Gansen, Fabia ; Severin, Franziska ; Schleidgen, Sebastian ; Marckmann, Georg ; Rogowski, Wolf

Lethal privacy: Quantifying life years lost if the right to informational self-determination guides genetic screening for Lynch syndrome

Journal Article	as:	peer-reviewed accepted version (Postprint)
DOI of this document*(secondary publication):		https://doi.org/10.26092/elib/3294
Publication date of this document:		06/09/2024

* for better findability or for reliable citation

Recommended Citation (primary publication/Version of Record) incl. DOI:

Fabia Gansen, Franziska Severin, Sebastian Schleidgen, Georg Marckmann, Wolf Rogowski, Lethal privacy: Quantifying life years lost if the right to informational self-determination guides genetic screening for Lynch syndrome, Health Policy, Volume 123, Issue 10, 2019, Pages 1004-1010, ISSN 0168-8510, https://doi.org/10.1016/j.healthpol.2019.08.015.

Lethal privacy: Quantifying life years lost if the right to informational self-determination guides genetic screening for Lynch syndrome

Fabia Gansen [a,*], Franziska Severin [b], Sebastian Schleidgen [c], Georg Marckmann [d], Wolf Rogowski [a,b]

[a] Department of Health Care Management, Institute of Public Health and Nursing Research, Health Sciences, University of Bremen, Bremen, Germany
[b] Institute for Health Economics and Health Care Management, Helmholtz Center München, German Research Center for Environmental Health, Neuherberg, Germany
[c] Department of Nursing Science, University of Philosophy and Theology Vallendar, Vallendar, Germany
[d] Institute for Ethics, History and Theory of Medicine, Ludwig-Maximilians-University Munich, Germany

1. Introduction

Recent developments in genome research include a better understanding of genetic diseases, advances in testing methods and growing attention for the cost-effectiveness of genetic tests [1]. The underlying objective of health economic evaluations is to analyze potential health gains and effects on health expenditures to inform health policy decisions and allow for an efficient allocation of resources in health care [2]. In the case of genetic testing, health gains are often measured in terms of the extent to which genetic relatives of the initially tested, so-called index patients, profit from test results. This is due to the fact that for genetically determined diseases, patients' relatives may have an increased risk of disease themselves [3]. Provided effective concepts of prevention exist – as is the case for hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome – it therefore may be beneficial to extend tests to them. In genetic diagnostics, testing relatives for family mutations with the goal of targeted prevention is known as cascade screening [4].

According to Juth and Munthe [5], justification of screening programs must be based on an assessment of their contribution to certain values. In their opinion, three basic values or goals are relevant for determining whether or not certain (cascade) screenings are justified: improvement of a) physiological health and b) psychological well-being as well as c) adequate consideration of (patient) autonomy. The authors discuss several conflicts that may arise within and between these goals when deciding about implementing screening programs.

In the present context, it is, in our opinion, vital that, while cascade screening may be beneficial with regard to physiological health, it implies transferring personal health-related information of the index patient to relatives and possibly medical service

* Corresponding author at: Grazer Str. 2a, 28359 Bremen, Germany.
E-mail address: gansen@ipp.uni-bremen.de (F. Gansen).

providers. There are circumstances, however, under which (for various reasons) unsolicited disclosure of information seems necessary. This, in turn, may violate the principle of adequate consideration of patient autonomy, either with regard to the index patients' informational self-determination or with regard to the relatives' right not to know. Such conflicts of patient autonomy on the one hand, and possible health benefits, especially for third parties, on the other, have been debated intensely in the ethical literature [5,6]. Less attention, however, has been paid to the fact that achieving efficient use of health care resources may also conflict with the right to informational self-determination as well as the right not to know – and how to deal with the resulting trade-offs.

In the following, this area of tension will be examined in the context of genetic testing for Lynch syndrome (LS). HNPCC or Lynch syndrome is a genetic disease of autosomal dominant inheritance originating from a mutation in a mismatch repair (MMR) gene. It is connected to an increased risk for several types of cancer and is estimated to cause between 2 and 3% of colorectal cancer cases [7]. As a consequence, universal LS testing of all colorectal cancer patients is recommended by several US and European guidelines on Lynch syndrome [8–10] but not practiced in Germany [11]. For the purpose of this analysis, a previously published health economic model of Lynch syndrome screening [12] illustrating current and potential screening practices from the perspective of the German statutory health insurance system was updated. Within this model, different strategies of test uptake and informing relatives about their potential risk are investigated and discussed using scenario analysis.

The research objective of this study is to analyze the ramifications of increased test uptakes by index patients and their relatives within the German setting. It does so by quantifying the economic impact of intensified cascade screening and using these results as a starting point to examine the ethical implications. In this way, the analysis provides insights into the question of whether or not a possibly more efficient use of health care resources could justify constraints of patient autonomy.

2. Materials and methods

2.1. Health economic model

The effects and implications of different screening strategies for Lynch syndrome were analyzed on the basis of a health economic model by Severin et al. published in 2015 [12]. The screening procedure investigated in the model is illustrated in Fig. 1. While the basic structure and specifics of the original model were maintained, it was updated by means of a literature search with a focus on cost parameters. An overview of the model parameters and updates underlying the analysis can be found in the Appendix (see Appendix Table 1 and Appendix Table 2). The decision-analytic model estimates the cost-effectiveness of screening for Lynch syndrome from the perspective of the German statutory health insurance. The effects of the different testing strategies are measured in life years gained through increased prevention. Costs are reported in 2016 euros (€). Costs are based on 2016 data, where available, or transferred to 2016 using consumer price indices and purchasing power parities (see Appendix Table 2).

With regard to its structure, the model consists of two parts: First, different strategies for testing index patients with colorectal cancer (CRC) for Lynch syndrome are modeled by decision trees. Subsequent Markov models estimate the life expectancy and life years gained by different screening strategies for index patients' first-degree relatives (FDRs). The model has a cohort size of 61,000 index patients which corresponds to the CRC incidence projected for Germany in 2016 [13]. With regard to the number of FDRs per index patient, every index patient is assumed to have approximately 4 relatives [14]. Including the strategy of no screening, the analysis takes a total number of 22 screening strategies into account. The strategies consist of a combination of several steps of tumor sample examination and genetic sequencing with and without preceding family-history assessment. Family assessment is conducted by application of either the revised Bethesda or Amsterdam II criteria. In comparison to the model by Severin et al. [12], the testing strategies included in the cost-effectiveness analysis were maintained.

Regarding the basic testing strategies, index patients with CRC are offered genetic counselling and testing for LS. For the strategies with family assessment, testing is only offered to those index patients who fulfill the revised Bethesda or Amsterdam II criteria. If (the identified) index patients agree to be tested, strategies 1 through 6 comprise testing of tumor material with a combination of microsatellite instability (MSI) testing, immunohistochemistry (IHC) analysis and tests for the BRAF V600E mutation. Positive tumor testing results in genetic sequencing using blood samples to identify which MMR gene – MSH2, MLH1, MSH6, or PMS2 – is affected by the mutation. Strategy 7 involves direct sequencing without prior tests on tumor material. If a mutation is detected in an index patient, his or her first-degree relatives are offered targeted screening for the family mutation. Details on the structure of the screening strategies can be found in Appendix Fig. 1. The two strategies representing the current screening recommendations in Germany are strategies B-4 and B-6 [11,12]. The German guidelines for CRC prevention and treatment recommend testing of index patients who meet the revised Bethesda criteria. Strategy B-4 then involves IHC analysis of tumor material. If IHC results are positive, genetic sequencing follows. In case of negative IHC results, DNA sequencing is only conducted if MSI results are positive. Strategy B-6 involves MSI testing of tumor material and DNA sequencing if these results indicate LS [11].

According to the model described by Severin et al. [12], relatives tested positive for LS are offered intensified surveillance by means of annual colonoscopies and aspirin prophylaxis starting at the age of 25. Relatives tested negative are assumed to be offered a colonoscopy every 10 years between the age of 55 and 75. The structure of the Markov models used to estimate CRC related mortality and costs can be found in the Appendix (see Appendix Fig. 2). Each Markov model consists of the main states well, initial CRC, metachronous CRC, well after cancer and death. The states initial and metachronous CRC are further divided into cancer stages I to IV according to the Union Internationale Contre le Cancer (UICC). Intensified surveillance is assumed to have a favorable effect on the stage distribution and cancer detection at an early stage [15]. With a 1-year cycle length, the model has a time frame of 120 years. Discount rates of 3% and half-cycle correction were applied to costs and effects [12].

Based on the model presented, the economic analysis of genetic screening for Lynch syndrome is divided into two steps. First, a base case analysis is conducted to determine the non-dominated strategies and their cost-effectiveness. For the identified non-dominated and German strategies, a scenario analysis then examines the effect of different test uptake rates in index patients and their relatives in a second step.

2.2. Base case analysis

In the base case analysis, it is assumed that 10% of index patients with CRC decide to be tested for LS according to expert opinion. With regard to the test uptake of first-degree relatives, approximately 30% of relatives of LS positive index patients decide in favor of testing for a family mutation [14]. To identify the non-dominated strategies, a deterministic analysis was performed to

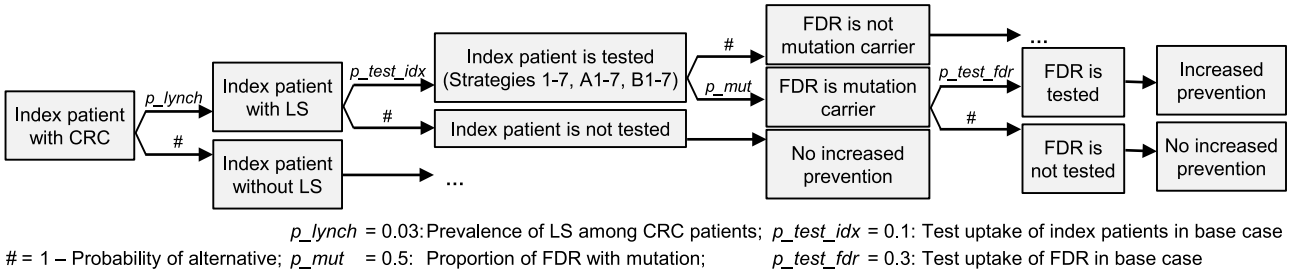

Fig. 1. Screening procedure for colorectal cancer patients and relatives of mutation carriers. Screening strategies 1–7 are without family-history assessment. Strategies with preliminary evaluation of the Amsterdam II criteria are abbreviated with A1–7 and those with revised Bethesda criteria are titled B1–7. CRC: colorectal cancer; FDR: first-degree relative; LS: Lynch syndrome.

estimate cost-effectiveness in the base case. The strategies currently recommended in Germany were also included in the further analysis. Besides their cost-effectiveness, testing costs, total costs (for testing, prevention and cancer treatment), number of mutation carriers detected and (undiscounted) life-years in FDRs in 2016 were estimated for the non-dominated and German strategies. The latter are included independently of their status of being non-dominated, dominated, or subject to extended dominance according to the deterministic analysis. Dominated strategies are more cost-intensive and less effective than alternatives and strategies subject to extended dominance are dominated by a combination of other strategies considered [12]. The parameter values applied in the model can be found in Appendix Table 1. All analyses of costs and effects were performed using TreeAge Pro 2017, R.2.1 (TreeAge Software, Williamstown, MA).

2.3. Scenario analysis

To estimate the effect and implications of different test uptake rates in index patients and relatives of LS patients, a scenario analysis was conducted. Within the model illustrated in Fig. 1, the two parameters for test uptake were varied. An overview of the four scenarios including the base case is shown in Table 1.

Research on CRC patients suggests that uptake of genetic testing for LS is relatively low in clinical practice [16–18]. Possible reasons for this reservation are missing information about testing options or doubts about the added value of testing for LS for index patients with regard to prevention. Compared to the low test uptake of 10% according to expert opinion in the base case scenario, Scenario 2 investigates the effects of routine testing in index patients assuming a test uptake of 100%. If relatives of positively tested index patients are not informed of their family member's diagnosis, they cannot profit from testing and intensified screening in the case of LS. For this reason, standardized contacting of first-degree relatives is investigated in Scenario 3. Contacting relatives could be implemented through attending physicians upon consultation with index patients using standardized letters recommending genetic counseling. Similar strategies have been introduced in Europe for hereditary diseases such as familial hypercholesterolaemia. In the UK, informing relatives by health care professionals led to an improvement in screening participation to 73% [19] as not all relatives contacted decided to get tested. This uptake rate as well as additional costs of contacting measures in the amount of approximately € 187 [20] are assumed in Scenario 3. To evaluate the implications of the combination of routine testing and contacting relatives, increased uptake rates of both index patients and relatives are investigated in Scenario 4.

3. Results

3.1. Base case analysis

In the base case, all screening strategies yield more life-years and higher costs than no screening for LS. Out of the 22 strategies considered, four strategies were not dominated according to the deterministic cost-effectiveness analysis of the base case. These strategies include Strategy 0 (no screening), Strategy B2, Strategy 2 and Strategy 7 (see Table 2). In Strategy B-2, IHC analysis follows assessment of the revised Bethesda criteria. If IHC analysis shows the MLH1 protein is absent, BRAF testing is conducted to rule out sporadic CRC cases. Negative findings for the BRAF mutation as well as other positive IHC results are followed by DNA sequencing. Strategy 2 entails respective testing without the revised Bethesda criteria. Strategy 7 involves direct genetic sequencing of the MMR genes.

As illustrated in Table 2, incremental cost-effectiveness ratios (ICERs) compared to the next most cost-effective strategy are € 46,494 per life-year gained (LYG) in Strategy B-2, € 154,431 per LYG in Strategy 2 and € 2,213,028 per LYG in Strategy 7. Regarding the overall testing costs for index patients and relatives and the number of mutation carriers identified in first-degree relatives, deterministic analysis results in the same non-dominated strategies. For the non-dominated and German strategies, testing costs range from € 1,422,747 (Strategy B-2) to € 14,358,255 (Strategy 7) while the number of mutation carriers detected is between approximately 73 (Strategy B-6) and 96 (Strategy 7) in the base case. The results for testing costs and number of mutation carriers detected are illustrated in the Appendix (see Appendix Fig. 3). Average testing costs per mutation detected are between € 19,369 for Strategy B-2 and € 148,973 for Strategy 7.

3.2. Scenario analysis

As demonstrated in Table 3, higher test uptake rates in index patients and their relatives increase the number of mutation carriers detected and undiscounted life years gained by FDRs in the reference year 2016. Direct comparison of Scenario 4 with the base case shows that routine testing of index patients and standardized contacting of FDRs could yield up to 2500 undiscounted LYG in Strategy 7. With regard to the additional mutation carriers detected in Scenario 4 – routine testing and contacting relatives – compared to the base case, numbers for the non-dominated and German strategies range from approximately 1723 (Strategy B-6) and 2290 (Strategy 7). Routine testing and contacting relatives also yield savings between € 11,098 (Strategy B-2) and € 88,278 (Strategy 7) in average testing costs per mutation carrier detected. Strategy B-6 results in saved testing costs of € 14,396 and Strategy B-4 of € 17,230 on average. Table 3 also indicates that

Table 1
Scenarios included in scenario analysis and their adjustments in test uptakes and costs.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Description	Base case	Routine testing of index patients	Contacting first-degree relatives	Routine testing and contacting relatives
Test uptake in index patients	10%	100%	10%	100%
Test uptake in relatives	29%	29%	73%	73%
Additional costs	–	–	€ 187 for contacting relatives	€ 187 for contacting relatives

Table 2
Results of cost-effectiveness analysis for non-dominated strategies. Incremental costs, life-years gained and ICERs are given in comparison to the next most cost-effective strategy. BRAF: BRAF V600E mutation testing; ICER: incremental cost-effectiveness ratio; IHC: immunohistochemistry; LYG: life-years gained.

		Total Cost	Total life years	Incremental Costs	Incremental LYs	ICER
Strategy 0	No screening	€ 116,510,159	5,023,554	–	–	–
Strategy B-2	Counseling including Bethesda, IHC, BRAF, sequencing	€ 117,972,159	5,023,586	€ 1,462,000	31.45	€ 46,494 per LYG
Strategy 2	Counseling, IHC, BRAF, sequencing	€ 118,630,232	5,023,590	€ 658,073	4.26	€ 154,431 per LYG
Strategy 7	Counseling, direct sequencing	€ 130,919,918	5,023,595	€ 12,289,686	5.55	€ 2,213,028 per LYG

Table 3
Results of the scenario analysis for the non-dominated and German strategies. The results include the undiscounted life years gained compared to the base case, the number of mutation carriers detected, the testing costs per mutation carrier detected and incremental cost-effectiveness ratios. BRAF: BRAF V600E mutation testing; FDRs: first-degree relatives; ICER: incremental cost-effectiveness ratio; IHC: immunohistochemistry; LYG: life-years gained; MSI: microsatellite instability analysis.

		Scenario 1: Base case	Scenario 2: Routine testing	Scenario 3: Contacting FDRs	Scenario 4: Routine testing & contacting FDRs
Undiscounted life years saved compared to the base case					
Strategy 0	No screening	–	0	0	0
Strategy B-6	Counseling including Bethesda, MSI, sequencing	–	713	117	1881
Strategy B-2	Counseling including Bethesda, IHC, BRAF, sequencing	–	722	118	1905
Strategy B-4	Counseling including Bethesda, IHC, MSI (if IHC-), sequencing	–	732	120	1932
Strategy 2	Counseling, IHC, BRAF, sequencing	–	820	134	2164
Strategy 7	Counseling, direct sequencing	–	947	155	2500
Number of mutation carriers detected					
Strategy 0	No screening	0	0	0	0
Strategy B-6	Counseling including Bethesda, MSI, sequencing	73	725	180	1795
Strategy B-2	Counseling including Bethesda, IHC, BRAF, sequencing	73	735	182	1818
Strategy B-4	Counseling including Bethesda, IHC, MSI (if IHC-), sequencing	75	745	184	1844
Strategy 2	Counseling, IHC, BRAF, sequencing	83	834	206	2065
Strategy 7	Counseling, direct sequencing	96	964	239	2386
Testing costs per mutation carrier detected					
Strategy 0	No screening	0	0	0	0
Strategy B-2	Counseling including Bethesda, IHC, BRAF, sequencing	€ 19,369	€ 18,693	€ 8544	€ 8271
Strategy B-6	Counseling including Bethesda, MSI, sequencing	€ 24,896	€ 24,212	€ 10,777	€ 10,501
Strategy 2	Counseling, IHC, BRAF, sequencing	€ 24,883	€ 24,288	€ 10,772	€ 10,532
Strategy B-4	Counseling including Bethesda, IHC, MSI (if IHC-), sequencing	€ 29,665	€ 28,998	€ 12,703	€ 12,434
Strategy 7	Counseling, direct sequencing	€ 148,973	€ 148,458	€ 60,903	€ 60,695
Incremental cost-effectiveness ratios of non-dominated strategies					
Strategy 0	No screening	–	–	–	–
Strategy B-2	Counseling including Bethesda, IHC, BRAF, sequencing	€ 46,494/LYG	€ 44,915/LYG	€ 21,207/LYG	€ 20,570/LYG
Strategy 2	Counseling, IHC, BRAF, sequencing	€ 154,431/LYG	€ 154,431/LYG	€ 64,811/LYG	€ 64,811/LYG
Strategy 7	Counseling, direct sequencing	€ 2,213,028/LYG	€ 2,213,028/LYG	€ 896,469/LYG	€ 896,469/LYG

incremental cost-effectiveness ratios are improved in the case of increased test uptake in both index patients and first-degree relatives for all non-dominated strategies. The main improvement can be seen for Scenario 3, which represents standardized contacting of relatives and higher test uptake of LS patients' family members. For Strategy 2 and 7, there is no change in ICERs for routine testing.

4. Discussion

4.1. Efficient use of resources

Our analysis of screening scenarios shows ways to redeem one of the key promises of personalized medicine: to generate additional health benefits at low costs or even reduce health expenditures. In

the case of LS screening, increased test uptakes of index patients and their relatives substantially improve both health gains and cost-effectiveness. While routine testing has a large impact on life years saved and the number of mutation carriers detected, contacting relatives entails lower testing costs and therefore makes a large difference in cost-effectiveness. From a health economic perspective, routine testing and contacting first-degree relatives – and especially the combination of the two – are therefore preferable. However, the evaluated scenarios have several ethical implications in need of further evaluation.

In principle, the implementation of cost-effective interventions allows for an efficient use of health care resources. This is an important criterion for ethically justified prioritization of health care services [21,22]: from a socio-ethical point of view, it is morally imperative to finance cost-effective health services. However, in the scenarios analyzed, cost-effectiveness is improved by routine testing and unsolicited disclosure of information. This may jeopardize proper consideration of patient autonomy.

4.2. Consideration of patient autonomy

The principle of appropriate consideration of patient autonomy is an essential prerequisite as well as starting point of numerous debates in modern medical ethics. It has been debated at different levels of justification and within the framework of various ethical approaches. Respect for patient autonomy as a *prima facie* valid principle, which is to be specified and, if necessary, weighed against other principles to justify decisions in morally relevant contexts [23] is probably the best-known variant. Alternatively – and more comprehensively –, an individuals' autonomy has been understood as an intrinsic value based on which corresponding obligations of its appropriate consideration were established [24]. A further possibility consists in characterizing individuals' autonomy – particularly expressed through autonomous decisions – as a necessary (and possibly sufficient) means for establishing and ensuring individual well-being and to derive a duty to appropriately consider autonomy as a secondary value [25].

Regardless of the theoretical provenance, there is broad agreement that the appropriate consideration of patient autonomy includes a right to informational self-determination. This right implies that patients are entitled to make their own decisions about which medical information they want to know and which personal health information they allow to be passed on to third parties (e.g. relatives or medical professionals). This entitlement, however, is obviously undermined in the case of routine testing and unsolicited disclosure of information to third parties. In addition, it is often argued that adequate consideration of patient autonomy must satisfy the right not to know, according to which a patient may determine which information he does not wish to receive. This right may also be violated in case of unsolicited disclosure of information to mutation carriers' relatives. The presented case therefore demonstrates the potential for a twofold conflict between the socio-ethically motivated demand for efficient use of health care resources and the norm of appropriate consideration of (patient) autonomy.

4.3. Dealing with resulting trade-offs

These conflicting commitments result in a trade-off between two poles: One the one hand, one could grant absolute priority to patient autonomy and disregard any demand for efficient use of resources. This corresponds to ethical positions giving absolute priority to the right to informational self-determination (or the right not to know) over any other (e.g. social-ethical) claims. As regards the scenarios, this would mean choosing the base case i.e. Scenario 1. On the other hand, one could grant absolute priority to the socio-ethical demand for optimal resource use and disregard the right to informational self-determination as well as the right not to know. This corresponds to ethical positions giving absolute priority to societal benefits or social justice. In the analyzed setting, this would require implementing the most cost-effective scenario which corresponds to Scenario 4 – routine testing and contacting relatives. A somewhat weaker position would be to grant *prima facie* priority to the right to informational self-determination or the right not to know over the demand for efficient use of resources (or vice versa). This would mean allowing for exceptions under certain conditions of overriding societal (or individual, vice versa) entitlements. The conditions of such exceptions as well as their implementation – possibly in the form of only routine testing (Scenario 2) or only contacting relatives (Scenario 3) – would require specifying. Finally, the two conflicting commitments could be weighed against each other by assigning respective weights.

For the process of weighing individual and socio-ethical considerations, different approaches exist. While prioritization criteria themselves can be derived in an analytically ethical manner, it is more plausible to base their weights on fair political decision-making processes or empirical preference elicitation [22]. Depending on the relative weights of the conflicting ethical obligations, different screening scenarios would be morally acceptable and preferable from an ethical perspective. Scenario 2, in which index patients are routinely tested for LS, only gradually improves cost-effectiveness but fully disregards the index patients' right to informational self-determination. Unsolicited disclosure of mutation carriers' health data in Scenario 3 limits the index patients' right to informational self-determination and their relatives' right not to know. In turn, Scenario 3 substantially improves cost-effectiveness. Despite its most favorable cost-effectiveness results, Scenario 4 seems particularly problematic due to its major infringement on the individual rights of index patients and their relatives. However, these rights could be given lower priority under certain conditions. Such conditions could include cases of identifiable and preventable health risks such as those associated with LS. Here, drawing the line between acceptable and unacceptable restrictions to patient autonomy would include assessing whether health benefits for relatives and improved cost-effectiveness could sufficiently justify limiting the above mentioned rights.

When assessing the trade-offs involved in LS screening, however, it has to be kept in mind that cost-effectiveness is not the sole criterion for ethically justified prioritization. Additional prioritization criteria include the added benefit of an intervention, its urgency and the expected health damage due to non-intervention [22]. In the present case, the health benefit for LS patients gained through increased prevention appears particularly relevant for consideration. The more a LS patient benefits from regular colonoscopies, the stronger the ethical argument to work toward high participation rates of index patients and relatives. Other factors relevant to the benefits of LS screening include the validity of the involved genetic tests and the risks associated to the above mentioned preventative measures. Following Juth and Munthe [5], the ethical evaluation of screening programs should also consider effects on psychological well-being. In the case of LS, this entails potential psychological burdens of the diagnosis LS which is connected to a higher lifetime risk of CRC and other types of cancer. These considerations are particularly relevant for female mutation carriers who are at risk of cancers which are less accessible to preventive measures [26]. To what extent other types of cancer reduce the health benefit gained through LS screening was beyond the scope of this study and constitutes an area of future research.

4.4. Implications

In this article, we have derived two main arguments. First, we have quantified the health gains and cost-effectiveness associated with increased screening by routine testing and informing first-degree relatives of their LS risk. As is routine for health economic evaluations, this result can be taken as a starting point to guide health policy decisions on appropriate screening programs for LS in Germany. However, the arguments made in this article go beyond the economic considerations and additionally assess the ethical implications and trade-offs associated to the analyzed screening scenarios. We suggest that the numerical results be taken as a basis for a weighing processes of informational self-determination on the one hand and efficient use of resources on the other. In any case, this analysis highlights the impact increased test uptake on a voluntary level – e.g. through intensified education and greater awareness – could have in the case of Lynch syndrome.

While the performed analysis included the economic and ethical implications of routine testing and contacting relatives, the investigated scenarios also affect legal rights of index patients and their relatives. Particularly in light of current developments in Germany due to the European General Data Protection Regulation (GDPR), the legal framework is highly relevant for the feasibility of routine testing and contacting relatives. According to the Genetic Diagnosis Act "Gendiagnostikgesetz" (GenDG), which is applicable for the mutation analysis of MMR genes performed in genetic sequencing [27], index patients are entitled to counseling before genetic testing is performed. The GenDG also stipulates index patients' right not to know and the need for their written consent before physicians may inform third parties about test results. The precise legal implications and challenging implementation of increasing test uptake rates for Lynch syndrome screening are to be investigated in future research.

5. Conclusions

The health economic analysis performed illustrates that both costs and effectiveness of LS screening substantially depend on the participation rates of index patients and their relatives. Routine testing and contacting FDRs by default could achieve health gains of up to 2500 undiscounted life years by FDRs and 2290 additional mutation carriers detected in the year 2016. Testing costs could be reduced by up to € 88,000 per mutation carrier detected. Furthermore, cost-effectiveness of the non-dominated testing strategies could be improved by approximately € 26,000, € 90,000 and € 1,317,000 per LYG respectively.

From an ethical point of view, the analysis illustrates a conflict between the efficient use of resources and appropriate consideration of patient autonomy. Notwithstanding the importance of the individual rights affected, it should be put up for discussion whether the right of informational self-determination should be waived in cases of clearly recognizable and preventable health risks for third parties. The dependence of informing genetic relatives on the consent of the patient should also be investigated further. If this information is of high medical value, as is the case for LS, the health protection of the relatives could have a greater weight than the right to informational self-determination of the index patient. There are, however, practical challenges to informing relatives such as gaining access to their contact information. Notwithstanding ethical and practical challenges as well as pending legal considerations, this analysis points out the importance of working towards a high voluntary test uptake in index patients and their relatives.

Funding

The research did not receive any grants from funding agencies in the public, commercial, or non-profit sector.

Declaration of Competing Interest

Franziska Severin is an employee of Amgen. Her contribution to this project largely consists of work she conducted during her PhD at Helmholtz Center München. Amgen did not provide any funding and was not involved in this study. All other authors have no conflict of interest to declare.

Acknowledgments

The authors would like to thank Simone von Hardenberg, Nikola Wilman and Ulrich Becker for their contribution to earlier versions of this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2019.08.015.

References

[1] Grosse SD. When is genomic testing cost-effective? Testing for lynch syndrome in patients with newly-diagnosed colorectal cancer and their relatives. Healthcare (Basel, Switzerland) 2015;3:860–78.

[2] Rogowski WH, Grosse SD, John J, Kääriäinen H, Kent A, Kristofferson U, et al. Points to consider in assessing and appraising predictive genetic tests. Journal of Community Genetics 2010;1:185–94.

[3] Schroder P. The status of genome-based information. Public-health-genomics and genetic exceptionalism. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2006;49:1219–24.

[4] Caswell-Jin JL, Zimmer AD, Stedden W, Kingham KE, Zhou AY, Kurian AW. Cascade genetic testing of relatives for hereditary cancer risk: results of an online initiative. Journal of the National Cancer Institute 2018;111:95–8.

[5] Juth N, Munthe C. The ethics of screening in health care and medicine: serving society or serving the patient? Dordrecht, Heidelberg, London, New York: Springer; 2012.

[6] Fulda KG, Lykens K. Ethical issues in predictive genetic testing: a public health perspective. Journal of Medical Ethics 2006;32:143–7.

[7] Steinke V, Engel C, Buttner R, Schackert HK, Schmiegel WH, Propping P. Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome. Deutsches Arzteblatt International 2013;110:32–8.

[8] Di Marco M, D'Andrea E, Panic N, Baccolini V, Migliara G, Marzuillo C, et al. Which Lynch syndrome screening programs could be implemented in the "real world"? A systematic review of economic evaluations. Genetics in Medicine 2018;20:1131–44.

[9] Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Diseases of the Colon and Rectum 2014;57:1025–48.

[10] Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013;62:812–23.

[11] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3-Leitlinie Kolorektales Karzinom, Langversion 2.0, 2017, AWMF Registrierungsnummer: 021/007OL; 2017.

[12] Severin F, Stollenwerk B, Holinski-Feder E, Meyer E, Heinemann V, Giessen-Jung C, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Genetics in Medicine 2015;17:765–73.

[13] Robert Koch-Institut (RKI). Beiträge zur Gesundheitsberichterstattung des Bundes: Krebs in Deutschland 2011/2012; 2015.

[14] Schneider R, Rummele P, Dechant S, Hofstadter F, Lorenz W, Furst A. Familial non-polyposis colorectal carcinoma (Lynch syndrome) in Germany—analysis of information, advisory service and family screening. Deutsche Medizinische Wochenschrift 2011;136:17–22.

[15] Engel C, Rahner N, Schulmann K, Holinski-Feder E, Goecke TO, Schackert HK, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clinical Gastroenterology and Hepatology 2010;8:174–82.

[16] Keller M, Jost R, Kadmon M, Wullenweber HP, Haunstetter CM, Willeke F, et al. Acceptance of and attitude toward genetic testing for hereditary nonpolyposis

colorectal cancer: a comparison of participants and nonparticipants in genetic counseling. Diseases of the Colon and Rectum 2004;47:153–62.
[17] Shia J. Evolving approach and clinical significance of detecting DNA mismatch repair deficiency in colorectal carcinoma. Seminars in Diagnostic Pathology 2015;32:352–61.
[18] Hampel H. Genetic counseling and cascade genetic testing in Lynch syndrome. Familial Cancer 2016;15:423–7.
[19] Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, et al. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Annals of Clinical Biochemistry 2009;46:24–32.
[20] Lairson DR, DiCarlo M, Myers RE, Wolf T, Cocroft J, Sifri R, et al. Cost-effectiveness of targeted and tailored interventions on colorectal cancer screening use. Cancer 2008;112:779–88.
[21] Zentrale Kommission zur Wahrung ethischer Grundsätze in der Medizin und ihren Grenzgebieten (Zentrale Ethikkommission) bei der Bundesärztekammer. Priorisierung medizinischer Leistungen im System der Gesetzlichen Krankenversicherung (GKV). Deutsches Ärzteblatt 2007;104. A-2750-4.
[22] Schleidgen S, Marckmann G. Kriterien für eine ethisch angemessene Priorisierung individualisierter Therapiemaßnahmen. Gesundheitswesen 2014;76:e57–64.
[23] Beauchamp TL, Childress JF. Principles of biomedical ethics. Oxford: Oxford University Press; 2013.
[24] Richardson HS. Autonomy's many normative presuppositions. American Philosophical Quarterly 2001;38:287–303.
[25] Brandt RB. A theory of the good and the right. Oxford: Clarendon Press; 1979.
[26] Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304–10.
[27] Schillhorn K, Heidemann S. Gendiagnostikgesetz: Kommentar für die Praxis. Heidelberg: medhochzwei Verlag; 2017.