J Community Genet (2014) 5:31–48
DOI 10.1007/s12687-013-0160-2

REVIEW

Patient compliance based on genetic medicine: a literature review

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Received: 26 December 2012 / Accepted: 2 July 2013 / Published online: 10 August 2013

Abstract For this literature review, medical literature data bases were searched for studies on patient compliance after genetic risk assessment. The review focused on conditions where secondary or tertiary preventive options exist, namely cancer syndromes (BRCA-related cancer, HNPCC/colon cancer), hemochromatosis, thrombophilia, smoking cessation, and obesity. As a counterpart, patient compliance was assessed regarding medication adherence and medical advice in some of the most epidemiologically important conditions (including high blood pressure, metabolic syndrome, and coronary heart disease) after receiving medical advice based on nongenetic risk information or a combination of genetic and nongenetic risk information. In the majority of studies based on genetic risk assessments, patients were confronted with predictive rather than diagnostic genetic profiles. Most of the studies started from a knowledge base around 10 years ago when DNA testing was at an early stage, limited in scope and specificity, and costly. The major result is that overall compliance of patients after receiving a high-risk estimate from genetic testing for a given condition is high. However, significant behavior change does not take place just because the analyte is "genetic." Many more factors play a role in the complex process of behavioral tuning. Without adequate counseling and guidance, patients may interpret risk estimates of predictive genetic testing with an increase in fear and anxiety.

This article is part of the special issue "Predictive Genetic Testing, Risk Communication and Risk Perception"

Electronic supplementary material The online version of this article (doi:10.1007/s12687-013-0160-2) contains supplementary material, which is available to authorized users.

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Keywords Genetic testing · Patient compliance · Medication adherence · Cancer screening · Genetic risk · Patient behavior

Introduction

A decade after sequencing the human genome, many genetic tests are now available that can modify the risk of developing a genetic disease or predict the individual response to drugs or allow other predictions based on discovered associations between certain genes and diseases. High expectations that such tests could improve patient health through enhancing patients' compliance with medical advice have been raised (Hunter et al. 2008; Harmon 2012). Factors expected to influence patient compliance based on genetic risk assessment include the predictive power of assessment measures, including genetic testing itself (Harmon 2012), severity of the condition in question, availability and burden of prophylaxis, third-party (especially family) relevance (Heshka et al. 2008b), and availability of appropriate genetic counseling (Heshka et al. 2008a). This view has been challenged by authors who are more skeptical about the power of genetic information to increase patient compliance. Marteau and Lerman (2001) reviewed evidence concerning behavioral responses to genetic information on risk and came to the conclusion that knowledge of DNA-derived information about health risks does not increase motivation to change behavior beyond that achieved with nongenetic information. In a critical review by McBride et al. (2010) on the behavioral response to personalized genetic information, genetic information with low numerical risk was observed to have little impact on behavior.

Public interest in genetics was fuelled by reports in the media. In 2007, the New York Times, for example published a blog on this issue (Parker-Pope 2007). Parker-Pope referred to twin studies which showed that while 30 % of our health differences can be explained by genetics, 70 % of

susceptibility to health problems are due to environmental factors. This leads to the interpretation that, "with the exception of certain rare diseases, a genetic predisposition just means a condition is possible, not that it's inevitable" (Parker-Pope 2007). That is the point where compliance after genetic testing may have its role. If one can positively influence the 70 % susceptibility to health problems, then not only an individual or their family members may benefit but also the whole health care sector.

The media are, however, also skeptical as to the benefits of genetic testing. The German news magazine "Der Spiegel" doubted that genomics will ever have the expected clinical relevance and thus benefit for patients (Blech 2009). The author argued that personalized medicine is far more complex, mainly due to unknown regulatory processes by epigenetic modification. It would perhaps be beneficial for the patient if regulatory processes could be indirectly influenced by behavioral changes or other health-related choices. Similarly, the New York Times pointed out that "Having a version of a gene may change the odds, making you more or less likely to have a trait… the actual outcome depends on a tangle of other circumstances as well" (Pinker 2009). The direct-to-consumer marketing of genetic testing created additional media interest, but the consumer and health care sector look critically at such business: "… personal genomics promises benefits and pitfalls that no one can foresee" (Pinker 2009).

In this review, we have systematically screened the scientific literature for reports quantifying patient compliance after any kind of genetic risk assessment, with or without genetic testing, focusing on conditions where secondary or tertiary preventative options exist. In addition, we evaluated compliance following physicians' advice in situations after nongenetic risk assessment. Of particular interest was the length of adherence to medication and frequency of clinical follow-up.

Methods

For this review, several literature databases, namely PubMed, Cochrane Database, MEDLINE, and Scopus were searched for relevant entries between January 1990 and February 2011. This review specifically includes the following syndromes and behavioral responses: hereditary nonpolyposis cancer (HNPCC), hereditary breast cancer (BRCA1/2), smoking cessation, thrombophilia, obesity, hemochromatosis (HFE), and medication adherence after receiving medical advice based on nongenetic risk information. Defined search terms were used in random relationships. Additionally, the disease/gene defect was added to the search terms. Thus, "colorectal cancer," "bowel cancer," "HNPCC," "Lynch syndrome," "patient compliance," "screening compliance," " screening behavior," "compliance after genetic testing," "BRCA1/2," " thrombophilia," "hemochromatosis," "haemochromatosis," "medication adherence," "smoking cessation," "obesity," " patient behavior after," "screening behavior after genetic testing for," "compliance genet*," "genetic testing," and "genet*" were used in combination. Moreover, reference lists and citations were searched. Only published articles written in English were included in this review. Clinical studies as well as analog studies were considered. This review does not include genetic testing relating to reproductive options such as carrier screening for recessive conditions.

A total of 290 different papers and studies were evaluated. Eighty-two studies directly addressed compliance before and after genetic testing and were eligible for comparison. Given the heterogeneity of the studies, no inclusion or exclusion criteria were set, except that studies with low numbers of participants (fewer than ten per group) or case reports were excluded. A structured analysis of these studies appeared not to be feasible because highly heterogeneous methods were used to collect data especially during follow-up. In addition, limited group sizes did not allow a high powered statistical analysis in the majority of publications. The heterogeneity of the studies prohibited any form of meta-analysis. Therefore, a descriptive approach was chosen, and the main findings for each condition are summarized in text form as well as in the detailed tables, added as supplemental material online only. Many studies deal with patient groups at elevated prior risk undergoing genetic testing. In these studies, mutation-negative patients are typically referred to as "noncarriers," even though their actual carrier status may not have been excluded. When reporting the results of these studies, we have retained the original terminology but wish to alert the reader to a potential source of confusion.

Results and discussion

Hereditary nonpolyposis colon cancer

Summary Most of the HNPCC mutation-positive study participants (about 60–70 %) showed greater adherence to screening guidelines than mutation-negative participants (about 10–15 %). In mutation-negative study participants, a progressive reduction of screening frequency was observed. When comparing compliance before and after genetic testing, most carrier participants showed a higher compliance after genetic testing. In particular, clinically unaffected risk carriers underwent regular screening (colonoscopy and gynecological screening) at much higher rates (70–80 %).

The evaluated studies regarding HNPCC are listed in Electronic supplementary material (ESM) 1.

Hereditary nonpolyposis colon cancer is an autosomal dominant trait which causes colon cancer at an early adult age and additionally predisposes to extracolonic cancers, mostly cancer of the endometrium, ovary, and stomach (Halbert et al. 2004). Prevalence among colon cancer patients varies from 1 to 3 % (Rahner et al. 2010). This cancer syndrome is caused by germline mutations of mismatch repair genes in particular *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Lifetime risk to develop the disease if these mutations are present is approximately 80 %. For individuals identified as a mutation carrier, annual/biennial colorectal cancer screening with complete colonoscopy from age 20 and yearly gynecological examination including transvaginal ultrasound in women, starting at age 30 years, is recommended (Rahner et al. 2010). One aspect one has to keep in mind is that the health care provider plays a highly important role when it comes to screening behavior and guidance of the patient. Not having had a health care provider recommend a sigmoidoscopy or colonoscopy was found to be the most important independent predictor of not recently having these tests (Kinney et al. 2007).

Johnson et al. (2002) questioned 65 clinically unaffected but with increased prior risk participants after genetic counseling (mutation positive, 7; mutation negative, 37; and test not taken, 21) about colonoscopy screening practices (mean follow-up time, 12.7±3.8 months after clinic visit). Mutation-positive patients were more likely to adhere at 100 % to screening guidelines vs. 40.5 % of mutation-negative and 57.1 % of untested patients. Of these 65 patients, 50 (76.9 %) had undergone at least one endoscopic colon exam prior to genetic risk assessment. At the time of genetic risk assessment, 37 of 65 (56.9 %) were overdue for colon examination, at follow-up only 15 of 65 (23.1 %) were still overdue. At follow-up, 52.3 % (34 of 65) had undergone colonic examination since their clinic visit.

In a prospective cohort study, Halbert et al. (2004) asked 98 clinically unaffected participants who were at higher familiar risk of HNPCC (22 mutation carriers, 49 noncarriers, and 27 not tested) about colorectal screening practices during a 12-month follow-up after genetic testing. At baseline, 37 (38 %) reported that they had never had a colonoscopy, whereas 61 (62 %) reported having had colonoscopy before genetic counseling/testing. After the 12-month follow-up, 73 % of carriers had colonoscopy, 16 % of noncarriers had colonoscopy, and 22 % of decliners had colonoscopy which demonstrates a significant difference between carriers and test decliners at follow-up. Within 2 years after the baseline survey, 36 % (8 of 22) of carriers, 27 % (13 of 49) of noncarriers, and 26 % (7 of 27) of decliners had colonoscopy, demonstrating a massive decrease in the group of mutation-positive participants. A higher educational level and in particular those who had been informed about increased cancer risk were significantly more likely to have had colonoscopy before genetic counseling and testing.

In a prospective survey by Hadley et al. (2004), 56 clinically unaffected participants with increased prior risk for HNPCC (17 mutation positive and 39 mutation negative) were studied concerning colonoscopy screening behavior during a 6- to 12-month follow-up. Before genetic testing, 30 of 56 (54 %) participants had had at least one colonoscopy at an earlier time point. This subgroup included participants with increased age and higher income level. After genetic testing, colonoscopy use correlates with a mutation-positive result and increasing age (53 % of mutation positive had at least one colonoscopy postgenetic testing vs. 8 % of mutation negative). Colonoscopy occurrence changed in patients relative to genetic test result. Mutation-positive patients showed an increase in undergoing colonoscopy from 41 to 53 % (nonsignificant increase); mutation-negative persons demonstrated a decrease from 59 to 8 % ($p<0.0003$, significant decrease).

Collins et al. (2005) surveyed 114 clinically unaffected participants at risk for HNPCC at baseline (32 carriers and 82 noncarriers) and 88 clinically unaffected participants after 12 months. Rates of colonoscopy screening (as well as transvaginal ultrasound, endometrial sampling, and prophylactic surgery for female carriers) at baseline and after 12 months were compared. After 12 months, 71 % of carriers and 12 % of noncarriers had had colonoscopy. Compared with colorectal cancer screening practices before genetic testing (25 % <25 years and 73 % >25 years had ever had colonoscopy before genetic testing) this demonstrates a nonsignificant increase in carriers and a significant decrease in noncarriers ($p<0.001$). Of the female carriers, 8 of 17 (47 %) had transvaginal ultrasound, whereas 9 of 17 (53 %) had endometrial sampling. Of the 39 female noncarriers, only 10 % underwent transvaginal ultrasound and only 5 % underwent endometrial sampling. In 2007, more follow-up data were published; the surveillance time was expanded to 3 years (Collins et al. 2007). All carriers had colonoscopy between 12 months and 3 years posttesting, and 7.4 % of the noncarriers had colonoscopy. After 3 years, 9 of 13 female carriers reported having had transvaginal ultrasound (69 %) and 7 (54 %) underwent endometrial sampling. Of the 32 female noncarriers, only 2 underwent transvaginal ultrasound and 1 underwent endometrial sampling during the previous 2 years.

Wagner et al. (2005) analyzed screening behavior with an average follow-up of 3.5 years of 70 mutation-positive participants, and 28 were clinically diagnosed of cancer (colorectal, endometrial, or both) at the time of testing. Before genetic testing, 31 % (13 of 42) of clinically unaffected risk carriers had regular colonoscopy (62 % every 2 years and 38 % less frequently). After testing, 88 % (37 of 42) of clinically unaffected carriers reported having colonoscopy screening every 1–2 years. Before genetic testing, gynecological screening was performed in 3 of 18 (17 %) unaffected

female risk carriers >35 years, at the time of the questionnaire 20 of 29 (69 %) female risk carriers >35 years had gynecological screening. To conclude, in this study genetic testing improved compliance for colonoscopy screening from 31 to 88 % and for additional gynecological screening from 17 to 69 % in clinically unaffected risk carriers.

Claes et al. (2005a) interviewed 72 clinically unaffected participants (29 females and 53 males) from mutation-identified families (36 carriers and 36 noncarriers) about screening adherence 1 year posttest. All mutation carriers adhered to the recommendations, whereas none of the noncarriers had colonoscopy in that year. Prior to genetic testing, 31 % of the later identified carriers had never had a colonoscopy. Ponz de Leon et al. (2004) analyzed medical data from 164 participants being tested for HNPCC (89 gene carriers and 75 mutation negative). Data included in this study were from 23 mutation-positive but cancer-unaffected individuals. They reported that 82.6 % of unaffected gene carriers had colonoscopy within 1–2 years from the test result. Hadley et al. (2008) surveyed 65 females at 50 % risk for carrying the HNPCC mutation. Testing identified 28 females as HNPCC carriers and 37 as noncarriers. The participants were unaffected by endometrial cancer but 15 % had a history of nonendometrial cancer. Screening behavior (colorectal cancer as well as endometrial cancer) at baseline, 6 months, and 12 months posttest was analyzed. Compared with 11 % of noncarriers, 61 % of carriers had colonoscopy posttest. Prior to testing, 36 of the 65 women (55 %) had undergone colonoscopy, leaving no significant difference between carriers and noncarriers. Additionally, endometrial cancer screening behavior was assessed and showed that 30 % of carriers and 32 % of noncarriers had endometrial cancer screening before testing. After testing 54 % of carriers underwent endometrial cancer screening procedures, compared with 14 % of noncarriers.

Ersig et al. (2009a) interviewed 69 participants personally affected by cancer (genetic test result, 38 mutation positive and 31 inconclusive). Sixteen mutation-positive participants had endoscopy in the year before receiving their genetic test result confirming their mutation-positive status. In the year of postgenetic testing, 69.9 % (30 mutation positive of a total of 48) had endoscopy. Overall, there were no differences between the groups in the year before receiving test results; however, after receiving test results patients with an inconclusive test were significantly less likely to have endoscopy than mutation-positive patients. Ersig et al. (2009b) emphasized that not only mutation status but also familial relationships play an important role. These authors found that time since last screening did not differ according to family mutation status. However, respondents who communicated about risk and received encouragement to screen from a greater proportion of named family members, and those who had a greater proportion of named family members involved in both communication and encouragement were found to be significantly more likely to have a shorter time interval since last colonoscopy.

Additionally, genetic counseling and testing itself was found to influence patients' behavior. Those actively undergoing genetic counseling and genetic testing for Lynch syndrome were more likely to comply with regular colonoscopic surveillance (Stoffel et al. 2010). Very high (98.8 %) long-term compliance to colonoscopy screening in HNPCC mutation-positive patients was demonstrated by Pylvänäinen et al. (2006). Medical data was collected on 415 HNPCC mutation-positive participants comprising 203 males and 212 females. Of the 415 patients, 49 % showed no colonoscopic findings. The reduction of mortality by colorectal screening (colonoscopy) due to earlier detection of colon cancer was also demonstrated by Järvinen et al. (2000), who examined 252 asymptomatic individuals belonging to HNPCC families being at 50 % a priori risk. They were divided into two cohorts, 133 in the study group and 119 in the control group. The research question concerned the efficacy of colorectal cancer screening over 15 years with a colonoscopy every 3 years for the study group. Colorectal cancer development was 6 % in the study group vs. 16 % in the control group. In this case, regular screening decreased overall mortality around 65 % in HNPCC families. In a cross-sectional survey by Kinney et al. (2007) on 150 participants being tested for familial adenomatous polyposis (71 clinical or genetic diagnosis and 29 remaining at greater risk because relatives were mutation positive or no cancer history), participants whose activated protein C (APC) mutation status was indeterminate or unknown were shown to be less likely to have had a recent endoscopy (59 %) than those who were carriers (42 %).

All of the aforementioned studies included information regarding screening behavior pre- and postgenetic testing, however, not always as a direct comparison. As already presented above, in most of the studies concerning colorectal screening practices in at-risk patients, mutation-positive participants showed greater adherence to recommended screening guidelines than mutation-negative participants. In addition, cancer-affected mutation-positive participants showed greater screening compliance and guideline adherence than cancer-affected mutation-negative participants (Halbert et al. 2004; Collins et al. 2005; Kinney et al. 2007; Ersig et al. 2009a; Stoffel et al. 2010; Loader et al. 2005; Bleiker et al. 2005) (Table1).

Familial breast cancer (BRCA1/2)

Summary Compliance before and after BRCA1/2 testing should be evaluated differently in female and male study participants. In general, male mutation carriers had a reduced screening frequency for colorectal and prostate cancer

Table 1 Studies examining compliance before and after genetic testing for HNPCC

Study	Prior to testing	After testing carriers	After testing noncarriers
Johnson et al. (2002)	At the time of genetic risk assessment, 56.9 % were overdue for colon exam	At follow-up, 23.1 % (unaffected at high risk) were still overdue	
Halbert et al. (2004)	36 % of carriers and 27 % of noncarriers had colonoscopy within 2 years of baseline survey. Participants with higher education level and informed about greater risk were more likely to have colonoscopy before testing	73 % had colonoscopy during 12 months after genetic testing	16 % had colonoscopy during 12 months after genetic testing
Hadley et al. (2004)	54 % of participants had at least one colonoscopy before genetic testing. Compliance was more likely with higher income level and age	53 % had colonoscopy in 12-month posttest	8 % had colonoscopy in 12-month posttest
Wagner et al. (2005)	31 % of unaffected risk carriers had regular colonoscopy before genetic testing (62 % every 2 years and 38 % less frequent)	88 % of healthy risk carriers intended to have colonoscopy screening every 1–2 years	
Wagner et al. (2005)	17 % of unaffected risk carriers, over 35 years before genetic testing had gynecological screening	69 % over 35 years old had gynecological screening at time of questionnaire	
Collins et al. (2005)	25 % <25 years old and 73 % >25 years old had colonoscopy	71 % had colonoscopy within 12-month posttest	12 % had colonoscopy within 12-month posttest
Claes et al. (2005a)	Prior to genetic testing 31 % of carriers never had a colonoscopy	After genetic testing 100 % of carriers were adherent to guidelines	
Hadley et al. (2008)	55 % had undergone colonoscopy pretest (no difference between carriers and noncarriers)	61 % of carriers had colonoscopy posttest	11 % of noncarriers had colonoscopy posttest
Hadley et al. (2008)	30 % of carriers and 32 % of noncarriers had endometrial cancer screening pretest	54 % of carriers had endometrial cancer screening posttest	14 % of noncarriers had endometrial cancer screening posttest
Ersig et al. (2009a)	33.3 % completed colorectal screening in the year before genetic test	In the year after test results: 69.6 % of index cases had colonoscopy, mutation positive more likely than inconclusive	

compared with women's screening frequency for breast and gynecological cancer. BRCA1/2 mutation-positive women were more likely than noncarriers to engage in risk management strategies, reaching statistical significance in some studies. When looking at patients regarding cancer affection status, there seems to be a trend that participants unaffected by cancer show greater behavioral differences. These surveillance strategies included not only regular or shorter screening intervals but also surgical removal of the potentially affected organs. Women in general showed higher baseline compliance to screening procedures. Over the last couple of years, genetic testing for BRCA1/2 has fallen in price and is discussed more openly in public. BRCA1/2 is a good example for influencing compliance after genetic testing because a quantitative risk assessment gives women a framework to decide about their own situation.

The evaluated studies regarding familial breast cancer are listed in ESM 2.

In Europe, breast cancer is the most frequent malignancy in women (Abdulrahman and Rahman 2012). Family history is the most important risk factor for developing breast cancer (Nelson et al. 2012; Protani et al. 2012). In about 2.5 % of the cases, mutations in the *BRCA1* or *BRCA2* genes are responsible for the disease. If identified as a carrier of a *BRCA1* mutation, there is a lifetime risk for breast cancer in women of 60–80 % and 40–55 % for ovarian cancer. Carrying a *BRCA2* mutation means a lifetime risk for women of 40–50 % for breast cancer and 10–20 % for ovary cancer. Additionally, carriers have an increased risk for other tumors in the prostate, pancreas, and intestine (Wieacker et al. 2008). Since breast cancer is the most prevalent cancer in women, much research has been conducted on the topic. Many studies analyze patient's behavior before and after receiving genetic test results for *BRCA1/2*. Additionally, patient behavior and compliance according to mutation status was evaluated.

In a study by Metcalfe et al. (2000), 58 % of carriers reported that screening behavior increased since receiving a test result, especially in women less than 59 years old and in women with no previous clinical diagnosis of cancer. Lerman et al. (2000) surveyed 216 females at risk for breast cancer (84 *BRCA1/2* carriers, 83 noncarriers, and 49 test decliners). Sixty of the participating females had a prior history of breast cancer. After 1 year, utilization of prophylactic surgery and surveillance behavior post-*BRCA1/2* test was analyzed (women with previous mastectomy were excluded from the mammogram test). In this case, adherence rates to mammogram in carriers were unchanged from baseline (68 % of carriers at baseline and after 1 year). However, carriers had significantly more mammograms than noncarriers (44 %) and decliners (54 %); (at baseline, 55 % noncarriers and 67 % decliners). Overall, the use of transvaginal ultrasound and CA125 at baseline was 10–11 % compared with 21 % of carriers undergoing CA125 and 15 % of carriers undergoing transvaginal ultrasound at follow-up. The difference in carriers and noncarriers reflected appropriate reduction in mammography in younger noncarriers. No evidence was found that motivation for screening behavior was increased by being mutation positive.

In a study by Scheuer et al. (2002), there was an overall increase in mean number of mammograms, clinical breast examinations, ovarian ultrasonograms, and CA125 determinations performed after genetic testing. However, the effect of genetic testing on breast cancer screening was found not to be statistically significant in the subset with prior breast cancer, which the authors attributed in part to a high incidence of baseline screening. A similar conclusion was reached by McInerney-Leo et al. (2006) who could not demonstrate any direct association between testing or test results and screening once other factors including baseline adherence, age, cancer history, worry, and distress were included in the model, although testers were more likely to undergo clinical breast exam than decliners.

Schwartz et al. (2003) interviewed 289 high-risk women (79 *BRCA1/2* positive, 44 *BRCA1/2* negative, 166 uninformative test results; 70 % were affected by breast cancer) at 1, 6, and 12 months posttest to assess ovarian cancer screening behavior and surgery decisions. At baseline, utilization of CA125 testing by carriers was 12 %, 16 % of all carriers had undergone transvaginal ultrasound. After 1 year, 43 % of carriers underwent CA125 testing compared with 9 % of noncarriers. Carriers clinically affected by breast cancer were more likely to obtain CA125 screening. Utilization of transvaginal ultrasound in carriers increased to 40 %, compared with 21 % in noncarriers. It was found that 27 % of carriers underwent bilateral prophylactic oophorectomy (34 % *BRCA1*, 9 % *BRCA2*) in 1 year compared with 5 % of participants with uninformative test results and 2 % of noncarriers. This demonstrates an increase in subsequent screening behavior and prophylactic surgery dependent on mutation status.

Botkin et al. (2003) interviewed 37 female carriers and 92 female noncarriers. Additionally, 15 participants with unknown mutation status were interviewed about their screening behavior and attitudes to prophylactic surgery decisions at baseline as well as at 1–2 weeks, 4–6 months, and 1–2 years posttesting. At baseline, mammogram was used by 22 % of carriers and 30 % of noncarriers. After 1 year, mammography use increased in carriers to 62 %, as well as in noncarriers to 53 %. After 2 years, use of mammogram was still elevated over baseline (carriers 57 % and noncarriers 49 %). Carriers and noncarriers additionally increased use of breast self examination. To conclude, carriers were not significantly more likely to obtain mammograms during the 1- or 2-year follow-up vs. noncarriers, but both groups showed a significant increase over baseline. No statistical difference was found between groups concerning use of

clinical breast examination or breast self examination after 2 years. No participants had a mastectomy within 2 years, but 46 % of carriers underwent oophorectomy.

Tinley et al. (2004) evaluated 112 returned questionnaires (33 mutation carriers and 79 at 50 % risk of being a carrier). Those women reported about their gynecological cancer screening behavior in the last 2 years. Adherence rates of the total group were 72 % for annual mammography, 21 % for biannual clinical breast exam, 29 % for monthly breast self exam, 19 % for annual transvaginal ultrasound, and 1 % for CA125 assay annually. In all cases, carriers were more adherent than participants who had a 50 % risk, but this was only statistically significant for clinical breast exam. This study also emphasized the findings by Loescher et al. (2009), that primary physician behavior had a significant independent association with adherence to mammography, clinical breast exam and ultrasound screening recommendations (Tinley et al. 2004).

Kinney et al. (2006) included 40 women (African Americans, 10 % of whom were affected by breast/ovarian cancer) with 10 being carriers for *BRCA1* mutations and 30 were noncarriers. Prior to genetic testing, 47 % of participants had undergone a mammogram (86 % of carriers reported having had a mammogram in the year before testing). One year after genetic testing, 71 % of carriers compared with 59 % of noncarriers adhered to mammography screening guidelines. There was no significant increase in carriers compared with the baseline interview. Before genetic testing, none of the participants had undergone ovarian cancer screening by tumor marker CA125 measurement. After genetic testing, 20 % of carriers reported CA125 screening and 25 % of carriers underwent transvaginal ultrasound in the year following genetic testing.

Lynch et al. (2006) showed that the rate of compliance with both breast and ovarian cancer screening recommendations was significantly increased among mutation carriers. Similarly, Antill et al. (2006b) found that mutation-positive women were more likely to adhere to clinical breast exam recommendations. Similar compliance was demonstrated by Loescher et al. (2009) who surveyed 107 women at risk for *BRCA1/2* mutations (84 % mutation negative, 8 % mutation positive, and 8 % inconclusive); of these, 90 % had a personal history of breast cancer. Participants were asked about gynecological cancer surveillance behavior (last mammogram, clinical breast exam, pelvic examination, etc.) 3 months after test disclosure. The authors found that 84 % performed minimum recommended or optimal breast cancer surveillance and 73 % performed suboptimal ovarian cancer surveillance. However, no association could be found between *BRCA1/2* test result and surveillance behavior. According to Loescher et al. (2009), a lack of a physician's recommendation was the most frequently reported reason for not undergoing surveillance procedures.

Some studies also included male participants when testing for mutations in BRCA susceptibility genes. This was the case of Foster et al. (2007) who published a prospective multicenter study analyzing cancer risk management 3 years posttesting. Included were 193 clinically unaffected patients from families with BRCA mutations. There were 154 female (53 carriers) and 39 male participants (18 carriers) and a total of 71 carriers (48 *BRCA1*, 22 *BRCA2*, 1 both) and 122 noncarriers. In females, 89 % of carriers had mammograms compared with 47 % of noncarriers, 43 % opted for oophorectomy, and 34 % for mastectomy. In males, 22 % of carriers compared with 5 % of noncarriers underwent colorectal cancer screening. Forty-four percent of male carriers were reported to have prostate cancer screening compared with 19 % of noncarriers. No differences in groups (mutation results) were found at baseline, but after 3 years carriers were more likely than noncarriers to engage in risk management strategies postgenetic testing.

Liede et al. (2000) included 59 male mutation carriers (41 *BRCA1* and 18 *BRCA2*; 12 of the men had a previous diagnosis of cancer) in a study on cancer screening practices after genetic testing for BRCA mutations with a mean follow-up of 2.2 years. The study showed that 43 % of all clinically unaffected men altered their cancer surveillance program after testing, and adherence to prostate screening was reported by approximately half of the men. Watson et al. (2004) found that men were not negatively affected by genetic testing regarding their general mental health. In women, the rate of prophylactic surgery after genetic testing was higher in carriers than in noncarriers (Schwartz et al. 2003; Lynch et al. 2006; Loader et al. 2004; Antill et al. 2006a; Meijers-Heijboer et al. 2003; Litton et al. 2009; Schwartz et al. 2004; Stolier and Corsetti 2005). Kauff et al. (2002) found that salpingo-oophorectomy in carriers of BRCA mutations would decrease the risk of breast cancer and BRCA-related gynecologic cancer. In 2008, the same author (Kauff et al. 2008) emphasized that after 3 years, follow-up risk reducing salpingo-oophorectomy was associated with a 72–85 % reduction in *BRCA1/2*-associated cancer risk. Prophylactic surgery was chosen over antihormonal therapy as shown by Metcalfe et al. (2005).

Several cofactors influence decision making as demonstrated by Lodder et al. (2002) who surveyed 63 cancer unaffected women (14 mutation-positive undergoing mastectomy, 12 mutation-positive undergoing surveillance, and 37 mutation negative) about prophylactic decisions, satisfaction, and emotional distress 1 year after genetic testing. Women opting for mastectomy were younger, had younger children, and had a longer awareness about cancer history in the family. Metcalfe et al. (2008) provided detailed evidence that family history plays an important role in decision making, especially for prophylactic surgery. Of a total of 517 (326 *BRCA1*, 186 *BRCA2*, and 5 *BRCA1+2*) participants,

249 (48.4 %) with a history of breast cancer were interviewed, and 30.2 % of women without a previous diagnosis of breast cancer was found to have undergone mastectomy (more likely if their sister had breast cancer). Women with *BRCA2* mutations were less likely to have oophorectomy than women with *BRCA1* mutations, however, if their mother or sister was affected by ovarian cancer then study participants were more likely to opt for surgery.

Some worries were expressed that genetic testing if receiving negative result would lead to false reassurance (with decreasing screening adherence) or to emotional distress. However, distress levels were found not to differ between carriers and noncarriers at 3-year follow-up (Foster et al. 2007). Lynch et al. (2006) found that even among noncarriers, breast cancer screening significantly increased after genetic testing. This matches the observations by Plon et al. (2000), where a negative *BRCA1* mutation result did not have a negative impact on mammography frequency 2 years after genetic testing. Regarding perceived seriousness and perceived control of breast and ovarian cancers, no differences were found between carriers and noncarriers 1-year after genetic testing for *BRCA1/2* (Claes et al. 2005c). One interesting aspect was identified in a paper published by Vos et al. (2011). In that study, participants were sent a questionnaire about their medical and psychological outcomes, perception and medical, and familial and psychological context 3 months after disclosure of BRCA test result. Of 248 cancer-affected women, 30 received a diagnosis of pathogenic mutations, 16 were found to have unclassified variants and 202 participants received uninformative results. The counselees' perceptions were found to predict medical intentions and decisions. The authors concluded that feeling at risk predicted the medical behavior and intentions of the counselees better than objective levels of risk (Vos et al. 2011).

Meiser and Halliday (2002) concluded in a meta-analysis that genetic counseling was able to reduce women's anxiety levels and improve the accuracy of their perceived risk. Most of the studies concerning cancer screening after genetic testing for *BRCA1/2* mutations report an increase in screening behavior, especially in carriers posttesting (Schwartz et al. 2003; Lynch et al. 2006; Foster et al. 2007; Claes et al. 2005b). In contrast to studies on HNPCC, the difference was not always significant (Scheuer et al. 2002; Tinley et al. 2004). Study conclusions on *BRCA1/2* testing are not as clear and defined. Behavior changes are not always statistically significant which may be explained by higher baseline compliance (Scheuer et al. 2002). Interestingly, mutation-negative patients or patients with an inconclusive test result still showed adequate screening behavior and did not downshift or neglect their risk potential (Botkin et al. 2003; van Dijk et al. 2005). In addition to this, distress levels that were elevated initially after genetic testing normalized in patients tested for BRCA and HNPCC mutations after 1 year (Lodder et al. 2002; Aktan-Collan et al. 2001). O'Neill et al. (2008)) found that women would not make spontaneous changes in diet and physical activity following the genetic testing and counseling processes. A multicenter randomized clinical trial on "behavioral and psychosocial effects of rapid genetic counseling in newly diagnosed breast cancer patients" is now being conducted by Wevers et al. (2011) (Table 2).

Familial HFE

Summary Patients with HFE mutations comply with maintenance therapy by phlebotomy at a rate higher than 90 % during the first year after genetic testing. This seems to be mainly due to the simplicity of intervention. There are no data available for long-term compliance.

The evaluated studies regarding familial HFE are listed in ESM 3.

Familial HFE is an autosomal-recessive disease characterized by accumulation of excess iron in body tissues, which consequently leads to organ dysfunction unless adequately treated. Resulting complications of excessive iron overload are liver cirrhosis, diabetes, cardiomyopathy, and musculoskeletal impairment, e.g., arthritis (Bacon and Sadiq 1997). The majority of people diagnosed with hereditary HFE are homozygous for the C282Y mutation, a genotype seen in more than 90 % of patients with typical HFE (Adams et al. 2005). Another HFE mutation is H63D, also contributing to iron overload when in the homozygous state or as compound heterozygote with C282Y (Burke et al. 2000). If an individual is found to be a mutation carrier, ferritin levels should be monitored regularly. Once identified as affected, treatment by iron depletion by phlebotomy is a simple and effective way to prevent iron overload and resulting complications.

Surprisingly, only two studies were found where patient compliance with HFE testing results was assessed. Hicken et al. (2003) analyzed the compliance with phlebotomy in patients diagnosed with HFE based on retrospective analysis of medical records. In this study, 142 patients were evaluated for maintenance therapy and 118 patients were evaluated for iron depletion, which was achieved in 96.6 % of patients. In the first year after achieving iron depletion, maintenance therapy reached an overall compliance rate of 84.5 %. It was further shown that 90.5 % of C282Y homozygotes compared with 75.9 % with other HFE genotypes or not tested patients participated in the first year of maintenance therapy (Hicken et al. 2003).

High compliance with clinical recommendations was also reported in a study by Allen et al. (2008) who screened 11,307 Australian workers at their workplace for HFE (C282Y mutation). Health behavior (clinical care, treatment compliance, and changes in diet) was assessed by questionnaire at baseline

Table 2 Studies examining compliance before and after genetic testing for BRCA1/2

Study	Prior to testing	After testing carriers	After testing noncarriers
Lerman et al. (2000)	Mammogram in the year before testing—carriers, 68 %; noncarriers, 55 %; and decliners, 67 %	Mammogram the year following testing—carriers, 68 %	44 % noncarriers and 54 % decliners
Plon et al. (2000)	BRCA 1 negative, unaffected with breast cancer, mammography at baseline the year prior to testing, 49.2 % (women, <50 years)		Women at <50 years, increase mammography in years 1, 62.7 % and 2, 67.1 %
Botkin et al. (2003)	Mammogram carriers, 22 % and noncarriers, 30 %	Mammogram in years 1, 62 % and 2 years, 57 %	Mammogram in years 1, 53 % and 2 years, 49 %
Schwartz et al. (2003)	Carriers CA 125 utilization at baseline 12 % and carriers TVU at baseline 16 %	After 1 year, 43 % of carriers CA 125 and 40 % of carriers TVU	After 1 year, 9 % of noncarriers CA 125 and 21 % of noncarriers TVU
Peshkin et al. (2002)	65 % women reported having obtained mammogram the year before testing	Mammography, 59 % of carriers	Mammography, 47 % of noncarriers
Kinney et al. (2006)	47 % of all groups had a mammogram prior to genetic testing (86 % of carriers reported having had mammogram in the year before testing)	71 % adherent to mammography screening guidelines	59 % adherent to mammography screening guidelines
McInerney-Leo et al. (2006)	Baseline, 77 % breast self examination	82 % at follow-up, no difference between groups, and no significant increase	
Lynch et al. (2006)	Before testing, 23.0 % of women underwent prophylactic mastectomy, oophorectomy, or both and 80 (53 %) of them then tested to be negative	52.9 % mutation carriers had prophylactic surgery after testing	No noncarriers underwent prophylactic surgery after testing

and at the time point of 1 and 12 months (up to 4 years for homozygotes) after receipt of the test result. A total of 40 of 47 newly identified C282Y homozygotes and 79 of 126 controls completed the questionnaire 12 months after diagnosis. It was reported that 93.6 % of homozygotes attended at least one dedicated follow-up clinic. In addition, 95.7 % of homozygotes had iron indices measured both at diagnosis and at least 12 months after diagnosis and all 22 patients requiring therapeutic phlebotomy complied with treatment for at least 12 months.

Obesity

Summary Compliance towards behavioral changes was higher in study participants who received a defined diagnosis (e.g., hypertension, diabetes mellitus, and risk of becoming obese). Overweight or obese patients showed higher weight loss in an intervention group which was led by a nurse and received individual repeated counseling. This allows to conclude that patients who left on their own will undergo a decrease in compliance. In general, individuals receiving personal risk information for becoming obese show a higher motivation to change diet. This could be shown also in analog studies where participants were confronted with a hypothetical test result.

The evaluated studies regarding obesity are listed in ESM 4.

Obesity and associated conditions such as hypertension, diabetes mellitus, and dyslipidemia (metabolic syndrome) are responsible for many preventable diseases and deaths (Arnlöv et al. 2010). They therefore play an important role economically and are a major aspect of public health concerns.

Zhao et al. (2009) analyzed weight control behavior and the attempts to lose weight in 143,386 obese patients diagnosed with or without diabetes and/or hypertension. Of these patients, 10,963 suffered from both conditions, 40,666 from hypertension only, 5,143 suffered from diabetes only, and 86,614 were obese with no other diagnosed condition. The results showed that 72.1 % of participants with both conditions, 57.8 % with hypertension, and 60 % with diabetes attempted to lose weight, compared with 49.8 % without hypertension or diabetes. The authors found that after adjustment for sociodemographic variables and the receipt of weight-loss advice, only participants with both hypertension and diabetes or with hypertension only were significantly more likely to try to lose weight (Zhao et al. 2009). Compliance was limited to patients with hypertension indicating that a life-threatening component adds to behavioral change.

Ter Bogt et al. (2009) compared changes in weight gain depending on supervision by either a general practitioner or by an intervention group led by a nurse. In the intervention

group led by a nurse, four individual visits to a nurse practitioner as well as one telephone feedback session was scheduled for counseling. Patients in the control group led by a general practitioner received usual care. Participating patients were obese or overweight. In the study, 52 % of 457 participants were women suffering from hypertension or dyslipidemia. After 1 year, the nurse group showed more patients with weight loss or stable weight. These participants also had significant reductions in waist circumference (2.8 cm; $p<0.05$). In this case, the kind and intensity of supervision influenced level of success. In the above studies, no genetic information was given to participants.

The potential influence of genetic information on weight loss was analyzed by Harvey-Berino et al. (2001) in a study of 30 white postmenopausal, nonsmoking women with a body mass index of >28 (18 mutation positive and 12 mutation negative for beta-3-adrenergic receptor gene). The women were asked by questionnaire (before and after genetic testing and before beginning a weight loss program) about their confidence in their ability to lose weight and control overeating. The authors concluded that a positive obesity gene status would not adversely affect people's confidence in their ability to lose weight or control their eating behavior in difficult situations. Frosch et al. (2005) published an analog study where 249 undergraduate students (BMI between 18.5 and 29.9) were asked about their attitudes, perceived behavior control and outcome expectancies towards eating a healthy diet after receiving a test result about a higher risk of becoming obese. Hypothetical test results were based either on a "genetic test" or on a "hormonal test" revealing increased or average risk of becoming obese. Those who were informed about an increased risk of becoming obese demonstrated higher intention to eat a healthy diet. The test type (genetic vs. hormonal) had no effect on perceived risk or on intentions to eat a healthy diet.

A similar approach was made in an analogue study by Sanderson et al. (2010). 191 participants were divided into five groups, either receiving no risk information of becoming obese, receiving a genetic test result for high-eating- or high-metabolism-based risk of obesity, or receiving an enzyme test result indicating high eating- or high-metabolism-based risk of obesity. After receiving test results, perceived risk and intention to eat healthily was assessed. Individuals who received a high-risk test result reported greater perceived risk and demonstrated higher intention to eat healthily than the group receiving no risk information. Regarding test type (genetic vs. enzyme), an effect was only shown for perceived risk of obesity. The genetic groups reported greater perceived risk than the enzyme groups. No other effects of test type were demonstrated on any other outcome. The authors concluded that their results would suggest that providing individuals with personal genetic risk information indicating that they are at a personally increased risk of obesity may increase their motivation to eat a healthy diet, and this holds true regardless of whether the genetic factor is described as acting through metabolism or eating behavior itself (Sanderson et al. 2010).

Smoking cessation

Summary Smoking cessation can be evaluated as compliance measure in individuals with increased risk for lung cancer as determined by GSTM-1 status. Genetic testing led to higher rate of smoking cessation up to 6 months posttesting. However, some results obtained after 12 months of follow-up showed no differences to controls. About 65 % of patients in one analog study expressed their intention to quit smoking after positive genetic testing for lung cancer or heart disease, compared with approximately 25 % of patients with negative genetic test result. This leads to the conclusion that patients are aware that smoking cessation is one measure to reduce risk of lung cancer, but no data are available for compliance after 12 months.

The evaluated studies regarding smoking cessation are listed in ESM 5.

Lung cancer is one of the leading causes of cancer-related death in the USA and Europe (Alberg et al. 2007; Tyczynski et al. 2003; Doblhammer et al. 2012). It represents one of the most focused issues in public health. Several approaches to promote successful smoking cessation have been made and the inclusion of genetics has been discussed to be a promising step to supplement and amend cessation programs. Several aspects of smoking-related genetics have been researched (including nicotine metabolism) regarding the risk of developing lung cancer (predominantly GSTM1 related) (Carlsten and Burke 2006). Here, the question arises as to how this information can be transferred to a public health context and the consequences that may follow application. Research, including genetic testing and genetic feedback concerning the risk for developing lung cancer, focuses on its impact on quit attempts and cessation rates, as well as comparing this genetic approach to usual cessation interventions, e.g., motivational interviewing, nicotine patches, and telephone counseling (Young et al. 2010).

McBride et al. (2002) published a study about a two-arm randomized trial on smoking cessation involving 557 African American smokers (40 % men). Of these smokers, 185 were treated with enhanced usual care (smoking cessation advice and nicotine patches). A further 372 belonged to the genetic testing (blood test for GSTM1) and telephone counseling arm with 308 agreeing to take the test (104 GSTM1 missing and 204 GSTM1 present). After 12 months, complete information was available for 316 participants. Prevalent abstinence was greater in the genetic testing arm (19 % compared with 10 %) at 6 months but not at 12 months. The rate of sustained abstinence was significantly higher

among those in the genetic feedback arm, but adjustment for baseline covariates diminished the significance of this result. Additionally, rates of prevalent and sustained abstinence for those with enzyme present or missing did not differ significantly at follow-up. Audrain et al. (1997) did a 12-month follow-up study on 426 male and female smokers in a randomized controlled trial. Follow-up information after 2 and 12 months on smoking cessation behavior was analyzed in three study arms: (a) minimal contact, (b) minimal contact+-exposure biomarker feedback, (c) same as item (b) plus genetic testing for CYP2D6. After 12 months, the genetic testing group was more than twice as likely to attempt to quit than the minimal contact group.

Two analog studies were published by Sanderson and coworkers (2005; Sanderson and Michie 2007) analyzing hypothetical smoking cessation rates and attitudes towards smoking behavior. In the study by Sanderson and Michie (2007) addressing genetic testing for heart disease susceptibility, 261 smokers were randomized into three groups. Of the participants, 96 received a genetic high-risk result for heart disease and 79 a genetic low-risk result for heart disease. Another 86 received an oxidative stress test high risk for heart disease. The group who received a hypothetical genetic high-risk result showed greater intention to quit smoking, compared with the oxidative high-risk test result. In the other study by Sanderson and Wardle (2005), 186 smokers of a cross-sectional survey were given a hypothetical genetic test result either for lung cancer or heart disease. In this study, 65 % of smokers would definitely quit smoking following a positive genetic test result (70 % cancer and 60 % heart disease) compared with 24 % if it was negative. Additionally, smokers viewed a positive result as more motivating than a negative result.

Genetic testing can be used by smokers as an additional motivational tool, in particular if participants are eager to quit (Sanderson and Wardle 2005). This was supported by another study by Sanderson et al. (2009) providing relative smokers of lung cancer patients with information about their GSTM1-status via online messaging. Before and after test result disclosure and again after 6 months, cessation related cognition as well as uptake of free smoking cessation services was monitored. Uptake of free smoking cessation services was high, irrespective of the genetic test result. Conversely, one must be careful of potential harm and side effects of genetic information. Failing cessation might reinforce low level or even loss of motivation due to genetic cause and can lead to fatalism. In the end, being identified as a nonelevated risk person might be interpreted as a permit to continue or start smoking despite other negative effects (Carlsten and Burke 2006; Sanderson et al. 2009).

Young et al. 2010 ranked smoking cessation as a very cost-effective intervention in clinical medicine. Much effort has been made to identify ways of supporting smoking cessation. In studies on genetic testing in smoking cessation, no unequivocal outcome has been found so far. "Scarcity and limited quality of the current evidence does not support the hypothesis that biomedical risk assessment increases smoking cessation as compared with the standard treatment" (Bize et al. 2007). However, there seems to be a suggestion that genetic testing leads to greater motivation and more attempts to quit (Audrain et al. 1997; Sanderson et al. 2008). Wright et al. (2008) assessed the impact of genetic testing for Crohn's disease, risk magnitude and graphical format on motivation to stop smoking in an experimental analog study. Risk-reducing behavior was strongly dependent on high percentage risk estimates.

Thrombophilia/factor V Leiden

Summary About 50 % of women who carry the Factor V Leiden mutation made lifestyle changes and about 70 % tried to make at least one specific health-related behavior change. Between 40- 80 % stopped using oral contraceptives. In noncarriers the awareness of genetic testing also led to lifestyle changes, however to a lesser extent. The use of oral contraceptives varied from high compliance to stop the hormonal therapy to continued use of oral contraceptives even after receiving a genetic test result of confirmation of Factor V Leiden mutation.

The evaluated studies regarding factor V Leiden associated thrombophilia are listed in ESM 6.

Factor V Leiden-associated thrombophilia is a disorder of coagulation caused by APC resistance, which leads to an increased risk of venous thromboembolism. Patients known to be affected should follow several clinical recommendations in order to reduce the risk of venous thromboembolism, e.g., avoid immobility, oral contraceptives, change in diet, and increased exercise. The condition is multifactorial and is characterized by exogenous risk factors and endogenous conditions (Kujovich 2011). Of these conditions, APC resistance can be identified by genetic testing. Inactivation of factor Va by activated protein C is impaired in mutation carriers. Lifelong risk of developing thromboembolism is about 7-fold higher (heterozygote) and 80-fold higher for homozygotes (Rosendaal et al. 1995).

Heshka et al. (2008a) examined 70 first-degree relatives (44 carriers and 26 noncarriers). Health care behavior 12-months posttesting was assessed by postal questionnaire. This found that 70.5 % of carriers compared with 61.5 % of noncarriers had tried to make at least one specific health-related behavior change (e.g., reduce risk of injury, avoid long trips, improve diet, etc.) but only 27.3 % of carriers and 19.2 % of noncarriers made these changes in order to reduce the risk of developing a blood clot. The authors' conclusion was that carriers were more likely than noncarriers to have

tried to avoid long trips since genetic testing and that there were no significant differences between carrier and noncarrier responses in regard to remaining health-related behavior (Heshka et al. 2008a). By contrast, Hellmann et al. (2003) found that from 110 affected individuals, 51 % made positive lifestyle changes, including avoidance of immobility, increase in exercise and altering dietary habits. Knowledge of Factor V Leiden status increased worry in 43 % of individuals. Legnani et al. (2006) observed that patients classified as carriers of thrombophilic alterations did not show any harmful psychological effects.

Regarding the use of oral contraceptives after genetic testing for Factor V Leiden, inconsistent results were found. Gartner et al. (2008) found that 80 % of women with Factor V Leiden were discouraged from oral contraceptive use compared with 16 % with wild-type Factor V, whereas 3 % of women with Factor V Leiden were encouraged to use oral contraceptives. Participants of the study were 161 women with Factor V Leiden and 63 women with wild-type Factor V. Use of hormonal contraception was recommended to 40 % with Factor V Leiden after diagnosis. In the present study, 41 % with Factor V Leiden used at least one hormone contraceptive method after diagnosis. In addition, 19 % who were advised to use nonhormonal methods did not adhere to this recommendation. This shows that a large proportion of women with Factor V Leiden continued to use oral contraceptives, despite recommendations to the contrary. Similar results and conclusions were affirmed by Eichinger (2009). In contrast to these findings Lindqvist and Dahlback (2003) analyzed changes in lifestyle in 215 women with APC resistance after 6–12 months and found that from 122 women who used oral contraceptives before testing, 84 % stopped using oral contraceptives in order to reduce their risk of thrombosis after genetic testing, while 16 % continued using oral contraceptives.

Medication adherence after receiving medical advice based on nongenetic risk information

Summary Most patients discontinue their medication in the first year, despite the recommendation to continue the prescribed medication. A higher compliance in taking prescribed drugs for a longer period of time is observed when a clearly defined clinical event such as myocardial infarction, had occurred. In general, compliance is better when the patient can understand and translate the test result and treatment recommendations into the personal situation. This underlines why proper and individual counseling of patients plays an important role to achieve better compliance.

The evaluated studies regarding medication adherence are listed in ESM 7.

How compliant are patients when it comes to medication intake and advice by their physician? Does it make any difference if the risk factor is genetic compared with common blood tests or clinical pathology testing?

Looking at studies analyzing patient's health behavior after diagnosis of hypertension, Neutel et al. (2008) interviewed 1,281 newly diagnosed hypertensive patients in five cycles at 2-year intervals. The main research question was the extent to which recently diagnosed hypertensive Canadians modify their lifestyles and to examine how lifestyle modification related to antihypertensive medication use. Patients not taking medication for hypertension were less likely to change their lifestyles; additionally, newly diagnosed hypertensive patients were more likely to be obese. The authors concluded that the main lifestyle modification associated with newly diagnosed hypertensive patients was smoking cessation, with an 18.6 % relative risk reduction (Neutel et al. 2008).

Mazzaglia et al. (2009) assessed the proportion of days covered by medication in 18,806 patients (mean age, 62 years; 41.6 % were males and 27.5 % had at least one cardiovascular risk factor) at baseline, which was 6 months after newly diagnosed hypertension. At baseline, 51.4 % showed low adherence, 40.5 % intermediate adherence, and 8.1 % high adherence. Patients were followed up until the first cardiovascular event or to the end of the study period 4–5 years later. At follow-up, 48.9 % showed low adherence, 32.3 % intermediate, and 18.8 % high adherence. Most documented cardiovascular risk factors led to high adherence to medication. Hasford et al. (2007) found similar results. They analyzed at 3-year follow-up the number of days that 13,763 newly diagnosed hypertensive patients (56 % females; mean age, 65 years) continued their initially prescribed antihypertensive drug. One year after initiation of treatment, between 87.1 and 64.4 % of all patients had discontinued treatment for at least 6 months. After 3 years, persistence varied between 11.2 and 31.2 % for any drug class; for initial drug class, persistence varied between 3.2 and 17.7 %. Overall, 25.2 % received three or fewer prescriptions within 3 years. This tendency was endorsed by Burke et al. (2006) who surveyed discontinuation rates in 109,454 newly diagnosed hypertensive patients. Discontinuation was defined as no prescription issued within 90 days following the most recent prescription expiration. Overall discontinuation was 20.3 % at 6 months and 28.5 % after 1 year. Median time to discontinuation was 3.07 years. One-year discontinuation ranged from 29.4 (angiotensin2 antagonist) to 64.1 % (potassium-sparing diuretics). It can be concluded that adherence rates also depend on substance classes and side effects.

The longest study timescale was used by Van Wijk et al. (2005) in a retrospective cohort study analyzing 2,325 patients who started antihypertensive drugs in 1992 (two or more prescriptions) and did not receive a prescription for any

antihypertensive drug within 365 days preceding the first prescription. During 10-year follow-up, 39 % used medication continuously and 39 % discontinued permanently. Overall, older patients were more persistent than younger patients. This study also shows that persistence depended on drug class, showing higher persistence with ACE/calcium blockers than with beta-blockers/diuretics.

Katz et al. (2009) surveyed 83 patients presenting with symptoms of acute coronary syndrome (ACS) at an observation unit. Patients were at risk for ischemic heart disease. Patients were interviewed at baseline and after 3 months about health behavior changes and compliance. Significant changes in behavior were found at follow-up. The present study reported a 0.5 % reduction in saturated fat intake, a 15-mg/day reduction in dietary cholesterol, a 0.4-serving/day increase in fruit and vegetable, and 4 cigarettes/day reduction on average. Furthermore, 40 % of participants reported having received clinician advice regarding diet/physical activity. These findings were supported by Simpson et al. (2003) who analyzed drug adherence in 14,057 elderly (>65 years) patients after acute myocardial infarction. High 1-year compliance rates and high persistence rates were found. Other smaller studies found high compliance rates—for example, Lopes et al. (2008), but sample sizes were much smaller (75 patients with confirmed metabolic syndrome, 54.66 % women; mean age, 63 years).

Looking at patients with dyslipoproteinemia and statin medication, the results showed similarities. Benner et al. (2002) surveyed the proportion of days covered by a statin in each quarter during the first year of therapy and every 6 months after in 34,501 patients who were 65 years and older. Mean proportion of days covered was 79 % in the first 3 months of treatment, 56 % in the second quarter, and 42 % after 120 months. Only one patient in four maintained a record of at least 80 % days covered after 5 years. Jackevicius et al. (2002) looked at statin therapy adherence in elderly patients with and without ACS. All patients were 66 years or older, 22,379 with ACS, 36,106 with chronic coronary artery disease (CAD), and 85,020 undergoing primary prevention. Adherence was defined as a statin being dispensed at least every 120 days after the index prescription for 2 years. Two-year adherence rate was 40.1 % for patients with ACS, 36.1 % in the CAD group, and 25.4 % in patients undergoing primary prevention. It was found that relative to the patients in the ACS cohort, nonadherence was more likely among patients receiving statins prescriptions in the CAD and primary prevention cohorts (Jackevicius et al. 2002). Similar findings were published by Chan et al. (2010) who measured the proportion of days covered by a statin from the index date to 1 year after the index date (full adherence was defined as at least 80 % proportion of days covered) in 14,257 patients (mean age, 51.6 years; 45.2 % females). Of those studied, 36.4 % were fully adherent, but patients with recent ACS showed better adherence compared with others.

A study by Claassen et al. (2010) combined both aspects, the patients being at risk and receiving medical advice as well as the genetic information of being a mutation carrier for familial hyperlipidemia. The study assessed 81 mutation carriers (screened positive in the preceding 2 years, 48 % men, and 57 % overweight or obese) for preventive behavior, perceived risks, and representations of cardiovascular disease. Almost optimal medication adherence (99 %) was found in participants, but only 49 % followed recommendations concerning diet and physical activity. The adoption of healthy lifestyle was positively associated with family history of cardiovascular disease and the experienced efficacy of a healthy lifestyle. Large numbers of patients were included in these studies, partly limited to a special age group. Follow-up time varies from a very short period of time up to 10 years. Medication adherence decreases with time and this surprisingly quite often already happens during the first year of treatment. Only a few studies show better compliance with medication and medical advice, but they are mostly limited by the number of patients included or limited to a special group of patients.

Conclusions

In this review, we have systematically screened the scientific literature for reports quantifying patient compliance after any kind of genetic risk assessment, with or without genetic testing. We have focused on “actionable” conditions, i.e., conditions where accepted secondary or tertiary preventive options exist. In comparison, we assessed compliance following physicians’ advice in situations after nongenetic risk assessment. To this end, we have evaluated medication adherence in relation to pathophysiological factors other than genetic risks.

The great majority of the studies assessed in this review dealt with the two most frequent familial cancer syndromes, namely hereditary nonpolyposis bowel cancer and hereditary breast and ovarian cancer. Both conditions are perceived as severe and are characterized by a high genetic contribution to disease risk. Most studies focused on individuals from affected families, i.e., typically individuals with grossly elevated prior disease risks. While one could have expected that compliance rates with advice regarding prophylactic action to be taken are already high prior to genetic testing, it can generally be observed that compliance rates are raised further in test-positive individuals. The effect seems to be more pronounced in the HNPCC group as compared with the BRCA group, perhaps related to a higher prior compliance rate in the latter. Genetic information, in particular positive results from genetic tests, generally enhanced patient compliance also in conditions likely to be

perceived as less threatening, namely HFE, thrombophilia, obesity, and being a smoker. However, nongenetic information such as routine therapeutic level tests and clinical information in relation to medication adherence does not appear to impact more or less than genetic information on patients' behavior.

Most studies attempting to measure the impact of genetic information on patient compliance suffer from methodological drawbacks, in particular small study groups and short observational periods. Thus, while often showing a trend that genetic information may influence behavior, the data showed wide confidence intervals or were often not significant. Furthermore, most studies are not directly comparable. Outcome measures included one or several of the following: adherence to established clinical follow-up after genetic testing (familial cancer syndromes and HFE), health promoting behavior aiming at lifestyle changes (obesity and smoking cessation) or other active behavioral changes (e.g., changes in diet and physical activity) to improve health. Objectifiable clinical benefits ensuing from patient compliance are typically not assessed in these studies.

While this review was conducted, a study by Marteau et al. (2010) on DNA-based risk information in view of health-promoting behavior was published. The results suggested that DNA-based risk estimates had little or no effect on smoking and physical activity. Participants did not feel motivated to change their behavior except small changes in diet. These conclusions were based on a small number of studies of limited quality. A similar view is held by Henrikson et al. (2009).

If the aim of providing patients with access to genetic testing is to effect significant behavioral change and increased compliance, then there is more to consider than simply the testing process itself. Before genetic testing is carried out, the expectations of patients are managed and this paves the way for future behavioral changes, compliance, and therapeutic options. Communication and interpretation of probabilities is important in the process of informed consent in genetic and genomic research (Rotimi and Marshall 2010). In this process, the psychosocial context is important for translation of genetic risk information. Often there is a correlation between the educational level as well as income level and the willingness to be compliant (Halbert et al. 2004; Hadley et al. 2004). Accordingly, the process of counseling patients about genetic testing is complex and should not exclusively be the responsibility of a geneticist in isolation. It has been commented that in any case genomic information should be returned to consenting individuals. The question is how to do this while avoiding harm, and in some cases positive genetic testing may decrease motivation to actively change lifestyle and behavior (Bredenoord et al. 2011; Offit 2011). This adds to the prevailing idea that genetic counseling is complex and should be understood as a multidisciplinary task.

Compliance also appears to be related to the perception of risk. It appears that patients pay more attention to higher risk estimates (higher percentage figure) than to the positive information on being a carrier of a defined genetic risk. It shows that a lower risk does not put enough psychological pressure on a patient to induce behavioral changes (Marteau and Weinman 2006). A similar conclusion was drawn by Collins et al. (2011), where no impact on the perceived effectiveness of behavioral intervention was observed. Another aspect is the perceived threat and the potential capability of handling a disease. For example in HFE patients high compliance with treatment and surveillance was demonstrated when being identified as mutation positive (Allen et al. 2008). This may be due to the simplicity of testing (blood sample) and treatment (phlebotomy), as well as the fact that the disease itself is not assumed to be very harmful when properly treated and monitored. Risk perception can change if the counseling process includes the offer of better screening practices or prophylactic surgery, for example.

A large number of patients were included in studies on medication adherence based on nongenetic information. It was generally found that medication adherence is weak and reduces over time, most evidently already during the first year of treatment (Hasford et al. 2007; Benner et al. 2002; Jackevicius et al. 2002). Additional factors such as cardiovascular risk factors, medication substance class, patient's age and recent morbidities such as ACS influence medication adherence (Mazzaglia et al. 2009).

Adherence rates to medication advice appear to improve when genetic information is being added. Thus, patients informed of being a mutation carrier for familial hyperlipoproteinemia displayed a very high adherence level to medication after genetic testing. In addition, almost half of the participants followed recommendations concerning diet and physical activity. The adoption of a healthy lifestyle was positively associated with family history of cardiovascular disease and the perceived efficacy of a healthy lifestyle (Claassen et al. 2010).

Similarly, when integrating genetic information in surveys about weight loss in obese patients, Harvey-Berino et al. (2001) could demonstrate that people's confidence in their ability to lose weight or control eating is not adversely affected by a positive genetic test result. When comparing genetic test results to other (nongenetic) biomarker results, those who were informed about an increased risk of becoming obese were found to have demonstrated higher intention to eat a healthy diet (Frosch et al. 2005). The test type (genetic or hormone test) had no effect on the perceived risk or intention to eat a healthy diet. Although no definite effect of genetic testing could be found, it emphasizes the important role counseling has. It shows that a positive genetic test result does not serve as an excuse for not trying to lose weight due to an attitude of fatalism.

One important aspect to bear in mind is that the primary care provider plays a key role in screening compliance. Several studies identified the "physician recommendation" as one of the most important factors in the patient's process of decision making about screening behavior (Hadley et al. 2004; Kinney et al. 2007; Tinley et al. 2004; Lerman et al. 1990; Geiger et al. 2008). Burton et al. (2010) concluded that genetic counseling offers a promising avenue for education and risk behavior reduction in persons at increased risk for cancer due to a familial or genetic predisposition and a teachable moment to introduce lifestyle modifications. Recently, DNA-based tests are beginning to be offered directly to consumers by the private genomic industry. Companies test for gene variants related to increased risk of complex diseases based on genome-wide association studies. Claims that such tests motivate behavior changes and increase compliance are not (yet) supported by empirical evidence (Bloss et al. 2011a, 2011b).

New genome sequencing technologies and integrated information on the genome and derivatives, such as transcriptome, proteome, and metabolome are generally expected to improve individual risk assessment, which could lead to disease prevention or at least earlier diagnosis and more tailored treatments for patients. Additionally, family, health history as a combination of shared genomic, environmental and lifestyle risk factors may also contribute to improved individual risk assessment. Benefit to the individual is expected to be highest if one can combine and interpret the information about family history, genomic, personal environment as well as metabolomics. The combination of technological advances in genetic testing, environmental assessment, and new routes of communication might lead to new understandings of genetic risk and subsequent favorably influenced health behavior (McBride et al. 2010). Compliance will remain dependent on the interaction between patient and physician or other medical personnel. A prerequisite for compliance is that patients are able to understand their medical situation and have collected enough information to make informed decisions for themselves or in certain conditions their family members as well. The more that clinical validity and utility of these tests can enable characterization of the disease and allow predictions, the better compliance can be expected from the individuals involved.

So far, in the majority of studies, patients were provided with predictive rather than diagnostic genetic profiles. Overlooking the last 10 years, the medical community including patients, physicians, and public health officials had a much higher expectation towards the usage of genetic information in relation to compliance and behavioral changes. There is currently no clear answer to the question if patient compliance is enhanced by genetic test results as such.

Acknowledgements We are greatly indebted to Professor Heather Skirton, Leigh Jackson, and Lesley Goldsmith, Plymouth University, for helpful discussions and reading an earlier version of the manuscript. The main conclusions of this literature survey were first presented at the symposium "Predictive genetic testing, risk communication and perception" at the Robert-Koch-Institute Berlin, 21st November 2011.

Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethics guidelines This study complies with current German laws.

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