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Final Technical Report (DE-FG02-95ER62048)

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Overview: The Sarah Lawrence College Human Genetics Program received Department of Energy funding to offer a continuing medical education workshop for genetic counselors in the New York metropolitan area. According to statistics from the National Society of Genetic Counselors, there are approximately 160 genetic counselors working in the tri-state area (New York, New Jersey, and Connecticut), and many of them had been working in the field for more than 10 years. Thus, there was a real need to offer these counselors an in-depth opportunity to learn the specifics of the major advances in molecular genetics, and, in particular, the new approaches to diagnostic testing for genetic disease.

As a result of the DOE Award DE-FG02-95ER62048 ($20,583), in July 1995 we offered the "Workshop on Molecular Methods for Genetic Diagnosis" for 24 genetic counselors in the New York metropolitan area. The workshop included an initial review session on the basics of molecular biology, lectures and discussions on past and current topics in molecular genetics and diagnostic procedures, and, importantly, daily laboratory exercises. Each counselor gained not only background, but also firsthand experience, in the major techniques of biochemical and molecular methods for diagnosing genetic diseases as well as in mathematical and computational techniques involved in human genetics analyses. Our goal in offering this workshop was not to make genetic counselors experts in these laboratory diagnostic techniques, but to acquaint them, by hands-on experience, about some of the techniques currently in use. We also wanted to provide them a technical foundation upon which they can understand and appreciate new technical developments arising in the near future.

Our experience with this workshop, which we classified as a great success (see **Outcomes from the 1995 Workshop**, below), accomplished several goals. First, we were able to provide some basic training for these counselors so that they may better understand the ever-evolving technology and thus will be better able to provide their clients with clearer, more accurate explanations of genetic testing methods. Second, the workshop provided an impetus to again request funding to run a similar workshop in the summers of 1996 and 1997. Third, experience with this Workshop has helped us build a model on which we can tailor future workshops that can cover a wider range of topics.

Attachment A presents the Workshop schedule. In order to assure participants full commitment to the workshop, an opening session informed counselors of the goals of the workshop and emphasized the tutorial nature of the sessions. Two classes, led by the PI, reviewed aspects of molecular biology, gene structure, nature of mutations, and recombinant DNA techniques. The first afternoon's laboratory, also led by the PI, included time to become reacquainted with basic laboratory techniques, and then went on to include PCR amplification of DNA from patients with sickle-cell anemia mutations. This particular laboratory introduced participants to basic diagnostic techniques, such as PCR, and set the stage for Day-3's laboratory of restriction-enzyme digestion and gel electrophoresis. At the end of each day, a one-half-hour group discussion was scheduled so that the day's information and technical content can be

reviewed and discussed. Workshop participants were encouraged to share areas of uncertainty during these sessions.

The theme of Day 2 was genetic markers and the use of molecular, statistical, and computer techniques for ascertaining linkage. The PI presented the first class of the day on the nature of molecularly determined genetic polymorphisms. This class was followed by a class, led by Dr. Susan Hodge (Columbia) on methods for determining linkage. These classes were reinforced by a laboratory session, in the morning of Day 3, in which participants utilized raw data to work on problems of linkage. These problems were supplemented with an exercise led by Dr. Allen Bale (Yale) in which participants worked with appropriate computer-analysis techniques to experience what goes into a linkage determination.

In the laboratory in the afternoon of Day 2, led by Dr. Sally Nolin (Institute for Basic Research, Staten Island), each participant extracted her own DNA from buccal scrapes. This exercise was supplemented by another PCR analysis, in which the Fragile-X gene was amplified from the participants' own DNAs. In addition, Dr. Nolin provided DNAs from fragile-X patients and carriers so that the participants gained experience in the amplification and analysis of expanding-repeat abnormalities.

The laboratory in the afternoon of Day 3, led by both the PI and Dr. Nolin, demonstrated how to analyze PCR products. The amplified globin genes from Day 1's lab were digested with appropriate restriction enzymes and run on agarose gels along with the PCR products from Day 2's lab. The group discussion ending Day 3 included a discussion of all of the diagnostic PCR results.

Day 4 explored both the revolution in techniques of gene identification as well as new developments in the marriage between molecular biology and cytogenetics. In the first class of the morning, Dr. Steve Somlo (Einstein) presented strategies and techniques of gene identification (e.g., by positional cloning) in the overall context of the Human Genome Program. Dr. Dorothy Warburton (Columbia), a noted cytogeneticist, then described some of the newest fluorescence *in situ* hybridization (FISH) techniques and their application to diagnostic cytogenetics. Dr. Warburton then directed a laboratory, on Day 4 afternoon and Day-5 morning, that enabled students to try out themselves both interphase and metaphase FISH techniques.

The final afternoon of the workshop was run by Dr. Harry Ostrer (NYU), who tied everything together by presenting two sessions on DNA testing strategies and new developments. This final afternoon presented a broad opportunity for the workshop participants to integrate some of what they have done or heard about during the week as well as bring up their own questions and comments. We hoped that it would also provide a means for them to relate some of the more basic techniques that they have just done in the laboratory during the week with technical advances foreseen for the future. Following this afternoon session, the participants were asked to fill out workshop evaluations.

Outcomes from the 1995 Workshop: We were very fortunate the first time this workshop was given to anticipate correctly the needs of the participants. All but one of the participants had no direct experience with any of the techniques used in the workshop laboratories, and most had not had any formal training in the basics of modern molecular biology and recombinant DNA technology. Immediately below, we list several of the major points made by workshop evaluations that have a direct impact on our thinking for planning future workshops of this type:

1. The molecular biology, recombinant-DNA, and genetic markers reviews were extremely useful and helped set the stage for the rest of the workshop. Likewise, the refresher lecture and lab on linkage (incorporating molecular markers) were clear, well done, enjoyable, and very useful.

Decision: Keep these sessions without change.

2. The sickle-cell anemia and Fragile-X PCR laboratories introduced most participants to the use of present-day molecular-biology-lab equipment and some of the basic strategies of molecular diagnosis. Everyone found these labs informative, useful, and fun. However, the labs were a bit hectic and ran overtime.

Decision: Keep these sessions, but spread out the gel running and data analysis sections of the two labs into separate days (partly at the expense of the "wet" FISH lab; see below).

3. The "dry" lab for molecular cytogenetics was extremely useful in helping counselors re-familiarize themselves with FISH/cytogenetics diagnoses. However, the "wet" lab, in which participants actually did a FISH hybridization, was not that well received because so much of the lab had to be done beforehand for the participants, they didn't get much out of it.

Decision: Delete the FISH "wet" lab, but keep the dry lab. In place of the "wet" lab, give extra time to the computer lab and to the analysis of data from the Fragile-X lab.

4. The computer software lab was extremely popular (in fact, this lab introduced some counselors to computers for the first time).

Decision: Double the time for the computer lab so that participants can fully explore the uses and applications of the Cyrillic software.

5. The lecture on positional cloning and the Human Genome program was too technical for counselors' needs.

Decision: Reformat this lecture to address general strategies and concepts in disease-gene discovery and the Human Genome program, with particular emphasis on showing counselors how they might explain such ideas to their clients if necessary.

6. The final afternoon session on "DNA Testing: Strategies and New Developments" was too long and repetitious in some places.

Decision: Condense this presentation into one lecture instead of two. This gives more time for a general wrap-up and the course evaluations.

Below we outline a more complete summary of the responses of participants to both the evaluation questionnaire filled out at the end of the workshop and the questionnaire sent to participants six months after completion of the workshop. The twenty-four participants were from the following institutions:

New York University Hospital
IVF America
Columbia Presbyterian Hospital
Norwalk Hospital (CT)
New York Hospital-Cornell University
New Jersey Medical School
Albert Einstein College of Medicine
Hospital for Joint Diseases
New York Medical College-Metropolitan Hospital
St. Lukes/Roosevelt Hospital
Strang Cancer Prevention Center
Hackensack Medical Center
Harlem Hospital
North Shore University Hospital
Jersey Shore Medical Center (NJ)
Montefiore Medical Center

We gave the participants of the workshop an evaluation form on the last day of the workshop.

Question #1 asked if they regarded the workshop as a useful experience. Twenty-three responded "yes", and one said "somewhat". The following quotes are representative responses:

"An excellent review and summary of developments in genetics that have occurred since I left school. Also, a good hands-on experience of what is involved in lab work that is done for our patients."

"The workshop provided me with an excellent review of molecular biology and the new technology used in DNA molecular research. It will be helpful in understanding journal articles, interpreting laboratory reports, and questioning the quality of different laboratories. Most importantly, it enables better communication of information for patients, other health professionals."

"Having graduated 15 years ago, these techniques were not available. Hearing the ins and outs of these new techniques is not only interesting, it is vital to any future understanding to have these basics in place. It will also be useful for counseling patients if I understand the nuances of these techniques. I would strongly recommend this workshop to a great many of my colleagues. Is it possible to consider CME credits?"

Question #2 asked participants to evaluate each lecture and laboratory, including presenter, content, organization, etc. Their responses have provided us with useful information with which to base modifications of future workshops (see **Outcomes from the 1995 Workshop**, above).

Questions #3: Did the workshop give you information that will help you in your direct patient service? Question #4: Do you feel that this workshop will help you better provide both general and technical information to physicians and other health professionals? Question #5: Did the workshop help you in the understanding of new diagnostic procedures?

Twenty-two participants answered "YES" to all these questions.

Question #6 asked participants to identify strengths of the workshop. The responses varied widely, but were consistently full of praise for the excellence of the presenters, the organization, and the fulfillment of the stated goals of the workshop. Some of these comments will be used in the planning of future workshops of this type (see **Outcomes from the 1995 Workshop**, above).

Question #7, on the weaknesses of the workshop, did identify a few minor ones: FISH wet lab not all that useful, Positional cloning lecture too technical. These concerns did help in our making minor modifications to this year's program (again, see **Outcomes from the 1995 Workshop**, above). Some of the negatives raised issues of time constraints--e.g., a week away from the office, more telephone facilities are needed, too much food, etc.

Approximately six months following the workshop, these participants were mailed another evaluation questionnaire. Ten participants have responded. For Question #1's query of how useful the workshop was now that they are a bit away from it in time, on a scale of 1-5, six have rated the workshop as a 5 (extremely useful); three persons gave a rating of 4; and one gave a rating of 3 (useful). No one rated the workshop as "not useful."

Some representative comments:

"The workshop provided me with the most current information about molecular methods being used for the Human Genome Program and disease analysis. This and the seminar on linkage analysis and lod scores have also enhanced my ability to interpret and understand journal articles better."

"Helped me to visualize in a concrete way just what it was that I was explaining to patients."

"I feel more comfortable with the concepts and terminology. Lab reports and journal articles are more accessible."

"The course provided the background educational material in molecular genetics which I felt I was lacking."

"Made abstractions and theoretical concepts concrete; helps in reading current journals. I considered that week a highlight of my 20+ years in this field." [PI's note: We are all particularly happy about this comment, and DOE ELSI should be too!]

Question #2, which asked if the material on new diagnostic procedures affected their practice revealed that the workshop influenced them **somewhat**, and most responded that they "can discuss the testing with greater confidence by deepening my understanding of 'how it works'."

Question #3, which asked if the participants got a better feel for the technical aspects and limitations of diagnostics tests, was answered "YES" by nine people and "NO" by only one.

Question #4, which asked whether participants were providing and explaining lab results differently with patients than they did before the training, was answered positively by most. The hesitancy on the part of a few people is summarized well by this particular participant: "Can't get too technical with patients, but [the training] probably makes what I say more comprehensible."

Question #5 asked if participants are now selecting labs differently after taking the workshop. Most responses were no, but a few gave a positive response. [This has made us question whether this is a valid workshop-evaluation question as stated because many genetic counselors do not have the option of selecting the labs that do the testing.]

Question #6 asked whether the workshop affected what the participant did with, and how they approached, primary-care physicians and other health-care professionals in their respective settings. Most participants answered "YES", and several comments were similar: "I clearly know more than they do; and can help guide them in decision-making."

Question #7 asked participants if they could identify additional topics about which they would like to have additional information. A few people gave substantial lists, including:

Levels of mosaicism and the lab controversy about interpretation
Complete genomic hybridization (as related to FISH)
Any new developments in gene sequencing
Other molecular techniques
Cancer genetics--techniques in lab
Cancer counseling and ethical issues
More lod scores
Practical application relating genetic counseling to the lab tests and techniques; explaining errors/ambiguity in tests.

We shall consider incorporating some of these topics into future workshops (especially genomic hybridization, new DNA sequencing developments, and more time spent in lab discussing testing errors and ambiguity). Some of these other areas (particularly ones dealing with cancer) could serve as issue-nucleation points in their own right for other smaller workshops (perhaps with not as large a lab component).

Question #8 asked if the workshop affected their participation in national genetics meetings. Half responded "YES", and half responded "NO". A representative comment: "The workshop helped me in understanding molecular techniques and its language better. As a result, I have a better understanding of presentations."

Significance of this Workshop: We are well aware of the daunting task of the Department of Energy's ELSI program in contributing to the bridging of the gap between the scientific/technical aspects of the Human Genome Project and educating the general public about the importance, relevance, and applicability of breakthroughs in genome research. In addition to the primary task of educating new genetic counselors in the Sarah Lawrence College's Human Genetics Master's program, we feel that offering a way, such as this Workshop, in which working counselors can be brought up to date in current techniques, strategies, and practices is an additional, powerful method of translating the technical promises and benefits of the Human Genome Program directly to the public.

The genetic counselors for whom this workshop was designed provide genetic services in over forty medical centers in the New York--New Jersey--Connecticut area. Their catchment areas, therefore, encompass millions of patients who need and deserve the most up-to-date medical genetic expertise available. Comprehensive genetic counseling incorporates not only the provision of risk figures for individual patients, but also an in-depth explanation of how a genetic diagnosis is achieved. Translating genetic technology for the consumer often involves sharing the concept of the testing capability, as well as its technical limitations. Only exposure to genetic testing itself can prepare genetic counselors to translate this information directly to consumers. A major tenet of genetic counseling is that patients must be given the tools to exercise informed consent. The lack of science sophistication prevalent in today's population makes truly informed consent an extremely challenging goal. Only through true comprehension of the diagnostic procedures themselves can a genetic counselor provide patients with the tools to understand their at-risk status. This understanding will enable patients to make personal choices based on their own values and cultural perspectives.

In addition to patient care, many genetic counselors are also engaged in the training of primary-care physicians and allied health professionals, and workshops of this type will probably be one of several mechanisms for providing them with the opportunity to obtain the latest available information in medical genetics. The majority of genetic counselors affiliated with clinical genetics centers also participate on a fairly regular basis with community education projects. These responsibilities include lectures to lay groups, teaching classes at the high-school level, and offering in-service training to public health nurses, nurse midwives, and occasionally the clergy. Thus, taking all of these factors into consideration, we envision that continuing education workshops, such as the one described here, can provide an important way of disseminating directly to the public the promises of the immediate future of Human Genetics.

As stated in the beginning of this report, the DOE's funding of this initial workshop allowed us to explore ways in which both lecture- and laboratory-based exercises can be used to provide continuing medical education for genetic counselors. This groundbreaking (for us) workshop provides us with the means for examining issues of content and logistics for the planning for similar workshops over the next ten years. As the Human Genome project continues to evolve, smoothly running, tried and tested workshops such as these can be an important part in the continuing education of these important health professionals.

Attachment A

WORKSHOP ON MOLECULAR METHODS IN GENETIC DIAGNOSIS

DAY I

9:00 - 9:30	WELCOME INTRODUCTION PROGRAM EXPLANATION	
9:30 - 10:45	Lecture	Molecular Biology Review Dr. Gene Rinchik
10:45 - 11:00	BREAK	
11:00 - 12:30	Lecture	Recombinant DNA Techniques Dr. Gene Rinchik
12:30 - 1:30	LUNCH	
1:30 - 4:30	Laboratory	Polymerase chain reaction Dr. Gene Rinchik
4:30 - 5:00	Recap	Group Discussion

DAY 2

9:00 - 10:30	Lecture	Genetic markers (RFLPs, microsatellites, VNTR, probes) Dr. Gene Rinchik
10:30 - 10:45	BREAK	
10:45 - 12:30	Lecture	Linkage Analysis; Dr. Susan Hodge
12:30 -1:30	LUNCH	
1:30 - 4:30	Laboratory	Preparation of Genomic DNA Fragile-X PCR Dr. Sally Nolin
4:30 - 5:00	Recap	Group Discussion

DAY 3

Split into two groups for each of the following morning laboratories

9:00 - 10:45	**Laboratory Group A**	**Linkage Problems Dr. Susan Hodge**
	Laboratory Group B	**Computer Programs for Linkage Dr. Allen Bale**
10:45 - 11:00	**BREAK**	
11:00 - 12:30	**Laboratory Group B**	**Linkage Problems Dr. Susan Hodge**
	Laboratory Group A	**Computer Programs for Linkage Dr. Allen Bale**
12:30 -1:30	**LUNCH**	
1:30 - 4:30	**Laboratory**	**Analysis of PCR products Restriction-enzyme digestion Gel Electrophoresis Dr. Gene Rinchik Dr. Sally Nolin**
4:30 - 5:00	**Recap**	**Group discussion**

DAY 4

9:00 - 10:45	**Lecture**	**Gene Identification, Positional cloning, Human Genome Program** **Dr. Stefan Somlo**
10:45 - 11:00	**BREAK**	
11:00 - 12:30	**Lecture**	**Molecular cytogenetics** **Dr. Dorothy Warburton**
12:30 - 1:30	**LUNCH**	
1:30 - 4:30	**Laboratory**	**Fluorescence *in situ* Hybridization** **Dr. Dorothy Warburton**
4:30 - 5:00	**Recap**	**Group Discussion**

DAY 5

9:00 - 12:30	**Laboratory**	**Fluorescence *in situ* Hybridization** **Dr. Dorothy Warburton**
12:30 - 1:30	**LUNCH**	
1:30 - 3:00	**Lecture**	**DNA Testing: Strategies and New Developments I** **Dr. Harry Ostrer**
3:00 - 3:15	**BREAK**	
3:15 - 4:30	**Lecture**	**DNA Testing: Strategies and New Developments II** **Dr. Harry Ostrer**
4:30 - 5:00	**EVALUATION**	