The information provided below may be useful in answering some questions.

The "Wobble" Rules of Codon-Anticodon Pairing	
5' Nucleotide of Anticodon	**3' Nucleotide of Codon**
C	G
A	U
U	A or G
G	C or U
I	U, C, or A
3' Nucleotide of Codon	**5' Nucleotide of Anticodon**
G	C, U
A	I, U
C	I, G
U	I, G, A

First position (5' end)	Second position U	C	A	G	Third position (3' end)
	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
U	Leu	Ser	Stop	Trp	G
	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
C	Leu	Pro	Gln	Arg	G
	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
A	Met	Thr	Lys	Arg	G
	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
G	Val	Ala	Glu	Gly	G

INFORMATION ON COMPONENTS OF RIBOSOMES

I. Prokaryotes (e.g. *E. coli*)

RIBOSOME (70S)

Large Subunit (50S) --- 5S and 23S rRNAs + many proteins
Small Subunit (30S) --- 16S rRNA + many proteins

II. Eukaryotes (e.g. human)

RIBOSOME (80S)

Large Subunit (60S) --- 5S, 5.8S, and 28S rRNAs + many proteins
Small Subunit (40S) --- 18S rRNA + many proteins

1) Which of the following is **not** a characteristic of most hereditary cancer syndromes?

A) Variable expressivity
B) Earlier age of onset
C) Codominant inheritance
D) Related to tumor-suppressor genes
E) Reduced penetrance

2) Lynch syndrome is associated with all of the following cancers **except**:

A) Endometrial
B) Prostate
C) Stomach
D) Ovarian

3) All of the following genes are associated with Lynch syndrome **except**:

A) BRCA2
B) PMS2
C) MSH2
D) MLH1
E) MSH6

4) Your patient has a strong family history of breast cancer and has elected BRCA1/2 analysis despite protests from her family, who themselves have not pursued such testing. Her results are negative. Your counseling session should include all of the following statements **except**:

A) The cancer in this family may be due to an identifiable mutation, but if so, this patient did not inherit it
B) The cancer in this family may be due to a mutation that is as of yet unidentified and the patient may or may not have inherited it
C) Testing of another affected family member is recommended to identify the causative mutation
D) This patient's risk for breast and ovarian cancer is unlikely to be increased above the general population risk
E) This patient should be considered at higher risk based on family history alone

5) Which of the following describe characteristics of BRCA1/2 families?

A) Male breast cancer
B) Bilateral breast cancer
C) Early onset breast cancer
D) Breast and ovarian cancer in the same patient
E) All of the above are characteristics

6) A 40-year-old woman presents with a strong family history of breast and ovarian cancer. She is interested in BRCA1/2 analysis but expressed significant concerns regarding insurance discrimination. Which of the following statements is **false** regarding her concerns?

A) The Americans with Disabilities Act (ADA) of 1990 will not protect the patient against employment discrimination if she has a mutation but remains cancer-free
B) Health Insurance Portability and Accountability Act (HIPAA) of 1996 will protect the patient from health discrimination based on genetic test results only if she remains part of a group health plan
C) Genetic Information Nondiscrimination Act (GINA) of 2008 will protect this patient from health insurance discrimination even if she develops cancer
D) None of these laws apply to life insurance

7) Predispositional genetic testing is BEST described as:

A) Genetic testing on someone who will develop the disease but is currently asymptomatic
B) Genetic testing on someone who does not and will not have the condition, but could be a carrier
C) Genetic testing to confirm the diagnosis in someone with symptoms of the condition
D) Testing for a condition with reduced penetrance or multifactorial inheritance

8) Michigan law requires informed consent be obtained in which of the following scenarios?

A) Predispositional testing
B) Carrier testing
C) Presymptomatic testing
D) A and C
E) All of the above

9) A woman with idiopathic epilepsy presents to you for her first obstetrician visit at 10 weeks gestation. She was on Dilantin but stopped at 6 weeks gestation at the time of pregnancy recognition. Which of the following statements is **true** regarding this scenario?

A) The fetus is not at increased risk for neural tube defects
B) Despite the risks, optimal seizure management with anticonvulsants is recommended to improve the odds of a positive pregnancy outcome
C) If the patient has remained seizure-free since discontinuing her medication, then she should not resume anticonvulsant therapy
D) Seizure disorders alone do not increase the risk of adverse pregnancy outcome

10) Which of the following factors does **not** influence the effect of a teratogen on embryonic development?

A) Stage in pregnancy when fetus is exposed
B) Dose of the substance
C) Combined effect of two different medications
D) Maternal age at time of conception

11) Which of the following statements is **false** regarding neural tube development?

A) Uncontrolled maternal diabetes is a risk factor for neural tube defects
B) The neural tube completes formation in the 8^{th} week post-conception
C) Folic acid decreases the risk for neural tube defects
D) Many anticonvulsants are associated with increased risk of neural tube defects

12) Your patient was prescribed lithium by her psychiatrist. She began taking this medication in the first trimester prior to pregnancy recognition and is now concerned about fetal risks. The fetus is at increased risk for which of the following?

A) Neural tube defect
B) Ebstein's anomaly
C) No risk, lithium is not associated with adverse fetal outcome
D) Growth restriction
E) Chromosome anomaly

13) A 30-year-old woman at 11 weeks gestation age has a positive First Trimester Screen with an increased risk of Down syndrome. Which of the following are reasonable options to present?

A) Alpha-fetoprotein (AFP) only in the second trimester to assess for neural tube defects
B) Chorionic villus sampling by 12 weeks
C) Amniocentesis at 15-16 weeks
D) Level II ultrasound at 20-22 weeks
E) All of the above are reasonable options

14) Your patient has her blood drawn for a Quadruple (Quad) Test as she is 16 weeks pregnant, but is unsure of her last menstrual period (LMP). The next day she has a sonogram that finds the fetus to really be 13 weeks. Which of the following statements are **false**?

A) She is too early for the Quad Test
B) She can have a First Trimester or Full Integrated Test if you can obtain a nuchal translucency (NT) measurement by a certified sonographer
C) A Quad can still be run but without neural tube risk assessment
D) She is too early for an amniocentesis

15) A lab that runs prenatal serum screening tests claims to have the lowest false positive rate compared to its competitors. This causes:

A) Lower sensitivity
B) More false negatives
C) Higher specificity
D) All of the above

For the following 4 questions: Select one of the following genetic diseases that <u>best</u> applies to the situation described. A choice can be used once, more than once, or not at all.

A) Fragile X Syndrome
B) Wolf-Hirschhorn Syndrome
C) Edwards Syndrome
D) Klinefelter Syndrome
E) Angelman Syndrome

16) This syndrome is due to the presence of an autosomal trisomy.

17) This syndrome is primarily due to trinucleotide expansions within the non-coding region of a gene.

18) Affected individuals could have a microdeletion present in the p-arm of chromosome 4.

19) This syndrome can be caused by lack of maternally derived chromosome 15q11.

20) Which of the following statements is **FALSE** regarding some of the molecular mechanisms underlying genetic diseases?

A) Expanded numbers of trinucleotide repeats are present in the protein coding region of patients affected by Huntington Disease.
B) Male individuals affected by Prader-Willi Syndrome due to 15q11 deletion are usually sterile, but hypothetically if they have a female child that inherited the deleted chromosome, the child would have Angelman Syndrome.
C) Myotonic Dystrophy is an autosomal dominant disorder with pedigrees demonstrating genetic anticipation.
D) Recessively inherited genetic diseases can demonstrate genetic anticipation
E) Beckwith-Weidemann syndrome can be due to overexpression of the insulin-like growth factor 2 gene.

21) Regarding conditions/diseases potentially attributed to multifactorial inheritance patterns and the liability/threshold models, which of the following statements is **TRUE**?

A) Recurrence of a congenital anomaly in a family is always due to dominant, recessive, or X-linked inheritance of a single mutated gene.
B) Familial clustering of diabetes, hypertension, and ischemic heart disease is not due multifactorial inheritance patterns.
C) The recurrence risk for a condition will be the same for males or females, if the condition is subject to gender dependent thresholds of liability.
D) Incidence of the condition will be higher in relatives of the less severely affected patients.
E) If more than one relative is affected, the risk for other members of the family to be affected is increased.

22) A 2 and 1/2 year old female child is brought to you with a previously confirmed diagnosis of Autism based on lack of normal speech development, lack of appropriate ability to interact socially, inappropriate focus on inanimate objects, repetitive movements, echolalia, hand-flapping when touched, and gaze avoidance. Which of the following statements is **FALSE**?

A) This child could have a normal chromosome analysis.
B) This child could have Fragile X syndrome
C) This child could have a normal Comparative Genomic Hybridization analysis.
D) This child could have a normal brother
E) This child does not require further evaluation for a genetic cause of her Autism.

23) A child is born that is small for gestational age, has a small chin, periorbital fullness, microcephaly, hypercalcemia, and a congenital heart (supra-valvular aortic stenosis) defect. Which of the following statements is **FALSE**?

A) High resolution banding karyotype analysis of the chromosomes may detect an abnormality in this child.
B) Use of a FISH probe specific for the centromeres of chromosome #7 would likely reveal two chromosome 7's in this child.
C) Comparative Genomic Hybridization array based assessment could not be used to detect the common mutation that causes this syndrome.
D) High resolution banding karyotype analysis of the chromosomes may not detect an abnormality in this child.
E) Use of a FISH probe specific for the centromeres of chromosome #22 would likely reveal two chromosome 22's in this child.

24) A normal-statured couple has a child with Achondroplasia, which is 100% penetrant and always caused by a specific point mutation in a single allele of the Fibroblast Growth Factor Receptor 3 (FGFR3) gene. They again conceive and have a second child with Achondroplasia and the same FGFR3 mutation, but neither parent carries the abnormal FGFR3 allele when their blood cells are appropriately analyzed. Which of the following statements is **TRUE**?

A) Achondroplasia must be due to autosomal recessive inheritance of two FGFR3 mutations.
B) Recurrence in this family is due to gonadal mosaicism for the FGFR3 mutation in one of the parents.
C) Recurrence in these families is usually attributable to non-paternity.
D) Recurrence in this family is caused by multifactorial inheritance of FGFR3 mutations.
E) Recurrence of Achondroplasia could not happen again.

25) TRUE or FALSE: Gene Therapy has never cured anyone of a genetic disease.

A) TRUE
B) FALSE

26) Concerning gene transfer technologies and their usage in human patients, which of the following statements is **TRUE**?

A) Only non-viral based methods for gene transfer have been utilized in human clinical trials.
B) Only gene transfer researchers in the United States have been undertaking human clinical trials.
C) Some of the clinical indications for gene therapy research efforts to date include rare, mono-genetic diseases, and other, more common diseases such as cancer or cardiovascular disease.
D) Greater than a thousand human clinical trials involving gene transfer research have been performed, but a small fraction (i.e.: less than 10%) of these involve Phase III level clinical trials.
E) Viral vectors cannot achieve high levels of gene transfer *in vivo* (ie: living animals).

27) Regarding recombinant protein/enzyme based therapies, which of the following statements is **FALSE**?

A) Only lysosomal storage diseases can be treated by infusion of recombinant proteins.
B) Recombinant lysosomal enzymes can be delivered to cells deficient for the respective enzyme, and cell surface uptake mechanisms present in the deficient cell can deliver the recombinant enzymes into the lysosomes of the deficient cell.
C) A form of systemic muscular weakness (Pompe myopathy) is now treated by enzyme replacement therapy.
D) Fabrazyme is a recombinant protein used to treat a X-linked disorder that affects the kidneys and heart.
E) Cerezyme is used to treat Gaucher Disease.

28) Which of the following statements is **FALSE** regarding gene therapy research?

A) More than one patient has gotten cancer due to an insertional mutagenesis that occurred subsequent to a clinical gene transfer attempt.
B) A patient has died after intravenous infusion of high doses of a gene transfer vector.
C) Patients have been injected with gene transfer vectors via a number of different routes, for example intravenously into their hepatic arteries, directly injected into their tumors, and directly injected into their retinas.
D) All human gene transfer trials have stopped due to side-effects that have occurred as a result of the gene transfer vectors utilized.
E) Some viral based gene transfer vectors do not need to integrate in order to deliver genetic information into target cells.

29) Which individual has the HIGHEST risk of having abnormal offspring?

A) A carrier of a paracentric inversion
B) A carrier of a Robertsonian 21q21q translocation
C) A carrier of a balanced reciprocal translocation.
D) A carrier of a pericentric inversion.

30) Which of the following human conditions is LEAST likely to be caused by aneuploidy?

A) Klinefelter syndrome
B) Turner syndrome
C) Down syndrome
D) Fragile X syndrome

31) Which of the following karyotypes represents an UNBALANCED chromosomal abnormality?

A) 46,XX,t(5;20)(q22.2;q31.2)
B) 45,XY,Rob(13;21)(q10;q10)
C) 46,XX,ins(6;4)(q13.1;q12q24)
D) 46,XY, del(10)(q23q25)

32) You are seeing a woman whose sister had a son with Tay-Sachs disease, an autosomal recessive condition. The gene frequency is 1/70. If this woman's partner is unrelated to her, what is their chance of having an affected child?

A) 1/560
B) 1/420
C) 1/280
D) 1/210

33) A man whose younger sister died with Canavan disease, an autosomal recessive condition, wants to know his chance of being a carrier, given that his carrier testing was negative. However, the detection rate of this testing is only 75%. What is his modified risk of being a carrier?

A) 0
B) 1/3
C) ½
D) 3/5

34) A man with tuberous sclerosis (an autosomal dominant condition) impregnates a woman with Crouzon syndrome (an autosomal dominant condition). What is the chance their child would have both conditions?

A) 25%
B) 50%
C) 75%
D) 100%

35) A couple has a male infant with an autosomal dominant, lethal form of skeletal dysplasia; testing reveals that this child is heterozygous for the causative mutation. The BEST explanation is to tell the family that this is the result of:

A) Variable expressivity
B) New mutation
C) Skewed X-inactivation
D) Reduced penetrance

36) A woman whose father and paternal uncle have hemophilia A, an X-linked recessive disorder, has what chance of being a carrier?

A) 100%
B) 50%
C) 25%
D) 0%

37) A man asks his cardiologist for an electrocardiogram (EKG) because his mother and daughter both have long QT syndrome, an autosomal dominant condition associated with episodes of dizziness, abnormal EKG findings, and increased risk of sudden death. He has the appropriate evaluation, with no abnormalities found. What is the BEST explanation for this finding?

A) Multifactorial inheritance
B) Variable expressivity
C) Reduced penetrance
D) Non-paternity

38) A family with multiple members affected by a form of migraine headache is seen by the local geneticist. Affected individuals include three children (two boys and one girl), their father, a paternal aunt and uncle, and two male cousins (offspring of the aunt). What is the most likely mode of inheritance?

A) X-linked recessive
B) X-linked dominant
C) Autosomal dominant
D) Mitochondrial

39) A woman and her daughter come to see you because they both have Robinow syndrome, an autosomal recessive condition. What is the BEST explanation for this finding?

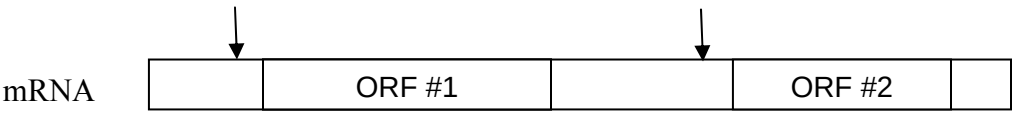
A) The woman has germline mosaicism for the gene
B) The woman and the daughter's father are related to each other
C) There is allelic heterogeneity for Robinow syndrome
D) The woman's parents are related to each other

40) A woman with type M blood and a man with type N blood have two children with type MN blood. What is demonstrated here?

A) Homozygosity
B) Codominance
C) Pleiotropy
D) Epistasis

41) Which of these is NOT a mitochondrial disorder?

A) Leber Hereditary Optic Neuropathy (LHON)
B) Myoclonic epilepsy with ragged red fibers (MERFF)
C) Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
D) Vertebral, anal, cardiac, tracheo-esophogeal, renal, and limb anomalies (VACTERL)



42) Given the above schematic of a bacterial mRNA, what element would most likely be located at the positions marked by arrows? (ORF = open reading frame)

A) Promoter elements
B) 5' cap structure
C) AUG start codon
D) Ribosome recognition site
E) Polyadenylation signal

43) Which of the following processes DO NOT take place in human cells?

A) Co-translational transport
B) Coupled transcription and translation
C) Post-translational modifications
D) RNA editing
E) Chaperone-aided protein folding

44) Which tRNA anticodon is LEAST likely to exist in nature?

A) 3'-ACC-5'
B) 3'-GAI-5'
C) 3'-CGI-5'
D) 3'-UAU-5'
E) 3'-CUU-5'

45) In monogenic inheritance, phenotypic characteristics are determined by

A) a single pair of alleles at a single locus
B) multiple pairs of alleles at multiple loci
C) the pseudo-autosomal genes on the maternal X chromosome
D) polyploidy as a result of an incomplete mitotic division.

Questions 46-52 refer to the case of Charlie X below. (Note: You can answer most of the questions WITHOUT the detailed information below. Suggest skimming the description, review the lab data, and carefully read the last 2 sentences of this page.)

Presenting complaint at first visit –

- 38 year old male factory worker, with stiffness and pain in the hands and wrists.
- Also complains of fatigue and loss of libido
- Radiographs are ordered, and show joint space narrowing of the metacarpophalangeal joints and chondrocalcinosis in the wrist joint

Family history reviewed – patient has three children, ages 12, 9, and 6, who are reportedly healthy and well. Patient reports that his older brother died of liver cancer, and a maternal uncle died of cirrhosis of the liver and heart failure at age 52; this was attributed to alcohol consumption, although patient states this individual really didn't "drink that much".

Rheumatoid arthritis considered as the diagnosis, and appropriate labs ordered

Two weeks later –

RA factor negative, so osteoarthritis considered as diagnosis, and aspirin recommended

6 months later –

Patient returns to see physician, because aspirin has no effect; nor do other over the counter pain relieving medications. Now complains of brownish tint to skin and increasing fatigue. Physical exam demonstrates mild hepatomegaly; echocardiogram done two weeks ago showed moderate ventricular enlargement. Patient mentions that he forgot to tell you last time that his wife's maternal uncle also died of cirrhosis at a relatively young age; he also didn't drink all that much. He didn't mention it last time because it was his wife's relative.

Additional blood tests ordered, with results shown below:

Lab test	Patient	Normal
Hematocrit (%)	44	40-54
Red blood cells (10^6/μl)	5.1	4.6-6.2
White blood cells (10^3/μl)	8	4.5-11
Platelets (10^3/μl)	380	150-450
Hemoglobin (g/dl)	8	13.5-18
Total protein (g/dl)	7.3	6-7.8
Albumin	2.9	3.2-4.5
Globulin	4.4	2.3-3.5
Prothrombin time (sec)	11	10-13
Glucose	240	70-110
BUN (mg/dl)	20	8-23
Bilirubin (mg/dl)	1.5	.1-1.2
Total iron-binding capacity (μg/dl)	330	250-400
Transferrin saturation (%)	92	20-55
Serum ferritin (ng/ml)	1080	15-200
Creatine kinase (U/l)	75	55-170
Alanine aminotransferase (U/l)	65	4-36
Alkaline phosphatase	160	20-130

Gastroenterology referral made; liver biopsy showed fibrous degeneration of moderate severity. Prussian blue staining showed extensive iron accumulation in hepatocytes, but with sparing of the Kupffer cells.

Genetics referral made – molecular testing demonstrated the patient was homozygous for the C282Y mutation in the *HFE* gene.

46) The *HFE* gene (on chromosome 6) codes for a protein that interacts with the transferrin receptor (TfR). Hereditary hemochromatosis can be caused by any of eleven different mutations in the *HFE* gene. This is an example of:

A) locus heterogeneity
B) allelic heterogeneity
C) pleiotropy
D) variable expressivity
E) genomic imprinting

47) The patient insists that his three healthy children also be tested. Which of the following statements is **false**?

A) The beneficence and nonmaleficence of this father outweighs his children's autonomy
B) Testing of asymptomatic children for autosomal recessive, adult-onset conditions is generally not recommended
C) Testing should be delayed until his children are adults to preserve their autonomy and provide informed consent
D) Test results could potentially make his children vulnerable to health insurance discrimination

48) The iron excess caused by hereditary hemochromatosis can have a beneficial effect by masking the iron deficiency that typically affects much of the world's population. Even heterozygotes for the Cys282Tyr mutation in the *HFE* gene have somewhat higher serum levels of iron than normal individuals. Which factor affecting the Hardy-Weinberg equilibrium principle would be most influenced by this?

A) geographic stratification
B) assortive mating
C) heterozygote advantage
D) new mutations
E) genetic drift

49) A nonsense mutation in the *HFE* gene might result in changes to both the size and the abundance of the protein encoded by that gene. Which of the following methods would best reveal these changes to the <u>protein</u>?

A) Southern blot
B) Western blot
C) Allele-specific oligonucleotide hybridization
D) Microarray analysis

50) Which of the following vectors would be able to carry the largest fragment (of about 1,000 kilobases) of human DNA surrounding the *HFE* gene?

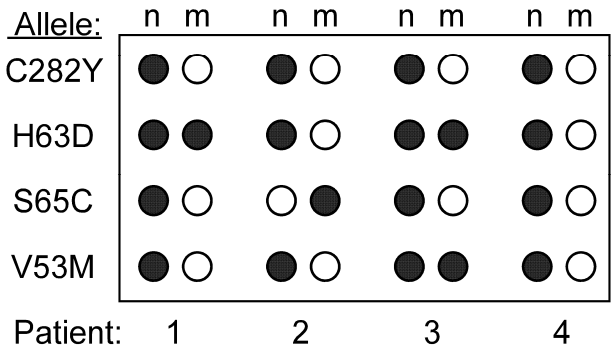
A) bacterial artificial chromosome
B) bacterial virus vector (phage)
C) cosmid
D) plasmid
E) yeast artificial chromosome

51) Which of the following regulatory signals would most likely be found within a cDNA clone of the *HFE* gene?

A) transcriptional promoter
B) enhancer
C) silencer
D) 5' splicing consensus
E) polyadenylation signal

52) The ASO panel (below) shows results of tests performed on four patients (1 through 4) for the four most common mutant alleles of the HFE gene. Given that hereditary hemochromatosis is an autosomal recessive condition, which pair of patients are most likely **not** affected by the disease? (n = normal; m = mutant; black dot = hybridization).

A) Patients 1 and 2
B) Patients 1 and 3
C) Patients 1 and 4
D) Patients 2 and 3
E) Patients 2 and 4



53) Which of the following statements regarding prokaryotic DNA replication is **correct**?

A) DNA polymerase III has a 5' to 3' exonuclease function.
B) DNA polymerase I synthesizes the DNA strand by extension from the primers.
C) The initiation stage is the regulated step.
D) DNA is synthesized in the 5' to 3' direction.
E) Helicase unwinds the DNA in front of the fork.

54) Which process takes place during anaphase I of meiosis?

A) reforming the nuclear membrane
B) exchange of material between homologous chromosomes
C) separation of chromatids to opposite poles of the cell
D) separation of homologous chromosomes to opposite poles of the cell
E) mitotic spindle attaches to the chromosomes

55) In the United States, ornithine transcarbamylase deficiency (an X-linked condition) has an incidence of about 1/40,000 affected males. What is the allele frequency in the United States for ornithine transcarbamylase deficiency?

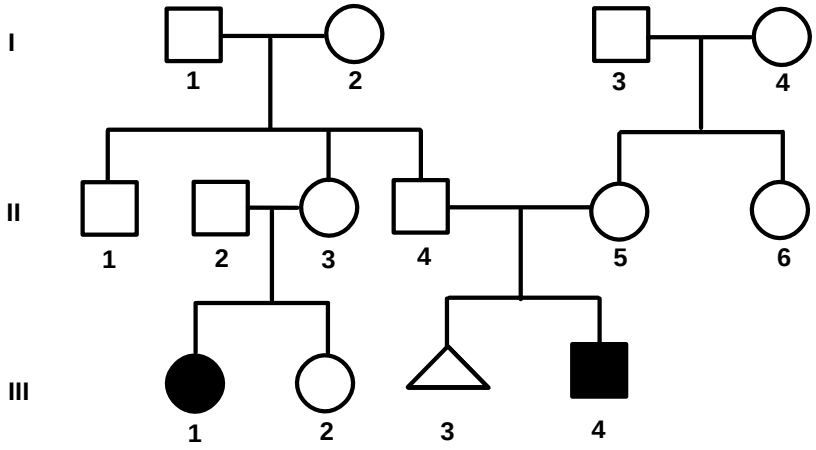
A) 1/200
B) 1/400
C) 1/20,000
D) 1/40,000
E) 1/ 1,600,000,000

56) In the African-American population, sickle-cell anemia (an autosomal recessive disorder) occurs in about 1/400 individuals. What is the approximate carrier frequency of sickle-cell anemia in this population?

A) 1/400
B) 1/160,000
C) 1/10
D) 19/20
E) 1

57) Assuming autosomal recessive inheritance in the pedigree below, which of the following individuals would be obligate carriers?

A) I-2
B) II-1
C) II-4
D) III-2
E) All of the above



END OF EXAMINATION Tear off this sheet and save to check your answers.

Please remember to:

- Write the letter corresponding to your **FORM** in the appropriate place on the **answer sheet**.
- **SIGN AND RETURN YOUR EXAMINATION** to an instructor **before leaving the exam room**.

FORM: A

1. _____	21. _____	41. _____
2. _____	22. _____	42. _____
3. _____	23. _____	43. _____
4. _____	24. _____	44. _____
5. _____	25. _____	45. _____
6. _____	26. _____	46. _____
7. _____	27. _____	47. _____
8. _____	28. _____	48. _____
9. _____	29. _____	49. _____
10. _____	30. _____	50. _____
11. _____	31. _____	51. _____
12. _____	32. _____	52. _____
13. _____	33. _____	53. _____
14. _____	34. _____	54. _____
15. _____	35. _____	55. _____
16. _____	36. _____	56. _____
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