AFTERWORD

Building the airplane while flying it: tracking the transformation of novel sequencing practices into clinical services

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“… sociological research approaches carve out a space for complicating our engagement with proliferating and expanding gene worlds.” Timmermans and Shostack 2016

Qualitative social scientists have long practiced methodological messiness in our empirical investigations of health and science. Sometimes we call ourselves “embedded anthropologists” or “shadowing sociologists”, the first drawn from the language of US military worlds as well as ELSI mixed methods discourse, the second from scripts of medical apprenticeship. Positioned in the heart of the research/clinical intersections we wish to study, qualitative researchers often find ourselves located on a continually receding horizon: the projects under study morph and move, on occasion in response to our presence/ findings despite our best efforts to avoid the Heisenberg Principle. This field-working instability in medical and STS empirical research is of course old news, and we prepare our graduate student researchers accordingly for the unanticipated directions that their investigations may well expose.

The reflexive element of qualitative research offers no clear direction forward, as the five articles placed into conversation in this special issue of \textit{New Genetics and Society} illustrate. These contributions to “Tracking the Transformation of Novel Sequencing Practices into Clinical Services” all reveal pedagogical paradoxes that are “good to think with” but harder to resolve into the clear-cut
policy recommendations that ELSI\textsuperscript{1} funding intends to promote. Indeed, these ethnographic essays (in the original meaning of the word: an attempt, an interpretation) highlight empirical examinations of the practices now developing at rapid rate and with substantial innovation in designing, recruiting, sharing, interpreting and even stabilizing genomic data. Widely hailed as “precision medicine,” this umbrella term signals the move from expansive databased scientific research tools to clinical patient-centered interventions that entails a very complicated “engagement with proliferating and expanding gene worlds,” as Timmermans & Shostack note (2016, 44).

Collectively, these five essays uncover the complexity of translating the rapidly-moving frontiers of genomic tumor testing and other databased forms of knowledge production not only to patients, but often to the very interdisciplinary clinicians and other medical stakeholders who are now being recruited to their use. Reflexivity is built into the methods of our social science research teams; and often into the musings of the many interlocutors whose production, circulation, and consumption of these new tests and tools they are tracking. Their partially-constructed protocols have entered the clinic in each of these essays, enabling these field-working social science authors to observe their development, checks, and transformations. The many respondents who speak to these researchers are quite forthcoming, perhaps because translation across interdisciplinary domains of expertise as well as empathic tutelage of the patients whose care is now being genomicized is so new. In Silicon Valley-speak, they understand that they are “building the airplane while flying it.”

Broadly speaking, a theme of always-emergent and unstable reflexivity unites these five papers. It is present in Outram and his colleagues’ concern that in interrogating what it means to “recruit underserved populations” to genomic research, they may contribute to reifying the very people whose treatment experiences they seek to understand.

They muse:

As embedded ethnographers we are left in a peculiar and uncomfortable position; recognizing the imperfections of the categories as they are enacted, but at the same time recognizing that such categories encompass important scientific and social objectives that cannot and should not be jettisoned … the position of the embedded ethnographer is to both reflect upon their role in this process and work to maximize the benefits of recruiting underserved populations while minimizing the potential for harm by constantly challenging the categories that are being created.

Reflexive work is also legible in the frustration that oncologists practicing in rural Maine clinics express toward the-always-ahead-of-the-curve urban and academic-centered research and clinical resources whose successes and limits they are too often barred from using by structural circumstances, as Darling and her co-authors tell us. We see that reflexivity again and again as the clinician-researchers in the WISDOM breast cancer machine-learning screening trial invoke their
mantra, “trust the trial,” despite their own ongoing doubts. And several oncologists involved in genomic tumor testing tell Ackerman that they worry about “the ethical problems that can arise at the unclear boundary between research and clinical care.” The very title of Gordon and Koenig’s article reveals a reflexive dilemma that is foundational to their analysis: The individualism built into American healthcare codes and bioethics, they discover through empirical research, is challenged by relatives of the tumor probands. Intimate kin think far more collectively and selectively about pancreatic cancer biobank data, opining that “If Relatives Inherited the Gene, They Should Inherit the Data.” This finding leads them to reflect on whether it is possible to bring “the Family into the Room Where Bioethics Happens”. On or off the record, reflection on the limits and uncertainty of the new knowledge in which they are both producers and consumers shadows all these reports.

Other themes, too, provide glue for this special issue: Here I index four additional topics beyond reflexivity. One is the rapidly dissolving boundary between clinical care and research, richly articulated in Ackerman’s article, as cited above: both clinicians and patients understand that they are helping to grow precision medicine even as their participation may contribute far more to research tools than to clinical breakthroughs from which participants may benefit. And of course, this dissolving boundary lies at the heart of the WISDOM machine-learning breast cancer screening trial, with all its complex protocols and “escape” clauses, allowing patients as well as their treating physicians to both use and overrule the screening recommendations that continually evolve as the machine learns and interprets. In Maine, oncologists serving a predominantly rural and small-town population are gratified to see their patients enrolled in cutting-edge tumor testing trials on par with their urban peers. Yet they understand very well that outcomes are likely to be delayed and may take the form of a NextGen promissory note in Maine. The discovery of incidental findings (IFs) in the pancreatic cancer banks leads to what Gordon and Koenig dub “a bioethical crisis”: research data may portend heightened risk associated not only with the tumor type of interest, but possibly also for diseases as diverse as breast and ovarian cancer, melanoma, and cystic fibrosis. Do family members have a right to know about these research findings as potentially affecting their clinical futures?

This dispersion of research into clinical care and vice-versa signals a second and related theme beyond reflexivity that is widely present in these analyses of precision medicine. Currently, it overwhelmingly produces “anticipatory knowledge” rather than many actionable uses of genome tumor testing (GTT), as all respondents to our authors’ queries attest. Indeed, this anticipatory knowledge is playing out most directly in the WISDOM trials, where James and Joseph pick up stakeholders’ uncertainties, despite enthusiastic participation: they know that they are wagering innovative near-future knowledge against real-time morbidity and mortality for the very people they are committed to serving, should the
algorithm prove inaccurate. As Darling tells us, “MCGI symbolized the future of biomedicine.” Outram and his colleagues make the dilemma of anticipatory medicine very clear in their discussion of recruiting “underserved” families and patients to biobanking:

To redress health inequalities we need to actively recruit populations that are poorly represented in the current biobanking and clinical research systems. The CSER consortium is actively engaged in this process, albeit indirectly through asking research enrollees if their data can be deposited in NIH genomic databases, for example a resource called “ClinVar,” which assembles data from multiple genetic studies. While it should be noted that patient-enrollees in this study will not benefit - as this will accrue through accumulated knowledge in future – the objective of reducing health inequalities is being met through this process of recruiting members of diverse populations.

This perception of an anticipated and better biomedical future for cancer patients in Maine, in urban neighborhoods of the Bay Area, and beyond surely animates all clinical trials, indeed one might opine broadly: all of scientific research. Yet it rings with particular poignancy in the treatment of intransigent cancers, “where the work of keeping a loved one alive through precision medicine is bound up in the work of keeping the promise of precision medicine alive” even though patients and their supporters can recognize its gaps and failures, as Ackerman puts it. And after the death of those whose tumors have been tested, anticipatory findings like the IFs identified in the pancreatic cancer databanks that set Gordon and Koenig’s analysis in motion may become an antechamber to new forms of care, a potential benefit and burden likely to be widely experienced in the shadow of biobanking.

Indeed, a third topic linking papers involves consequential new forms of care now appearing along the hovering-horizon of anticipatory knowledge. While the frustrations of experimental failure are par-for-the-course in scientific research, this is hard for many physicians to accept as they try to do their very best for their cancer patients. For example, the Maine oncologists who are the subject of Darling et al’s analysis are learning on the job; many are frankly excited about it, but they worry that their participation in new learning communities is unlikely to directly benefit their current patients whose tumor testing rarely yields actionable results. “Most clinicians,” Ackerman tells us, “were able to accommodate the push and pull of genetic sequencing conceived as an investment in research, and the future of precision medicine …” But of course, their commitment to caring for patients also leads them to mobilize the moral support of team-work, even if genomic testing nets little of use; at least they have then pursued every path in sight. The interdisciplinary teams of research-clinicians contributing to the WISDOM trials also express concern about patient support in response to research findings that jar their own professional as well as some patients’ sense of being adequately screened for a disease most women find frightening. In Ackerman’s study, patients,
too, experience the new care demands this anticipatory participation demands: “The efforts also required contributions and sacrifices from patients and caregivers, who often dedicated themselves to understanding ‘the whole clinical trial ecosystem,’ as one patient phrased it.”

She goes on to say,

We found that clinicians, patients, and caregivers worked together to create a form of care that would extend the patient’s time horizon … Many of (their) activities reinforced relations of mutual obligation and re-invigorated the expectation that precision medicine will eventually offer broad benefits for human health.

They are thus caring for a potential future, as well as laboring to sustain presently-new practices. Indeed, we may read Gordon and Koenig’s reflection on downsizing American bioethics’ commitment to individual privacy in favour of a potentially more-evolved form of relational care when clinical genomics acknowledges this dilemma: “If Relatives Inherited the Gene, They Should Inherit the Data.”

Beyond these themes of reflexivity, dissolving research-clinical boundaries, the move toward anticipatory medicine, and new modalities of care, I note a fifth concern that precision medicine hides as well as reveals. The famous four Ps that characterize precision medicine—participation, prediction, prevention, leading to more personalized interventions (Flores et al. 2013)—encounter many historical and structural barriers that suggest we add a fifth P: “profit”, now provoking rapid investments in healthcare interventions at remarkable velocity. This 5th P is a key starter-engine in the U.S., where market solutions are powerfully advertised as the ideal flight-plan for “our” future (cf. (Murphy 2017)). Gale-force commercial gusts now blow vigorously across the runway where the Dreamliner of precision medicine is always about to take off: this is a site of global investment, “lively capital,” to borrow anthropologist Kauchik Sunder Rajan’s alluring title (Rajan 2012). Here, the intensity and speed of investment/destruction/corporate take-over is expansive, as a cursory glance at any of the many industry aggregators shows. Yet the weather for take-off is always turbulent. The dream of near-future profits surely animates the hope and the hype of “bench to bedside” interventions (Brown 2003) (Hoyer 2007). For example, the Maine oncologists interviewed and observed by Darling are acutely aware that building databased genomic medicine in their economically-depressed state may lead to a goldmine of public-private investment, a future that would both bring more jobs as well as inflated healthcare costs.

At the same time, this vision reflects what former U.S. Surgeon General David Sackett classically deemed “the arrogance of preventive medicine.” He is speaking to the assumption that the frictionless and rational world envisioned by an advertised and idealized genomic medicine reflects the potential experiences of heterogeneous human subjects (Sackett 2002). The authors in this special issue offer glimpses of that more complex real-time world within which their genomic researcher-clinicians and patients actually operate. Ackerman, for example, shows how the political
economy of what some dub “the medical-industrial complex” influences patient participation in genomic somatic cancer panels. She tells us that.

... the fragmented structure of U.S. healthcare puts the burden of tissue and data tracking and transfer on clinicians and patients. Many patients obtain care at multiple institutions, change health insurance frequently, or do not have a trusted clinician willing or able to devote time to managing data and tissue across institutions. ... Clinicians worked to render a genetic mutation actionable through emotional labor, negotiation skills, scientific knowledge, and disposition - including righteous anger at insurers and pharmaceutical companies.

Darling notes the longstanding suspicion of some Maine oncologists who worry about patients being conscripted into hidden financial costs that means they are indirectly paying for becoming research subjects. For now, a combination of generous private funding and public networking encourages a remarkable state-wide experiment in genomic tumor testing and database sharing, coordinated through the global-facing Jackson Laboratory. Researcher-clinicians recognize “The value of biobanking infrastructures that could foster Maine’s bio-pharmaceutical and healthcare industries.” She tells us that

Stakeholders used language like “capitalizing”, “selling” and “business opportunity” to describe the work of building a platform for precision oncology that could be economized in for-profit and non-profit models of biomedicine. “Some also recognized” … the ethical ambiguities of contemporary biomedical research and practice (that) dwell within … systems they viewed as flawed, unsustainable and unethical in themselves; they were questions about the multiple conflicted interests and incentives baked into paradoxes of U.S. biomedical institutions.

In her discussion of an innovation-oriented bioeconomy, Ackerman cites Catherine Waldby’s critique of the concept of “a biological citizen” as an “entrepreneurial subject of health” whose consumption and creation of medical innovation are deeply entangled. The emerging enterprise of molecular oncology offers a compelling example of a bioeconomy in which production and consumption, and research and clinical care, have become meshed.

Outram and his colleagues return us to some important basic public health insights: they highlight that “The focus upon genomics may detract from the many social interventions that could reduce racial health inequalities.” While health disparities face all countries, the U.S. is home to a particularly ferocious organization of healthcare as a profitable sector that leaves our social inequalities frighteningly intact.

These authors go on to say:

Indeed, with successful recruitment we can at least make some narrative inroads by describing what it is like to care for a child with genetic condition and be living on an income well below federal poverty levels in the San Francisco Bay area, and whether transport and parking costs impact the ability of families to get to clinical appointments. We can also talk to families about how important genetic results are to
their lives. Indeed, we can talk to families seeking access to physical therapies or special education programs, learning whether they can get time off work for the clinical consultations needed to care for a child with chronic health conditions.

A romance with molecularized medicine eclipses these basic concerns and practices of social inequality, as many critics have taught us. The rapid move of lively capital into precision medicine now forces us to consider many questions: what does it mean to investigate potential illnesses and disability as if they could be understood as individual risks without recourse to the social realities in which “at risk” people already excluded from the benefits of basic public health resources now live? How do we want new biomedical knowledge financed, produced, distributed, and its interventions governed? The voices of “blue skies” investment in precision medicine in the U.S. are increasingly loud while those calling for public health structural investments that will improve the outcomes of vulnerable populations are too-often deemed old-fashioned.

For now, we all stand on that runway of genomic medicine, participant-observer-participants in the departure lounge where the promises of biobanking cannot be redeemed without a more evolved social fund of health disparities knowledge and commitment to its transformation. Given the potent combination of lively capital, scientific curiosity and research accomplishments, we will collectively be living on this genomic runway for the foreseeable future, albeit in all our health-stratified diversity. Anthropologists are quite good at identifying social and cultural dilemmas, and this is surely one. But we are notoriously bad at constructing policy interventions into them, a brave goal that many of our authors espouse. We need all the interdisciplinary collective discussion we can mobilize to wake up from the imprecision of the dream of precision medicine, insisting that the fifth P—profit—also frame our analysis.

Notes

1. Initially labeled ELSA in the EU, many European genome-oriented ethics projects were then folded into RRI/ RI, Responsible Research and Innovation. For brief histories, see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480351/; https://lsspjournal.biomedcentral.com/articles/10.1186/2195-7819-9-3.

2. This state-wide model program is described at: https://www.jax.org/clinical-genomics/maine-cancer-genomics-initiative

Quotes from within this paper referring to the current Special Issue were derived from earlier versions of these papers – some of these quotes have been edited in the finalized papers.

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References

Brown, Nik. 2003. Hope Against Hype - Accountability in Biopasts, Presents and Futures. Science & Technology Studies. https://sciencetechnologystudies.journal.fi/article/view/55152, accessed July 12, 2018.

Flores, Mauricio, Gustavo Glusman, Kristin Brogaard, Nathan D. Price, and Leroy Hood. 2013. “P4 Medicine: How Systems Medicine Will Transform the Healthcare Sector and Society.” Personalized Medicine 10 (6), doi:10.2217/pme.13.57

Hoyer, Klaus. 2007. “Person, Patent, and Property: A Critique of the Commodification Hypothesis.” Biosocieties, 327–348. doi:10.1017/S1745855207005777

Murphy, Michelle. 2017. The Economization of Life. Durham, London: Duke University Press Books.

Rajan, Kauchik Sunder. 2012. Lively Capital. Durham: Duke University Press. www.dukeupress.edu/lively-capital, accessed July 12, 2018.

Sackett, David L. 2002. “The Arrogance of Preventive Medicine.” Canadian Medical Association Journal 167 (4): 363–364.

Timmermans, Stefan, and Sara Shostack. 2016. “Gene Worlds.” Health: An Interdisciplinary Journal for the Social Study of Health, Illness and Medicine 20 (1): 33–48. doi:10.1177/1363459315615394