Screening Programs for Lynch Syndrome in Italy: State of the Art and Future Challenges

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Colorectal cancer (CRC) is the third leading cause of cancer death worldwide, accounting for 774.000 deaths in 2015 [1]. The estimated annual worldwide incidence of CRC is 1.4 million new cases and, of which, approximately 3-5% will have Lynch syndrome (LS) [2]. When applying this frequency to the Italian prevalent cases of CRC, it can be estimated that in our country almost 9,000 cases have LS.

LS, previously known as hereditary non polyposis colorectal cancer, is an autosomal dominant disorder caused by mutations in DNA mismatch repair (MMR) genes that have the role to maintain genomic integrity during DNA replication. Inactivation of MMR genes causes an increased mutation rate (genomic instability) and a microsatellite instability [3].

LS has an estimated prevalence in the general population of 1 in 440 [4], and is characterized by an increased risk for CRC (life-time risk: 54–74% males and 30–52% females) and extracolonic cancers, including endometrial (life-time risk: 28–60% females) and ovarian cancer [5].

Intensive cancer surveillance has been shown to reduce CRC incidence and related mortality in individuals with LS [6]. Current CRC screening recommendations include colonoscopy every 1–2 years beginning at age 20–25 years [7]. Annual transvaginal ultrasound of the uterus and ovaries and endometrial sampling are also recommended, although efficacy remains to be documented as does the utility of screening for other LS cancers. Furthermore, evidence supports the efficacy of prophylactic surgery, and guidelines suggest offering this surgery as an option for women with LS [8]. Additionally, epidemiological data shows that regular, long-term aspirin use reduced incidence and mortality due to CRC [9], and the highest impact of chemiopreventive strategies is expected in patients with defined hereditary predisposition as LS [10].

Since recognition of LS and related implementation of appropriate cancer surveillance strategies can reduce morbidity and mortality from cancer, the interest on LS identification through screening programs has been increasing, as underscored in one of the agenda items in Healthy People 2020: *"Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome"* [11].

In the last years, different international guidelines prompted the universal LS screening for all newly diagnosed CRC patients [3, 12-14], regardless the age or the clinical criteria. The tumor screening is performed through immunohistochemistry (IHC) staining or the microsatellite instability (MSI) molecular testing, two laboratory procedures with comparable sensitivity and specificity [15]. A positive screening test is followed by genetic counseling and germline testing for MMR mutations to establish the diagnosis of LS.

Moreover, it has been shown that universal tumor screening is also cost effective versus no screening, because it allows to reduce the costs related to morbidity and mortality from CRC from the early identification of LS-carriers among family members [16].

However, the implementation of the guidelines at a universal CRC scale requires a multidisciplinary and multiprofessional approach that might be not feasible in all clinical contexts. Furthermore, genetic services are not always established as part of diagnostic and therapeutic pathways in the EU Member States, and in resource-limited settings, a universal tumor screening

could be hardly achievable. All these issues contribute to the great variability in the practice and recommendations about LS screening [17].

In this framework, the Italian Ministry of Health is strengthening the efforts to implement adequate diagnosis and management programs of the highly penetrant hereditary forms of cancers within the National Prevention Plan 2014-2018 [18]. In order to support decision-makers with a feasible approach toward setting health priorities, we are currently revising the published diagnostic pathways for LS performed internationally and assessing the cost-effectiveness of different testing strategies to identify LS from the Italian National Health Service perspective.

To date, no organized screening pathways are in place in Italy to identify LS, nor economic evaluations in the Italian context have been reported.

The cost-effectiveness analysis is ongoing, but the preliminary results revealed that universal testing for all newly diagnosed CRC patients versus no testing is cost effective.

In conclusion, the crucial point, now, for LS screening has shifted from "could we" to "how can we" implement it. Its feasibility has been demonstrated in research, but coordinated efforts in educating all key stakeholders and addressing public concerns are necessary to ensure that public health needs are satisfied through appropriate and sustainable healthcare services.

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