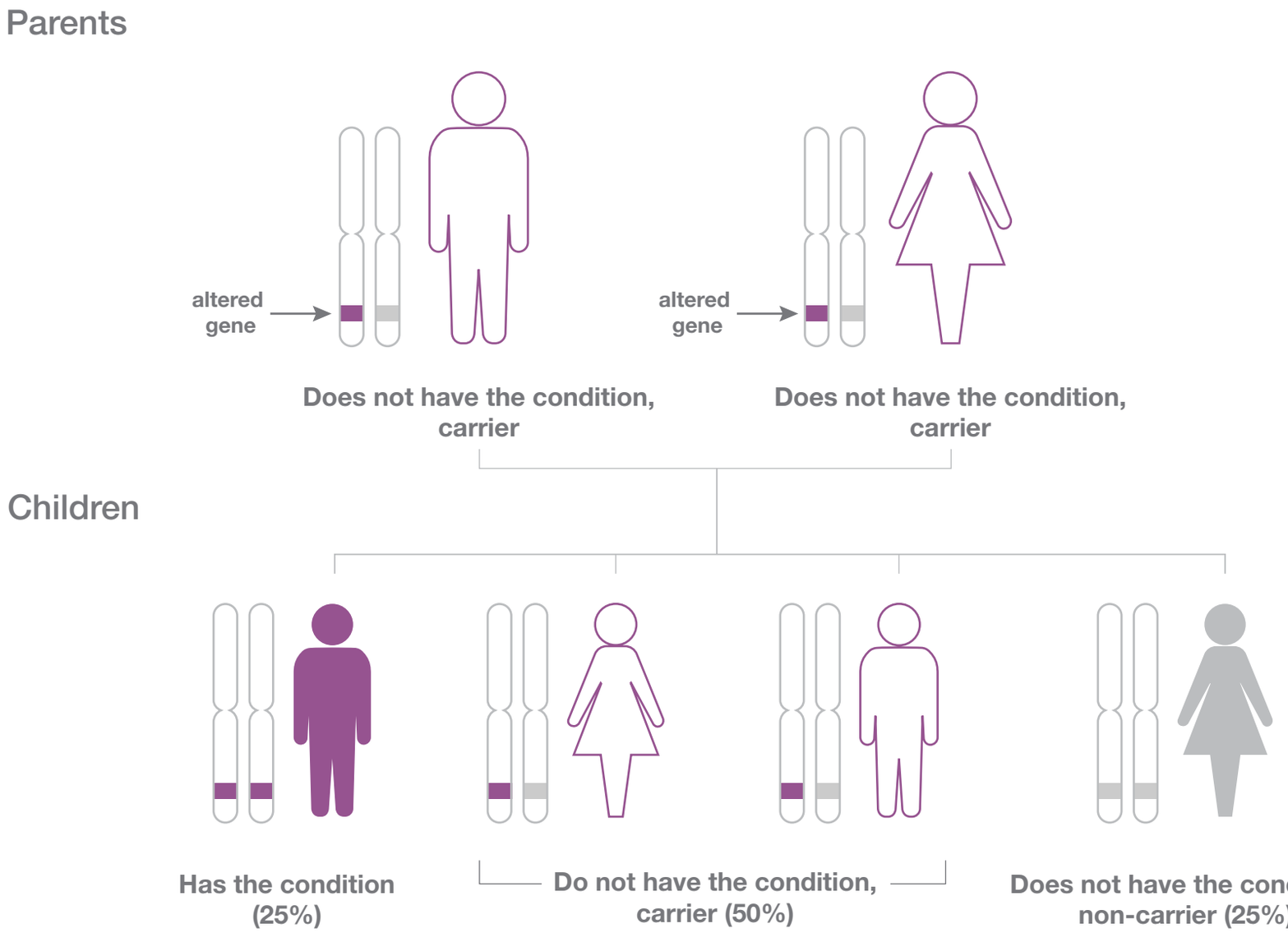
Autosomal dominant inheritance

- With autosomal dominant inheritance, only one copy of an altered allele is necessary for the condition to be present
- An affected parent has the following reproductive risks with each pregnancy:
  - 50% chance to have a child affected with the condition
  - 50% chance to have a child without the condition (unaffected)
  - Males and females are at equal risk



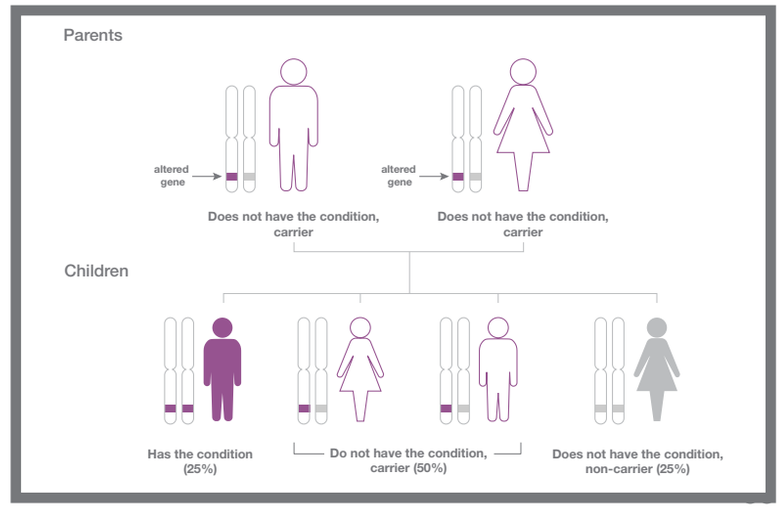
US National Library of Medicine. Help Me Understand Genetics: Inheriting Genetic Conditions. https://ghr.nlm.nih.gov/primer/inheritance.pdf. Published June 6, 2016. Accessed June 7, 2016.

Autosomal recessive inheritance



Autosomal recessive inheritance

- With autosomal recessive inheritance, two copies of the altered allele are necessary for the condition to be present
- Individuals with only one copy of the altered allele are called carriers and are typically unaffected
- If both parents are carriers of the same condition, they have the following reproductive risks with each pregnancy:
  - 25% chance to have a child with the condition (affected)
  - 50% chance to have a child who does not have the condition (unaffected) and is a carrier of the condition
  - 25% chance to have a child without the condition (unaffected) and a non-carrier
  - Males and females are at equal risk



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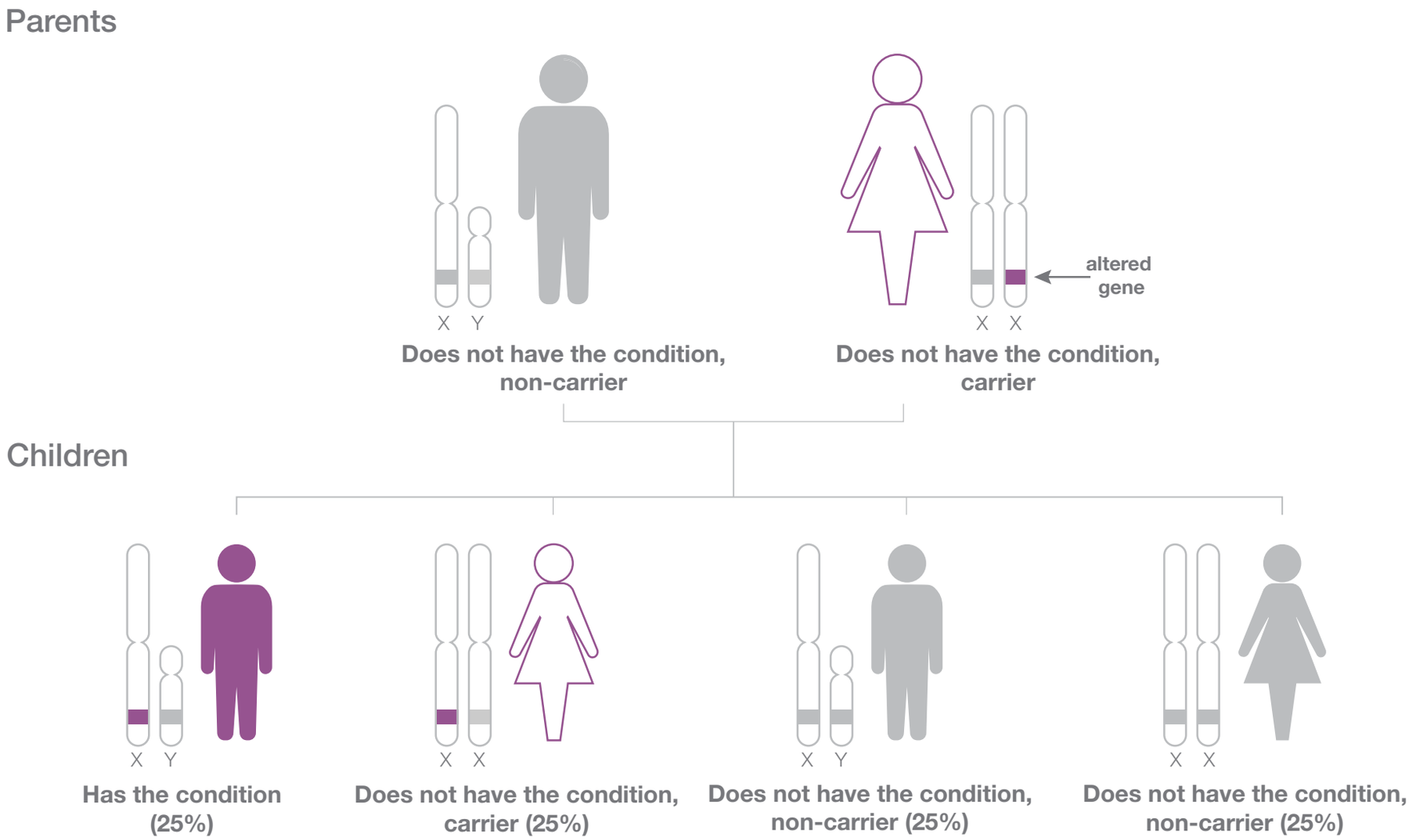
X-linked recessive inheritance



X-linked recessive inheritance

- X-linked recessive inheritance involves an altered allele that occurs on the X chromosome
- Males with an altered allele on their X chromosome will have the condition (affected)
- Females with a gene variant on one of their two X chromosomes are called carriers of the condition
  - Female carriers are typically unaffected; however, some may display some characteristics of the condition
- Carrier females have the following reproductive risk with each pregnancy:
  - 25% chance of a male with the condition (affected)
  - 25% chance of a carrier female without the condition (unaffected)
  - 25% chance of a male without the condition (unaffected)
  - 25% chance of a non-carrier female without the condition (unaffected)

US National Library of Medicine. Your guide to understanding genetic conditions: What are the different ways in which a genetic condition can be inherited? https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns. Published May 31, 2016. Accessed June 3, 2016.

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