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Direktor/in: Prof. Dr. Jacqueline Müller-Nordhorn

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Using an epidemiological tool for medical and public health practice: Conceptual and ethical considerations on the use of individualized risk estimates

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Dr. phil. Christine Holmberg, M.A., M.P.H.

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Dekanin: Professor Dr. med. A. Grüters-Kieslich

1. Gutachter/in: Professor Dr. Wolfgang Hoffmann, Greifswald

2. Gutachter/in: Professor Dr. Claudia Bausewein, München

Content

1   Introduction

Today, the most common diseases worldwide are cardiovascular disease and cancer. The rise in the incidence of these diseases in the 20th century is to a large extent attributable to modifiable risk factors, mostly lifestyle factors. This led to a significant shift in research methods and study designs in 20th century epidemiology in order to better understand chronic disease development. Epidemiology, which originally focused solely on infectious diseases, had to change its focus to include diseases that are slow to develop, and for which exposure to the disease-initiating agents and the resulting disease might lie many years apart. This changing focus necessitated new study designs that could investigate multiple risk factors simultaneously over a long period of time; one of which was the "cohort study."

The first cohort study, the Framingham Heart Study, began in the 1940s and is still ongoing. The Framingham Heart Study's goal has been to examine the development of cardiovascular disease (CVD) in a population that was healthy at the study's beginning [1, 2]. It has been extremely successful, in that it was the first to describe most of the lifestyle-related risk factors for CVD and could quantify their effect on disease development, two contributions which remain important for health messages and further study today. We now believe that 80% of heart disease, stroke, and type-2 diabetes mellitus could be prevented with the elimination of smoking, physical inactivity, and unhealthy diet [3]. Increased risk for some cancers has also been associated with a sedentary lifestyle, particularly television watching [4]. Similarly, a lifestyle that includes a healthy diet, high levels of physical activity, and low alcohol consumption has been shown to reduce the risk of cancer, type-2 diabetes mellitus, and cardiovascular disease [5, 6].

Data collected in cohort studies and related epidemiological study designs also lend themselves to the development of so-called "individualized risk estimates." Individualized risk estimates (or models) are statistical tools based on risk functions that predict a person's risk of developing a disease in a given time frame, taking into account certain risk factors [7]. Variables in such

models may include both modifiable and non-modifiable risk factors, including the environmental, behavioral, genetic, or psychological attributes of a person.

Individualized risk models have been developed for a range of diseases, including cardiovascular disease, type-2 diabetes mellitus, and a variety of cancers. For example, two risk models are used for cardiovascular disease prevention in clinical practice in Germany: the HeartScore, which was developed as part of the Systematic Coronary Risk Evaluation (SCORE) project, with data from 12 European cohort studies, and the ARRIBA score that uses the Framingham risk function from the US as basis for its calculations [8, 9]. Both aim to aid clinical and patient decision-making to reduce the risk of cardiovascular disease. The National Cancer Institute in the US started an initiative to increase research into the development of risk scores for a variety of cancers [7], with the result that risk prediction models now exist for a range of cancers (http://epi.grants.cancer.gov/cancer_risk_prediction/#risk, accessed July 25, 2014).

Many guidelines for prevention decision-making recommend the use of risk scores to better identify whom to target for risk reduction, prevention, and health behavior change [10-12]. For example, the HeartScore is part of the European Society of Cardiology's guidelines for cardiovascular disease prevention in clinical practice. The use of individualized risk estimates are promoted for use in health education to improve risk perception and health decision-making among laypeople [13]. Some argue that individualized risk models, if accurate, can not only predict future disease burden and thus inform health policy, but can aid in motivating individual behavior change [10, 14, 15].

Individualized risk models typically fall into two broad categories: those that are intended to be used by patients with the help of their healthcare providers, and those that may be used by individuals on their own. Models in the first category may include medical information that is not readily available to patients, such as cholesterol levels. Models in the second category include information that a person usually knows already or where a "work around" is built in for missing information, and thus can be used by individuals on their own, without the help of healthcare providers. For the purposes of this habilitation, I will focus on individualized risk estimates, which are readily

available online, in particular individualized risk models for type-2 diabetes mellitus and sporadic breast cancer [16-19].

1.1   Risk prediction for type-2 diabetes mellitus

Type-2 diabetes mellitus is one of the diseases whose worldwide rise is attributed to lifestyle factors [20, 21]. Today in Germany, approximately 7.2% of the adult population lives with a diagnosis of type-2 diabetes mellitus, a 2% rise from 1998, according to German health monitoring (http://tinyurl.com/pem66sl, accessed October 23, 2014). The worldwide prevalence of type-2 diabetes mellitus was 8% in 2011, and it is predicted to rise to 10% by 2030 [22]. Several recent studies have found that undiagnosed type-2 diabetes mellitus is common both in Germany and elsewhere, suggesting that actual rates of the disease may be even higher [21, 23, 24].

It is important to develop good measures for identifying individuals at risk for of developing type-2 diabetes mellitus [25-27] since it is associated with severe morbidity and disability, as well as with an increase in myocardial infarction, especially when uncontrolled [28, 29]. There is evidence that a Mediterranean diet [30], regular consumption of foods with high quality nutrients [31], low alcohol consumption [6], and remaining physically active [32, 33] may reduce an individual's risk of developing the disease. Thus, once high-risk individuals are identified, they may be able to lower their risk of developing type-2 diabetes mellitus, as well as the associated morbidity and disability, through lifestyle changes.

Several risk prediction models for type-2 diabetes mellitus are available, but few are readily usable by laypeople [34]. In Germany, the most prominent model is the Diabetes Risk Score (DRS) [19], which is based on data from the European Investigation into Nutrition and Cancer (EPIC) [35, 36]. The German DRS can also be used outside of a medical context [37], as it has been adapted for a publicly available website (www.drs.dife.de, accessed October 23, 2014). In addition, a paper version has been created that can be distributed through print media or other promotion activities [37].

The German DRS in its original version included age; height; waist circumference; history of high blood pressure; levels of physical activity; consumption of red meat, wholegrain bread, coffee, and alcohol; and smoking status. The most updated version of the DRS also factors in family history of diabetes [38]. In addition, because the DRS includes modifiable risk factors, it is considered an ideal tool not only to alert individuals to their risk of type-2 diabetes mellitus, but also to initiate behavior change.

1.2   Risk prediction for breast cancer

Breast cancer is the leading cancer in females and responsible for most cancer deaths among women worldwide (http://www.who.int/cancer/detection/breastcancer/en/, accessed July 25, 2014), including Germany [39] and the US (http://seer.cancer.gov/statfacts/html/breast.html, accessed July 25, 2014). In the US, 12.3% of women will be diagnosed with breast cancer during their lifetime, according to 2008-2010 data collected in the Surveillance, Epidemiology, and End Results Program (SEER). Known risk factors for breast cancer include age, early menarche, older age at first live birth, late menopause, and obesity [39]. There is conflicting evidence as to whether changing behavioral factors such as a sedentary lifestyle, smoking, or regular alcohol consumption can reduce the risk of breast cancer [40-43]. Risk reduction efforts for breast cancer are therefore challenging, as the most effective options for breast cancer prevention (young age at first live birth and multiple children) conflict with other public health messages and efforts. In contrast to individualized risk models for type-2 diabetes mellitus, very few breast cancer risk models include behavioral factors that would be amenable to change. Indeed, while today a variety of individualized risk models for breast cancer are available that include modifiable risk factors, none of them sufficiently predict breast cancer incidence to warrant intervention [15]. As a result, breast cancer prevention efforts have instead focused on drug development.

Two large prevention studies have been conducted in the US: the Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) [44-47], both of which investigated the effect of selective estrogen-receptor modulators (SERMs) on the incidence of breast cancer in women with a high risk for it. Both of the tested SERMs, tamoxifen and raloxifene, reduced breast cancer risk for these high-risk women [44-46]. Other prevention trials, such as the International Breast Cancer Intervention Study (IBIS-I), have also investigated the effect of tamoxifen on breast cancer incidence and found that it reduced cancer risk [48]. The IBIS-II study has further shown that the aromatase inhibitor Anastrozole reduces the risk of developing breast cancer in high-risk postmenopausal women [49].

Such prevention focused clinical trials use individualized risk models to identify individuals at a high risk of disease, to target them for study participation. While the IBIS studies used the Tyrer-Cuzick risk prediction model for breast cancer to identify risk-eligible women for their studies [50], BCPT and STAR used an absolute risk of 1.7% or higher of developing breast cancer, as calculated by the modified Gail score [16, 17, 51], to identify risk-eligible women. The modified Gail score for breast cancer risk prediction is a risk prediction model that has been validated for a range of different populations [52, 53]. In the US, it is the most widely used individualized risk model for the general female population. The Gail score includes variables such as age, age at menarche, age at first live birth, mother or sister with breast cancer, number of biopsies, and race/ethnicity [16, 17]. The Gail model can be easily used by women outside of a medical context, as the assessed factors are likely to be already known to them and it is readily available online (e.g. http://www.cancer.gov/bcrisktool/, accessed October 10, 2014).

1.3   Concerns regarding the use of individualized risk prediction

Identifying individuals at high risk for diseases like type-2 diabetes mellitus and cancer is considered necessary for prevention interventions and treatment decision-making. Such a perceived necessity has partially driven the development of individualized risk estimates like the ones described above [54].

However, many individualized risk estimates in use may not accurately predict risk in target populations other than the specific population for which they were originally developed. The performance of risk models that are currently used for both breast cancer and type-2 diabetes mellitus varies considerably when transferred to other populations [15, 55].

Individualized risk estimates are also commonly used in health communication to improve individuals' risk perception. Accurate risk perception is seen as an important component in motivating behavior change. Models such as the Gail score are used as objective risk measures, with which a patient's subjective risk perception should ideally align [13, 56]. In this realm, extensive research has been conducted on how to present risk estimates in order for individuals to best understand the information [14, 57]. However, there is evidence that even when individuals understand the risk information from the individualized risk estimates presented to them, they do not necessarily consider this information relevant [13, 58, 59] and it may have limited influence on their risk perception of their own risk [60].

With the current increase in knowledge of risk factors and the progress in information technology, the development of individualized clinical guidelines is under way [61-63]. The core of such guidelines includes the calculation of individualized risk estimates based on data that is available through electronic health records and the calculation of decrease in risk with the uptake of medications or change in risk factors. Electronic health records that capture the health information necessary to calculate common individualized risk estimates for CVD, type-2 diabetes mellitus, and other diseases [64] are therefore necessary for such an approach in routine health care. While there is an increasing push towards such automated individualized risk calculations, their effects are yet to be determined [65].

1.4   Aim of the study and research questions

The continued development of information technologies and the increase in risk knowledge are driving an increased focus on individualized risk estimates to aid and guide risk reduction efforts and the identification of intervention groups.

This push is reinforced by current efforts of the WHO and others to increasingly refocus health care systems onto prevention, to reduce the burden of chronic diseases such as CVD and cancer. In this effort, individualized risk estimates may be able to aid health care providers in their efforts to introduce prevention measures to their patients, especially if such calculations are automated via the use of electronic health records. Individual risk assessments have also found their way into guideline medicine as an important means to identify target persons for risk reducing efforts in medical care. In addition to the practical application of individualized risk estimates in clinical practice, individual risk assessments are seen to play an important role in improving risk perception and motivating behavior change in individuals.

There are, however, concerns about the use of many individualized risk estimates for populations other than those for which they were originally developed. Similarly, evidence is conflicting regarding whether individualized risk information has a long-term impact on risk perception and health behavior. In the face of this increase in the use of individualized risk estimates and the conflicting evidence of their effects, it is the aim of this habilitation to interrogate the use of individualized risk estimates by individuals and by health care providers in the clinical setting. In addition, in order to scrutinize further the conceptual concerns raised by the increased focus on individualized risk estimates, an analysis of how individualized risk estimates are developed follows, including an investigation of the ethical considerations regarding individual risk estimates. In particular, this habilitation addresses the following questions:

- In what ways are individualized risk estimates used by individuals?

- How are individuals' characteristics and behaviors represented in individualized risk estimates? What conceptual and ethical implications does the use of individualized risk estimates have for health communication and health decision-making?

- What are the perspectives of physicians, particularly primary care physicians, on the use of individualized risk estimates? Do they use other tools to introduce primary prevention into their patient care?

To answer these questions, this habilitation will engage different perspectives on the topic. First, in a paper by Holmberg et al. (2011), users' activities on an interactive DRS website were analyzed to understand real-time use of an individualized risk estimate calculator [66]. Second, a study by Holmberg, Daly and McCaskill-Stevens (2010) is presented that investigated the narratives of two women at increased risk of breast cancer considering STAR participation, in order to understand how individuals may use individualized risk information for health decision-making [67]. Third, in a study conducted by Holmberg, Bischoff and Bauer (2014), we followed the development of the DRS, with a particular focus on how individuals become research subjects and how they come to be represented in the DRS, in order to understand the type of knowledge that risk scores produce at a population level [68]. Fourth, in a study conducted by Holmberg and Parascandola (2010), we investigated the conceptual and ethical implications of the use of individualized risk estimates [69]. Fifth, in a study conducted by Müller-Riemenschneider et al. (2010), we investigated if and how individualized risk estimates are used in primary care and general practice by health care professionals [70]. Lastly, in a study conducted by Holmberg et al. (2014), we studied the perspectives of general practitioners on the policy-directed reorientation of the health care system towards primary prevention, in order to investigate the possibilities to induce behavior change through medical care without the explicit use of individualized risk estimates [71].

2 Own Works

2.1 Navigation and use of a website that includes an individualized risk estimate

To learn about the use of individualized risk estimates in the public realm, we monitored a website that allows visitors to calculate their type-2 diabetes mellitus risk score. The internet provides an important venue for present-day health communication. In 2013, 1 in 3 people in the US used the internet to search for health information [68, 72]. Websites are ideal for the dissemination of individualized risk estimates, because visitors can easily calculate their risk. Thus, many individualized risk models are freely available online. However, little is known about real-time use of such websites. We conducted a study to monitor and understand the use of a website on which the German DRS is presented.

To disseminate the use of the DRS, a website was created on which a person's risk score can be calculated (www.drs.dife.de, accessed August 4, 2014). The website has a welcome page with information on the DRS and for whom the DRS can offer reliable risk prediction information. This page is followed by the DRS itself, with six pages asking about the included risk factors (age; height; waist circumference; history of high blood pressure; physical activity; consumption of red meat, wholegrain breads, coffee, and alcohol; and smoking status), a summary page of the entered data, and finally a score page. In addition to the actual score, a comparison score is displayed, in which all the modifiable risk factors are set to the optimal value, to show the reduced risk that an individual could achieve through behavior change.

To study user information-seeking behavior and gain knowledge of the use of individual web pages, we conducted a transaction log analysis with the log information that was recorded by the web server software. This approach allowed for a real-life analysis of web server traffic. From March to August 2007, 32,055 unique visits were recorded. Unique visits were defined as a series of requests from a uniquely identified user via IP address within one hour. Interestingly, only 3.3% of users came through search engines such as Google.

Most users accessed the website directly (61%). This suggests that the promotion of the website through other media, such as newspapers and journals, successfully sparked interest in the website. In addition, we found that few people read the information pages that were provided on type-2 diabetes mellitus (6%), known risk factors (10%), and the calculation of the DRS (11%). Furthermore, 14% of users filled out the DRS more than once; 29.2% of high-risk users calculated the DRS more than once, compared to 17.9% of low-risk users.

These results point to the importance of using a range of public media to raise awareness of risk information tools. They also show that high-risk users are more likely to calculate their risk several times. While we cannot know why they do so, it is not unlikely that such "playing" with the score may lead to increased understanding of how different levels of a risk factor influences diabetes. These findings suggest that the internet may provide a good environment for targeted prevention efforts among high-risk groups that cannot otherwise be easily identified.

The limitations of the findings include the fact that we do not know why users chose to navigate the website as they did or why high-risk users calculated the DRS more often. Similarly, we cannot be certain that the unique visits we counted are attributable to different individuals. Additional studies are necessary to answer these questions. However, it remains one of the few published studies with real data on the use of a live risk website.

Work I

Holmberg, C., Harttig, U., Schulze, M., Boeing, H. (2011) The potential of the Internet for health communication: The use of an interactive on-line tool for diabetes risk prediction. **Patient, Education, and Counselling 83** (1), 106-12.

http://dx.doi.org/10.1016/j.pec.2010.04.021

2.2 The role of individualized risk estimates in lay decision-making

A different perspective from which to answer the question of how individuals use individualized risk estimates is to focus on individual treatment decision-making when individualized risk estimates are implicated. Thus in this study, we investigated how two women who were identified as being at an increased risk of developing breast cancer and who were offered to participate in a prevention clinical trial decided on their treatment venue. In particular, we were interested in the role that the individualized risk estimate, in this case the Gail model, played in this decision-making process.

Much research has been invested into identifying the best way to present risk information in a manner that it is understood by laypeople, as probabilities are considered to be important tools for health care decision-making [73, 74]. However, some studies have shown that even in cases where women understand their risk and the benefits of taking tamoxifen to reduce their risk, they are not interested in taking it [58]. There is also evidence that the presentation of individualized risk information does not change risk perception in the long term [60]. Thus, we were interested in investigating how individualized risk information is incorporated into an individual's treatment decision-making. We conducted a detailed case study of two women's decision-making narratives during the STAR recruitment process [45-47].

In a qualitative interview study, we collected the narratives of 40 women who conducted a risk assessment using the modified Gail model [17]. Of these 40 women, only one remembered her 5-year-risk of developing breast cancer, as calculated by the Gail model, without referring to her documents. Another interviewee demonstrated a clear understanding of the risk assessment that she conducted in order to qualify for STAR participation. Both women decided not to participate in STAR, and neither took tamoxifen outside of the trial. To understand how both women made their decision and the role that the Gail score played in the decision-making process, we analyzed the women's narratives for information on how they contextualized and justified their decisions, and the role that the individualized risk estimate played in their narratives.

Both women had previously had a breast biopsy, and they considered themselves "at risk" for breast cancer. As a result, they had long-term relationships with a clinical center, had participated in a family risk assessment program at a cancer center, and received a twice-yearly breast check-up. Thus, by the time they received the epidemiological risk information as part of STAR recruitment, they were already living with the conscious possibility of a breast cancer diagnosis. The interviewee who remembered her risk score, whom we will call Mrs. Wiler, considered her risk of 5% as a small risk, which is why she ultimately decided not to participate in STAR. In contrast, the other interviewee, whom we will call Mrs. Wayne, found the concept of risk unsettling. She feared breast cancer as much as she feared the unintended effects of tamoxifen intake. Her sister and mother, both of whom had had breast cancer, experienced significant side-effects from tamoxifen. The epidemiological concept of risk and the associated risk-benefit table that was given to Mrs. Wayne were intended to help her consider the situation. However, Mrs. Wayne saw that there were "risks" on all sides, as some risks increase and others decrease with medication intake. The uncertainty involved in this risk-benefit table left her unable to make a decision.

For Mrs. Wayne, the decision of whether or not to take tamoxifen may well have mattered. Did she need the risk reducing capacities of tamoxifen, or didn't she? Unfortunately, this question can only be answered in hindsight. She was unable to translate the probabilities that she received from the clinical center into her personal life, and her decision was made more complicated by her mother's and sister's experiences with cancer and cancer drugs. In this respect, Mrs. Wayne's narrative exemplifies the situation that women face when they are asked to make real-life decisions based on probabilities.

Work II

Holmberg, C., Daly M., McCaskill-Stevens, W. (2010) Risk Scores and Decision Making: The Anatomy of a Decision to Reduce Breast Cancer Risk. **Journal of Nursing and Healthcare of Chronic Illness 2** (4), 271-280.

http://dx.doi.org/10.1111/j.1752-9824.2010.01068.x

2.3 Representing individuals' characteristics in the development of individualized risk estimates

In the previous paper, in-depth analysis of two narratives demonstrates how statistical information that is precise on a population level can create uncertainty on the individual level. To characterize the interconnectedness and difference of an individual in relation to a (statistical) population, we need to understand how individuals come to be represented in individualized risk estimates; or to be more precise, how individuals' characteristics and behaviors come to be represented in individualized risk estimates. Thus in this paper, we investigated the creation of prediction information in epidemiological studies. In particular, we analyzed how individual information comes to be represented in individualized risk estimates and how the risk information constructed is returned to the social sphere of everyday life.

Sociological and philosophical theories argue that statistical means of "representing" reality actually reshape that reality. Studies have been conducted to address the social and political implications of this argument. However, studies have yet to address the question of how individuals become part of the populations from which statistical statements are computed, and how the transformation of individual information into the standardized information that becomes part of statistical computations influences the reshaping of the everyday world.

In order to investigate the transformation of an individual into a "research subject," from whom information is extracted and compiled with other data for statistical computations, we focused on the development and use of the DRS [19]. The DRS was developed from data collected as part of the European Investigation into Cancer and Nutrition (EPIC).

Data collection and verification processes in epidemiological studies are critical to ensure that the information is collected and entered into a database in such a way that it can be considered "reliable." These processes are detailed in an international protocol to which all centers involved in this study adhere. To ensure that the centers follow this protocol, control measures and site visits are in place.

Before analyzing the data, so-called "analysis files" are created, which anonymize the information and retrieve the information that is needed for the computation. Only these analysis files (not the raw data) are shared by centers for research purposes. Thus the information collected at a local level from an individual is transformed into standardized information that can be combined with data from other areas, making statistical calculations possible. At this stage, variables of interest become the organizing principle of the data and are used to characterize "populations." Individual information is transformed in such a way that patterns across many individuals can be described in terms of distributions of a variable within or between study groups. In this sense, epidemiological procedures can only calculate population health and not individual health from a data set [75]. It is through the predictions derived from such computations that the information originating from individuals is fed back to society and individuals in transformed ways [76].

Work III

Holmberg, C., Bischof, C., Bauer, S. (2012) Making Predictions: Computing Populations. **Science, Technology & Human Values 38** (3), 398-420.

2.4   Conceptual and ethical implications of the increase in use of individualized risk estimates

As was shown in the previous paper, to develop individualized risk estimates, a significant amount of work goes into "cleaning" individual information to make it comparable across time and space with other information. Based on this process of "populationisation" [68], individualized risk estimates can be computed and fed back to society. However, this feedback loop has triggered critique from within both epidemiology and the social sciences. In this paper, we first analyzed the debate that was sparked particularly by the Gail model and its use as a decision-making aid for breast cancer risk reduction treatment. We then applied some of the more general critique to other individualized risk estimates and developed a framework for a more general critique of individualized risk estimates. Finally, we delineated the consequences thereof.

In our analysis, we show that the critique that we identified in the literature on the Gail model can partly be extended to individualized risk estimates more generally. Ethical and conceptual concerns regarding the use of individualized risk estimates are related to: 1) validation procedures using discriminatory accuracy; 2) the fact that responsibility for risk reduction is transferred to an individual, while more complex causes including environmental, political, and economic factors may be neglected; 3) the conflation of risk *prediction* with risk *reduction*; and 4) the fact that threshold values are set as to when to recommend interventions and behavior change without communicating or providing the information on why the particular threshold value was chosen.

While many risk prediction models exist, the Gail model in particular has been targeted in the literature [16-18, 51, 77-82]. Critique from within epidemiology focused on the low discriminatory accuracy of the model and on the use of the model for populations other than the one for which it was developed. In addition to these methodological limitations, others have questioned how probabilistic concepts apply to individuals. The Gail risk score, as well as other scores, are derived from population aggregate information and are designed to fit the population rather than an individual [83]. In an individual's

life, a person deals with single events rather than multiple ones (either you do or you do not get breast cancer). Finally, critiques contend that individualized risk estimates lead to a shifting of the responsibility for health onto the individual, as they suggest that individual risk can be changed [84]. They thereby exclude other factors that influence disease risk, which may lead to a favoring of pharmaceutical interventions.

While we would argue that there are models with much better discriminatory accuracy than the Gail model, such as the DRS, there remains a more general problem that concerns the statistical question of the probability of a single event versus multiple events. Discriminatory accuracy assesses how often a person who develops a given disease has a higher score compared to a person who does not develop the disease. It does not say anything about the magnitude of the score in order to identify who may develop the disease. This lies in the nature of probabilistic information. It is mathematically precise, but indeed introduces quite some uncertainty when applied at the individual level [85].

Similarly, the statement that the use of individualized risk estimates transfers the responsibility for risk reduction onto the individual can also be applied to other risk models. Indeed, we argue that it is quite important to make the distinction between risk *prediction* and risk *reduction*. This means that the change of risk factors in an individualized risk model changes the *statistical* risk. However, in order to know whether such changes also influence actual risk, intervention studies are necessary. Furthermore, the decision regarding the risk level at which the threshold should be set in order to define the target group is qualitative in nature and involves many factors that may influence the decision [37, 69]. These factors are usually obscured and unknown to those who receive a recommendation. For example, the threshold level of 1.7% for developing breast cancer in the next five years, which was set to indicate tamoxifen intake for breast cancer risk reduction, was based on sample size calculations for the BCPT trial [84]. This value is now often used to qualitatively label women with a Gail score of 1.7 or higher as at "high-risk" of developing breast cancer. Thus, while it may be a useful way to guide individual decision-making, there are ethical concerns that the different factors involved in setting a threshold are

often neither communicated in the decision-making process nor are they known to those who use these thresholds in practice.

Finally, it may well be possible that the use of individualized risk estimates may obscure the fact that successful prevention efforts have thus far always included changes at the social and political level as much as at the individual level. However, to evaluate the effects of individualized risk estimates on individuals and on general prevention efforts, further studies are necessary to investigate the use and effect of individualized risk estimates in practice. Such studies will be presented in the following.

Work IV

Holmberg, C., Parascandola, M. (2010) Individualized Risk Estimation and the Nature of Prevention. **Health, Risk, and Society 12** (5), 441-452.

2.5 The use of individualized risk estimates in primary care

As discussed above, the use of individualized risk estimates for individual decision-making is not well understood and may not influence individual health decision-making in significant ways. Nevertheless, the use of individualized risk estimates in clinical practice has been implicated in prevention guidelines for CVD. Thus, for a comprehensive understanding of the use of individualized risk estimates, it is important to study the perspectives of physicians, particularly general practitioners (GPs), as they may be at the forefront of prevention in clinical practice.

The goal of this paper was to identify the current uses, and potential barriers to use, of individualized risk estimates in primary care. We conducted a mixed-method study that included a mail survey of all GPs residing in Berlin, Germany, and focus groups with a select group of GPs.

The surveyed GPs regularly assessed the risk of their healthy patients, mainly with regards to CVD and type-2 diabetes mellitus, with or without the use of individualized risk estimates. Less frequently, they reported using risk assessments for osteoporosis, fracture risk, depression, dementia, and falls. Individualized risk estimates were mostly used for CVD (60%). The low usage rates of individualized risk estimates in practice has been demonstrated in several other studies [86, 87]. In focus group discussions, GPs did not differentiate between a more general risk assessment and quantifiable individualized risk estimates. Keeping this confusion of definitions in mind, the surveyed GPs suggested that they used risk estimates as counseling and educational tools, as diagnostic instruments to aid decision-making, and as screening instruments.

Overall, the focus group participants identified several barriers to regular use of individualized risk estimates. First, they described risk models that do not include modifiable risk factors as useless, since they cannot be used as counseling tools in primary care. Second, the reimbursement scheme in Germany does not allow for more detailed counseling and follow-up for primary prevention, thus GPs lack incentives to identify high-risk patients for further counseling or treatment. Third, discussants believed that the nature of the

patient–physician relationship precludes regular use of risk scores in general practice. Patients are active in shaping this relationship, and doctors cannot "simply" introduce diagnostic tools that are unrelated to the reason for the patient's visit. Similarly, physicians have their own ways of assessing the risks of their patients based on their experience and knowledge of the patients, and were not all convinced that standardized risk estimates are suitable substitutes for their clinical judgment. From the view of focus group participants, the environment of the health care system, which is shaped by health policies, needs to change before it makes sense for GPs to calculate individualized risk estimates for their patients on a routine basis. The focus group participants voiced several suggestions for making individualized risk estimates more compatible with primary care, such as the inclusion of modifiable risk factors in these models and visualization tools, in order to help patients understand how changing their behavior may lower risk. However, such an approach carries its own ethical and conceptual problems [69].

Work V

Müller-Riemenschneider, F., Holmberg, C., Rieckmann, N., Kliems, H., Rufer, V., Müller-Nordhorn, J., Willich, S.N. (2010) Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. **Archives of Internal Medicine 170** (8) 719-24.

http://dx.doi.org/10.1001/archinternmed.2010.66

2.6 Primary prevention in general practice in Germany

As the previous paper showed, primary care physicians assess their patients' risks based on their long-standing relationship and what they know about the patients. They did not differentiate between precise quantitative individualized risk estimates and more general risk assessments, including ones based on their clinical judgment. In the light of such definitional confusion and lack of awareness of individualized risk estimates, it seems crucial to investigate more generally the methods, if any, that GPs use to integrate prevention efforts into their patient care, in order to gain a full understanding of prevention approaches in general practice. As a first step to do so, we investigated whether and how GPs include primary prevention in their patient care.

Since many chronic diseases are considered preventable through major health behavior changes [3], the WHO and other health service bodies have argued for a shift in health care delivery from disease treatment to a focus on behavior change and health promotion [88-93]. However, surveys show that while GPs find health promotion important, they have not incorporated it into their practice to the extent envisioned by the WHO. To understand current practices of primary prevention in general care, and the attitudes and beliefs that GPs hold about primary prevention in Germany, we conducted a mixed-methods study using a survey and focus group methodology.

GPs indicated that physical activity was the behavior change that they addressed most frequently in practice. Alcohol consumption and smoking habits were discussed less frequently, even when they thought that behavior change was indicated. They reported using the reason for the health care visit as a trigger to initiate discussions of health behavior change. The examples that the GPs used to demonstrate this practice were mostly derived from the field of secondary prevention.

Analysis of the focus group discussions revealed that GPs took their relationship with a patient into account when deciding whether or not to address behavior change. Some feared that an unwanted discussion of behavior change may threaten such a relationship because the role of the physician would change to become that of the "health police."

Findings from this study suggest that introducing standard approaches of primary prevention into general practice would not only add additional burdens to the practice, but would change the role of the GP in relation to the patient. The relationship would become a moral one, in which GPs explain to their patients how they should live their lives.

The GPs did consider the promotion of primary prevention as part of their role; however, they also believed that other societal institutions (e.g. daycare centers, schools, and communities) need to engage in these efforts. They suggested a much broader coalition for behavior change that included the social and the political by adding communities and social institutions to the network. Such multi-level approaches have indeed proven successful in effecting long-term behavior change such as smoking cessation [94].

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3 Discussion

The aim of this habilitation was to investigate the use of individualized risk estimates from the perspective of lay and health care professional users and from a theoretical and ethical perspective. Furthermore, this habilitation investigated the current practice of primary prevention in general practice, which does not explicitly include the use of individualized risk estimates.

The WHO and other health bodies have worked towards redirecting the focus of health care systems onto prevention efforts in order to reduce the burden of many chronic diseases. It is now assumed that 80% of heart disease, stroke, and type-2 diabetes mellitus could be prevented with the elimination of smoking, physical inactivity, and unhealthy diet [3]. Lifestyles that include a healthy diet, high levels of physical activity, and low alcohol consumption reduce the risk of developing cancer, type-2 diabetes mellitus, and cardiovascular disease [5, 6] . It is such findings that have led to an array of interventions targeting the health behaviors of individuals to improve health outcomes. Because risk perception is seen as an integral part of behavior change in many health behavior theories, it is now assumed that personalized risk information is an important prerequisite to engage individuals in positive health behaviors. Individualized risk estimates provide one means of providing such personalized information. However, research has been conflicting in terms of the ways in which such information may influence and change risk perception or health behaviors. At the same time, there has been critique from within epidemiology on individual-level approaches to prevention [75, 95], as well as from the social sciences on the use of individualized risk estimates [84]. However, there is little known about the actual uses of such individualized risk estimates in practice. It was the aim of this habilitation to understand qualitatively how individualized risk estimates may be used in practice and what ethical and conceptual concerns may be warranted based on such uses. In the following, we discuss these findings.

3.1   The use of individualized risk estimates by individuals

The analysis of the online use of the DRS indicated that lay individuals readily use risk scores available online and some calculate a risk estimate more than once with changed values. The study design did not allow for assumptions about why individuals may have calculated several scores in one session. However, we may assume that while doing so, individuals learned something about how changes in values of risk factors influence the calculated individualized risk estimate.

        While individuals seem to have an interest in calculating their risk and "playing" with their risk level, it may be less commonly used for actual health decision-making [67]. In a situation in which both risks and benefits were involved in a treatment for something that had not yet occured, it appeared difficult to use probabilistic information for *individual* decision-making. Mrs. Wayne, who was concerned both about developing breast cancer and about taking tamoxifen, could not know from the probabilistic information given to her whether she would suffer from side-effects of the medication or whether she would actually profit from taking the drug. The probabilistic information cannot tell an individual whether taking the medicine will actually prevent a disease that he or she may or may not get. This case example highlights the problematic nature of probabilistic information at the individual level: a risk estimate can only give a degree of likelihood, but it cannot predict whether an individual will or will not get the disease. This problem of the use of probabilistic information for single events remains unresolved [86, 96].

        Thus while individuals may have an interest in knowing their risk levels, they may still prefer heuristic-based decision-making over risk-based decision-making, even when they have risk information available [58, 59, 87]. While this is well known in decision-making theory [97], efforts persist to guide individuals to more risk-based decision-making. Considering the difficult task of translating probabilistic information for an individual's life, as evidenced by Mrs. Wayne's narrative, aversion to risk-based decision-making may be a reasonable approach for some. To further understand the relationship between an

individual and a population, we then investigated the development of individualized risk estimates from conceptual and ethical perspectives.

3.2 Conceptual and ethical considerations concerning individualized risk estimates

In order to calculate individualized risk estimates, large data sets are necessary that consist of data that is comparable across time and space, in order to aggregate the information and make computations. This process of "populationisation" enables computations that can show patterns of disease with associated variables across and within study populations [68]. In this sense, such computations can only give probabilities on population fractions rather than individuals. It is this distinction of an individual from a population fraction that raises ethical concerns regarding the use of the term "individualized" [69]. Individualized may suggest a level of accuracy of the risk estimate for particular individuals that may be misleading. There exists a difference between an individual's true risk and individualized risk estimates that is obscured by the use of such language. In addition, the use of individualized risk estimates for health communication may conflate risk prediction with risk reduction. "Playing" with risk scores and changing one's risk by inserting different values for risk factors is firstly a mathematical calculation and not a change in actual risk. In order to discern whether indeed such a change in risk factors leads to the calculated reduction in risk of the model, this would necessitate the implementation of intervention studies on individualized risk estimates. Such studies are quite challenging to design and conduct.

Risk prediction models depend on the availability of data in terms of what factors can be included into a model. For example, the original DRS did not include family history, a well known risk factor for type-2 diabetes mellitus, because EPIC did not have that information in its database. Only later, with the help of another epidemiological study, could family history be included in the model [38]. Aside from the availability of data, the selection of risk factors for risk modeling is based on statistical reasoning. This means that the risk factors included may not necessarily lie on the causal pathway of disease development

[69]. For example, the Gail score includes the number of biopsies in its calculation, a factor that is *associated* with developing breast cancer – which is why it is considered a risk factor in the Gail model – but it does not lie on the causal pathway of developing breast cancer.

Thus when one considers using individualized risk estimates, not only to calculate the future burden of disease of populations but also for health education and individual behavior change, several factors need to be carefully evaluated. First, what factors are amenable to change on an individual level? Second, for which of these factors does evidence exist, as derived from intervention studies, that a change of the value reduces the risk of the disease? How can one best communicate that the change in statistical risk may be different than the change in actual risk? And finally, it should be carefully considered which of the available individualized risk models are best suited for such individual interventions, based on the risk factors they include. The DRS clearly is more favorable in this respect compared to the Gail model.

3.3   Primary prevention in general practice

The use of individualized risk estimates in clinical practice is suggested for CVD prevention, for example through the use of scores such as ARRIBA or others that are intended to aid health care providers to identify patients for which health behavior change or the use of Statins is recommended. In countries such as the UK, there are now projects under way that take advantage of electronic health records to automatically calculate scores as well as potential benefits through Statin use or health behavior change, which are given to patients on a routine basis to inform their treatment decision-making [63, 98]. In Germany, such an approach is not feasible as there is no standardized way of keeping health records, and patients are not obliged to have a GP in order to access the health care system. Furthermore, in Germany we found that many GPs did not use individualized risk estimates, because they felt that the estimates did not provide them with additional information and may obscure information they already knew and had about their patients [70]. At the same time, GPs did not have a clear understanding of what individualized risk estimates signified, and

used a range of qualitative, subjective, and quantitative means of assessing risks and discussing them with their patients. Most importantly, GPs found a standard approach to risk assessments in practice detrimental to the patient-physician relationship.

In those instances in which GPs were interested in using individualized risk estimates, some indicated that they would appreciate visual tools with which they could show patients how their risk levels could change based on changes in the risk factors. Thus they saw the value of individualized risk estimates in terms of their ability to visually show the effect of a change in risk factors. However, as we have discussed above, the preciseness of this quantified risk reduction is unlikely to reflect actual risk reduction.

Considering this uncertainty involved when using individualized risk estimates at an individual level and the limited evidence thus far that their use significantly influences behavior change, this suggests that other approaches should be researched in order to investigate prevention efforts in clinical practice. With such a broadened perspective on prevention efforts in practice, Holmberg et al. [71] found that GPs discussed health behavior change mostly in relation to the reason for the patient's health care visit, in order not to jeopardize the relationship with the patient and to ensure continued care. GPs' offices seemed better suited for secondary and tertiary prevention rather than primary prevention, based on the patient population in German GP offices. In addition, GPs who participated in focus group discussions suggested that an approach confined to the health care sector that solely focuses on the individual would not be sufficient to initiate behavior change. They suggested multi-level interventions to successfully target behavior change in populations, which should include structural aspects such as the availability and accessibility of swimming pools and physical activity facilities, as well as schools and other societal institutions, in order to provide an environment that promotes and fosters healthy behavior.

3.4 Individual intervention versus multi-level intervention to change the burden of disease

At the heart of debates concerning the use of individualized risk estimates stands the question of how to improve patients' and population health. The two examples used in this habilitation, the DRS and the Gail score, represent two very different scenarios. For breast cancer, there is little evidence that risk can be reduced by individual lifestyle changes, thus an increased focus is put on pharmaceutical or surgical interventions. The use of the Gail score may further foster a focus on pharmaceutical intervention, as Rockhill and Fosket have argued [84, 99]. Such a narrow risk approach may lead to a neglect of the many environmental factors that are implicated in breast cancer incidence, as a variety of studies, including migration studies, have shown [100], several of which hint to a relative importance of early life events in terms of influencing breast cancer risk. Thus if the increased development and use of individualized risk estimates would lead to such a narrow focus on the cause and prevention of disease, this is likely to be problematic. The approach used in individualized clinical guidelines also has an emphasis on Statin use for CVD risk reduction, however they also include other risk reducing possibilities or focus on thresholds for interventions [63, 98]. While it is important to set thresholds to give an indication of who may profit from an intervention, be it behavioral or pharmaceutical, such decisions involve many factors, including political and economic ones. These should be communicated in order to make the setting of thresholds more transparent in practice.

The use of the DRS, which includes modifiable risk factors, may be less prone to result in pharmaceutical interventions, especially because there is strong evidence of the importance of lifestyle factors for type-2 diabetes mellitus incidence. In this case, what remains from the critique voiced by Rockhill [75, 99, 101] is the focus on individuals' behaviors in the use of the DRS. Rockhill [75, 99] argues that Western philosophy and cosmology favors a focus on the individual rather than on societies or populations, and that these "hidden" values drive current research efforts. The continued focus on the improvement of individualized risk estimates that use current information technology may be influenced by such values [61-63].

A longstanding debate in the literature has arisen around Geoffrey Rose's prevention paradigm [102]. Rose suggested that different prevention approaches are necessary to target population health in contrast to individual health. He argued against a "high-risk" approach to prevention, since the bulk of disease happens in the general population. A contrasting approach suggests that in the 1980s and 1990s at the time when Rose developed his arguments sufficiently developed tools were not yet available to differentiate different risk groups. Since this has changed, it is argued that risk reduction should be guided in diverse sets of populations by incorporating risk identification tools into prevention efforts and developing novel methods for risk prediction [103-105]. The two examples used in this habilitation, individualized risk estimates for breast cancer and type-2 diabetes mellitus, show that one should factor the disease in question into these debates. For some a high-risk approach may be more appropriate than for others. It may also be necessary to develop novel approaches to the evaluation of risk models used for individual decision-making [106]. Similarly, one needs to take into consideration ethical concerns in the communication of individualized risk prediction, and more importantly the difference between risk prediction and risk reduction.

From a public health perspective, it is important to realize that an approach solely focused on individuals and individual behavior change is unlikely to be successful. Individual behavior is deeply intertwined in social, economic, and cultural structures and cannot be viewed in isolation [65]. Public health efforts that have been successful in the long-term behavior change of a population with an effect on incidence rates – such as tobacco smoking in the US or reduction of traffic-related injuries in Australia – were successful because they involved different intervention levels, including a focus on individual behavior change, policy decisions, and structural changes [60, 94].

4 Conclusion

With the current increase in knowledge of risk factors and advances in information technology, the development of individualized clinical guidelines is under way [61-63]. The spreading of such guidelines is dependent on the existence of electronic records that capture the health information necessary to calculate common individualized risk estimates for CVD, type-2 diabetes mellitus, and other diseases [64]. The core of these guidelines is individualized risk estimates. The use of electronic records and the possibility of calculating individualized risk estimates on a routine basis bring the standardized approach of individualized risk estimates to the heart of medical practice, something that the GPs in our studies resisted. It is likely that the push to use such risk prediction tools on a routine basis will persist. Such consideration will, however, need to take into account the active role of patients and the likely change in the patient-physician relationship in German general practice [70, 71].

The effects and changes that routine use of individualized risk estimates has in terms of the patient-physician relationship, as well as individual decision-making, should be further scrutinized. Finally, policy-level studies should be initiated that investigate whether an increased focus on the development and application of individualized risk estimates indeed leads to a narrowing of prevention efforts, as some suggest [75, 95].

If we consider the accumulated evidence that some simple health recommendations may successfully reduce the risk of major chronic diseases simultaneously [5, 6, 32], as well as the discussed problems with the use of individualized risk estimates, it may be worthwhile to focus on structural factors that will enable individual sustained behavior change in order to reduce the burden of disease in society, rather than focusing on improved risk prediction, particularly as its effects on risk reduction are as yet unknown.

5 Summary

In this habilitation, I focused on studies that investigated the ethical and conceptual considerations of using individualized risk estimates in medical care, particularly the use of individualized risk estimates in medical practice and for individual decision-making. The aim was to learn about the ethical implications that arise when a tool that is developed within one discipline, epidemiology, is moved into medical and public health practice for health communication and decision-making purposes. Conceptual concerns, such as the difference between populations and individuals, as well as how an individual comes to be represented in a population, were of further interest in order to understand the implications of the use of individualized risk estimates. Finally, the studies analyzed how such individualized risk estimates may be used (or not) in real-life settings, including their use by laypersons and health care professionals.

The findings suggest that the critiques of individualized risk estimates include problems associated with using information on population fractions to suggest precise *individual* prediction, conflating risk prediction and risk reduction, and translating probabilistic information onto a single event in an individual's life. Indeed, one cannot yet quantify on an individual level how an individual's risk may change when he or she changes his or her risk factors.

Case studies of how individualized risk estimates may be used in lay decision-making found that it was impossible for a woman to transform the statistical information into personally relevant information, as the probabilities could not tell her whether she would get the disease. Physicians, in turn, were not overtly enthusiastic about the use of individualized risk estimates because they perceived them as adding only a limited amount of new information about their patients.

The main goal of using individualized risk estimates outside of epidemiology is to guide health decision-making and help identify individuals who should be targeted with risk-reducing measures. The findings suggest that this may be of importance at a population level in terms of targeting interventions, but not for individual health communication, as individuals may know qualitatively that they are at risk (or not) and may not use the quantified

risk information in the manner that health care policy would like [87]. The nature of probabilistic information and the manner in which individualized risk estimates are developed suggest that this may indeed be a reasonable approach by individuals and health care providers.

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Erklärung

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