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RESEARCH ARTICLE

Artificial intelligence in human genomics and biomedicine

Dynamics, potentials and challenges

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Abstract • The increasing availability of extensive and complex data has made human genomics and its applications in (bio)medicine an attractive domain for artificial intelligence (AI) in the form of advanced machine learning (ML) methods. These methods are linked not only to the hope of improving diagnosis and drug development. Rather, they may also advance key issues in biomedicine, e. g. understanding how individual differences in the human genome may cause specific traits or diseases. We analyze the increasing convergence of AI and genomics, the emergence of a corresponding innovation system, and how these associative AI methods relate to the need for causal knowledge in biomedical research and development (R&D) and in medical practice. Finally, we look at the opportunities and challenges for clinical practice and the implications for governance issues arising from this convergence.

Künstliche Intelligenz in der Humangenomik und Biomedizin.
Dynamiken, Potenziale und Herausforderungen

Zusammenfassung • *Die zunehmende Verfügbarkeit umfangreicher und komplexer Daten hat die Humangenomik und ihre Anwendungsbereiche in der (Bio-)Medizin zu einem attraktiven Bereich für künstliche Intelligenz (KI) vor allem in Form von fortgeschrittenen Methoden des maschinellen Lernens (ML) gemacht. Diese Methoden sind nicht nur mit der Hoffnung verbunden, Diagnosen und die Medikamentenentwicklung zu verbessern. Sie könnten auch darum, Kernthemen in der Biomedizin voranzubringen, z. B. zu verstehen, wie individuelle Unterschiede im menschlichen Genom bestimmte Merkmale oder Krankheiten verursachen können. Wir analysieren die zunehmende Konvergenz von KI und Genomik, das Entstehen eines entsprechenden Innovationssystems und wie diese assoziativen KI-Methoden mit dem Bedarf an kausalem Wissen in der biomedizinischen Forschung und Entwicklung und in der medizinischen Praxis zusammenhängen. Schließlich betrachten wir die Potenziale und Herausforderungen für die klinische Praxis und die sich aus dieser Konvergenz ergebenden Implikationen für Governance-Fragen.*

Keywords • *artificial intelligence, biomedicine, genomics, governance, knowledge*

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Introduction

The increasing availability of extensive and complex data has made human genomics and its application areas in (bio)medicine an attractive domain for artificial intelligence (AI) in the form of advanced machine learning (ML) methods (Wainberg et al. 2018). The focus of interest is on sequence data of the human genome as well as on data of genes that are read (transcribed) or proteins that are produced in various body cells and organs. These can be combined with clinical data from biobanks or electronic patient records, among others. The use of ML in

human genomics and biomedicine is associated with the hope of obtaining answers to a key question in these domains, namely how individual differences or mutations in the genome cause specific traits or diseases. This would allow predictions about functional consequences of genetic differences, diagnoses, prognoses about therapy options or the development of new drugs at an unprecedented pace and scope.

With AI and human genomic research, two emerging techno-scientific domains appear to converge, both being linked to hopes and fears on issues such as new diagnosis and therapy options, health economics, autonomy, discrimination, privacy, or accountability – all of which will likely be judged against the background of different interests, values, or worldviews of people. To develop policies helping to align innovations with societal needs and expectations, (1) an understanding of scientific-technical potentials and challenges, and (2) (mutual) learning on perspectives through dialog activities on the technologies and possible applications involving various stakeholders and publics will be needed.

Given the nascent state of the convergence of both domains, in this article we mainly focus on the first step, by exploring and using evidence from the literature as well as perspectives from stakeholders involved in current scientific-technical developments. This work may inform discussions on policy issues as well as realistic scenarios in societal dialog activities in the required second step towards the further development of AI in human genomics according to societal expectations.

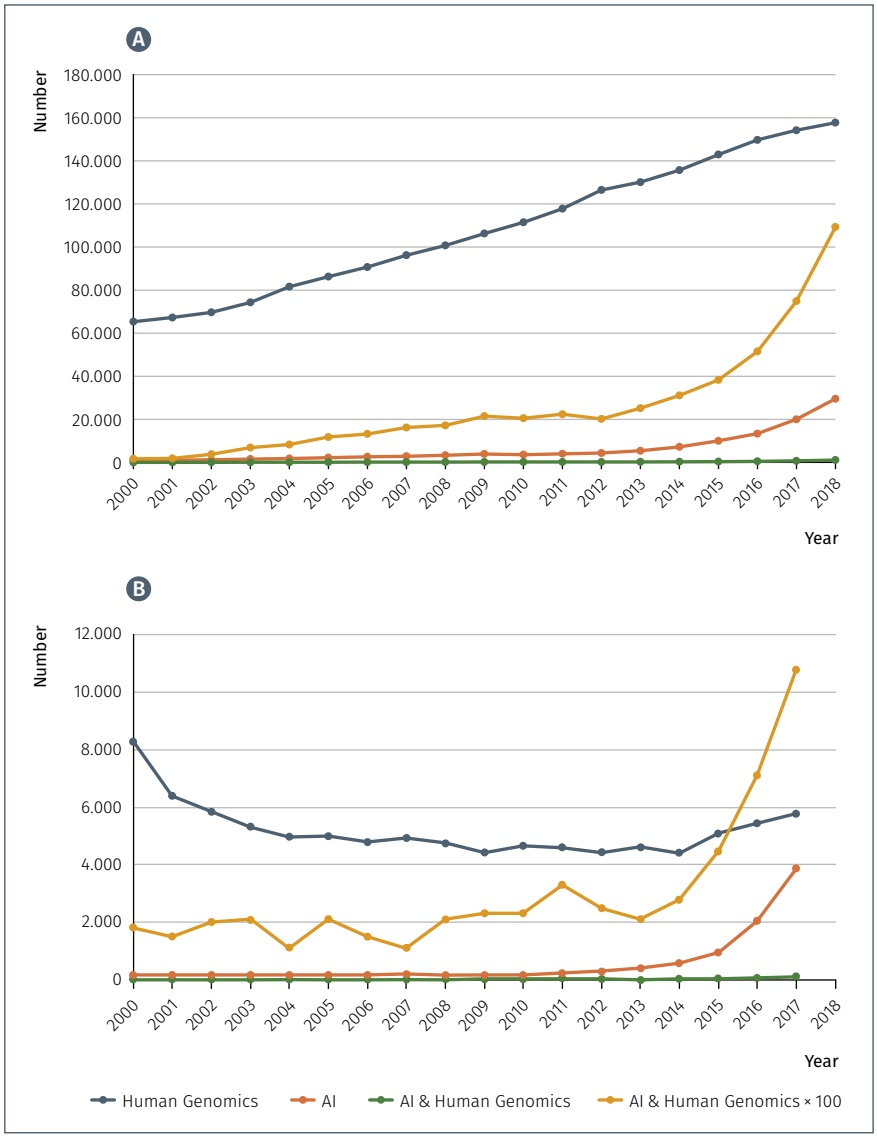

Fig. 1: Number of publications and patents worldwide over time.
A: Number of publications *(Source: Web of Science 2019. Authors' own calculations)*, **B:** Number of transnationally registered patents *(Source: World Patents Index 2019. Authors' own calculations).*

Number of publications and patents, respectively, in the domain 'AI in human genomics' (green curves), human genomics (blue) and AI (orange). To better visualize the dynamic development, publication and patent numbers of the green curves were multiplied by 100 (yellow curves).

Methods

As basis for identifying potentials and challenges, the current state of research as well as existing and emerging applications were examined and mapped by reviewing peer-reviewed scientific publications, conference proceedings, and patents (König 2020). In addition, the emerging innovation system at the intersection of AI and human genomics was analyzed through a mapping of international key actors, a review of international policy strategies, and a publication and patent analysis. The results of these steps were presented and discussed at a two-day workshop (held in November 2019 in Heidelberg) with twelve international experts from academic research, industry and the venture capital sector. Subsequently, the literature was evaluated with regard to ethical, social and regulatory challenges. These results informed a one-day workshop (held online in October 2020) with eight experts from Germany representing clinical research, genetic counseling, patient associations, medical and technical ethics, and jurisprudence. Finally, the results of all mentioned steps were reviewed and summarized for this article.

Results and Discussion

Innovation system analysis

Our analyses of the publication and patent statistics show that the use of AI-based methods in human genomics and biomedicine has boomed in recent years, both in academia and industry. Thus, the number of scientific publications and patents rapidly increased since 2014 (Figure 1 A/B; yellow curves). However, if one compares these activities to those in the domains of AI or of human genomics overall, it becomes clear that they still represent a relatively small niche with a limited number of key players and application areas (Figure 1 A/B; green curves). However, if this momentum continues, research and development (R&D) in human genomics will be heavily influenced by AI in the next years.

In the future, there could be a shift from scientific explanation based on experimentally validated causal relationships towards explanation largely derived from AI predictions.

Looking at different world regions, the publication analysis suggests that Europe as a whole plays a significant role in the global research domain (with the UK and Germany as the most prominent European countries) alongside the two dominant countries USA and China. In contrast, the statistics of transnational patents (suggesting a particular commercial relevance) show that the USA is well ahead of all other countries and regions in utilizing relevant research for commercial purposes.

The dynamics in global publication and patent activities at the intersection of AI and human genomics point to the emergence of a new innovation system. Our analyses suggest various factors and actors that have contributed to this development. These are in particular the widespread (also clinical) use of and demand for whole genome sequencing and corresponding platform technologies as well as the engagement of venture capital companies, big tech companies, pharma companies, and startups. The latter (especially in the USA) are significantly driving technological innovations for drug discovery and development (DKA 2019). In addition, numerous public research organizations, international research consortia (e. g., the International Cancer Genome Consortium) or local research clusters (such as Boston, MA, USA) are important drivers.

Potentials of AI for human genomics and biomedicine

Basic and translational research: Deep learning (DL), a form of ML which relies on software-simulated multiple layers of so-called artificial neurons (deep neural networks), is increasingly used to explore how individual differences in the human genome may cause traits or diseases. Several recent studies suggest that DL models, via analysis of large data sets, can be of decisive help in rapidly and comprehensively identifying putative causative genetic alterations and molecular mechanisms for diseases. These include common diseases such as neurological diseases (e. g., Alzheimer's disease, autism or schizophrenia), inflammatory bowel diseases (e. g., Crohn's disease) and diabetes (König et al. 2021; Zou et al. 2019). Similarly, potential pathogenic mutations that could facilitate diagnoses or prognoses have been identified for various cancer types and rare genetic diseases (Bailey et al. 2018; Brasil et al. 2019).

Drug development: ML methods are increasingly developed and used, especially by start-up companies, to make predictions of molecular properties (such as protein structures and interactions, or toxicity) from genomic data, which are used to identify drug candidates (virtual screening), to use existing drugs for new purposes (drug repurposing) or to design new drugs (Paul et al. 2021).

Clinical practice: ML has enabled new diagnostic methods by linking genomic data with clinical data (such as on disease progression or medical images). Such new methods include the diagnosis of rare genetic diseases in children by linking altered facial features, symptoms and genetic changes (Gurovich et al. 2019) or methods to analyze minute amounts of DNA and other tumor cell components in body fluids (liquid biopsies) (Heidrich et al. 2021). Another strand of development aims to improve risk predictions by combining and weighing very large numbers of individual genetic variants (genome-wide polygenic scores) for a range of important and common diseases to such an extent that they may be widely used clinically (Lello et al. 2019).

Challenges and fields of action

AI-based understanding, quality of knowledge, and potential implications: Although causality and causal modeling have become an active area of research in AI, currently established ML methods for analyzing large and complex data are still based on statistical modeling and do not reflect true causal relations but correlative associations (Schölkopf 2019). In contrast, current self-understanding of scientific explanation and associated quality criteria for (causal) knowledge in biomedical research rely on experimental intervention to reveal causal processes and interactions that lead to the event (e. g., a disease) to be explained (MacArthur et al. 2014; Soldner and Jaenisch 2018). Accordingly, rigorous validation of such correlation-based model predictions on putative gene functions or physiological pathways by interventions in molecular and cellular processes remains necessary. Due to the very large and increasing numbers of genetic

variants associated with complex traits and the complexity of implicated gene and protein networks, such validation is costly and dependent on the availability of suitable human cell models or model organisms.

In the future, there could thus be a shift from scientific explanation based on experimentally validated causal relationships towards explanation largely derived from AI predictions. This would not only challenge the current self-conception in basic research regarding scientific understanding and the quality of knowledge, but also pose challenges for application-oriented research. The latter is supported by retrospective studies of drug approvals, suggesting that demonstrating a causal genetic link between the drug target and the disease significantly increases the likelihood of successful drug development (King et al. 2019).

It remains unclear what influence explainability actually has on trust in and acceptance of AI-based systems.

While causal mechanistic accounts of understanding prevail in basic and translational biomedical research, in clinical practice and evidence-based medicine difference-making probabilistic concepts of causation are the centerpiece. Using randomized controlled trials as their most important tool, they usually only provide black-box causal claims about the (statistical) effectiveness of interventions in a studied population, without providing a mechanistic explanation (König et al. 2021). Therefore, and as the value of mechanistic knowledge is controversial among practitioners (Andersen 2012; Reiss and Ankeny 2016), the impact of a potential quality loss in causal-mechanistic knowledge through AI is much less clear. Yet causal knowledge on mechanisms can play a role in the interpretation of clinical trials (Andersen 2012) as well as in diagnosis when cases are rare or complex (Brush Jr. et al. 2017).

Research and data infrastructures as well as data governance: Large amounts of high-quality genomic and other 'omic' data as well as health data are essential for ML methods (Saunders et al. 2019; Wainberg et al. 2018). Harnessing possible benefits from these techniques for biomedicine would thus require the (further) development of large and diverse biobanks (Denny 2019) as well as international initiatives which link national genome and health data and allow as many researchers as possible to share and access data (Powell 2021; Saunders et al. 2019). This poses considerable challenges linked to sufficient data processing and storage capacity, broad implementation of common technical standards, such as the FAIR principles (Wilkinson et al. 2016), high data security, and solutions that enable data sovereignty (Phillips et al. 2020; Powell 2021; Saunders et al. 2019).

Although commercial or 'community' cloud computing services can in principle solve these challenges (Langmead and Nellore 2018), problems may arise regarding regulation and/or privacy aspects, e. g., if the cloud services are located outside a certain geographical area and data are subject to less strictly regulated access by security and law enforcement authorities (Dove et al. 2015; Kolata and Murphy 2018). Possible privacy issues that may lead to (re-)identification and discrimination risks of data donors also pose a major challenge beyond ethical and legal issues, because academic as well as industrial research relies on a sufficiently high representativeness of data sets. This requires that as many patients and study participants as possible make their data available. Ethnic groups in particular must not be underrepresented in the databases (Sirugo et al. 2019) in order to avoid biases and to generate benefits for as many people as possible.

In the area of private R & D, in addition to big tech companies, large pharmaceutical companies have increasingly invested in AI for diagnosis and drug development and have entered into numerous collaborations with innovative start-up companies. While data might become concentrated in pharmaceutical companies, start-ups are better placed to produce innovative approaches to using data, as they are usually more agile. They can take risks, pivot, focus on niche markets and be disruptive. Large companies often become sustainers as they chase quarterly results. They concentrate on incremental innovations that support their business models. Operating like a start-up through largely autonomous entities or collaborating with real start-ups is considered essential for new AI developments in the biomedical domain (DKA 2019). Large companies thus need to engage directly with start-ups by providing equity as well as access to resources such as technology and data. In Europe, however, the financing of such start-ups is a structural weakness due to various problems generally associated with the European venture capital landscape (DKA 2019).

Explainability, evaluation, and approval: Important ML methods for genomic medicine, especially DL models, have a distinct 'black box' character. They are difficult for humans to explain or interpret in terms of how and/or why a result is produced (Lipton 2018). This challenge is particularly severe for systems that are continuously learning and changing (Babic et al. 2019). The lack of explainability or interpretability is widely considered to be particularly important in the medical domain because of the high risks for human lives associated with potential errors and biases in models and data. Expectations are therefore high for so-called explainable AI systems (Arrieta et al. 2020). Despite the importance often attributed to explainability or interpretability, existing and proposed guidelines and regulations for AI in general, as well as for software as a medical device in particular (Ordish et al. 2019), currently lack clear standards for explainability or interpretability in both Europe and the USA. For

instance, in the USA, guidelines by the U. S. Food and Drug Administration (FDA) urge developers to provide information such as an "explanation of how the software works" (FDA 2019 b, 26), and physicians' ability to "independently review the basis for the recommendations" is considered important in determining whether software should be regulated (FDA 2019 a, 8). Similarly, the recently proposed EU Regulation on AI (AI Act) demands that high-risk AI systems are designed in a way "that their operation is sufficiently transparent to enable users to interpret the system's output and use it appropriately" (EC 2021, Article 13).

However, it remains largely unclear how information toward such transparency should look like in practice. In addition, the conceptual problem arises that for current ML systems it is only possible to explain how correlations and the predictions based on them are obtained, but not to draw causal conclusions (Pearl 2010). Thus, policy makers and regulators need to agree on more concrete information developers should provide with regard to the functionality of AI systems and on what role explainability can or should play for the approval of AI systems in comparison to complex, rigorous clinical trials (and possibly post-market monitoring).

Ethical and social implications: In the application of AI-based procedures in medical care, like diagnosis or treatment selection, trust and acceptability on the part of physicians and patients are seen as being of decisive importance (Arrieta et al. 2020; Kelly et al. 2019). Various EU policy documents, including the Ethics Guidelines for Trustworthy AI (HLEG 2019) and the European Commission's White Paper on AI (EC 2020), as well as the recent proposal for the EU's AI Act (EC 2021) aim at trustworthy AI. Transparency in the form of explainability or interpretability of AI systems (in the AI Act, in particular) is delineated as an important element to achieve this aim and the ethical use of AI.

However, given rather weak and contradictory empirical evidence, it remains unclear what influence explainability or interpretability actually have on trust in AI-based systems or their recommendations, compared to other factors, such as marketing, clinical trial data, or the regulatory environment. Studies on the diffusion or adoption of medical innovations also indicate that the adoption of applications is a complex social process (Azoulay 2002; Lublóy 2014). Thus, there is currently a lack of empirical evidence on how AI applications and their governance need to be designed in order to create and deserve sustainable trust and acceptance in medical AI systems. Before thinking about creating trust and acceptance, it is, of course, paramount that the AI system in question can or will actually improve the quality of care for specified patient groups. Trust is closely related to acceptance and both may be generated by explainability. However, since explainability cannot replace validation of AI systems with regard to medical outcomes and patient benefits by clinical trials, the generation of trust by 'plausible' explanations on how AI systems work just for the sake of pushing the diffusion of AI systems is highly problematic.

If risk predictions and disease progression prognosis, both in the direct-to-consumer and the regulated domain, should become available for a growing number of diseases and people, further challenges on the societal, health care system and individual level may arise. There would be a growing need for trained human genetic counselors who can help healthy and diseased individuals to make informed decisions (Heyen 2016), considering uncertainties arising from the potentially changed understanding of knowledge through AI systems. Already known social and psychological issues of health predictions or diagnoses based on genetics – such as societal pressure on individuals with regard to lifestyle related diseases or the right not to know (also of biological relatives) in case of a lack of therapeutic options (Voorwinden et al. 2020) – may be exacerbated if such AI systems are widely adopted. Health inequalities may be increased in case of a lack of financial support by health insurances for effectively health enhancing but costly genetic testing and AI-based diagnoses or prognoses. Research on these issues, especially by actively involving patients or the broader public is still scarce compared to the rapidly increasing technological possibilities.

The generation of trust by 'plausible' explanations on how AI systems work just for the sake of pushing the diffusion of AI systems is highly problematic.

Conclusion

In view of the epistemological, economical, technical, ethical and social challenges outlined above, as well as the current scarcity of evidence on how to best govern them, more research and efforts to experimental policy making are urgently needed. Given the complexity and wide scope of these challenges, broad societal debate and mutual learning by different forms of inclusive dialog activities, will be needed to improve research agendas and current regulatory proposals. These activities should involve stakeholders and publics – in order to harness the potentials and minimize risks for improved quality of care and life. By exploring and providing an overview of possible applications, actors and challenges, the article strives to help to identify and discuss most realistic scenarios in the needed societal dialogue.

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