European Journal of Human Genetics

Eur J Hum Genet 1997;5(suppl 2):25–30

D. Stemerding[a]
L. Koch[b]
P. Bourret[c]

[a] Department of Philosophy of Science and Technology, University of Twente, Enschede, The Netherlands;
[b] Department of Social Medicine, University of Copenhagen, Denmark;
[c] Université de Bourgogne, Département de Sociologie, Dijon, et Unité INSERM 379, Marseille et LEST-CNRS, Aix-en-Provence, France

DNA Diagnosis and the Emergence of Cancer Genetic Services in European Health Care

Introduction

As a result of rapid advances in molecular genetics, diagnostic capabilities in clinical genetics are rapidly increasing. One of the most significant characteristics of the emerging new genetics is the extension of options for predictive gene testing from 'classic', and relatively rare hereditary disorders to common diseases like cancer [1–3]. This development is generally seen as a major challenge to existing health care systems and to the organisation of clinical genetic services in particular [4, 5].

In this chapter we focus on cancer genetics as a field in which the extension of options for predictive genetic testing is already clearly visible and which thus allows us to study the implications of this development at an empirical level. The basis for this chapter is a more extensive study of the introduction of DNA diagnosis in the field of cancer genetics in three European countries – Denmark, France and The Netherlands. In the following we discuss two of the cancer genetic services examined in our study, one relating to familial adenomatous polyposis (FAP), the other to hereditary breast (and/or ovarian) cancer (HB(O)C). FAP is a rare, well-defined hereditary disease predisposing to colorectal cancer. HB(O)C is linked to a more widespread genetic susceptibility to breast and ovarian cancer.

Comparison of these two cases allows us to follow the extension of predictive genetic testing from rare hereditary disorders to more widespread genetic susceptibilities within the field of cancer genetics itself. To understand the implications of this development, our analysis relates the introduction of DNA diagnosis to a context of clinical practices already established in the field. In these practices we find particular configurations of skills, institutional and professional relations, definitions of demand and guidelines, to which the introduction of DNA diagnosis adds new elements. Depending on the situation the introduction of DNA diagnosis will imply a more or less radical reconfiguration and redefinition of the elements constituting current practices in the field [6, 7]. Seen from this perspective, the two cases are clearly different. In comparing them we will see a development from relative simplicity towards greater complexity, and identify a number of technical, organisational, ethical and political issues which deserve special attention in this context.

FAP

FAP is a rare dominantly inherited syndrome leading to colon cancer. Gene carriers have a lifetime risk of nearly 100%. The syndrome is primarily characterised by the appearance of hundreds to thousands of adenomatous polyps in the colon, with a high risk of developing cancer before the age of 45. In several countries, including Denmark and The Netherlands, registries have been created in which data are collected from FAP patients and family members at risk. On the basis of these registries, national screening programmes have been established in these countries [8–10]. First-degree relatives have a 50% chance of developing the disease and are usually screened every 2 years through internal inspection of the rectum. Screening usually starts at the age of 10–12 years and may be continued to the age of 60. When adenomatous polyps develop, the colon is removed in patients in order to minimise the risk of cancer.

KARGER

E-Mail karger@karger.ch
Fax + 41 61 306 12 34

Dr. Stemerding
Department of Philosophy of Science and Technology
University of Twente
PO Box 217
NL–7500 AE Enschede (The Netherlands)

Among medical specialists involved in the diagnosis and treatment of FAP, there is a high level of consensus about diagnostic criteria for FAP and about guidelines for screening individuals at risk and treating patients [11]. Moreover, there is generally accepted evidence showing the effectiveness of screening and prophylactic treatment in terms of lower morbidity and mortality rates [8, 9]. The establishment in several countries of registries to promote screening not only reflects agreement on these matters. It has also created a structure which has reinforced consensus about and commitment to current screening practices.

Introduction of DNA Diagnosis

In 1987, the gene for FAP, the so-called APC gene, was localised, and then identified in 1991. Thus FAP was one of the first hereditary cancers for which presymptomatic DNA diagnosis was introduced [12–17]. In the context of established screening programmes for FAP, the introduction of DNA diagnosis in the early 1990s was generally seen as an opportunity to improve the organisation of screening [10, 18]. It opened the possibility to divide a known population at risk for FAP into a carrier group which could be followed with traditional clinical screening methods, and a non-carrier group which might be excluded from risk. Individuals in the non-carrier group thus could be reassured and relieved from participation in a burdensome and protracted screening programme.

For those found to be carriers, DNA diagnosis may have additional value in decisions about prophylactic interventions, and is available in the form of prenatal diagnosis, an option which, however, seems to be rarely used [18, 19]. In other words, in the case of FAP, established practices of screening have served as a 'niche' in which options for DNA diagnosis were readily accepted as an improved diagnostic tool. Given a well-defined and nearly completely registered risk population, and the availability of a well-organised and effective screening programme, neither the potential demand for DNA tests nor the ethical and social implications of presymptomatic testing were perceived as especially critical issues. The introduction of DNA diagnosis for FAP has not, however, remained completely without debate. One frequently mentioned issue is that, with the advent of DNA diagnosis, members of families at risk for (rare) hereditary tumours are confronted with more complex choices, which implies that in genetic counselling, ethical questions and psychosocial implications deserve particular attention [18, 20]. In this context, it is often emphasised that the introduction of DNA diagnosis requires close co-operation between medical specialists, clinical geneticists and, possibly, patient organisations. Indeed, with DNA diagnosis now being available for most family members at risk for FAP, the question of how to co-operate in offering this service has become a point of concern among medical specialists and clinical geneticists.

Hereditary Breast (and/or Ovarian) Cancer

HB(O)C is a dominantly inherited cancer which, in the early 1990s, began to attract a great deal of attention in the field of cancer genetics. It is primarily characterised by the development of breast cancer in premenopausal women. The lifetime risk for carriers in high-risk families is about 85%. On the basis of clinical examination, it is impossible to distinguish patients with HB(O)C from sporadic cases of breast (or ovarian) cancer. Recognition of HB(O)C depends on the observation of a particular family history of the disease. Although the importance of hereditary factors in the development of breast cancer has been pointed out by geneticists for a long time, this phenomenon has been mostly neglected by the general clinician [21].

The rapidly growing interest in HB(O)C in the early 1990s has largely been the result of activities in the field of DNA analysis. As a result of an intense gene-hunting effort, two breast cancer genes – BRCA 1 and 2 – were identified in the first half of the 1990s, and are thought to account for most cases of HB(O)C [22–26]. Since breast cancer is the most frequent cause of cancer deaths among women, and 5–10% is commonly attributed to inheritance, HB(O)C is considered as one of the most common genetic diseases in the industrialised world [27]. In this context, the isolated breast cancer genes have been welcomed as the first genes for which widespread presymptomatic testing might be appropriate [28].

In other words, in the case of HB(O)C, the introduction of DNA diagnosis has followed a pattern which is different from that seen with FAP. Whereas in countries like Denmark and The Netherlands, the introduction of DNA diagnosis of FAP took place in a situation in which practices of registration and screening had already been established on a national scale, the situation in the field of HB(O)C was rather the reverse. Initiatives to organise and co-ordinate registration and screening of HB(O)C families are being undertaken particularly in response to a growing interest in DNA analysis of HB(O)C. Because of

this different pattern, the implications of the introduction of DNA diagnosis of HB(O)C appear to be far more complex and profound than in the case of FAP.

Questions to Be Resolved

One issue is the technical feasibility and reliability of large-scale testing. The two BRCA genes are very large and complex and a wide array of mutations have been identified. The development of highly sensitive and specific DNA diagnostic tests will thus be difficult and costly [29, 30]. However, it would be a serious mistake to imagine that the only barriers to DNA testing of BRCA mutations are technical ones [31]. As technical problems are being overcome, DNA diagnosis will become more and more a means enabling identification of BRCA mutations in individuals without a striking family history. Thus, the question arises as to who is to be offered a test. Should a test be offered for example to all women (below a certain age or not) with newly diagnosed breast cancer in order to track down relatives who are at risk? A point of serious concern in this context is that hardly any knowledge of the effectiveness of preventive strategies for women at risk is available at the moment [32–34]. Regular screening by mammography and physical examination is one option offered to these women, prophylactic mastectomy is another (but controversial) option. Neither of these options is considered a proven effective strategy. Indeed, although the technical feasibility to perform DNA tests may improve rapidly, options for screening and prevention can be offered only in the hope that, in the long run, these options will prove to be effective. Decision-making about these options is further complicated by the fact that about 15% of all women carrying a mutation may not develop breast cancer and this figure may be higher for those women who prove to be carriers without having a family history of breast cancer. Indeed, the individual risk of carriers, and thus the meaning of a test result, will depend on multiple and complex interactions involving both genes and the environment in a way which is currently largely unknown [35–37].

Strategies of Introduction

Given current estimates of the carrier rate of BRCA mutations, which range from 1:200 to 1:800, it is often expected that screening for BRCA mutations is likely to become the first widespread presymptomatic genetic test that finds its way into general medical practice [38]. Thus the introduction of a presymptomatic DNA test of HB(O)C holds the promise of a radical process of change in which early diagnosis and prevention, based on extensive DNA testing, may become a new standard in health care. However, many observers also agree that the introduction of BRCA testing should proceed with caution [31, 34]. For the time being, that is, tests should be provided only in a research context. At the same time, efforts should be focused on preparing for 'a complex series of challenges' to the health care system [38]. The establishment of multidisciplinary cancer family clinics offering specialist counselling and the establishment of registries of individuals at risk are generally perceived as necessary steps in this direction. Current models of future (cancer) genetic services also emphasise the role of general practitioners in identifying women with a family history of breast cancer and in educating and counselling them about their personal risk factors. General practitioners will act as 'gatekeepers' who may refer women to more specialised (cancer) genetic services on the basis of guidelines that may be used to assess breast cancer risk in relation to family history [34].

Thus, the introduction of DNA diagnosis of HB(O)C is linked to initiatives which will further enhance awareness of familial breast cancer risks and which are likely to generate increasing demand for a DNA diagnostic test. This strategy of introduction is primarily considered as a way to increase women's options and choices, but it has other implications as well. With the introduction of BRCA testing, clinical genetic care is going to expand from a relatively small number of families who have already been identified as being at risk – as in the case of FAP – to large numbers of individuals with no prior knowledge of their risk status. In the first situation, the DNA test is primarily perceived as a means which made it possible to exclude individuals from risk. In the latter situation, the availability of a test implies that more and more individuals will be confronted with the possibility of being at risk. A large-scale introduction of presymptomatic testing of HB(O)C in medical practice thus will not only bring new options and choices for a large group of women, but will also generate anxiety and place women in dilemmas that will be especially difficult to cope with as long as the effectiveness of available options remains to be established. At the same time, as those involved in the introduction of BRCA testing emphasise, a careful approach which involves registration of carriers, retainment of testing in a controlled research setting for as long as possible and long-term follow-up of women making different treatment

choices will create the opportunity to assess in the future the effectiveness of preventive strategies [32].

Conclusion and Discussion

In our account of recent developments in cancer genetics, we have emphasised the different patterns of introduction of DNA diagnosis which emerge from the cases we have studied in this field. Indeed, when comparing the two cases, we see a reversal taking place in the way in which DNA diagnosis has been introduced in clinical practice. In the case of FAP, an infrastructure of registries and screening programmes had been established to advance care of patients and relatives at risk, before the advent of DNA analysis. Within this infrastructure, the introduction of DNA diagnosis was a relatively straightforward development. Both the implications of and the demand for DNA tests could be relatively easily anticipated. What we see here is a process of incremental change taking place without major modifications of the existing infrastructure in which services are provided. In the case of HB(O)C, on the other hand, the advent of DNA analysis has preceded the emergence of a systematic organisation for the care of patients and relatives at risk. As a result, demand for DNA diagnosis of HB(O)C is taking shape in a highly undetermined situation. Implicated in this situation is a more complex and radical process of sociotechnical change including the establishment of registries, multidisciplinary clinics, counselling, guidelines and a new role for general practitioners.

In relation to the reversal noted above, we also see a shift taking place in the meaning given to DNA diagnosis. In the case of FAP, presymptomatic DNA diagnosis is generally perceived as an improved diagnostic tool which makes it possible to divide a well-defined and known population at risk into carriers and non-carriers. However, with the extension of options for genetic testing to more common cancers, presymptomatic DNA diagnosis is given another meaning as well. It is not only accepted as a means to divide a well-known risk population into carrier and non-carrier, but is also perceived as a means which makes it possible to identify individuals at risk beyond established risk groups.

The rising prospect of large-scale genetic testing for cancer susceptibilities in the population has generated extensive debate about conditions and standards that should apply to the introduction of new options for genetic testing in society [39–41]. What is emphasised most in this debate is the need for education and counselling which should allow individuals at risk to cope with the implications of genetic testing on a well-informed basis. In the debate on DNA diagnosis for HB(O)C, for example, both leading researchers and patient representatives make clear that tests should be made available, but not without thoroughly informing women about the many unresolved questions surrounding the test [32, 42–44]. In other words, debates on the introduction of genetic testing in society are dominated by a counselling response. In terms of this counselling response, the acceptability of practices of genetic testing depends primarily on the question of whether conditions have been created which allow individuals to make an autonomous and well-informed choice. Thus dilemmas and tensions relating to the introduction of new tests in society should be managed by informing potential users as fully as possible about options, limitations and implications of testing. This involves the need for pretest education, informed consent, posttest counselling, and long-term follow-up of individuals at risk. It also involves the need for education of health professionals and for counselling facilities.

However, with different patterns of introduction of DNA diagnosis and different meanings of DNA diagnosis involved in these patterns, the notion of individual autonomy underlying the counselling response cannot simply be taken for granted. On the one hand, DNA diagnosis is introduced in clinical practices which, as in the case of FAP, involve a relatively small number of families who have already knowledge of their risk status and for whom well-established options for screening and intervention are available. The introduction of DNA diagnosis in this situation adds an option which may help to exclude individuals from risk. Indeed, in this context, it will be relatively straightforward to make this option available in a way in which individuals can make informed choices about its use. On the other hand, DNA diagnosis may in the future more often be introduced according to the pattern observed in the case of HB(O)C. Thus it becomes a means to identify genetic susceptibilities to cancer (or other adult disorders) in individuals who have no prior knowledge of their risk status. Especially when there is, as in the case of HB(O)C, little or no experience with the options available for those identified as carriers, DNA diagnosis may become a source of uncertainty and anxiety rather than a source of help or relief [45–48]. In this context, the aim of 'informed choice' will be very difficult to achieve as both information and choice are becoming more complex. Thus, it is only to a limited extent that the complexities of the new genetics can be solved by 'a high dose of education and counselling' tailored to the autonomous individual [49].

The changing pattern of introduction of DNA diagnosis and the related prospect of more extensive practices of genetic testing also raise the issue of the broader social implications of the new genetics. Predictive genetic testing and screening obviously not only concerns the individual, but also has wider implications, involving the content and use of basic medical concepts such as 'disease' and 'risk'. Indeed, in the context of cancer genetics, the concept of disease is being extended to genetic 'susceptibilities' which may never manifest clinically.

In the case of HB(O)C, as in other hereditary cancers, a substantial minority of gene carriers may never develop manifest disease. Nevertheless, gene carriers are diagnosed as having a health problem, which does not involve symptoms of disease, but a risk factor 'opening up a space of future illness potential'. This may lead to new and wide-ranging practices of 'surveillance medicine', monitoring healthy populations in order to identify and prevent possible future abnormalities [50]. Such practices obviously also involve difficult ethical dilemmas. Should the genetic status of an individual be disclosed to family members potentially at risk, or should doctors act according to traditional medical ethical standards and exclusively treat the individual patient? A host of issues on which there is no basic agreement at the moment concerning consent, confidentiality, and handling and banking of genetic information need to be reconsidered in this light.

The current debate on BRCA testing clearly reflects concern about the various issues implicated in the emerging new genetics, as is apparent from pleas to proceed with caution, and to offer BRCA tests as yet only in a research context. For the time being, researchers involved in BRCA testing seek to maintain a protected space of academic centres and co-operative trials in which answers may be sought to various technical, organisational, educational and ethical questions before tests are moved into clinical practice on a larger scale [31, 42]. This raises the question of how in the near future the results of these learning processes are going to be evaluated. Currently, the debate on BRCA testing is mainly taking place in professional circles.

In this debate, the preservation of individual autonomy serves, as we have seen, as the gold standard in assessing the acceptability of the introduction of new options for genetic testing in society. But, as genetic tests for cancer susceptibilities begin to move into clinical practice on a larger scale, such tests will gradually enter into a grey zone between small-scale testing in high-risk families on the one hand and large-scale population screening on the other. Thus, there is a growing need for evaluation of these options, based on a broad set of standards, including those relating to population screening. Indeed, both internationally and nationally, general guidelines have been recently proposed with regard to population-based genetic screening [51, 52], but the implications of such guidelines in relation to a field like cancer genetics have yet to be discussed. In other words, what we need in reaction to the emerging new genetic in society is not only an adequate counselling response, based on a well-organised and high-quality system of genetics services. We also need an adequate regulatory response, based on a well-organised, high-quality system of assessment, evaluation and debate, involving the perspectives of a variety of actors, such as professionals, (potential) users, social scientists, ethicists and policy makers.

References

1 Grody WW: The coming era of cancer genetic screening. Diagn Mol Pathol 1994;3:145–146.
2 Nowak R: Genetic testing set for takeoff. Science 1994;265:464–467.
3 Smith O: Genetic testing: Out of the bottle. Nat Med 1996;2:613–614.
4 Harris R, Harris H (eds): Genetics in Primary Care: Workshop of EC Concerted Action on Genetics Services in Europe. Central Manchester Healthcare Trust, 1995, pp 4–6.
5 Julian-Reynier C, et al: L'émergence sociale des consultations de génétique pour l'adulte. Vers une colonisation génétique de la médecine? Sociol Soc 1996, pp 28.
6 Koch L, Stemerding D: The sociology of entrenchment: A cystic fibrosis test for everyone? Soc Sci Med 1994;39:1211–1220.
7 Rip A: Introduction of new technology: Making use of recent insights from sociology and economics of technology. Technol Anal Strat Manage 1995;7:417–431.
8 Vasen HFA, et al: The value of screening and central registration of families with familial adenomatous polyposis: A study of 82 families in The Netherlands. Dis Colon Rectum 1990;33: 227–230.
9 Bulow S, Søndergaard JO, Moesgaard F: Familiår adenomatøs polypose. Ugeskr Lager 1990;152:2628–2632.
10 Bulow S, Myrhoj T: Arvelig kolorektal cancer. Ugeskr Lager 1996;158:2959.
11 Thomson JPS: Leeds Castle Polyposis Group Meeting. Dis Colon Rectum 1988;31:613–616.
12 Bodmer WF, et al: Localization of the gene for familial adenomatous polyposis on chromosome 5. Nature 1987;328:614–616.
13 Tops GMJ, et al: Presymptomatic diagnosis of familial adenomatous polyposis by bridging DNA markers. Lancet 1989;ii:1361–1363.
14 Houlston RS, et al: Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. BMJ 1990;301: 366–368.
15 Gorden J, et al: Identification and characterization of the familial adenomatous polyposis coli gene. Cell 1991;66:589–600.
16 Kinzler KW, et al: Identification of FAP locus genes from chromosome 5q21. Science 1991; 253:661–665.

17 Nishisho I, et al: Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 1991;253:665–669.
18 Vasen HFA, Muller HJ: DNA-onderzoek in families met erfelijke vormen van kanker. Ned Tijdschr Geneeskd 1991;135:1620–1623.
19 Vasen HFA, et al: Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. Lancet 1996;348:433–435.
20 Lips CJM, et al: De ontdekking van genen verantwoordelijk voor erfelijke tumorsyndromen; klinische en maatschappelijke gevolgen. Ned Tijdschr Geneeskd 1994;138:60–63.
21 Vasen HFA, Devilee P: Periodiek onderzoek van families met een erfelijke predispositie voor mammacarcinoom. Ned Tijdschr Geneeskd 1993;137:2350–2354.
22 Hall JM, et al: Linkage of early onset familial breast cancer to chromosome 17q21. Science 1990;250:1684–1649.
23 Easton DF, Bishop DT, Ford D, Crockford GP: Genetic linkage analysis in familial breast and ovarian cancer: Results from 214 families. Am J Hum Genet 1993;52:678–701.
24 Miki Y, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71.
25 Wooster R, et al: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994;265:2088–2090.
26 Wooster R, et al: Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–792.
27 King M-C: Breast cancer genes: How many, where and who are they? Nat Genet 1992;2:89–90
28 Roberts L: Zeroing in on a breast cancer susceptibility gene. Science 1993;259:622–625.
29 Shattuck-Eidens D, et al: A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene: Implications for presymptomatic testing and screening. JAMA 1995;273:535–541.
30 Plummer SJ, Casey G: Are we any closer to testing for common malignancies? Nat Med 1996;2:156–158.
31 Collins FS: BRCA1 – lots of mutations, lots of dilemmas. N Engl J Med 1996;334:186–188.
32 King M-C, Rowell S, Love SM: Inherited breast and ovarian cancer. What are the risks? What are the choices? JAMA 1993;269:1975–1980.
33 Vasen HFA et al: Clinical heterogeneity of hereditary breast cancer and its impact on screening protocols: The Dutch experience on 24 families under surveillance. Eur J Cancer 1993;29A:1111–1114.
34 Hoskins KF, et al: Assessment and counselling for women with a family history of breast cancer: A guide for clinicians. JAMA 1995;273:577–585.
35 Nowak R: Breast cancer gene offers surprises. Science 1994;265:1796–1799.
36 Friend SH: Breast cancer susceptibility testing: Realities in the post-genomic era. Nat Genet 1996;13:16–17.
37 Hubbard R, Lewontin RC: Pitfalls of genetic testing. N Engl J Med 1996;334:1192–1193.
38 Biesecker BB, et al: Genetic counselling for families with inherited susceptibility to breast and ovarian cancer. JAMA 1993;269:1970–1974.
39 National Advisory Council for Human Genome Research: Statement on the use of DNA testing for presymptomatic identification of cancer risk. JAMA 1994;271:785.
40 Kommission fur Öffentlichkeitsarbeit ethische Fragen der Gesellschaft für Humangenetik. Stellungnahme zur Entdeckung des Brustkrebsgens BRCA1. Med Genet 1995;7:8–10.
41 Statement of American Society of Clinical Oncology: Genetic testing for cancer susceptibility. J Clin Oncol 1996;14:1730–1796.
42 Cotton P: Prognosis, diagnosis or who knows? Time to learn what gene tests mean. JAMA 1995;273:93–95.
43 Wadman M: Panel softens cancer gene test warning. Nature 1996;380:573.
44 Geller G, et al: Genetic testing for susceptibility to adult-onset cancer: The process and content of informed consent. JAMA 1997;277:1467–1474.
45 Ponder M, Green JM: BRCA1 testing: Some issues in moving from research to service. Psychooncology 1996;5:223–232.
46 Julian-Reynier C, et al: Risk perception, anxiety and attitudes toward predictive testing after cancer genetic consultations. Am J Hum Genet 1995;57:A296.
47 Niermeijer MF: Medical genetics and primary care in The Netherlands; in Harris R, Harris H (eds): Genetics in Primary Care: Workshop of EC Concerted Action on Genetics Services in Europe. Central Manchester Healthcare NHS Trust, 1995, pp 15–18.
48 Coghlan A: Hopelessness is key result of gene test. New Sci 1996;152(14 Sep):8.
49 Nelson NJ: Caution guides genetic testing for hereditary cancer genes. J Nat Cancer Inst 1996;88:70–72.
50 Armstrong D: The rise of surveillance medicine. Sociol Health Illness 1995;17:393–404.
51 Nederlandse Gezondheidsraad (Dutch Health Council). Genetische screening. Den Haag, 1994.
52 World Health Organisation: Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services (draft). Geneva, WHO, 1995.