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Living laboratory: Whole-genome sequencing as a learning healthcare enterprise

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Abstract

With the proliferation of affordable large-scale human genomic data come profound and vexing questions about management of such data and their clinical uncertainty. These issues challenge the view that genomic research on human beings can (or should) be fully segregated from clinical genomics, either conceptually or practically. Here we argue that the historical sharp distinction between clinical care and research is especially problematic in the context of large-scale genomic sequencing of people with suspected genetic conditions. Core goals of both enterprises (e.g., understanding genotype-phenotype relationships; generating an evidence base for genomic medicine) are more likely to be realized at a population scale if both those ordering and those undergoing sequencing for clinical reasons are routinely and longitudinally studied. Rather than relying on expensive and lengthy randomized clinical trials and meta-analyses, we propose leveraging nascent clinical-research hybrid frameworks into a broader, more permanent instantiation of exploratory medical sequencing. Such an investment could enlighten stakeholders about the real-life challenges posed by whole-genome sequencing, e.g., establishing the clinical actionability of genetic variants, returning “off-target” results to families, developing effective service delivery models and monitoring long-term outcomes.

Keywords

Whole-genome sequencing; whole-exome sequencing; human subjects; research participation; governance; personalized medicine

Introduction

With the precipitous drop in large-scale sequencing costs over the last few years, the $1000 genome appears imminently achievable if not already a reality (1). Quantum advances in sequencing technology, coupled with government-funded mandates and commercial initiatives to carry out large-scale clinical-grade sequencing in diverse patients, have

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allowed whole-exome sequencing (WES) to be used for an expanding range of clinical purposes (2–5). With the help of NIH funding, research-based whole-exome and genome sequencing (WES/WGS) has also become more common.

The current framework for WES is labor-intensive, costly, and fraught with uncertainty. Moreover, scaling up from whole exomes to whole genomes (~50 times more data than exomes) poses even more daunting interpretive and informatics challenges (6). Reliable estimates of the true workflow costs involved in WES/WGS remain unknown (7), while measuring the health outcomes of sequencing remains a difficult, long-term undertaking for which no standards exist (8). The issue of returning "off-target" results (those seemingly unrelated to the original reason for testing) has raised concerns over liability exposure (9–11). Despite these obstacles, the pace of clinical and research sequencing is unlikely to slow anytime soon (12).

An expanding knowledge-base of social and behavioral research has accompanied the growth of large-scale sequencing in both clinical and research settings (13–16). It is becoming clear that both patients and research participants have heterogeneous attitudes about the genetic information they may receive from clinicians and investigators (14). The heuristics people employ with respect to this type of decision-making are complex (17, 18). However, a clear majority would like at least some "off-target" test results back, a desire that places their expectations at odds with the dominant policies and norms in research ethics (19–22).

Assuming that WES/WGS will be carried out at a population level in the next decade, we believe it is time to confront: 1) the inadequate evidentiary base relating to WGS/WES; 2) the opacity faced by clinicians ordering clinical sequencing from commercial laboratories; and 3) the alienation of research participants undergoing clinical-grade sequencing, who are denied access to data about themselves under the regulatory status quo and late twentieth-century norms of human subjects research. To contend with these realities, we see a need to relax the hard-and-fast distinction between research and clinical care. We envision a system that focuses less on "protection" and mitigation of liability and more on providing high-quality WES/WGS and developing responsible service delivery models for genomic medicine. Like others, we envision a health system where generalizable knowledge derived from genotypes and phenotypes is produced not in isolation or as an abstraction, but as an intrinsic part of the practice of medicine under carefully monitored circumstances (23–25).

The research-treatment distinction and its application to large-scale sequencing

For a variety of historical, political and logistical reasons (26), the "segregation model" that draws a sharp distinction between research and clinical practice became permanently embedded in U.S. bioethical oversight policy with the drafting of the *Belmont Report* in 1978 (27). The fault line upon which this distinction rested—and continues to rest—is the notion that *research* is distinguishable from *practice* by virtue of the former's intent to create "generalizable knowledge" (26, 27). However, as Beauchamp and Saghai point out, the National Commission for the Protection of Human Subjects of Biomedical and

Behavioral Research, the body charged with drafting what became the *Belmont Report* (27) in the 1970s, never argued: 1) that research is riskier than clinical practice; 2) that clinical practice should be exempt from similar oversight to research; 3) that the research-treatment distinction can be made based upon whether a given intervention was aimed at a single individual (clinical practice) or many individuals (research); or 4) that the two activities cannot be carried out simultaneously (26).

A recent analysis by Kass and colleagues points out that systematic data collection is already ubiquitous if not obligatory in clinical medicine, and that collection will likely increase with the widespread instantiation of electronic health records (28, 29). They counter the argument that research is riskier than clinical care by showing that clinical care is rife with examples of dangerous procedures (gastric freezing, carotid bypass, postmenopausal estrogen, among others) that were long regarded as safe and effective before eventual recognition that they were neither (30).

In our view, this critique is readily applicable to the use of large-scale sequencing in human beings with undiagnosed conditions, whether in “medicine” or “research.” In both settings, WGS/WES yields generalizable knowledge: it is only by aggregation of such large-scale sequencing data that we can begin to reach robust conclusions about causal relationships between variants and phenotypes (31). In large-scale human sequencing projects of people and families with undiagnosed conditions, whether the laboratory is academic or commercial, a goal of both researchers and physicians is to identify mutations relevant to their patient-participants’ health. Even those who insist on maintaining a sharp distinction between research and clinical care concede that research results from WGS/WES assays can make their way into the participants’ medical records and that many genomics personnel are both researchers and members of a clinical team (32). As Wolf has observed, in genomics, research and clinical care now exist along a translational continuum: “Instead of a wall between the two, we now have a permeable membrane.” (33)

Does academic, research-based WGS/WES of undiagnosed patients and families necessarily present greater physical risk and offer less clinical benefit than commercial clinical WGS-WES? We are not aware of any data suggesting that it does. Similarly, there is little reason to believe that so-called “research” sequencing participants are at any greater a priori psychological risk than “clinical” sequencing patients. An uncertain result in a patient is surely no less uncertain in a research participant, the main difference being that the former result may never be subject to rigorous follow-up study or placed in the public domain. Conversely, in the “research” case, any potentially health-related variant must be confirmed in a CLIA/CAP laboratory before it is returned to clinicians and families. The potential of genomic sequencing to truncate diagnostic odysseys is becoming clear (4, 5, 34–36). What is even clearer is that the clinical application of WGS/WES will be hamstrung as long as the evidence base underlying it remains both incomplete and too often wrong (37).

Accumulating—and sharing—evidence to improve clinical care

Much uncertainty is still attached to the analysis and interpretation of genetic variants, even in genes known to cause Mendelian disorders. Alleles found in genes associated with

conditions of various stripes, from cancer (38–40) to metabolic disorders (41) to cardiovascular disease (42, 43) and more (44), include large numbers of variants of unknown significance (VUS) (45).

Closely related to the VUS problem is that of reduced penetrance, which often confounds our ability to make phenotypic predictions based on genotype. In all likelihood, there are many good reasons for this, ranging from stochasticity to modifier genes to ascertainment bias to population structure (46, 47). Consequently, alleles defined as pathogenic and sometimes life-threatening turn up with some regularity in the genomes of ostensibly healthy individuals (48, 49).

In silico prediction tools, a necessary part of assessing variant causality, are useful but nevertheless limited. Sensitivities and specificities are often less than desired and, given the same variant, different programs can produce discordant results (50). Newer iterations appear to do better at predicting pathogenicity (51, 52), but as MacArthur et al note, multiple *in silico* prediction algorithms should not be regarded as either independent or strong lines of evidence supporting disease causation (53).

Obviously one cannot draw robust conclusions about pathogenicity without well-populated and carefully annotated databases harboring the current state of knowledge, or ideally, “one database to rule them all.” But much like downstream *in silico* prediction tools, the current variant database ecosystem is both inadequate and highly heterogeneous. Public databases vary greatly with respect to depth, annotation, curation, and nomenclature, to say nothing of ease of use (54), while private databases continue to harbor significant numbers of pathogenic variants (55). Given this fractured ecosystem, the dream of a single freely available comprehensive electronic resource harboring known genetic variants and their phenotypic associations has gone unfulfilled (37) and, we suspect, is likely to remain so for some time. Together, these problems can confound even the most skillful genome interpreters (56).

Meanwhile, the desired health outcomes of genetic and genomic testing remain contested and there is limited evidence available concerning the impact of genetic information results on both physician behavior and human wellbeing. In our view, the ongoing uncertainty surrounding management, interpretation and outcomes of WES/WGS strengthens the case for allowing data generated in clinical settings to be re-used in research more easily, contingent upon the voluntary authorization of the individuals from whom it originated. In the interests of both scientific advancement and public health, variants found in all settings should be easily accessible without regard for commercial and/or intellectual property considerations (55, 57). Aggregation and study of these variants in hybrid clinical-research settings should advance our understanding of the relationship between genotype, phenotype, and human health.

Returning “off-target” research results: The inadequacy of “It’s only research”

The notion that clinicians and researchers could continue to ignore individual “off target” results from WES/WGS was dispelled in 2013 when the Presidential Commission for the Study of Bioethical Issues signaled its belief in the importance of dealing straightforwardly with incidental findings in research, clinical medicine and commercial testing. The Bioethics Commission emphasized the need to “anticipate and communicate” how such findings will be handled to patients and participants before they underwent large-scale sequencing (58). Subsequently it issued primers aimed at helping researchers, clinicians and direct-to-consumer services manage incidental/secondary findings in an ethically responsible fashion (59). Beyond calling for careful deliberation, the Bioethics Commission punted on the long-debated (if no longer highly contentious) question of whether clinicians ever have an absolute duty to return such findings. It opted to emphasize the importance of the distinction between research and clinical care as a way of managing participant expectations (58). To the extent that it did so solely as a proxy for distinguishing between the levels of evidence associated with a particular test, this distinction may in fact be misleading, particularly when those undergoing “research” WES/WGS are nevertheless patients and families seeking to end diagnostic odysseys.

Setting aside the contested notions of “actionability” and “clinical utility”, we begin from the premise that offering to return individual research results to study participants is an act of respect and good faith (60, 61) that both fulfills the principle of justice (62) and is likely to redound to the investigator by engendering good will among participants (63, 64). It has become increasingly clear that the majority of patients and genetic research participants are interested in receiving off-target data (19, 60, 65–68). Return of such data is often portrayed mainly as a financial, legal and/or regulatory burden (9, 11, 69–71). Conversely we see it as an opportunity to 1) change the relationship between researchers/clinicians and participants/patients in ways that benefit both sets of stakeholders; and 2) learn how people respond to this information, track their responses to it over time, and measure it in the context of an evolving knowledge-base and competing personal considerations. Indeed even the US Food and Drug Administration conceded recently that, “People have every right to get their [genomic] data.” (72)

We recognize that investigators’ resources are limited and there are few incentives to return results, while there are ample incentives not to do so (e.g., institutional liability fears; lack of time, money and expertise). The instantiation of a hybrid model, wherein WES/WGS is conducted on a more routine basis in clinical settings, would allow for the return of individual research results embedded within clinical protocols, with supportive and safety monitoring structures that can be tested, refined, and gradually scaled.

Learning healthcare systems for genomic medicine: will a thousand flowers bloom?

Among the existing templates for de-compartmentalizing research and clinical sequencing is the Clinical Sequencing Exploratory Research Program, an initiative sponsored by the National Human Genome Research Institute and the National Cancer Institute. The CSER network, launched in 2011, includes six projects aimed at assessing the impact of large-scale sequencing in a range of clinical settings (https://cser-consortium.org/projects). These projects may take different approaches to: the demographic characteristics of the populations they sequence (2, 70); informatics and analysis research (73), social and behavioral studies (20); physician education (2, 74); and return of results (68, 75).

Other models of learning-based integration of genomics into the clinic can be found at Geisinger Health System; Baylor College of Medicine; Children's Mercy Hospital in Kansas City; the Medical College of Wisconsin; Vanderbilt University; and among members of the eMERGE Consortium (25). What these initiatives share are nascent but growing programs in which large-scale sequence information can be leveraged to inform patient care and attached to electronic health records. They apply iterative approaches to clinical sequencing in practice and document what works, what does not, how physicians and patients understand and respond to genomic information, and identify opportunities to improve practices in sustainable and granular ways.

Just as it would be foolish to expect every large municipality to embrace the same approach to public transit, there is no reason to envision a homogeneous future for genomic medicine embedded within academic medical centers, community hospitals and independent medical practices. As has been the case with the CSER consortium, we can expect a variety of approaches to physician education, patient recruitment, data generation, informatics analysis, genetic counseling, return of results, and clinical follow-up. All healthcare systems must negotiate a combination of political, financial, socioeconomic and demographic circumstances that are peculiar to the communities they serve. It would behoove us to seed genomic medicine in a representative sample of these communities.

Remaining challenges

We have tried to show how large-scale sequencing of human beings with undiagnosed conditions highlights the increasing impracticality of the rigid distinction between clinical care and research. This distinction has exacerbated the evidentiary shortcomings of WES/WGS as a tool to end diagnostic odysseys and inhibited the return of off-target genomic results. Here, we review some challenges associated with the integration of genomic research and clinical care. Although one cannot dismiss these significant challenges out of hand, we believe there are ways each of them may begin to be addressed with the help of further empirical study.

Re-evaluating the therapeutic misconception

One rationale for segregating research from clinical care is to avoid propagating the so-called "therapeutic misconception," in which research participants erroneously believe

research is intended to benefit them directly (76). Yet recent scholarship suggests that the therapeutic misconception may be an unhelpfully reductive concept, and that participants enroll in research for a nuanced mix of reasons including salutary optimism and hope (77–80). In other cases it seems clear that consent-form language itself ("Who will be my doctor on this study?") can explicitly promote the therapeutic misconception (64). Regardless, it strikes us as perverse to conclude a priori that benefitting research participants is somehow an undesirable byproduct of the research process, as long as the nature and likelihood of any prospective benefits are made clear to research participants and are reasonable given competing demands on finite resources.

A related view is that physicians and investigators have distinct moral duties to patients and research participants, respectively. While we do not underestimate the complexity physicians and investigators must confront when asked to "bridge" the divide between them (81), such confrontations are unavoidable given the nature and scope of WES/WGS results. There is evidence that many WES/WGS researchers want to return at least some results to participants in their studies, both to improve their health and as an expression of respect; one reason they refrain from doing so is because they lack access to clinicians and other necessary resources (82, 83).

We believe the thoughtful integration of research and clinical WES/WGS can help to overcome challenges researchers and clinicians face when using these tools, by allowing them to benefit mutually from their complementary expertise. However, any effort to increase the synchronicity of research and clinical care will necessitate clear communication with patient-participants, to manage their expectations from WES/WGS and develop new approaches to both oversight and ongoing multiple-stakeholder collaboration.

Reconciling the informed consent process with the realities of big data

In genomic research, clinical care and hybrid settings, there are enormous challenges to obtaining truly informed consent from patients undergoing large-scale sequencing. Many participants are asked to consent to future studies with unspecified aims, broad data-sharing policies, questionable data de-identification practices, and lack of clarity about investigators' return of results policies. These realities have led some to question whether the current reigning mechanism of informed consent is itself "broken" (84).

Given the large evidence gaps in genomic medicine and forceful implications genomic test results can have for individuals and families, we do not believe it would be appropriate to forego informed consent altogether for genomic research in clinical settings, as has been suggested for low-risk comparative effectiveness research (85). That said, we agree that most current informed consent practices are inadequate, static, mired in legalese, and come with unacceptably high administrative burdens. There is an urgent need to develop innovative ways of addressing patients' expectations of genomic sequencing and communicating its nuances and uncertainties. Dynamic informed consent, in which individuals can tailor and manage their own preferences, is one emerging strategy for lowering the burdens of continually communicating with patients that merits closer investigation (86). It is incumbent upon our community to develop, explore, and empirically

test others (87) in order for integrated genomic research and clinical care to proceed in ways that privilege respect for persons over mitigation of institutional liability.

Who will pay? A "coverage with evidence development" approach

Whatever the future integrative framework of sequencing ultimately looks like, in the near term the question of "Who will pay?" will likely loom large (as it does for virtually every new medical procedure/intervention). Even for testing of highly penetrant, rare and sometimes-actionable single-gene disorders and other targeted molecular diagnostic assays, payers have long demanded evidence of clinical validity, clinical utility and cost-effectiveness (88, 89). Recent anecdotal reports suggest that large-scale sequencing will be no different (90). Thus, it may be a long, uphill climb to persuade payers to cover technology- and labor-intensive "fishing expeditions" whose current yields are on the order of twenty-five percent (4, 91) and for whom clinical actionability is typically uncertain at best.

This situation—when an intervention holds promise but has yet to prove its clinical utility and/or justify its expense—lends itself to Coverage with Evidence Development (CED), a form of conditional insurance reimbursement in which restricted third-party coverage is available while targeted data collection on the intervention continues in parallel. The goal of CED is to characterize the clinical and/or cost effectiveness of the intervention and thereby reduce material uncertainty associated with it (92). Successful applications of CED include cases of various surgical procedures (93), medical devices and imaging techniques (94, 95), and pharmaceuticals (96) characterized by great potential and high costs.

That said, CED is not a panacea: in the United States, for example, the government-sanctioned CED scheme does not offer blanket reimbursement for a targeted intervention in all settings, but rather only those that meet the needs of the Centers for Medicare and Medicaid Services in making national coverage decisions (97). In some cases the data may be so incomplete or the methodology so flawed that payers cannot reach robust conclusions (98). Unsurprisingly, there is also evidence suggesting that both corporate and political interests may exert undue influence over CED deliberations (99).

Despite these caveats, we argue that CED is an appropriate framework for measuring the large-scale potential of WES/WGS without sacrificing its "N-of-1" benefits. Others have made this argument: At a 2011 workshop sponsored by the Institute of Medicine (US), participants called for a conditional reimbursement scheme for genome-based diagnostic tests contingent upon gathering of further cost and efficacy data (100).

The risk of exacerbating genomic health disparities

Until recently, the study of human genotype-phenotype relationships has focused almost entirely on populations of European descent (101). Although efforts to rectify this imbalance are now underway (102), they will take considerable time to bear fruit. Meanwhile, the negative impacts of this imbalance are evident from ethnic disparities in genomic medicine (103). For example, African American women are more likely to receive variants of uncertain significance from clinical testing of cancer-related genes than women of European descent (104). Existing strategies for ameliorating genomic health disparities have had

underwhelming results, and the task of doing so remains daunting given the need to design especially well-powered studies in more genetically heterogeneous populations (105).

Genetic-test uptake has been found to vary by social group (106, 107) and clearly, not everyone is comfortable with the idea of using clinical data in research (108). In light of these realities, there is a valid concern that the hybrid clinical-research systems we propose could exacerbate existing disparities in both research and clinical care.

At the same time, we note that there is a growing interest in using public engagement as a mechanism for improving the health of diverse populations and involving them in research on ethical terms (109). Any institution proposing to integrate research and clinical genomics more closely would do well to review the evolving literature on public engagement models, with special attention to those that have and have not worked well in the contexts of genomics and biobanking (110, 111). Robust public engagement may help to determine how hybrid clinical-research frameworks will affect people on the margins of our health and research systems and to better define their unmet needs.

Barriers to institutional data-sharing

In genomics, data-sharing is generally regarded as a virtue, if not “a scientific and ethical imperative.” (112) Nonetheless, data-sharing faces real obstacles, which, in some cases are similar to those inhibiting return of results in WES/WGS. Institutions are concerned about sample and data ownership (113), patient privacy, and security breaches (114) potentially exacerbated by the inherent identifiability of genomic data (115) and the prospect of liability exposure (9, 116). Moreover, genomic data can be perceived by commercial interests to be of greater value if kept as trade secrets rather than shared broadly (55). ClinVar, a presumptively universal human variant database (117), has thus far seen a disappointing level of participation from commercial laboratories in many instances. For example, of 78 labs offering testing for the hereditary breast and ovarian cancer genes BRCA1 and BRCA2 (whose commercial rights were subject to exclusive patent licenses held by a single commercial lab that kept BRCA data as trade secrets until 2013), just six (8%) had made their BRCA variant data available in ClinVar (http://www.free-the-data.org/ accessed 29 June 2014).

Novel frameworks that allow patients themselves to manage their own samples and information are now an increasingly realistic option in both clinical and research settings (61, 86, 118). As genetic diagnostic laboratories’ major customers, hospitals are in a unique position to leverage their economic power to demand that labs operate transparently and contribute the variants they find to the community knowledge-base. Alternatively (and perhaps concurrently), communities can reverse-engineer the variant knowledge base, as the Free the Data! movement has begun to do, by amassing test reports of commercially claimed BRCA variants that predispose to hereditary breast and ovarian cancer and depositing them in the public domain (57).

Conclusion

The WES/WGS enterprise continues to be dogged by an inflexible divide between research and clinical care that limits both; lack of evidence to support genotype-phenotype correlations and a preponderance of VUSes; inadequate databases; lack of incentives/institutional will to return results; and opacity/intransigence with respect to control of variant data. The abiding problems constraining clinical sequencing will not be ameliorated by data silos and static approaches carried out in isolation. Rather, carefully integrating WES/WGS in carefully selected aspects of routine practice is a promising mechanism for getting clinical sequencing right. The sequencing enterprise will be better served in a learning healthcare framework, where data are pooled, shared and used to inform practice and engage with patients and families for a long journey that, we hope, will deliver more robust science and better health on a much larger scale.

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