

## Guidelines and Recommendations

Josep Queraltó, Jennifer Brady, Anna Carobene, Evgenija Homšak and Gijsbert Wieringa\*

# The European Register of Specialists in Clinical Chemistry and Laboratory Medicine: code of conduct, version 3 – 2023

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**Abstract:** Whilst version 2 focussed on the professional conduct expected of a Specialist in Laboratory Medicine, version 3 builds on the responsibilities for ethical conduct from point of planning to point of care. Particular responsibilities that are outlined include:

- The need for evidence when planning a new service, providing assurance that a new test does not do harm
- Maintaining respect for patient confidentiality, their religious/ethnic beliefs, the need for informed consent to test, agreement on retrospective use of samples as part of governance envelopes in the pre-analytical phase
- Ensuring respect for patient autonomy in the response to untoward results generated in the analytical phase
- Supporting the safety of patients in the post-analytical phase through knowledge-based interpretation and presentation of results
- The duty of candour to disclose and respond to error across the total testing process
- Leading initiatives to harmonise and standardise pre-analytical, analytical and post-analytical phases to ensure more consistent clinical decision making with utilisation of demand management to ensure more equitable access to scarce resources
- Working with emerging healthcare providers beyond the laboratory to ensure consistent application of high standards of clinical care

\*Corresponding author: **Gijsbert Wieringa**, European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), Via Carlo Farini 81, 20159 Milan, Italy, E-mail: [eflm@eflm.eu](mailto:eflm@eflm.eu)

**Josep Queraltó**, SEQC<sup>ML</sup> – The Spanish Society of Laboratory Medicine SEQC<sup>ML</sup> Barcelona, Spain

**Jennifer Brady**, Department of Paediatric Laboratory Medicine, UCD School of Medicine, Children's Health Ireland (CHI) Dublin, Ireland

**Anna Carobene**, Laboratory Medicine Department, IRCCS San Raffaele Hospital Milan, Italy

**Evgenija Homšak**, European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Milan, Italy

In identifying opportunities for wider contributions to resolving ethical challenges across healthcare the need is also highlighted for more external quality assurance schemes and ethics-based quality indicators that span the total testing process.

**Keywords:** clinical efficacy; ethical conduct; Specialist in Laboratory Medicine; total testing process.

## Introduction

Whilst version 2 [1] focussed on the standards of personal conduct, attitudes and behaviours expected of Specialists in Laboratory Medicine version 3 focusses on their contributions and responsibilities for ensuring ethical conduct in the practice of laboratory medicine. Although a specialist may not have direct clinical responsibility for a patient, his/her ethical responsibilities extend to that patient whether in the pre-analytical, analytical or post-analytical phase. In taking that responsibility the specialist brings a knowledge, skills and competence base that goes beyond the laboratory guiding colleagues on ethical approaches in diagnostic testing that reflect the moral values and laws/regulations of his/her society. Given the multi-cultural and multi-ethnic backgrounds amongst the 40 European member states with professional societies affiliated to the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) the examples of ethical challenges presented here may prompt different responses from different populations.

Precedents for codes of conduct, consent and conditions emerged after the second world war in the Nuremberg Code (1947) which laid down 10 standards to which physicians must conform when carrying out experiments on human subjects [2]. Shortly thereafter the Geneva Declaration [3] reaffirmed the physician's Hippocratic oath of dedication to the humanitarian goals of medicine. In drawing the two together the Declaration of Helsinki (1964) set the ethical principles of the right to self-determination and informed consent when participating in human research [4]. In subsequent revisions concepts such as patient well-being

prevailing over the interests of science and society emerged; the need for written consent; the role of research ethical committees; the use of placebo; ensuring greater access to benefits of research. Following exposure [5] of *The Tuskegee Study of Untreated Syphilis in the Negro Male* in which consent to participate was not sought the United States-led landmark Belmont report [6] identified 3 core principles for the protection of human subjects participating in biomedical and behavioural research:

- “Respect for persons” (protecting the autonomy of all people; treating people with courtesy and respect)
- “Beneficence” (the philosophy of “Do no harm” while maximizing benefits of research and minimizing risks to the research subjects)
- “Justice” (ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly and equally).

In bringing together a substantial proportion of the biomedical scientific community through its member organizations The Council for International Organizations of Medical Sciences (CIOMS) was established jointly in 1949 by the World Health Organisation and the United Nations Educational, Scientific and Cultural Organization with the overarching aim of advancing public health through guidance on health research including ethics, medical product development and safety [7]. The extensive revisions in their guidance that have since taken place perhaps reflect the voluntary nature of international codes and different perspectives on ethical conduct. This may be of particular relevance when considering and comparing possible responses to case studies across Europe where nation-based values and legislation may sometimes supplant such consensus guidance. Whilst this paper sets out ethical challenges in supporting patients before, during and after analysis of their sample, it also emphasises wider responsibilities supporting people and society in their access to laboratory medicine services.

## Ethical issues in planning new services

### Screening and case finding

Because they affect large numbers of people, screening and case finding programmes are amongst the most hotly debated topics in medical ethics. In Wilson and Jungner’s original principles there should be a suitable test or examination; the test should be acceptable to the population; there should be an agreed policy on whom to treat as patients; and there should

be an accepted treatment for patients with recognized disease [8]. A key contribution and responsibility for the Specialist in Laboratory Medicine is to understand the value and the limitations of the test and to use this knowledge in guiding planning. For example, in ultrasound/biomarker-led Down’s syndrome screening the decision as to where to set “cut-offs” between “higher chance” and “lower chance” pregnancies in turn determines the false positive and negative rates. A false positive result, as well as causing unnecessary anxiety, may lead to a woman being offered an invasive amniocentesis or chorionic villus sampling, procedures associated with a 1–2% miscarriage risk; a false negative result provides false assurance and may endure an unwanted pregnancy. In planning a service knowledge of the underlying prevalence of the condition is key to understanding the negative and positive predictive values for a given population and, therefore, the ability of the test to mitigate potential risk and meet cost-benefit criteria. In this regard the diagnostic accuracy of recent advances in genetic testing technology have created openings for pilot/opportunistic screening programmes that still meet Wilson and Jungner’s original criteria and may provide cost-effective alternatives to biomarker-led programmes. As well as the shift in Down’s syndrome screening to non-invasive pre-natal testing of cell-free foetal DNA, key examples of emerging programmes include the detection of Tay-Sachs disease [9] and Cystic Fibrosis [10] where the deployment of relatively simple point mutation detection techniques has allowed a paradigm shift in parental decision making from an unknown outcome in a neonatal programme to a highly predictive pre-natal outcome that enables pre-conception, earlier intervention and/or termination decisions to be made. Such advances have raised the ethical challenge of ensuring that the shift to determining a pre-natal outcome is matched by a shift in parental counselling from supporting post-natal reactions to guiding pre-natal actions.

When Wilson and Jungner set their benchmarks in 1968 the authors never expected these to remain static. Challenges to the original criteria (for example the need for costs of case-finding to be balanced against expenditure on medical care, and for a test to be acceptable to the population) have in part been raised by ready access to advances in genetic testing technology [11]. With the rate at which new technologies and data are being generated society increasingly confronts a challenge in keeping pace with converting data into the information that assesses risks and benefits of revealing incidental, unwanted or predictive findings for which there may not (yet) be opportunities for disease prevention or treatment [12, 13]. A recent example of a negative consequence of such challenge has come with the fraud perpetrated by Theranos’ failed blood testing start-up in which inaccurate results on unvalidated technology were reported to people and patients

[14]. Governments, and the citizens who support their decision making, are therefore faced with the difficult task of managing the challenge of technology advances in the light of increasing expectations from their populations for better health, better care, and faster access to services.

Most recently the Covid-19 pandemic has required rapid, sometimes difficult decisions to be made on issues such as the allocation of testing resources, deliberation on the value of mass testing and its impact on society, whether testing should be mandatory or voluntary, and which tests should be carried out [15]. The allocation of testing resources, particularly in the early phase of a pandemic when capacity is likely to be limited, may give rise to triage challenges in balancing the needs of those who stand most to lose, the need to protect those who support them, and the societal need to gather more evidence. Whilst mass testing may provide valuable information about those most vulnerable to the virus, its direction and rate of spread, and the targeted/medical resources needed to combat the outbreak, the requirement to test may not be welcomed by individuals minimally affected by the virus whose livelihoods may be adversely affected by national directives [16]. The voluntary approach with informed consent adopted by many countries reflected an overwhelming societal wish for protection against infection and the likelihood that an obligatory approach may have been less successful in driving individual ownership in health [17]. Arguably, the same may not have been the case with a less infectious virus. Fortuitously the initial spread of Covid took place in countries with well-developed laboratory resources and with ability to invest in mass testing with innovative technologies. In this regard clinical laboratories have played key roles in guiding their governments on the value and deployment of a plethora of testing platforms that rapidly emerged ranging from (sometimes less reliable) hand held, self testing devices to central lab based, high capacity platforms. Whilst higher income countries have benefited from the opportunity to invest on behalf of their own citizens a wider responsibility emerges in sharing resources to combat this global pandemic to which all countries have been equally vulnerable [18]. The value conflicts learned during the Covid pandemic may be unique to Covid but the ethical issues and the response to them are likely to be prescient irrespective of the nature of a future pandemic.

### Ensuring clinical efficacy and evidence for an *in vitro* medical technology

To date, regulatory requirements for introducing new medical devices have been relatively weak. Whilst the European Union's (EU) CE benchmark set general safety and

performance requirements (GSPR) for a product to meet all relevant European Medical Device regulations, no clinical evidence of performance whether in screening, diagnosis, management, monitoring or prognosis has until recently been required. In a repeal of EU's 1998 *In Vitro* Diagnostics (IVD) Directive 98/79/EC, new regulations (2017/746/EU) for *in vitro* medical devices came into force on 26th May 2017 with a 5 year transition up to 26th May 2022 [19]. An *in vitro* medical "device" here describes any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body. The definition thus includes point of care and self-testing devices, companion diagnostics, and the software, for example, that predicts drug response or diagnosis/disease risk from genetic or phenotypic testing. The regulations now require manufacturers to provide clinical evidence that devices meet claimed benefits and safety. The clinical evidence may include diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, and expected values in normal and affected populations. Gathering evidence may therefore extend to the need for clinical trials with requirements for ethical oversight and scientific protocols. Whilst the repeal of Regulation 98/79/EC has not been without controversy [20, 21] the new regulations create a robust, transparent and sustainable framework that improves patient safety by requiring manufacturers' prospective clinical evidence rather than users' retrospective evidence. Special exemptions may apply to devices manufactured within health institutions (in-house devices) that are not transferred to another legal entity and whose manufacture and use is governed by appropriate quality management systems.

### The pre-analytical phase

Perhaps the phase with the most ethical challenge phase given it is almost the last step at which choices to test are taken, the pre-analytical phase is also one which preoccupies literature commentaries twice as frequently as the analytical and post-analytical phases [22]. Issues facing healthcare professionals before an examination is carried out include:

- The justification for obtaining a sample
- The need for an invasive procedure such as venepuncture and other fluid/tissue sampling procedures
- The assurance of informed patient consent

- Ensuring right patient, right tests(s), right times(s), right sample(s)
- The protection of patient confidentiality and autonomy during the sample's journey

The Specialist is a custodian of the sample and an integral contributor to assuring the patient of ethical conduct throughout its journey. For the laboratory, the “consent to test” is often implied, and for many services will be encompassed within organisational governance envelopes. The “consent to test” envelope may include:

- An *a priori* explanation of the limitations, risk and benefits of testing such that patient expectations can, as far as possible, be managed in light of the knowledge of the test's value. In this regard national frameworks and guidance may provide safety nets for both the clinician and the patient. Guiding patients in the light of an incomplete knowledge base has growing relevance in the provision of clinical genetics services where a spectrum from certainty to uncertainty may pertain depending on the investigation technique used, the level of understanding of the significance of variants, and the expertise provided in pre-test counselling. The approach to investigation of the heritable BRCA1/2 gene, for example, may take a route of searching for a limited number of known cancer pre-disposition sequences during which the number of secondary findings may provide a manageable albeit incomplete risk picture. Alternatively, a whole genome sequencing approach may identify more variants of unknown significance but possibly with less accurate overall risk stratification given the cumulative uncertainty in reaching a diagnosis and/or guiding treatment [23]. Throughout, the patient's autonomy in “The right to know” and “The right not to know” needs to be taken into consideration but balanced against the needs of societal health, economic costs and benefits.
- The retrospective use of samples for clinical and laboratory research (e.g. new method evaluation, quality assurance support). Many countries have now initiated “BioBank” projects [24] for samples that may be used for future research potentially deploying future technologies which, for example, may provide earlier diagnosis, more informed personal profiling and more accurate predictive testing. Storage of samples may therefore raise prospective ethical dilemmas such that, with the benefit of hindsight, the individual's opportunity to participate may have been bypassed when faced with a late, unwanted diagnosis [25, 26].
- Provision for proxy consent to test, for example a parent/guardian on behalf of a child not yet at an age of self-determination, an unconscious patient e.g. due to

drug overdose or aphasia as a result of dementia, stroke, severe head injury or brain tumour

- Exemption from testing on religious/ethnic belief grounds, for example refusal of a blood transfusion by Jehovah's Witnesses who believe it is against God's will to receive blood, including their own. Whilst a frequently carried ‘No blood’ card may define the response for the healthcare team the same would not apply in the absence of a card or when a decision needs to be taken on behalf of a child. Whilst Jehovah's Witnesses have fought for the right to refuse blood on behalf of their children courts across the western world do not recognise these rights as absolute and mandate their overriding right to determine children's welfare [27]. Although consistency has applied in the case of younger children, judicial inconsistency both within and across countries has arisen in the case of adolescent Jehovah's Witnesses who have argued the right to refuse medical treatment independent of their parents/guardians [28]. The inconsistencies in approach highlight the ethical dilemma a healthcare team may face in real time situations, the need for multi-disciplinary consultation and, in extremis, resorting to case law/legal jurisprudence.

## The analytical phase

Ethical considerations may arise when the laboratory unintentionally generates a test result that was not part of an initial request but which might indicate a risk to health or risk of disease that had not yet been considered by the patient's clinician. A *prima facie* example emerged in the 1990s with Apolipoprotein E (Apo E) phenotyping and genotyping techniques that provide zygosity profiles for the Apo E4, Apo E3 and Apo E2 isoforms/alleles. Test requests have historically been initiated for the detection of Apo E2 zygosity, its link to type 3 hyperlipidaemia having been known since the 1950s [29]. More recently, the link between Apo E4 and Alzheimer's disease has been extensively reported since the 1990s (E4 homozygosity is associated with a 12 fold increased risk of Alzheimer's disease) [30]. The response of many laboratories and their requesting clinicians has been to suppress E4 zygosity reporting with confidential retention of results in the laboratory unless result dissemination is separately requested. Historically, however, many patients will have been left with unwanted reports that may cause anxiety and may have consequential implications for their insurance policies and the providers of their policies [31].

The unintentional unmasking of a hitherto unsuspected agent during drugs of abuse screening in a clinical or workplace setting may pose a particular ethical dilemma

given the potential legal and social ramifications for the patient [32–34]. It dictates the need for closely defined chains of custody that include consent/authorisation policies, an understanding of the implications of methodological limitations (e.g. interference, missed substances, lack of correlation between urine concentration and effect), policies on reporting, and the clinical liaison required between all stakeholders to ensure a fair outcome [35].

More intentionally, the laboratory may initiate reflex testing in which a second line investigation is carried out on the basis of a first line result. Whilst this may offer laboratory-added value the practice may raise controversy when policy and practice has not been agreed with patients and the service's clinical users. Examples include the detection of a paraprotein on serum electrophoresis initiated following a raised total protein, the unmasking of a possible haematological malignancy on a differential film, the finding of a possible pregnancy on initiation of a serum B-hCG when LH and FSH are suppressed. Murphy [36] has highlighted the need for threshold parameters to be set beforehand with clinicians but, additionally, that the practice is in need of harmonisation given there is no consensus on the panel of tests to which reflex testing might apply nor is there consensus on the test thresholds/cut-off that should be deployed. A reflection on UK practice recently revealed a mixed picture of likely patient benefit [37].

To err is human – people make mistakes. A central tenet of the Institute of Medicine's landmark publication *To Err is Human: Building a Safer Health System* [38] is that a system-based approach of shared accountability is one more likely to motivate and support individual ethics in error disclosure (e.g. whether due to technology error, personal disregard, fear of disciplinary measures/litigation) than a “blame and shame” approach. In practice, error attributable to laboratory medicine is small, some estimates suggesting that the rate in the analytical phase may be less than 0.002% of the total error that may happen along a patient's journey [39]. Whilst within the total testing process analytical error may constitute 7–13%, the most frequent errors have been reported to occur before a sample reaches the laboratory (46–68.2%) and after the results have left the laboratory (25–45.5%), phases usually less under the influence of the laboratory [40]. In part driven by earlier exploration of quality and safety through service accreditation, Laboratory Medicine has a track record of instigating risk assessment, incident reporting, audit, training programmes and quality assurance systems. More recently, initiatives such as grading seriousness of errors on the basis of patient care/outcomes may help prioritise quality improvement initiatives and switch a team's focus to pro-active prevention rather than reactive intervention [40].

## The post-analytical phase

The post-analytical stage may call on specialist expertise to determine what further action, if any, should be taken on reports. Example actions might include urgent communication of results when patient safety/management might be compromised, initiation of further investigations, addition of interpretive comments/reflective testing. Reflective testing (often in conjunction with reflex testing) is widely seen as an opportunity to add value [41, 42] that is welcomed by patients. In protecting patients' safety assurances should be sought that such “added value” contributions are provided by individuals with the knowledge, skills and competence that is appropriate for the undertaking. In many countries this may be demonstrated through awards/qualifications, recognition of competency through registration schemes and/or statutory regulation in which standards of practice and scope of practice are defined. Assurance of ongoing ability may typically be sought through evidence of continuing professional development, participation in external quality assurance schemes for results interpretation. Increasingly, also, schemes are being established for revalidation of practice (including, for example, assessment of appraisal records, feedback from patients/colleagues, learning lessons from significant events, reflections on personal practice). In the absence of statutory/mandatory infrastructures local decisions within wider governance envelopes (at within organisation, regional, national or international level) may pertain, the recognition of Specialist in Laboratory Medicine practice measured against key standards of knowledge, skills and competence by the European Federation of Laboratory Medicine providing a key example of a currently voluntary register that also acts as a forerunner to the recognition of professional qualifications under European Union Directive 2013/55/EC [43, 44]. Throughout, the evolving infrastructures signal the ethical expectation that patients' safety be protected.

In a reflection of changing times, the principle of patients having the right to view online, download, print and share their health information is increasingly accepted as part of a digital health age and is enshrined in law in some countries [45]. Indeed, patients are being encouraged to use their health information to manage their health and their providers being expected to offer online access to that information. In the European Union (and United Kingdom) the principle builds on rights enshrined in General Data Protection Regulations (GDPR) that people have access to their personal data. As such laboratories may now face the challenge of directly conveying results in the absence of a wider picture traditionally sought through a patient's clinician. In practice the challenge may prove a “double edge sword” by empowering the laboratory to take a more direct role in patient care and recent surveys

across Europe suggest patients welcome such direct support [46]. Patient care may in turn be enhanced: failure to follow up on community and out-patient test results has been reported to occur at anything between 6.2% and 62% with implications for delayed diagnosis, otherwise avoidable hospital admission and adverse drug reactions [47]. Direct access may also enable faster support, in turn allaying anxiety and encouraging greater engagement in clinical care [48]. In providing direct access alternative ways of presenting reports may need to be considered. Reference ranges prove a challenge to many people [49]. Rather, colour coded charts annotated with appropriately worded interpretive comments and hyperlinks to further information have been shown to add value in a number of studies [50, 51].

## Discussion

Ethical dilemmas occur when an issue challenges individual and societal values. They are characterised by the need to make a decision when faced with choice of more than one action for which a personally held standard or value may be compromised. In healthcare the challenges include the balance between patient autonomy and patient safety (respect), the need to act in the best interest of the patient (beneficence), and the obligation to treat people fairly and equally in terms of benefit. Whilst examples have been presented from pre-analytical, analytical and post-analytical phases, the principles cut across the total testing process. The authors' intent is to highlight the diversity of circumstances and situations the specialist in laboratory medicine may come across and their opportunities to contribute to reaching outcomes. The intent also is to highlight opportunities to avert ethical challenges before they arise. The need for greater harmonisation and standardisation across laboratory medicine has been variously highlighted as a key means for ensuring more consistent clinical decision making, better patient protection and more equitable access to resources [52–54]. The need comes at a time of universal shortfalls amongst an internationally transient healthcare work force faced with differing approaches to service provision [55]. The reasonable expectation of patients and clinicians is that a test carried out in one laboratory should give the same result in another laboratory and is interpreted in the same way. Some ongoing initiatives have recently been summarised [56]. Pre-analytically, opportunities include the harmonisation of test request formats, patient identification and preparation protocols, and sample transport systems [57]. In the analytical phase, there is an *a priori* need to standardise

those assays linked to diagnosis, patient management options and treatment eligibility thresholds [58]. Post analytically, taking opportunities to unify reporting units, harmonising fit-for-purpose reference ranges and reaching consensus on results interpretation [36, 37, 59]. Throughout all phases, ensuring appropriate test utilisation, challenging inappropriate use, and instilling demand management to encourage better use of scarce resources [60]. As measures of success the need to establish more external quality assurance schemes and quality indicators that focus on harmonised practice across the total testing process [61–63].

Beyond the laboratory, diagnostics are seen as key catalysts in taking care closer to home, reducing hospital admission, encouraging greater interest in individual health and supporting self-management. In working with new and emerging providers of direct-to-consumer diagnostics new responsibilities emerge for the specialist: shaping end points with stakeholders beyond and within the healthcare sector such that the outcome is better health and best care; ensuring the application of local, national, international clinical standards; ensuring seamless comparability of practice by integrating digital solutions into current healthcare systems; recognising the need for data and confidentiality guardians; building solutions that mitigate errors within and across partners; ensuring the provider-patient dynamic is preserved through local stakeholder engagement [64]. Such principles equally apply to emerging opportunities to apply artificial intelligence-driven solutions whether as research or quality management tools in the laboratory or at the point of care in algorithm-led/machine learned diagnostics pathways [65]. Here, a particular challenge is ensuring ethical conduct in the deployment of artificial intelligence-driven solutions and machine learned protocols when enforcing national/international regulatory frameworks and legislation are not yet in place [66, 67].

## Summary

Whilst Specialists in Laboratory Medicine may not have direct contact with patients they have a duty to safeguard them and protect their autonomy. This review underlines their ethical responsibilities from the point of planning new services to their responsibilities across the total testing process, and then beyond the laboratory at the point of care to ensure that people, patients and healthcare professionals have safe, equitable, valuable and informed access to services that make best use of scarce resources. The emphasis is on leadership and the opportunities for specialists to contribute.

## Note

During the preparation of this paper, we learned of the passing of our highly valued friend and colleague, Josep Maria Queralto, a man of integrity, humility, high values and standards who took the initiative to start the manuscript. His wise contributions to EFLM will be greatly missed.

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