NIST Physical Standards for DNA-Based Medical Testing

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As DNA and RNA become major targets for clinical laboratory analysis, benchmark reagents will play an increasingly important role in standardization. Reliable national and international nucleic acid standards promote automation and third-party reimbursement for clinical testing. Furthermore, nucleic acid standards provide materials for quality assurance and quality control (QA/QC), and proficiency testing. Standard methods and training initially evolved from consensus guidelines endorsed by professional societies and governmental agencies. The National Institute of Standards and Technology (NIST), a nonregulatory agency of the U.S. Department of Commerce, develops and certifies

physical and chemical standards in support of national commerce, manufacturing, and science. In its role supporting U.S. science and industry, the NIST responds to specific standards needs, most recently for medically and biologically important analytes. Broad-based consensus developed through interdisciplinary NIST workshops initiated development of NIST-certified DNA standards. Such materials serve the diagnostic community and help manufacturers benchmark a variety of DNA diagnostic testing platforms. Here we summarize the NIST experience and programs for development of national standards for DNA-based medical diagnostic testing. *J. Clin. Lab. Anal.* 16:5–10, 2002. © 2002 Wiley-Liss, Inc.

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INTRODUCTION

The National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards (NBS), is the U.S. federal agency whose mission addresses national needs for standards and measurements in science and the economy (1). Its goal is to promote the competitiveness of U.S. industry by the development and application of technology, measurements, and standards.

Each year, as the need for new standards arises in the private sector or in other governmental agencies, Standard Reference Material® (SRM®) proposals from NIST scientists are developed in response. Following scientific review, high-priority applications receive NIST funding to support development and production phases. In some cases, outside groups participate in cost sharing to expedite standards production at the NIST.

The need for nationally accepted clinical laboratory stan-

dards has often been unforeseen until issues arise. There is frequently a lag before technical and research innovations find their way to clinical application. Early in the process, it may be unclear which technologies will survive market selection and secure a permanent place in the clinical diagnostic testing laboratory. This is especially true during times of rapid technological development. Few areas of clinical testing have developed as rapidly as DNA-based molecular diagnostics. The consequence is that material standards follow discovery, implementation, and validation of most diagnostic technolo-

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gies. The role of the NIST in developing national DNA standards for medical diagnostics illustrates this.

NIST Organization: Standards and Measurements Capabilities

The first commercial research laboratory was established at the General Electric Company in the late 1800s. Shortly thereafter, advocacy by prominent American scientists and industrialists led to the creation of the NBS (1901), the first federal physical science laboratory. This new federal institution was organized to aid manufacturing, commerce, makers of scientific apparatus, and the scientific work of government, schools, colleges, and universities (2). Since then, the NBS and its successor the NIST diversified as the U.S. technology base steadily expanded and changed during the course of the 20th century.

The NBS mission was implemented by recruiting research scientists as original NBS staff. NBS laboratories were constructed on Connecticut Avenue in Washington, D.C. Soon after, a publicly accessible collection of standard reference materials was initiated. This formed the basis for a remarkable expansion of the NIST collection of reference materials over the succeeding 95 years (2). Since initiation of the program, Standard Reference Material® and SRM® have become registered trademarks owned by the NIST.

Currently, four program areas and several laboratories implement the NIST mission. Measurement and Standards Laboratories are the major research and technology components at the NIST. They include the Electronics and Engineering Laboratory, Manufacturing Engineering Laboratory, Chemical Sciences and Technology Laboratory, Physics Laboratory, Materials Science and Engineering Laboratory, Building and Fire Research Laboratory, and the Information Technology Laboratory.

Additional programs promulgate the NIST mission. The Advanced Technology Program (ATP) oversees matching funds awards for governmental support of emerging technologies in private sector–government partnerships. The Manufacturing Extension Partnership administers support for small manufacturing concerns. The Baldrige Quality Program is an outreach award that recognizes performance excellence and quality achievement in business. The NIST Office of Measurement Services provides intramural funding for invention, development, and production of NIST SRMs®. This office maintains an inventory and an online catalog of currently available NIST reference materials.

NIST SRMs®

Consistent with the NIST mission, the current SRM® catalog (Table 1) is an outgrowth of the first “Standard Samples” sold by the NBS in 1905. The SRM® program originated with 17 types of steel provided to NIST for validation at the request of the Association of American Steel Manufacturers.

The NBS undertook certification and distribution of these, the precursors of numerous NIST SRMs® (2).

SRMs® are federally developed and distributed material standards produced at the NIST. Each SRM® comes with a certificate detailing conditions for use and associated characterization data. Terms such as “NIST-certified” and “NIST-traceable” have formal definitions that are detailed in NIST Special Publication 260-136 (3). Whereas only those primary standard SRMs® produced at NIST are “NIST-certified,” secondary standards manufactured with appropriate direct linkage to NIST standards can be “NIST-traceable.” The statistical treatment of NIST SRMs® is described in NIST Special Publication 260-125 (4).

Standards for heavy industry were followed by standards development and production in diverse technical fields. The first health-related SRM®, a cholesterol standard, was produced in 1967. This was followed by other crystalline standards and serum-based SRMs®, as well as serum supplemented with known concentrations of vitamins and cholesterol, and various drugs for urine analysis in medical and forensics settings (5,6).

Today, health is one of many market sectors for which NIST standards are available. Additional SRM® program information can be viewed online at <http://www.nist.gov/srm>.

With new DNA diagnostic tests for various human diseases, and the growth of businesses that focus on genetic diagnostics, new standards needs have emerged during the last decade. The basis for NIST activities in human DNA diagnostics was established during a March 15–18, 1998, meeting at Gaithersburg entitled “Workshop on Standards for Nucleic Acid Diagnostic Applications.” This conference on the NIST campus brought together practitioners of human genetics, pathology, infectious disease, and human genetic identification to discuss common technology and standards issues. A standing committee was established following the workshop to periodically review progress and future directions.

In related work, DNA-based SRMs® have been completed and additional SRMs® are under development (Table 1). The focus of this review is NIST DNA standards for medical diagnostics. Nucleic acid standards and methods for diagnosis of infectious disease (7–12), human genetic identification and forensic applications (13,14), human medical genetic diagnostics (15), and cancer diagnostics (16) have been discussed elsewhere.

Biomedical Research and Standards Development at NIST

Early work on biomedical standards for commercially available surgical materials, such as dental amalgams, was initiated at NBS in 1919 in response to needs of the U.S. military. The variability in quality of restoration materials from private vendors caused problems for military dentists (1). This research and development program, formalized with the National Institute of Dental Research at the National Institutes

TABLE 1. NIST SRMs[®] for forensic analysis, human genetic identification and medical diagnostics

Application/technology	SRM [®] physical form	NIST SRM [®] number	Use	Availability	Reference
DNA profiling standard, RFLP Analysis (Genomic DNA)	Cells, isolated DNA, cleaved DNA	2390	F/I	Yes	Duewer et al. [2000] ^a (19)
PCR-based profiling standard, PCR analysis (genomic genotyping)	Genomic DNAs	2391	F/I	Yes	UP ^b
DNA mitochondrial sequencing, PCR analysis (mt DNA/sequencing)	Cellular DNAs	2392	F/I/M	Yes	Levin et al. [1999] ^c (20)
PCR analysis: TP 53 gene mutations	12 DNA clones	2393	M	UD	O'Connell et al. [1998] (22)
PCR heteroplasmy detection (mt DNA mixtures)	Mixtures of PCR products	2394	F/I/M	UD	UP
PCR analysis (Y chromosome genotyping)	Male cell lines	2395	F/I	UD	UP
Characterization of DNA damage	Pure modified nucleic acid bases	2396	M/T/C	UD	UP
Fluorescence intensity standard	Validated fluorescein solution	1932	M/C	Yes	Gaigalas et al. [2001]

^a<http://ois.nist.gov/srmcatalog/certificates/2390.pdf>^b<http://ois.nist.gov/srmcatalog/certificates/2391a.pdf>^c<http://ois.nist.gov/srmcatalog/certificates/2392.pdf>

F, forensics; I, human identification; M, medical; T, toxicology; UD, under development; UP, unpublished; C, instrument calibration.

of Health (NIH) in 1984, is an example of a governmental interagency collaboration for research and development of standard materials that has spanned more than 80 years.

There are other early examples of NIST technological expertise being directed toward medical science in research as well as standards development. NIST involvement in biomedical imaging research included early computer-assisted cytometric analyses of cortical brain sections (17). These pioneering research studies were also undertaken as a collaborative effort between the NIST and the NIH.

In other collaborations with the NIH, the NIST has been actively engaged in developing clinical chemistry standards. A series of blood analyte SRMs[®] are available as a result of over 10 years of work (5,6).

The need for calibration and fluorescence intensity standards in the clinical flow cytometry community and in the DNA array community was motivation for the NIST fluorescence intensity standards program (18). This program will produce a precisely characterized liquid fluorescence intensity standard based on fluorescein (SRM[®] 1932), and plans are underway to develop corresponding standards for DNA array quantitation.

These precedents for NIST activity in biomedical research and standards development followed a similar pattern when the need for technology and standards arose in the government and private sector. The NIST responded by providing specialized technical and scientific expertise to provide for those expressed needs, fostering economic and scientific development in the process.

Standards for Forensic Analysis at the NIST

Current DNA work at the NIST owes its origin to the need for benchmark standards in forensic analysis and human genetic identification. NIST involvement came in response to

requests from the U.S. military and the private sector. This area of research continues as an active program within the DNA Technologies Group in the Biotechnology Division, Chemical Science and Technology Laboratory, at the NIST. In addition to research papers, a resulting product of this activity takes the form of DNA-based SRMs[®].

More than eight decades after the first SRMs[®], the NIST established the DNA profiling standard (SRM[®] 2390) in 1992 (19), and a PCR-based profiling SRM[®] in 1995 (SRM[®] 2391) for human genetic identification (Table 1). The details of DNA mitochondrial sequencing SRM[®] 2392 (20) are listed on the Internet and describe a standard NIST kit for sequence analysis of mitochondrial DNAs (Table 1).

For several research and certification SRM[®] projects, corresponding publicly accessible Internet-format databases have been developed. For example, STRbase summarizes information on the DNA sequence short tandem repeats (STRs) (21) for use in forensic analysis and human genetic identification at <http://www.cstl.nist.gov/biotech/strbase/>.

Additional SRMs[®] for DNA analysis under development include a characterized standard set of p53 gene mutations (SRM[®] 2393) (22), an SRM[®] for detection of mitochondrial DNA heteroplasmy (SRM[®] 2394), a set of additional STRs for genetic fingerprint analysis of the human Y chromosome (SRM[®] 2395), and a collection of certified DNA base variants for analysis of oxidatively damaged DNA (SRM[®] 2396) (Table 1).

While developing physical and chemical standards, the NIST has also conducted extensive interlaboratory validation trials to characterize performance of DNA markers and to improve analytical methods in forensic analysis and human genetic identification (23–29). This activity will be expanded as the NIST works with the National Cancer Institute (NCI) on collaborative validation projects.

In parallel with its DNA diagnostic standards work, the NIST is active as a biomarker validation site for the NCI's early detection research network (EDRN) (30). This joint NIST-NCI program evaluates promising biomarker assays for early detection of cancer, especially those based on molecular genetic, cytogenetic, and in situ hybridization (ISH) technologies. Technical validation activities for medical diagnostic testing are thus closely integrated with NIST work in standards and measurements in several areas of technology, with direct impact on the medical diagnostics laboratory.

Genetic and Infectious Diseases: The Need for Standard DNA and RNA Analytes

The advent of recombinant DNA in the 1970s set the stage for molecular cloning of a large number of human genes of clinical relevance, and the recently completed sequencing of the entire human genome (31). As genes were integrated into a physical human genome map and the genome effort moved into its applied phase, opportunities for extensive medical genetics diagnostics emerged.

Parallel with the U.S. federal government and the related international consortium of genome laboratories, the private sector took a leading role in accomplishing this feat (32). This brought to public attention the recent trend that biotechnology research and development have evolved in the private sector in parallel with (and increasingly independently of) academic laboratories. With expanding economic impact, the biotechnology market has grown considerably in the past 25 years.

As genetic sequence information expanded, opportunities for DNA-based diagnostics also grew. Along with genetic diseases, infectious diseases can also be diagnosed through nucleic acid analytes.

Technologies such as polymerase chain reaction (PCR), reverse transcription (RT)-PCR, and, more recently, quantitative (Q)-PCR encouraged clinical applications of nucleic acid-based methods for detecting infectious agents (7). Molecular diagnostic tests, such as those with in-house verification only, utilized molecular technologies developed to detect and identify a wide variety of human pathogens. Increasingly, the private sector is involved in such testing. The U.S. Food and Drug Administration (FDA) has been called upon to evaluate many of the innovations of the biotechnology revolution for commercial development.

Although some have received FDA approval, commercially available kits for microbiological testing are still relatively rare. The trend is toward better standards, QA/QC, and automation with miniaturization where practicable. Developments in related applications of nanotechnologies, such as microfluidics, will accelerate the evolution of new test platforms. For example, while they are available from private-sector vendors, HIV test kits often rely on synthetic or artificial standards developed for these assays. Laboratories that imple-

ment their own locally developed assays (so-called "home brews") use synthetic controls, poorly standardized controls from vendors, or specimen samples from their own patient populations. There is a clear need for universally acceptable RNA-based consensus standards in this and other infectious diseases. To date, the NIST has not been involved with DNA- or RNA-based SRMs[®] for detection of infectious disease. However, needs in this area are emerging.

Standard live biological substrates are another emerging area in which institutions other than the NIST take the lead. Except for frozen cells as components of SRMs[®], the NIST does not maintain a "standard" cell bank. Several excellent private foundations and institutions maintain frozen stocks of viable human cells and various microorganisms. The American Type Culture Collection in Manassas, Virginia, is an example. Some professional organizations also maintain similar materials for their own QA/QC needs. An illustration is the set of standard cell lines for transplantation validation and standardization work that is available from the American Society for Histocompatibility and Immunogenetics.

When the need for specific standards is identified in such areas, the NIST may take a role, but only in response to an expressed consensus on which needs are of the highest priority.

Appropriate Applications and Use of NIST SRMs[®]

Table 1 gives a brief overview of DNA-based physical standards available or under development at the NIST laboratories at the Gaithersburg, Maryland, campus. A few comments on their use and intended applications are in order, especially in the context of how these reagents were envisioned. Kit packaging and NIST SRM[®] certificates are available to the public on the Internet (see Table 1). These clearly elaborate the uses, with supporting NIST data for these strictly defined applications.

The need addressed by the earliest DNA-based SRMs[®] was for benchmark reagents to promote the standardization of human genetic identification technology in the U.S. forensics community. Although many similar or identical DNA probes are used for medical purposes, most NIST SRMs[®] have not been intended, developed, validated, or cleared for such applications. In the NIST certificate that accompanies each SRM[®] (Table 1), the conditions and limitations for the use of NIST SRMs[®] are detailed.

Thus, applications beyond those specified by the NIST—for example, medical diagnostic applications for which NIST forensic analytical reagents might be used—are made with liabilities assumed by the user.

Published Standards, Guidelines, and Recommendations for DNA-Based Diagnostics

Concurrent with development of material SRMs[®], such as NIST-certified DNAs and fluorescence intensity standard solutions, an increasing awareness of emerging technologies

among professional organizations inspired the development of position papers on standards for clinical training, practice, and proficiency testing in molecular diagnostics. As a consensus-driven institution serving U.S. commerce, the NIST has worked with several such groups to solicit guidance and advice through ad hoc intramural committees, NIST workshops, and NIST scientific representation on committees of the American Society for Testing and Materials (ASTM) and the NCCLS (formerly the National Committee for Clinical Laboratory Standards).

Formal position papers bearing on standards for DNA-based diagnostics have been developed by the NCCLS, a voluntary organization (8,16,33), and governmental agency committees such as the Molecular and Clinical Genetics Panel of the FDA's Medical Devices Advisory Committee, the Centers for Disease Control and Prevention (34), the National Institutes of Health, and the U.S. Department of Energy (15).

Among professional groups contributing to consensus and nationally accepted guidelines for DNA-based molecular diagnostics, the American Society of Human Genetics and the American College of Medical Genetics (15,35) took the lead in developing written guidelines for DNA-based testing. A few studies of human molecular genetics QA/QC have appeared (36,37). Other organizations, such as the College of American Pathologists (CAP), the American College of Obstetrics and Gynecology (ACOG), and the new Association for Molecular Pathology (AMP), have fostered professional awareness of molecular diagnostic standards, technology, and proficiency issues in publications, at their annual meetings, and through listserv postings and online discussions.

A more broad-based approach to industry standards is embodied by the ASTM (West Conshohocken, PA). This encompasses standards for industry in general, including medical applications. Some ASTM committees focus on definitions for emerging biomedical work in the private sector, such as tissue engineering. ASTM subcommittee E-48.02 focuses on general PCR standards for detection of nucleic acids, and PCR detection of certain bacteria and viruses.

The ASTM is a voluntary organization that is increasingly global in emphasis. It seeks to be a primary source of voluntary consensus standards, methods, and practices related to technical information and services. Although it originated in the U.S., the ASTM strives for internationally recognized standards of quality and applicability. ASTM standards promote public health, safety, and overall quality of life; contribute to the reliability of materials, products, systems, and services; and facilitate commerce along a continuum of local to international applications.

Globalization of DNA Standards for Clinical Diagnostics: Organizations and Agencies

Whereas the NIST produces material (chemical and physical) standards to address national needs in the U.S., other orga-

nizations share the task of garnering consensus for written standards. The two organizations mentioned above, the ASTM and the NCCLS, are both moving toward global membership and an internationally relevant focus.

Like the ASTM, the NCCLS is a voluntary organization that solicits community input to develop guidelines for clinical testing procedures and reagents (see Refs. 8, 16, and 33 for examples). NCCLS guidelines are developed by committees of scientific and clinical experts. These are technically detailed presentations of the background, use, and standard of practice for laboratory medicine. Current NCCLS documents include several areas of molecular diagnostics.

Large institutions whose primary mission is national medical or DNA-based standards are rare. As is the NIST, such activities are usually under the aegis of institutions with a broader purpose. Although a few institutions offer standards for DNA-based medical testing, consensus work and development of standards for biomedical research and clinical diagnostics are carried out in the context of wider missions at several sites in Europe. A complete survey of these organizations is beyond the scope of this short review.

SUMMARY

We have presented a brief overview of the development and production of DNA standards for human medical genetics at the NIST. The NIST is a science and technology research institute of the U.S. Department of Commerce. In a climate of increasingly globalized efforts to develop benchmark standards and reagents for molecular diagnostics, the NIST assumes a role among U.S. and international organizations that promote common, universally acceptable biomedical standards for the betterment of U.S. and global health, and industries whose business derives from molecular genetic testing.

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Certain commercial equipment and materials were identified in this work in order to adequately specify the experimental procedures. Such identification does not imply recommendation or endorsement by the NIST or the U.S. FDA, nor does it imply that the materials and equipment identified are necessarily the best available for the purpose.

Although we have worked to solicit input on all DNA standards from as many sources as possible, omissions are inevitable and inadvertent. Organizations and institutions in the U.S. and abroad that wish to include contact information in a publicly available compilation of nucleic acid standards resources are welcome to contact NIST staff scientists at peter.barker@nist.gov or coc@nist.gov.

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REFERENCES

- Schooley JF. Responding to national needs: the National Bureau of Standards becomes the National Institute of Standards and Technology, 1969–1993. Washington, D.C.: U.S. Government Printing Office; 2000.
- Cochrane RC. Measures for progress—a history of the National Bureau of Standards. Washington, D.C.: U.S. Government Printing Office; 1976.
- May W, Parris R, Beck C, et al. Standard Reference Materials®. Definitions of terms and modes used at NIST for value-assignment of reference materials for chemical measurements. NIST Special Publication 260-136. Washington, D.C.: U.S. Department of Commerce; 2001.
- Schiller SB. Standard Reference Materials: statistical aspects of the certification of chemical batch SRMs. NIST Special Publication 260-125. Washington, D.C.: U.S. Department of Commerce; 1976.
- Schaffer R, Bowers Jr GN, Melville RS. 1995. History of NIST's contributions to development of standard reference materials and reference and definitive methods for clinical chemistry. *Clin Chem* 41: 1306–1312.
- Welch M, Colbert J. Certification strategies for health-related SRMs at NIST. *Fresenius J Anal Chem* 1998;360:312–316.
- Persing DH, Smith TF, Tenover FC, White TJ. Diagnostic molecular microbiology: principle and application. Washington, D.C.: American Society for Microbiology, 1993.
- NCCLS. Molecular diagnostic methods for infectious diseases, approved guideline. NCCLS document MM3-A (ISBN 1-56238-288-8). Wayne, PA: NCCLS; 1995.
- Saldanha J, Leliec N, Heath A. Establishment of the first international standard for nucleic acid amplification technology (NAT) assays for HCV RNA. *Vox Sanguinis* 1998;76:149–158.
- Saldanha J, Heath A, Lelie N, et al. 2000. Calibration of HCV working reagents for NATY assays against the HCV international standard. *Vox Sanguinis* 2000;78:217–224.
- Saldanha J. Validation and standardization of nucleic acid amplification technology (NAT) assays for detection of viral contamination of blood and blood products. *J Clin Virol* 2001;20:7–13.
- Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH, editors. Manual of clinical microbiology. 7th ed. Washington, D.C.: American Society for Microbiology; 1999.
- Budowle B, Smith J, Moretti T, DiZinno J. DNA typing protocols: molecular biology and forensic analysis. Natick, MA: Eaton; 2000.
- Levin BC, Reeder DJ. Reference materials for DNA analysis. In: Stoeppler M, Wolf WR, Jenks PJ, editors. Reference materials for chemical analysis—certification, availability and proper use. New York: Wiley-Liss, Inc.; 2000. p 160–172.
- Holtzman NA, Watson MS. Promoting safe and effective genetic testing in the United States. Final report of the task force on genetic testing, NIH-DOE working group on ethical, legal and social implications of human genome research. Washington, D.C.: U.S. Government Printing Office; 1997.
- NCCLS. Immunoglobulin and T cell receptor gene arrangement assays; approved guideline. NCCLS document MM2-A (ISBN 1-56238-289-6). Wayne, PA: NCCLS; 1995.
- Lipkin LE, Watt WC, Kirsch RA. The analysis, synthesis and description of biological images. *Ann N Y Acad Sci* 1966;128:984–1012.
- Gaigalas AK, Li L, Henderson O, et al. The development of fluorescence intensity standards. *J NIST* 2001;106:381–389.
- Duewer DL, Richie KL, Reeder DJ. RFLP band size standards: NIST standard reference material 2390. *J Forensic Sci* 2000;45:1093–1105.
- Levin, BC, Cheng H, Reeder DJ. A human mitochondrial DNA standard reference material for quality control in forensic identification, medical diagnosis, and mutation detection. *Genomics* 1999;55:135–146.
- Ruitberg C, Reeder DJ, Butler J. STRBase: a short tandem repeat DNA database for the human identity testing community. *Nucl Acids Res* 2001;29:320–322.
- O'Connell CD, Tian J, Juhasz A, Wenz H-M, Atha DH. Development of standard reference materials for diagnosis of p53 mutations: analysis by slab gel electrophoresis. *Electrophoresis* 1998;19:164–171.
- Duewer DL, Currie LA, Reeder DJ, Leigh SD, Liu HK, Mudd JL. Interlaboratory comparison of autoradiographic DNA profiling measurements. II. Measurement uncertainty and its propagation. *Anal Chem* 1995;67:1220–1231.
- Duewer DL, Currie LA, Reeder DJ, et al. Interlaboratory comparison of autoradiographic DNA profiling measurements. IV. Protocol effects. *Anal Chem* 1997;69:1882–1892.
- Duewer DL, Lalonde SA, Aubin RA, Fournery RM, Reeder DJ. Interlaboratory comparison of autoradiographic DNA profiling measurements: precision and concordance. *J Forensic Sci* 1998;43:465–471.
- Duewer DL, Lalonde SA, Aubin RA, Fournery RM, Reeder DJ. Interlaboratory comparison of autoradiographic DNA profiling measurements: precision and concordance. *J Forensic Sci* 1998;43:465–471.
- Stolorow AM, Duewer DL, Reeder DJ, Bael E, Herrin Jr G. Interlaboratory comparison of autoradiographic DNA profiling measurements. III. Repeatability and reproducibility of restriction fragment length polymorphism band sizing, particularly bands of molecular size >10 K basepairs. *Anal Chem* 1996;68:1941–1947.
- Kline MC, Redman JW, Reeder DJ, Duewer DL. Intercomparison of DNA sizing ladders in electrophoresis separation matrices and their potential for accurate typing of the D1S80 locus. *Appl Theor Electrophor* 1996;6:33–41.
- Kline MC, Duewer DL, Newall P, Redman JW, Reeder DJ, Richard M. Interlaboratory evaluation of short tandem repeat triplex CTT. *J Forensic Sci* 1997;42:897–906.
- Srivastava S, Kramer BS. Early detection cancer research network. *Lab Invest* 2000;80:1147–1148.
- International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;409:860–921.
- Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science* 2001;291:1304–1351.
- NCCLS. Molecular diagnostic methods for genetic diseases; approved guideline. NCCLS document MM1-A (ISBN 1-56238-396-7). Wayne, PA: NCCLS; 2000.
- Williams LO, Cole EC. General recommendations for quality assurance programs for laboratory molecular genetic tests. Morrisville, NC: DynaCorp; 1999.
- Standards and guidelines: clinical genetics laboratories. 2nd ed. Rockville, MD: American College of Medical Genetics; 1999.
- Matteson KJ, Barker PE, Kaplan GC, et al. Regional evaluation of DNA diagnostic laboratories. *Am J Hum Genet* 1989;46:182–183.
- McGovern MM, Benach MO, Wallenstein S, Desnick RJ, Keenlyside R. Quality assurance in molecular genetic testing laboratories. *JAMA* 1999;281:835–840.