

Development and Implementation of A LIS-Based Validation System for Autoverification Toward Zero Defects in The Automated Reporting of Laboratory Test Results

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Abstract

Background

Validation of the autoverification function is the most critical step to confirm its effectiveness before use. It is crucial to verify whether the programmed algorithm follows the expected logic and produces the expected results. In recent years, this process has always been centered on the assessment of human-machine consistency and mostly takes the form of manual recording, which is a time-consuming activity with inherent subjectivity and arbitrariness, and cannot guarantee a comprehensive, timely and continuous effectiveness evaluation of the autoverification function. To overcome these inherent limitations, we independently developed and implemented a laboratory information system (LIS)-based validation system for autoverification.

Methods

We developed a correctness verification and integrity validation method (hereinafter referred to as the "new method") in the form of a human-machine dialogue. The system records the personnel's review steps and determines if the human-machine review results are consistent. If they are inconsistent, the laboratory personnel analyze the reasons for the inconsistency according to the system prompts, add to or modify the rules, reverify, and finally improve the accuracy of autoverification.

Results

The validation system was successfully established and implemented. For a dataset consisting of 833 rules for 30 assays, 782 rules (93.87%) were successfully verified in the correctness verification phase, and 51 rules were deleted due to execution errors. In the integrity validation phase, 24 projects were easily verified, while the other 6 projects still required the addition of new rules or changes to the rule settings. From setting the rules to the automated report, the time difference between manual validation and the new method, was statistically significant ($\chi^2=11.06$, $p=0.0009$), with the new method greatly reducing validation time. Since 2017, the new method has been used in 32 laboratories, and 15.8 million reports have been automatically reviewed and issued without a single clinical complaint.

Conclusion

To the best of our knowledge, this is the first report to realize autoverification validation in the form of a human-machine interaction. The new method can effectively control the risks of autoverification, shorten time consumption, and improve the efficiency of laboratory verification.

Background

Autoverification is a powerful tool for the batch processing of test results and has been widely used in recent years. It has obvious advantages in reducing reporting errors, shortening turnaround time and improving audit efficiency[1-5]. Based on the American Clinical and Laboratory Standards Institute (CLSI)

AUTO-10[6] standards and current review processes, we established an autoverification system including 11 rule categories. Technicians set the rules according to audit requirements and rule categories. Each item can set multiple rules, including single value judgment, combined mode judgment, historical record query and calculation, sampling time validity judgment, sample abnormality (hemolysis, lipemia) judgment, etc. The autoverification system determines whether the report is abnormal according to the rules. Tests that did not trigger contradiction mode are displayed in green, while failed tests (triggering rules, contradictory modes set by the rules) are displayed in red, and the cause of the contradiction is indicated. If all the tests in the report are green, the bar code of the report is also green; if any test in the report is red, the report shows a red barcode, which signals a warning in the system.

According to the above steps, the autoverification system displays colors and abnormal prompts after judging the rules, a process called automatic early warning. The automatic warning is only for judgment and is not involved in the decision to issue a report. Based on this, the system automatically sends out a report with a green barcode, a process called automatic reporting. Automatic early warning and automatic reporting comprise the automatic review. This system is especially useful in the review of complex diagnostic projects (molecular testing, pathological testing). These projects prompt absurd values from personnel. For some moderately complex projects (biochemical, blood), the combination of report review, automatic warning and automatic reporting is equivalent to the autoverification system in a large number of literature reports and the laboratory information system (LIS) automatic reports. The autoverification process used by our laboratory is shown in Figure 1.

Current status and challenges

The autoverification system developed by Kingmed Diagnostic Co. has been used in many disciplines, such as biochemistry, immunology, hematology, microbiology, molecules and pathology. To date, 25,487 rules have been set. The system judges test results 1.1 million times a day and provides audit recommendations for 250,000 report forms, accounting for 87% of the total number of report forms. Approximately 80,000 reports are automatically generated every day. The College of American Pathologists clauses GEN43875[7] and ISO 15189:2012[8] 5.9.2b both require that autoverification systems undergo functional verification before use.

According to published studies, almost all laboratories have performed personnel-based and automatic system audits with the same results, manually recorded consistency, and reached a conclusion after a statistical analysis of the results[2, 4, 9, 10]. This method is simple to implement but has limitations:

1. Lack of implementability. Based on the requirements of WS/T 616-2018 (China Health Organization recommended standard) [11]for the validation of the autoverification of quantitative clinical laboratory test results, every test and every sample type involved in the autoverification procedure should be tested; the validation time should be no less than 3 months and/or the number of reports released should be no less than 50000; and periodic verification should be performed every year for no less than 10 working days and/or for no less than 5000 reports. The validation workload is large,

and it is difficult to rely on manual comparison and recording, which greatly increases the postanalytical workload.

2. Reporting risk. During manual verification, personnel are prone to inertia or judgment errors. The lack of a system control mechanism for this kind of validation can generate reporting risks and directly affect clinical diagnosis and treatment.

Therefore, there is an urgent need to design a verification method that minimizes the workload and systematically controls risks. We report on a rule verification system with a small workload and ease of operation that can be used as a reference for self-built and automatic test auditing for laboratories and manufacturers.

Methods

Validation scheme

On the premise that automatic audits are divided into automatic warnings and automatic reports, we divide the verification system into two stages. The first stage is called correctness verification, which verifies that the operation of the rules is consistent with the expectations set by the personnel. If there is a problem, the responsible party may be the program development department. The second stage is called integrity validation. Based on the results from the first stage, this stage verifies whether the set rules include all the elements from the personnel's audit report. The functional design of the two-stage system is shown in Table 1.

Table 1. Two validation methods designed for two parts of the autoverification system

Phase	Object	Validation method	Explanation	Inconsistent solutions
Automatic warning	Warning rules	Correctness verification	To verify that the warning rules behaves as expected and produce the expected outcome.	If the warning rules setting is wrong, delete and reset the rules.
Automated reporting	Laboratory tests	Integrity validation	To confirm that the laboratory test results that pass the automatic warning can be reported automatically	Add more warning rules according to the laboratory report criteria.

Correctness verification

The correctness verification phase confirms whether the execution of a single rule is correct. It is implemented as follows: 1. For newly added rules, the system adds the label "Pending Verification". 2. When the report is reviewed, the system displays the rule judgment result, and a purple color block is displayed to remind the staff to judge whether the execution result of the "Pending Verification" rule is correct. 3. The staff input the judgment result. 4. The system changes the rule status according to the

staff input. If it is consistent, the rule label is set to "verified", prompting the personnel to continue to the next stage of verification. If it is inconsistent, the staff are prompted to delete the rule. Figure 2 is a schematic diagram of the correctness verification using the example of a C-reactive protein (CRP). The CRP test result was 1.8 mg/l and passed the quality control. The autoverification system searched all the rules for the CRP and hit two of them, No. 001879 and No. 002009. The No. 001879 rule(verified) is to check whether the CRP result has passed the quality control. The No. 002009 rule(pending verification) is to intercept the result greater than or equal to 5. Therefore, when No. 002009 is triggered, the warning information of the sample appears purple, indicating that the technician needs to confirm whether the warning result is consistent with the manual judgment. In the correctness verification interface as shown in Figure 3, the system provides two options, the human-machine judgment is consistent, or the system judges incorrectly. The technician can confirm that the rule is performing correctly and change its status to "verified".

Integrity validation

Integrity validation can only be started after the correctness verification of all rules of a project is completed. It is implemented as follows: 1. After the report shows the result of the automatic warning step, if the system monitoring finds that the report sheet has been changed, a dialog box will pop up and ask the reviewer to select the reason for the modification. These reasons include a) a rule execution error, b) a rule setting value that is inappropriate, c) the required addition of new rules, d) the lack of involvement of other issues related to automatic review, and e) automatic warning and prompt modification. the LIS records the modified content and the reasons for personnel analysis. 2. If the laboratory wants to implement automatic reporting, a verification number, such as 5000, can be set according to the complexity of the project review. 3. If the automatic warning result of the report is green (approved), the personnel will issue the report directly, and the verification number of the report will automatically increase by 1. 4. If the verification number of all items on the report exceeds the set number, the report will be automatically released. 5. If the automatic warning result of the report is green (approved), the report is modified, and the reason selected is any of a, b, or c. The LIS will clear the verification number for the related items and stop automatic reporting. **Fig 4.** shows the verification goals and verification numbers for six projects.

Results

Validation results of the autoverification system

Data from the autoverification function validation of 30 assays from Ji Nan Kingmed Diagnostic Co. from October 2019 to January 2020 were collected, and a total of 833 early warning rules were obtained.

Correctness verification results

Among the 833 rules, 782 (93.88%) were successfully verified for correctness, with a total of 3814 validations, including 2230 (58.47%) released tests and 1584 (41.53%) intercepted tests. The

inconsistencies were verified, and 51 (0.06%) error rules were deleted. The reasons for verification failure are shown in Table 2.

Table 2. List of reasons for correctness verification failure

Error type	Proportion (%)	Sample	Solution
Human error	63.3	Incorrect English letter case in the text of the rules, resulting in no warning	Reset the rules
Specific warning target	24.9	Early warning of diagnostic results and microscopy results in a special report interface for pathology	Add a supplementary algorithm code
Algorithm code error	8.4	HPV typing results could not be verified with the Delta Check; the results of the microbial project identification could not be correlated with a variety of drug sensitivity combinations	Fix the algorithm code
Software compatibility problem	3.4	Problem with the precision of the number comparison script	Fix the algorithm code

Integrity validation results

The integrity of all projects was verified within one month, and the problems found are shown in Table 3. The reasons provided for rule modification were automatic warning prompt and rule modification (5, 10.6%), rule execution error (0, 0%), improper setting values (15, 31.9%), new rule added (18, 38.3%), no automatic warning involving other questions (9, 19.2%).

Table 3. List of reasons why integrity validation failed

Test	Reason for not passing	Solution
HPV genotyping	There was no comprehensive analysis of the combined thin-layer cytology results	Analyze the results associated with thin-layer cytology
Urea	The limit range was too wide	Reduce the limit range
Albumin	Review of the detection system produces an error	Specify the detection system
CBC	Test results were only checked on the same day as the barcode	Extend the backdating of the historical results
HBsAg HBsAb HBeAg HBeAb HBcAb	Not all composite mode scenarios were covered	Add a joint audit of the portfolio project results
Cortisol	There was no warning of abnormal rhythms	Add a rule about checking sampling time

Comparison of the two methods

The comparison of manual record analysis and the new method for different steps is shown in Table 4. The new method performs 4 automation steps, reduces personnel workload, and automatically controls the enabling and disabling of automatic report release through system monitoring report modification. The increased accuracy verification can quickly eliminate rule setting exceptions and development loopholes while reducing the time needed for personnel analysis. The two methods took 452 hours and 275 hours, respectively, to complete.

Table 4. Comparison of the two methods in verifying HBV reports for 3000 cases (hours)

Steps	Manual verification	New Method
1. Set 65 rules	1.5	1.5
2. Perform Rule 130 test	2.5	2.5
3. Correctness verification	0	0.25 ^a
4. Personnel comparison report and results review	240	240
5. Record comparison result	100	0 ^b
6. Analysis of the verification number	10	0 ^b
7. Determine whether to activate automatic approval	5	0 ^b
8. Personnel analysis of the reasons for inconsistent audit results	90	30
9. Add and modify rules	1	1
10. Determine whether to turn off autoverification	1	0 ^c
Total	452	275

Note: For automatic implementation, the time is calculated as zero.

a: Reasons for invalid locking rules; b: Reduced workload; c: Controlled risks

Real-time effect of the two methods with multiple projects

The results for measuring the actual time required from setting the rules to automatic report generation for 24 automatically reported items are shown in Figure 5. The shortest time difference is 69 hours, the longest is 324 hours, and the median is 174 hours, for a total time savings of 4631 hours. The log-rank test shows that the verification time difference between the two methods is statistically significant ($\chi^2=11.06, p=0.0009$). In addition, a survey conducted after half a year of use shows that 94.6% of laboratory personnel believe that the new method greatly reduces the workload and effectively controls reporting risks.

Discussion

The core of the use of autoverification lies in the validation of system functions and rules. Due to the complexity of these rules, it is impossible to find all the functional defects by relying solely on function validation before the system goes online, and even human input errors cannot be carried out in the validation[12]. Such functional defects must be found in actual application scenarios with multiple different rule settings, such as the incorrect input of full-width symbols, that is, correctness verification; the premise of rule verification is to include a review of the logic of all reviewers in the system, which can

only be discovered in actual application scenarios. Additionally, integrity validation can be performed in actual application scenarios to truly find problems[13, 14].

We initially designed the system into two parts, automatic warning and automatic reporting, to allow complex detection items (molecular and pathological examination, final human report, system prompt error) to be included in the automatic review. The laboratory technicians can then choose to address the needs of different measurements. These two parts correspond to two verification steps: the automatic warning part performs correctness verification, and the automatic reporting part performs integrity validation.

Compared with the traditional method, the true positives and false positives of the "personal and machine-based audit results" are easy to understand, but if the indicators are abnormal, it can be difficult to find the cause of this abnormality, especially after all the reasons are verified after thousands of reports are released[15]. The audit scene has become blurred in the auditor's memory, and it becomes inefficient to check the problems one by one. The process-based validation scheme we developed is more practical and advantageous: 1. It can be easily operated and quickly initialized; 2. Its self-traction and control of online functions can ensure that every rule is fully verified; 3. The amount of manual work is small, allowing the technicians to complete the verification steps during their daily work.

We divided the entire validation into two modules, correctness verification and integrity validation, based on the concept of process management. Rules are the basic unit of the entire autoverification system. If basic rule verification is not performed at the beginning of the entire process, when the human-machine judgment is inconsistent, it is difficult to confirm whether the problem is caused by algorithm error, execution error or another reason, inevitably increasing the analysis workload. In contrast, if correctness verification is completed when the rules are established, the only reason for an inconsistency between man and machine during the release of the report issuance would "rule omission", requiring the technician to only add the corresponding rules.

During the entire verification process, we implemented human-computer interaction, which includes the following:

1. An "expected sense of play": Before the laboratory personnel view the results, they already possess a logical expectation, and in the process, establish a comparison of the rules and effects;
2. The use of visual stimulation methods (red, green, purple backgrounds) that can be quickly identified and relax the laboratory personnel;
3. System pull: Once the verification succeeds or fails, it is automatically counted with the click of a button, which automatically opens the automatic report function. All the functions ensure that laboratory personnel, particularly those born after 1990, can derive enjoyment from completing the verification process, thus increasing its core value[16].

Conclusions

In the two years that the online validation has been in use, there have never been any defects or reporting risks due to autoverification. We believe that for both intermediate and self-built autoverification systems, online validation is a useful tool for controlling the risks of autoverification and improving the quality of the reports. The detailed process for this method can serve as reference for the development and implementation of LIS-based autoverification systems.

Abbreviations

LIS:Laboratory information system;TAT:Turnaround time;CLSI: American Institute of Clinical and Laboratory Standardization;AUTO 10-A: Autoverification of Clinical Laboratory Test Result 10-A; Approved Guideline;CRP:C-reactive protein;CBC: Complete blood cell count; HBsAg : Hepatitis B virus surface antigen; HBsAb : Hepatitis B virus surface antibody ; HBeAg : Hepatitis B virus e antigen ; HBeAb : Hepatitis B virus e antibody ; HBcAb : Hepatitis B virus core antibody ;HBV: Hepatitis B virus; HPV: Human papilloma virus;

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All of the authors had full access to all of the data in the study and taking responsibility for the content of the manuscript.RT conceived and designed the study. DJ ,QW,BJL, DZP and JJW performed the case and sample collection,analysis,and interpretation of the data. YTC, XYD and NXM performed the analysis with constructive discussions.DJ wrote the first draft of the paper.RT reviewed and approved the final manuscript.All authors have read and approved the final manuscript.

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Ethics approval and consent to participate

This study was approved by the ethics review board of KingMed Diagnostics. The study adhered to relevant guidelines and regulations. The patient consent was waived by the approving ethics review board, as utilization of anonymized history data does not require patient consent.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article. The data underlying this study are available and researchers may submit data requests to the corresponding author on reasonable request.

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Figures

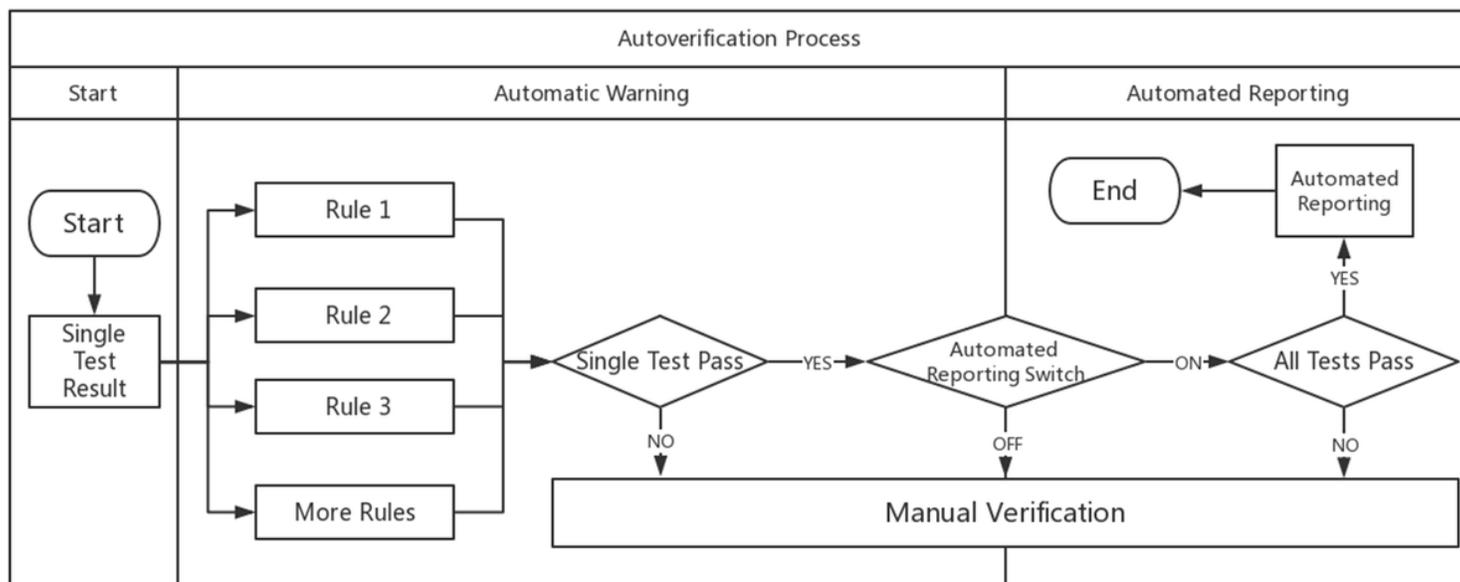


Figure 1

Autoverification process. Single test results must meet all the warning rules at the same time. The autoverification algorithm can identify those samples requiring manual review that do not meet the laboratory's criteria for autoverification. If the automated reporting switch is not activated, then reports that pass the automatic warning step are manually issued. If the automated reporting switch is turned on and all tests on the report pass their warning rules, then the system automatically releases the report.

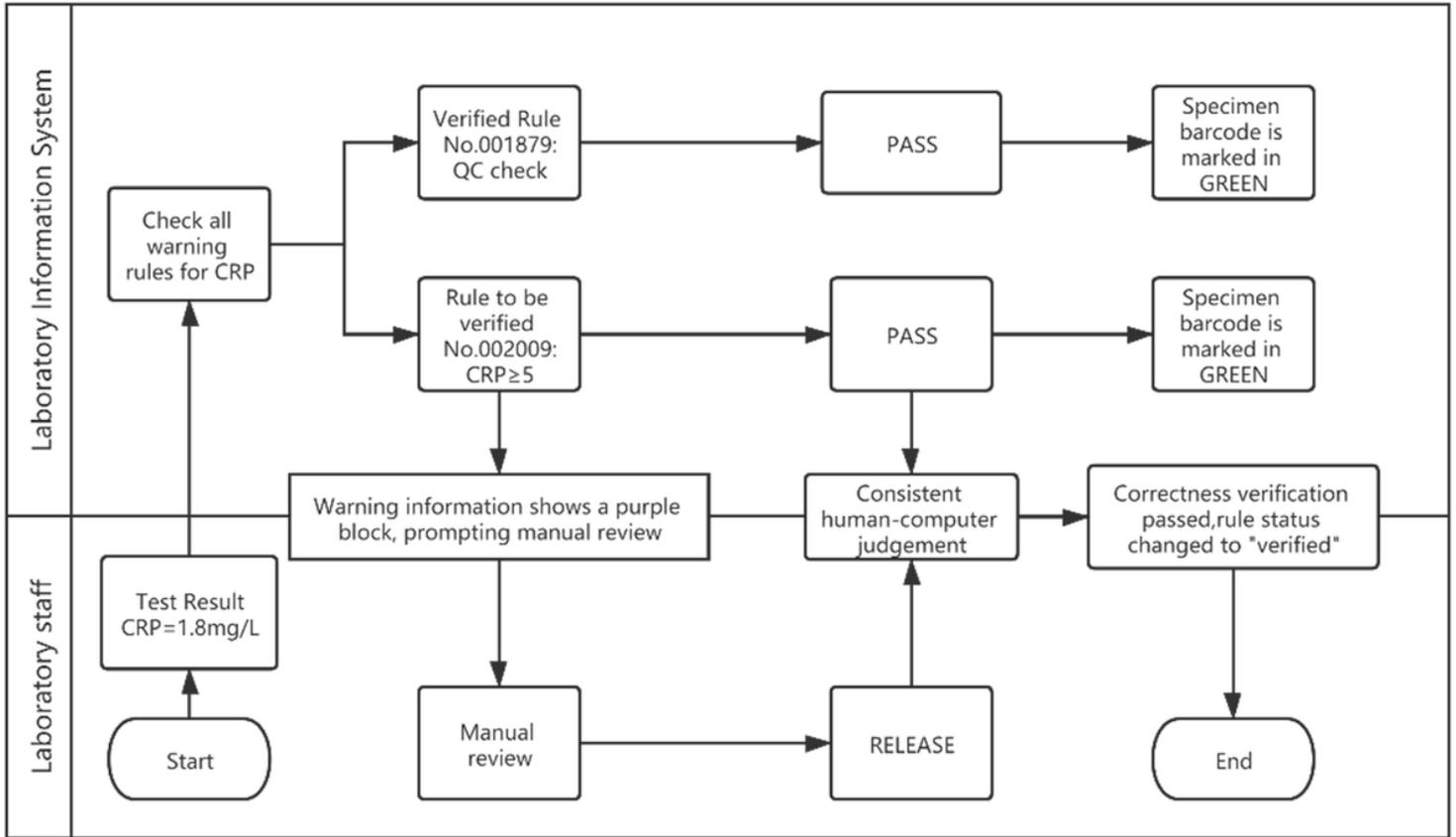


Figure 2

The logic of the human-machine interaction for correctness verification

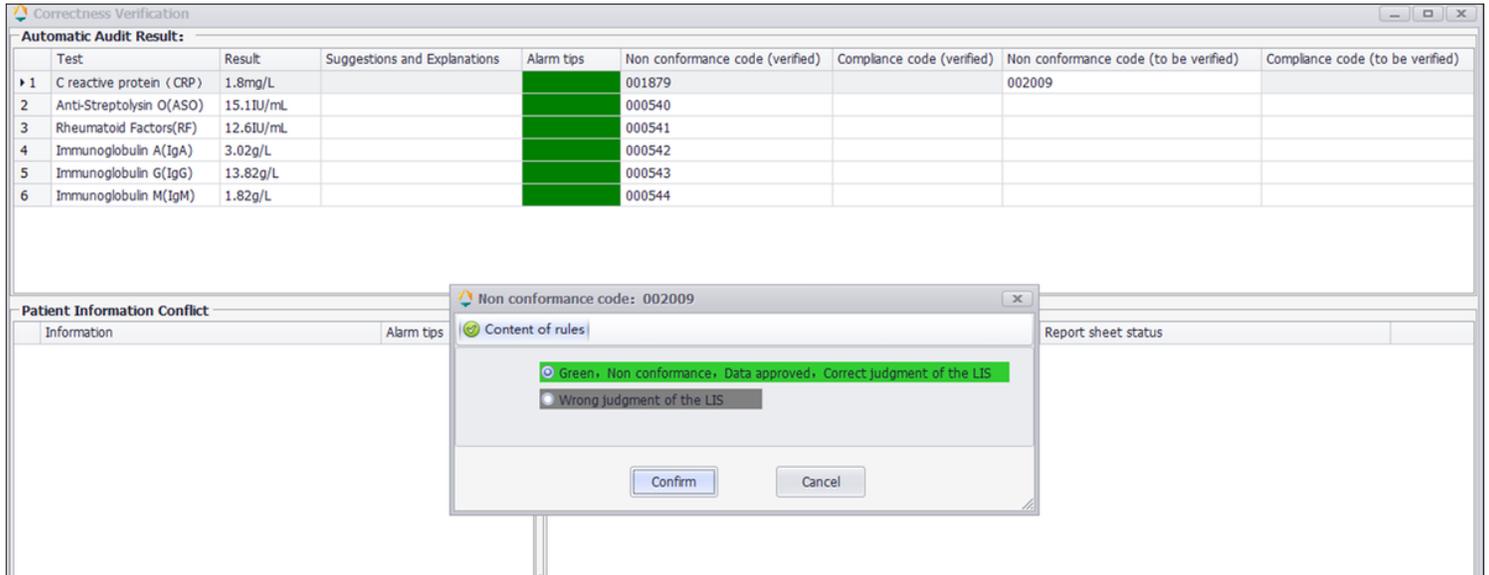


Figure 3

Correctness verification interface

Post	Test	Equipment	Model	Reagent manufacturer	AutoPublish	Rule last modified	Target number	Validation number	
<input type="checkbox"/>	Routine bioche...	C-reactive Protein (CRP)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	2155
<input type="checkbox"/>	Routine bioche...	Anti-Streptolysin O(ASO)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	2235
<input type="checkbox"/>	Routine bioche...	Rheumatoid Factors(RF)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	2455
<input type="checkbox"/>	Routine bioche...	Immunoglobulin A(IgA)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	2633
<input type="checkbox"/>	Routine bioche...	Immunoglobulin G(IgG)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	1976
<input type="checkbox"/>	Routine bioche...	Immunoglobulin M(IgM)	Roche bioche...	Cobas c702	Reagent manufacturer Roche	NO	2019-06-06	3000	2278

Figure 4

Integrity validation target number settings and recording interface. The validation targets of the six projects in the above figure are all 3000, and the verification number is between 1900 and 2500. The corresponding reports cannot be released automatically.

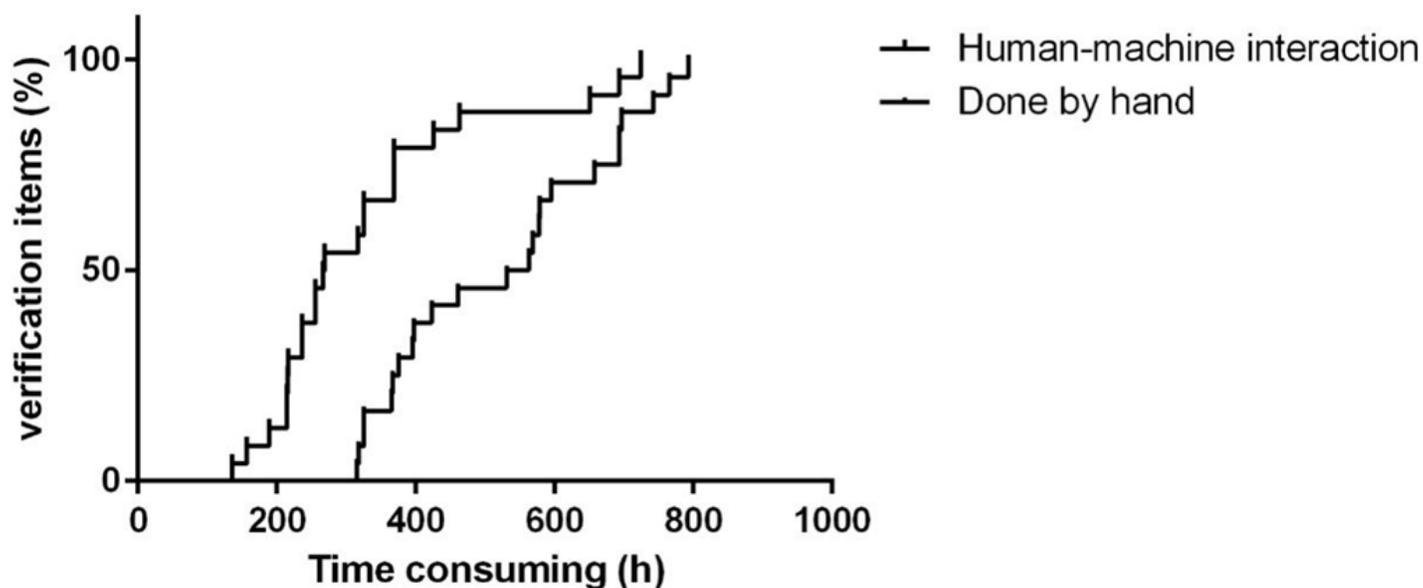


Figure 5

Comparison of the difference in time consuming between human-machin interaction and manual validation.