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Ensuring Consistent European-Wide Urological Care by the Use of Evidence-Based Clinical Practice Guidelines: Can We Do Better?

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Abstract
The European Association of Urology (EAU) annually updates 21 clinical practice guidelines in which summaries of the evidence base and best practice recommendations are made. The methodology applied to achieve this and integrate stakeholder opinion is continuously improving. However, there is evidence to suggest wide variation in clinical practice indicating that many patients receive suboptimal and heterogeneous care. Studies from certain countries suggest that 2 out of 5 patients do not receive care according to the current scientific evidence, and in 1 out of 4 cases the care provided is potentially harmful. Clearly, the harmonisation of care in alignment with evidence-based best practice recommendations is something to strive for. Development of robust methods to disseminate and implement guideline recommendations and measure their impact is an objective the EAU is committed to improving. An important strategy for achieving harmonisation in urological care across Europe is to ensure the availability of high-quality clinical practice guidelines and to actively promote their implementation by clinicians and healthcare providers.

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Introduction

Urological diseases, both oncological and benign, are highly prevalent medical conditions affecting virtually everyone at some stage in their lives. They affect the prostate, bladder, kidneys, and genitalia impacting not only patient life expectancy but also quality of life. The most prevalent oncological conditions include prostate, bladder, and kidney cancer. Together, these cancers represent roughly a third of all malignancies diagnosed in men [1].

Prostate cancer is the most common cancer diagnosed in men in Europe and the third commonest cause of death from male cancer in Europe, representing 1 out of 10 of all cancer deaths in men and corresponding to 71,000 deaths in Europe alone in 2012 [2]. Prostate cancer healthcare costs were estimated at EUR 8.43 billion per year in the EU in 2009 and accounted for 7% of all cancer costs in Europe [3].

Bladder cancer is the fifth commonest cancer when all cancers in both sexes are considered collectively. Bladder cancer was diagnosed in 124,000 people and accounted for approximately 40,000 deaths in Europe, in 2012 [4]. Healthcare costs related to bladder cancer in Europe were EUR 4.9 billion in 2012 and accounted for 3% of all cancer costs, although this is likely to be an underestimate given the recurrent nature of the disease necessitating frequent hospital admissions. Of note, the 5 most populous countries (i.e., France, Germany, Italy, Spain, and UK) accounted for 73% of all costs [4]. Productivity losses and informal care represented 23 and 18% of bladder cancer costs, respectively.

Kidney cancer is the seventh commonest cancer, occurring in both sexes and accounting for 115,000 cases in Europe in 2012 [2] and causing more than 12,000 deaths annually. Currently, there is no up-to-date cost estimation for kidney cancer healthcare costs in Europe, but in the US kidney cancer costs approximately USD 38,000 per patient in the first year after diagnosis and USD 6,000 per year thereafter.

In terms of benign urological conditions, the two most prevalent conditions are urinary incontinence and urinary tract infections. The prevalence of urge urinary incontinence was estimated to be approximately 30% in the European population [5]. A 2005 multinational study found that the annual direct cost of illness estimate for urge urinary incontinence in Canada, Germany, Italy, Spain, Sweden, and the UK was EUR 2 billion on average per country [6].

A survey conducted by the World Health Organization showed that 2.4 million European patients suffer hospital-acquired infections every year. Community acquired urine infections account for approximately 4 out of 10 hospital acquired infections and are directly responsible for the deaths of 30,000 people in Europe annually. The associated annual direct cost for managing community-acquired urine infections is approximately USD 2 billion per country across Europe [7]. In addition, growing antimicrobial resistance is estimated to cause approximately 25,000 deaths each year across Europe, and over EUR 1.5 billion in healthcare expenses and productivity losses [8].

Importance of Clinical Practice Guidelines

Healthcare strongly depends on the translation of scientific evidence into clinical practice guidelines (CPGs) to ensure patients receive the best possible care. CPGs are defined as "statements that include recommendations intended to optimise patient care that are informed by a systematic review of scientific evidence and assessment of the benefits and harms of alternative care options" [9]. There is an established body of evidence showing that the use of guidelines:

- improves practice in terms of quality and outcomes of healthcare [10];
- optimises healthcare results by encouraging interventions of proven benefit and discouraging ineffective interventions [11–13];
- improves the consistency of healthcare, promoting homogeneity in levels of care for similar clinical problems independently of the healthcare professional, institutional setting or country [14].

In the era of personalised medicine, guidelines empower patients to make more informed healthcare choices and to consider their personal needs and preferences when selecting the best treatment option for them. Furthermore, evidence-based guidelines can demonstrate the most pressing knowledge gaps as well as previous research flaws, redirecting research questions and shaping the policies of funding agencies. Ultimately, healthcare systems, governments, and private insurers depend on guidelines to optimise the effectiveness and cost-effectiveness of healthcare [15, 16].

Variation in Practice and Consequences of Non-Adherence to CPG

Adherence to national and international guidelines is suboptimal throughout Europe [17–19]. This is particularly true when considering urological diseases. In fact, despite the availability of comprehensive urological guidelines based on standardised and high-quality methodology, a significant gap currently exists in terms of their application and use in clinical practice.

For example, when considering adherence to the European Association of Urology (EAU) guidelines on the prescription and use of androgen deprivation therapy (ADT) in Italian men with prostate cancer, approximately 1 out of 4 patients received ADT when this was not recommended by evidence-based guidelines [18]. This, in turn, increased the risk of short- and long-term side effects, and the costs related to disease management. In fact, the costs related to the inappropriate management of localised prostate cancer in relation to radiological imaging alone is reported to be in excess of EUR 5 million per year in Italy alone [18].

Another example pertains to the management of low-risk non-muscle invasive bladder cancer (NMIBC) which requires the use of intravesical chemotherapy after surgical resection, as recommended by the EAU NMIBC guidelines [20]. This treatment has a proven therapeutic role in significantly reducing bladder cancer recurrence rates and delaying time to recurrence [21]. However, numerous studies in the US and in Europe have reported that despite clear guideline recommendations advocating use of intravesical chemotherapy, adherence to these guidelines is low and varies widely, with estimates ranging from 0.33 to 28.4% in the US [22, 23], and from 22% (France) to 71% (UK) in a sample of 5 EU countries (mean 43%) [24]. The consequence of such non-adherence is increased bladder cancer recurrence and increased cost for management of recurrence [25, 26].

There are also similar concerns regarding non-adherence to non-oncological guidelines in urology. A study conducted to assess adherence levels to the Guideline on Urinary Incontinence of the Dutch College of General Practitioners found that approximately only a third of surveyed clinicians complied with treatment recommendations [27].

Similarly, when considering urinary tract infections, significant variation exists in the use of antibiotic prophylaxis before urological procedures between countries, regions, and types of hospitals [28]. Antibiotic prophylaxis usage varied from 86% in Asia to 67% in Europe. These variations are significant given recent evidence highlighting that adherence to EAU guidelines on antibiotic prophylaxis would reduce antibiotic use without increasing the rate of postoperative infections [17]. Moreover, interventions aimed at increasing adherence to

guidelines on antibiotic prophylaxis would eventually reduce the prevalence of multi-resistant bacteria [17] and would therefore be associated with potential significant cost savings.

Taken together, these data highlight that there is still wide variation in clinical practice and that adherence to guidelines is suboptimal in several settings. Ultimately, the lack of widespread adoption of guidelines has detrimental effects on patient outcomes and increases costs for healthcare systems [17–19, 29, 30].

Reasons for Variation in Practice and Non-Adherence to Guidelines

Guidelines are ideally informed by systematic reviews of the evidence, and those systematic reviews are in turn informed by primary research of treatment effectiveness. A major hurdle for conducting systematic reviews occurs when outcomes are not defined, measured, and reported in the same way and at the same time point across the included studies. This heterogeneity means that synthesising and creating meaningful and impactful evidence summaries is often difficult in urology [31, 32]. For guideline panels, it is difficult to make strong recommendations for or against clinical care practices in the most transparent way because they must rely on suboptimal summaries of the evidence. Furthermore, it is unclear which of the variety of outcomes reported in primary research and guidelines are important to all stakeholders.

This highlights another limitation in relation to guidelines which is, that guideline panels are often limited to those with clinical and methodological expertise. The voice of the other stakeholder groups in the design and delivery of healthcare (e.g., patients, carers, charitable organisations, and industry) is often missing from these discussions. Given the emphasis on patient-focused outcomes and the need for guidelines to be responsive to stakeholder needs, strong arguments exist for the inclusion of all of the key stakeholder groups in the guidelines development process [33]. Achieving true stakeholder engagement in the Guidelines development, delivery, and implementation process will:

- guarantee that all stakeholders have confidence in the guidelines development process and as such the resulting recommendations;
- ensure that the recommendations are appropriate, achievable, and can be translated into corresponding health behaviour leading to better treatment compliance and better health outcomes;
- result in recommendations and guidelines which facilitate person-centred care.

The need for a model that facilitates the effective engagement of all key stakeholders in healthcare delivery as well as the need for evaluation to be built into any process of stakeholder engagement to establish the value of this approach has been highlighted [34].

In addition, guideline developers need to ensure that guidelines have a clear structure and local applicability in order for guidelines to be useful in different settings and healthcare systems [35, 36]. Although guidelines have the potential to improve care by promoting effective interventions and discouraging ineffective ones, publication of guidance alone is unlikely to optimise practice [37]. Development of guidelines must be supported by an effective dissemination and implementation strategy. Dissemination should be an active process in which tailor-made information is actively imparted to the appropriate audience [36, 38]. Effective implementation of guidelines involves the identification of barriers to knowledge transfer, or, more importantly, the identification of the optimum interventions to limit or overcome such barriers, ensuring that the most appropriate treatments are targeted at and delivered to patients who will benefit the most, allowing for the optimisation of healthcare resources whilst eventually improving patient outcomes [36].

The EAU have successfully developed an effective mass dissemination platform through Twitter [39]. The EAU Twitter platform has also been used to estimate adherence to EAU guidelines recommendations.

Finally, the gap between evidence-based recommendations and evidence-based care may be due to barriers that exist at different levels within healthcare systems including structural (e.g., financial disincentives), organisational (e.g., inappropriate skill, lack of facilities or equipment), peer group, professional, and cognitive barriers. Differences among how healthcare systems are paid for and administered [3], as well as differences in clinician and patient profiles, represent some of the reasons for the lack of uniformity in the adoption of guidelines and evidence-based recommendations [19, 40]. The EAU Guidelines Office "IMAGINE" project (IMpact Assessment of Guidelines Implementation and Education) has been developed to effectively tackle the issues of non-adherence and implementation with the ultimate goal of ensuring all patients across Europe receive the best evidence-based standardised care [41, 42].

Why Should We Improve CPG Adherence?

If evidence-based best practice recommendations are not disseminated effectively and knowledge is not actively transferred, variations in practice are likely to occur. Where variations in practice occur, healthcare is unequal within nation states and across European Member States, and health systems may most likely be inefficient. Furthermore, if all stakeholders, including patients, are not meaningfully included in consultations to prioritise research areas, to determine which outcomes are the most important, and to ensure recommendations are phrase appropriately, then they are denied informed shared-decision making.

Therefore, there is an urgent need to harmonise clinical practice throughout Europe, and guidelines are the ideal tool for doing so. The key to this is to ensure the availability of high-quality European-wide guidelines, which are robustly established, fit for purpose and comprehensive. The EAU guidelines are an excellent demonstrator model for achieving harmonisation across all EU Member States. It is fundamentally important that such guidelines have a high degree of visibility, uptake, and adherence by clinicians and healthcare providers. Whilst the EAU guidelines are now endorsed by all EU Member States, European Union/European Commission endorsement would undoubtedly increase the recognition of the importance of guidelines in general, as well as their visibility, dissemination, and implementation. There is a responsibility to formally assess the impact of more effective implementation of guidelines EU wide because current (albeit limited) evidence suggests that the benefits would be: (1) harmonisation of patient management across the EU Member States; (2) a reduction in unnecessary costly diagnostic and therapeutic approaches; (3) optimisation of healthcare resources; and (4) improving patient outcomes.

If this integrated model for the development, dissemination, and implementation of European-wide guidelines for urology could be achieved the potential for other clinical areas to apply this cohesive model would be promising, with the prospective overwhelmingly positive impact on harmonisation and a far more effective healthcare provision in Europe.

Disclosure Statement

Emma Jane Smith certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript are the following. All authors are involved in the guidelines production process

of the European Association of Urology (EAU) Guidelines; James N'Dow, Anders Bjartell, Alberto Briganti, Thomas Knoll, Tillmann Loch, Maria J. Ribal, Richard Sylvester, and Hein Van Poppel sit on the EAU Guidelines Office Board; Richard Sylvester chairs the EAU Guidelines Methods Committee of which Steven MacLennan is a member; Emma Jane Smith is a member of the EAU Guidelines Office.

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