Cytogenetic Laboratory Management
Chromosomal, FISH and Microarray-Based Best Practices and Procedures

Susan Mahler Zneimer

WILEY Blackwell
CYTOGENETIC LABORATORY MANAGEMENT
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I dedicate this book to my daughters, Mira and Alana, who since they were born have changed my life forever and for the better. They have given me strength, inspired me to do great things, and have given me abounding love. I hope I have done the same for them.

Mira and Alana, I wish you both a life of good health, happiness, and profound significance. And may you strive for Tikkun Olam.

And to my dear friend and colleague, Lauren Jenkins, whom I have known for most of my life. Your time on this earth was much too short. I miss you with all my heart.

Lauren died on Rosh Hashanah 5776 (September 14, 2015).
For the last 25 years, I have been the director of different cytogenetic laboratories. Like most directors, I started out in academia for my American Board of Medical Genetics fellowship, but then moved on to various commercial laboratories for the next 20 years, and now currently to consulting for different genetic laboratories, both commercial and academic. After all these years, I realize that my daily work consists of two main tasks, signing out cytogenetic cases and managing the clinical laboratory. I wrote my first book, *Cytogenetic Abnormalities, Chromosomal, FISH and Microarray-Based Clinical Reporting*, published by Wiley Publishers in 2014, to reflect all the information that I have learned in signing out cases throughout my career. In this book I want to focus on the other aspects of my laboratory duties, namely, laboratory management. Managing or directing a lab requires vastly different skills than what we learn as scientists who need to perform, review, and interpret cytogenetic laboratory results. As scientists, we generally receive little training in the field of management, let alone laboratory management. As geneticists, we rely on our scientific knowledge base and experience in genetic procedures to perform and sign out test results. We acquire those skills after years of working in the laboratory in graduate school and postdoctoral programs.

However, laboratory management uses other skills that we usually learn “on the job.” We learn that to be a good director or manager, we need to be good at interpersonal relations, organization, and time management. We learn to be supportive of the laboratory staff yet be good disciplinarians when performance is not acceptable. We learn to be innovative and strive to be as productive as possible. We learn to be conscious of interpreting patient results and performing genetic analyses with complete accuracy, yet to also be aware of the “bottom line” in order to be within a specific budget. It is a balancing act that we must perform daily and get right every time. Genetic results require 100% accuracy in diagnostic testing as well as being business savvy to be always within a budget; otherwise, our jobs may be in jeopardy.

For these reasons, I decided to write this book on laboratory management. I know what most lab directors and managers face with regards to “running a lab.” So I want to share as
much as possible to make life easier for those just starting out, as well as for labs that can use ways to improve their laboratory processes to meet the demands of patient care and their institution’s requirements.

One of the most important things I have learned in management skills (from my father actually) is that as a director or manager of a laboratory or department, one does not manage people; instead, one manages a laboratory or department, and one guides or leads people. There are many different management styles for leaders or leadership. My style is to engage the staff in the processes and procedures of the laboratory and to provide the tools necessary to empower the staff to do their work correctly and efficiently and as independently as possible. I am often the most vocal cheerleader in the laboratory, supporting the staff as best I can in order to give them the assistance and encouragement they need to do their work well and simultaneously enjoy it. Happy employees are generally the most productive employees. By keeping good employees happy in their job, they also tend to have a greater sense of loyalty to their leaders and will support decisions made by the managers. Throughout the years, I have enjoyed great relationships with my present and past employees and companies by keeping a positive demeanor in the laboratory and knowing that I am part of the laboratory team, not above it.

After all these years, I am also aware of some of the possible mistakes that can be made. There is no room for sentimentality as a lab director or manager. Being too hard a leader can cause resentment or shutting down communication between staff and leader of the lab. However, being too soft a leader can be as difficult as being too hard on staff. Staff will certainly take advantage of a leader who is too sympathetic when given the chance. I also know that stress on the job often comes, not necessarily from the daily operations of the laboratory, but often from the demands placed on the directors from those who are higher in the organization hierarchy. It is so easy to feel that as the director of a genetics laboratory, we know best how to run the department, and no one knows better than we do about the testing we perform. However, that often creates conflict with those who place demands on us that differ from our own beliefs in how to direct the laboratory. So how do we resolve these conflicts? That is exactly what I have been analyzing during my years as a laboratory director.

I do know that being too vested in the decisions of the laboratory can be as detrimental as being too aloof when handling conflicting objectives, that is, what is imposed on us versus what we believe. Being so sure of oneself and one’s decisions can lead to arrogance and stubbornness, which often are not in the best interests of the laboratory, its processes, and staff. So this is truly a balancing act that either leaves one feeling elated when it works well or too stressed or “burned-out” when it does not.

In this book, I am providing information on various topics in laboratory management for those of us who are continually trying to improve ourselves and our laboratories. This book has gray and boxed sections for CAP guidelines, and condensed ACMG guidelines, and other boxes for lists of information for easier reading.

The first section of the book focuses on best practices for laboratory operations, which contains chapters on quality and safety processes that are common in cytogenetic labs; reagent lists and an SOP on reagent verification for clinical use; quality control, quality assurance, and quality improvement SOP’s that are needed for College of American Pathologists (CAP) and Clinical Laboratory Improvement Act (CLIA) regulatory agencies; and ways to perform both internal and external proficiency tests, such as for CAP. This section also includes ways to prepare for a CAP inspection, to “pass with
flying colors,” by giving tools on how to make an inspection go smoothly and provide the necessary information to inspectors. This section also discusses calibration verification and how it is used in a cytogenetics laboratory, especially on how it pertains to deriving FISH cutoffs for DNA probes and how to keep up to date with this process, since it is a CAP requirement.

More relevant information to laboratories regarding other aspects of laboratory management, including designing laboratory developed tests (LDTs), FDA guidelines for LDTs, and preclinical validation studies, is also provided in this section. We know in cytogenetic testing that we need to have all of our tests validated, with the exception of FDA-approved tests, which only need the performance characteristics confirmed in the laboratory when tests are performed “on-label.” Since most cytogenetic tests are not FDA approved or are FDA-approved tests that are “off-label,” these tests need proper validations performed before clinical use, with a validation plan and SOP and a validation report. Therefore, I have provided templates and example validation plans and reports that can be downloaded for laboratory use.

The second section of the book describes best practices for staffing and training employees in a cytogenetics laboratory. So much of what we do as directors are ensuring that staff are trained, competent, and efficient in their work. That requires a lot of dedication to the staff and a great deal of paperwork to document their performance in the laboratory. My goal here is to provide template benchmarks and documents, including spreadsheets that can be downloaded so that laboratories do not have to generate new forms for each item required, and to also provide the necessary steps for each test to prove training and competency of staff. I have also provided template “Training Programs” for cytogenetic and molecular genetic technologists (that comply with California standards—currently the most stringent of all the states in training and licensing technologists).

A chapter on Six Sigma for process improvement is also provided. Six Sigma is a sophisticated approach to improving processes, which applies well to cytogenetic laboratories. As a certified “green belt” in Six Sigma and Lean Processes, I give examples of how to improve processes in a business manner that organizations like to see for the purpose of being able to buy essential equipment, increase staffing where needed, and improve efficiency in a laboratory.

The third section of this book focuses on standard operating procedures. This is not an attempt to be comprehensive of all the possible procedures in every aspect of cytogenetic testing, since there are many other sources for this information. Rather, I am putting together common practices used in most laboratories, mainly to offer prototypes of each procedure as templates which can be used as is or with one’s own variations. These SOPs will help labs acquire procedures that can be “downloaded” into their laboratory, which can then be modified for one’s own use, rather than starting from scratch. As a result, a director’s job will be much easier by being able to use these SOPs in the correct format for regulatory purposes and to provide the necessary steps for each SOP that cytogenetic laboratories need. We most often focus our SOPs on each individual step of the process, but we also need to understand the format that is required and include the pre- and postanalytic steps of processes which may be overlooked. Also, many labs do not process all sample types or all the various tests that are available. In that case, when adding new tests, it is often hard to start writing a new SOP in the correct format from scratch. This is true especially for microarrays, where there is relatively little information on SOPs for this type of testing. I have not included a detailed microarray assay for this very reason. I have found
no SOP to date that applies equally well for any laboratory since I believe there is too wide a variety of processes that can be used in this technology. Thus, there is no real standard SOP as yet to share with laboratories.

My goal is that when you read this book, it will be a handbook for you, and you will use it for practical purposes. I have provided many spreadsheets, forms, and SOP’s that can be downloaded, saving time in developing these documents on your own. I also hope that this book can give ideas on how to save time, use good time management and organization, help enhance management skills, and improve your laboratory processes. Please feel free to contact me if you have information you would like to share on this topic.

Sincerely,

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ACKNOWLEDGMENTS

I wish to thank those who have graciously read my manuscript for content and coherence. Special thanks go to Nancy Wold and Martin Chetlen for all their assistance and guidance throughout the duration of this product.

I would also like to thank the many cytogenetic directors and laboratory staff who have inspired me with their work and knowledge to write this book. All these people and their laboratories have provided me with invaluable information throughout my career.

My deep appreciation goes to the directors and staff of the following laboratories:

- Alfigen (The Genetics Institute): Omar Alfi, Veronica Ward
- Texas A&M University: James Womack
- University of Texas Southwestern Medical Center: Nancy Schneider, Golder Wilson, Debra Cohen, Rene Payne
- Genetrix: John Stone, Robert Wassman; Denise Main, Debra Giroux
- Kaiser Permanente Laboratories: Lauren Jenkins, Mehdi Jamshed, Britt Ravnan, John Mann, JoAnn Bergoffen, Lloyd Maxwell, Michael Tiffert, Angela Lim, and so many more
- Quest Diagnostics/Smith-Kline Beecham: JoAnn Kelly, Dwanna Stewart, James Ray, Mervat Ayad, and so many more
- City of Hope: Joyce Murata-Collins, Popsie Gaytan
- CombiMatrix: Karine Hovanes
- Genzyme: Bing Huang, Maya Thangavelu, Neng Chen
- ARUP Laboratories: Sarah South, Art Brothman
- University of California, San Francisco: Jingwei Yu
- Signature Genomics: Lisa Shaffer, Beth Torchia
- PathCentral: Mansoor Mohammed, Elaine Luckey
• LabCorp of America: Martin Sasaki, Ati Girgin, Monika Skapino, Rosa Thompson, Jose Navarro, and so many more
• Natera: Catherine Medina, Rosina Tao, Jonathan Sheena, Hanz Olanan, Anne Nguyen, and so many more
• Sterling Pathology: Changyau Yang, Jackie Puma, Kimberly Woodward, Tasha Le, Evelyn Prestano
• Epic Sciences: Tara Martinez, Deanna Fisher, Sarah Orr
• Allina Health: Sue Kang, Bill Wyatt
• Virtual Scientific: Allie Johns

I also wish to acknowledge the College of American Pathology for granting me permission to use their checklist items in this book. I truly appreciate the collegiality of CAP and all its endeavors.
ABOUT THE COMPANION WEBSITE

This book is accompanied by a companion website:

www.wiley.com/go/Zneimer/CytogeneticLabManagement

The website includes

- Figures
- Tables
- Textboxes
- Standard Operating Procedures/Protocols
- Proforma
- Guidelines
SECTION I

BEST PRACTICES FOR LABORATORY OPERATIONS
Good clinical laboratory practice (GCLP) is an essential part of starting and maintaining a clinical laboratory. It is imperative for all of us who direct, manage, and work in clinical laboratories follow certain guidelines encompassing ethical and safety practices in addition to the level of efficiency we desire. GCLP contains standards derived from a combination of Clinical Laboratory Improvement Amendments (CLIA) (portions of 21 CFR part 58 (GLP) and 42 CFR part 493), accrediting bodies such as the College of American Pathologists (CAP) and the International Organization for Standardization (ISO) 15189, and other regulatory authorities and organizations. The British Association of Research Quality Assurance (BARQA) takes a similar approach by combining good clinical practice (GCP) and laboratory practices that are involved in laboratory research activities in Great Britain.

The GCLP standards developed by CLIA were done with the objective of providing a single, unified document that incorporates requirements to guide the conduct of laboratory testing for human clinical trials. However, they are also used in clinical laboratory testing of patients for the diagnosis, prognosis, and screening of human diseases. The intent of GCLP guidance is that when laboratories follow these processes, it ensures the quality and integrity of data, provides accurate reproducibility of experiments and testing, monitors data quality, and allows comparison of test results at any testing facility.

The information that follows synthesizes the GCLP standards based on the guidelines of CAP, CLIA, and ISO in order to facilitate implementation of GCLP for clinical laboratories. A comprehensive version of the GCLP standards with accompanying templates and examples is available at https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf.
By recognizing these standards as the minimum requirements for optimal GCLP, compliance will result in consistent, reproducible, auditable, and reliable laboratory results for clinical testing.

In addition to these good laboratory practice (GLP) standards, other laboratory processes or plans need to be implemented, such as for the instruction of safety, biosafety, and chemical hygiene standards in the laboratory. Also, in the United States, patient health information is protected by law (Health Insurance Portability and Accountability Act (HIPAA)) and a plan must be developed in the laboratory for ensuring the security of patient information. These plans are necessary elements for GCLP and are required before clinical testing can be performed. The following standards for GCLP are outlined in this chapter:

- Safety Plan
- Biosafety Plan
- Chemical Hygiene Plan
- HIPAA Plan

These plans can be used by cytogenetic laboratories in order to comply with most regulatory agencies.

### 1.1 PHYSICAL FACILITIES

For GCLP, it is important to examine the facility you plan to use for your clinical laboratory in a myriad of ways. First, the environment in which laboratory testing is performed must allow efficient operations that do not compromise the safety of the staff or the quality of the preanalytical, analytical, and postanalytical processes. Developing new laboratory space or reconstructing current space needs to be carefully planned to account not just for efficiency and cost, but for the well-being of the staff and specimen processing. This would include implementing measures to avoid common errors seen in laboratories, such as ensuring enough walkway space, color-coding, and labeling areas for identification of processing, eliminating clutter, and adding storage space and personal space for the staff.
The laboratory design must account for equipment placement and proper ventilation. It must have a designated area for reagent storage and archiving of data in a secure fireproof, fire-resistant, or fire-protected environment with access only to authorized personnel, if possible.

Laboratory work areas must have sufficient space so there is no hindrance to the work or employee safety. Laboratory room (ambient) temperature and humidity must be controlled so that equipment and testing are maintained within the tolerance limits set by the manufacturer or laboratory. Ambient temperature logs should be used to document the acceptable ambient temperature range, record daily actual temperatures, and allow for documentation of corrective action should the acceptable temperature ranges be exceeded. All floors, walls, ceilings, and bench tops of the laboratory must be clean and well maintained.

Molecular amplification procedures within the laboratory that are not contained in closed systems must have a unidirectional workflow. This must include separate areas for specimen preparation, amplification, detection, and reagent preparation to avoid contamination and mix-ups between test and control specimens.

1.2 SPECIMEN TRANSPORT AND MANAGEMENT

The accuracy of all laboratory test results depends on the identity and integrity of the specimen submitted. We all know how difficult cytogenetic testing can be when an inappropriate or insufficient quantity of a sample is received for testing or if a sample gets lost in transit or is missing within the laboratory facility. Therefore, it is important to establish a sound specimen tracking system in the laboratory from collection to reporting test results in order to ensure the highest quality data and results. It is also important to ensure that clients sending samples to the laboratory know the laboratory specimen requirements.

The laboratory must also have documented procedures for collection, transportation, and receipt of specimens because the accuracy of all laboratory tests is dependent on specimen quality. A laboratory can only ensure specimen integrity when following appropriate specimen management and transportation procedures.

A properly completed requisition form must accompany each patient sample to the laboratory. The requisition form must contain unique patient identifiers, specimen collection date and time, patient demographics, and specimen type. Laboratory staff should verify that the specimen container with label information matches the requisition form and any log sheet that is present. Any discrepant or missing information must be verified promptly before specimens are processed or stored by the laboratory.

The laboratory must have documented specimen acceptance and rejection criteria for evaluation of sample adequacy and integrity. The laboratory must maintain an audit trail for every specimen from collection to disposal or storage. Audit trails must verify the date and time testing was performed and the personnel responsible for testing. All audit trails must be documented and accessible to auditors.

A shipping procedure must be documented that addresses preparing shipments by following all federal and local transportation of dangerous goods regulations (e.g., International Air Transport Association). Laboratory personnel handling specimens should be trained in hazardous materials/dangerous goods transportation safety regulations. Twenty-four hour monitoring of storage conditions, using manual and/or electronic monitoring with alert systems, and standard operating procedures (SOPs) for response to alerts must be in place to ensure that the integrity of samples is maintained.
1.3 PERSONNEL SAFETY

The safety of all laboratory staff is essential to avoid laboratory accidents and to prevent the acquisition of infectious agents through handling of specimens. Although exposure cannot always be avoided, every precaution must be taken to provide a safe working environment. Safety policies that are defined according to regulatory organizations, such as the Occupational Safety and Health Administration (OSHA) or the ISO, must be present in the laboratory.

THE FOLLOWING POLICIES MUST BE IN PLACE TO ENSURE THE SAFETY OF LABORATORY STAFF

- Standard universal precautions
- Chemical hygiene
- Hazard communication
- Waste management
- Safety equipment
- General safety and biosafety

These policies are described in more details later in this chapter. However, in general, fire extinguishers, emergency showers, eyewashes, and sharps containers must be present in each laboratory and in compliance with general safety and local laws. Periodic inspections and/or function checks of applicable safety equipment must be documented. The employer must provide the use of personal protective equipment (PPE) and provide access to PPE to all laboratory staff during clinical testing on human specimens. All laboratory employees must use PPE if there is a potential for exposure to blood or other potentially infectious material through any route (e.g., skin, eyes, other mucous membranes). The laboratory must have Safety Data Sheets (SDSs) or equivalent in the workplace for each hazardous chemical they use.

All laboratory staff must also receive safety training. See the Safety Plan further in the chapter for details.

AT A MINIMUM, SAFETY TRAINING MUST INCLUDE INSTRUCTION IN THE FOLLOWING AREAS

- Blood-borne pathogen handling
- Personal protective equipment (PPE) use
- Chemical hygiene/hazard communications
- Use of safety equipment in the laboratory
- Use of cryogenic chemicals (e.g., dry ice and liquid nitrogen)
- Transportation of potentially infectious material
- Waste management and biohazard containment
- General safety and related local laws
1.4 LABORATORY INFORMATION SYSTEM (LIS)

The laboratory information system (LIS) is an essential tool to manage complex processes and ensure regulatory compliance and good practice for clinical laboratories. The LIS should be capable of integrating various processes in the laboratory into a single platform with comprehensive specimen processing, reporting, surveillance, and networking capabilities.

The laboratory must maintain a written SOP for the operation of the LIS which should be appropriate and specific to the day-to-day activities of the laboratory staff as well as the daily operations of the information technology (IT) staff. Documentation must be maintained, indicating that all users of the computer system received adequate training both initially and after any system modification. Documented procedures and a disaster preparedness plan must exist for the preservation of data and equipment in the case of an unexpected destructive event (e.g., fire, flood, or earthquake), software failure, or hardware failure, allowing for restoring service as quickly as possible.

The purpose of the LIS, its functions, and its interaction with other devices or programs must be documented with validation data and results including data entry, data transmission, calculations, storage, and retrieval. Since patient management decisions are based on laboratory data, appropriate documentation in the LIS must exist to ensure data quality and integrity. Both abnormal and normal data must be used to test the system. Any changes or modifications to the system must be documented, and the laboratory director or designee must approve all changes before they are released for use. Computer time-stamped audit trails must be used by the LIS. The laboratory’s LIS policies must ensure that LIS access is limited to only authorized individuals.

1.5 QUALITY MANAGEMENT

An overarching quality management (QM) program is essential to ensure the safety of patient samples and maintenance of quality laboratory operations. The QM program is a systematic approach to plan the achievement of quality objectives, comply with approved procedures, and assign specific functional responsibilities to laboratory staff. The QM program should also include a quality assurance (QA) program, which is set up to evaluate the laboratory’s analytical performance by comparing test performances. The following information is an overview of the major components of a good QM program. More detailed information on QM is described in Chapter 2.

The laboratory QM program should be developed as an overall laboratory scope as well to monitor, assess, and correct specific problems identified in each of the preanalytic, analytic, and postanalytic steps in the laboratory testing process. As previously stated, a key component of the QM program is quality assurance (QA). QA must monitor for GCLP compliance, oversee the development of the QM program, and resolve quality-related problems as described earlier. The QA program should submit status reports to management and must prepare and respond to external audits. It must include evidence of appropriate follow-up actions taken as a result of monitoring in addition to evaluating the effectiveness of corrective actions.

The laboratory must provide evidence of implementation of the QM program (e.g., minutes of committee meetings, results of ongoing detection of errors, and documented complaint investigations). The laboratory must also be able to provide evidence of appraisal
of its QM program. That is, an annual written QM program with revisions including laboratory policies and procedures. QM program documentation must demonstrate at least annual review by the laboratory director or designee. The laboratory’s QM program must include results of ongoing measurement of key quality indicators of laboratory operations compared to internal or external benchmarks and must be monitored for trends over time. The laboratory must be able to use the QM program for guidance when conducting annual appraisals of effectiveness and must provide evidence of the program’s implementation.

THE QM PROGRAM SHOULD INCORPORATE THE FOLLOWING ELEMENTS

- Goals and objectives
- A design to monitor, evaluate, and correct quality problems
- The monitoring of complaints and incidents
- The monitoring of all aspects of the laboratory’s scope of care
- Addressing problems that interfere with patient care
- Describing procedures for collection and communication of quality and safety information (e.g., QC and QA)
- Key quality indicators of laboratory operations that target quality improvements (QI measures), such as test turnaround time, specimen acceptability, and test result accuracy
- Evidence of a regular review by the laboratory director or designee

The laboratory’s monitoring of the QM program must include an internal audit schedule that contains a comprehensive comparison of the actual practices within the laboratory to the laboratory’s policies and procedures (e.g., personnel files, training documentation, quality control (QC) performance, review of SOPs). Internal audits involve an individual or a group of laboratory personnel performing periodic self-assessment of actual laboratory practices to see if it matches the laboratory’s policies and procedures. All findings (compliance, noncompliance, or deficiencies) from an internal audit should be documented to allow for appropriate corrective action and follow-up through resolutions when appropriate. The laboratory should monitor that the QA Program covers all testing assays. The laboratory director or designee must document review of all external quality assurance data, and corrective action should be taken with appropriate preventive measures in response to any unacceptable results, which must be documented.

The laboratory must have a list of assay turnaround times readily available to all laboratory staff as well as laboratory customers. The laboratory must also have a nonretaliatory policy for employees to communicate concerns to laboratory management regarding testing quality or laboratory safety.

Within the QM program, all laboratories must include a QA program.