Payvand

Clinical Specialty Lab.

Quality Management System in Molecular Lab. with emphasis on Quality Assurance

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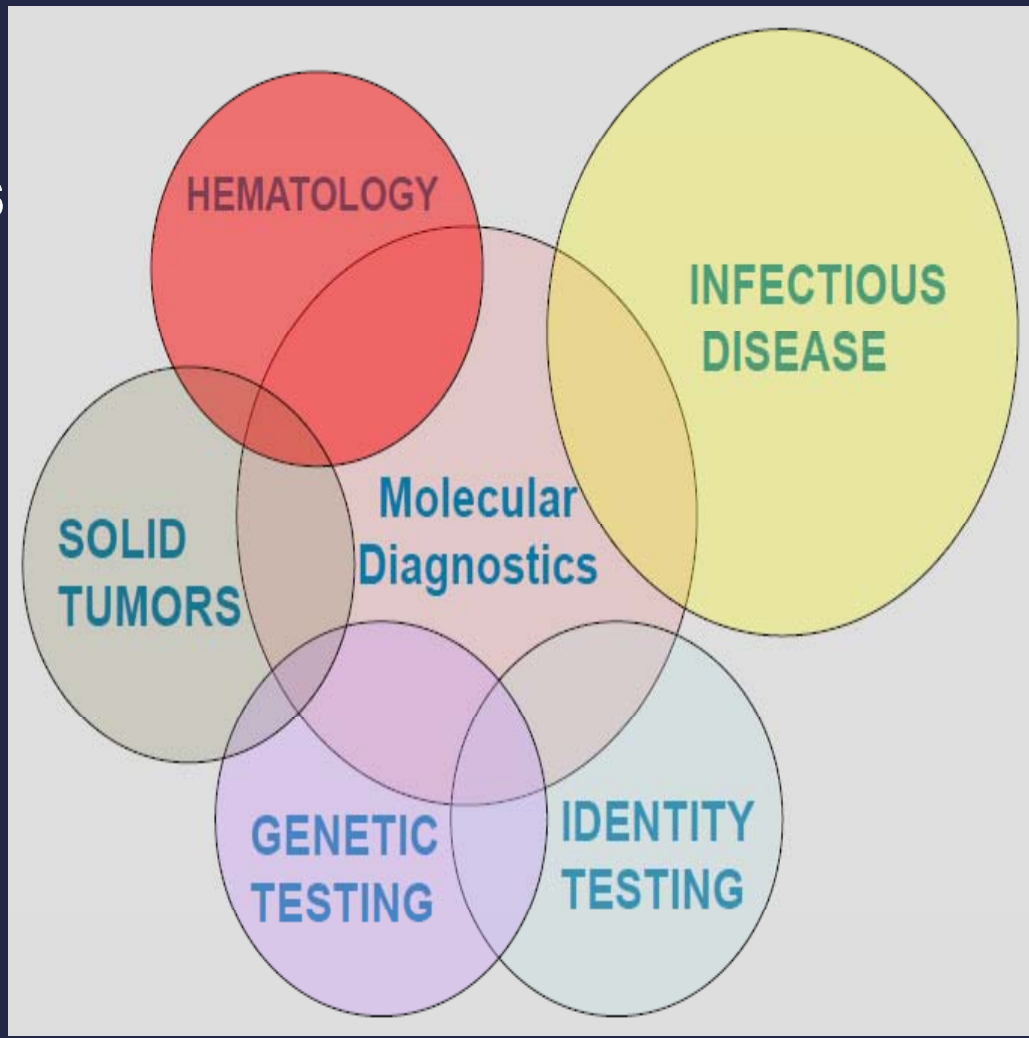
Advances in molecular diagnostics

- **Considerable advances** in molecular diagnostics in recent years.
- **Rapid introduction** means that ***quality issues have often been neglected***
- **Inter-laboratory** and **inter-technology variation** in results remains an issue of concern
- There is a **lack of international standards** for a wide range of Molecular Tests

MOLECULAR Diagnostics

An Interdisciplinary Field in Laboratory Medicine

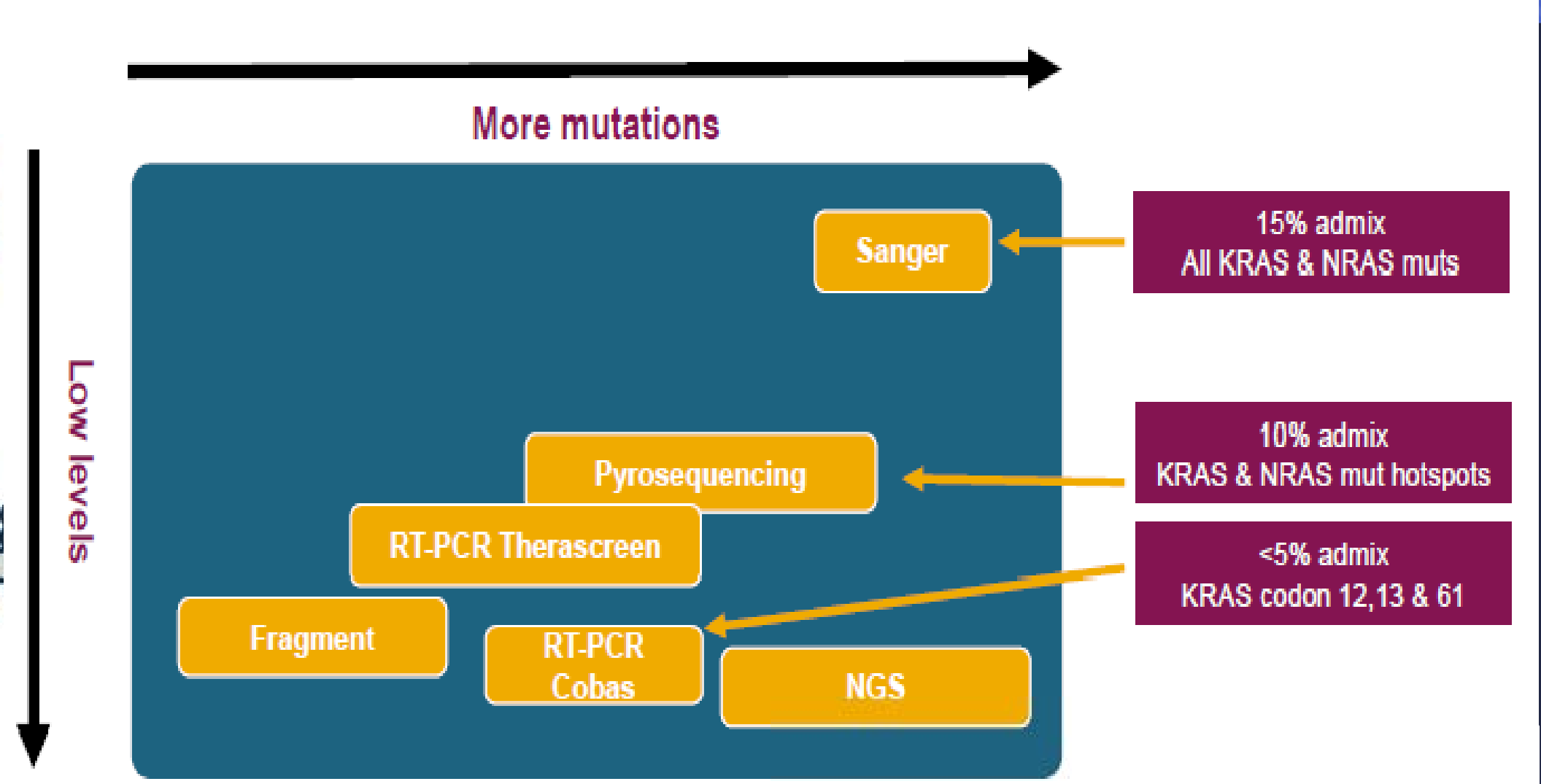
- Detection, quantitation, genotyping of infectious agents
- Detection of defective genes and variations in the genome
  - *Molecular genetics*
  - *Molecular oncology*
  - *Pharmacogenetics*
  - *Genomics*
- Identification and characterization of individuals



Molecular Diagnostics Laboratories

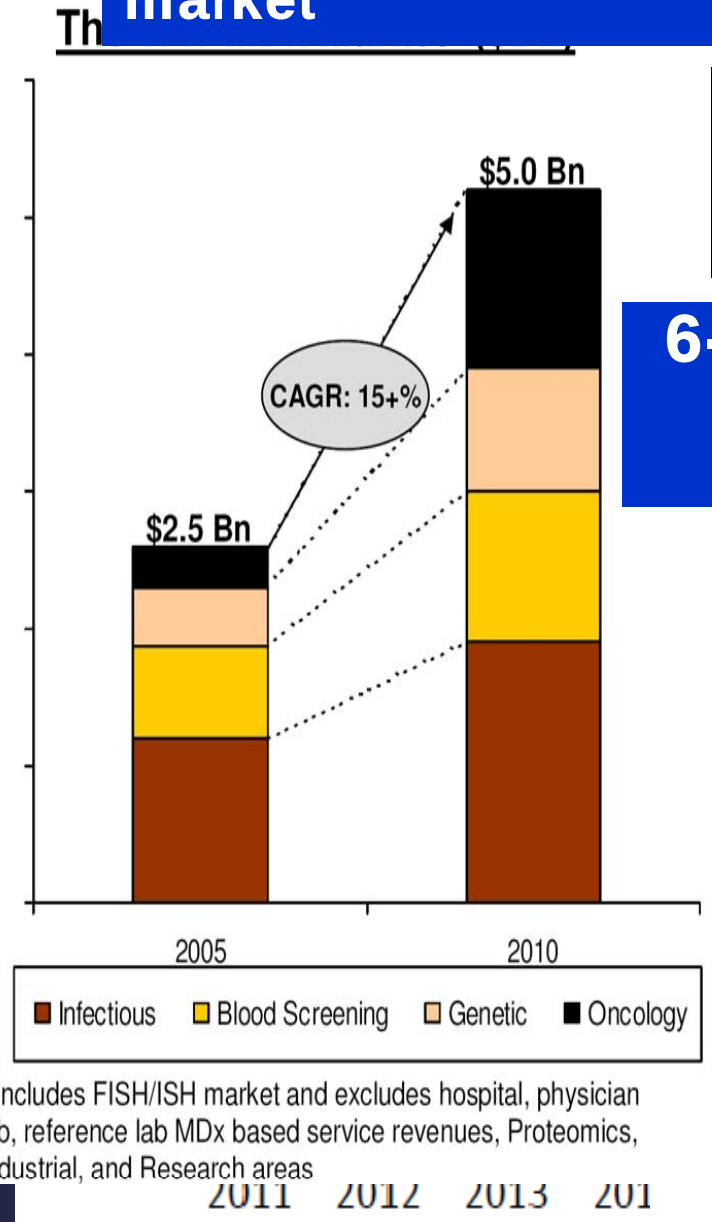
- **Test types**
  - ***Laboratory-Developed Molecular Tests (LDMTs)***
  - ***Lab-modified FDA-approved molecular tests***
  - ***FDA-approved molecular tests***
- **Clinical validity** & **utility** of Molecular tests
- Providing ***clinical interpretation*** of test results
- **Staffing** & **technical expertise**
- **Regulatory oversight** & **best practice** considerations

Different technologies, different LOD



~$34 billion world-wide market

Global MDx Market (2011)

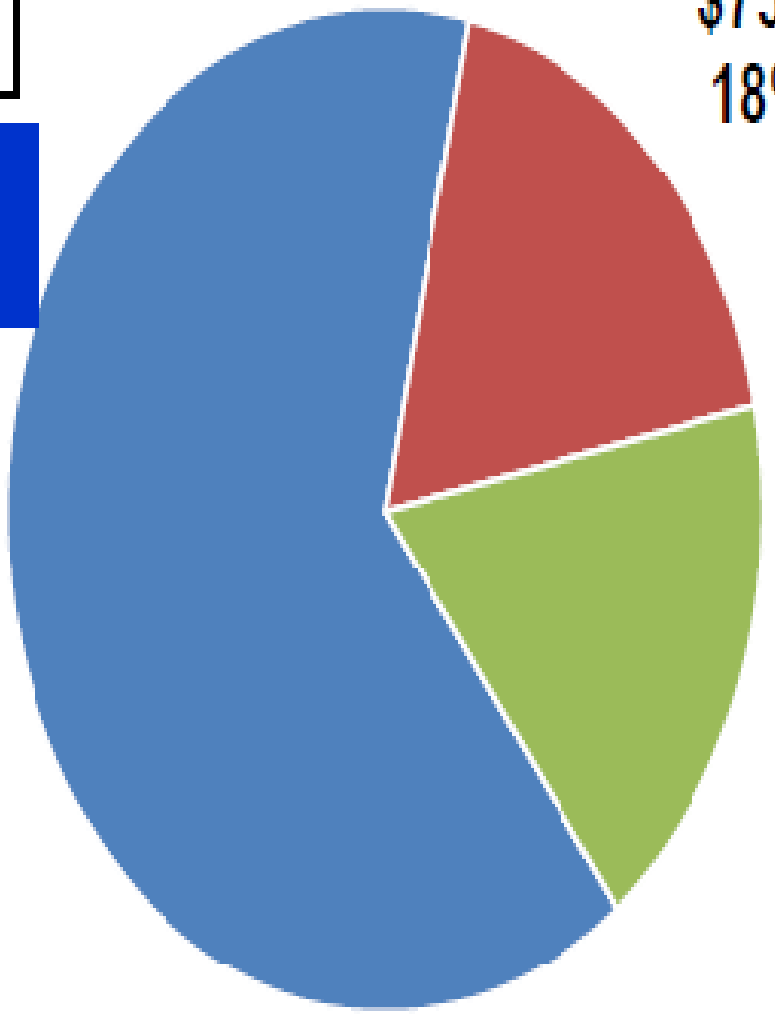


ncludes FISH/ISH market and excludes hospital, physician
o, reference lab MDx based service revenues, Proteomics,
dustrial, and Research areas

2011 2012 2013 201

$-Million

6-8% annual growth



Quality Management System Definition

Coordinated activities to direct and control an organization with regard to quality (ISO CLSI)

All aspects of the laboratory operation need to be addressed to assure quality; this constitutes a quality management system.

Quality Control, QC is method control
Quality Assurance, QA is process control

Quality System is the process of building quality into the entire system

Molecular tests vs. other clinical tests

- the quality system principles & quality considerations of Molecular Lab. are **the same as** other clinical lab disciplines.
- Molecular tests are subjected to the same CLIA regulations as other **highly complex laboratory tests**.
- There are some **quality assurance challenges** that are unique to molecular, and are different than chemistry and hematology.
- No matter what your background, ***a lab director must become thoroughly familiar with molecular techniques and the associated quality assurance challenges***.

Clinical Scientists in Molecular Pathology

Dutch Society for Pathology (www.pathology.nl), each pathology laboratory performing molecular diagnostics is recommend to have a **certified CSMP** (clinical scientists in molecular pathology)

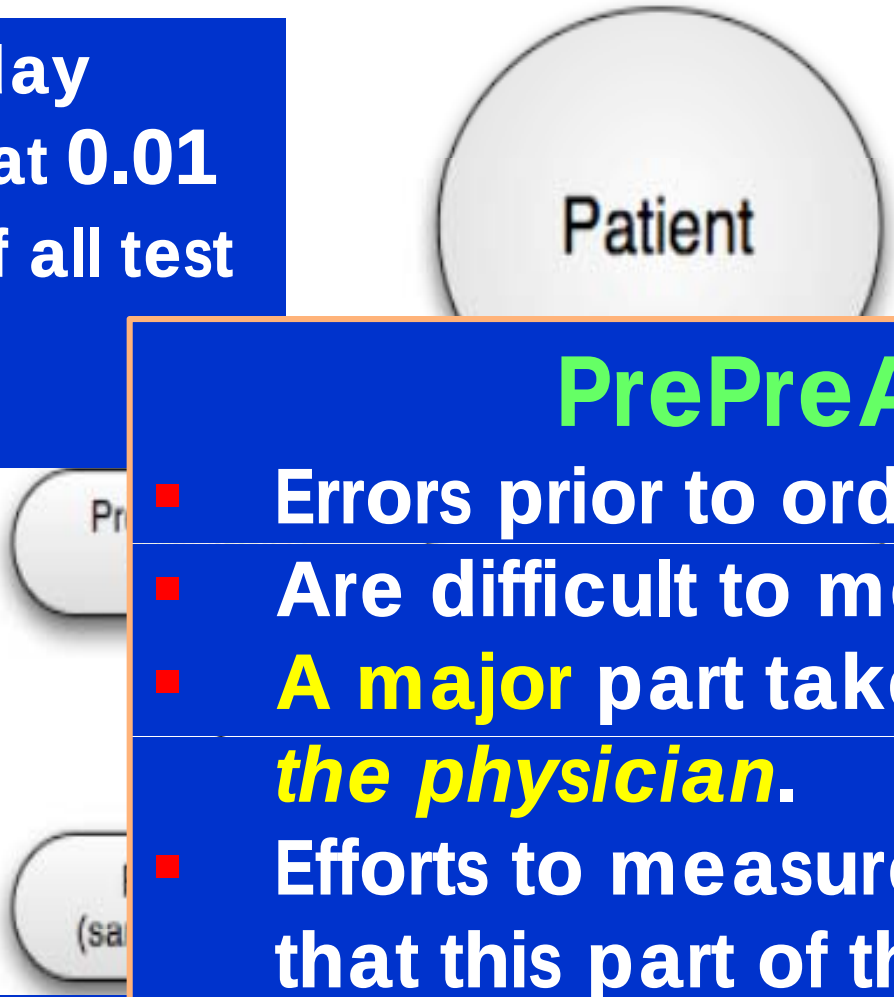
- **CSMP** is responsible for **development** and **supervision** of the molecular pathology diagnostics.
- This CSMP is a **PhD** or **MD/PhD** in molecular biology and/or molecular pathology and/or genetics,
- Completed a 2-year training in molecular pathology, covering design, analysis and evaluation of molecular tests, tissue/cell based diagnostic possibilities and quality management.
- In the **UK** there is a Royal College of Pathologists ***5 year Clinical Scientist specialist training program in Molecular Pathology of acquired disease*** which focuses on service delivery and development specifically for diagnosis of solid tumors within health care science (http://www.rcpath.org/)

The Total Testing Process (TTP)

- TTP is the total process from the **ordering of a test** to the **interpretation of a test result.**
- The TTP **starts** and **ends** with the ***patient***,
- Errors can occur in every step of the TTP.
- Of all errors in the TTP, approximately **25%** have consequences for the patient

The Total Testing Process, TTP

Studies today suggest that 0.01 to 0.5% of all test results are erroneous



Many errors detected by QC systems in the lab. & corrected before they produce an erroneous

The actual error rat
probably higher, s
estimating errors in
is a difficult task

PrePreAnalytical

- Errors prior to ordering of the test
- Are difficult to measure,
- A major part takes place in the *brain o the physician*.
- Efforts to measure these errors indicate that this part of the TTP process can cause a *large number of errors* , including over-utilization of laboratory tests

Total Testing Process

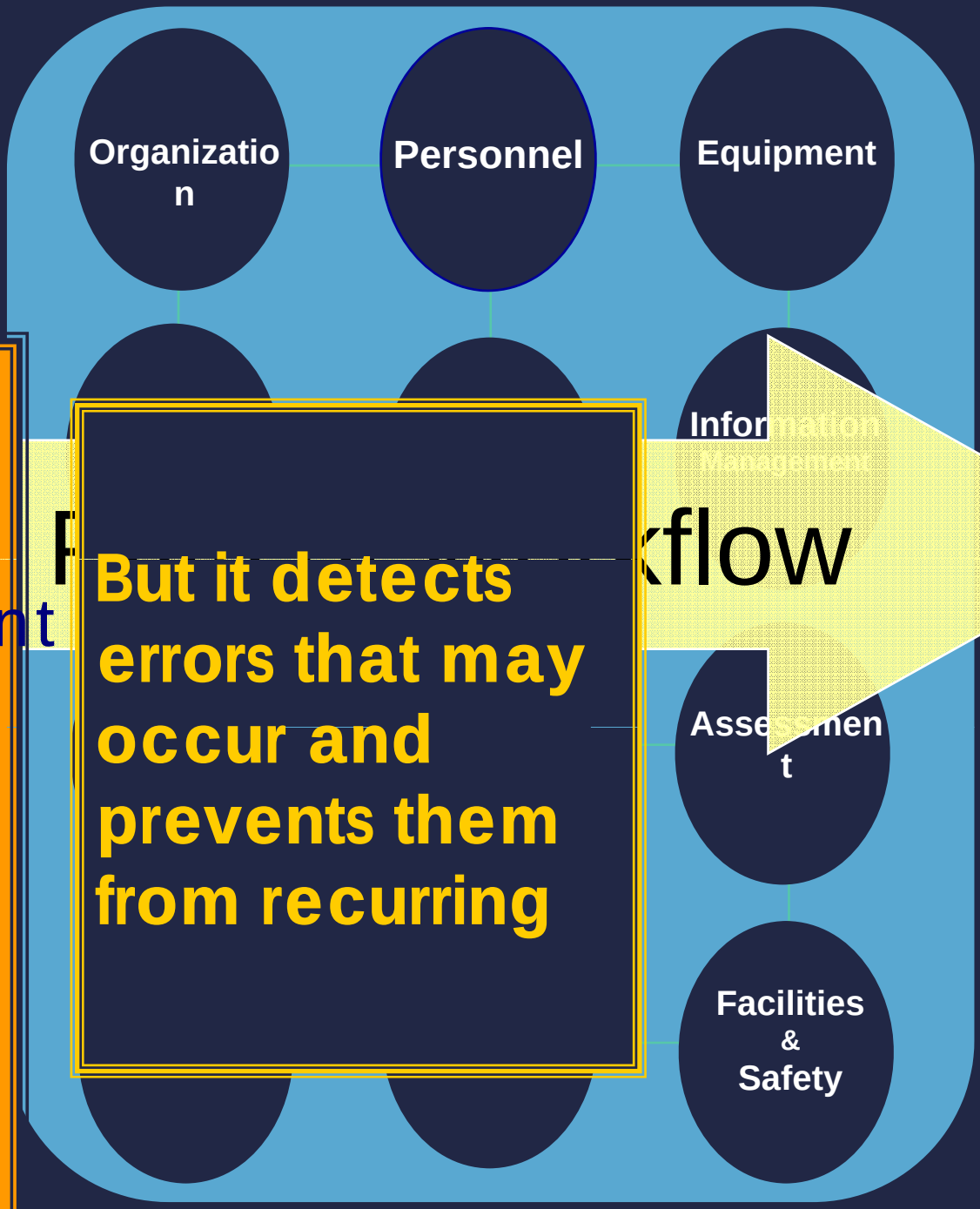
Phases of the TTP	Definition	Examples of Activities in Phase	Estimated contribution to TTP errors
Pre-Pre Analytical	Activities associated with initial selection of the test	Inappropriate test request, order entry, patient/specimen misidentification, inappropriate sample collection, inappropriate container, handling, storage or transportation.	46–68%
Pre-Analytical	Pre-test laboratory activities	Errors in sorting, pipetting, labeling, centrifugation	3–5%
Analytical	Testing-associated activities	Equipment malfunction, sample mix-ups, assay interference, undetected failure in quality control	7–13%
Post-Analytical	Post-test laboratory activities	Erroneous validation of analytical data, excessive turn-around-time, improper data entry or manual transcription error, failure/delay in reporting critical values	13–20%
Post-Post Analytical	Activities associated with interpretation of test results by the clinician	Delayed/missed reaction to laboratory reporting, incorrect interpretation, inappropriate/inadequate follow-up plan, failure to order appropriate consultation	25–46%

Quality assurance systems in molecular genetic testing

- Governments and regulatory bodies should recognize that **accreditation** of medical laboratories is **an effective procedure for assuring quality**.
- All molecular Lab. testing results for clinical care purposes should be reported by **competent laboratories**, as established by accreditation or other equivalent recognition consistent with these Guidelines.

Quality Management System (QMS), Es

Implementing Quality Management **does not** guarantee an ***ERROR-FREE*** Laboratory



But it detects errors that may occur and prevents them from recurring

Six steps for quality Assurance in the molecular lab.

- Plan Carefully
- **Train Properly**, requires experienced personnel

  - Both technicians and supervisors should have an adequate theoretical and technical training in molecular biology techniques
- Know the Risks
- Consider the Costs
- Practice Prevention (It is wise to practice preventive quality control)
- Stay Current (with quality issues, lab directors and techs need to utilize various **resources**.)

MOLECULAR ONCOLOGY 8 (2014) 830–839

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Review

Next generation diagnostic molecular pathology: Critical appraisal of quality assurance in Europe

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Quality assurance for diagnostic laboratories

- Implications of molecular analyses **on treatment** of patients a **high quality of test-** and **lab. performance** is required.
- Procedures for ***continuous measurement & improvement*** of laboratory performance should be fully integrated.
- Ensure a consistently ***high standard of performance***.
- External quality assurance (**EQA**) programs, are inevitable for monitoring of performance

Internal Quality Assurance (IQA)

- **IQA is necessary:**
  - To ensure **high assay reproducibility** and performance
  - enable detection and correction of **errors** in daily practice.
- Using **SOP** with appropriate **Pos. & Neg. controls**.
- **New tests** requires a **validation procedure**
- Dedicated trained personnel
- A manageable, easy to use quality management system
- A ***laboratory quality manager*** is essential to take charge of participation and performance in quality assurance schemes and to organize internal and external audits.

Table 2 – External quality assessment schemes for molecular pathology in Europe.

Provider	Tissue	Scheme	Type	Starting year
European Society for Pathology	Colon cancer	KRAS	Mutation detection	2009
	Colon cancer	KRAS, NRAS and BRAF	Mutation detection	2014
	Lung cancer	EGFR, KRAS	Mutation detection	2012
	Lung cancer	ALK	Rearrangement (ISH, FISH)	2012
	Lung cancer	Digital ALK	Rearrangement, digital cases	2012
European Molecular Genetics Quality Network	Colon cancer	KRAS, NRAS and BRAF	Mutation detection	2014
UK National External Quality Assessment Services	Adult Molecular Neuropathology	1p/19q FISH, MGMT promoter methylation, IDH	Translocations, methylation and mutation detection	2012
	Colon cancer	KRAS	Mutation detection	2009
	Colon cancer	KRAS, BRAF, PIK3CA and NRAS	Mutation detection	2013
	Gastrointestinal stromal tumor	KIT, PDGFRA	Mutation detection	2008
	Lung cancer	EGFR	Mutation detection	2010
	Lung cancer	EGFR, KRAS, BRAF and PIK3CA	Mutation detection	2013
	Lung cancer	ALK	Rearrangement (ISH, FISH, RT-PCR)	2013
	Melanoma	BRAF	Mutation detection	2012
	Melanoma	BRAF, NRAS, KIT	Mutation detection	2013
	Sarcoma	Common translocations	Translocations (FISH, RT-PCR)	2014
Dutch Foundation for Quality Assessment in Medical Laboratories[a]	B-cell clonality	IG heavy and light chain gene rearrangements	Rearrangement detection (Fragment analysis)	2003, 2004, 2008, 2010
	Breast cancer	ERBB2 (HER2)	Amplification	2005, yearly
	Colon cancer	KRAS	Mutation detection	2012
	Lymphoma	BCL2, BCL6 and MYC translocations	Translocation detection	2005, 2011
	Lynch prescreening	MSI	Fragment analysis	2006
	Lung cancer	EGFR, KRAS	Mutation detection	2009
	Lung cancer	EGFR	Mutation detection	2010
	Melanoma	BRAF	Mutation detection	2012
	Sarcoma	Common translocations	Translocations (FISH, RT-PCR)	2002 and 2009
	Solid tumor clonality	TP53	Mutation, LOH detection	2001
	Tissue identification	Polymorphic markers	Fragment analysis	2002–2007
French nationwide initiative	Melanoma	BRAF	Mutation detection	2012

a EQA schemes provided in the years indicated.

Iranian J Publ Health, Vol. 42, Supple.1, Jan 2013, pp: 119-124

Original Article

Quality Assurance Program for Molecular Medicine Laboratories

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(Received 05 Jun 2012; accepted 11 Nov 2012)

Quality Assurance program

- **50 labs.** with the highest receiving samples per day in Tehran
- **Self evaluation** before attending auditors at laboratories for molecular accreditation

Asked question and subject Frequency (%)

1 Quality control of applied material before use	83
2 Use of reference materials	91
3 Use of independent freezer for molecular tests	91
4 Regular calibration of instruments	100
5 Regular calibration of thermal cyclers	96
6 Regular calibration of micropipette	100
7 Policy of confirmation results	
- Repeating the test on the original specimens	32
- Repeating the test on the new specimens	29
- Repeating the test with alternative protocols	13
- Sending to other laboratory	13
8 Intending to participate in external quality assurance program	95

Analyzed data of Molecular Tehran Bench marking (%)

	Inspected Items	Frequency (%)
1	Dedicated Space	61.5
2	Provided Instruments	23
3	Storage conditions	77
4	Disposing the Swage	93
5	Extraction Procedures	83
6	SOPs for instruments	33
7	SOPs for protocols	77
8	Considered Correction Policies	30.7
9	Quality Control	7.7
10	Documentations of the tests	7.7
11	Documentations of Quality Control Experiments	7.7

European Journal of Human Genetics (2012) 20, 1118–1126

www.nature.com/ejhg

ARTICLE

Quality assurance practices in Europe: a survey of molecular genetic testing laboratories

Sarah Berwouts[1,4], Katrina Fanning[1,4], Michael A Morris[2,4], David E Barton[3,4] and Elisabeth Dequeker*[,1,4]

- **910** human molecular genetic testing labs. surveyed ,**32%** from **29** European countries responded.
- The majority of Labs were in the public sector (81%), university hospital (60%).
- ***Minority accredited*** (**23%**), and 26% was certified.
- **22%** of labs. did not participate in **EQA** and 28% did not use reference materials (RMs).

Quality Assurance in Europe, Molecular Labs.

- In **accredited laboratories**,
  - participation in EQA (P<0.0001),
  - use of RMs (P=0.0014) and
  - availability of continuous education (CE) on medical/scientific subjects (P=0.023),
  - specific tasks (P=0.0018), and quality assurance (P<0.0001)

  were significantly higher than in non-accredited laboratories.
- **They conclude that quality practices vary widely in European genetic testing laboratories.**

European Journal of Human Genetics (2012) 20, 1118–1126; doi:10.1038/ejhg.2012.125;
published online June 2012

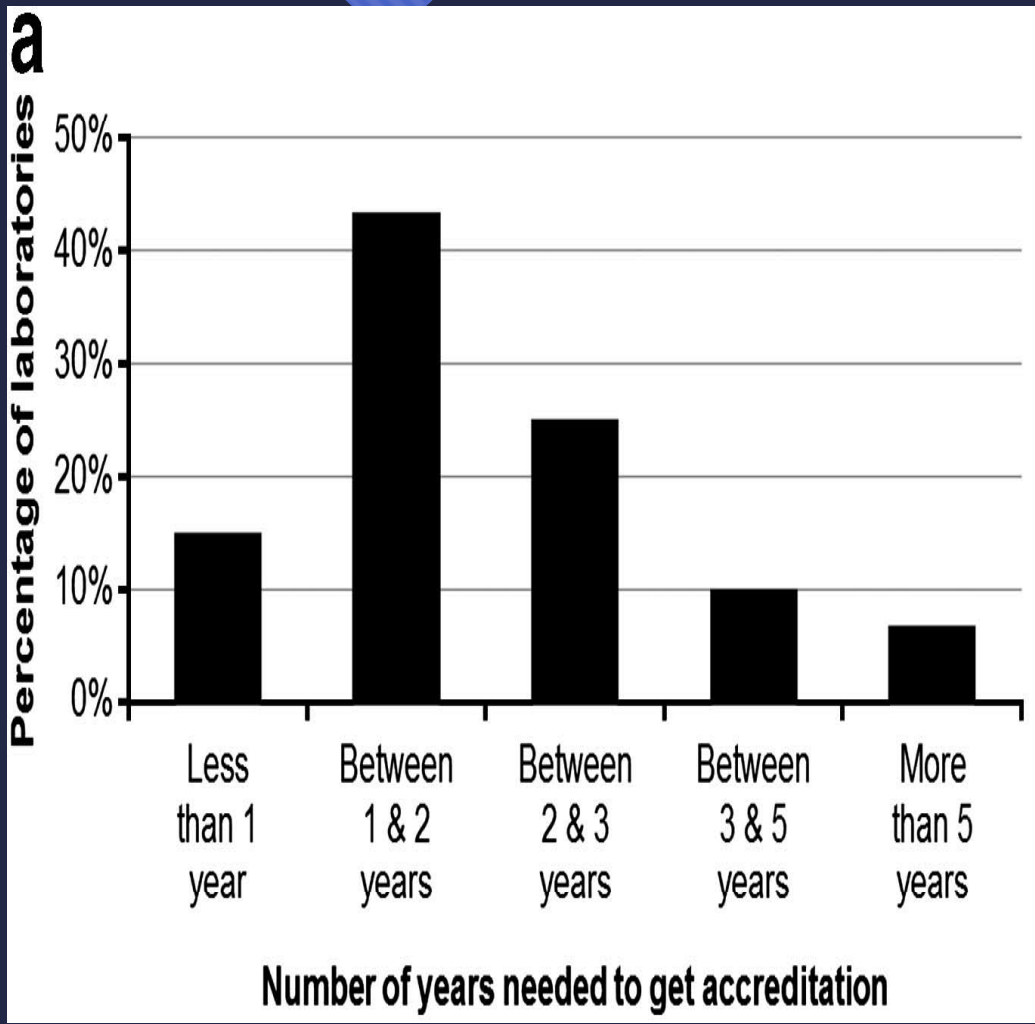
Degree of implementation of different Management & Technical Quality Indicators in accredited and non-accredited laboratories

Quality indicator	Degree of implementation (%)			P-value		
	Acc	Cert	None	Acc vs Cert	Acc vs None	Cert vs None
Management						
SOPs	100	99	69	1.00*	≤0.01	≤0.01
Document control	100	93	62	0.06*	≤0.01	≤0.01
Diagnostic log books	98	82	58	≤0.01	≤0.01	≤0.01
Quality manual	98	78	43	≤0.01	≤0.01	≤0.01
Maintenance/calibration log books	98	77	50	≤0.01	≤0.01	≤0.01
Training records	98	76	37	≤0.01	≤0.01	≤0.01
Following turnaround times	97	76	46	≤0.01	≤0.01	≤0.01
Recording of nonconformities	97	76	46	≤0.01	≤0.01	≤0.01
Recording complaints and compliments	97	71	40	≤0.01	≤0.01	≤0.01
Documented internal audits	97	66	18	≤0.01	≤0.01	≤0.01
Recording diagnostic errors	95	77	61	≤0.01	≤0.01	0.02
Recording complaint response times	78	66	31	0.18*	≤0.01	≤0.01
Technical						
Participation in EQA	100	77	65	≤0.01	≤0.01	0.09**
IQC	98	91	55	0.07*	≤0.01	≤0.01
Validation of instruments	97	84	54	≤0.01	≤0.01	≤0.01
Systematic corrective/preventive actions	97	73	46	≤0.01	≤0.01	≤0.01
Performing internal audits	97	68	21	≤0.01	≤0.01	≤0.01
Validation of methods	95	86	66	0.08*	≤0.01	≤0.01
Performing annual management reviews	94	66	19	≤0.01	≤0.01	≤0.01

Abbreviations: Acc, accredited laboratories; cert, certified laboratories; EQA, external quality assessment; IQC, internal quality control; none, non-accredited and noncertified laboratories.
*No significant difference between accredited and certified laboratories ($P>0.05$).
**No significant difference between certified laboratories and laboratories with no certification and no accreditation ($P>0.05$).

(a) Years (n=60) needed from **decision to prepare** for accreditation to being accredited.

(b) **Accreditation standards** implemented over the years (n=62) in Europe



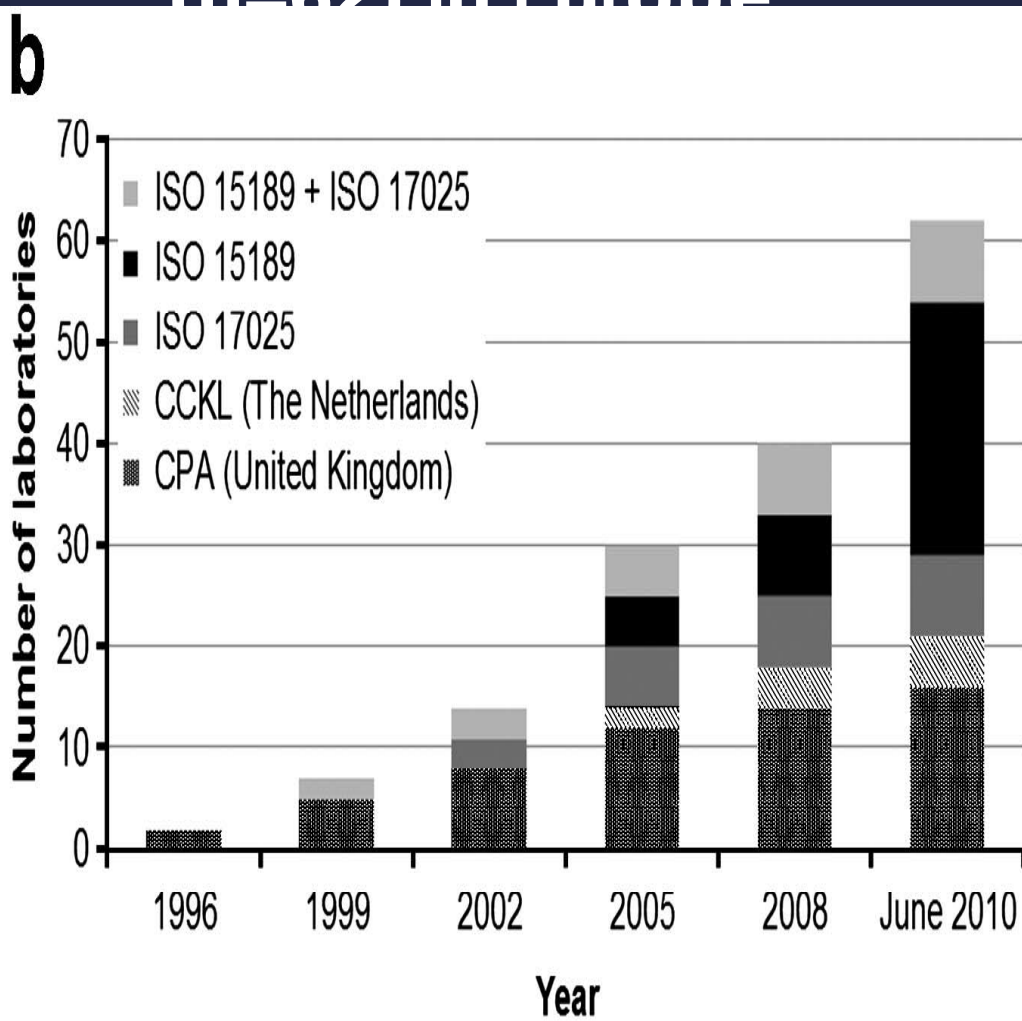


Table 2. Information Collected and Reviewed for CLIA Certification/Recertification Surveys

- Services offered—the list of tests and specialties/subspecialties
- Standard operating procedure manual with all test procedures (e.g., package inserts and supplemental information, as necessary)
- Reference laboratory's client services manual, if applicable
- Records of tests referred to other laboratories
- Personnel records, including diplomas, certificates, degrees, training and experience, continuing education, competency assessment, duties/responsibilities, and personnel changes
- Quality control records, including remedial action information, calibration and calibration verification records, statistical limits, and instrument maintenance and function checks records
- Proficiency testing (PT) reports, including test runs with PT results, direct printouts, and remedial actions for unsatisfactory results
- Quality system assessment plan and documentation; for each of the systems:
    - Policies and procedures to monitor, assess, and correct identified problems
    - Documentation of ongoing assessment activities, including review of the effectiveness of corrective actions taken, revision of policies and procedures to prevent recurrence of problems, and discussion of assessment reviews with staff
- Safety information
- Patient testing records including requisition (patient charts may be used), work records (direct printouts), and patient test reports (patient charts may be used)

Table 3. Key Quality Control Requirements Relevant to Molecular Testing

- For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytical process.(42 CFR 493.1256 (a)) The control procedures must:
  - detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance (42 CFR 493.1256 (c)(1)) and
  - monitor over time the accuracy and precision of test performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance. (42 CFR 493.1256 (c)(2))
- The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified or established by the laboratory. (42 CFR 493.1256 (b))
- Each laboratory that introduces a test system not subject to FDA clearance or approval—including methods developed in-house—must, before reporting patient test results, establish for the test system the performance specifications for the following performance characteristics, as applicable:
  - accuracy,
  - precision,
  - analytical sensitivity,
  - analytical specificity to include interfering substances, reportable range of test results for the test system,
  - reference intervals (normal values), and
  - any other performance characteristic required for test performance. (42 CFR 493.1253 (b)(2))
- For test systems developed in-house, a laboratory must establish a maintenance protocol, and perform and document the maintenance activities, to ensure test system performance to produce accurate and reliable test results (42 CFR 493.1254 (b)).
- Each test system that has an extraction phase, include two control materials, including one that is capable of detecting errors in the extraction process. (42 CFR 493.1256 (d)(3)(iv))
- Each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting the inhibition. (42 CFR 493.1256 (d)(3)(v))

Conclusion

Quality Improvement of Molecular Diagnosis in Iran

1. Government & Regulatory roles:

- Define exactly the requirements for establishing the molecular lab.
- Monitoring on scientific & regular basis
- Promote referral to reference Labs.

2. Lab. Director roles:

- Plan Carefully for Molecular section establishment
- Education & Training are necessary for GLP
- Note to the Risks
- Practice Prevention (IQC & EQA are essential)
- Stay Current

Thank you,

- ***"Improve constantly and forever the system of*** *production and* ***service*** *to* ***improve quality & productivity****, and thus* ***constantly decrease costs."*** (**W. Edwards Deming**)