Genetic Testing Research Literatures

Ma Hongbao, PhD

Brookdale University Hospital and Medical Center, Brooklyn, New York 11212, USA
ma8080@gmail.com

Abstract: Genetic testing, also known as DNA testing, allows the determination of bloodlines and the genetic diagnosis of vulnerabilities to inherited diseases. In agriculture, a form of genetic testing known as progeny testing can be used to evaluate the quality of breeding stock. In population ecology, genetic testing can be used to track genetic strengths and vulnerabilities of species populations. In humans, genetic testing can be used to determine a child's parentage (genetic mother and father) or in general a person's ancestry or biological relationship between people. In addition to studying chromosomes to the level of individual genes, genetic testing in a broader sense includes biochemical tests for the possible presence of genetic diseases, or mutant forms of genes associated with increased risk of developing genetic disorders. Genetic testing identifies changes in chromosomes, genes, or proteins. The variety of genetic tests has expanded throughout the years. In the past, the main genetic tests searched for abnormal chromosome numbers and mutations that lead to rare, inherited disorders. Today, tests involve analyzing multiple genes to determine the risk of developing specific diseases or disorders, with the more common diseases consisting of heart disease and cancer.[2] The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed. Because genetic mutations can directly affect the structure of the proteins they code for, testing for specific genetic diseases can also be accomplished by looking at those proteins or their metabolites, or looking at stained or fluorescent chromosomes under a microscope.
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Introduction

Genetic testing, also known as DNA testing, allows the determination of bloodlines and the genetic diagnosis of vulnerabilities to inherited diseases. In agriculture, a form of genetic testing known as progeny testing can be used to evaluate the quality of breeding stock. In population ecology, genetic testing can be used to track genetic strengths and vulnerabilities of species populations. In humans, genetic testing can be used to determine a child's parentage (genetic mother and father) or in general a person's ancestry or biological relationship between people. In addition to studying chromosomes to the level of individual genes, genetic testing in a broader sense includes biochemical tests for the possible presence of genetic diseases, or mutant forms of genes associated with increased risk of developing genetic disorders. Genetic testing identifies changes in chromosomes, genes, or proteins. The variety of genetic tests has expanded throughout the years. In the past, the main genetic tests searched for abnormal chromosome numbers and mutations that lead to rare, inherited disorders. Today, tests involve analyzing multiple genes to determine the risk of developing specific diseases or disorders, with the more common diseases consisting of heart disease and cancer.[2] The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed. Because genetic mutations can directly affect the structure of the proteins they code for, testing for specific genetic diseases can also be accomplished by looking at those proteins or their metabolites, or looking at stained or fluorescent chromosomes under a microscope.

The following introduces recent reports as references in the related studies.

Berg, A. T., et al. (2017). "Early-Life Epilepsies and the Emerging Role of Genetic Testing." JAMA Pediatr **171**(9): 863-871.

Importance: Early-life epilepsies are often a consequence of numerous neurodevelopmental disorders, most of which are proving to have genetic origins. The role of genetic testing in the initial evaluation of these epilepsies is not established. Objective: To provide a contemporary account of the patterns of use and diagnostic yield of genetic testing for early-life epilepsies. Design, Setting, and Participants: In this prospective cohort, children with newly diagnosed epilepsy with an onset at less than 3 years of age were recruited from March 1, 2012, to April 30, 2015, from 17 US pediatric hospitals and followed up for 1 year. Of 795 families approached,

775 agreed to participate. Clinical diagnosis of the etiology of epilepsy were characterized based on information available before genetic testing was performed. Added contributions of cytogenetic and gene sequencing investigations were determined. Exposures: Genetic diagnostic testing. Main Outcomes and Measures: Laboratory-confirmed pathogenic variant. Results: Of the 775 patients in the study (367 girls and 408 boys; median age of onset, 7.5 months [interquartile range, 4.2-16.5 months]), 95 (12.3%) had acquired brain injuries. Of the remaining 680 patients, 327 (48.1%) underwent various forms of genetic testing, which identified pathogenic variants in 132 of 327 children (40.4%; 95% CI, 37%-44%): 26 of 59 (44.1%) with karyotyping, 32 of 188 (17.0%) with microarrays, 31 of 114 (27.2%) with epilepsy panels, 11 of 33 (33.3%) with whole exomes, 4 of 20 (20.0%) with mitochondrial panels, and 28 of 94 (29.8%) with other tests. Forty-four variants were identified before initial epilepsy presentation. Apart from dysmorphic syndromes, pathogenic yields were highest for children with tuberous sclerosis complex (9 of 11 [81.8%]), metabolic diseases (11 of 14 [78.6%]), and brain malformations (20 of 61 [32.8%]). A total of 180 of 446 children (40.4%), whose etiology would have remained unknown without genetic testing, underwent some testing. Pathogenic variants were identified in 48 of 180 children (26.7%; 95% CI, 18%-34%). Diagnostic yields were greater than 15% regardless of delay, spasms, and young age. Yields were greater for epilepsy panels (28 of 96 [29.2%]; P <.001) and whole exomes (5 of 18 [27.8%]; P =.02) than for chromosomal microarray (8 of 101 [7.9%]). Conclusions and Relevance: Genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies regardless of key clinical features. Thorough genetic investigation emphasizing sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations and poor outcomes.

Domanjko-Petric, A., et al. (2008). "Polycystic kidney disease: a review and occurrence in Slovenia with comparison between ultrasound and genetic testing." J Feline Med Surg **10**(2): 115-119.

Polycystic kidney disease (PKD) is an inherited autosomal kidney disease which is most commonly identified in Persian and Persian related cats. Positive cats have multiple cysts of various sizes that occur in the renal cortex and medulla and occasionally in other abdominal organs. PKD often leads to renal failure which occurs from mid to late in life. Renal cysts can be diagnosed ultrasonographically after 7 weeks of age by an experienced ultrasonographer and a high resolution machine. However, ultrasonography is now being replaced by genetic screening. A total of 340 cats of variable breeds aged from 5 months to 18 years were ultrasonographically examined in the past 7 years at the University Veterinary Small Animal Clinic. Of these, 13.8% were PKD positive with very high prevalence in Persian cats (36%). There was no sex predilection identified. The C>A transversion at position 3284 on exon 29 of PKD1 gene, resulting in a stop mutation has been identified in the heterozygous state in eight affected cats examined (Persian breed). All heterozygous cats were also ultrasonographically positive.

Duncan, R. E., et al. (2007). ""Holding your breath": interviews with young people who have undergone predictive genetic testing for Huntington disease." Am J Med Genet A **143A** (17): 1984-1989.

Guidelines recommend that predictive genetic testing for Huntington disease (HD) should be deferred until the age of majority (18 years in most countries). However, opposition to these guidelines exists, with some professionals arguing that testing may be beneficial for young people, and should be considered much earlier. Empirical evidence is unable to substantiate either position. We aimed to (1) explore the experience of predictive genetic testing for HD from the young person's perspective and to (2) document the impact that testing has upon various aspects of young people's lives. Eight young people who had undergone predictive genetic testing for HD were interviewed. They ranged in age from 17 to 25 years at the time of their test. Four were female and two had received a gene-positive test result. Interviews were taped, transcribed and analyzed thematically. Three themes emerged related to the time before the test was performed: "Living as though gene-positive," "Risk behaviors," and "Complex pasts." Two themes emerged related to the time after testing: "Identity difficulties" and "Living again." When the young people spoke about their experiences of predictive testing, they placed these within a broader context of growing up in a family affected by HD. For some of the young people, uncertainty about their genetic status constituted a barrier in their lives and prevented them from moving forward. Testing alleviated these barriers in some cases and helped them to move forward and make significant behavioral changes. Not one of the young people interviewed regretted undergoing predictive testing.

Duncan, R. E., et al. (2008). ""You're one of us now": young people describe their experiences of predictive genetic testing for Huntington disease (HD) and familial adenomatous polyposis (FAP)." Am J Med Genet C Semin Med Genet **148C** (1): 47-55.

There has been much debate about the psychosocial effects of predictive genetic testing in minors. The majority of this debate has been theoretical, with little empirical evidence published. We conducted in-depth interviews with 18 young people who had undergone testing, to explore the range of harms and benefits that they perceived were associated with their tests. Participants were eight individuals who were tested for Huntington disease (two gene-positive, six gene-negative) and ten who were tested for familial adenomatous polyposis (five gene-positive, five gene-negative). At the time of their test they ranged from 10 to 25 years of age. When interviewed they ranged from 14 to 26 years of age. Harms described included knowledge of future illness, witnessing distress in parents, negative effects on family relationships and friendships, effects upon employment and school, experiencing regret, feeling guilty and having to confront difficult issues. Benefits included knowledge of gene-negative status, relief from uncertainty, witnessing relief in parents, feeling able to plan for the future, positive effects on family relationships and friendships, feeling empowered and experiencing a sense of clarity about what is important in life. Harms were described in relation to gene-negative test results, as were benefits in relation to gene-positive test results. The testing process itself had several positive and negative effects for young people, distinct from the actual test result. Future research concerning the effects of predictive genetic testing in young people must remain broad and should aim to measure the beneficial as well as the harmful effects that resonate for young people themselves.

Duncan, R. E., et al. (2010). "The challenge of developmentally appropriate care: predictive genetic testing in young people for familial adenomatous polyposis." Fam Cancer **9**(1): 27-35.

Predictive genetic tests for familial adenomatous polyposis (FAP) are routinely offered to young people during early adolescence. While this is not controversial, due to the medical benefit conferred by the test, it is nonetheless challenging as a consequence of the stage of life of the young people, and the simultaneous involvement of multiple family members. Despite these challenges, it is possible to ensure that the test is offered in such a way that it actively acknowledges and facilitates young people's developing autonomy and psychosocial well-being. In this paper we present findings from ten in-depth interviews with young people who have undergone predictive genetic testing for FAP (four male, six female; five gene-positive, five gene-negative; aged 10-17 years at the time of their predictive test; aged 12-25 years at the time of their research interview). We present five themes that emerged from the interviews which highlight key ethical challenges associated with such testing. These are: (1) the significance of the test; (2) young people's lack of involvement in the decision to be tested; (3) young people's limited understanding; (4) provision of the blood test at the first visit; and (5) group testing of family members. We draw on these themes to make eight recommendations for future practice. Together, these recommendations highlight the importance of providing developmentally appropriate care to young people undergoing predictive genetic testing for FAP.

Eisinger, F. and J. P. Moatti (2007). "[Diffusion of genetic testing in oncology: what criteria for regulation?]." Med Sci (Paris) **23**(3): 327-332.

Does gene testing indicate a switch from an histopathological to a molecular approach of human diseases? Disease management in oncology is already improved by gene testing, at least for some specific cancers. It is however necessary to distinguish the analysis of genes specific to the tumour which gives clues about the fate of the tumours, from those unique to the patients, which gives clues about the future of the person. For the latter so-called germline mutations, wide scale gene-default screening would put pressure on resource allocation from the health care systems of developed countries. Currently the cost of detecting of 700 genes in the whole French population would exceed the whole health budget of the country for the next 10 years. Even if we can anticipate a dramatic decrease in the unit cost of these genetic tests in the future, their diffusion should not be controlled exclusively by technological and market forces. In this paper, we propose to discuss four main parameters for regulating these genetic tests, using as an archetypal example their application to cancer prevention and treatment: (1) which specific cancer disease is targeted by the test (prevalence, incidence, likelihood of cure with current therapeutics, number of years of life potentially saved...); (2) what are the characteristics of the genes tested and which level of evidence is required about the predictive value of the test; (3) what are the size and characteristics of the population who will be offered the test, and (4) which process and public control are necessary before market approval of the test and reimbursement of related expenditures by health care insurance schemes.

Etchegary, H., et al. (2015). "'It had to be done': genetic testing decisions for arrhythmogenic right ventricular cardiomyopathy." Clin Genet **88**(4): 344-351.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable disease of the heart muscle, causing life-threatening ventricular arrhythmias, sudden cardiac death and/or biventricular

heart failure. Little research examines ARVC genetic test decisions, despite the gravity of the condition. This qualitative study used semi-structured interviews to explore the testing decisions of 21 individuals across 15 families segregating a well-studied, particularly lethal form of ARVC caused by a p.S358L TMEM43 mutation. Genetic testing decisions were rarely described as 'decisions' per se, but rather 'something that had to be done'. This perception was attributed to personality type or personal suspicion of carrying the TMEM43 mutation, but most often was described in the context of testing for other family members, usually children. Participants related a strong need to rule out risk, more for children than for themselves, but lingering doubts remained about personal and children's risk for ARVC, even when gene test results were negative. Study findings highlight the interdependent nature of genetic test decisions and suggest that an individualistic conception of autonomy in genetic services may not meet the needs of affected families. Findings also suggest the need for follow-up support of families affected by ARVC, including for those individuals testing negative for the family mutation.

Freeman, B. D., et al. (2006). "Genetic research and testing in critical care: surrogates' perspective." Crit Care Med **34**(4): 986-994.

OBJECTIVE: Genetic testing is increasingly a component of clinical research in critical illness and has potential for integration into routine care. This study explored the perspectives of surrogate decision-makers (SDMs) for acutely ill patients with respect to social, legal, and ethical aspects of genetic testing. SETTING: Medical and surgical intensive care units in an urban tertiary care hospital. INTERVENTION: Questionnaires administered to SDMs for critically ill patients over a 12-month period. MEASUREMENTS AND MAIN RESULTS: A majority of eligible SDMs participated (117/146; 80.8%). SDMs were more likely to permit genetic testing for purposes of diagnosing a treatable life-threatening disease (114/117; 97.4%) or chronic disease (111/117; 94.9%) than for an untreatable life-threatening illness (95/117; 81.2%) (p <.001). SDMs were receptive to testing to explain familial traits (112/117; 95.7%) or ethnic traits (105/117; 89.7%) (p =.131). SDMs were concerned about potential for economic discrimination, with a majority expressing reluctance to permit testing if employers (93/117; 79.5%), health insurers (90/117; 76.9%), or life insurers (92/117; 78.6%) could access results. There was a greater willingness to allow participation in studies in which data were collected anonymously (90/117; 76.9%) vs. nonanonymously (75/117; 64.1%) (p =.04). Finally, SDMs placed greater trust in universities and nonprofit organizations (107/117; 91.4%) than either the federal government (75/117; 64.1%) or pharmaceutical companies (46/117; 39.3%) to perform genetic research (p <.01). CONCLUSIONS: SDMs expressed concerns regarding economic discrimination, confidentiality of data, and trust in entities conducting clinical investigation that may represent barriers both to performing studies in which genetic information is collected and to implementation of gene-based technologies in the critical care environment.

Gago-Diaz, M., et al. (2017). "Postmortem genetic testing should be recommended in sudden cardiac death cases due to thoracic aortic dissection." Int J Legal Med.

BACKGROUND: Acute thoracic aortic dissections and ruptures, the main life-threatening complications of the corresponding aneurysms, are an important cause of sudden cardiac death. Despite the usefulness of the molecular diagnosis of these conditions in the clinical setting, the corresponding forensic field remains largely unexplored. The main goal of this study was to explore and validate a new massive parallel sequencing candidate gene assay as a diagnostic tool for acute thoracic aortic dissection autopsy cases. MATERIALS AND METHODS: Massive parallel sequencing of 22 thoracic aortic disease candidate genes performed in 17 cases of thoracic aortic dissection using AmpliSeq and Ion Proton technologies. Genetic variants were filtered by location, type, and frequency at the Exome Aggregation Consortium and an internal database and further classified based on the American College of Medical Genetics and Genomics (ACMG) recommendations published in 2015. All prioritized results were confirmed by traditional sequencing. RESULTS: From the total of 10 potentially pathogenic genetic variants identified in 7 out of the 17 initial samples, 2 of them were further classified as pathogenic, 2 as likely pathogenic, 1 as possibly benign, and the remaining 5 as variants of uncertain significance, reaching a molecular autopsy yield of 23%, approximately. CONCLUSIONS: This massive parallel sequencing candidate gene approach proved useful for the molecular autopsy of aortic dissection sudden cardiac death cases and should therefore be progressively incorporated into the forensic field, being especially beneficial for the anticipated diagnosis and risk stratification of any other family member at risk of developing the same condition.

Guerrini, R. and R. Carrozzo (2001). "Epileptogenic brain malformations: clinical presentation, malformative patterns and indications for genetic testing." Seizure **10**(7): 532-543; quiz 544-537.

We review here those malformations of the cerebral cortex which are most often observed in epilepsy patients, for which a genetic basis has been elucidated or is suspected and give indications for genetic testing. There are three forms of lissencephaly (agyria-pachygyria) resulting from mutations of known genes, which can be distinguished because of their distinctive imaging features. They account for about 85% of all lissencephalies. Lissencephaly with posteriorly predominant gyral abnormality is caused by mutations of the LIS1 gene on chromosome 17. Anteriorly predominant lissencephaly in hemizygous males and subcortical band heterotopia (SBH) in heterozygous females are caused by mutations of the XLIS (or DCX) gene. Mutations of the coding region of XLIS were found in all reported pedigrees, and in most sporadic female patients with SBH. Missense mutations of both LIS1 and XLIS genes have been observed in some of the rare male patients with SBH. Autosomal recessive lissencephaly with cerebellar hypoplasia has been associated with mutations of the reelin gene. With few exceptions, children with lissencephaly have severe developmental delay and infantile spasms early in life. Patients with SBH have a mild to severe mental retardation with epilepsy of variable severity and type. X-linked bilateral periventricular nodular heterotopia (BPNH) consists of typical BPNH with focal epilepsy in females and prenatal lethality in males. About 88% of patients have focal epilepsy. Filamin A (FLNA) mutations have been reported in some families and in sporadic patients. Additional, possibly autosomal recessive gene (s) are likely to be involved in causing BPNH non-linked to FLN1. Tuberous sclerosis (TS) is a dominant disorder caused by mutations in at lest two genes, TSC1 and TSC2. 75% of cases are sporadic. Most patients with TS have epilepsy. Infantile spasms are a frequent early manifestation of TS. Schizencephaly (cleft brain) has a wide anatomo-clinical spectrum, including focal epilepsy in most patients. Familial occurrence is rare. Heterozygous mutations in the EMX2 gene have been reported in some patients. However, at present, there is no clear indication on the possible pattern of inheritance and on the practical usefulness that mutation detection in an individual with schizencephaly would carry in terms of genetic counselling. Amongst several syndromes featuring polymicrogyria, bilateral perisylvian polymicrogyria had familial occurrence on several occasions. Genetic heterogeneity is likely, including autosomal recessive, X-linked dominant, X-linked recessive inheritance and association to 22q11.2 deletions. FISH analysis for 22q11.2 is advisable in all patients with perisylvian polymicrogyria. Parents of an affected child with normal karyotype should be given up to a 25% recurrence risk.

Guerrini, R. and R. Carrozzo (2002). "Epileptogenic brain malformations: clinical presentation, malformative patterns and indications for genetic testing." Seizure **11 Suppl A**: 532-543; quiz 544-537.

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Gwyn, K., et al. (2003). "Intention to pursue genetic testing for breast cancer among women due for screening mammography." Cancer Epidemiol Biomarkers Prev **12**(2): 96-102.

Because few studies have addressed the intention to pursue testing for breast cancer susceptibility among women in the general population, we examined whether women due for routine mammography would want such testing and what factors might impact on their decision to pursue testing. A questionnaire was mailed to women > or =50 years of age who had undergone a screening mammogram 12 to 14 months before the study. Univariate and multivariable analyses were conducted to identify factors associated with intention to pursue genetic testing. Approximately 41% of respondents probably or definitely intended to pursue testing. In univariate analysis, the intention to undergo testing was not significantly associated with age, education, marital status, potential effects on health or life insurance, or physician recommendation. Although significant in univariate analysis, family history of breast cancer and ethnicity were not significant in multivariable analysis. In both univariate and multivariable analysis, factors significantly associated with intention to undergo testing included awareness of genetic testing, cancer worry, and insurance coverage of testing cost. Intention also was associated with the respondent wanting to know whether she possessed the susceptibility gene, even if that knowledge would not impact on options for early detection or treatment. Given the relatively high level of interest in testing among women at average risk of breast cancer, these results may help health care professionals educate and counsel women regarding the appropriate use of genetic testing as well as breast cancer risk factors.

Hess, J. E., et al. (2016). "Genetic basis of adult migration timing in anadromous steelhead discovered through multivariate association testing." Proc Biol Sci **283**(1830).

Migration traits are presumed to be complex and to involve interaction among multiple genes. We used both univariate analyses and a multivariate random forest (RF) machine learning algorithm to conduct association mapping of 15 239 single nucleotide polymorphisms (SNPs) for adult migration-timing phenotype in steelhead (Oncorhynchus mykiss). Our study focused on a model natural population of steelhead that exhibits two distinct migration-timing life histories with high levels of admixture in nature. Neutral divergence was limited between fish exhibiting summer- and winter-run migration owing to high levels of interbreeding, but a univariate mixed linear model found three SNPs from a major effect gene to be significantly associated with migration timing ($p < 0.000005$) that explained 46% of trait variation. Alignment to the annotated Salmo salar genome provided evidence that all three SNPs localize within a 46 kb region overlapping GREB1-like (an oestrogen target gene) on chromosome Ssa03. Additionally, multivariate analyses with RF identified that these three SNPs plus 15 additional SNPs explained up to 60% of trait variation. These candidate SNPs may provide the ability to predict adult migration timing of steelhead to facilitate conservation management of this species, and this study demonstrates the benefit of multivariate analyses for association studies.

Hollands, G. J., et al. (2012). "Patient accounts of diagnostic testing for familial hypercholesterolaemia: comparing responses to genetic and non-genetic testing methods." BMC Med Genet **13**: 87.

BACKGROUND: Continuing developments in genetic testing technology together with research revealing gene-disease associations have brought closer the potential for genetic screening of populations. A major concern, as with any screening programme, is the response of the patient to the findings of screening, whether the outcome is positive or negative. Such concern is heightened for genetic testing, which it is feared may elicit stronger reactions than non-genetic testing. METHODS: This paper draws on thematic analysis of 113 semi-structured interviews with 39 patients being tested for familial hypercholesterolaemia (FH), an inherited predisposition to early-onset heart disease. It examines the impact of disease risk assessments based on both genetic and non-genetic information, or solely non-genetic information. RESULTS: The impact of diagnostic testing did not seem to vary according to whether or not genetic information was used. More generally, being given a positive or negative diagnosis of FH had minimal discernible impact on people's lives as they maintained the continuity of their beliefs and behaviour. CONCLUSIONS: The results suggest that concerns about the use of genetic testing in this context are unfounded, a conclusion that echoes findings from studies in this and other health contexts.

Hubner, D. (2006). "Genetic testing and private insurance--a case of "selling one's body"?" Med Health Care Philos **9**(1): 43-55.

Arguments against the possible use of genetic test results in private health and life insurance predominantly refer to the problem of certain gene carriers failing to obtain affordable insurance cover. However, some moral intuitions speaking against this practice seem to be more fundamental than mere concerns about adverse distributional effects. In their perspective, the central ethical problem is not that some people might fail to get insurance cover because of their 'bad genes', but rather that some people would manage to get insurance cover because of their 'good genes'. This paper tries to highlight the ethical background of these intuitions. Their guiding idea appears to be that, by pointing to his favourable test results, a customer might make an attempt to 'sell his body'. The rationale of this concept is developed and its applicability to the case at issue is critically investigated. The aim is to clarify an essential objection against the use of genetic information in private insurance which has not yet been openly addressed in the academic debate of the topic.

Ikeda, K., et al. (2017). "[Implementation and Evaluation of Genetic Testing Seminars about Lifestyle-related Disease Prevention in Pharmacy Insurance-The Need for Cooperation between the Pharmacy and the University in Genetic Testing]." Yakugaku Zasshi **137**(12): 1517-1531.

A seminar titled "Implementation and evaluation of genetic testing of lifestyle-related disease genes" was held for pharmacists, medical clerks, and clerks of pharmacy insurance, with the aim of holding seminars led by pharmacists for the general public (including patients) in the future. The subject of the seminar was single nucleotide polymorphisms in obesity-related genes and alcohol metabolism-related genes. The purpose of the seminar was to contribute to the prevention of lifestyle-related diseases of the general public. We evaluated it by administering a questionnaire to the participants before and after the seminar. After the seminar, 55% of pharmacists answered that they would like to or would strongly like to participate in genetic testing (for lifestyle-related diseases and drug metabolism-related genes) of the general public. However, some participants did not wish to do so. A customer satisfaction (CS) analysis found that this was mainly because they did not want to know the results of genetic testing of others, which they felt should be private. Most (82%) of the pharmacists answered that assistance and advice was "very necessary" or "necessary" in the participation of genetic testing. These findings show that collaboration between pharmacies and universities will be important for future seminars to the general public.

Ingles, J., et al. (2012). "A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy." Heart **98**(8): 625-630.

BACKGROUND: Traditional management of families with hypertrophic cardiomyopathy (HCM) involves periodic lifetime clinical screening of family members, an approach that does not identify all gene carriers owing to incomplete penetrance and significant clinical heterogeneity. Limitations in availability and cost have meant genetic testing is not part of routine clinical management for many HCM families. OBJECTIVE: To determine the cost-effectiveness of the addition of genetic testing to HCM family management, compared with clinical screening alone. METHODS: A probabilistic Markov decision model was used to determine cost per quality-adjusted life-year and cost for each life-year gained when genetic testing is included in the management of Australian families with HCM, compared with the conventional approach of periodic clinical screening alone. RESULTS: The incremental cost-effectiveness ratio (ICER) was $A785 (pound510 or euro587) per quality-adjusted life-year gained, and $A12 720 (pound8261 or euro9509) per additional life-year gained making genetic testing a very cost-effective strategy. Sensitivity analyses showed that the cost of proband genetic testing was an important variable. As the cost of proband genetic testing decreased, the ICER decreased and was cost saving when the cost fell below $A248 (pound161 or euro185). In addition, the mutation identification rate was also important in reducing the overall ICER, although even at the upper limits, the ICER still fell well within accepted willingness to pay bounds. CONCLUSIONS: The addition of genetic testing to the management of HCM families is cost-effective in comparison with the conventional approach of regular clinical screening. This has important implications for the evaluation of families with HCM, and suggests that all should have access to specialised cardiac genetic clinics that can offer genetic testing.

Itin, P. H. and S. K. Fistarol (2003). "[Genetic counseling and DNA testing in patients with increased risks for malignant melanoma]." Ther Umsch **60**(8): 469-472.

There are numerous risk factors for the development of malignant melanoma. It has been documented that genetic predisposition exists but exogenous factors are also very important. In familial melanomas it has been well established that mutation in the CDKN2A gene which is located at chromosome 9 leads to a marked risk for malignant melanoma. This tumor-suppressor gene is important for the regulation of the cell cycle and mutation in this gene is associated

also with an increased rate of pancreas cancer. The penetrance of this mutation is influenced by UV-energy. In addition it has been shown that a second cluster for the familial atypical nevus syndrome is located at chromosome 1p36. Patients with the rare disease xeroderma pigmentosum have a defect in the DNA-repair mechanism inherited in an autosomal recessive trait and therefore develop within the first 20 years of life numerous malignant skin tumours including malignant melanomas. But also in non-syndromic patients a decrease of DNA-repair ability may occur. It has been shown recently that reduced DNA-repair ability is an independent risk factor for malignant melanoma and may contribute to susceptibility to sunlight-induced melanoma among the general population. Other constitutional risk factors for the development of malignant melanoma are fair skin, red hair and blue eyes. The most important exogenous risk factor is UV-exposition. Extensive and repetitive sunburns before the age of 15 years are especially predisposing to malignant melanoma. The most important preventive measures are continuous sun-protection including avoidance of sun in noon time on tropical and subtropical places, wearing a hut and sunglasses and application of sun-screens with high sun-protection factor. Furthermore a regular check for changing moles is indicated in persons with multiple atypical nevi or a familial melanoma syndrome. Nowadays molecular genetic screenings are available within research projects for members of melanoma-prone families. The controversy of such possibilities is discussed.

Jones, K. and B. A. Minassian (2014). "Genetic testing in infantile spasms identifies a chromosome 13q deletion and retinoblastoma." Pediatr Neurol **50**(5): 522-524.

BACKGROUND: Infantile spasms is an epileptic encephalopathy and the common final manifestation of numerous disparate insults to the developing brain during infancy. The varied etiologies may be structural, metabolic, genetic, or unknown. Etiological diagnosis is important as it may lead to specific therapy, which may affect developmental outcome. PATIENT: We report a case of infantile spasms of unknown etiology with dysmorphic features, in which genetic copy number variation microarray testing was included in the investigation of the cause of the disease. RESULTS: A large deletion of chromosome 13 was identified in the region 13q13 to 13q21.3 encompassing the retinoblastoma gene (13q14.2). Urgent ophthalmological evaluation revealed an asymptomatic retinoblastoma of the left eye, leading to early treatment. CONCLUSION: This is the first case report of infantile spasms specifically associated with a chromosome 13q deletion. Chromosomal region 13q13 to 13q21.3 may contain one or more genes whose hemizygous loss leads to infantile spasms. Copy number variation testing for cryptogenic infantile spasms led to the discovery of a mutation responsible for retinoblastoma, enabling early diagnosis and treatment of a potentially life-threatening cancer. High-sensitivity molecular diagnosis improves health care and substantially reduces expenses. This shift in diagnostic evaluation is broadly relevant to health care.

Kaduri, L., et al. (1999). "Genetic testing of breast and ovarian cancer patients: clinical characteristics and hormonal risk modifiers." Eur J Obstet Gynecol Reprod Biol **85**(1): 75-80.

OBJECTIVES: Carriers of the mutations 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene have a substantial life-time risk for breast and ovarian cancers (BC and OC). The aim of the study was to identify the clinical features and the hormonal risk modifiers in mutation carriers and the implication in suggested guidelines for treatment decisions in BRCA1/2 carrier patients. STUDY DESIGN: Breast and/or ovarian cancer patients from the Oncology and Cancer Genetic clinics were tested for the three Ashkenazi founder mutations: 87 patients were identified as carriers of one of these mutations. Clinical presentation and age at onset were correlated with the mutations, in patients with bilateral BC or BC and OC, the length of time that elapsed between the diagnosis of the two cancers was recorded. We compared BC and OC patients with regard to ages at menarche, first pregnancy and menopause, number of pregnancies and deliveries, the use of oral contraceptives, hormonal replacement therapy and fertility treatments. RESULTS: The carriers of the three BRCA1/2 Ashkenazi founder mutations did not differ in clinical presentation nor age at onset. Forty-three patients (74.1%) of 58 BC patients were diagnosed between the ages 30 and 50, only four (6.9%) patients were diagnosed after age 60. Of BC patients diagnosed before age 35, 63.6% developed second BC as compared to 25.5% of those diagnosed after age 35. Ovarian cancer was diagnosed after age 45 in 89.7% of the patients, only one patient was diagnosed under the age of 40. Oral contraceptives use was documented in 61.3% of BC patients as compared to 11.8% of OC patients. Other hormonal factors did not differ between the two groups. CONCLUSIONS: The carriers of the three Ashkenazi founder mutations should be considered at the same risk for BC and for OC and treatment options should be the same. Mutation carriers diagnosed with BC before the age of 35 are at a very high risk for developing second breast cancer. Most ovarian cancers in carriers were diagnosed after age 45, and

prophylactic oophorectomy should be postponed to the age of 45. Oral contraceptives might elevate the risk of BC in mutation carriers.

King, C. H., et al. (2002). "Will genetic testing alter the management of disease caused by infectious agents? A cost-effectiveness analysis of gene-testing strategies for prevention of rheumatic Fever." Clin Infect Dis **34**(11): 1491-1499.

Cost-effectiveness analysis was done to evaluate the potential health and economic effects of a genetic screening program to identify individuals at risk for rheumatic fever (RF). The current RF prevention strategy was compared with a new, primary prevention strategy involving early genetic testing and intensive prophylaxis to prevent a first attack among individuals at high risk for RF. When analysis of a hypothetical 2000 birth cohort was done from a societal perspective, the prevention strategy involving genetic screening and prophylaxis for high-risk persons reduced the number of RF cases and increased life span at an estimated discounted cost of $7900 per quality-adjusted life-year gained. Genetic screening became the preferred (least expensive) strategy if the test specificity was >/=98%, the annual cost of prophylaxis was <$550, or the annual cost of caring for an individual with severe rheumatic heart disease increased to >$32,000. When used with available antibiotic prophylaxis, genetic testing has the potential to provide a cost-effective strategy for the primary prevention of RF and its sequelae.

Koikawa, K., et al. (2017). "A Case of Hyperparathyroidism-jaw Tumor Syndrome Confirmed by Preoperative Genetic Testing." Intern Med.

We herein report the case of a young woman who was diagnosed with primary hyperparathyroidism and in whom genetic testing confirmed a diagnosis of hyperparathyroidism-jaw tumor syndrome. Familial hyperparathyroidism was suspected based on the patient's young age at the onset of the disease. Thus, genetic testing was performed.It showed a germline mutation in the HRPT2/CDC73 gene and confirmed the diagnosis of hyperparathyroidism-jaw tumor syndrome. Total parathyroidectomy was performed to prevent recurrence. In patients with early-onset hyperparathyroidism, genetic testing should be considered to facilitate the selection of a proper surgical procedure based on the consideration of future life expectancy.

Lala, A., et al. (2013). "Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis." J Thromb Haemost **11**(1): 81-91.

BACKGROUND: The CYP2C19 genotype is a predictor of adverse cardiovascular events in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) treated with clopidogrel. OBJECTIVES: We aimed to evaluate the cost-effectiveness of a CYP2C19*2 genotype-guided strategy of antiplatelet therapy in ACS patients undergoing PCI, compared with two 'no testing' strategies (empiric clopidogrel or prasugrel). METHODS: We developed a Markov model to compare three strategies. The model captured adverse cardiovascular events and antiplatelet-related complications. Costs were expressed in 2010 US dollars and estimated using diagnosis-related group codes and Medicare reimbursement rates. The net wholesale price for prasugrel was estimated as $5.45 per day. A generic estimate for clopidogrel of $1.00 per day was used and genetic testing was assumed to cost $500. RESULTS: Base case analyses demonstrated little difference between treatment strategies. The genetic testing-guided strategy yielded the most QALYs and was the least costly. Over 15 months, total costs were $18 lower with a gain of 0.004 QALY in the genotype-guided strategy compared with empiric clopidogrel, and $899 lower with a gain of 0.0005 QALY compared with empiric prasugrel. The strongest predictor of the preferred strategy was the relative risk of thrombotic events in carriers compared with wild-type individuals treated with clopidogrel. Above a 47% increased risk, a genotype-guided strategy was the dominant strategy. Above a clopidogrel cost of $3.96 per day, genetic testing was no longer dominant but remained cost-effective. CONCLUSIONS: Among ACS patients undergoing PCI, a genotype-guided strategy yields similar outcomes to empiric approaches to treatment, but is marginally less costly and more effective.

Lerman, C., et al. (1995). "Interest in genetic testing among first-degree relatives of breast cancer patients." Am J Med Genet **57**(3): 385-392.

The recent cloning of a breast-ovarian cancer susceptibility gene (BRCA1), and determination of the locus of a related gene (BRCA2), offers potential for clinical genetic testing for breast cancer susceptibility. This study examined interest in and expectations about an impending genetic test among first-degree relatives (FDRs) of breast cancer patients. One hundred five females completed two structured telephone interviews to assess demographics, breast cancer risk factors, psychological factors, and attitudes about genetic testing for breast cancer susceptibility. Overall, 91% of FDRs said that they would want to be tested, 4% said they would not, and 5% were uncertain. The most

commonly cited reasons for wanting genetic testing were to learn about one's children's risk, to increase use of cancer screening tests, and to take better care of oneself. Women with less formal education were motivated by childbearing decisions and future planning to a greater degree than were women with education beyond high school. Most women anticipated a negative psychological impact of positive test results, involving increased anxiety (83%), depression (80%), and impaired quality of life (46%). In addition, 72% of women indicated that they would still worry if they tested negative. In multivariate regression analysis, level of baseline depression was the strongest predictor of an anticipated negative impact of genetic testing (Beta =.15; P,.0001). These results suggest that the demand for genetic testing for breast cancer susceptibility may be great, even among women who are not likely to have predisposing mutations. (ABSTRACT TRUNCATED AT 250 WORDS)

Li, G., et al. (1999). "Molecular and clinical study of familial adenomatous polyposis for genetic testing and management." J Exp Clin Cancer Res **18**(4): 519-529.

Familial adenomatous polyposis (FAP) is an inherited predisposition to colorectal cancer characterized by the development of numerous adenomatous polyps, predominantly in the colorectal region. Germline mutations of the adenomatous polyposis coli (APC) gene are responsible for familial adenomatous polyposis. We examined germline mutations of the APC gene and clinical features among eighty-seven individuals who consisted of thirty-nine FAP-patients, thirty-seven of their family members with a 1 in 2 risk of predisposition to this disease, and eleven normal persons. We accurately identified nine heterozygotes, among individuals with a 1 in 2 risk by genetic testing, without the uncertainty of the recurrence risk calculated by Bayes' theorem. Six of the nine heterozygotes were confirmed to have colorectal polyps by colonoscopic examination. Since they were diagnosed at 12.7 years-of-age on average, and were no more than 20 years old, they could be treated to prevent colorectal cancer. Based on the genotype-phenotype correlation, we concluded that the germline mutations responsible for the sparse polyps phenotype of FAP-patients tend to locate from codon 1055 in the proximal region of the APC gene, while those for the profuse type locate from codon 1102 in the distal region. Among the thirty-nine FAP-patients, we found that those with the germline mutations within codon 1055 and codon 1262 had colorectal carcinomas of an advanced stage, at a high rate (71.4%). Special attention and aggressive intervention is needed in these patients and relatives at risk. With reasonable and appropriate management, it should be possible to prolong and improve the quality of life of those family members both affected and at risk.

Lickleder, C., et al. (2008). "Mental health and quality of life after genetic testing for Huntington disease: a long-term effect study in Germany." Am J Med Genet A **146A** (16): 2078-2085.

Predictive genetic testing for Huntington disease (HD) might cause severe short-term psychological reactions in patients with poor mental health. Very few studies exist on the long-term effects of genetic HD testing. The aim of this study was to assess mental health and quality of life in persons who were tested for HD mutation, to compare mental health depending on the result of the genetic test (non-carriers, gene carriers, and patients with HD) and to identify predictors of mental health and quality of life via linear regression. The data were collected by self-report questionnaires. In total, 121 individuals participated in this study: 52 were non-carriers, 54 were gene carriers, and 15 were gene carriers suffering from HD. Non-carriers and gene carriers showed better mental health and quality of life than HD-patients but did not differ from each other. In non-carriers four variables predicted increased depression and low mental quality of life: low perceived social support, no intimate relationship, female sex and younger age. For gene carriers three predictors were found: low perceived social support, the expectation of an unfavorable genetic test result before the testing procedure and being childless. To prevent detrimental effects of HD testing on mental health and mental quality of life, specific attention should be paid to persons with limited social networks during genetic counseling. Assessment of expectations related to the test result and mental health prior to a genetic testing procedure may help to identify gene carriers at risk of poor coping after an unfavorable test result.

Lips, C. J., et al. (2001). "Medullary thyroid carcinoma: role of genetic testing and calcitonin measurement." Ann Clin Biochem **38**(Pt 3): 168-179.

All patients with a thyroid nodule should have their plasma CT measured. Stimulated CT is generally better than basal, but in the lower ranges false negatives and false positives still occur. In families with hereditary MTC, RET gene mutation analysis has superseded measurement of plasma CT in the detection of asymptomatic disease gene carriers. All individuals with apparently sporadic MTC, but in whom there is some suspicion of familial disease, should also have RET genetic analysis. A negative DNA result practically excludes the possibility of hereditary MTC in families where an index case has been investigated and obviates the need for further

biochemical evaluation. Disease gene carriers may be divided into three distinct risk groups depending on the specific RET gene mutation in the family. The age at which presymptomatic surgery has to be performed depends on the risk group to which the patient belongs. Compared with the results of DNA analysis, the results of CT stimulation tests have become less important in the assessment of timing of surgery. During follow-up of patients who underwent surgery, measurement of plasma basal CT is still useful. The high sensitivity of measuring stimulated CT levels does not outweigh the burden of life-long periodic stimulation tests and the limited clinical consequences of slightly elevated levels. Stimulation tests are inevitable for persons at risk who prefer not to have genetic testing.

Lovric, S., et al. (2016). "Genetic testing in steroid-resistant nephrotic syndrome: when and how?" Nephrol Dial Transplant **31**(11): 1802-1813.

Steroid-resistant nephrotic syndrome (SRNS) represents the second most frequent cause of chronic kidney disease in the first three decades of life. It manifests histologically as focal segmental glomerulosclerosis (FSGS) and carries a 33% risk of relapse in a renal transplant. No efficient treatment exists. Identification of single-gene (monogenic) causes of SRNS has moved the glomerular epithelial cell (podocyte) to the center of its pathogenesis. Recently, mutations in >30 recessive or dominant genes were identified as causing monogenic forms of SRNS, thereby revealing the encoded proteins as essential for glomerular function. These findings helped define protein interaction complexes and functional pathways that could be targeted for treatment of SRNS. Very recently, it was discovered that in the surprisingly high fraction of approximately 30% of all individuals who manifest with SRNS before 25 years of age, a causative mutation can be detected in one of the approximately 30 different SRNS-causing genes. These findings revealed that SRNS and FSGS are not single disease entities but rather are part of a spectrum of distinct diseases with an identifiable genetic etiology. Mutation analysis should be offered to all individuals who manifest with SRNS before the age of 25 years, because (i) it will provide the patient and families with an unequivocal cause-based diagnosis, (ii) it may uncover a form of SRNS that is amenable to treatment (e.g. coenzyme Q10), (iii) it may allow avoidance of a renal biopsy procedure, (iv) it will further unravel the puzzle of pathogenic pathways of SRNS and (v) it will permit personalized treatment options for SRNS, based on genetic causation in way of 'precision medicine'.

Malinowski, M. J. (2000). "Separating predictive genetic testing from snake oil: regulation, liabilities, and lost opportunities." Jurimetrics **41**(1): 23-52.

This article explores the extent to which completion of maps of the human genome, coupled with the introduction of technology that will accelerate the identification of gene and protein function, have introduced immeasurable potential to advance life science and health care through genetic profiling. In light of definitional uncertainty, the regulatory and legal environment surrounding predictive genetic testing threatens to impede clinical utilization of genetic profiling technologies that could significantly improve human health. Especially given that genetic testing technologies have been stigmatized in the public and medical community, they must enter the marketplace with a regulatory framework that assures safety, efficacy, and market responsibility.

Marcuzzi, A., et al. (2013). "Clinical genetic testing of periodic fever syndromes." Biomed Res Int **2013**: 501305.

Periodic fever syndromes (PFSs) are a wide group of autoinflammatory diseases. Due to some clinical overlap between different PFSs, differential diagnosis can be a difficult challenge. Nowadays, there are no universally agreed recommendations for most PFSs, and near half of patients may remain without a genetic diagnosis even after performing multiple-gene analyses. Molecular analysis of periodic fevers' causative genes can improve patient quality of life by providing early and accurate diagnosis and allowing the administration of appropriate treatment. In this paper we focus our discussion on effective usefulness of genetic diagnosis of PFSs. The aim of this paper is to establish how much can the diagnostic system improve, in order to increase the success of PFS diagnosis. The mayor expectation in the near future will be addressed to the so-called next generation sequencing approach. Although the application of bioinformatics to high-throughput genetic analysis could allow the identification of complex genotypes, the complexity of this definition will hardly result in a clear contribution for the physician. In our opinion, however, to obtain the best from this new development a rule should always be kept well in mind: use genetics only to answer specific clinical questions.

McCune, C. A., et al. (2006). "Iron loading and morbidity among relatives of HFE C282Y homozygotes identified either by population genetic testing or presenting as patients." Gut **55**(4): 554-562.

BACKGROUND AND AIMS: Although most cases of hereditary haemochromatosis are associated with homozygosity for the C282Y mutation of the HFE gene, clinical penetrance varies and other genes

may modify disease expression. If so, relatives from clinically affected families, by inheriting such genes, may accumulate more iron. To seek evidence for this, we compared iron status and morbidity in unselected first degree relatives of two groups of index cases from South Wales, namely asymptomatic C282Y homozygotes identified by genetic screening of blood donors (n = 56) and C282Y homozygous haemochromatosis patients presenting clinically (n = 60). METHODS: All participating relatives had a structured interview, clinical assessment, and laboratory investigations. Health related quality of life was measured (SF-36 version 2). RESULTS: In total, 92% of 180 eligible first degree relatives were interviewed in the "screened" family group and 85% of 143 eligible relatives in the "patient" group. Of 59 relatives homozygous for C282Y, 76% of men and 32% of women had the "iron phenotype" (raised transferrin saturation and serum ferritin). Logistic regression modelling of the iron phenotype risk showed that 42% of the initial model deviance could be explained by homozygosity for C282Y, another 6% by lifestyle factors, and 6% by being male. Family group membership was not a significant risk factor. Morbidity and SF-36 scores did not differ significantly either between C282Y homozygotes and relatives lacking C282Y, or between C282Y homozygotes from the "screened" and "patient" groups. Serious morbidity (including cirrhosis) was low in both groups of relatives. CONCLUSIONS: HFE C282Y homozygosity has a high penetrance for iron accumulation but a low clinical penetrance. Lack of excess morbidity among C282Y homozygous relatives of index cases who presented clinically suggests that residual unknown genetic or environmental factors do not greatly influence clinical outcome among C282Y homozygotes.

McCusker, E. A. and C. T. Loy (2017). "Huntington Disease: The Complexities of Making and Disclosing a Clinical Diagnosis After Premanifest Genetic Testing." Tremor Other Hyperkinet Mov (N Y) **7**: 467.

The management of patients and families affected by Huntington disease (HD) is complicated by several factors, both practical and ethical. It can be difficult to determine the onset of clinically manifest HD (mHD). In addition, it can be challenging to decide when to disclose the diagnosis to the affected individual. Firstly, the features of HD, an incurable, inherited, neurocognitive disorder that often manifests in young adulthood, influence how the person presents and accepts a diagnosis. Secondly, a positive genetic test for HD may result in a genetic diagnosis, sometimes years before the development of clinical features and the diagnosis of mHD. Thirdly, observational studies of unaffected gene expansion carriers documented HD manifestations up to 10 years before the typical presentation for diagnosis. These developments may permit earlier genetic diagnosis and information regarding the patient's likely status with respect to the development of clinical disease. Making the genetic diagnosis of HD and providing information regarding disease status, earlier rather than later, respects the person's right to know and preserves honesty in the doctor/patient relationship. Conversely, delaying the diagnosis respects the right not to know, avoids potential discrimination, and permits the person to live a "normal" life for longer, in the context of a disease without cure. This discussion has implications for other inherited and neurocognitive disorders.

McRae, C. A., et al. (2001). "Interest in genetic testing in pallido-ponto-nigral degeneration (PPND): a family with frontotemporal dementia with Parkinsonism linked to chromosome 17." Eur J Neurol **8**(2): 179-183.

The specific mutation on the tau gene responsible for a neurodegenerative disease known as pallido-ponto-nigral degeneration (PPND) was recently located. PPND family members are at risk for an autosomal dominant form of frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). This study investigated whether individuals in this family would consider presymptomatic genetic testing. Surveys were sent to 66 at-risk individuals in the family; replies were received from 20 (30%). Family members were asked if they would consider having testing now or in the future, and to indicate their reasons for and against proceeding with testing. Fifty per cent (n=10) of those who were at risk and who responded indicated they would consider testing now, and 55% (n=11) would think about it in the future. The most frequently cited reasons to proceed with testing were to 'collaborate with research' (70%) and to 'know if my children are at risk' (45%). The most frequently cited reason not to pursue testing was 'I can enjoy my life more fully by not knowing' (50%). Results suggest that interest in determining whether they will manifest PPND is generally low among at-risk members of this family, despite wide support and participation in other research studies.

Meisel, S. F., et al. (2015). "Genetic susceptibility testing and readiness to control weight: Results from a randomized controlled trial." Obesity (Silver Spring) **23**(2): 305-312.

OBJECTIVE: To test the hypothesis that adding obesity gene feedback (FTO) to simple weight control advice at a life stage with raised risk of weight gain (university) increases readiness to control weight. METHODS: Individually randomized controlled trial

comparing the effect of: (i) simple weight control advice plus FTO feedback (FA) and (ii) simple weight control advice only (AO) on readiness to engage with weight control. Differences in stage of change by genotype and differential weight control behaviors were secondary outcomes. RESULTS: Of 1,016 participants randomized, only 279 completed follow-up, yielding 90% power to detect a small effect for readiness to control weight. As predicted, FA participants were more likely to be in the contemplation stage than AO participants (P = 0.023). Participants receiving higher-risk genetic results were at a higher stage of change than controls (P = 0.003), with a trend toward a higher stage of change than those getting lower-risk results (P = 0.051). Lower-risk results did not decrease weight control intentions compared with controls (P = 0.55). There were no group differences in adherence to recommended weight control behaviors (P = 0.87). CONCLUSIONS: Adding FTO feedback to weight control advice enhanced readiness to control weight, without evidence for genetic determinism, but had no more effect on behavior than weight control advice alone.

Muller, H. (2003). "[Genetic testing when tumor susceptibility, especially for colorectal cancer, is suspected]." Ther Umsch **60**(8): 445-453.

Approximately 5-10% of all tumours can be explained by inherited susceptibilities. While some of the underlying traits are rare, the total number of subjects at an increased genetic tumour risk is quite large in our population. Genetic testing has gained considerable importance in the identification of persons with such traits allowing their systematic medical surveillance and early detection and treatment of tumours. Predisposition for tumour development has to be considered in the following cases, 1) when the onset of the neoplasm was at an age earlier than the average of that for the general population, 2) if synchronous or metachronous foci occur in the same organ or organs at an increased risk due to the same trait, 3) if the tumour displays typical histological pecularities or occurs at an unusual position within an organ, 4) if the patient suffers from a genetic disorder with an increased tumour risk, 5) if several relatives were/are suffering from the same or genetically associated tumours and/or 6) a "tumour gene" has already been identified in a relative by molecular genetic testing. Thanks to the progress of the genome project, the number of genes identified has led to a steady increase in the detection of mutations which may lead to tumourigenesis. Identification and characterisation of a mutated "tumour gene" in a patient allows the verification of a clinical and/or genealogical diagnosis. Genetic testing is indicated if medical non-heroic measures are available to identify a tumour at an early state and to prevent its progression to an incurable disease. Also, healthy relatives can profit from the identification and characterization of the tumour trait. If they have inherited the same gene mutation they also need a systematic medical surveillance to improve their life expectancy and quality. Because gene testing raises a broad spectrum of medical, social, psychological, and ethical issues, genetic counselling has to be offered before, during and after molecular genetic analysis. In particular in genetic counselling related to tumour risks, problems often develop due to the involvement of an unusually large number of experts representing various medical disciplines who may hold different views. If several professionals are involved in the diagnosis and the genetic workup it is advisable for them to communicate directly with each other and not to misuse the patient as their "go-between". In this paper special emphasis is given to genetic testing for predispositions to colorectal cancer.

Mvundura, M., et al. (2010). "The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer." Genet Med **12**(2): 93-104.

PURPOSE: To estimate the cost-effectiveness of genetic testing strategies to identify Lynch syndrome among newly diagnosed patients with colorectal cancer and to offer targeted testing to relatives of patients with Lynch syndrome. METHODS: We calculated incremental costs per life-year saved for universal testing relative to no testing and age-targeted testing for strategies that use preliminary genetic tests (immunohistochemistry or microsatellite instability) of tumors followed by sequencing of mismatch repair genes. We also calculated incremental cost-effectiveness ratios for pairs of testing strategies. RESULTS: Strategies to test for Lynch syndrome in newly diagnosed colorectal tumors using preliminary tests before gene sequencing have incremental cost-effectiveness ratios of <or=$45,000 per life-year saved compared with no testing and <or=$75,000 per life-year saved compared with testing restricted to patients younger than 50 years. The lowest cost testing strategies, using immunohistochemistry as a preliminary test, cost <or=$25,000 per life-year saved relative to no testing and <or=$40,000 per life-year saved relative to testing only patients younger than 50 years. Other testing strategies have incremental cost-effectiveness ratios >or=$700,000 per life-year saved relative to the lowest cost strategies. Increasing the number of relatives tested would improve cost-effectiveness. CONCLUSION: Laboratory-based strategies using preliminary tests seem cost-effective from the US health care system perspective. Universal testing detects nearly twice as many cases of Lynch

syndrome as targeting younger patients and has an incremental cost-effectiveness ratio comparable with other preventive services. This finding provides support for a recent US recommendation to offer testing for Lynch syndrome to all newly diagnosed patients with colorectal cancer.

Nguyen, H. V., et al. (2017). "Incremental cost-effectiveness of algorithm-driven genetic testing versus no testing for Maturity Onset Diabetes of the Young (MODY) in Singapore." J Med Genet **54**(11): 747-753.

BACKGROUND: Offering genetic testing for Maturity Onset Diabetes of the Young (MODY) to all young patients with type 2 diabetes has been shown to be not cost-effective. This study tests whether a novel algorithm-driven genetic testing strategy for MODY is incrementally cost-effective relative to the setting of no testing. METHODS: A decision tree was constructed to estimate the costs and effectiveness of the algorithm-driven MODY testing strategy and a strategy of no genetic testing over a 30-year time horizon from a payer's perspective. The algorithm uses glutamic acid decarboxylase (GAD) antibody testing (negative antibodies), age of onset of diabetes (<45 years) and body mass index (<25 kg/m (2) if diagnosed >30 years) to stratify the population of patients with diabetes into three subgroups, and testing for MODY only among the subgroup most likely to have the mutation. Singapore-specific costs and prevalence of MODY obtained from local studies and utility values sourced from the literature are used to populate the model. RESULTS: The algorithm-driven MODY testing strategy has an incremental cost-effectiveness ratio of US$93 663 per quality-adjusted life year relative to the no testing strategy. If the price of genetic testing falls from US$1050 to US$530 (a 50% decrease), it will become cost-effective. CONCLUSION: Our proposed algorithm-driven testing strategy for MODY is not yet cost-effective based on established benchmarks. However, as genetic testing prices continue to fall, this strategy is likely to become cost-effective in the near future.

Olry de Labry Lima, A., et al. (2008). "[An economic assessment of genetic testing for familial adenomatous polyposis]." Rev Esp Enferm Dig **100**(8): 470-475.

OBJECTIVE: To analyze the cost-effectiveness of genetic testing for first-degree relatives of patients with colon cancer to identify mutations in the APC gene (Adenomatous Polyposis Coli). METHODOLOGY: Analyses were performed from the perspective of the health system. We used a Markov model. We compared genetic testing for the APC gene, the cause of familial adenomatous polyposis (FAP), which results in colon cancer, versus no genetic testing for said gene. The effectiveness measure used was quality-adjusted life-years (QALYs), and costs were measured in euros for 2005. The costs of interventions were extracted from the costs of health services provided by centers under the Andalusian Public Health System, and other parameters were obtained from the literature. RESULTS: The performance of genetic testing is the dominant strategy when compared to the absence of genetic testing given the latter option has an incremental cost of 7,676.34 euros and is less effective. A sensitivity analysis found that genetic testing remains the dominant strategy for a plausible range of costs of the test itself, and for the probability of developing adenocarcinoma. CONCLUSIONS: Our analysis showed that in this patient group genetic testing to detect APC gene mutations is on average less costly and improves QALYs versus no testing.

Penchaszadeh, V. B. (1993). "Reproductive health and genetic testing in the Third World." Clin Obstet Gynecol **36**(3): 485-495.

New reproductive genetics means recently developed techniques to prevent the birth of children with specific defects or genetic diseases by testing individuals for sickle cell anemia, the thalassemias, Tay-Sachs disease, cystic fibrosis, or Down syndrome. Third World health services have many deficiencies with high maternal mortality rates (30-40 fold higher than in developed countries), the low percentage of births delivered by health personnel, the high rates of low birth weight babies, and high child malnutrition and infant mortality rates. The main issues in women's reproductive health are fertility regulation, abortion, maternal mortality, sexually transmitted diseases, and infertility. As a result of expansion in contraceptive use worldwide, the total fertility rate in developing countries has declined from 6.1 in 1965 to 3.9 in 1990. It is estimated that, worldwide, 36-53 million induced abortions are performed each year, most of them in developing nations. WHO estimates that more than 500,000 women die each year because of complications of pregnancy, most in developing countries. More than 95% of the 13 million estimated deaths of children under 5 years of age have occurred in these countries. Approximately 200 million people carry a potentially pathologic hemoglobinopathy gene, and about 250,000 children are born every year with hemoglobinopathy, most of them in the developing world. Reproductive genetic testing in big cities and in private for-profit ventures cater to the socioeconomic elite. Amniocentesis is often misused for fetal sex determination to abort female fetuses in India. Currently, in Cuba virtually every pregnant woman is tested for sickle cell trait and maternal serum alpha-

fetoprotein levels between 15 and 20 weeks of gestation. It is predicted that the judicious use of reproductive genetic testing will be possible when health and quality of life issues are addressed properly.

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Peterson, S. K., et al. (2008). "Psychological functioning in persons considering genetic counseling and testing for Li-Fraumeni syndrome." Psychooncology **17**(8): 783-789.

OBJECTIVE: Li-Fraumeni syndrome (LFS) confers an increased risk of multiple types of cancer in both children and adults. Clinical genetic testing for deleterious germline p53 gene mutations can identify most LFS-affected families. We evaluated factors associated with cancer-specific distress and perceived self-efficacy in coping with a positive genetic test result among persons at risk of having deleterious p53 mutations. METHODS: One hundred thirty-five persons from 15 LFS-affected families were invited to take part in a study that offered p53 genetic counseling and testing and to complete psychosocial measures. RESULTS: Participants (n=92) were more likely to be younger and female than nonparticipants (n=43). In multivariate analyses, greater cancer-specific distress was associated with having a lower quality of life, a higher perceived risk of having a p53 mutation, no personal history of cancer and a greater number of first degree relatives (FDRs) affected with cancer. Lower perceived self-efficacy in coping with a positive test result was associated with greater cancer worry, higher decisional conflict about p53 testing and having no personal history of cancer. CONCLUSIONS: Individual perceptions about cancer risk and p53 genetic testing, as well as personal experience with FDRs' cancer diagnoses and deaths, should be addressed during the counseling and testing process for LFS-affected families.

Powell, T. M. (1998). "Genetic testing: can it predict the lived experience of individuals and families? A personal testimony." Community Genet **1**(3): 180-182.

An individual's and family's experience with a genetic disease is too complex and diverse to be totally predicted using genetic testing. Stigmatization and discrimination of gene carriers can occur if society chooses to utilize genetic technology to eliminate 'disease and disability' without accepting human variation and devoting any possible efforts for ameliorating the life of individuals faced with disabilities. In this paper I use Friedreich's ataxia (FA) to illustrate some ways in which a disease experience can differ from what is expected from textbook descriptions of a given condition. I describe the expected medical characteristics with FA and some of my own personal experience with the disease as well as that of my family.

Prince, A. E., et al. (2017). "Is there evidence that we should screen the general population for Lynch syndrome with genetic testing? A systematic review." Pharmgenomics Pers Med **10**: 49-60.

BACKGROUND: The emerging dual imperatives of personalized medicine and technologic advances make population screening for preventable conditions resulting from genetic alterations a realistic possibility. Lynch syndrome is a potential screening target due to its prevalence, penetrance, and the availability of well-established, preventive interventions. However, while population screening may lower incidence of preventable conditions, implementation without evidence may lead to unintentional harms. We examined the literature to determine whether evidence exists that screening for Lynch-associated mismatch repair (MMR) gene mutations leads to improved overall survival, cancer-specific survival, or quality of life. Documenting evidence and gaps is critical to implementing genomic approaches in public health and guiding future research. MATERIALS AND METHODS: Our 2014-2015 systematic review identified studies comparing screening with no screening in the general population, and controlled studies assessing analytic validity of targeted next-generation sequencing, and benefits or harms of interventions or screening. We conducted meta-analyses for the association between early or more frequent colonoscopies and health outcomes. RESULTS: Twelve studies met our eligibility criteria. No adequate evidence directly addressed the main question or the harms of screening in the general population. Meta-analyses found relative reductions of 68% for colorectal cancer incidence (relative risk: 0.32, 95% confidence interval: 0.23-0.43, three cohort studies, 590 participants) and 78% for all-cause mortality (relative risk: 0.22, 95% confidence interval: 0.09-0.56, three cohort studies, 590 participants) for early or more frequent colonoscopies among family members of people with cancer who also had an associated MMR gene mutation. CONCLUSION: Inadequate evidence exists examining harms and benefits of population-based screening for Lynch syndrome. Lack of evidence highlights the need for data that directly compare benefits and harms.

Qiu, J., et al. (2016). "Quality of Life and Psychological State in Chinese Breast Cancer Patients Who Received BRCA1/2 Genetic Testing." PLoS One **11**(7): e0158531.

BACKGROUND: This study aims to understand the quality of life (QOL) and psychological state (PS) of Chinese breast cancer patients who received

BRCA1/2 genetic testing; to examine the psychological changes between BRCA1/2 mutation carriers and non-carriers; and to further explore the psychological experience of BRCA1/2 mutation carriers. METHODS: This study was combined with quantitative and qualitative designs. First, we performed a quantitative investigation using FACT-B (Chinese version) and Irritability, Depression and Anxiety scale (IDA) to assess the QOL and PS in breast cancer patients who received BRCA1/2 genetic testing. Then semi-structured in-depth qualitative interviews among 13 mutation carriers were conducted in hospital. RESULTS: Results from the quantitative study showed QOL scores were relatively high and the IDA scores were relatively low among the patients, and there was no significant difference in the QOL or IDA scores between non-carriers and carriers. Based on the qualitative analysis, four main themes emerged: (1) Finding the reason for having breast cancer; (2) Negative emotions; (3) Behavioral changes; (4) Lack of information. CONCLUSIONS: The present study showed that QOL and PS are good among the breast cancer patients who received genetic testing. Genetic testing itself does not cause long psychosocial effects. BRCA1/2 mutation carriers may have certain negative emotions at the first stage they knew the testing results and may initiate behavioral and lifestyle changes. The patients with a BRCA1/2 mutation desire knowledge with regard to genetic aspects in mainland China. Professional information and advice can be provided to relieve the patients' negative emotions when they were informed of gene defect.

Rasmussen, A., et al. (2010). "Uptake of genetic testing and long-term tumor surveillance in von Hippel-Lindau disease." BMC Med Genet **11**: 4.

BACKGROUND: von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome caused by germline mutations in the VHL gene. Patients have significant morbidity and mortality secondary to vascular tumors. Disease management is centered on tumor surveillance that allows early detection and treatment. Presymptomatic genetic testing is therefore recommended, including in at-risk children. METHODS: We tested 17 families (n = 109 individuals) for VHL mutations including 43 children under the age of 18. Personalized genetic counseling was provided pre and post-test and the individuals undergoing presymptomatic testing filled out questionnaires gathering socio-demographic, psychological and psychiatric data. Mutation analysis was performed by direct sequencing of the VHL gene. Mutation-carriers were screened for VHL disease-related tumors and were offered follow-up annual examinations. RESULTS: Mutations were identified in 36 patients, 17 of whom were asymptomatic. In the initial screening, we identified at least one tumor in five of 17 previously asymptomatic individuals. At the end of five years, only 38.9% of the mutation-carriers continued participating in our tumor surveillance program. During this time, 14 mutation carriers developed a total of 32 new tumors, three of whom died of complications. Gender, education, income, marital status and religiosity were not found to be associated with adherence to the surveillance protocol. Follow-up adherence was also independent of pre-test depression, severity of disease, or number of affected family members. The only statistically significant predictor of adherence was being symptomatic at the time of testing (OR = 5; 95% CI 1.2 - 20.3; p = 0.02). Pre-test anxiety was more commonly observed in patients that discontinued follow-up (64.7% vs. 35.3%; p = 0.01). CONCLUSIONS: The high initial uptake rate of genetic testing for VHL disease, including in minors, allowed the discontinuation of unnecessary screening procedures in non mutation-carriers. However, mutation-carriers showed poor adherence to long-term tumor surveillance. Therefore, many of them did not obtain the full benefit of early detection and treatment, which is central to the reduction of morbidity and mortality in VHL disease. Studies designed to improve adherence to vigilance protocols will be necessary to improve treatment and quality of life in patients with hereditary cancer syndromes.

Rauscher, E. A. and M. Dean (2017). ""Take your time, then follow your heart:" Previvors' advice for communicating about family planning after testing positive for a BRCA genetic variant." Fam Syst Health **35**(4): 486-497.

INTRODUCTION: The purpose of this study was to identify previvors' strategies for communicating about family planning after testing positive for a variant of the "breast cancer gene" (BRCA). METHOD: Semistructured interviews were conducted with 20 women currently in committed romantic relationships, but who had not yet completed family planning upon finding out about their BRCA mutation status. RESULTS: Data analysis produced three categories of participant advice given to newly diagnosed previvors. Participants advised the following: (a) the importance of engaging in two-way dialogue with their partners/spouses across the life span of the partnership, (b) seeking information on new technologies and information regarding family-planning and genetic-cancer-prevention decision-making, as well as recognizing where to go for different support needs, and (c) managing and acknowledging emotions surrounding their BRCA-related health decisions. DISCUSSION: Previvors who have already had family-planning and genetic-cancer-risk conversations had important advice for

newly diagnosed previvors. Practical advice for starting and managing conversations with partners/spouses, family members, and friends are discussed. (PsycINFO Database Record).

Ream, M. A. and M. A. Mikati (2014). "Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study." Epilepsy Behav **37**: 241-248.

RATIONALE: The utility of genetic testing in pediatric drug-resistant epilepsy (PDRE), its yield in "real life" clinical practice, and the practical implications of such testing are yet to be determined. GOAL: To start to address the above gaps in our knowledge as they apply to a patient population seen in a tertiary care center. METHODS: We retrospectively reviewed our experience with the use of clinically available genetic tests in the diagnosis and management of PDRE in one clinic over one year. Genetic testing included, depending on clinical judgment, one or more of the following: karyotype, chromosomal microarray, single gene sequencing, gene sequencing panels, and/or whole exome sequencing (WES). RESULTS: We were more likely to perform genetic testing in patients with developmental delay, epileptic encephalopathy, and generalized epilepsy. In our unique population, the yield of specific genetic diagnosis was relatively high: karyotype 14.3%, microarray 16.7%, targeted single gene sequencing 15.4%, gene panels 46.2%, and WES 16.7%. Overall yield of diagnosis from at least one of the above tests was 34.5%. Disease-causing mutations that were not clinically suspected based on the patients' phenotypes and representing novel phenotypes were found in 6.9% (2/29), with an additional 17.2% (5/29) demonstrating pharmacologic variants. Three patients were incidentally found to be carriers of recessive neurologic diseases (10.3%). Variants of unknown significance (VUSs) were identified in 34.5% (10/29). CONCLUSIONS: We conclude that genetic testing had at least some utility in our patient population of PDRE, that future similar larger studies in various populations are warranted, and that clinics offering such tests must be prepared to address the complicated questions raised by the results of such testing.

Reyes, S., et al. (2012). "Presymptomatic genetic testing in CADASIL." J Neurol **259**(10): 2131-2136.

Genetic counselling has been poorly investigated in cerebrovascular diseases. Characteristics, motivations and long-term outcome of presymptomatic tests (PT) in subjects at risk of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) were investigated at the National Centre for Rare Vascular Diseases of the Brain and/or Retina (CERVCO). Sociodemographic, motivational and psychological variables were collected between 2003 and 2010 for PT applicants. Multidisciplinary consultations (with a geneticist, neurologist and psychologist) were proposed over a 6 month period. When PT showed a deleterious mutation of the NOTCH3 gene, cognitive performances, mood, autonomy and quality of life were also assessed. Over 7 years, only 33 subjects asked for a PT of CADASIL. They were predominantly women, lived as a couple, had children and were of high sociocultural level. The dropout rate after the first step of the procedure was 63%. The characteristics of the 11 subjects who reached the end of the procedure did not differ from the 22 who dropped out. Six were carriers of the deleterious mutation and were still asymptomatic after a mean follow-up of 19 months. They did not experience any particular negative event and all of them indicated a high score of overall quality of life. Indeed, two carriers gave birth to their first child. These initial data in CADASIL show that PT is rarely requested and that there is a high dropout rate. Our study also highlights that a multidisciplinary and multistep procedure in genetic counselling testing appears useful to obtain minimal harmful consequences of genetic testing.

Romanowicz, M., et al. (2012). "Testing a diathesis-stress model: potential genetic risk factors for development of distress in context of acute leukemia diagnosis and transplant." Psychosomatics **53**(5): 456-462.

OBJECTIVE: Brain-derived neurotrophic factor (BDNF) is a nerve growth factor that has antidepressant-like effects in animals and may be implicated in the etiology of mood-related phenotypes, specifically in the context of stressful life events. We hypothesized that this single-nucleotide polymorphism will predict the development of psychological distress among patients diagnosed with acute leukemia and preparing for hematopoietic stem cell transplant (HSCT). We also explored the relationship of other genetic factors to psychological distress, including 5HTTLPR and STin2, FKBP5, and the CRHR1 TAT haplotype. METHOD: In a retrospective cohort design, 107 adult acute leukemia survivors preparing for HSCT at a major medical center completed a pre-HSCT psychological evaluation and volunteered to donate blood to the HSCT Cell and Serum Research Repository for future research studies. RESULTS: There was evidence of a potential association between BDNF (Val66Met) and psychological distress. More specifically, rs6265 was related to both personal mental health history (P = 0.09, 0.06 adjusted) and diagnosis of depression/adjustment disorder at time of pre-transplant evaluation (P = 0.11, 0.09 adjusted). Other genetic factors were unrelated to distress.

CONCLUSION: The BDNF Val66Met polymorphism may contribute to development of depressive symptomatology in patients undergoing stressful life events, such as diagnosis of acute leukemia and preparation for HSCT. The SNPs in BDNF might be applicable in identifying patients at risk for developing psychological distress and depression in the context of coping with stressful medical conditions. Polymorphism in other genes (FKBP5, CRHR1, and 5HTT) did not show any significant relationships. Replication studies are needed with larger samples of people undergoing similar significant life stressors.

Rudd, A., et al. (2013). "Co-existence of hereditary coproporphyria and porphyria cutanea tarda: The importance of genetic testing." Australas J Dermatol **54**(2): e50-52.

The porphyrias are a group of inherited disorders that result in defects in the enzymes of the haem biosynthetic pathway, causing photosensitive bullous skin eruptions or abdominal and neurological attacks. Enzymatic defects result in specific porphyrin excretory patterns that are diagnosed biochemically and can be confirmed by genetic testing. Defects in the coproporphyrinogen oxidase (CPOX) enzyme result in the autosomal dominant hereditary coproporphyria. Multiple mutations have been identified in the CPOX gene and incomplete penetrance is noted. Latent carriers without clinical evidence of disease are at risk of life-threatening attacks. Porphyria cutanea tarda may be inherited, but is more commonly acquired. Occasionally two forms of porphyria may co-exist. The importance of genetic testing is discussed.

Saffroy, R., et al. (2017). "Impact of country of birth on genetic testing of metastatic lung adenocarcinomas in France: African women exhibit a mutational spectrum more similar to Asians than to Caucasians." Oncotarget **8**(31): 50792-50803.

BACKGROUND: Limited data are available on the prevalence of oncogenic driver mutations in Caucasian populations, and especially in Europeans. AIM: To evaluate the targetable mutational spectra in unselected patients with lung adenocarcinoma in routine clinical practice from several French hospitals, using the same molecular platform. PATIENTS AND METHODS: Samples from 2,219 consecutive patients with histologically-proven advanced lung adenocarcinoma were centrally analysed at a referenced and certified diagnostic platform in order to test for activating and resistance mutations in EGFR, KRAS, BRAF, ERBB2 and PI3KCA. Demographic and clinical features were retrieved from the medical charts. Multivariate binary logistic regression was used to determine the independent predictive factors for the occurrence of specific mutations, in the whole study population or in selected subgroups. FINDINGS: The overall respective incidence of EGFR, KRAS, BRAF, ERBB2 and PI3KCA mutations was 10.5%, 0.9%, 25%, 1.5%, 2.1% and 1.4%, in our study sample including 87.4% white Caucasians, 10.8% Africans and 1.8% Asians; 60.6% men, 30.7% never smoker (median age: 68.3 years). Ethnicity was an independent predictor for EGFR, KRAS and ERBB2 gene abnormalities. In all cases, a significantly higher prevalence of targetable EGFR and ERBB2, and a lower prevalence of resistance KRAS mutations were observed in African women as compared to African men or Caucasians. CONCLUSIONS: In real life conditions of routine genetic testing, we have identified subsets of patients with specific targetable activating somatic mutations according to ethnicity, who could preferentially benefit from anti-EGFR and anti-ERBB2 targeted therapies.

Savulescu, J. (2001). "Why genetic testing for genes for criminality is morally required." Princet J Bioeth **4**: 79-97.

This paper argues for a Principle of Procreative Beneficence, that couples (or single reproducers) should select the child, of the possible children they could have, who is expected to have the best life, or at least as good a life as the others. If there are a number of different variants of a given gene, then we have most reason to select embryos which have those variants which are associated with the best lives, that is, those lives with the highest levels of well-being. It is possible that in the future some genes are identified which make it more likely that a person will engage in criminal behaviour. If that criminal behaviour makes that person's life go worse (as it plausibly would), and if those genes do not have other good effects in terms of promoting well-being, then we have a strong reason to encourage couples to test their embryos with the most favourable genetic profile. This paper was derived from a talk given as a part of the Decamp Seminar Series at the Princeton University Center for Human Values, October 4, 2000.

Scotet, V., et al. (2005). "Impact of HFE genetic testing on clinical presentation of hereditary hemochromatosis: new epidemiological data." BMC Med Genet **6**: 24.

BACKGROUND: Hereditary hemochromatosis (HH) is a common inherited disorder of iron metabolism in Northern European populations. The discovery of a candidate gene in 1996 (HFE), and of its main mutation (C282Y), has radically altered the way to diagnose this disease. The aim of this study was to assess the impact of the HFE gene discovery on the clinical presentation and epidemiology of HH. METHODS: We studied our cohort of 415 patients

homozygous for the C282Y allele and included in a phlebotomy program in a blood centre in western Brittany, France. RESULTS: In this cohort, 56.9% of the patients were male and 21.9% began their phlebotomy program before the implementation of the genetic test. A significant decrease in the sex ratio was noticed following implementation of this DNA test, from 3.79 to 1.03 ($p < 10(-5)$), meaning that the proportion of diagnosed females relatives to males greatly increased. The profile of HH patients at diagnosis changed after the DNA test became available. Serum ferritin and iron values were lower and there was a reduced frequency of clinical signs displayed at diagnosis, particularly skin pigmentation (20.1 vs. 40.4%, OR = 0.37, $p < 0.001$) and hepatomegaly (11.0 vs. 22.7%, OR = 0.42, $p = 0.006$). In contrast, fatigue became a more common symptom at diagnosis (68.0 vs. 51.2%, OR = 2.03, $p = 0.004$). CONCLUSION: This study highlights the importance of the HFE gene discovery, which has simplified the diagnosis of HH and modified its clinical presentation and epidemiology. This study precisely measures these changes. Enhanced diagnosis of HFE-related HH at an early stage and implementation of phlebotomy treatment are anticipated to maintain normal life expectancy for these patients.

Serretti, A., et al. (2011). "A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders." World J Biol Psychiatry **12**(7): 501-515.

OBJECTIVE: To evaluate the benefit of pharmacogenetics in antidepressant treatment. METHODS: In a simulated trial 100,000 subjects in a current episode of major depressive disorder (MDD) received citalopram or bupropion based on the clinician's decision (algorithm A) or following indications from 5-HTTLPR genetic testing (algorithm B), which effect size of was estimated from a meta-analysis of pharmacogenetic trials. A and B were compared in a cost-utility analysis (12 weeks). Costs (international $, 2010) were drawn from official sources. Treatment effects were expressed as quality-adjusted life weeks (QALWs). Outcome was incremental cost-effectiveness ratio (ICER). RESULTS: Under base-case conditions, genetic test use was associated with increases in antidepressant response (0.062 QALWs) and tolerability (0.016 QALWs) but cost benefit was not acceptable (ICER = $2,890; $1,800-$4,091). However, when the joint effect on antidepressant response and tolerability was analyzed in two recurrent episodes, ICER dropped to $1,392 ($837-$1,982). Cost-effectiveness acceptability curve (CEAC) showed a >80% probability that ICER value fell below the commonly accepted 3 times Gross Domestic Product (GDP) threshold (World Health Organization) and therefore suggesting cost-effectiveness. CONCLUSION: Notwithstanding some caveats (exclusion of gene-gene and gene-environment interactions; simple 5-HTTLPR architecture), this simulation is favourable to incorporate pharmacogenetic test in antidepressant treatment.

Shiffman, D., et al. (2012). "Cost-effectiveness model of use of genetic testing as an aid in assessing the likely benefit of aspirin therapy for primary prevention of cardiovascular disease." Clin Ther **34**(6): 1387-1394.

BACKGROUND: Aspirin use for the primary prevention of cardiovascular disease (CVD) is controversial because of the need to balance the risk of major bleeding events caused by aspirin with the benefit of CVD events prevented by aspirin. The United States Preventive Services Task Force (USPSTF) proposed guidelines that use CVD risk thresholds, based on the Framingham Risk Score, to identify patients likely to benefit from aspirin use. Genetic information could be used to modify this CVD risk assessment; for example, 2 variants of the LPA gene, which encodes apolipoprotein (a), are associated with increased risk of CVD. OBJECTIVES: To estimate the incremental cost-effectiveness of using genetic test results for 2 LPA variants to derive modified Framingham Risk Score estimates and to use these estimates to identify patients likely to benefit from aspirin use according to USPSTF guidelines for aspirin use in the primary prevention of CVD. METHODS: A cost-effectiveness model of 1 million patients representative of the US population was developed based on the association of 2 LPA variants (rs3798220 and rs10455872) with CVD. The cost of testing was estimated for patients whose 10-year CVD risk would exceed the USPSTF treatment threshold if they were to test positive for the LPA variants. Patient utility estimates for myocardial infarction and stroke, and cost estimates (using a 3.5% annual discount rate) for myocardial infarction, stroke, and gastrointestinal bleeding events were based on published estimates. RESULTS: Recommending aspirin to patients whose CVD risk surpassed the risk threshold when LPA information was included in their risk assessment would prevent an estimated 65 CVD events over 10 years. At a genetic test cost of $150, the incremental cost-utility of testing for LPA variants is estimated at $24,942 per quality-adjusted life-year. CONCLUSIONS: LPA genotyping in the context of the aspirin use guidelines for primary prevention of CVD could be cost-effective.

Spencer, C. C., et al. (2003). "Testing an 'aging gene' in long-lived drosophila strains: increased

longevity depends on sex and genetic background." Aging Cell **2**(2): 123-130.

Molecular advances of the past decade have led to the discovery of a myriad of 'aging genes' (methuselah, Indy, InR, Chico, superoxide dismutase) that extend Drosophila lifespan by up to 85%. Despite this life extension, these mutants are no longer lived than at least some recently wild-caught strains. Typically, long-lived mutants are identified in relatively short-lived genetic backgrounds, and their effects are rarely tested in genetic backgrounds other than the one in which they were isolated or derived. However, the mutant's high-longevity phenotype may be dependent on interactions with alleles that are common in short-lived laboratory strains. Here we set out to determine whether one particular mutant could extend lifespan in long-lived genetic backgrounds in the fruit fly, Drosophila melanogaster. We measured longevity and resistance to thermal stress in flies that were transgenically altered to overexpress human superoxide dismutase (SOD) in the motorneurones in each of 10 genotypes. Each genotype carried the genetic background from a different naturally long-lived wild-caught Drosophila strain. While SOD increased lifespan on average, the effect was genotype- and sex-specific. Our results indicate that naturally segregating genes interact epistatically with the aging gene superoxide dismutase to modify its ability to extend longevity. This study points to the need to identify mutants that increase longevity not only in the lab strain of origin but also in naturally long-lived genetic backgrounds.

Surbone, A. (2001). "Ethical implications of genetic testing for breast cancer susceptibility." Crit Rev Oncol Hematol **40**(2): 149-157.

The identification of gene mutations involved in hereditary breast cancer is a major recent scientific discovery, enabling us to identify women at very high risk, and also providing the means to understand the biology of breast cancer and to explore novel preventive strategies. Yet, it carries medical, psychological, ethical and social implications. This paper is a review of all the ethical implications of genetic testing for breast cancer predisposition, as well as an attempt to discuss the more philosophical questions of women facing BRCA testing. To what extent does the individual benefit from genetic knowledge? Some women look with trepidation upon the potential of planning their life in view of a risk, while others believe that only through knowledge and awareness we can improve control of our life. The risk of breast cancer may be qualitatively so important to justify all the potential risks of finding out about it.

Sureka, A. (2000). "Improved genetic testing: a new impetus toward universal coverage." Princet J Bioeth **3**(1): 20-34.

As the Human Genome Project increases the predictive power of human genetics, emerging gene chip technology and other advances of genetic testing will give more information to people about their genetic predilections. If insurance companies were allowed to use this information, they would set premiums such that many who need life-saving medical treatment would have no access to it. Americans would not accept this disparity; instead, genetic information will likely remain private, making the modern health insurance system unprofitable for companies and thus pushing the United States towards a universal health care system in the near future.

Uhrova, T., et al. (2013). "Importance of psychiatric examination in predictive genetic testing for Huntington disease." Neurol Neurochir Pol **47**(6): 534-541.

BACKGROUND AND PURPOSE: Huntington disease (HD) is an au-tosomal dominant hereditary neurodegenerative disease with multiplication of CAG triplet in the short arm of chromoso-me 4, manifested by motor symptoms, cognitive dysfunction progressing to dementia, and various types of neuropsychiat-ric disorders. The diagnosis of HD is confirmed by a gene-tic test, which may also be carried out presymptomatically. MATERIAL AND METHODS: We studied differences in psychiatric examination and psychometric measures among the 52 people at risk of HD, who were recommended to postpone or to continue in the predictive protocol. In addition to the psychiatric examination, we administered the Eysenck Personality Questionnaire (EPQ-A), the Symptom Checklist 90 (SCL-90), and quality of life questionnaire (MANSA). RESULTS: People at risk of HD with the recommended test postponement showed lower rate of neuroticism and EPQ-A lie score, higher values on the phobia and the so-called 'positive symptom distress index' in SCL-90 and lower quality of life than people at risk of HD with the recommendation to continue. CONCLUSIONS: Our results indicate that the formalized testing does not bring significant information whereas the clinical psychiatric examination remains the main decisive factor in the recommendation to perform a predictive genetic test. The motivation of applicants is considered as the most important factor in the decision-making process.

Vernon, S. W., et al. (1999). "Intention to learn results of genetic testing for hereditary colon cancer." Cancer Epidemiol Biomarkers Prev **8**(4 Pt 2): 353-360.

INTRODUCTION: This report investigates the correlates of intention to find out genetic test results in colorectal cancer patients undergoing genetic counseling and testing for hereditary nonpolyposis colon cancer. Specifically, we investigated whether intention to learn genetic test results was associated with sociodemographic factors, medical history, psychosocial factors, attitudes, beliefs, and decisional considerations related to genetic testing. MATERIALS AND METHODS: Among 342 colorectal cancer patients who went through an informed consent process and gave blood for genetic testing and who were eligible for a psychosocial questionnaire study, 269 cases completed a baseline interview. Patients were contacted in person during a routine clinic visit or by letter and follow-up telephone call and were interviewed either in person or by telephone. RESULTS: In univariate analysis, intention to learn test results was positively associated with income, quality of life, a belief that being tested will help family members prevent cancer, being worried about carrying an altered gene, and a belief that one has the ability to cope with test results. It was negatively associated with a belief that genetic counseling is too much trouble relative to the benefits. Intention also was positively associated with scales measuring the pros of learning test results and the pros of informing relatives about test results; it was negatively associated with the cons of learning test results. In multivariable analysis, the belief that testing would help family members prevent cancer, being worried about carrying an altered gene, and the pros of learning test results remained statistically associated with intention when other variables were included in the model. CONCLUSIONS: Our findings showed that the positive aspects of genetic testing were more strongly associated with intention than were the negative aspects. They also showed that persons who stated an intention to learn their genetic test results were more likely than persons who did not to affirm both the benefits and the importance of such testing. These results are consistent with the literature on psychosocial aspects of genetic testing for breast cancer.

Wahlin, T. B., et al. (1997). "Reactions to predictive testing in Huntington disease: case reports of coping with a new genetic status." Am J Med Genet **73**(3): 356-365.

A predictive testing program for Huntington disease has been available in Stockholm, Sweden since October 1990. Psychosocial assessments were performed throughout the testing program to evaluate the impact of the risk situation itself and the effect of predictive testing, and to identify those individuals who were most vulnerable to severe stress and anxiety reactions. All subjects underwent neurological, neuropsychological, and psychiatric examinations. Individuals undergoing predictive testing were assessed twice by a genetic counsellor before receiving their results, and at 10 days (gene carriers only) and then 2, 6, 12, and 24 months after receiving the results. The process of coping with the test results and the psychological adjustment to knowledge about new genetic status have been shown to vary considerably. In this report, we describe the results obtained from two gene carriers and two noncarriers. The four persons chosen represent different ways of coping with the outcome of the test and of integrating knowledge about their genetic status into everyday life. These cases illustrate common themes and recurrent problems often surfacing during the counselling and testing process. The longitudinal evaluations provide information about the impact, adaptation, and long-term effects of living with a new genetic status.

Wevers, M. R., et al. (2011). "Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial." BMC Cancer **11**: 6.

BACKGROUND: It has been estimated that between 5% and 10% of women diagnosed with breast cancer have a hereditary form of the disease, primarily caused by a BRCA1 or BRCA2 gene mutation. Such women have an increased risk of developing a new primary breast and/or ovarian tumor, and may therefore opt for preventive surgery (e.g., bilateral mastectomy, oophorectomy). It is common practice to offer high-risk patients genetic counseling and DNA testing after their primary treatment, with genetic test results being available within 4-6 months. However, some non-commercial laboratories can currently generate test results within 3 to 6 weeks, and thus make it possible to provide rapid genetic counseling and testing (RGCT) prior to primary treatment. The aim of this study is to determine the effect of RGCT on treatment decisions and on psychosocial health. METHODS/DESIGN: In this randomized controlled trial, 255 newly diagnosed breast cancer patients with at least a 10% risk of carrying a BRCA gene mutation are being recruited from 12 hospitals in the Netherlands. Participants are randomized in a 2:1 ratio to either a RGCT intervention group (the offer of RGCT directly following diagnosis with tests results available before surgical treatment) or to a usual care control group. The primary behavioral outcome is the uptake of direct bilateral mastectomy or delayed prophylactic contralateral mastectomy. Psychosocial outcomes include cancer risk perception, cancer-related worry and distress, health-related quality of life, decisional satisfaction and the perceived need for

and use of additional decisional counseling and psychosocial support. Data are collected via medical chart audits and self-report questionnaires administered prior to randomization, and at 6 month and at 12 month follow-up. DISCUSSION: This trial will provide essential information on the impact of RGCT on the choice of primary surgical treatment among women with breast cancer with an increased risk of hereditary cancer. This study will also provide data on the psychosocial consequences of RGCT and of risk-reducing behavior. TRIAL REGISTRATION: The study is registered at the Netherlands Trial Register (NTR1493) and ClinicalTrials.gov (NCT00783822).

Wilhelm, K., et al. (2009). "Issues concerning feedback about genetic testing and risk of depression." Br J Psychiatry **194**(5): 404-410.

BACKGROUND: Recent studies show that adverse life events have a significantly greater impact on depression onset for those with the s/s allele of the genotype for the 5-HT gene-linked promoter region. Research in genes related to risk of depression leads to the question of how this information is received by individuals. AIMS: To investigate factors related to the response to receiving one's own serotonin transporter genotype results. METHOD: Predictors of the impact of receiving individual genotype data were assessed in 128 participants in a study of gene-environment interaction in depression onset. RESULTS: Two-thirds decided to learn their individual genotype results (receivers) and prior to disclosure this decision was associated with a perception of greater benefit from receipt of the information (P=0.001). Receivers completing the 2-week (n=76) and 3-month follow-up (n=78) generally reported feeling pleased with the information and having had a more positive experience than distress. However, distress was related to genotype, with those with the s/s allele being most affected. CONCLUSIONS: There was high interest in, and satisfaction with, learning about one's serotonin transporter genotype. Participants appeared to understand that the gene conferred susceptibility to depression rather than a direct causal effect.

Yoshida, K., et al. (2002). "[Analysis of 14 individuals who requested predictive genetic testing for hereditary neuromuscular diseases]." Rinsho Shinkeigaku **42**(2): 113-117.

Predictive genetic testing for hereditary neuromuscular diseases is a delicate issue for individuals at risk and their families, as well as for medical staff because these diseases are often late-onset and intractable. Therefore careful pre- and post-test genetic counseling and psychosocial support should be provided along with such genetic testing. The Division of Clinical and Molecular Genetics was established at our hospital in May 1996 to provide skilled professional genetic counseling. Since its establishment, 14 individuals have visited our clinic to request predictive genetic testing for hereditary neuromuscular diseases (4 for myotonic dystrophy, 6 for spinocerebellar ataxia, 3 for Huntington's disease, and 1 for Alzheimer's disease). The main reasons for considering testing were to remove uncertainty about the genetic status and to plan for the future. Nine of 14 individuals requested testing for making decisions about a forthcoming marriage or pregnancy (family planning). Other reasons raised by the individuals included career or financial planning, planning for their own health care, and knowing the risk for their children. At the first genetic counseling session, all of the individuals expressed hopes of not being a gene carrier and of escaping from fear of disease, and seemed not to be mentally well prepared for an increased-risk result. To date, 7 of the 14 individuals have received genetic testing and only one, who underwent predictive genetic testing for spinocerebellar ataxia, was given an increased-risk result. The seven individuals including the one with an increased-risk result, have coped well with their new knowledge about their genetic status after the testing results were disclosed. None of them has expressed regret. In pre-test genetic counseling sessions, we consider it quite important not only to determine the psychological status of the individual, but also to make the individual try to anticipate the changes in his/her life upon receiving an increased-risk or a decreased-risk result. Sufficient time should be taken to build a good relationship between the individual and his/her family and the medical staff during pre-test counseling sessions. This will help the individuals feel satisfied with their own decisions for the future, whether they receive genetic testing or not.

Zara, F., et al. (2013). "Genetic testing in benign familial epilepsies of the first year of life: clinical and diagnostic significance." Epilepsia **54**(3): 425-436.

PURPOSE: To dissect the genetics of benign familial epilepsies of the first year of life and to assess the extent of the genetic overlap between benign familial neonatal seizures (BFNS), benign familial neonatal-infantile seizures (BFNIS), and benign familial infantile seizures (BFIS). METHODS: Families with at least two first-degree relatives affected by focal seizures starting within the first year of life and normal development before seizure onset were included. Families were classified as BFNS when all family members experienced neonatal seizures, BFNIS when the onset of seizures in family members was between 1 and 4 months of age or showed both

neonatal and infantile seizures, and BFIS when the onset of seizures was after 4 months of age in all family members. SCN2A, KCNQ2, KCNQ3, PPRT2 point mutations were analyzed by direct sequencing of amplified genomic DNA. Genomic deletions involving KCNQ2 and KCNQ3 were analyzed by multiple-dependent probe amplification method. KEY FINDINGS: A total of 46 families including 165 affected members were collected. Eight families were classified as BFNS, 9 as BFNIS, and 29 as BFIS. Genetic analysis led to the identification of 41 mutations, 14 affecting KCNQ2, 1 affecting KCNQ3, 5 affecting SCN2A, and 21 affecting PRRT2. The detection rate of mutations in the entire cohort was 89%. In BFNS, mutations specifically involve KCNQ2. In BFNIS two genes are involved (KCNQ2, six families; SCN2A, two families). BFIS families are the most genetically heterogeneous, with all four genes involved, although about 70% of them carry a PRRT2 mutation. SIGNIFICANCE: Our data highlight the important role of KCNQ2 in the entire spectrum of disorders, although progressively decreasing as the age of onset advances. The occurrence of afebrile seizures during follow-up is associated with KCNQ2 mutations and may represent a predictive factor. In addition, we showed that KCNQ3 mutations might be also involved in families with infantile seizures. Taken together our data indicate an important role of K-channel genes beyond the typical neonatal epilepsies. The identification of a novel SCN2A mutation in a family with infantile seizures with onset between 6 and 8 months provides further confirmation that this gene is not specifically associated with BFNIS and is also involved in families with a delayed age of onset. Our data indicate that PRRT2 mutations are clustered in families with BFIS. Paroxysmal kinesigenic dyskinesia emerges as a distinctive feature of PRRT2 families, although uncommon in our series. We showed that the age of onset of seizures is significantly correlated with underlying genetics, as about 90% of the typical BFNS families are linked to KCNQ2 compared to only 3% of the BFIS families, for which PRRT2 represents the major gene.

Zick, C. D., et al. (2000). "Genetic testing, adverse selection, and the demand for life insurance." Am J Med Genet **93**(1): 29-39.

The dramatic increase in genetic testing for adult-onset diseases has created a debate regarding whether or not insurance companies should be able to use genetic test results in underwriting. We use data from women who have been tested for the BRCA1 gene mutation along with data from otherwise comparable untested women to assess the potential for adverse selection in the life insurance market when tested individuals know their genetic test results but insurers do not. Our analyses show that women who test positive for the BRCA1 gene mutation do not capitalize on their informational advantage by purchasing more life insurance than those women who have not undergone genetic testing.

Zoller, H. and T. M. Cox (2005). "Hemochromatosis: genetic testing and clinical practice." Clin Gastroenterol Hepatol **3**(10): 945-958.

The availability of a facile treatment for hemochromatosis renders early diagnosis of iron overload syndromes mandatory, and in many instances genetic testing allows identification of individuals at risk of developing clinical disease before pathologic iron storage occurs. Numerous proteins implicated in iron homeostasis have recently come to light, and defects in the cognate genes are associated with iron storage. Although most adult patients with hereditary iron overload are homozygous for the C282Y mutation of the HFE gene, an increasing number with hereditary iron storage have an HFE genotype not characteristic of the disease. Heterozygosity for mutations in the gene encoding ferroportin 1 (FPN1) is probably the second most common genetic cause of hereditary iron storage in adults; here the primarily affected cell is the macrophage. Rare defects, including mutations in the transferrin receptor 2 (TFR2) gene, have also been identified in pedigrees affected with "non-HFE hemochromatosis." Homozygous mutations in the newly identified genes encoding hemojuvelin (HFE2) and hepcidin (HAMP) cause juvenile hemochromatosis. At the same time, heterozygosity for mutations in these genes can modify the clinical expression of iron storage in patients predisposed to iron storage in adult life. Hemochromatosis might thus be considered as a polygenic disease with strong environmental influences on its clinical expression. As our mechanistic understanding of iron pathophysiology improves, our desire to integrate clinical decision making with the results of laboratory tests and molecular analysis of human genes poses increasing challenges.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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