PRACTICAL GENETIC COUNSELING FOR THE LABORATORY

edited by

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Practical Genetic Counseling for the Laboratory

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Foreword

CATHERINE A. REISER

As I reflect upon my 30-plus years of professional practice. this book is significant not only in imparting practical information but also because it documents that the laboratory genetic counselor is permanently and formally recognized as a vital and necessary part of our workforce. As a program director, I have read thousands of applications from prospective genetic counseling students. Their motivation or reasons for wanting to enter our ranks can always be distilled to a bottom line: a love of genetics and a passion for helping people. This has been true since the beginning, when most counselors' primary work setting was in a clinic and seeing patients was their primary function.

I vividly remember a time when helping people and working in a laboratory setting seemed, at least to some, incongruent. A laboratory-based counselor was seen as having turned away from patient care. We couldn't have been more wrong, then and now. Patient welfare is primary for all genetic counselors regardless of work setting. Incoming students and new graduates understand this and are increasingly interested in the laboratory role, recognizing that laboratory-based genetic counselors also work to serve the best interests of patients. This is apparent in the following students' reflections written during their training after contact with laboratory-based genetic counselors and others in a nonclinical setting:

> ". . . lab genetic counselors have a central obligation as liaison between the lab and the ordering physician. They are responsible for ensuring that the appropriate test has been ordered for patients and for translating results to physicians. [She] used her more variable role to expand her professional boundaries, producing education materials for physicians, drafting consent forms and creating useful templates for clinicians. Essentially, however, it seems any position of a lab genetic counselor retains the central component of genetic counseling: translating genetic information to palpable information applicable to a patient's situation."
>
> "She emphasized the importance of having genetic counselors working for laboratories like these to advocate for patients and remind all the other

> researchers, business people, and scientists that there are real patients behind their test results."

An article in the winter 2005 *Perspectives in Genetic Counseling*, titled "Nontraditional is the new mainstream," advocated that the term *nontraditional* "be eliminated when discussing the scope of genetic counseling practice" (Steinberg et al. 2005). The authors noted that training programs must prepare students for the job market, which includes the ability to take advantage of new opportunities when they arrive. Training programs accomplish this by adhering to the Accreditation Council of Genetic Counseling (ACGC; formerly the American Board of Genetic Counseling) standards, which require we teach to the domains of the practice-based competencies and provide relevant experiences. This provides our graduates with a skill set that they can transfer to the many diverse settings within the genetic counseling profession. We are teaching students to be genetic counselors who, in addition to providing genetic counseling directly to patients, can provide services to a broader client base that may be encountered in the laboratory setting, such as physicians and other genetic counselors. Although they work in different settings (clinic vs. lab) and with different clients (patients vs. professionals), all genetic counselors use the same skills and are guided by the same values as outlined in our professional practice-based competencies (ACGC 2013a). The ACGC has specifically recognized the importance of laboratory-based experiences, as seen by the change in standards to which programs must adhere. The recently revised standards (compliance effective June 2014) state that "Trainees must be exposed to multiple clinical and fieldwork settings (B3.2.6)," which includes the laboratory-based genetic counselor (ACGC 2013b). The laboratory-based experience requirement is further expanded and requires programs "to provide students with instruction in, and observation of, genetic laboratory activities, and ensure opportunities for the students to interface with professionals involved in the performance and interpretation of genetic/genomic tests (B4.2.1)." While the laboratory-based genetic counselor is considered together with genetic counselors in other nonclinical settings, the change in language regarding this group of genetic counselors is significant. No longer are we simply "encouraged" (American Board of Genetic Counseling 1996) to provide exposure to laboratory-based genetic counselors and other nonclinical sites and practice areas, we "must" do so, indicating a shift in the importance of laboratory and other nonclinical settings in our future.

From students:

> "I recognize that the skills of a genetic counselor are widely applicable and valuable in a number of contexts."
>
> ". . . the counselors [in the lab] clearly demonstrated many situations in which they used ethical reasoning, communication and attending skills . . ."
>
> "My interview with [her] was a refreshing glimpse into the numerous possibilities for genetic counselors and a reaffirmation that skills we are acquiring in our training hold tremendous value outside of a clinic."

The laboratory-based genetic counselor has been on a relatively fast trajectory from being viewed as someone in a nontraditional role to becoming a mainstream position in one of the fastest-growing specialty areas. Consider the trends seen in the professional status surveys collected biannually by the National Society of Genetic Counselors (NSGC). The "Summary of Membership Trends: 1980–2002" listed 11 different primary specialty areas; laboratory counseling was not among them (NSGC 2004a). Diagnostic laboratory does appear, however, in the 2004 survey, when 74 (7%) respondents indicated this as their primary work setting (NSGC 2004b). By 2016, 297 (20.9%) respondents reported they are employed by a diagnostic laboratory (commercial or academic) (NSGC 2016). Even if those respondents who are employed by a diagnostic laboratory and also counsel patients are removed from these data, that represents more than a threefold increase (74 to 254). In addition, according to the 2016 survey, 7.5% of genetic counselors considered laboratory support as a primary role—that is, a function in which they spend more than 50% of their time (NSGC 2016). While the categories are neither exactly equivalent (primary work setting vs. primary specialty areas) nor clearly defined (the 2014 survey: clinical counselor vs. nonclinical counselor and the 2016 survey: counsels patients vs. does not counsel patients), it can be reasonably concluded that laboratory-based genetic counseling is an area of practice that has grown dramatically.

Equally important to the growth of this specialty area is the high degree of job satisfaction reported in the 2016 survey by genetic counselors who identify as working in nonclinical settings versus those who identify as working in a clinical setting. Of 1,525 respondents who counsel patients, the mean overall job satisfaction was 2.17 (with 3 being very satisfied, 2 satisfied, and 1 dissatisfied) compared to a mean of 2.38 for the 508 respondents in a nonclinical setting (those who do not counsel patients). Job satisfaction was significantly higher ($p < .001$) in the nonclinical setting in nearly all measured aspects, including autonomy, salary, opportunity for advancement, and supervisor and institutional support. The report's authors concluded that "Overall, non-clinical genetic counselors express more satisfaction with the various aspects of their work than do clinical genetic counselors; this finding continues a pattern seen in 2012 and 2014, and almost all of the differences were statistically significant" (NSGC 2016, p. 2).

Students increasingly recognize that laboratory-based genetic counseling is a satisfying professional role and one in which they can see themselves. From students:

> "I recognize that a genetic counselor can work and thrive in a nonclinical setting."
>
> "She says she really enjoys her position . . . and has never thought about going back to clinical genetic counseling ever since."
>
> "I would strongly consider a laboratory genetic counseling position . . ."
>
> ". . . a career as a laboratory counselor is also a path I could see myself pursuing someday."

In accordance with the standards put forth by the ACGC, our profession requires that we maintain a level of proficiency across a defined set of skills called the

practice-based competencies (ACGC 2013a). We are expected to have expertise in genetics and genomics core concepts and principles, be effective communicators and educators, and be committed to continued professional development and practice. These attributes describe all genetic counselors regardless of work setting or practice area. The chapters and topics in this resource for laboratory counselors easily line up with the current competencies. The initial chapters (1 through 3) include information about the types of laboratories and business relationships, infrastructure, and the regulatory bodies that guide laboratory practice. Understanding of this content supports a genetic counselor's ability to work across the healthcare system and promote responsible use of genetic/genomic technologies, which supports Domain IV of the competencies, Professional Development and Practice. Chapters 4 through 7 cover testing technologies and related issues in molecular, biochemical, prenatal, and cytogenetics. Domain 1 of the competencies, Genetics Expertise and Analysis, includes a specific and parallel skill requiring genetic counselors to "identify, assess, facilitate, and integrate genetic testing options in genetic counseling practice." Chapter 12, "Genetic Counselor Communication and Counseling Skills for the Laboratory," and Chapter 14, "The Laboratory Genetic Counselor as an Educator," align perfectly, and respectively, with Domain II (Interpersonal Skills) and Domain III (Education). The remaining chapters can similarly be connected to a specific competency (e.g., Chapter 13, "Ethical Considerations in the Genetic Testing Laboratory," with Domain IV skill 17, "act in accordance with the ethical . . . principles and values of the genetic counseling profession"). The breadth and depth of the chapters all contribute to a text that is valuable resource that will ensure that practicing and future genetic counselors have the necessary tools to develop and maintain competence as a laboratory-based counselor.

All genetic counselors are vital to the future of our profession and our place in the healthcare system, especially if we are to make any progress toward the NSGC vision of "integration of genetics and genomic health care for all." This book, and the future editions that are certain to follow, is important not only for laboratory counselors as they work to enhance and maintain their skills within the competencies but also for clinic-based genetic counselors and those still in training as they work toward a deeper understanding of the work performed by their laboratory colleagues.

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Introduction

As relative veterans of the laboratory genetic counseling field, we have witnessed, experienced, promoted, and in some cases initiated great change in the roles and responsibilities of the genetic counselor in support of diagnostic laboratories. Laboratory genetic counseling was once perceived as a nontraditional role given the lack of direct patient interaction. The original movement of genetic counselors from the clinic to the laboratory grew from the recognition of the need for a high level of communication between laboratories and clinicians, particularly as testing menus expanded rapidly. The overwhelmingly successful application of the genetic counselor's core skills and competencies acquired during graduate training and clinical experiences to the laboratory environment has been the impetus for a great paradigm shift toward "nontraditional" work settings and has naturally led to a significant increase in the number of genetic counselors practicing in this specialty area.

As the number of laboratory genetic counselors has grown over the last 15 years, both nationally and within our own institution, laboratory genetic counselors have largely relied on networking and internal conversations for professional development, education specific to this specialty, and growth of the laboratory genetic counselor role. With the continued onboarding of new laboratory genetic counselor colleagues, we recognize an important literature gap with regards to this area of genetic counseling. In 2010, the number of peer-reviewed publications specific to the practice of laboratory genetic counseling within the entirety of the genetic counseling body of literature numbered less than five articles. There has since been an increase in published literature and educational content presented via professional venues, but practical studies, educational material, and publications geared toward the professional development of laboratory genetic counselors are less common than in many other clinical specialties of the genetic counseling practice.

The opportunities for new graduates within the laboratory are significantly greater than ever before; however, only a few training programs incorporate formal laboratory genetic counseling rotations into their curriculum. We endeavor to help synthesize existing literature and further contribute to the educational material available to graduate programs in the training and exposure of new genetic counselors to laboratory genetic counseling. In addition, this text is meant to provide a reference base to those currently practicing as laboratory genetic counselors and clinical genetic counselors alike as the standard of practice in laboratory genetic counseling.

With that, we are excited to introduce the first laboratory genetic counseling text. The content was contributed by genetic counselors, geneticists, and laboratorians from over 30 institutions and laboratories, representative of the various genetic testing laboratory types, including major reference laboratories, commercial laboratories, academic laboratories, and government institutions. The content highlights the important background knowledge necessary to navigate a diagnostic laboratory, the technical aspects and nuances of the various forms of genetic testing, and the specifics regarding the diverse roles of the laboratory genetic counselor. We hope you enjoy this text as much as we enjoyed being part of its creation.

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McKinsey L. Goodenberger
Teresa M. Kruisselbrink

1

Types of Laboratories and Business Relationships

STEVEN KEILES, MARGARET LILLEY, AND HEATHER MACLEOD

There is a growing need for genetic counselors (GCs) to fulfill increasing roles in genetic testing laboratories. This chapter focuses on the types of laboratories that may employ a GC in addition to the function and importance of business relationships and billing and reimbursement in the laboratory.

Types of Genetic Laboratories

Laboratory GCs work in many different laboratory settings, including commercial laboratories, academic laboratories, hospital-based laboratories, and research labs. The labels used for the types of laboratory settings are not exclusive, and many laboratories are a combination of such types. For example, an academic or commercial laboratory that performs testing on a wide range of diseases may also follow up on clinical results with related research studies. A laboratory's specialty and setting will determine who its clients are and is directly related to its business model. A laboratory's goals and business model can range from supporting local researchers to transitioning genetic testing for rare disease into clinical testing to providing routine genetic testing for a wide range of genetic disorders.

A survey of laboratory GCs found the most common work setting is a university-based hospital, followed by a private laboratory. Other laboratory settings include provincial or regional health services and public laboratories (Christian et al. 2012; Waltman et al. 2016). Regardless of the setting, a primary role of the laboratory GC is to serve as client liaison. This role includes addressing questions from clients about test algorithms, discussing results with clients and providers, and working with clients to facilitate appropriate testing and manage high-priority cases and specimens. The laboratory GC often notifies clients of results and may reach out to obtain additional clinical or family history information used in results interpretation (Christian et al. 2012; Waltman et al. 2016). Client-facing roles are a key component of the laboratory GC role and are the focus of this chapter. Other roles are explored in more detail in other chapters, such as in Chapter 8, "Genetic Counselor Role in Laboratory Case Management."

CLINICAL LABORATORIES

Clinical laboratories issue clinical testing reports and are accredited by a governing body. The primary role of a clinical laboratory is to provide a clinical testing service for its clients. All clinical laboratories charge for their testing services, but business models vary considerably. Certification and accreditation are formal processes that ensure robust quality control and quality assurance programs, appropriate technical competencies, the participation in proficiency testing, and documentation standards. In Canada, laboratories are accredited at a provincial level by the College of Physicians and Surgeons. Genetics laboratories and clinics are also accredited by the Canadian College of Medical Genetics. In Europe, laboratory accreditation is obtained from the European Molecular Genetics Quality Network. A laboratory may have more than one accreditation. The role of various regulatory bodies is covered in more detail in Chapter 2, "Regulation of Laboratory Genetic Testing."

There are many different types of clinical labs, including large commercial reference laboratories, specialized commercial labs, hospital-based laboratories, and academic laboratories. This categorization of laboratories is based on their business model and a number of other factors, including the size and content of the test list, the types of clients they serve, and their funding source.

A laboratory may be private or publicly funded. Private laboratories may be either not-for-profit or for-profit organizations. Publicly funded laboratories are funded by the government or a government agency. For example, many genetic laboratories in Canada are funded by the provincial government. A private laboratory is not supported directly by a funding body but rather relies on the revenue it generates. Academic laboratories will generate some revenue through reimbursement but are often supported in large part by the host institution. Private organizations may choose a not-for-profit business model where revenue is used to support the company's objectives or a for-profit business model.

Commercial reference laboratories are typically for-profit companies with large test menus. They provide testing for a fee to a broad number of healthcare providers. Customer liaison is likely to be a predominant role for a GC as there is a significant amount of direct contact between the GC and the healthcare provider (Christian et al. 2012; Waltman et al. 2016). In this type of lab, the GC may be more likely to have a role in creating educational or other testing materials, such as test algorithms to help navigate the larger test menus. An increasing number of GC positions include some sales and marketing roles (Christian et al. 2012; Waltman et al. 2016), and many GCs are now filling sales and marketing positions in these laboratories. Due to the large volume of testing performed in these laboratories, there is great opportunity for the publication of results of large-scale testing for a given gene or condition.

Specialized laboratories are typically privately funded but may be either for-profit or not-for-profit entities. These laboratories tend to provide testing for a limited number of conditions, such as neurological, metabolic, or ocular conditions, for example. Given their niche testing menu, they typically provide testing for a broad client population, receiving national and international samples alike. GCs in these laboratories have the opportunity to become subject matter experts in these niche areas and create educational materials in addition to providing direct client support. Due to the

specialized nature of the testing, there is a great opportunity for clinical research in these GC roles.

Hospital-based laboratories may be privately or publicly funded. Typically, these laboratories have a small menu of genetic tests and serve a limited client population, such as patients seen at a specific hospital or within a group of hospitals. Such laboratories tend to offer testing only for common or high-volume tests such as cystic fibrosis. Given the limited testing provided in house, hospital-based laboratories often refer many samples to larger reference laboratories. GCs in a hospital-based laboratory will spend a significant amount of their time coordinating the send out of samples to other testing laboratories (Waltman et al. 2016). They may also have significant involvement in testing utilization management, which is further reviewed in Chapter 10, "Genetic Counselor Role in Hospital Test Utilization." There may be limited opportunity for test development or research in these settings due to the limited volumes and scope of testing.

Academic laboratories are generally publicly funded and are linked directly to a university or other academic institution. An academic laboratory may be a research laboratory or may choose to be accredited and provide clinical testing. This business model allows for more flexibility regarding the test menu available and the corresponding clientele. Typically, they function similarly to a specialized laboratory with a focused testing list but potentially geographically broad client base. GCs in an academic laboratory may have many research opportunities in addition to the customer liaison role (Waltman et al. 2016). The laboratory GC in this setting may be involved in the selection of new tests and the development of interpretations and educational materials for such tests.

RESEARCH LABORATORIES

Research laboratories are not accredited by a recognized accrediting body and cannot issue clinical reports. The testing performed in a research laboratory is regulated by hospital or university ethics boards. Depending on the research focus of the laboratory, testing may be performed on patient samples and the results published to further the scientific community's understanding of a given condition, gene, or natural phenomenon. In such situations, testing is performed anonymously and research participants are not routinely provided with genetic test results. In some cases, patients may elect to be notified of research results and can opt in or opt out of this option during the informed consent process. If the research protocol allows, participants may be contacted to confirm clinically significant findings. Research results should not be used for clinical purposes. However, due to the complexity of genetic testing, the rarity of many genetic conditions, and the rapid pace of knowledge acquisition, it is possible that the only available testing for a given condition is in a research laboratory. Therefore, clinicians may request research studies despite the recommendation not to use the results for medical management. This illustrates the complex relationship between research and clinical testing for rare genetic disease. Reports issued based on research testing should clearly indicate that the testing was not performed in a clinical laboratory and that the results should be confirmed in an accredited laboratory when possible (Das et al. 2008).

GCs in a research laboratory may perform duties similar to those of a clinical laboratory GC with respect to customer service and laboratory support. In addition, they may write research grant applications, research ethics board applications, research consent forms, and peer-reviewed publications. GCs may also participate in the recruitment and informed consent process for research participants and the disclosure of results.

Business Relationships and Interactions

Given their client-facing role, GCs working in the laboratory will build important relationships with colleagues from within their own company as well as competitors, clients, and others they work with externally. The nature of these relationships will influence the types of contacts developed and who the primary contacts are and will also influence billing practices. These relationships will most certainly include physicians, nurses, GCs, and other lab send-out coordinators who submit their specimens for testing. They can also include affiliated institutions, health systems, managed-care plans, and utilization review committees for third-party payers.

Several factors are incorporated into how labs market their services to prospective new clients. The scale of the marketing strategies employed depends largely on the size of the lab and the budget and resources designated to sales and marketing efforts. Labs with limited resources for "feet on the street" may rely mostly on exhibiting at educational meetings and national conferences, maintaining a small field-based team. Many of the larger reference labs will have significant resources dedicated to sales and marketing, with hundreds of field-based representatives who optimize face-to-face meetings with potential clients. This will also change how they market their products. For years, labs have focused on marketing directly to the providers who are most likely to be seeing the patients requiring genetic testing. In more recent years, however, labs have started marketing more generally to nurses and primary care physicians and even directly to the public.

INTERACTIONS BETWEEN LABORATORY AND CLIENT

When a laboratory is approached by potential clients, the following are important discussion points for both parties to consider:

1. What certifications does the laboratory hold?
2. How will communication between the client and the laboratory be accomplished?
3. Who are the key contacts for clinical versus logistical questions?
4. Are GCs employed by the laboratory?
5. What tests are needed by the client, and does the laboratory offer these tests?
6. What is the lab's experience with the technology and testing being performed?
7. Is testing performed in house or sent out?
8. What are the laboratory's billing practices (patient insurance [third-party billing] or institutional billing only)?

9. What do the test reports look like? Are sample reports available?
10. How are results attained (portal, manual delivery, electronic transfer)?
11. What is the process for report updates, including variant reclassification?

As with all businesses, the most successful labs are in tune with their clients' testing needs. Many new test suggestions come from clinical providers who state what they need in order to provide the best care for their patients. Sometimes a test may not be commonly ordered or profitable, but a lab may choose to add it to its test menu to keep current clients satisfied. As the test menu evolves, it is important that there is ongoing communication with all current and potential clients to ensure they are aware of all the offerings.

INTERACTIONS BETWEEN LABORATORIES

Many labs choose to have a relationship with another reference lab to allow them to focus on tests they do not have the expertise or inclination to perform themselves. This is especially likely for a lab that focuses on performing more common high-volume tests while sending out more esoteric testing to a lab that specializes in such testing. In this way the first lab can respond to the needs of their clients without needing to dedicate resources for test development that are not consistent with their business model. These relationships often result in a mutually beneficial relationship.

If a lab does not perform the testing in house and refers it to another lab, this must be noted on the clinical report. Offering send-out testing options enables a lab to make it easier on its clients by not having to obtain and send an additional patient sample to more than one lab. It is also possible that a lab may be unable to keep up with current volumes and may use an outside lab for overflow to eliminate a backlog situation.

To expand a business, new customers will need to be converted. One relatively easy investment to encourage clinicians to switch is to add new tests to the test menu. In addition, with increasing competition it is sometimes necessary to continue to evaluate lab offerings to stay competitive in the market. This is where market research on current customer ordering patterns and voice of customer data in the field are crucial to a laboratory's success. Adding a new test that targets the current client base would be easier for marketing purposes while also keeping the current client base satisfied and would increase the likelihood of a successful launch. This would not require additional marketing and advertising expenses to a whole new audience, an investment that some companies might not wish to make. Again, as the test menu evolves, ongoing communication with all current and potential clients is important so they are aware of all the offerings.

INTERACTIONS BETWEEN LABORATORY AND RESEARCHERS

Many clinical laboratories may also develop relationships with researchers and form partnerships with clinical research organizations (CROs), pharmaceutical companies,

and other biotech companies. A clinical laboratory may also participate in research by performing testing for one of these organizations. Such testing may be performed by a research lab located within the company or in the Clinical Laboratory Improvement Amendments (CLIA) lab itself, thus ensuring that all testing meets CLIA requirements (Centers for Disease Control and Prevention 2015). A common partnership may be formed in the context of drug development for companion diagnostics purposes, in which a new drug will only benefit patients with or without a specific genotype. This type of testing is typically performed in partnership with CROs or directly with a pharmaceutical company involved in clinical trials.

Billing and Reimbursement

CPT CODES AND REIMBURSEMENT RATES

Billing and reimbursement for genetic testing is based on Current Procedural Terminology (CPT) codes. These codes were first developed by the American Medical Association in1966 and are used as "reliable nationwide communication among healthcare providers, patients, and third parties." Medicare publishes new codes and updates to existing CPT codes every year in the Federal Register, the official daily publication for rules, proposed rules, and notices of federal agencies and organizations (Office of the Federal Register 1994).

Reimbursement rates for CPT codes are set by the Centers for Medicare and Medicaid Services (CMS). CMS is an arm of the federal government's Health and Human Services Department. CMS is responsible for the administration and funding of Medicare and Medicaid programs (Centers for Medicare and Medicaid Services 2016a). The Coverage and Analysis Group at CMS determines coverage by requesting Technical Assessment Reports through the Agency for Healthcare Research and Quality that serve as a guide for coverage of genetic testing (Centers for Medicare and Medicaid Services 2016c). Genetic testing coverage is assessed based on the clinical utility of genetic tests in the Medicare population, and therefore it is not necessarily supportive of testing for conditions that typically occur at an earlier age. Although CMS develops guidelines and recommendations for testing, the coverage determination for these tests is processed by Medicare Administrative Contractors (Centers for Medicare and Medicaid Services 2016e) such as Palmetto or Noridian.

Many insurance companies base their reimbursement policies and rates on those of CMS. Third-party payers or health insurance plans use the CMS reports as a major source of evidence for determining coverage for specific genetic tests and emphasize evidence-based coverage decision making (National Institutes of Health 2016). Currently, evidence used in other areas of medicine (randomized trials, clinical utility) is not routinely available for most forms of hereditary genetic testing. The assessment of a genetic test involves assessing the analytic validity, clinical validity, and clinical utility of tests used in specific clinical scenarios (Evaluation of Genomic Applications in Practice and Prevention Working Group 2014). Sources for this data can include published literature, professional organization statements, and data review sites such as Evaluation of Genomic Applications in Practice and Prevention. Another group that

assesses the evidence-based utility of genetic testing is the U.S. Preventive Services Task Force. When these sources are not available, expert opinion can serve as a data source.

In the past CPT codes for genetics used stacked codes based on the methodology. This system is still used in certain genetic testing settings like cytogenetics. In 2012, new CPT codes more specific to molecular genetic tests were developed to replace stacking of codes. The process to implement these new codes based on the gene being tested rather than the technology began in 2013. In 2015, CMS announced that the Medicare Program adopted the 2013 American Medical Association's Molecular Pathology (MoPath) CPT codes. To address the rapidly changing diagnostic testing options, Genomic Sequencing Procedure codes for both current and future diagnostic technologies have been created and are being implemented. These codes are designed to focus on the clinical indications for and clinical utility of the genes included on the panel rather than specific to an exon or gene. Monetary reimbursement for specific codes is set by CMS's Clinical Laboratory Fee Schedule (Centers for Medicare & Medicaid Services 2016b). Reimbursement for outpatient clinical laboratory services is paid based on a fee schedule in accordance with Section 1833(h) of the Social Security Act. Reimbursement is increased each year in accordance with inflation but can also be modified by legislation in Congress. Insurance payments such as copayments and deductibles do not apply to services paid under the Medicare clinical laboratory fee schedule.

Each payer has its own pricing strategy for determining reimbursement. Models for pricing strategies may include using the CMS schedule or a percentage of posted fees from the CMS schedule; paying a percentage of billed charges from the laboratory; or setting pricing rates for a specific CPT code. In cases of third-party billing, the details of how reimbursement will happen between a laboratory and payer are predetermined in their contract (if they are contracted). If a laboratory is "in network" for a specific insurer, the contract and/or explanation of benefits must be followed for billing. If a laboratory is out of network, the patient can be billed for the balance once reimbursement is issued by the payer. Refer to the billing practices described below for details on the reimbursement of the performing laboratory for genetic testing services.

BILLING PRACTICES

Billing options used when working with genetic testing laboratories include institutional, U.S. government, third-party payers (commercial insurance), self-pay, and international. The size and success of different billing and reimbursement strategies can affect the specific services a laboratory offers. Labs that are profiting entities are more easily committed to offering services such as preauthorization and/or direct patient or insurance billing. For smaller, grant-funded laboratories, these services may not be offered.

Institutional Billing

Institutional billing occurs when a genetic testing laboratory directly bills a referring institution. The referring institution then bills the patient and may add on additional charges to the patient's bill depending on the state laws allowing markup pricing. This

can be a successful model, particularly if a hospital or institution has a clinical laboratory send-out or referral department. An advantage of this method of billing can include negotiating reimbursement based on volume.

Government Billing

Laboratories that are approved government vendors have the ability to expand their business opportunities. Labs that want to become government vendors must fill out an application (National Institutes of Health 2006). Being a government-approved vendor opens opportunities for a laboratory when requests for proposals are posted for laboratories. Examples of requests for proposals for government vendors include contracts for newborn screening and being a provider for VA hospitals and the various state Departments of Health.

Medicare/Medicaid/Tricare

Medicare is a U.S. government insurance program available to individuals 65 years and older. Medicare reimbursement depends on local and national coverage criteria. Medicare may have criteria for specific tests (Centers for Medicare & Medicaid Services 2016d). An Advanced Beneficiary Notification, which may be required for billing through Medicare, is a written notification to a patient stating that Medicare may not cover services and that a patient may be personally financially responsible if Medicare does not cover the service. Medicaid provides insurance coverage for low-income families. Medicaid coverage is determined by state policies. If Medicare or Medicaid does not cover the cost of the test, either the patient or the lab covers the cost of testing. In some cases, patients may have secondary insurance. Some laboratories are not in-network providers for government-funded insurers.

Tricare is a healthcare program of the U.S. Department of Defense Military Health System. Specific coverage criteria should be reviewed (Tricare 2015).

Third-Party Payers/Commercial Insurance

Billing to a commercial insurance company requires complete insurance information provided by the patient. Insurance verification/preapproval practices vary among laboratories, insurance companies, and patient preferences. Verification of insurance can mean the patient has insurance benefits, the insurance coverage is active, and/or the benefit being requested is covered. Insurance preauthorization is a determination by an insurer if a medical service (genetic testing) is medically necessary. If insurance preauthorization is required, the preauthorization must be requested and received before the service is provided. Typically preauthorization is not a guarantee of payment. Patients should also verify their responsibilities, including deductibles, co-payments, and benefit limitations, in assessing the costs associated with genetic testing. Labs may set up contracts with private insurance companies as in-network providers of genetic testing services. Reimbursement rates are negotiated based on the specific contract.

Self-Pay

For patients who do not have insurance or do not want genetic testing to go through their insurance, many laboratories allow self-pay options. This typically involves

patients providing a credit card number, money order, or other upfront payment for genetic testing. Many laboratories have financial hardship payment options requiring financial documentation of need.

International Billing

In Canada, healthcare is funded by the federal government but managed at a regional or provincial level. Residents of a given province are assigned a provincial healthcare number allowing them access to publicly funded healthcare services. Most Canadian provinces have molecular, cytogenetic, and biochemical genetic testing laboratories, although the test menus vary significantly between provinces. Testing performed within the provinces and does not require preauthorization. There is no standardized system for the review or approval of referred-out genetic testing (Christian et al. 2015). The authorization may be through a medical genetics clinic, a genetics laboratory, or the Ministry of Health. The authorization may be at the discretion of a single individual, a committee, or a number of independent reviewers. Regardless of the system in place, written notice of preauthorization is provided to the ordering healthcare provider and would accompany a sample to the testing laboratory. If a request for preauthorization is declined by the provincial approval body, a patient may choose to pay for testing out of pocket. Some individuals have access to private supplementary health insurance, which may cover some or all of the cost of testing. Any country with publicly funded health care, such as Australia or the United Kingdom, faces the challenge of funding testing that is performed outside of its jurisdiction and has a system in place for reviewing such requests. Specific billing information for customers outside the United States will be similar to self-pay options but will vary by laboratory.

Future Directions

The availability of advancing technologies such as genome and exome sequencing will drive changes to laboratory test menus, research and clinical laboratory functions, and their relationships to one another. Laboratories are consistently expanding their testing menus with large multigene panels. However, there will be an increasing demand for labs to focus on determining the clinical implications of a given gene or genetic variant identified by clinical testing. In parallel, new business collaborations and models will follow.

As new CPT codes for multigene panels are developed, third-party payers or health insurance companies are updating their policies to address the rapidly expanding use of such testing. GCs will continue to play a vital role in educating payers about the genes being included on these panels and the clinical utility of multigene testing. It will be most important to assess the clinical utility for all testing, as that has become the single most important factor in assessing coverage decisions for all payers. Educating payers about the value of testing to reduce overall cost to their company is an important part of achieving reimbursement for genetic testing. Many positions already exist in test utilization management. A growing number of insurance companies are using GCs to assess their coverage policies for genetic testing and to provide

input on approving coverage decisions. For all of these reasons, the opportunities for GCs will only continue to expand.

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2

Regulation of Laboratory Genetic Testing

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The many aspects of laboratory regulation affect genetic counselors (GCs) working in both the clinical and laboratory settings. Clinical GCs play a significant role in determining which tests to offer patients, which laboratories to consider for testing, and which phenotypic information to provide to the clinical laboratory to improve the interpretation of test results. Given their client-facing role as well as their involvement in the testing process, laboratory GCs must maintain awareness of the laboratory regulations pertinent to the type of testing offered and the specimens received in their laboratory. To serve adequately in these roles, clinical and laboratory GCs alike should understand the regulatory oversight of genetic testing, including the strengths and limitations of current regulation.

Laboratory regulations provide rules to establish consistency, provide the basis for evaluation of performance, and describe the qualification and experience requirements of laboratory staff to fulfill the regulatory descriptions. They may originate from tenets of expert opinion, consensus positions, or evidence-based studies to incorporate guidance, recommendations, and best practices. The development of regulation (the regulatory process) involves identifying a problem, developing policy alternatives, translating those into legislation, researching the feasibility or impact of implementing the proposed rules (regulatory impact analysis), formalizing the regulations, and establishing agency authority to implement and oversee compliance with regulations. The purposes of regulations are to ensure the safety of the public, define standards for effective practices, produce meaningful results for decision making, improve the health of the public, and provide a framework for compliance oversight.

Genetic testing includes several types of laboratory specialties and many methods and technologies, and regulation and test performance specifications can be specific to different types of genetic testing. For laboratory genetic testing these regulations describe performance specifications to ensure patient safety, standardization of laboratory test performance specifications (e.g., accuracy, sensitivity, specificity, precision, reproducibility, reliability), and clinical decision support. Test performance specifications are usually evaluated as analytic validity, clinical validity, and clinical utility. The clinical value and impact of the genetic test will depend on the intended use of the findings and the type of testing available. The genetic information may support disease screening, disease diagnosis, carrier testing, preimplantation diagnosis, prenatal diagnosis, predictive or presymptomatic testing, or pharmacogenomics. A single assay

type may not serve all of these roles, nor may it be suitable for all populations of patients or families.

Cytogenetic tests for chromosome abnormalities such as aneuploidy, large deletions, insertions, duplications, and inversion and translocation rearrangements, have also been widely used for diagnosis of genetic conditions. Historically this relied on microscopy to analyze chromosome number, size, morphology, and banding patterns to identify karyotypes. More recent technologies using fluorescent detection and molecular methods such as chromosomal microarrays for comparative genomic hybridization are considered the standard of care. Many syndromes with multiple symptoms and abnormalities may be characterized with chromosome abnormalities.

Molecular genetic testing detects DNA variations associated with a specific disease or condition by interrogating a single gene, many genes (a gene panel), or the entire genome. Clinical molecular genetic testing includes disease diagnosis, asymptomatic carrier detection (preconception and prenatal), predictive disease risk assessment, disease prognosis, and treatment selection.

Federal Regulating Agencies

Three federal agencies—Centers for Medicaid and Medicare Services (CMS), Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA)—are responsible for regulating all clinical laboratories, including genetic testing labs, to ensure compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA), legislation enacted to improve the quality of laboratory practices (Fig. 2.1). CMS regulates the education requirements for laboratory personnel, defines the quality control of laboratory processes, monitors laboratory performance in proficiency testing, conducts inspections, and enforces regulatory compliance. CMS also issues laboratory certificates, collects user fees, publishes CLIA

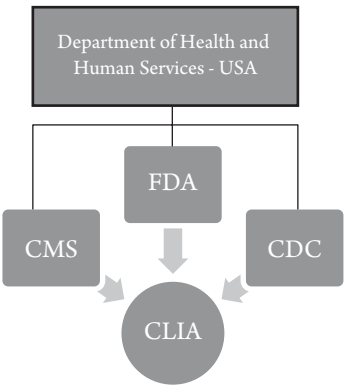

Figure 2.1 The Centers for Medicaid and Medicare Services (CMS), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA) jointly regulate the Clinical Laboratory Improvement Amendments (CLIA) program.

rules and regulations, and approves private accreditation organizations (e.g., the Joint Commission and the College of American Pathologists) and state exemptions (New York and Washington).

CDC provides scientific analysis, research, and technical assistance in developing standards and laboratory practice guidelines. These are accomplished by conducting laboratory quality improvement studies and monitoring proficiency testing practices. The findings are communicated directly to CMS and other federal, state, and local agencies; to many professional organizations for laboratory and healthcare experts; to policymakers, partner certification organizations, and stakeholders; and to educational institutions. CDC also manages the Clinical Laboratory Improvement Advisory Committee, which provides recommendations to the federal Health and Human Services Secretary about possible changes to CLIA requirements.

FDA regulates the safety and effectiveness of laboratory tests under the authority of the Medical Devices Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act. FDA develops the rules and guidance for defining the CLIA categories of tests by complexity, reviews requests for CLIA Waiver by Application for simple devices or test categories, and regulates test use according to how the test comes to market. Waived tests are those that are simple to perform, those that require no special training or controls, and those for which an inaccurate result is unlikely to cause serious harm to patients. Examples are home pregnancy kits or home HIV detection tests. FDA oversight is based on the intended use of the test or device and the risks posed to the patient as a result of an inaccurate test result. Medical devices include in vitro diagnostics (e.g., laboratory tests, test kits, implantable artificial organs) and are categorized into one of three risk-based classes according to the level of regulatory control necessary to ensure safety and effectiveness:

- Class I represents a relatively low risk of harm to the patient and uses general quality controls (no specific analytes) to ensure accuracy and quality.
- Class II includes devices or tests that pose a moderate to high risk of harm to the patient if performed or used incorrectly and require some special controls and premarket review to provide assurance of safety and effectiveness.
- Class III devices pose the highest risk of harm to the patient and require the greatest level of premarket review and scrutiny (usually because the test result leads to a clinical treatment decision or intervention).

FDA requires premarket review of test data and testing claims prior to use and reporting of patient results as well as postmarket reporting of adverse events or product recalls.

Certification Process

CLIA legislation enacted in 1988 requires that all laboratory testing performed in the United States on human clinical specimens intended for diagnostic or therapeutic purposes be performed in CLIA-certified laboratories. International laboratories are exempt from these regulations, as are research, forensics, and waived

tests. CLIA regulates laboratories to ensure accurate and reliable test results by focusing on the requirements for quality laboratory operations. All laboratories that perform testing on human specimens must be CLIA certified as the legal requirement to releasing information "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" (U.S. Government Publishing Office 2015), and this includes research laboratories that return individual patient results. Enforcement of the requirement for certification is achieved by a Medicare requirement that any claim for reimbursement of a laboratory test must include the CLIA certificate number. Also, any citizen complaint about a laboratory is likely to produce an enforcement visit. Laboratories are exempt from CLIA requirements if they are research laboratories that test human specimens but do not report patient-specific results. Laboratories that report patient specific results associated with personal identifiers to research study participants should obtain CLIA certification even if they do not charge for the testing. Similarly, even if they provide a disclaimer statement that the test was performed on a research basis, a CLIA certificate should be obtained. CLIA-certified laboratories are required to ensure that the laboratories they send samples to for clinical testing are also CLIA certified.

The CLIA regulations recognize that different tests require different levels of scrutiny, and consequently certification requirements vary with the complexity of the testing being performed. To differentiate between different tests, categories of tests are defined based on the complexity of the analytic process. Categories are (a) waived tests, (b) Provider Performed Microscopy (PPM) cytology tests performed by a physician or advanced practitioner using microscopy (not cytogenetics), (c) moderately complex tests, and (d) highly complex tests. This classification determines the level of oversight (including proficiency testing, quality control, and personnel qualification) and depends on the type of test being performed.

Certification is structured according to the nature and complexity of the testing the lab performs. Waived testing (Certificate of Waiver) includes "tests so simple and accurate that error is unlikely, or pose no reasonable risk of harm" to the person being tested. No pretreatment of the clinical specimens is involved. No calculations or expert interpretations are required. Untrained individuals may perform the waived test by following the manufacturer's instructions described in the product insert. Proficiency testing is not required. Examples of waived tests include over-the-counter pregnancy tests or personal glucose monitoring devices.

Laboratories that perform moderate- or high-complexity tests must be issued a Certificate of Compliance by CMS or a Certificate of Accreditation by a CMS-approved accreditation organization. These CMS-approved accreditation organizations include the College of American Pathologists (CAP), the Joint Commission (formerly JCAHO), the American Association of Blood Banks, the American Society for Histocompatibility and Immunogenetics, and others. Laboratories in the states of New York and Washington or in the Veterans Administration system are exempt from CLIA regulations because they have separate regulatory oversight programs that satisfy the CLIA requirements. Often the state regulatory oversight programs have additional requirements. A laboratory that is certified to perform only waived testing (Certificate of Waiver) may not perform moderate- or high-complexity testing under

this same certificate, but a Certificate of Compliance lab may perform both high-complexity and waived tests.

The CLIA certification process for genetic testing laboratories includes (1) an application to CMS describing the types and volume of laboratory testing services, (2) the payment of a biennial fee structured according to the annual volume of testing performed, and (3) on-site laboratory inspection to verify compliance with CLIA regulations. The CLIA fee is proportional to the complexity and the test volume of the laboratory, ranging from $150 for a laboratory performing only waived tests to almost $8,000 for a laboratory performing more than a million tests annually. Compliance is reviewed in areas of personnel qualifications, successful proficiency testing performance (or alternate external quality assessment), quality control, maintenance of operations, and testing records. All must be aligned with the type of testing allowed under the laboratory's certificate. Medicare-approved billing requires that a laboratory has a CLIA certification; failure to comply may incur penalties or sanctions regarding billing practices. Institutions may have a single CLIA certificate, or laboratories in an institution may have their own separate CLIA certificates.

Regulated Specialty Areas

Most molecular genetics tests are classified as moderate or high complexity by CLIA. There is no specific CLIA specialty category for most genetic testing, except clinical cytogenetics, but this is limited to karyotyping and does not include fluorescence in situ hybridization (FISH) or chromosomal microarray methods. All genetics labs must comply with general CLIA requirements for moderate- or high-complexity laboratory testing. These tests require qualified, trained personnel to both perform and interpret high-complexity testing. Proficiency testing must be performed for all test types through proficiency survey programs, inter-laboratory comparisons and specimen exchanges, or alternative performance assessment schema. Specific and complex reagents and reference materials are usually required to ensure quality test performance specifications are sustained. Specialized knowledge and expertise is necessary for appropriate and meaningful results interpretation and reporting. These test systems are not automated and must be monitored for equipment maintenance and intervention.

The FDA determines the CLIA complexity level of diagnostic tests by reviewing package insert instructions during premarket approval. Seven criteria required for test performance are evaluated during this review:

- Knowledge—Is minimal or specialized knowledge required to perform the test? To interpret the test results?
- Training and experience—Is minimal or specialized laboratory training required for performing the testing? Is limited or substantial experience in laboratory testing necessary?
- Reagents and materials preparation—Are reagents and materials prepackaged or premeasured? Do they require special handling? Are the reagents stable or labile? Are manual preparation steps required prior to use?

- Operational steps—Is implementation of the testing process automatically executed and easily controlled? Is close monitoring of the test system, special specimen preparation, precise temperature control or exact timing of operational steps, or extensive calculations necessary to ensure good test performance?
- Calibration, quality control, and proficiency testing—Are these materials readily available and stable when stored?
- Test system troubleshooting and maintenance—Are these systems automatic or self-correcting? Is instrument maintenance easy to perform or provided by the manufacturer? Does maintenance or troubleshooting require special knowledge, skills, and abilities of the laboratory personnel?
- Interpretation and judgment—Are there minimal or extensive requirements for interpretation and judgment throughout the testing process? Does resolution of problems require extensive independent knowledge or experience?

Scores of 1 to 3 are assigned to each parameter, with a score of 1 representing the lowest level of complexity for that criterion and 3 as the highest level of complexity. Typically a compiled score of 12 or less represents moderate complexity and greater than 12 represents high complexity. The FDA has an online CLIA categorizations database (U.S. Food and Drug Administration 2014) that provides detailed information about test categorization for FDA-cleared and FDA-approved assays. These are typically commercial test kits and analytic instruments including interpretive software.

Genetic test kits or systems that are FDA cleared or FDA approved are assigned to a subset of medical products called in vitro diagnostic (IVD) devices: "reagents, instruments, and systems intended for use in the diagnosis of disease or other condition, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae" (U.S. Food and Drug Administration 2002, 2015a). These devices are intended for use in the collection, preparation, and examination of specimens taken from the human body. The manufacturer has submitted extensive documentation (and a fee) to FDA prior to marketing the product about the safety and efficacy of the device, its intended use, and the quality of the design and manufacturing process that was followed in the IVD production.

IVDs are classified into Class I, II, or III according to the level of regulatory control necessary to ensure safety and effectiveness. This classification also determines the appropriate degree of scrutiny or premarket review process that FDA will follow. For example, Class I devices require only general controls, Class II devices require general and special controls, and Class III devices require all of the Class II criteria plus premarket approval. There are no Class I genetic tests. A complete list of approved human genetic tests is listed by the FDA (U.S. Food and Drug Administration 2016a). Device classification depends on the intended use of the test and the indications for use. Devices that are FDA cleared have been through the 510(k) review process, while those that are FDA approved have been through the Premarket Approval (PMA) review process. The same IVD may have different levels of risk depending on the intended use. For example, a genetic test that screens asymptomatic individuals for a condition is higher risk than the same test used for individuals who already have a clinical diagnosis; the burden of proof is higher in the absence of disease symptoms.

There are many more detailed descriptions and resources available at the FDA website to describe the application and review processes. Most genetic tests offered currently have not been through the FDA review process and have not been assigned to these categories. The primary reason is that manufacturers have not developed in vitro diagnostic tests for many genetic disorders because they are relatively rare (compared to infectious disease testing, for example) and do not represent significant return on investment. This is one of the quality areas that the currently planned oversight of laboratory-developed tests (LDTs) will clarify and define.

Areas of Regulatory Focus

A central challenge for a genetic testing laboratory is spanning the gap from general CLIA requirements for high-complexity testing to defining and implementing specific quality practices necessary for accurate genetic testing. This may be achieved through several models of service delivery. For example, the laboratory may choose to perform only FDA-cleared or FDA-approved assays to minimize the experience and resources required to provide testing (Table 2.1). Before putting these assays into clinical use the labs must perform and document test verification to demonstrate that the assay and clinical lab personnel perform the test to the same specifications that the manufacturer claims. The same acceptable specimen type(s) and collection tube or matrix must be used as specified by the manufacturer's instructions. Deviations from or modifications of the manufacturer's specifications will require a full and detailed test validation by the clinical laboratory. There are many resources that describe the details of laboratory test verification and validation, which are beyond the scope of this chapter. Examples of FDA-cleared genetic tests include CFTR Gene Mutation Detection System, a Class II device (U.S. Food and Drug Administration 2005) that involves multiplex polymerase chain reaction (PCR) amplification of specific DNA variants in the CFTR gene using non–sequencing-based methods. Another example is Factor V Leiden DNA Mutation Detection System, a Class II device (U.S.

Table 2.1 **In Vitro Diagnostic Device Classification**

IVD Category	*FDA Regulatory Oversight*	*Review Criteria*
Laboratory-developed test (LDT)	Enforcement discretion, no FDA review prior to use*	CLIA requirements for lab performance and test validation**
FDA cleared (Class II)	Premarket notification, 510(k) review process	Analytic performance specifications reviewed to support claims and clinical use
FDA approved (Class III)	Premarket authorization (PMA)	Clinical utility, safety, and effectiveness

* Current as of May 2016

** Not lab test manufacture

Food and Drug Administration 2004) that involves closed-tube PCR amplification and direct detection of a single base change. Few genetic tests fulfill these criteria. Class III genetic test examples include those that determine a specific therapy or clinical follow-up procedures such as a nucleic acid–based test for DNA methylation in colorectal neoplasia (U.S. Food and Drug Administration 2016b). A positive result with this test should be followed with a diagnostic colonoscopy. Extensive clinical trial data were required for the premarket approval of this very complex test.

Labs with more experienced personnel and resources to perform test validation may perform FDA-cleared tests, FDA-approved tests, and LDTs, which are designed in the laboratory with quality analyte specific reagents (ASRs) that confer specificity for detection of an analyte. ASRs are not diagnostic tests or kits by themselves. Reagents and materials labeled as Research Use Only (RUO) or Investigational Use Only (IUO) may not be used for clinical testing purposes. A thorough validation of the LDT performance throughout the total testing process (preanalytic, analytic, and postanalytic phases) must be demonstrated and documented prior to testing clinical specimens. For preanalytic systems, CLIA requires laboratories to establish quality systems for processing test requests and submitting, handling, and referring specimens. Analytic performance specifications to be defined and measured include accuracy, analytic sensitivity, analytic specificity, precision, reportable range, reference intervals, and limit of detection (Table 2.2). The validation process should include comparison to an existing reference method to assess the trueness of the results. Interfering substances and environmental conditions must also be described. Reproducibility between duplicate samples within a testing batch as well as between testing batches performed by different operators or in different lab settings may also be required. All reagents, specimen types, instruments, and software must be evaluated in the validation process. A full range of positive controls for each genetic variant type (i.e., allele or base change), negative controls (absence of a genetic variant), and no substrate (DNA) controls are necessary to monitor possible cross-contamination of reagents or specimens. For LDTs that will report a quantitative result, such as cancer diagnostics or genetic mosaicism, some additional precision criteria must be validated for the linearity of the data across a range of concentrations, the lower and upper limits of measurement linearity, and the lowest amount of analyte that may be distinguished from the "background" signal of a negative control (limit of detection) with clinical significance.

Postanalytic quality systems must ensure that test results and other patient-specific data are transmitted accurately and reliably. The test report information must be maintained in a readily available manner, with record retention of 25 years recommended for genetic testing to inform testing for offspring of the affected patients. Follow-up notification of authorized persons—either healthcare professionals, patients, or designated family members—of any errors detected in reported patient test results is also facilitated by record retention policies.

There are several sources of both expert and consensus guidance documents that describe recommended laboratory practices to facilitate quality testing as well as regulatory compliance. Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions (Chen et al. 2012a) and Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening of Inherited Metabolic Disorders (Chen et al. 2012b), published by CDC, provide detailed descriptions

Table 2.2 **Laboratory Test Performance Specifications**

Term	*Definition*
Accuracy	Closeness of agreement of measured quantity value and a true quantity value
Analytic validity	Assessment of the performance characteristics of an assay (accuracy, precision, specificity, limits of detection and quantitation, linearity and range, repeatability and reproducibility)
Analytic sensitivity	Smallest amount of a substance that can be reliably measured
Analytic specificity	Ability of test to measure solely the detectable analyte
Positive control	Sample that will give the desired measurement or genotype
Negative control	Sample that will not have the desired measurement or genotype
Precision	Closeness of agreement between measured values obtained by replicate measurements
Repeatability	Measurement precision of replicates under repeated and same conditions (same system, same operator, same procedure, same location)
Reproducibility	Measurement precision of replicate measurements under reproducible but different conditions (different system, operator, procedure, location)
Reportable range	A set of measured values for which the lab has established the accuracy of the test
Limit of detection	Lowest amount of analyte that can be detected with stated probability
Clinical validity	The accuracy with which a test predicts the presence or absence of a clinical condition or predisposition
Clinical utility	Value or benefit assigned to diagnostic information (test result) that contributes to diagnosis of condition or disease
Positive predictive value	The likelihood that a positive test result will correctly detect the presence of a disease
Negative predictive value	The likelihood that a negative test result will correctly detect the absence of a disease

of these criteria. Many genetics laboratory guidance documents are also available from professional laboratory organizations such as the American College of Medical Genetics and Genomics (2007), the Association for Molecular Pathology (n.d.), and the Clinical and Laboratory Standards Institute (CLSI 2005, 2008, 2011, 2012a, 2012b, 2013, 2014, 2015).

Laboratory directors are responsible for determining whether an LDT meets the performance requirements to be implemented as a clinical test. The specific design of an LDT validation will vary with the type of assay, the complexity of the assay, the prevalence of the target or genetic variation in the patient population, the analysis required for reporting the data in a clinically meaningful format, and the established accuracy for the reference method (Sloan 2007; Jennings et al. 2009; Burd 2010).

Analytic validation is distinctly different from clinical validation and clinical utility. All three of these values define how well the genetic variants relate to the presence, absence, or risk of specific disease and whether the test provides clinically actionable information about the disease. These values are determined by the intended use of the test and the test findings for supporting patient care decisions for diagnosis, treatment selection, and management or prevention of symptoms that will be of use to the healthcare provider. These are also values required of tests that are submitted for FDA review but are not specifically required for CLIA certification. Frequently genetic testing laboratories cite data published in peer-reviewed journals to document clinical validity and clinical utility because randomized control trials are impractical for rare genetic disorders, particularly those with genetic heterogeneity.

Clinical utility is defined by the impact or usefulness of the test result on the patient or public health and is affected by aspects of disease presentation. For example, the relative prevalence of a disorder can affect the significance of the test result in terms of the positive and negative predictive values. For low-prevalence disorders the predictive value of a positive test result may be low but the predictive value of a negative test to rule out disease is high. However, for high-prevalence disorders the positive predictive value may be high but the negative predictive value to rule out disease is low. In addition, the frequency of the genetic variant, allelic and genetic heterogeneity, penetrance, expressivity, genotype–phenotype correlations, and founder effects must be considered when interpreting the relative significance of a negative test result and the possible residual risk that a mutation not included in the test scope may be present in the patient. For example, a cystic fibrosis genetic test that includes alleles that are prevalent in an Irish population may not detect alleles present in people of Ashkenazi Jewish descent with equal sensitivity. For genotypes with 100% penetrance, a positive test result is 100% specific for disease phenotype. Detection of a positive result for genotypes with reduced penetrance, however, is less than 100% predictive of disease phenotype. These criteria must be considered in applications for specific populations of patients both in the design of the test and in the interpretation of the findings.

In the past few years the use of LDTs has come under increased scrutiny by Congress and the FDA. LDTs were traditionally designed with simple test methods