

Participatory Genomic Research: Ethical Issues from the Bottom Up to the Top Down

Heide Aungst,¹ Jennifer R. Fishman,²
and Michelle L. McGowan^{3,4,5}

¹Center for Pediatric Genomics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229; email: heide.aungst@cchmc.org

²Biomedical Ethics Unit, Department of Social Studies of Medicine, McGill University, Montreal, Quebec H3A 1X1, Canada; email: jennifer.fishman@mcgill.ca

³Ethics Center, Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229; email: michelle.mcgowan@cchmc.org

⁴Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio 45229

⁵Department of Women's, Gender, and Sexuality Studies, University of Cincinnati, Cincinnati, Ohio 45221

Annu. Rev. Genom. Hum. Genet. 2017. 18:357–67

First published as a Review in Advance on April 19, 2017

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

<https://doi.org/10.1146/annurev-genom-091416-035230>

Copyright © 2017 by Annual Reviews.
All rights reserved

Keywords

participatory genomic research, citizen science, patient advocacy, crowdsourcing, public engagement with science, research ethics

Abstract

Participatory approaches to genomic research manifest along a continuum from bottom-up citizen-science initiatives designed to liberate scientific inquiry from the constraints of traditional research institutional contexts and professional practices to top-down investigator-initiated studies designed to expose the public to scientific research processes and build its support and enthusiasm for genomic research. With foundations as varied as open science, crowdsourcing, patient advocacy, social media, the digitization of health, and the neoliberalization of academic research, a range of ethical frameworks inform the modes of participatory genomic research. Using illustrations from citizen genomic science, patient advocacy, and investigator-led and government-initiated genomic research efforts, we argue that as participatory genomic research pushes the conventional research boundaries toward a more democratizing ethos, it challenges scientific practices and the ethical conduct of genomic research both within and outside of the traditional sites of biomedical innovation.



ANNUAL REVIEWS Further

Click [here](#) to view this article's online features:

- Download figures as PPT slides
- Navigate linked references
- Download citations
- Explore related articles
- Search keywords

INTRODUCTION

Interest in individual health management, advances in mobile technologies, and the ubiquity of social media platforms have led to heightened expectations for individuals to acquire more self-knowledge with the aim of managing their health. Whether through wearable biomonitoring tracking devices, direct-to-consumer genetic testing, or emerging models of shared decision making in the clinic, health care is moving from top-down paternalism to a patient-centered focus—no longer asking just “What’s the matter with you?” but also “What matters to you?” (4).

Paralleling this trend, biomedical research is also expanding out of the ivory tower and into garages and community laboratories, challenging the traditional academic models of science to include citizen science and scientists. Many in the traditional genomics research community have willingly embraced this expansion as a win-win—working with individuals or patient advocacy groups on their agendas; creating open, accessible data platforms; and encouraging participation through crowdsourcing for large-scale data collection.

Such novel approaches have been called public-participation, citizen-driven, crowdsourced, participant-led, participant-centric, and participant-driven genomic research, and they have varied in terms of the aspects and degrees of participation of nonscientific experts in research initiatives (13, 22, 46). As Woolley et al. (49) argued, participatory approaches to genomic research manifest along a continuum from bottom-up citizen-science initiatives designed to liberate scientific inquiry from the constraints of traditional research institutional contexts and professional practices to top-down investigator-initiated research designed to acquaint the public with scientific research processes and build its support and enthusiasm for them. With foundational values as varied as open science, crowdsourcing, patient advocacy, social networking, the digitization of health to generate both individual and aggregate data, and entrepreneurial academic research, a range of ethical frameworks inform the modes of participatory genomic research that we describe here. Using illustrations from citizen genomic science, patient advocacy, and investigator-led and government-initiated genomic research efforts, we argue that as participatory genomic research pushes the conventional research boundaries toward a more democratizing ethos, it challenges both scientific practices and research ethics in novel and uneven ways.

BOTTOM-UP APPROACHES TO PARTICIPATORY GENOMIC RESEARCH

Do-it-yourself (DIY) genomic sequencing may seem far-fetched—not many people can set up the technology in their home or garage and sequence their own genomes. However, bottom-up approaches to participatory genomic research start with the premise that genomic information and science should be available and accessible to anyone, regardless of their level of training or affiliation with traditional hubs of biomedical research in academia and industry (29). Bottom-up approaches to participatory genomic research are characterized by participants playing central roles in setting research agendas and priorities, funding research, and collecting, analyzing, and disseminating data (2, 19, 37). These participatory genomic researchers often work from laboratories that consist of servers and computing devices as much as wet lab apparatus, relying on information-processing software for data-driven, discovery-based analysis rather than hypothesis-driven experimentation (29). For example, the group DIYbio, which was founded on the belief “that biotechnology and greater public understanding about it has the potential to benefit everyone” (11), teaches participants to sequence their own data from cheek swabs to discover predisposition to diseases.

Given the decreasing costs and sizes of sequencing equipment, DIY whole-genome sequencing might not be as far off as it once seemed. Clive Brown believes that he is the first person to use next-generation sequencing on his own DNA (17, 18). Of course, he works for Oxford Nanopore,

the British biotech company that sent the first sequencer into space. But, he says, he is working toward making it possible for everyone to do this on their own: “With self-sequencing you are in control. Part of that means asserting your right to understand your own biology, and, in this case taking ownership of your own genetic profiles” (18). He believes that self-sequencing could become a powerful health monitoring tool, tracking changes over time and generating a baseline for health. “We could then look for meaningful perturbations from those baselines, both within individuals and also between groups (if they share their data) and also across geographical domains,” he explains (18). By making the argument that self-sequencing can aid in health monitoring, Brown is advocating an ethic of personal responsibility for monitoring and managing one’s health and risk susceptibilities, an example of what Michel Foucault has called “technologies of the self” (15).

But with an assertion of personal responsibility for one’s own health comes the potential for individuals and groups to be compelled to take on that responsibility, perhaps because public and private institutions that have historically monitored and managed population health are scaling back their roles (14). Furthermore, as has also been argued about direct-to-consumer genomic testing (30), the progress and potential of DIY sequencing could become a means to better health yet simultaneously creates a process that challenges traditional power relations within health care, with individuals obtaining personal health information before most primary care doctors even know how to work with genomic data. Likewise, in research, kitchen- or garage-based DIY whole-genome sequencing may compel researchers to go where the data are—and that means finding people who have genomic sequencing data and are willing to share them.

Another form of DIY participatory genomic research involves data collection through the Internet. Researchers are enlisting people who are willing to share personal health information through websites such as PatientsLikeMe (<https://www.patientslikeme.com>) by uploading data gathered from tracking devices or smartphones. This type of crowdsourcing gives researchers unprecedented access to large amounts of data from willing participants unbounded by geographical region. As this type of research has increased in popularity, so have numerous organizations that feed into it, such as DIYgenomics, HiveBio, Indie Biotech, and SNPedia. One recent study that examined these and similar groups argued that the missions underpinning the work of these organizations are not uniform but draw to varying degrees from a set of overlapping principles, including democratizing access to genomic information; deinstitutionalizing scientific practices, education, and outreach; increasing the affordability of genomic technologies; and reenvisioning research participation and funding (29). By seeking to redefine genomic expertise and the ownership of data and deinstitutionalizing scientific research and its priorities, these bottom-up approaches to participatory genomic research clearly challenge the existing ethos guiding the conduct of genomic research in traditional settings in a way that is both subversive and entrepreneurial (5, 9, 10, 21). By disrupting the hierarchy of scientific knowledge production, agenda setting, professionalism, and scientific spaces, bottom-up participatory genomic research approaches are poised to challenge the norms of the well-established genomic research enterprise (29).

PATIENT-CENTRIC APPROACHES TO PARTICIPATORY GENOMIC RESEARCH

Whereas bottom-up participatory genomic research has emerged largely in contrast to and outside of traditional academic and commercial genomic research contexts (29), patient advocates have long called for cooperative involvement and open governance strategies with both academic and commercial researchers through the mantra “no data about me, without me” (12). In this vein, a recent editorial headline in *Science Translational Medicine* read “The Study Is Open: Participants Are Now Recruiting Investigators” (45). In the editorial, Sharon Terry, a cofounder

of PXE International and Genetic Alliance, calls for an end to the patient-versus-researcher model, deriding the classic image of a patient “sitting on the exam table in a flimsy johnnie—the epitome of information and power asymmetry” (45, p. 1). Instead, she advocates for the creation of “authentic” partnerships between participants and researchers on the research continuum from study design to dissemination of results, concluding, “It is my hope that we can take a new tack and use the power of grassroots leadership and disruption, crowdsourcing, and citizen science to capitalize on the best of the current system’s expertise and passion” (45, p. 3).

Since the 1980s and 1990s, patient advocacy groups have partnered with scientists to build the evidence base for their causes, becoming indispensable to the scientific knowledge production process (26, 38, 39). Although patient advocacy has historically involved starting a support group or foundation, working to empower affected individuals, and challenging scientific expertise on rare diseases, more recently patient advocacy groups have begun to use the language of collaboration to describe their interactions with genetic and genomic researchers (26, 38, 39). Today, especially in genomics and for rare diseases, participants are finding their own investigators and raising funds for research, searching a growing number of open databases to find others whose children have a mutation in the same gene, leveraging direct-to-consumer genomic test results, and even conducting the research or experiments on their own as citizen scientists. As with coproduction in patient care, which has moved along a continuum from awareness to participation to contribution to ownership (43), some families and patient advocacy groups are now formulating research questions and designing studies, assembling research components, disseminating findings, locating willing researchers, and acting as contributors and coinvestigators, thereby asserting more control over the genomic research process (26). Such a movement in biomedical research is palatable to some researchers, but for others it may be received as a direct challenge to the existing order of scientific knowledge production in which the research process and data quality can be managed by certified experts (26, 29). Nevertheless, patient-centric approaches to participatory genomic research are poised to challenge how genomic research is designed and conducted—and, ultimately, depending on how participants use their data, could transform the notions of scientific expertise and collaboration (26). This potential will be mediated by professionals’ willingness to receive genomic information in these ways and by the utility and robustness of the genetic knowledge itself.

In a collaborative approach, rare disease patient advocacy often includes individuals using social media or public databases to connect with others who might have mutations in the same gene. This participant-driven matchmaking has evolved from social media searches of parents trying to find other children with similar phenotypic features or mutations in the same gene to more formalized open-source databases. Parents are not only participating in matchmaking, but are also trying to connect with others to solve a diagnostic odyssey for their child. One early example was *My Daughter’s DNA*, which was developed by a father, Hugh Reinhoff, as he tried to find more about his daughter’s undiagnosed condition (41). Reinhoff has been lauded as a trailblazer in inspiring other parents to participate in online communities to discuss and investigate complicated diagnoses (28). Efforts such as this have benefited from the availability of web-based social networking platforms and the phenomenon of crowdsourcing to engage patients and their families in collecting and analyzing data (47).

One of the most famous cases is Matt Might’s 2010 blog post “Hunting Down My Child’s Killer,” which began with these powerful words:

I found my son’s killer. It took three years. But we did it. I should clarify one point: my son is very much alive. Yet, my wife Cristina and I have been found responsible for his death. My son Bertrand has a new genetic disorder. (32)

This post eventually led to 15 more verified cases of *NGLY1* deficiency worldwide. As the network of parents grew, Might and another father, Matt Wilsey, documented the power the parents have had in the journey of researching the disorder:

As untrained people, we are not qualified to analyze whole-exome/whole-genome data. We cannot develop a therapeutic compound. We cannot design a diagnostic assay. That being said, parents can offer observations and ideas, and we can push for solutions. Nineteen months after the initial report . . . five viable approaches to treatment are under active consideration, thanks to relentless digging by afflicted families. One parent found a compound that seems to have measurably raised the quality of life in one *NGLY1* child. Another parent read about a novel (but relevant) fluorescent assay and shared it with the *NGLY1* team. The team had not heard about it, but it has become a fundamental tool in the functional analysis of *NGLY1*. One parent has formed and funded a multi-institutional network of researchers to tackle specific projects. The capabilities of parents and the social media are frequently underestimated; we are here to say: join us! As the discovery of new diseases explodes with the deployment of NGS, we hope clinicians will consider this model seriously. (33, pp. 736–37)

Chong et al. (6) reported on a similar case, a family that established the website Milo’s Journey (<http://milosjourney.com>), a Facebook page, and a Twitter account to document phenotypic features of their child and variants of unknown significance on the *KDM1A* gene and to find other families, while simultaneously emailing investigators to try to persuade them to study their child’s condition. This experience led the family to connect with researchers at the University of Washington Center for Mendelian Genomics, which in turn led the investigators to start a web-based portal, MyGene2 (<https://mygene2.org>), for families to submit phenotypic information and sequence data that would then be accessible to researchers worldwide. The researchers concluded that using this type of infrastructure to empower families will accelerate the pace of gene discovery for Mendelian conditions and that “the rapid translation of these discoveries into diagnostic tests and new starting points for repurposing or developing therapeutics would, in turn, improve the overall care of families with rare disease” (6, p. 794).

Like MyGene2, other research facilities have started databases to serve as matchmakers between patients or families and researchers. The database Genomes in Need (<https://sequencing.com/knowledge-center/genomes-in-need>) is an open-source database for parents that describes itself as “the first time crowdsourcing has been used to leverage the combined brainpower of the world to help decipher the genomes of children that have an undiagnosed illness” (44).

GenomeConnect (<https://www.genomeconnect.org>) is a patient portal supported by the Clinical Genome Resource (ClinGen), a National Institutes of Health–funded resource that curates and annotates the clinical relevance of genomic variants for use in precision medicine and research. GenomeConnect “was developed to empower patients to help researchers and clinicians in the effort to understand the genetic contribution to health and disease . . . [and] to engage patients as partners in data sharing efforts” (1). Participants receive a unique identifier code to securely share genomic and health data and to connect with researchers, laboratories, and other patients. Approved personnel can later reidentify participants to recontact them (25). The developers of GenomeConnect recognize that self-reported patient data are valuable resources for research and can serve as an essential educational tool, making patients aware of the importance of sharing health and genetic data in order to improve understanding, research, and development of genetic tests or therapies.

With increasing numbers of parents armed with whole-genome and whole-exome data, many new genomic matchmaking models have been created to connect people with similar phenotypes and/or mutations. One is Matchmaker Exchange (<http://www.matchmakerexchange.org>),

which is supported by the Global Alliance for Genomics and Health, the International Rare Diseases Research Consortium, and ClinGen (27). However, as Lambertson et al. (27) have pointed out, most of the people involved at this level are geneticists and informaticists, which omits a key component that can make such a network successful—participant-led matchmaking. They have further argued that participant-led matchmaking and research may be advanced by parents' use of multiple forms of communication, development of expertise, and capacity to make decisions and share information in a way that extends “beyond what institutional data holders—irrespective of their dedication—are legally and ethically allowed to disclose” (27, p. 968). Although families involved in patient-centric participatory genomic research may feel ethically compelled to use whatever tools are available to them to optimize their life chances, Lambertson et al. (27) argued for a flexible approach to participant-led genomic matchmaking that would allow participants to determine the degree of privacy risk they are willing to assume in engaging in genomic research and would allow them to change their thresholds for risk over time. Such an approach may be at odds with existing codes of research ethics that frame protecting genomic research participants' privacy as of primary importance and not worth risking for the sake of data sharing (27). This could pose challenges for patients and families hoping to collaborate with academic and industry researchers, who are held to specific regulatory standards for the management of human subjects research data and personal health information and who pride themselves on protecting patient privacy, confidentiality, and personally identifiable information (29).

For many years, Genetic Alliance has led the way by providing a model for advocates of genetic research, with the philosophy that biological data belong to the affected individuals. Genetic Alliance and Private Access have now developed the Platform for Engaging Everyone Responsibly (PEER) to give individual research participants access to health information and the capacity to decide how much and with whom to share data. This participant-centric approach engages individuals at various points throughout the research project, which may be particularly valuable to those with rare diseases or parents on a diagnostic odyssey. Lambertson et al. (27, p. 973) argued that “it is time we not only encourage this engagement, but also build the resources to sustain it.”

When individuals or families find a handful of other people—or even just one other person—with similar mutations and phenotypic features and then engage investigators to advance research and discover therapies, it can be mutually gratifying to see the realization of the goals of precision medicine when a researcher is unraveling the health complexities of an individual or group affected by a rare disease. As the above examples show, patient advocacy groups and parents of patients with rare disorders use a wide range of tools to contribute to genomic discovery and research, from initial study design through receipt of aggregate (and, more rarely, individual) study results. The approaches that these groups take range from bottom-up layperson-initiated genomic research efforts to top-down investigator-initiated research in partnership with affected families, but what they have in common is a clear focus on improving the health and lives of patients and families living with rare or undiagnosed genetic and genomic conditions. This personal and familial lens contributes to the sense of urgency in moving genomic discovery and research forward through what social theorist Patricia Hill Collins (8) has called coalitions of convenience and coalitions of conscience to give patients and families a voice at the table and to highlight the personal significance of genomic research. Coalitions of convenience may emerge out of expediency and affinity for specific issues, but shared ethics may not be central; coalitions of conscience are more likely to emerge out of necessity, commitment, and personal or collective identity, and ethics is central to the formation and critical praxis of a participatory coalition. Collins argues that coalitional politics requires recognition that different constituencies may have independent and intertwined struggles that motivate their interests in coalition building (8). Hence, an ethos of flexible solidarity ought to constitute a core principle of coalition building in patient-centric participatory genomic research.

TOP-DOWN APPROACHES TO PARTICIPATORY GENOMIC RESEARCH

Although personal motives drive families with rare conditions to contribute to genomic research, other motives, such as altruism and the wish to contribute to wider societal knowledge, propel those willing to contribute to larger, investigator- or government-initiated genomic research efforts (23, 35, 36). These altruistic motives are what many large national initiatives, including the Precision Medicine Initiative (PMI), depend on for their ultimate success. One advantage of aggregating the information into large databases, as the PMI proposes, is to stratify “empiric genomic disease risk associations, and to lesser degrees, [make] generalizations from racial and ethnic ancestry” (20, p. 23). Announced by President Barack Obama in January 2015, the PMI plans to enroll a cohort of one million volunteers, which would make it the largest longitudinal study in the United States (42). In a rhetorical twist, in October 2016 the PMI changed the cohort’s name from the PMI Cohort Program to the *All of Us* Research Program, evoking a sense of collective responsibility for participation in the research and altruistic actions for the public good (31). The shift from technical words, like cohort, to the easily understood phrase “all of us” is also clearly a way for researchers to encourage public participation by avoiding stilted academic rhetoric in favor of commonly understood and accessible language. However, as Juengst et al. (20) have argued, this move may also suggest not only collective stakes, but collective obligations to participate in genomic research, which may be stronger for groups whose genomic characteristics are of particular interest to genomic researchers, such as racial and ethnic minorities who have been underrepresented in genomic research.

Another critical word choice in the PMI is its proposition to engage one million “partners.” The PMI has been framed as an effort to “change the way we do research,” and its promoters argue that “participants will be partners in research, not subjects, and will have access to a wide range of study results” (7). The agreement with participants reads as if it is an all-or-nothing, take-it-or-leave-it endeavor, so even though the PMI is engaging “partners,” it is unclear what degree of control they will have over what happens with their genomic, phenotypic, and lifestyle information. Participants “must be willing to contribute data freely, generously, regularly, and longitudinally, including 1) agreeing to ongoing accessibility of their electronic health records; 2) participating in and sharing results of additional clinical and behavioral assessments; 3) contributing DNA samples and other biologic specimens; and 4) participating in mobile health (mHealth) data-gathering activities to collect geospatial and environmental data” (42, p. 744). How much engagement will each partner/participant have—or will it be up to them? Will they simply donate their biospecimens and give consent for access to their health records, or will they engage in a type of citizen science? Will they be given access to some form of technology to examine their own genomes, or will active participation be limited to some type of field reporting on health or environmental data?

Whether or not a top-down strategy to engage the public will lead to participants driving the research questions and study design remains to be seen, although there are precedents for top-down investigator-led participatory genomic research approaches. Harvard University’s investigator-led Personal Genome Project calls participants in its open-access whole-genome sequencing initiative “co-drivers of the project” (3, p. 693) who work in partnership with the investigator (29). Large initiatives like the PMI fall on one far end of the participatory genomic research spectrum, one that has been initiated and will be managed by investigators whose success hinges on significant participation and buy-in from the population. This will require the organizers of the PMI and other such initiatives to invest heavily in recruitment efforts, addressing how privacy, confidentiality, and stewardship of participants’ data will be managed and protected. Trust is well understood as an essential component for prospective participants in research (49). Loss of trust in their government puts national research projects—especially in sensitive areas, like genomics—at risk.

One example of stakeholders joining together to promote participatory genomic research is the Melbourne Genomics Health Alliance in Australia, which brings together government support, leading health and research organizations, patients and their families, clinicians, and researchers. The alliance even engaged a community advisory group, which provided stories to patients and worked on creating an understandable consent document that resulted in 90% of participants agreeing to share genomic information for research purposes (48). Moreover, 96% said that they felt they had enough information to make a decision about testing. These are rough measures of success but seem to corroborate the idea that a collaborative approach to genomic research endeavors can successfully enroll the number of participants that researchers need.

The participatory turn in the approaches of the PMI and the Melbourne Genomics Health Alliance acknowledges that traditional sites of biomedical research increasingly require growing pools of research participants, and government, academic, and corporate researchers are embracing populist approaches to increase the appeal of participating in genomic research processes (49). Approaches taken vary from inviting the public to participate in online games that help solve scientific problems to tapping the public for data sampling, research funding, and knowledge transfer (24, 29).

The top-down approaches to participatory genomic research described here illustrate the goal to “propel science within the constraints of its traditional institutional contexts, and under the supervision of professional scientists” (49, p. 3). However, cultural critic Henry A. Giroux (16) has characterized the entrepreneurial approach that academics have taken to their research in recent decades as a reflection of the neoliberal ideology embraced by universities as state and federal funding for higher education has diminished. Within the neoliberal university, research ideas are assessed instrumentally and deemed successful if they obtain external funding and increasingly strong ties between academic researchers and corporate entities are promoted (16). The increasing neoliberalization of academic research has thus required rethinking how to fund and ensure adequate participation in genomic research, beyond the conventional government and market-based sources of corporate and industry funding. Indeed, academic researchers explain that the instrumentalist neoliberal ideology of the university has in part led them to adopt populist and entrepreneurial participatory genomic research strategies to achieve their professional and career goals (29, 34). As genomic researchers adapt through calculation and entrepreneurialism, and perhaps even a social responsibility to their participants, their practices raise new regulatory and ethical questions related to who constitutes an investigator, ethical research practices, conflicts of interest, credit sharing, and ownership of and responsibility for data and findings that have not been addressed systematically (29, 40).

CONCLUSION

Participatory genomic research describes a diversity of projects with various degrees of engagement in crafting research agendas, study design, contribution of and access to data, and control of personal genomic information. At a minimum, these projects claim to want to democratize and promote public engagement with genomic science. For some groups promoting participatory genomic research, the goal is more about deinstitutionalizing science itself by “creating an alternative technical-knowledge infrastructure for genomic research and knowledge production that operates outside traditional modes” (29, p. 27). An example is Terry’s (45, p. 3) call for “a disruptive revolution from the outside,” and her hope, as quoted above, that we can “take a new tack and use the power of grassroots leadership and disruption, crowdsourcing, and citizen science to capitalize on the best of the current system’s expertise and passion.”

There are certainly some who want researchers to continue to keep data in the ivory tower and behind corporate walls, and others who want to take data into their own garages, to experiment at will, even if that means going against recommendations in important areas, like dissemination of genetically modified organisms, or against norms in research ethics. But to move genomic research forward on sound footing, we must recognize that participatory genomic research is already under way at various points along this spectrum and that such research may even be necessary in order to gather data from the large numbers of people needed for robust genomic studies. We should be attentive to the similarities and differences in the ethos of these efforts, which will raise new challenges for the ethical conduct of genomic research both within and outside of the traditional sites of biomedical innovation (29). Accepting that both coalitions of convenience and coalitions of conscience can make valuable contributions to the pursuit of genomic knowledge may alleviate some of the tension to settle upon a single code of ethics and governance for participatory genomic research—whether it emerges from the bottom up, the top down, or somewhere in between.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

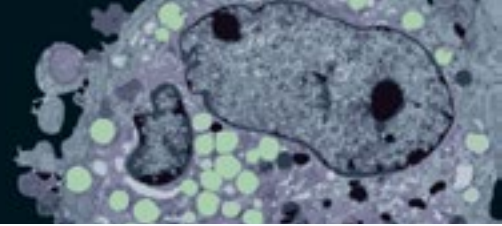
Support for the preparation of this article was provided by National Human Genome Research Institute grant R01 HG005277.

LITERATURE CITED

1. AltaVoice Patient Insights Netw. 2017. *About GenomeConnect*. <https://www.genomeconnect.org/about-connect/genomeconnect.html>
2. Anderson NB, Caleb C, Hartzler A, Edwards K. 2012. Participant-centric initiatives: tools to facilitate engagement in research. *Appl. Transl. Genom.* 1:25–29
3. Angrist M. 2009. Eyes wide open: the Personal Genome Project, citizen science and veracity in informed consent. *Pers. Med.* 6:691–99
4. Batalden M, Batalden P, Margolis P, Seid M, Armstrong G, et al. 2016. Coproduction of healthcare service. *BMJ Qual. Saf.* 25:509–17
5. Bennett G, Gilman N, Stavrianakis A, Rabinow P. 2009. From synthetic biology to biohacking: Are we prepared? *Nat. Biotechnol.* 27:1109–11
6. Chong J, Yu J, Lorentzen P, Park K, Jamal S, et al. 2016. Gene discovery for Mendelian conditions via social networking: De novo variants in *KDM1A* cause developmental delay and distinctive facial features. *Genet. Med.* 18:788–95
7. Collins FS. 2015. Building the Precision Medicine Initiative National Research Cohort—the time is now. *NIH Director*, Sept. 15. <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/building-precision-medicine-initiative-national-research-cohort-time-now>
8. Collins PH. 2017. *Taking a stand: anti-black racism and coalitional politics*. Presented at Cincinnati Proj. Annu. Symp., 3rd, Cincinnati, OH, Feb. 17
9. Delfanti A. 2011. Hacking genomes. The ethics of open and rebel biology. *Int. Rev. Inf. Ethics* 15:52–57
10. Delfanti A. 2012. Tweaking genes in your garage: biohacking between activism and entrepreneurship. In *Activist Media and Biopolitics: Critical Media Interventions in the Age of Biopower*, ed. W Sützl, T Hug, pp. 163–77. Innsbruck, Austria: Innsbruck Univ. Press
11. DIYbio. 2017. Homepage. <https://diybio.org>
12. Downing A. 2016. *No data about me, without me*. Presented at Festiv. Genom., Boston, MA, June 28–29

13. Eriksson N, Macpherson J, Tung J, Hon L, Naughton B, et al. 2010. Web-based, participant-driven studies yield novel genetic associations for common traits. *PLoS Genet.* 6:e1000993
14. Fishman JR, McGowan ML. 2014. Will personal genomic information transform one's self? In *Genetics as Social Practice: Transdisciplinary Views on Science and Culture*, ed. B Prainsack, S Schicklanz, G Werner-Felmeyer, pp. 29–42. Farnham, UK: Ashgate
15. Foucault M, Martin LH, Gutman H, Hutton PH. 1988. *Technologies of the Self: A Seminar with Michel Foucault*. Amherst: Univ. Mass. Press
16. Giroux HA. 2008–2009. Academic unfreedom in America: rethinking the university as a democratic public sphere. *Works Days* 26/27:45–71
17. Harley L. 2016. First “DIY” human genome offers a new approach to conventional genomics. *Front Line Genomics*, Dec. 14. <http://www.frontlinegenomics.com/news/8993/first-diy-human-genome>
18. Harley L. 2016. Truly personal genomics – Clive Brown, Oxford Nanopore. *Front Line Genomics*, Dec. 14. <http://www.frontlinegenomics.com/opinion/8995/clive-brown-personal-genomics>
19. Irwin A. 1995. *Citizen Science: A Study of People, Expertise and Sustainable Development*. New York: Routledge
20. Juengst ET, McGowan ML, Fishman JR, Settersten RA Jr. 2016. From “personalized” to “precision” medicine: the ethical and social implications of rhetorical reform in genomic medicine. *Hastings Cent. Rep.* 46:21–33
21. Kelty C. 2010. Outlaw, hackers, Victorian amateurs: diagnosing public participation in the life sciences today. *J. Sci. Commun.* 9:C03
22. Kelty C, Panofsky A. 2014. Disentangling public participation in science and biomedicine. *Genome Med.* 6:8
23. Kerath S, Klein G, Kern M, Shapira I, Witthuhn J, et al. 2013. Beliefs and attitudes towards participating in genetic research—a population based cross-sectional study. *BMC Public Health* 13:114
24. Khatib F, Cooper S, Tyka M, Xu K, Makedon I, et al. 2011. Algorithm discovery by protein folding game players. *PNAS* 108:18949–53
25. Kirkpatrick B, Riggs E, Azzariti D, Miller V, Ledbetter D, et al. 2015. GenomeConnect: matchmaking between patients, clinical laboratories, and researchers to improve genomic knowledge. *Hum. Mutat.* 36:974–78
26. Koay PP, Sharp RR. 2013. The role of patient advocacy organizations in shaping genomic science. *Annu. Rev. Genom. Hum. Genet.* 14:579–95
27. Lambertson K, Damiani S, Might M, Shelton R, Terry SF. 2015. Participant-driven matchmaking in the genomic era. *Hum. Mutat.* 36:965–73
28. Maher B. 2013. Father's genetic quest pays off. *Nature* 498:418–19
29. McGowan ML, Choudhury S, Juengst ET, Lambrix M, Settersten RA Jr., Fishman JR. 2017. “Let's pull these technologies out of the ivory tower”: the politics, ethos, and ironies of participant-driven genomic research. *BioSocieties*. In press. <https://doi.org/10.1057/s41292-017-0043-6>
30. McGowan ML, Fishman JR, Lambrix M. 2010. Personal genomics and individual identities: motivations and moral imperatives of early users. *New Genet. Soc.* 29:261–90
31. Meagher KM, McGowan ML, Settersten RA Jr., Fishman JR, Juengst ET. 2017. Precisely where are we going? Charting the new terrain of precision prevention. *Annu. Rev. Genom. Hum. Genet.* 18:369–87
32. Might M. 2010. *Hunting down my son's killer*. <http://matt.might.net/articles/my-sons-killer>
33. Might M, Wilsey M. 2014. The shifting model in clinical diagnostics: how next-generation sequencing and families are altering the way rare diseases are discovered, studied, and treated. *Genet. Med.* 16:736–37
34. Mirowski P. 2017. *What is “open science” supposed to fix?* Presented at Milieux Inst. Arts Cult. Technol., Concordia Univ., Montreal, Feb. 16
35. Neidich A, Joseph J, Ober C, Ross L. 2008. Empirical data about women's attitudes towards a hypothetical pediatric biobank. *Am. J. Med. Genet. A* 146A:297–304
36. Porteri C, Pasqualetti P, Togni E, Parker M. 2014. Public's attitudes on participation in a biobank for research: an Italian survey. *BMC Med. Ethics* 15:81
37. Prainsack B. 2013. Citizen science in health domain. In *Encyclopedia of Creativity, Invention, Innovation and Entrepreneurship*, ed. EG Carayannis, pp. 206–11. New York: Springer
38. Rabeharisoa V. 2003. The struggle against neuromuscular diseases in France and the emergence of the “partnership model” of patient organisation. *Soc. Sci. Med.* 57:2127–36

39. Rabeharisoa V, Callon M, Filiped A, Nunes J, Patersona F, Vergauda F. 2014. From “politics of numbers” to “politics of singularisation”: patients’ activism and engagement in research on rare diseases in France and Portugal. *BioSocieties* 9:194–217
40. Rajan K. 2006. *Biocapital: The Constitution of Postgenomic Life*. Durham, NC: Duke Univ. Press
41. Rienhoff HY. 2016. Reflections on my daughter’s DNA. *Appl. Transl. Genom.* 8:45–48
42. Sankar PL, Parker LS. 2017. The Precision Medicine Initiative’s All of Us Research Program: an agenda for research on its ethical, legal, and social issues. *Genet. Med.* 19:743–50
43. Seid M, Margolis P, Opiari-Arrigan L. 2014. Engagement, peer production, and the learning healthcare system. *JAMA Pediatr.* 168:201–2
44. Sequencing.com. 2017. *Helping children, together*. <https://sequencing.com/knowledge-center/helping-children-together>
45. Terry SF. 2017. The study is open: Participants are now recruiting investigators. *Sci. Transl. Med.* 9:eaaf1001
46. Vayena E, Tasioulas J. 2013. Adapting standards: ethical oversight of participant-led health research. *PLOS Med.* 10:e1001402
47. Vayena E, Tasioulas J. 2013. The ethics of participant-led biomedical research. *Nat. Biotechnol.* 31:786–87
48. Watson L. 2016. Making it real – the impact of consumer co-production. *Consumers Health Forum of Australia*, Nov. 10. <https://chf.org.au/blog/making-it-real-impact-consumer-co-production>
49. Woolley J, McGowan ML, Teare H, Coathup V, Fishman JR, et al. 2016. Citizen science or scientific citizenship? Disentangling the uses of public engagement rhetoric in national research initiatives. *BMC Med. Ethics* 17:33



New From Annual Reviews:

Annual Review of Cancer Biology

cancerbio.annualreviews.org • Volume 1 • March 2017

ONLINE NOW!

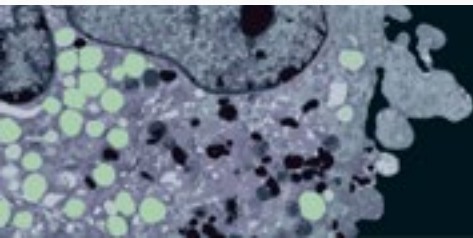
Co-Editors: **Tyler Jacks**, *Massachusetts Institute of Technology*

Charles L. Sawyers, *Memorial Sloan Kettering Cancer Center*

The *Annual Review of Cancer Biology* reviews a range of subjects representing important and emerging areas in the field of cancer research. The *Annual Review of Cancer Biology* includes three broad themes: Cancer Cell Biology, Tumorigenesis and Cancer Progression, and Translational Cancer Science.

TABLE OF CONTENTS FOR VOLUME 1:

- *How Tumor Virology Evolved into Cancer Biology and Transformed Oncology*, Harold Varmus 
- *The Role of Autophagy in Cancer*, Naiara Santana-Codina, Joseph D. Mancias, Alec C. Kimmelman
- *Cell Cycle-Targeted Cancer Therapies*, Charles J. Sherr, Jiri Bartek
- *Ubiquitin in Cell-Cycle Regulation and Dysregulation in Cancer*, Natalie A. Borg, Vishva M. Dixit
- *The Two Faces of Reactive Oxygen Species in Cancer*, Colleen R. Reczek, Navdeep S. Chandel
- *Analyzing Tumor Metabolism In Vivo*, Brandon Faubert, Ralph J. DeBerardinis
- *Stress-Induced Mutagenesis: Implications in Cancer and Drug Resistance*, Devon M. Fitzgerald, P.J. Hastings, Susan M. Rosenberg
- *Synthetic Lethality in Cancer Therapeutics*, Roderick L. Beijersbergen, Lodewyk F.A. Wessels, René Bernards
- *Noncoding RNAs in Cancer Development*, Chao-Po Lin, Lin He
- *p53: Multiple Facets of a Rubik's Cube*, Yun Zhang, Guillermina Lozano
- *Resisting Resistance*, Ivana Bozic, Martin A. Nowak
- *Deciphering Genetic Intratumor Heterogeneity and Its Impact on Cancer Evolution*, Rachel Rosenthal, Nicholas McGranahan, Javier Herrero, Charles Swanton
- *Immune-Suppressing Cellular Elements of the Tumor Microenvironment*, Douglas T. Fearon
- *Overcoming On-Target Resistance to Tyrosine Kinase Inhibitors in Lung Cancer*, Ibiayi Dagogo-Jack, Jeffrey A. Engelman, Alice T. Shaw
- *Apoptosis and Cancer*, Anthony Letai
- *Chemical Carcinogenesis Models of Cancer: Back to the Future*, Melissa Q. McCreery, Allan Balmain
- *Extracellular Matrix Remodeling and Stiffening Modulate Tumor Phenotype and Treatment Response*, Jennifer L. Leight, Allison P. Drain, Valerie M. Weaver
- *Aneuploidy in Cancer: Seq-ing Answers to Old Questions*, Kristin A. Knouse, Teresa Davoli, Stephen J. Elledge, Angelika Amon
- *The Role of Chromatin-Associated Proteins in Cancer*, Kristian Helin, Saverio Minucci
- *Targeted Differentiation Therapy with Mutant IDH Inhibitors: Early Experiences and Parallels with Other Differentiation Agents*, Eytan Stein, Katharine Yen
- *Determinants of Organotropic Metastasis*, Heath A. Smith, Yibin Kang
- *Multiple Roles for the MLL/COMPASS Family in the Epigenetic Regulation of Gene Expression and in Cancer*, Joshua J. Meeks, Ali Shilatifard
- *Chimeric Antigen Receptors: A Paradigm Shift in Immunotherapy*, Michel Sadelain



Contents

The Clinic Is My Laboratory: Life as a Clinical Geneticist <i>Judith G. Hall</i>	1
A Conversation with Kurt and Rochelle Hirschhorn <i>Kurt Hirschhorn, Rochelle Hirschhorn, and Joel N. Hirschhorn</i>	31
Gene Regulatory Elements, Major Drivers of Human Disease <i>Sumantra Chatterjee and Nadav Abituv</i>	45
The Microbiome and Human Biology <i>Rob Knight, Chris Callewaert, Clarisse Marotz, Embriette R. Hyde, Justine W. Debelius, Daniel McDonald, and Mitchell L. Sogin</i>	65
Recent Advancements in DNA Damage–Transcription Crosstalk and High-Resolution Mapping of DNA Breaks <i>Valerio Vitelli, Alessandro Galbiati, Fabio Iannelli, Fabio Pessina, Sheetal Sharma, and Fabrizio d’Adda di Fagagna</i>	87
Cognitive Dysfunctions in Intellectual Disabilities: The Contributions of the Ras-MAPK and PI3K-AKT-mTOR Pathways <i>Sarah C. Borrie, Hilde Brems, Eric Legius, and Claudia Bagni</i>	115
Tailoring Medulloblastoma Treatment Through Genomics: Making a Change, One Subgroup at a Time <i>Borja L. Holgado, Ana Guerreiro Stucklin, Livia Garzia, Craig Daniels, and Michael D. Taylor</i>	143
The Yin and Yang of Autism Genetics: How Rare De Novo and Common Variations Affect Liability <i>Pauline Chaste, Kathryn Roeder, and Bernie Devlin</i>	167
Advances in Preimplantation Genetic Testing for Monogenic Disease and Aneuploidy <i>Nathan R. Treff and Rebekah S. Zimmerman</i>	189
Application of Panel-Based Tests for Inherited Risk of Cancer <i>Payal D. Shah and Katherine L. Nathanson</i>	201
Gene and Variant Annotation for Mendelian Disorders in the Era of Advanced Sequencing Technologies <i>Samya Chakravorty and Madhuri Hegde</i>	229

Recent Advances in Mitochondrial Disease <i>Lyndsey Craven, Charlotte L. Alston, Robert W. Taylor, and Doug M. Turnbull</i>	257
The Genetic Diversity of the Americas <i>Kaustubb Adbikari, Juan Camilo Chacón-Duque, Javier Mendoza-Revilla, Macarena Fuentes-Guajardo, and Andrés Ruiz-Linares</i>	277
On the Evolution of Lactase Persistence in Humans <i>Laure Séguérel and Céline Bon</i>	297
A Robust Framework for Microbial Archaeology <i>Christina Warinner, Alexander Herbig, Allison Mann, James A. Fellows Yates, Clemens L. Weiß, Hernán A. Burbano, Ludovic Orlando, and Johannes Krause</i>	321
Participatory Genomic Research: Ethical Issues from the Bottom Up to the Top Down <i>Heide Aungst, Jennifer R. Fishman, and Michelle L. McGowan</i>	357
Precisely Where Are We Going? Charting the New Terrain of Precision Prevention <i>Karen M. Meagher, Michelle L. McGowan, Richard A. Settersten Jr., Jennifer R. Fishman, and Eric T. Juengst</i>	369
Sharing Data to Build a Medical Information Commons: From Bermuda to the Global Alliance <i>Robert Cook-Deegan, Rachel A. Ankeny, and Kathryn Maxson Jones</i>	389

Errata

An online log of corrections to *Annual Review of Genomics and Human Genetics* articles may be found at <http://www.annualreviews.org/errata/genom>