

What happens when the emergence of new medical technologies does not depend on industry?

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Abstract:

The development of many new medical technologies has relied on new industrial actors and their collaboration with clinicians (for example see Blume 1992 on diagnostic imaging instruments, and Martin 1998, on gene therapy). This study shows that in some cases the development of medical technologies is not reliant on clinician-industry links, as previous authors suggest. As a result such technologies may follow a markedly different 'career' than medical technologies brought to the clinic by firms. It is argued that by deconstructing the technology into its component parts (techniques, artefacts, and regimes) we can distinguish between artefact-led and technique-led innovations in medical services, and begin to explore the characteristics of the later. This is demonstrated through empirical research on genetic testing services within the UK National Health Service (NHS).

Genetic testing services in the UK's NHS are made up of three distinctive networks of laboratories reliant on different technologies, with distinct technological platforms and specialist staff: biochemical genetics, molecular genetics, and cytogenetics. Based on historical accounts and research interviews, this paper reviews the development of cytogenetic techniques and explores how these techniques facilitated the development of novel services. It is argued that while we have an understanding of artefact-led technological innovation (the traditional industry-dependent route), technique-led innovation follows a different dynamic, which requires an extension of existing model of medical innovation presented by Blume. This is demonstrated by showing how services develop from basic scientific research and instrumentalities (DeSolla-Price 1984) through the 'tinkering' (Knorr-Cetina 1981) and persistence of university and hospital laboratory staff. The results also inform the literature concerning producer-user interactions, e.g. Lundvall (1992).

Introduction

This paper seeks to add to our understanding of the dynamic processes through which novel medical services are developed and delivered. An understanding of the processes of medical innovation becomes more important as medical technology and its supporters are increasingly called to account. Despite historical successes in areas such as managing contagious diseases (eg. antibiotics, vaccines), modern medicine has been criticized as being increasingly expensive and relatively ineffective against a host of diseases (heart disease, cancer, dementias) (Weatherall 1995) (LeFanu 1999) (Porter 1999). Healthcare costs account for an average of 6.8% of GDP in developed countries and ultimately affect almost all the families therein (add ref: Development Indicators, 2000). This high cost, linked to an apparent increasing dependence on high-tech solutions (Blume 1992: pp13-21) together with increased public disappointment with medicine goes some way to explaining why medical innovation is an activity involving diverse groups of actors in wide ranging political, economic, social and ethical debates.

Given the importance of medical innovation, it seems odd that over the years the Innovation Studies literature on the subject has often been referred to as underdeveloped (Roberts 1981; Blume 1985) (Gelijns and Rosenberg 1994). Recent initiatives such as the UK ESRC's Innovative Health Technologies Program and the 'Medical innovation at the crossroads' series by the USA's Committee of Technological Innovation in Medicine may begin to redress the balance, however there are notable gaps in our understanding of how medical innovation occurs. To show these, it is helpful to deconstruct the term 'technology' into its component parts.

Authors have identified three elements of which technology is comprised: artefacts, techniques and institutional structures (Fleck 2000) (Winner 1977) although the terminology used to describe these elements varies as illustrated in Table 1.

Table 1: The constitution of technology

Element	Examples
Artefacts	Hardware, apparatus, products
Techniques	Skills, methods, routines, processes
Institutional structures	Laws, regulations, ethics, codes of conduct

To be clear and concise¹, we will use to the term *regime* rather than institutional structure, and our definitions of these core terms will be as follows:

- An *Artefact* – an object made by a human being
- A *Technique* – a way of carrying out a particular task
- A *Regime* – a system or a planned way of doing things (i.e. a set of rules within which techniques and artefacts are used)

Thus when we examine a ‘Technology’ we must be aware of an entire sociotechnical system composed of artefacts, techniques and regimes. The formulation of these components results from processes of negotiation, conscious or otherwise, between groups of actors within the confines of social and technical limitations which constrain choice. In defining the term ‘technology’ we refer to the application of knowledge within a regime, using a set of artefacts whether derived from scientific knowledge, or ‘tinkering’. Fleck puts forward a mechanism for the evolution of technology through change in either an artefact or an activity (the artefact-activity couple) (Fleck 2000), and therefore we suggest that technological change results from developments in artefacts, techniques or regime as defined above.

At present medical technologies are often divided into three categories: drugs, devices and techniques (Gelijns 1990). There is a long history of literature exploring the dynamics of drug use, for example (Coleman, Katz et al. 1966) (Finkelstein and Gilbert 1985) and more recently the pharmaceutical innovation that produces them, for example see (Pisano 1997), (Nightingale 2000). Technological change in medical devices have also been well addressed in the literature (Blume 1992), (VonHippel and Tyre 1995) (Shaw 1998) (Gelijns and Rosenberg 1999). However the dynamics of medical

¹ And to avoid confusion with Blume’s term ‘inter-organisational structure’ which will be introduced later.

innovation resulting from change in medical techniques remains largely unexplored, with the one or two exceptions, for example (Casper and Clarke 1998) perhaps partly because the dynamics of medical techniques can be difficult to monitor p.184 (Gelijns 1990). Nonetheless, by focusing on artefacts such as drugs and devices, much of the above literature becomes dedicated to the studies of interactions between clinical users and industrial producers, thus neglecting other possible forms of medical innovation, especially those not driven wholly or partly by firms. It is entirely possible that in some circumstances clinical users are able to adapt existing artefacts and extend their use to create entirely new technologies. They can introduce new types of services through the development of novel techniques and create entire new forms of technology together with associated specialist practitioners and bodies of knowledge. We suggest this is a distinct process from the more incremental change that occurs when, for example, a surgical laser or endoscope is put to use against a disease it had not been tried against previously, as that would be only the extension of a recognised medical technology, rather than the creation of an entirely new technology. The mode of innovation investigated here will be called ‘technique-led technological change’ to distinguish it from change resulting from the introduction of novel drugs or devices that we refer to as artefact-led technological change². Equally, we might imagine innovation in medical services can be spurred by a change in regime – as has been explored by Bartlett-Foote in a study of forty years of American policy on medical devices (Bartlett-Foote 1992). In this paper we will focus solely on exploring some of the characteristic of technique-led technological change through examination of the following hypotheses³:

² This seems similar to Barras’s Reverse Product Cycle p.165 Barras, R. (1990). "Interactive Innovation in Financial and Business Services: The Vanguard of the Service Revolution." Research Policy **19**: 215-239. The Reverse Product Cycle has three stages: 1. New product introduced to help *existing* service, 2. New product improves quality of services 3. Technology of new product is used to transform next generation of services.

³ H1 and H2 are similar to postulations made by Geljins in Gelijns, A. C. (1990). Comparing the Development of Drugs, Devices and Procedures in Medicine. Modern Methods of Clinical Investigation. A. C. Gelijns. Washington DC, National Academy Press: 147-201. However these remain to be tested against full case studies.

H1: In technique-led innovation users introduce new medical services through the adoption of non-medical artefacts, put to new purposes through the creation of novel techniques.

H2: Technique-led innovation can diffuse unchecked and with little associated financial costs, as commercial interests and regulatory systems are absent.

H3: Industry will attempt to join the new sociotechnical system by offering to automate manual techniques, standardise reagents, or optimise existing artefacts for the new activities when an attractive market appears.

A suitable theoretical framework with which to test the above hypotheses is provided by Blume (Blume 1992). Blume's framework draws heavily on the sociology of technology literature, for example (Bijker 1995), (MacKenzie and Wajcman 1999), which views technologies as developing through the selection of options by relevant actor groups, engaged in processes of negotiation. Blume is rather pragmatic in his approach to conceptual tools, which consequently present fewer difficulties in operationalising than the frameworks provided by other authors in the STS field, especially when it comes to the question of generalisation between case studies. Blume's central conceptual tools are the *career*, *inter-organisational structures*, and the *problematization* of aspects of the new technology or its environment by actors involved in shaping it. The *career* is an analytical approach that follows the development of a technology, through distinct phases indicated by milestones, such as completion of a prototype or the first clinical use. Blume identifies these phases as experimentation, development, diffusion and feedback. Its purpose is to aid generalisation between case studies. Analysis of relevant actors and their role in the shaping of the technology is facilitated through the exploration of the *inter-organisational structures* they form with other groups of actors, such as contractual obligations, or informal agreements to collaborate, and the problems they attach to the technology (i.e. the form of *problematization* that occurs) for example in debates, institutional records, or at interview. Blume has employed these conceptual tools on a set of case studies within the field of diagnostic imaging instruments (X-ray, C-T, MNR,

Ultrasound, and Thermography), and identified three types of career that medical technologies appear to follow (see table 2). He also notes that some technologies such as CT Scanners can ‘switch’ between careers – and as such careers are not rigid.

Table 2: Blume’s Technological Careers in Diagnostic Imaging

Type of career	Central actors involved in innovation network	Example
Conformist	Existing firms and their customers (users)	CT Scanners (late)
Non-conformist	New firms and new users	Ultrasound, MNR, X-Ray
Contested	Mixture of new and old users and/or new and old firms	CT scanner (early), Thermography

It is clear from Blume’s accounts that, although the ways in which these instruments are used are often described as techniques, the clinical techniques could not be developed until an instrument had been designed, and that design took place with a clinical application in mind. In this sense the technologies associated with these various diagnostic scanners are artefact-led technologies. If we wish to extend Blume’s framework, and assign other medical innovations their ‘careers’, we will need to include forms of medical innovation besides artefact-led technological change. Through the addressing of the above hypotheses, it may become necessary to define new types of careers.

Selection of a technique-led innovation to study

To explore the dynamics of technique-led technological change in medicine, the case study of genetic testing technologies in the UK’s National Health Service has been selected. The choice of UK genetic testing services is appropriate for several reasons. Firstly, in addressing Blume’s theoretical framework it is good practice to compare like with like. Blume’s cases are based on diagnostic imaging equipment, and by focusing on genetic testing we remain within the field of diagnostic medicine, rather than looking at therapeutic technologies, such as surgical techniques. This is important for the study of the dynamics of technological change because complex diagnostic technologies often

exhibit a ‘user split’. For example, surgeons requiring X-ray images of patients refer the patient to a radiologist who conducts the procedure; hence both are users of the technology in some sense – while the patient might be distinguished as a consumer. In the case of genetic testing, the clinical geneticist or other specialist, such as a paediatrician, sends samples for testing, then undertaken by clinical scientists. The role of both users is crucial, but distinct, as we shall see in the case study. Secondly, the choice of genetic testing offers a ‘clutch’ of technologies that share their institutional environment, and have similar economic, political, social and technical circumstances. This allows comparisons between the examples studied, and provides a similar structure to that of Blume’s own work on diagnostic imaging technologies. The thesis from which this paper is derived focuses on three genetic testing technologies (cytogenetics, molecular genetics and biochemical genetics). Each of these technologies employs a distinct group of specialists, trained and reporting to separate professional bodies, and using very different techniques and instruments. Only the data from the case study on Cytogenetics is reported here.

A third reason for the selection of genetic testing technologies is that they are relatively young technologies, meaning many key figures are still available for interview. The advantage of a new, and still evolving technology is that we can examine the ‘science in action’ (Latour 1987) p.258, before controversial technologies are ‘blackboxed’. Fourthly, the choice of genetic testing as a case study may be considered timely. With the near-completion of the human genome project, the public and politicians are increasingly aware of genetic testing services⁴ and as a result new pressure groups have formed to pursue regulatory change and other service developments.

Finally, the choice to focus on genetic testing in the UK is largely governed by resource limitations. It should be noted that the shaping of genetic testing technologies used in the NHS is to some extent dependent on developments outside the NHS and indeed the UK, as genetics is an activity conducted by an international scientific community. This limitation can only be addressed to an extent through referring to available literature.⁵

⁴ Genetic testing has even been covered extensively the leading UK consumer magazine - See Copeland, E. (2002). "All in the genes." *Health Which?*(June): 10-13.

⁵ Detailed histories of genetic testing services in the Netherlands [Nelis, 1999 #83], and Canada [Leeming, 2001 #265] have been published previously as well as broad comparative studies by clinicians [Harris,

Research Method

The broad nature of the research questions required a complex method to be developed, as the case studies involved diverse and heterogeneous groups of actors, some of whom have been active for several decades, while the roles of others have only recently emerged. The result has been a mixed methodology drawing on the use of histories and archival research, semi-structured interviews, participant observation, ethnohistory, and survey techniques to produce a series of case studies (see annex 1 for matching of research method to research problems).

Cytogenetic testing in the UK's National Health Service

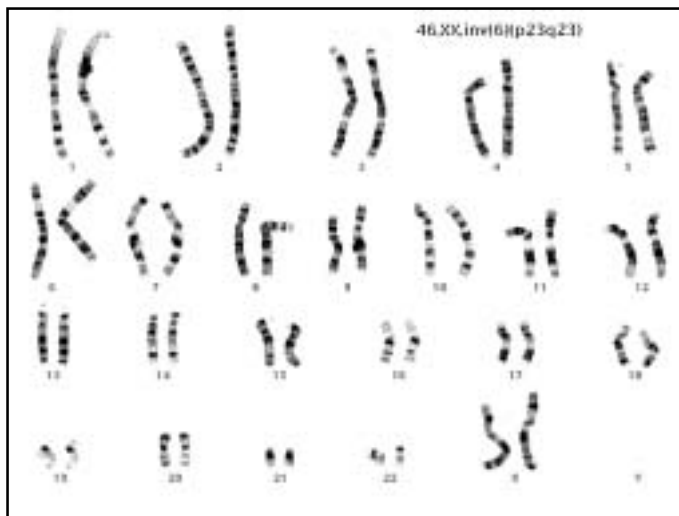
Cytogenetics has been defined as the study of inheritance in cells through determination of the presence or absence of changes in chromosome structure. (p.181 (Isaacs, Daintith et al. 1991)). It has a long history that begins with the study of cells, cytology. For the purpose of this paper we can understand the development of this technology through a crude illustration. In picture 1: we see a twisted and tangled mass of chromosomes, the role of which we do not understand. In picture two, we see an adept scientist has taken an inventory of a set of chromosomes from which they have been able to distinguish a barely visible fault (noted in top right hand corner) which may be diagnostically valuable.

1997 #100]. Other histories such as Harris Harris, H. (1995). The Cells of The Body. New York, Cold Spring Harbour Laboratory Press. and Kevles Kevles, D. (1985). In the name of Eugenics: genetics and the uses of human heredity. New York, Knopf. also go beyond the scope of UK developments.

Picture 1: Unsorted human chromosomes



Picture 2: A set of 'karyotyped' human chromosomes



The first diagnostic services based on cytogenetics emerged in the early 1960s. They were offered by research scientists with knowledge of cytogenetics to a small number of clinical geneticists and other medical specialists with an interest in genetics, such as paediatricians, who had patients they suspected of having abnormalities caused by chromosomal errors. However only in the last ten to twelve years have firms begun to focus on producing products exclusively for clinical users of the technology. Through a

historical analysis of the field we will address the implications of this case study for Blume's framework.

The Origins of Cytogenetics

Cytogenetics grew out of cytology, and cytology's origins are intimately connected with the development of the microscope. It is important to emphasise the non-technical aspects of the era of microbiological discovery that run parallel with the technical achievements of Leeuwenhoek and others. At the time the field was populated by philosopher-scientists who have been accused of wild speculation based on their observations, and diehard beliefs in the spontaneous generation of life. These views took almost seventy years to give way to more modern beliefs (Harris 1995: p.1). Thus when progress came it was not because of advances in lens making, but because of changes in the theoretical concepts microbiologists used their microscopes to address p.1 (Hughes 1964). After the metaphysical debates were resolved, cytology developed to the stage at which the significance of the sperm and egg fusing was realised. By 1877 microbiologists had watched cell divide, and witnessed the formation of thread-like structures they called *chromosomes*, meaning coloured bodies, because they appeared thick and dark, in the nucleus prior to cell division. They observed these structures multiplied, and separated out during cell division and then melted away to become indistinct during the rest of the cell cycle p.41 (Judson 1992). In 1892 the German physiologist August Weismann settled the age-old debate about the contribution of each parent to the embryo - both parents contribute half the contents of the nucleus. In 1896 Edward Wilson, a cell biologist at Columbia University, suggested the chromosomes played a role in inheritance p.42 (Judson 1992). The Austrian monk Gregor Mendel is generally credited with deciphering the mechanism of heredity, and publishing a set of laws that could be observed in breeding experiments with the common pea plant. He observed the passage of characteristics from one generation to another in the common pea plant and hypothesized the existence of hereditary 'particles', deducing such particles must work in pairs judging by the changing ratios of those displaying or not displaying a given

characteristic.⁶ His work languished for around 35 years before being rediscovered, tested and held to acclaim by biologists, who in the intervening years had acquired a greater grasp on other both the tools of cytology and statistics. These could now be used to examine patterns of inheritance.

By 1905, within three years of Mendel's work being discovered, Wilson had observed that characteristics such as sex (male or female) were determined (using the fruit fly as an experimental model) in a pattern consistent with Mendel's laws. He concluded this implied that genetic information must be carried on chromosomes. For more than twenty years, Wilson, his students, and later his students' students led the international scientific community (for which they collected two Nobel prizes) in the study of genetics. The 'genetics' was coined in 1906, and subsequently used by experimental geneticists who focused on fruit flies⁷ to distance themselves from Eugenicists, whose studies of Humans they saw as 'unreliable and reckless' (Kevles 1985: p.122).

Exploratory phase

It is difficult to elucidate the exact time the idea of cytogenetics as a medically useful activity first emerged. Certainly by 1932, it was apparent to the visionary UK geneticist Haldane, that chromosomal abnormalities could be common in humans, even though cytology was not his field, (Polani 1997: p.118). By this time a number of research scientists in Europe, the USA and elsewhere were already working on solving crucial problems that stood in the way of the identification of such abnormalities, even if they may not have been considering medical applications at the time.

⁶ For example he observed that when tall stemmed and short stemmed plants were bred, the offspring were all tall, but in the subsequent generation, for each short stem, three tall stems were present. P.42 Kevles, D. (1985). In the name of Eugenics: genetics and the uses of human heredity. New York, Knopf.

⁷ Although human genetics remained little explored, partly due to the stigma of eugenics, geneticists favoured the fruit fly, *Drosophila melanogaster*. They were chosen because they reproduced quickly and in large numbers, as was essential for a science that relied on probability and statistics to produce results. It follows that if one needs a large number of such organisms, they must be small and easy to keep (Kevles: 1985: p.194). When heritable changes in individuals were discovered, the scientists were rapidly able to segregate the affected individuals and form stocks of mutations. Using traits such as long and short wings, and red or white eye colour experimental geneticists were able to achieve rapid progress in understanding the nature of genes and their patterns of inheritance.

Work on human chromosomes did not progress as fast as in other experimental organisms as scientists could not agree on the correct number of human chromosomes that should be present in a normal cell. This is of course the most basic problem one would need to solve to undertake any form of chromosomal analysis – for research or applied purposes. The problem lay in the relatively large number of chromosomes humans appeared to have, and the serious technical problems facing those preparing samples. At first, slides had to be prepared using thin slivers of the types of tissue⁸ where one would expect to find dividing cells – necessary because chromosomes are visible only immediately prior to cell division⁹. Although it was possible to keep such tissue alive *in vitro*, it was every difficult to maintain cell growth.

By 1923 the confusion surrounding human chromosomes was such that a cytogeneticist at the University of Texas, Theophilus Painter, was able to list 26 publications concerned with identification of the correct number of human chromosomes, none of them accurate by today's measure (Harris 1995: p.58-61). The problem partly resulted from counts being made on thin tissue sections that contained many portions of bisected cells. Analysis was further complicated as the numerous human chromosomes appeared twisted, crowded and stacked (Kevles, 1985: pp.240-241). Painter was able to access testes tissue he obtained from the Texas State Insane Asylum that he hoped would give good results as they were fresh¹⁰. From this source he concluded the correct number of chromosomes in a Human diploid (non-germline) cell should be 45-48, with sex chromosomes XX or XY determining sex of the offspring, although his was disputed at the time (Polani 1997) p.119. Nonetheless Painter's final estimate of 48 chromosomes that was favoured among his peers and endured for the next thirty years.

The difficult task of examining human chromosomes continued to encourage cytogeneticists to try novel preparative techniques, and this was the core problematization behind the technology until the late 1950s. During this time cytogenetics was of interest

⁸ The tissue had to be thin enough for the microscope's light source to pass through.

⁹ Dividing cells can be found in many types of tissue while growth is underway, but in adult animals these are limited to organs producing white blood cells (e.g. bone marrow, spleen tissue, or white blood cells themselves), and in organs producing germline cells, i.e. sperm or eggs.

¹⁰ Luckily for Painter, the asylum doctor thought that removal of the testes was desirable because it calmed the inmates.

only to research scientists, some of whom it should be noted, worked in hospitals and had clinical training. We will describe four distinct techniques, three of them borrowed from other fields, that when used together, increased the repeatability and reduced the subjectivity of chromosome counting.

During the 1920s Belling, a plant cytologist developed the 'squash technique', a simple trick of pressing the sex cells of plants under the cover slip of the microscope slide so that the chromosomes appeared in the same visual plane when viewed under the microscope. In 1927 he applied this technique to human tissue, however he concluded that chromosome clumping made it difficult to get anything other than a rough estimate (Harris 1995: p.60) and he claimed his best preparations favoured Painter's number, 48 (Kevles, 1985: p.239). He was wrong. Painter's error was repeated in study after study, and even when researchers counted 46 chromosomes they discarded their results because they differed from Painter's number and all the work that had subsequently agreed with it (Prof. Polani, interview, 2001), (Kevles 1985: p.241).

The next important advance in method came in 1929 when Kemp, came to work on chromosomes multiplying '*in vitro*'. He worked in Copenhagen with a group of embryologists developing techniques for culturing cells outside the body¹¹ (especially in chicks). Kemp saw the value of using isolated (and therefore whole) cells rather than using tissue slices for cytogenetics. The technique he developed was a response to the problem that in tissue samples only a few cells out of many hundreds would have been at the correct point in the cell cycle to count a full set of chromosomes at the time the sample was analysed. Kemp managed to obtain human tissue from the spleen, liver and heart of four fetuses. By using fluctuations in temperature he was able to synchronize the cells' cycles, and produce an elevated number of divisions at the desired point in time

¹¹ The development of a media in which cells could continue to grow and flourish outside the body was an important parallel line of research to cytogenetics and other disciplines requiring live tissues that ran for many years and developed from the 1920s to the 1950s, culminating in the identification of recipes including sugars, vitamins and minerals that best encouraged growth p39-44. [Harris, 1995 #248], and subsequently lead to the establishment of firms such as Microbial Associates (USA) being founded by research scientists to produce the first commercial media in 1947, produced for the research market (see www.Cambrex.net, 2002, the parent company web site).

(Harris, 1995: p.60). Yet still when reporting his results he could not resist the allure of Painter's number 48 (Polani 1997: p.119).

By the early 1930s cytogenetics had advanced through the study of several plant species with conveniently small number of large chromosomes, such as *Vicia* and *Trillium*, to the stage at which the methods of analysis were considered developing into "a fine art" (Harris, 1995). One book in particular, 'Recent Advances in Cytology' written by Prof. C. D. Darlington of the UK's John Innes Institute in 1932, became a cytogeneticist's "bible" particularly for providing preparation techniques (Interview - Prof. Polani, 2001). Meanwhile, progress in animal models continued through studies of chromosomal banding. Painter was the pioneer of these experiments, and in 1933 he published a paper in *Science* explaining how bands could be observed using the giant chromosomes found in larval salivary glands of *Drosophila*¹². The bands appeared as light or dark, thick or thin, pinched or bulging features and although each chromosome had its own appearance, this did not vary in the majority of flies (i.e. Chromosome 1 in one fly had the same shape and patterns of banding as chromosome 1 in other healthy flies). For the first time researches could tell most chromosomes apart.

Although tissue culture provided a method of obtaining more cells at the required stage of the cell cycle the resolution of the sample was not much improved, especially human cells, with their crowded nuclei. By the late 1930's this problem was being addressed by the introduction of a chemical, Colchicine, again borrowed from plant cytology. Animal cell cultures treated with Colchicine began their cycles of division, but were unable to complete the stage known as metaphase as Colchicine arrests this process, leaving the newly copied chromosomes neatly paired together (Harris, 1995: p.61).

The next technical advancement came through serendipitous circumstance, appearing not once but twice before it was recognised. Tao-Chiuh Hsu, was a Chinese student working in the USA after completing his PhD. One day in 1952, he observed the chromosomes in

¹² The chromosomes in the salivary glands are especially large and visible, but unfortunately such giant chromosomes did not occur frequently in other research models.

his tissue culture where 'beautifully scattered' p.240 (Kevles 1985). However he did not know for some time that an accidental exposure of the cells to a hypotonic¹³ solution had occurred. He could not repeat his results although the effects of hypotonic solutions on cells had been reported to the scientific community previously. Harris notes Makino and Nishimura, a contemporary group of cytologists in Japan, had also made the same mistake as Hsu by rinsing their tissue sections in tap water for too long. They too had observed an improvement in clarity (Harris 1995: p.63).

Hsu published some of the clearest pictures of chromosomes seen at that time, but still he managed only to confirm Painter's number of 48 chromosomes. After some months Hsu's serendipitous discovery became evident through trial and error attempts to repeat the previous success. Rapidly the four techniques of tissue culturing cells, treatment with Colchocine, preparation with a hypotonic, and squashing became widely used and combined (Harris 1995: p.64) (Polani 1997: p.117). Nevertheless, it was not until 1956 that Joe-Hin Tjio and Albert Levan working in Sweden, bravely published a paper refuting Painter's number and demonstrating they had counted 46 chromosomes in the diploid cells derived from four different aborted human fetuses. Within weeks, Charles Ford, a cytologist from the John Innes Centre (a UK research institute) and student of Darlington, repeated the experiment and confirmed Tjio and Levan's findings. Ford and his co-worker Hamerton wrote in their paper confirming Levan and Tjio's work, "the crux lies no longer in the microscopy but in the preparative technique." (Polani 1997: p.119). From that time on, the human 'Karyotype' was 46 chromosomes in diploid (non-germline) cells, and 23 in Haploid cells (i.e. sperm and eggs).

Development Phase

Almost immediately after the publication of Tjio and Levan's work, clinical implications became possible. This poses an interesting point for the utility of Blume's career structure in technique-led technological change. His characterization of the development phase typically describes a period where one would expect 'significant industrial development

¹³ A hypotonic solution is one in which the concentration of salts is lower than that of the fluid within the cell. Cells exposed to hypotonic solutions, thus absorb water through osmosis becoming swollen in the process. [Isaacs, 1991 #252]

work' p.69 (Blume 1992). However in the history of cytogenetics, this phase is markedly short, and with no industrial activity, no formal clinical trials or commercial 'product launch'. Instead, the development phase blends rather indistinctly into the diffusion phase. The important inter-organisational structures in this phase remain informal agreements between scientists to collaborate. The research scientists, not necessarily based in medical institutions, required access to tissue samples, and the researchers with clinical experience still lacked the full set of techniques necessary to obtain the best results from their samples.

With the benchmark of 46 human chromosomes in normal tissue established, the task of linking chromosomal abnormalities with particular congenital diseases could begin.

In 1958 Polani, a practicing paediatrician at Guy's Hospital in London was almost unique as he had access to sources of tissue from patients affected with rare syndromes¹⁴, and an interest in cytogenetics. However his work had effectively been held up:

"We had both [patients with] Turner [syndrome] and controls, but never got counts higher than 45 [in the Turner patients]. Because the dogma was then that there were 48 chromosomes, we thought we were miserable, and we can't do it" (interview, Polani 2001)

After reading a paper by Ford and others describing a culture technique for bone marrow, Polani forged a research relationship with Ford and sent him bone marrow samples from patients at Guy's Hospital with Klinefelter syndrome and Turner Syndrome. When a set of results came back indicating a Klinefelter male had two X chromosomes, rather than an X and a Y, Polani writes, "*that was really* the very first human developmental chromosome anomaly ever documented... and reported [by the laboratory back to the referring physician]" (Polani's emphasis) (Polani 1997: p.120).

In late 1958, Ford was eager to undertake more research on karyotype anomalies, and had made arrangements to examine a Down syndrome patient's bone marrow but the parental approval process was delayed, and an outbreak of flu at the hospital the patient was in further delayed things. By early 1959, a French doctor, working in Hospital

¹⁴ A syndrome is a group of symptoms that occur together, or a condition characterised by the presence of several associated symptoms.

Trousseau, Paris under one of the few French physicians interested in genetics at the time¹⁵, had published his discovery, of 47 chromosomes in patients with Down syndrome¹⁶. The Frenchman, Jérôme Lejeune was working on a worn out microscope discarded by the pathology department, with the most basic facilities. Nonetheless he had discovered a chromosomal anomaly that caused Down syndrome. Lejeune had suspected a chromosomal abnormality might be found, as syndromes had been associated with the absence of entire chromosomes in *Drosophila*, in experimental studies (Kevles 1985: p.246). Indeed Lejeune was not the first to suspect this was the case. A Dutch physician P.J. Waardenburg, and a US physician, Adrien Bleyer, first thought of this possibility in the 1930s. Penrose, one of the earliest practicing clinical geneticists in the UK, had also suspected such an error might have been found, but in 1952 his staff were using ineffective techniques and had failed to find abnormal counts of chromosomes in the sperm of an affected male (Kevles, 1985: p.244).

Harris notes the beginning of Clinical cytogenetics as being 1959, as indicated by a spate of publications reporting associations between syndromes and chromosomal changes. Now the diagnostician (whether they were a university researcher or a clinician) had something to look for.

Diffusion phase

We focus here on the adoption of techniques that led to the wider use of cytogenetics in a clinical context, eventually resulting in its routine use (for post-natal and pre-natal screening) by centres in the early 1970s. The actors that drove this process problematized the technology in a set of ways that can loosely be divided into those of early diffusion and late diffusion. In early diffusion, cytogeneticists - who were at the time research scientists driven by a spirit of discovery, concerned themselves with the problem of tissue

¹⁵ Lejeune's supervising professor was a paediatrician, Raymond Turpin, who had obtained government funding for radiation genetics, a topical field that flourished after various governments began to wonder about the effects atomic bombs might have on populations in future conflicts.

¹⁶ Lejeune had actually presented his findings to the tenth International Congress of genetics in Montreal in 1958, but the audience where unconvincing and Lejeune returned to gather more evidence p.247[Kevles, 1985 #229].

availability, and broadening their repertoire of diagnostic powers. In the late diffusion phase and feedback phase, many research scientists had become clinical scientists, with their university funding being slowly replaced by hospital funding (Interview, Prof. of Medical Genetics 1, 2002; Interview, Director of Clinical genetics 1, 2002). They grew more concerned with the speed of service delivery, and the quality of the service they offered to patients. These 'late diffusion' problematizations are more fully explored in the next section, the feedback phase.

By 1960 the Galton laboratory, run by Prof. Penrose in London, was receiving a steady flow of clinical samples (Weatherall, Wellcome Witness seminar, 2001), and Polani had accepted a generous endowment from the Spastic Society, a large charity at the time, to form a specialist unit at Guy's Hospital to investigate the causes of congenital birth defects. These funds allowed him to establish a multidisciplinary center that would become a model for future regional genetic testing centres (Interview -Prof. Polani, 2001). It was composed of both research and diagnostic service laboratories, and also employed staff who acted as genetic counsellors¹⁷. In the early days, many of the staff performed several roles, researcher, clinical scientist, and counsellor and this was a common feature of other laboratories performing early diagnostic service work (Interview – Prof. of Medical Genetics 1, 2002).

1960 was also an important time for technical reasons. To assure continuity of both diagnostic and research results, a series of international standardisation meetings were called, with the aim of settling nomenclatures and individual chromosomal identification patterns (Polani 1997) p.121. Around this time another technique became widely used that opened up opportunities for diffusion of cytogenetics. This was an extract from the kidney bean, called phytohaemagglutinin. Before phytohaemagglutinin, there were three methods of obtaining suitable samples from patients, These were sections of

¹⁷ The counselors talked to patients and their families about the risks of abnormalities recurring within their family, although even at the time this was acknowledged to be a very imprecise process p.254 Kevles, D. (1985). In the name of Eugenics: genetics and the uses of human heredity. New York, Knopf..

testicular material, tissue culture, particularly of skin biopsies¹⁸, and bone marrow culture, all of which were not popular with patients for obvious reasons.

In 1958, it was observed that this substance had the unexpected effect of simulating the growth of white blood cells. Moorland and Hungerford developed its use and the technique spread rapidly around the world partly because it was easy to use (Harris 1995). The possibility of using cells taken from the blood meant that a scientist could undertake cytogenetic analysis more easily, as blood was readily accessible p.249 (Kevles 1985).

In the 1960s a range of chromosomal abnormalities and their corresponding phenotypic syndromes were documented, although this process slowed once the obvious syndromes linked to having too few or too many chromosomes had been accounted for (these are collectively known as aneuploidies). Attempts to identify further chromosomal errors using radiographic labelling methods were deemed to complex and more or less abandoned (Polani 1997) p.121. However, more simple apparatus seemed amply able to meet the requirements of the cytogeneticists, and once again it was existing technology that was brought to bear. Caspersson of the Karolinska Institute, Sweden, introduced cytogeneticists to a method of staining chromosomes that produced a clear pattern of banding. This could be used to identify each chromosome independently, using a staining substance known as quinacrine mustard, a plant extract that was used in other areas of biology for many years and fluoresced under ultra violet light (Interview – Prof. Polani, 2001). Even at this stage none of the equipment or reagents used in cytogenetics were new to microscopy in general (interview – Prof. of Medical Genetics 1, 2002). Once Caspersson's banding patterns were recognised by others as providing a means of consistently identifying particular chromosomal regions, they were very useful. Cytogeneticists could look for alterations in the banding patterns and therefore find abnormalities of small parts of the chromosome, as hypothesised and proven in fruit flies by Muller and Painter in previous decades. However the use of quinacrine (Q-banding)

¹⁸ The skin of the subject was abraded, and after several days, the scab lifted and area beneath swabbed to collect the dividing skin cells.

soon gave way to Geimsa (G-Banding), another stain based on a recipe of organic chemicals used as far back as the nineteenth century for microscopy stains. Geimsa which had been introduced to cytogenetics in the late 1950s, and could be used without a UV microscope, had been under-exploited (Polani 1997) p.121. At a 1971 conference in Paris, comparison of different recipes and procedures were found to favour Geimsa banding, because its bands were equivalent to Q-bands in experimental resolving power, but did not require UV equipment to visualize (Harris 1995) p.81.

Until the end of the 1960s, cytogenetics had been confined to diagnosing patients born with genetic abnormalities. However around this time, Obstetricians realised the potential value of cytogenetics for providing prenatal testing to women who were considered at risk of having a baby affected with a chromosomal abnormality. This was enabled through the use of a technique called amniocentesis¹⁹ to obtain tissue from the unborn foetus using a needle to obtain fluid from the amniotic sac surrounding the foetus. It appears this became a highly demanded procedure by at-risk pregnant women (Reid 1991) p.12. The technique coupled with legislation allowing abortion in the UK, opened up a very large new stream of clinical users.

Before the introduction of amniocentesis the patients whose tissue had been tested by cytogeneticists were seen at informal clinics. These were established and conducted by physicians who spanned both the fledgling clinical cytogenetic and clinical genetics groups, and the research and clinical communities. By 1972, small laboratories were operating from the major teaching hospitals, Great Ormond St, Guys, Manchester, Oxford, Sheffield, Glasgow, Edinburgh, Birmingham and Bristol and one or two other hospitals such as Salisbury (Interview - Prof. of Medical Genetics 1, 2002). Throughout the 1970s, the increase in sophistication in the use of amniocentesis, with better quality samples, and improved guidance of the needle through ultrasound, raised the use of the technique to become routine in major UK hospitals (Interview - Prof. of Obstetrics and Gynaecology 1, 2002). However the amniocentesis procedure carries a risk of

¹⁹ This was conceived and developed in the 1950s, but not used widely until the late 1960s (see Coventry, P. (2000). *The Dynamics of Medical Genetics: the development and articulation of clinical and technical services under the NHS, especially at Manchester c.1945-1979.* Faculty of Science and Engineering. Manchester, University of Manchester. ,Reid, M. (1991). *The Diffusion of Four Prenatal Screening Tests Across Europe.* London, King's Fund Centre.)

miscarriage, and was mainly restricted to older women who were identified as being at higher risk of having an affected foetus.

By 1980 10% of pregnant women who were likely to be at high risk were offered amniocentesis. Although this was a more cautious and sparing use of the technology than was seen the USA, where 50% of at risk women were able to access the procedure (Kevles 1985) p.291, it still provided a high workload for a growing number of cytogeneticists.

By the early 1970s growth in the number of laboratories and workload of services was very strong and the diagnostic labs were gradually brought more formally under the control of the NHS (Interview – Director of Clinical Genetics 1, 2002). At around the same time groups of cytogeneticists were linking up via mutual contact with microscope sales representatives – the first industry influence admitted by the cytogeneticists at interview (Interview - Director of Clinical Genetics 1, 2002). They formed the Human Chromosome Group, later named the Association of Clinical Cytogeneticists (ACC). The ACC was formally established in 1978 to protect the interests of the growing community of specialists as they felt they needed a better career structure to attract and maintain staff, and a unified voice to argue on their behalf (Interview - Director of Clinical Genetics 1, 2002). In particular this was felt to be necessary because those without medical qualifications were excluded from the clinical genetics society when this formed in the mid-1970s (Interview - Prof. of Medical Genetics 1, 2002).

“[The ACC] set up a training and accreditation structure and they did it very well. They had a strangle hold on cytogenetics, and if you wanted to get in, it was through them. When they had a problem in getting (less skilled staff), they loosened up and allowed them in.” (Interview - Prof. of Medical Genetics 1, 2002)

By 1982 the ACC was organising meetings and an annual audit to improve services through establishment of feedback mechanisms in the clinical cytogenetics community. The problematizations formed by actors at the time focused on the variable quality of services, the lack of standardised practices, and failure to apply to date techniques, such as G-banding, to all samples processed (ACC annual survey, 1983-5). The laboratory

network was estimated to be around 40 (ACC annual survey, 1983), and cytogenetic testing was well established for pre-natal and postnatal diagnostic work, with a small number of specialist laboratories also using the techniques for characterization of tumours.

Feedback phase

Blume classifies the feedback phase as being a time when medical technologies are adapted and improved after initial usage. This typically involves the launch of improved products aimed at existing users. At this stage, the history of cytogenetics appears to move closer to the careers Blume describes as industry becomes an important producer of artefacts for use in cytogenetic services, and even provides testing services to physicians.

In cytogenetics, the feedback phase began in earnest with the incremental improvement in performance through ACC's influence on *regime* rather than *technique* or *artefact*. Documentation in the ACC's archived annual survey shows the actor's problematization of the technology is focused on the speed at which samples are processed and results reported back to referring physicians. This was important because ultimately patients and their families are waiting anxiously for these results.

The new professional organization of the ACC pushed its members to reduce the average sample-processing time. Subsequently they also act as a channel through which appraisal of innovations in techniques and artefacts are made. By the early 1980s, inter-organisational structures are fairly well established in the pattern observed today. Cytogenetics laboratories are organised in a regional framework – with clinical genetics providing advice and support to patients where needed, although most of the laboratory workload comes from other specialists including obstetricians, gynaecologists, pediatricians, neurologists, haematologists and Oncologists (Interviews – Head of Cytogenetics laboratories 1,2 & 3, 2002). These specialists are tied to the laboratories they send samples to through contracts agreed by the hospitals they work for (Interview – Director of Company 1, 2002). Cytogenetics laboratory staff are linked nationally through the ACC – now responsible for a formalised training program involving a two

year apprenticeship scheme, and more informally to international networks of research and clinical scientists through their membership of organizations European Society of Human Geneticists, and their institution's subscription to various medical journals.

At the start of the 1980s, the service offered could be described as fairly simple in format:

“Skilled people looking down a microscope are actually remarkably good at...pattern recognition...but it was really a one trick business, once you had grown the chromosomes from various preparations and stained them in various ways.”
(Interview, Prof. of Medical Genetics 1, 2002)

This was by no means a satisfactory situation for the users of the service. The amniocentesis samples, regarded as urgent because the detection of an abnormality could result in an abortion, were taking an average of over 22 days to be processed and reported (ACC audit data, 1983). Thus measures to reduce waiting time were pursued, primarily through influence of the physicians using the service on behalf of their patients (interview XXX). The existence of long waiting times offered an opportunity for a small private firm. In 1982, following the consolidation of two London laboratories, one of the ex-NHS laboratory staff formed the start-up to exploit the high concentration of private doctors whose patients would be willing to pay for faster service. This firm now processes two to three times as many samples as an average NHS laboratory, with a higher output per member of staff (Interview -company Director 1, 2002) (ACC Audit data). The company is a powerful influence on NHS laboratory uptake of new technology, as it competes for contracts with local NHS hospitals (interview – Company Director 1, 2002), (Interview - Cytogenetics Laboratory Head 2, 2002). Thus when they began to use techniques and artefacts from another technology (Molecular genetics), NHS laboratories followed (Interviews – Company Director 1, 2002, Cytogenetics Laboratory Head 2, 2002, Cytogenetics Principle Scientist 1, 2002).

The primary reason for both the private firm and NHS laboratories becoming interested in molecular genetic technologies, such as Fluorescent In-Situ Hybridisation (FISH), and Quantitative Fluorescence Polymerase Chain Reaction (QFPCR) is because they allow

laboratories to avoid the longest single stage of sample preparation - waiting for cells sampled to establish cultures of healthy dividing cells that can be prepped for analysis. In ideal circumstances both of these techniques can supply the patient with their answer in one or two days. The evolution of molecular genetic techniques and their effect on genetic testing services will be covered in the author's Thesis. For the purposes of this paper it is only important to reflect that these techniques were developed by a new group of research scientists with different skills to cytogeneticists. They developed molecular 'probes' that could be used to tag the DNA that makes up chromosomes in very precise ways, providing a resolving power beyond that possible with staining techniques. The synthesis of these highly specific probes, which could be used on very small numbers of cells at any point in their cell cycles, is highly complex and prone to failure (Interview – Principle Clinical Scientist 1, 2002). This provided an opportunity of the creation of start-up firms in both the USA and UK to produce these probes (see annex 2). Cytogeneticists favour commercial probes over 'home-made' probes where available.

“If you are doing research you can make your own probes and it's not the end of the world if they don't work, but if you are doing diagnostic stuff, you have embryos that you are testing, you can't just say, 'the probe didn't work, what a shame'. You have to have a result. You need a reliable product that you are absolutely positive about.”
(Interview – Principle Clinical Scientist 1, 2002)

Clinical cytogenetics is now a well-established discipline in the UK. Table 3 charts its rising usage year by year. Forty years after clinical testing began it employs 400 clinical scientists (Harris, 1997) in 40 laboratories (ACC audit data) and many more worldwide, firms have been keen to offer FISH probes. Additionally firms are attempting to speed up the analysis process by using software (see annex 2), and sample prepping using automation (see annex 2).

“There are one or two companies that think there may be niche for them to work alongside [cytogeneticists] and develop [new artefacts].... the only other area is image analysis, where there have been companies that have actually specifically been set up and established themselves to sell in a cytogenetic market.”
(interview – Head of Cytogenetics Laboratory 1, 2002)

There is evidence that even the microscope manufacturers (see Annex 2) who have been supplying the cytogeneticists' key artefact almost without questioning its use for decades, have recently begun to take note of this market and have attempted to produce novel artefacts to improve the quality of service.

Discussion:

We posed three hypotheses in the introduction section. These were that in an example of technique-led innovation, users would adopt pre-existing artefacts rather than relying on industry to supply novel artefacts, and that from these artefacts they would develop new services. We suggested that these services could develop relatively unchecked by regulatory bodies that in the UK at least, examine only drugs and devices. The techniques could spread quickly through scientific communities with little hindrance from commercial interests. Finally we suggested that industry would eventually attempt to enter the market by selling products or services focused on improving the existing services.

In the case study of cytogenetics we suggest we have found agreement with each of these hypothesis. De Solla price described how 'instrumentalities' wound between science and technology, i.e. the instrumentalities facilitate both scientific discovery and provide the basis for new commercial products and services(DeSolla-Price 1984). It appears that the cytogenetic techniques fit this description rather well, and that in terms of adapting the artefacts and techniques themselves from research to applied use, the 'tinkering' (Knorr-Cetina 1981) of scientists, was all that was needed to bring about these new services, rather than industrial forces. It was activities of these research scientists that allowed the slow accumulation of a body of knowledge on inheritance and disease. These same activities provided the impetus to form a new clinical discipline with its own techniques, and regime, based on existing artefacts such as the microscope, stains (e.g. Geimsa) and other reagents (e.g. Colchocine). This new technology, was able to progress through Blume's stages of exploration, development and diffusion without the push of

Industry. Instead progress in cytogenetics was driven by inter-organisational structures between scientists and a small group of clinicians. These links were intensive at the local network level, but also stretched across the international scientific community.

Only when opportunities for the improvement of the technology appeared, long after the user market had become established did commercial organisations appear to take a direct role in the shaping of technological options on which clinical services were based. There are several possible reasons for this. First of all, cytogenetics was originally established to research genetic abnormalities, which affected only a small percentage of births, hence this was not a large market and perhaps not very enticing for firms. Secondly, the novel set of capabilities that cytogenetics is based on are the tacit skills of the cytogeneticist. They are skills of pattern recognition and delicate sample preparation. To suggest that industry stayed away because cytogenetics was a quiet activity hidden in hospital laboratories belies the complexity of this craft-based technology. It is a technology that relies in essence on a highly complex set of skills that are difficult to crystallise into an artefact – often an important stage in the evolution of technologies (Fleck 2000). We suggest that at present it is a complex task to create instrumentation to replace even in part the skills of the cytogeneticist, and in the UK, artefacts embodying forms of automation are often viewed as providing only marginal performance enhancement (Interview – Prof. of Medical Genetics 1, 2002). One might predict that now industry has begun to attempt this, if they are successful, cytogenetics will revert to a more familiar pattern of development with the laboratory scientists displaced, and the industry-clinician links re-instated at the centre of any technological change. However it is also possible that these skills will continue to be too complex to fully automate and that clinical scientists will maintain their control of the technology leaving firms at the periphery.

Conclusions:

We conclude by suggesting that Blume's framework for medical innovation would benefit from the introduction of at least one new type of career, so as to accommodate technique-led technological change as well as artefact-led technological change in diagnostic medical technologies (see table 4, for an extended taxonomy). We note that

this new career is close to the ‘non-conformist’ career Blume describes, in the sense that it does not build on pre-existing networks. However it does not involve industry in the early stages.

Table 4: An expanded taxonomy of diagnostic medical technology careers

Type of technological career	Central actors in innovation network	Example
Artefact-led conformist	Established firms & customers (users)	CT scanners (late)
Artefact-led non-conformist	New firms and new user groups	Ultrasound, MNR
Artefact-led contested	Established users and firms vs. new firms and/or users	CT scanner (early)
Technique-led non-conformist	New users and late entering firms	Cytogenetics

The dynamics of technique-led technological change are commensurate with Lundvall’s description of user-producer relationships and their role in innovation (Lundvall 1992). Using Lundvall’s ‘four dimensions of space’²⁰, we can see the user (the physician) and the producer (or the service provider – the cytogeneticist) are closely linked both geographically and culturally. They are often within the same hospitals and they share the values and norms of the medical and scientific research community. Furthermore in the public sector NHS, the user and the service provider are not separated by a true market (or economic space), and service providers are not exposed to the full competitive pressures and secrecy of a commercial market place, at least until industrial competition arrives. These conditions foster innovation, and provide an environment where the potential for rapid diffusion exists. The rate of this diffusion will of course depend on other factors such as utility of the technology and the available resources. However, within the public sector, relatively conducive conditions exist: with no industry involvement, the new technological advance is not encumbered by the need to repay

²⁰ Lundvall notes these as being Economic, Organisational, geographical, and cultural dimensions

development costs, or by the costs of industrial infrastructure, and the need to generate profits to the user's expense. Also because the technique has been developed within the medical community, it is already effectively within the regulatory perimeter that industrial products must attempt to pass through after gaining the approval of agencies for the control of devices and drugs. Although these factors allow set up costs to be relatively low, so too is the requirement to prove the new technology is appropriately applied. For example, Nelkin provides a cautionary tale of doctors in the USA who offer abortion in cases where chromosomal abnormalities are detected, whether or not they are certain the abnormality will manifest itself in the child in an unpleasant way (Nelkin 1996). We conclude that for this reason alone, policy makers need to be aware of rapid technique-led technological change, especially as once in routine use, medical technologies and their proponents have proved to be difficult to dislodge (McKinlay 1981).

Table 3: Mean Annual Workload of UK Cytogenetic Laboratory Services from 1982-1999

Sample Type	1982*	1983	1984*	1985*	1986	1987	1988	1989	1990	1991 [▼]	1992	1993	1994	1995	1996	1997	1998	1999
Amniocentesis	649	667	703	785	794.6	867.8	886	845	929	957	1014	1112	1130	1169	1171	1083	1119	1132
CVS	0	0	0	0	0	0	0	135	161	137	145	167	217	211	220	293	283	285
Blood	1029*	1050*	819	888	883	910	980	922.6	993.6	1185	1296	1325	1507	1515	1667	1791	1823	1991
Solid tissue	0	0	0	0	0	0	0	0	179	206	221	252	266	219	326	332	322	325
Haematological	0	0	0	0	0	0	274	0	277	308	332	393	428*	457	506	619	657	721

Source: The data above are mean values generated from UK NEQAS annual audit with returns from 30-40 UK laboratories (NHS regional labs, specialist labs, and a private lab).

* Original data for the years 1982,1984,and 1985 were only collected for 100 working days & annual is workload estimated here on the basis of 252 working days per year.

♦ The data for these two years were titled 'other' i.e. non-amniocentesis but were mainly Blood samples. As a result these data are not directly comparable with future years.

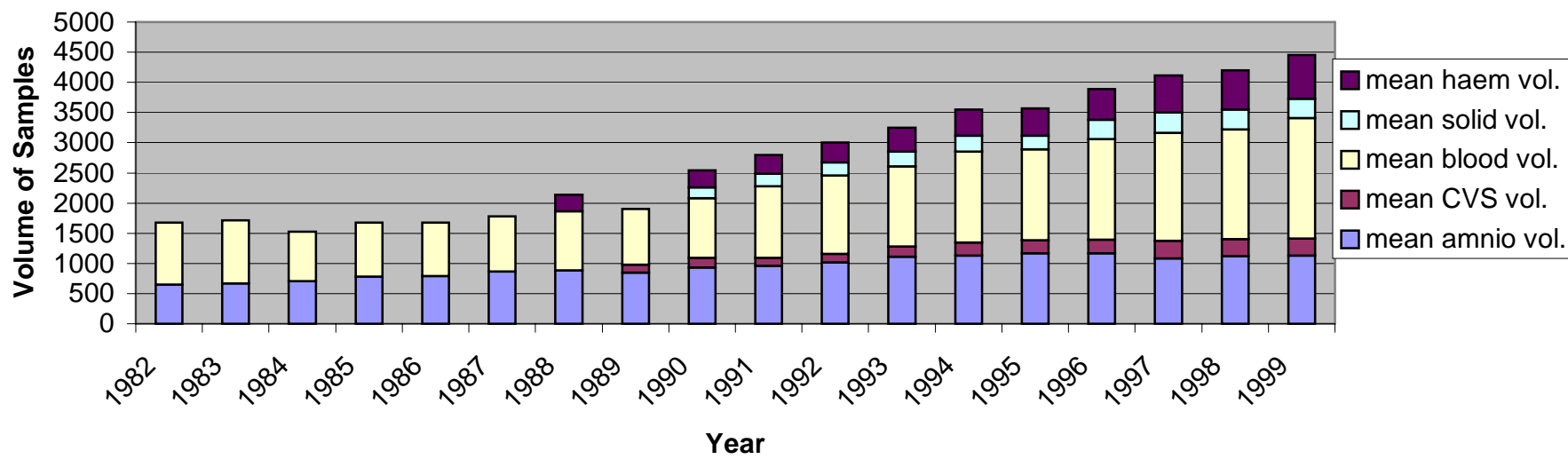
CVS work began in the early 1980's but data was not collected until 1989. Solid tissue and Hematological work was undertaken for many years prior to appearing in the data series as a distinct category.

▼ From 1991 the survey changed from collecting data per calendar year to per financial year

* figure calculated on the basis of a 9% reported rise in audit, but exact figure absent in my copy.

Note: data for CVS and Haematological workload only become available several years after the practices are introduced.

Fig 1: Mean workload per UK cytogenetic lab: 1982-1999



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Annex 1: Research Problems and Methods

Problem	Solution	Method	Limitation
Mapping influence of key actors	Interviewee snowball, ask interviewees to identify/ rank actor groups	Ethnoscience ranking process	Radically different opinions are lost as output is based on mean values
Low interviewee recall of dates Low participation in historically distant events of interviewees	Review of literature	Use of histories	Histories are selective, and scientific histories are often uncritical of scientists p.28 (Hughes 1997)
In-depth understanding of problematizations involved with the technologies	Detailed and tailored questioning of selected actors	Semi-structured interviews	Objectivity of the subject, recall, access.
Understanding role of tacit knowledge and grasping technically complex subject.	Sustained exposure to environment studied	Participant observation in a regional genetic testing centre	Only two weeks access was secured. Time was spend predominantly with junior staff
Accessing nationwide data on service provision while remaining within budget	Obtain permission to access NHS Trust-held data, Ask selected questions to wider group	E-mail survey	Low initial response rate - increased by telephone interviewing (to 50%)
How to combine evidence to produce representative and cohesive synthesis	Triangulation of evidence	Case study	Selection of data to stay under word count limit!

Appendix 2: Firms supplying equipment & instruments for Cytogenetics

Company (delete quoted ref – write in text)	Year Established	First Cytogenetics product	Subsequent Cytogenetic Products	Attempting Automation for cytogenetics?	Primarily a cytogenetics enterprise?	Website
Microbial Associates (USA)	1947	Cell culture Medium	-	No	No	www.Cambrex.net
Gibco (now part of Invitrogen)	1962	Cell culture media	Broad range of Reagents/ Equipment	No	No – Broad range of reagents for Life sciences	www.invitrogen.com
Cambio Ltd. (Cambridge UK)	Early 1980's	FISH probes	-	No	No – reagent supplier for molecular genetics	www.cambio.co.uk
Genzyme Inc. (Cambridge MA, USA)	1981	Cytogenetic testing services	-	No	No – integrated producer of Biopharmaceuticals, biomaterials and diagnostics.	www.genzyme .com
Cytogenetic DNA services Ltd.	1982	Service (first commercial service)	-	Yes (via molecular genetics)	Yes –but now do molecular genetic testing	
ADIR (now owned by Applied Imaging Corp) Austin Texas USA	1984	Imaging software/ Equipment	-	Yes (partial analysis)	No – supply imaging solutions for industry	
Metasystems (Allusheim De)	1986	Imaging Software	Probes	Yes (partial analysis)	Yes – now developing other pat. recognition software	www.metasystem.de
Qbiogene Inc. (Carlsbad, CA, USA)	Late 1980's	FISH Probes (pioneer of technology)	-	No	Yes – but now supply reagents and contract research for Life sciences	www.qbiogene.com
Kreatech (Amsterdam, Netherlands)	1990	Probes	-	No	No – develop broad applications of molecular labels	www.kreatech.com
Cytocell Ltd.	1991	FISH Probes	Stains, Culture Media, Ancillaries (slides, etc.)	No	Yes	www.cytocell.com
Vysis (Downers Grove II, USA) Subsidiary of Abbott Laboratories	1991	FISH probes	-	Yes – Sample preparation	Yes – but now developing various genomics platforms	www.vysis.com
ID Labs Inc. (London, Ontario Canada)	1991	Probes	Cell growth media	No	No – supply a broad range of reagents for life sciences research	www.idlabs.com
Applied Imaging Corp.	?	Software for analysis	-	Yes (image analysis)	Yes?	www.aii.com
MatTek Inc. Ashland MA USA()	?	Glassware	-	No	No – generic glassware for microscopy	www.glass-bottom-dishes.com
Nikon (Japan)	?	Microscopes, cameras	Digital imaging solutions	Yes (via imaging)	No – diverse optical goods	

Note: This is not a comprehensive list of global reagent distributors, and so excludes firms such as **Sigma-Aldrich** St. Louis, MO, USA (www.sigma-aldrich.com) and **Pierce Biotechnology** Rockford, IL USA (www.piercenet.com). It focuses instead on specialist suppliers important in cytogenetics.