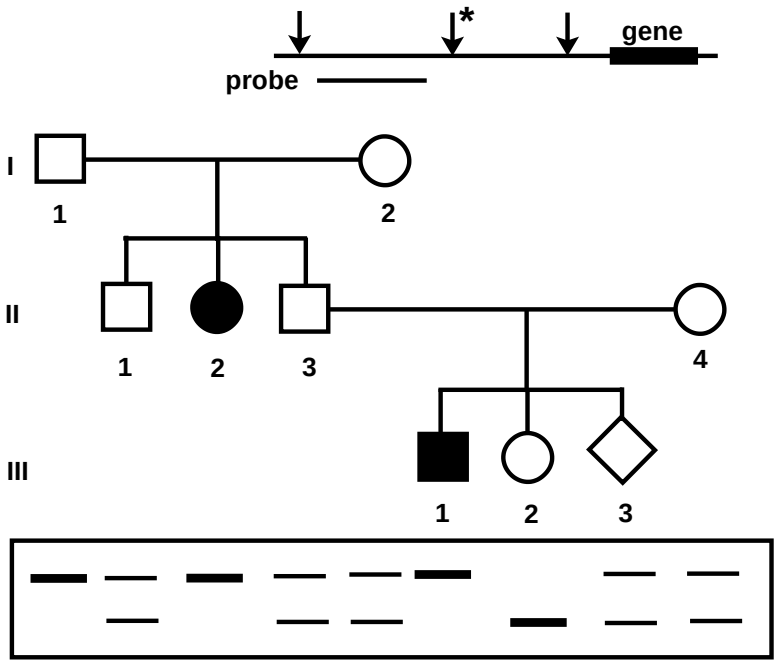
Use the diagram below to answer questions 1 and 2.

The diagram below depicts DNA (indicated by the line) and restriction endonuclease sites (indicated by the arrows) in a marker region near a gene. The asterisk represents a polymorphic restriction site. The DNA probe is indicated by a line below the DNA.

An RFLP analysis is performed on a family. Both the pedigree and the Southern blot results (below each individual) are shown, with the largest fragments at the top and the smallest towards the bottom of the blot. The analysis detects two different polymorphic marker alleles (m1 and m2) linked to the gene implicated in the disease. The disease is autosomal recessive, and all affected family members are shown in the pedigree by the shaded symbols.



1) What is the predicted status of the unborn child III-3? Assume no recombination has occurred.

A) Affected
B) Heterozygous for the disease gene, inheriting the disease allele from the father
C) Heterozygous for the disease gene, inheriting the disease allele from the mother
D) Heterozygous for the disease gene, but cannot determine from which parent the disease allele was inherited
E) Homozygous normal

2) What is the predicted carrier status of individual III-2? Assume no recombination has occurred.

A) Unaffected carrier, inheriting the disease allele from the mother
B) Unaffected carrier, inheriting the disease allele from the father
C) Unaffected and homozygous for the normal gene
D) Marker is uninformative for predicting the carrier status of III-2

Choose the best answer from the following choices to answer questions 3 and 4.

A) Northern blot
B) Western blot
C) ASO (allele-specific oligonucleotides) blot
D) STR (short tandem repeat) analysis
E) PCR (Polymerase chain reaction)

3) This assay uses a labeled nucleotide probe to detect relative amounts of mRNA transcribed from a gene in different patients.

4) This assay could detect the presence of specific single nucleotide mutations in an individual.

5) Which of the following cells are LEAST suitable for cell culture?

A) T-lymphocytes from peripheral blood
B) B-lymphocytes from lymph nodes
C) Cells from buccal swabs
D) Fetal cells from amniotic fluid

6) 46,XY,del(20)(q13.1) refers to or may lead to (upon gamete formation):

A) A karyogram
B) An interstitial deletion
C) Chromosome #20, long arm, sub-band #13
D) Partial monosomy
E) All of the above

7) Which of the following has the LOWEST risk of generating abnormal offspring?

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

8) Which of the following karyotypes is an example of euploidy?

A) 47,XXX
B) 45,X
C) 68,XXX,-21
D) 92,XXXX
E) 48,XX,+21,+22

9) A woman with Wilson disease, an autosomal recessive condition, is found to have the following mutations: H1069Q/R778L. The BEST description of what this genotype exhibits is:

A) Homozygosity
B) Genotype-phenotype correlation
C) Locus heterogeneity
D) Compound heterozygosity

10) PTPN11 maps to 12q24, and SOS1 maps to 2p22. Mutations in either gene cause Noonan syndrome, an autosomal dominant condition. This is an example of:

A) Allelic heterogeneity
B) Genetic modification
C) Epistasis
D) Locus heterogeneity

11) A boy and his sister have oculotrichoanal syndrome, an exceptionally rare recessive condition. What would be the MOST likely finding in the family history?

A) Only maternal relatives would be expected to be affected
B) The maternal grandmother and paternal grandmother are sisters
C) If tested, the mother would be expected to have skewed X-inactivation
D) The paternal grandfather and paternal grandmother are cousins

12) Individuals with Kabuki syndrome have the combination of long palpebral fissures (eye openings), congenital heart defects, hearing loss, fingertip pads, and cognitive impairment. This illustrates which concept?

A) epistasis
B) homoplasmy
C) heteroplasmy
D) pleiotropy

13) A boy with Kearns-Sayres syndrome is found to have different proportions of the mitochondrial mutation in different tissues examined. For example, there are no abnormal mitochondria in the skin, but 80% of the muscle mitochondria are abnormal. He is exhibiting

A) Heteroplasmy
B) Homoplasmy
C) Pleiotropy
D) Variable expression

14) A 30 year old woman comes for counseling because she has breast and ovarian cancer. Her 65 year old mother is unaffected, although her mother's sister and mother's mother also had breast and/or ovarian cancer in their 30's. What phenomenon does this family history illustrate?

A) homoplasmy
B) incomplete penetrance
C) variable expressivity
D) allelic heterogeneity

15) A woman with Stickler syndrome has the combination of hearing loss, cataracts, and cleft palate. Her son with Stickler syndrome has glaucoma, Pierre-Robin sequence (small chin and cleft palate), and joint pains, whereas her daughter with Stickler syndrome has hearing loss and small chin. This family demonstrates:

A) Variable expressivity
B) Locus heterogeneity
C) Reduced penetrance
D) Allelic heterogeneity

16) You are seeing a couple whose newborn son has a severe form of osteogenesis imperfecta, an autosomal dominant trait. The apparently unaffected father states that he had previously had a child with a different partner who had also been diagnosed with a severe form of osteogenesis imperfecta, and who had died soon after birth. What is the BEST explanation for this family?

A) Pleiotropy
B) Epistasis
C) Variable expressivity
D) Germline mosaicism

17) A couple has a daughter with classic Duchenne muscular dystrophy (DMD), an X-linked recessive condition. The mother's brother also had DMD. A karyotype shows that the girl has a deletion of part of the paternally inherited X chromosome. The girl's phenotype is BEST explained by:

A) Epistasis
B) Random X-inactivation
C) Variable expressivity
D) Skewed X-inactivation

18) A 42 year old woman relates to her doctor that her mother developed early-onset Alzheimer disease (EAD) at age 40. Her sister is showing evidence of memory loss and mild cognitive decline. Her maternal grandmother died at age 60, but had been diagnosed with EAD 15 years before her death. The chance that this woman will develop EAD is closest to:

A) 0%
B) 3%
C) 25%
D) 50%

19) A six year old boy, who had previously been well, develops stroke-like episodes, seizures, frequent headaches, and recurrent vomiting. The boy's mother reports that she has frequent migraines and a recent onset of diabetes, and that her sister died at 2 years of age with some condition that caused progressive deterioration and seizures. What is the BEST explanation for the disease pattern in this family?

A) Mutation in a mitochondrial gene
B) Mutation in an X-linked dominant gene
C) Somatic mosaicism in the mother
D) Germline mosaicism in the father

20) A woman who is heterozygous for hemophilia (an X-linked recessive trait) marries a man who is not a hemophiliac. What is the chance a **son** will be a hemophiliac?

A) 0 %
B) 25 %
C) 50 %
D) 75 %
E) 100 %

21) A man has been diagnosed with a mitochondrial disorder characterized by myopathy, hearing loss, ataxia, and depression. His sister, father, paternal aunt, and paternal grandmother are similarly affected. What is the risk to his daughter and son, respectively?

A) 0%, 0%
B) 50%, 0%
C) 0%, 50%
D) 50%, 50%

22) A couple has a son with an X-linked condition characterized by widely spaced eyes, genital anomalies, and swallowing difficulties. The mother's maternal uncle and brother also have this condition. Given that the penetrance of this condition is 75%, the chance of the couple having another affected son is closest to:

A) 19%
B) 25%
C) 38%
D) 50%

23) Women with oral-facial-digital syndrome type I (OFDSI), an X-linked dominant condition, have a 20% chance of having brain abnormalities as a component manifestation. A pregnant woman with OFDSI wants to know the chance that her female fetus will have OFDSI and brain abnormalities. You respond that the chance is:

A) 50%
B) 25%
C) 20%
D) 10%

24) A 45 year old asymptomatic man has a father with a confirmed diagnosis of Huntington disease (HD), a late-onset autosomal dominant condition. You know that at age 45 years, 50% of those with an HD mutation show clinical evidence of having the disease. The chance that this man inherited the HD mutation from his father is CLOSEST to:

A) 50%
B) 33%
C) 17%
D) 0%

25) Regarding X chromosomes, which of the following statements is FALSE?

A) In normal females, the inactivated X-chromosome has most, but not all of its gene expression extinguished as a result of X-inactivation.
B) Klinefelter Syndrome is due to unbalanced gene expression derived from the presence of an extra X chromosome in males.
C) Severe Turner Syndrome (i.e. with severe intellectual impairments) due to a very small ring X chromosome 46,Xr(X), is caused by lack of expression of the Xist gene, resulting in functional disomy for genes present on the r(X).
D) Barr bodies are only seen in cells with 2 or more X chromosomes, and not, for example, in cells from normal males.
E) The *Tsix* gene is expressed from the inactivated X chromosome in females.

26) Which of the following statements is FALSE in regard to concordance rates and heritability?

A) If the concordance rate for a trait or phenotype is identical between identical twins and fraternal twins, then the Heritability of that trait is low.
B) High Heritability for a trait indicates that a single gene is responsible for the trait.
C) Measles infection rates show high concordance between identical and fraternal twins, likely due to similar environmental exposure risks.
D) Schizophrenia has a High Heritability, suggesting that genetic factors are responsible for its presence in an affected individual.
E) Concordance rates for Autism in identical twins are much higher than the rates in fraternal twins, suggesting that environmental causes are not as important as genetic causes for Autism.

27) Several members of a family are affected by Myotonic Dystrophy, a genetic disease involving various degrees of muscular weakness. A male (Male A) in the family is only slightly affected, having just corneal opacities (cataracts). His daughter (Female B) is slightly more affected, with onset of myotonia as an adult. Female B has a son (Male C) who is severely affected with Myotonic Dystrophy, i.e.: he has congenital muscle weakness that is so severe that he requires mechanical respiratory support. This family BEST represents an example of which genetic phenomenon?

A) Multifactorial inheritance
B) Genetic Anticipation
C) Autosomal Recessive variability
D) Phenocopies
E) Locus heterogeneity

28) Concerning Down Syndrome, which of the following is TRUE?

A) Most cases are due to a microdeletion within the q-arm of chromosome 21.
B) Heart defects always occur in Down Syndrome.
C) The incidence of children with Down Syndrome born to women increases with maternal age, but this increase in incidence only begins after the maternal age of 36.
D) The rate of recurrence for some forms of familial translocation Down Syndrome can be as high as 100%.
E) Physical features of Down Syndrome are so obvious and characteristic that a chromosome analysis is not required to be performed in these individuals.

29) Which of the following statements regarding trinucelotide repeat mutations causing Fragile X syndrome is FALSE?

A) Typically, in family pedigrees affected by Fragile X syndrome, males are affected, and they are related by unaffected or mildly affected females.
B) The trinucleotide repeats are located within the 5' untranslated region of the Fragile X gene.
C) The mutations are considered to be loss of function.
D) Expansion is more likely to occur when the repeat is inherited from the mother rather than from the father.
E) Males with abnormal Fragile X trinucleotide gene expansions cannot have children.

30) Which of the following would not routinely be detected by comparative genomic hybridization analysis performed on a patient's blood sample?

A) Down Syndrome
B) Trisomy 13
C) Williams Syndrome
D) Klinefelter Syndrome
E) A balanced chromosomal translocation

31) Consider evaluation of a spontaneously aborted fetus that was miscarried at week 5 of gestation. Which of the following statements is FALSE?

A) The fetus may have had holoprosencephaly due to trisomy 21
B) The fetus may have had holoprosencephaly and been chromosomally normal
C) Diagnosing trisomy 16 in the fetus is more likely than diagnosing trisomy 16 in a newborn infant
D) Diagnosing Turner syndrome in the fetus is less likely than diagnosing Turner syndrome in a newborn infant
E) The fetus may have had acardia (absence of the heart) and trisomy 18

32) A newborn patient is found to be affected by four rare, minor congenital anomalies. It is known from the medical literature that these specific anomalies are typically found to occur together at a higher frequency than would be predicted by their individual occurrences in the general population. Which of the following statements about this patient, or the patient's biological relatives, is FALSE?

A) The patient could be affected by a known Association.
B) The patient could be affected by a known Sequence.
C) The patient could be affected by a known Syndrome.
D) The patient could be affected by a teratogen exposure during gestation, such as the Fetal Alcohol syndrome.
E) This child is not likely (<3% risk) to be affected by a major congenital malformation such as heart disease.

33) Which of the following statements is FALSE?

A) Some children with Retinoblastoma (tumor of the retina) have deletions in the q-arm of chromosome 13.
B) Some children with the renal tumor known as Wilms Tumor, are also affected by iris abnormalities, genito-urinary abnormalities, retardation of growth, and a micro-deletion in the p-arm of chromosome 11.
C) Some children with microdeletions in the p-arm of chromosome 17 demonstrate congenital heart disease, scoliosis, deafness, and abnormal behaviors such as head banging, inserting objects into body orifices, and pulling out their own nails.
D) If a trait demonstrates multi-factorial inheritance and male sex predisposition, then first-degree female relatives of an affected male are at lower risk of being affected by the trait.
E) Hypomelanosis of Ito can be a skin manifestation of mosaicism for diploidy/triploidy.

34) Which of the following statements is TRUE?

A) Most forms of Diabetes (Type I, Type II) are due to single gene defects.
B) Autism and Autism Spectrum Disorders are highly heritable, and can be due to a recognized syndrome.
C) Fragile X Syndrome is primarily caused by hyperexpansion of trinucleotide repeat sequences present in the fibrillin gene.
D) Female individuals affected by Prader-Willi Syndrome due to 15q11 deletion are usually sterile, but if they hypothetically gave birth to a child that inherited the deleted chromosome, the child would also have Prader-Willi Syndrome.
E) Thrombosis risk decreases in individuals carrying a Factor V Leiden gene variant.

35) Concerning molecular analysis of tissue samples derived from clinical patients, which of the following statements is FALSE?

A) Multi-plexed, sub-telomeric FISH probes can detect sub-microscopic deletions in children with intellectual impairments.
B) Array based Comparative Genomic Hybridization Techniques could be used to detect Trisomy 18.
C) Amplification-refractory Mutation System (ARMS) based PCR techniques utilize PCR primers that bind either to mutant or normal alleles, amplifying mutant or normal DNA sequences present in a test sample.
D) Lack of FISH probe based detection of deletions in chromosome 15q11 rules out a diagnosis of Angelman syndrome in a suspected case.
E) Multiple PCR primers can be pooled into a single reaction mixture, allowing for detection of multiple DNA sequences simultaneously.

36) Which of the following statements is FALSE, in regards to genetic evaluation of a 2 year old child with seizures, microcephaly, cleft lip and palate, severe developmental and growth delay, a major congenital heart defect, and 2-3 toe syndactyly?

A) The child could have a normal routine karyotype.
B) The child could have a normal sub-telomeric FISH probe analysis.
C) The child could have Down Syndrome.
D) The child could have been normal until deprived of oxygen during the birth process, the latter causing all of the medical problems noted.
E) The child could be mosaic for Trisomy 13.

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. _____	11. _____	21. _____	31. _____
2. _____	12. _____	22. _____	32. _____
3. _____	13. _____	23. _____	33. _____
4. _____	14. _____	24. _____	34. _____
5. _____	15. _____	25. _____	35. _____
6. _____	16. _____	26. _____	36. _____
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10. _____	20. _____	30. _____	