Curriculum Item #6 Qualification of molecular-genetic laboratory personnel

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ISO 15189 Accreditation Support Course

'Educational Curriculum, Qualification, and Career Development of Laboratory Professionals in Molecular Biology'

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1. Laboratory Personnel in Quality Assurance of Molecular-Genetic Testing

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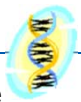
Expanded Use and Global Standards



Sequencing and biological significance of the human genome
→individual drug responses or future disease risks
→genome-based medicine (individualized, preventive)
Entry of clinical laboratories into service for routine tests
Entry of molecular/genetic scientists into commercial service
Genetic information service
Uses are expanded: Medicine→Health industry
Services and products: Regional→Global
Care providers: Untrained

Quality?

Needs for global standards:
OECD (2007)→ISO★, CDC, CLSI, CAP, etc.
★ISO/TC212 Clinical laboratory testing and *in vitro* diagnostic testing systems

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Recent Trends in Molecular-Genetic Testing in Japan

- Promotion of the use of genomic medicine for treating cancer and rare intractable diseases.
- Introduction and expansion of the following by covering under national health insurance for medical care:
  - Companion diagnostics
  - Cancer gene panel testing
  - Genetic testing for heritable diseases
- Expansion and penetration in not only the medical but also healthcare field
  - Items not applicable to national health insurance
  - Items not covered by health insurance (NIPT, personal identification)
- Health check-up
- DTC/OTC

OECD Guidelines for Quality Assurance in Molecular-Genetic Testing (2007)

（OECD: Organization for Economic Cooperation and Development）

General Principles and best practices
1) Quality assurance systems
2) Proficiency testing
3) Quality of result reporting
4) Education and training standards for laboratory personnel

Methods and Best Practices (Highlights) (OECD 2007)

Quality assurance framework is important.
Totality of the mechanisms that directly or indirectly affect the quality of a laboratory service.
Mechanisms may include statutory, non statutory, regulatory and/or professional ones such as code of practices and clinical guidelines.

Methods	**Best Practices** (selected)
1) Quality assurance systems	
2) Proficiency testing	Acceptable performance levels Timely corrective actions Assess all phases Scheme for every disease or alternative methods
3) Quality of result reporting	Effectively communicable information with non-specialist health care professional
4) Education and training standards for laboratory personnel	Measures to ensure professional competence Directors: MD, PhD, or equivalent Continuing education and training program

Guideline for Best Practice in Molecular-Genetic Testing issued by JCCLS (JCCLS 2012)

Scope: Quality assurance of testing offered in a clinical context

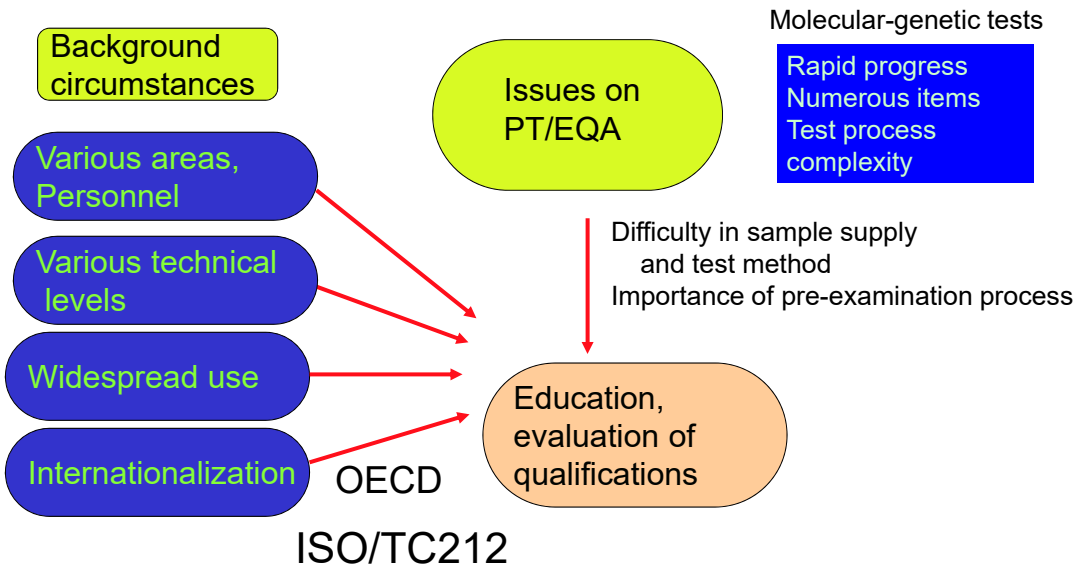
All three categories of molecular-genetic testing for DNA sequence variations in pathogens, somatic cells, and the germ line

General Principles and best practices
1) Quality assurance systems
2) Proficiency testing
3) Quality of result reporting
4) Education and training standards for laboratory personnel

Current Issues and Challenges in Japan, according to Japan Best Practice Guideline for Molecular-Genetic Testing (JCCLS 2020)

Major approaches	Current situations	Issues	Challenges
① Quality Assurance System	Clinical Research Core Hospital (2015) Cancer Genome Core Hospital (2018)	Accreditation not mandatory (recommendation) Health insurance (2016)	ISO 15189 Guidance Pilot Audit (2019) →Accreditation Program (2020)
② Proficiency Testing/EQA	CAP EQA available Obligation to make effort (2018)	Few items Caucasian-specific Costly	Onsite PT Plan for Japan EQA Japan GetRM
③ Quality of Result Report	Best Practice Guideline	Recruitment of Expert physicians Incentive	Transition of research to clinical laboratories
④ Education and Training of Laboratory Personnel	JSLM/CJLM Molecular Analysts (2007) /Specialists (2012)	Regulatory requirement (2018)	Training and qualification (directors and personnel)

Basic requirements for Laboratory Professionals to Ensure Quality



2. Qualification Examination of Laboratory Technologists in Molecular-Genetic Testing

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5.1.2 Personnel Qualifications (ISO 15189: 2012)

- Laboratory management shall document personnel qualifications for each position.
  The qualifications shall reflect the appropriate education, training, experience, and demonstrated skills needed, and be appropriate to the tasks performed.
- The personnel making judgments with reference to examinations shall have the applicable theoretical and practical background and experience.

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Laboratory Careers in Molecular Pathology in the USA

Types of Careers

- Laboratory Assistant
- Technologist:
  - Cytogenetic
  - Molecular
- Manager/Administrative Director
- Medical Director

Manager/Administrative Director and Medical Director

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Manager/Administrative Director
Managers and Administrative Directors in molecular laboratories typically have experience of working as a technologist in the field of molecular technology and often have a Master's degree in a technical area or in business. Their responsibilities may include benchwork but will always include managing staffing and operations for the laboratory. In larger laboratories, specific aspects of laboratory management, such as operations, quality, or education may be overseen by specific managers within the management team. Depending on the state in which the laboratory is located, there may be two laboratories with operations overseen by the Administrative Director, i.e., a research laboratory where the tests are developed and a clinical laboratory where diagnostic testing is performed.

Medical Director
The Medical Director typically has a doctorate with fellowship, postdoctoral, or other training in molecular diagnostics. Often, the Medical Director is board-certified in the technical area that he/she oversees. MDs and PhDs both qualify for this position; however, different states have specific requirements regarding the qualifications for this role.

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Types of Certifications for Technologists in the USA

MB (ASCP): Molecular Biologist
MDT(AMT): Molecular Diagnostics Technologist (American Medical Technologist)

SMB (ASCP): Specialist in Molecular Biology

Specialist in Molecular Biology Board Certification (provided by the American Society for Clinical Pathology)
& MT(AAB) Molecular Biology Board Certification (provided by the American Association of Bioanalysts)

Importance of Qualifications and Training of Personnel

In Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions.
MMWR June 12, 2009/58(RR06);1-29

Studies indicate that qualifications of laboratory personnel, including training and experience, are critical for ensuring quality performance of genetic testing, because human error has the greatest potential influence on the quality of laboratory test results.

Laboratory Technologist Certifications Issued by the College of Laboratory Medicine of Japan (CLMJ)

Technologist in Microbiology	Specialist in Microbiology
Technologist in Pathology	Specialist in Pathology
Technologist in Chemistry	Specialist in Chemistry
Technologist in Hematology	Specialist in Hematology
Technologist in Immunology	Specialist in Immunology
Technologist in Cardiology	Specialist in Cardiology
Technologist in Neurology	Specialist in Neurology
Technologist in Respiratology	Specialist in Respiratology

Technologist in Emergency Laboratory

Operator in POCT (2020)

Molecular Analysis Technologist (2007)

Molecular Analysis Specialist (2012)

The Objectives of the Molecular Analysis Technologist/Specialist System

- Foster laboratory professionals who have specialized knowledge in the field of molecular-genetic analysis science and can internalize advanced technology.
- Promote the development and dissemination of molecular-genetic analysis and analytical technology.
- Contribute to the nation's health and science and technology development by promoting the improvement and standardization of the technical methodology and providing high-quality results in molecular-genetic tests.

Eligibility Criteria for the Post of Molecular Analysis Technologist/Specialist

More than 3 years of work experience in laboratory testing and more than 3 years of work experience in quality control.

Studied molecular biology-related subjects at graduate schools, universities, colleges, vocational colleges, or colleges of technology.
(molecular biology, genetic testing, cell genetics, human genetics, microbiology, biochemistry, immunology, hematology, physiology, pathology, anatomy, animal cell engineering, biological science, etc.)

Definition of Molecular Analysis Technologist/Specialist

Definition: Genetic technologists for genomic material derived from all living organisms and organism-derived substances. The individual is certified as having the academic knowledge and skills necessary to responsibly carry out molecular analysis and genetic testing.

Molecular Analysis Technologist

Has basic knowledge and skills and can perform molecular-genetic analysis and testing.

Molecular Analysis Specialist

Has already acquired certification as a Molecular Analysis Technologist and has advanced knowledge and sufficient experience and can teach juniors.

Certification Registry Board

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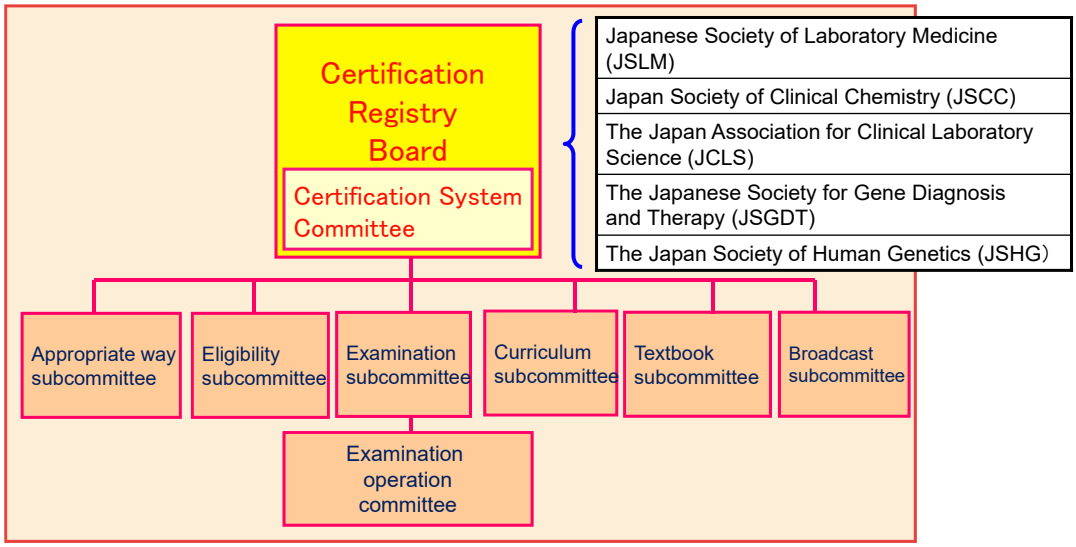
College of Laboratory Medicine of Japan (CLMJ)



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Related Rules for the System for Certified Molecular Analysis Technologist/Specialist

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Rules	Content
Rules for system	Registry board, designated curriculum, application, certification, registration, renewal and cancellation, etc.
Detailed rules for system enforcement	Application qualifications, examination criteria, designated training, examination, renewal, etc.
Examination Committee internal rules	Examination implementation, content, pass/fail judgment, etc.

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A Certified System with Two Stages and Renewal

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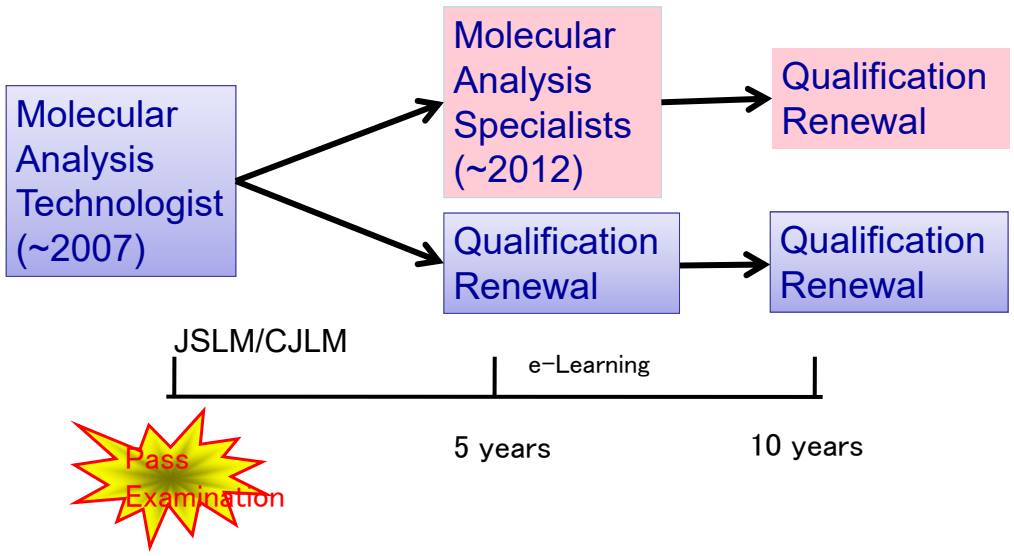

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Educational Curriculum for Molecular Analysis Technologist

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Levels	Major items	Medium item
Basic version	Basic medical knowledge	Biochemistry, physiology, anatomy
	Knowledge required to carry out molecular-genetic tests	Equipment handling, reagent preparation method, sample handling method, quality control of molecular-genetic/chromosome test, law on gene/chromosome
	Genetic testing	Search for responsible genes, interpretation of test results, usage of tests
Advanced version	Molecular-genetic tests technology	How to handle test reagents, nucleic acid extraction, nucleic acid amplification, detection technology, troubles and countermeasures, advanced technology
	Practice of genetic testing	Genetic medicine, genetic information, ethics
	Evaluation of molecular-genetic test results	Infectious diseases, blood diseases, solid tumors, hereditary diseases, lifestyle-related diseases, personal identification, regenerative medicine
	Chromosome testing technology	Structure and function, classification and nomenclature, human chromosomal map
	Chromosome test practice	Cell culture method, sample preparation, banding method, karyotype analysis, fluorescence *in situ* hybridization
	Evaluation of chromosomal test results	Types of chromosomal abnormalities, tumors and chromosomal abnormalities, environmental variants and chromosomal abnormalities

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Educational Curriculum for Molecular Analysis Specialist

Major items	Medium item
Basic Knowledge of Molecular-Genetic Testing	Molecular Analyst/Specialist Certification System, General Considerations in Molecular-Genetic Testing, Basics of Gene and Chromosome
Basic Technology of Pre-examination	Handling of Specimens, Handling of Reagents and Equipment, Quality Assurance
Nucleic Acid Extraction	Specimen Pretreatment, DNA/RNA extraction (Animal/Plant/Human), Usage of Testing
Nucleic Acid Amplification	Significance and Principles, PCR Methods, Other Nucleic Acid Amplification Technologies
Detection Technology	DNA/RNA Analysis and Other Detection Technologies
Advanced Technology	Genomics, Proteomics, Regenerative Medicine, Bioinformatics
Other Genetic Testing Techniques	Animal Gene Analysis, Plant Gene Analysis, Human Chromosome Map
Practice of Medical Care Based on Molecular-Genetic Testing	Genetic Abnormalities and Diseases, Genetic Diagnosis, Gene Therapy, Genetic Counseling, Genetic Information, Ethics
Evaluation of Genetic Test Results	Infectious Diseases, Blood diseases, Solid Tumors, Hereditary Diseases, Lifestyle-related Diseases, Personal Identification, Pharmacogenomics
Chromosome Test Practice	Cell Culture Method, Specimen Preparation, Banding Method, Karyotype Analysis, Fluorescence *in situ* Hybridization
Evaluation of Chromosomal Test Results	Types of Chromosomal Abnormalities, Tumors and Chromosomal Abnormalities, Environmental Variants and Chromosomal Abnormalities, Ethics
Molecular-Genetic/Chromosome Testing Operation	Operation Management, Consultation, Education and Training, Quality Assurance/Management, Safety Management, Quality Control, Genetic Testing Business, Clinical Trials, Development of Diagnostic Reagents, Guidelines

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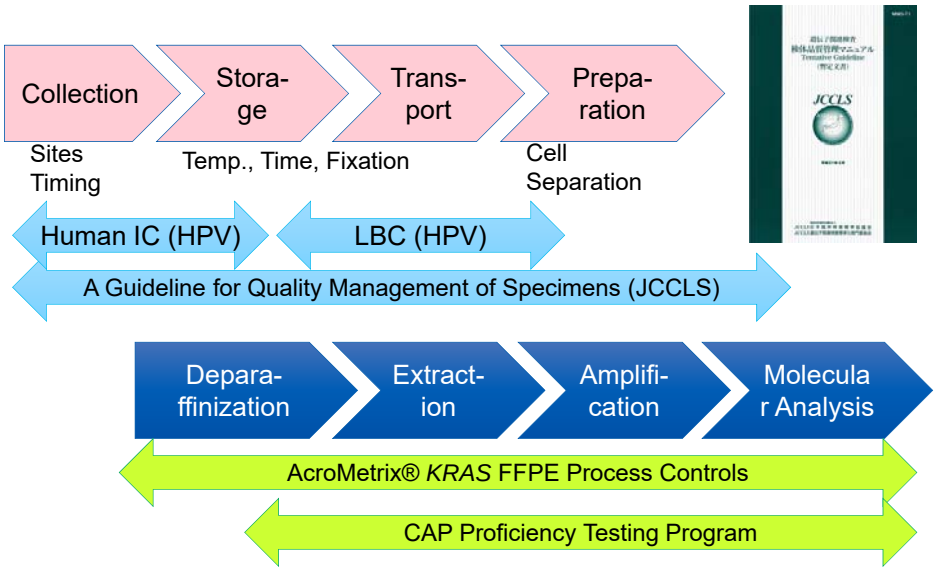
Quality Assurance for Pre-examination



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CAP Proficiency Testing (Molecular Oncology)

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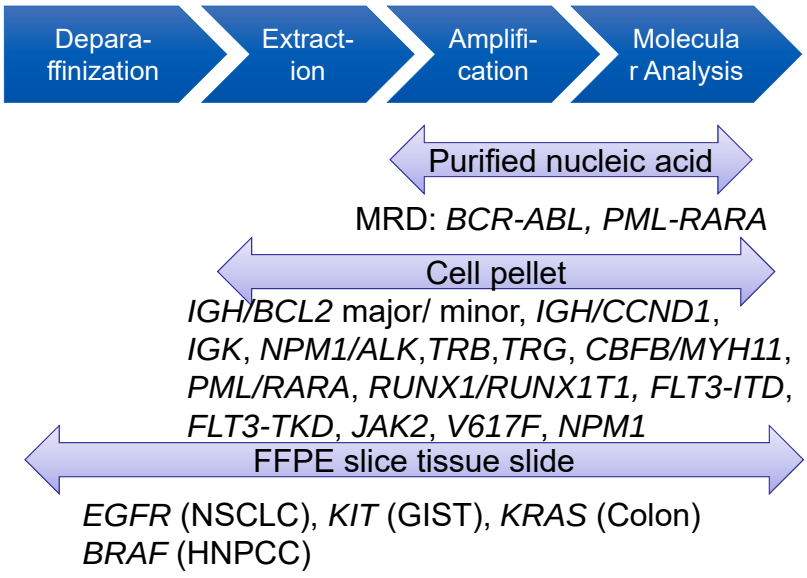

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Updated: Addition to Minor Items

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Medium item	Minor Item
Molecular Analyst/Specialist Certification System, General Considerations in Molecular-Genetic Testing, Basics of Gene and Chromosome	microRNA
Handling of Specimens, Handling of Reagents and Equipment, Quality Assurance	Biobank, LBC, Liquid biopsy
Specimen Pretreatment, DNA/RNA extraction (Animal/Plant/Human), Usage of Testing	
Significance and Principles, PCR Methods, Other Nucleic Acid Amplification Technologies	Cancer-gene panel test
DNA/RNA Analysis and Other Detection Technologies	
Genomics, Proteomics, Regenerative Medicine, Bioinformatics	iPS
Animal Gene Analysis, Plant Gene Analysis, Human Chromosome Map	
Genetic Abnormalities and Diseases, Genetic Diagnosis, Gene Therapy, Genetic Counseling, Genetic Information, Ethics	Genome editing, Genome and personal information, Secondary findings
Infectious Diseases, Blood Diseases, Solid Tumors, Hereditary Diseases, Lifestyle-related Diseases, Personal Identification, Pharmacogenomics	Companion diagnostic test
Cell Culture Method, Specimen Preparation, Banding Method, Karyotype Analysis, Fluorescence *in situ* Hybridization	
Types of Chromosomal Abnormalities, Tumors and Chromosomal Abnormalities, Environmental Variants and Chromosomal Abnormalities, Ethics	
Operation Management, Consultation, Education and Training, Management, Safety Management, Quality Control, Genetic Testing Business, Clinical Trials, Development of Diagnostic Reagents, Guidelines	

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Process of Cancer Gene Panel Test

https://www.thermofisher.com/jp/ja/home/life-science/sequencing/next-generation-sequencing.html

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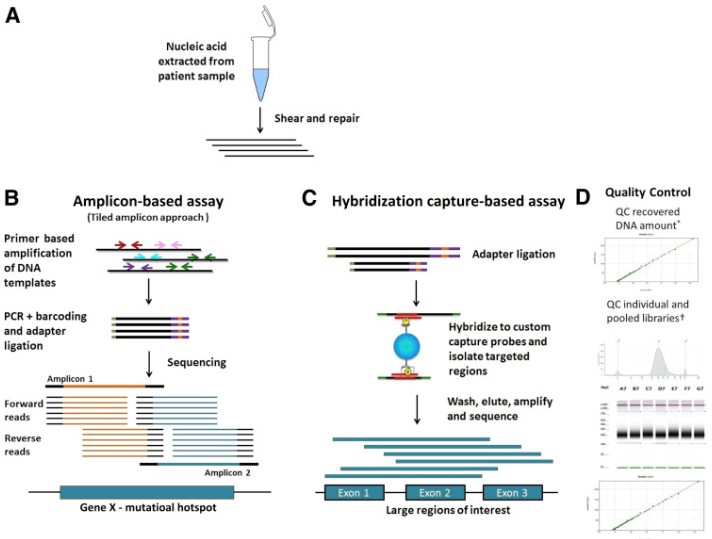
Target Enrichment Process Flow



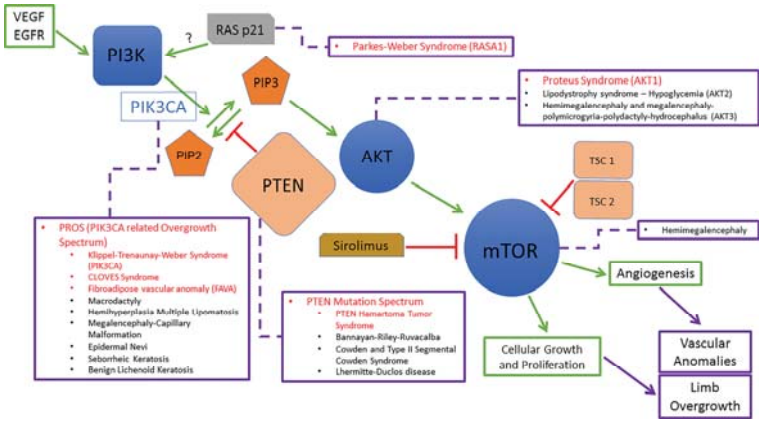
Jennings LJ, et al. J Mol Diagnostics 2017; 19: 342

Primary and Secondary Findings of Cancer Gene Panel Tests

1. Detection of activated oncogenes, e.g., *EGFR*, *KRAS*, and *ALK*, which are candidates for molecular targeted therapy.
2. Detection of variants of suppressor genes, e.g., *TP53* and *APC*, which facilitate diagnosis of inherited tumors.
3. Detection of deletion of genes responsible for homologous recombination, which indicate selection of poly ADP-ribose polymerase (PARP) inhibitor.
4. Evaluation of microsatellite instability (MSI) and tumor mutation burden (TMB), which are indicators of immune checkpoint inhibitors.

Involvement of Cancer-related Genes in Intractable Diseases

PI3K/AKT/mTOR pathway and
associated limb overgrowth syndromes



(Frederic Bertino, et al. RadioGraphics 2019; 39:491–515)

Question Criteria and Methods

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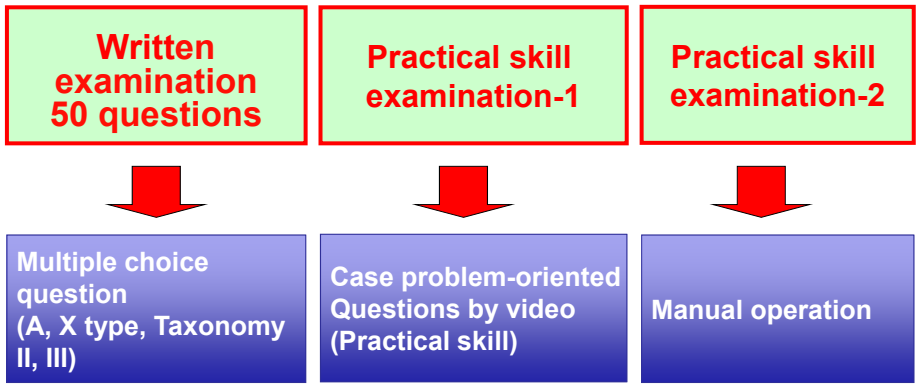

Written Examination→ Content of Educational Curriculum

Practical Skill Examination→ Achievement of Goal

Question Criteria for Practical Skill Examination: Achievement of Goal

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1) Be able to select the optimum testing items, sampling, pretreatment method, and testing method considering appropriate operation of the test and the roles of various nucleic acid amplification technologies.
2) In carrying out the test, understand proper work and procedures, and be able to avoid the influence of inappropriate operations on test result values.
3) Be familiar with the theoretical background and limits of each operation and be able to properly grasp and solve measurement problems.
4) Be able to extract artificially abnormal results (sampling, measurement) and abnormal samples from the test results (list), estimate the cause, and instruct retesting.
5) Be able to judge the measurement result for the general target of detection encountered in the routine test, to select/instruct additional test, evaluate or interpret the result, and report it to the user.
6) Be able to obtain information on gene structural abnormalities specific to the target of detection, select efficient analysis techniques for the detection, and design individual specific tests.
7) When implementing a new test, be able to evaluate the basic performance of the test and ensure sufficient measurement accuracy based on the appropriate evaluation.

Examinees of Molecular Analysis Technologists

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3. Qualification of Laboratory Director in Molecular-Genetic Testing

Personnel Requirements

CLIA requires laboratories performing moderate- and high-complexity tests to have specific expertise available.
- **Laboratory director**: The director is responsible for the overall operation and administration of the laboratory. The laboratory director ensures that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation regarding specific patient conditions. CLIA sets out specific qualification requirements for laboratory directors, depending on the complexity of tests performed by a laboratory.
- **Technical consultant/technical supervisor**: For laboratories performing moderate- complexity testing, one or more persons must be qualified to provide technical consultation for each specialty and subspecialty for which the laboratory is accredited. For high- complexity testing, laboratories must have a technical supervisor for each such specialty and subspecialty. These persons are responsible for ensuring appropriate test methodology, verifying test procedures, and establishing quality control programs.
- **Clinical consultant**: Laboratories performing moderate- and high-complexity testing must employ a clinical consultant who is qualified to consult with and render opinions to laboratory clients regarding the diagnosis, treatment, and management of patient care.
- **General supervisor**: For high-complexity testing, laboratories also must employ one or more general supervisors to provide day-to-day supervision of testing personnel and reporting of test results. Specific qualifications apply depending on the specialty and sub-specialty testing performed by the laboratory.

Certification Boards for Laboratory Directors of High Complexity Testing

Most molecular-genetic tests are classified as moderate or high complexity.

For high complexity testing at 42 CFR 493.1443(b)(3)(i), the laboratory director must hold an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution and be certified and continue to be certified by a board approved by HHS (Department of Health and Human Services).

The current approved boards are as follows:
ABB – American Board of Bioanalysis
ABB public health microbiology certification
ABCC – American Board of Clinical Chemistry
ABFT – American Board of Forensic Toxicology (limited to individuals with a doctoral degree with Fellow status)*
ABMGG – American Board of Medical Genetics and Genomics (formerly known as American Board of Medical Genetics (ABMG))
ABMLI – American Board of Medical Laboratory Immunology
ABMM – American Board of Medical Microbiology
ACHI – American College of Histocompatibility and Immunogenetics (formerly known as American Board of Histocompatibility and Immunogenetics (ABHI))
NRCC – National Registry of Certified Chemists (limited to individuals with a doctoral degree) *

* These boards certify non-doctoral individuals also.

Roles and Responsibilities of Laboratory Director in NGS

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Test Development, Optimization, and Familiarization

Choosing Sequencing Platform and Sequencing Method

Considerations: size of the panel (number of genes and extent of gene coverage); expected testing volume; required test turnaround time; availability of bioinformatics support; provider's degree of technological innovation, platform flexibility, and scalability; and laboratory resources, technical expertise, and manufacturer's level of technical support.

Reference cell lines or reference materials
PPA and PPV
Depth, sample type, and number

Test Validation Confirmation

Approval of methods, LLOD, Repeatability/reproducibility

Acceptance of minor modification and report a supplemental validation in additions or changes to a validated NGS test
Selection of confirmation test

Implementation and Quality Control Metrics

Validation Documentation and Summary

Laboratory Director

Entire Process Error-based Approach

①Test Design Validation Quality Management

②Error→Patient Outcome

(Jennings LJ, et al. J Mol Diagnostics 2017; 19: 342)

Roles and Responsibilities of Laboratory Directors

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Laboratory Director

①Laboratory Practice Quality Assurance

②Patient Practice Safety

Laboratory director

Technical supervisor

Clinical consultant

General supervisor

Staff Staff Staff Staff

(Code of Federal Regulations, USA)

Roles and Responsibilities of a Laboratory Director in the New Era

	Roles and Responsibilities	
1	Ensuring quality in all aspects of laboratory	Particularly in validation of laboratory developed tests on emerging technologies, implementation and evaluation of clinical validation, and allocation and training of personnel
2	Ensuring compliance with confidentiality of patient information and life ethics	Compliance with ethical codes and guidance
3	Ensuring quality in judgment, interpretation, and reporting of a test result	Clinical competence and knowledge, with specialty and experience as necessary, when judging, interpreting, and reporting
4	Ensuring multi-discipline collaborative approach	Recruiting of and collaborating with experts as necessary

Outline of Training Curriculum for Laboratory Medicine (JSLM 2014, revised)

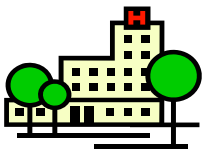
- Overall Goals of Training Curriculum
- Competencies Shared among All Rotations
- Basic Schedule of Rotations
- Curriculum for Subdiscipline-Specific Rotations

Overall Goals of Training Curriculum for the Laboratory Medicine (JSLM 2014, revised)

1. Career development
   To have the fundamental skills and knowledge as a basic medical specialist (generalist in laboratory medicine) and the competency to become an expert in a subspecialty.
2. Laboratory management
   To communicate as a medical consultant with other clinicians and to optimally direct the management of the clinical laboratory enterprise.
   To understand the science and technology of the clinical laboratory and ensures the quality, clinical appropriateness, and usefulness of the data produced by the laboratory.
3. Patient management
   To understand and consult on methods of diagnostic test development, test utilization in the context of generally applicable and patient-specific clinical settings, and assay interpretation in the clinical management of patients.

Competencies Shared among All Rotations

1. Expert Consultation in Patient Care Provision
2. Medical Knowledge
3. Practice-Based Learning and Improvement
4. Interpersonal and Communication Skills
5. Professionalism
6. Systems-Based Practice



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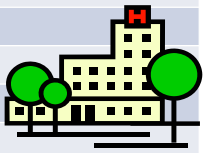
Basic Schedule of Rotations

The achievements that are required for minimal competency as a generalist in laboratory medicine would be acquired in 36 months of training.
It is generally recommended that the core rotations be structured as subdiscipline-specific, concentrated, and protected rotations.

	Subdiscipline	Duration (months)
1	General Laboratory and Clinical Chemistry	3–5
2	Clinical Hematology	3–5
3	Clinical Microbiology	3–5
4	Transfusion Medicine	1–2
5	Clinical Immunology	1–2
6	Molecular Pathology/Genetics	1–2
7	Medical Imaging and Physiology	1–2
8	Laboratory Management, Informatics	1–2



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4.8 Molecular Pathology/Gene-related Testing

	Competence
4.8.1. Basic Knowledge of Specific Tests Using Molecular Biology Methods	
4.8.1.1 Basic of Molecular Pathology and Genetics	1) Understand structure and function of gene/chromosome. 2) Understand synthesis of protein. 3) Understand inheritable diseases and mode of inheritance. 4) Understand categories of gene-related tests. 5) Understand genetic testing of mono-gene diseases. 6) Understand pharmacogenomics-based tests. 7) Understand personal differentiation tests.
4.8.1.2 Understand ethics in genetic tests.	
4.8.2 Molecular Biology Technology	1) Have awareness of sample types, preparation, and storage for molecular tests. 2) Have knowledge of extraction and handling of nucleic acid. 3) Understand principle and limitations of PCR. 4) Understand nucleic acid amplification methods and others. 5) Understand DNA sequencing and microarray methods 6) Understand variations of genome sequence.
4.8.3. Judgment and Interpretation of Gene-related Tests	1) Be able to interpret results of molecular tests for hematopoietic neoplasms 2) Be able to interpret results of molecular tests for mono-gene diseases. 3) Be able to interpret results of molecular tests for infectious diseases. 4) Be able to make a report of results of molecular tests.

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Increased Roles of Subspecialization

In an era of ever-increasing medical complexity, the role of subspecialization by a subset of laboratory physicians is increasing, and fellowship-trained subspecialists are likely to become increasingly important in medical care delivery systems.

General Laboratory
Clinical Chemistry
Clinical Hematology
Clinical Microbiology
Transfusion Medicine
Clinical Immunology
Molecular Pathology
Medical Imaging and Physiology
Laboratory Management, Informatics
Laboratory and Patient Safety

Generalist in Laboratory Medicine

↓

Genetic Medicine
Ultrasound Medicine
Preventive Medicine

4. Education and Training of Auditors in ISO 15189 for NGS-based tests

Issues to be challenged

1. Monitoring scheme of external quality assessment
   Japanese version of EQA and GetRM
2. Linkage with clinical (and research) biobank
3. Expansion of accredited laboratories
4. Qualification and training of auditors
5. Training of laboratory professionals

Usage of ISO 15189 Guidance for Molecular-Genetic Laboratories

Molecular-Genetic Laboratories

- Introduction of quality management (validation and verification
  →performance parameters
  →internal quality control)
- Documentation of operational procedures
- Education and training of laboratory staff

Accreditation body

Basis for accreditation criteria
Education of auditors
Harmonization among auditors

Development of a new accreditation program for molecular-genetic laboratories

Career Development of Molecular Analysis Technologist

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Molecular Analysis Technologist

a person who has basic knowledge and skills and can perform molecular-genetic analysis and testing.

Molecular Analysis Specialist

a person who already has acquired certification for Molecular Analysis Technologist and has advanced knowledge and sufficient experience and can teach juniors.

Career Development

Auditor of conventional molecular laboratories

Auditor of laboratories performing NGS

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Candiates of Auditors for Molecular Laboratories

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Types of Labs	Methods/Panels	Candidates for an Auditor	
		Certificated as Molecular Analysis	In Combination with Certified Technologist
Conventional Molecular Laboratories	PCR-based Sanger-Sequencing FISH	Technologist	Pathology, Hematology, or Microbiology
Molecular Laboratories Performing NGS-based Test	Inherited Diseases	Specialist	
	Solid Tumor		
	Hematopoietic Tumor		
	Microbial Pathognes		

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Auditor Training: Uniform and Unification Level of Audit

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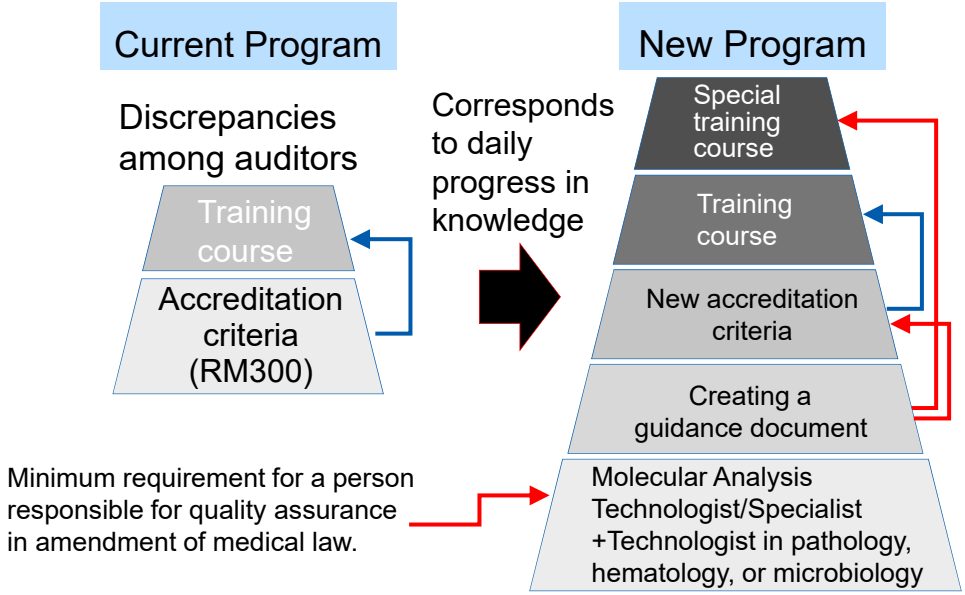

External Quality Assessment (EQA) or Proficiency Testing (PT) (IFCC, 2017)

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- External quality assessment (EQA) or proficiency testing (PT) describes the process of comparing the laboratory's test results to an outside source.
- There are four methods for EQA/PT:
  Rechecking or retesting samples that were previously tested by a reference laboratory,
  On-site evaluation,
  Inter-laboratory exchange of samples (typically between a few laboratories), and
  Proficiency testing.
- In proficiency testing, an organization provides unknown samples for testing to a set of laboratories, and the results from all laboratories are analyzed and reported to the laboratories.
- EQA identifies systematic errors in testing, training needs, and objective evidence of testing quality.

Issues and Challenges

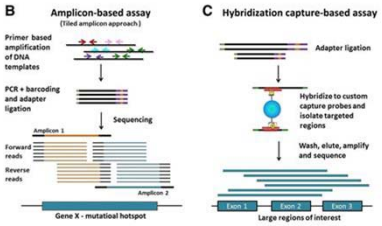
in Competence Evaluation of Laboratories Performing NGS-based tests

Diversity of NGS-based Tests

Specimen types
Purpose of use
Assay platforms
Detection targets of interest

Samples Prepared

Genome-based
DNA-based
Cell-based



Guidelines for Validation of Next-Generation Sequencing–Based Oncology Panels
J MolDiagn. 2017 May;19(3):341-365

Forms of NGS On-Site Evaluation

Report of self-assessment

Test item
DNA preparation
Library construction results
Sequencing results
Interpretation and discussion
Auditor assessment

Presentation and discussion
→internal process improvement

Competence of laboratory professionals

Instruction for auditors

★1 Diversity of NGS-based tests
Purpose of use
Assay platforms
Detection targets of interest
Three types of sample are delivered.
As necessary, an alternative approach is allowed.
★2 On-site evaluation is conducted to assess the routine laboratory work.
Routine lab. practice and competence is to be evaluated.
In the presentation and discussion, information and suggestions can be given to ensure the quality of the laboratory.

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Potential Sources of Error Affecting NGS Assays

Designed for Formalin-Fixed, Paraffin-Embedded Tissue

Step	Assay design considerations	Quality assessment during Validation
DNA yield	Optimize extraction	Measure yield
DNA purity and integrity	Optimize DNA library preparation	Monitor DNA library preparation
Deamination or depurination	Ung treatment, duplex reads	Confirm all positives with orthogonal method
Contamination	Change blades during tissue dissection	No template control
Stochastic bias	Increase input, multiple displacement amplification, single-molecule barcoding	Sensitivity control
Amplification errors	High-fidelity polymerase, duplex reads	Confirm all positives with orthogonal method
Capture bias	Optimize enrichment, long-range PCR	Define minimum coverage, back-fill with orthogonal method
Primer bias and allele dropout	Assess causes of false-negatives, design overlapping regions	Bioinformatically flag homozygosity of rare variants

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Inconsistent Test Results in AF among Laboratories (IonPGM)

		Tokai	B	C
BRAF	COSM467	11.4	21.9	22.7
EGFR	COSM21683	19.6	18.4	23.2
	COSM21687	22.4	21.6	23.1
	COSM21690	21	20.8	20.5
	COSM6239	25.4	23	24.9
	COSM6213	19.8	8.5	5.2
MET	COSM700	21.3	20.1	20.2
	COSM691	21.6	20.4	8.0
AKT1	COSM33765	5.5	6.2	8.6
ALK	COSM28056	11.6	8.7	7.9
	COSM28055	10.3	8.5	8.7
FGFR2	COSM36912	10.4	9.2	5.2
	COSM36906	8.9	7.6	9.0
	COSM36904	8.8	7.5	8.8
	COSM36903	9.3	8.8	8.5
FGFR3	COSM715	6	6.8	8.1
	COSM719	7	4.5	7.1
	COSM24802	6.8	7.9	9.8
HRAS	COSM499	8	9.3	9.1
	COSM483	9.3	5.1	8.8
KRAS	COSM19940	8.2	6.9	8.4
	COSM554	8.3	10.1	5.5
	COSM546	8.2	10.2	8.6
	COSM521	8.6	8.8	8.1
NRAS	COSM564	9	9.1	7.6
PDGFRA	COSM22415	7.2	7.5	7.4
	COSM736	7.6	7	8.4
PIK3CA	COSM27497	10.1	0	0.0
	COSM13570	10.1	0	0.0
	COSM754	8.7	7.7	8.6
	COSM757	9	9	8.5
	COSM759	8.8	8.7	7.1
	COSM760	8.6	8.6	7.1
	COSM763, COSM125370	8.7	8.6	7.2
	COSM778	9.7	8.5	7.4
	COSM94986, COSM775	11	9.2	7.1

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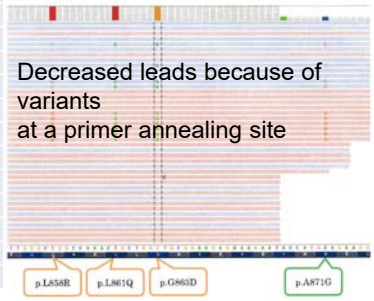

Causes of a Failure of Detection by NGS-based Cancer Gene Panel Tests

- Decreased leads because of variants at a primer annealing site.
- Decreased leads because of a panel property.
- Decreased leads because of pseudogenes.
- Filtering of pathogenic variants because of complex sequences/misalignment.

Plan for correcting internal processes
Inform the limitation to users

Outcomes of On-Site Evaluation

Advantages

・Self-assessment, discussion, and feedback effectively improved quality of various NGS-based tests.
・ Quality indicators in each process allowed evaluation of the appropriateness.
・ Each laboratory made a plan relevant to its own system (dummy RNA, matched pair analysis with reference genome).
・Particularly, this worked for cancer companion diagnostics.

Limitations and challenges

・Various specimens and applications of NGS-based tests such as circulating cell-free nuclear acid.
・Development and evaluation (assigned values) of all types of samples are costly.
・For diverse applications, combination with alternative approaches is accepted.

Summary

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Summary

1) Because of the highly complex process of molecular-genetic testing and important impact of test results on decision-making for patient care, the importance of Laboratory Personnel in Quality Assurance has been underscored.

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4) In the ISO 15189 accreditation for NGS-based tests, auditors were trained, based on new accreditation criteria and the implementation guidance document ISO 15189, as well as development of on-site evaluation for persons certified as Molecular Analysis Technologists/Specialists.

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