


## Developing new frameworks to value genomic information: accounting for complexity

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First draft submitted: 21 February 2021; Accepted for publication: 14 April 2021; Published online: 11 May 2021

**Keywords:** [economics](#) • [genomics](#) • [methodology](#)

### Current frameworks & their limitations

Decisions have to be made about how to allocate the finite resources available to healthcare systems. Frameworks exist that can aid decisions about whether a new healthcare intervention should be approved for use in a healthcare system. These frameworks are typically underpinned by a formal approach to economic evaluation called cost-effectiveness analysis (CEA) and are primarily driven by the tenet that population health should be maximized.

In a CEA, two or more interventions are assessed in terms of their costs and outcomes to determine the relative cost-effectiveness of an intervention compared with its alternatives. To enable comparisons between different types of healthcare interventions in a CEA, it is preferable to use a standard, common outcome measure: the quality-adjusted life-year (QALY). Mortality effects and quality of life attributable to 'health' are captured by the QALY with 'health' being narrowly defined by the scope of recommended survey tools such as the EQ-5D [1].

Generally speaking, the frameworks have proved useful for resource allocation decision making and have been successfully adopted in a number of jurisdictions across the world. There are, however, specific situations in which QALY-based frameworks, as currently applied, are inadequate. Notably, limitations have been identified where genomic information forms part of a complex intervention, for example, in precision medicine initiatives [2,3]. Interventions which utilize genomic information are complex, in that multiple elements combine to produce multifaceted outcomes. Importantly, these outcomes can extend beyond the confines of 'health' as conceptualized in the QALY.

### The role & complexity of genomic information

Genomic information can be used for a variety of purposes. In a precision medicine context it can guide treatment decisions. The extent to which these decisions are driven by the providers and/or users of healthcare is dependent on the specific application of precision medicine.

In other applications, genomic information can confer a diagnosis or provide a likely prognosis of disease progression. The distinction between genetic and genomic information is brought into sharp relief in this respect; over the last decade, new diagnostic technologies have provided a means of identifying the etiological basis of rare diseases for which older genetic tests were ill-equipped [4]. Juxtaposing the 'precision' label, it should be noted that a residual uncertainty often accompanies diagnostic and prognostic information because phenotypic traits can vary in how they present in individuals who share a common genomic diagnosis.

Uncertainty can also be seen in relation to the provision of individualized risk information. Genomic-based data can be used to estimate a person's likelihood of experiencing a health condition over a given period of time. The inherent uncertainty in this likelihood is further compounded by concerns about how risk information is interpreted by individuals.

Taking a broader system-wide perspective, complexity in genomic medicine also manifests in bureaucracy, infrastructures and dynamic relationships between multiple stakeholders. Jurisdictions differ in their approaches to the approval and delivery of healthcare. Within healthcare systems, variations in working practices are evident [5] and

have resulted in apparent inequities in, for example, the provision of genomic testing [6]. Technological innovation, ostensibly beneficial, has the potential to re-inforce existent negative elements or introduce new system-wide problems.

### Addressing challenges

Limitations with decision-making frameworks ascribable to these complexities could be addressed by refining approaches to the economic evaluation of interventions reliant on genomic information. A White Paper from 2016 [2] highlighted challenges with a particular focus on issues to consider, relating to the evaluation of ‘complementary diagnostic’ technology. The report describes how existing frameworks fail to account for the true comprehensive value of diagnostic technologies and, consequently, do not provide adequate incentives – from an industry perspective – to foster technological innovation [2].

The focus, in CEA, on a narrowly defined conception of health maximization means that current frameworks may not adequately account for the true value of diagnostic technology as perceived by individuals [2,7]. For example, genomic test information *per se* can confer value irrespective of any associated treatments; it has been demonstrated that people attach value to genomic-based diagnostic information in relation to untreatable familial conditions [8]. Qualitative and quantitative approaches have been combined to define and measure how people value genomic-based diagnostic information. It is considered useful in aiding informed decision-making and is also valued in its ability to reduce uncertainty about a family’s condition. Importantly, for inherited conditions, individuals value genomic test information because it may have implications for others as well as themselves [9]. These types of value attributable to genomic information, using a QALY-based framework, would not inform approval decisions.

As well as offering gains in perceived value, genomic information has the potential to impact upon individuals’ behavior. For example, clinicians from an increasing range of disciplines are being confronted with new ways of working as more and more treatment-guiding genomic tests become available. In dedicated clinics, genetic counselors use genomic information to tailor their intervention aimed at helping people come to terms with a diagnosis, understand its implications and to help them make plans for the future. In principle, effects of such behavior change could be predicted, measured and incorporated into economic evaluation but, again, the extent to which the true value of genomic information is captured rests on approaches to outcomes measurement.

Algorithms to predict risk of preventable disease can be augmented with genomic information. The expectation here is that, armed with knowledge, individuals might alter their behavior to maximize health outcomes. However, current evidence does not support this expectation; the provision of genetic risk information in isolation does not appear to effectively change behavior [10]. More work is needed to understand and, if appropriate, quantify the impact on individuals’ behavior of genomic information as a complex intervention component.

Genomic information is used for different purposes in different settings, can be used as a complement to other interventional components and can produce varied outcomes. More broadly, resource allocation decision-making in this area is further complicated by various factors including the involvement of multiple stakeholders with distinct agendas. As alluded to earlier, one key factor of complexity relates to the failure of current frameworks to account for the often synergistic effects of interventions attributable to genomic information. This has served to stifle technological innovation and – alongside the inadequate measurement of value from the individual’s perspective – has undoubtedly hindered the development and timely approval of novel diagnostics. A framework which accounted for the true value of genomic information and which was fairly set up to reward innovation would accelerate the diffusion of benefits deriving from novel technologies across the healthcare system.

### New approaches

Progress has been made. It has followed from the identification of certain areas of concern [2,11,12]. But the key issue, running through each of these individual concerns, has yet to be addressed. Complexity is also manifest throughout the overarching systems in which decisions are made and where healthcare is provided. As indicated in the White Paper [2], it is possible to address each area of concern by measuring additional elements of value but the real challenge is to combine evidence in order to construct a new fit-for-purpose framework which is cognizant of system-wide complexity.

The characterization of each area of concern as a distinct problem to fix before a new framework can be developed, might serve to compound the current unacceptable situation. It does not promote a holistic approach which would allow the targeting of multiple issues simultaneously. Such an approach could address areas of complexity which are currently unknown or difficult to target. For example, dynamic relationships between industry-based stakeholders,

approval bodies and individuals would represent a useful focus of enquiry. A recognition that the implementation of new interventions within healthcare systems might apparently produce only slight changes in the short term will be required. An understanding of the value and impact of genomic information from multiple perspectives could also play a role. Complex systems approaches have been used in the field of public health research to consider the interconnectedness of system elements and how interventions have the potential to effect change across these systems over extended periods of time [13].

The specific implications of systems theory approaches for economic evaluation have been explicitly considered [14]. Primarily, there is a need to recognize when traditional economic evaluation methods will suffice (i.e., in the case of complex interventions applied in a noncomplex system) and when characteristics of a complex system demand that alternative approaches be enlisted [14]. The scope for interventions to redefine and shift values held within a system is a characteristic to consider in the development of frameworks seeking to incentivize innovation in diagnostic technologies used to synergistic effect.

Using a complex systems theory approach to framework development will require multidisciplinary working, employing mixed-methods techniques. Where progress has been made to date, it has arisen with methodological input from a range of disciplines including health economics and health psychology. Advances in genomic technologies have been mirrored by methodological innovation in the evaluation of precision medicine initiatives and much has been learned. To capitalize on these lessons, a fundamental shift in approach is now required so that new frameworks can be developed. In doing so, the true value of genomic information will be realized within healthcare systems both despite and because of inherent complexity.

#### Financial & competing interests disclosure

M Eden has completed a National Institute for Health Research (NIHR) Doctoral Research Fellowship. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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