Dealing with uncertainty in diagnostic practices:
A comparison of mammographic screening and DNA-diagnostics for breast cancer

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[Note: unfinished draft; especially the conclusions in section 5 are very preliminary and references are incomplete or missing]

Fighting breast cancer by examining apparently healthy women: this is the goal that connects the diagnostic practice of mammographic screening with the practice of DNA-diagnostics for hereditary breast and/or ovarian cancer (HBOC). In professional and public debate, however, these practices are hardly seen as related to each other. Contrary to expectations at the start of the genomics era, genetic and medical professionals now consider DNA-diagnostics for breast cancer irrelevant for breast cancer in general. The advent of DNA-diagnostics has reinforced the separation of 'hereditary' and 'sporadic' breast cancer. These are now considered as different diseases with different causal mechanisms, to be diagnosed with different technologies and often treated in different ways.

The perceived difference between both diagnostic practices is strengthened as well by specific ideas associated with the technologies used. Whereas mammography is thought of as a well developed and broadly accepted technology, DNA-diagnostics is usually conceived of as radically new and problematic. Both the novel character and the genetic basis of DNA-diagnostics seem to lead to many uncertainties, which make it difficult to decide whether this technology is acceptable or not.

In this paper I will argue that it might be fruitful to compare the diagnostic practice of mammographic screening with DNA-diagnostics for HBOC, exactly because uncertainty is not unique to DNA-diagnostics. A comparison of both practices might make us realize that uncertainties (in plural) are always implicated in technology. The relevant question in debating the desirability of a diagnostic technology than should not be: 'is this technology hampered by uncertainty?', but rather 'how are uncertainties dealt with in this technological practice?'.

I will start with a reconstruction of the experiences of individual women participating in both practices, based on ethnographic field work done in the Netherlands in 2002 and 2003 (1). Subsequently, I will focus first on the main differences that can be observed and present

two explanations often cited to account for these differences, both focusing on the role of uncertainty in the technologies used (2). Next, I will argue why these explanations do not hold (3 & 4) and that both diagnostic practices, as far as uncertainties are concerned, have more in common than is usually supposed (5). I will finish by drawing some conclusions as to the relevance of these observations and analyses for debating the desirability of new diagnostic technologies in general (6).

1. Diagnosing breast cancer in a-symptomatic women: two stories

Going to the 'mammabus'[1]

On a parking lot next to the sporting grounds, just outside the village, a large white bus is standing. Mrs. A., a middle aged woman, climbs some stairs leading to its door and enters a small waiting room. She is welcomed here by an assistant who asks her to show her invitation letter and the form she was asked to fill out in advance. While the assistant checks her name and appointment, mrs. A. greets some familiar faces from the neighborhood sitting in the room. She is asked to sit down as well. After some time she is invited by another attendant to go into one of the three dressing rooms, to undress the upper part of her body and to wait until she is fetched. Immediately after having undressed, mrs. A. is invited to enter the imaging room on the other side of the dressing room.

" You are mrs. A, born on July 12, 1953?" the assistant says. "I see it is your first time here. Do you have any complaints or have you noticed anything strange in your breasts lately? No? Well, I will ask you to do some physical exercises first, so I can visually inspect your breasts. And then we will proceed to make the photographs". Mrs. A. puts her arms in the air, akimbo, then bows forward as asked by the assistant. "It's like aerobics!", she laughs. The assistant then proceeds to place mrs. A. in the right position behind the X-ray machine: her breast is laid on a glass plate and the upper part of the apparatus is lowered, until the breast is pressed quite heavily on the plate. "I hope it doesn't hurt too much? Can you stay in this position for a few seconds?" The attendant retreats behind a screen to press a button. The position of mrs. A. and of the apparatus are changed to make another X-ray from a different

[1] The stories in this section are based on, but not directly taken from observations of both practices and interviews with participants and professionals I did in 2002 and 2003. The spoken texts are condensed representations of what might have been said, but no literary citations. I want to thank the professionals and the clients of Bevolkingsonderzoek Borstkanker Noord Holland and of the Outpatients Department for Clinical Genetics involved for their hospitality and openness. The professionals of the Clinical Genetics Department deserve special thanks here, because they were the ones who suggested that comparing their practice to more 'traditional' diagnostic practices might be useful.

perspective, and then the procedure is repeated with the other breast. “You may dress yourself”, says the attendant. “…but please do not leave immediately. We want to check whether the photo’s quality is good enough; if not, we may ask you in again, so we can try once more. This does not mean at all that we have seen something suspicious, so there’s no reason to worry.”

Mrs. A. dresses and within a moment the attendant is back to tell her she may go now. “You will receive the result by letter, within a week or two.” “See you two years after today, then!”, mrs. A. greets jokingly before she leaves the bus. The whole procedure has taken about 15 minutes.

Visiting the outpatient clinic for DNA-diagnostics

Mrs. G., a lean and healthy looking woman in her forties, enters the academic hospital and follows the signs leading to the outpatient department for clinical genetics. Some time ago, she saw a program on TV about a DNA-test for hereditary breast cancer. Since both her grandmother and her mother have had breast cancer, while several other relatives suffered from other cancers, she visited her GP to ask whether it might be sensible to apply for this test. Her GP warned her that doing such a test might confront her with difficult questions: does she really want to know in advance whether she runs a heightened risk of breast cancer? And if so, would she be prepared to have her breasts surgically removed to prevent breast cancer? Mrs. G. admitted that she could not answer these questions right now, but said she wanted at least to know more about the possibilities. To her relief, the GP agreed that her family history was serious enough, so she referred mrs. B. to the Clinical Genetics Department. To her surprise, mrs. G. did not immediately get an appointment when she phoned the department. She had to answer a whole bunch of questions about her family’s history of disease, and she was told that only if the geneticists thought her family history serious enough, she would get an invitation to a consultation at the outpatient clinic. Luckily, she received a letter inviting her to today’s appointment. In the letter she was asked to fill out the form attached, asking again, but now more extensively, about the names, birth and death dates, diseases and causes of death of her family members. It has taken her quite some time to collect all this information, and she had to leave blank some lines.

After some waiting, she is invited to the doctor’s room. When she sits down and unfolds the form, the geneticist, dr. Z. says: “I see you have done some home work!” She explains that she will first ask mrs. G. about her family (once again) and will draw a pedigree, after which she will be able to say more about both the family’s risk and mrs. G.’s personal

risk of getting breast cancer. Drawing the pedigree takes a lot of time, but after about half an hour, dr. Z. thoughtfully summarizes the work by saying: “Well, we do not yet have all the information that might be useful, but there are indeed more breast cancer cases in your family than you would expect on average, so there might be a genetic factor at work. You probably thought so yourself, isn’t it, that’s the reason you are here, I guess.” She then continues to explain that geneticists use definitions to distinguish ‘hereditary’ from ‘familial’ and ‘sporadic’ cancers and that Mrs. G.’s family shows a pattern of disease that can be identified as hereditary breast cancer. “This hereditary disease is caused by a specific error in the DNA of your family. In the past, we could not see this error, so we had to estimate the risk of individuals in a family on the basis of the pedigree and epidemiological information. In your case, this would result in an estimate of about 35 % that you will get breast cancer. However, we now have this DNA-diagnostic technology, which enables us to investigate who does and who does not carry the error, or the mutation, in her DNA. If you are a carrier, you may have a risk of 55 – 85 % of getting breast cancer, but if you do not carry the mutation, your risk is just as high as that of anyone else, that is, about 10-12 %. Are you still with me, or are these numbers and percentages dazzling you? No? I will give you this brochure, everything I have told you is in it, so you may read it through at your leisure at home. But the next question is, of course, what are your options if you are a carrier? Well, you may choose to have yourself examined regularly, for example by yearly mammograms and physical examinations by a surgeon twice a year. But you may also opt for preventive surgery. However, I should warn you that this new DNA-technology is not yet able to see everything. At this moment, in about 25 % of all families diagnosed with hereditary breast cancer, a mutation is found. So in a lot of cases, we do think something hereditary is at work, whereas we cannot pin it down completely. Thus, if we do not find a mutation in your blood, we are not sure what this means. Maybe your family does not carry a mutation at all. But it may equally well be that there is a mutation unknown to us, for example on a gene that is not yet identified as being related to breast cancer. And in this case, you might or might not carry the unknown mutation. So it would not be very useful to test your blood immediately. However, if your mother and your grandmother, who have had breast cancer, would be willing to donate some blood, we can examine their DNA first, and if we identify a mutation in one of them, we may search your blood for this mutation as well. So, what I am asking is, would your mother or grandmother be willing to have their DNA diagnosed? If so, we would like to speak to them personally before they have this test. But the first issue now is: are you prepared to ask them?”

Mrs. G. leaves the room after an hour, provided with a brochure of about 30 pages with information about hereditary breast cancer, the diagnostics and preventive possibilities. She also carries forms to give to several family members, asking for their consent to retrieve their medical file, and some additional forms for her mother and grandmother, on which they may indicate their consent to cooperate in DNA-diagnostics. She has gotten a bit numb by all the information poured over her and all the information she had to give herself. Moreover, there are many issues she should think over in the time coming. DNA-testing is no simple matter, that much has become clear to her in the last hour.

2. Fighting breast cancer: comparing diagnostic practices

At first sight the scenes described above show that two diagnostic practices in preventive health care could hardly differ more, even if they both aim at reducing (mortality from) breast cancer. Although the differences are manifold, what struck me most as an observer of both practices, were the different roles of and the relation between 'technology' and 'talk'.

Mrs. A. is physically examined in a relatively fast, routine procedure with a minimum of talk; the X-ray machine plays the leading part while the behavior of both mrs. A and the assistants seems to be guided by the desire to optimize the machine's functioning. Mrs. G., on the other hand, is orally examined by a doctor who extensively questions her about her motives for wanting DNA-diagnostics and her resources for dealing with this technology and the possibilities it opens up; the technology itself does not come into view at all: in the end mrs. G. leaves without even having donated blood. The effect of this difference on the observer (and probably on the people involved as well) is that, whereas mammography seems to be self-evident and leaves hardly any room to voice doubts concerning its use, DNA-diagnostics comes to the fore as fraught with uncertainties and ambivalences.

This impression of diagnostic practice concurs with the public image of both technologies. Both mammography in the narrow sense and the screening program using it appear to be widely accepted as an asset for the early detection of a serious disease by professionals, patients and regulating bodies alike. The images produced may present us with a certainty concerning one's health that cannot be attained by other means. The usefulness and desirability of DNA-diagnostics for HBOC, by contrast, is as yet surrounded by doubts and debate. Wholehearted enthusiasm is alternated with critical and doubtful voices.

Explaining the difference

How to account for the differences between these practices? Why is there so much talk in the one and not in the other? One obvious answer seems to be that DNA-diagnostics is accompanied by talk because it is (considered as) problematic. In a more general vein, one might even suggest that the unproblematic character of technology and talk are communicating vessels: the less problematic a technology is, the less talk it is surrounded with. The lack of talk in and about screening practice, then, means that it is not seen as problematic. This begs the question, though, why DNA-diagnostics is problematic whereas mammographic screening is not.

Two explanations seem to suggest themselves[2]. Both have to do with uncertainties in the technology at stake. The *first* one points to the apparent anachronism implicit in comparing these practices. Mammography of the breasts was developed in the 1960's and 70's and has been used in screening programs in the Netherlands from the 1980's onwards, whereas DNA-diagnostics for HBOC entered the floor only in the midst of the 1990's and thus is a relatively new technology. It need not surprise, then, that mammography is more broadly accepted; it has simply had more time to develop. Whereas DNA-diagnostics is a *technology in development*, hampered by all kinds of uncertainties because of its relative novelty, mammography is a relatively *successfully developed technology*. The claim behind this explanation is, of course, that mammography in its initial phase has known its problems too (concerning, for example, validity and reliability, containment of radiation risk, etc.); at the start, it was probably hotly debated and accompanied by a lot of talk as well. Talk and debate now have receded indeed, but this is just an indication that the uncertainties and difficulties of the initial phase in this case apparently have been resolved in a satisfactory way. Scientists and designers have done their best to enhance validity and reliability and to reduce radiation doses, and thus in due time developed a problematic device into a valuable diagnostic instrument.

The *second explanation* refers to the specific character of DNA-diagnostic technology and the information it produces. This type of diagnostics, so it is argued, differs from more traditional types of diagnostic technology (including mammography) in at least three respects. First, it produces knowledge that *predicts* your *future* health *risk* (instead of *informing* you about your *current* health *state*). This knowledge, secondly, is inherently uncertain. It is

[2] These explanations, by the way, are not completely mutually exclusive; they may qualify one another.

framed in statistical statements that are difficult to translate to the individual level. This is inherent in the type of technology, so this characteristic will not vanish when it is developed further. Third, the test results are not just meaningful for the person tested, but also for his/her relatives, because genetic information by definition tells something about them as well. The claim behind this explanation is that of what is called 'genetic exceptionalism': we are confronted with difficult questions because of the specific character of genetic knowledge.

Thus, whereas the first explanation (the 'novelty-explanation') suggests that most uncertainties and problems pertaining to DNA-diagnostics will vanish in due time, and that this will be the result of professional and technical efforts, the second ('genetic exceptionalism') explanation suggests that these uncertainties and problems are here to stay as long as we keep using this knowledge and these technologies. From this perspective, there is good reason for being reticent in using DNA-diagnostic technology and for talking things over: psychological and ethical support will probably remain indispensable.

I have discussed these arguments in some detail, because they appear in many public and professional debates on the ethics of DNA-diagnostics (for HBOC, but also for other diseases). Analyzing both practices (and some of their history) in more detail, however, suggests that they do not hold. I will first discuss the 'genetic exceptionalism'-thesis, and then continue with the 'novelty'-explanation.

3: Genetic exceptionalism and uncertainty in test results

Many studies concerning the ethical and social impact of genetic technologies, are predicated on the assumption of 'genetic exceptionalism': genetic technologies deserve special consideration because they produce an exceptional type of knowledge, compared to more traditional biomedical technologies [REF – Chadwick and others]. If we confine ourselves to DNA-diagnostic technologies, the assumption of genetic exceptionalism hinges on its predictive character and on the uncertain, statistical content of the information it produces. DNA-diagnostic technologies, that is, are thought to differ from diagnostic tools like chemical analysis of urine or blood samples and from diagnostic imaging techniques like X-rays or MRI-scans, because DNA-characteristics do not inform us about our current state of health. Whereas the presence of a specific protein in our blood may tell us we suffer from bowel inflammation at this very moment, the presence of specific DNA-characteristics *predicts* our

future health [REF – de Vries]. In the case of breast cancer, it may tell the client that as a mutation carrier, she has a 60 % chance of getting this disease somewhere during her lifetime. As this percentage indicates, DNA-diagnostic technologies usually do not produce digital results: either positive (you will be diseased) or negative (you will be healthy). They issue *statistical estimates*, implying that the client has a X times heightened or lowered risk, compared to some reference group, of contracting a specific disease [REF]. This implies that translating these risk estimates to the individual will always be uncertain: this individual mutation carrier may belong to the minority of carriers who do not contract the disease. As a result, DNA-diagnostic technology provides the client with inherently uncertain knowledge about the future. DNA-diagnostics is predictive, and its predictions may or may not come true.

The idea that this makes DNA-diagnostics exceptional, however, only makes sense if traditional diagnostic technologies do produce certain knowledge concerning current health. This assumption does not hold. To see this, we should focus on the character of disease and on the difference between diagnosis of people with and without complaints.

Diagnostic tools like urine analysis or MRI-scans apparently tell us something about our bodily state. They show we have a heightened level of a specific protein, or that we have a lesion in our veins. In the case of mammography, a white knot on an X-ray image of breast tissue may signify a tumor. Perceiving such signs, let alone identifying them as deviant and thus as indicators of disease, requires extensive knowledge about other bodies. We may only identify a specific body characteristic as deviant, that is, if we know what a 'normal' body state is. What is normal and what is deviant, however, hinges on our definition of disease, which in turn hinges on statistics, which in turn depends on the technical possibilities to produce specific information. This implies that what counts as disease varies between populations and may change over time. [REF] Heightened blood pressure, for example, has become a disease on its own relatively recently in the Western world, and since then the definition of normal blood pressure has changed quite radically because of the availability and the expanding knowledge on the effectiveness of treatment [Sackett 2000, 70] Thus, the idea that diagnostic tests produce unambiguous signs of a pre-existing disease is too simplistic, even for simple and long-lived diagnostic tests like chemical analysis of urine [REF Horstman]. This is not meant to deny that disease does have an existence of its own, but to stress that the meaning of the signs and symptoms making up the disease cannot be found outside a culturally, historically and technologically mediated frame of reference. As a much

used handbook on evidence based medicine says: “diagnosis is not about finding absolute truth but about limiting uncertainty.” [Sackett 2000, 92]

Diagnostic tests, that is, produce statements on our bodily state, but these statements are related to diseases only on the basis of statistical (epidemiological) information, and thus indicate the *probability* of a specific diagnosis.[3] Because test results often are seen and acted on as relatively unambiguous, we tend to forget that their meaning depends on statistics and is uncertain nevertheless.

This statistical character becomes outright *predictive* when diagnostic technology is applied to individuals without complaints. This includes application of DNA-diagnostic technology for, for example, Huntington’s disease or breast cancer, but also screening tools like measurement of cholesterol level, X-rays of the lungs in case of screening for tuberculosis, as well as mammographic screening for breast cancer. In these cases, the individuals who are examined do not have complaints: they are ‘a-symptomatic’. Application of diagnostics to these individuals is considered useful nevertheless, because they belong to ‘risk groups’: groups of individuals with specific characteristics (for example age, sex, or family history of disease) that have been identified by epidemiological research. A significant percentage of this group will contract the disease somewhere during his/her lifetime. The diagnostic technology is then used to refine the predictions by singling out individuals with an even higher chance of getting the disease.

DNA-diagnostics for HBOC is a clear example of such predictive diagnostics: within the group of families at risk, individuals are singled out who have a heightened risk because they carry a mutation. The predictive character of this test, however, is not unique to DNA-diagnostics. Just the fact that someone’s family history of disease includes several cases of breast cancer sufficed for a long time to include her in the group that is at heightened risk for breast cancer. It was predicted that a significant number of these women would get breast cancer during her lifetime (usually 30 – 40 %). Now that the blood of an individual may be searched for specific DNA-characteristics, prediction is more refined. By looking for the presence of specific mutations the group identified as at risk because of family history can be divided in two. Those carrying a mutation have a substantially higher risk than assumed before (50 – 85 %), whereas the risk of the group of non-carriers is probably no more than

[3] This is a somewhat simplified picture of making a diagnosis, of course: usually information produced by a diagnostic technology is combined with information from other sources, like the complaints presented by the patient and the results of physical examination by the physician. To construct an informative diagnosis, the relevant information from these different sources has to be coordinated [REF Mol 2002].

that of the average population (10-12 %). Despite this refinement, the test result remains statistical and predictive nevertheless; even mutation carriers do not all get breast cancer.

Predictive diagnoses are not new, then, nor are they limited to the domain of genetics. As indicated above, mammography is usually not perceived of as producing a predictive diagnosis. Mammography is associated more with diagnostic tests like chemical urine or blood analysis: it produces an image of our bodily state at a given moment in time. However, as the American Committee on Technologies for the Early Detection of Breast Cancer (instituted by the National Cancer Policy Board) stated in 2001:

> "Although most patients and physicians would consider a histological diagnosis of breast cancer, even when it is totally in situ, a "disease," a more precise definition of disease is "a condition that causes morbidity and mortality." In this sense, breast cancer is only a disease when one of these two conditions exists. Morbidity and mortality occur almost exclusively in the setting of clinically detectable metastases. Thus, all other stages of breast abnormalities are shown here as having variable levels of risk for the development of morbidity and mortality (i.e., disease)." (2001, 49, Fig. 1-6)

And they continue:

> " (I)n more modern times, most patients are diagnosed with aysmptomatic breast cancer. In this setting, almost all treatment for breast cancer (…) could be considered prophylactic or preventive. Such treatment s are applied to reduce the chances that the patient will develop morbidity or mortality (or "disease")." (ibidem, 50)

Moreover, since in 'more modern times' women diagnosed with asymptomatic breast cancer are almost always treated, we do not really know whether all women with positive (deviant) mammograms would have developed disease (that is, morbidity and/or mortality) in due time. With the advent of new imaging techniques, more abnormal lesions may be identified, but their clinical meaning is unclear. Usually they are treated, but since we cannot be sure that they are precursors of disease, this may in fact be overtreatment. In professional literature there has been a lot of debate about 'ductal carcinoma in situ' (DCIS) in particular. DCIS refers to a lesion in a breast tissue duct that has not spread to its environment. Some of these, but apparently not all, will develop into breast cancer, and there is no way to distinguish them

at an early stage. Most cases of DCIS (possibly accounting for 30 % of all breast cancer cases identified by mammographic screening (Ernster et al. 1996, see Nass et al. 2001, 46)) are treated by mastectomy or lumpectomy followed by radiation, so the question wether DCIS should be considered as (leading to) a disease is highly relevant, both in terms of preventing unnecessary suffering and of health care efficiency.

Thus, the meaning of the result of mammography when applied to individual women without complaints is not at all certain. However, in practice screening mammography results are not treated as uncertain predictions, but as relatively certain diagnoses.[4] What is important here, is to note that screening mammography and DNA-diagnostics for HBOC in this respect have much more in common than is usually thought: the uncertainty of the knowledge produced by DNA-diagnostics is not exceptional or unique to genetics after all.

It is remarkable, though, that this uncertainty is dealt with in completely different ways in both practices. Whereas women asking for DNA-diagnosis are confronted with the uncertainty of future test results beforehand and thus have the opportunity (and the obligation) to decide themselves whether and how this uncertainty affects their choices, in screening mammography this uncertainty is played down: it is actively promoted as good to have. Moreover, the uncertainty of results in DNA-diagnosis is treated as relevant to decision making on the basis of these results as well: it is considered perfectly legitimate for women identified as mutation carriers to choose for less drastic options such as periodical examinations. In screening mammography, this is hardly an option for women with a positive result.

Comparing both practices, in sum, enables us to identify relevant similarities between DNA-diagnostics and screening mammography. In doing so, it undermines the thesis that DNA-diagnostics as a genetic technology is exceptional, at least as far as the statistical and predictive character of test results is concerned. Finally and most importantly, the comparison opens up possibilities for mutual learning how to deal with uncertainty of test results.

4. New diagnostic technologies and uncertainties concerning technology itself

Having discussed the genetic exceptionalism-thesis, I now turn to the ‘novelty-thesis’, which suggests that the uncertainties that characterize new technologies (like DNA-diagnostics) will

[4] It would be interesting to investigate how this practice has come into being, but this question is beyond the scope of this paper.

vanish in due time when they are successfully developed (like screening mammography). It is important to note that the uncertainties relevant here differ from those discussed in the preceding section. Even if we accept that diagnostic technologies (be it mammography or DNA-diagnostics) produce uncertain, statistical results, the question remains whether these results are reliable and whether the technology is safe. To become accepted as a useful diagnostic tool, new technologies have to prove that their results can be trusted to be accurate and without serious side-effects. In our time, with many diagnostic procedures already existing, this usually means that the new technology should at least match the results of a reference diagnostic procedure that is perceived as the 'golden standard' at a specific moment and have less or less serious side effects. Whether a new diagnostic technology can live up to this criterion is of course usually uncertain for at least some time. The thought implicit in the novelty-explanation is that uncertainties of this kind will usually be resolved by technological developments; if not, the new technology will probably be abandoned.

Although this explanation is not altogether implausible, it risks one sidedness nevertheless. First, it suggests that screening mammography is free of the reliability problems pertaining to DNA-diagnostics. Second, it suggests that reduction of this type of uncertainty hinges on technological development, or, the other way round, that technological development may be seen as a steady reduction of uncertainties. There is good reason to reject both suggestions.

Countering the first suggestion: mammography is a reliable technology

DNA-diagnostics for HBOC is, as set out in the scene at the beginning of this paper, hampered by severe reliability problems. The predictive value of this test is quite low. At this moment, it succeeds in identifying a mutation only in about 25 % of all families diagnosed as having HBOC. (The criterion for reference or 'golden standard' being used here is good old pedigree analysis.) Therefore, when a healthy individual whose relatives have not (yet) been examined tests negatively, the meaning of this result is uncertain. Either the individual tested may not carry a mutation at all, whereas some family members are carriers; or an unknown mutation (or complex interaction between gene(s) and environment) is running in the family, which means that the individual tested may or may not be a carrier of this unknown mutation.

It is enticing to interpret these problems as start up problems, and clinical geneticists often tend to frame the issue as such in counseling conversations. The large number of false negatives is then attributed to a lack of knowledge: "until now, only two genes, BRCA 1 & 2,

have been identified, but probably other genes play a role as well…". The suggestion is that this problem will be solved in due time when all the relevant genes and mutations (and, if recent scientific insight is accounted for, their interactions with each other and with the environment as well) will be identified. Scientific and technological progress, that is, will make this problem obsolete somewhere in the future.

This perspective suggests, moreover, that diagnostic technologies ideally are completely reliable: the rate of false positives and negatives should approach the 100 %, and thus imply complete certainty. This ideal is, however, quite distant from everyday medical practice. In this context, we often settle for diagnostic technologies that are very uncertain indeed. There may be good reasons for doing so: DNA-diagnostics for HBOC is a case in point. Although it does not succeed in identifying all individuals at high risk, it may clear at least some family members who were until then considered 'high risk' on the basis of pedigree analysis. By using both technologies side by side, we may have the best of both worlds.

That we are often able to make do with (much) less than complete certainty regarding the reliability of diagnostic technologies, is illustrated by the case of screening mammography as well. When X-ray technology was developed (at the end of the 19th and the beginning of the 20th century), attempts to use it for the imaging of breast tissue were considered a failure because the softness of the tissue did not produce enough contrast to enable reliable interpretation. Attempts to adjust X-ray-devices in such a way as to make it useful for breast imaging resurfaced only in the 1960's and '70's . Better film, new emulsions, breast compression, (etc.) all contributed to more reliable images. However, interpretation of mammograms remained an uncertain business.

Notwithstanding these problems, mammography was quite soon seen as a useful technology for screening women at risk of breast cancer. In the Netherlands two pilot projects of breast cancer screening started in the mid 1970's already (that is, when mammography was a relatively young technology). To be sure, the reliability of the technology played a large role in the debate about the desirability of a screening program, next to radiation risk and effectiveness. Especially the number of false positives and the worries and stress these might induce in the women involved were mentioned as drawbacks of such programs. However, in one of the advisory reports commissioned by the Dutch government, the Health Council concluded that technical developments went so fast that progress on this domain was to be

expected on short term. (Gezondheidsraad 1981 en '84) [5] In the end the Health Council thought mammography was at least sufficiently reliable to be used in screening programs, provided that adequate measures would be taken to optimize and guarantee the highest possible reliability. (Gezondheidsraad 1987) Nevertheless, the numbers of false positives and negatives in present-day screening programs are still substantial.[6]

After the Dutch screening program was introduced on a national scale from 1991 onwards, the uncertainties regarding reliability and effectivity were hardly spoken of anymore. When two Danish researchers in 2001 published a Cochrane report claiming that the effect of breast cancer screening programs on mortality reduction is quite limited, partly because of mammography's low reliability, this stirred some public and professional debate. . (Olsen & Gotzsche 2001a, 2001 b) This subsided rather soon after the Health Council issued a report stating that the effect on mortality might be smaller than expected, but that there was no reason to abort the screening program right now. This does not mean, however, that the uncertainties regarding mammography's reliability have been solved: in the same report, the Health Council states that the Dutch screening program has rates of 70 % for sensitivity and 50 % for specificity. (Gezondheidsraad 1987)

To conclude, uncertainties regarding the reliability and general functioning of a diagnostic technology need not prevent its use: even imperfect and uncertain technologies may become widely used. Mammography is, again, a case in point: thousands of women in the Netherlands are screened bi-annually and even more in other countries. Apparently its low specificity is not seen as a problematic issue. One might speculate on the reasons for this. An important explanation is that the stakes and hopes are simply too high: breast cancer is a widespread disease causing a lot of suffering. If mammography is able to prevent some of this suffering, we are glad to give it a try, even if its functioning is hampered by uncertainties. Arguments like these probably carry a lot of weight in discussions about diagnostic technologies in general.

Countering the second suggestion: technological uncertainty is to be reduced by technological development

[5] With the benefit of hindsight one might now even conclude that the introduction of screening programs has served as an incentive to ameliorate mammography technology. (REF)

[6] Current international numbers: sensitivity (the percentage of breast cancers correctly identified by a positive test result) is estimated to be between 90-98 %), and specificity (the percentage of healthy breasts correctly identified by a negative result) between 83-95 % (Nass et al. 2001, 39, 40). However, these numbers have been established in quite controlled experimental contexts. Screening practice in the Netherlands shows a sensitivity of about 70 % and a specificity of 50 % (Gezondheidsraad 2002, 16-17). That is, especially the rate of false positives is high.

As I said above, the suggestion of many professionals working in genetics is that the uncertainties hampering DNA-diagnostic tests like those for HBOC right now, will not only be reduced in due time, but that this will be realized by scientific and technological progress. Instead of sequencing just the BRCA 1 and –2 genes, future DNA-diagnostics will sequence all the relevant genes, is the (implicit) promise. This line of thinking is widespread in reflection on new diagnostic technology. The Dutch Health Council, for example, at the end of the 1970's had a strong faith in technological progress as well when discussing the value of mammographic technology.

Although scientific and technological developments often do contribute to the reduction of uncertainties in technology, they are on no account the only means. As numerous studies of technological practice have shown, technological devices need a fitting environment to function well. The case of mammography will be used again as an illustration here.

Reliable images of the breast are not just produced by the X-ray machine, but also depend on the way this device is used and embedded in practice. First, of course, the images produced require human interpretation to become meaningful. This means that images and interpreters have to be geared towards one another: images have to fit the capabilities of the human eye (for example by enhancing contrast and resolution), whereas humans (especially radiologists) have to be adjusted to the images produced (for example by developing discernment by way of training programs and regular feedback). Bias may be partly neutralized by installing procedures of double judgment. In addition, measures may be taken that aim at simplifying interpretation by embedding it in specific contexts and therefore limiting interpretive possibilities (for example by limiting use of mammography to specific age groups and by asking additional information about use of hormones or family history of disease)

If we look at the history and current practice of mammographic breast cancer screening once more, it becomes clear that the diagnostic reliability of screening actually has been enhanced by a whole array of organizational and social measures. In most countries, quality standards have been installed to guarantee that optimal diagnostic results will be produced. Organizations offering screening are required to take many different measures, both technical, social and organizational. In many countries these quality regulations have been tied to a licensing system.

Here another reason why mammography is trusted, notwithstanding its uncertainties, becomes visible. Even though technology is imperfect, the practice in which it is embedded is

designed in such a way as to keep these uncertainties in check. Uncertainties implied by the technological device may be balanced by assigning specific roles and responsibilities to other actors (human or non-human) involved in the practice.

This is even more clear in the case of DNA-diagnostics for breast cancer. The uncertainty caused by the low predictive value of this technology discussed in the preceding section, is in Dutch practice limited by refraining from testing healthy family members immediately. If a healthy women from a family that has not been examined before asks for DNA-diagnostics, this request will not be granted at once. She will be asked (as mrs G. in the second story) to mobilize her diseased family members and ask them to submit themselves to DNA-testing first. Only if this relative tests positive, the healthy woman will be tested herself. This procedure makes the test result somewhat easier to interpret, since the meaning of a negative test result in healthy women is much more clear if a mutation has been found in family members (and of the chance of finding a positive result is larger in diseased family members). Thus, to reduce the uncertainty implied by DNA-diagnostic technology, the healthy women involved have to play a very specific role. In the interviews I conducted with these women, many of them indicated that this procedure had surprised them: they had not anticipated either that family members had to be involved, nor that they would have to play an active role in approaching these relatives themselves. Most of them noted that they had experienced this as a heavy responsibility. [Boenink 2003]

What is at stake here, to conclude this section, is the conception of technology. The idea that uncertainties implied by technology will be reduced by scientific and technological development is not only quite optimistic, but it also presupposes a conception of technology that is too narrow. A diagnostic device does not produce results all on its own; results are a co-production of the complex interaction between many different (material, human, social, organizational) elements in the diagnostic practice. This means that uncertainties may be both produced and reduced by many different elements as well. Relatively well developed technologies, like mammography, do not differ from new technologies (lie DNA-diagnostics) in that they produce completely certain results. They may, however, have been embedded in a practice in a more successful way, either because this practice as a whole reduces the uncertainties to an acceptable level, and because the roles and responsibilities implied by this practice are not considered problematic.

5. Dealing with uncertainty in diagnostic practices

The first lesson from this comparison between the diagnostic practice of mammographic screening and the practice of DNA-diagnostics for breast cancer is, then, that they may have more in common than is usually supposed. Uncertainties abound in both technologies, whether or not they are new, and whether or not they have their foundation in genomic knowledge. It seems that the hype surrounding genomics has led both professionals, policy makers and the broader public astray by suggesting that genetic diagnostic technologies are unique, and so are their problems. We can now say that they are not, at least not as far as the uncertainties discussed in this paper are concerned.

The second lesson is that both practices have developed in a specific way to mitigate or reduce uncertainties of interpretation and reliability, and that they might learn from each other in this regard. Whereas the uncertainties are discussed quite openly in DNA-diagnostics, the way they are dealt with is attributing an important role and a heavy responsibility on the individual healthy women involved. In mammographic screening the uncertainties are much more covert, but here the responsibility for reducing them is located much more with the professionals involved, partly as a result from public policy choices. I do not think that any of these practices has succeeded in making uncertainties completely unproblematic (this might be an illusionary ideal anyway). But comparing practices may give us some idea of better and worse ways to deal with uncertainty. When the women involved in DNA-diagnostics criticize current practice for the role it attributes to them, one might look at screening practice to see whether alternative distributions of responsibilities would be feasible.

Generalizing from this comparison, we might suggest that diagnostic technologies in general are hampered by uncertainties one way or another. They are always based on statistical knowledge that is difficult to translate into conclusions on the individual level; moreover, their reliability and predictive value may be quite low. Thus, the functioning and the results of diagnostic technology will usually be uncertain to at least some extent.

It is clear by now, I suppose, that this need not prevent a diagnostic technology of being used, since these uncertainties may be mitigated in a myriad of ways. The roles of devices, users, procedures et cetera are being fitted to each other, or tinkered with, to construct a situation in which uncertainty is reduced to an acceptable level, and in such a way that the roles and responsibilities involved are acceptable as well.

A third and last observation is that the uncertainties involved need not diminish when a technology is developed further. Reducing uncertainty is not only an issue of gathering more or more certain knowledge, nor of designing material artifacts in such a way that they act

more reliably. Uncertainty is often reduced by reorganizing technological practice, that is, by social and organizational regulations. Imperfect artifacts may be very useful, if they are used in clearly circumscribed ways. Responsibility for reducing a technology's uncertainty than is relocated to additional artifacts, individual users or complete organizations.

The continuous and reciprocal fitting of artifacts, users, procedures etc. is a complex process that has been the focus of research by both Science and Technology Studies and Philosophy of Technology. It might be described as 'continuous experimenting' (Latour), and is probably one of the explanations of technology's 'indeterminacy' (Ihde). Both concepts suggest that we should cast away the spell of 'perfect technology' or the ' technological fix' and become technical realists: uncertainty is here to stay, even (or especially) in a technological culture.

In addition to these more general analyses, I hope to have shown that studying these processes at the level of specific practices induces us to ask different questions. The relevant question is not whether or not a technology is hampered by uncertainties. Much more relevant is the question how to deal with uncertainties. Which types of uncertainty are and which ones are not bearable? And how acceptable are the roles and responsibilities created to reduce uncertainty?

We should be aware, however, that judgment concerning the acceptability of a specific distribution of roles and responsibilities is not an issue of applying general criteria. It is an issue of tinkering to fit all the different kinds of requirements to each other in a satisfactory way. What is a good result in this regard is usually context dependent. One way to become more skillful and creative in this tinkering process is to learn from other practices. And this is, of course, exactly why comparing practices such as mammography and DNA-diagnostics is highly relevant, even though they may be very different at first sight.