1. A woman has a son with an X-linked recessive lethal disorder, and her maternal half-brother had the same X-linked recessive lethal disorder. There is no other family history of the condition. Her daughter has one healthy son. What is the daughter’s chance to be a carrier?

A. 1/4  
B. 1/3  
C. 1/2  
D. 2/3  
E. 5/6

2. You evaluate a 6-day-old term girl in the emergency room with an unremarkable prenatal and family history. She was discharged home at 2 days of age on regular infant formula. For 24 hours she has been eating poorly (<1 ounce per feed) and seems “sleepy.” She has vomited once. Her CBC is normal, her electrolytes show a metabolic acidosis and the ammonia level is 500 mg/dl. Which of the following metabolic laboratory results are you the most likely to find?

A. Elevated plasma glycine with 3-OH-propionate, methylcitrate present on urine organics acids  
B. Low citrulline on plasma amino acids along with high orotic acid in urine  
C. Markedly elevated citrulline on plasma amino acids and normal urine organic acids  
D. Markedly elevated plasma glycine with normal urine organic acids  
E. Normal plasma amino acids and large suberylglycine peak on urine organic acids

3. Genome-wide chromosomal microarray analysis (CMA) detects losses and gains across the genome. Various methods have been developed for CMA, including the use of arrays that contain single nucleotide polymorphism (SNP) probes. Which of the following test characteristics represents an advantage for detecting genetic abnormalities by using an array that contains SNP probes, compared to an array that contains only copy number detection probes?

A. Balanced rearrangements can be detected  
B. Exon-level imbalances can be detected  
C. Imbalances of the sex chromosomes can be detected  
D. Smaller imbalances can be detected  
E. Uniparental disomy can be detected

4. You are adjusting the cutoffs for a Newborn Screening (NBS) test for a metabolic condition. Your adjustments increase the number of true positive results and reduce the number of false positive results. Both of these changes will increase which of the following NBS test parameters?

A. False negative rate  
B. False positive rate  
C. Positive predictive value  
D. Sensitivity of the test  
E. Specificity of the test
5. A young child has recently been diagnosed as having cystic fibrosis and is found to have one G551D allele. Which of the following medications might be appropriate to offer as a treatment?

A. everolimus  
B. ivacaftor  
C. losartan  
D. methotrexate  
E. vemurafinib

6. A four-year-old girl presents to the emergency room with rectal bleeding and rectal prolapse. The gastroenterologist removes a bleeding polyp and stabilizes the patient. A geneticist evaluates the patient and recommends genetic testing for a next generation panel test for polyposis/GI cancer genes. Which of the following gene tests is most likely to be positive given the child’s clinical presentation?

A. APC  
B. MUTYH  
C. MSH2  
D. PTEN  
E. SMAD4

7. You are scheduled to see a woman whose family history is consistent with inheritance of an autosomal dominant RB1 mutation with reduced penetrance. Your patient’s brother, maternal uncle, and maternal grandmother all had bilateral retinoblastoma. However, your patient and her mother have both had a normal ophthalmologic exam. Review of the literature reveals that RB1 mutations with 90% penetrance have been documented. If an RB1 mutation with 90% penetrance is segregating in this family, what is the chance for your patient’s offspring to inherit the RB1 mutation?

A. 0  
B. 1/40  
C. 1/22  
D. 1/11  
E. 1/2

8. A 4-year-old girl has sparse hair, abnormal teeth, and absence of sweating. Which of the following genes is most likely to be responsible for this disorder?

A. EDA1  
B. EDAR  
C. GJB6  
D. MSX1  
E. SLC45A2
9. Mrs Smith is a 40-year-old G2 P1 at 18-week gestation, with an ultrasound report indicating a neural tube defect was found in the fetus. She had a 12-week cell free fetal DNA (cffDNA) study which was "normal" for chromosomes 13, 18, 21 and X, Y. She remains concerned about the fetus so she decides to proceed with an amniocentesis. Which of the following findings is most likely from her amniocentesis?

A. Autosomal aneuploidy (other than chromosome 13, 18, 21)
B. Autosomal aneuploidy (of chromosome 13, 18, 21)
C. Microdeletion syndrome
D. Normal karyotype
E. Sex chromosome aneuploidy

10. You provide a clinical description of a patient to the molecular cytogeneticist at your facility including: a prominent nasal root, bulbous nasal tip, hypocalcemia, immunodeficiency, and conotruncal heart abnormality. Which of the following laboratory techniques is best used to confirm the suspected diagnosis in this patient?

A. Next-generation sequencing
B. Routine cytogenetic testing
C. Southern Blot
D. Fluorescence-in-situ hybridization (FISH) or DNA microarray
E. Sanger sequencing of the TBX1 gene

11. An 8-year-old boy and his family recently moved to the United States from Russia. His parents report their son has a genetic disorder and needs a special diet. Newborn screening was never performed. On physical examination you note macrocephaly and choreoathetotic movements. Height and weight are 25-30th centile for age. The parents note he has some mild cognitive deficits, but attended regular school in Russia. Which of the following metabolic disorders is the most likely diagnosis?

A. Canavan disease
B. Glutaric academia Type I
C. Isovalericacidemia
D. Medium chain acyl-CoA dehydrogenase deficiency
E. Phenylketonuria

12. A woman has retinitis pigmentosa (RP) and is found to be heterozygous for two unlinked genes, each of which has been implicated in RP. Her partner does not have RP and is unrelated. The chance for a child of this couple to have RP is?

A. 0
B. 1/8
C. 1/4
D. 1/2
E. 1
13. Your laboratory offers chromosomal microarray testing and you were asked to test an individual who has a known cytogenetic abnormality, which was detected by G-banding, to further define the abnormality. Which of the following karyotypes represents an individual who would not benefit from this additional characterization by microarray analysis?

A. 47,XY,+mar  
B. 47,XY,+21  
C. 46,XX,t(3;7)(p24;q22)dn  
D. 46,XY,add(11)(q25)  
E. 46,XX,der(6)t(1;3)(q32;q27)

14. Based on the clinical presentation and nuclear study, a diagnosis of Hereditary Paraganglioma-Pheochromocytoma syndrome was considered in a 36-year-old woman. The eight exons of the succinate dehydrogenase complex, subunit B (SDHB) gene were sequenced and the variant c.434 C>T (p.R115X) was detected in the fourth exon of this gene. What is the most likely outcome of the mRNA transcribed from this allele?

A. mRNA will be translated into truncated protein that has deleterious gain of function  
B. mRNA will be translated into truncated protein that has dominant negative effect  
C. mRNA will undergo nonsense mediated mRNA decay (NMD)  
D. mRNA will be translated into full-length protein  
E. This variant will inhibit the transcription of mRNA from this allele

15. A 34-year-old woman was recently diagnosed with breast cancer and comes for a consultation. Which of the following options describes the most appropriate use of the current models and guidelines?

A. The Amsterdam criteria can be used to predict the likelihood that she carries a PALB2 mutation.  
B. The Chompret criterion including additional family history data can determine the likelihood that she carries a BRCA1/2 mutation.  
C. The Claus tables can be used to predict her likelihood of developing ovarian cancer.  
D. The Gail model can be used to predict her likelihood of developing a second primary breast cancer.  
E. The NCCN guidelines suggest reflex TP53 testing if BRCA1/2 testing is negative.

16. A nasal sample was sent on a patient that was seen in clinic who you suspect has a problem with ciliary function. The results found abnormalities in the dynein arms of the cilia. Which of the following diagnoses is most consistent with this finding?

A. Bardet-Biedl syndrome  
B. Grieg cephalopolysyndactyly syndrome  
C. Holoprosencephaly  
D. Joubert syndrome  
E. Situs inversus
17. In your obstetric practice, you obtain a detailed second trimester fetal ultrasound survey to assess for the risk of Down syndrome. Which of the following ultrasound findings would have the highest relative risk for trisomy 21?

A. Choroid plexus cyst  
B. Echogenic bowel  
C. Echogenic cardiac focus  
D. Renal pyelectesis (4.0 mm)  
E. Shortened femur

18. As you evaluate a 4-day-old boy with a blood sugar of 37, an anion gap of 21, 4+ urinary ketones and an ammonia level of 197, the State Newborn Screening (NBS) Lab contacts you to report an emergency NBS result. The emergency result is most likely to reveal an increase in which of the following levels?

A. Biotinidase enzyme activity  
B. C3 acylcarnitine  
C. C6, C8 & C8/C10  
D. GALT enzyme activity  
E. Succinylacetone

19. A case-control study shows that an allele is present in 20% of controls and 40% of affected individuals. What is the odds ratio of an allele carrier having the disease compared with a non-carrier?

A. 0.66  
B. 0.75  
C. 2.0  
D. 2.66  
E. 3.0

20. You see a 4-year-old boy and his parents for a follow-up visit in genetics clinic. He was initially referred from craniofacial clinic for a sub-mucous cleft, delayed speech, a ventricular septal defect, and characteristic facial features. The parents were told these features may be consistent with a deletion of chromosome 22q11.2, and the syndrome was briefly described. The chromosomal microarray analysis you obtained following his initial visit revealed a 22q11.2 deletion and the family comes to discuss the results. After disclosing the confirmation of the diagnosis to the parents, which of the following actions is the most appropriate next step?

A. Assess the parents’ reaction to this diagnosis, and then ask if they want to hear more information.  
B. Describe the 22q11.2 deletion syndrome and the clinical features associated with this diagnosis.  
C. Explain how 22q11.2 deletion syndrome is inherited and discuss testing for other family members.  
D. Inform the parents of the limitations and potential benefits of chromosomal microarray testing.  
E. Provide support and reassurance for the parents that everything will be okay.
21. Known pathogenic variants are found in a variety of genetic databases available electronically through the internet. In searching for the implications of a de novo variant found on exome sequencing of a patient with unexplained developmental delay and dysmorphic features you find the exact same variant reported in the Human Genetic Mutation Database (HGMD) associated with a milder phenotype. However, a search of the Online Mendelian Inheritance in Man (OMIM) database and LOVD (Locus Specific database) does not confirm this relationship. Which of the following is the best explanation for the differences in the information available in these databases?

A. Cancer causing changes (somatic mutations) are not included in these databases.
B. Each database has a unique way of identifying which variants to include and call pathogenic
C. Mitochondrial mutation data is only included in some of these databases.
D. Sources of identified variants are the same across these databases.
E. Splice-site and regulatory regions of human nuclear genes are not included.

22. A couple, who had a previous child with classic Hurler syndrome who died of disease complications, comes to you for pre-conception counseling. Each parent has been molecularly confirmed to carry a known pathogenic mutation. Which of the following interventions will likely provide the best outcome for a future affected pregnancy?

A. HLA matched (66%; 4/6) unrelated donor bone marrow transplant in the early postnatal period
B. HLA matched liver transplant when the infant reaches a weight of 10 kilograms
C. Institution of chaperone therapy as early as possible in the postnatal period
D. Institution of enzyme replacement therapy at the first sign of neurologic regression
E. Unrelated donor, HLA matched (100%; 6/6) cord blood transplant in the early postnatal period

23. A 10-year-old boy presents with distal muscle weakness and atrophy associated with mild glove and stocking sensory loss, depressed reflexes, and pes cavus. Array CGH analysis demonstrates an abnormality in chromosome 17 at band p12 shown in the plot below. What is the diagnosis of this patient?

A. Williams syndrome
B. Hereditary neuropathy with liability to pressure palsies (HNPP)
C. Miller-Dieker syndrome
D. Charcot-Marie-Tooth syndrome type 1A (CMT1A)
E. Neurofibromatosis type 1 (NF1)
24. A 3-year-old boy from Southeast Asia has a seizure disorder and it is determined that he should be treated with carbamazepine. Before starting this medication, which of the following genes should be checked for pharmacogenetic polymorphisms?

A. CYP2D6  
B. HLA-B  
C. RYR1  
D. SLCO1B1  
E. TPMT

25. A couple who are first cousins ask about their risk of having a child with a rare autosomal recessive disorder that affected the sister of their common grandmother. The grandmother was not affected by this condition that exhibits complete penetrance. What is the risk to their child?

A. 1/128  
B. 1/96  
C. 1/32  
D. 1/24  
E. 1/6

26. A 5-year-old boy was referred for delays in language development. He had no functional communication, but was able to repeat words and phrases. He displayed some repetitive behavior and did not play with toys in the typical manner. Testing for Autism Spectrum Disorder was recommended. Which of the following analyses is likely the first tier test to be performed on this child?

A. Chromosomal analysis  
B. Expanded CGG repeat in FMR1 (Fragile X)  
C. Expanded CCG repeat in FMR2 (FRAXE)  
D. Non-syndromic autism gene panel  
E. Syndromic autism gene panel

27. A 20-year-old woman presents with a pheochromcytoma of the adrenal gland. Further work-up reveals hearing loss and an endolymphatic sac tumor. Genetic testing using an available pheochromcytoma/paragangioma panel is ordered. A positive mutation in which of the following genes is most likely to be identified?

A. NF1  
B. RET  
C. SDHB  
D. SDHD  
E. VHL
28. Early enzyme replacement therapy has dramatically altered the prognosis for infantile Pompe disease. Which of the following represents an unexpected clinical finding in long-term treated survivors?

A. Development of sensorineural or conductive hearing loss
B. Lack of development of antibodies in treated patients
C. Loss of visual acuity and retinal detachment
D. Normal gross motor skills after 12 months of therapy
E. Progressive cardiac enlargement

29. Susan Smith is a G1 at 22 weeks gestation. Her medical history is significant for obesity (BMI 40), Type 2 diabetes and anxiety. She drinks a glass of wine with most dinner meals. She started metformin preconception and has continued on it through the pregnancy. First trimester hemoglobin A1C was slightly elevated (7.0, normal < 6.1). She took Ampicillin for 7 days at 10 weeks gestation for a urinary tract infection. She presents to your office with an ultrasound finding of a fetus with a neural tube defect. From her history, which of the following factors conveys the highest relative risk for a fetus with a birth defect, especially a neural tube defect?

A. Alcohol consumption during pregnancy
B. Ampicillin use
C. Maternal obesity (BMI ≥ 40)
D. Metformin use
E. Type 2 diabetes A1C = 7.0

30. Two unrelated patients are evaluated in genetics clinic. One of the patients has sickle cell anemia phenotype and the other has a thalassemia phenotype. Molecular analysis detected homozygous mutations in beta globin for each patient. In the first patient, the homozygous mutation was consistent with sickle cell anemia (coding for the Glu6Val substitution), while the second patient was homozygous for a stop codon in the beta-globin gene. Which of the following concepts best describes these findings?

A. Allelic heterogeneity
B. Incomplete penetrance
C. Locus heterogeneity
D. Pleiotropy.
E. Variable expressivity
31. You evaluate a 2-year-old boy, Ethan, with multiple fractures after mild trauma. The family pedigree (below) reveals additional family members with a similar clinical phenotype. Ethan’s two sisters have no history of fractures.

![Family Pedigree](image)

The most likely cause of fractures in this family is a mutation in which of the following genes?

A. `COL1A1/2`
B. `IFITM5`
C. `LEPRE1`
D. `RPIB`
E. `SERPINF1`

32. Mr and Mrs Jones are both in their early thirties and seeking prenatal genetic counseling at 18 weeks gestation. This is their first pregnancy, conceived by IVF following 4 years of infertility, etiology undetermined. They are worried about the possibility of abnormal findings on their upcoming ultrasound. If an ultrasound abnormality were identified, which of the following findings is most likely to be seen on their pending ultrasound?

A. Dysplastic kidney and absent stomach bubble
B. Omphalocele and nephromegaly suggesting Beckwith Weideman Syndrome
C. Shortened long bones consistent with a skeletal dysplasia
D. Tetralogy of Fallot
E. Ventriculomegaly and adducted thumbs suggesting X-linked aqueductal stenosis

33. A 7-year-old with NF1 develops an acute left hemiparesis. Which of the following clinical findings is the most likely cause of acute stroke in NF1?

A. Blood clotting abnormality
B. Cardiac rhabdomyoma
C. Embolus from cardiac arrhythmia
D. Moyamoya syndrome
E. Optic glioma
34. Non-allelic homologous recombination (NAHR) mediated by segmental duplications is a mechanism known to cause recurrent deletions and duplications across the genome. Deletions of 22q11.2, which have been associated with DiGeorge syndrome and Velocardiofacial syndrome, are the most common recurrent imbalance. Which of the following syndromes is also caused by a NAHR-mediated mechanism?

A. 1p36 deletion syndrome  
B. Cri du Chat syndrome  
C. Miller-Dieker syndrome  
D. Potocki-Lupski syndrome  
E. Wolf-Hirschhorn syndrome

35. You are seeing a 4-day-old girl with abnormal Newborn Screening (NBS) result. She has a 2-day history of emesis and diarrhea. On physical examination she is quite icteric with hepatomegaly. Which of the following abnormalities is most likely to be found on the NBS report?

A. C0 acylcarnitine level is decreased  
B. C5DC level is increased  
C. Citrulline level is decreased  
D. GALT level is decreased  
E. Phenylalanine level is increased

36. A 15-year-old healthy girl is running long distances as a member of her high school track team. The morning after a 10-mile run on a hot day, she notices a red color to her urine. She is referred to you to exclude an inborn error of metabolism. Her creatine kinase is markedly elevated at 15,000 U/L and urine myoglobin is positive. Which of the following disorders of fatty acid oxidation is most compatible with this presentation?

A. Carnitine palmitoyltransferase I (CPT I) deficiency  
B. Carnitine palmitoyltransferase II (CPT II) deficiency  
C. Long chain 3-OH Acyl-CoA dehydrogenase deficiency  
D. Medium chain acyl-CoA dehydrogenase deficiency  
E. Short chain acyl-CoA dehydrogenase deficiency

37. You evaluate an 8-year-old girl with eczema since 3 months of age, recurring boils and cyst forming pneumonia since 1 year of age but no significant problems with diarrhea. Which of the following disorders is the most likely cause of her problems?

A. AR Severe Combined Immune Deficiency  
B. Common Variable Immune Deficiency  
C. Hyper IgE Syndrome  
D. Hyper IgM Syndrome  
E. XL Severe Combined Immune Deficiency
38. You are counseling a couple where both parents are affected with NF1. They have just had a baby, who at birth has no signs of the disorder. You explain that although NF1 follows is autosomal dominant disorder, features such as café-au-lait spots may not appear at birth, so their child still needs to be followed clinically, and that genetic testing is possible. You also note that homozygotes for NF1 mutation do not survive in utero. The couple asks you to estimate the chance that the baby has inherited an NF1 gene mutation. You quote the family which of the following risks?

A. 1/4  
B. 1/3  
C. 1/2  
D. 2/3  
E. 1  

39. The 35-year-old woman shown in the pedigree (noted by a star) is concerned about her risk of kidney cancer based on her family history of a brother who died of kidney cancer (clear cell RCC) at age 45. Given the pedigree you order genetic testing using a kidney cancer panel. Which of the following genes is most likely to have a pathogenic mutation?

A. BHD  
B. FH  
C. MET  
D. PTEN  
E. VHL
40. You are following a 30-year-old pregnant woman with von Hippel-Lindau syndrome. Which of the following findings is the most important to monitor her for during the pregnancy?

A. Endolymphatic sac tumor  
B. Pheochromocytoma  
C. Renal Cancer  
D. Retinal hemangioblastoma  
E. Vestibular schwannoma

41. Chromosomal microarray analysis (CMA) has replaced conventional G-banding as the first-tier test for cytogenetic analysis. Comparative genomic hybridization (CGH) is one type of CMA that can be used to detect copy number variants, however there are still limitations to this method. Which of the following test characteristics is a limitation of this methodology compared to a G-banded karyotype?

A. All polyploidy cannot be detected  
B. Cells need to be cultured for DNA extraction  
C. Resolution is lower than a G-banded karyotype  
D. Single copy number differences (i.e., loss or gain) cannot be detected  
E. Unbalanced translocations cannot be detected

42. A skin biopsy is done on a young woman with severe scarring due to epidermolysis bullosa. Which of the following sites is most likely to demonstrate skin separation in this biopsy?

A. Below basement membrane  
B. Epidermis  
C. Multiple layers in skin  
D. Sub-dermis  
E. Within basement membrane

43. You are evaluating Paul who is a 5-day-old boy. Paul has a large hematoma at his Vitamin K injection site and he continues to ooze after initial bleeding from his circumcision three days ago. He has a normal prothrombin time, von Willebrand and F9 factor levels and no family history of coagulation problems. You suspect hemophilia A. Which of the following mutations in the F8 do you predict is most likely to explain Paul’s problems?

A. Deletion/duplication  
B. IVS1 inversion  
C. IVS22 inversion  
D. Missense  
E. 51 promoter
44. A 6-month-old with unilateral retinoblastoma has genetic testing including sequencing and deletion analysis performed. The results of the tumor and blood analysis at the RB1 locus are shown below. What is the likelihood that a future sibling will develop retinoblastoma?

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Allele 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoblastoma tumor</td>
<td>c.7510C&gt;T (p.R261X)</td>
</tr>
<tr>
<td>Blood</td>
<td>normal</td>
</tr>
<tr>
<td></td>
<td>Homozygous C&gt;T substitution that causes an immediate termination codon in exon 8 of tumor DNA</td>
</tr>
</tbody>
</table>

A. <1% 
B. 1% 
C. 6% 
D. 25% 
E. 50%

45. A newborn with severe weakness is evaluated in the nursery. He is intubated and moves very little. Exam reveals little movement but weakly elicitable deep tendon reflexes. On taking a family history it is noted that his mother has visible mild facial weakness. What is the most likely diagnosis for the infant?

A. Charcot-Marie-Tooth disease 
B. Congenital muscular dystrophy 
C. Duchenne muscular dystrophy 
D. Myotonic dystrophy 
E. Spinal muscular atrophy

46. You offer your patient noninvasive prenatal testing (NIPT) as a screening test for aneuploidy at 10 weeks into her pregnancy. Which of the following conditions would have excluded her from this testing?

A. Demise of twin gestation at 8 weeks 
B. Diabetes type 1 
C. Diabetes type 2 
D. Miscarriage within past year 
E. Obesity (BMI > 30)

47. A newborn has failed her hearing screen. An electrocardiogram is ordered and is found to be abnormal. Which of the following findings is most likely?

A. Elevated P wave 
B. Elevated R wave 
C. Elongated PR interval 
D. Elongated QT interval 
E. Right bundle branch block
48. You are asked to evaluate a small child with asymmetric head shape, midface hypoplasia and digital anomalies. You obtain a head CT with 3-D reconstruction that demonstrates the finding below. 

Which of the following genetic defects is the most common cause of the radiographic finding seen on this 3-D CT image?

A. Chromosomal anomaly
B. DNA repair enzyme mutation
C. Fibroblast growth factor receptor mutation
D. RAS pathway component mutation
E. Sonic hedgehog mutation

49. A couple comes to you for genetic counseling because the husband had two siblings who died from cystic fibrosis (CF; an autosomal recessive disease with an incidence of approximately 1 in 2,500 livebirths). No molecular testing was done for either of his siblings. Both members of the couple choose to have carrier testing, using a mutation panel test which detects 90% of CF mutation carriers in their population. You are surprised to find that the wife receives a positive result, and is a carrier of the Phe508del mutation. However, the husband’s test is negative; no mutations are identified. What is probability that their first child will be affected?

A. 1/2500
B. 1/150
C. 1/44
D. 1/24
E. 1/6
50. Next Generation Sequencing (NGS) technology is being widely adopted in clinical laboratories. As a part of the guidance documents from CAP, CDC and ACMGG tests are evaluated for several parameters which include ability to detect insertion and deletion. NGS based tests tend to have a reduced analytical sensitivity for small insertions and deletions (in/dels) as a result of which of the following characteristics of in/dels detection?

A. In/dels negatively influence cluster generation on the flow cell
B. In/dels lead to altered chromatin structure
C. In/dels tend to have strand bias and reads containing them are filtered out
D. Short reads containing in/dels are more difficult to map unambiguously
E. The polymerases used do not sequence efficiently through in/dels