

Biobanking for Public Health

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Abstract Genome-based biobanking requires a new governance model which integrates the personal values of the people concerned, the medical knowledge necessary to define a “genomic indication” as well as the procedural law which enables those professions and families involved to make an ethically and legally acceptable prioritisation of dissenting interests in genomic services and data. Thus, almost all healthcare systems are currently facing fundamental challenges. New ways of organizing these systems based on genomic health information and technologies and stakeholders’ different needs are essential to meet these challenges in time.

The issue of biobanking has become a specific challenge having major implications for future research and policy strategies as well as for the healthcare systems in general. The various stakeholders in public health play a key role in translating the implications of genome-based research deriving from biobanks for the benefit of population health. In setting the epidemiological research agenda, in balancing individual and social concerns, by promoting meaningful communication about genomics among researchers, professionals, policymakers, public health agencies, and the public, public health organizations will enhance the potential return on public investment in genomic research. Whereas medicine is currently undergoing remarkable developments from its morphological and phenotype orientation to a molecular and genotype orientation, promoting the importance of prognosis and prediction, the discussion about the role of genome-based biobanking for public health still is at the beginning.

The following chapter contributes to this discussion by focussing on the use of genome-based biobanking for public health research, surveillance systems, health policy development, individual health information management and effective health services.

1 Introduction

The development of target-oriented health promotion, prevention and new treatments in common complex diseases requires the elucidation of the molecular processes involved, the understanding of the causal pathways and the establishment of predictive and diagnostic patterns. To date, epidemiological research and public health practice have been concerned with environmental determinants of

health and disease and have paid scant attention to genomic variations within the population as well as between populations. The advances brought about by genomics are changing these perceptions (Peltonen and McKusik 2001, Khoury 1997). Many predict that this knowledge will not only enable clinical interventions but also health promotion messages and disease prevention programmes to be specifically directed and targeted at susceptible individuals as well as subgroups of the population, based on their individual genomic profile and risk stratification. For example, nowadays, it is known that coding variants in DNA determine not only the cause of single-gene disorders, which affect millions of people worldwide, but also predisposition (“susceptibility”) (Baird 2000), based on genotype and haplotype variants (Lai et al 2002, Gibbs et al 2002, Probst-Hensch et al 1999), to common complex diseases. The new technologies will allow researchers to rapidly and comprehensively investigate the whole human genome at the level of individual genes (Gutmacher and Collins 2002). Furthermore, there will also be a better understanding of the significance of environmental factors such as chemical agents, nutrition or personal behaviour (Antonovsky 1987) in relation to the causation not only of diseases like osteoporosis, cardiovascular diseases (Sing et al 2003), cerebrovascular diseases, cancer and diabetes, which account for 86% of all deaths and 77% of burden of disease in Europe in 2005, but also of psychiatric disorders, allergies and infectious diseases (Dorman and Mattison 2000, Little 2004, Brand and Brand 2005).

In the past, there had been a narrowed focus looking mainly at the role of inheritance in monogenetic diseases and genetic testing for more than 1000 diseases in that context (human genetics setting). At present, the role of genetic susceptibilities and other biomarkers in common complex diseases is discussed (medical, community health as well as public health setting). In the future, the focus will be even broader by looking at genome-phenomena data sets (Barabasi 2007) and analyzing the role of genomic variants together with other health determinants such as social or environmental factors in health problems (public health setting).

Thus, regarding the understanding of diseases the following “trend” due to novel genome-based knowledge can already be identified (Barabasi 2007, Motter et al 2008, Loscalzo et al 2007, Lunshof et al 2008): recent advances in systems and network biology indicate that specific cellular functions are infrequently carried out by single genes, but rather by groups of cellular components, including genes, proteins, and metabolites. Such a network-based view changes the way of thinking about the impact of mutations and other genomic defects: the damage caused by malfunctioning protein or gene is often not localized, but spreads through the cellular network, leading to a loss of cellular function by incapacitating one or several functional modules (“diseasomes”). New technologies and experimental tools support the systematically mapping of various cellular interactions while enabling to focus not only on the individual components, but also to monitor and analyse the global changes in the cellular network induced by the defective gene or protein. This results in the death of the organism, a finding that may be useful for the design of antibiotics or cancer drugs. Yet for most (genetic) diseases the goal is

not to kill the cell, but to recover the lost cellular function or limit the existing damage by asking whether network-based strategies can be developed to predict how to recover function that may have been lost due to defective genes. Research is already starting to change nosology. Seemingly dissimilar diseases are being lumped together. What were thought to be single diseases are being split into separate ailments, i.e. “diseasomes”. Just as they once mapped the human genome, scientists are currently trying to map these diseasomes (Barabasi 2007, Motter et al 2008), which can be defined as the collection of all diseases and the genes associated with them. Thus, we are in a unique position in the history of medicine to define human disease precisely, uniquely and unequivocally. It is only a matter of time until these advances will start to affect medical practice as a new field such as “network medicine”. The purpose of this perspective is to provide a logical basis for a new approach to classifying human disease that uses conventional reductionism and incorporates the non-reductionist approach of systems biomedicine. What would be the potential of such a systems-based network analysis for the understanding of diseases and their treatments? Loscalzo, Kohane and Barabasi recently identified at least five benefits of the disease network analysis (Loscalzo et al 2007):

1. It can identify those determinants (nodes) or combinations of determinants that strongly influence network behaviour and disease expression or phenotype.
2. It provides unique insight into disease mechanism and potential therapeutic targets.
3. It provides the opportunity to consider the interaction within the network genome, environmental exposures and environmental effects on the posttranslational proteome that define the specific pathophenotype. Thus, disease can be understood as the result of a modular collection of genomic, proteomic, metabolomic and environmental networks that interact to yield the pathophenotype.
4. It provides a mechanistic basis for defining phenotypic differences among individuals with the same disease through consideration of unique genetic and environmental factors that govern intermediate phenotypes contributing to disease expression.
5. It offers a notably method for identifying therapeutic targets or combinations of targets that can alter disease expression.

Overall, the approach offers a novel method for human disease classification, since it defines disease expression on the basis of its molecular and environmental elements in a holistic and fully deterministic way. Although the application of these principles to specific diseases is still in its infancy, the early concepts are internally consistent and the results are encouraging. In addition, the integration of genome-based knowledge into epidemiological and public health research, policies and health services for the benefit of all can be considered as one of the most important future challenges that our health care systems will face (Barabasi 2007, Lunshof et al 2008, Collins et al 2003, Childs and Valle 2000, Collins and McKusick 2001, Burke 2003, Ellsworth and O’Donnel 2004).

Besides that novel biomedical knowledge, also accompanying novel technologies are already triggering the shift in the comprehension of health and disease as well as in the understanding of new approaches to prevention and therapy (Khoury 1996, Brand 2002a, French and Moore 2003). For example, high-throughput and next generation technologies such as tissue microarrays (so-called TMAs) have the potential to screen large numbers of molecular targets in tumor samples for rapid causal, prognostic, diagnostic or therapeutic purposes (Torhorst et al 2001). Complementary to the conventional microarray gene expression profiling, population-based TMAs can be implemented to quickly validate gene expression microarray data in a larger and unselected population of tissue samples (Hoos et al 2001). Through population-based TMAs, it will be possible to assess multiple genomic and protein differences among malignancies such as colorectal cancer, breast cancer, gliomas or rhabdomyosarcoma and thus studying the molecular and cytogenetic changes associated with these malignancies, including human carcinogenic infections (Kononen et al 1998).

Another example of the potential of novel genome-based technologies is the use of nano-chips, which allow the detection of gene activity and genomic pattern by measuring messenger RNA (mRNA). By this, it will be possible to predict with higher accuracy and even quicker the response to certain therapies such as interferon therapy.

One of the key questions in all health care systems is whether “the right” interventions and services are provided by the various stakeholders: are the current public health strategies evidence-based? That is, are we assuring the “right” health interventions and innovations (based on combined concepts of health needs assessment and health technology assessment) in the “right” way (based on concepts of quality management and policy impact assessment) in the “right” order and at the “right” time (based on concepts of priority setting and health targets) in the “right” place (based on concepts of integrated health care and health management)?

There has been almost no systematic integration of genome-based knowledge into all of these concepts so far. Current public health strategies are therefore lacking important evidence-based aspects. Thus, with regard to genomics the public health agenda demands a novel vision that reaches beyond the research horizon to arrive at application and public health impact assessment of this novel technology (Brand and Brand 2005, Yoon 2001).

2 The Role of Genome-based Biobanking for Epidemiological Research

The definition of biobanking is very wide and has a twofold character comprising both samples and data. Since biobanks cover therapeutical and population-representative biobanks like blood and tissue banks, including umbilical cord blood banks, semen banks as well as organ collections, they can be defined as collec-

tions of samples of human body substances (e.g. cells, tissue, blood, or DNA) that are or can be associated with individual data and information such as clinical, socioeconomic, demographic, lifestyle, behavioural and environmental health determinants.

Biobanking not only allows to store probes of the human body, it also assures the standardisation of sampling processes and data collection. By this, target-orientated preventive, diagnostic and therapeutic interventions can be developed to promote personalized medicine and health care. In the long run, this will result in the provision of more effective and efficient health services.

Furthermore, the already mentioned rapid development of biotechnological research such as population-based TMAs as well as bioinformatics has stimulated the use of biobanks. Although it has been recognized that population-based data on genome-disease and genome-environment interactions are the primary point for assessing the added value of genome-based information for all health interventions in the different health care settings, this approach is not new at all. Human body substances of all kinds have been collected, stored and used for a variety of purposes for many years. Large epidemiologic cohort studies such as EPIC (European Prospective Investigation into Cancer and Nutrition), ARIC (Atherosclerosis Risk in Communities) (ARIC 1989), ALSPAC (Avon Longitudinal Study of Parents And Children), ISAAC (International Study of Asthma and Allergies in Childhood), EUROCAT (European Surveillance of Congenital Anomalies) or various cancer registries and neonatal screening programmes (e.g., in Denmark or Western Australia) have already been able to perform genotyping to expand their existing databases for studying disease incidence and prevalence, natural history and risk factors (Peltonen and McKusick 2001). In addition, large cohort studies such as in the UK (Wright et al 2002) or even involving whole populations such as in Iceland or Estonia (Hakonarson et al 2003) have been initiated to establish repositories of biological materials for the study and characterization of genomic variants associated with common diseases. These biobanks will allow quantifying the occurrence of diseases and risk patterns in various populations and subpopulations as well as to understand their natural histories and risk factors, including genome-environment interactions (Khoury, Little and Burke 2004, Khoury et al 2004).

Nevertheless, the majority of existing biobanks are still relatively small collections of tissue samples related to specific diseases such as cancer. They have been established, for example, in university departments (e.g., in clinics for pathology) or in cancer registries and contain a few hundred up to a few thousand human biospecimen. These biobanks will remain important in the future. But in addition large-scale population-based biobanks have to be established enabling research not only to study single diseases but also “diseasomes” based on individual genome-phenomena data sets (Loscalzo et al 2007, Lunshof et al 2008) and also approaches to a wide range of other health-related issues.

In most countries, besides poor access to human biospecimen, one major bottleneck for large-scale biomedical research is the fragmentation of biorepositories. Biobanks may be organized in different clinical settings, in the public sector or in

pharmaceutical companies. Irrespective of the responsible institution for biobanking, they may be funded from public or private resources and they may also have been established and used to serve a variety of interests – for instance, purely scientific interests, the interests of donors or commercial interests.

In addition, for most common complex diseases, the collection of body samples for genome-based association studies has often been retrospective in nature and has also been limited to cases of a particularly pronounced phenotype, or with a strong family history. But in order to be able to evaluate the relative risk of a given genomic variant retrospectively from case-control studies, its background frequency in the sample population must be known. Thus, there is a need to recruit large samples of unselected controls from the populations of interest as well as to extend the common cross-sectional or retrospective ascertainment of phenotypes for the prospective follow-up of at least a subset of cases, defined for example by an incidence cohort.

This means that on the one hand long running cohort studies – starting as early as possible in life and including nested case-control studies at various ages and at various occasions – have to be established. This will be a costly, long-lasting, but nevertheless essential public health task. On the other hand another – less costly and less time-consuming – public health task could be the implementation of case-control studies in the very old population to generate hypotheses on genomic-environmental associations, on epigenomic effects as well as on pleiotropic effects.

One specific biobank which has not often been recognized in most countries as an already existing nationwide genome-based biobank is the newborn screening. It has been established for decades in the public sector, in private hand or in public private partnership. Recently, not only the possibility of reanalysing up to 25-year-old Guthrie cards has been discussed. There will be a discussion about shifting from newborn screening exclusively on metabolic diseases to a DNA-based newborn screening for genomic variants as well. A major point of societal discussion will be the question for which validated genomic variants, in addition to metabolic diseases, should newborns be tested for in the future. Should they be screened for complex diseases with the highest burden of disease (e.g., for cardiovascular diseases, cerebrovascular diseases, diabetes, cancer and osteoporosis accounting for 77% of burden of disease in 2005 in Europe), or for orphan diseases (accounting for 10% of all diseases in the whole population and having involved highly validated genomic variants) by developing a resequencing chip for orphan diseases?

Based on these needs the future challenges for biobanks with respect to epidemiological research and public health are comprehensive as well as manifold. They include the promotion of public private partnerships, the linkage of records (e.g., perinatal quality assurance programs, hospital discharge data, data from registries) with data from (genome-based) samples in addition to population-based (mega)biobanks. They also include the integration of genome-based information into the many already existing population-based surveillance systems such as into surveillance systems for infectious diseases, congenital malformations or even into

health observatories and the integration of genome-based knowledge into future surveillance systems covering health problems and linking individual information during the whole lifespan (record-linkage based surveillance). Thus, genome-based biobanks can be used as a basis for individual genomic profiling as well as a tool for individual health information management.

Population-based data on genome-disease association and genome-environment interaction form the basis for studying the added value of genome-based health information in various health care settings. They will help to better understand the contribution of genomic variants to common diseases. In the meantime, there is a need to consider how best to collect and monitor information stemming from genome-based research and technologies, to close gaps and to frame the policy development of evidence-based strategies in that field. Thus, the argument of biobanking in the context of public health surveillance systems seems to be crucial.

3 From Epidemiological Research to Population-based Surveillance Systems and Public Health

So far, biobanking and surveillance systems have been looked at independently from each other. This is astonishing, since in the last decades, the concept of surveillance has been quite successfully developed and implemented in various fields of public health. Considerations of problems like data protection or data sharing and also the development of processes and methods in the context of surveillance programs could be easily translated to biobanks.

The idea of observing, recording and collecting facts, analyzing them and considering reasonable health interventions is very old and stems already from Hippocrates (Eylenbosch and Noah 1988). However, before a large-scale organized system of surveillance can be developed, certain requirements need to be fulfilled such as an organized health-care system, a classification system for diseases as well as appropriate methods of measurements. Currently, surveillance is defined as the ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in planning, implementation and evaluation of public health practice (Langmuir 1963). It includes the functional capacity for data collection and analysis as well as the timely dissemination of these data to persons who can undertake effective prevention and therapy. Surveillance data tell where the problems are, who is affected and where effective and efficient health interventions should be directed. Such data can also be used for defining public health priorities in a quantitative manner and to evaluate the effectiveness of programmes. Furthermore, the analysis of surveillance data enables researchers, especially epidemiologists, to identify areas of interest for further investigation.

The uses of surveillance systems are numerous involving quantitative estimates of the magnitude of health problems in a population at risk, analyzing the natural history of diseases, assessing differences by geographic areas, detecting and

documenting the spread of health events, identifying research needs to facilitate epidemiologic and laboratory research, testing hypotheses about the etiology of diseases, identifying differences in health status within racial or other subgroups of the population, evaluating health interventions such as preventive or curative strategies, monitoring changes in the nature of diseases, long-term trends or changes in health practices as well as fostering strategic health planning.

Especially the use of registries for surveillance and other medical or public health interventions has increased in the last few years. Registers such as cancer registries differ from other sources of surveillance data in that information from multiple sources is linked for each individual over time. Information is collected systematically from diverse sources including hospital-discharge data, treatment records, pathology reports and death certificates. This specific type of registry is also suitable to monitor health events in groups with increased exposure to hazardous agents. Nevertheless, population-based registries are particularly useful for surveillance because, using incidence rates, the occurrence of a health event can be estimated over time in different geographic areas and subgroups of the population.

The availability and value of data for surveillance depend on a number of factors. These factors include the extent to which classification schemes are used to categorize diagnosis, signs, symptoms, procedures, and reasons for health care, the extent to which information for individuals from different administrative sources over time periods can be linked using a unique personal identifier such as in Denmark or Western Australia. Here, the integration of genome-based biobanks and technologies such as TMAs or nano-chips will be a specific challenge.

In the future, several developments are expected to contribute to the evolution of surveillance systems such as the implementation of bioinformatics, the ability to make more effective use of sophisticated epidemiological and statistical tools to detect changes in patterns of health problems, the electronic dissemination of surveillance data and – last but not least – novel knowledge and innovations such as genome-based knowledge and technologies. The critical challenge, however, is the need to regard surveillance as a scientific enterprise. To do this properly, the principles of surveillance and their role in guiding epidemiologic research and in influencing other aspects of the overall mission of public health have to be fully understood. In addition, new epidemiological methods based on public health surveillance have to be developed. Bioinformatics for efficient data collection, analysis and dissemination have to be applied. Ethical, legal and social concerns have to be addressed right in time, the benefit of surveillance systems has to be reassessed on a routine basis, and surveillance practice has to be translated into emerging areas of public health practice such as the integration of genome-based biobanks.

The success of these surveillance systems including genome-based biobanks will heavily depend on the quality of the information into the system (i.e., on validated population-based genomic variants) and on the value of the information to its intended users. A clear understanding of how policymakers, voluntary and pro-

fessional groups, researchers, the commercial sector and other stakeholders might use surveillance data is valuable in gathering the support of these audiences for the surveillance system.

Regarding data sharing, it has to be stressed that different sources of information need to be accessed and compared with or added to the data collected in its own system, e.g., laboratory results, tissue results, epidemiological information for specific conditions, population estimates and mortality records. Through responsible planning and coordination on the part of managers on reporting systems, standard coding schemes can be adopted as data systems evolve. These actions, for example, have the potential to facilitate the sharing and use of data.

European and US public health institutions and platforms like the Public Health Genetics Foundation in Cambridge (PHGF), UK, the European Centre for Public Health Genomics in Maastricht, the Netherlands, the Turkish Center for Public Health Genomics and Personalized Medicine (TOGEN) in Ankara or the US National Office of Public Health Genomics (NOPHG) at the Centers for Disease Control and Prevention in Atlanta (CDC), who work closely together with researchers from genetic and molecular science (“modern biology”) as well as from population science, humanities and social science, are optimistic and clear about the relevance of the integration of genome-based biobanks into surveillance systems and thus, for public health in general (Brand et al 2004, Khoury et al 2000, Omenn 2000, Walt 1994). Interestingly enough, they all have strong links or are even part of the respective national genome research projects in these countries and are translating genome-based knowledge from biotechnology and biobanks through genetic epidemiology or “classical” epidemiology into public health (“translational research”). By using methods like horizon scanning, fact finding and monitoring to identify research trends as early as possible, they are already doing a prospective evidence-based evaluation. That is an evaluation that is already carried out in the process of basic research and not just in the (retrospective) process of the implementation of public health strategies and policies (Williams 2005), which always will tend to lack behind.

4 Public Health Ethics as a New Paradigm

The present discussion about ethical aspects of biobanking is dominated by the conventional and individual-centered moral categories of medical ethics and bioethics. But especially in this context of biobanking, focussing always on individual rights and protections such as informed consent, confidentiality, discrimination, stigmatization or the “right not to know” in the end will undermine individual rights and interests in ways that benefit some organized interests, because important social, political and scientific questions will be hardly considered (Schröder 2007).

Regardless of the question of whether in the situation of “informed consent” the promises and information that potential research subjects are given are accu-

rate indeed, and regardless of the point that informed consent is irrelevant to many groups of potential research subjects, the biggest concern is that by focussing on individual consent to research, the importance of statutory research like for example epidemiological and public health research or the monitoring of the effectiveness and efficiency of specific health interventions, that poses few risks to individuals but is essential to the assurance and improvement of (collective) health care provision, is neglected. This focus on individual decision-making not only ignores contexts of choice but also is connected to a view of ethics that is separated from politics.

Moreover, if ethics in the context of biobanking is further promoting informed consent and confidentiality, then ethics is no longer concerned with the scientific validity of research, balancing likely benefits of research and establishing research priorities. Thus, the question of whose health and whose interests will be served by research is critical. Public policy principles such as institutional oversight and competing political priorities, ethical principles such as solidarity, justice and good governance as well as the concepts of benefit-sharing and informed contract will be able to provide an appropriate public health ethics framework (Schröder 2004, Sass 2001, Knoppers 2005). But continuing to make an artificial division between ethical and political aspects on the one hand and between individual rights and public goods on the other hand, will impede any innovative future use of biobanking.

Since policy development in the field of biobanking must take contextual as well as cultural factors into consideration, “both collective and individual rights and interests are at stake in creating or assessing genomic databases for public health research” (Coughlin 2006). At the same time, a public health ethics framework (Knoppers 2005)¹ must be based on norms beyond the legal and ethical criteria of autonomy and privacy. Furthermore, new models are needed to offer robust moral guidance while keeping the reality of a dynamic science such as the concept of diseasesomes in mind (Loscalzo et al 2007).

Also, since biobanks require an ongoing contribution from the potential research subjects, if not samples, then at least health information and possible lifestyle data need to be collected over an indefinite period of time. It becomes obvious, that in this situation complete anonymisation of data is impossible, as this would prevent new data being linked to the old and to tissue samples or genome-based information.

Clarifying the general conditions under which genome-based knowledge and technologies can be put to best practise in the field of biobanking, epidemiological research and public health surveillance, paying particular consideration to the public health specific ethical, legal and social implications (ELSI) (Brand et al 2004, Omenn 2000, Michigan Center for Genomics and Public Health 2004), is currently the most pressing task and thus has been stressed by public health genomics (PHG). Aiming the application of genetic and molecular science to the promotion

¹ Cf. <http://www.ete-online.com/content/3/1/16>, Accessed 15 July 2008.

of health and disease prevention through the organised efforts of society, integral to its activities is dialogue with all stakeholders in society, including industry, governments, health professionals and the general public (Walt 1994).

Policymakers must be aware of the current challenge to improve consumer protection, to monitor the implications of genome-based knowledge and technologies for health, social and environmental policy goals and to assure that genomic advances will be tailored not only to treat medical conditions, but also to prevent disease and improve health (Beskow et al 2001). Sound and well reflected genetics policies and programs require a timely and coordinated process for evidence-based policy making that relies on scientific research and ongoing community consultation (Frankish et al 2002). An acceptable and maybe delicate balance between providing strong protection of individuals' interests (O'Neill 2002, Geier and Schröder 2003) and enabling society to benefit from the genomic advancements at the same time must be found (Brand et al 2004, Beskow et al 2001, Tauber 2003, UNESCO 2003).

Interestingly enough, research in biobank-related fields such as for example in the field of genetically modified food has been able to distinguish between trust in governance, trust in government and trust in non-governmental organizations (NGOs), since trust is an important predictor of the attitude of individuals towards innovations, public acceptance, technological optimism, and various forms of behaviour. Public trust as a rather complex social and political phenomenon remains an important issue in the near future, especially in the context of the integration of genome-based biobanks into public health surveillance systems. It is not just the restoring of public faith in government, industry, NGOs or other stakeholders. It is related to the way government or politicians are willing to involve the public within decision-making, how industry is handling consumer interests and individuals' perception of the way biotechnology may influence their lives (Hansen et al 2001). With higher levels of trust in governance, even more important than trust in government or NGOs, people have a more positive attitude towards an innovation, are more likely to accept new knowledge and technologies, and are more optimistic about technological developments (Gutteling et al 2006). E.g., also regarding the implementation of population-based biobanks policy-makers and clinicians should consider how to narrow the gap between expectations and reality (Coulter and Jenkinson 2005).

Since the effectiveness and efficiency of biobanks depend very much on people's willingness to contribute samples for both research and storage, public support is thus essential in assuring long-term realisation and potential of biobanks. It is also based on the assumption that the complex issues surrounding biobanks are managed appropriately by the responsible authorities. Although the majority of the general public is willing to donate a sample to a biobank (Kettis-Lindblad et al 2005), the willingness is mainly driven by altruism and depends on the public well-informed and having trust in experts and institutions. In general, there is an overwhelming positive attitude towards genomic research. Nevertheless, the trust in authorities' capability to evaluate the chances and risks of genomic research

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