Quiz!

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2023

Risk Calculation

Q&A

A woman has a brother and a maternal uncle who both died of severe hydrocephalus due to X-linked recessive aqueductal stenosis. The woman has two healthy sons and is currently pregnant. What is the probability that her child will be affected by the same disease?

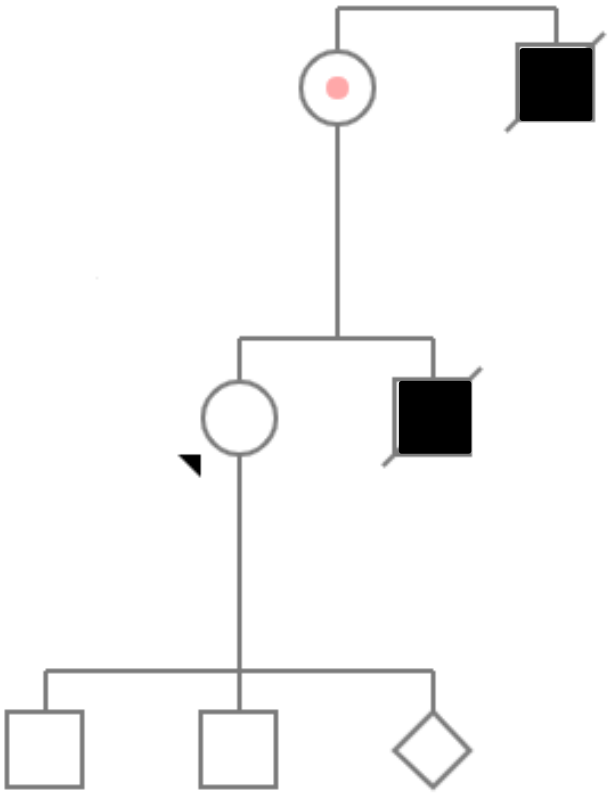
A. 1/5

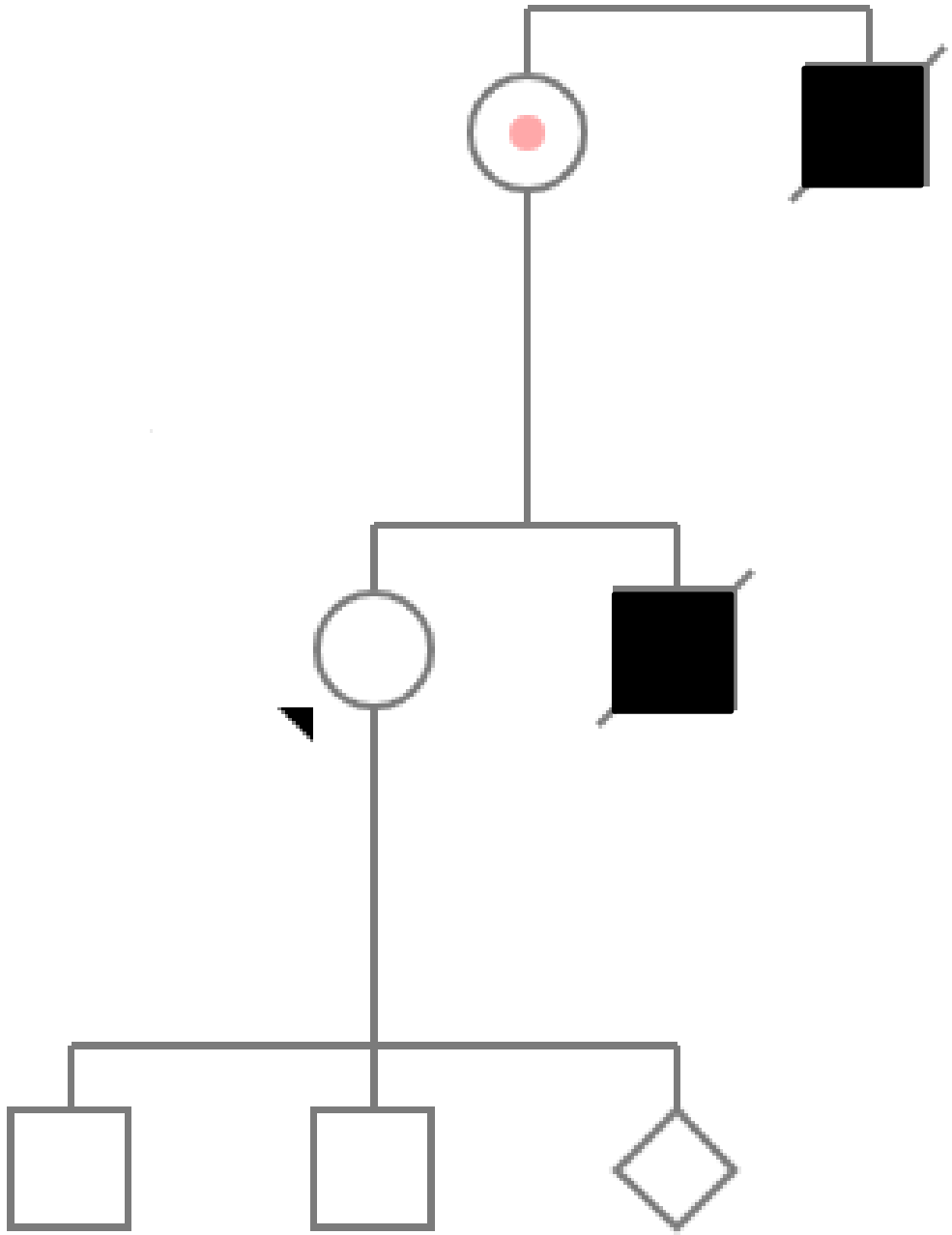
B. 1/8

C. 1/10

D. 1/20

E. 1/32





She is	A carrier	Not a carrier
Primary risk (*a priori)*		
Condition (affected)		
Product		
Final risk (*a posteriori*)		

She is	A carrier	Not a carrier
Primary risk (*a priori)*	½	½
Condition (affected)	½ x ½	1
Product	½ x ½ x ½ = 1/8	½ = 4/8
Final risk (*a posteriori*)	1/5	4/5

What is the probability that the child is a boy?
½
What is the probability that this boy will inherit the defective gene?
½

Final step: 1/5 x ½ x ½

A woman has a brother and a maternal uncle who both died of severe hydrocephalus due to X-linked recessive aqueductal stenosis. The woman has two healthy sons and is currently pregnant. What is the probability that her child will be affected by the same disease?

A. 1/5

B. 1/8

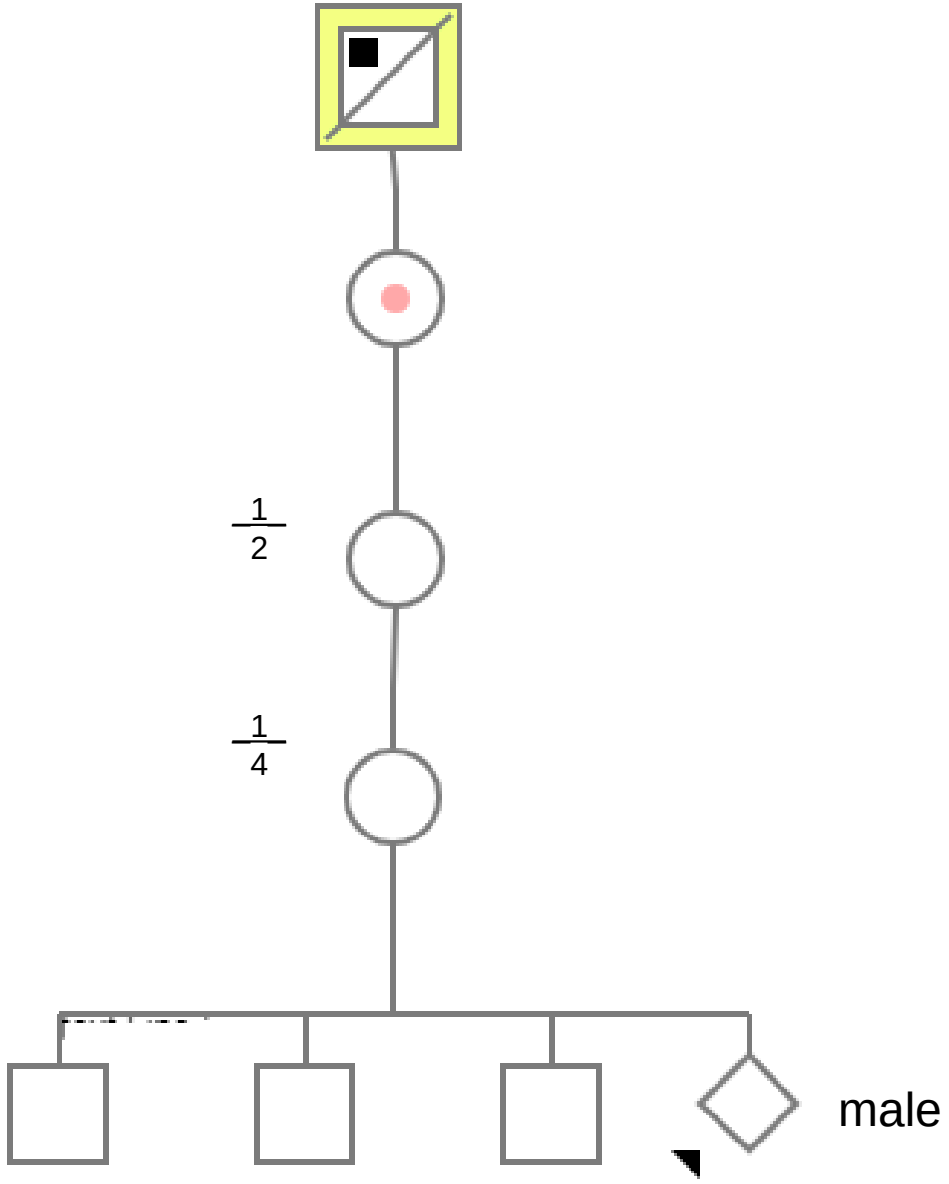
C. 1/10

D. 1/20

E. 1/32

The father of the mother of the mother of a female patient has Hemophilia. The patient has 3 healthy sons and is currently pregnant with her 4th son. What is the probability that this boy will be affected?

A. 1/4
B. 1/8
C. 1/9
D. 1/18
E. 1/50


1/2
1/4
male

She is	A carrier	Not a carrier
Primary risk (*a priori*)		
Condition		
Product		
Final risk (*a posteriori*)		

She is	A carrier	Not a carrier
Primary risk (*a priori*)	¼	3/4
Condition	½ x ½ x ½ = 1/8	1
Product	¼ x 1/8 = 1/32	24/32
Final risk (*a posteriori*)	1/25	24/25

What is the probability that this boy will inherit the defective gene?
½

Final step: 1/25 x ½ = 1/50

The father of the mother of the mother of a female patient has Hemophilia. The patient has 3 healthy sons and is currently pregnant with her 4th son. What is the probability that this boy will be affected?

A. 1/4

B. 1/8

C. 1/9

D. 1/18

E. 1/50

A nonconsanguineous, healthy couple comes for genetic counseling. The female's brother was diagnosed with an autosomal recessive condition with a population frequency of 1/400. What is the risk to this couple's offspring will be affected?

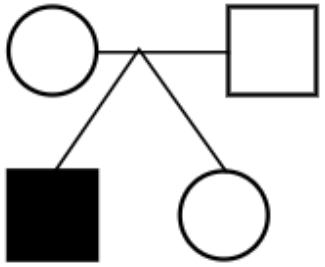
A. 1/40

B. 1/60

C. 1/80

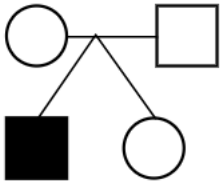
D. 1/100

E. 1/120



	A	a
A	AA	Aa
a	Aa	aa

$p^2+2pq+q^2=1$



What is the risk that the mother is a carrier?

….

What is the risk that the father is a carrier?

….

Assuming the mother is a carrier, what is the risk she will pass down the defective gene?

….

Assuming the father is a carrier, what is the risk he will pass down the defective gene?

	A	a
A	AA	Aa
a	Aa	~~aa~~

$p^2+2pq+q^2=1$

What is the risk that the mother is a carrier?

2/3

What is the risk that the father is a carrier?

1/10

Assuming the mother is a carrier, what is the risk she will pass down the defective gene?

½

Assuming the father is a carrier, what is the risk he will pass down the defective gene?

½

Last step:

2/3 x 1/10 x ½ x ½ = 1/60

A nonconsanguineous, healthy couple comes for genetic counseling. The female's brother was diagnosed with an autosomal recessive condition with a population frequency of 1/400. What is the risk to this couple's offspring will be affected?

A. 1/40

B. 1/60

C. 1/80

D. 1/100

E. 1/120

Given a gene frequency of 1 in 50 for an autosomal recessive disorder, what is the probability that the first child born to a couple will be affected?

A. 1/625
B. 1/1,250
C. 1/2,500
D. 1/10,000
E. 1/25,000

$p^2+2pq+q^2=1$

What is the risk that the mother is a carrier?

….

What is the risk that the father is a carrier?

….

Assuming the mother is a carrier, what is the risk she will pass down the defective gene?

….

Assuming the father is a carrier, what is the risk he will pass down the defective gene?

$p^2+2pq+q^2=1$

What is the risk that the mother is a carrier?

1/25

What is the risk that the father is a carrier?

1/25

Assuming the mother is a carrier, what is the risk she will pass down the defective gene?

½

Assuming the father is a carrier, what is the risk he will pass down the defective gene?

½

Last step:

1/25 x 1/25 x ½ x ½ = 1/2500

Given a gene frequency of 1 in 50 for an autosomal recessive disorder, what is the probability that the first child born to a couple will be affected?

A. 1/625

B. 1/1250

C. 1/2500

D. 1/10000

E. 1/25000

Assume the following frequencies for the AB0 blood group. The A allele 0.3, the B allele 0.1, and the 0 allele 0.6. What percent of people should be group A?

A. 9%

B. 18%

C. 27%

D. 36%

E. 45%

$p^2+2pq+q^2$

AA?

….

A0?

….

Thus

….

$p^2+2pq+q^2$

AA?

0.3x0.3

A0?

2x0.3x0.6

Thus

AA+A0

Assume the following frequencies for the AB0 blood group. The A allele 0.3, the B allele 0.1, and the 0 allele 0.6. What percent of people should be group A?

A. 9%

B. 18%

C. 27%

D. 36%

E. 45%

What is the chance that these first cousins once removed will have an affected child with an AR disease? (No family member is affected)

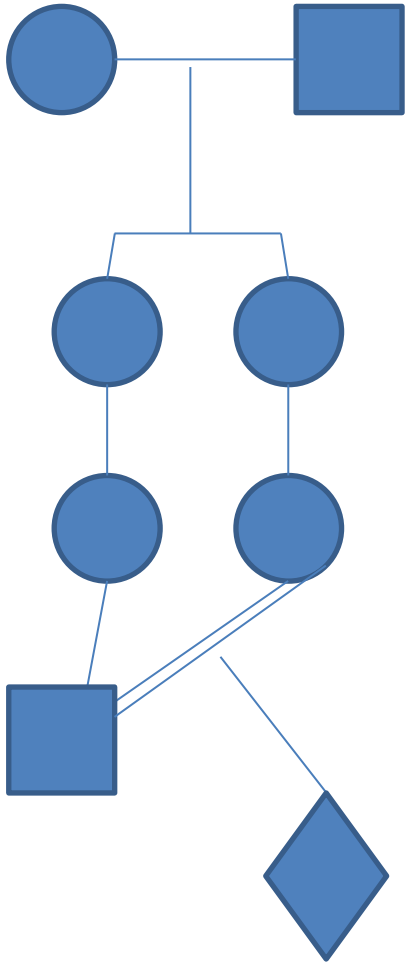
A. 1/4

B. 1/8

C. 1/16

D. 1/32

E. 1/64



What proportion of common genes do siblings have?

….

Go through the pedigree

….

Thus

….

What proportion of common genes do these cousins have? Go through the pedigree

1/16

Assuming the mother is a carrier, what is the risk she will pass down the defective gene?

½

Assuming the father is a carrier, what is the risk he will pass down the defective gene?

½

Last step:

1/16 x ½ x ½ = 1/64

What is the chance that these first cousins once removed will have an affected child with AR disease?

A. 1/4

B. 1/8

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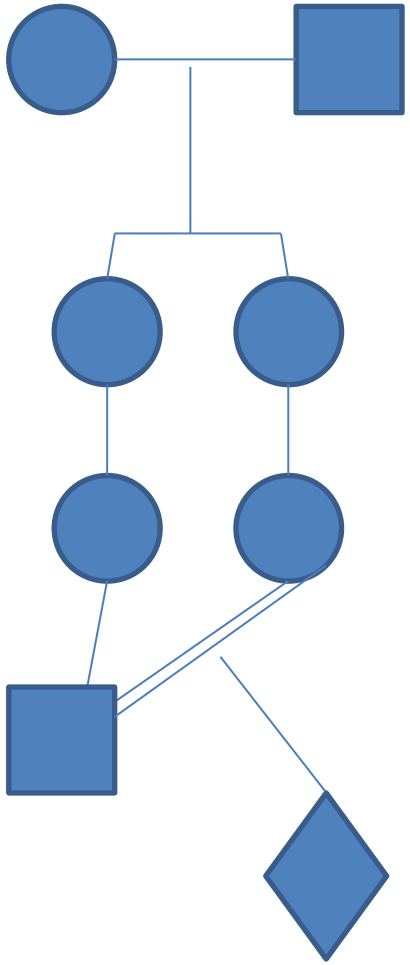
D. 1/32

E. 1/64



Clinics

Q&A

Abdominal US done in an otherwise healthy neonate reveals a unilateral multicystic kidney. What is the most likely karyotypic finding in this individual?

A. 47,XXY

B. 45,X

C. 46,XY

D. 46,XY.ish del(7)(q11.23q11.23)(ELN-)

Answer: C

This can be unilateral multicystic dysplastic kidney (UMCDK) as an isolated finding or autosomal recessive polycystic kidney disease (ARPKD) or rarely dominant (ADPKD)
BUT KARYOTYPE WOULD INVARIABLY BE NORMAL AS FIRST ANOMALY IS MULTIFACTORIAL WHILE OTHER TWO ARE SINGLE GENE DISORDERS
Answer D? Williams Syndrome: genetic disorder affecting many body parts of the body. Dysmorphia, "elfin“ appearance.

The diagnosis of chromosome aberration or microaberration is **MOST** likely in an individual with:

A. Isolated intellectual disability (ID)

B. ID + microcephaly

C. ID + congenital heart disease

D. ID + multiple congenital anomalies + dysmorphism

Answer: D (a typical 'chromosomal phenotype')

It's been a busy day in your Genetics Clinic in San Sebastian. At the end of it you are approached by a couple with both a bride and a groom coming from the same village in a remote mountainous region of Basque country. They are healthy and report no family history of serious genetic conditions but wish to know if they're at risk of a serious genetic disorder in their kids. What is your next **MOST** appropriate step?

A. Assuring the couple that everything's fine and risks involved are negligible

B. Look up the most common severe recessive disorders for that population, calculate risks and let them choose if they want carrier genetic testing

C. Offer genetic testing for a highly penetrant dominant disorder running in this population

D. Make them rethink their wedding plans as they have a 25%-risk of a serious genetic condition in their offspring

Answer: B (possible consanguinity issues)

A 9yo male is referred by a neurologist for evaluation of a 6 month history of decreasing intellectual performance. An MRI shows prominent white matter changes. There is biochemical evidence of mild adrenal dysfunction. The gene responsible for this disorder encodes a:

A. Lysosomal enzyme
B. Transcription factor
C. Peroxisomal enzyme involved in fatty acid oxidation
D. Peroxisomal membrane protein
E. Mitochondrial enzyme involved in fatty acid oxidation

X-LINKED ADRENOLEUKODYSTROPHY

Responsible gene: ABCD1
Protein: ATP-binding cassette sub-family D member 1
Cytogenetic locus: Xq28
Inheritance: XLR
Clinical Features and Diagnostic Criteria:
a. Childhood cerebral: ADHD -> total disability within 2 yrs
b. Adrenomyeloneuropathy: late 20's progressive paraparesis, sphincter disturbance, adrenocortical dysfunction
c. Adrenocortical insufficiency (only); majority by age 7.5 (seen in 20% carrier females
Clinical Tests: Brain MRI, VLCFA (not reliably abnl in carrier females)
Molecular Tests: ABCD1 seq (92%); ABCD1 del/dup (6%)
Disease Mechanism: Peroxisomal disorder, accumulation of saturated VLCFA
Treatment/Prognosis: Corticosteroid replacement, BMT if diagnosed after changes visible on brain MRI but before significant neuropsych problems develop (Lorenzo's Oil)

A 9yo male is referred by a neurologist for evaluation of a 6 month history of decreasing intellectual performance. An MRI shows prominent white matter changes. There is biochemical evidence of mild adrenal dysfunction. The gene responsible for this disorder encodes a:

A. Lysosomal enzyme

B. Transcription factor

C. Lipoxygenase enzyme

D. Peroxisomal membrane protein

E. Mitochondrial enzyme involved in fatty acid oxidation

Penicillamine is useful in treatment of:

A. Menkes disease
B. Homocystinuria
C. Cystinuria and Wilson disease
D. Tyrosinemia type 1
E. Cholesterol ester storage disease

Cystinuria and Wilson disease

Which of the following is not a feature of metabolic syndrome?

A. Hypertension
B. Insulin resistance
C. Elevated triglycerides
D. Increased abdominal circumference
E. Decreased C reactive protein

CRP is increased in metabolic syndrome.
PHATS mnemonic:
Pressure, HDL, Abdomen, Triglycerides, Sugar

A concerned mother brings her 18-month-old daughter to the pediatrician's office because she has been intermittently constipated. Her mother became alarmed while changing her diaper after straining to have a stool, she found some red, tissue bulging from the rectum. Which of the following procedures or laboratory studies is most like to identify the appropriate diagnosis?

A. Colonoscopy for Crohn’s disease

B. Molecular analysis for Duchenne muscular dystrophy

C. Rectal biopsy for Hirschsprung disease

D. Renal US for Beckwith-Wiedemann syndrome

E. Sweat chloride test for Cystic fibrosis

Imatinib is used in the treatment of which of the following disorders?

A. Asthma

B. Chronic myelogenous leukemia

C. Coronary artery disease

D. Diabetes

E. Hypertension

A man with a right-sided triphalangeal thumb and left sided absent thumb has a child with bilateral absence of the radius and an atrioventriculoseptal defect. Which of the following genetic concepts accounts for this clinical history?

A. Genetic heterogeneity
B. Multifactorial inheritance
C. Phenotypic pleiotropy
D. Variable expression with complete penetrance
E. Variable penetrance with incomplete expressivity

Important definitions:

- **Genetic heterogeneity:** a single clinical disorder is caused by several genes.
  - *Example:* Tuberous sclerosis - mutation in a gene on chr 9 or 16
- **Multifactorial inheritance:** many factors involved in causing a birth defect – both genetic and environmental.
  - *Example:* individual cases - neural tube defects, cleft palate.
- **Phenotypic pleiotropy:** 1 mutation affects several unrelated phenotypic traits.
  - *Example:* Marfan syndrome – *FBN1* mutation, tall & thin fingers.
- **Expression:** what are the symptoms of the disease? (When considering the whole pedigree)
- **Penetrance:** how many people in the whole pedigree are ill?

Chromosome analysis would be most helpful in diagnosis of which of the following syndromes?

A. Marfan syndrome
B. Neurofibromatosis 1
C. Smith-Magenis syndrome
D. Pfeiffer syndrome
E. Williams syndrome

The most common autosomal dystonia 1 (DYT1) mutation is found in which ethnic group?

A. African-Americans
B. Ashkenazi Jews
C. Finns
D. Mennonites
E. Southeast Asians

A 10-year-old boy visits an ophthalmologist for the first time after complaining to his parents that he is having trouble seeing the interactive whiteboard at school. The ophthalmologist finds a mild refractive error, but is most concerned about finding Lisch nodules. The presence of iris Lisch nodules is a helpful diagnostic feature of which of the following syndromes?

A. Gardner syndrome
B. Neurofibromatosis type 1
C. Sturge-Weber syndrome
D. Tuberous sclerosis complex
E. Von Hippel-Lindau disease

Cheat sheet!

Buzzwords:

- Lisch nodules = NF1 (Neurofibromatosis)
- Periungual fibromas = Tuberous Sclerosis
- Colon polyps = Gardner syndrome
- Meningioma + epilepsy = Sturge-Weber Syndrome
- Kidney tumors = von Hippel-Lindau Syndrome

A young girl with new onset seizure disorder is examined by a neurologist and found to have non-traumatic periungual and subungual fibromas. These clinical features are a primary diagnostic feature of which of the following syndromes?

A. Gardner syndrome
B. Neurofibromatosis type 1
C. Sturge-Weber syndrome
D. Tuberous sclerosis complex
E. Von Hippel-Lindau disease

A 30-year-old woman with a complicated medical history dies of renal cell carcinoma. Renal cell carcinoma is a primary cause of death in which of the following syndromes?

A. Gardner syndrome
B. Neurofibromatosis type 1
C. Sturge-Weber syndrome
D. Tuberous sclerosis complex
E. Von Hippel-Lindau disease

A newborn infant has extreme hypotelorism, microcephaly, midline cleft, poor temperature regulation, seizures, and no anomalies below the neck. The most likely diagnosis is:

A. Trisomy 13

B. Trisomy 18

C. Holoprosencephaly

D. Meckel-Gruber syndrome

E. Ellis van Creveld syndrome

Holoprosencephaly

HOLOPROSENCEPHALY

Spectrum of congenital structrural brain anomalies defined by different degrees of frontal lobe fusion
Impaired midline cleavage of the embryonic forebrain
‘Face pedicts brain’ = severe midline anomalies
Clinical severity relates to degree of hemispheric fusion

A newborn infant has cleft lip and palate, postaxial polydactyly, microphthalmos, and congenital heart disease. The most likely diagnosis is:

A. Trisomy 13

B. Trisomy 18

C. Holoprosencephaly

D. Meckel-Gruber syndrome

E. Ellis van Creveld syndrome

Patau syndrome

Patau syndrome

- **Inheritance**: 90% *de novo*, 5-20% translocation event
- **Clinics**: rarest trisomy in liveborn, holoprosencephaly, polydactyly, seizures, HL, microcephaly, cleft lip and/or palate, omphalocele, heart and kidney anomalies, ID. In mosaics: clinial heterogeneity: from typical to milder ID degree and longer survival
- **Diagnostics:** PRENATAL: US+biochemical screening, amnio-karyotype, cell-free fetal DNA 80%, POSTNATAL: MRI, EEG, audiogram, echocardiogram, kidney US, karyotype
- 44% does not survive to 1mth, >70% die in the first year. In others severe ID.

What is the most common karyotype seen with hypoplastic left heart?

A. 47,XXY
B. 45,X
C. 46,XX
D. 46,XX,del(22)(q11.2;q11.2) – DiGeorge=Velocardiofacial=CATCH22
E. 46,XY.ish del(7)(q11.23q11.23)(ELN-)

46,XX

Factor V Leiden mutation testing is **not** recommended for which of the following conditions:

A. Screening in the general population to determine risk for deep venous thrombosis

B. Pts with venous thrombosis at usual sites or recurrent venous thrombosis

C. Relatives of individuals with venous thrombosis under the age of 50

D. Pts with pregnancy-associated venous thrombosis

E. Women with recurrent pregnancy loss or unexplained severe preeclampsia, placental abruption, intrauterine fetal growth retardation, or stillbirth.

The probability that a trisomy 21 (DS) conception will be born alive is estimated to be:

A. 1%

B. 20%

C. 70%

D. 90%

E. 100%

The risk of pregnancy loss is considered to be the highest following which procedure?

A. First trimester nuchal translucency determination

B. Chorionic villus sampling

C. Standard amniocentesis (at least 15wks)

D. Early amniocentesis (up to 12wks)

2-4%

The earliest dx of a karyotype abnormality?

If a fetus has a nuchal translucency increased to 2 standard deviations at 11-14 wks, the most likely karyotype finding is:

A. 47,XX,+21

B. 45,X

C. 46,XX

D. 47,XX,+18

The causes of increased Nuchal Translucency! **Up to 80% choromosomally normal…**

Genetic testing of an asymptomatic at-risk 10yo girl would be **least** appropriate in which of the following hereditary cancer syndromes?

A. Breast/ovarian cancer syndrome

B. Familial adenomatous polyposis **10yrs**

C. MEN2B **5yrs**

D. Li-Fraumeni syndrome **Tumours and malignancies**

E. Familial retinoblastoma **Retinoblastoma**

What are the ages?

The thiopurine-S-methyltransferase polymorphism is important in treatment of:

A. Hypertension
B. Pain
C. Cancer
D. Asthma
E. Diabetes

6-mercaptopurine metabolism = leukemia treatment

The most common presenting complaint in individuals with hemochromatosis is:

A. Joint pain

B. Fatigue

C. Change in skin pigmentation

D. Nausea and vomiting

E. Decreased libido