

A market in the making: the past, present and future of direct-to-consumer genomics

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It is just over two decades since a small start-up firm called University Diagnostics launched a mail-order genetic testing service in the UK in 1996. That same year, the US-based Genetics and IVF Institute began marketing its BRCA tests for breast and ovarian cancer directly to consumers via newspaper ads. Two years later, Myriad Genetics (by then the sole provider of BRCA testing in the USA) launched a consumer advertising campaign that encompassed TV, radio and popular magazines (Parthasarathy 2007). By 2001, when UK nutrigenetics firm Sciona began marketing to consumers via its website, a new trend was emerging: the growth of the direct-to-consumer genetic testing (DTCGT) market was now interlinked with the increasing use of the internet as a medium for retail shopping. Genetics was beginning to move out of the clinic and into the marketplace.

Despite little evidence of significant consumer uptake, the consumerisation of genomics has garnered extensive media coverage, provoked much public controversy and stimulated considerable academic research. Some twenty years since its inception, and a decade since the second wave of DTCGT firms launched, this is an opportune moment to take stock of the past, present and future of what remains a market in the making. The articles that follow tackle a variety of topics: regulation, rhetoric, venture capital financing, and the attitudes of consumers and healthcare professionals. The contributions situate DTCGT firms in their historical and geographical contexts, highlighting continuities between generations of firms and critically evaluating how claims to innovation, novelty and disruption are used to legitimate their practices.¹

DTCGT in a historical perspective

Since 1996, there have been two main waves of DTCGT firms: before 2005, the first wave of firms, such as Sciona, largely focused on nutrigenetic testing, testing for genes linked to nutrient metabolism and providing tailored dietary recommendations; from around 2007, a second wave of larger firms, such as Navigenics and 23andMe, began offering polygenic risk tests for a range of common diseases such as asthma, diabetes and stroke as they sought to capitalise on gene-disease associations emerging from the new wave of large-scale Genome-Wide Association

¹ Some terminological clarity is required. The term “direct-to-consumer” has been used to describe two distinct models: firstly, where a firm advertises direct to the public, but the test must still be ordered by (and the results delivered to) a healthcare professional; and secondly, the more common model where a consumer buys directly from a firm, without the involvement of the consumer’s healthcare provider (in some instances the test may, in strict legal terms, be “ordered” by a healthcare professional employed by the firm solely for this purpose, but this does not establish a doctor-patient relationship with the consumer).

Studies (GWAS). Navigenics and 23andMe were better capitalised than their predecessors in the DTCGT market (see Hogarth this issue), and both firms had links to highly-respected DNA chip makers (Affymetrix and Illumina respectively), which were looking to shift from the biomedical research market to the clinical market; and collaborative partnerships with global software firms (Microsoft and Google respectively), which were interested in DNA as big data (see Saukko this issue) and the opportunities in the burgeoning electronic healthcare records market.

In the last decade the DTCGT market appears to have grown further, at least in terms of the number of firms that have entered the market: Philips' (2016) survey identified 246 firms. The heterogeneity of product offerings has also expanded: DTCGT firms specialise in different areas such as ancestry, athletic traits, character/personality, familial relatedness, nutrigenetics, and quirky traits such as a propensity towards ear wax. Health-related testing covers a diverse range of tests including carrier testing for genetic diseases; polygenic susceptibility tests; and pharmacogenetic tests that seek to guide drug dosage decisions. The lexicon of terms these firms use to describe their services has also expanded: terms like recreational genomics, informational genomics and lifestyle genomics may demonstrate a diversity of product differentiation strategies, but they also perform boundary work, distancing DTCGT firms from the clinical domain (Saukko, Reed, Britten and Hogarth 2010) and functioning as a form of regulatory arbitrage (Hogarth this issue).

In parallel with this commercial growth, there has been an explosion in scholarly research on the ethical, legal and social implications (ELSI) of DTCGT. To give but one metric that indicates the scale of this research field, an early review of the ELSI landscape published in 2008 now has 221 citations (Hogarth, Javitt and Melzer 2008). Like Myriad Genetics' patents on the BRCA 1/2 genes, DTCGT has become a lightning rod for broader concerns about the commercialisation of genetic testing (Caulfield et al. 2006). Why has the topic of DTCGT proved so popular? The relatively low cost of analysing the content of firm websites (Phillips and Saukko this issue) or media coverage of DTCGT (Hogarth and Saukko this issue) cannot be overlooked. The emergence of the second wave of DTCGT in 2006/7 came at a time when, it might be argued, ELSI researchers had begun to exhaust the possibilities of examining established paradigms of genetic testing: the domain of clinical genetics, the emerging market for pharmacogenomics, the first wave of genetic risk tests like BRCA for breast/ovarian cancer and APOE4 for Alzheimer's. Each of these had been the subject of intensive scrutiny and DTCGT was seized upon with enthusiasm as fresh grist to the ELSI analytic mill. Although tackling a novel topic, this new wave of scholarship pursued many familiar research themes – geneticisation (e.g. Harris and Wyatt 2011), genetic subjectivities (e.g. Reardon 2011), informed consent (e.g. Hawkins and Ho 2012), regulation and governance (e.g. Borry, Cornell and Howard 2011), and the promissory nature of personalised medicine (e.g. Tutton 2014).

Looking at a number of these topics in turn, we identify some of the key issues and approaches of the ELSI literature on DTCGT and highlight the original contributions made by papers in this collection. To begin, we consider DTCGT's struggle for legitimacy and its entanglement with regulatory authorities.

Regulation

As has become typical for emergent biotechnologies, the ethical, legal and social implications of genetic testing have been the subject of much academic research, policy deliberation and public

debate in the mass media over the last two decades, and much of this normative scrutiny has focused on the issue of regulation. Deliberation around how DTCGT might be regulated is thus just one dimension of a much broader debate about the governance of genetic testing that can be traced back to the early 1990s when newborn screening for monogenic disease was the topic of concern (see for instance, Nuffield Council on Bioethics 1993). The regulatory debate has periodically changed focus in response to technological innovations (most recently non-invasive prenatal testing and next-generation sequencing), new diagnostic modalities (such as companion diagnostics to identify patient sub-populations eligible for targeted cancer therapeutics) and changes in test delivery mechanisms (exemplified by DTCGT) (Hogarth forthcoming). Indeed, one might suggest that DTCGT combines all three drivers of regulatory debate: *technological innovation*, since second-wave firms relied both on advances in array-based high throughput genotyping and the emergence of Web 2.0 technologies (see Saukko this issue); and *new diagnostic modalities*, in this case polygenic risk assessment, which the DTC firms pioneered; as well as obviously a change in test delivery models. Given this powerful convergence, it is perhaps unsurprising that DTCGT became a lightning rod for discussion of longstanding regulatory concerns.

Concerns have been raised about whether it is appropriate to offer genetic testing without medical supervision; about the accuracy and utility of the tests being offered; and about the veracity of marketing claims made by firms. Whilst the first of these concerns is broadly applicable across much of the field of genetic testing - from well-established tests for single-gene disorders to pharmacogenetic tests - the latter concern has been primarily focused on susceptibility tests for common diseases. In this respect, concern about DTCGT converged with more longstanding concerns about susceptibility testing that first emerged with the discovery of the link between the APOE gene and Alzheimer's Disease in 1992. The discovery of the BRCA 1/2 genes two years later, and subsequent rapid commercialisation of genetic risk assessment for breast and ovarian cancer in the USA, focused the regulatory debate onto predictive genetic testing. A series of policy reports were produced across the globe, highlighting concerns about the predictive value and clinical utility of genetic risk tests, and warning about the psycho-social harms that these new technologies might generate.

Common policy recommendations emerging from this phase of policy deliberation included the need for informed decision-making, supported by appropriately qualified healthcare professionals (often encompassing genetic counselling), and the need to ensure rigorous, independent evaluation of tests before they enter routine clinical use. As the second wave of DTCGT was emerging in 2007/8, these recommendations were being enshrined in transnational standards generated by international bodies such as the Council of Europe's 2008 Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, and the Organisation for Economic Cooperation and Development's 2007 Best Practice Guidelines for Quality Assurance in Molecular Genetic Testing (Ibaretta and Hogarth 2010). The need for the involvement of a healthcare professional in genetic testing is also enshrined in legislation in a number of European countries such as France, Germany and Portugal (Borry et al. 2012). However, thus far it remains unclear how many states have implemented the standards they signed up to when developing the OECD guidelines, and in those European states with national legislation there is little evidence of enforcement of the regulations.

One branch of ELSI scholarship has sought to provide empirical evidence of the potential for consumer harm. As Philips notes in this issue, a recurrent theme has been the asymmetries of information between firm and consumer and the failure of firms to provide accurate and comprehensive information about their tests (see for instance, Geransar and Einsiedel 2008 and Hennen, Sauter and Van Den Cruyce 2010). A second strand of research has analysed the loopholes in existing regulatory regimes and proposed ways to address them to ensure pre-market evaluation of new tests using medical device regulation, either through legislative reform or stricter enforcement of existing powers (see for instance, Hogarth, Javitt and Melzer, 2008).

However, when regulators have acted in the DTCGT market, their actions have proven controversial. The US Food and Drug Administration's efforts to regulate DTCGT firms as manufacturers of medical devices have been characterised by some ELSI scholars as premature (Prainsack et al. 2011), unnecessary (Wright, Hall and Zimmern 2011), or even an infringement of constitutional rights (Farahany 2014). These regulatory sceptics question whether there is evidence of harm, and some suggested that further empirical research was needed to identify the impact of DTCGT on consumers. The subsequent research literature on consumer attitudes is addressed in the section on geneticisation below, but we note in passing that this research agenda, which sought to investigate the actual harms and benefits of DTCGT services, in particular genetic risk profiles, has put the evidentiary cart before the horse, interrogating questions of clinical utility in the absence of evidence of clinical validity (i.e. the accuracy of the risk assessments). Typical of the way that this latter concern is effaced in this literature is the argument advanced by Caulfield et al. (2013), who suggest that the lack of evidence that genetic risk testing causes psychological harm demonstrates that calls for enhanced regulation are an example of "ELSI hype". This conclusion neglects longstanding scientific concerns that genetic susceptibility tests provide inaccurate and misleading risk scores. Janssens et al. (2008) reviewed meta-analyses of gene-disease associations relevant to DTGT risk tests and found "significant associations with disease risk for fewer than half of the 56 genes that are tested in commercially available genomic profiles" (595).

Until two years ago the debate about the impact of using medical device regulation to govern DTCGT firms was largely conjectural, with much uncertainty about the scientific standards that might be applied or what types of tests regulators would allow firms to offer directly to consumers. Since 2015, the FDA has approved two regulatory submissions from 23andMe (the first for carrier testing and the second for genetic risk assessment), and a clearer picture of how regulation might shape this market is beginning to emerge. These developments occurred at the same time as this special issue took shape, and Curnutte's paper provides the first ELSI analysis of the new regulatory paradigm. Curnutte characterises DTGT as a disruptive technology that challenged existing regulatory arrangements but which ultimately has been folded within the established regulatory regime. Curnutte describes how the FDA allowed 23andMe's tests to be down-classified as Class II, medium risk devices, permitting them to use a less onerous regulatory pathway than Class III, high-risk devices, based on the firm's ability to provide evidence on the analytic and clinical validity of the tests and to demonstrate consumer comprehension of test results. She concludes that the boundaries of this new regulatory paradigm are not yet clear; it remains to be seen, for instance, whether 23andMe will seek FDA approval for the pharmacogenetic tests it once offered (and continues to offer in other

jurisdictions). Moreover, as Hogarth (this issue) points out, the genetic risk tests that FDA have approved are all for single-gene risk markers which, although their clinical utility is questioned, are supported by a body of evidence that has established their predictive accuracy (i.e. clinical validity). The FDA has yet to approve a polygenic risk score of the type that was central to the product offer of firms like 23andMe and Navigenics, and over which much scientific doubt remains. Whether the FDA will approve such tests, and what evidentiary standard will be applied, remains to be seen.

Like Curnutte, Hogarth is interested in the intersection of disruption and regulation, but for Hogarth disruption is an ideological construct and a commercial strategy, rather than a quality inherent in DTCGT services. Hogarth describes 23andMe's strategic shift from regulatory arbitrage to a combination of regulatory compliance and political lobbying as the firm responded to the FDA's decision to exercise its authority over the DTCGT market. In situating 23andMe in the tradition of Silicon Valley disruptor firms, Hogarth provides a broader context for understanding the regulatory strategies of DTCGT firms.

Approaching the governance question from a quite different perspective, Phillips shifts the focus away from medical device regulation and towards more generic consumer protection legislation. Issues of consumer comprehension, hitherto discussed in terms of genetic literacy, are recast as matters of legal expertise, as attention shifts from misleading product claims to confusing contract terms. Just as Hogarth's paper demonstrates how 23andMe's practice of regulatory arbitrage is a strategy generic to self-styled dotcom disruptor firms operating in many different consumer markets, so Phillips draws our attention to how DTCGT exemplifies the broader governance challenges of internet-based commerce. Her focus is the common recourse to clickwrap and browsewrap contracts that mitigate against consumer comprehension by dint of the complexity of their terms and their length (23andMe's terms of service is 9,081 words, and its privacy statement is even longer at 15,807 words). Phillips points to the UK Competition & Markets Authority (CMA) as the regulatory agency with the power to remedy these problems. What impact might this have? Drawing on a 2016 CMA report on unfair terms in cloud computing contracts, Phillips provides a typology of terms commonly found in her sample of DTCGT contracts, that the CMA's report suggested might be in breach of consumer legislation.

Geneticisation: past and present

A long-standing debate vis-a-vis DTCGT is the concern that such tests fuel 'geneticisation,' i.e. the idea that genes determine health and life processes. In her classic article on women's health and geneticisation Lippman (Lippman, 1991) argued that genes have become the 'lens' through which health is understood. So, low birth weight came to be seen as resulting from genes rather than poor nutrition and prenatal healthcare, illustrating how geneticisation is also frequently coupled with individualistic notions of health and illness, downplaying social and environmental causes and solutions. Deterministic metaphors for genes, such as 'blueprint' or 'book of life,' analysed also on the pages of this journal (Nelkin, 1994; Nerlich & Hellsten, 2004) have proved enduring in popular and scientific media, even if new scientific approaches, such as epigenetics, have generated new metaphors, such as genes as musical scores that can be played differently (Stelmach & Nerlich, 2015). Analyses of the websites of DTC genetic testing companies have noted that they represent genes in deterministic fashion (Nordgren & Juengst, 2009) and foster the neo-liberal notion of health as an individual responsibility (Harvey, 2010).

Saukko's paper in this issue continues these conversations and compares the representation of genes on the websites and media coverage of the now defunct nutrigenetic testing company Sciona and the current personal genome service 23andMe. Sciona represented genes as coding for predisposition for disease, which could be offset by eating specific foods or micronutrients. 23andMe represented genes in a new way, as digital big data to be browsed, uploaded and shared by consumers and companies online. On closer inspection, however, 23andMe continued to represent genes as coding for predisposition for disease to be mitigated by individual lifestyle change and targeted drugs, both in its genetic test results and the research it supported by selling its customers genetic and survey data to private companies. Yet, the metaphor of big data, which cast genes as digital big data to be circulated, shared, pooled and correlated by consumers and companies alike to produce new 'discoveries', was novel in social and economic terms, legitimising 23andMe's business model of consumer genetics and private biobanking. The way in which 23andMe mobilises discourses of open access, sharing and participatory science to support selling its customers' DNA for private gain has been noted by various scholars (Harris, Kelly, & Wyatt, 2016; Van Dijck & Poell, 2016). What Saukko's article adds to this discussion is the observation that, regardless of its claims to be a 'disruptive' actor (Hogarth, this issue), 23andMe represented genes in conventional terms as coding for disease at the same time as adopting the metaphor of genes as digital data to be shared and traded online. Genetic determinism has also raised concerns about lay understanding, with some authors suggesting that predictive genetics might give consumers false reassurance or generate undue anxiety or even fatalism. In this respect studies on the effects of DTCGT on consumers have found the tests to have null effects (for a synthesis, see Saukko 2013): consumers in these surveys do not interpret DTCGT genetic tests deterministically (Kaphingst et al. 2012); they do not suffer long-term anxiety, but neither do they adopt healthier behaviours (Bloss, Schork, & Topol 2011; James et al. 2011). A qualitative study of early adopters in the USA found them to be interested in health but aware of the limitations of the tests (McGowan, Fishman, & Lambrix 2010), and a study of Finnish consumers found them to be interested in genetics but also sceptical about the tests, or making sense of them through alternative interpretive frameworks, such as religion (Ruckenstein 2016). This survey data notwithstanding, anecdotal evidence points to the very profound impact that predictive genetics can have, as Messner's (2011) account of patients who had undergone APOE4 testing for Alzheimer's Disease demonstrates. Finley's paper in this issue provides a similarly compelling anecdote of patient anxiety recounted by a UK clinician.

The article by Finley in this issue explores attitudes towards DTCGT amongst UK consumers and clinicians working in the National Health Service (NHS). Clinicians have been amongst the most vocal critics of DTCGT, and Finley's clinician interviewees were similarly sceptical, although they acknowledged that their fears that DTCGT consumers would take up NHS clinician time had not yet become a reality (perhaps unsurprising given the low rate of consumer uptake (see Hogarth this issue)). Some of the consumer interviewees, on the other hand, had bought into the notion of commercial personalised medicine, wanting to acquire personalised information about themselves, and portraying clinicians as "pretty stuck in the past". Framing these views as a conflict between collective and personalised medicine, Finley locates this dichotomy in the contemporary politics of the NHS in a period of austerity economics.

Promissory capitalism: the political economy of DTCGT

Attention to questions of political economy has been scant in the ELSI genomics literature, which, even when addressing matters of governance, has paid more attention to upstream research (in particular biobanking) than downstream commercialisation. Research on the DTCGT market is a rare exception to this rule, but even this body of work pays limited attention to how the firms in this emergent market seek to create and capture value. Paradoxically, although much of the ELSI interest in DTCGT is generated by the controversy around the commercialisation of genomics, it seems that there is limited interest in the commercial realities of DTCGT.

Whether this expanding market is creating or destroying financial value is moot, and thus far the ancestry testing market seems the most successful in terms of known customer numbers. The market leader Ancestry DNA has more than 2 million customers, however the firm has integrated vertically with so many other firms in the genealogy market that its commercial worth is only partially tied to its genotyping service. Firms offering health-related testing have struggled to establish sustainable business models (see Hogarth this issue), a problem common to many emergent biotechnologies (Plagnol, Rowley, Martin and Livesey 2009).

One approach to the economics of DTCGT has been to focus on the relationship between firm and consumer. Harris, Wyatt and Kelly (2013) draw on the concepts of clinical labour and free labour to understand how 23andMe seeks to derive financial value from the work that their customers perform as research participants. In this issue Hogarth offers a different approach, focusing on the relationship between venture capitalists and DTCGT firms. Examining 23andMe's status as a self-styled 'disruptor' firm, Hogarth explores issues of worth and value in the bioeconomy, and what Paul Martin (2015) has called "the promissory character of contemporary capitalism". Situating 23andMe in its geographical setting of Silicon Valley, Hogarth describes how the firm is typical of the distinctive local culture of entrepreneurialism that has developed in the area since the 1980s. Hogarth suggests that in Silicon Valley the relationship between moral worth and economic value is mediated through the concept of disruptive innovation, which functions as both ideological construct and a set of commercial practices utilised by the founders of start-up firms and the venture capitalists (VC) who invest in them. Drawing attention to 23andMe's success in attracting the support of VC investors, he points to the recent massive increase in private capital available for start-ups in Silicon Valley and describes the controversy the new era of 'unicorn' firms has created: the crisis of corporate governance that surrounds disruptor firms like Theranos and Uber, and the warnings many experts are now raising that the growth in unicorn firms signals a new high-tech investment bubble.

And beyond?

Taken together, the papers in this special issue identify some key trends and developments that may shape the future of DTCGT. In the USA, the FDA is pushing the DTCGT sector toward more validated tests and asserting greater control over consumer information and test accuracy. To the extent that regulation may now be acting as a barrier to market entry, it is likely that 23andMe has gained a major competitive advantage in being the only FDA-approved DTCGT firm, a significant development given the firm's ambitions for market dominance.

Aside from the changing regulatory environment, there are other important contextual shifts. Firstly, much of the hype in consumer diagnostics has shifted from genomics to mobile digital health (mHealth) technologies. As with DTCGT, the issue of technology validation has been

raised, with the US Federal Trade Commission recently sanctioning one health app developer for making unsubstantiated medical claims and stating that the device must be tested in a Randomised Control Trial (Wicklund 2016). However, as with DTCGT, there is uncertainty about the applicability of the established regulatory paradigm for medical devices to this new generation of technologies that straddle the space between the consumer market for wellness/lifestyle products and the clinical market for medical devices.

As Saukko's paper indicates, the integration of genomics into this new technology paradigm of mHealth is predicted, not least by 23andMe, but at the moment most mHealth applications are focused on other types of biomarker, which suggests that geneticisation of healthcare remains a partial and contested process that both competes with, and is dependent on, convergence with other socio-technical trajectories. As personalised medicine has been rebranded as precision medicine, there is growing acceptance that other types of 'omics markers may be more clinically useful than germline DNA, and that the utility of genomic markers may be enhanced by integration with other biomarkers (Anonymous 2012).

How DTCGT firms will fare in this changing socio-technical landscape remains to be seen. Consumer surveys have shed light on the attitudes of early adopters, but the attitudes of the lay public can be clearly read from the sales figures: given the very low uptake of DTCGT, the prevailing attitude amongst the general public is at best indifference. Whether FDA approval provides a form of reassurance that can quicken the pace of consumer uptake also remains to be seen. Given the slow progress of the broader project of personalised/precision medicine (Green and Guyer 2011), it is perhaps unsurprising that DTCGT firms have yet to realise their vision of a mass market for genomic knowledge .

However, even amongst those sceptics who believe that the business models of DTCGT firms are as shaky as their scientific claims, there can be little doubt that the second wave of firms has enjoyed one notable success: they have been able to shift the discursive terrain on which the future of genomics is contested. In the face of a variety of regulatory efforts, and in defiance of a decade of policy angst about the potential harms of predictive genetics, they have persuaded many that genomic knowledge is fascinating rather than scary; and they have asserted the principle that individuals have a right to their genome. It is an indication of the power of this principle that the FDA has been at pains to publicly state that they do not wish to contest it (see both Saukko and Curnutte in their contributions to this issue). As Hogarth's paper suggests, the future of DTCGT may hinge as much on winning the ideological battle and the ability of firms to generate compelling visions of social transformation, as it does on technological advances or managerial competence. In this respect the growth of the mHealth market represents not simply an opportunity for new forms of technology convergence and commercial synergy, but the emergence of new allies in the ideological struggle to advance the cause of routine consumer health monitoring as a new individualised form of preventive medicine. However, the commercial push has been met with increasing professional critique: the Choosing Wisely campaigns and the international *Preventing Overdiagnosis* conference series, now in its fifth year, exemplify increasingly vocal and organised scepticism about screening/early disease detection as a public health goal. If DTCGT remains a market in the making, then the future progress of DTCGT will in part be determined by the contest between these two contrasting visions.

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