



# Translating genetics beyond bench and bedside: A comparative perspective on health care infrastructures for ‘familial’ breast cancer



Erik Aarden

Department of Science and Technology Studies, University of Vienna, Universitätsstraße 7/II/6, 1010 Vienna, Austria

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## ABSTRACT

Developments in genomics research are considered to have great potential for improving health care – making genomics an urgent site for translational efforts. Yet while much emphasis is put on the technical challenges of translation, there is less scholarly attention for the social infrastructures through which novel medical interventions may be delivered to patient populations. Reflecting the idea that cancer is at the frontier of genomic applications in health care, this paper explores how the assessment of familial breast cancer risks was ‘translated’ into routine health care in Germany, the Netherlands and the United Kingdom. The paper identifies regulation, institutionalization and standardization as key mechanisms of translation that find distinct expression in particular sociocultural contexts and shape both the social and technical making of genomics into routine clinical practice. Translation is therefore an area of social as well as technical concern, and therefore requires collective decision-making.

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## 1. Introduction

Recent achievements in basic genomic science are widely heralded as carrying great clinical potential – and therefore in need of translational support. Knowledge on the molecular mechanics and pathways of disease should contribute to more tailored forms of individual medical care, but it is widely acknowledged that this cannot happen without considerable investment in bringing advances from the laboratory ‘bench’ to the clinical ‘bedside’ (Niederhuber, 2010). In particular, the detailed understanding of human biological complexity at the molecular level is expected to contribute to further patient stratification and the delivery of care tailored to biologically differentiated patient groups. Rooted in genomics and systems biology, the future of medicine is often sketched in terms of the *preservation* of individual health, rather than *treating disease* in the aggregate population (Hood and Friend, 2011). Yet to arrive there, various technical and social challenges to translation need to be addressed to ‘bridge the gap’ between bench and bedside.

In recent years, the intricate complexity of such ‘bridging’ has increasingly been recognized, and translation reconsidered as a two-way road (Marincola, 2003) that should involve broader communities around bench and bedside (Cohrs et al., 2015). The challenge of making scientific knowledge beneficial for overall population health has consequently been defined as a continuum of various translational phases – especially in the context of genomics (Khoury et al., 2007; Schully and Khoury, 2014). For translation to proceed through the various phases,

medical researchers call for investments in all of them, ranging from translation of basic science to clinical application (T1); on to evidence based practice guidelines (T2); evaluation in practice (T3); and population level evaluation of health outcomes (T4), respectively. Yet even while this approach to translation acknowledges the work that remains to be done for novel diagnostics or therapeutics to contribute to population health, the multi-phase model of translation remains attached to a technical (i.e. evidence-based) understanding of the problem (for a broader critique around this point, see (Van der Laan and Boenink, 2015)). Research in the social sciences, by contrast, has shown how translation efforts are always closely entangled with a broader social context that shapes how medical innovation, its application and its integration in health care delivery arrangements take shape (Vignola-Gagne and Biegelbauer, 2013). Moreover, the various phases of translation may relate and unfold very differently considering both the social configuration of research and clinical care and the specific domains of genomic research and medicine in which these efforts unfold (Gardner and Webster, 2016; Merriman and Molina, 2015). A more detailed understanding of specific sociocultural understandings of health and diseases and social preferences vis-à-vis the incorporation of particular novel (genomic) technologies in health care distribution is therefore required to fully understand how translation may benefit population health (Aarden et al., 2010).

This paper aims to contribute to a more detailed understanding of the intersections between social and technical dimensions of translation by investigating how genomic advances are delivered to populations in different health care contexts. It explores this question through a comparison of services available for risk assessment and follow-up for

E-mail address: [erik.aarden@univie.ac.at](mailto:erik.aarden@univie.ac.at).

familial breast cancer predispositions in Germany, the Netherlands and the United Kingdom. Applications of genomics in the oncological domain are at the forefront of translating genomics from research to medical care (Dolsten and Soegaard, 2012; Bombard et al., 2013), both in terms of genomic approaches to cancer risks (related to germline mutations) and the development and characteristics of tumors (somatic mutations). While germline and somatic approaches to cancer genomics are different, they share certain characteristics of interest from the viewpoint of translation. Both (should) allow more sophisticated classification of disease (risk) into distinct subcategories and earlier intervention more tailored to affected sub-populations (Bydoun et al., 2014). At the same time, a focus on familial cancer risks allows us to see how uses of genomics are established as routines, how the limits of molecular technologies are confronted (since only around 30% of familial breast cancers has a known genetic background (Shiovitz and Korde, 2015; Foulkes, 2008)), and how technicalities of risk stratification intersect with the social dimensions of health care infrastructures to bring genomics to the population. Approaching translation of genomic technologies to patient care from this vantage point provides insight into the mutual influence between risk classification and health care delivery infrastructures and the social and technical dimensions of translation in distinct contexts.

## 2. The importance of health care infrastructure

The technocratic nature of much of the translation discourse – particularly in the domain of bench-to-bedside (Woolf, 2008) – reflects a ‘technological imperative’ that suggests that new technologies will by definition reshape health care. Yet various studies of the development of technologies in health care and beyond have shown how these commonly develop in close interaction with their social environment, with both technology and society coproducing each other (Jasanoff, 2004). In the context of complex health care environments that both shape and are shaped by advances in medical technology, a framework that understands the roads new technologies travel to become available to patients in particular clinical settings may be fruitfully understood in terms of *health care infrastructures*. This notion of infrastructure expands on Parthasarathy’s study of ‘architectures’ for genetic testing for breast cancer in the United States and the United Kingdom (Parthasarathy, 2005). While she helpfully notes how structures of regulation, technology development and health care delivery influence how genetic tests are delivered in distinct forms to different segments of the population in these countries, the notion of infrastructure more explicitly considers the wider context of genetic tests and the more extensive range of issues that characterize ‘translation’. These issues include culturally specific responses to how medical knowledge is made and incorporated in health care, which configurations of actors and mechanisms are involved in evaluating new diagnostics and therapeutics, how they are distributed, etc. (Daemmrich, 2004). These diverse socio-cultural elements collectively shape an infrastructure for translating genomics to patient care, a process that involves a balancing act between full development of technological possibilities and improving health for as large a part of the population as possible (Aarden et al., 2011).

The infrastructures that shape the translation of genomic technologies to health care delivery are highly context-specific. A powerful way to gain insight into the role of infrastructures in the later phases of translation is therefore to compare between different infrastructural environments. The comparison in this paper includes three Western-European countries – Germany, the Netherlands, and the United Kingdom – that are similar in many ways, but differ in several respects that are important to our purpose here. In particular the organizational structure of health care delivery and sociopolitical responses to advances in medical applications of genomics color the ways familial understandings of breast cancer have been adopted in health care delivery. We will encounter some of these differences in detail when discussing the infrastructures for delivering familial breast cancer

diagnostics below, yet in broad terms we may identify two axes of difference. On the one hand, health care delivery in Germany and the Netherlands is based on (social) health insurance, where individuals pay a premium to an insurance company that purchases medical services on behalf of their collective membership. In the UK health care is funded through general taxation, with funds for the National Health Service (NHS) redistributed to regional purchasing authorities (Van der Zee and Kroneman, 2007). These different structures affect how financial resources are distributed, how decisions about reimbursement are made, and who is involved in making health care policies (Van Hoyweghen, 2014). At this structural level, Germany may further be distinguished from the other two countries by having a so-called ‘double structure’ of physicians employed by hospitals and those that are self-employed (a differentiation that roughly overlaps with the delivery of inpatient and outpatient care). Where it comes to political responses to the advent of genomics, the Netherlands and the United Kingdom may be grouped together as well, since in both countries the health ministries developed elaborate strategies for integrating genomics in health care. For various reasons, no strategy of that sort was developed in Germany. As we will see, these and more specific characteristics constitute the infrastructures that give shape to the translation of genomics to routine medical interventions – affecting both the social and technical configuration of genomics’ contributions to population health.

## 3. Developing a comparative perspective

This paper deliberately takes a step back from the frontier of developments in cancer genomics to focus on the assessment of hereditary breast cancer risks and genetic testing for BRCA mutations in three European countries. It thereby seeks to answer a question that has received relatively little attention in discussions on how the translation of genomic knowledge can contribute to the improvement of population health. While various social scientists have pointed to the changes that affect research communities, clinical practitioners and the relations between genomics research and the attribution of meaning to genomic findings in the clinic (Rabeharisoa and Bourret, 2009; Harvey, 2011), the broader infrastructures for health care delivery, access and reimbursement of genomic technologies remain more obscure (Aarden, 2016). To address this void, the paper neither seeks to address only the cutting edge of advances in the field, nor does it seek to be comprehensive with regard to contributions genomics has made to understanding the complexity of breast cancer predispositions and progression of disease. The paper instead provides empirical evidence for the complex intersections between social and technical dimensions of how diagnostics are distributed. On that basis it proposes a way to explore the social dimensions of translation from, as it were, bedside to health care infrastructures. We may thereby gain insight into the establishment of health care delivery routines and how some of these routines may affect further incorporation of genomics in health care delivery in the future.

The paper focuses on the establishment of routines for the delivery of diagnostics and follow-up services for familial breast cancer risks in the first decade of the present century. Empirical material was primarily collected between 2005 and 2010, complemented with a short literature reviews to assess whether guidelines and standards for risk assessment have changed to a significant degree since the initial data collection was completed. While this should not imply that no important developments in breast cancer genomics have taken place since, medical evidence suggests that no radical change has taken place in the main risk categories (based on family history and identifiable gene mutations; (Shiovitz and Korde, 2015)). Moreover, taking a few years of distance allows us to clarify the origins of routines in specific contexts, without having them obscured by ‘incomplete’ evidence from recent and experimental approaches that are highly prevalent in health care systems’ attempts to grapple with the significance of genomics for the future of medicine.

The empirical evidence presented in this paper was obtained through the analysis of relevant documents and interviews with medical professionals and public officials involved in the integration of genomics in health care delivery. The documents, which include regulations, standards and guidelines as well as opinion articles and perspectives in medical journals in all three countries, were identified through searches of online databases of regulations and national medical journals. Interview respondents were identified either from these publications, by contacting relevant organizations (ministries, medical professional organizations – both generic and specialized in relevant fields – national expertise centers, etc.), and by asking respondents for further suggestions (so-called snowball sampling). A total number of 33 professionals was interviewed; 11 of them in Germany, 9 in the Netherlands and 12 in the United Kingdom. Materials from both document analysis and interviews were coded for particular themes of interest such as risk classification, indications for genetic testing, follow-up procedures, availability and distribution of services, etc. Results were constantly compared across national borders to gain more pronounced insight into national specificities. While the approaches in each of the countries presented an internally coherent (even if sometimes paradoxical) logic, the discussion below structures the presentation of materials along thematic rather than national lines – in order to advance our insight into the roles distinct infrastructures play in, respectively, classifying familial risks, applying molecular genetic diagnostics, and providing subsequent follow-up and prevention. In the ensuing [discussion and conclusion](#) section, we will address the social mechanisms of translation these countries share, their different contextual manifestations and what this implies for the social and technical shape translation takes in cancer genomics and beyond.

#### 4. Translation infrastructures for risk assessment

The question whether and how hereditary factors play a role in cancer has a long history that predates scientific and technological capabilities for understanding why cancer is more prevalent in some families than in others. In more scientifically and clinically useful ways, familial dimensions of cancer were uncovered from the 1970s onwards; initially through registration and the analysis of statistical correlations, and through the identification of direct links between genetic mutations and increased likelihoods of developing the disease from the 1990s onwards ([Mukherjee, 2010](#)). Despite these advances, the clinical adoption of knowledge about correlations between gene mutations and cancer remains a challenge due to the fact that (for most cancers) not all mutation carriers develop the disease and vice versa, not all cases of cancers (even those clustering in families) can be accounted for in molecular genetic terms. As we will see, a core issue to the translation of genomics to health care is therefore how to account for this plurality of risks. Usually, the first step is therefore risk classification based on family history analysis.

##### 4.1. Classifying familial risks

Even though health care services in these three countries are based on shared scientific insight into increased likelihoods of cancer on the basis of family history and genetic mutations, categories and criteria used in clinical practice are remarkably different. Not only are classificatory boundaries drawn differently, but approaches to risk assessment are shaped by the distinct health care infrastructures in ways that are deeply incongruent. Not only are the risk categories and criteria for assessment different or are guidelines developed by vastly different organizations, even the purposes of risk assessment in terms of the forms of risk they seek to distinguish are fundamentally different.

To begin, risk assessment in the Netherlands is to a large degree continuous with family classifications that preceded the advent of genetic testing. Since the early 1980s, an independent organization called StOET (a Dutch acronym that stands for Society for the Detection of

Hereditary Tumors) runs a registry of familial cancers and, in collaboration with the Dutch Society of Clinical Geneticists, produces diagnostic guidelines for assessing individual risks ([Stichting Opsporing Erfelijke Tumoren and Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2010](#)). This organization was originally funded by the Ministry of Health, but currently finances its activities through direct payment for services it delivers to hospitals.

Current guidelines for risk assessment no longer primarily use statistical percentages and categories (as they used to), but instead describe scenarios to identify women who should receive additional monitoring, those who should be referred to a specialist geneticists and distinguishes between moderate and high risks for the purpose of monitoring. The group eligible for additional monitoring (see also [Section 4.3](#)) consists of women who have a lifetime risk that is more than twofold that of the general female population. This group includes women who have two first-degree relatives diagnosed with breast cancer before the age of 50, or women who have a first or second degree relative with ovarian cancer and a first or second degree relative diagnosed with breast cancer before the age of 60. The guideline for referral to a genetics specialist additionally includes women diagnosed with breast cancer before the age of 35, women with a brother/father with breast cancer and a female relative with breast or ovarian cancer on the same side of the family, or with three or more first or second degree relatives with breast cancer, at least one of which was diagnosed before the age of 50 (for more details on these guidelines see ([Stichting Opsporing Erfelijke Tumoren and Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2010](#))).

For follow-up, the Dutch guidelines refine these categories and distinguish between a category of moderately (2–3 times population risk) and strongly (3–4 times population risk) increased risks (without specifying how to distinguish between these two types of risk), referring the former to a general practitioner (GP) for monitoring purposes, and the latter to a specialist physician. Furthermore, the Dutch guidelines are the only ones making a sharp distinction between what is called familial risk (based on family history assessment) and hereditary risk (based on the identification of a genetic mutation). As we will see below, this distinction in terms of the presence or absence of a genetic mutation has particular consequences in the context of follow-up.

The guidelines in the Netherlands are produced by organizations that specialize in genetics and hereditary tumors, while a national standard setting body for all of health care issues similar instructions in the United Kingdom (technically only England and Wales, although interview respondents argued that Scotland and Northern Ireland largely concur). This organization, the National Institute for Health and Care Excellence (NICE) has issued several revisions of its guidelines for familial breast cancer. The most recent version appeared in 2013; according to NICE regulations, the guideline is up for revision again in 2017. The guidelines are written by a committee of experts in a particular field and are supposed to serve as best practice standards for health care throughout the country. NICE guidelines are also developed as a management tool for the health service as a whole, especially in comparison to the guidelines developed by more specialized professional organizations in the Netherlands and Germany.

The familial breast cancer guideline consequently links distinct risk categories explicitly to different segments of the National Health Service (NHS) ([NICE, 2013](#)). It distinguishes between women at or near population risk (<17% lifetime risk at age 20, <3% between age 40 and 50), who should be seen by their GP and in the national population screening program between the ages of 50 and 70; women at moderate risk (between 17 and 30% lifetime risk, 3–8% between 40 and 50), who should be attended to by a secondary care specialist like a surgeon or radiologist for regular surveillance; and high risk women (lifetime >30%, >8% between 40 and 50; including BRCA and TP53 mutation carriers) who should be referred to a tertiary care specialist in genetics. As we will see, this particular configuration and distribution of risk categories has

clear implications for the role of genetic testing and the application of monitoring and early detection services in the UK.

Compared to the Netherlands and the United Kingdom, the diagnostic strategy in Germany has a different aim. Rather than to stratify the likelihood of developing breast cancer for all women on the basis of their family history, initial risk assessment in Germany is oriented towards distinguishing women who do or do not qualify for a genetic test. This is a result of the recommendations of two leading medical organizations in Germany – the Federal Chamber of Physicians and the Society for Human Genetics – to proceed carefully after the identification of the BRCA genes in the 1990s (Bundesärztekammer, 1998; Gesellschaft für Humangenetik, 1995). In response to these guidelines, several university hospitals set up a consortium to develop best practices for genetic testing (see Section 4.2), an important element of which was to identify women for whom testing would have clinical value. Similarly, a guideline for risk assessment developed by German cancer organizations and the cooperative association of medical scientific associations AWMF recommends genetic counseling and testing in specialized centers (meaning those in the consortium) for women meeting one of several criteria (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2012).

This so-called S-3 guideline (which have the highest level of confidence in the related evidence base) thus equally focuses on ways to distinguish between women who should and those who should not receive a genetic test. Criteria include the presence of three or more women in the family diagnosed with breast cancer, one or more women diagnosed with breast cancer before the age of 35 or two or more women diagnosed with ovarian cancer (scenarios that are virtually identical with those used in the Netherlands). Furthermore, on its website the consortium provides a form to medical professionals that allows them to tick boxes for the presence of breast and ovarian cancers in first degree relatives and further relatives in the paternal or maternal line. Ticked boxes are linked to certain point values, which may be added up and, when the score is three or higher, indicate a need to refer a woman to one of the consortium centers (see [http://www.konsortium-familiaerer-brustkrebs.de/medien/user\\_upload/8\\_Checkliste.pdf](http://www.konsortium-familiaerer-brustkrebs.de/medien/user_upload/8_Checkliste.pdf); accessed 14 July 2016).

Any further risk assessment on the basis of family history is secondary to genetic testing, and only applied to women who have undergone a genetic test. In case that test comes back inconclusive or negative, women are offered breast monitoring on the basis of their statistical risk – which has to be >30% lifetime risk of developing breast cancer or a 20% risk of carrying an (as yet unidentifiable) gene mutation (Zylka-Menhorn, 2013).

#### 4.2. Applying molecular genetic diagnostics

The German Consortium for Familial Breast and Ovarian Cancer ([www.konsortium-familiaerer-brustkrebs.de](http://www.konsortium-familiaerer-brustkrebs.de), accessed 14 July 2016) consists of (presently) seventeen university clinics that joined together to develop a joint concept for genetic testing, monitoring and further studies on the significance and implications of genetic testing for breast cancer predispositions. The consortium started out with financial support from the German Cancer Society, but was incorporated in regular health care reimbursement under Germany's statutory health insurance within a few years (Schmutzler et al., 2006). Yet the reimbursement of patient care through the collective sickness funds that cover the majority of medical expenses for German patients was only possible due to a recent amendment to health care regulation in Germany. Only since 2004 can hospitals provide certain highly specialized or experimental outpatient procedures with funding from public health insurance funds. This includes the services provided by the consortium.

The role of regulatory change in facilitating the establishment of the consortium – or at least the accessibility of its services for the average German woman – points to the particular status of clinical genetics in Germany. Whereas clinical genetics was originally established in close

association with research in academic hospitals, its services of genetic counseling and testing are in principle outpatient procedures – roughly distinguished by the fact that they do not require overnight admission –, which are traditionally provided by self-employed, 'private' physicians (not to be confused with privately financed medical care). The majority of genetic tests in Germany is consequently provided in independent genetics clinics. Similar to the academic consortium, these clinics are primarily oriented towards offering genetic testing, but employ criteria unlike those proposed by the consortium. In interviews, private geneticists presented themselves as service providers for their patients – women concerned about their risk – and they considered an offer of genetic testing legitimate if it could help alleviate a woman's concerns. Consequently, private geneticists do not necessarily limit genetic testing to women with a family history indicating a significant increase in risk. Moreover, despite the principle of cost-effectiveness that is central to health care financing in Germany, insurance funds have no instruments to restrict this practice, since the catalogue for reimbursement of outpatient care states that any genetic test prescribed by a qualified professional ought to be reimbursed, regardless of indication – a point that is of great importance for medical professional's sense of autonomy.

The contrast between this German practice and the situation in the Netherlands is perhaps the greatest, since genetic services in the latter are by law restricted to eight centers associated with academic hospitals (see <http://wetten.overheid.nl/BWBR0014594/2009-03-05>, accessed 14 July 2016). Only those eight centers are allowed to provide genetic counseling and perform genetic tests. While the aforementioned guidelines for familial cancer risk assessment do not provide distinct criteria for genetic testing, a genetic test is an option for all women who do qualify for referral to a genetics clinic. Yet the forms of care offered at a genetics clinic may also consist of one or more counseling sessions only. An earlier version of the diagnostic guideline prescribes DNA diagnostics when there is a > 10% chance of finding a BRCA 1 or 2 mutation (STOET and Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2005) – although clinicians indicated in interviews that they took this number as a rule of thumb rather than a strict line and that they used various calculation methods, the results of which they would synthesize on the basis of experience and their tacit beliefs about accuracy of the various methods. In terms of reimbursement, insurance companies and the Dutch Society of Clinical Genetics drew up an agreement in 1995 that still largely applies today, despite reforms to the Dutch insurance and health care financing structures in the interim. According to this agreement, genetics clinics can bill either simple (one counseling session) or complex consultations (anything more comprehensive), although material costs of e.g. laboratory procedures are listed independently.

As indicated before, the Dutch guidelines further distinguish between familial and hereditary cancer risks on the basis of the proven presence of a BRCA mutation. While clinicians we interviewed questioned the significance of this distinction in biological and clinical terms, it does have consequences for the forms of follow-up offered to individual women at risk, as we will see below.

This sharp distinction between women at a statistically high risk with or without a mutation stands in stark contrast with the recommendations by NICE in the UK, where the follow-up services for these two groups are largely the same. This may perhaps be related to the limited availability of genetic testing for BRCA mutations within the NHS. Although the Department of Health committed to solid establishment of genetic services in the NHS in the context of a policy strategy for genetic medicine issued a few years after the completion of the Human Genome Project (Department of Health, 2003), breast cancer charity Breakthrough Breast Cancer published a report only a few years later that reflected critically on the availability of genetic diagnostics and the time between testing and availability of results (Breakthrough Breast Cancer, 2006). Geneticists shared the report's observations in interviews, and often gave additional examples of problems with genetic

testing, such as the practice of testing only a segment of the BRCA genes in order to reduce costs.

Concerns about the precarious status of genetic testing for breast cancer predispositions in the NHS are reflected in Breakthrough's subsequent campaign to improve service delivery. On its website the organization therefore takes credit for some of the changes made to NICE's familial breast cancer guidelines in its most recent revision (see <http://breastcancer.org/news-and-blogs/blogs/changing-the-policy-on-genetic-tests-for-breast-cancer>). As of 2013 NICE recommends the use of carrier probability scores to establish whether women at risk should be offered genetic testing. The guideline further reduces the threshold for such an offer from a 20% of finding a mutation to only 10% and extends this advice to also include women with no clear family history or no relative with diagnosed breast cancer who can be tested first. It remains to be seen whether these changes in recommendation do in fact improve the availability of genetic testing, due to particularities of health care financing in the UK, which we encounter in more detail in the next section.

#### 4.3. Providing follow-up and prevention

For women identified to be at increased risk of developing breast cancer due to their family history or a genetic mutation, few options to actually prevent cancer exist. One of the more radical options is prophylactic surgery to remove breast tissue or ovaries, but this is only recommended for a small minority of women at risk. Beyond that, intense monitoring of breast tissue through (self-)examinations, mammography and MRI is recommended in all three of the countries, but to different degrees. These forms of monitoring are often complementary to population breast screening offered to women over the age of fifty in each of these countries. Monitoring guidelines for hereditary risks often do include referral to the screening programs as well as additional monitoring at earlier ages.

The various follow-up options are most extensively described in the NICE guideline in the UK, which distinguishes between what physicians should actively offer, should consider as options and should not offer to different categories of women (NICE, 2013). To give only one example, annual mammography should be offered to (among others) women at moderate or high risk between the ages of 40 and 49; be considered for women aged 30 to 39 with a BRCA 1 or 2 mutations; and not be offered to women aged 29 or under. For the latter age group, MRI is recommended only for women who have a proven TP53 mutation or >30% likelihood thereof. These recommendations apply to women without a personal history of breast cancer; more stringent recommendations apply to women who have (had) the disease. For most women over the age of 50, the guidelines recommend participation in the population screening program (including those over 70 with a BRCA mutation) and more regular screening for e.g. women with a TP53 mutation. The guideline further specifies the criteria for offering prophylactic surgery and recommends prescriptions of Tamoxifen for five years for certain groups of women.

But even though the guideline indicates that women attended to in secondary care settings such as breast care centers or family history clinics should receive access to monitoring, it is in exactly this context that British clinicians see the limitations of NICE guidance. As several of them indicated in interviews, NICE guidelines aim to set standards but come with neither formal power nor financial incentives to force implementation. Since most funding for the NHS is allocated to particular medical services by regional NHS authorities, there are considerable regional differences in available resources and hence availability of the recommended interventions. This problem is especially attributed to secondary care physicians who supposedly prefer to use their limited resources for mammography screening for women referred with suspect results from the population screening program over women with raised familial risks (although this may have changed in recent years, since a study conducted with the exact purpose to assess the efficacy

of mammography for women aged 40–49 with increased risk, sponsored by Cancer Research UK, suggests such monitoring reduces breast cancer mortality; see (FH01 Collaborative Teams, 2010)).

While the problem in the United Kingdom is thus rooted in the insufficient funds available for implementing early detection recommendations, the issue appears to be more fundamentally about what appropriate medical care is in Germany. The aforementioned S3 guideline for breast cancer care recommends breast examinations and ultrasound at six month intervals, and annual mammography and MRI from the age of 25, or five years before the earliest case of breast cancer in the family, onwards (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2012). In line with the general orientation towards genetic breast cancer risks in Germany, these recommendations apply to women with a BRCA mutation or a risk >30% or a mutation chance >20%. In addition, only mutation carriers should be offered prophylactic mastectomy and be recommended to undergo prophylactic oophorectomy around the age of forty. All of these forms of early detection and prevention are clustered in the seventeen consortium clinics; private geneticists are asked to recommend these options primarily when they themselves have established their clinic in a conglomerate of private clinics that include radiologists and/or surgeons who can offer these procedures.

But even though this is what medical professional organizations advise, several clinicians indicated that insurance funds sometimes refuse to reimburse monitoring – as well as genetic testing. The arguments insurance funds use to reject reimbursement of breast monitoring and genetic testing follow the same logic and refer to the central principle of cost-effectiveness in German health care. In both cases, the funds argue, there is no specific clinical indication to perform a medical procedure – a laboratory test or clinical examination. Insurers argue that the intervention is then a form of generic screening for which efficacy is not scientifically established and insurers carry no financial responsibility. While physicians claim that this argument relies on a misunderstanding of genetic diagnostics and preventive medicine, a conviction shared by the majority of insurance funds and their association, these examples suggest that in individual cases women may not get access to the forms of diagnostics and preventive measures recommended for them. This is a problem not exclusive to Germany, although the discrepancies between recommendation and delivery take different shapes elsewhere.

Still different are the recommendations for follow-up in the Netherlands, where each risk category gets its own set of recommendations (Stichting Opsporing Erfelijke Tumoren and Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2010). Women with a moderately increased risk should receive an annual mammography through their GP between the ages of 40 and 50 and participate in population screening until the age of 75. With a strongly increased risk, women should receive annual mammography and breast examinations from a specialist physician and subsequently participate in the screening program until the age of 75. For both categories, in cases where breast cancer was diagnosed at very young age in the family, the guideline further suggests monitoring may start at age 25, although no mammography should be offered before the age of 30. For women with a hereditary (i.e. genetically confirmed) risk and their female relatives who have not been tested, breast examinations and MRI should start at age 25 and MRI and mammography at age 30. Between ages 60 and 75 these women should also participate in the screening program. Starting at age 35 these women should further be offered various gynecological examinations for early detection of ovarian cancer (although, the guideline adds, women should be counseled that the chance of actual early detection is small). In addition, mutation carriers should be advised to consider prophylactic mastectomy from age 25 onwards, and prophylactic oophorectomy from age 35–40 for BRCA1 and 40–45 for BRCA2, respectively. The various preventive interventions should be offered in interdisciplinary settings in university hospitals, called Outpatient Clinics for Hereditary Tumors.

Clinicians express concern about the difference between monitoring for strongly increased familial and hereditary risks, especially with regard to the different settings in which these services should be provided. While they are generally positive about the efforts to establish integrated services for mutation carriers, they argue that similar measures should be taken for the highest risk category that does not have a demonstrable genetic predisposition. According to clinicians, these women also carry a considerable risk of developing cancer, but since they are supposed to be monitored in their own local hospitals it is difficult to follow up on whether they actually receive the forms of monitoring that are recommended for them. Nevertheless, it is not an option to include these women in the specialized outpatient clinics, since their number is about three times that of the mutation carriers and university hospitals do not have the budget to see such large numbers of women at risk in that particular setting. Geneticists are therefore worried about the fate of these women.

The fragmentation of services provided to women with similar statistical risks consequently shows how measures to promote translation, or the incorporation of genomics in routine health care, are negotiated with the constraints of existing health care infrastructures and resources. As a consequence, the contribution of translational efforts to population health is always contested and incomplete, excluding differently constituted segments of the population in different contexts.

## 5. Discussion and conclusion

In the preceding discussion we have seen how insights into the correlation between family history, genetic mutations and individual breast cancer risk was translated into the delivery of diagnostic services and follow-up in distinct ways in Germany, the Netherlands and the United Kingdom. Despite the differences between these settings, we can distill three elements of context-specific health care infrastructures that influence the shape of genomics in routine health care delivery. First, *regulation and policy*, such as the legal restrictions on clinical genetics in the Netherlands or the regional allocation of funding to medical disciplines in the UK produce a broad framework within which genomic medicine is established. Second, *institutionalization* of, for example, diagnosis and monitoring in a consortium of university clinics in Germany and monitoring specifically for mutation carriers in the Netherlands have an impact on how robust the availability of particular services is. Finally, *standardization and guidelines*, perhaps most prominent in the central standard setting role of NICE in the UK, but equally important in the more specialized context of a registry for hereditary tumors in the Netherlands, specifies how scientific evidence can and should be applied to individual clinical cases.

But while we find similar mechanisms of translation vis-à-vis health care infrastructures in each three of these countries, they shape up in highly specific ways that speak to the sociocultural specificity of the infrastructures at stake. The particular configurations of actors and institutions that shape trajectories for genomics from bench to bedside and beyond are rooted in both particular national histories and traditions of health care organization and chance events that steer developments in certain ways. Consider for example the establishment of the German consortium of university clinics with the support of the German Cancer Society and in response to policy statements by medical professional organization, the formation of a registry for hereditary tumors largely independent from existing infrastructures in the Netherlands, or the top-down, centralized role of NICE in the UK. These are very divergent organizations that each produces the diagnostic guidelines for particular national settings. In addition, an important area of difference between these countries is the autonomy physicians have in setting out a course of risk assessment and monitoring for their patients and the degree of influence external actors such as insurers and the state have on whether these services get reimbursed. While medical doctors in Germany appear to have a relatively large degree of autonomy in Germany, their discretionary space is much more circumscribed in the

Netherlands and especially through NICE and regional budgeting in the NHS in the United Kingdom. At the same time, gaps and controversies in service delivery are equally specific to each setting, as reflected in the struggles between inpatient and outpatient delivery of genetic testing in Germany; the contested distinction between familial and hereditary risks in the Netherlands; and the regional differences in availability of services in the UK. The contributions of translation to population health thus depend to a significant degree on national responses to technical novelties.

These context-specific manifestations of genomics' contribution to population health imply that the impact of infrastructures on translation cannot be seen as exclusively social. Just like translation processes run in both directions between bench and bedside, clinical practices of risk assessment and infrastructures of health care delivery mutually shape each other. To understand the translation of novel medical interventions into routine health care, the process of translation therefore has to be understood as socio-technical. Consequently, and even though they largely rely on the same scientific evidence of familial and genetic factors contributing to individual breast cancer risks, the three countries discussed here turn familial breast cancer into something that is also clinically different across borders. While risk assessment in all three countries combines statistical risk calculation and genetic testing, the balance between these methods may be significantly different. In Germany, there is much more emphasis on identifying women who can undergo a genetic test; in the Netherlands, genetic risks are most explicitly understood and treated as different from familial ones; and in the United Kingdom genetic testing is of lesser importance for deciding on follow-up monitoring than statistical risk categories are. This is not to say that all applications of genomics in health care in these countries necessarily shape up like this; they may in fact be very different for other diseases, where different actor configurations, regulations and sets of standards and guidelines are involved (see e.g. (Aarden et al., 2011)). Nevertheless, it suggests that the indicators of population health that translation is expected to contribute to are affected by processes to establish new technologies in health care as much as regulations, institutions and standards are. Definitions of health and disease change together with the incorporation of new diagnostics and therapeutics in established routines.

One may argue that things are different with the advent of genomics (as distinct from the largely genetic predispositions discussed here). For one, it appears that in the years since the completion of the initial study presented here, guidelines in these three countries have converged somewhat (although that does not imply convergence of health care delivery). Moreover, both biological-technical and social-institutional dimensions of genomic medicine continue to undergo rapid and interconnected transformations. New diagnostic techniques, including next generation sequencing, as well as shifting perspectives on stability and change in the genome are likely to complicate any straightforward notions of 'genetic predispositions' (Lappe and Landecker, 2015). At the same time, private industry and venture capital play an increasingly important role in the development of new medical technologies (Lehoux et al., 2016), with as yet unclear consequences for health care delivery infrastructures. Nevertheless, even the most recent development of new diagnostic markers, sequencing tests and other new technologies applied in the oncological field similarly involves negotiation of technical, social and regulatory dimensions (Kohli-Laven et al., 2011; Nelson et al., 2013). This means that the translation of new technologies to health care delivery, as well as the delivery of care to particularly defined populations will continue to unfold in context specific ways, with potential residues of how things are done at present.

In order to truly understand and be able to anticipate the translation of genomics to health care in the interest of population health, we therefore need to attend to the specific mechanics of translation in different medical-technological and infrastructural contexts. This implies that translation in the interest of population health is a question that can neither exclusively be solved on the basis of scientific evidence, nor

through the established administrative routines of health care delivery. Genomic technologies and their translation to routine health care present a number of challenges – both medical and organizational – of which the exact breadth and depth are uncertain. As genomics promises a personalization of health that intersects in complex ways with political trends towards increased individual (financial) responsibility for obtaining medical care (Bella, 2010), the question of translation is paradoxically a question of collective choice. It requires attention to the evolving knowledge base on the genomic dimensions of disease as well as explicit and inclusive considerations of uncertainties and social preferences and priorities regarding resource distribution. The translation of genomics from bedside to population health care delivery is consequently an issue that requires informed democratic deliberation (Bijker et al., 2009; Brown, 2009). Only through collective, balanced deliberation about the social as well as technical dimensions of translation may genomics fully realize its promising potential for improving population health.

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## References

- Aarden, E., 2016. Constitutions of justice in genetic medicine: distributing diagnostics for familial hypercholesterolemia in three European countries. *Crit. Policy Stud.* 10 (2), 216–234.
- Aarden, E., Van Hoyweghen, I., Horstman, K., 2010. Solidarity in practices of provision: distributing access to genetic technologies in health care in Germany, the Netherlands and the United Kingdom. *New Genet. Soc.* 29 (4), 369–388.
- Aarden, E., Van Hoyweghen, I., Horstman, K., 2011. The paradox of public health genomics: definition and diagnosis of familial hypercholesterolemia in three European countries. *Scand. J. Public Health* 39 (6), 634–639.
- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2012. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Leitlinienprogramm Onkologie Deutsche Krebsgesellschaft, Berlin.
- Bella, L., 2010. In sickness and in health: public and private responsibility for health care from Bismarck to Obama. In: Harris, R., Wathen, N., Wyatt, S. (Eds.), *Configuring Health Consumers. Health Work and the Imperative of Personal Responsibility*. Palgrave-Macmillan, Basingstoke, pp. 13–29.
- Bijker, W., Bal, R., Hendriks, R., 2009. *Paradox of Scientific Authority; or the Role of Scientific Advice in Democracies*. The MIT Press, Cambridge, MA.
- Bombard, Y., Bach, P., Offit, K., 2013. Translating genomics in cancer care. *J. Natl. Compr. Cancer Netw.* 11 (11), 1343–1353.
- Breakthrough Breast Cancer, 2006. *Testing times, Waiting for Genetic Test Results*. Breakthrough Breast Cancer, London.
- Brown, M., 2009. *Science in democracy. Expertise, Institutions, and Representation*. The MIT Press, Cambridge.
- Bundesärztekammer, 1998. Richtlinien zur Diagnostik der genetischen disposition für Krebserkrankungen. *Dtsch. Arztebl.* 95 (22), 1396–1403.
- Bydoun, M., Marcato, P., Dellaire, G., 2014. Breast cancer genomics. In: Dellaire, G., Berman, J., Arceci, R. (Eds.), *Cancer Genomics. From Bench to Personalized Medicine*. Academic Press, London, pp. 213–232.
- Cohrs, R., et al., 2015. Translational medicine definition by the European Society for Translational Medicine. *New Horiz. Transl. Med.* 2, 86–88.
- Daemmrich, A., 2004. *Pharmacopolitics: Drug Regulation in the United States and Germany*. University of North Carolina Press, Chapel Hill.
- Department of Health, 2003. *Our inheritance, our future. Realising the Potential of Genetics in the NHS*. Department of Health, London.
- Dolsten, M., Soegaard, M., 2012. Precision medicine: an approach to R&D for delivering superior medicines to patients. *Clin. Transl. Med.* 1(7).
- FH01 Collaborative Teams, 2010. Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. *Lancet* 11, 1127–1134.
- Foulkes, W., 2008. Inherited susceptibility to common cancers. *N. Engl. J. Med.* 359 (20), 2143–2153.
- Gardner, J., Webster, A., 2016. The social Management of Biomedical Novelty: facilitating translation in regenerative medicine. *Soc. Sci. Med.* 156, 90–97.
- Gesellschaft für Humangenetik, 1995. Stellungnahme zur Entdeckung des Brustkrebsgens BRCA1. *Med. Genet.* 7, 8–10.
- Harvey, A., 2011. From lab to lifestyle: translating genomics into healthcare practices. *New Genet. Soc.* 30 (4), 309–327.
- Hood, L., Friend, S., 2011. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat. Rev. Clin. Oncol.* 8, 184–187.
- Jasanoff, S., 2004. *States of knowledge. The Co-production of Science and Social Order*. Routledge, London.
- Khouri, M., et al., 2007. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet. Med.* 9 (10), 665–674.
- Kohli-Laven, N., et al., 2011. Cancer clinical trials in the era of genomic signatures: biomedical innovation, clinical utility, and regulatory-scientific hybrids. *Soc. Stud. Sci.* 41 (4), 487–513.
- Lappe, M., Landecker, H., 2015. How the genome got a lifespan. *New Genet. Soc.* 34 (2), 152–176.
- Lehoux, P., et al., 2016. How venture capitalists decide which new medical technologies come to exist. *Sci. Public Policy* 43 (3), 375–385.
- Marincola, F., 2003. Translational medicine: a two-way road. *J. Transl. Med.* 1 (1), 1–2.
- Merriman, B., Molina, S., 2015. Variable conceptions of population in community resource genetic projects: a challenge for governance. *New Genet. Soc.* 34 (3), 294–318.
- Mukherjee, S., 2010. *The emperor of all maladies. A Biography of Cancer*. Scribner, New York.
- Nelson, N., Keating, P., Cambrosio, A., 2013. On being "actionable": clinical sequencing and the emerging contours of a regime of genomic medicine in oncology. *New Genet. Soc.* 32 (4), 405–428.
- NICE, 2013. *Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People With a Family History of Breast Cancer*. National Institute for Health and Care Excellence, London.
- Niederhuber, J., 2010. Translating discovery to patient care. *JAMA* 303 (11), 1088–1089.
- Parthasarathy, S., 2005. Architecture of genetic medicine. Comparing genetic testing for breast cancer in the USA and the UK. *Soc. Stud. Sci.* 35 (1), 5–40.
- Rabeharisoa, V., Bourret, P., 2009. Staging and weighting evidence in biomedicine: comparing clinical practices in cancer genetics and psychiatric genetics. *Soc. Stud. Sci.* 39 (5), 691–715.
- Schmutzler, R., et al., 2006. Familiärer Brust- und Eierstockkrebs. Von der Forschung zur Regelversorgung. *Dtsch. Arztebl.* 102 (50), A 3486–A 3488.
- Schully, S., Khoury, M., 2014. What is translational genomics? An expanded research agenda for improving individual and population health. *Appl. Transl. Genomics* 3, 82–83.
- Shiovitz, S., Korde, L., 2015. Genetics of breast cancer: a topic in evolution. *Ann. Oncol.* 26 (7), 1291–1299.
- Stichting Opsporing Erfelijke Tumoren, Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2010. *Erfelijke Tumoren. Richtlijnen voor Diagnostiek en Preventie*. Stichting Opsporing Erfelijke Tumoren & Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, Leiden.
- STOET and Vereniging Klinische Genetica Nederland Werkgroep Klinische Oncogenetica, 2005p. *Erfelijke Tumoren: Richtlijnen voor diagnostiek en preventie*.
- Van der Laan, A., Boenink, M., 2015. Beyond bench and bedside: disentangling the concept of translational research. *Health Care Anal.* 23 (1), 32–49.
- Van der Zee, J., Kroneman, M., 2007. Bismarck or Beveridge: a beauty contest between dinosaurs. *BMC Health Serv. Res.* 7(94).
- Van Hoyweghen, I., 2014. On the politics of calculative devices. *J. Cult. Econ.* 7 (3), 334–352.
- Vignola-Gagne, E., Biegelbauer, P., 2013. Translational research. In: Carayannis, E. (Ed.), *Encyclopedia of Creativity, Invention, Innovation and Entrepreneurship*. Springer, New York, pp. 1834–1843.
- Woolf, S., 2008. The meaning of translational research and why it matters. *JAMA* 299 (2), 211–213.
- Zylka-Menhorn, V., 2013. Jeder Fall ist Anders zu Bewerten. *Dtsch. Arztebl.* 110 (21), 1020.