

**Title**

Hidden Innovation: Examples from the emergence of novel genetic testing technologies in the UK's National Health Service

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## 1. Introduction

Technological innovation takes many forms, and inevitably some are more obvious to observers than others. The launch of a new consumer product such as a multi-media platform like a new iPhone will be accompanied by much advertising, and so will be readily observable. The physical size and cost of many other technologies makes some innovations quite apparent, such as new types of military equipment. However other innovations are less tangible, such as those based on new methods, techniques, or novel forms of social arrangements, so called social innovations (Nelson 2008). Observers can use databases of patents to find product or process innovations, but not all inventors seek to protect their innovations in this way (Patel 2012). Thus it appears that some innovations are poorly served by traditional measures of innovative activity, which may lead to incorrect assumptions about where and how innovation takes place (NESTA 2006). One sector where this is particularly apparent is in healthcare, where as we will explore, there is a strong contrast in modes of innovation between the private and public sectors.

On the one hand the linear model of pharmaceutical innovation suggests basic research and pre-clinical research undertaken in the public sector is followed by expensive clinical trials, regulatory approval and marketing launch, all of which are resource intensive activities, usually funded by private sector risk-capital. These innovations often enter medical use via processes of regulatory approval and health technology assessment. Health insurers may or may not decide to reimburse their costs, but certainly the profile of these innovations is high with industry apparently driving the innovation process. Industry has also played a key role in the innovation in medical imaging technologies (Blume 1992).

On the other hand medical advances stemming from new techniques such as surgical techniques supporting organ transplantation (starting with kidney, liver and later then heart, face, legs and hands) do not require firms, nor extensive regulatory or marketing expertise to bring to market. They emerge within a hospital-based innovation system driven by clinicians. These innovations are internal to the hospital-based research system, rather than externally created innovations whose creators must build a network and enroll institutional support to bring their innovations within the system.

This raises the question of how 'hidden innovations' may create new technologies within hospital-centred networks of actors? What are the institutional arrangements that accommodate these technologies and how do they differ from those that result from firm-led efforts?

This topic was initially approached as part of a doctoral study (Hopkins 2004) however hidden innovations emerging from hospital-based research systems remain relatively neglected by scholars of innovation (Lander and Atkinson-Grosjean 2010). The present paper returns to the subject bringing new insights and a previously unpublished case to add to prior published accounts (Hopkins 2006, Hopkins and Nightingale 2006).

## 2. Conceptual approach and method

Technologies may be usefully conceptualized as sociotechnical ensembles (Bijker 1995) made up of physical artefacts, operated through techniques which are embodied in people, who in turn operate within a regime of norms, regulations and organizational constraints (Hopkins 2006). The composition of technologies and the networks of people using them change over time as groups of stakeholders ('actor groups') adopt, amend or abandon the technology according to their needs. Blume (1992) provides a straight forward framework (the '*career*') to facilitate comparison of different technologies according to milestones such as their proof of principle or first adoption, as well as a tool kit of concepts, emphasizing the importance of *problematizations* by actor groups of the technology, the coordinating *visions* these groups express in relation to how the technology may be used, and the *inter-organizational links* that are formed between firms, hospitals, and other groups that influence the emergence of the technology.

Fieldwork involved interviews with over 50 clinicians, scientists, industry executives, and patient groups, two weeks of participant observation at a regional genetics centre in a major London hospital, a laboratory survey, and archival research in the records of professional bodies. This, together with historical literature review, allowed detailed accounts to be constructed of the careers of cytogenetic testing, biochemical genetic testing and molecular genetic testing.

## 3. Empirical Account

The final paper will focus on comparing and contrasting the emergence of cytogenetic testing and molecular genetic testing in the UK. Unlike, biochemical genetics (excluded for reasons of space) both these technologies are based on direct analysis of genetic material (DNA) to determine whether deleterious mutations associated with disorders are present. Cytogenetics studies DNA *in situ* in the cell using a body of cell culture and microscope-based techniques to visualize relatively large changes in the chromosomes that make up the genome of patients. By contrast molecular genetics can be used to detect even the smallest of changes in the genome by using biochemical reactions to replicate or disassemble genes in preparation for sorting DNA fragments by size and electrostatic charge. A summary of the main empirical findings below shows that these technologies emerged at different times (see Tables 1 and 2), relied on distinct sets of techniques, were practiced by different groups of scientists with distinct training by separate professional bodies and (although there were some notable overlaps) specialized in providing testing services for different genetic conditions.

### The career of cytogenetic testing technology in the NHS

	<b>Exploration: early 20<sup>th</sup> century – 1956</b>	<b>Development: 1956-1959</b>	<b>Adoption: 1959-late 1960s</b>	<b>Early growth: late 1960s-early 1980s</b>
New actor groups (new inter-organisational structures indicated in brackets)	Research scientists (international exchange of knowledge)	Research scientists and early clinical geneticists (exchange of samples and test results)	Funding bodies and charities, clinical scientists (funding to support the establishment of laboratories and clinics)	Other physicians (referrals sent to clinical scientists and results reported back) Professional bodies (networks of laboratories and clinics form and discuss best practice, and lobby for resources)
<b>Visions (in bold) &amp; Problematisations</b>	<b>Research scientists: Chromosomal changes are linked to disease might be detected in patients</b>  How many chromosomes do humans have? How can consistent experimental results be achieved?	Which conditions are caused by chromosomal abnormalities?	With the 'conquest of environmental disease', where is medicines' new focus? Heritable disease? Can we discover more conditions caused by chromosomal abnormalities if we increase the resolution of analysis? How can samples be obtained more easily for analysis?	<b>Clinical geneticists: offer parents reproductive options but contain such services in a dedicated clinical genetics network</b>  Can we reduce the impact of abortion on patients? Can we increase detection rate of technology by: 1) better referral criteria? 2) resolving power of tests?
Artefacts recruited/ configured, or developed	Configuration of microscopes with tissue samples from model organisms/ humans. Colchicine adopted from plant cytologists.	-	phytohaemagglutinin Geimsa stains, fluorescent microscopes are all adopted from other fields	-
Change in techniques	Sample preparative techniques developed and combined – cell culture methods, squash technique, hypotonic solution	Analytical development i.e. spotting missing chromosomes	Cell culture techniques for white blood cells, staining techniques are developed.	Karyotyping linked to Amniocentesis and amniocyte culturing
Change in regime	No relevant clinical regime	No relevant clinical regime beyond informal exchanges of tissues	Ad hoc clinical laboratory regime established International consensus on scientific nomenclature	Wider professional acceptance of 'therapeutic abortion' with genetic counseling Association of Clinical Cytogeneticists established for training and lobbying.
Outcomes	Human karyotype established as 46 in diploid cells.	Down's associated with chromosomal abnormality	Dedicated clinical cytogenetics laboratories established	Cytogeneticists gain more NHS funding - screening for Down's established on a regional basis, Clinical genetics centres develop

### The career of molecular genetic testing technology in the NHS

	<b>Exploration - mid 1970s</b>	<b>Development mid-1970s-early 1980s</b>	<b>Adoption Early 1980s-start 1990s</b>
New actor groups (and new inter-organisational structures)	Research scientists (multidisciplinary/international collaborations)	Clinical geneticists, other physicians (research collaborations with laboratories, first reporting of results) Patient groups (financial links, supply material, information to physicians/ laboratories)	Clinical molecular geneticists & their professional body (CMGS) (linked to clinical genetics depts, supported by MRC, informally networked for co-operation)
<b>Visions &amp; Problematisations</b>	What is a gene? Where are genes located? How do genes work? How can DNA be analysed?	<b>Physicians: carrier detection or prenatal detection of rare severe disease aimed at prevention (e.g. thalassaemia).</b> <b>Research geneticists: prediction of more common diseases</b>  <b>Find linkage markers to track genes</b>	<b>Clinical geneticists: continue to offer special clinics and informed choice over reproductive issues using new technologies</b>  Careful management of genetic knowledge Increase breadth of services: -Discover more genes -increase resolving power of techniques -decrease laboriousness of techniques
Artefacts recruited/ configured, or developed	Restriction enzymes DNA probes/ cDNA libraries	Novel probes	-----PCR machines -----Automated sequencing ----- Commercial kits
Change in techniques	Electrophoresis hybridisation Southern blotting Auto-radiography	RFLP analysis and linkage combined Prenatal application via combination with CVS, Manual sequencing developed	Development of protocols for new diseases using existing techniques PCR introduced, manual sequencing
Change in regime	Clinical genetics established (see Chapter 4)	Clinical application of tests meet no formal regulation	NHS 'internal regime' forms: First dedicated NHS molecular laboratories. Ad hoc network of CMGS laboratories develops, counseling established for management of 'genetic knowledge' for increasing number of conditions
Milestones	DNA structure and code unravelled. Repeatable fragments of DNA generated/ cloned	First prenatal tests and discovery of first genes/ markers for rare disorders (CF, HD, DMD)	Human genome project begins, 'core services' established in CMGS laboratories

#### 4. Discussion

The tables summarise key events and illustrate that both cytogenetics and molecular genetic testing emerged out of fundamental scientific research, undertaken by a community of researchers, some of whom had clinical training seeking to use new technologies to understand genetic inheritance. The artefacts (such as the microscope and some laboratory reagents) were pre-existing and where industry supplied these, their focus was on the research market, rather than clinical application.

The association of particular genetic abnormalities with (relatively) rare disease that was considered to be severe enough to warrant intervention provided a stimulus for clinical involvement by a small number of pediatric clinicians. They worked even in sensitive prenatal cases, bringing the new technologies into use in a small niche.

There was no external regulation of the technologies, as clinicians had sufficient authority to use procedures and health authorities could be told technologies were cost saving rather than adding to expenses (i.e. reducing births of disabled and therefore expensive children by informing parents about their 'reproductive options').

Research scientists became clinical scientists and established a new network of laboratories to offer testing services within the NHS. Clinicians facilitated this process and over saw the governance of testing through the establishment of a professional body. Genetic counseling is seen as important part of genetic testing process to protect patient's well being. Industry involvement in testing services is absent until the early 1980s and is limited in scope when it emerges, following accepted practice in NHS labs. Industry involvement in production of artefacts for clinical testing market is also limited until the growth phase (see Hopkins 2006).

After initial adoption for niche applications both cytogenetics and molecular genetics expand their usage to wide spread use (still relatively small field) with, collectively, hundreds of testing protocols developed.

## **5. Conclusions**

The emergence of cytogenetic and molecular genetic testing services in the UK NHS demonstrates how trusted clinicians were able to mediate the introduction of new technologies even into highly sensitive prenatal care without an external regulator. Existing artefacts and techniques were brought together in novel configurations and together with a hospital-based governance regime developed locally via professional bodies, the technologies grew in use to a wide range of applications. Industry played little role, and technology adoption appears to have been relatively rapid. Elsewhere we note that industry found it more difficult to access the UK market for commercial genetic testing services due to consumer group suspicion and the dominant position of NHS testing laboratories (Hopkins and Nightingale 2006). Thus NHS genetic testing services have become part of a distinct hospital-centred innovation system generating a series of 'hidden innovations' within their own 'internal regime' while firms remain part of the 'external regime'. It is notable that since 2003 these arrangements have been formalized in the EU with the in vitro diagnostics directive that expressly excludes hospital services from the same regulatory controls as firms. In recent years NHS laboratories also tend to ignore IP claims of firms on genetic tests (HGC 2011) further demonstrating the isolation of the internal regime from the external.