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The International Journal of Biomedical Laboratory Science (IJBLS) is an on-line peer-reviewed journal published bi-annually by International Federation of Biomedical Laboratory Sciences (IFBLS).

The journal is intended to disseminate information and knowledge to the international laboratory community by accepting a variety of manuscripts for publication. Those manuscripts should be original research articles, literature or mini-reviews, case studies, brief communications and letters to the editor describing original investigations in all fields of biomedical laboratory sciences.

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Editorial

Pressing Concerns in the Clinical Laboratory and Potential Impact

Patricia Tille Ph.D MLS(ASCP) AHI (AMT) FASCs
IJBLS Editor in Chief

Today's social, economic and political environment is challenged with several pressing concerns for the clinical laboratory that impact healthcare systems, professionals and patients. A brief review of those concerns includes funding and reimbursement, regulation and compliance, workforce shortages, telemedicine and remote diagnostics, data security and privacy, global health and access to testing as well as the political divides on public health responses.

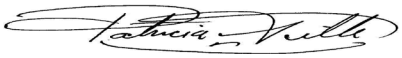
The laboratory has persistently struggled with funding and reimbursement with budget cuts in some areas and reduced reimbursements. Healthcare, including the clinical laboratory must move towards value-based care to improve services, patient outcomes and reduce costs. This can only be accomplished through more efficient and evidence-based practices, often without additional funding.

Laboratory regulations vary globally, however, there is on-going pressure to standardize laboratory testing. Control of laboratory regulations often limits and encumbers these processes. This is only exacerbated by the growing workforce shortages. This shortage is magnified by the aging workforce, insufficient recruitment and challenges in retaining staff.

In addition to staffing, digitization of health information raises concerns about data security and privacy. This is fueled by the increasing use of artificial intelligence (AI) in laboratory diagnostics and the growing volume of data. Both digitization and AI are also impacted by the rapid expansion of telemedicine and the regulatory gaps for at-home testing and monitoring of patients.

Lastly, but most certainly not the least of the challenges is the global disparities in testing access. This is even more evident with political decisions that are affecting international relations and trade policies that impact the availability and distribution of diagnostic texts. This may disrupt the global supply chain that could affect public health not only on a daily basis but in critical emergencies such as pandemics.

In order to address these issues, laboratory professionals, policymakers and the public must collaborate to ensure the laboratory services continue to meet the needs of patients, improve health outcomes and remain sustainable. The intersection of the clinical laboratory and healthcare policy is complex and are all influenced by the ever-changing political environment globally. As laboratory professionals we must remain steadfast and committed to quality diagnostic testing for all and continue to support our communities of professionals!



Patricia Tille Ph.D. MLS(ASCP) AHI(AMT) FACSc

Research article

An Analysis of the Updated Estimated Glomerular Filtration Rate Among African American Patients Diagnosed with Chronic Kidney Disease in an Acute Care Setting

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Purpose: **The issue of under-diagnosis among African Americans was a precipitant factor for the exclusion of race in the revised estimated glomerular filtration rate formula (eGFR) in 2021. Prior to the revision, using race in the eGFR formula was seen by many in the medical community to contribute to fewer nephrology referrals among African Americans. The purpose of the study was to determine if implementation of the updated eGFR resulted in significant differences in chronic kidney disease (CKD) classification among African American patients.**
Materials and Methods: **A retrospective cohort study was conducted utilizing African American patients newly registered with a CKD diagnosis between January 1, 2022, and January 31, 2024, at a large, public academic hospital in the southern United States.**
Results: **This study included 568 patients with a median age of 67 years. We found a significant difference in CKD staging when comparing the race-free eGFR and the race-inclusive eGFR, with patients demonstrating an upward staging trend.**
Discussion: **This study found that the revised, race-free eGFR formula categorizes African Americans in an acute care setting at CKD stage 3 and higher compared to the prior, race-inclusive eGFR formula. This potentially impacts staging of African American patients, as well as resulting in higher numbers of nephrology referrals.**

Keywords: Chronic kidney disease, CKD, eGFR, glomerular filtration rate, African American

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Introduction

Of the approximately 15% of adults in the United States with chronic kidney disease (CKD), 808,000 are estimated to be living with end-stage renal disease (ESRD).[1,2] CKD occurs due to several conditions such as diabetes and hypertension, and poor control of these conditions increase the risk for ESRD.[1,3] To compound matters, a vicious cycle often ensues whereby CKD further complicates cardiac health, with a 2-fold risk increase for cardiovascular diseases like atherosclerosis.[1,3] The incidence of CKD is higher among women compared to men, blacks and Hispanics compared to whites, and adults older than 65 years.[1] As the population ages, chronic conditions will become more prevalent and difficult to manage as individuals acquire multiple chronic comorbidities. Rates of unawareness among individuals with CKD both in the US and worldwide remain alarmingly high, with an estimated 82%-90% of those with stage 1 CKD being unaware and up to 40% of individuals with stage 4 CKD (i.e., ESRD) being unaware.[2,4] With respect to ESRD, treatment options are limited to dialysis and transplant procedures.[1] The under-diagnosis of CKD represents a looming public health crisis pointing not only to a need for earlier detection but improved predictive monitoring to prevent ESRD – particularly among those with predisposing conditions.

The issue of under-diagnosis, particularly among African Americans, was a precipitant factor for the exclusion of African American race in the revised formula for estimated glomerular filtration rate (eGFR) in 2021. Inclusion of race in the previous formula entailed higher eGFR values among patients identifying as African American compared to those identifying as another race, even though the creatinine values were equal.[5] On the other hand, the mean creatinine value among African Americans is approximately 9% higher when compared to the means from other demographic groups.[6] The etiology of this is not well understood. In spite of this, and prior to the formula's revision in 2021, using race in the eGFR formula was seen by many in the medical community as a major contributing factor for fewer nephrology referrals among African American patients, even though they have (on average) higher risk for CKD and ESRD compared to other racial/ethnic groups.[5,7] The novelty of the revised eGFR necessitates a timely review of CKD patients who were diagnosed and stratified following its implementation. Figure 1 includes the eGFR formulas prior to 2021 and updated as of 2021, respectively.[8,9]

Formula prior to 2021 (with African American race as a variable)

- GFR = 141 * min(Scr/κ, 1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]

Formula as of 2021 (without African American race as a variable)

- eGFRcr = 142 * min(Scr/κ, 1)α * max(Scr/κ, 1)-1.200 * 0.9938Age * 1.012 [if female]

Note: GFR = glomerular filtration rate; Scr = serum creatinine; κ = 0.7 if female and 0.9 if male; α = -0.241 if female and -0.302 if male

Figure 1: CKD-EPI GFR formulas without and with African American race as a variable, respectively

There have already been noticeable differences in CKD classification in other studies. For example, in a study of African American kidney donors, 17.7% were reclassified with a higher CKD stage using the revised eGFR without race prior to donation.[7] In the same study, 25.5% of African American donors were reclassified with a higher CKD stage following donation. With respect to kidney recipients, the race-free eGFR equation performed slightly better than the previous versions.[10]

At present, CKD is diagnosed and scored by eGFR; values below 60 mL/min/1.73 m^2 are diagnostic.[11] There are additionally multiple analytes, indices, and ratios currently used in the routine screening and assessment of renal function, such as serum creatinine, blood urea nitrogen (BUN), 24-hour urine creatinine concentration, and urine protein-to-creatinine

Table 1: Current Chronic Kidney Disease (CKD) Nomenclature used by KDIGO

Prognosis of CKD by GFR and albuminuria categories: Kidney Disease | Improving Global Outcomes (KDIGO) 2012				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30 - 300 mg/g 3 - 30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60 - 89			
	G3a	Mildly to moderately decreased	45- 59			
	G3b	Moderately to severely decreased	30 - 44			
	G4	Severely decreased	15 - 29			
	G5	Kidney failure	< 15			

Adapted from https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

ratio.[11] Taken together, these provide a snapshot of an individual's present renal capacity. Over time, monitoring these results is also helpful in determining progression of kidney disease or injury. However, the ordering and performance of these tests for at-risk patients depend on a host of factors, including clinician experience, knowledge, and resource availability. As of 2023, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Table 1) used eGFR and urine albumin levels to categorize CKD.[12]

The purpose of the study was to determine if implementation of the updated eGFR in 2021 resulted in significant differences in CKD diagnosis or classification among African American patients at the University of Texas Medical Branch (UTMB). The study hypothesized that the revised, race-free eGFR formula is more sensitive at staging African Americans in an acute care setting at a higher stage when compared to the prior, race-inclusive eGFR formula.

Materials and Methods

A pre- and post-study involving a cohort of all African American patients enrolled in TMB's EPIC Electronic Health Record (EHR) between January 1, 2022, and January 31, 2024, with a new CKD diagnosis was conducted. Patients not categorized as African American in the EHR were not included in the study since the updated eGFR differs from the previous formula in the lack of African American race as a variable. Patients diagnosed with CKD in Epic prior to implementation of revised eGFR in 2021, prisoners, pregnant females, and patients below age 18 were also excluded. Data analysis for CKD staging was conducted using Wilcoxson's signed-ranks test. The International Classification of Diseases (10th revision) (ICD-10) codes for CKD diagnoses were used to identify patients with CKD in the EHR (Table 2). A *p*-value of <0.05 was considered significant.

Prior to commencement of study activities, the approval of the institution's IRB was obtained. All patient data, to which only the principal investigator and their co-authors have access, were deidentified and stored in a password-protected computer. The anticipated level of risk to study participants was none to minimal.

Table 2: International Classification of Diseases (10th revision) codes for chronic kidney disease

Code	Stage of Disease	Severity Level
N18	Chronic kidney disease (CKD)	
N18.1	CKD, stage 1	
N18.2	CKD, stage 2	Mild
N18.3	CKD, stage 3	Moderate
N18.30	CKD, stage 3	Unspecified
N18.31	CKD, stage 3a	
N18.32	CKD, stage 3b	
N18.4	CKD, stage 4	Severe
N18.5	CKD, stage 5	
N18.6	End-stage renal disease (ESRD)	
N18.9	CKD	Unspecified
E08.22	Diabetic CKD	
E09.22	Diabetic CKD	
E10.22	Diabetic CKD	
E11.22	Diabetic CKD	
E13.22	Diabetic CKD	
I12	Hypertensive CKD	
I12.0	Hypertensive CKD with stage 5 CKD or ESRD	
I12.9	Hypertensive CKD, stage 1-4 or unspecified	

Note: Reprinted from "ICD-10-CM Codes > N00-N99 > N17-N19 > Chronic kidney

Table 3: Population characteristics (N = 548)

Variable	n (%)
Gender	
Female	340 (59.9)
Male	228 (40.1)
History of smoking	
Yes	141 (24.8)
No	339 (59.7)
Unknown	88 (15.5)
History of hypertension	
Yes	494 (87.0)
No	74 (13.0)
History of diabetes	
Yes	258 (45.4)
No	310 (54.6)
Median age (years)	**Standard deviation**
67	13.5

Results

Of the total number of 568 patients, the patient characteristics, as displayed in Table 3, include median age of 67 years (standard deviation of 13.5); 59.9% female vs. 40.1% male; 59.7% non-smokers and 24.8% smokers; 87% with a history of hypertension; and 54.6% with a history of diabetes. There was a significant difference in staging at all levels of CKD (each with a *p*-value <0.05) when comparing the race-free eGFR and the race-inclusive eGFR, with patients demonstrating a mostly upward staging trend, as displayed in Table 4.

Table 4: GFR[1]-based CKD[2] stages

CKD stage			Comparison of race-free and race-inclusive GFRs	
	Race-free GFR	GFR w/race	Wilcoxson Signed Ranks Test *(Effect Size: 0.72)*	
Stage	n (%)	n (%)	Z	p-value
1	9 (1.6)	30 (5.3)	-4.58	<0.001*
2	120 (21.1)	246 (42.8)	-12.00	<0.001*
3a	204 (35.9)	155 (27.3)	-9.75	<0.001*
3b	169 (29.8)	100 (17.6)	-5.10	<0.001*
4	43 (7.6)	22 (3.9)	-2.24	0.025*
5	23 (4.0)	18 (3.2)		
Overall			-17.06	<0.001*

1. GFR = glomerular filtration rate; 2. CKD = chronic kidney disease

Discussion

The hypothesis that the revised, race-free eGFR formula is more sensitive at staging African Americans at CKD stage 3 and higher in an acute care setting when compared to the prior, race-inclusive eGFR formula was supported by this study's findings. This seems to suggest that there is a significant staging difference overall and in staging of CKD with the use of the retired race-based eGFR vs. the race-free eGFR. However, it is important to note that this study was confined to the UTMB patient population, which is a limitation because of the higher acuity of patients in the teaching hospital.

Recent findings elsewhere continue to recommend the use of a race-based stratification method for GFR calculation because of

the conclusion that adoption of a race-free eGFR exaggerates racial disparities between African Americans and other racial groups.[13] Their basis is that the revised formula's ability to identify undiagnosed CKD among African Americans is not supported by studies using kidney failure replacement therapy and mortality as proxies for initial CKD values.[13] Regardless, an analysis of multiple studies concluded that race-based eGFR provides more benefits because it does not systematically overestimate GFR values among African Americans, which could lead to higher stage CKD diagnoses going undetected.[14] A prospective cohort study across seven centers in the United States examined 16 years' worth of data on almost 3900 patients and found that the race-free GFR was superior at predicting ESRD.[15]

Conclusion

Based on this study's findings, there is a significant difference in sensitivity for CKD diagnosis and staging when using the revised eGFR formula as opposed to the previous eGFR formula. This potentially impacts how African American CKD patients are staged, and it could also result in higher numbers of nephrology referrals and kidney transplants within the African American population. A primary recommendation is to advocate for consistency in which type of eGFR formula is used to mitigate the exaggerated differences in CKD staging between and among facilities and regions. It is important to note that this study was confined to the UTMB patient population, which is a limitation because of the higher acuity of patients in the teaching hospital.

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Research article

Evidence Based Practice in Biomedical Laboratory Science Education. A Dedicated Module to Improve Danish BLS Undergraduate Students EBP Competences

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Objective: **This study evaluated the effect of the Introduction, Methods, Results and Conclusion (IMRAD) module on the knowledge, skills, and attitudes towards evidence-based practice (EBP) in third-year biomedical laboratory science (BLS) students at the University College South Denmark. Additionally, it examined students' perceptions of EBP competencies post-education and their importance for future job searches.**

Materials and Methods: **The IMRAD module, integrated into the sixth semester of the BLS curriculum, spans six weeks and includes theoretical and practical components on the IMRAD format. The study involved two consecutive groups of students (BA19, n=23; BA20, n=32). Data were collected using a self-reported questionnaire (Q1) at three points: baseline, post-module, and end of semester. A second questionnaire (Q2) was administered six months post-module to assess long-term EBP competency retention and job relevance.**

Results: **Both groups exhibited significant improvements in EBP attitudes, knowledge, and skills post-module. The mean subscale scores for attitudes increased significantly from 25.7 to 28.8 (BA19) and from 25.1 to 28.0 (BA20). Knowledge and skills scores also showed significant increases from 44.5 to 63.2 (BA19) and from 48.9 to 64.8 (BA20). These improvements were maintained at the end of the semester. The Q2 results indicated that students felt confident in applying EBP competencies in their professional practice and valued these skills for future job opportunities.**

Conclusion: **The IMRAD module effectively enhances EBP competencies in BLS students, with sustained improvements in attitudes, knowledge, and skills. Students recognize the relevance of EBP in their future careers, highlighting the module's success in preparing them for professional practice.**

Keywords: EBP (Evidence based practice), BLS (Biomedical laboratory Science), IMRAD (introduction, methods, results and discussion), Undergraduates, MLS (Medical Laboratory Scientist), Quality improvement

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Introduction

The importance of evidence based practice (EBP), its implementation in healthcare undergraduate curricula, and the impact of teaching evidence-based healthcare have been a topic of investigation for many years.[1,2] Implementing the learned EBP competencies is essential for all practicing healthcare professionals.[3] Teaching EBP at the undergraduate level and identifying the best teaching strategies are crucial aspect of this process.[4] In this respect, several interventions and methods for teaching EBP to health students have been documented.[5]

The Sicily statement defines a five-step process that is fundamental for both clinical practice and teaching EBP. This process includes formulating questions to address uncertainty (ask), retrieving the best available evidence (search), critically appraising the evidence (appraise), applying the results in practice (integrate) and evaluating performance (evaluate).[6]

Teaching EBP has revealed several strategies that seem to favor the acquisition of some of these five-step elements. These strategies include clinical collaborations and educational interventions where both framing and teaching interventions are described.[5]

BLS professionals play a crucial role in the health system, and therefore an EBP approach during their undergraduate education would be beneficial.

Although health professionals like nurses and physiotherapists have discussed the strengths and challenges of implementing EPB in education and practice, the reality for BLS remains to be elucidated. A thorough database search for BLS or medical laboratory scientists (MLS) on EBP teaching for undergraduate students retrieved no peer-reviewed articles.[1,5] Articles about EBP and BLS/MLS students are rare[7,8], illustrating the need for publications on this important topic.

In 2018, the BLS educators at the University College South (UCS) developed a compulsory six-week module to introduce BLS undergraduate students to various skills and knowledge regarding the IMRAD format. The module integrates several chosen EBP steps and employs different teaching strategies to help the students acquire the necessary tools for their semester-graded assessment and final bachelor project.

This study investigated the effect of the IMRAD module in the knowledge, skills, and attitudes towards EBP in third year BLS students from two consecutive yearly cohorts at UCS. Additionally, this study investigated the students' perception of the EBP appraised competencies after their education and the importance of these competencies for future job searches.

Materials and methods

Module description

The objective of the IMRAD module is to equip students with the necessary tools to conduct a semi-independent bibliographical work on a self-chosen topic within endocrinology. This module is included in the students' sixth semester, which comprises 30 European Credit Transfer System (ECTS) credits, including a seven-week period at school (12 ECTS) followed by a 14-week clinical placement (18 ECTS). The six-week IMRAD module takes place at school and is designed to provide students with theoretical knowledge on the IMRAD topic sections and practical skills. Students become familiar with bibliographic searching, critical appraisal of evidence, documentation, and the practical use of a journal club (JC). The module concludes with a written bibliographical assignment and an oral presentation that includes peer feedback. Throughout the process, both compulsory and voluntary guidance is scheduled to assist students. The module is conducted in parallel with other activities and is assessed on a pass/fail basis.

The module was facilitated by the same educators, and the number of lessons, content, learning activities, and assignments was consistent for the enrolled groups. The distribution of the activities throughout the module is shown in Figure 1, along with the number of

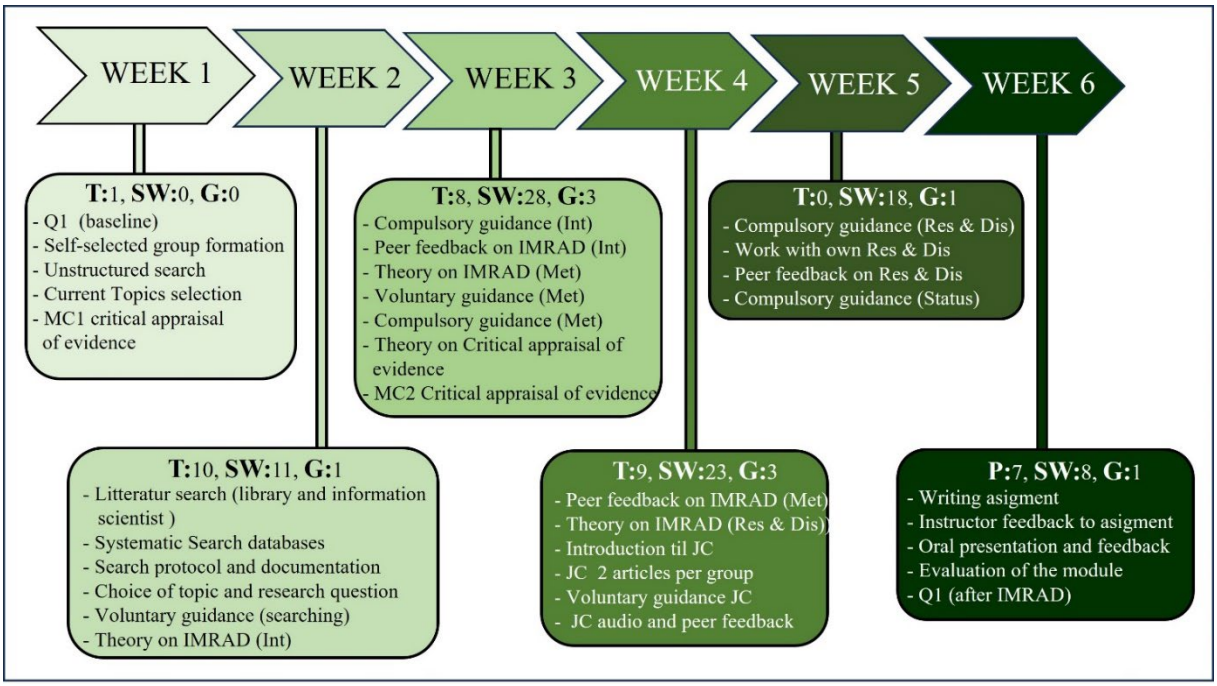

Figure 1: Detailed description of the IMRAD module.
The different teaching activities are presented for each week. The number of planned lessons (45 minutes per lesson) are indicated under each week. T: Teaching, SW: independent Student Work, G: Guidance, P: final oral Presentation. IMRAD topic sections: Introduction (Int), Methods (Met), Results and Discussion (Res &Dis). Questionnaires and tests: EBP questionnaire at two different points Q1 (baseline, and after IMRAD module completion), critical appraisal of evidence MC1 (baseline), MC2 (after dedicated lessons).

planned lessons per week allocated for teaching, independent student work and guidance.

In week one, self-selected groups (3-4 students) are formed by the students and, if necessary, facilitated by the educators. Prior to the start of the module, students completed the EBP questionnaire Q1 (baseline) and a multiple-choice test on critical appraisal of evidence (MC1). This test was applied to subjectively evaluate one specific skill in contrast to the self-reported questionnaires Q1 and Q2.

The Q1 questionnaire is described below, and the MC test is a publicly available online training test.[9]

The course timetable is presented to the students, and the practical work begins with an unstructured search. The groups search and choose topics within the overall theme of endocrinology. The remainder of the week is devoted to other unrelated activities. The chosen endocrinology topics become the starting point for the second week.

In week two, systematic literature search begins. Students attend two lessons on bibliographical searching conducted by a library and information scientist and decide on the final endocrinology topic for remainder of the module. The search must be documented, and the use of a searching protocol and PICO (patient or population, intervention, comparison and outcomes) or similar models is compulsory. Teacher guidance is available during the week. The groups are paired with one sparring group for future joint activities. Additionally, the theory on the IMRAD introduction topic is presented as described in the section below following Juhl and Lindahl.[10]

In week three, the work on the introduction concludes. The first compulsory group guidance takes place. Students start working on the theory of the IMRAD method. Additionally, critical appraisal of evidence theory is presented, and students take the same multiple-choice test as in week one immediately after the lessons (MC2).

In week four, students complete the method topic section. They then start working on the theory of IMRAD´s results and discussion. Additionally, they are introduced to JC. To illustrate the JC concept all students are given an article. The teacher then runs the JC with one student from each group and the rest of the class observe its development. Later in week four, the different groups run two JCs on their own on self-selected articles and create an audio product based on the outcome of the JC. The groups use their assigned sparring group to exchange the audio product and provide a peer feedback to each other following a predefined template. Voluntary guidance on JC is available throughout the week, and a compulsory guidance is scheduled at the end of the JC activity.

In week five, the groups continue working on the results and discussion topic section. Guidance is available a couple of times during the week. Week five concludes with a compulsory group status guidance meeting with the educator to monitor the progress of their respective IMRAD projects.

In week six, the groups work on their written project assignment, which is delivered before the oral presentation. The educators provide brief feedback of the written assignment, which students may consider for their final oral presentation. The oral presentation includes a peer feedback element involving two sparring groups: the sparring group they have had throughout the module and another one. Once the presentation is finished, students complete the Q1 questionnaire (after IMRAD). The final week concludes with an oral evaluation of the module.

Detailed description of the learning strategy

During the module, students are introduced to the IMRAD topic sections, Introduction, Materials and Methods, Results, and Discussion. They subsequently work on these sections in their groups. The learning process for the different IMRAD sections is structured as follows:

1. Instruction on relevant content in topic sections based on the IMRAD format.[10]
2. Reflections on an example of the section from selected BLS previous bachelor theses in smaller groups, followed by shared reflections on the quality of this section in class. This work is facilitated by an educator.
3. Independent group work on the particular topic section as part of their self-chosen bibliographical work.
4. Voluntary guidance. Group work resumes.
5. Compulsory guidance on the working topic section.
6. Submission of the topic section to the sparring group for peer feedback review.
7. Written peer feedback to the sparring group according to a specified model of peer feedback developed by the educators of the module, followed by oral elaboration and discussion of feedback in the groups.
8. Use of received peer feedback to qualify the topic section.

Participating students

Two groups, named BA19 (n=23) and BA20 (n=32), were included in this study. All students participated throughout the entire semester, where attendance to class was mandatory. This implied that no control group could be allocated. Students belonged to two consecutive yearly promotions and represented typical BLS student groups at the school. Both groups were in the same semester (sixth) and academic year (third) and continued right after to their final semester, which ended with their bachelor project. BA19 completed the sixth semester in 2022 and BA20 in 2023. Students were made aware that answering the questionnaires was not compulsory.

Effect of the module. EBP questionnaire (Q1)

To investigate the effect of the designed IMRAD module on students' learning of EBP elements, a questionnaire was developed as the basis of a quasi-intervention study without a control group.

The self-reported questionnaire was inspired by the previously published works of

Martinez EBP-COQ [11] and Upton S-EBPQ [12] validated questionnaires. Newly formulated questions necessary for this research were included. The questionnaire begins with a brief introduction stating that EBP requires decisions about healthcare to be based on the best available, current, valid, and relevant evidence.[6] Additionally, students were informed that some of the concepts might not be known to them at the beginning of the module.

The questionnaire consisted of 22 items divided into two subscales: one on attitude (7 items) and one on knowledge and skills (15 items). All items followed a five-point Likert scale ranging from strongly agree to strongly disagree. The questions were translated into Danish from international references directly by the authors. The questionnaire was not validated.

The questionnaire was distributed to the students via e-mail at three different points during the semester; at the beginning of the IMRAD module (baseline), immediately after the end of the module (after IMRAD), and at the end of the semester (end of semester) The baseline and after IMRAD responses were completed at school, with time scheduled during the lessons to complete the task. The last one (end of semester) was announced on their learning management system, distributed, and reminders for completion were sent within one week after initial distribution. Students did not complete their questionnaires at school. Students were not informed of the questionnaire distribution before the IMRAD module started.

Coupling to the clinical institution

After their seven-week school period, sixth-semester BLS students join a 14-week clinical placement.

During the clinical placement, students must conduct a self-chosen clinical project concerning the development of their biomedical practice. The project consists of three days of project planning followed by three weeks of data collection, data processing, and preparation of a written assignment according to the IMRAD structure. This is followed by an oral assignment, and students are assessed according to a 7-point grading scale.

Self-evaluation, bachelor project contribution and intention to use EBP competences after graduation (Q2).

Six months after completing the sixth semester and immediately after submitting their bachelor thesis, students received a new questionnaire composed of four questions (Q2).

The questionnaire covered different subjects. The first topic was a self-reported questionnaire (five questions) about the students' perception of the five Sicily steps after completing their education and before the final bachelor exam.

The second topic asked students for their self-perception of their bachelor project's contribution to new knowledge and its applicability in the clinical context. The questions on these first two topics followed a five-point Likert scale ranging from "to a large extent" to "not at all".

The third topic (six questions) referred to their future job, job status after graduation, and whether some of the EBP competences acquired could be important for their future job search considerations. In this topic, two of the questions had a Yes/No answer and the remaining followed a five-point Likert scale ranging from "extremely" to "not at all."

Data analysis

To measure internal consistency of the Q1 questionnaire, the Cronbach alpha coefficient was calculated using all students at baseline. The coefficient was calculated for the entire questionnaire and for each of the two subscales, attitude (items 2-8) and knowledge and skills (items 9-22 and 1).

To elucidate an attitude and knowledge and skills profile for each item, Likert scale responses at the three points of Q1 (baseline, after IMRAD, end semester) were coded (1 to 5) and descriptive statistics (mean, standard deviation) were calculated for each item, attitudes and knowledge and skills.

To analyze the effect significance on both subscales, a total subscale score was calculated for questions regarding attitudes (items 2-8) and knowledge and skills (items 9-22 and 1) for each student at all three points. Scores at baseline were compared to scores after IMRAD and at the end of the semester using a paired t-test.

For the critical appraisal test data MC1 and MC2 (before and after the dedicated lesson), mean, standard deviation, and a paired t-test were calculated.

The level of significance for all paired t-tests was set at $p < 0.05$.

For the self-evaluation, bachelor contribution, and intention to use EBP (Q2), mean value, standard deviation and answer percentage were calculated. Statistical analysis was performed using Excel version 2401.

Results

Demographics and Q1 completion rate

The two groups BA19 (n=23) and BA20 (n=32), were very similar, with an average age of 26.6 (BA19) and 26.3 (BA20) years, respectively. The gender distribution showed a slightly higher proportion of males in BA20 (21.9 %) compared to BA19 (17.4%). No students dropped out during the study.

The completion rate of Questionnaire Q1 was 100% at baseline and after IMRAD module in both groups. By the end of the semester, the completion rate was 62.5 % and 65.5 for BA19 (n=15) and BA20 (n=21), respectively.

IMRAD module self-reported EBP questionnaire Q1

The internal consistency of the questionnaire Q1 (n=55) was measured by calculating the Cronbach's alpha coefficient for the entire questionnaire (0,9) and the two subscales: attitudes (0,6) and knowledge and skills (0.9).

Attitudes and knowledge and skills profiles

Attitude profiles (items 2-8)

BA19 and BA20 had similar mean positive overall attitude towards EBP at baseline, with scores of 3.7 and 3.6, respectively. For BA19 students, the relevance of EBP (4.3) and the awareness of EBP´s impact on clinical practice (4.0) scored highest, while for BA20, relevance

Table 1: Attitudes and knowledge and skills profiles

Data is included forBA19 (n=23) and BA20 (n=32) students using questionnaire Q1. A total of 22 items were divided into two subscales: attitudes towards EBP (7 items) (1A), and EBP knowledge and skills (15 items) (1B). The questionnaire was administered before the start of the module as a baseline (before), after completion of the IMRAD module (after IMRAD), and at the end of the semester (after end semester). Numbers are presented as Mean (M) and standard deviation (SD) for each item and each subscale.

	BA19			BA20		
Items Attitudes (1A)	M (SD) Baseline n=23	M (SD) After IMRAD n=23	M (SD) After end semester n=15	M (SD) Baseline n=32	M (SD) After IMRAD n=32	M (SD) After end semester n=21
2. EBP is relevant for me as a BLS	4,3 (0,4)	4,4 (0,7)	4,6 (0,5)	4,0 (0,8)	4,7 (0,5)	4,4 (0,6)
3. I like reading scientific articles	3,6 (1,0)	4,0 (0,7)	4,2 (0,4)	4,0 (0,6)	4,1 (0,7)	4,0 (0,9)
4. I'm confident that I will be able to evaluate critically the quality of a scientific article	3,4 (1,1)	4,1 (0,3)	4,2 (0,4)	3,5 (0,8)	4,2 (0,4)	4,2 (0,4)
5. My awareness of EBP has an impact on clinical practice	4,0 (0,2)	4,3 (0,5)	4,6 (0,5)	3,5 (0,7)	4,1 (0,8)	4,3 (0,6)
6. EBP helps to make decisions in clinical practice	3,9 (0,7)	4,2 (0,4)	4,4 (0,5)	3,6 (0,8)	4,0 (0,8)	4,1 (0,5)
7. In the future as BLS I wish to apply EBP	3,8 (0,8)	4,3 (0,4)	4,3 (0,5)	3,8 (0,6)	4,1 (0,7)	4,1 (0,9)
*8. I stick to tried and trusted methods instead of changing to something new	2,7 (1,0)	2,9 (0,9)	2,9 (0,9)	2,7 (1,0)	2,8 (0,7)	3,0 (0,7)
Overall Attitudes towards EBP (Items 2-8)	3,7 (0,9)	4,0 (0,8)	4,1 (0,8)	3,6 (0,9)	4,0 (0,9)	4,0 (0,8)

Items knowledge and skills (1B)	M (SD) Baseline n=23	M (SD) After IMRAD n=23	M (SD) After end semester n=15	M (SD) Baseline n=32	M (SD) After IMRAD n=32	M (SD) After end semester n=21
1. I know what EBP is	2,6 (1,2)	4,2 (0,7)	4,4 (0,6)	2,6 (1,0)	4,3 (0,5)	4,3 (0,6)
9. I feel able to formulate a study question to start the searching of the best scientific evidence	3,0 (0,8)	4,2 (0,9)	4,2 (0,6)	3,8 (0,8)	4,3 (0,5)	4,3 (0,6)
10. I feel able to formulate a clinical question to start the searching of the best scientific evidence	3,1 (0,8)	3,9 (1,0)	4,3 (0,6)	3,8 (0,8)	4,2 (0,5)	4,3 (0,6)
11. I have knowledge of the relevance of different health sciences databases	3,4 (0,8)	4,3 (0,6)	4,1 (0,7)	3,8 (0,6)	4,4 (0,6)	4,3 (0,5)
12.I know what a MESH term is	2,5 (1,3)	4,7 (0,5)	4,7 (0,6	2,7 (1,1)	4,5 (0,6)	4,4 (0,6)
13. I am able to conduct a systematic search for scientific evidence in health sciences data bases	3,0 (0,8)	4,2 (0,7)	4,5 (0,6)	3,8 (0,6)	4,6 (0,6)	4,4 (0,7)
14. I am able to use the specifically issued search protocol for my literature search	2,9 (1,1)	4,2 (0,7)	4,4 (0,6)	3,5 (0,7)	4,3 (0,5)	4,2 (0,5)
15. I am able to conduct a systematic literature search using the PICO format	2,1 (0,8)	4,3 (0,9)	4,4 (0,6)	2,6 (0,8)	4,3 (0,5)	4,2 (0,7)
16. I know the most important characteristics of the principal clinical research designs	2,8 (1,0)	4,0 (0,4)	4,1 (0,6)	3,1 (0,9)	4,2 (0,5)	4,2 (0,4)
17. I know the different levels of evidence of the clinical research designs	2,8 (1,2)	4,0 (0,6)	4,3 (0,7)	2,9 (0,8)	3,9 (0,7)	4,0 (0,7)
18. I am able to assess whether the obtained results of a clinical study are valid	3,2 (0,8)	3,8 (0,7)	4,1 (0,7)	3,6 (0,9)	4,2 (0,4)	4,0 (0,5)
19. I am able to assess the applicability of a scientific article and relate it to my study question	3,6 (0,9)	4,1 (0,4)	4,2 (0,7)	3,9 (0,5)	4,5 (0,5)	4,3 (0,6)
20. I have knowledge of the IMRAD format	3,4 (1,0)	5 (0,2)	4,8 (0,6)	2,7 (0,9)	4,8 (0,4)	4,8 (0,4)
21. I am able to disseminate the content of a practice-oriented study question aided by the IMRAD format	2,8 (1,0)	4,5 (0,5)	4,7 (0,6)	2,6 (0,9)	4,3 (0,4)	4,4 (0,5)
22. I am able to assess the relevance of a change in clinical practice based on empirical data-collection and existing evidence	3,3 (0,8)	4,0 (0,6)	4,5 (0,6)	3,5 (0,7)	4,1 (0,4)	4,2 (0,4)
Overall knowledge and skills (Items 1,9-22)	3,0 (1,0)	4,2 (0,7)	4,4 (0,7)	3,3 (1,0)	4,3 (0,5)	4,3 (0,6)

and reading articles were highly considered (4.0). Both groups scored lowest on sticking to tried and trusted methods (2.7). After completing the IMRAD module, there was a slight improvement in all questions for both groups, reflected in their mean scores. At this stage, the relevance of EBP was the most agreed-upon item for both groups 4.4 and 4.7, respectively, (Table 1A).

For BA20, there was a notable increase in confidence to critically evaluate the quality of scientific articles and the relevance of EBP, from 3.5 at baseline to 4.2 after IMRAD module.

By the end of the semester, both groups maintained the same attitudes as after completion the IMRAD module, (Table 1A).

Knowledge and skills (items 1, 9-22)

In terms of mean overall knowledge and skills score both BA19 and BA20 started at the middle of the Likert scale at base line, with average scores of 3.0 and 3.3, respectively. At this point, students did not seem to have much knowledge of EBP, MeSH terms or the PICO

Table 2: Effect of the IMRAD module on attitudes, and knowledge and skills.

Data represents student groups by total subscale score using the Likert scale coding (1 to 5): after IMRAD and end of semester BA19 (2A) and BA20 (2B).

2A BA19	Baseline M (SD) =23	After IMRAD M (SD) n=23	p-value	Baseline M (SD) n=15	After end semester M (SD) n=15	p-value
Items attitudes (items 2-8) (max score 35)	25,7 (3,7)	28,2 (2,6)	$2,5 *10^{-3}$	26,0 (3,5)	29,3 (2,4)	$6,4*10^{-4}$
Items knowledge and skills (items 1, 9-22) (max score 75)	44,5 (10,4)	63,2 (6,0)	$2,9 * 10^{-9}$	43,1(11,4)	65,8 (7,4)	$5,2*10^{-8}$

2B BA20	Baseline M (SD) n=32	After IMRAD M (SD) n=32	p-value	Baseline M (SD) n=21	After end semester M (SD) n=21	p-value
Items attitudes (items 2-8) (max score 35)	25,1 (2,6)	28,0 (2,9)	$1,8*10^{-6}$	25,3 (2,8)	29,1 (3,2)	$4,8*10^{-4}$
Items knowledge and skills (items 1, 9-22) (max score 75)	48,9 (6,7)	64,8 (4,5)	$2,9*10^{-14}$	49,1 (7,0)	64,4 (4,9)	$2,9*10^{-9}$

model. Interestingly, BA20 students also lacked knowledge of the IMRAD format (Table 1B).

After completing the IMRAD module, both groups increased their skills and knowledge to 4.2 (BA19) and 4.3 (BA20) on average. By the end of the semester, BA20 maintained the same overall average score 4.3, while BA19 increased slightly to 4.4, (Table 1B).

Effect of the IMRAD module

Attitudes (items 2-8)

Most students in both groups exhibited an improvement in subscale score for attitudes both after the IMRAD module and by the end of the semester.

After the IMRAD module, three BA19 students showed no change in attitude subscale scores, and another three students showed a decrease (≤1 point). The mean subscale score at baseline was 25,7 (SD=3.7), which increased significantly to 28.8 (SD=2.6, p=0.0025). By the end of the semester, two students showed a decrease in the subscale score (≤1 point) while others increased. The mean subscale score increased significantly to 29.3 (SD=2.4, $p=6.4*10^{-4}$) by the end the semester, (Table 2A).

After the IMRAD module, three BA20 students showed no change in subscale scores, and another three students showed a decrease (≤3 point). The mean subscale score for attitudes at baseline was 25.1 (SD=2.6), which increased significantly to 28.0 (SD=2.9, $p=1.8*10^{-6}$). By the end of the semester, three students showed no change in subscale scores, while two students showed a decrease (≤3 point). The mean subscale score increased significantly to 29.1 (SD=3.2, $p=4.8*10^{-4}$) (Table 2B).

Knowledge and skills (items 1, 9-22)

Only one BA19 student showed no change in subscale scores for knowledge and skills after IMRAD module, while the rest of the students showed an increase (≥9 points). The mean subscale score at baseline was 44.5 (SD=10.4), which increased significantly to 63.2 (SD=6.0, $p=2.9*10^{-9}$) after the IMRAD module.

By the end of the semester, all students exhibited an improvement in the subscale scores (≥8 points). The mean subscale score increased significantly to 65.8 (SD=7.4, $p=5.2*10^{-8}$) (Table 2A).

All BA20 students exhibited an increase in subscale scores (≥3 points) both after the IMRAD module and at the end of the semester. the mean subscale score at baseline was 48.9 (SD=6.7), which increased significantly to 64.8 (SD=4.5, $p=2.9*10^{-14}$) after the IMRAD module and was 64.4 (SD=4.9, $p=2.9*10^{-9}$) at the end of the semester (Table 2B).

Measurement of critical appraisal knowledge

The comparison of both tests (MC1 and MC2) was used to elucidate the impact of the theoretical lessons on the students' knowledge of critical appraisal.

BA19 (n=23) scored an average of 8.8/16 at the start of the IMRAD module and 9.1/16 after the dedicated lessons. The difference was not significant (p=0.66). In this group, it was noticeable that half of the students (n=10) had an increase in their scores after the lesson (from 8.6 to 10.7 on average) while the other half (n=11) had a decrease in their scores (9.2 to 7.6 on average).

BA20 (n=29) scored an average of 7.9/16 at the start of the module but significantly increased this score after the dedicated lessons (10.4/16, p=0.0006). All the students except two increased their scores.

Bachelor result contribution, EBP competences and intention to use them after graduation. Questionnaire Q2

BA19 had a completion rate of 100% while BA20 reached 63%.

The students self-graded their ability to ask, retrieve, appraise, apply, and evaluate different aspects of their profession and practice on a five-point Likert scale ranging from "to a great extent" to "not at all," based on their completed BLS education. Both BA19 and BA20 reported their ability in all five steps to a large extent (>4) (Table 3A).

In terms of occupation, 52.2% of the students from the BA19 group already had a job by the time they answered the questionnaire while 73.9 % had sent a job application. For BA20, 35% of the students had a job and 45% had applied for a job.

When asked about the possible contribution of their bachelor project results, BA19 students considered on average "to a large extent" (>4), that their bachelor results could contribute to confirming existing clinical practice, assessing the implementation of new practice, and qualifying the development of bioanalytical practice. For BA20 students, assessing the implementation of new practice was considered slightly lower (3.7 on average, "somewhat"), while the other items were the same as for BA19 students (Table 3B).

Table 3: Students responses to the questionnaire Q2.

The students answered using a five-point Likert scale, ranging from "to a great extent" (best) to "not at all" (worst). They assessed their ability to ask, search, appraise, apply, and evaluate different aspects in the context of their profession and clinical practice (3A). The students responded to questions about: 1) the contribution of their bachelor project new knowledge, 2) the importance of the competences ask, apply and evaluate in work assignments on their future job as BLS (3B).

3A		
Based on your BLS education, to which extent are you able to:	BA 19 (n=23)	BA20 (n=20)
ASK questions that can contribute to solve professional problems or challenges	4,2 (0,7)	4,2 (0,7)
RETRIEVE existing best available evidence that can contribute to solve professional problems or challenges	4,1 (0,7)	4,3 (0,6)
Critically APPRAISE the quality, usefulness or clinical relevance of the best available evidence	4,1 (0,6)	4,2 (0,6)
APPLY new evidence or knowledge in relation to your praxis.	4,3 (0,6)	4,3 (0,6)
EVALUATE whether the implementation of new initiatives can contribute to increase the quality or improve the current clinical practice.	4,1 (0,7)	4,5 (0,5)

3B		
To which extent can your bachelor project contribute to knowledge that can be used to:	BA 19 (n=23)	BA20 (n=20)
Confirm existing clinical practice.	4,2 (0,7)	4,2 (0,9)
Assess the implementation of new practice in clinical practice.	4,1 (0,7)	3,7 (0,8)
Quality development of the bioanalytical diagnostic in clinical practice.	4,2 (0,7)	4,2 (0,7)
To which extent does it make sense for you that in your future job as a BLS, you get work assignments where you be involved in:		
Critically APPRAISING the quality, usefulness, or clinical relevance of the best available evidence	4,1 (0,8)	3,7 (1,0)
APPLYING new evidence or knowledge in relation to your praxis.	4,0 (0,6)	4,2 (0,7)
EVALUATING whether the implementation of new initiatives can contribute to Increase the quality or improve the current clinical practice.	4,2 (0,7)	4,1 (0,9)

Finally, BA19 and BA20 students reported that it made sense to them, “to a large extent,” to get a job where they could undertake assignments involving applying new evidence and knowledge to practice and evaluating the contribution of new evidence implementation in clinical practice. The two groups differed slightly in their assessment of critically appraising the quality, usefulness, or clinical relevance of the best available evidence. BA19 considered it to a large extent (4.1), while BA 20 only “somewhat” (3.7) (Table 3B).

Discussion

The IMRAD module

A teaching module was developed to introduce students to the IMRAD format. In the module, different aspects of the EBP process were considered; specifically, three steps of the five-step process (ask, search, and appraise) were included. A comprehensive and well-defined framework of the module facilitated the students' learning progression, transitioning from an educator-guided start to more independent student group work by the end of the module (Figure 1). The format, which divides different elements into short educational units, supports students' confidence and allows time for immersion and reflection. Educators' guidance was available to help the students throughout the module. This is an important part of the process, as the students can feel frustrated at the beginning and often require some guidance. Guidance meetings also help the educators to follow up on the students' progress facilitating individual learning processes and creating a positive, safe zone of proximal development.[13,14] During the guidance sessions at the final stages of the module and the final evaluation, the students exprressed a high degree of satisfaction with the module contents, its structure, and the development of a critical sense towards primary literature. This positive feedback and the students' progress are particularly rewarding and motivating for the educators.

The design of the module took into consideration different approaches that have previously reported their effectiveness. Self-selected groups were encouraged based on published theory[15] and references therein. The students had suggested their involvement in group formation in previous evaluations, pointing out that at this stage of their education they knew each other well. It is important to add that the educators may help with group formation if needed.[15] Sparring groups were matched by the instructors considering similar academic levels and expectations.[16]

The module combines several effective teaching methods to achieve better outcomes: case lectures, group work, peer-feedback, educator guidance, test analysis, JC, written and oral assessments and collaboration with a library and information scientist for learning searching strategies.[2] The combination of teaching methods and collaborations has been reported as an effective method to achieve the skills required to practice EBP.[5]

Students begin their clinical placements immediately after completing the module. As part of the clinical work, they can apply their new knowledge by carrying out a mini IMRAD project that becomes the main part of the semester's final graded assessment. In this way, they learn about the last two steps of the EBP process (integrate and evaluate), stressing the importance of close collaboration with the clinic, a method previously stated as key[1] and particularly beneficial for MLS students.[8]

Collaboration between the clinical institution and the school has been pointed out as the most prominent facilitator for teaching EBP in our institution [17] and Ghaffari et al. argue that integrating EPB teaching into clinical education can enhance students' knowledge and skills.[18]

Questionnaire results

In general, the results from questionnaire Q1 indicated that students from both groups experienced a moderate increase in their EBP attitudes and a significant increase, with a narrower SD in their knowledge and skills after completing the IMRAD module. This outcome could be expected, as the module is an intensive six-week course, and the students

tend to focus on it due to the necessity of these skills and knowledge for the final semester exam and the future bachelor project. Interestingly, this effect was maintained after the clinical period, as shown by the results at the end of the semester. Despite no longer being in contact with the educators and shifting their focus to practical work and semester assignments, the students' improvement persisted. However, these results should be interpreted with precaution, as the completion rate of the questionnaire at the end of the semester dropped to 62.5% (BA19) and 65.5% (BA20). The fact that e-mail questionnaire distribution typically results in a moderate mean response rate[19] was key to scheduling the baseline and after IMRAD questionnaire measurements during lessons at the school, which explains the 100% completion rate.

As a specific measure of the IMRAD module´s effect, we tested the students' knowledge on one item, critical appraisal of evidence (MC1 and MC2). The results showed that while BA19 students did not achieve a better score, BA 20 students showed significant improvement. These results suggest a possible self-reported bias in Q1.[20,21]

Moderate correlation between self-reported questionnaires and objective assessments for the EBP-COQ in undergraduate nursing students has been reported previously.[22] In this study, the lack of a control group and a validated questionnaire limits the interpretation of the data. However, the fact that the results obtained after completing the IMRAD module and the end of the semester, along with the answers from questionnaire Q2, demonstrated the same higher degree of the Likert scale, suggests that the IMRAD module had a positive effect in the students' EBP competences and their subsequent use in practical and bachelor contexts. Additionally, using two groups accounts for both motivated and unmotivated students.

It is important to mention that many students expressed "to a large extent" that it makes sense to them to apply for future jobs where some of these competences could be utilized.

In a global context where health professionals increasingly quit their jobs[23] or are difficult to retain,[24] the Danish public health service is unable to recruit 20% of their BLS positions with BLS professionals.[25] Bearing this in mind, the interests and job satisfaction factors of young, recently graduated BLS students pursuing their first job may need to be considered in the near future.

Methodological considerations

There are several considerations regarding the methods used in this article. The number of students in each group and the absence of a control group considerably limit the interpretation of the data. The completion rate after the end of the semester for BA20 Q2 is low. Questionnaire Q1 has not been validated, and the translation of the questions was performed by the authors without further considerations. However, the internal consistency of the questionnaire was estimated using the Cronbach alpha coefficient and the calculated coefficients were similar to those reported in previous studies.[17]

This study accounts for a fraction of the BLS students in Denmark, representing a small institution, and therefore cannot necessarily account for the education across the entire country.

Conclusion

We have detailed a module designed to introduce and familiarize Danish BLS students, early in their bachelor's degree, with both EBP and the IMRAD format. Two independent groups self-reported a significant improvement in their EBP attitudes, knowledge, and skills after completing the module. This effect was sustained at the end of their clinical placement. Upon completion of their bachelor project, students reported the ability to apply EBP competences to ask questions, retrieve evidence, appraise quality, apply evidence or knowledge, and evaluate the implementation of new initiatives within their current clinical practice to a large extent. Additionally,

students indicated that it would be logical to receive work assignments that allow them to utilize their newly acquired competences.

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Research article

Raising the Bar in the Diagnosis of Non-Small Cell Lung Cancer (NSCLC): The Impact of Automated FISH Technology

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Purpose: **The MET gene, which encodes a receptor tyrosine kinase, is crucial in cancer cell proliferation and survival. Fluorescence in situ hybridization (FISH) is vital for assessing MET-gene amplification in non-small cell lung cancer (NSCLC). Manual FISH assays are time-consuming, and results are critical for treatment decisions; automation could reduce turnaround time. This study evaluates the potential benefits of the automated FISH-system, Oncore Pro X (Biocare Medical USA), by assessing factors including results, turnaround time, and cost.**

Materials and Methods: **A method comparison was conducted using 20 NSCLC formalin fixed paraffin embedded (FFPE) specimens. Manual FISH-assays (ZytoLight® FISH-Tissue Implementation Kit with ZytoLight® SPEC MET/CEN 7 Dual Color Probe) were compared to automated assays (Oncore Pro X with MET (7q31) Orange + Copy Control 7 Green Probe). Concordance of MET-parameters was evaluated for both categorical and numerical data.**

Results: **Categorical data showed 80% concordance with a Cohen's Kappa coefficient (k=0.86), indicating near-perfect agreement. A Bland-Altman plot for numerical data revealed no noteworthy bias. A radar chart based on scoring (0-5) of relevant categories rated the manual assay at 15 and the automated at 21 out of 25.**

Discussion/Conclusion: **The automated assay reduced turnaround time, allowing for faster treatment initiation. Despite minor discrepancies, the high concordance indicates that the Oncore Pro X system has strong potential to replace manual FISH in clinical settings, significantly reducing turnaround time. Future research should focus on expanding probe availability and further cost optimization.**

Keywords: Fluorescence in situ hybridization, Gene amplification, Automation, Non-Small-Cell Lung Carcinoma

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Introduction

Since its introduction in the 1980s, FISH has become essential for detecting chromosomal abnormalities, including amplifications and deletions in cancer diagnostics. The method utilizes fluorescently labeled DNA probes that hybridize to specific targets of DNA within the nucleus which is then traditionally detected using a fluorescent microscope. FISH can be performed on FFPE tissue samples resulting in a rapid output with high sensitivity and specificity.[1] In NSCLC mapping of dysregulations in the proto-oncogene MET located on chromosome 7q31.2 have proved significant in prognosis and treatment. The MET-gene encodes a transmembrane tyrosine kinase receptor c-Met also known as hepatocyte growth factor receptor (HGFR), which when activated by the natural ligand hepatocyte growth receptor (HGF) results in the activation of several signaling pathways in relation to cell proliferation, survival, apoptosis, invasion and angiogenesis.[2]

Dysregulation of the MET-gene can occur in many ways including MET amplification detectable via FISH analysis.[2] Despite its comparative speed in genetic analysis, FISH remains labor-intensive and time-consuming, prompting interest in automated alternatives.[1] Oncore Pro X Automated Slide Staining System, Biocare Medical USA, is a fully automated staining system for paraffin-embedded and frozen tissue samples, cytospins, cell smears and fine needle aspirates. The system is able to perform FISH along with other *in situ* hybridization techniques as well as routine immunehistochemistry staining (IHC) techniques.[3] This automated system minimizes hands-on time, optimizes workflow, and notably accelerates assay turnaround times—critical for expediting treatment decisions in clinical settings.[4]

Using the probe MET (7q31) Orange + Copy Control 7 Green from Biocare Medical, potential amplification of the gene can be detected through FISH-analysis on Oncore Pro X with a turnaround time of approximately 5 hours.[5] This study aimed to verify the automatic FISH-system Oncore Pro X from Biocare Medical by comparing it to a gold standard manual assay from ZytoVision through assessing paired results of levels of MET-amplification and MET/CEN7-ratios. Additionally, key factors such as probe availability, time consumption efficiency and labor intensity was investigated to comprehensively assess the system's performance and feasibility in clinical diagnostics.

Materials and methods

Tissue specimens

The tissue used in this study originates from patients with lung cancer and consists of both primary tumors and suspected metastases.

In total 20 tissue samples including 14 from the thorax, three from the gastrointestinal canal, two from neurological tissue and a single sample of ear-neck-throat-tissue were analyzed. These 20 samples represented all levels of amplification.

The FFPE blocks were retrieved as residual blocks (2023) from the Department of Pathology (Rigshospitalet, Denmark) and specimens were cut into sections of 2 µM and mounted on TOMO glass slides (Matsuanmi Glass Ind. Lt.d., Osaka Japan) before being subjected to heat at 60°C for 60 min. For each specimen HE (hematoxylin and eosin) and IHCstained slides were obtained (if available), the majority with the cancerous tissue marked by a pathologist to better locate area of interest.

Data collection and storage was performed in compliance with the Danish Data Protection Agency. All samples were controlled in the Danish Tissue Utilization Register (Vævsanvendelsesregisteret (VAR)).

Controls

Along with the specimen each slide was mounted with an established in-house xy control consisting of healthy tonsil tissue from a male. This is used as a control to ensure that a reaction is seen in the expected signal pattern as well as an adequate signal intensity for both fluorophores.

MET-probes

In this study two different probes were used for manual and automatic FISH. For automatic FISH the prediluted FISH probe Oncore Pro MET

(7q31) Orange + Copy Control 7 Green, FISH Probe (902-OPPR7341-020322, Biocare Medical, Concord, CA) for the specific use on Oncore Pro X (Biocare Medical) was used. This probe includes an orange fluorophore targeting a 440 kb sequence at locus 7q31.2 harboring the MET gene, along with a green fluorophore targeting the 7p11.1-q11.1 sequence encoding the alpha satellite centromeric region of chromosome 7.

For the manual verification slide a ZytoLight® SPEC MET/CEN7 Dual Color Probe (Z-2087–50, ZytoVision GmbH, Bremerhaven, Germany) was used in a ZytoVision FISH-assay. This probe targets similar regions of interest and is labeled with comparable fluorescent dyes, however the MET-region and CEN7-region have inverted labeling. Furthermore, the targeted sequence on the MET-region is significantly longer in that it targets a sequence of 795 kb relative to 440 kb.

Zyto*Light* FISH-Tissue Implementation Kit

As a gold standard, manual FISH was performed using the ZytoLight FISH-Tissue Implementation Kit (Z-2028-20, ZytoVision GmbH, Bremerhaven, Germany). The kit contains all reagents necessary for manual FISH and is intended to be used in combination with ZytoLight FISH probes on FFPE specimens. Slides performed with this kit were considered verifycation slides. This procedure was carried out in the span of two days.

First day

Initially specimens were dewaxed using xylene followed by rehydration with a decreasing concentration of ethanol (99-70%). Specimens underwent heat pretreatment using a microwave oven set for 13 min. followed by treatment with 2-4 drops of Pepsin Solution (stored at <10 °C) for 10 min. at 37 °C. Specimens were then washed with Wash Buffer SSC (saline, sodium, citrate) and afterwards dehydrated with an increasing concentration of ethanol (70-99%) in preparation for hybriddization.

Approximately 10 µL ZytoLight ® SPEC MET/CEN 7 dual color probe was then applied to each specimen, covered with a coverslip, and sealed with rubber cement. Denaturation was performed at 75 °C for 10 min. followed by hybridization at 37 °C for at least 18h (overnight) by using the TDH-500 Hybridization System (Hangzhou Allsheng Instruments Co. Ltd., Hangzhou China).

Second day

After hybridization, coverslips were removed, and specimens underwent stringent washing with diluted Wash Buffer A at 37 °C for 12 minutes. Specimens were then dehydrated with increasing concentrations of ethanol (70% to 99%), dried, and mounted with ZytoVision DAPI before being cover slipped.

Oncore Pro X Automated Slide Staining System

Automatic FISH was performed using the automated system Oncore Pro X from Biocare Medical utilizing reagents supplied by the manufacturer. The system was operated in accordance with Biocare Medical protocols using the MET (7q31) Orange + Copy Control 7 Green probe also from Biocare Medical. Each run had an approximate turnaround time of 5.5 h varying based on workload. Upon completion of each run slides were air dried and mounted using Fluoro Care Anti-Fade Mountant (901-FP001-062023, Biocare Medical, Concord, CA).

Cell counting

The slides were assessed using the Olympus fluorescent microscope system BX63 at magnifications of 10x, 60x and 100x equipped with filters suitable for the specific fluorescent dyes used. Cell counting was performed by experienced biomedical laboratory scientists in the FISH-laboratory at the Department of Pathology, Rigshospitalet, Denmark.

By default, signals from one hundred cells total were enumerated and specimens were placed into one of four categories based on established research recommendations.[6]

High level amplification (A): MET/CEN7-ratio ≥2 or MET/cell ≥6 or ≥10% of tumor cells with ≥15 MET signals (clusters).

Intermediate level amplification (B): ≥50% tumor cells with ≥5 MET signals.

Low level amplification (C): ≥40% of tumor cells ≥4 MET signals.
No amplification (D): none of the above criteria was met.

However, if a sample showed a clear signal of clusters in a large number of cells a preliminary screening of the slide was deemed sufficient to diagnose 'high level amplification' (A) and no numeric result would be obtained.

Minor and major discrepancies/evaluation of category disagreements

The categories mentioned above serve as diagnostic criteria upon which potential patient treatment decisions are based. Therefore, a distinction of possible disagreements between the two assays is crucial in evaluating the clinical relevance and thus the performance of Oncore Pro X for diagnostic purposes. As observed in previous studies, e.g., Manion et al., classifications minor- and major discrepancies are utilized.[7] A minor discrepancy is defined as a disagreement between categories that will not present a clinical relevance as the disagreement does not alter patient treatment. Contrary, a major discrepancy is defined as a significant disagreement that influences both treatment decisions and patient prognosis.

Wash out period and blinding

To prevent intentional or unintentional bias during cell counting, either a washout period or blinding of slides was implemented, given that knowledge about how the staining was obtained may lead to a subconscious modification of results.[8] The washout period was set at a minimum of 14 days based on recommendation from the College of American Pathologists Pathology and Laboratory Quality Center (CAP) guidelines.[9]

Sample 1-14 had a previous manual MET FISH-analysis approximately 1 to 10 months earlier. The previous result was retrieved for correlation. For these slides a wash out period of at least 14 days occurred naturally and it was therefore determined that earlier opinions would not influence subsequent count.[9]

Samples 15-20 had no prior MET FISH-result and both the manual and automated staining was therefore performed during this study. As a result, a wash out period of at least 14 days was unattainable. Thus, blinding of the tests before counting was chosen as a suitable method to prevent bias.[8]

Consequently, these slides were blinded within pairs to ensure that assessments could not be influenced by prior knowledge.

Statistical analysis

To compare the manual gold standard ZytoVision FISH assay with the automated FISH assay on Oncore Pro X, a method comparison was performed. The concordance between assays was investigated by cross-tabulation and by calculating a Cohen's K coefficient based on results from the categorical data (levels of amplification). Additionally, the levels of amplification were visualized in a graph based on classifications from both the manual and automatic assays.

Furthermore, numerical data (when available) for the MET/CEN7 ratios from cell counting were evaluated and visualized in a graph, as well as a Bland-Altman plot, to assess potential systematic tendencies.

This study systematically evaluated operational parameters of FISH methods using constructive technology assessment (CTA).[10] Multivariate data were analyzed using a radar chart to assess both automated FISH on the Oncore Pro system and manual FISH methods according to five categories: turnaround time (within a 25-hour limit) specified in hour (h), hands-on time (evaluating resource efficiency) specified in hour (h), exposure to hazardous chemicals (addressing safety concerns), probe availability (examining variety), cost per slide in Danish kroner (DKK) (analyzing economic feasibility), and usability (considering ease of training and operational efficiency).

Differences, challenges, and benefits of both manual and automated FISH methods were thoroughly assessed through CTA. Each category received a score ranging from 1 to 5, with definitions provided in Table 1. Assessment criteria were selected based on clinical

Table 1. Definitions and Elaboration of Categories for Method Comparison

Definition and elaboration of the categories used for method comparison: Turnaround Time specified in hour (h), Hands-on Time specified in hour (h), Exposure to Hazardous Chemicals, Number of Available Probes, Cost per Slide specified in Danish kroner (DKK) and Usability.

		Definition of each score				
Category	**Elaboration**	1	2	3	4	5
Turnaround Time	Time passed from start of assay to slide is ready for microscopy	20-25 h	15-20 h	10-15 h	5-10 h	0-5 h
Hands-on Time	Amount of time actively spent performing FISH	4-5 h	3-4 h	2-3 h	1-2 h	0-1 h
Exposure to Hazardous Chemicals	Based on exposure to formamide in the handling of probes	Long exposure	Moderate exposure	Fair exposure	Minimal exposure	No exposure
Number of Available Probes	Number of available probes provided by the manufacturer	0-40	40-80	80-120	120-160	160-200
Cost per Slide	Total cost per slide based on reagents required in DKK	1200-1500 DKK	900-1200 DKK	600-900 DKK	300-600 DKK	0-300 DKK
Usability	Based on amount of Jakob Nielsen five usability criteria[11] met: 1) Learnability 2) Efficiency, 3) Memorability 4) Errors, and 5) Subjective satisfaction	0-1/5	2/5	3/5	4/5	5/5

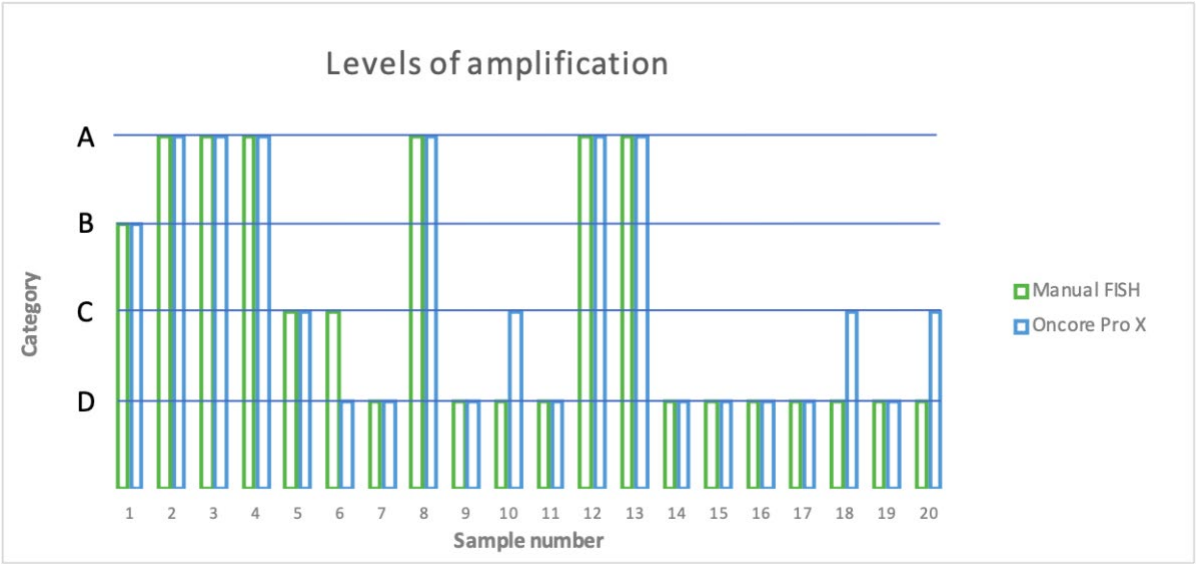

Figure 1. Amplification Levels Across Samples in Manual FISH vs. Oncore Pro X Assays

Levels of amplification for all samples, with the sample number on the x-axis and the assigned category on the y-axis. Green represents the category based on the manual FISH assay, while blue represents the category based on the Oncore Pro X assay.

relevance and variations in typical laboratory settings. Categories turnaround time and available probes were chosen based on key components of a FISH-analysis in a clinical setting where timely reporting of results and a wide selection of probes are crucial for patient diagnosis and treatment. Furthermore, categories hands-on time, exposure to hazardous chemicals and usability, based on Jakob Nielsen five usability criteria[11], were assessed with the purpose of evaluating the individual employee's health and comfort in this regard. Lastly, cost per slide was calculated, as different laboratories have different means, meaning that more costly solutions might not be an option for any given laboratory.

For all mentioned statistical analysis Excel version 16.79.2 was used.

Results

Levels of amplification

Amplification status was classified based on enumeration of signals from one hundred cells and placed into categories **A** - high level of amplification (MET/CEN7- ratio ≥2 or MET/cell ≥6 or ≥10% of tumor cells with ≥15 MET signals (clusters)), **B** - intermediate level of amplification (≥50% tumor cells with ≥5 MET-signals), **C** - low level of amplification (≥40% of tumor cells ≥4 MET-signals) or **D** when none of these criteria were met. In total 20 samples were categorized, and results are presented in Figure 1.

The cross tabulation of amplification status obtained by manual assay and automatic assay is shown in Table 2. In total amplification status from 20 specimens was obtained, six of which fell into category A, one into category B, one into category C and eight into category D, for both manual and automatic assay respectively.

Disagreement was noted in four cases, three of which showed an amplification status in category D for manual FISH-assay and category C for automatic FISH-assay, and a single case that showed the opposite. Thus, agreement was found in 16 out of 20 cases resulting in a concordance rate of 80.0%.

Concordance in amplification status was further assessed by calculating Cohen's Kappa with linear weighting, which, according to the criteria established by Landis and Koch (1977), indicated an almost perfect level of agreement (K = 0.86).[12]

MET/CEN7-ratios

For samples representing categories B, C and D, the ratio between MET-signals and CEN7-signals for 100 cells counted were obtained. This numerical data consists of a total of 14 samples and is presented in Figure 2.

Furthermore, agreement and possible systematic tendencies of obtained MET/CEN7 ratios from manual and automatic assays was investigated by creating a Bland Altman plot which can be seen in Figure 3.

Representative microscopy images

Selected microscopy images of FISH-stained slides performed on the Oncore Pro X can be seen in Image 1. Image 1a shows a representative image of tumor cells with cluster formation, indicated by a high number (>15) of red signals in several of the cells. In contrast,

Table 2. Cross-Tabulation of MET Amplification Status Between ZytoVision and Oncore Pro X Assays

Cross tabulation of MET-amplification status obtained using the manual ZytoVision assay and the automated Oncore Pro X assay. Amplification levels: A – high (MET/CEN7 ratio ≥2, MET/cell ≥6, or ≥10% tumor cells with ≥15 MET signals/clusters); B – intermediate (≥50% tumor cells with ≥5 MET signals); C – low (≥40% tumor cells with ≥4 MET signals); D – no amplification (criteria not met).

Levels of amplification						
		Automated assay - Oncore Pro X				
		A	B	C	D	Total
Manual assay - ZytoVision	A	6	0	0	0	6
	B	0	1	0	0	1
	C	0	0	1	1	2
	D	0	0	3	8	11
	Total	6	1	4	9	20

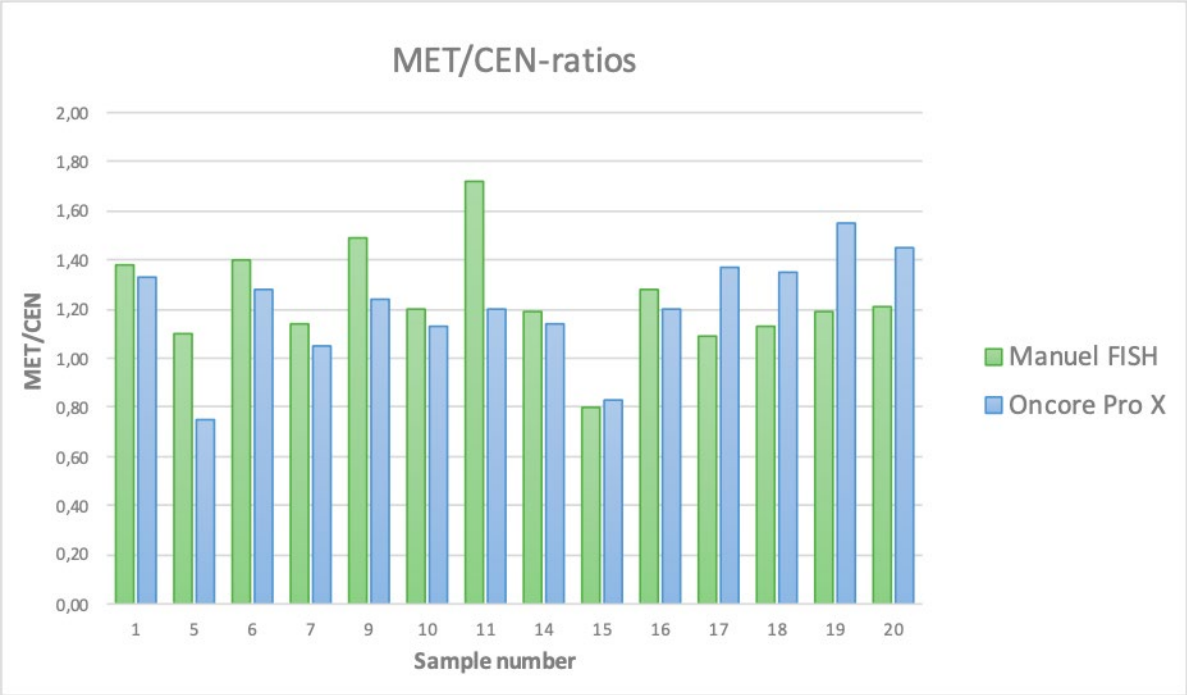

Figure 2. Comparison of MET/CEN Ratios in Manual FISH vs. Oncore Pro X Assays

MET/CEN ratios for samples 1, 5–7, 9–11, and 14–20, with sample number on the x-axis and MET/CEN ratio on the y-axis. Green represents the ratio based on the manual FISH assay, while blue represents the ratio based on the Oncore Pro X assay.

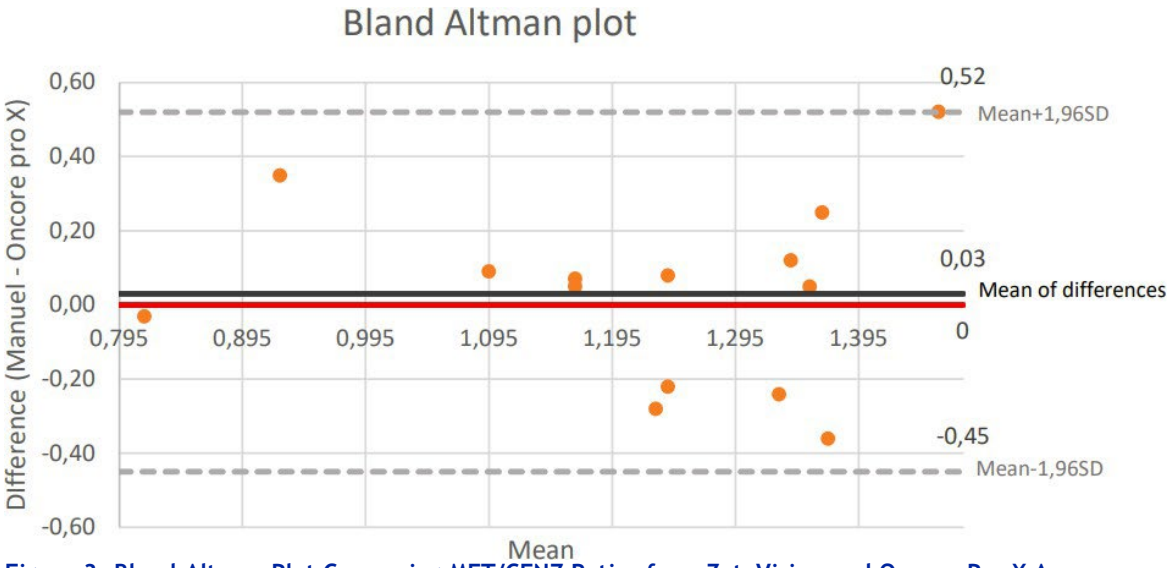

Figure 3. Bland-Altman Plot Comparing MET/CEN7 Ratios from ZytoVision and Oncore Pro X Assays

Comparison of MET/CEN7 ratios obtained from the gold standard manual ZytoVision assay and the automated Oncore Pro X assay. The plot includes 14 samples (orange dots), the 0-line (red line), the mean of differences (black line), and the mean ± 1.96 standard deviations (dashed gray lines).

image 1b shows a representative image of tumor tissue without MET amplification, where approximately two red and two green signals are seen in each cell. Images 1c and 1d both depict controls, consisting of healthy tonsil tissue from a male without MET amplification, with around two red and two green signals in each cell. Slides stained on the Oncore Pro X all showed faint green signals in comparison to slides stained with ZytoVision test-kit as evident in said images. However, it is worth noting that the green signals, albeit faint, still allowed for confident enumeration of samples as the fluorescence appeared much stronger

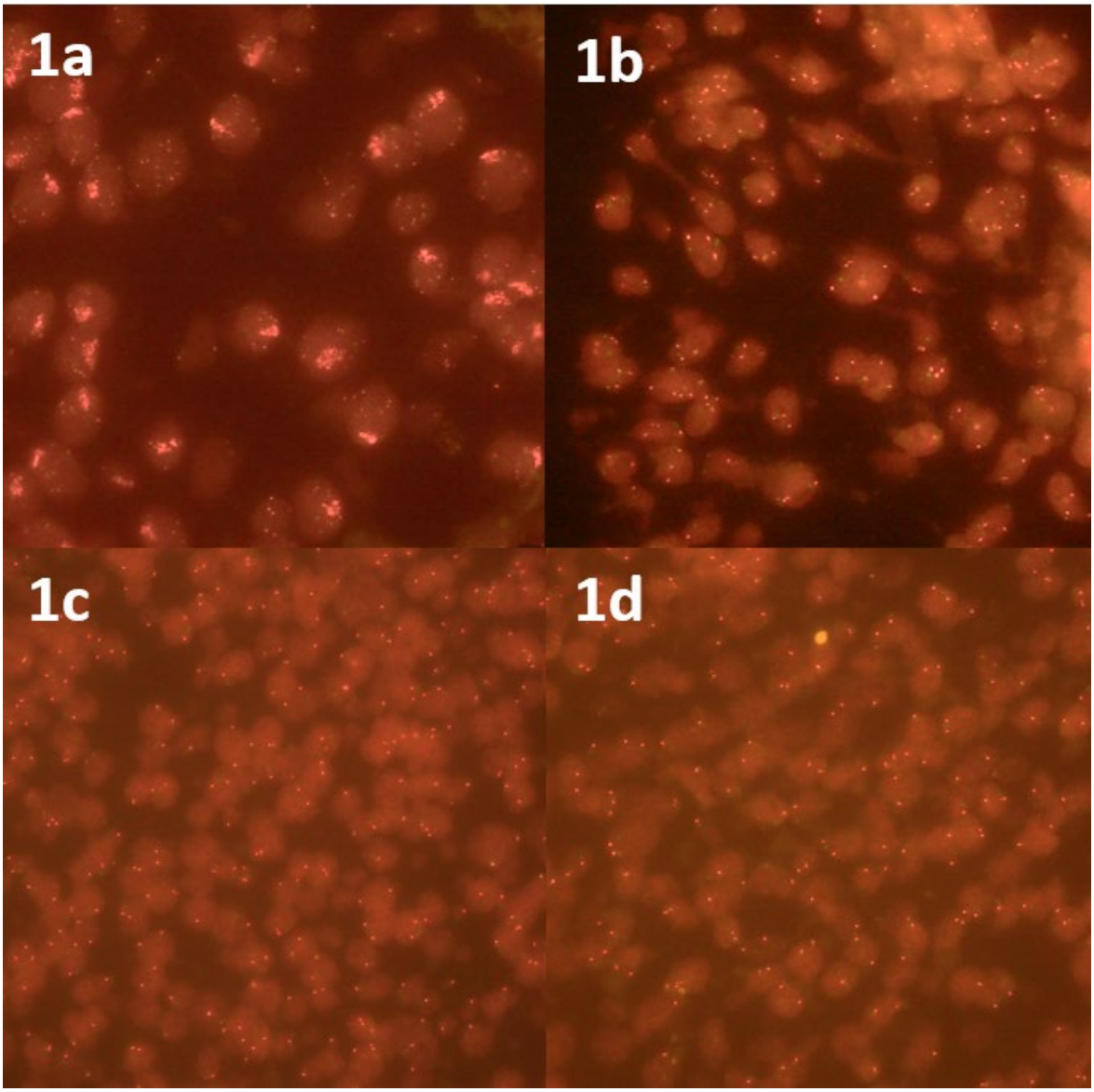

Image 1. FISH Analysis of MET and CEN7 Signals in Different Samples

Areas from different FISH performed on the Oncore Pro X showing MET signals (red) and CEN7 signals (green). 1a: Sample number 13 showing cells with cluster formation with <15 MET signals per cell. 1b: Sample number 10 showing cells without MET amplification. 1c and 1d: Controls consisting of tonsil tissue from a male, showing cells without MET amplification. Magnification x1000 with red/green dual filter.

Table 3. Comparison of Manual ZytoVision and Automated Oncore Pro X Assays Based on Explicit Scoring Categories

Comparison of manual ZytoVision assay and automatic Oncore Pro X assays based on categories Turnaround Time specified in hour (h), Hands-on Time specified in hour (h), Exposure to Hazardous Chemicals, Number of Available Probes, Cost per Slide specified in Danish kroner (DKK) and Usability.

Categories	Score given		Specific result	
	ZytoVision	Oncore Pro X	ZytoVision	Oncore Pro X
Turnaround Time	1	4	24 h	5,5 h
Hands-on Time	2	5	3-4 h	0,5 h
Exposure to Hazardous Chemicals	2	4	Moderate	Minimal
Cost per Slide	3	2	621.85 DKK	972.2 DKK
Number of Available Probes	5	1	188	13
Usability	1	5	1/5	5/5

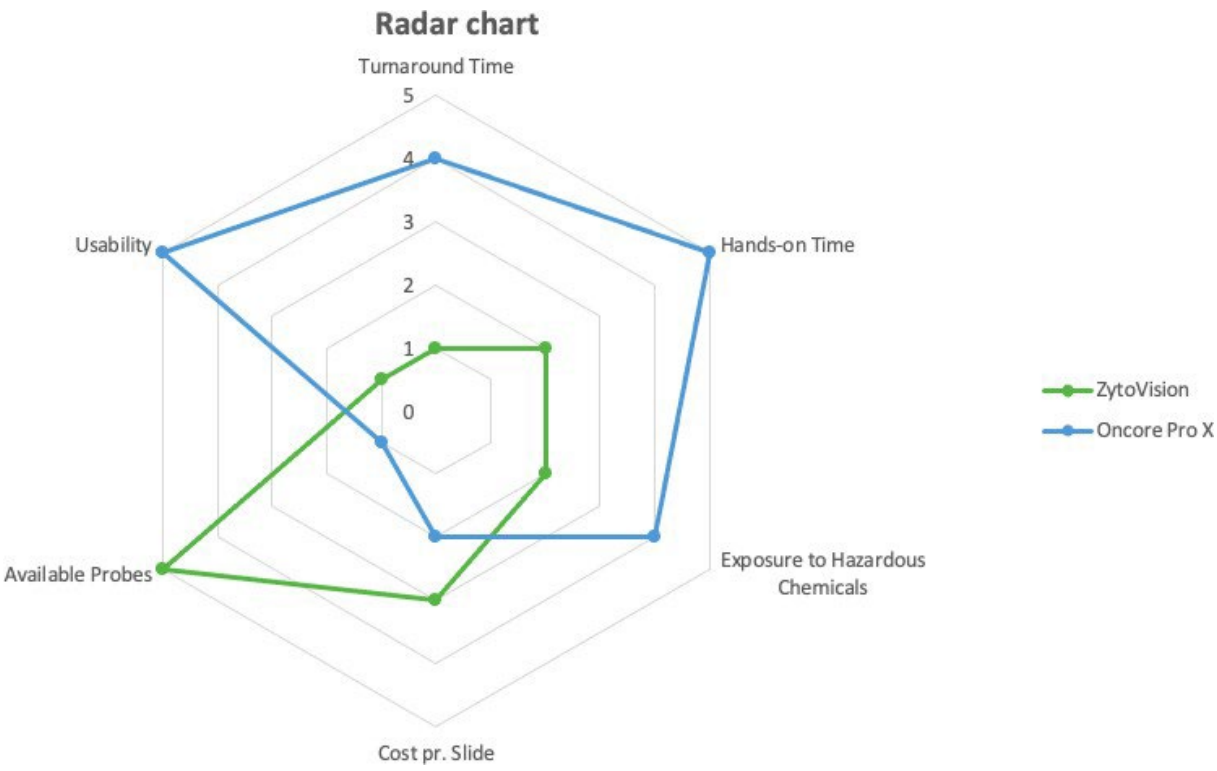

Figure 4. Radar Chart Comparison of Assay Scores Across Categories
Radar chart displaying the score given to each assay in the 6 categories.
Turnaround Time specified in hour (h), Hands-on Time specified in hour (h), Exposure to Hazardous Chemicals, Number of Available Probes, Cost per Slide specified in Danish kroner (DKK) and Usability. The green lines representing the ZytoVision assay and the blue lines representing the Oncore Pro X assay.

under a fluorescent microscope.

Assessment of other variables

To visually display assessment of other factors each assay was given a score from 1-5 for each following category. This score is seen in Table 3 and a radar chart visualizing this data is seen in Figure 4.

Discussion

Levels of amplification

In total MET amplification status from 20 samples were obtained for manual ZytoVision FISH-assay and automatic Oncore Pro X FISH-assay respectively. Of these cases concordance between amplification status was found in 16 cases resulting in a concordance rate of 80%. Disagreement was found in 4 out of 20 cases, however in tese 4 cases, disagreement was between categories 'low level amplification' (C) and 'no amplification' (D), which is deemed a minor discrepancy. Consequently, a diagnosis of either no MET amplification or low levels of MET-amplification does not result in treatment with tyrosine kinase inhibitors (TKIs) due to an inadequate response to this form of treatment suggesting that the disagreement in these cases have little to no clinical relevance.[13] Had disagreement been observed between polar categories 'no amplification' (D) and 'high level of amplification' (A) as well as 'intermediate level of amplification' (B) this would be deemed a major discrepancy in that misdiagnosis would result in unnecessary and harmful treatment or inadequate/absent treatment, which could be detrimental to the patient's health with a possible fatal outcome. The disagreements found between these two assays however did therefore not cause any harm to the patient.

This overall agreement of diagnostic data between the two assays is reflected in the calculated Cohen's Kappa coefficient of 0.86 indicating an almost perfect level of agreement.[12] Since the data is compiled of more

than two ordinally scaled categories this has been calculated as a linear weighted Cohen's Kappa taking the degree of disagreement into account. Consequently, the result of this statistical analysis factors in the disagreement between categories C and D in these 4 out of 20 cases being minor discrepancies and the Cohen's Kappa coefficient must therefore be perceived as accurate hence reliable.

It is however important to note that the weighted Cohen's Kappa assesses the reliability, not the validity, of the two methods. The high-level agreement indicates that both methods measure the same parameter, but not necessarily accurately. The validity of the Oncore Pro X FISH assay must be established by comparison to the manual ZytoVision FISH assay, the gold standard. New assays, including the Oncore Pro X, must demonstrate validity through method comparison, proving the results align with the gold standard used for verification.

As previously mentioned, sample 1-14 already presented a MET-result from prior manual FISH-analysis performed from one to ten months earlier. In addition, subsequent testing such as polymerase chain reaction (PCR) and next generation sequencing (NGS) was performed on samples from these blocks in between manual and automatic FISH-analysis, which meant that the method comparison was performed at different depths of the tissue section. Consequently, the area of analysis may have moved further into or further out of the tumor area, which ultimately could result in a higher or lower estimated level of amplification than previously estimated.

The counting of signals is very dependent on the observer's ability to locate the tumor or cancerous tissue which introduces a bias especially in heterogeneous cases with a high fraction of normal cells. This in particular may result in a falsely lower level of amplification if the area from which enumeration of signals was carried out represents an increased number of normal cells. This bias however was in many cases lessened by the utilization of HE- and IHC-stained slides with the cancerous tissue or tumor marked by pathologists for quick identification of the area of interest, minimizing bias. For some cases HE and IHC slides were not available however posing a risk for bias.

Furthermore, enumeration of signals also depends on the observer's individual counting tendencies which can be affected by personal experience and preference. One individual may count a fainter signal, and another may count more isolated cells making it easier to distinguish one cell from another. The individual variability in personal experience and preference can result in different diagnostic data and consequently affect the patient's follow-up treatment. In this study the enumeration of signals was conducted by two experienced observers working in the same FISH-laboratory (and not several observers across multiple FISH-laboratories). Due to standardized policies within the same laboratory, the study assumed that the same general guidelines were followed for every enumeration minimizing individual variation.

MET/CEN7-ratios

Based on MET/CEN7 ratios obtained from a total of 14 samples for both manual ZytoVision and automatic Oncore Pro X assays, a Bland-Altman plot was constructed. The plot indicated a slight trend towards higher MET/CEN7 ratios in the manual ZytoVision assay compared to the automatic Oncore Pro X assay, as evidenced by a predominance of ratios above the line representing no difference between the two methods (null difference line). However, several samples also fell below this line, and with a mean difference of 0.03, close to zero, overall concordance between the two assay methods suggests a strong correlation. Moreover, all ratios fell within the limits of Mean ±1.96 SD, further supporting this likelihood.

Considering that this analysis is based on a small sample size of only 14 samples, any observed tendencies should be interpreted cautiously, and no definitive conclusions can be drawn from this plot alone.

Assessment of other variables

Turnaround Time

The turnaround time of a FISH assay is critical as it significantly impacts diagnosis, treatment, and prognosis for NSCLC patients.[4] As shown in Table 3 and Figure 4, the Oncore Pro X system produces FISH-stained slides ready for microscopy in approximately 5.5 hours, whereas the manual FISH assay requires approximately 24 hours. It is important to note that the manual assay does not run continuously over weekends, potentially extending its turnaround time to over 72 hours if hybridization occurs from Friday to Monday, highlighting a significant disparity between the two methods.

For patients, waiting for test results, whether positive or negative, can adversely affect overall well-being and mental health.[14] A faster assay not only enables quicker initiation of treatment but also provides patients with prompt clarity, reducing stress and anxiety.[14]

The Oncore Pro X software does offer an option to start a delayed run which could optimize turnaround time with the implementation of overnight processing followed by microscopy the next morning. However, this option is not recommended as this may lead to probe inconsistencies due to solution separation. Would this have been an option though, the Oncore Pro X might have had an even larger advantage.

Hands-on Time

Turnaround time is not the sole factor to consider when comparing the timelines of the two assays; the required hands-on time is equally crucial. In busy laboratories handling numerous routine samples daily, maximizing hands-off intervals is essential. Therefore, assessment of hands-on time for the available assays plays a major role in selecting the best option for the specific workplace. Table 3 and Figure 4 shows how the manual ZytoVision FISH-assay has around 3-4 hours of hands-on time, whereas the Oncore Pro X requires as little as half an hour. Automation in general has proven effective in eliminating manpower and thereby giving the opportunity for redefining employees' time towards more value-added tasks.[15] For laboratories aiming to enhance productivity by reallocating time for tasks such as microscopy or other critical laboratory activities, the Oncore Pro X offers significant advantages.

This surplus of free hands-off time combined with a shorter turnaround time enhances the potential for workflow optimization in a FISH laboratory. It allows laboratories to maximize time, ultimately benefiting patients. Manual microscopy of FISH-stained slides is labor-intensive and time-consuming, potentially leading to delays in sample readings during periods of high workload. Minimizing hands-on time ensures an optimized workflow with more time available for microscopy, ensuring timely results without postponements.

Exposure to Hazardous Chemicals

In working with chemicals in general, precautions always need to be taken or at least considered. When operating FISH, the probe in particular might prove a health hazard since these usually contain the carcinogenic substance formamide, as is also the case with the two probes used for this comparison.[16,17] Therefore, the time working in direct contact with the probe is used as the assessment for exposure to hazardous chemicals. For Oncore Pro X the only contact with the probe is unscrewing the cap before loading it on the reagent rack; therefore, this has been categorized as minimal exposure. When performing the manual ZytoVision assay however the probe must be manually pipetted onto the slide; therefore, this has been categorized as moderate exposure. Furthermore, automated systems in general present lower biological risk for operators regarding both hazardous chemicals but also by removing them from potential high-risk tasks.[15] In concordance, the use of the automatic Oncore Pro X FISH assay provides the least amount of exposure to hazardous chemicals and prioritizing staff health and well-being.

Available Probes

When performing FISH-staining on Oncore Pro X it is recommended to use the manufacturers ready-to-use (RTU) probes designed specifically for the instrument. Diluting other probes for this purpose is both costly as a large amount is needed and can result in an increase in human error. Currently 13 different probes are available for the Oncore Pro X system.[5] On the contrary ZytoVision has 188 probes available.[18] The choice between systems depends on the laboratory's specific probe requirements. While the fewer probes available for Oncore Pro X may suffice for some laboratories, ZytoVision's extensive range offers greater flexibility to meet diverse testing needs. Therefore, laboratories requiring a wide variety of probes may find Oncore Pro X less suitable despite its other advantages.

Cost per Slide

Laboratories must consider cost and overall economics when implementing new or improved equipment, assays etc. Both assays in this comparison utilize kits containing necessary reagents alongside the specific probe. Based on the current market price the cost per slide was calculated for each assay (Table 3). This illustrates that staining one slide with ZytoVision costs approximately two-thirds of the price of one slide on Oncore Pro X when evaluating reagent and probe costs alone.

Other economic factors include the initial cost of purchasing the Oncore Pro X instrument, additional equipment required for manual FISH not provided in kits, potential service agreements, labor costs, electricity usage, and other operational expenses. These factors collectively influence the overall cost-effectiveness of manual versus automatic methods in the laboratory setting.

Usability

Usability in this study is defined across five components: learnability, efficiency, memorability, errors, and subjective satisfaction.[11] Each component was assessed to compare the usability of the two assays.

The ZytoVision assay was given a score of 1 out of 5 indicating it was only considered easy to learn (learnability). As this manual assay involves complex and lengthy procedures it was deemed to be both difficult to apply (efficiency) and problematic to remember (memorability). The high degree of manual labor also increases the risk of human errors, impacting the accuracy of the results. Lastly the constant need for close proximity and the requirement for some tasks to be performed in a dark room pose health and safety hazards, diminishing subjective satisfaction.[19]

In contrast, the Oncore Pro X assay was given a score of 5 out of 5 indicating it excels in all five components of usability. The system is easy to learn and the simple and manageable software makes it straightforward to both remember and apply repetitively. The automatic approach furthermore decreases the likelihood of human error and the small quantity of manual tasks and thereby more availability for other laboratory work adds to the subjective satisfaction.

Previous studies have highlighted that automating tasks allows staff to reallocate saved time to more intellectually stimulating and value-added activities, enhancing overall productivity and staff morale.[15] Considering these factors, the Oncore Pro X assay demonstrates superior usability compared to the manual ZytoVision assay, making it the preferred choice when prioritizing the usability aspects.

Other observations

Fading green signals

When enumerating signals on slides with automatic FISH performed using Oncore Pro X observers noted a fading of the green signals (CEN7-signal). This did not pose an issue with parallel slides that had manual FISH performed as the signals on the slides remained stable. Enumeration of signals on slides with one of the signals being less clear than the other could result in a skewed ratio between the two. Consequently, weak green signals in the

automated Oncore Pro X assay may attribute to a falsely higher level of MET-amplification, which could ultimately result in a more aggressive form of treatment for the patient.

Consequently, enumeration of signals with automatic FISH had to be performed within a certain time frame to ensure reliable results, which also meant that slides might not be suitable for repeated viewing on the microscope. This could pose the risk that if someone needed to go back and recount the slide this could potentially not be an option-preventing recounting. In cases where a recount is vital this could mean a longer process time since a new slide would need to be prepared and analyzed or the patient would need to have a new sample collected in cases where excess specimen was no longer accessible.

Limitations

This study was conducted over the course of approximately five weeks which meant that a sample size of >30 could not be obtained due to the short time frame.

Furthermore, it was only possible to obtain numerical data from 14 samples total due to a change in national counting procedures, which meant that samples could not precede 2023.

This low number of samples also meant that only a single sample exhibited an intermediate level of MET-amplification (category B). Therefore, future studies on the capabilities of the automated system Oncore Pro X should be based on a wider range of levels of MET-amplifications along with a larger number of samples in general.

Conclusion

This comparison between the manual ZytoVision assay and the automated Oncore Pro X using MET/CEN7 parameters demonstrated a substantial overall agreement of 80%. While minor discrepancies in amplification levels were observed in 4 out of 20 cases and did not influence patient treatment decisions. The Bland-Altman plot revealed a slight trend towards higher MET/CEN7 ratios in the manual assay, though the small sample size limits definitive conclusions.

In addition to assay agreement, key operational factors were considered, including turnaround time, hands-on time, chemical exposure, probe variety, cost per slide, and usability. The Oncore Pro X assay significantly reduced turnaround time to 5.5 hours compared to approximately 24 hours for the manual ZytoVision assay, potentially allowing for faster treatment decisions. Automation also minimized hands-on time, improved efficiency, and streamlined workflow.

However, the Oncore Pro X system is limited by the availability of only 13 probes, compared to 188 probes for ZytoVision, potentially restricting its use in comprehensive testing. Additionally, the higher cost per slide (972.2 DKK for Oncore Pro X vs. 621.85 DKK for ZytoVision) presents a financial consideration.

These factors should be carefully weighed when considering the adoption of the automated system as a replacement for the manual gold standard in specific laboratory settings. Nevertheless, the Oncore Pro X demonstrates comparable diagnostic accuracy to the manual ZytoVision assay and offers significant operational advantages, suggesting strong potential for adoption in laboratories where these factors align with institutional needs.

Disclosure

The authors have no conflicts of interests to declare.

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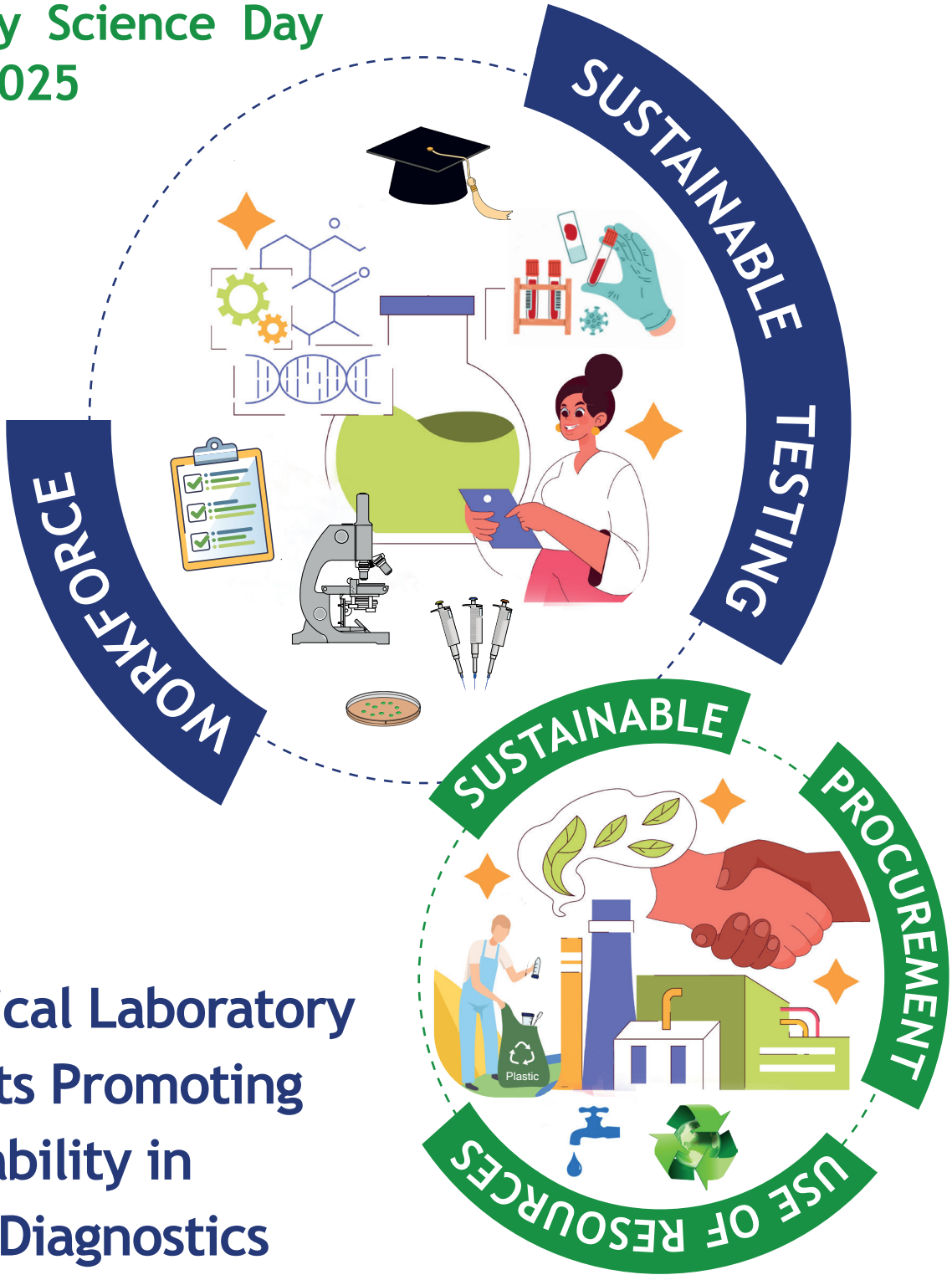

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