Introduction

We finalize this book on the 'time of BRCA' at a pivotal moment in the history of breast cancer genetics. The BRCA genes are configured amidst dynamically interacting medical, scientific, cultural, socio-political and economic parameters, which are essential to understanding this continually evolving terrain.

Using BRCA as a case study, this book sheds light on transformations that are occurring in the wider field of genomic science and medicine as a result of new technological possibilities, transnational research collaborations and ever-widening parameters and definitions of risk. Our focus on time-economies illustrates how temporal notions of past, present and future are built into genomic developments, and as such facilitates a re-reading of core concepts like risk, prevention, kinship and heredity. We begin, however, by highlighting some key recent developments in the field of BRCA genetics that illustrate this shifting terrain.

The first and perhaps most highly anticipated development is the recent US Supreme Court decision regarding the patentability of genes. The two breast cancer genes BRCA1 and 2 were sequenced in the mid 1990s through the efforts of multiple international research teams, and shortly thereafter patented by one of the US teams managed by Mark H. Skolnick, co-founder of Myriad Genetics Inc. (Salt Lake City, US). Since then, debates about the commercialization of biological knowledge and the proliferation of the ownership of genes have continued to be highly controversial. In June 2013, the US Supreme Court announced their decision to outlaw patents on naturally occurring genes (but not on cDNA) putting an end to Myriad Genetics' long-held and contentious monopoly on BRCA testing in the US (see van Zimmeren *et al.*, this volume).[1] Significantly, several companies that were already providing genetic testing of other genes associated with breast cancer were ready to launch their own BRCA tests the day after the decision was announced (e.g. see the Ambry press release the day of the Supreme Court Announcement, www.ambrygen.com/press). The defeat of Myriad's patent monopoly could make genetic testing without threat of litigation more financially feasible and therefore a more widespread option, or lead to an increase in research by groups previously hindered by concerns about patent infringement. Of course, the ramifications of the court's decision both inside and outside the US remain to be seen, and may take years to fully unfold while also having repercussions in global arenas.[2]

Second, the emergence of Next Generation panel tests (e.g. Ambry Genetics' BreastNext panel and the University of Washington's BROCA panel), and the increasing turn towards whole genome/exome sequencing, signals another change in the landscape of genetic testing. Next Generation panel tests, which became commercially available in 2011, examine numerous genetic changes associated with elevated breast cancer risk, including those that confer moderate and relatively low risk. As Next Generation testing becomes more widely available and financially feasible (some of the panel tests cost approximately the same as or less than Myriad's BRCA test), the criteria for testing related to hereditary breast cancer syndromes will likely widen. At the same time, the decreasing cost of whole exome/genome sequencing will likely have even broader implications, as in the future individuals may have their entire genomes sequenced rather than portions of it (such as the BRCA genes only). One potential consequence is that many more individuals will learn they carry a BRCA mutation (and many other disease-associated mutations) as a result of sequencing carried out for some other purpose – a scenario that is directly explored by Sandra Lee in this volume, in the context of BRCA testing in the direct-to-consumer setting. While Next Generation panel tests and advanced sequencing technologies predate the recent Supreme Court decision on gene patents, they will likely be informed by this decision in complex ways, thereby paving the way for expanded and broader BRCA testing. This constantly changing technological landscape which now includes whole genome sequencing has exponentially increased the initial concerns raised by BRCA testing, such as those regarding privacy, incidental findings, variants of unknown significance and return of results (Green *et al.* 2013; Kohane, Masys, and Altman 2006, Pyeritz 2011).

Third, BRCA genetics has been and continues to be a test case in the field of genomic medicine (Gibbon *et al.* 2010b; Palfner 2009): a symbol of 'success' whilst also being at the forefront of challenging the new genetics. Nevertheless, in thinking about BRCA as a barometer for the shifting space and evolving trajectory of predictive medicine, it is important to stress the gendered and gendering nature of these medical interventions that are aimed primarily at women (such as the prophylactic removal of breasts and ovaries; also see Pelters, this volume). Thus as BRCA evolves and spreads into new medical arenas, women continue to find themselves the subjects of increasing medical and scientific practices. These dynamics coexist with well-established medical practices aimed at women such as annual gynecological exams and mammographic screening programmes, and are entangled with deeply gendered life-worlds in which women function as 'genetic housekeepers' (Richards 1996: 261). Furthermore, if we consider BRCA genetics to be a test case in the field of genomic medicine, then women are the experimental field on which such endeavors are taking place (Gibbon *forthcoming;* Happe 2006, 2013; Palfner 2009).

We can see the intersection of gender and genomics with the recent high-profile announcement by Hollywood star Angelina Jolie in a New York Times op-ed that she had undergone a preventive double mastectomy due to a 'faulty' BRCA1 gene, bringing BRCA genetics to international attention. Jolie's decision was particularly striking given her status as an international sex symbol, and contributed to

increased interest in testing among many women around the world. Indeed, those of us based in cancer centres can attest to 'the Angelina effect': the increased volume in calls and inquiries from members of the public following the announcement. On the other hand, media debate, and the comments from readers of the *New York Times* and many other news outlets took up questions about access to the test and the recommended screening and prevention practices (Jolie's announcement arrived just weeks prior to the Supreme Court's decision on Myriad's patents), and about the appropriateness of 'proactive' measures like the preventive double mastectomy surgery that Jolie had. Jolie's announcement about her decision thus provoked polemical discussion about prevention and risk reduction, access to testing, gene patents the options available to women identified at risk in this way, and in some cases, the right 'not to know' about genetic risk. Her announcement serves to both highlight the way that gendered idioms of female nurturance and empowerment continue to be central to this domain, and the ongoing impact of BRCA on women.

These developments and the recent intense media attention to BRCA that has resulted provide an opportune moment for us as social scientists to engage and explore the shape-shifting present and future terrain of BRCA genetics. The confluence of events, while each of a different scale and magnitude, has heightened interest and attention to genetic testing for hereditary cancer and related matters. This book thus provides a timely contribution which reflects on the diverse socio-cultural spaces as well as the scientific and medical practices that constitute genomics in the era of BRCA.

BRCA histories

The identification of the BRCA genes in the mid 1990s was accompanied by an enormous amount of expectation, hype and hope, and swiftly led to the establishment of predictive genetic testing and specific medical programmes for those at high risk of developing breast cancer in many countries, particularly the US, Canada and Europe. Carriers of mutations in the BRCA genes are thought to have a higher risk of breast and ovarian cancer, although risk estimates vary from 45–80 per cent for breast (compared to 10 per cent for an average woman) and 10 to 60 per cent for ovarian cancer (compared to 1.8 per cent for an average woman). While they do not account for the majority of breast cancers, BRCA mutations are thought to be responsible for 5 to 10 per cent of breast cancers. Although BRCA1 and 2 have been primarily discussed in the context of familial breast and ovarian cancer, since their initial identification there has been a concurrent hope that the knowledge gained from BRCA research would have relevance for, and be transferable to, the treatment of sporadic breast cancers, which affect many more women than the rare instances of familial breast cancer (Palfner 2009). However the establishment of a robust connection between the clinical utility of BRCA and the sporadic cancer domain emerged only recently, in 2004–2005, when the concept of 'BRCAness' took hold, as discussed by Bourret and co-authors in this collection.

Since their discovery, the medical institutionalization of BRCA knowledge-practices and accompanying techniques for assessing risk have advanced at a rapid pace, involving different scientific or medical specialties, routinizing programmes of genetic testing, developing risk assessment for breast cancer and increasing health management options for those identified at increased cancer risk. The availability of BRCA samples obtained through programmes of genetic testing and risk assessment has facilitated further research (Gibbon *et al.* 2010b; Mozersky 2013; Palfner 2009), illustrating the mutually constitutive interactions between BRCA research and clinical practices. The emergence and use of BRCA genetic knowledge in clinical settings has raised questions about the social consequences of genomic information for 'patients', family and their kin as well as the scientific and clinical utility of novel knowledge of genetic risk for breast cancer. Social scientists have studied these developments in different countries from diverse perspectives, which include: examining the historical dimensions of genetic research and the related medical practices or the laboratory life that surrounds novel techniques linked to BRCA genetics (Bourret, 2005; Löwy, 2010; Palfner, 2009; Parthasarathy, 2007); analyzing the social consequences for health, identity and perceptions of risk for women undergoing assessment in cancer genetic clinics (Gibbon, 2007; Hallowell, 1999; zur Nieden, 2010, 2013) or comparing the cultural and institutional specificity of these developments, demonstrating the unevenness of the complex global intersections that are forming across a diverse field of genomic knowledge and technology (Gibbon *et al.* 2010a, Gibbon 2013; Mozersky and Joseph 2010; Shkedi-Rafid *et al.* 2012).

While the medical and laboratory practices surrounding the BRCA genes expand, their scientific and medical bases, on the other hand, continue to raise questions. In fact, very shortly after the sequencing of BRCA1 and 2, predictive genetic testing made it apparent that very few people actually carry the BRCA1 or BRCA2 mutations (5–10 per cent as previously mentioned), and many mutations were found in families without increased incidences of breast cancer. This variability in risk and penetrance estimates reflects gaps in medical knowledge about the BRCA genes which are based on databases of known mutations and previously identified 'at risk' families and/or populations. This variability has become increasingly apparent particularly in national contexts outside the US, Canada and Europe (see Mozersky and Gibbon, this volume), and highlights the role of nongenetic and epigenetic factors in determining risk.

At the same time, the BRCA genes have led to new avenues of medical research, particularly in the use of genetic technologies for the diagnosis and treatment of breast cancer (e.g. clinical trials of targeted drug therapies for BRCA mutation carriers; see also Section 3 in this volume) and raised questions concerning the medical management of female mutation carriers and women at high risk, such as the effectiveness of mammography, the benefits of tamoxifen in chemoprevention and prophylactic mastectomy. Thus this field of medical practice and scientific engagement continues to evolve, in part as a response to the *limitations* of BRCA genetic testing. In this sense, breast cancer genetics provides a vital arena for examining how scientific stability or transition is achieved in different contexts,

for example from lab to clinic or from BRCA genetics to other research arenas (e.g. epigenetics, 'Next Generation' panel testing and whole genome/exome sequencing). In other words, BRCA shifts and spreads in various directions far beyond the very limited medical programmes for familial breast and ovarian cancer.

Time-economies

As the title of this book and the chapters within indicate, we are living in the time of BRCA. In this sense, BRCA not only stimulates enormous research and pushes it in various directions; it also reconfigures the life-worlds of many women (and men), enhances specific medical programmes and puts economic, legal and ethical issues on the agenda of many health care systems. However, BRCA genes do not hold innate agency or power; rather as Palfner (2009), drawing on Haraway (1997) and Latour (2004) suggests, we should understand BRCA as an assemblage. For Haraway (1997: p. 142), 'a gene is not a thing, much less a "master molecule" or a self-contained code but rather the term gene signifies a node of durable action where many actors, human and nonhuman, meet'. Latour (2004: p 233) underlines that the word *thing* also means 'assembly': 'A thing is, in one sense, an object out there and, in another sense, an issue very much in there, at any rate, a gathering'. In terming the breast cancer gene an assemblage, we aim to heighten awareness of how it orchestrates and performs biomedical practices, stimulates socio-political discourses and connects various medical and research arenas through times and spaces, as the essays throughout this volume demonstrate.

Temporality is a theme that weaves through all three sections of the collection, from looking back at history and genealogy (Section I), to the ways in which risk is embodied and lived in the present (Section II), to the changing landscape and future developments of BRCA testing (Section III). While the principal aim of this book is to give an overview of BRCA research and medical practices in different countries, the contributing authors also analyze the theme of temporality as it emerges in the varied contexts they explore. The political scientist Wolf-Dieter Narr reminds us that time is a social product and intersects with relations of power: 'Ruling power is always characterized by its own calendar, its own hierarchy, its own assignment of time and its own quality of this assigned time, regardless of whether every ruling power, such as the brief rule of the Jacobins during the French Revolution, literally had their own calendar' (2003: 239; author's [SP] own translation). In other words, time itself is heterogeneous and performative, and we suggest that living in the time of BRCA should encourage us to take into account time itself and recognize that understanding time is a precondition for better understanding the ongoing research and multiple medical practices related to BRCA. Thus, we think it is appropriate to speak about BRCA 'time-economies', seeing these as social matters and hence infused with power in different ways and making it vital to understand more deeply the interplay of various temporalities.

In the context of biomedicine, the matter of time materializes clearly in the notion of disease prevention. In her commentary (this volume), Martina Schlünder argues that the most important epistemic change from medicine to biomedicine is

the reconfiguration of the relation between the normal and the pathological with an increasing emphasis on health instead of disease (Clarke *et al.* 2010; Keating and Cambrosio 2003). The prevention of diseases is now seen as one of the most urgent tasks in medicine as opposed to limiting actions to the treatment of pathological events that have already happened (in an unalterable past) or are still ongoing in the present. According to Adams *et al.* (2009: 248), disease prevention and predictive medicine are practices that occur in a mode of anticipation and the attempt to envision, control and manage the future and its risk of possible pathological events: 'Crucially, the future increasingly not only defines the present but also creates material trajectories of life that unfold as anticipated by those speculative processes. Anticipation is rapidly reconfiguring technoscientific and biomedical practices as a totalizing orientation.' Following this, we begin to understand the discursive power to name genes 'breast cancer genes'. On the one hand, BRCA1 and 2 are understood as tumor suppressor genes, with a single germ line mutation increasing the risk for developing breast and/or ovarian cancer; such genes thus protect cells from one step on the path to cancer. On the other hand, to call a gene a 'breast cancer gene' implies the opposite, namely that this gene is responsible for the cancer and carrying the gene means having cancer. In other words, this overlap of the pathological and the normal rolls out through the anticipation of breast cancer in the gene.

This unfolding in the identification of 'risk' for breast and ovarian cancer via BRCA testing has resulted in the normalization of preventive procedures (Robson *et al.* 2010) such as prophylactic mastectomy and *prophylactic oophorectomy* (see Pelters and Gordon, this collection, for discussions of prophylactic mastectomy), *chemoprevention* as well as Preimplantation Genetic Diagnosis (PGD) to screen embryos at risk of carrying a BRCA mutation (Rubin and de Melo-Martin, this volume). Although the acceptance and use of these preventive measures varies significantly within and across national contexts, these practices must be situated within this biomedical maelstrom in which prospective diseases are pushed into the present and thereby have a major impact on present life-worlds including the meaning of patienthood and cancer survivorship (Bell 2013).

The increasing focus on prevention in biomedicine shows up in BRCA-related practices in other ways too. In some instances, the shift toward prevention is constituted by a move toward wider screening for deleterious BRCA mutations in particular populations. For example, a recent study of African American women with breast cancer which found high rates of deleterious mutations in BRCA and other 'breast cancer genes' (e.g. CHEK2, PALB, PTEN) suggested screening for all these genes in women of African descent with breast cancer diagnosed at a young age, with a family history, or with triple negative breast cancer (Churpek *et al.* 2013). In both Israel and Canada, population-wide screening of all Ashkenazi Jews (regardless of family history) has been proposed as a viable method to identify BRCA carriers who might not otherwise come to clinical attention (Levy-Lahad *et al.* 2011; Metcalfe *et al.* 2009). On another track, public health scientists and practitioners in the US are making efforts to identify potential BRCA carriers prior to a diagnosis by screening – in both clinical and community settings – for

family history and appropriate referrals to genetic counseling (rather than genetic testing) for a full assessment of BRCA risk (e.g. Bellcross *et al.* 2009; Joseph 2012 and this volume). Thus the categories of who is at risk continue to encompass more and more people, in the name of prevention, as does the notion of being at risk for breast cancer itself.[3] In other words, the enormous potential for BRCA research to be applied to a wide range of arenas of medical research and treatment and to incorporate different clinical disciplines has made and continues to make BRCA genetics significant.

The shift toward prevention also reflects breast cancer activists' and researchers' increasing attention to the causes of breast cancer rather than only treatment and survivorship. While some argue that treatment for breast cancer has improved over recent decades in terms of the survivorship rates, others suggest this is due to overdiagnosis (e.g. Esserman *et al.* 2013). Most agree, however, that the treatments themselves remain terribly damaging with enormous side effects. As a result, the goal of preventing breast cancer in the first place has become more prominent in certain national contexts. In addition, the failure to identify the causes of breast cancer to date, particularly the environmental factors that contribute and may intersect with hereditary susceptibility, is recognized as a huge barrier to reducing morbidity and mortality due to breast cancer – and as a failure of the research community. The politics of environmental pollution and the lack of regulation of polluters has also become a target for activists, particularly in the US, who have shifted their focus to prevention as discussed by Kirsten McHenry in her paper at the Brocher Conference where this volume originated (not included in this volume; see also BreastCancerAction.org).[4] While epigenetic research holds out the promise that the parameters of research related to prevention of breast cancer may eventually encompass a more biopolitical framework that addresses collective responsibilities for disease and health, this is unlikely to mean the disappearance of individualized framings of risk. As Landecker and Panofsky (2013) point out, this may in fact paradoxically entail an intensification of the moral framing of gendered health responsibilities given that the 'critical windows' at stake in epigenetic research often relate to nutrition in early childhood and maternal-fetal health exposures (see also Mansfield 2012).

Transnational perspectives

By offering perspectives on the transnational arenas in which BRCA genetics is now evolving, this collection directly responds to the vital need for social science to engage with genomics in the context of globalizing health care agendas *and* local moral worlds of practice. Some of the chapters directly take up the task of providing a comparative perspective with reflections on the way that for instance the so called 'Ashkenazi mutations' associated with the BRCA genes are being configured differently in Brazil and the UK (Mozersky and Gibbon) and in Germany (zur Nieden). The varying ways that questions of race and ethnicity are being drawn into the developments surrounding breast cancer genetics are also highlighted in the contrasting perspective on these issues provided by

papers reflecting how different national histories concerning the politics of inclusion and discrimination play out in Germany (zur Nieden) and the US (Joseph). For example, in Germany, the history of racial hygiene and the Holocaust as well as a specific tradition of perceiving the nation as 'ethnically homogenous' continue to have an effect on contemporary medical discourse. In the US, historical and ongoing discrimination experienced by African Americans affect how risk of genetic breast cancer and interventions may be viewed. Other chapters in this volume provide a reflection on the space which BRCA occupies, or rather does *not* occupy in contexts such as India (Macdonald) and Italy (Gordon), providing an important reminder of the 'absent spaces' that BRCA also constitutes. In Alison Macdonald's discussion, we see how this absence relates to overwhelming socio-economic challenges and lack of resources in treating those with breast cancer, but also very specific beliefs about disease risk and its transmission between gendered bodies, as well as 'biomoral' concerns around family relations. Deborah Gordon similarly reminds us of the way a comparative perspective can illuminate the diverse routes through which BRCA has emerged. Gordon highlights how discourses of disease risk related to BRCA genetics and the temporal anxieties they have provoked elsewhere (especially the US) have not resonated in Italy where different cultural logics of 'risk' are at play. This is reflected, for example, in the limited institutionalization of some BRCA medical practices such as prophylactic mastectomy in the Italian context.

At our Brocher workshop, we were fortunate to have participants who offered further contrasting reflections on the way that BRCA research and medical practices were evolving in Greece, Israel and Uruguay, providing additional illuminating and invaluable perspectives not present in this volume. Eirini Kampriani's work in Greece has been and continues to be central to discussions in the BRCA group (see Kampriani 2009). Her presentation at the Brocher meeting showed the complex ways that religious philanthropy and gendered ideologies have been a key dimension of BRCA medicine in Greece against a backdrop of limited and finite public health resources – an issue that is also addressed in a number of papers in the collection concerning BRCA genetics in India (Macdonald) and Brazil (Mozersky and Gibbon). Shiri Shkedi-Rafid provided fascinating perspectives on the field of BRCA in Israel where the prospect of identifying BRCA carriers through population screening of Ashkenazi Jewish individuals without a family history is emerging as a viable avenue of intervention. Her work on the meaning of 'carrierness' for those identified in this way has important implications, particularly given the expanded possibilities of Next Generation sequencing for identifying individuals with BRCA mutations without a significant family history (Shkedi-Rafid *et al.* 2012). Finally, Ana Egana's work as part of a transnational collaborative initiative in Uruguay examined the relationship between ancestry and breast cancer. She highlighted the extent to which, for participants and also local researchers in Uruguay, socio-economic factors rather than ancestry per se were as important if not sometimes more relevant in perceptions of disease risk, raising important challenges to the homogenizing potential of global research paradigms, an issue that is also discussed by Mozersky and Gibbon.

Challenges of being engaged/positioned/situated in our research fields

In the course of our discussions at Brocher, one of the themes that recurred was our own embeddedness in the medical and scientific field of BRCA genetics. As social scientists analyzing, engaging and sometimes even collaborating with what has become a multi-million-dollar industry that is now expanding across a global terrain of medical practice and scientific research, there is an awareness (for some uncomfortably so) that our own research trajectories have been informed (and in many cases funded) because of the high public profile that BRCA genetics continues to garner. As Haraway (1988: 581) pointed out, there is of course no view 'from nowhere' and we are all necessarily 'situated' by working in the domain of BRCA genetics, whether we carry out research at the clinical interface, in the laboratory or with patient or activist populations. Entering and acknowledging the complexity of our situatedness in the context of interdisciplinarity or collaborative research is part of the challenging task of social scientists examining developments in the life and medical sciences, and one that others have begun to address. Prainsack and colleagues (2010) note the ever-present ambiguity of conducting social science research in such settings, highlighting the challenges of creating the space for critical social science perspectives and negotiating differences in authority and the legitimacy of contrasting methodological approaches. Barry *et al.* (2008) suggest the need for a more complex understanding of interdisciplinarity and stress that interdisciplinarity has diverse histories and can take a multiplicity of forms. They interrogate how different modes of interdisciplinarity come into play and intersect, and raise valuable questions about the conditions under which particular styles of interdisciplinary practices appear and the ways they inform the outcomes of scientific knowledge production.[5] Drawing on their approaches and reflecting on our own embeddedness as social science researchers in the field of BRCA genetics the following questions emerge: When – or even – is it possible to reach a synthesis of natural scientific and social scientific knowledge? Under which conditions does our own social science research function in a 'service-mode' to facilitate the research goals of the life and medical sciences? And how can the existing disciplinary epistemological and ontological assumptions be contested in such interdisciplinary collaborations? While these issues are implicit in many of the chapters presented, the questions raised about the ethics and politics of doing social science research at the interface with BRCA genetic research remain ongoing challenges that are of central interest to a number of the book's contributors, and which we suggest are crucial to social science research more generally in the field of genomic science and medicine, beyond BRCA.

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The book is organized across three sections interspersed with a foreword from Rayna Rapp, commentaries from Nina Hallowell and Martina Schlünder and an afterword from Susanne Bauer, all of whom who we were fortunate to have in attendance at the Brocher workshop. The first section, 'Practices of population

politics and history in the production of BRCA', brings together three papers that place concerns with temporal pasts and presents centre stage. Collectively these papers tease out some of the complex questions concerning genetic research and categories of race/ethnicity and populations in the context of BRCA genetic research and medical interventions in different national contexts and/or for various 'under-served' populations. The second section, entitled 'Risk, personhood and subjectivity', provides the framework for three papers that consider core issues of politics, gender and identity in the way that BRCA research and medical practice is enacted, whilst also importantly revealing the spaces where it is absent or resisted. The third section of the book, 'Shifting terrains of BRCA knowledge and practices', brings into view the emerging horizons of this dynamic domain of genetic research as it becomes incorporated into direct to consumer testing, translational research and pre-implantation diagnosis and is informed and potentially transformed by the recent decision in the US on the patentability of genes.

Notes

1. cDNA is complementary DNA and refers to a form of DNA that is artificially synthesized.
2. Within weeks of the Supreme Court decision, Myriad sued two competitors (Ambry Genetics and Gene by Gene), who began offering BRCA testing claiming violation of some of their remaining patents not invalidated by the Supreme Court (*New York Times*, July 10, 2013, www.nytimes.com/2013/07/11/business/2-competitors-sued-by-genetics-company-for-patent-infringement.html). At the same time, Myriad has pledged that it 'will not impede non-commercial, academic research that uses patented technology licensed or owned by us'. (www.myriad.com/responsibility/myriads-pledge/)
3. See for instance the new UK NICE guidance on the preventative use of Tamoxifen or raloxifene for those with a family history of breast cancer as part of a strategy of chemoprevention. The same guidelines have suggested reducing the threshold for BRCA genetic testing for women from 20 per cent chance of having a BRCA gene mutation to 10 per cent, greatly widening the number of women eligible for genetic testing in the UK (www.nice.org.uk/newsroom/news/MoreTreatmentOptionsWomenRiskBreastCancer.jsp)
4. See Preface.
5. Barry *et al.* 2008 suggest three difference interdisciplinary modes – *integrative-synthesis* mode, *subordination-service* mode and *agonistic-antagonistic* mode.

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