Opinion Paper

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Applying the Milan models to setting analytical performance specifications – considering all the information

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Abstract: Analytical performance specifications (APS) are used for decisions about the required analytical quality of pathology tests to meet clinical needs. The Milan models, based on clinical outcome, biological variation, or state of the art, were developed to provide a framework for setting APS. An approach has been proposed to assign each measurand to one of the models based on a defined clinical use, physiological control, or an absence of quality information about these factors. In this paper we propose that in addition to such assignment, available information from all models should be considered using a risk-based approach that considers the purpose and role of the actual test in a clinical pathway and its impact on medical decisions and clinical outcomes in addition to biological variation and the state-of-the-art. Consideration of APS already in use and the use of results in calculations may also need to be considered to determine the most appropriate APS for use in a specific setting.

Keywords: analytical performance specifications; laboratory quality; state of the art; biological variation

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Introduction

Analytical performance specifications (APS) are used to evaluate the testing systems for different measurands in laboratory medicine [1]. The definition for APS included in the Milan consensus is as follows: "Criteria that specify (in numerical terms) the quality required for analytical performance in order to deliver laboratory test information that would satisfy clinical needs for improving health outcomes" [2].

As with any topic, clear terminology, definitions and agreement on the fundamental concepts are required to allow advancement and application in the area. A Task Group of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) for example required the understanding of six aspects of APS for appropriate use in External Quality assurance (EQA) for routine laboratories [3]. Various groups have developed APS for the same measurand and often it is difficult for the end users to decide which APS they should use in their own setting [4].

How APS should be determined also remains under active debate. This topic is becoming particularly relevant in

the era of the new European IVD Regulation that requires evidence on the clinical performance of *in vitro* diagnostics which is inevitably linked to their analytical performance. As any "APS" without further explanation is unusable, we would like to outline a more general set of required supporting information when discussing APS and provide some guidance on the actual approach that helps define APS in an evidence- and risk-based process that better fulfils the Milan definition of APS.

Required elements for a general description of APS (Table 1)

When APS are defined, the first aspect to be considered is the **setting** for the APS. The definition above refers to laboratory test information to meet clinical needs. This means that the APS primarily is for laboratories providing clinical testing to patients. If an APS is designed for a different setting, this needs to be stated. Examples for different settings may include analytical performance requirements for higher order reference materials, measurement procedures and measurement services and EQA organisations supporting these services. The APS for reference measurement procedures or services would be expected to be tighter than for routine use. Alternatively, a wider APS may be accepted, for example by EQA when combining data from multiple sources, recognising that data from multiple laboratories and methods are unlikely to reach the standard for a single laboratory.

Any APS needs to describe the **property** to which it should be applied, and this linked to the data analysis that defines the property. Typical examples are APS for bias, applied to the average of a number of measurements; APS for imprecision, applied to the dispersion (e.g. SD or CV) of a data set; and APS for total error, applied to individual measurement results.

Another key aspect that needs to be clearly stated is the **aim** of the APS. Typically, wider APS have been used in regulatory EQA programs, where only severely underperforming laboratories may be expected to fail. Progressively tighter limits might be described as "maintenance", when the current performance is acceptable, and the goal is to avoid deterioration. The aim of APS can be "tail-end improvement", i.e. to flag poorer performing methods and laboratories to promote adoption of performance achieved in other laboratories or "overall improvement" i.e. flagging performance that is outside of what is only achievable by the best performing laboratories The aim of APS can also be "aspirational" i.e. the analytical performance may not be achievable at this time, however a higher level of performance should be sought with future developments. This type of APS is more of an analytical performance *goal* (i.e. desirable to be achieved at some stage with more advanced technology) than an analytical performance *requirement* that should be achieved (as it is achievable by current technology).

Analytical performance specifications are required to make informed decisions about the suitability of different methods and can be applied at the time of method selection, method validation and verification, assessment of lot-to-lot variation, and the laboratory's performance in internal quality control and EQA. While commonly applied to the analytical properties of precision, bias and measurement uncertainty, they are also used to assess the impact of other factors that may affect laboratory results such as analytical specificity (selectivity), common interferences (e.g. haemolysis, icterus, lipaemia), collection container type, and analyte stability under various conditions. As well as their utility for clinical laboratory service, they can provide vital information for manufacturers in developing and marketing assays, calibrators and standards.

Table 1: Required elements for a general description of APS.

Key elements	Examples
Setting for the use of APS	Clinical laboratory and point of care service; higher order reference materials, measurement procedures and measurement services by standardisation bodies; manufacturers; or EQA organisations
Property to which the APS should be applied	Bias, imprecision, total error analytical sensitivity and specificity/selectivity
Aim of the APS	Regulatory, maintenance of existing quality, tail-end improvement, overall improvement, aspirational

International initiatives for setting APS

Building on pioneering work from 1999, known as the Stockholm Hierarchy [1], the Milan Criteria, in 2015, described three models which may be used to set APS [2]. In brief these are Model 1, based on clinical outcome; Model 2, based on biological variation, and Model 3, based on currently available assay performance ("state of the art"). Since that time there has been further work under the auspices of EFLM to bring these concepts into practical use, with

the final goal being, where possible, concrete agreed APS for most routinely used laboratory tests. As part of this process there has been ongoing work to further refine the understanding and application of each of the models including reviewing existing data and generation of newer, higher quality data.

The EFLM has also established a working group for setting APS based on clinical outcome studies (Milan Model 1) [5]. This can, in principle, be seen as the gold-standard criteria as the final metric for pathology testing is impact on the patient's health. The ideal approach is direct evaluation through comparative studies assessing health outcomes when assays with different performances are utilised (Milan Model 1A). Given the extreme difficulty in undertaking such studies, indirect evaluation (Milan Model 1B) may also be considered. This may be done by modelling the effect of changes in analytical performance on health outcomes (using empirical data to underpin the models) [6]; or by surveying clinicians about their likely actions in response to different scenarios based on laboratory results to measure potential changes to clinical decision making [7]. Although more feasible than direct evaluation, indirect clinical outcome studies are still challenging to identify and to perform.

The approach to setting APS based on biological variation (Milan Model 2) has seen a dramatic improvement in the methodology and available data [8]. Important developments include the Biological Variation Critical Appraisal Checklist (BIVAC) on how to evaluate the quality of studies on biological variations [9], and the EFLM database for biological variation (biologicalvariation.eu) where available data are collated and assessed for quality [10]. The EFLM European Biological Variation Study (EuBIVAS) has delivered rigorously determined biological variation data of many clinically important measurands [11].

Assessment of state of the art (Milan Model 3) also remains an area of work in progress. An example of using the best performing routinely available methods as a benchmark to promote assay improvement that can be reached with current technology has been described for CRP [12]. A contrasting view may be to use a standard that, for example, 80 % of laboratories can achieve, providing impetus to improve or replace inferior methods while recognising the current performance of most laboratories. Data for this type of assessment often comes from EQA programs, and the quality of the data, including the nature and number of samples and the statistical analysis, may be variable.

Before establishing an APS for a measurand, a range of factors need to be considered (Table 2) [13]. Inherent in considering these, is the possibility that different APS may be needed in different settings and for different purposes making it difficult to use one common APS for a measurand. For example, in a clinical laboratory the same measurand can be used for different clinical purposes, each of which may require a different APS; in this case the application of the more stringent APS can be proposed, unless the applications can be clearly separated. For example, rapid semi-quantitative cortisol testing during adrenal venous sampling has shown to improve diagnostic outcomes, whilst this analytical performance is inadequate for diagnosing conditions with cortisol excess [14]. For appropriate use and comparison with other APS for the same measurand, the numerical values of an APS require a detailed description (Table 1).

Table 2: Factors to be considered when setting criteria for APS (adapted from [13]).

- Aim of the test (i.e. intended use, purpose and role of test in clinical pathway, including the role of the tests in calculations used for diagnosis or assessing risk or prognosis)
- Clinical needs and risks associated with the test result
- Test environment (e.g. prevalence of the condition, setting, point-of-care vs. laboratory based assay)
- Relevant data and quality of data from all three Milan models (outcome studies, biological variation, state of the art)
- Preanalytical variables impacting test results
- Economic considerations
- Practical/organisational aspects

The process

Determining the optimum process for applying the Milan models to propose specific APS for individual measurands is ongoing. One approach which has been proposed is to select the most appropriate model for a measurand and use that model alone to establish APS [15]. The selection of the model is based on a number of factors, with Model 1 proposed for measurands that have a central and specified role in a clinical decision; Model 2 for measurands under homeostatic control; and Model 3 where models 1 or 2 cannot be applied.

In this paper we present arguments why, even if a measurand is assigned to one Milan model, data from all three models should be considered when setting APS for a measurand. For some measurands there may also be additional factors which need consideration beyond those specified in the Milan criteria. Our proposal is based on the concept that there are interactions between the models and so it may be wrong to use them in isolation. It may be that one model is selected to provide the final criteria for setting the APS for a measurand, but the other models still need to

be considered to assess possible relevance on the final decision. It is also important to consider the mentioned key aspects (Table 1) including the aims and how and by whom the APS will be used in practice. Do we think about a theoretical, aspirational goal or a practical goal for routine use e.g. in an EQA program for clinical laboratories? When selecting the most appropriate model, the quality of the evidence for a model also needs to be considered [2] as well as the impact of the assessed analytical performance on the actual clinical management of patients. Some of the above-mentioned relationships between the different Milan models are described below.

Interactions between Model 1 and Model 3

Model 1 is based on the effect of analytical performance on actual or modelled clinical outcomes (health outcomes or clinical decisions), and Model 3 represents current analytical performance. The most obvious interaction here is if a certain analytical performance is proposed to meet a clinical need, but existing assays are not able to meet that need. In such cases a "clinical need"-based specification is limited by the existing analytical state-of-the-art. For example, during treatment of moderate hypernatraemia (150–169 mmol/L), it is advised to avoid overly rapid decrease of serum sodium (>0.5 mmol/L/h or 0.3 %/h) to prevent iatrogenic brain oedema caused by rapid correction of a chronically developed hyperosmotic state [16]. This protocol recommends 6 hourly testing, however, if there was a new evidence-based recommendation to monitor changes at hourly intervals as that would improve patient outcome, then currently available sodium assays with an average analytical imprecision (CV_A) of 0.5 % are unable to reliably detect this change, making such a recommendation impossible to implement.

The same issue can arise when clinician's opinion is sought on clinically important changes in results, with current assays often unable to meet the performance determined by such surveys [7]. For example, in one study, clinicians frequently interpreted changes in HbA_{1c} results as being clinically significant when the change was within the analytical variation of the method [17]. It is also possible that "state of the art" may affect clinicians' surveyresponses as their experience is based on the performance of currently available assays. Using the example of treatment of hypernatraemia above [16], clinicians aware of the performance of current serum sodium assays may not recommend more frequent monitoring, even though it is possible that this may provide better outcomes if better assays were available. However, in practice it is likely that there is unawareness of current assay performance by clinicians [18]. A clear limitation to such surveys is that an opinion that a better outcome may be achieved with a better performing assay than is currently available cannot be based on actual experience.

Interactions between Model 1 and Model 2

Model 2, based on biological variation has two components, assessing assay imprecision against within-subject biological variation, and assay bias against combined within- and between-subject variation. This second component may be questioned for two reasons: 1/the model for calculation is based on the modification of the percentage of subjects misclassified in a reference population due to the effect of bias, and this approach may not fit with other applications such as the use of clinical decision points other than reference limits, and 2/because the between-subject variation is frequently large, which is associated with skewed distributions thus makes the use of Gaussian statistics inappropriate. For assessment of imprecision, this model compares analytical performance based on its effect on the final variability in result seen by the clinician, sometimes referred to as the diagnostic variation. If an assay meets a high-level imprecision goal based on biological variation (e.g. the optimal or desirable level), then a proposed clinical outcome-based analytical performance set by Model 1 should not be tighter than this criterion set by Model 2, as the inherent variation in the patient significantly outweighs the variation of the assay.

To put this into an assessment, for a measurand that has the characteristics for the application of Model 1, the definition of APS for imprecision lower than those obtained according to the criteria of biological variation is not valid as further reduction in assay imprecision will have minimal effect on the total uncertainty of the result and therefore on the interpretation of the results. Put another way, if an assay's existing performance meets a biological variation-based optimal imprecision criterion, then there is no need for a tighter limit. For example, serum triglycerides have a within-subject biological variation of 19.7 % according to the EFLM database (biologicalvariation.eu) and an analytical variation for an entire country of below 3.5 % [19], which adds less than 2 % to the diagnostic variation. Thus, any study which concludes that a smaller analytical variation may be needed is unlikely to be valid. A limitation here is if the available estimates of within-subject biological variation are inadequate. If reduced overall variation is required, then the solution may be to take the average of the measurement of more than one sample as improving the assay imprecision will have minimal effect.

Interactions between Model 2 and Model 3

Similar to the interaction between Models 1 and 3, setting an APS based on biological variation which is not achievable can be set as an aspirational theoretical target, but is not useful for assessing routine assay performance. Thus, assigning a measurand to Model 2, without consideration of the state of the art, may not be realistic for routine laboratories. However, it can remain important for future method development. For example, current routine assays for serum sodium are generally unable to meet the minimal APS under Model 2 with respect to imprecision due to the very low within-subject biological variation of the measurand [20]. This implies that a sodium assay with improved imprecision is desirable (see also the previous paragraph), and while this is an attractive proposition, it may be better to consider this as a testable hypothesis rather than a given truth that requires evidence from clinical studies whether a tighter APS leads to improved patient management and outcomes.

Additional factors

The original Stockholm hierarchy also included a level recognising "published professional recommendations from (a) national and international expert bodies, or (b) expert local groups or individuals" [1]. However, these levels are always based on one (or more) of the three Milan models either directly or indirectly. For most of the models the final decision has to be taken by "expert bodies". For example, the College of American Pathologists APS for HbA_{1c} have informed manufacturers and other decision makers over many years and led to improved assay performance and more accurate diagnosis and more efficient monitoring of diabetes mellitus. Any change in the APS for this measurand should take this history and effects into account [21]. At the least, managing a transition to a different APS would benefit from understanding of the rationale behind the previous paradigm and the current influences on laboratory performance.

As in many areas of laboratory medicine, establishment of APS needs to consider all aspects with regard to decision making [13]. To this end the actual aim of the test and all uses of a measurand should be considered and some use case scenarios may lead to different requirements. An example of this is the use of the same test for clearly different clinical purposes. The example of rapid semiquantitative cortisol testing during adrenal venous sampling has been given above [14].

Laboratory results are also used as inputs to a range of calculated values. This might be simple calculations such as osmolar or anion gaps or calculated LDL cholesterol. More complex equations may include area under the curve calculations for therapeutic drug monitoring (TDM), for example with vancomycin dosing [22], or highly complex risk prediction equations including laboratory data, for example for the risk of developing acute liver failure in the setting of chronic liver disease [23]. The effect of bias and imprecision of a measurand on the outcomes of such calculations needs to be considered, for example by simulation studies under Model 1B. Using the example of AUC estimation based on TDM results, the effect of assay result variation changes depending on the time the sample is taken within the dosing interval. The effect of analytical variation on drug dosing decisions using pharmacokinetic models has recently addressed this complex area [24]. Even with a simple ratio, the different assay performances at different concentrations can give different uncertainties although the final calculated result is the same. An example is the aldosterone:renin ratio used for screening for primary hyperaldosteronism where the uncertainty of the ratio, and therefore its interpretation, depends on the uncertainties of the input measurements.

Another factor may be the effect of pre-analytical factors or assay interferences (Table 2). For example, if a measurand has a significant, unavoidable pre-analytical variability, then a better analytical performance may be required to keep results within a total error budget. Similarly, more assay interference, e.g. from sample haemolysis, may be allowable if an assay has better precision than indicated by biological variation.

Conclusions

The purpose of APS is to provide guidance for assessing the analytical performance of laboratory assays. This assessment takes place in many environments, including individual laboratories, EQA providers and *in vitro* diagnostics manufacturers as well as reference material and reference measurement service providers with the aim of improving the clinical performance of diagnostic testing. We believe that the assessment of required analytical performance should take all factors that impact the overall variation of measurement results into account, as well as non-analytical factors such as those listed in Table 2. This information is best interpreted in the context of the clinical use of the test, applying an evidence- and risk-based approach to assess the impact of the desired analytical performance of the measurand on clinical decisions and outcomes. This process includes formal assessment of available information for all three models of the Milan criteria, and at the same time, identifies areas of limited knowledge that can be marked for

future research. The APS derived in this way can, for example, be presented in a table summarising the available data for all 3 models, along with relevant factors about the use of the measurand and the nature and the purpose of the APS. For this summary the headings in Tables 1 and 2 should be considered. An importance hierarchy can then be applied to the models based on availability, quality and relevance of available information for all models and, importantly, attention given to possible interactions between the models. Some specific factors that may arise may be considered as "boundary conditions" that should always be considered. Examples of these would be that assay imprecision does not need to be better than required against biological variation criteria, and that APS for routine laboratory use should be achievable by current state of the art. Together with these, consideration should be given to any other factors that may be relevant in the total testing process including the clinical use of the measurand and the decisions which will be influenced by the APS.

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