ATLAS Project
ISO 15189 Accreditation Support Course

ISO 15189 Clinical Laboratory Accreditation —Accreditation of gene-related testing—

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Brief biography: Tokiko Nishimura

Work History

- Nippon Medical School
  Head of Physiological Function Testing Center, Clinical Laboratory Department, Chibahokuso Hospital (1993-2016)
- National Research and Development Agency, Center Hospital of the National Center for Global Health and Medicine
  Head of Physiological Testing Department, Laboratory Testing Department (2016-2017)
- Public Interest Incorporated Foundation, Japan Accreditation Board
  Manager of Clinical Laboratory, Technical Department (2018-2022)
- SRL, Inc.
  Section Manager, Quality Assurance Department, Quality Assurance Headquarters (2022-2023)
- Public Interest Incorporated Foundation, Japan Accreditation Board
  LAB Accreditation Unit, BB/Physiological Testing Manager (2023-)
- Saitama Prefectural University
  Part-time Lecturer, Laboratory Sciences, Department of Health Sciences (2020-)

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1 Comparison between ISO 15189 and CAP accreditations

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Accreditation of clinical laboratories

Clinical laboratory accreditation is defined as "third-party attestation to confirm and certify that a clinical laboratory has met specific standards."
There are two standard accreditations for clinical laboratories: ISO, primarily used in Europe, and CAP, in the United States.

- ISO (International Organization for Standardization 15189)
- CAP (College of American Pathologists Laboratory Accreditation Program: CAP-LAP)

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Comparison between ISO 15189 and CAP accreditations

	ISO accreditation	CAP accreditation
Purpose	• To assess the quality management system provisions and testing capabilities of a clinical laboratory • To verify the competency of clinical laboratories to laboratory clients, regulators, and accreditation bodies	• To improve the quality of clinical laboratory services and promote laboratory safety through education, establishment of standards, and assurance that clinical laboratories comply with regulatory requirements
Accreditation organization	Member institutions of the International Laboratory Accreditation Conference (ILAC)	College of American Pathologists (CAP)
Applicable standards and related requirements	• ISO 15189 Medical laboratories - Requirements for quality and competence • Domestic laws, etc.	• Clinical Laboratory Improvement Amendments (CLIA) • Clinical and Laboratory Standards Institute (CLSI) Guidelines, etc.

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Comparing accreditation programs (CAP)

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CAP accreditation program

PROCESS	Details
1. Request Application	Participate in proficiency test 6 months before application
2. Review Welcome Kit	Preparation of application documents
3. Complete Application	Completion of application form and document review
4. Receive Customized Checklists	Checklist preparation
5. Schedule Inspection Date	Confirmation of inspection schedule
6. Host Inspection Day	Conduct inspection
7. Respond to Deficiencies Within 30 Days	Corrective response to identified items
8. Support CAP Review of Responses	Review of corrective response and committee approval
9. Receive Certificate of Accreditation	Receipt of certificate
10. Perform Self-inspection and Maintain Continuous Compliance	Implementation of self-inspection (1 year after accreditation)

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Comparing accreditation programs (ISO 15189)

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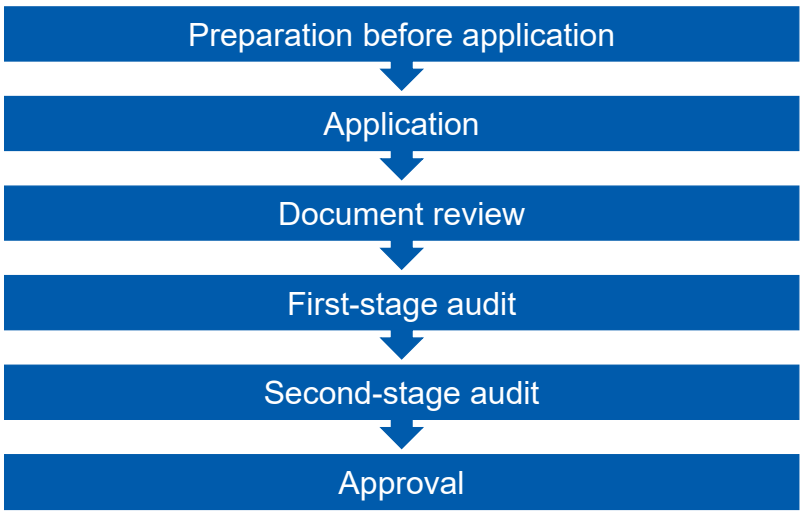

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Comparing accreditation programs (ISO 15189)

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Applicant institution (clinical laboratory)	Process	Accreditation inspection institutions and inspection teams
• Participation in interlaboratory comparisons • Documentation of procedures and creation of records • Operation and evaluation of quality management system • Creation of application form	Pre-application preparation	
• Submission of application • Response and correction of missing documents	Application	[Accreditation Inspection Institution] • Confirmation of application documents • Acceptance of application • Selection of inspectors and formation of the inspection team
• Submission of additional requested documents • Submission of corrective response to the identified issues	Document review	[Inspection team] • Document review • Preparation of additional submission request form for missing documents and submission to the applicant institution • Preparation of inspection results report • Creation of an indication list (if there are non-conformities) • Evaluation of submitted corrective action responses and determination of whether to proceed to the next process [Accreditation inspection institution] If the inspection team decides that it cannot proceed to the next process, it will notify the applicant institution of the termination of inspection.

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Comparing accreditation programs (ISO 15189)

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Applicant institution (clinical laboratory)	Process	Accreditation inspection institutions and inspection teams
• Submission of required documents • Submission of corrective response to the issues	First-stage inspection	[Inspection team] • Adjustment of inspection schedule and preparation and submission of detailed audit plan • Implementation of the inspection (if there are any deviations, a list of findings will be created and explained at the closing meeting of the inspection) • Preparation of the first-stage audit report • Evaluation of submitted corrective responses and determination of whether to proceed to the next process [Accreditation inspection institution] • If the inspection team decides that it cannot proceed to the next process, it will notify the applicant institution of the termination of the review.
• Adjustment of audit schedule and preparation and submission of detailed inspection plan • Implementation of the inspection (if there are any deviations, a list of findings will be created and explained at the closing meeting of the inspection) • Preparation of the first-stage audit report • Evaluation of submitted corrective responses and determination of whether to proceed to the next process	Second-stage inspection	[Inspection team] • Adjustment of audit schedule and preparation and submission of detailed audit plan • Implementation of inspection including on-site skills inspection (if there are any deviations, a list of findings will be created and explained at the closing meeting of the inspection) • Preparation of the second-stage audit report • Evaluation of submitted corrective responses and determination of whether to proceed to the next process [Accreditation inspection institution] • Send the proficiency test samples to the applicant institution in advance if there is a review of gene-related tests (in the case of NGS) • If the inspection team decides that it cannot proceed to the next process, it will notify the applicant institution of the termination of the inspection.

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Comparing accreditation programs (ISO 15189)

Applicant institution (clinical laboratory)	Process	Accreditation inspection institutions and inspection teams
• If accreditation is approved, a certificate will be issued. • The accreditation period validity is 4 years, during which two surveillances and one re-examination must be taken to maintain the accreditation status.	Judgment of accreditation	• The accreditation inspection institution discusses the approval of accreditation based on the report submitted by the inspection team and informs the applicant of the results.

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2 Key points of ISO 15189 accreditation

Quality assurance, process approach, PDCA cycle

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2 Key points of ISO 15189 accreditation

1. Quality assurance
2. Process approach
3. PDCA cycle

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2.1 Quality assurance

Quality assurance can be thought of as substantive performance that satisfies the intended use.

The final product (product) that clinical laboratories should work on with an awareness of quality is…

"Test report"

The test report is used for the following:
- Confirmation or assistance with diagnosis,
- Assistance in decision and selection of treatment policy,
- Judgment of therapeutic effect, etc.

Clinical laboratories need to demonstrate that they maintain performance consistent with their intended use.

Proving quality = Quality assurance

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2.1 Quality assurance

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Why should clinical laboratories use ISO 15189, and obtain ISO 15189 accreditation?

- ISO 15189 serves as a guideline for clinical laboratories to maintain quality assurance.
- Achieving ISO 15189 accreditation is proof of competence of the laboratory to users.

Overview of ISO 15189

- Roles and initiatives of top management and the organization, construction of the PDCA cycle
  → Contents related to quality management system (ISO 9001)
- Building technical initiatives to influence test results
  → Contents for managing personnel, equipment and reagents, measurement specimens (samples), measurement methods, quality control, and result reporting (ISO/IEC 17025)

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2.1 Quality assurance

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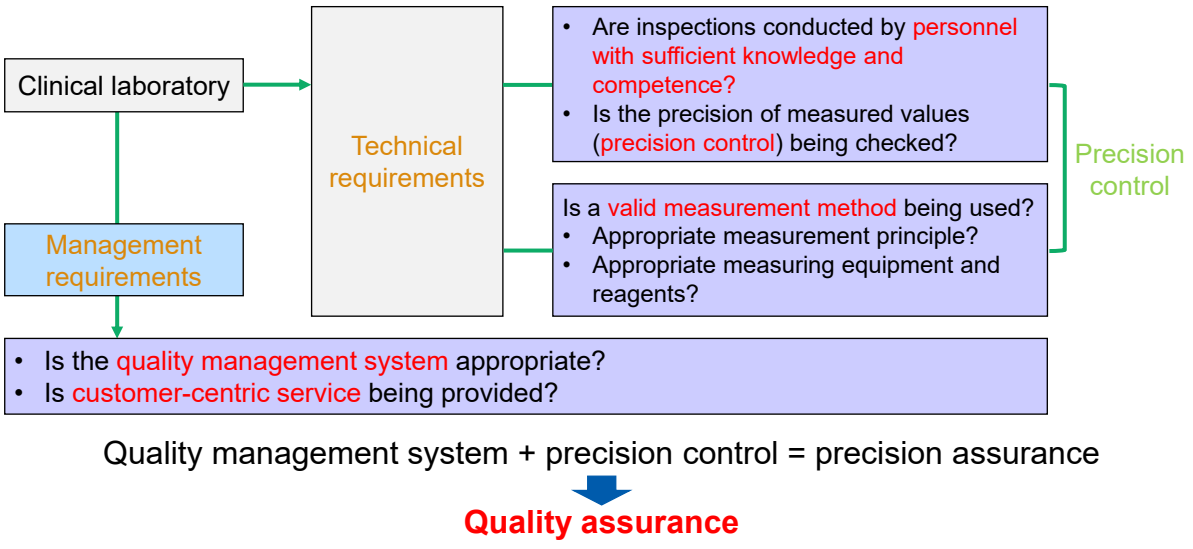

Quality management system + precision control = precision assurance

Quality assurance

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2.2 Process approach

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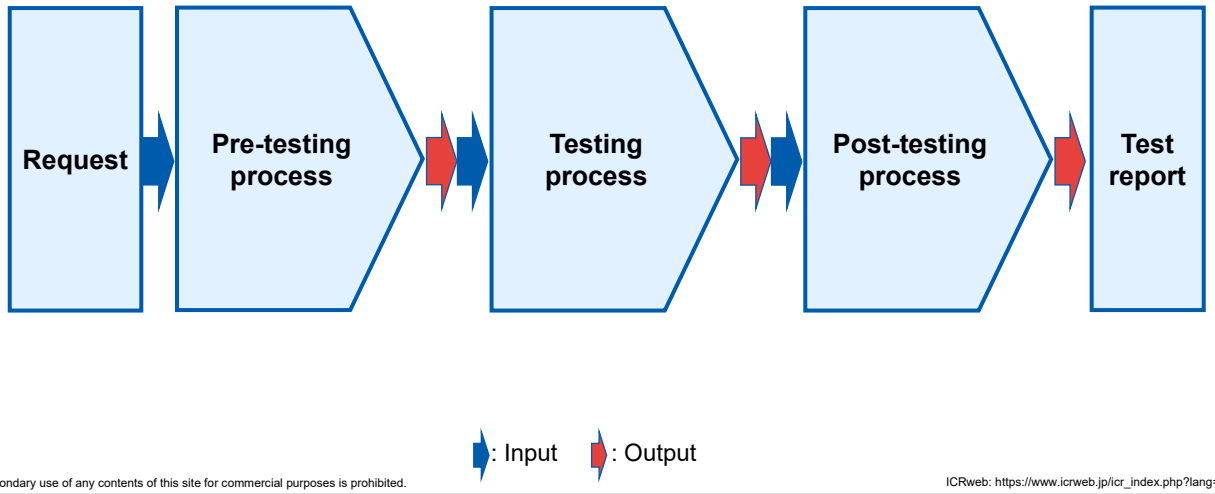
The work of clinical laboratories consists of a chain of processes.



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2.2 Process approach

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What are the necessary elements that make up the process?

- Man
- Machine (environment and infrastructure)
- Method (Operation methods)
- Material

4M

Before establishing a quality management system, top management must investigate and understand the organization's resources, including the 4Ms.

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The standard requires that you have the resources necessary to meet the customer's needs.

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2.2 Process approach

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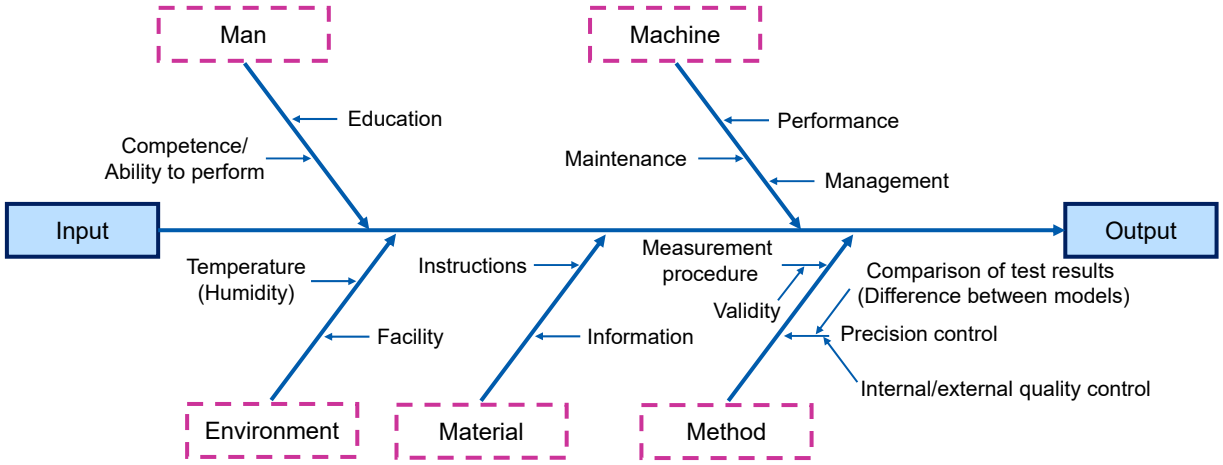

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2.2 Process approach

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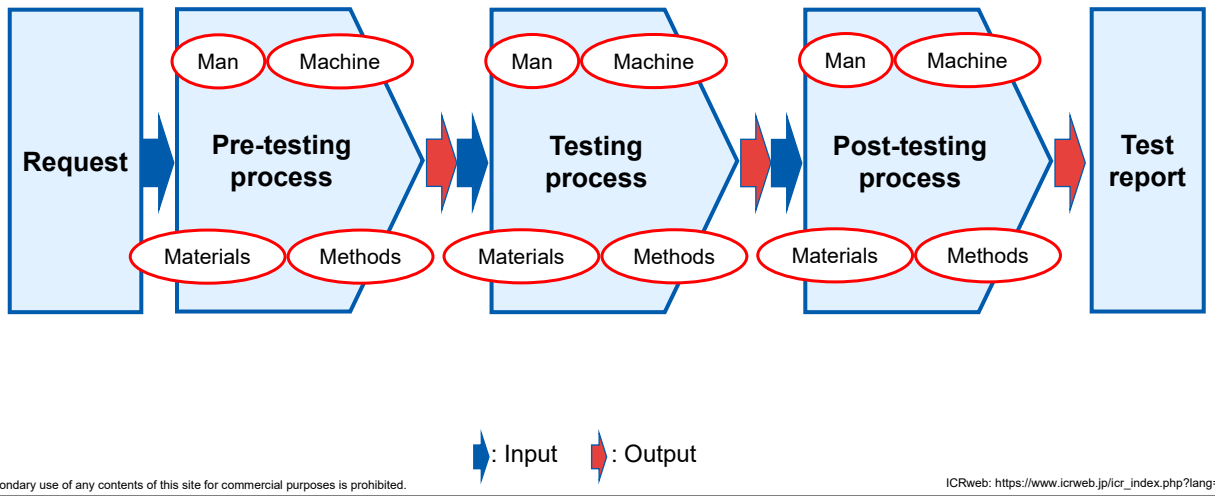

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2.2 Process approach

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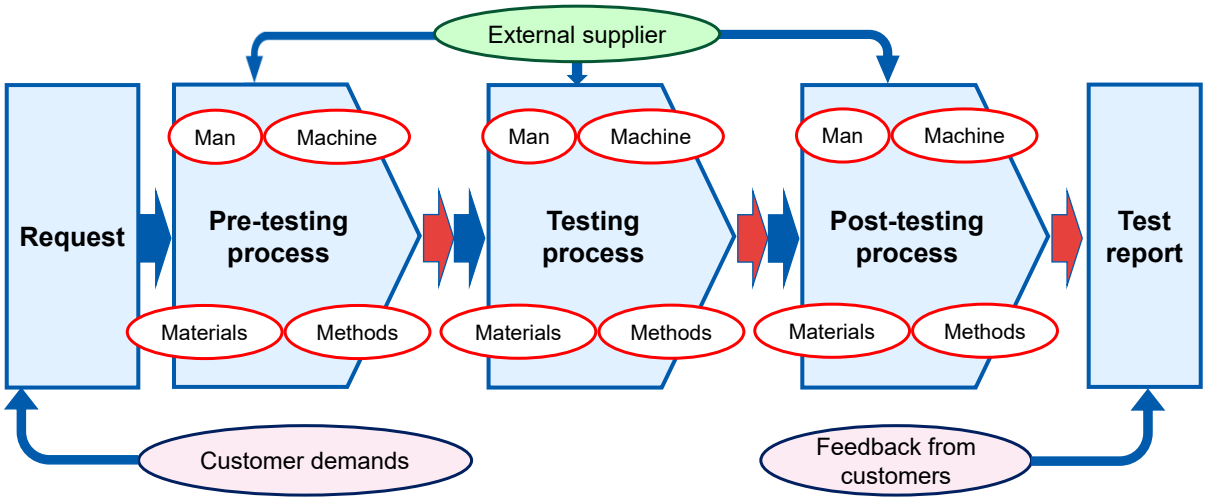

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2.2 Process approach

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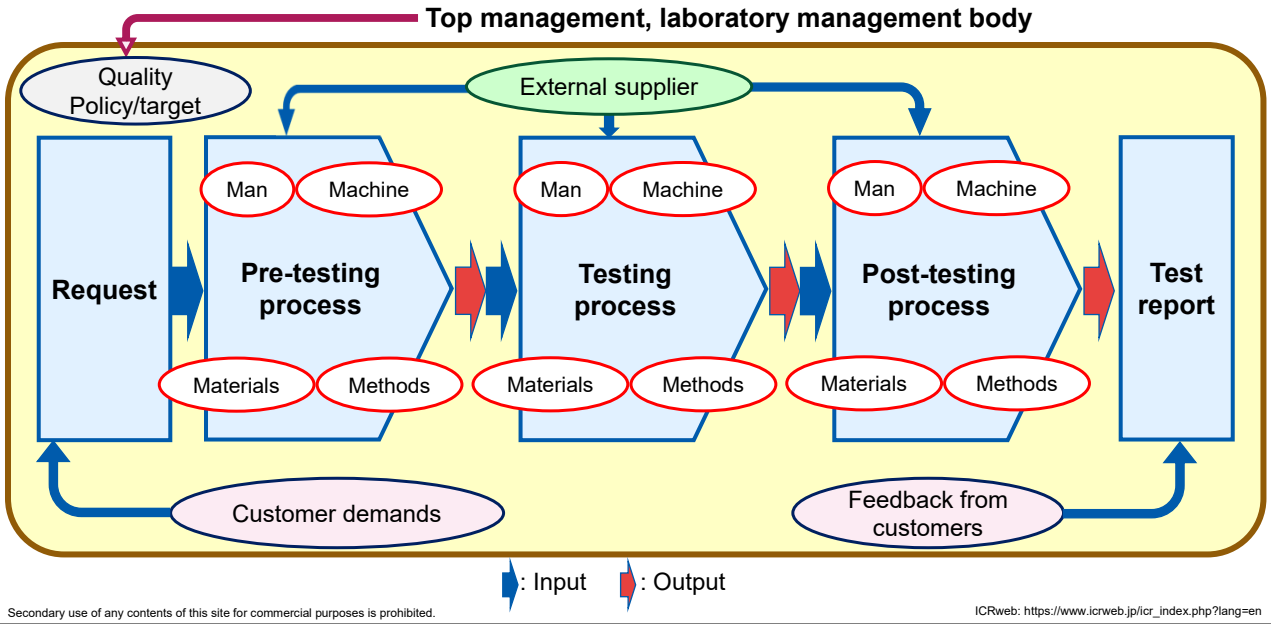

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2.3 PDCA Cycle

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[Plan]

- Goal setting
- Create an action plan to achieve your goals
  (Creating procedures and mechanisms)

* In planning, consider the “why”, “who”, “when”, “what”, and “how”.

* Targets are indicated numerically so that the degree of achievement can be easily grasped.

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2.3 PDCA Cycle

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[Do]

Execute according to the planned goals and action plans.

*** It includes not only the meaning of “steadily carrying out work according to the plan”, but also the meaning of “trial”.**

1. Record progress and results against goals.
2. If things don’t go according to the plan, record it.
   (Defects and non-conformance cases are also recorded.)

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2.3 PDCA Cycle

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[Check]

- Were the set goals and action plans achieved? (**Assessment of progress**)
- Was it executed as planned?
- Were there deviations from procedures and mechanisms? (**Assessment of eligibility**)

*** Avoid ambiguous expressions and show specific evaluation results.**

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2.3 PDCA Cycle

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[Act]

Consider improvement points for analysis and verification issues clarified in the previous stage Check (evaluation).

*** When considering improvements, it is important to have multiple options.**

1. Continue as planned
2. Improve some points of view while continuing the plan
3. Cancel or postpone the plan

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2.3 PDCA Cycle

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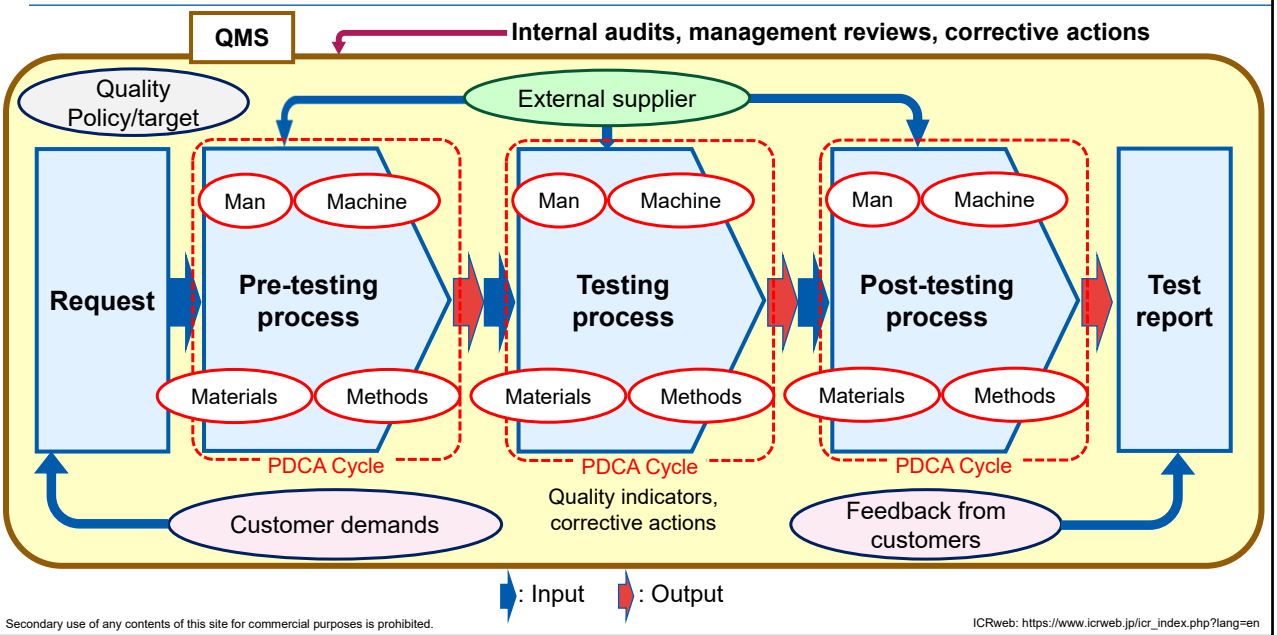

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3 Key points of gene-related testing

Quality assurance required by ISO 15189

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3 Key points of gene-related testing

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[What is included in the quality assurance framework for gene-related testing]

- Training of technicians and professionals
- Protocol standardization and quality assurance plan (including equipment used, reagents, and consumables)
- Obtaining reference materials
- Interlaboratory proficiency testing for laboratories
- Providing customers with information regarding indications and interpretation of gene-related testing

It encompasses all work that directly or indirectly affects the quality of inspection work. In other words, not only the technical aspects of testing but also the safety, validity, and usefulness of medical and healthcare aspects related to testing are subject to evaluation.

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3 Key points of gene-related testing

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1. Service agreement

- Regarding gene-related and chromosomal testing, if the testing process is long and there are cases where specimens cannot be tested at each stage, it is necessary to clarify each non-testability standard and contact method at the stage of signing a contract with the customer.
    1. Discrepancies between request and sample and defect in sample at sample acceptance
    2. Insufficient the amount of nucleic acid
    3. Unmeasurable sample

- Reporting scope of test results

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3 Key points of gene-related testing

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2. Selection and evaluation of outsourced laboratories and consultants

- Even when subcontracting some parts of the process of gene-related testing and chromosome testing, the laboratory should assess the subcontractor.
- Subcontracting some parts of the process means that only NGS wet bench or bioinformatics processes are outsourced.

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3 Key points of gene-related testing

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3. Control of records

- The conditions and factors associated with complex processes and algorithms involved in analytical performance and interpretation should be documented. This record must be maintained within a comprehensive framework in which all reagents, primers, sequencing chemistries, and platforms used in the analysis of each patient sample (specimen) should be maintained.
- A description of the test, including the nature of the target sequence (e.g., genome, exome, target panel specific gene, transcriptome, or methylome) and coverage (e.g., range and mean), should also be maintained.

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3 Key points of gene-related testing

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4. Workforce management

- Clarification of responsibilities and authority of each staff member
- Proof of competence to perform the work of each process and its record
  Record of education and training
  Record of acquired professional qualifications, etc.

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3 Key points of gene-related testing

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5. Laboratory environment (prevention of contamination)

- Type of contamination
  1. Cross contamination
  2. Carry-over contamination
- Area
  The room should be divided into two: the preparation room for reagents for nucleic acid extraction/amplification and the amplification/detection room.
- Instruments and device
  Pipettes, etc. should be kept in designated areas.
  UV irradiation and sodium hypochlorite solution should be applied before and after use to prevent contamination.

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3 Key points of gene-related testing

6. Appropriateness of inspection procedures

For gene-related testing, the following are required for validation:

- The principle of validation is to establish reliable sequence analysis across the target genomic region through testing.
- Validation of testing is to establish a system that correctly identifies the mutated genomic region associated with the disease. However, the profiling testing is not limited to this.
- Validation of the informatic pipeline means establishing an algorithm capable of accurately identifying sequences, suited to the application, using reliable analysis-based data.

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3 Key points of gene-related testing

7. Estimation of the measurement uncertainty associated with the value of the measured quantity is required.

- If it is difficult to estimate the measurement uncertainty, creation a cause-and-effect diagram is also necessary in gene-related testing.
- The appropriate components of measurement uncertainty are those related to the actual measurement process.
- The flow of creating a cause-and-effect diagram begins with the submission of a sample (specimen) to the measurement operation and ends with the output of the measured values.

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3 Key points of gene-related testing

8. Assurance of test results

- Internal quality control

  What to do in the process of sample handling, measurement, and management of measurement results

- External quality control (proficiency test provided by an external organization)

  Confirm the competence of the laboratory by measuring the priced samples and comparing the measurements.

  The following are the interlaboratory comparison substances that can be used in evaluating the competence of laboratories in gene-related tests.

  1. NMIJ
  2. CRM 6204-b, 6205-a, etc.

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3 Key points of gene-related testing

8. Assurance of test results

- Alternative approaches (other than commercially available substances)

  1. Appropriately preserved samples (specimens) used in previous inter-laboratory comparison programs
  2. Exchanging samples (specimens) with other laboratories
  3. Previously inspected samples (specimens)
  4. Materials from stored cells or tissues

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3 Key points of gene-related testing

9. Specimen storage

- Setting and managing sample (specimen) storage conditions
- Establishment of safe disposal procedures for samples (specimens) that have passed their storage period

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3 Key points of gene-related testing

10. Reporting of results

- Genetic laboratories should have a policy regarding the reporting of secondary findings unrelated to clinical purposes.

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3 Key points of gene-related testing

10. Information security

- In genetic laboratories, policies and procedures should describe processes to ensure patient confidentiality and security with respect to internal and external storage and transfer of sequence data and should ensure the following.

1. Laboratories have rigorous processes to protect information and ensure privacy.

2. Laboratories have robust policies for transferring genomic information to other healthcare institutions and third-party vendors that provide cloud-based computer-related services and sanitary laboratory services.

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3 Key points of gene-related testing

10. Information security

3. Procedures to ensure confidentiality include data encryption, secure data transfer, user authentication with limited access to protected medical information, and audit trails tracking data transmissions with recipients and/or users.

4. Laboratories performing large-scale genomic sequencing analysis for clinical examination should be aware of the ongoing research activity on the medical and ethical implications of returning NGS secondary findings. They should be considered when developing a policy for reporting on those outcomes.

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4 Key points of next-generation sequencing accreditation

Actual on-site proficiency tests

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4 Key points of next-generation sequencing accreditation

Regarding NGS, key points of gene-related testing are confirmed through the inspection process.

Especially for NGS, certified reference materials are sent during the inspection process to the facility that wishes to be accredited. The facility measures them and sends back the results to the accreditation inspection implementing body/inspection team before the accreditation review (second-stage inspection).

- Sending NGS preliminary samples (one month before inspection)
- Return the measurement results of preliminary samples (1-2 weeks before the inspection)
- Inspection team meeting based on returned results (7-10 days before the inspection)
- Discussion of the measurement results between the technical inspectors and measurers

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4 Key points of next-generation sequencing accreditation

Discussion points on the day of inspection

- Validity of measurement results
  In particular, it is necessary to thoroughly discuss on the mutated genes present in the sample and measured as negative.

- Reporting scope of measurement results

At the discussion, all records related to measurement, such as the condition of the measuring machine on the day of measurement, should be provided.

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4 Key points of next-generation sequencing accreditation

On the day of the audit, observation of daily work is also done as following.

- Equipment inspection and recording at the beginning of work
- Specimen reception (compliance with reception standards)
- Pre-testing process (specimen handling and contamination prevention, etc.)
- Testing process (compliance of procedures, pipette handling, prevention of contamination)
- Post-testing process (compliance with test result release procedures, sample storage)

Especially regarding pipette handling, it is important to have multiple staff perform the actual procedure and to confirm that there are no differences among personnel, as pipette handling can have a large impact on test results.

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5 Summary

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Summary

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- Certifications for clinical laboratories include ISO 15189 and CAP.
- ISO 15189 standard describes how clinical laboratories meet customer needs and address quality assurance themselves.
- ISO 15189 takes a process approach, allowing processes to be managed individually. When a problem occurs, it is possible to distinguish whether it is a problem specific to a process or a problem of the QMS as a whole and to respond accordingly.
- For gene-related testing, the handling of unacceptable specimens and untestable specimens found in the testing process should be agreed with the customer at the time of the contract. It is also necessary to share the scope of reporting.
- In gene-related testing, it is important to prevent contamination, which greatly affects quality.

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Summary

- For gene-related tests, it is necessary to implement an alternative approach because external quality control has not been established.
- Information security is important for gene-related testing because it handles a large amount of personal information.
- For gene-related tests (including NGS), it is necessary to eliminate inter-personnel differences in pipetting techniques that affect test results.