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Preparing for the American Board of Pathology (ABPath) Examination of Fundamental Knowledge and Skills

Molecular Genetic Pathology

Content Specifications

Overview:

Molecular Genetic Pathology Content Specifications

This guide outlines the content related to molecular pathology that may appear on the American Board of Pathology Anatomic and Clinical Pathology exam, as well as the Molecular Pathology Subspecialty exam. It provides a framework based on the knowledge and skills that the trainee is expected to know or be able to perform ranging from the early learner through the Fellow-level.

Key to Designations:

C = Core/Foundational Knowledge

AR = Advanced Resident Knowledge

F = Fellow/Advanced Practitioner Knowledge

The exam assesses the knowledge, judgment, skills, and abilities necessary to identify specific entities, properly process specimens, and diagnose and monitor diseases using molecular methods. The specific diseases, tests, and concepts listed in this document are important for candidates to know, but it is not possible to create a fully comprehensive list of all the material needed for certification and effective practice. Candidates should use this guide as a reference for preparing for certification and professional practice.

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1. Normal Structure and Function

a. Chromosomes	C
b. Genes	C
c. DNA	
i. Exons, Introns, Non-Coding DNA	C
ii. Repetitive Elements (e.g., STRs, Microsatellite)	AR
d. RNA	
i. mRNA and tRNA	C
ii. miRNA and IncRNA	AR
e. Transcription, Translation, and Post-Translational Modification	C
f. Mitosis	C
g. Meiosis	C
h. Nomenclature	
i. Gene Nomenclature	C
ii. Protein Nomenclature	C
iii. Variant Nomenclature	AR

2. Molecular Genetic Principles

a. Mechanisms and Types of Genetic Alterations/Defects	
i. Ploidy	C
ii. Copy Number Variants (CNV)	C
iii. Translocation and Other Rearrangements, including	
1. Deletions, Duplications, Inversions	C
iv. Single Nucleotide Polymorphisms (SNPs)	C
v. Methylation, Epigenetics	C
vi. Trinucleotide Repeats	C
1. Stabilizing Interruptions	F
vii. Multifactorial Events	C
viii. Mismatch Repair	C
ix. Point Mutations	C
x. Mosaicism	C
b. Inherited Defects	

i. Mendelian Inheritance		C
ii. Non-Mendelian Inheritance		C
iii. Oncogenes		C
iv. Tumor Suppressor Genes		C
v. Risk Calculations		C
vi. Hardy Weinberg Principle		AR
vii. Founder Mutations		F
viii. Bayes Analysis		F
c. Somatic Defects		
i. Oncogenes		C
ii. Tumor Suppressor Genes		C
iii. Loss of Heterozygosity (LOH)		AR
iv. Microsatallite Instability (MSI)		AR
v. Clonality		AR
vi. Genomic Instability		AR
vii. Chromothripsis		F

3. Techniques and Methods

a. Cytogenetics	C
b. PCR, RT-PCR, and other NAAT	C
c. FISH	AR
d. Nucleic Acid Isolation & Quantitation	AR
e. Restriction Enzyme Digestion	AR
f. Fragment Analysis (i.e., Gels, Capillary Electrophoresis)	AR
g. Quantitative PCR and RT-PCR	AR
h. Nucleic Acid Sequencing (i.e., Sanger & Pyrosequencing)	AR
i. Next Generation Sequencing	AR
j. Constitutional Arrays (aCGH, SNP, and Oligo Arrays)	AR
k. Somatic Arrays (aCGH, SNP, and Oligo Arrays)	AR
l. Melt Curve Analysis	AR
m. Tumor Mutational Burden	AR
n. MLPA and Other Mutation Scanning Methods	F
o. Methylation Analysis	F
p. Mass Spectrometry	F
q. Proteomics	F

4. Assay Performance and Validation

a. Proficiency Testing	AR
b. Validation versus Verification	AR
c. Preanalytical Considerations	AR
d. Analytical Considerations	AR
i. Stability	AR

	ii. Specimen Selection	AR
	iii. Specimen Collection	AR
	iv. Anticoagulant	AR
	v. Fixation	AR
e.	Postanalytical Consideration, including	
	i. Results, Interpretation, & Follow-up Testing	AR
f.	Variant Classification	AR
g.	Reporting	AR

5. Quality

a.	Quality Assurance	AR
b.	Quality Control	AR
c.	Controls	
	i. Internal Controls	AR
	ii. Quantitative Controls	AR

6. Ethical, Legal, and Regulatory Issues

a.	Ethical	
	i. IRB	C
	ii. Consent	C
	iii. Secondary & Incidental Findings (e.g., ACMG List)	F
b.	Legal	
	i. HIPAA	C
	ii. Genetic Information Non-Discrimination Act (GINA)	C
	iii. Gene Patent	AR
c.	Regulatory	
	i. CLIA	AR
	ii. CAP	AR
	iii. CMS	AR
	iv. FDA: LDT/LDP, IUO, RUO	AR
d.	Coding and Reimbursement	
	i. CPT	AR
	ii. ICD	AR
	iii. Laboratory Utilization	AR

7. Indications for Testing

a.	Presymptomatic / Predictive	C
b.	Diagnostic	C
c.	Prenatal Diagnosis, including	
	i. preimplantation genetic diagnosis (PGD)	C
d.	Screening	

i. Carrier Screening	C
ii. Newborn Screening	C
iii. Molecular Cancer Early-Detection Screening	F
e. Cancer Monitoring (e.g., minimal residual disease, resistance)	F

8. Inherited Diseases

a. Coagulation Disorders	
i. Factor V Leiden (FVL)	C
ii. Prothrombin	C
iii. Factor VIII	C
iv. Protein C	AR
b. Non-Neoplastic Hematology	
i. Thalassemia	C
1. Methods of Detection	F
ii. Hemophilia	C
iii. Sickle Cell Disease	C
iv. Hemochromatosis	C
1. Penetrance	F
2. Less Common Disease Producing Alleles	F
c. Cardiovascular	
i. Coronary Artery Disease; Hyperlipidemia	C
ii. Heritable Cardiomyopathy	AR
iii. Heritable Arrhythmias (e.g., Long QT)	AR
d. Renal	
i. Renal Cystic Disease	C
e. Endocrine	
i. Thyroid	C
ii. Parathyroid	C
f. Gastrointestinal	
i. Hirschsprung Disease	AR
ii. Celiac Disease	F
g. Pulmonary	
i. Cystic Fibrosis	C
1. Variant Associated Therapy	F
2. Genotype-Phenotype Correlation	F
3. Residual Risk Based on Testing Method & Ethnicity	F
ii. Alpha-1-Antitrypsin Deficiency	C
h. Immunologic	
i. Severe Combined Immunodeficiency (SCID)	C
i. Biochemical Genetics	
i. Metabolic Disorders (e.g., Phenoketonuria (PKU), galactosemia, and fatty acid oxidation disorders)	C

ii.	Storage Disorders	C
	(e.g., Gaucher, Tay-Sachs, glycogen storage disorders)	
iii.	Leukodystrophies	C
	(e.g., Krabbe, Canavan)	
j.	Mitochondrial Disorders	
i.	Inheritance Patterns	C
1.	Nuclear versus Mitochondrial Genes	F
ii.	Heteroplasmy	C
k.	Neuromuscular Disorders/Dementia	
i.	Huntington	C
ii.	Alzheimer	C
iii.	Parkinson	C
iv.	Muscular Dystrophy	C
v.	Freidreich Ataxia	AR
vi.	Dystonia	F
vii.	Myotonic Dystrophia	F
viii.	Spinal Muscular Atrophy (SMA)	F
l.	Neurodevelopmental Variants	
i.	Down Syndrome	C
ii.	Fragile X	C
iii.	Autism Spectrum	F
m.	Cutaneous/Connective Tissue Disorders	
i.	Osteogenesis Imperfecta	C
ii.	Marfan Syndrome	C
iii.	Ehlers-Danlos Syndromes	AR
iv.	Epidermolysis Bullosa	AR
n.	Imprinting Disorders and Congenital Growth Disorders	
i.	Angelman/Prader-Willi Syndromes	C
ii.	Beckwith-Wiedemann/Russel-Silver Syndromes	F
iii.	Proteus Syndrome	F

9. Inherited Cancer Syndromes

a.	Gastrointestinal Tumor Syndromes	
i.	Lynch Syndrome	C
ii.	*APC*-Associated Polyposis Conditions (e.g., FAP, GAPPS)	C
iii.	*MUTYH* Polyposis	AR
iv.	Peutz-Jeghers	AR
v.	Juvenile Polyposis Syndrome	AR
vi.	Hereditary Diffuse Gastric Cancer	AR
vii.	EPCAM Deletions	F
b.	Breast Cancer	
i.	BRCA 1 & 2	C
ii.	HRD Pathway Genes	AR

iii.	Cowden Syndrome	AR
iv.	Hereditary Diffuse Gastric Cancer	AR
v.	Reversion Mutations, Germline versus Somatic	F
vi.	Therapeutic and Management Implications	F
c.	Prostate Cancer (e.g., HRD Pathway, MMR)	F
d.	Pancreatic Cancer (e.g., HRD Pathway)	F
e.	Renal Cell Carcinoma	C
i.	*SMARCB1*-Deficient Renal Medullary Carcinoma	AR
f.	Endocrine	
i.	von Hippel-Lindau	C
ii.	Multiple Endocrine Neoplasia (MEN) 1 & 2	C
g.	Soft Tissue & Bone	
i.	Neurofibromatosis	C
ii.	Li-Fraumeni Syndrome	C
iii.	Carney-Stratakis Syndrome	AR
h.	Hematologic	F
i.	Müllerian	
i.	*BRAC 1* & *2*	C
ii.	Lynch Syndrome	C
iii.	*POLE* & *POLD1*	F

10. Solid Tumors, Sporadic

a.	Breast	
i.	HER2 Status	C
ii.	HER2 FISH Interpretations	AR
iii.	Prognostic Gene Expression Panels	AR
iv.	HER2 Detection by Other Methods	F
1.	(e.g., *ESR1*, *PIK3CA*)	
b.	Uterine, Cervical	
i.	HPV Status	C
ii.	HPV Molecular Methods	F
c.	Müllerian	
i.	TP53 Diagnostic Classification	AR
ii.	MMR Status	AR
iii.	*POLE* Mutation	AR
iv.	HER2 Amplification	AR
v.	HRD Pathways, including BRCA 1 & 2	AR
vi.	*KRAS* Mutation	F
d.	Lung	
i.	EGFR	C
ii.	*KRAS* Mutation	C
iii.	Guideline Recommended Gene Targets	AR

iv.	On versus Off Resistance Mechanisms	AR
v.	Biomarkers for Adjuvant Therapy (e.g., EGFR)	F
vi.	DNA versus RNA for Biomarker Assessment (e.g., *MET* Exon 14)	F
e. Gastrointestinal (GI)		
i.	Upper GI	
1.	HER2	AR
2.	MMR	F
ii.	Colorectal	
1.	MMR	C
2.	Sporadic MSI/MLH1	AR
3.	*RAS/RAF* Mutation Testing	AR
4.	HER2	F
5.	*POLE*	F
iii.	Pancreas	
1.	*RAS*	F
2.	Fusion	F
f. Genitourinary		
i.	Prostate	
1.	*TMPRSS2::ERG* Fusion	AR
2.	Homologous Recombination Deficiency (HRD)	F
ii.	Bladder	
1.	*FGFR* Mutations	F
2.	*TP53* Mutation Status	F
g. Central Nervous System		
iii.	Molecular Classification	AR
1.	(e.g., *TERT* Promoter Mutations, *IDH1* & *2*, *BRAF* Fusion)	
iv.	*MGMT* Promoter Methylation	AR
v.	Methylation-Based Classifiers	F
h. Endocrine		
i.	Thyroid	
1.	*BRAF* Status	C
2.	*RET* Fusion Status	C
3.	*RAS* Family Variants	AR
4.	Targetable Alterations	F
5.	Multigene Classifiers (e.g., for indeterminate cytology)	F
ii.	Pheochromocytoma	F
1.	*SDH* Gene Family Deficiency	F
iii.	Neuroblastoma	AR
1.	N-*MYC*	AR
i. Bone and Soft Tissue (including GIST)		
i.	Diagnostic Genetic Alterations	AR
j. Cutaneous		
i.	Melanoma	C
1.	*BRAF*	C

2. Site Specific Mutations (i.e., Cutaneous, Mucosal, Uveal) AR
3. UV Mutational Signatures F
4. Molecular Classifiers (e.g., Microarray, FISH, TERT) F

ii. Merkel Cell Carcinoma AR

iii. Squamous and Basal Cell Carcinomas F

k. Pan-Tumor Markers (e. g., Tumor Mutational Burden (TMB), MSI, *NTRK* Fusions) F

11. Hematopathology

a. Clonality (e.g., IGH, IGK, TRB, TRG) AR

b. Disease Monitoring AR

c. Specific Disorders

i. Lymphoid

1. B-ALL
   a. *BCR::ABL1* AR
   b. *ETV6::RUNX1* F
   c. *TCF3::PBX1* F
   d. *KMT2A::AF4* F
   e. *Ph*-Like ALL (e.g., *CRLF2-Rearranged*) F
2. Mature T cell
   a. *NPM1::ALK* AR
   b. *JAK-STAT* Pathway F
3. Mature B cell
   a. Common Translocations
      i. (e.g., *BCL2, BCL6, CCND1, MYC*) AR
   b. Recurrent Mutations
      ii. (e.g., *BRAF, MYD88, TP53*)
   c. *JAK-STAT* Pathway F
   d. *IGH* Somatic Hypermutation F
   e. Predictive Biomarkers (e.g., *BTK, PLCG2, EZH2*) F
4. Plasma cell F

ii. Myeloid

1. *MPN*-associated mutations (e.g., *JAK2, CALR, MPL, CAF3R*) C
2. Clonal hematopoiesis (e.g., DNMT3A, TET2, ASXL1) AR
3. *MDS*-associated mutations (e.g., *SF3B1, EZH2, TET2*) AR
4. Kinase Fusions (e.g., *PDGFR A/B, FGFR1, JAK2, ABL1*) AR
5. AML
   a. Associated mutations (e.g., *NPM1, FLT3, CEBPA*) AR
   b. Associated translocations AR
      (e.g., *PML::RARA, RUNX1::RUNX1T1, CBFB:MYH11)*
6. CML
   a. Diagnostic studies C
   b. Monitoring studies AR

c. Mastocytosis-associated mutations		AR
d. Resistance		F

12. Pharmacogenetics

a. Cytochrome P450 (e.g., CYP2D6, CYP2C9, CYP2C19)	C
b. Other Drug Metabolizing Enzymes (e.g., UGT1A1, Thymidine Kinase, DPYD, TPMT)	F
c. HLA-associated Pharmacogenetics (e.g., abacavir, carbamazapime).	F

13. Infectious Disease

a. Detection	C
b. Differentiation/Subtyping	AR
c. Antimicrobial Resistance	AR
d. Sequencing	F
e. Molecular Epidemiology	F
f. Viruses	
i. Hepatitis	C
ii. HIV	C
iii. HPV	C
iv. Viral Infections of Immunocompromised Hosts	AR
v. CNS Viral Infections	AR
vi. Respiratory Viruses	AR
vii. Gastrointestinal Viruses	AR
g. Bacteria	
i. *Staphylococcus aureus* and MRSA	C
ii. *Clostridioides difficile*	C
iii. Respiratory Bacteria	AR
iv. Mycobacteria	AR
v. Gastrointestinal Pathogens	
1. *E. coli*	AR
2. *Campylobacter*	AR
vi. Sexually Transmitted Pathogens (e.g., GC/CT, *Trichomonas*)	AR
vii. Central Nervous System Pathogens	AR
viii. Microbiome / Metagenomics	F
h. Fungi	AR
i. Parasites	AR

14. Identity Testing

a. Chimerism	AR
b. Maternal Cell Contamination Studies	AR
c. Sample Contamination	AR

d.	Paternal/Relationship Testing	F
e.	Forensic Applications	F
f.	Gestational Disease (Molar Pregnancy)	F

15. Histocompatibility F

16. Informatics

a.	Genomic Databases (e.g., CoSMIC, gnomAD, ClinVar)	AR
b.	NGS Bioinformatics Pipelines	F

17. Gene Therapy

a.	Therapeutic mechanisms	
i.	Gene Editing (e.g., CRISPR)	F
ii.	Gene Transfer (e.g., Viral Constructs)	F
iii.	Gene Modifying (e.g., CFTR, DMD, SMA)	F
b.	Adverse Events	F
c.	Ethical Considerations	F