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# Hereditary or sporadic polyposis syndromes

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A B S T R A C T

Polyposis syndromes are encountered in endoscopy practice, and are considered rare entities, accounting for ≤1% of colorectal cancer. Polyposis can occur within inherited syndromes or as "sporadic" cases of unknown etiology. Their proper characterization is relevant for patient management, and should nowadays drive appropriate genetic tests which have a key role in clinical practice for driving surveillance and colorectal cancer prevention, enlarged to relatives. Polyposis classification is based upon polyp number and histology, familial and personal history. This review will explore the polyposis nosology and their genetic determinants in the emerging scenario of Next Generation Sequencing which allow testing multiples genes in parallel. This capability will likely continue to increase the range of polyposis predisposing genes, contributing to define new clinical entities.



## Introduction

Colonic polyps can present as part of inherited polyposis syndromes in which their number varies greatly according the type of gene damage, and clinical pictures of multiple polyps are often encountered, in clinical practice, yet the term polyposis is largely misused. We come from a culture telling us how frequent polyposis is the soil for colorectal cancer (CRC) development that returns a figure ≤1% in our conventional cultural background [1–3]. Yet how frequently is polyposis encountered in endoscopy practice, nowadays? Can we draw an estimate of polyposis frequency in the era of screening? It is difficult to draw such picture, as also emerging entities add low numbers (most recent data bring up a prevalence ≪1% for serrated polyposis in screening populations), while standards for detection and histopathology reports may vary [4–6]. Overall, we continue to base most of our frequency estimates on *post hoc* evaluations based upon cancer development. Rather, in an evolving perspective, we should move from the encountered precancerous lesions, and then pursue the best clinical and molecular diagnoses to avoid cancer development. This gap need to be overcome; an effort than in modern era will require connecting different types of data. Such data should encompass individuals having an established diagnosis of inherited predisposition and their relatives, those who underwent genetic testing (and the reason why) without conclusive results, individuals that for their phenotype at colonoscopy (plus other features) are amenable to genetic testing [7]. It would be advisable that these data will increasingly become included in screening programs, yet we cannot draw a reasonable prevision of times for such a comprehensive approach.

In appropriate terms, the definition should not be applied to the occurrence of less than 10 polyps [8], otherwise better described as oligo-polyposis [9]. Polyps may occur in very large number (i.e. above 100, sufficient for clinical diagnosis), alike in florid pictures of classic familial adenomatous polyposis (FAP), or in so-called "attenuated" amounts (that is below 100), alike in attenuated FAP (aFAP). Properly reporting the number of polyps is often overruled by non-quantitative description of the polyp burden in clinical practice. Time is part of the issue, as multiple polyps should occur synchronously to meet the definition, although this represents a limitation; the incidence of polyposis based upon metachronous development remains poorly addressed [10]. Thus, endoscopy practice clearly impacts on proper case allocation, and should prompt a specialty opinion concerning appropriate molecular investigations that are seminal to a modern clinical process in defining diseases beyond phenotype and anamnestic description. It

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might appear disappointing, but this approach is still largely disregarded [11]. This perspective is instrumental to proper clinical management, including testing relatives and defining the best preventive strategy, through proper endoscopy surveillance and/or surgical management, whenever correctly specified [8].

Considering the issue from a historical perspective, phenotype discrimination was seminal in defining genetic predispositions to colorectal cancer (CRC), specifically dividing those patients in which polyposis is the main feature preceding CRC development, from those in which cancer occurs in the absence of overt polyposis. In fact, the latter scenario, that is Lynch syndrome (LS) [2,12], has previously been referred to as "hereditary non-polyposis colorectal cancer" (HNPCC), in that polyps occur (and continue to develop through carrier life, possibly evolving into CRC) not yet in the amount that identifies polyposis syndromes. This situation should not be underestimated, as the occurrence of oligo-polyposis may herald the occurrence of Lynch syndrome. Depending upon patient age, the occurrence of oligo-polyposis may thus lye at the cross-road between LS and aFAP. The issue is relevant for appropriate patient management, as the presence of given clinical pictures should nowadays prompt appropriate genetic testing, as inherent part of the clinical workup. The ordering of genetic tests not always grew alongside clinical practice, if not in academic centers with a focus on inherited CRC predispositions [13]. Gastroenterology as a specialty field has been in a peculiar situation, as its contribution to the understanding of the genetic basis of tumors has been quite relevant with respect to other branches of medicine. Recognition of classic polyposis (i.e., Familial Adenomatous Polyposis, FAP) as a model for cancer development, alongside with its peculiar bases genetically driving cancer development, could be traced back to the forties of the previous century [14]. Discovery of the molecular mechanisms of gene damage in inherited predispositions took place after decades, and was parallel to the development of the notion that a similar gene damage occurs in most sporadic cases [15,16]. So that, the study of predispositions paved the road for the concept that in molecular medicine cancer can be considered a genetic disease, either at the somatic or at the germ-line level, possibly classified by the type and amount of genetic damage [17,18]. The main difference between sporadic CRC and its predisposing syndromes resides in the fact that in truly sporadic cancer all gene damages are somatic in their nature, while individuals with an inherited predisposing trait already bear a predisposing gene damage in their germ-line DNA (often referred to as "first hit", according to Knudson model). The amount of scientific notions in the field increased enormously since the seminal era of late Eighties-early Nineties, yet knowledge gaps still exist. As to the content of the present review, the main question is as to what extent a polyposis picture can be considered sporadic in its occurrence, after genetic tests score negative for germ-line mutations. In the latter instance, we should refer to colonic adenomatous polyposis of unknown etiology [8,19], and the key point is the amplitude of available genetic tests that need to score negative to label a polyposis case as sporadic (beside family history), to explain for a polyposis picture otherwise of unclear genetic bases [20]. This is particularly relevant in the emerging scenario of next generation sequencing (NGS), which allows testing multiple genes in parallel. Assuming we can answer this issue, we are clearly going to face the next one: do exist specific (somatic) molecular defects responsible for truly sporadic cases? While in some instances, we know that specific molecular defects (i.e. Gene promoter methylation and MSI) may resemble the molecular phenotype of gene damage observed in inherited predispositions, work remains too done in this area [21].

At any event, the current era is marked by an acceleration of molecular genetic testing into the real world of clinical medicine, after years of engine warm-up, also driven by patients awareness linked to media coverage of "faulty genes", as exemplified by the Angelina effect [22–25]. Accordingly, we need to endorse genetic testing as an integral part of clinical management, as NGS helps to bring up new genetic entities, meanwhile trying to avoid over-interpretation, over-diagnosis, and potentially overtreatment [26].

## Polyposis syndromes: a multifaceted problem

Polyposis syndromes can be approached under several perspectives, each having its own methodological bases. In framing a case of polyposis, one should consider: polyp number and histology, familial and personal history, which are clue to the potential inheritance pattern, and the gene changes therein more likely to be pathogenic. Having in mind these components of the puzzle largely helps to solve it, alike fixing a Rubik cube (Fig. 1). Obviously, different situations may occur, some more frequent, while others, although having been for a long time on text-book pages (let say Peutz-Jeghers syndrome to make a simply perceived example), are exceedingly rare.

The relevant point is that inherited predispositions to cancer have often being perceived by clinicians as a grey area, marked by uncertainty and a some-how anecdotic nature [27] as opposed to the high technicality required by genetic analyses and interpretation. In medical reality, this view is likely going to be swapped by the up-surging use of diagnostic tests for inherited predispositions to cancer (not only to CRC) that parallels the diffusion of genetic tests into daily clinical practice. As knowledge increases in couple with technology, more and more tests will become available for clinical use, and costs will progressively to go down, leading to their dissemination. It remains true that the laboratory competence required to face the issues coming with inherited cancer predisposition requires clinical and molecular genetic backgrounds that need to be made broadly available to build bridges rather than gaps to implement the management of clinical problems. Costs and competence have clearly been a problem contributing to enlarge the gaps between clinicians and field specialists. While it is easily advocated that a multidisciplinary approach would help to fix problems, it likely will not. Only dissemination of a different culture in the clinical arena will, increasing the awareness that genetic background is part of the cultural heritage of a modern clinician. In an era facing exponential development and diffusion of technology, genetics will continue to pave the road to cancer understanding and better clinical management [18,28].

It remains that the field of predispositions to gastroenterological malignancies has been a major player in contributing to relevant discoveries, becoming a cornerstone in making genetic an integrating part of oncology, thus spreading knowledge that integrates the molecular bases of diseases in their management in the daily clinical practice (Fig. 2).

However, it should not be oversimplified that generating more data will lead *per se* their easier interpretation. As an example, contemplate that the more patients we investigate by NGS sequence, the more information we obtain, including incidental findings associated with variable risks [29], and variants of uncertain significance (i.e. VUS) [30]. Overall, the prevalence of such variants may account for up to more than 15% of series sequenced by using multi-gene panels [30]. Under this respect, it should be considered that this has always been an arduous challenge for researchers, physicians and consultants involved in the field. So that, the identification of hereditary polyposis syndromes implies the evaluation of the pathogenicity of VUS. Accordingly, data stratification is mandatory to progressively characterize the clinical significance of VUS. Consider that whenever a germ-line pathogenic mutation is identified in a family, a double advantage is obtained: