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.

Table of Contents

Contents

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
iii.	Splicing	F
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.	Mutations, including but not limited to:	

a.	Point Mutations	C
b.	Synonymous vs Non-Synonymous	C
c.	Missense	C
d.	Nonsense	C
e.	Indels / Frameshift Mutations	C
f.	Non-Coding (e.g., promoter, UTR, deep intronic splice sites)	C
g.	Mosaicism	C
h.	Splice mutations	AR
x.		
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.	Microsatellite 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.	Arrays	
i.	Chromosomal Microarray Analysis, Constitutional	AR
ii.	Chromosomal Microarray Analysis, Acquired	AR
iii.	SNP Array Analysis	AR
iv.	Oligo Array Analysis	AR
k.	Melt Curve Analysis	AR

l. Tumor Mutational Burden AR
m. MLPA and Other Mutation Scanning Methods F
n. Methylation Analysis F
o. Mass Spectrometry F
p. Proteomics F

4. Assay Performance and Validation

a. Proficiency Testing AR
b. Validation versus Verification per Standards and Guidelines AR
c. Preanalytical Considerations
    i. Stability AR
    ii. Specimen Selection AR
    iii. Specimen Collection AR
    iv. Anticoagulant AR
    v. Fixation AR
d. Analytical Considerations AR
    i. Assay Optimization 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, including 'housekeeping' genes AR
    ii. Quantitative Controls (e.g., gene expression, minimal residual disease) 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
e. Specific Topics		
i.	Genetic Testing of Children	F
ii.	Pre-Implantation Genetic Testing	F
iii.	Reporting	F
iv.	Re-Evaluation/Re-Classification (e.g., VUS)	F

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 (e.g., Gaucher, Tay-Sachs, glycogen storage disorders)	C
	iii. Leukodystrophies (e.g., Krabbe, Canavan)	C
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.	Congenital Hearing Disorders	F
m.	Neurodevelopmental Variants	
	i. Down Syndrome	C
	ii. Fragile X	C
	iii. Autism Spectrum	F
n.	Cutaneous/Connective Tissue Disorders	
	i. Osteogenesis Imperfecta	C

ii.	Marfan Syndrome	C
iii.	Ehlers-Danlos Syndromes	AR
iv.	Epidermolysis Bullosa	AR

o. Imprinting Disorders and Congenital Growth Disorders

i.	Angelman/Prader-Willi Syndromes	C
ii.	Beckwith-Wiedemann/Russell-Silver Syndromes	F
iii.	Proteus Syndrome	F

9. Inherited Cancer Syndromes

a. Gastrointestinal Tumor Syndromes

i.	Lynch Syndrome	C
	a. Mismatch Repair	
	Homozygous Variants	AR
	Heterozygous Variants	AR
	EPCAM	AR
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 Disease

a.	Pancreatic Cysts and Genomic Classifiers	F
b.	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
b.	Uterine, Cervical	
i.	HPV Status	C
ii.	HPV Molecular Methods	F
c.	Müllerian	
i.	Diagnostic Classification	
1.	TP53 Status	AR
2.	MMR Status	AR
3.	POLE Status	AR
ii.	HER2 Amplification	AR
iii.	HRD Pathways, including BRCA 1 & 2	AR
iv.	*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)	AR
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.	PIK3CA	AR
5.	HER2	F
6.	*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

l. Testing Cancers of Unknown Primary 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*) AR
   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 F
   (e.g., UGT1A1, Thymidine Kinase, DPYD, TPMT)
c. HLA-associated Pharmacogenetics (e.g., abacavir, carbamazepine). 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