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Diffusion of complementary evolving pharmaceutical innovations: The case of Abacavir and its pharmacogenetic companion diagnostic in Italy

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ABSTRACT

Innovation is increasingly important in the delivery of efficient healthcare; however, the pathways through which medical innovation reach clinical practice are fraught with uncertainty. Further scientific investigation and technological development are normal in medical innovation even when drugs, diagnostics or medical procedures are already adopted. Diffusion studies rarely admit such possibilities as a fundamental element of their conceptual frameworks. This paper explores the diffusion process of an antiretroviral drug (Abacavir) and the introduction of its companion pharmacogenetic test into clinical practice in Italy. This is a landmark case of translational medicine where the principles of pharmacogenetics made an important - applied - contribution to medical innovation shifting the focus away from the diffusion of a complete technology (the drug) towards that of a dynamic technology (Abacavir + developing companion diagnostics). We adopt the historical method to analyse the sequence of events. Key findings show that the diffusion process of a dynamic technology does not fit in the widely accepted S-shaped model for a complete technology. The diffusion phase presents complex interactions amongst the stakeholders involved, each operating on the basis of their own competences within the environment and the regulatory system; the analysis of the diffusion process should proceed through the correct identification of the dynamic technology – the therapy – and cannot be de-coupled from scientific discovery and technological development.

1. Introduction

Innovation is becoming increasingly important in the delivery of efficient healthcare; however, the pathways through which medical innovation is embedded in clinical practice are fraught with uncertainty and littered with failure. Even when innovation appears to be initially successful, its wide diffusion sometimes results in unforeseen outcomes that may not match the innovators or indeed, the wider societal expectations. This aspect is rarely tackled in the literature dealing with diffusion of innovation.

Ever since the classical work on innovation diffusion of Rogers (1962) the theme of diffusion has attracted the attention of scholars in many domains. Coleman et al. (1957) was one of the first studies to develop a framework analysing the diffusion of a new medicine. Here the concern was on understanding the social processes leading to the wider adoption of tetracycline across four American cities by general practitioners. The study found that diffusion followed a contagion-like trajectory wherein professional and personal networks of medical practitioners were important drivers of the widening use of the drug.

Since these pioneering works, innovation diffusion studies grew in scope extending towards forecasting of diffusion paths (Bass, 1969; Bass et al., 2001) and in terms of sophistication (Cho et al., 2012; Semitiel-Garcia and Noguera-Mendez, 2012), increasingly uncovering important aspects in the process of diffusion of innovation. More recent studies, in fact, have uncovered inextricable links between technological diffusion and socio-economic characteristics (Ilonen et al., 2006); the dynamic saturation limits of the diffusion process in technologies with substitution effect (Michalakelis et al., 2010); the impact of information dynamics on diffusion trajectories (Yücel and van Daalen, 2011) and the impact of market segmentation and population heterogeneity on technology diffusion (Ferreira and Lee, 2014; Guseo and Guidolin, 2015).

A common feature of these studies is that the diffusion trajectory follows the classical sigmoid shape. Moreover, the vast literature on the diffusion of innovation usually focuses on well-defined technologies either considered through vintage updates or battling for market with substitutes. Increasingly, we may see however, that more and more evolving technologies are hitting the market (Homer, 1987). These are

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technologies that do have clear market applications but are embedded in complex systems where exogenous and endogenous factors drive or hinder diffusion. As a result of these influences, the diffusion trajectory may not be S-shaped. Moreover, many technologies embedded in these systemic arrangements may not be fully formed though fulfilling their purposes (Greer, 1988). In these cases, further scientific investigation and technological development are necessary. This is normal procedure in medical innovation even when drugs, diagnostics or medical procedures have been introduced in clinic. Yet, mainstream innovation diffusion studies rarely admit such possibilities as a fundamental element of their conceptual frameworks.[1]

This paper aims at exploring the diffusion pattern of one such case. We look at the diffusion of the antiretroviral drug Abacavir (marketed as Ziagen®), and its companion pharmacogenetic test. It is a well-documented landmark case in HIV/AIDS where the historical reconstruction highlights a 'point of entry' of pharmacogenetics into mainstream pharmaceuticals (Martin and Kroetz, 2013). We use it to unravel some of the complexities associated with the diffusion process of the drug and the test as complementary therapeutic devices. The diffusion process in this case is even more interesting in that it involves many domains of competences and, within each domain, scientific discovery and technological development is ongoing as the case unfolds. The deliberate approach targets the integration of pharmaceuticals core-activities either in pharmaceutical science and/or research and development with the science-base outside the pharmaceutical industry in order to benefit from advances in pharmacology, diagnostics and clinical procedural.

The paper is organised as follows. In the next section we provide a review of medical innovation literature in particular of the diffusion of medical innovations. Our interpretative framework is sharpened in the light of relevant theoretical contributions. In Section 2 we profile the methodology used. In Section 3 we develop the case study. In the last section we provide a discussion of the elements that contributed to the implementation of the pharmacogenetic test and its successful diffusion over the Italian territory, highlighting some indications of future research.

2. Theoretical background

Innovation in medicine is a complex process. However in the medical innovation literature, the innovation process has been reduced to a sequence of tightly defined and discrete activities (Fig. 1). Diffusion of innovation in clinical practice occurs at the last stage of the innovation process which begins after the science had been resolved, clinical research had demonstrated the effectiveness and efficacy (including cost efficacy) and regulatory approval gained.

Whilst in the classical diffusion tradition various factors affecting the adoption of an innovation[2] relate to distinctive phases of diffusion (from early/lead adopters to mass markets), in the medical domain Mckinlay (1981) identifies several stages that are partly different from those described in the mainstream literature (Pullen et al., 2012). Differences are primarily due to issues related to the stringent regulation and the knowledge/skill intensity necessary for the adoption and integration of medical innovation in the medical profession and to institutionalised routines (to be discussed later). However, Mckinlay, 1981identifies the starting point of a successful diffusion trajectory in the publication of 'promising reports' i.e. studies or demonstrations highlighting that a technology or a practice may provide a relative advantage with respect to existing technologies or practices. Diffusion of medical innovation then gain momentum through 'professional and organisational adoption'; in this phase, the scattered support of the innovation in the first phase gains commitments within the profession and some institutional support. The third stage consists of 'public acceptance and state/payer endorsement'. At this stage, the innovation gains recognition from the wider stakeholder base and early users and organisations are legitimatised for their early adoption. The innovation is then formally accepted and eventually reimbursed by the state or third-party payers (i.e. insurance). Finally, a medical innovation is integrated into standard procedures (routines); observational reports are then conducted on what has been adopted as "the most appropriate way of proceeding with a particular problem or situation" (p. 387). The author points out that not all stages in the envisaged sequence need to be successfully dealt with in order to confirm the success of a medical innovation in clinical practice. Confirmation would come from randomised clinical trials.

Greenhalgh et al. (2004) differentiate between two alternative diffusion modes: i) diffusion as a process through which new or improved knowledge may spread within a system in an unplanned, informal, decentralised and horizontal manner – mediated by peers and ii) active dissemination whereby the diffusion of innovation is planned, formal and often centralised – likely to occur through hierarchical structures. They posit that between the two modes there exists a continuum where elements of the first mode, diffusion in the sense of Rogers (1995) may overlap with those of the second, planned dissemination. In a later paper, Greenhalgh et al. (2005) report that in evidence-based medicine the provision of implementation guidelines assumes a central role in the diffusion process. In particular, the process of diffusion is seen as the final stage of a substantially linear progression not unlike the process described by Swen et al. (2007) and operationalised once the 'funnel model' still used by the pharmaceutical industry has successfully run its course (Paul et al., 2010, p 2006; Calcoen et al., 2015, p. 162).

Within the rationalist science tradition, supporters argue that the translation of scientific evidence into clinical practice is relatively unproblematic (Dawson, 1995). If problems were to occur, they would be due to knowledge or behavioural gaps somewhere along the linear sequence (Haines and Jones, 1994). Consistently, numerous publications focused on providing solutions or alternative pathways to plug the gaps so that sound and context-neutral research could reach clinical practice and change clinical behaviour.

However, this model has been challenged by many authors. Grol (2001), for example, argues that evidence-based diffusion strategies may be unsuccessful given that guidelines, based on a restricted view of the research conducted in any specialist field, may translate in ambiguous practices. Guidelines, tainted by the fragmentation of knowledge deriving from collating specialist research work from various fields, often result too generalist i) for single/unique patients presenting individual health problems[3]; ii) usually disruptive of the routine of the learned and tested clinical practices and organisations and iii) generally, are not cost-neutral. Within this context, Ferlie et al. (2001) argued that evidence-based practices in diffusion should be incremental and adaptive since they are based on a complex evolution of medical knowledge which needs to be explored in its multifaceted domains, understood and internalised by the scientists as well as by the clinicians and contextualised before it can be operationalised. According to Greenhalgh et al. (2005) the implementation of clinical guidelines should be complemented by information and education campaigns to

[1] One exception may be the study of Barberá-Tomás and Consoli (2012) where the authors look at uncertainty and technological hybridisation (i.e. the embodiment of multiple competing operational principles within a technology) in the diffusion of innovative technologies in medical implantable devices.

[2] These may be summarised by the followings factors exerting a positive effect on diffusion: 1) relative advantage over existing technologies, 2) fit with users' values, 3) availability to trials and 4) result of the adoption of innovation may be easily observable. Complexity, on the other hand, is seen as factor hindering diffusion.

[3] On a more fundamental matter: personalisation of medicine and the promise of genomics for individually formulated therapies, Tutton (2012) observes that a shift towards a vision of patient as an individual as opposed as the 'average patient' in current medicine may embody a fundamental change in perspective from the universalist approach to a more experimental setting that considers technological advances as well as environmental and societal aspects associated to illness.