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Genetic testing in England: ROI, cost-effectiveness analysis or both to evaluate intervention?

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Last year, the UK Genetic Testing Network issued over 200,000 genetic test results for more than 3,000 disorders and their associated genes.[1] A majority of these tests were primarily targeting cancer mutations. The rapid uptake of genetic testing within the National Health Service (NHS) and current debate around genetics make evaluating these tailored interventions increasingly more relevant to ensure an efficient use of NHS spend.

Return on investment (ROI) is used in many business areas to evaluate competing investment strategies with potential future financial implications. In healthcare, ROI can be used to measure the effectiveness of various disease management programmes, particularly those targeting patients with chronic conditions, or even to determine the potential value of health risk assessments to insurers. Often, calculating ROI can be fraught with methodological challenges or other logistical constraints, mostly around definitions of data required and evaluation methodology, but the math behind it and overall principles remain straightforward.

ROI provides a framework to help determine whether additional funds should be allocated to a particular activity or alternatively, whether these funds should be withdrawn and allocated elsewhere. By nature, ROI strictly focuses on financial metrics and will most often be compared against a pre-defined threshold; thus, interventions with a ROI above the threshold would normally be funded whereas interventions with a ROI under the threshold may warrant further investigation.

ROI and genetic testing

Through an observational study, we can assess the financial impact of genetic testing on healthcare resource use between comparable populations that have and have not undergone testing in England. This financial analysis would project the upfront cost for providing genetic testing to the eligible population by considering factors such as how the cost and take-up of genetic testing may change over time.

a) For instance, we can look at real-world data from two distinct population groups with a similar risk profile before and after a particular genetic test becomes available. Under this approach, we would use the year a specific test was introduced in the NHS as a marker and select populations as close to the marker as possible to reduce potential bias and externalities (i.e., new technologies uptake).
b) We would follow patients for an established duration, yet the observation period timing for the two groups would differ. Ultimately, this approach requires looking at two distinct population cohorts.
c) While in theory it is possible to control for health status in a similar way to other demographic factors, in practice risk adjustment mechanisms for health status are not perfect, and ultimately may add a level of complexity to the modelling.

An alternative study design could focus on a single population group which did not undergo genetic testing but fits the clinical (eligibility) criteria.

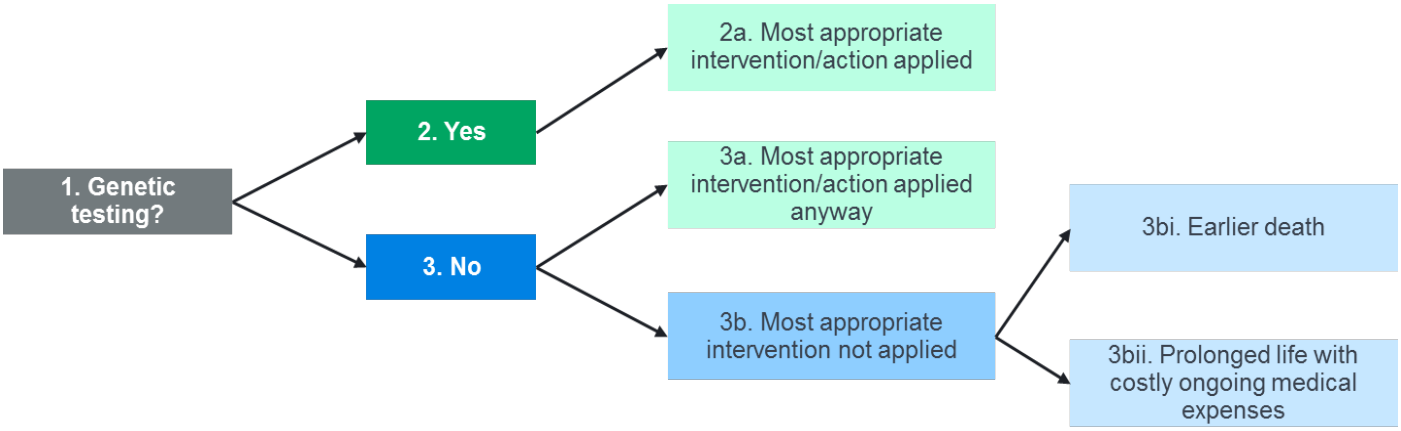
a) Using this group as baseline, we then would apply adjustments for the expected impact of genetic testing directly onto medical resource utilisation to establish a theoretical “treatment” group. We recommend the use of peer-reviewed literature and other external sources to supplement findings from real-world data and help provide additional input into the potential financial impact of testing on overall healthcare utilisation and cost by disease area.

b) This approach has the advantage of reducing the level of bias and potential confounding factors as the analysis is performed using a single cohort of patients over a single time period. However, this study design corresponds to a modelling exercise rather than being a true observational study.

Ultimately, irrespective of the method selected, the aim will remain to compare patient populations with and without genetic testing as summarised in Figure 1.

[1] Promoting gene testing together (March 2017). Retrieved June 8, 2017, from https://ukgtn.nhs.uk/fileadmin/uploads/ukgtn/Documents/Resources/Library/Reports_Guidelines/UKGTN_Biennial_report_2017.pdf

FIGURE 1: POTENTIAL EVALUATION PATHWAY FOR POPULATION ELIGIBLE FOR GENETIC TESTING



Once the study design is chosen, we then move on to select our population of interest. Focusing on a particular cancer type, for instance, a ROI framework can help health and care commissioners and payers determine whether tests currently used within the NHS for a specific condition are creating savings or incurring further costs elsewhere in the system. The process can be replicated for other types of cancer or multiple disease areas where genetic testing is currently being used. A potential benefit of widening the scope of the analysis includes the ability to measure the effect of genetic testing at a population level, yet a proof-of-concept on a smaller scale can sometimes demonstrate what can and cannot be achieved given available data.

Timeframe and financial projections

Similarly, choosing the right time horizon is important. A longer timeframe-- for example, 15 to 20 years-- will allow quantification of the potential foregone medical costs over time as well as any additional surveillance and other costs incurred due to genetic testing. Additionally, while NHS budgets are set annually, the potential benefits linked to testing will accrue over the long term. Therefore, ROI can be an appropriate measure to evaluate a given intervention over that timeframe.

Further, presenting medical utilisation and cost of the control and treatment groups in a structured way can provide insights into the areas that may be affected the most by genetic testing. As a starting point, tools like the Milliman *Health Cost Guidelines*™ (HCGs) can be used to categorise medical data for selected populations into service categories, breaking down healthcare utilisation by hospital inpatient, outpatient and primary care as well as other tertiary care settings in England. This stratification will help pinpoint the differences in medical utilisation and costs between a control group (no genetic testing) and a treatment group (genetic testing), ultimately laying the foundation to derive ROI for a given intervention and support any benchmarking exercise. While only direct medical costs are typically captured in the analysis, a wider scope could, for example, consider other societal costs (i.e., productivity loss) and social care costs, but the approach once again would be similar.

Once base year data are set, we would adjust projections of medical resource utilisation and cost for demographic changes such as ageing and population growth. This will create more representative cost models in line with population projections for England. Where available, modelling should rely on real-world data from England. However, data limitations may require the use of larger and more readily accessible real-world datasets from external settings. Finally, once the financial projections are populated, we can assess the financial impact of genetic testing by comparing experience in the treatment group against that of the control group. An analysis by service category will highlight the areas in the system which are the most affected by the intervention.

Population segmentation and ROI

Another relevant consideration is the relationship between the selection of the population group subject to genetic testing and the overall level of return from this intervention. Similar to disease management programmes, it is important to risk stratify your population of interest, ideally using a method that will produce reliable results given the data available and without requiring resources or investment beyond the value gained from the method applied, to really hone in on the population most likely to benefit from testing. While offering genetic testing to the whole population of England is unlikely to yield a positive ROI, a more granular analysis may identify the sub-populations most responsive to testing, and thus most likely to benefit from tailored interventions.

For instance, the prevalence of certain genetic predispositions within the population at large may be low, but may be particularly high within a given disease area. Targeting these selected individuals is likely to influence the ROI by potentially reducing the number of people subject to genetic testing (and overall cost of testing) while increasing the estimated number of people likely to benefit from the interventions recommended by genetic testing. The hypothetical example below (Figure 2) illustrates how selecting 100 patients at random versus carefully selecting 100 patients for genetic testing may produce very different financial outcomes to payers in tailoring treatment interventions to patients. We note applications of genetic testing may extend beyond the simplified scenario presented

below and may also offer better dosage guidance, screening and surveillance practices to patients.

FIGURE 2: ILLUSTRATIVE EXAMPLE OF POTENTIAL FINANCIAL REWARDS DUE TO GENETIC TESTING

DESCRIPTION	SCENARIO 1 POPULATION AT RANDOM	SCENARIO 2 POPULATION SEGMENTATION
COST OF 1 GENETIC TEST	£600	£600
COST OF 1 TREATMENT	£5,000	£5,000
NUMBER OF PATIENTS AT RISK OF TREATMENT NON-RESPONSIVENESS	1 IN 100	20 IN 100
POTENTIAL TREATMENT COST AVOIDED DUE TO GENETIC TESTING	1 * £5,000 = £5,000	20 * £5,000 = £100,000
TOTAL COST OF GENETIC TESTING	100 * £600 = £60,000	100 * £600 = £60,000
FINANCIAL REWARDS DUE TO TESTING	(£55,000)	£40,000

Note on cost-effective analysis as an alternative evaluation tool

The scope of a cost-effective analysis (CEA) is by definition wider than the scope under ROI because it allows non-financial outcome metrics in the modelling. The primary aim of a CEA is to assess whether additional benefits to patients are worth the extra investment required to fund an intervention. Therefore, data on quality of life (utility) and other clinical outcome metrics will generally supplement financial data. Particularly, medical costs and outcome measures for populations that have and have not undergone genetic testing are compared against each other, ultimately producing a cost-effectiveness ratio used to inform reimbursement decisions and potential adoption in the NHS.

Recent NICE guidance on the use of molecular testing (genetic testing) for Lynch syndrome in patients with colorectal cancer demonstrates how CEA can be applied to diagnostics in a similar way to medical technologies. While new medical technologies are typically used to treat a particular condition and provide an alternative treatment to existing therapies, diagnostics are normally used to rule out a specific disease, assess the degree of severity of a particular disease or even look for specific conditions in patients without symptoms. Therefore, diagnostics have the potential to tailor care interventions to individual patients.

From the point of view of care commissioners and payers, however, CEA will fall short of estimating the potential current and future budget impact of new interventions because the aim is to demonstrate cost-effectiveness. CEA rarely accounts for population dynamics and changes in the age/gender structure to inform decisions on technology adoption. Nonetheless, CEA modelling can identify the diagnostic strategies and care pathways likely to be more cost-effective, which can in turn inform any further ROI analysis.

Actuarial approaches to understand key uncertainties and guide risk management processes

Similarly to other interventions, evaluating the financial implications of genetic testing includes uncertainties, notably around the future cost and uptake of genetic testing and the level of sophistication of new tests as well as future spend allocated to genetic testing. As technology evolves, the future medical costs of providing standard and alternative care, as well as the costs of treating adverse events, are also uncertain and may fluctuate from current levels. In this context, both ROI and CEA frameworks can benefit from actuarial approaches and other risk management principles as these emphasise sensitivity analysis and scenario testing to determine key modelling assumptions. Main considerations include:

i. Actuarial design applied to healthcare will typically adopt a population-level perspective. This provides a more holistic view of the financial benefits and costs accrued to the whole system and measured against external benchmarks.
ii. Additional population segmentation by age band, gender and the number of co-morbidities can provide further insights into the variations in medical utilisation and cost by these factors.
iii. As mentioned above, projections rely on real-world data and incorporate demographic changes over time.
iv. Another benefit is to demonstrate cost and benefit implications under various trend scenarios, including extreme scenarios, to understand key sensitivities and uncertainties in the model.
v. Actuarial approaches are dynamic; therefore, they can help monitor actual versus expected as new experience in the model inputs emerge.

Conclusion

We describe above some of the advantages and limitations of ROI and CEA frameworks and highlight how each may require its own source of data and methodology to evaluate the benefits of a given intervention. Focusing strictly on financial metrics such as the ROI example can assist local commissioning bodies, national care commissioners and other payers address whether the potential future financial rewards of genetic testing to the NHS are worth the extra upfront investment. Alternatively, CEA provides an evaluation framework that highlights the relationship between the cost of a new intervention and its associated clinical outcomes over time.

Ultimately, it remains increasingly important that the findings be interpreted in an appropriate NHS context and be relevant and meaningful to stakeholders. Actuarial approaches can add value to the evaluation of genetic testing by focusing on the main sources of uncertainty under a variety of projection scenarios while adjusting for demographic changes over time.

Note about the authors

Didier Serre joined the Milliman London healthcare practice in 2015 and is responsible for applying actuarial principles to health economics and pharmaceutical products.

His current role is to develop ways to better allocate financial risk and financial uncertainty of new health technologies between payers and drug manufacturers. He is also involved in designing alternative reimbursement and evaluation models, notably for high cost drugs and novel antibiotics, and developing cost models drawing on real-world evidence and claims data.

His previous work assignments in Toronto and New York include roles in risk management for two leading global reinsurers and in pharmacy benefit consulting, respectively.

Joanne Buckle is the lead consultant in the Milliman London Healthcare practice. She has been at Milliman since 2001, including 18 months in the New York City office.

While in the United States, she was involved in several assignments for healthcare providers, including analyses of reimbursement structures and assessment of the adequacy of capitation arrangements. Her experience also includes wider applications of actuarial techniques for UK and US healthcare companies:

- Bed-demand projections for a new hospital
- Return on investment models for preventative medicine and screening services
- Estimates of the impact of disease-management services on medical cost trends
- Benchmarking of claims experience against best-practice protocols
- Building of models to project healthcare demand for government payers
- Investigation of actuarial approaches to assessing new drugs and technologies

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