New sequencing methods: New data and new challenges (Introduction)

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INTRODUCTION

New sequencing methods

New data and new challenges

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Abstract • Today, DNA sequencing is part of the standard repertoire of biological and medical research. Next generation sequencing (NGS), established around the mid-2000s, was the main catalyst for this development. NGS has led to major knowledge gains in the molecular life sciences. However, the new technology provides data that pose new challenges that both science and society still must learn to deal with. A technology-driven dynamic can already be observed in this field, leading to transformation processes in science, where new fields of research are emerging, but also in society, where questions of identity are increasingly being negotiated based on genetic analyses.

Neue Sequenzierungsmethoden. *Neue Daten und neue Herausforderungen*

Zusammenfassung • *Die Sequenzierung von DNA gehört heute zum Standardrepertoire der biologischen und medizinischen Forschung. Das um die Mitte der 2000er-Jahre etablierte Next Generation Sequencing (NGS) war der wichtigste Auslöser für diese Entwicklung. NGS führte zu großen Erkenntnisgewinnen in den molekularen Biowissenschaften. Die neue Technologie liefert allerdings Daten, die Wissenschaft und Gesellschaft vor neue Herausforderungen stellen. Schon jetzt lässt sich in diesem Feld eine technikgetriebene Eigendynamik feststellen, die zu Transformationsprozessen in der Wissenschaft führt, wo sich neue Forschungsfelder herausbilden, aber auch in der Gesellschaft, in der Fragen von Identität zunehmend anhand von genetischen Analysen verhandelt werden.*

Keywords • *NGS, technoscience, transformation processes, archaeogenetics*

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Introduction

These days, everyone is talking about genomes, mutants, variants, DNA, and sequencing. Most people, at least here in Germany, are now familiar with cryptic rows of letters and numbers such as B.1.1.7, B.1.351, and P1 – these are three variants of the SARS-CoV-2 coronavirus, which has been running rampant worldwide since 2020. In January 2021, as many other countries had already done, the German government and the Robert Koch Institute (RKI) decided to carry out more extensive genome sequencing of SARS-CoV-2 in order to discover new virus variants and to track their frequency and spread. This expansion of what is known as "molecular surveillance" in Germany is linked to the goal of increasing the rate of genome sequencing and ensuring that approximately five percent of positive samples are sequenced (Robert Koch Institut 2021, p. 1). The current success of rapid and, above all, mass sequencing of SARS-CoV-2 is in part due to the methods of next generation sequencing (NGS), which have been "adapted to the SARS-CoV-2 paradigm" and have been "shown to be applicable to a wide variety of associated biological questions. The rate of data production and analysis has been unprecedented and would have been inconceivable only a few years ago." (Chiara et al. 2021, p. 626)

Without any doubt and as this example illustrates well, DNA sequencing has become part of the common toolkit of biological and medical research. NGS, which emerged in the mid-2000s, was the most important catalyst for this development. NGS procedures allow for the sequencing of many DNA molecules simultaneously and cost-effectively. This new procedure and the rapidly decreasing costs of sequencing generated significant impacts. The rate of knowledge generation expanded rapidly in molecular-based biosciences, particularly evolutionary research but also pharmacogenomics, oncology, reproductive medicine, and epigenetics.

When this TATuP special topic was conceived in the winter of 2019/20, SARS-CoV-2 had not yet reached Central Europe. Our focus was on the social, cultural, economic, and political

consequences of the "molecularization of science and society" (Bösl 2017, p. 339, our translation) that accompanied the emergence of NGS. Thus, even then, we had less in mind the 'classical' sectors for the application of gene sequencing such as medicine, pharmacology, and forensics. On the contrary, from the interdisciplinary perspective of technology assessment (TA) we were specifically looking for contributions relating to fields of application that defy disciplinary classification and cross traditional boundaries, as well as papers dealing with the consequences for these fields.

Consequently, the focus of the published papers is not on NGS per se or conflicts relating to its implementation. Rather, the authors deal with the data obtained by means of NGS and the associated scientific, social, and ethical impacts and challenges. Ultimately, the new technology provides new data that science and society still have to learn to deal with. The impact of the technology becomes apparent indirectly – both through the data obtained and the way we deal with it. In terms of science and technology studies, NGS can be considered a new 'actor' that has emerged, that is 'getting involved' in many fields – some of which are far removed from medicine – and that has changed "the way different groups imagine human identities, such as race, gender, kinship, citizenship and disease risk" (McGonigle and Benjamin 2016, p. 1). The papers published in this TATuP special topic engage with debates of this kind.

Next generation sequencing provides new data that science and society still have to learn to deal with.

New cross-cutting fields

NGS is used in many fields today. The medical sector is undoubtedly central, but there are, in addition, several research areas and cross-cutting fields that first emerged as a result of NGS. Thanks to technological innovation, these new interdisciplinary fields have acquired a place in academia in just a few years. The field alternately known as archaeogenetics or palaeogenetics, which traces the historical biological development of not only humans but also animals and other fossil organisms through the changes in their DNA, is part of this development. Research based on sampling and sequencing ancient DNA (aDNA) has triggered a great deal of "hype" (Jones and Bösl 2021) within and outside the academic world in the last ten years. Archaeogenetics, with its "combination of enticing cultural imagery and the authority of genetics" is proving to be a successful formula for drawing attention to the new field (Källén et al. 2019, p. 83; see also Samida 2020, 2021, pp. 86–111).

Archaeogenetics thus challenges the established historical sciences on two accounts: first, by claiming to conduct historical research and second, by producing provoking headlines about historical issues. One of its most prominent representatives, David Reich (2018, p. xxiii), emphasized predictively that the "ancient DNA revolution is rapidly disrupting our assumptions of the past". However, the extent to which these "assumptions" are actually 'blown up' is currently the subject of intensive debates. These debates are accompanied by discussions on disciplinary self-conceptions and epistemological issues, including discussions of a fundamental nature, e. g., the relationship between the 'two cultures' – the sciences and the humanities – in terms of C. P. Snow (Bösl 2017; Meier and Patzold 2021; Samida 2021). As a laboratory science, archaeogenetics also makes claims to objectivity and credibility, which in turn provokes criticism from well-established disciplines such as history and (prehistoric) archaeology (see, for example, debates in special issues of Medieval Worlds 2016, NTM 2018 and 2019, World Archaeology 2019, and recently Journal of Social Archaeology 2021).

Struggles over the interpretation of findings and disciplinary boundaries as well as heated debates about terms and concepts are evident. Moreover, the fabrication of ethnicities by archaeogeneticists as immediately disseminated in the media, whether intentionally or not, creates not only a false impression of stable and collective identities from prehistoric times to the present day, but is also increasingly misused in debates over identity politics (Maran, in press). Recently, Catherine J. Frieman and Daniela Hofmann (2019) impressively analyzed how right-wing and racist activists make use of the results of archaeogenetic studies. In the context of contemporary debates on migration, these activists simultaneously propagate an invasion from the east while also promoting "a narrative of (biological and social) domination by pale, blue-eyed men" (ibid. p. 529). Arguments that rest on ethnic essentialism and biological determinism are increasingly prominent (Furholt 2020). This is a matter of concern not only for scientific discussions but also for social and political debates.

Lab technologies and established disciplines

In practical terms, NGS is just a new technology that is being put to use in fields with long research traditions. It is being used to approach questions and hypotheses that, in many cases, have long been part of these fields. In archaeogenetics, for example, the techniques of taking and processing samples were developed in the late 1980s and the 1990s and have not undergone much modification since then. Moreover, the methodol-

ogy associated with stratigraphy, dating, prospection, i. e. the entire field of archaeology, is not new either, nor has it been revised or altered because of or to better suit NGS. Sequencing also relies on samples being collected, stored, and processed, as archaeogenetic studies are inconceivable without archaeological context information. While archaeological methodology is obviously also subject to historical change in general, there is much more of the old than the new in NGS-based archaeogenetics. The importance of substantial context information is by no means diminished by NGS. On the contrary, the whole business of archaeogenetics is coming to rely even more on 'old', established methodologies, precisely because new sequencing techniques are producing new source material in hitherto unknown quantities. The incorporation of the new into the old in this way is a phenomenon widely known to historians of technology, even though historiography itself has long been so focused on innovation that it has ignored old, tried-and-trusted approaches (Edgerton 2006; Möser 2010).

As much as geneticists would like to, they cannot solve the paramount problem of archaeology and historiography – no technological advance or ingenuity can overcome the lack of source material and its characteristic selectivity, fragmentariness, and perspectivity. Neither NGS nor any other technoscience can eliminate such fundamental limitations, which are as old as the disciplines themselves. In most cases, the problems to which geneticists are applying their state-of-the-art technology have been there for a long time. And while high-end technology can often offer alternative ways to look at them, the basic problem remains. Moreover, just like the technologies that preceded it, NGS has limits. One of these limits, or rather a characteristic of lab technology in general, is that it can only help to produce proxy data which, later on, has to be interpreted using a different set of methods.

The importance of substantial context information is by no means diminished by next generation sequencing.

Technology-driven processes

The example of archaeogenetics stands pars pro toto for other, very similar developments that to a certain extent are all manifestations of the same technology-driven momentum. What do we mean by this? TA proposes the "systematic identification and evaluation of technical, environmental, economic, social, cultural, and psychological effects associated with the production, use, and exploitation of technologies" (Renn 2011, pp. 64, our translation). However, TA's promise to assess technological effects in advance is hardly feasible. This applies equally to methods such as NGS, in particular, and to the "uncanny development of genomic investigations" (Hagner 2012, p. 49, our translation) in general. Ambivalence, complexity, and uncertainty, as Ortwin Renn (2011, p. 65) has put it, are part of the attendant circumstances of TA, because opportunities and risks become apparent only gradually over time. In terms of NGS, this means that every new technical procedure is *ambivalent* – there are never only positive aspects, but also always negative ones. At first glance, the current sequencing of the coronavirus to uncover potential mutants falls into the 'positive' category and is rarely questioned. However, police investigations using DNA to identify the skin color of a suspect are sensitive and trigger critical questions. *Complexity* and *uncertainty*, in turn, are reflected in, among other things, computational operations, statistical procedures, and modeling of new data sets.

An example from the arts illustrates this quite impressively. Heather Dewey-Hagborg's 2017 installation "Probably Chelsea" presents thirty different possible portraits of the famous whistleblower Chelsea E. Manning. These portraits, however, were algorithmically modeled based on an analysis of Manning's DNA before being 3D printed. This example shows not only "how subjective the act of reading DNA really is" (Dewey-Hagborg 2017, p. 11) but also that "there exists an array of possible identities that are all simultaneously correct" (Schrock 2017, p. 7).

The novel methods of NGS, which were developed in molecular biology, do not only matter for medical research and diagnostics and for archaeogenetics. NGS makes the use of DNA analysis possible in numerous fields and has led to increasing commercialization in the private sector. This includes the hobbyist arena of genealogical research, which – once considered dusty and outdated – has become a rapidly growing market. Private genetic analyses (*direct-to-consumer genetic testing*) – including medical services – are in great demand and have become everyday commodities. Enterprises such as "MyHeritage" and "Ancestry DNA" not only act as large-scale collectors of genetic data, but also create specific concepts of ancestry and heredity in their marketing activities. This sort of 'entertainment genetics' is closely connected to questions of identity, which undoubtedly both draw from and impact on current identity discourses. This concerns individual as well as collective dimensions of identity formation (Sommer and Krüger 2011). Accordingly, 'biogeographical narratives' certainly create and convey forms of evidence but often remain unquestioned and unreflective.

Recently, quite a few empirical studies have made an effort to research how individuals deal with this information and incorporate it into their identity work. A new cultural studies paper (Strand and Källèn 2021) studied how genetic ancestry testing (GAT) clients from the UK, USA, and Sweden interpreted their

test results. The interviewees, including some accomplished genealogists, all had at least vaguely imagined a priori that they were testing for genetic traces of their 'Scandinavian' origin. As it turned out, they dealt selectively and quite differently with the genetic data they obtained, which suggests that identity work is an individual and rather ambivalent process, one that depends on an individual's preconceptions, interests, and very specific goals. Interestingly, however, most brought up the concept of the 'Viking' and attributed traits of their own character and behavior and aspects of their own biographies to their concept of a typical 'Viking'. Those concepts varied, however, between an image of Vikings as brutal conquerors and plunderers, and one that sees them as ingenious inventors, seafarers, and skilled traders. Some attributed family violence to what they thought of as their Viking ancestry. The contrasting popular concepts and images of the Viking reproduced here have, in fact, no empirical basis in archaeology or history. The image of Vikings as an ethnic group of violent, brave, adventurous conquerors was created in the 19th century in Northern Europe under the influence of Romantic nationalism. There is however no evidence from archaeological and historical sources that an ethnically cohesive group of this kind ever existed in Northern Europe. The groups that did live there did not even usually see themselves as forming a socio-cultural unity. And it is not possible to define 'the Viking' in genetic terms. Although the interviews had fairly varied ideas about the characteristics of Vikings, they all regarded these as determined by genetics. The test results were used to reinforce preexisting identity constructs. Another remarkable result of the study is that some participants described feeling physically close to the Vikings – even though the latter never actually existed in the way the interviewees perceived them (Strand and Källèn 2021).

Technoscience and transformation processes

The example of genetic ancestry testing also sheds light on how we experience the world around us through technoscience. Not only are our lives completely saturated with technology, we also make sense of the world via technologies (Nye 2006; Böhme 2007; Nordmann 2008). While this may be obvious when we consider a phenomenon such as surfing the web, it is also true for technologies such as NGS. NGS appears to give us access to the molecular dimension of the world, which would otherwise be out of reach. The world of molecules is becoming tangible for many now, as molecular genetic data is being communicated to the public via a growing variety of channels.

As the above clearly shows, DNA sequencing methods developed in molecular genetics have triggered transformation processes for both the general public, and in established fields of research. Nevertheless, one has to ask how much old there really is in all the new. As several authors in this TATuP special topic suggest, NGS has brought about a change of perspectives: from the taxonomic or phylogenetic dimension, i. e. the genetic relationships among various biological species, to the (meta-) genomic dimension of organisms in microbial ecology and from a symptoms-based clinical stance to a molecular-genetic-virological-epidemiological perspective in the research and management of a pandemic. NGS provides a genomic view of organisms. Such shifts in perspective change what we think a certain phenomenon consists of and also determine how researchers and practitioners deal with it. Obviously, NGS has made sequencing fast and cheap and has given access to a new level – the genome. Whether one needs to regard this as revolutionary, as Frieman and Brück do in their contribution to this issue, is certainly debatable.

Contributions to this TATuP special topic

Since DNA sequencing is significant for numerous fields, this special topic of TATuP brings together a broad range of perspectives from a variety of disciplines and cross-cutting fields. The authors discuss discourses and practices, actors and their networks, as well as concepts and specific (research) interests. In doing so, all address the various benefits, limitations, and inherent ambivalences of technoscience as manifested in NGS. They analyze how new technological options bring new social challenges and commitments as well as unintended effects.

Karen Kastenhofer addresses the molecular-genetic dimension of the Covid-19 pandemic from the perspective of TA and the sociology of science and technology. In our everyday experience of the pandemic, Polymerase chain reaction (PCR) is on everyone's lips and features prominently in the media. The PCR test, in particular, may become an icon of our time. NGS-based practices are far less present in everyday life but are of special importance to virology and epidemiology, as they capture the entire viral genome and thus enable scientists to detect variants and mutations. Geneticists and virologists are constantly trying to analyze the virus at the genetic level, to track its mutations, and to chart its genetic evolution. This molecular genetic knowledge is being used to develop not just test methods and novel vaccines but also new risk management concepts. NGS plays an essential role in this, as only it allows genome-wide study of the virus and the investigation of mutations. NGS leads to enormous increases in knowledge in a short time as well as to huge amounts of data made available in international databases. This happens within a new and potentially limitless network of actors, instruments, practices, rules, ontologies, and objects where SARS-CoV-2 is processed and as a knowledge artifact co-produced. Kastenhofer uses the idea of the "seamless web" to classify this phenomenon. The weak point of this highly efficient network, she points out, is the exclusion of clinical practice. Kastenhofer argues that while the new virus is thus conceptualized and stabilized as a molecular-genetic-virological-epidemiological event and the molecular genetic dimension of the pan-

demic is central to our understanding and management of the pandemic, other dimensions take a back seat.

Historians of science may find this an interesting parallel to the shift in focus that occurred after Alexandre Yersin, a Swiss and French physician, identified the causal agent of plague in 1896, a bacillus that was later named *Yersinia pestis*. In the case of plague, the diagnosis of the disease shifted from the clinical symptoms towards the bacteriological evidence. What plague is and what it means has been largely considered on the bacteriological level ever since. In the meantime, in the last 30 years, the focus in plague research and practice has again shifted: towards the perspective of molecular genetics.

Metagenomics, i. e., the analysis of the collective genomic content of a certain sample containing a variety of organisms (microbial communities), has only become feasible because of NGS. Robert Meunier and Saliha Bayır discuss the transformation processes that have affected microbial ecology (the study of microorganisms in relation to their environment and to one another) and especially agricultural soil research as a consequence. From their philosophy-of-science perspective, they argue that metagenomcis is greatly impacting agricultural research and practice because it gives access to other aspects of microbial life than the earlier culture-based or PCR methodologies. Metagenomics has changed both basic science and, consequently, design science, i. e., the type of science that produces recommendations for interventions in, in this case, agricultural practice. While culture-based approaches focused on taxonomies and physiology and PCR sequencing produced data on the phylogeny of single organisms, metagenomic approaches allow the focus to move onto interacting microbial communities, the microbiome, and their genetic structures and functions. NGS made possible a systems approach and a shift from studying structure to studying the integrated functional units of microbial communities, which were now understood to a large extent through the lens of their collective genome. These were then transferred to and adopted by agricultural science, whose focus now is on the genomic dimension of microbes rather than their taxonomy or phylogeny. This change of perspectives shaped the perception of ecosystems and thus the interventions devised by agricultural science and the technical norms proposed to farmers, politics, and businesses. While many of these intervention concepts are still to be put into real-world practice, situation assessment including, e. g., soil quality indicators has already been changed by the metagenomic approach, as have the goals and values of agricultural studies.

The sociologists Alexander Lang and Florian Winkler explore aspects of direct-to-consumer genetic testing, while focusing particularly on elements of co-construction and the process by which ancestry is 'produced'. Their analysis of this kind of 'doing ancestry' is based, on the one hand, on a review of existing empirical studies and, on the other, on an explorative qualitative inquiry that includes analysis of relevant websites of popular companies (e. g. "MyHeritage"), qualitative expert interviews, and auto-ethnographic self-observation. Using this mix of methods, the authors present interesting results concerning the companies and their users. In their self-portrayal, the companies seek to present themselves as apolitical and promote their products as tools that produce objective facts. The users, in turn, (re)interpret the test results in an open and playful manner, while incorporating them into their genealogies and lives.

Using the example of 'Jewishness', Noa Sophie Kohler points to ways in which genetic ancestry testing is used for political and religious purposes. A large number of immigrants from the former Soviet Union are seeking to legally 'prove' their 'Jewishness' to the State of Israel, as this has consequences for their civil rights. However, most of them do not have any evidence about their maternal ancestors, which, in accordance with traditional law, the Chief Rabbinate considers to be the main determining factor. Here, genetic testing not only comes to the fore as a central method, but also becomes an important tool for re-claiming Jewish identity. In this respect, DNA is an important actor in this process of negotiation.

From an archaeological point of view, Stefan Burmeister deals with the concept of genetic ancestry. Instead of the concept of race that has been problematized in biology and the social sciences for decades, the term "genetic ancestry" seems at first glance as a harmless alternative. However, Burmeister observes its increasing influence on public discourse, particularly when it comes to identity politics. Archaeogenetics is not entirely innocent in this process, because the careless and often largely unreflecting use of archaeological, ethnic, and genetic categories and concepts opens the door for xenophobic and racist discourses.

Next generation sequencing poses massive challenges to science and society.

Catherine J. Frieman and Joanna Brück discuss archaeogenetic approaches to both horizontal and vertical aspects of kinship. NGS has accelerated the process of generating data on genetic relations and has provided geneticists with an abundance of high-resolution data for a growing number of individuals, a fact that Frieman and Brück call revolutionary. However, as they point out, NGS does not mean that kinship research is now a closed book, but rather that a new class of evidence is available. Genetic evidence of purely genetic relationships between individuals and groups has to be put into relation with other kinds of evidence, such as those generated by archaeology, ethnogra-

phy, and social anthropology. The authors highlight the fact that genetic data alone cannot contribute anything to the understanding of non-genetic relations between people. This data may, however, form part of an integrated, multi-perspective approach to kinship. Kinship, they argue, is likely to be composed by a variety of factors such as care, obligations, beliefs, dependencies, and genetics. The relative importance of these components may vary by period and culture. So neither should genetic relations be equated with kinship in general nor can kinship itself be considered universal. Frieman and Brück also stress that studies on genetic relations inevitably rely on heterosexual reproduction and thus have an inevitable heteronormative tendency. Geneticists working on lineages and ancestry cannot address anything but biological reproduction. And this is a very limited perspective. That is problematic, because as social anthropology and ethnography suggest, there have been many other forms of kinship in past and present societies in which heterosexual reproduction is not the most significant factor at all. So, the authors dig in their heels to protest against reductionism and promote a more complex concept of kinship instead, one that encompasses both genetic and non-genetic relations. Frieman and Brück make another important point: Genetic research into kinship, recently refined and accelerated by NGS, means that archaeologists need to become more active. They should take recent advances in genetics as an incentive to put more effort into researching kinship themselves. Studies should be set up that analyze housing, hoards, food-sharing, burials and other practices to see what these may tell us about how kinship was perceived and practiced. The authors present recent examples of archaeological papers that consider such social practices as part of making kin. From their article it is obvious that the combined efforts of archaeology and genetics may produce complex pictures of kinmaking and thus overcome the concept of people simply being kin by birth.

All the contributors to this special edition point, at least implicitly, to the vital role of bioinformatics. NGS is unthinkable without close collaboration with expert bioinformaticians, not least because of the enormous amounts of data that it generates. NGS technologies result in proxy data – which is pretty meaningless in itself. It is only made significant by means of tools from the computational sciences, statistics, and the modeling expertise of population genetics. While this was also true for PCR-based studies, the sheer amount of data being produced by NGS has increased the importance of bioinformatics. In archaeogenetics, the ongoing refinement of approaches and scenarios is in a way more due to bioinformatics and statistics than to advances in molecular biology, or, to put it another way, advances in molecular biology and population genetics are due at least as much to bioinformatics as they are to new sequencing techniques.

To sum up, NGS influences a huge range of fields and applications and it certainly shows enormous potential. However, as we have seen, it also poses massive challenges to science and society. Continuous reflection from various perspectives therefore remains an important task and many more debates – particularly public debates – on NGS and its (social) implications in the future remain to be carried out.

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[Bildquelle: Petra Höglmeier-Wübert]

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