Integration of Risk Assessment Strategies and Quality Control Plans for Next-Generation Sequencing-based Assays at a Time of Evolving Quality Assurance and Regulatory Frameworks

AMP 2016
#12530

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Introduction

Next generation sequencing (NGS) is key for the implementation of personalized medicine into diagnostics. Most NGS diagnostics assays are developed as Laboratory Developed Test (LDTs). The Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations remains the main regulatory framework for LDT testing.

Professional stakeholders and regulatory agencies are actively working on evolving NGS assays Quality Assurance (QA) frameworks and regulatory requirements. As the U.S. Food and Drug Administration (FDA) continues its work on a NGS LDTs Policy, parallel discussions on modernizing CLIA LDT oversight are in progress by additional stakeholders such as the Centers for Medicare & Medicaid Services (CMS), the College American of Pathologist (CAP), the American College of Medical Genetics (ACMG), the American Medical Association (AMA), and the Association for Molecular Pathology (AMP).

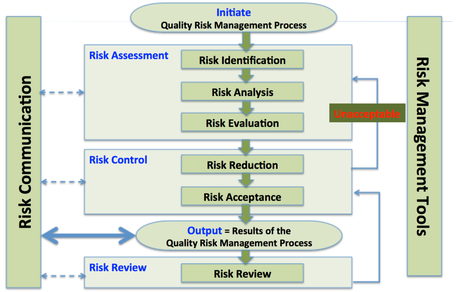
Nonetheless, the CAP checklists currently assure Quality Standards for LDTs, at a time when the same definition of LDT is challenged.

Methods

CDC/CMS, CAP, ISO 15189, and CLSI EP23 guidelines are used.

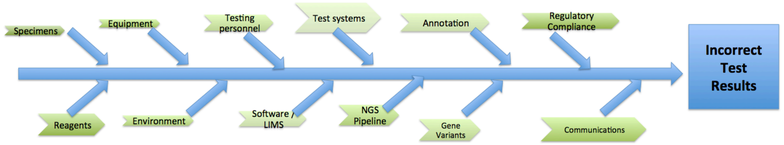
Personalis Risk Management Approaches

Risk Management at Personalis follows the approach depicted below:



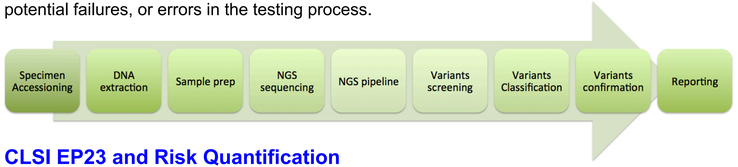
Source of Errors identification through Fish*(-like)* Diagram

Risk points, sources of potential failures or errors are charted through process maps. Risk Assessment (RA) spans all key pre-, post- and –analytical phases of testing and critical components not limited to specimens, test systems, reagents, environment, testing personnel, software and LIMS, communications and regulatory compliance.



Test (Assay) Performing Map *(not comprehensive*

Maps are charted to dissect assay processes and identify risk points, sources of potential failures, or errors in the testing process.



CLSI EP23 and Risk Quantification

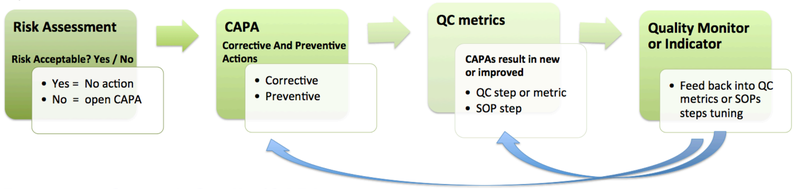
Means of failure detection are charted in relation to different types of controls, and risk quantified and controlled.

	Severity				
Probability of Harm	Negligible	Minor	Serious	Critical	Catastrophic
Frequent	unacceptable	unacceptable	unacceptable	unacceptable	unacceptable
Probable	acceptable	unacceptable	unacceptable	unacceptable	unacceptable
Occasional	acceptable	acceptable	acceptable	unacceptable	unacceptable
Remote	acceptable	acceptable	acceptable	unacceptable	unacceptable
Improbable	acceptable	acceptable	acceptable	acceptable	acceptable

Results

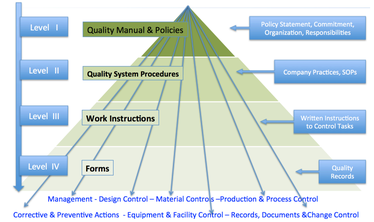
Risk Assessment, Quality/CAPAs and Quality Management Plans

Tuning of Quality Control (QC) plans allowed for risk mitigation and successful resolution of Corrective and Preventive Actions (CAPAs) initiated as RA. New QC steps are added or modified in relation to the severity of identified sources of risk in relation to patients testing at critical process nodes. QA is then set to monitor and assess quality over time through non-conforming reports and trends.



Document Control, Quality/CAPAs and Quality Management Plans

An advanced Product Life Management (PLM) environment is configured to support Document Control and redline traceability of procedural changes, thus providing structured compliance and auditability. As a result of RA, Procedures are then modified to reduce risks by tailoring of QC plans.



Conclusion

At the present time multiple RA analyses have resulted into the successful creation of new procedures, QC steps or other process improvements. Comprehensive NGS QC plans have been evolved in relation to key process steps such as annotation, databases, software, testing personnel competency, reagents and environment.

Advanced PLM Management and Document Control is key in orchestrating compliance across multiple Quality Systems and distinct Regulatory Standards dictated by different organizations or Agencies. This approach is successful in de-convoluting LDT NGS-based assays complexity and key to Quality and NGS QC Metrics definition. It is anticipated that the integration at a minimum of CLIA'88, CAP and ISO 15189 standards into LDT NGS based assays will provide pivotal, especially at a time of multiple and evolving Quality and Regulatory Standards.

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