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Special Report

Goals and Objectives for Molecular Pathology Education in Residency Programs

The Association for Molecular Pathology Training and Education Committee

Increasing knowledge of the molecular basis of disease and advances in technology for analyzing nucleic acids and gene products are changing pathology practice. The explosion of information regarding inherited susceptibility to disease is an important aspect of this transformation. Pathology residency programs are incorporating molecular pathology education into their curricula to prepare newly trained pathologists for the future, yet little guidance has been available regarding the important components of molecular pathology training. We present general goals for pathology training programs for molecular pathology education. These include recommendations to pathology residents for the acquisition of both basic knowledge in human genetics and molecular biology and specific skills relevant to microbiology, molecular oncology, genetics, histocompatibility, and identity determination. The importance of residents gaining facility in integrating data gained via nucleic acid based-technology with other laboratory and clinical information available in the care of patients is emphasized. ***(J Mol Diag 1999, 1:5–15)***

The practice of anatomic and clinical pathology is being transformed by new knowledge in molecular pathology and human genetics and by advances in the application of molecular biology technology. As this trend accelerates, pathology residency programs must address the need to incorporate molecular pathology training and education within their curricula. This is true not only of traditional resident rotations within the anatomic and clinical laboratories such as hematopathology, microbiology, and histocompatibility, but also in new areas of human genetics.[1–3] On one hand, the ability to replace traditional methodologies with more sensitive nucleic acid-based assays is changing clinical laboratories from within. On the other hand, new knowledge of the mutations responsible for classical inherited disorders and mutations defining inherited susceptibility and resistance to common multifactorial disorders is providing novel roles for the clinical laboratory in disease diagnosis and patient management. This new understanding of the genetics of complex diseases such as neurodegenerative and thromboembolic disorders will find use in diagnosis, prognosis, and therapy.[4,5] Similar information about inherited and acquired genetic alterations in neoplasia will alter pathology practice and clinical management of these disorders.[6,7]

The importance of pathologists gaining facility with advances in molecular pathology and human genetics and incorporating this information within the routine practice of pathology is difficult to overstate. Pathologists must be adequately prepared to offer these clinical services and assume leadership roles in molecular pathology research and education. Pathology residency programs have responded to this challenge by devising a number of strategies for preparing residents for practice in this new era. A survey conducted by the Association for Molecular Pathology (AMP) polled United States pathology training programs regarding their efforts at molecular pathology education.[8] More than 80% of programs indicated that they have already instituted educational programs for molecular pathology. These programs are quite variable in form, ranging from formal 2- to 3-month clinical rotations in a general molecular pathology laboratory to short didactic sessions organized cooperatively with other departments. This variability is likely due in part to the heterogeneous nature of training programs and the residents they serve. However, program directors completing the survey frequently pointed out the need for more information concerning what constitutes appropriate molecular pathology education and the infrequent discussion of this topic in the literature.[2,3]

In this report, the Training and Education Committee of AMP provides an outline of important elements of resi-

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Table 1. Basic Concepts in Molecular Biology

Structure and biochemistry of nucleic acids
DNA and RNA structure
Physical chemistry of nucleic acids
DNA and RNA hybridization
DNA replication and repair
Gene organization and expression
Gene structure
Transcription
RNA processing
Translation, post-translational modification
Regulation of gene expression

Table 2. Concepts in Human Genetics

The human genome
Genomic organization
Chromatin and chromosome structure
Human genetic variation, polymorphisms
Molecular basis of inherited disease
Deletion, duplication, and insertion mutations
Missense, nonsense, null, and frameshift mutations
Mutations affecting RNA splicing and stability
Mutations altering transcription
Patterns of inheritance
Autosomal dominant and recessive disorders
De novo mutations
Consanguinity
Sex-linked disorders
X inactivation
Multifactorial inheritance
Mitochondrial inheritance
Nonclassical patterns of single gene inheritance
Mosiacism
Imprinting
Uniparental disomy
Trinucleotide repeat disorders
Expression of phenotypes
Penetrance and variable expressivity
Anticipation
Genetic, allelic, and locus heterogeneity
Quantitative genetics
Population genetics, Hardy-Weinberg equilibrium
Laws of probability, Bayesian analysis
Linkage analysis

dent molecular pathology education. Training requirements for fellowships in molecular pathology are not delineated in this paper. Residency directors may wish to consider this outline as they implement and refine the molecular pathology components of their programs. We have focused on broad concepts important to education in this field rather than compiling extensive lists of the numerous diagnostic assays now available. Literature references given in the text and reading suggestions for residents linked to specific areas within molecular pathology are intended as representative examples and entry points to the relevant literature for molecular pathology education, rather than as a comprehensive listing of available teaching materials or citation of the primary literature.

Concepts, Technologies, and Instrumentation for Molecular Pathology

The practice of molecular pathology requires understanding of general concepts and technologies that are common to specific applications in each area of the clinical laboratory. Access to this basic information will serve residents well not only during their training but also as practicing pathologists as new areas of molecular pathology are developed.

Basic Molecular Biology and Human Genetics Concepts

Many residents enter pathology training with sophisticated backgrounds in molecular biology and human genetics obtained from research experiences, graduate programs, and medical school courses.[9] However, a significant fraction of pathology residents do not share this background. In the absence of such experiences, and in light of the fact that human genetics and molecular biology education in United States medical schools remains uneven, an emphasis on concepts underlying molecular pathology is helpful to many pathology residents. Knowledge of the basic molecular biology information listed in Table 1 will aid residents in understanding the technology employed for molecular pathology practice in general and for specific applications in areas such as infectious disease diagnosis and hematopathology.[10] Knowledge of the concepts in human genetics given in Table 2 will be useful to residents as they encounter molecular pathology applications in histocompatibility and human identification and is essential for clinical applications in inherited disease diagnosis and cancer genetics.[11,12] As noted above, the increasing role of the clinical laboratory in the detection of alleles associated with multifactorial disease resistance and susceptibility requires that pathology residents have a relatively sophisticated understanding of human genetics.

Basic Technologies and Instrumentation

Methods for molecular pathology are increasingly automated and rapid, facilitating high through-put. Residents should understand the underlying principles and practical aspects of classic and more recently developed techniques employed in molecular diagnostic applications (Table 3).[13–17] In order to understand problems associated with specific assays and issues of test sensitivity, specificity, and cost in a molecular pathology laboratory, residents should understand the major instrumentation commonly employed. These include spectrophotometers, gel electrophoresis equipment, thermal cyclers, automated DNA sequencers, oligonucleotide synthesizers, and hybridization apparatus.[18]

We have not included in Table 3 molecular biology techniques such as library screening by hybridization, subcloning, the transformation of *Escherichia coli* with plasmids, and the isolation of cloned DNA fragments from hosts, since these are generally labor intensive methods which are not commonly used in contemporary clinical molecular pathology laboratories. However, resi-

Table 3. Technology for Molecular Pathology

Basic technology
Isolation and quantitation of DNA and RNA in cells
Enzymatic digestion of DNA
Electrophoretic separation of nucleic acids
Probe production and labelling of DNA and RNA
In vitro amplification of DNA and RNA
Polymerase chain reaction
Non-PCR based methods for amplification
Allele or sequence specific polymerase chain reaction
Solid phase and solution hybridization reactions
Southern and Northern blot analysis
Forward and reverse dot/slot blot/line analysis
ELISA plate or microwell arrays
In situ hybridization
Microchip and array technology
Nucleic acid detection methods
Ethidium bromide staining
Fluorescence
Chemiluminescence
Radioisotopes
Enzyme linked colorimetric assays
Other techniques for mutation screening and detection
Single-stranded conformation polymorphism analysis
Denaturing gel electrophoresis
DNA sequencing
Capillary electrophoresis
Computer-based analyses
Genetic databases
Sequence analysis and comparison

dents will wish to familiarize themselves with these methods, at least through their readings.[10] These methods provide a conceptual and historical basis for the techniques in Table 3 and are useful today for research purposes and for occasional diagnostic problems.

Education within Specific Areas of Molecular Pathology

Opportunities to provide educational experiences in molecular pathology for residents most often occur in areas of the clinical laboratory in which molecular technology and concepts are having a major impact. Examples include, but are not limited to, the diagnosis of inherited disease, leukemia and lymphoma diagnosis and monitoring, solid tumor analysis, infectious disease testing, HLA allele identification for transplantation, and identity and paternity determination. Some programs will not be able to provide a complete array of diagnostic experiences for residents. If clinical services in a particular training program are limited to a single area or application within molecular pathology, it may be difficult to construct an educational program of adequate breadth. Programs in which at least three molecular pathology areas or applications are represented in the clinical laboratory, especially when one involves inherited disease diagnosis, are likely to provide adequate case material for resident education. For each major area of molecular pathology, it is possible to define important elements of resident education.

Infectious Disease Testing

The molecular pathology tests performed most frequently in clinical laboratories today are in the field of infectious diseases. The marked improvement in sensitivity of nucleic acid-based detection of infectious agents and the rapid turnaround time as compared with some culture or antigen detection methods has argued for a stronger representation of molecular techniques in many laboratories. Molecular methods for quantitation of infectious agents, identification of difficult or impossible to cultivate agents, identification of antibiotic or antiviral resistance genes, and identification of toxin genes are becoming commonplace in laboratories. On the other hand, traditional microbiologic methods continue to be the appropriate approach for identifying most infectious agents, particularly from a cost-effectiveness perspective. The management of microbiology and virology laboratories now requires that laboratory directors have appropriate training in molecular biology so that they effectively make choices among the variety of technologies, including nucleic acid-based tests, available to them. Clinical rotations in these disciplines in residency training programs should be designed to accommodate this reality. Residents need to have basic understanding of the following:

- Organization of the DNA/RNA genomes of infectious agents
- Evolutionary relationships among microorganisms
- Species and genus specific sequences
- Genetic basis of pathogenesis and drug resistance

Examples of commonly employed DNA/RNA-based infectious disease tests include those designed to detect and quantitate human immunodeficiency virus-1, hepatitis C virus, cytomegalovirus, herpes simplex virus types I and II, Epstein-Barr virus, *Chlamydia trachomatis*, *Neisseria gonorrhea*, and *Mycobacterium* species.

Many training programs function in clinical settings where a subset or only a few of these assays are offered as diagnostic tests; however, a limited array of molecular microbiology assays can still serve as a reasonable basis for teaching residents important general concepts relevant to the use of nucleic acid-based tests. The concepts taught should be beyond the issues of organism detection and quantitation, since molecular techniques are also useful for other purposes in the microbiology laboratory. For example, residents should gain an appreciation of the clinical utility of differentiating among strains of fungi and bacteria with technology such as pulsed-field gel electrophoresis, ribotyping, and restriction fragment length polymorphism analysis in epidemiological studies. Similarly, direct and indirect DNA sequence analysis for purposes of genotyping and assessing drug resistance is clinically relevant.

Correlation of diagnostic and quantitative molecular test results with standard microbiological methods and clinical findings should be emphasized for best appreciation of the important applications of each. Training should include opportunities to discuss a variety of examples of the use of molecular methods to identify and characterize infectious agents. Residents should have experiences which allow them to do the following:

Table 4. Selected Readings: Infectious Disease

Black CM: Current methods of laboratory diagnosis of Chlamydia trachomatis infections. Clin Microbiol Rev 1997, 10:160–184
Carroll KC, Lenoard RB, Newcomb-Gayman PL, Hillyard DR: Rapid detection of the staphylococcal mecA gene from BACTEC blood culture bottles by the polymerase chain reaction. Am J Clin Pathol 1996, 106:600–605
Clementi M, Menzo S, Bagnarelli P, Valenza A, Paolucci S, Sampaolesi R, Manzin A, Varaldo PE: Clinical use of quantitative molecular methods in studying human immunodeficiency virus type 1 infection. Clin Microbiol Rev 1996; 9:135–147
Diagnostic Molecular Microbiology: Principles and Applications Edited by DH Persing, TF Smith, FC Tenover, and TJ White. Washington, D.C., American Society for Microbiology, 1993
Forns X and Bukh J: Methods for determining the hepatitis C virus genotype. Viral Hepatitis 1998, 4:1–19
Hjelle B: Hantavirus pulmonary syndrome. Laboratory Diagnosis of Viral Infections, ed 3 ch. 21. Edited by EH Lennette and TF Smith. New York, Marcel Dekker, pp 421–442
Krarup HB, Jacobsen SE, Varming K, Drewes AM, Madsen PH: Performance of hepatitis C virus (HCV) antibody test systems in relation to HCV-RNA detection in the diagnosis of HCV infection. Dan Med Bull 1998, 45:89–91
Lakeman FD, Whitley RJ: Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Gorup. J Infect Dis 1995, 171:857–863
Morse SS: Importance of molecular diagnostics in the identification and control of emerging infections. Emerg Infect Dis 1996, 1:201–206
Pfaller MA: Application of new technology to the detection, identification, and antimicrobial susceptibility testing of mycobacteria. Am J Clin Path 1994, 101:329–337
Relman DA, Loutit JS, Schmidt TM, Falkow S, Thompkins LS: The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. N Engl J Med 1990, 323:1573–1580
Schmitz FJ, Steiert M, Hofmann B, Verhoef J, Hadding U, Heinz HP, Kohrer K: Development of a multiplex-PCR for direct detection of the genes for enterotoxin B and C, and toxic shock syndrome toxin-1 in Staphylococcus aureus isolates. J Med Microbiol 1998, 47:335–40
Tang YW, Procop GW, Persing DH: Molecular diagnostics of infectious diseases. Clin Chem 1997, 43:2021–2038
Tompkins LS: The use of molecular methods in infectious diseases. N Engl J Med 1992, 327:1290–1297
van Vliet KE, Glimaker M, Lebon P, Klapper PE, Taylor CE, Ciardi M, van der Avoort HG, Diepersloot RJ, Kurtz J, Peeters MF, Cleator GM, van Loon AM: Multicenter evaluation of the Amplicor Enterovirus PCR test with cerebrospinal fluid from patients with aseptic meningitis. The European Union Concerted Action on Viral Meningitis and Encephalitis. J Clin Microbiol 1998, 36:2652–2657
Versalovic J, Woods CR, Georghiou PR, Hamill RJ, Lupski JR: DNA-based identification and epidemiologic typing of bacterial pathogens. Arch Pathol Lab Med 1993, 177:1088–1098
Whelen AC, Persing DH: The role of nucleic acid amplification and detection in the clinical microbiology laboratory. Annu Rev Microbiol 1996, 50:349–373

- Interpret the detection of the nucleic acids of an infectious agent that should not be present in a clinical sample
- Interpret the meaning of an infectious agent detected in a clinical sample for which it may or may not be a pathogen (pathogen *versus* colonization or carrier)
- Interpret the results of a method designed to quantitate infectious burden in clinical samples
- Interpret the results of a method designed to identify sequence variation associated with antimicrobial or antiviral resistance
- Interpret the results of a method designed to classify a microbe based upon phylogenetic data
- Interpret the results of a molecular epidemiological investigation as to the likelihood of a common point exposure
- Interpret the results of *in situ* hybridization in the context of morphologic features and clinical data

The trainee should become familiar with the importance and unique aspects of quality control and proficiency testing required for molecular tests for infectious agents that are also potential environmental contaminants. Emphasis should be placed on aspects of appropriate specimen selection, integrity of samples, specimen preparation, contamination prevention, and monitoring the sensitivity and specificity of assays. Table 4 provides selected readings in molecular microbiology which residents may find useful.

Molecular Oncology

Substantial advances in knowledge of the biology of leukemias and lymphomas, embodied in part in the increasingly detailed information regarding the genetic alterations contributing to the development of these neoplasms, have been particularly important in the field of hematopathology. Similar advances in our understanding of the molecular genetics of solid tumors are having a significant impact on the pathologist's approach to these neoplasms. Finally, recent discoveries of inherited alterations in tumor suppressor genes and genes encoding proteins responsible for DNA repair and their association with neoplasms such as breast and colon adenocarcinomas have opened a new and controversial arena of clinical assays for cancer predisposition assessment. It is essential that pathologists understand the molecular basis of neoplasia including the contribution of both inherited and acquired genetic alterations to tumor development. Important concepts relevant to molecular oncology include the following:

- The clonal origin of neoplasms and the phenomenon of clonal evolution
- The multistep pathogenesis of neoplasia involving:
  - inherited predisposition
  - activation of oncogenes
  - inactivation of tumor suppressor genes

- alterations of genes regulating apoptosis
- mutations of DNA repair genes

Residents should understand the spectrum of genetic alterations associated with neoplasia and be conversant with techniques for detecting different classes of mutations. They should be aware of the variety of means by which oncogene activation and tumor suppressor gene inactivation contribute to malignant cell growth. They should have some familiarity with specific examples of gene alterations found in common neoplasms. Residents should discuss the phenomenon of loss of heterozygosity including its detection and consequences. Residents should be familiar with chromosome translocations associated with specific neoplasms. This is particularly true for translocations involving genes such as PML/RAR-α, EWS/Fli1, bcr/abl, bcl-2, and the T cell antigen receptor and immunoglobulin loci which have played important roles in the development of improved understanding of the pathogenesis of neoplasia and which are useful in making diagnostic, prognostic, and therapeutic decisions. The advantages and disadvantages of detecting chromosome translocations and their chimeric products via traditional cytogenetics, molecular cytogenetics, and amplification techniques such as reverse transcriptase-PCR should be discussed.

Residents will wish to gain experience in the detection of clonality in lymphoproliferative lesions via immunoglobulin and T-cell receptor gene rearrangement analysis and the integration of these results with morphologic and other clinicopathologic data to produce a cohesive diagnostic report. Residents should review the process of normal rearrangement of the immunoglobulin and T-cell antigen receptor genes during B- and T-cell development. The advantages and disadvantages of detection of clonal rearrangements via Southern hybridization *versus* PCR approaches should be discussed. The value of gene rearrangement analysis in the context of morphologic, immunohistochemical, and flow cytometric study of lymphoproliferative lesions should be considered.

Diagnostic molecular oncology goes beyond the detection of translocations, identification of mutations in oncogenes and tumor suppressor genes, and clonality studies. Residents should gain familiarity with the use of amplification-based tests to detect minimum residual disease and should consider how one judges the clinical relevance of these data. They may gain exposure to microsatellite allele assessment for purposes of assessing genomic instability associated with DNA repair enzyme mutations or to determine the success of engraftment following allogeneic bone marrow transplantation. Finally, the promises and pitfalls of the ability to make predictions of the future risk of cancer by detecting inherited mutations in genes such as *BRCA-1* will be of interest. Predisposition testing for the inherited cancer syndromes raises many of the issues discussed in the subsequent inherited disease section. Table 5 and 6 give selected examples of readings in solid tumor and hematopathology molecular oncology which residents may find useful.

Inherited Disorders

Diagnostic assays are now available to detect mutations responsible for many classic inherited syndromes. Mutations which contribute to several common multifactorial disorders are also known. Like other sections within the clinical laboratory, molecular pathology laboratories performing tests to detect mutations associated with inherited disease have responsibilities beyond the production of a test result. Laboratory programs offering human genetic analysis must be designed and managed with great care, since these services very often involve prenatal diagnosis, presymptomatic diagnosis, implications for families as well as individuals, frequent consultation with referring non-specialist providers, and unique ethical issues. Resident education in inherited disease diagnosis should emphasize these issues in addition to teaching useful technologies.

In this regard, training programs should offer residents opportunities for significant interaction with human geneticists, genetic counselors, and other clinicians providing genetic services. These interactions should be designed to offer exposure to issues relevant to genetic diagnosis and counseling, risk assessment, explanation of testing and results to patients, psychosocial assessment, and support services. The resident should be exposed to clinical experiences which illustrate the problem of obtaining meaningful informed consent, the potential for genetic discrimination, issues concerning predictive testing in presymptomatic individuals, and the implications of genetic testing in minors. In some cases experiences on clinical genetics services may provide this exposure. In other settings, interdisciplinary conferences may be more suited to this purpose. These experiences should be designed to prompt the resident to consider the inherent complexities in the use of genetic information in the care of patients and families.

An introduction to inherited disease diagnosis should include a number of concepts and practical issues which build upon residents' knowledge of the basic information in Table 2:

- The use of standard molecular laboratory methods to detect point mutations, deletions, and other mutations responsible for disorders such as cystic fibrosis, Factor V Leiden associated hypercoagulability, hemochromatosis, and the muscular dystrophies should be studied.
- The transmission of genotypes and phenotypes in families with classic Mendelian disorders as well as non-classical disorders which display genetic imprinting or anticipation should be studied.
- The benefits and drawbacks of the use of samples other than peripheral blood such as buccal smears for inherited disease diagnosis should be considered.
- Potential problems such as maternal contamination associated with diagnostic tests performed with samples such as amniocytes obtained for prenatal diagnosis should be emphasized.

Table 5. Selected Readings: Molecular Oncology (Solid Tumors)

Barr FG, Chatten J, D'Cruz CM, Wilson AE, Nauta LE, Nycuym LM, Biegel JA, Womer RB: Molecular assays for chromosomal translocations in the diagnosis of pediatric soft tissue sarcomas. J Am Med Assoc 1995, 273:553–557
Barr FG: Translocations, cancer and the puzzle of specificity. Nature Genet 1998, 19:121–124
Blackwood MA, Weber BL: BRCA1 and BRCA2: From molecular genetics to clinical medicine. J Clin Oncol 1998, 16:1969–1977
Brodeur G, Seeger R, Sather H, Dalton A, Siegel S, Wong K, Hammond D: Clinical implications of oncogene activation in human neuroblastomas. Cancer 1986, 58:541–545
Castilla LH, Couch FJ, Erdos MR, Hoskins KF, Calzone K, Garber JE, Boyd J, Lubin MB, Deshano ML, Brody LC, Collins FS, Weber BL: Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer. Nature Genet 1994, 8:387–391
Evan G, Littlewood T: A matter of life and cell death. Science 1998, 281:1317–1322
Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. Cell 1990, 61:759–767
Fearon ER: Human cancer syndromes: Clues to the origin and nature of cancer. Science 1997, 278:1043–1050
Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Deville P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998, 62:676–689
Harris CC, Hollstein M: Clinical implications of the p53 tumor-suppressor gene. N Engl J Med 1993, 329:1318–1327
Hibshoosh H, Lattes R: Immunohistochemical and molecular genetic approaches to soft tissue tumor diagnosis: A primer. Semin Oncol 1997, 24:515–525
Ionov Y, Peinado MA, Malkhosyan MS, Shibata D, Perucho M: Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993, 363:558–561
Kinzler K, Vogelstein B: Lessons from hereditary colon cancer. Cell 1996, 87:159–170
Ladanyi M: The emerging molecular genetics of sarcoma translocations. Diagn Mol Pathol 1995, 4:162–173
Liu B, Nicolaides NC, Markowitz S, Willson JK, Parsons RE, Jen J, Papadopolous N, Peltomaki P, de la Chapelle A, Hamilton SR, Kinzler KW, Vogelstein B: Mismatch repair gene defects in sporadic colorectal cancers with microsatellite instability. Nature Genet 1995, 9:48–55
Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990, 250:1233–1238
Menke A, McInnes L, Hastie ND, Schedl A: The Wilms' tumor suppressor WT1: approaches to gene function. Kidney Int 1998, 53:1512–1518
Mulligan G, Jacks T: The retinoblastoma gene family: cousins with overlapping interests. Trends Genet 1998, 14:223–229
Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King M-C: Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. J Am Med Assoc 1998, 279:915–921
Persons DL, Borelli KA, Hsu PH: Quantitation of HER-2/neu and c-myc gene amplification in breast carcinoma using fluorescence in situ hybridization. Mod Pathol 1998, 10:720–727
Philipson L: Cell cycle exit: growth arrest, apoptosis, and tumor suppression revisited. Mol Med 1998, 4:205–213
Ponder B: Genetic testing for cancer risk. Science 1997, 278:1050–1054
Powell SM, Petersen GM, Krush AJ, Booker S, Jen J, Giardiello FM, Hamilton SR, Vogelstein B, Kinzler KW: Molecular diagnosis of familial adenomatous polyposis. N Engl J Med 1993, 329:1982–1987
Schwab M: Amplification of oncogenes in human cancer cells. Bioessays 1998, 20:473–479
Sidransky D: Nucleic acid-based methods for the detection of cancer. Science 1997, 278:1054–1059
Singleton TP, Strickler JG: Clinical and pathologic significance of the c-erbB-2 (HER-2/neu) oncogene. Pathol Annu 1992, 27 (Part 1): 165–190
Staunton MJ, Gaffney EF: Apoptosis: basic concepts and potential significance in human cancer. Arch Pathol Lab Med, 1998, 122:310–319
Thibodeau SN, Bren G, Schaid D: Microsatellite instability in cancer of the proximal colon. Science 1993, 260:816–819
Willman CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, Gilliland DG: Langerhans'-cell histiocytosis (histiocytosis X)—a clonal proliferative disease. N Engl J Med 1994, 331:154–160

- Risk assessment in families via linkage analysis when direct mutation detection is not possible or feasible should be discussed.
- Concepts of risk analysis should be reviewed for selected disorders with an emphasis on the general characteristics of Bayesian analysis and computer-based risk assessment.
- Problems posed for interpretation of the consequence of mutations detected in single gene and multifactorial disorders displaying incomplete penetrance or variable expressivity should be considered.

Cloned disease genes and specific mutations are now known for a large number of inherited disorders, making molecular diagnosis feasible in many cases. Table 7 includes a highly selected set of readings which residents may initially employ as they introduce themselves to this field.

Histocompatibility

Laboratories providing support for transplantation programs have undergone a major transformation during the past decade as DNA-based forms of HLA Class II allele identification have replaced serologic detection of Class II antigens for routine characterization of organ and hematopoietic stem cell recipients and donors. Allele identification, rather than antigen detection, will become routine for the Class I loci as well during the next few years. These changes are driven by nucleic acid-based typing's heightened accuracy and precision in comparison to serology. A diverse array of methods has been applied to clinical HLA allele identification, including sequence specific PCR, sequence specific oligonucleotide hybridization, and DNA sequencing of PCR products. The adoption of these methods in the HLA laboratory has implications for resident education. Residents need to

Table 6. Selected Readings: Molecular Oncology (Hematopathology)

Bakels V, van Oostveen JW, van der Putte SCJ, Meijer CJLM, Willemze R: Immunophenotyping and gene rearrangement analysis provide additional criteria to differentiate between cutaneous T-cell lymphomas and pseudo-T-cell lymphomas. Am J Pathol 1997, 150:1941–1949
Biernaux C, Loos M, Sels A, Huez G, Stryckmans P: Detection of major bcr-abl gene expression at a very low level in blood cells of some healthy individuals. Blood 1995, 86:3118–3122
Chhanabhai M, Adomat SA, Gascoyne FD, Horsman DE: Clinical utility of heteroduplex analysis of TCR gamma gene rearrangements in the diagnosis of T-cell lymphoproliferative disorders. Am J Clin Pathol 1997, 108:295–301
Cline MJ: The molecular basis of leukemia. N Engl J Med 1994, 330:328–336
Coad JE, Olson DJ, Lander TA, McGlennen RC: Molecular assessment of clonality in lymphoproliferative disorders: I. Immunoglobulin gene rearrangements. Mol Diagn 1996, 1:335–355
Coad JE, Olson DJ, Lander TA, McGlennen RC: Molecular assessment of clonality in lymphoproliferative disorders: II. T-cell receptor gene rearrangements. Mol Diagn 1997, 2:69–81
Corradini P, Astolfi M, Cherasco C, Ladetto M, Voena C, Caracciolo D, Pileri A, Tarella C: Molecular monitoring of minimal residual disease in follicular and mantle cell non-Hodgkin's lymphomas treated with high-dose chemotherapy and peripheral blood progenitor cell autografting. Blood 1997, 89:724–731
Drexler HG: Review of alterations of the cyclin-dependent kinase inhibitor INK4 family genes p15, p16, p18, and p19 in human leukemia-lymphoma cells. Leukemia 1998, 12:845–859
Gribben JG, Neuberg D, Freedman AS, Gimmi CD, Pesek KW, Barber M, Saporito L, Woo SD, Coral F, Spector N, Rabinowe S, Grossbard ML, Ritz J, Nadler LM: Detection by polymerase chain reaction of residual cells with the bcl-2 translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 1993, 82:3449–3457
Grignani F, Fagioli M, Alcalay M, Longo L, Pandolfi PP, Donti E, Biondi A, Lo Coco F, Grignani F, Pelicci PG: Acute promyelocytic leukemia: from genetics to treatment. Blood 1994, 83:10–25
Knowles DM: Immunophenotypic and immunogenotypic approaches useful in distinguishing benign and malignant lymphoid proliferations. Semin Oncol 1993, 20:583–610
Look AT: Oncogenic transcription factors in the human acute leukemias. Science 1997, 278:1059–1064
Mackinnon S, Barnett L, Heller G: Polymerase chain reaction is highly predictive of relapse in patients following T cell-depleted allogeneic bone marrow transplantation for chronic myeloid leukemia. Bone Marrow Transplant 1996, 17:643–647
McClure JS, Litz CE: Chronic myelogenous leukemia: Molecular diagnostic considerations. Hum Pathol 1994, 25:594–597
Nowell PC: The clonal evolution of tumor cell populations. Science 1976, 194:23–28
Provan D, Bartlett-Pandite L, Zwicky C, Neuberg D, Maddocks A, Corradini P, Soiffer R, Ritz J, Nadler LM, Gribben JG: Eradication of polymerase chain reaction-detectable chronic lymphocytic leukemia cells is associated with improved outcome after bone marrow transplantation. Blood 1996, 88:2228–2235
Radich J, Thomson B: Advances in the detection of minimal residual disease. Curr Opin Hematol 1997, 4:242–247
Rowley JD, Aster JC, Sklar J: The clinical applications of new DNA diagnostic technology on the management of cancer patients. J Am Med Assoc 1993, 270:2331–2337
Sawyers CL, Timson L, Kawasaki ES, Clark SS, Witte ON, Champlin R: Molecular relapse in chronic myelogenous leukemia patients after bone marrow transplantation detected by polymerase chain reaction. Proc Natl Acad Sci USA 1990, 87:4563–4567
Schwartz RS: Hodgkin's disease—time for a change. N Engl J Med 1997, 337:495–496
Siebert R, Matthiesen P, Harder S, Zhang Y, Borowski A, Zuhike-Jenisch R, Metzke S, Joos S, Weber-Matthiesen K, Grote W, Schlegelberger B: Application of interphase fluorescence *in situ* hybridization for the detection of the Burkitt translation t(8;14)(q24:q32) in B-cell lymphomas. Blood 1998, 91:984–990
Sukpanichnant S, Vnencak-Jones CL, McCurley TL: Detection of clonal immunoglobulin heavy chain gene rearrangements by polymerase chain reaction in scrapings from archival hematoxylin and eosin-stained histologic sections: implications for molecular genetic studies of focal pathologic lesions. Diagn Mol Pathol 1993, 2:168–176
Tsujimoto Y, Finger LR, Yunis J, Nowell PC, Croce CM: Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation. Science 1984, 226:1097–1099
Zelenetz AD, Chu G, Galili N, Bangs CD, Horning SJ, Donlon TA, Cleary ML, Levy R: Enhanced detection of the t(14;18) translocation in malignant lymphoma using pulsed-field gel electrophoresis. Blood 1991, 78:1552–1560
Zwicky CS, Maddocks AB, Andersen N, Gribben JG: Eradication of polymerase chain reaction detectable immunoglobulin gene rearrangement in non-Hodgkin's lymphoma is associated with decreased relapse after autologous bone marrow transplantation. Blood 1996, 88:3314–3322

understand and work with a variety of concepts and issues relating to molecular histocompatibility (see Table 8 for selected readings). These include:

- The organization of the major histocompatibility complex on chromosome 6
- The nature and consequences of the extensive polymorphism of the Class I and Class II genes
- Nucleic acid-based methods for identifying HLA alleles and appropriate choices of methods tailored for specific clinical applications
- The relationship of alleles to antigens expressed on cell surfaces as detected by serologic methods and problems posed by alleles which are not expressed (null alleles)
- The utility of Class I and Class II allelic information gathered at various levels of resolution and its clinical value in hematopoietic stem cell, renal, and the other forms of solid organ transplantation
- The consequences of allelic mismatches in terms of failure to engraft, graft rejection, and graft versus host disease

Identity Determination

The recent characterization of an extensive array of microsatellite, minisatellite, and single nucleotide polymorphisms distributed throughout the human genome has yielded many loci useful for distinguishing among indi-

Table 7. Selected Readings: Inherited Disorders

Andrews LB, Fullarton JE, Holtzman NA, Motulsky A (Eds): Assessing Genetic Risks. Washington, DC National Academy Press, 1994
ASHG/ACMG Report: Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet 1995, 57:1233–1241
ASHG Statement: Professional Disclosure of Familial Genetic Information. Am J Hum Genet 1998, 62:474–483
Beutler E, Gelbar T, Kuhl W, Zimran A, West C: Mutations in Jewish patients with Gaucher's disease. Blood 1992, 79:1662–1666
Bothwell TH, MacPhail AP: Hereditary hemochromatosis: etiologic, pathologic, and clinical aspects. Semin Hematol 1998, 35: 55–71
Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR: The likelihood of being affected with Huntington disease by a particular age, for a specific CAG size. Am J Hum Genet 1997, 60:1202–1210
Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, Hunter K, Stanton VP, Thirion JP, Hudson T: Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3′ end of a transcript encoding a protein kinase family member. Cell 1992, 68:799–808
Cai SP, Chang CA, Zhang J-Z, Saiki RK, Erlich HA, Kan YW: Rapid prenatal diagnosis of beta thalassemia using DNA amplification and nonradioactive probes. Blood 1989, 73:372–374
Clement K, Vaisse C, Lahiou N, Cabrol S, Pelloux V, Cassuto D, Gourmeien M, Dina C, Chambaz J, Lacort J-M, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998, 392:398–401
Collins FS, Patrinos A, Jordan E, Chakravarti A, Gesteland R, Walters L, and the members of the DOE and NIH planning groups: New goals for the human genome project: 1998–2003. Science 1998, 282:682–689
Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993, 261: 921–923
Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, Rimmler JB, Locke PA, Conneally PM, Schmader KE, Small GW, Roses AD, Haines JA, Pericak-Vance MA: Protective effect of apolipoprotein E type 2 alleles for late onset Alzheimer disease. Nature Genet 1994, 7:180–184
Deloukas P, Schuler GD, Gyapay G, Beasley EM, Soderlund C, Rodriguez-Tomé P, Hui L, Matise TC, McKusick KB, Beckmann JS, Bentolila S, Bihoreau M-T, Birren BB, Browne J, Butler A, Castle AB, Chiannilkulchai N, Clee C, Day PJR, Dehejia A, Dibling T, Drouot N, Duprat S, Fizames C, Fox S, Gelling S, Green L, Harrison P, Hocking R, Holloway E, Hunt S, Keil S, Lijnzaad P, Louis-Dit-Sully C, Ma J, Mendis A, Miller J, Morissette J, Muselet D, Nusbaum HC, Peck A, Rozen S, Simon D, Slonim DK, Staples R, Stein LD, Stewart EA, Suchard MA, Thangarajah T, Vega-Czarny N, Webber C, Wu X, Hudson J, Auffray C, Nomura N, Sikela JM, Polymeropoulos MH, James MR, Lander ES, Hudson TJ, Myers RM, Cox DR, Weissenbach J, Boguski MS, Bentley DR: A physical map of 30,000 human genes. Science 1998, 282:744–746
Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R Jr, Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikang E, Wolff RK: A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nature Genet 1996, 13:399–408
Fu Y, Kuhl DP, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJ, Holden JJ, Fenwick RG Jr, Warren ST: Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1991, 67:1047–1058
Gelbart WM: Databases in genomic research. Science 1998, 282:659–661
The Huntington's Disease Collaborative Research Group: A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's Disease chromosomes. Cell 1993, 72:971–983
Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC: Identification of the cystic fibrosis gene: genetic analysis. Science 1989, 245:1073–80.
Kiechle FL, Kaul KL, Farkas DH: Mitochondrial disorders. Methods and specimen selection for diagnostic molecular pathology. Arch Pathol Lab Med 1996, 120:597–603
La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH: Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 1991, 352:77–79
Miller RG, Hoffman EP: Molecular diagnosis and modern management of Duchenne muscular dystrophy. Pediat Neurogenet 1994, 12:699–725
Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN, Eismann JA: Prediction of bone density from vitamin D receptor alleles. Nature 1994, 367:284–287
Multiple contributors: J Am Med Assoc 1997, 278:1209–1294 (Multiple articles addressing genetics and molecular diagnosis of Alzheimer disease, breast carcinoma, prostate cancer, multiple sclerosis, retinoblastoma, beta thalassemia, colorectal cancer and other disorders)
Poort RS, Rosendaal FR, Reitsma PH, Bertina RM: A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996, 88:3698–3703
Press RD, Flora K, Gross C, Rabkin JM, Corless CL: Hepatic iron overload: direct HFE (HLA-H) mutation analysis vs quantitative iron assays for the diagnosis of hereditary hemochromatosis. Am J Clin Pathol 1998, 109:577–584
Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielinski J, Lok S, Plavsik N, Chou JL, Drumm ML, Iannuzzi MC, Collins FS, Tsui LC: Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989, 245:1066–1073
Risch N, Merikangas K: The future of genetic studies of complex human diseases. Science 1996, 273:1516–1517
Risch N: Haemochromatosis, HFE and genetic complexity. Nature Genet 1997, 17:375–376
Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui LC, Collins FS: Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989, 245:1059–1065
Sutcharitchan P, Embury SH: Advances in molecular diagnosis of inherited hemoglobin disorders. Curr Opin Hematol 1996, 3:131–138
Warren ST, Nelson DL: Advances in diagnosis of fragile X syndrome. J Am Med Assoc 1994, 271:536–542
Wivel NA, Walters L: Germ-line gene modification and disease prevention: some medical and ethical perspectives. Science 1993, 262:533–538

Table 8. Selected Readings: Histocompatibility

Beatty PG: The immunogenetics of bone marrow transplantation. Transfusion Med Rev 1994, 8:45–58
Begovich AB, Erlich HA: HLA typing for bone marrow transplantation. J Am Med Assoc 1995, 273:586–591
Bunce M, Young NT, Welsh KI: Molecular HLA typing—the brave new world. Transplantation 1997, 64:1505–1513
Hurley CK, Schreuder GMT, Marsh SGE, Lau M, Middleton D, Norreen H on behalf of multiple contributors: The search for HLA-matched donors: a summary of HLA-A*, -B*, -DRB1/3/4/5* alleles and their association with serologically defined HLA-A, -B, -DR antigens. Tissue Antigens 1997, 50:401–418
Martin S, Dyer PA: The case for matching MHC genes in human organ transplantation. Nat Genet 1993, 5:210–213
Matas AJ: Is MHC matching as a primary criterion for kidney allocation justified? Nat Genet 1993, 5:210–213
McDevitt H: Evolution of MHC Class II allelic diversity. Immunol Rev 1995, 143:113–122
Olerup O, Zetterquist H: HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens 1992, 39:225–235
Parham P, Adams EJ, Arnett KL: The origins of HLA-A, B, C polymorphism. Immunol Rev 1995, 143:141–180
Petersdorf EW, Longton GM, Anasetti C, Martin PJ, Mickelson EM, Smith A, Hansen JA: The significance of HLA-DRB1 matching on clinical outcome after HLA-A, B, DR identical unrelated donor marrow transplantation. Blood 1995, 86:1606–1613
Saiki RK, Walsh PS, Levenson CH, Erlich HA: Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. Proc Natl Acad Sci USA 1989, 86:6230–6234
Suthanthiran M, Strom TB: Renal transplantation. N Engl J Med 1994, 331:365–376
Wu J, Griffith BB, Bassinger S, Moehlenkamp C, Brodie SG, Wu Y, Gribble GG, Troup GM, Williams TM: Strategies for unambiguous detection of allelic heterozygosity via direct DNA sequencing of PCR products: Application to the HLA DRB1 locus. Mol Diagn 1996, 1:89–98
Troup GM, Williams TM: HLA: The molecular age. Principles of Transfusion Medicine, ed 2. Edited by EC Rossi, TL Simon, GS Moss. Baltimore, Williams and Wilkins, 1995, pp 813–824

viduals. Serologic-based red blood cell and HLA antigen detection for purposes of paternity and forensic identification has been supplanted by Southern hybridization and amplification mediated analysis of polymorphisms. Identifying alleles at polymorphic loci is also useful for assessing engraftment in allogeneic transplantation, performing linkage analysis in families, detecting loss of heterozygosity in tumors, and for resolving diagnostic specimen mixups. A variety of nucleic acid-based methods have been developed for these purposes (Table 9, selected readings).

- Residents should understand the nature of polymorphisms occurring in the genome and the means available for analyzing polymorphic loci.
- Residents should be familiar with the uses of polymorphism assessment to conduct genetic linkage analysis and paternity and forensic analyses.
- Residents should understand the statistical concepts useful for calculating the probabilities of relatedness and identity.

Clinical Correlation

The importance of training residents in the appropriate interpretation of molecular pathology test results and their integration with other laboratory data in the clinical context has been illustrated in the discussions of individual applications above. The need for close attention to clinical correlation of molecular pathology data is highlighted by the relative novelty of many molecular technologies and the recent introduction of many molecular pathology tests. Education in molecular pathology should offer opportunities for residents to critically examine what, if any, additional valuable information a nucleic acid-based test will provide in a particular clinical situation over traditional methodologies:

- How is the proposed molecular test more sensitive or more rapid than an established test?
- When is the contemplated nucleic acid-based test the only practical way to obtain the needed information?

Table 9. Selected Readings: Identity Determination

Alfort RL, Hammond HA, Coto I, Caskey CT: Rapid and efficient resolution of parentage by amplification of short tandem repeats. Am J Hum Genet 1994, 55:190–195
Budowle B, Allen RC: Analysis of amplified fragment-length polymorphisms (VNTR/STR loci) for human identity testing. Methods Mol Biol 1998, 98:155–171
Chakroborty R, Kidd KK: The utility of DNA typing in forensic work. Science 1991, 254:1735–1739
Gill P, Jeffries AJ, Werrett DJ: Forensic application of DNA fingerprints. Nature 1985, 318:577–579
Hammond HA, Jin L, Zhong Y, Caskey CT, Chakraborty R: Evaluation of 13 short tandem repeat loci for use in personal identification applications. Am J Hum Genet 1994, 55:175–189
Housman D: Human DNA polymorphism. N Engl J Med 1995, 332:318–320
Inman K, Rudin N: An Introduction to Forensic DNA Analysis. Boca Raton, CRC Press, 1997
Lander ES, Budowle B: DNA Fingerprinting dispute laid to rest. Nature 1994, 371:735–738
O'Brian DS, Sheils O, McElwaine S, McCann SR, Lawler M: Sorting out mix-ups: the provenance of tissue sections may be confirmed by PCR using microsatellite markers. Am J Clin Pathol 1996, 106:758–764
Olaisen B, Bar W, Brinkmann B, Budowle B, Carracedo A, Gill P, Lincoln P, Mayr WR, Rand S: DNA recommendations 1997 of the International Society for Forensic Genetics. Vox Sanguinis 1998, 74:61–63
Weedn VW: Forensic DNA tests. Clin Lab Med 1996, 16:187–196

- If not appropriate as a general approach to a clinical problem, when is the DNA-based assay most suited to a particular diagnostic niche? For example, detection of HIV-1 RNA via amplification strategies may be ideal in neonates because of the presence of maternal antibodies, but not appropriate as an initial approach in the general population.
- When do the very specific questions answered by nucleic acid-based methodologies merit their substitution for broader traditional screening methods?
- How well do assays for known mutations associated with inherited disorders adequately address the possibility of unexpected genetic heterogeneity?
- Does the detection of the genome of a microorganism via a DNA amplification technique precisely correlate with the presence of a clinical significant infection?
- What are the implications for family members of a patient with a positive result for a specific genetic disease?
- How does a DNA-based test result correlate with other available laboratory and clinical data?

Well designed molecular pathology education programs should allow ample opportunity for discussion of and practical experiences relevant to these and related questions.

Laboratory Management

Like other laboratory rotations, molecular pathology residency training should include opportunities to learn about quality management, test reimbursement, and the efficient organization of the laboratory.[19,20] However, molecular pathology laboratories also offer several distinctive laboratory management teaching opportunities. Residents can learn how priorities are set for the local development and validation of new genetic tests based on information only recently available in the literature. They can develop some facility in using computer technology and internet-based databases which provide gateways to exponentially accumulating information regarding the sequence of the human genome, mRNAs present in various cell types, DNA polymorphisms, and correlations between specific genetic variations and disease states.[21] Residents can consider strategies for recruiting and training molecular pathology technologists given the reality that few medical technology programs include molecular pathology training. Finally, the fact that blood, cell, and tissue specimens constitute banked DNA samples[22,23] linked to individual patients raises important management issues which should be addressed. These include discussion of means for preserving patient privacy, maintaining confidentiality, and appropriately protecting and compartmentalizing access to clinical genetic results stored and communicated in paper and electronic forms.[24]

Curricular Choices for Resident Molecular Pathology Education

Molecular pathology education experiences for residents will necessarily vary among programs. These differences are driven by variation in faculty expertise, the mix of specific molecular diagnostics services offered, residents' prior experiences and interests, and opportunities for coordinated programs with other departments within the institution. While substantially different approaches are taken, it is apparent from the survey of residency directors referred to above that a substantial majority of training programs across the United States consider it necessary to offer residents formal education in molecular pathology. Appropriate programs would reasonably include various combinations of didactic sessions, rotations within molecular pathology laboratories, participation in conferences, and experiences on relevant clinical services. While didactic sessions may substitute for practical experience in the laboratory because of the lack of a particular molecular pathology service at a training institution, the wholesale teaching of molecular pathology through written materials and lectures seems as inappropriate in this field as for any of the traditional anatomic and clinical pathology rotations. The physical location of molecular pathology education will also reasonably vary among programs secondary to differences in the organization of molecular pathology services. Some institutions have developed centralized molecular pathology facilities while others provide these services in preexisting sections of the clinical laboratory. For example, topics in molecular virology might be addressed either in the microbiology laboratory rotation or in the molecular pathology laboratory rotation or both depending on where the relevant tests are offered. In institutions in which molecular tests are performed in a molecular pathology laboratory, many of the educational goals discussed in this report can be achieved in rotations through that laboratory. However, an added emphasis on appropriate integration of data from other sections of the laboratory and clinical correlation will be necessary. Conversely, in institutions in which molecular pathology practical experience is gained in dispersed laboratories, a coordinated strategy for providing the general training in basic technologies and concepts in molecular and human genetics described above must be devised.

Pathology residency programs may wish to develop educational experiences which allow residents to meet several goals:

- Understand the basic concepts of human genetics, molecular biology and cell biology
- Develop a familiarity with the principles and techniques used in the design and validation of molecular patient tests[25]
- Understand the specimen requirements for molecular tests[26,27"]
- Develop competency in test interpretation
- Understand the clinical applications of molecular testing and the appropriate role of nucleic acid-based testing relative to other methodologies
- Develop familiarity with personnel requirements and management strategies necessary for efficient operation of a molecular pathology laboratory
- Be aware of important legal, ethical, and social implications of the availability of tests which assess human genetic variability

Resources for Molecular Pathology Education

Many residency programs will not be in a position to directly expose residents to all major areas of molecular pathology. This fact suggests that external resources for molecular pathology education will be important supplements to case material available within each program. Several textbooks dealing with molecular pathology are currently available.[18,28–30] These subjects are also addressed in texts specific to disciplines such as hematopathology. However, texts dealing with topics in molecular pathology become rapidly outdated given the rate of change in the field. Professional organizations within pathology such as the American Society of Clinical Pathology (ASCP), the College of American Pathologists, the American Association of Clinical Chemistry, the International Academy of Pathology, and the Association for Molecular Pathology (AMP) provide a number of excellent molecular pathology courses at annual meetings. An intensive, practical course in molecular pathology has been offered for several years by the American Society for Investigative Pathology. The ASCP's Check Sample series on Molecular Pathology and Applied Technologies provides instructive relevant case material. Each of these resources is valuable; however, educational materials for molecular pathology are somewhat limited in number and scope. The development by interested organizations and institutions of additional patient case-based resources useful to training programs and residents, especially materials that could be made available in electronic format, would be of substantial benefit.

Summary

Education in molecular pathology is an important component of modern pathology training programs. We have presented a view of general topics and issues specific to fields within molecular pathology which should be addressed in residency rotations. Few, if any, programs will be able to offer residents all of the experiences which we have outlined above. Programs should not interpret the goals and objectives outlined in this paper as ones which must be comprehensively satisfied in order to offer successful education in molecular pathology to residents. However, creative and selective coverage of this material in designated molecular pathology rotations in conjunction with traditional anatomic and clinical laboratory rotations and appropriate clinical experiences outside the pathology laboratory should enable many programs to devise adequate programs. We expect that training programs will draw upon the diverse nature of their clinical services and faculties to create a rich variety of approaches to resident molecular pathology education, linked by a goal of preparing new pathologists to succeed in the era of molecular medicine.

References

1. Collins FS: Preparing health professions for the genetic revolution. J Am Med Assoc 1997, 278:1285–1286
2. Kant JA: Training in molecular pathology. Hum Pathol 1995, 26:1051–1054
3. Arber DA, Battifora H, Brynes RK, Chang KL, Weiss LM, Wilczynski SP: Certification and training in molecular pathology (letter). Hum Pathol 1996, 27:430–431
4. Mayeuz R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, Hyman BT, Crain B, Tang MX, Phelps CH: Utility of the apolipoprotein E genotypes in the diagnosis of Alzheimer's disease: Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med 1998, 338:506–511
5. Dahlback B: New molecular insights into the genetics of thrombophilia. Resistance to activated protein C caused by Arg506 to Gln mutation in factor V as a pathogenic risk factor for venous thrombosis. Thromb Hemost 1995, 74:139–148
6. O'Sullivan MJ, McCarthy TV, Doyle CT: Familial adenomatous polyposis: from bedside to benchside. Am J Clin Pathol 1998, 109:521–526
7. Cannon-Albright LA, Skolnick MH: The genetics of familial breast cancer. Semin Oncol 1996, 23(1Suppl 2):1–5
8. Association for Molecular Pathology: Survey of molecular pathology education in pathology residency programs. (In preparation)
9. ASHG Report: Report from the ASHG Information and Education Committee: Medical School Core Curriculum in Genetics. Am J Hum Genet 1995, 56:535–537
10. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD: Molecular Biology of the Cell. New York, Garland Publishing, 1994
11. Gelehrter TD, Collins FS, Ginsburg D: Principles of Medical Genetics. Baltimore, Williams & Wilkins, 1998
12. Jorde LB, Carey JC, Bamshad MJ, White RL: Medical Genetics. St. Louis, Mosby, 1998
13. Southern ME: Detection of specific sequences among DNA fragments separated by gel electrophoresis. J Med Biol 1975, 98:503–507
14. PCR, The Polymerase Chain Reaction. Edited by KB Mullins, F Ferré, R Gibbs. Boston, Birkhäuser, 1994
15. Ben-Ezra JM: Amplification methods in the molecular diagnosis of genetic diseases. Clin Lab Med 1995, 15:795–815
16. Saiki RK, Walsh PS, Levenson CH, Erlich HA: Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. Proc Natl Acad Sci USA 1989, 86:6230–6234
17. Chee M, Yang R, Hubbell E, Berno A, Huang XC, Stern D, Winkler J, Lockhart DJ, Morris MS, Fodor SPA: Accessing genetic information with high-density arrays. Science 1996, 274:610–614
18. Rapley R, Walker MR: Molecular diagnostics. Oxford, Blackwell Scientific Publications, 1993
19. Ferreira-Gonzalez A, Garrett CT: Pitfalls in establishing a molecular diagnostic laboratory. Hum Pathol 1996, 27:437–440
20. Farkas DH, Ed.: Molecular Biology and Pathology: A Guidebook for Quality Control. Academic Press, San Diego, 1993
21. Killeen AA: Overview of current Internet resources for molecular pathology. J Clin Lab Anal 1996, 10:375–379
22. Shibata D, Martin WJ, Arnheim N: Analysis of DNA sequences in forty-year-old paraffin-embedded thin-tissue sections. a bridge between molecular biology and classical histology. Cancer Res 1988, 48:4564–4566
23. Kleiner DE, Emmert-Buck MR, Liotta LA: Necropsy as a research method in the age of molecular pathology. Lancet 1995, 346:945–948
24. Holtzman NA, Watson MS, Eds.: Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing. National Human Genome Research Institute (http://www.nhgri.nih.gov/ELSI/TFGT_final/)
25. Association for Molecular Pathology: Recommendations for in-house development and operation of molecular diagnostic tests. Am J Clin Pathol 1999, 111:449–473
26. Kiechle FL, Chambers LM, Cos RS, et al. (Eds): Patient Preparation and Specimen Handling Fascicle VIII: Reference Guide to Diagnostic Molecular Pathology and Flow Cytometry. Northfield, IL, College of American Pathologists, 1996
27. Farkas DH, Drevon AM, Kiechle FL, DiCarlo RG, Heath EM, Crisan D: Specimen stability for DNA-based diagnostic testing. Diagn Mol Pathol 1996, 5:227–235
28. Heim RA, Silverman LM (Eds): Molecular Pathology: Approaches to Diagnosing Human Disease in the Clinical Laboratory. Durham, NC, Carolina Academic Press, 1994
29. Coleman WB, Tsongalis GJ (Eds): Molecular Diagnostics for the Clinical Laboratorian. Humana Press, 1997
30. Farkas DH, Drevon AM, DiCarlo RG: Molecular Pathology: Basic Methodologies and Clinical Applications: A Self-Study Guide. Washington, DC, AACC Press, 1998