

# Molecular Diagnostics Clinical Laboratory Science Course Design: Making It Real

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The ability of a clinical laboratory scientist (CLS) to perform molecular diagnostic testing has become critical to the profession. Knowledge of methodology associated with detection of pathogens and inherited genetic disorders is imperative for the current and future CLS. CLS programs in the US teach human genetics and molecular diagnostics in various components and formats. Integrating these sometimes expensive methods into the curriculum can be challenging. This article provides a commentary with specific details associated with our experience in designing a dedicated CLS molecular diagnostics course. It offers a flexible template for incorporating a lecture and laboratory course to address theoretical and practical knowledge in this dynamic area of the laboratory.

**ABBREVIATIONS:** ACMG = American College of Medical Genetics; ASCLS = American Society for Clinical Laboratory Science; CAP = College of American Pathology; CLIA = Clinical Laboratory Improvement Amendment; CLSI (formerly NCCLS) = Clinical and Laboratory Standards Institute; CLS = clinical laboratory science; MD = molecular diagnostics; NAACLS = National Accrediting Agency for Clinical Laboratory Science; PCR = polymerase chain reaction; QA = quality assurance; QC = quality control.

**INDEX TERMS:** clinical laboratory science; education methods; molecular diagnostics; teaching techniques.

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Personnel in clinical laboratories around the world are being asked to provide rapid identification of emerging and reemerging disease-causing agents associated with both “common” disorders and bioterrorism preparedness activities. The clinical laboratory has always been an evolving environment in which personnel are constantly challenged to implement new diagnostic tests designed to provide more sensitive and specific tests for detecting and monitoring disease.<sup>1</sup> Clinical laboratory scientists (CLS) are being challenged yet again by the introduction of complex molecular diagnostic techniques that were formerly performed only in research settings. Historically, the prevention, control, and treatment of infectious diseases are improved by early and accurate identification of the causative pathogenic organism. Many detection procedures require the pathogen to be grown in culture, followed by analytical testing in differential media for proper identification. These tests, although usually effective, can be slow and costly. Further, the organisms (especially bacteria and parasites) can be fastidious or cannot be cultivated at all, leading to severe limitations in pathogen detection, and ultimately, delayed patient treatment. To overcome these

major constraints, molecular diagnostic (MD) techniques are being developed and introduced into routine laboratory practice.<sup>2</sup> For a MD approach to succeed in a clinical setting, it is critical that CLS, residents, and clinicians be well trained in performing, troubleshooting, and interpreting the assays. They must understand the limitations (e.g., false positives, false negatives, cross-reactivity, contamination issues, and inhibition of amplification) of both the technology and the results produced from MD tests.<sup>1</sup>

MD testing has shifted dramatically in the past decade from the research arena to the clinical arena. The success of the Human Genome Project, forensic applications, genetic identification of various disease-causing microbes, establishment of the Laboratory Response Network (LRN) for detection of bioterrorism agents,<sup>3</sup> and expanded public health epidemiology and surveillance activities have all contributed to the incorporation of MD into the routine practices of medical and public health laboratories at a rapid pace.<sup>4</sup> CLS programs in the US have been asked to educate the future laboratory professional with the goal of being knowledgeable in the basic principles and uses of MD technology.<sup>5</sup> An informal telephone survey in 1992 of CLS program directors<sup>6</sup> and a formal survey in 1993<sup>7</sup> indicated that only 8% to 16% of the responding programs required a genetics course as part of their curriculum or as a prerequisite. A more recent survey in 2002 of 263 CLS programs indicated that over 92% of programs teach human genetics and MD in varied formats. Briefly, this survey found that more programs teach theory than hands-on wet laboratories. Importantly, there was noted dissatisfaction in the education provided in the MD area with respect to time issues, lack of knowledgeable faculty, associated costs, and implementation.<sup>5</sup>

The following is a review of how the CLS program at Texas State University – San Marcos introduced a dedicated MD course (lecture/laboratory) in the spring of 2002. This overview focuses on the dynamic nature of the course resources that are used to teach the concepts of MD and prepare CLS students for entry level skills. Students are required to take a prerequisite genetics course prior to the CLS MD course. During the spring semester of the senior CLS academic year, the students receive dedicated MD didactic lectures and laboratory exercises to achieve active learning. MD topics are also intermittently discussed throughout the two year curriculum with specific topics (e.g., Gen Probe assays in microbiology, Factor V Leiden deficiency in hematology, viral load and genotyping for HIV in immunology, etc.). The evolution of lecture and laboratory components of this dedicated course will also be discussed.

## RESOURCES FOR MOLECULAR DIAGNOSTICS INFORMATION

With the lack of specific guidelines for molecular testing in the Clinical Laboratory Improvement Amendments (CLIA) final rule, one must turn to the recommendations of the National Accrediting Agency for Clinical Laboratory Science (NAACLS),<sup>8</sup> American College of Medical Genetics (ACMG), Clinical and Laboratory Standards Institute (CLSI) and College of American Pathology (CAP).<sup>9</sup> NAA-CLS describes the programmatic accreditation process for the institution of the diagnostic molecular scientist by providing competencies and requirements for this professional. CLIA defines many of the basic quality systems required for laboratories, but lack specific guidelines pertaining to molecular genetic testing.<sup>10</sup> These standards and practice guidelines can be applied to many areas of molecular testing regardless of the field of study. The ACMG Standards and Guidelines cover cytogenetics, biochemical genetics, and molecular genetics.<sup>11</sup> In addition, the ACMG has developed disease-specific guidelines to address specific technical problems frequently seen in complex assays. Together, these guidelines cover general laboratory practices, assay validation, and method-specific and disease-specific technical issues.

The Clinical and Laboratory Standards Institute (CLSI), formerly known as National Committee on Clinical Laboratory Standards (NCCLS), used field-specific experts to develop a number of guidelines for molecular diagnostics, including molecular genetic testing,<sup>12</sup> molecular hematopathology,<sup>13</sup> DNA sequencing,<sup>14</sup> diagnostic microarrays,<sup>15</sup> and proficiency testing.<sup>16</sup> The College of American Pathologists (CAP) is the main accrediting organization for molecular laboratories. The inspection checklists for General Laboratory and Molecular Pathology are good references for the type of quality systems and procedures that should be operating in a molecular laboratory.<sup>17</sup> These documents provide expert opinions on standard practices in a molecular laboratory. They offer guidance on specific techniques and appropriate controls. Furthermore, molecular testing is becoming more complex as an increasing number of analytes are now being measured on microarray platforms. In addition to the CLSI guidelines for microarrays, the ACMG is working on guidelines for genomic microarrays. These guidelines will continue to be developed and updated as more applications of microarrays move into clinical practice. Importantly, the position of ASCLS is that “the profession (of a CLS) includes generalists as well as individuals qualified in a number of specialized areas of expertise” including MD.<sup>18</sup>

## IMPLEMENTATION OF MD IN THE CLS CURRICULUM

### Didactic lectures

While some have integrated MD topics and laboratories in different CLS courses throughout the curriculum, a dedicated MD lecture/laboratory course was introduced at Texas State University in 2002. The faculty at Texas State University takes advantage of the opportunity to present appropriate MD clinical applications in other courses (e.g., viral load and genotyping for HIV in immunology); however, an *immersion* in a dedicated course is critical to allow for deeper learning and understanding of the content. A variety of textbooks has been utilized for this course and is listed in Table 1. Regardless of the textbook, the topics selected in the lecture have remained fairly stable and are listed in Table 2.

**Table 1.** Textbook resources for MD course

1. Buckingham L, Flaws ML, editors. Molecular diagnostics: fundamentals, methods, & clinical applications. Philadelphia: FA Davis ; 2007.
2. Coleman WB, Tsongalis GJ, editors. Molecular diagnostics for the clinical laboratorian, 2<sup>nd</sup> edition. Totowa NJ: Humana Press; 2006.
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8. Farkas DH. DNA from A to Z, 3<sup>rd</sup> edition. Washington DC: AACC Press; 2004.
9. Bruns DE, Lo YMD, Wittwer CT, editors. Molecular testing in laboratory medicine. Washington DC: AACC Press; 2002.

The course begins with a review of molecular biology “basics” (central dogma) surrounding DNA, RNA, and proteins. The lecture topics follow with extraction/isolation techniques, amplification techniques such as polymerase chain reaction (PCR), and mutation events. The latter topics introduce post-analytic techniques (e.g., sequencing) and detection (inherited disorders, infectious disease, oncology), and conclude with quality assurance and control (QC/QA) in MD. The lectures are supplemented with case studies associated with MD data sets (gel images, dendograms) and problem sets requiring student calculations (concentration, purity, primer design). Students are evaluated on the material based on their answers to problem sets, case studies, and several unit exams.

A special assignment for course credit involves student groups conducting a literature review of a MD technology as it applies to a “real world” CLS case. This assignment coincides with our College of Health Profession Faculty – Student Research Forum. Students are required to submit an abstract detailing their topics with a final poster presentation

**Table 2.** Topics for molecular diagnostic (MD) lectures

### Unit number and topics

1. DNA: An Overview
2. RNA & Proteins: An Overview
3. Nucleic Acid Extraction Methods
4. Resolution, Detection, & Analysis
5. MD Amplification
  - PCR
  - qPCR
  - Reverse-transcriptase PCR
6. Chromosomal Structure & Mutations
7. Gene Mutations
8. DNA Sequencing
9. DNA Polymorphisms & Human Identity
10. Detection & Identity of Microbes
11. Detection of Inherited Diseases
12. Molecular Oncology
13. QA & QC
  - Agency oversight
  - Regulations
  - FDA approved testing

(in class and at the research forum) of their findings. For example, a recent topic chosen from the literature, “Real-time PCR for *Chlamydia pneumoniae* Utilizing the Roche Lightcycler and a 16s rRNA Gene Target”, was awarded the 2008 Outstanding Student Educational Poster. The student groups are evaluated on content, meeting guidelines/deadlines, presentation, and professionalism.

The major limitation of the lecture format is that students are at different stages of understanding basic genetic concepts. Due to this concern, the Texas State University CLS program now includes a prerequisite genetics course. However, students still can be at different “levels” of understanding due to the prerequisite being satisfied at different institutions and by different instructors. For example, some instructors focus on classic genetics with brief topics on current clinical applications while other courses are lecture-based only without offering the student any laboratory experience. Another limitation is in the area of calculations associated with MD. Some students struggle with calculations due to differences in their backgrounds and cognitive skills in math and statistics. This is especially noticeable with students who have not taken these types of courses recently. Texas State University, like others, has also seen this issue with our clinical research course that requires method validation and correlation cognitive skills.<sup>19</sup> To help the students master the material with respect to these issues, the instructor (and other CLS faculty) will meet with students independently or in small groups to review or practice these topics.

### Laboratory component

The laboratory component of the MD course is taught concurrently with the didactic component. Concurrent lecture and laboratory sessions allow the student to be involved in the actual generation of data using clinically relevant MD tools and techniques. Senior students are also beginning their clinical rotations in various community laboratories during this semester which permits possible observation and experience with MD equipment and methods in the hospital and reference laboratory setting. Finally, the concurrent MD laboratory helps reduce the problem of lecture topics becoming abstract or distant before the student has an opportunity to “practice” what’s being covered in the didactic lecture.

During the initiation of the course, the laboratory component was a mixture of online “virtual” experiences from a variety of websites (e.g., DNA from the Beginning

at <http://www.dnaftb.org/dnaftb/>, Cold Spring Harbor Laboratory Dolan DNA Learning Center at <http://www.dnalc.org/ddnalc/about/>) or training CDs from the Roche Education Program (e.g., Genetics, Hepatitis C, MRSA/VRE, Regulatory and Molecular Technology). These virtual laboratory experiences were followed by selected molecular kits (available from a variety of suppliers) covering areas such as (1) isolating the student’s DNA from cheek cells with PCR of particular genes, (2) mock crime scene investigation with PCR and restriction fragment analysis, and (3) PCR of known controls. Each of these modules incorporated the use of typical extraction kits, PCR thermocyclers, and post PCR work via gel electrophoresis and analysis of products.

In 2008 we collaborated with a local biotechnology company (Embark Scientific, Austin TX) to incorporate a “beginning to ending” real world application of clinical MD in our laboratory component. The specific exercise was planned to integrate the application over the entire semester between student clinical rotations. The assay design process was discussed broadly with the students with respect to *mecA* and *femA* genes in Methicillin-resistant *Staphylococcus aureus* (MRSA) and for the *iroB* gene in *Salmonella enterica*. The *iroB* gene was chosen for the laboratory exercise because it has been extensively documented in the literature. Sequence data for the *iroB* gene was obtained at the National Center for Biotechnology (NCBI) website (<http://www.ncbi.nlm.nih.gov/>) and publication<sup>21</sup> for utilization of specific primers and for student exercises in primer design techniques.

Each student was provided an overnight culture of *Salmonella enterica* (Central Texas Medical Center, San Marcos TX) for total DNA isolation/purification using the DNeasy Blood and Tissue kit (Qiagen Inc., Valencia CA). PCR design and troubleshooting was reviewed and each student performed PCR amplification of *iroB* utilizing primer *iroB* F1: TGGACTGCTATAACCCTGTGC and primer *iroB* R1: GCAGTATGCTCATGCTGGGC which yields a 493bp PCR fragment. Primers (Integrated DNA Technologies, Inc., Coralville IA) were resuspended at 100µM. The DNA template (3µL) was added to a PCR mixture (Promega, Madison WI) with a total volume of 50µL and a final MgCl<sub>2</sub> concentration of 2mM. PCR cycling was performed as recommended by Embark Scientific. PCR products and DNA markers (Amresco Inc., Solon OH) were separated by agarose gel electrophoresis (Amresco Inc., Solon OH) to confirm correct *iroB* gene size (493bp) with photodocumentation (Figure 1).

PCR products were treated with ExoSAP-IT (USB Corporation, Cleveland OH) to provide clean template for DNA sequencing. Sequencing reactions were prepared by adding 5.0µL of each sample or positive control (pUC19), 2.0uL sequencing primers (1.6uM), 8.0uL DTCS Quick Start Master Mix and ddH2O for a total volume of 20µL (Beckman Coulter, Inc., Fullerton CA). Sequencing reaction amplification was performed with 30 cycles of one minute at 94°C, 20 seconds at 96°C, 20 seconds at 50°C and four minutes at 60°C. Sequencing reaction cleanup by ETOH precipitation was performed on final products.

DNA sequencing was performed using a capillary array instrument (Beckman Coulter Genomic Analyzer acquired by R Rohde via an Education/Research Grant from Beckman Coulter and matching grant from Texas State University). Students were instructed on how to create databases and project folders to manage the sequencing data and to enter necessary sample information into the instrument software program. Instrument startup and shut down procedures were performed including: installing, removing or replacing Capillary Arrays, installing Gel Cartridges, priming the system (Manifold Purge, Gel Capillary Fill and Optical Alignment), installing gel waste bottle, preparing plates for run, loading Wetting Tray, Sample Plate and Buffer Plate and system cleanup. Students exported sequencing data of their samples (Figure 2) and analyzed it utilizing typical sequencing analysis software.

This laboratory component is critical to the students' understanding of mathematical operations (calculating DNA concentrations, PCR master mix) and interpretation of data (troubleshooting gels, controls). Students are evaluated on technique by the instructor (pipetting, gel loading, maintenance of equipment, QA/QC) during the entire semester and are given a concluding final exam. The final exam includes theory of basic concepts and synthesis/critical problem solving of data interpretation (Table 3).

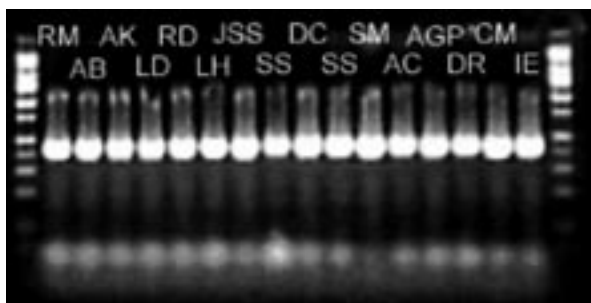
**Clinical practicum**

Due to the limitation of MD applications in the clinical laboratories in our geographic location, the students may spend time only in some laboratories doing MD assays and QC/QA of equipment associated with molecular techniques.

**Table 3.** Topics for molecular diagnostic (MD) laboratory

1. Assay Design: An Overview
  - Define/obtain target sequence
  - Primer design
2. DNA Isolation/Purification Methods
3. PCR Method: An Overview
  - Assay design
  - Reaction component interactions
  - Troubleshooting
  - PCR amplification
4. PCR Analysis
  - Agarose gel electrophoresis
  - Photodocumentation
5. PCR Cleanup Method
6. DNA Sequencing: An Overview
  - DNA sequencing reaction setup & amplification
  - DNA sequencing reaction cleanup procedure
  - Instrument setup & reaction run procedures
  - Instrument startup & shut down procedures
  - Data Management
7. DNA Sequence Analysis
  - Review analyzed data
  - Export data
  - Data analysis

**Figure 1.** Agarose gel of student PCR *iroB* gene amplicons (493bp)



DNA markers are shown on the far left and right lane and student samples (capital letters depict student samples) are between the DNA markers.

The clinical practicum is an area that we feel can be nurtured and grown with our area affiliate laboratories as they incorporate MD into their testing menus. It is important to mention that hospitals, upon finding out about our dedicated MD course, actively recruit our students to “help set up” that type of testing as future employees.

**SUMMARY**

Molecular diagnostics is the fastest growing area of clinical medicine. Current CLS students and working CLS professionals need to be proficient in this area of the laboratory. MD often allows for faster turnaround times with increased sensitivity and specificity. However, this testing must be integrated with strict QC/QA with respect to the types of controls, standards, and limits.<sup>16</sup>

By including a dedicated MD course in the CLS curriculum, we are preparing our students with the knowledge and background they need to be competent in applying this skill set in the workforce. The course has strengthened our students’ “job attractiveness” in clinical, reference, research, and public health laboratories. The future of CLS students in MD has arrived and they need the strong background in this exploding diagnostic area of the medical world to effectively and accurately perform the growing number of FDA approved clinical testing platforms (e.g., cystic fibrosis, Factor V, and non-culturable microbes). Having a course in MD and gaining work experience in molecular techniques post-CLS degree also allows CLS professionals who meet the proper requirements to obtain certification from a variety of organizations, for example technologist in molecular pathology (MP) from ASCP.<sup>20</sup>

It is important to mention the challenges associated with the endeavor of pursuing this type of course in the CLS

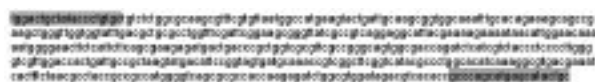
curriculum. The major obstacles that we encountered were (1) dedicated space (clean area outside of typical routine CLS teaching laboratories), (2) faculty expertise, (3) time of placement within CLS curriculum, (4) student preparation for course rigor (prerequisites), (5) reagent and equipment cost, and (6) a MD clinical experience for the student.

These obstacles were addressed in a variety of ways. As we acquired funding and gained recognition within our College of Health Professions and university about the importance of this course, additional dedicated laboratory space was provided to support this course and the research expertise of the faculty member. Faculty expertise was met in the initial year (2002) of the course implementation by employing a new faculty member with MD skills. Subsequently, the faculty member augmented the laboratory component of the course by collaborating with a local biotechnology company (Embark Scientific) to assist in the course development from a real world perspective. The placement of the MD course in the curriculum and student preparation will be different for each CLS program. In our experience, the course was best placed in the senior year so that students would have the opportunity to finish prerequisites and build their skills in critical areas (pipetting, calculations, etc.). The financial costs associated with the course can be problematic. However, a program can reduce this issue by using home-brew assays, utilizing molecular equipment that is available in other departments on their respective campus (or laboratories with clinical affiliations), and using expired or donated kits from companies. Acquiring a MD clinical practicum or rotation for students is an ongoing challenge for our program. However, by reaching out to local biotechnology companies, research laboratories, and hospitals, we are finding more possible sites to place students for experience in molecular techniques.

A dedicated course in MD provides CLS programs with the unique opportunity to become flexible in the face of a growing clinical need. While molecular biology theory and general laboratory work is taught in a variety of university and college departments (biology, biochemistry, forensics), CLS programs can become *the* leader in preparing clinically competent CLS professionals by providing them with training in MD.

*Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to brodak@iupui.edu. In the subject line, please type “CLIN*

**Figure 2.** A sample student *iroB* gene sequence identified by capillary electrophoresis on the Beckman Coulter Genomics Analyzer



The shaded areas indicate the forward primer and reverse primer areas.

*LAB SCI 22(1) CP ROHDE*". Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

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