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ORIGINAL ARTICLE

Estimated prevalence of hereditary cancers and the need for surveillance in a Norwegian county, Telemark

ASTRID T. STORMORKEN[1], GEIR HOFF[2,3], JARLE NORSTEIN[2], INGER MARIE BOWITZ-LOTHE[4], ELDBJØRG HANSLIEN[1], ELI GRINDEDAL[1] & PÅL MØLLER[1]

[1]*Section of Genetic Counselling, Department of Cancer Genetics, The Norwegian Radium Hospital, Oslo, Norway,* [2]*The Cancer Registry of Norway,* [3]*Department of Gastroenterology, Telemark Hospital, Skien, Norway, and* [4]*Department of Pathology, Ullevål University Hospital, Oslo, Norway*

Abstract

Objective. The aim of the study was to estimate the prevalence of hereditary cancers and the need for surveillance in Telemark county, Norway. ***Material and methods***. All persons attending the Norwegian Colorectal Cancer Prevention (NORCCAP) trial in Telemark were interviewed about cases of cancer in the family. Diagnoses were verified, pedigrees constructed and families classified according to preset criteria aiming at identifying hereditary cancer. Mutation analyses were performed in kindreds at risk for breast cancers when possible. Immunohistochemistry of tumors in assumed inherited colorectal cancer families was undertaken. ***Results***. The screening examination was attended by 7224 persons among whom 2866 had cancer in the family. Of these, 2479 had no suspicion of any known inherited cancer syndrome. Family information questionnaires were mailed to 387 persons and returned by 191. Sixty-four of these 191 met the clinical criteria for familial cancer by family history after verification of diagnoses. Observed prevalences for being at risk for hereditary breast and breast–ovarian cancer (HBOC) or hereditary non-polyposis colorectal cancer (HNPCC) were 2.8‰ and 0.77‰, respectively. ***Conclusions***. The number of colonoscopies and mammograms obtained per year serving those who needed them was limited and reduced by clinical genetic work-up from 2866 with a family history of cancer to 64 proven cases. Continued surveillance of an unnecessarily high number leads to unjustified cancer worry, is costly and uses up health-care facilities. Genetic work-up is a one-time job that reduces input numbers to surveillance programs, provides a starting-point for mutation testing and is economically cost beneficial if inherited cancers are prevented or cured by the health-care programs offered.

Key Words: *BRCA1, cure, family history, genetic work-up, hereditary cancer, HNPCC, Norway, prevalence, prevention, surveillance*

Introduction

Individuals in families where cancers have occurred previously have themselves an increased risk of developing cancer. They may develop cancer at a young age (30–40 years) and have an increased risk of multiple primaries [1–6]. First-degree relatives of those affected are invited to participate in surveillance programs to provide early diagnosis and improved prognosis [7–10].

In recent years a number of genes causing susceptibility to cancer have been identified. Among these are the breast cancer genes BRCA1 and BRCA2 [11,12], and in hereditary non-polyposis colorectal cancer (HNPCC) the mismatch repair (MMR) genes MLH1, MSH2, MSH6, PMS1 and PMS2 [13–18]. Complete mutation analyses are expensive and only available in specialized centers. There is a high incidence and uneven geographical distribution of hereditary cancer in the Nordic countries owing to founder mutations [19–24].

Obtaining an accurate history of cancer in the family is the first step towards identify persons at risk. A family history of cancer may, *per se*, give a rationale for surveillance aiming at early diagnosis and treatment, and it may initiate mutation testing. This has implications for the individual persons and

Correspondence: Pål Møller, Section of Genetic Counselling, Department of Cancer Genetics, The Norwegian Radium Hospital, NO-0130 Oslo, Norway. Tel: +47 22 935 675. Fax: +47 22 935 219. E-mail: pal.moller@medisin.uio.no

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financial/capacity implications for the national health system [25].

The Norwegian Colorectal Cancer Prevention (NORCCAP) trial is a large-scale, randomized, controlled trial for prevention of colorectal cancer (CRC) performed between 1999 and 2001 in Telemark county, Norway. The aim of the present study was to estimate the prevalence of hereditary cancers and the need for surveillance.

Material and methods

In Telemark, with a population of 165,855 persons [26], a total of 10,411 men and women, aged 50–64 years, were selected randomly from the population registry and invited to have a flexible sigmoidoscopy (FS) screening examination with or without (1:1) a fecal occult blood test (FOBT) in the NORCCAP trial [27]. Two hundred and ninety individuals were excluded in accordance with preset medical criteria [27]. Forty-eight of these had CRC. The overall attendance rate in Telemark was 7224 of 10,411 (71%). Sigmoidoscopy screening was performed between 1999 and 2001 at Telemark Hospital, Skien.

In principle, we estimated observed prevalences for inherited cancer in the cohort studied. In addition, we scored the information in a "worst-case" analysis, as described below.

All persons attending for screening were interviewed by a nurse about cases of cancer in the family and a written questionnaire was completed. All persons who had one or more 1st-degree relatives with cancer diagnosed before the age of 60 or four relatives with any cancer irrespective of age at diagnosis were asked to give the Section of Genetic Counselling, Department of Cancer Genetics, The Norwegian Radium Hospital, permission to contact them for further investigation.

Classification of families

The pedigrees of all participants' families were constructed by using information from the questionnaires. All known cancer syndromes were looked for in the constructed pedigrees. Initially, the diagnoses were often unspecific. A worst-case approach was applied: for example, "abdominal cancer" was considered as endometrial cancer to meet the criteria for HNPCC [28,29] and considered as ovarian cancer to meet the criteria for hereditary breast- and breast–ovarian cancer (HBOC) [30,31]. As a consequence, some female participants were classified twice; both as meeting the criteria for HNPCC (if the abdominal cancer was endometrial) and the criteria for HBOC (if the abdominal cancer was ovarian). In males "abdominal cancer" was considered as CRC to meet the criteria for HNPCC or late onset colorectal cancer (LO CRC) [32]. In this way, the families were classified according to preset criteria aiming at detecting those with hereditary breast-, ovarian-, colon- or other types of cancer (see Table I). Families not meeting the criteria, but who were close to doing so ("HBOC-, HNPCC- or LO CRC-like" families = familial cancer) were identified. These families were also subjected to further investigations for meeting the criteria for inherited cancer.

Calculated probabilities for MLH1 and MSH2 mutations

Probabilities for mutations in the mismatch repair (MMR) genes MLH1 and MSH2 were calculated based on information in the tentative pedigrees and thereafter recalculated based on the information from the verified pedigrees. Fulfillment of the classical Amsterdam criteria I (Table I), number and mean age of CRCs in the family and presence of endometrial cancer were entered into a multivariate logistic regression model to calculate the probability of the affected patient carrying an MLH1 or MSH2 mutation [33]. A probability of 20% or higher has been proposed as a cut-off to justify germline mutation analyses in MLH1 and MSH2 [33–35]. Initially, we applied a cut-off as low as 5% to include families for further investigations.

Verification of family history

Participants belonging to families that were suspected of meeting one or more of the clinical criteria discussed above or were classified as familial cancer and/or had $\geq 5\%$ calculated probabilities for mutation in MLH1 or MSH2 were selected for further investigations. They were sent a family information questionnaire by mail and asked to supply information about their closest relatives, including names, date of birth, cancer diagnoses, year of diagnosis and hospital treatment, and date of death of the deceased. If the family questionnaire was not returned, one reminder was mailed. Once the questionnaires were returned, the site and classification of all cancers and polyps and age at diagnosis were verified in the medical files and/or in the Cancer Registry of Norway whenever possible. All verifications were subject to written consent from living relatives and from the descendants if the relatives had died. After verification of diagnoses the families were reclassified. Family members at risk were offered surveillance programs according to our ordinary health-care routines.

Table I. Clinical criteria for hereditary cancer.

A. Hereditary breast-and breast-ovarian cancer (=HBOC)
   1. Four affected family members with breast cancer who were 1st- or 2nd-degree relatives.
   2. Two affected family members with breast cancer who were 1st-degree relatives or 2nd-degree relatives related through a male, both ≤55 years of age at diagnosis.
   3. One affected family member with bilateral breast cancer ≤60 years of age.
   4. One affected family member with breast and another cancer ≤60 years of age.
   5. One relative with ovarian cancer and one relative with breast cancer ≤60 years of age, both of them being 1st-degree relatives or 2nd-degree relatives through a male.
   6. One 1st-degree relative or 2nd-degree relative through a male with both ovarian and breast cancer, the breast cancer diagnosed at ≤60 years of age.
   7. Two 1st-degree relatives with ovarian cance (Møller et al. 1993, 1999)

B. Hereditary non-polyposis colorectal cancer (=HNPCC)
   1. The Amsterdam criteria I: At least three relatives in two successive generations with histologically verified colorectal adenocarcinoma, at least one being diagnosed at <50 years of age. Familial adenomatous polyposis (FAP) excluded (Vasen et al. 1991)
   2. The Amsterdam criteria II: Extension of the Amsterdam criteria I by including cancers of the endometrium, duodenum, ureter and renal pelvis in addition to colorectal cancers (Vasen et al. 1999)

C. Late onset hereditary gastrointestinal cancer (=LO CRC)
   1. Four or more HNPCC-related cancers all diagnosed at over 50 years of age. (NGICG 1999)

Registration of colorectal cancers diagnosed in the NORCCAP screening trial

Information about CRC cases diagnosed in the screening trial was obtained and family history was re-evaluated.

Immunohistochemistry

In families with aggregation of HNPCC-related cancers, formalin-fixed, paraffin-embedded tissue sections from adenocarcinomas identified in one affected individual in each family were collected whenever possible. Immunohistochemistry for the presence of MLH1, MSH2 and MSH6 gene products was performed using standard procedures ([36,37], unpublished observations). The slides were evaluated by a pathologist (IMBL).

Mutation analyses

All families meeting the HBOC criteria were tested for the frequent Norwegian BRCA1 and BRCA2 mutations if living affected kin were available. The resources available to us did not allow mutation analyses for MMR genes. Immunohistochemistry of tumors with loss of MMR protein expression was used to increase sensitivity in order to identify HNPCC kindreds.

Estimation of observed prevalence and "worst-case" prevalence of hereditary cancer risk

Observed prevalence of at-risk persons meeting the clinical criteria for hereditary cancer was calculated by dividing the number of persons with a verified history of hereditary cancer by the total number of persons invited to the trial, assuming high compliance in persons with a family history of cancer [38]. "Worst-case" prevalence was calculated by dividing the number of persons with a suspected history of hereditary cancer by the number that actually responded and participated in the trial.

Estimation of number of persons requiring surveillance for hereditary cancer

The number of persons requiring surveillance was calculated by multiplying the observed and "worst-case" prevalence of persons having an increased risk of hereditary cancer by the number of persons in Telemark belonging to the age cohorts relevant for screening [26]. In Amsterdam positive families lifelong surveillance starts at the age of 25–30 years. Colonoscopy is recommended every second year, because of the possibly more aggressive nature of polyps associated with HNPCC [8,39,40]. In late onset hereditary CRC, lifelong surveillance is recommended every five years from the age of 40 [32]. For the calculations, we assumed surveillance until 80 years of age. The annual need for colonoscopies was calculated as the number at risk divided by the number of years between colonoscopies for HNPCC and late onset hereditary CRC, respectively. In families with HBOC, surveillance of the breasts is recommended every year from 30 years of age until 60 years of age, and from that age on the national mammography screening program is recommended [31].

Ethics and informed consent

The study was part of the NORCCAP trial. The NORCCAP protocol had been approved by the regional ethics committee. Written informed consent

was given by all NORCCAP participants before entering the trial. The medical files verifying diagnoses were obtained with written permission from all living persons, or with permission from the descendants of the deceased. Similarly, written informed consent underlay all requests for tumor specimens. Informed consent and blood samples for diagnostic mutation analyses and informed consent in writing following genetic counselling for healthy family members were obtained according to national legislation. All information obtained was approved as health care. All information was kept in our medical files. No research registry was erected.

Results

Classification of families

The Section of Genetic Counselling received 2866 completed questionnaires for participants with cancers in their families. Management of the questionnaires and the primary results are described in Figure 1. Frequencies of participants belonging to families suspected and verified as meeting the clinical criteria are presented in Table II. Among the 387 participants that were asked for more detailed family information, 46 were previously registered or belonged to families already under investigation for suspected family cancer syndromes. In all, 191 participants complied with the detailed documentation of all cancer cases in the families, giving a response rate of 49%.

Calculated probability for HNPCC

Among the responders, 29 belonged to families that met the criteria for HNPCC or LO CRC. They had a median calculated probability for mutation of 0.8% (0–14.5%) before and of 0.2% (0–37%) after verification of diagnoses. Only one participant had a probability >20% (proposed cut-off) for mutation. Among the non-responders, 49 were suspected of meeting the criteria for HNPCC or LO CRC. They had a median calculated probability for mutation of 0.6% (0–15.3%).

Verification of family history

We were able to verify cancer diagnoses in the families of 167 participants. Among these families 93 were suspected of meeting one of the criteria for hereditary cancer, and 4 were suspected of meeting the criteria for both hereditary colorectal- and hereditary breast-ovarian cancer. After verification of diagnoses, it was found that 64 participants belonged to families that met one or two of the criteria: 55 families met the criteria for hereditary colorectal or hereditary breast-ovarian cancer and two participants belonged to families meeting both of these criteria. We identified three families with skin cancers, two families with multiple pulmonary cancers, one family with multiple endocrine neoplasia (MEN2) and one with hereditary papillary thyroid carcinomas. Of the 64 participants belonging to families verified as meeting the criteria for hereditary cancer, 30 (47%) had been registered previously, or belonged to families already registered in the Section of Genetic Counselling. Eighteen participants belonged to families with HBOC, 10 to families with hereditary CRC, 1 to both of the previous families and 1 belonged to a MEN2 family.

The initial classification was verified in 47 (47%) and changed in 54 (53%). Details are presented in Table II.

10411 persons (♂**=5164,** ♀**=5247), age 50--64 years, randomized to the NORCCAP trial**
↓→ 290 persons (♂**=161,** ♀**=129) excluded according to exclusion criteria**
10121 persons (♂**=5003,** ♀**=5118) invited to screening examination**

↓→ 2897 non-responders (♂**=1529,** ♀**=1368)**
7224 persons (♂ **= 3474,** ♀ **= 3750) attended screening examination**
↓→ 4358 persons did not meet requirements for cancer in the family
2866 persons (♂ **= 1169,** ♀ **= 1697) met requirements for cancer in the family**
↓→ 2479 persons had no suspicion of inherited cancer in the family and were excluded from further investigations
387 persons (♂ **= 133,** ♀ **= 254) were mailed a family information questionnaire**
↓→ 196 did not return the family information questionnaire
191 persons returned the questionnaire
↓→ 24 persons did not return consent to verify diagnoses
167 persons (♂ **= 53,** ♀ **= 114) had a verified family history**
↓→ 103 persons did not meet the clinical criteria after verification of diagnoses
64 persons (♂ **= 21,** ♀ **= 43) met clinical criteria for inherited cancer in the family after verification of diagnoses**

Figure 1. Flowchart demonstrating study design and numbers in groups. Abbreviation: NORCCAP = Norwegian Colorectal Cancer Prevention.

Table II. Frequency of persons belonging to families suspected and verified to meet clinical criteria[1].

Classification (number of persons)	HBOC	HNPCC	LO CRC	Others	Familial
Total, suspected (387)	161	23	63	16	171
Suspected, non-responders (220)	101	15	38	8	98
Suspected, responders (167)	60	8	25	8	73
Total verified to meet $\geq$1 of the criteria (64)	30	8	21	7	
Verified = suspected (47)	28	4	12	3	

Abbreviations: HNPCC = hereditary non-polyposis colorectal cancer; LO CRC = late onset colorectal cancer; HBOC = hereditary breast- and breast–ovarian cancer.
Others = other hereditary cancer; Familial = HBOC-like, HNPCC-like or LO CRC-like aggregation of cancers, not meeting any of the criteria.
[1]Some persons can have a family history that meets more than one of the criteria.

Colorectal cancers diagnosed in the sigmoidoscopy screening trial

In the sigmoidoscopy screening trial 29 participants were diagnosed as having CRC. None of these findings changed the classification of the families.

Immunohistochemistry

We were able to obtain tissue sections from adenocarcinomas in 40 out of 46 families with an aggregation of HNPCC-related cancers. Tumors from those affected in 32 families showed the presence of all three proteins. Eight tumors showed absence of one or more proteins: MLH1 protein = 3, MSH2/MSH6 proteins = 1 and MSH6 protein = 4.

Mutation analyses

Those affected from the HBOC kindreds were offered testing for the frequent BRCA1 and BRCA2 mutations. BRCA1 mutations were detected in 7 participants. Six participants had an 1135insA mutation and one had a 1675delA mutation. All the mutation-positive participants had been identified by our genetic health-care effort prior to the present study. Those affected from 8 families had loss of MMR protein in tumor, mutation analysis has not yet been completed in one, while the remaining participants were deceased and DNA was not available. One participant with clinically detected MEN2 was previously registered with us, but so far no mutation has been detected.

Estimation of prevalence and number of persons requiring surveillance for hereditary cancer

A total of 10,411 persons were invited to the trial, 7224 of whom participated. Prevalence rates are presented in Table III. The observed and "worst-case" numbers of colonoscopies required annually were 70 and 293, respectively. The observed and "worst-case" numbers of mammograms required yearly were 95 and 737, respectively. The observed prevalence of BRCA1 mutation carriers was 0.07% (7/10,411) and "worst-case" prevalence was 0.1% (7/7224).

Discussion

As expected, most cancer kindreds had HBOC, some had HNPCC, and in addition a few rare syndromes were seen. We identified a limited need

Table III. Estimated prevalence and numbers of persons in Telemark county recommended surveillance for hereditary cancer.

Classification	Observed prevalence, ‰ (V/10411)	"Worst-case" prevalence, ‰ (S/7224)	Age cohorts in Telemark, (age group) (gender)	Surveillance, observed no. of persons	Surveillance, "worst-case" no. of persons	Yearly examinations, observed no.	Yearly examinations, "worst-case" no.
HBOC	2.88 (30/10,411)	22.29 (161/7224)	33,077 (30–60) (♀)	95	737	95	737
HNPCC	0.77 (8/10,411)	3.18 (23/7224)	105,677 (25–80) (♀+♂)	81	337	41	167
LO CRC	2.02 (21/10,411)	8.7 (63/7224)	72,348 (40–80) (♀+♂)	146	631	29	126
Others	0.67 (7/10,411)	2.21 (16/7224)					

Abbreviations: HNPCC = hereditary non-polyposis colorectal cancer; LO CRC = late onset colorectal cancer; HBOC = hereditary breast- and breast–ovarian cancer.
Number of families verified (=V)/suspected (=S) meeting the clinical criteria.
*Statistics Norway.

for follow-up for breast or intestinal cancer risk. The relatively high number of families possibly at risk was reduced substantially by a proper genetic work-up. Future mutation analyses in the affected kindreds will further reduce these numbers. Thus, proper genetic work-up of families will reduce, not increase, the need for follow-up resources. The cost-effectiveness of CRC surveillance of HNPCC gene carriers has been analyzed, and surveillance is effective and less costly than no CRC surveillance [41]. It has also been demonstrated that this kind of activity is beneficial to the psychosocial well-being of the persons at risk [42–47].

The health authorities ask for prevalence rates in planning health care – this report is the best answer that we can give today. We obtained the calculated prevalence rates, and below we discuss the extent to which methodological problems may have influenced the results. Forty-eight persons were excluded due to previous CRC. However, a number of CRC cases ($n=29$) were detected by NORCCAP during the study, and none of them was found to be a member of an HNPCC kindred. Using the prevalence rates reported by others, we should have found zero or one person with HNPCC among the 48 persons excluded because of previous CRC surgery. Some of the 48 excluded persons were already dead, and for practical and ethical reasons it was decided not to ask for their family history.

Only 49% of the participants returned the family information questionnaire. There was no significant difference in response rate between females (45%) and males (40%), as reported by others [48]. In our regular health service we use the same procedure, and in 1999 the response rate was 74% (unpublished data). Most likely, in our regular health service the families contain more extreme features such as multiple cancers or several family members diagnosed at an early age (38). This might give an increased awareness of risk, resulting in a high response rate. Our patients were part of a research population with older probands being invited to take part in CRC screening. They may have limited the motivation to provide family history information. This has also been suggested by others [49]. Persons at risk may be overrepresented in screening programs [50]. Those who are aware of possible risk factors, such as, for example, familial predisposition, may be motivated to attend [50]. Under Norwegian legislation, persons at risk should make the initial contact with the proper health personnel, and not vice versa. Accordingly, we were not allowed to look up those who did not respond. It was expected that families with a true history of familial cancer would be more responsive than those with only a few cancer cases among their relatives, which means that non-responders in the final round of verification of families may have lower prevalence of cancer syndromes than those who did comply. The 29 families in the present study that met the criteria for HNPCC or LO CRC had a median calculated probability for an MMR mutation as low as 0.2%, compared with 3.7% and 2%, respectively, for the previously reported families from our general health service ([5], unpublished observations). Again, this indicates a low prevalence in the cohort studied, resulting in a relatively high prevalence of chance clusters in families included, which subsequently gives a low probability of the families harboring a deleterious mutation.

After verification of diagnoses, the number of times the criteria for HBOC or HNPCC were met was reduced from 101 (divided among 97 participants) to 66 (divided among 64 participants). In 47/101 (47%) the verified results were as initially scored. This seems to be in agreement with previous reports [52,53]. The accuracy of the diagnoses varied according to the site of cancer. Many patients do not discriminate between the different internal organs. This is in accordance with the findings of other researchers [25,49,54] and may partly explain why only 30 of the 60 participants who tentatively met the criteria for HBOC did so after verification of their diagnoses. Breast cancers are often accurately reported [25,54]. Inaccurate reporting increases when more complex criteria are used [53] and may be more extreme when family history is obtained in a busy gastroenterology, surgery or general practice clinic [54]. Family studies are not reliable unless diagnoses are verified from official sources [53]. In sum, our results verified that a family history to determine risk for cancer is not reliable until properly done.

Underreporting of cancer cases could not be addressed, as only claimed cases could (by legislation) initiate a search for confirmation.

Prevalence rates for hereditary cancers depend on the clinical criteria employed as well as differences between populations. Families with accumulated cancer due to incidental clustering or shared environmental factors will influence the estimations. Self-referred families may have more extreme features and contribute to an overestimation of prevalence. Small families may be missed because the number of affected relatives tends to be low when the number of relatives is low.

The results for HBOC confirmed our previous reports that Telemark is part of the East-Norwegian population where the BRCA1 1135insA mutation is prevalent and the high number of previously detected mutation carriers confirmed that we had made contact with a substantial proportion of the BRCA1 mutation-carrying kindreds in Telemark prior to this

study [19]. The observed and "worst-case" prevalences of BRCA1 mutation carriers were 0.07% and 0.1%, respectively. The Anglian Breast Cancer Study Group has estimated a prevalence of BRCA1 mutation carriers of 0.07 or 0.09%, depending on the calculations used [55]. Prevalence of HNPCC reported by others [38,56–61] varied between 0.3% and 2.6% compared with the observed prevalence of 0.08% and "worst-case" prevalence of 0.32% in this study. The previous reports were based on consecutive CRC patients. All consecutive cancer series may overestimate the prevalence of young patients and the studies mentioned here were undertaken in areas known to have a high prevalence of HNPCC founder mutations. We had expected to arrive at lower estimates than these reports.

To adjust for the low sensitivity of the Amsterdam criteria, we applied immunohistochemistry also in families not meeting the clinical criteria for HNPCC. In sum, 8 out of 40 patients available for immunohistochemistry had abnormal findings and 5 of them most probably represented non-inherited cases. This was expected, and is considered to be caused either by MLH1 promoter hypermethylation, which is seen in 10–15% of sporadic cancers [62,63] and is strongly associated with increasing age [64], or by technical problems, as tumors from other affected persons in the family showed the presence of all three proteins. Concurrent loss of MSH2 and MSH6 protein is most likely the result of abrogation of the MutSα complex formed by MSH2 and MSH6 proteins [37,51,63,64]. Blood samples for mutation analyses are only available from one of these patients, and mutation testing is currently not available in Norwegian health care.

In conclusion, 47% of all at-risk persons identified as needing surveillance were included for follow-up prior to the study, which indicates the efficacy of our general population-based family history approach. The initial "worst-case" approach need for health service was substantially reduced by validating the family history. This will be further reduced by genetic testing removing the non-mutation carriers within the families from the surveillance programs in the future. Because the genetic work-up is a one-time job, and because continued surveillance of an unnecessarily high number is costly, clinical genetic activity is efficient and confers a favorable long-term benefit [41]. In addition, the benefit will increase if inherited cancers are prevented or cured. In contrast, a low-quality genetic service will mean that many cases will be offered health care under the "worst-case" strategy. This will use up health-care facilities and personnel and create unjustified cancer worry in many persons.

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