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Evaluating the economic impact of technological advances in diagnostics: The case of high throughput sequencing for hereditary breast cancer

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Abstract

This paper describes an application of discrete event simulation (DES) modelling approach to evaluate the economic impact of new diagnostic technologies using the case study of BRCA1/2 genetic testing to diagnose the risk of breast cancer. Diagnostic benefits are generally centred on test accuracy measures but additional benefits of diagnostics may include: reduced laboratory time; reduced time to results and capacity to increase the number of tests performed. Current BRCA1/2 testing technologies are limited by long (one-year) turnaround times, which together with limited resources to increase the volume of tests and associated genetic counselling, has driven the use of a 'risk threshold' to target women eligible for BRCA1/2 testing. New technological development, called high throughput sequencing (HTS), offer the opportunity of decreased turnaround time and increased volume of BRCA1/2 tests, which will impact on the benefits and costs associated with the diagnostic service. Systematic reviews have identified Markov-type models as the dominant modelling methodology for the assessment of genetic testing. In this paper we propose that discrete event simulation (DES) is the appropriate model type to quantify the economic impact of HTS BRCA1/2 testing as it allows evaluation of the impact of capacity constraints and increased turnaround time on the costs and benefits of this new diagnostic technology. Importantly, DES also allows for the assessment of structural uncertainty by considering changes in patient pathways when using a new diagnostic technology. The paper described the implications of using DES in this context and the type of data required.

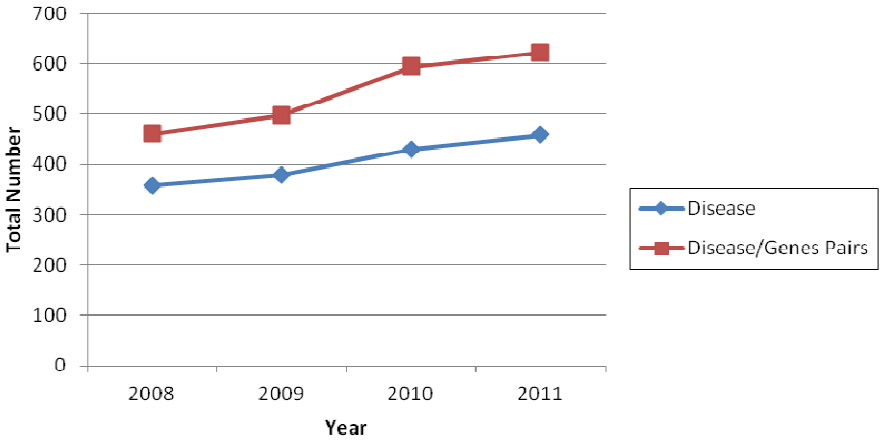
Contents

1 Background

The late 1970s and early 1980s witnessed the introduction of some of the first genetic tests analysing DNA within the UK NHS. These pioneering tests were often for rare disorders, such as hemoglobinopathy (genetic blood disorders), the majority of which were conducted in specialised laboratories at Oxford or London in the UK (1). The emergence of the molecular genetics field following this period allowed for the more widespread use of DNA diagnostic tests within the NHS for conditions such as Duchenne and Becker muscular dystrophy, cystic fibrosis and Huntington's disease. These tests would be conducted outside the first specialised genetics laboratories of Oxford and London to newly established regional molecular genetics laboratories (2).

Today, genetic testing within the NHS is organised by the UK Genetic Testing Network (UKGTN), whose responsibility is to promote more formal cooperation between member laboratories providing tests to the NHS. Currently available data indicates that genetic tests are available for 458 diseases covering 622 disease/gene pairs as of 2011 (3). Figure 1 displays the yearly increase in the number of genetic tests available from UKGTM member laboratories for the period between 2008 and 2011, which represents a crude yearly increase of ≈33 diseases per year.

Figure 1: Total Number of Disease and Disease/Gene Pairs within UKGTN



Source: Adapted from UKGTN NHS Directory of Genetic Testing (3–6)

The vast majority of these genetic tests are produced using Sanger sequencing technology. Indeed, this is essentially the same technology that has been in use since the 1970s in the provision of DNA analysis. While there has been advancements upon the original technology which has led to more automated testing procedures. Fundamentally, this technology is limited both in terms of the amount of data it can produce and in the length of time required to produce this data (7–9). Continuing advancements in the knowledge of the genetic basis for human disease through the field of genetic medicine has placed increasingly greater demands upon the current Sanger sequencing technology; both in terms of an increase in number of tests provided in addition to an increase in the amount of data required for each test (9). The pace of the increase of these demands on current technology is guaranteed to become greater into the future. However, it can be argued that continued investment in Sanger sequencing technology may not be appropriate given the time consuming and labour intensive nature of the testing procedure.

In response to the increased demands for genetic tests, a novel technology representing a departure from Sanger sequencing is currently in development. High-throughput sequencing (HTS) technology promises the ability to provide both a larger number of genetic tests and a greater volume of data (8). HTS represents the most recent advancement in medical science which opens the possibility to understanding the impact of genetic variation not just in a single gene but across multiple genes or even the entire genome; all within a single diagnostic test. This has the potential to transform the delivery of healthcare within the NHS by improving our ability to determine disease risk prediction, provide more accurate diagnosis and inform the selection of more individual therapeutic options.

Regardless of the potential benefits of HTS, this newly developed diagnostic technology will be introduced into a healthcare system which is funded by a finite budget, generally agreed on an annual basis. Currently, HTS remains a relatively expensive technology in comparison to the latest automated Sanger sequencing technology platforms (7,8); and as a component of the overall cost of HTS, capital expenditure on equipment forms a significant proportion which must be borne at the outset when introducing HTS into clinical service. Decision makers, such as the

member laboratories of the UKGTN, are charged with allocating scarce healthcare resources and must make an informed choice about the possible introduction of HTS and consider the opportunity cost of this funding decision.

Methods of economic evaluation are a potentially useful source of information to help decision makers delibrate on whether to introduce HTS into routine clinical service. Economic evaluations consider the incremental costs and benefits of a new technology compared with current practice. Unfortunately, there are relatively few robust economic evaluations of genetic services and tests. However, two key systematic reviews have attempted to identify and assess the quality of published economic evaluations (10,11).

The review conducted by Carlson and colleagues (11) identified studies published between the years 1990 and 2004. The authors identified 149 articles, of which 63 met the defined inclusion criteria and identified as comparative economic evaluations where costs and consequences were included. The authors report that cost-effectiveness analysis was the most common type of study, representing approximately 59% of included studies with the remaining 25% identified as cost-utility analysis. Additionally, the authors identified cancer and chromosome abnormalities as the most common disease areas examined. Finally, the authors noted the increasing trend in the number of publications examining genetic tests and services between 1990 and 2004.

Djalalov and colleagues (10) aimed to build upon the previous systematic review by Carlson et al. (11) and identify more recent trends in the literature concerning the economic evaluation of genetic services. The review covered publications in the time period between 2004 and 2009. A total of 631 publications were identified where 26 met the inclusion criteria defined by the authors. The previous trend indicating an increase in the number of publications detailing genetic technologies over time was confirmed by the authors. Similarly, a majority of the studied included in the review were categorised as cost-effectiveness analysis. In addition, the type of modelling technique employed was extracted from the studies where a decision tree type methodology was identified as the most common type of model used, representing 46% of studies which reported utilising health economic modelling techniques. This

may suggest a trend towards a more limited approach to modelling genetic technologies in comparison to other, more established disease areas where modelling techniques have been more frequently used.

In the absence of a clear direction from the literature in terms of the economic evaluation of genetic technologies, a European Commission Seventh Framework Programme funded project titled TECHGENE[1] included a work package tasked with exploring economic evaluation techniques that may be used to assess the economic impact of HTS technology for current clinical practice. The following case study presents an application of HTS for the identification of genetic mutations associated with hereditary breast cancer.

2 Introduction to the Case Study: Hereditary Breast Cancer

Breast cancer is defined as the abnormal and malignant growth of breast tissue and constitutes the most common form of cancer among women. In 2008, 39,681 new cases of breast cancer were diagnosed in England, representing the most common site for the development of malignancy within the overall population (12). The cause of the majority of breast cancer cases is unknown, but risk factors associated with the disease have been well documented (13). Evidence suggests that family history of the disease is a known risk factor for subsequent development (14).

Predisposition for breast cancer, as determined by genetic mutations, does not invariably lead to the subsequent development of the disease. However, it has been estimated that a significant proportion of women, up to 10%, can be identified as having an inherited predisposition for the disease (13). Indeed, studies have estimated that between 4 and 10% of the total number of cases of breast cancer may be attributed to familial history (15). The major genes associated with breast cancer risk are BRCA1 and BRCA2, where the presence of faults within these genes indicates an increased risk for an individual of developing breast cancer.

[1] TECHGENE [www.techgene.org]

Genetic testing for BRCA1 and BRCA2 gene mutations has been available commercially since 1996 (15). The majority of these tests are conducted by UKGTN laboratory members and use some platform variation of the Sanger sequencing method (Personal Communication: Dr. Rob Elles, Manchester, 2012). These tests are conducted in conjunction with genetic counselling appointments with either a genetic counsellor or consultant geneticist. Typically, each patient requiring predictive testing for cancer will require on average three genetic counselling appointments (16). Testing for mutations within the BRCA1 and BRCA2 genes is complex. Several hundred mutations in these genes have been identified, occurring almost throughout their sequence (13). Using Sanger sequencing technology to assess these gene mutations can therefore be a lengthy process. In some cases, results turn-around times for up to a year have been noted in the UK (Personal Communication: Dr. Rob Elles, Manchester, 2012).

Current NHS practice is to refer individuals who have been deemed at 'high risk' of developing breast cancer to a specialist genetics service (17). Currently, a high risk individual in the United Kingdom is identified as possessing a greater than 8% risk of developing breast cancer between 40 and 49 years or a lifetime risk of ≥30% or a ≥20% chance of carrying a BRCA1 or BRCA2 gene (Table 1). Once received into a specialist genetics service, the decision to offer a BRCA1/2 test is based on the criteria of a possessing ≥20% chance of carrying a BRCA1 or BRCA2 gene (17). The risk assessment percentages are provided by clinical assessment with the aid of computerised risk-assessment models.

Table 1: NHS Breast Cancer Risk Classification Levels

Risk Class	10-Year Risk (40-49 Years)	Lifetime Risk	BRCA1/BRCA2 Gene Fault Risk
Near Population Risk	<3%	<17%	-
Raised Risk	3-8%	≥17% - <30%	-
High Risk	>8%	≥30%	≥20%

Source: NICE Familial Breast Cancer Guideline 41, 2006 (17).

The application of risk thresholds appears, in part, as response to the limited number of BRCA1/2 tests that may be provided by a typical genetics laboratory. In this

instance, the risk classification criteria act as a rationing mechanism for the existing stock of genetic tests. Unfortunately, the clinical evidence for the application of these thresholds is lacking (18).

The potential benefits of applying HTS technology to genetic testing for hereditary breast cancer are believed to be a reduction in the turn-around time between submission of sample for testing and receipt of results from the test. In addition, HTS may simultaneously increase the number of tests that may be provided by a typical laboratory employing HTS or next-generation sequencing (HTS) (Personal Communication: TECHGENE Expert Panel, 2011). This may allow for the provision of genetic services to a much wider population group with equivalent or shorter turn-around time for results than is currently possible with Sanger sequencing technology.

It is believed that the comparative cost of providing HTS in relation to Sanger sequencing is likely to change over the short to medium term (8) with the diffusion of this technology from development to implementation stage. Replicating cost reduction patterns of previous technology variants. Therefore, it is believed that in the medium terms the cost of providing genetics tests using HTS could be assumed equivalent to that of current technologies. Furthermore, a new diagnostic test using HTS will only be provided for use in a clinical setting if the technology meets current levels of sensitivity, specificity and predictive values.

Table 2: Benefits of HTS Technology

Potential Benefits of HTS Genetic Testing in Comparison to Current Technology
1. Decreased Turn-Around Time;
2. Increase in testing capacity (number of individual tests possible);
3. Equivalent test performance (sensitivity, specificity, predictive values);
4. Equivalent cost (in the medium term).

Given the potential benefits (Table 2) of HTS in terms of cost and test performance, which may be considered the traditional effectiveness measures of a diagnostic technology; current modelling approaches to evaluate the incremental costs and benefits of HTS would show that, on face value, HTS offers no benefits over current Sanger sequencing methods and the costs to the healthcare service associated with

providing HTS would be the same. Current economic evaluation use particular types of economic modelling methods, such as decision trees and Markov models (10,11), which may not potentially capture the true impact of introducing HTS in terms of costs and benefits to the health service and patient population. A systematic review conducted for the TECHGENE project (18) identified and critically appraised published economic models relevant to hereditary breast cancer. Again, the review did not identify methodologies that have previously been published which would incorporate the potential benefits of HTS.

The selection of an appropriate modelling methodology for the calculation of the benefits and costs of HTS technology was aided by a number of key articles (19–21). The criteria for which each of the methodologies could be judged were centred around the main benefits of HTS technology. These included, turn-around time for genetic tests which would need to be incorporated in terms of days. Resultant from this are the activity and queues which are required to be incorporated to simulate turn-around and waiting time data. Finally, the genetic test itself may also induce subsequent demand for the genetics and laboratory services from family members of individuals tested may also request counselling and/or a genetic test. Application of the guidance and selection criteria provided by to HTS testing for hereditary breast cancer risk suggested a modelling methodology which incorporates individual level data and allows for interaction between individuals (Table 3).

Table 3: Decision Matrix for Modelling Methodology

	Decision Trees	Markov-Type	Individual-Level
Time	Not Explicit	Cycle Based	Discrete Time
Structure	Simple	Health States	Event Based
Individual Data	Possible	Possible	Fully Incorporated
Capacity Constraints	Not Possible	Not Possible	Fully Incorporated
Dynamic Population	Possible	Not Possible	Fully Incoproated

Therefore, it was decided to utilise a discrete event simulation (DES) methodology with the ability to explicitly incorporate time in discrete units. It would also be capable of representing a complex diagnostic pathway, incorporating individual level data such as risk and simulating the queuing behaviour of waiting for a test and the

results from a test. DES would also have the ability to change the model population based on the estimated activity within the model.

3 Methods

3.1 Model Overview

3.1.1 Relevant Study Population

The study population is defined as individuals who may be considered for referral to a genetics service due to concerns regarding hereditary breast cancer. The population group is widely defined so as to represent the total population that may be eligible for a genetic test but do not currently meet the established risk thresholds.

3.1.2 Study Perspective

The perspective of the model will take the viewpoint of the health care system and therefore will only consider the costs incurred to the system rather than those borne by the wider society. The health care system is defined as that of the NHS in the United Kingdom.

3.1.3 Study Time Horizon

The model time horizon is dependent on the selection of the outcomes for extrapolation. In the case where the effectiveness of the genetic test is being examined in isolation, in terms of turn-around time and queue lengths, a comparatively short time horizon is sufficient to account for the benefits of HTS in comparison to Sanger sequencing. In the current instance, the model time horizon is 1 year.

3.2 Defining the Model Structure

An overview of the care pathway for patients with suspected hereditary breast cancer predisposition in the UK was sought from both clinical practice guidelines (17) and interviews with expert personnel working in a regional genetics service in Manchester, UK[2]. Based upon a soft elicitation technique, a preliminary care pathway was identified and described.

Initially, patients are referred into a genetics service typically at the primary care level by a general practitioner or at a secondary care level by a surgeon or oncologist. The group of patients referred querying concerns about hereditary cancer include those who have previously or currently have breast cancer while others will have no history or symptoms of the disease, but have concerns about their family history following development of the disease or identification of a breast cancer susceptibility gene within their family. The decision to refer a patient to the genetics service is typically based upon a discussion surrounding the known clinical and family history to form a risk estimation for developing breast cancer.

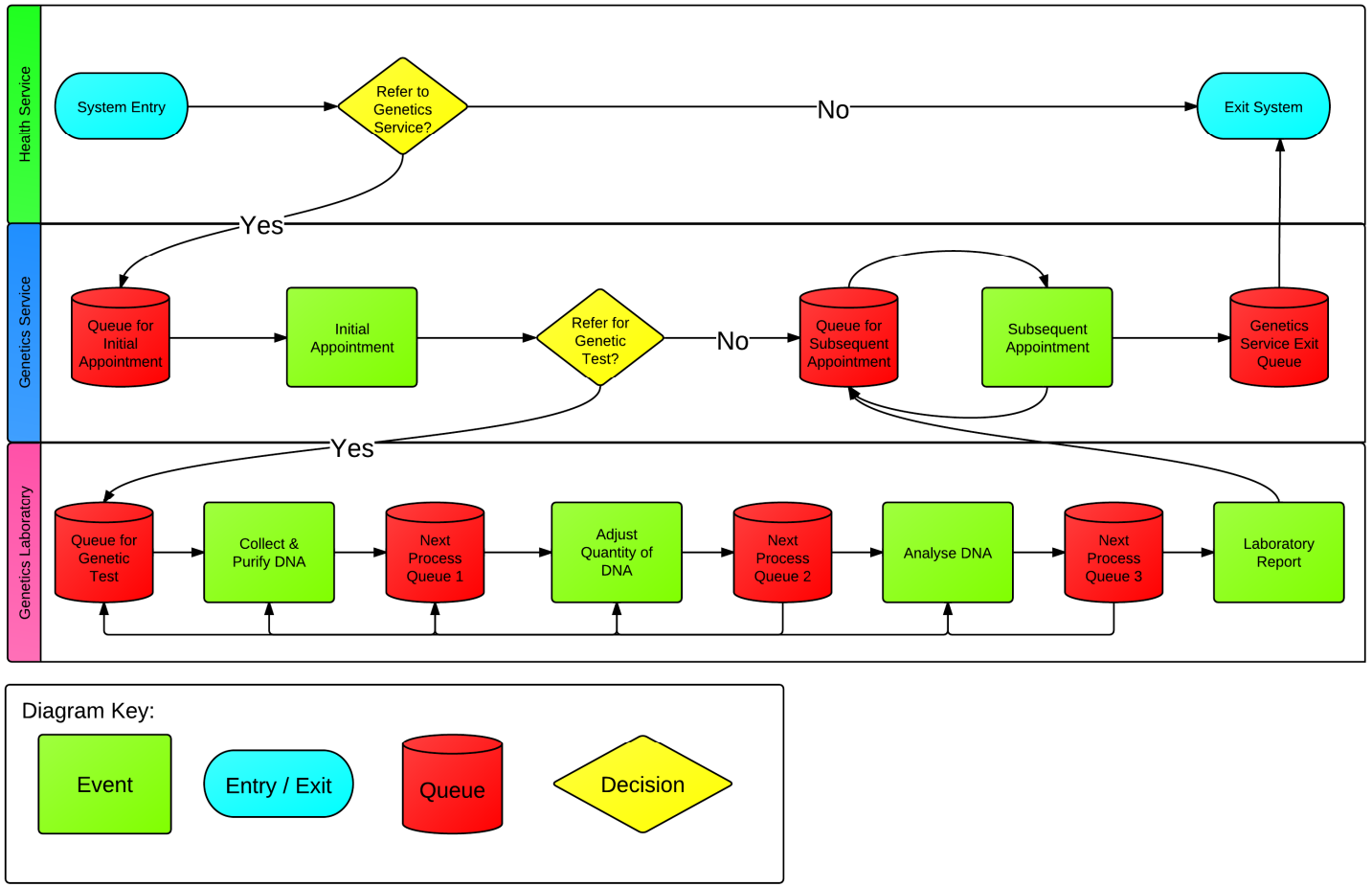
Once received at the genetics service, a risk assessment of the patient is conducted by examining their family history, personal medical records and medical records of family members, if available, who may have used the service previously. It is at this point that an initial risk assessment will determine whether a genetic test is provided by the service and/or accepted by the patient. Currently in the UK, the decision to offer a genetic test is based upon a decision rule whereby women must be deemed to be at high-risk and a ≥20% risk of detecting a BRCA1 or BRCA2 mutations before qualifying for a genetic test. This rule represents a rationing mechanism for the limited number of BRCA1/2 tests currently made available by Sanger sequencing technology. An additional capacity constraint is imposed on the service via the need for genetic counselling throughout the testing process. A determination of risk is made in the final assessment, with or without the genetic test.

A formalised discrete event simulation model structure was then constructed from the details provided and validated with expert personnel. The DES model structure is formed from four activity types: entry/exit, event, queue, decision. The possible

[2] Manchester Regional Genetic Centre, Genetic Medicine, St. Mary's Hospital, Manchester UK. [http://www.mangen.co.uk]

diagnostic pathways between each of the activity types are then mapped (Figure 2). The model comprises three distinct systems representing the health service, the specialist genetics service and the genetics laboratory. Simulated patients (entities) progress through the model while possessing information (attributes) which determine the direction of their progress. Decision activities, examine a individual patients attributes and decide on subsequent path, for example the decision to refer to the genetics service is based upon the determined risk category of an individual simulated patient. Events within the model include patient interactions with the genetics service in terms of appointments. The events also represent key stages in the genetics laboratory testing process. While waiting for an event activity to become available, a patient waits and accumulates time in a preceding queuing activity. As the model time progresses, all individuals reach the system exit point at which all the available information concerning the simulated individual is recorded.

Figure 2: Model Structure



3.3 Defining the Model Parameters

A key feature of discrete event simulation is the incorporation of stochastic components for each individual patient within the model structure. These components are specified in as input parameters; typically in the form of probability distributions. Each of these input parameter distributions are then randomly sampled to provide a unique value for each individual or the value for the next 'moment' in time upon which an event, activity or process occurs. The input parameters for the model structure defined in Figure 2 can be broadly classified as 1) those pertaining to the individual patients (entities) in the model and 2) those representing the model system.

3.3.1 Input Parameters for Model Entities

The input parameters associated with individual entities simulated within the model can be envisaged as patient attributes. These include age, gender, medical history and family history. A unique value from each of the parameters is determined for each individual entity at the system entry activity of the model. Each of the parameters are sampled independently, with the exception of the true BRCA1 and BRCA2 status input parameters; the values of which are dependent upon the previous sampled values of characteristics, medical history and family history.

Table 4: Model Input Parameters for Entities

Parameter	Sampling Relationship	Distribution Type	Value Determined At
Age	Independent	Continuous	System Entry
Gender	Independent	Binary [Male, Female]	System Entry
Ashkenazi Jewish Ancestry	Independent	Binary [No, Yes]	System Entry
Current/Previous Breast Cancer	Independent	Binary [No, Yes]	System Entry
Current/Previous Ovarian Cancer	Independent	Binary [No, Yes]	System Entry
No. 1st-Degree Relatives with Breast Cancer	Independent	Discrete	System Entry
No. 1st-Degree Relatives with	Independent	Discrete	System Entry

Ovarian Cancer			
No. 2nd-Degree Relatives with Breast Cancer	Independent	Discrete	System Entry
No. 2nd-Degree Relatives with Ovarian Cancer	Independent	Discrete	System Entry
True BRCA1 Status	Dependent	Binary [No, Yes]	System Entry
True BRCA2 Status	Dependent	Binary [No, Yes]	System Entry
Acceptability of Genetic Test	Independent	Binary [No, Yes]	System Entry

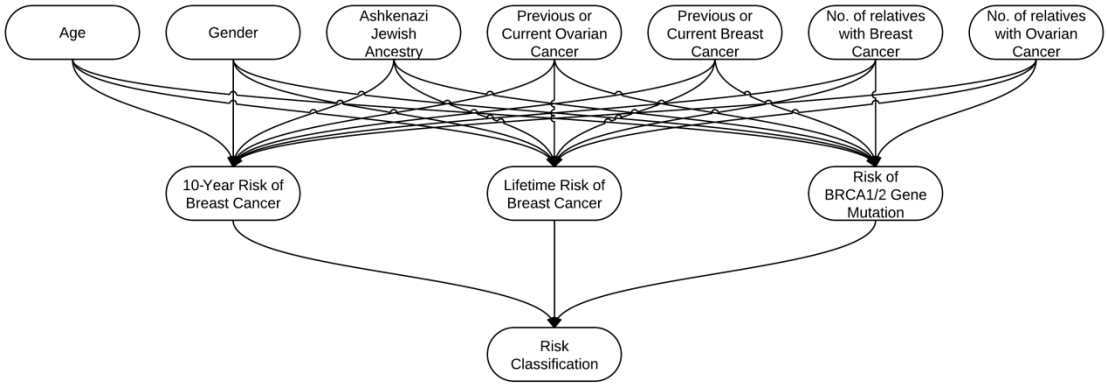
The values sampled for the above model input parameters also determine the resulting values of variables which also determine the direction of an individual patient diagnostic pathway within the model (Table 5).

Table 5: Variables Determined Within the Model

Variable	Distribution Type
10-Year Risk of Breast Cancer	Fixed Probability
Lifetime Risk of Breast Cancer	Fixed Probability
Risk of Carrying a BRCA1/2 Gene Mutation	Fixed Probability
Risk Classification	Fixed Categorical [Population, Raised, High]
Genetic Test Result	Binary [Negative, Positive]

The influence of the model input parameters and variables is displayed in Figure 3. This shows how the determination of subsequent variable values, which are unique to each model entity (patient) are determined based upon preceding random sampling of parameter input distributions.

Figure 3: Parameter Input and Variable Influence Diagram for Individual Attributes



3.3.2 Input Parameters for Model System

The input parameters associated with the model system represent the performance of the health service, genetics service and genetics laboratory. These parameters may determine the unique amount of time taken to conduct an activity or the direction through the model for an entity.

Table 6: Model Input Parameters for System

Parameter	Sampling Relationship	Distribution Type	Value Determined At
Inter-Arrival Rate	Independent	Continuous	System Entry
Initial Appointment Time	Independent	Continuous	Initial Appointment
Subsequent Appointment Time	Independent	Continuous	Subsequent Appointment
Collect & Purify DNA Time	Independent	Continuous	Collect & Purify DNA
Adjust Quantity of DNA Time	Independent	Continuous	Adjust Quantity of DNA
Analyse DNA Time	Independent	Continuous	Analyse DNA
Laboratory Report Time	Independent	Continuous	Laboratory Report
Collect & Purify DNA Failure	Independent	Fixed Value Probability	Collect & Purify DNA
Adjust Quantity of DNA Failure	Independent	Fixed Value Probability	Adjust Quantity of DNA

Analyse DNA Failure	Independent	Fixed Value Probability	Analyse DNA
Laboratory Report Failure	Independent	Fixed Value Probability	Laboratory Report
Sensitivity of HTS Test	Independent	Fixed Value Probability	Laboratory Report
Specificity of HTS Test	Independent	Fixed Value Probability	Laboratory Report
Sensitivity of Sanger Test	Independent	Fixed Value Probability	Laboratory Report
Specificity of Sanger Test	Independent	Fixed Value Probability	Laboratory Report

3.4 Model Assumptions

All models representing a simplification of the 'real world' require the statement of assumptions to allow for the operationalisation of the model. The following assumptions apply for the current hereditary breast cancer model.

Where variables are identified as having an independent sampling relationship, it is assumed that the values sampled for each entity are independent of the values of other parameter samples. For example, the acceptability of a genetic test for an individual is independent of the number of 1st-degree relatives with breast cancer that has also been sampled.

The structural assumptions within the model assume that a decision to refer for a genetic test is made immediately after the initial appointment with a genetics service. An individual may then experience one subsequent appointment but must await a third subsequent appointment until results of genetic test are available. Once an individual has experienced two subsequent appointments within the genetics service they are assumed to exit the system.

It is also assumed that the available working time within each of the systems is based on a working five day week for fifty weeks per year. Allowing for 250 days per

year in which events can occur. In addition, it is also assumed that the system is operating based on an eight hour day from 9am to 5pm.

Finally, it is assumed that the total available time within the system is devoted entirely to BRCA testing. No other genetic testing demands are assumed for the genetics service or laboratory. Additionally, it can be assumed that the outputs from the model are dependent upon the currently assigned technology and labour resources, where increases in either (i.e. addition of additional testing facilities, or addition of more genetic councillors) would result in service improvement for both HTS and Sanger sequencing test comparisons.

4 Results

The aim of the DES model is to create a series of unique patient diagnostic pathways for individuals who experience HTS tests and compare that to individuals who experience Sanger sequencing testing. The simulated data for individual patients can then be analysed in addition to the performance measures of the modelled system as outlined in Table 7.

Table 7: Possible Model Outputs for Comparison

Model Outputs
1. Number of individuals referred to genetics service;
2. Number of individuals referred for genetic testing;
3. Queue (Wait) time for initial appointment;
4. Queue (Wait) time for subsequent appointment;
5. Laboratory results turn-around time
6. Cost per individual

Additionally, scenario analysis may be performed by varying the currently imposed risk thresholds which ration genetic tests. This can allow for the comparison of differences in model outputs between technologies for a variety of defined risks.

5 Discussion

This paper represents work in process with the aim of evaluating the economic impact of HTS for hereditary breast cancer. The unique challenges posed by the technology have lead a departure from the more traditional modelling methodologies employed by previous technology evaluations. However some issues remain outstanding.

5.1 Diagnostics Evaluation: A Data Free Environment

HTS represents a technology that is still currently in development. As a consequence, the data available to researchers is still being collected and analysed. Regardless of the stage of development, diagnostics in general do not undergo a rigorous trial evaluation as required by their therapeutic counterparts. The absence of a formal clinical trial evaluation has led to the situation where data is simply lacking. This data free environment can be contrasted against the amount of data provided by a HTS test. To assess the impact of a genetic test, alternative sources of data may be required. It is envisaged that for the current evaluation, extensive use of expert option will be required to populate the parameter inputs for which no data is available.

5.2 The Cost Cliff: Capital Costs for Genetic Diagnostics

This current paper did not directly address costing for HTS and Sanger sequencing testing but it can be noted that a significant capital investment is required before testing can be made available. This capital investment results in a fixed maximum amount of tests that are available to an optimal testing laboratory. To breach this threshold, a near doubling of investment may be required to establish the resources required for any tests above the maximum available. The consequence of this for decision-makers for this may need to be quantified and included in scenario analysis for a discrete event simulation.

5.3 Multiplex Use of Technology

The current evaluation assumed that the typical genetics laboratory, as defined in the model structure, concentrated entirely on providing BRCA1/2 tests. No other competing uses of the technology were incorporated. This is an extreme oversimplification of the current use of the technology and proposed use of HTS. The results from the model provide an estimate of the amount of the resource that is required to meet the simulated demand with a given level of resources (technology and labour). Decision-makers may infer from this the total capacity required when considering other used of the technology. However, this is not directly incorporated in the model or subsequent analysis and consideration must be given to this.

5.4 The Benefits of a Diagnostic Technology

The benefits of the current genetic testing technology were only considered to be in terms of turn-around time and capacity. This limits the comparison of the technology to identical outcome measures. It could also be assumed that HTS and Sanger sequencing do not alter the therapeutic pathway, except for perhaps reaching in at an earlier stage. However, it is possible to extrapolate beyond the current diagnostic pathway to a subsequent therapeutic pathway for hereditary breast cancer. Invariably, as noted this would require yet much more information and data which may indicate the potential impacts of HTS and Sanger sequencing tests on the subsequent therapeutic pathway.

5.5 KISS for DES

The above discussion points hint at the possibilities of increasing the complexity of discrete event simulation model. This, at first sight, may appear an easy prospect. However, increases in the scope of the model structure results in ever increasing demands on the amount and quality of the parameter inputs required for such a model. Therefore, much consideration should be given for each expansion in the

model capabilities. The KISS principle “Keep it simple, Stupid!” may be the most overriding principle when implementing a DES model for diagnostic tests.

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