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ISSUE BRIEF

The Ethics of Research at the Intersection of Functional Genomics and Artificial Intelligence

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The Problem

The field of functional genomics aims to examine the biological systems that contribute to particular phenotypes based of varying genomes.[1] Functional genomics builds off the Human Genome Project's legacy of discovery-driven scientific inquiries to understand how and when genes are expressed, regulated, and interconnected.[2] Recently, functional genomics researchers have sought to couple high-throughput experimental technologies with computational methodologies based on machine learning and artificial intelligence (AI). This has brought to light a confluence of novel ethical tensions,[3] arising from the intersection of basic biology, computer science, and AI.[4] Much attention has been dedicated to the ethical, legal, and social implications (ELSI) and challenges associated with implementing interventions that result from genomics-related research, such as those advancing precision medicine. The ethical issues associated with bench science at the early stages of the AI lifecycle have received less attention and merit further examination, as addressing issues early on can mitigate downstream challenges, including those related to equity and privacy.

Background

Functional genomics aims to examine "how genes and intergenic regions of the genome contribute to different biological processes."[4] These components consist of different cell biology systems examined as different "omics," such as genomics, transcriptomics, proteomics, and metabolomics, among others. The multi-omics nature of functional genomics facilitates the understanding of how the various layers of molecular information bridge genotypic and phenotypic characteristics.[5] This integration of diverse omics data enables researchers to uncover complex interactions within biological systems, offering a more holistic view of how genetic (and ultimately environmental) factors contribute to observable traits. By leveraging these insights, functional genomics has the potential to identify novel biomarkers, predict individual responses to interventions, and uncover therapeutic targets, thereby addressing challenges in understanding rare diseases and population-level variations.

Structural Impacts on Decision Making

Multiple structural factors implicitly or explicitly influence how functional genomics research is conducted. These factors need to be considered when evaluating the moral integrity of scientific practices, especially as the application of AI may increase the risk of exacerbating historically biased practices. These structural factors include, but are not limited to:

- Scientists' high level of expertise and specialization in a specific topic may guide their choice of which conditions to investigate, which methods to use, and which patient populations to prioritize.

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- Funding agencies' priorities, which can be based on societal values, may impact which research areas benefit from investment and which ones are neglected.
- Scientists may prefer a particular cell line because it is more accessible, less expensive, or more conducive to experimental manipulation. Furthermore, scientists may choose a cell line because it has been used by many others in the past and hence it is associated with large amounts of previous data useful for integration and cross-comparison. Such factors can result in an ethically problematic underrepresentation of cell lines from minority populations or rare diseases.
- The majority of widely available cell lines are derived from individuals of European descent. This parallels other commercial and open genomic databases, such as the Personal Genome Project,[6] and sets the stage for training AI models on historically biased datasets.

Ethical Points to Consider *(see Table 1)*

1. Implications for Generalizability

When AI-aided functional genomic research examines the multi-omics characteristics of a small number of cell lines, the generalizability of the project has a defined scope. This aspect follows the trend set by the Human Genome Project's legacy of focusing on discovery-driven science, while also implicitly contributing to the contemporary "precision medicine" movement that has been growing since the early 2010's.[7,8] In general, precision medicine strives to acquire large amounts of health information from patients with the goal of finding each individual's optimal treatment. The mantra that "knowledge is power" may result in patients being considered increasingly responsible for their own health, as increasing amounts of data are collected from them regardless of causative, external sociologic factors that may be out of their control.[9] In the research context, precision medicine is also challenging traditional clinical trial methodology—which relies on large cohort studies to evaluate a treatment's safety and efficacy—as cohorts are stratified into smaller and smaller sample sizes based on the unique physiologic presentation of patients.[10,11] As such there have been novel clinical trial designs, like basket trials, implemented in their stead.[12]

2. Incorporating Diversity into Functional Genomics Research

Following public calls for systemic changes in the summer of 2020, there has been increasing pressure on the field of functional genomics to "get race right."[13] Given the biases that racial categories entail, it's tempting to simply try and remove the socially constructed notion of race from science altogether. However, some structural practices of science are built to perpetuate it.[14] Despite this challenge, an honest pursuit of genetic diversity in research studies, such as using race and/or ethnic categories as imperfect guides to increasing inclusivity, helps balance the pursuit of objective scientific findings in an inherently biased world. For example, in the case of the increased mortality from triple negative breast cancer among African American women, research is ongoing to parse environmental causes of genomic instability from underlying inequalities in healthcare access.[15] Going beyond the need for genomic diversity, it remains unclear for the omics field where the ethical imperative to strive for inclusive samples becomes outweighed by the objective nature of the research being conducted. Given the insights that different populations can contribute to scientific knowledge, it makes sense to strive for genomic diversity; however, it may be less clear why there should be such a requirement for scientists studying the basic, fundamental science of protein-protein interactions. Thus, which omics level(s) ought to incorporate diversity remains a topic open for further examination.

3. The Value of Interpretability

The absence of explainability or interpretability in AI-based research may reduce the trustworthiness of the science, which represents an ethical challenge.4 Recently, visible neural networks (VNNs) that use experimentally derived maps of cellular architecture as the foundation for machine learning approaches have been developed and successfully applied to mitigate some of the "black box" nature of AI-driven predictions.[16,17] However, it remains unclear where else interpretability should be prioritized in any given project. For example, which component of the omics data ought to be easily interrogatable and why? Additional empirical social science research (e.g., clinical surveys and interviews) is necessary to explore whether transparency (i.e., explainability or interpretability) has an impact on trust in and trustworthiness of interventions that are based on AI-powered research. Moreover, empirical research is needed to explore methods of engagement with users and characterize how these methods may impact trust. This is especially important in the context of a healthcare system with a racist and classist history that continues to influence the present.[18]

4. Impact of Legacy Cell Lines on Consent Practices

The informed consent documentation associated with many legacy cell lines is vague and often non-existent. Even though the Common Rule does not currently require that de-identified specimens be obtained with informed consent,[19] such a standard is becoming harder to rely on as AI improvements continue to increase the capacity for patient re-identification through their genomic information.[20] Thus, it is strongly recommended that, when possible, researchers use cell lines with clear, documented consent. Such a principle is not absolute, as it is also understood that such ethical considerations must be balanced against availability of resources, reliability of the cell line, and prioritization of underrepresented demographics and diseases. Researchers should continue to consider all these variables carefully, weighing them against one another, while aiming to select cell lines that have clear, documented consent. However, as the medical landscape continues to adjust to the integration of AI technologies, simply relying on informed consent could prove insufficient in a few decades. Thus, in the spirit of transparency that consent fosters, scientists are encouraged to interact with the relevant communities regarding their research endeavors (e.g., tissue sample donors or their descendants, patient populations, disease specific advocacy organizations, etc.).

5. The Role of Ethics in Basic Research

There are several examples of successful collaborations between ethicists and laboratory scientists, such as determining whether a product of stem cell research should be classified as an embryo and how to best describe nervous system organoids of varying morphologies.[21] Such collaborations strive to address ethical issues as they emerge in basic science, to respect ethical values, and to improve practices that may have downstream implications in terms of resulting products. Ethics plays a critical role not as a restrictive force, but as an enabler of responsible innovation by embedding moral considerations early in the research lifecycle. Neglecting ethics can result in the unintentional incorporation of biases into AI models, further exacerbating inequalities and reducing public trust. Successful collaboration between scientists and ethicists needs to occur over time to foster mutual trust through co-reasoning, where each person openly participates in shared decision making.[21,22] Such collaboration can help integrate ethics into AI research in ways that facilitate responsible innovation, rather than exacerbating the perception that ethics “polices” scientific research.[23]

Conclusion

The ethical tensions associated with functional genomics research that employs AI deserve more dedicated scholarship. Prioritizing this multidisciplinary research helps tease apart the inherent structural factors that influence value-laden decisions in the scientific process, the commitments that come with research relying on small sample sizes, the ambiguities surrounding diversity and interpretability requirements within multi-omics research, and the challenges of utilizing legacy cell lines and de-identified specimens moving forward. Integrating ethical considerations into these areas—such as ensuring transparency in AI models, incorporating diverse datasets, and balancing consent practices—helps mitigate potential downstream challenges in resulting medical applications. Proper integration of ethics into the research ecosystem, particularly early on in the lifecycle, ensures that research practices benefit from insights before ethical challenges are imprinted into the resulting products of such labor-intensive work.

Table 1.
Ethical Points to Consider in Functional Genomics Research Using AI

Ethical Point	Description	Key Implications
1. Implications for Generalizability	Functional genomics research often relies on small, specific datasets, raising concerns about the generalizability of results. The rise of precision medicine emphasizes personalized data but may unfairly shift responsibility for health outcomes to individuals while ignoring broader sociological factors.	■ Risk of bias in precision medicine. ■ Challenges to traditional clinical trial models due to smaller, stratified cohorts.
2. Incorporating Diversity	While genomic diversity is essential for understanding population-specific traits and addressing health disparities, the need for diversity at other "omics" levels (e.g., proteomics) is less clear. Structural scientific practices perpetuate racial biases, making it vital to approach diversity as an ethical imperative.	■ Ethical tension in balancing inclusivity with scientific objectivity. ■ Need to ensure that research benefits all populations, especially underrepresented groups.
3. Value of Interpretability	AI research's "black box" nature can undermine trust and transparency. Efforts to improve interpretability, such as using Visible Neural Networks, are promising but require further empirical research to determine where transparency matters most in omics studies.	■ Trustworthiness of AI-powered research depends on transparency. ■ Engagement with stakeholders (e.g., clinicians, patients) needed to improve trust and acceptance.
4. Consent and Legacy Cell Lines	Many legacy cell lines lack clear consent documentation. As AI advances increase re-identification risks, reliance on de-identified specimens raises ethical concerns. Researchers are encouraged to use cell lines with documented consent while balancing resource availability and inclusion of underrepresented groups.	■ Growing ethical challenges in using legacy cell lines. ■ Need for evolving consent practices in response to AI's data re-identification capabilities.
5. Ethics in Basic Research	Collaboration between ethicists and scientists fosters responsible innovation. This includes co-reasoning on emerging issues like the classification of stem cell research products or nervous system organoids. Ethics should be integrated early in research to avoid downstream ethical conflicts.	■ Encourages trust-building and ethical foresight in research. ■ Avoids perceiving ethics as a "policing" mechanism, ensuring mutual respect and integration in workflows.

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