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# Genetic screening by DNA technology: A systematic review of health economic evidence

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**Objectives:** The Human Genome Project has led to a multitude of new potential screening targets on the level of human DNA. The aim of this systematic review is to critically summarize the evidence from health economic evaluations of genetic screening in the literature.
**Methods:** Based on an extensive explorative search, an appropriate algorithm for a systematic database search was developed. Twenty-one health economic evaluations were identified and appraised using published quality criteria.
**Results:** Genetic screening for eight conditions has been found to be investigated by health economic evaluation: hereditary breast and ovarian cancer, familial adenomatous polyposis (FAP) colorectal cancer, hereditary nonpolyposis colorectal carcinoma (HNPCC), retinoblastoma, familial hypercholesterolemia, hereditary hemochromatosis, insulin-dependent diabetes mellitus, and cystic fibrosis. Results range from dominated to cost-saving. Population-wide genetic screening may be considered cost-effective with limited quality of evidence only for three conditions. The methodology of the studies was of varying quality. Cost-effectiveness was primarily influenced by mutation prevalence, genetic test costs, mortality risk, effectiveness of treatment, age at screening, and discount rate.
**Conclusions:** Health economic evidence on genetic screening is limited: Only few conditions have properly been evaluated. Based on the existing evidence, healthcare decision makers should consider the introduction of selective genetic screening for FAP and HNPCC. As genetic test costs are declining, the existing evaluations may warrant updating. Especially in the case of hereditary hemochromatosis, genetic population screening may be about to turn from a dominated to a cost-effective or even cost-saving intervention.

**Keywords:** Costs and cost analysis, Genetic screening, Genetic predisposition to disease, Nucleic acid amplification techniques, Review

Scientific knowledge on human genetics is growing at a fast pace (17;19). The "Online Mendelian Inheritance in Man" (OMIM), a catalog of human genes and genetic disorders, lists approx. 1,700 gene sequences known to be associated with a disease (as of September 2004) (28). Scientific progress concerning gene function corresponds with an increasing number of clinics and laboratories offering genetic testing for various diseases (19;35).

Deoxyribonucleic acid (DNA) testing can detect a disease-causing gene mutation when the gene in question is known and gene changes can be found and interpreted (35). Independently from patient age or phenotypic pathogenesis, it provides the opportunity to diagnose monogenic diseases or risk factors for polygenic and multifactorial diseases. At high sensitivity and specificity, tests may be conducted very

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early in life, and due to new technologies such as DNA chips, potentially at prices of a few cents per tested mutation. It is, therefore, well suited for screening programs that substitute risk calculation based on family history and may provide individual answers on whether preventive intervention is appropriate or not (43).

For "genetics," a variety of definitions can be found in the literature, ranging from the Mendelian analysis of heredity in a narrow sense to modern biology in a broad one (51). Accordingly, "genetic screening" can be used to refer to various diagnostic interventions from directly examining the DNA to analyzing certain metabolites (35). The PubMed Medical Subject Heading "genetic screening" also includes family analysis (31). To answer the interests of technology-based test laboratories, genome researchers, geneticists, and diagnostics manufacturers, a technology-based approach was chosen where "genetic" refers to "DNA technology."

For this review, genetic screening is defined as *the systematic application of a genetic test, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder* (33). Mass screening targets individuals on a population or subpopulation level; selective screening targets individuals in specific high-risk groups (45). An effective screening program must be capable of detecting the disease (earlier than it would otherwise be detected), and there ought to be effective therapies or alternative courses of action capable of changing the outcome that would otherwise eventuate (6). With consideration to the ethical implications of screening and the psychological consequences resulting from both false-positive and false-negative tests, screening programs should offer choices to individuals and each individual should appreciate the risks and benefits of the screening program for them as an individual (32).

Various criteria can be applied to investigate the appropriateness of genetic screening (21). This review takes a healthcare economic perspective and investigates the evidence provided by health economic evaluations of screening by DNA technology in the literature. Current reviews in this field are restricted to either single or few conditions to be tested for; technology-based reviews are available only for tandem mass spectrometry (36).

## METHODS

### Exclusions

As the issue of therapeutic abortion is subject to controversial ethical discussion, preconceptive, preimplantation, and prenatal screening programs that involve termination of pregnancy were excluded. Focusing on human germ-line mutations, molecular pathology (e.g., in cancer diagnosis and diagnosis of infectious agents) also was excluded. To follow the technology-based approach and to consider only economic evaluations conducted after discovery of the genetic causes of the hereditary diseases investigated, diagnoses solely on the phenotype level were also excluded from this review. For pharmacogenetics, a related field of health technology, a review was conducted recently by Phillips and Bebber (37).

The health economic evaluation of screening programs involves the systematic assessment of the costs and the benefits of screening compared with a well-defined alternative, for example, reliance on symptomatic presentation of disease (6). Only full health economic evaluations where both quantitative health outcomes and the associated costs were reported from a third party payers, a healthcare sector, or societal perspective were considered for inclusion. Other publication types were excluded from this review but were used for reference tracking. Only publications in German, English, French, Dutch, or Spanish languages were included.

### Systematic Database Search

The major challenge of this review was the high number of indications susceptible to genetic screening and, therefore, within the scope of this review. To identify an appropriate search strategy more than 1,000 titles and abstracts were identified and investigated in opportunistic searches by various control terms and abstract text words. Databases searched were PubMed, BIOSYS, Cochrane, DAHTA, EMBASE, IHTA, Medline, NHS-HTA-DARE, NHS-CRD-HTA, NHS-EED, SOMED. Additionally, the internet was searched by Google, and references of economic evaluations and recent reviews were tracked.

The exploratory search generated a set of seventeen economic evaluations of genetic screening as defined for this review. All but one were available in Medline/PubMed (the remaining one in EMBASE). An investigation of the database references for further similarities revealed that all could be retrieved by the following combination of Medline medical section heading (MeSH) control terms or equivalent terms for EMBASE: ((“economics”[Subheading] OR “costs and cost analysis”[MeSH Terms]) AND (“genetic screening”[MeSH Terms] OR “genetic predisposition to disease”[MeSH Terms] OR Genetic Diseases, Inborn/diagnosis[MAJR])) AND Journal Article[PT] AND 1994[PDAT] : 2005[PDAT].

The systematic database search followed this algorithm, and 946 publications were identified (updated on July 19th, 2005). The full text of articles was investigated if from title and abstract the health technology appeared to be genetic screening and if quantitative economic results were reported. Sixty-one publications were selected for full-text investigation, approximately fifty evaluations of prenatal interventions or phenotype screening by tandem mass spectrometry were excluded. Twenty-one publications met the definition of

health economic evaluation of genetic screening for this review. All were published in the English language. No further economic evaluation was identified by reference tracking or hand search in the journals where one of the selected evaluations was published. Details on the search algorithm and a list of excluded studies are available from the author upon request.

### Appraisal of Studies

Different groups of authors suggest checklists for the appraisal of health economic evaluations (e.g., 8;12;45). For this appraisal process, the well-known checklist of Drummond and Jefferson developed by a working party of leading health economists for the British Medical Journal (12) was applied by two independent reviewers. If one of the twenty-six items of an economic evaluation was identified, but with limited transparency only, a score of .5 was assigned. Literature references, for example, in the case of cost data taken from other evaluations, were not included in the appraisal. A detailed overview of study appraisal can be obtained from the author. From the high number of quality criteria, only the most substantial characteristics and irregularities are reported here.

## RESULTS

### Overview of Target Conditions Investigated by Economic Evaluation

Only eight conditions were identified for which genetic screening was economically assessed. An overview of the indications and genes tested is given in Table 1. The table is structured by the corresponding parts or subsections in *Harrison's Principles of Internal Medicine* (18) where further information on the conditions can be found. The order corresponds to the number of conditions per disease category. As the costs of genetic testing are substantially lower if defined sequences and not the whole gene are tested, the number of mutations tested is given as well. An estimation of the burden of disease would be a desirable addendum in this overview. Yet the burden strongly depends on ethnicity and family background, and especially in the case of genetic risk factors, it is still subject to scientific discussion. Thus, only a brief description of each condition is given.

### Neoplasms

***Hereditary Breast and Ovarian Cancer.*** The Hereditary Breast and Ovarian Cancer syndrome is a clinical condition associated with the transmission of germline mutations in the *BRCA1* or *BRCA2* genes. Three heterogeneous evaluations on *BRCA1/2* investigated genetic screening of different female risk groups for preventive mastectomy and/or oophorectomy (48), population screening among Ashkenazi Jewish women also for prophylactic surgery (15), or screening of high-risk women for increased prophylactic surveillance (2). The papers unanimously conclude or assume that decision makers are highly unlikely to find population-wide testing for mutations in the *BRCA1/2* cancer susceptibility genes cost-effective. Yet also their more favorable conclusions on the cost-effectiveness ratios for the selected risk groups are based on limited evidence only: The evaluations are heterogeneous in their assumptions on cancer risks and treatment effectiveness and their health economic transparency is comparatively low (among the lowest 25 percent of quality scores) (2;15) or they lack a widely acceptable treatment alternative (48). Further details are given in Table 2.

***Familial Adenomatous Polyposis.*** Familial adenomatous polyposis (FAP) is a hereditary form of precancerosis caused by mutations of the Adenomatous Polyposis Coli gene (*APC*). Regular colonoscopic screening of at-risk family members is recommended, and DNA testing primarily serves to exclude healthy first-degree or other relatives from conventional colonoscopy. Before screening family members, the FAP index patient is screened for an *APC* mutation. If the index patient is *APC*-positive, first-degree relatives (FDRs) are tested to determine whether they have inherited

**Table 1.** Overview of Target Conditions Investigated by Health Economic Evaluation

| Disease category | Condition | Gene mutation(s) tested for |
|---|---|---|
| Neoplastic disorders | Hereditary breast and ovarian cancer | Breast and ovarian cancer susceptibility genes (*BRCA1/2*), three defined mutations (15); whole coding gene sequence (2;48) |
| | Familial adenomatous polyposis colorectal cancer | Adenomatous Polyposis Coli gene (*APC*), only protein-truncating mutations (7;10); including two defined mutations (3) |
| | Hereditary nonpolyposis colorectal carcinoma | DNA mismatch repair genes *MSH2/MLH1*, whole coding gene sequence (22;38;39;40) |
| | Retinoblastoma | Tumor suppressor gene *RB1*, whole coding gene sequence (34) |
| Endocrinology and metabolism | Familial hypercholesterolemia | Low-density lipoprotein (*LDL*) receptor gene, whole coding gene sequence (25-27;49) |
| | Hereditary hemochromatosis | *HFE* gene, one defined mutation (1;4;44) |
| | Insulin-dependent diabetes mellitus | *HLA-DQB1* risk alleles, two defined mutations (16) |
| Diseases of the respiratory system | Cystic fibrosis | *CF* gene, one defined mutation (24) |



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**Table 2.** Overview of Health Economic Evaluations of Genetic Screening

| Condition | Source | Country, year | Target population (mutation prevalence) | Screening alternatives compared | Treatment for selected subgroup | Perspective | Type of study | Results & unit (Base case) | Evidence for the condition |
|---|---|---|---|---|---|---|---|---|---|
| Hereditary breast and ovarian cancer | Balmana et al. (2) | Spain, 2004 | Women from high-risk families (20%) and FDR (10%) | Selection of breast cancer patients according to clinical criteria; DNA test of index case; if +, test of family members vs. no screening | Intensified screening: monthly self-palpation, annual clinical breast examination with mammography for m+ | Healthcare system | CE | 4,294 €/LYG ($5,591[a]) | Limited[b,c,d] |
| | Tengs & Berry (48) | USA, 2000 | 30 year old at-risk women (>5%) | Genetic testing for at-risk women vs. no genetic screening | Oophorectomy, mastectomy for m+ | Society | CU | <34,000 $/QALY | |
| | Grann et al. (15) | USA, 1999 | Ashkenazi Jewish women (2.5%) | DNA testing for three frequent mutations vs. no genetic screening | Combined prophylactic oophorectomy and mastectomy for m+ | Healthcare system | CE | 20,717 $/LYG | |
| FAP | Chikhaoui et al. (7) | Canada, 2002 | FDR of FAP patients (50%) | Family tracing, proband DNA testing, FDR PTT vs. family tracing only | Colonoscopy or flexible sigmoidoscopy only for m+ and mutation-unknown FDR | Healthcare system | CM | Savings of 922 Can$/s.p. aged 12 ($768[a]) | High (cost saving) |
| | Bapat et al. (3) | Canada, 1999 | FDR of FAP patients (50%) | Family tracing, proband DNA testing and FDR PTT testing vs. family tracing only | Flexible sigmoidoscopy only for m+ and mutation-unknown FDR | Third party payer | CM | Savings of 3,056 Can-$/family[f] ($2,568[a]) | |
| | Cromwell et al. (10) | USA, 1998 | Apparently healthy FDR of FAP patients (50%) | Family tracing, two different DNA testing strategies vs. family tracing only | Flexible sigmoidoscopy only for m+ and mutation-unknown FDR | Third party payer | CM | Savings of 583 $/s.p. aged 12 | |
| Hereditary Nonpoly-posis Colorectal Carcinoma | Kievit et al. (22) | Netherlands, 2005 | CRC patients (approx. 5%) & siblings and children of m+ (50%) | Application of four clinical selection criteria, MSI, DNA testing vs. family based selection criteria, MSI, DNA testing | Increased colonoscopic surveillance with polypectomy for m+ | Healthcare system | CE | 2,184 €/LYG ($2,376[e]) | High (cost-effectiveness to be assessed) |
| | Ramsey et al. (38) | USA, 2003 | CRC patients (approx. 5%) & FDR of m+ (50%) | Family analysis (Bethesda guidelines), MSI, DNA testing vs. three other screening strategies | Prophylactic colorectomy/ increased colonoscopic surveillance for m+ | Healthcare system | CE | 11,865 $/LYG | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Reyes et al. (40) | USA, 2002 | CRC patients (approx. 5%) & FDR of m+ (50%) | Application of Amsterdam selection criteria, tumour MSI analysis, germ-line DNA testing vs. three other strategies | (comparison of cost per mutation detected only) | Healthcare system | CE | 6,441 $/c.d. | |
| | Ramsey et al. (39) | USA, 2001 | US-CRC patients (approx. 5%) & FDR of m+ (50%) | Family analysis (Bethesda guidelines), MSI, DNA testing vs. no screening | Prophylactic colorectomy/ increased surveillance for m+ | Society | CE | 7,556 $/LYG | |
| Retinoblastoma | Noorani et al. (34) | Canada, 1996 | FDR of bilaterally affected infants (10% assumed) | Molecular selection of m+ vs. family tracing only | Clinical investigation of m+ vs. clinical investigation for at-risk FDR | Third party payer | CM | Savings of 22,756 Can$/ family ($19,123[a]) | Limited[b] |
| Familial Hyper-cholesterolemia | Wonderling et al. (49) | Netherlands, 2004 | Relatives of diagnosed FH patients in the Netherlands (50%) | DNA testing subsequent to clinical diagnosis of FH; screening of relatives for detected mutation vs. no screening | Cholesterol-lowering statin treatment for m+ | Healthcare system | CE | 8,800 $/LYG | High (genotype screening dominated by phenotype screening) |
| | Marang-van de Mheen et al. (25) | Netherlands, 2002 | Relatives of diagnosed FH patients in the Netherlands (50%) | DNA testing subsequent to clinical diagnosis of FH; screening of relatives for detected mutation vs. no screening | Statin therapy for m+ who fulfil treatment criteria | Healthcare system | CE | 25,500 €/LYG ($27,687[a]) | |
| | Marks et al. (27) | United Kingdom, 2002 | Different population groups in England and Wales aged 16-54 (50%-1/500) | Cholesterol testing and genetic diagnosis vs. cholesterol testing and phenotype diagnosis for five different target groups | Statin therapy for m+ | Healthcare system | CE | Dominated | |
| | Marks et al. (26) | United Kingdom, 2000 | Different population groups in England and Wales aged 16-54 (50%-1/500) | Cholesterol testing and genetic diagnosis vs. cholesterol testing and phenotype diagnosis for five different target groups | Statin therapy for m+ | Healthcare system | CE | Dominated | |

**Table 2.** Continued

| Condition | Source | Country, year | Target population (mutation prevalence) | Screening alternatives compared | Treatment for selected subgroup | Perspective | Type of study | Results & unit (Base case) | Evidence for the condition |
|---|---|---|---|---|---|---|---|---|---|
| Hereditary Hemochromatosis | El-Serag et al. (14) | USA, 2000 | Siblings and children of affected proband (25%) | Three genetic screening alternatives vs. phenotype and no screening | Phlebotomy, annual serum ferritin control for m+ | Healthcare system | CE | 508-3,665 $/LYG | Limited[b,c] |
| | Schöffski et al. (44) | Germany, 2000 | Male Caucasians aged 25 (2.5/1,000) | Population-based DNA testing vs. no screening | Counseling, Phlebotomy, annual serum ferritin control for m+ | Healthcare system | CE | 4,441 €/LYG ($4,724[a]) | |
| | Adams & Valberg (1) | Canada, 1999 | Voluntary blood donors (3/1,000) and siblings of the identified homozygotes (25%) | Genotypic (DNA and serum ferritin) screening vs. phenotypic (transferrin saturation, serum ferritin) and no screening | Phlebotomy for m+ with elevated serum ferritin level | Third party payer | CU | Dominated | |
| | Bassett et al. (4) | Australia, 1997 | Australian population (3/1000) | Transferrin saturation, DNA testing vs. Transferrin saturation, liver biopsy | n.a. | Societal | CM | Savings of >669 $/c.d. | |
| Insulin-dependent Diabetes Mellitus | Hahl et al. (16) | Finland, 1998 | Finnish newborns (13%) | Repeated protein test for diabetes only for mutation positives vs. repeated protein test to all | n.a. | Healthcare system | CM | Savings of 402 $/s.p. | Limited[b] |
| Cystic Fibrosis | Lee et al. (24) | USA, 2003 | US newborns (.8–2.9/10,000) | Newborn blood immunoreactive trypsinogen test; DNA testing; sweat test added to existing screening program vs. sweat test at age 3–4 | n.a. | Healthcare system | CM | Savings of 2.47 $/s.p. | Limited[d] |

[a] US$ converted by purchasing-power parity (gross domestic product) rates of the publication year.
[b] Unstable results/low epidemiologic evidence.
[c] Incongruent results among different studies.
[d] Inappropriate methodology.
[e] The purchasing-power parity conversion rate for 2004 was used as 2005 was not available.
[f] The currency was assumed to be of the country of authors.

c.d., case detected; CE, cost-effectiveness analysis; CM, cost-minimization analysis; CRC, colorectal carcinoma; CU, cost-utility analysis; DNA, deoxyribonucleic acid; FAP, familial adenomatous polyposis; FDR, first-degree relatives (parents, siblings, offspring); LYG, life-year gained; m+, mutation-positive; MSI, microsatellite instability testing, a diagnostic method to identify potential hereditary nonpolyposis colorectal carcinoma mutation carriers at lower cost than by gene sequencing; n.a., not applicable; PTT, protein-truncated testing; QALY, quality-adjusted life year; s.p., screened person.

the mutation. If the index patient is *APC*-negative, subsequent FDR testing is not performed and conventional screening is applied according to family analysis (7;10). Three homogenous cost-minimization analyses were identified, which all compare genetic testing with conventional colonoscopy or sigmoidoscopy based on family risk only (3;7;10). The authors unanimously favor genetic testing based on protein truncated testing (PTT) with supplementing DNA analysis.

***Hereditary Nonpolyposis Colorectal Cancer.*** Hereditary nonpolyposis colorectal carcinoma (HNPCC), or Lynch syndrome, is a cancer susceptibility syndrome without overt symptoms or signs before onset of the associated malignancies. Several groups have proposed algorithms that focus testing efforts on subjects who are at high risk for HNPCC, mostly persons with newly diagnosed colorectal cancer who meet clinical and family history criteria. Four heterogeneous cost-effectiveness analyses (22;38–40) compared selection of high risk colorectal cancer (CRC) patients eligible for genetic testing by alternative algorithms (22;38;40) or screening according to the Bethesda guidelines (41) to no screening (39). The number of cases detectable by the investigated testing strategies varied substantially between the evaluations and no publication consistently compared all available screening algorithms. The unanimous result of the authors was that genetic screening compared with not screening had a cost-effectiveness ratio that may be acceptable to healthcare providers, but only if based on defined selection criteria.

***Retinoblastoma.*** Retinoblastoma is a childhood cancer of the retina, which can result from inactivation of the tumor-suppressor gene *RB1*. The siblings, nephews/nieces, and first cousins of bilaterally affected children are conventionally recommended for screening by repeated ophthalmological examinations under general anesthetic (EUA). The oldest economic evaluation identified, a cost-minimization analysis published in 1996, compared conventional EUA to genetic testing of the index case and genetic testing of relatives for an identified mutation before EUA (34). Based on published and unpublished effectiveness data, the authors constructed a decision tree and concluded that the genetic screening strategy is cost-saving compared to conventional screening.

## Metabolic Diseases

***Familial Hypercholesterolemia.*** Familial hypercholesterolemia (FH) is associated with pronounced atherosclerosis leading to premature cardiovascular disease and untimely death. It is a potential target condition for screening programs, as treatment with statins is effective and delays or prevents the onset of coronary heart disease (27;49). Screening can be conducted for mutations of the low density lipoprotein receptor (*LDL*) gene as well as for characteristic lipid profiles. Four cost-effectiveness analyses (25–27;49) including one British health technology assessment (HTA) report (26) on genetic screening for familial hypercholesterolemia were identified. Two controversial publications evaluated the cost-effectiveness of a screening program conducted in the Netherlands without considering the alternative of phenotype screening. The two remaining similar evaluations (26;27) investigate five screening strategies for the UK population. They compared genotype with phenotype screening and concluded that genetic screening is dominated by the latter.

***Hereditary Hemochromatosis.*** Hereditary hemochromatosis (HH) is an autosomal recessive disorder characterized by an over absorption of iron and the progressive accumulation of iron in most body tissues, which results in severe cellular and organ damage, in particular of the liver. HH is an outstanding screening target, as iron removal by phlebotomy is highly effective at a comparatively low cost (47). The four economic evaluations that met the inclusion criteria (1;4;14;44) were very heterogeneous concerning the alternatives investigated, their methodological quality, and their conclusions. Phenotype screening was both calculated to be dominating and dominated by genetic screening. Genetic screening was cost-saving, with limited quality of evidence when it substituted confirmatory liver biopsy (4). It showed a cost-effectiveness ratio potentially acceptable to healthcare deciders when it was applied to at-risk relatives and thus substituted regular serum iron studies (14). Falling costs of genetic tests may be about to make genetic screening the unanimously preferred option: At genetic test costs of $173, valid at the time of the publications, genetic testing was calculated to be cost-saving only compared to liver biopsy for confirmatory testing but dominated as a primary screening test. Yet, a recent costing study on genetic screening for HH (47) found direct test costs currently to be below the threshold for cost-savings of $20 in one of the studies (1).

***Insulin-Dependent Diabetes Mellitus.*** Insulin-dependent diabetes mellitus (IDDM) is a multifactorial autoimmune disease of high incidence in the Western world, which is associated with sizeable life-long costs. As prevention of IDDM may soon become a reality, one cost-minimization analysis assessed two options of selecting target subjects for preventive programs based on a trial with 11,721 newborns (16): A pure immunological strategy where markers of autoimmunity were repeatedly analyzed in the entire population was compared to a genetically targeted strategy where the markers were only analyzed in a genetically determined high-risk population. The authors concluded that the genetically targeted strategy was cost-saving, yet as the oldest trial propositi were aged slightly over 2 years at the time of publication, evidence on genotype–phenotype association was limited.

## Respiratory Tract Disease

***Cystic Fibrosis.*** Cystic fibrosis is the most common serious hereditary disorder among Caucasians characterized

by progressive respiratory and gastrointestinal problems. Modern treatment with physiotherapy, antibiotics, and enzyme supplements delays disease progression, and average survival is now predicted to exceed 40 years (29). Most of the studies dedicated to CF investigated the cost-effectiveness of prenatal screening, which was excluded from this review. One study compared the costs of newborn DNA screening for the most frequent mutation, delta F508, and the blood immunoreactive trypsinogen test to the cost of the traditional practice of diagnosis by the sweat chloride test at a mean age of 3 to 4 years (24). Based on data of 70,797 newborns from the Wisconsin newborn screening program in the year 2000, additional screening effects and costs for a nationwide U.S. newborn screening program were estimated. Based on a calculation with limited transparency, the authors concluded that newborn screening was cost-saving. Costs for a nationwide CF screening program were estimated to be around $10,000,000.

### Methodology of the Economic Evaluations

Most of the evaluations were based on a decision tree, some incorporating Markov chains. In half of the fourteen evaluations, where the modeling software was stated, DATA TreeAge Software was used. The evaluations were of varying quality and frequently deviated from current standards of health economic evaluation. In many cases, the perspective was not stated correctly or justified and no economically relevant decision-making context was made transparent. Also, quantities of consumed resources or details on currency or on discounting often were not given. Probabilistic sensitivity analysis, currently the method recommended for dealing with uncertainty in economic modeling by several good-practice guides and regulatory agencies (5;30), was only conducted in an appropriate way in three of the twenty-one economic evaluations (15;38;39). Most of the economic evaluations relied on one-way sensitivity analyses (52 percent), one-way sensitivity analysis with best/worst case scenario (8 percent) or two-way sensitivity analysis (24 percent). In none of the studies, the clinical evidence was solely based on the gold standard of randomized, clinical trials. Instead, cost-effectiveness was frequently modeled based on experimental and observational data and, in some cases, supplemented by author's assumptions.

### Overview of Economic Evaluations of Genetic Screening

Table 2 details condition, country of authors and year of publication, target population and assumed mutation prevalence within the target population, screening alternatives compared, treatment for the selected subgroup, perspective, type of economic evaluation, results, and the quality of evidence for the condition of all publications included in this review. Within the conditions, the publications are listed chronologically. If more than two alternatives were investigated, the information given in the table refers to the base case scenario when the finally recommended screening strategy was chosen and the recommended treatment was conducted for the selected mutation carriers. Numerical results were converted to US$ by the gross domestic product (GDP) purchasing-power parity (PPP) conversion rate of the publication year. The results were not adjusted for inflation, as within the conditions, the publication years only span a period of 5 years or less.

The appraisal of the evidence favoring or opposing the use of genetic tests for the condition ("high" or "limited") was based on three criteria: methodological transparency and quality, stability of results in the sensitivity analyses, and consistency among different evaluations. If one or more criteria were not met, the evidence was appraised as limited.

## DISCUSSION

### Systematic Search

Neither extensive reference tracking nor hand search revealed additional economic evaluations to those detected by the index-based search strategy. As earlier literature on review methodology concluded that electronic searches of the literature identify only 50 percent of all relevant articles (11;23), this intermediate result may be taken as a sign of improving database indexing quality and, thus, decreasing indexing bias. Two of the evaluations were identified in EMBASE (44;48). Therefore, from this search process, it cannot be recommended to follow the conclusions of Sassi et al. (42) and to limit the scope of a review to Medline alone.

### Results

The health economic literature on genetic screening is limited: Only a minuscule part of the approximately 1,700 gene sequences known to be associated with a disease (28) or the approximately 800 diseases for which clinical testing is available in the United States (35) have been investigated by health economic evaluation of genetic screening. Yet the literature is not only limited due to the novelty of the screening options but also due to the low prevalence of most genetic disorders with sufficient penetrance and expression for effective genetic screening (9;50).

No dominant scientific platform has evolved yet where the cost-effectiveness of this new and growing field of medical intervention is discussed. The twenty-one economic evaluations identified in this review have been published in nineteen different journals (with two evaluations only in Gut and the Annals of Internal Medicine).

The assessment of the methodology by Drummond's quality criteria confirmed the results of earlier quality assessments of economic evaluations, which report methodological deficiencies (20). Frequently, economic evaluations of screening for hereditary diseases lack clinical studies due to their low population prevalence (9).

There was no unanimous judgment on the cost-effectiveness of genetic screening, but results vary by condition and target group and range from dominated to cost-saving. Apart from one study investigating newborn screening across the United States, all evaluations were restricted to certain risk groups selected by ethnicity or clinical/family criteria. Population screening was considered cost-effective with limited quality of evidence only in the case of screening for *BRCA1/2* founder mutations among female Ashkenazi Jews and of hemochromatosis screening among Caucasians. It was considered cost-saving compared with current practice in newborn screening for cystic fibrosis in the United States.

Genetic screening was considered cost-saving for familial adenomatous polyposis with high health economic evidence and for retinoblastoma and insulin-dependent diabetes mellitus with limited evidence. For hereditary nonpolyposis colorectal carcinoma, another condition with high health economic evidence, the authors concluded that the cost-effectiveness of genetic testing is below their assumed benchmark. As the cost-effectiveness ratios are below most of the currently proposed and applied thresholds (13), healthcare providers may be assumed to share this conclusion. It was dominated by phenotype screening in the case of familial hypercholesterolemia.

## Factors Influencing Cost-Effectiveness

To summarize the sensitivity analyses, the following factors were most influential on cost-effectiveness of genetic screening: The cost-effectiveness of genetic screening compared with no screening primarily depended on *mutation prevalence* in the defined target population. As in most cases, the prevalence among the general population was prohibitively low, and ethnic (e.g., Ashkenazi Jews for *BRCA1/2* mutations), family (e.g., family history of colorectal cancer), and clinical selection (e.g., microsatellite instability for HNPCC) criteria for screening candidates were defined. Second, *genetic test costs* compared with phenotype test costs strongly influenced cost-effectiveness of genetic screening. As genetic test costs have fallen substantially in the past years, the existing studies may warrant re-evaluation. Third, variations in *mortality risks and effectiveness of treatment* played an important role in sensitivity analyses. Due to the novelty of genetic diagnosis and limited clinical data, in some cases, authors had little evidence on the effectiveness and, therefore, even less evidence on cost-effectiveness of genetic screening. Fourth, the *age at screening* was influential: The younger the screened person, the more effective is the treatment or the higher are the cost savings due to omitted surveillance (e.g., for mutation-negative family members of hereditary cancer probands). Fifth, the *discount rate* was of strong influence, as costs and effects frequently arise over long periods. Further important influence factors were family size, drug and counseling costs, compliance, and test sensitivity and specificity.

## Limitations of This Study

"Genetic screening" in medicine is a fuzzy term applied for various medical interventions ranging from DNA analysis to family anamnesis. The DNA technology-based approach allows for generalizing statements due to the similarity of the interventions investigated but may be criticized as being too narrowly focused.

The appraisal of health economic evaluations followed a well-known checklist on methodological transparency to rate the evaluations only by widely applicable criteria potentially known to the authors. Yet a good economic evaluation is more than the sum of its parts (46), and quality and content validity can hardly be appraised by a checklist oriented at transparency issues. Even if the appraisal is based on consensus of two independent reviewers, it is additionally restricted by their subjectivity.

## Implications of This Review

***Implications for Healthcare Deciders and Policy Makers.*** Based on the existing evidence, healthcare deciders should consider the introduction of genetic screening of at-risk patients for familial adenomatous polyposis, because it is cost saving compared to no screening. Healthcare providers may be inclined to consider genetic screening for HNPCC in colorectal cancer patients to be cost-effective. In the case of familial hypercholesterolemia, under current conditions, genetic screening is dominated by phenotype screening.

***Implications for the Genetic Diagnostics Industry.*** With falling prices for genetic tests, not only screening for high-risk groups but also population-based screening for selected genetic disorders is close to widely accepted cost-effectiveness, especially in the case of hereditary hemochromatosis. Given that economic evidence on cost-effectiveness is an increasingly important condition for market entry, health economic evaluations can guide marketing decisions as well as provide benchmarks to be reached in further research and development.

***Implications for Further Health Economic Research.*** There is further need of health economic evaluations in the field of genetic screening. Areas that especially warrant further research are the potentially cost-saving fields of newborn screening for cystic fibrosis and retinoblastoma as well as the potentially cost-effective screening for hereditary hemochromatosis. Due to falling prices of genetic test costs, existing economic evaluations may need re-evaluation and new indications may become worthwhile screening targets.

The research targets for sound health economic evaluation are limited by a lack of epidemiological evidence and treatment options. Especially in the field of hereditary cancer and insulin-dependent diabetes mellitus, medical and epidemiologic research should be conducted before further health economic evaluation.

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