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The cost-effectiveness of DNA testing for sudden cardiac death

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1. INTRODUCTION

Cardiovascular disease (CVD) is responsible for almost half (48%) of all deaths in Europe and the European Union (41%). Such figures create the need for evidence on cost-effective ways to provide primary and secondary disease prevention for CVD. For primary prevention, specialist cardiology care has tended to focus on reducing risk factors such as smoking and obesity and use clinical tests such as electrocardiogram (ECG) and echocardiography (ECHO) to diagnose CVD. However, there is now the potential to use a genetic approach (DNA testing and genetic counselling) to help identify asymptomatic individuals at risk from cardiac events within families. Those at risk from sudden cardiac death represent such a group.

2. SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) accounts for approximately 50% of the mortality from CVD in the United Kingdom (UK) and the incidence is around 0.1% to 0.2% per annum (1). The factors predisposing individuals to SCD include: lifestyle behaviour, including smoking and over-consumption of alcohol; obesity and clinical history, such as previous myocardial infarction or coronary artery disease. In addition, there are also inherited genetic diseases which predispose individuals to SCD. Hypertrophic cardiomyopathy (HCM) is one of these diseases and is the focus of this paper.

HCM is the most common *genetic* CVD and is characterised by unexplained hypertrophy of the left ventricle (asymmetric thickening of the heart in the absence of hypertension etc). The prevalence of the disease amongst UK adults is around 0.2% (1:500) (2), with a mortality rate at approximately 1% (3). The disease is genetically transmitted by *affected* individuals and is caused by mutations in at least ten different genes. Each child of an affected parent has a 50% chance of inheriting the disease(2;4-6).

A large part of the interest in this particular form of CVD, relates to it being the most common cause of sudden cardiac death in the young, with numerous examples of young

athletes dying in this way. Furthermore, the majority of patients have few symptoms and diagnosis is often made incidentally.

HCM diagnosis and treatment

The traditional process of diagnosis and treatment of HCM in the UK (and other SCD linked diseases) is clinical management within cardiology services. Clinical investigations, including ECHOs, ECGs and 24-hour ambulatory (Holter) ECGs, are used to help diagnose the disease. Where there is a known family history of HCM this can also contribute towards diagnosis. For those who are diagnosed with HCM by this clinical approach, there are a number of alternative prevention options for SCD including lifestyle changes (e.g. smoking cessation, competitive athletes are encouraged to stop competing etc), antiarrhythmic drug therapy such as amiodarone, or an implantable cardioverter defibrillator (ICD).

Genetic approach to HCM

To date the use of genetic tools (DNA testing and genetic counselling) for diagnosing HCM has been limited to a research setting. However, the Oxford Genetics Knowledge Park (Department of Health and Department of Trade and Industry funded initiate), is currently assessing whether a genetic approach for HCM should be translated from research laboratories into routine clinical practice. This 5 year assessment includes a National Pilot Study, where blood samples referred from UK Regional Genetics Centres (cohort of around 1000 SCD families) are being tested within a NHS laboratory. More specifically, the Oxford assessment is using cascade screening to:

- Identify affected, but undiagnosed individuals;
- Identify clinically unaffected, but genetically at risk individuals;
- Discharge those without mutation.

The aim of this paper is to present the methods and results of part of the health economic component of the Oxford Genetics Knowledge Park SCD assessment. More specifically,

to examine the long-term costs and effects of alternative approaches to diagnosing and managing HCM for those at risk of SCD.

3. ECONOMIC EVALUATION

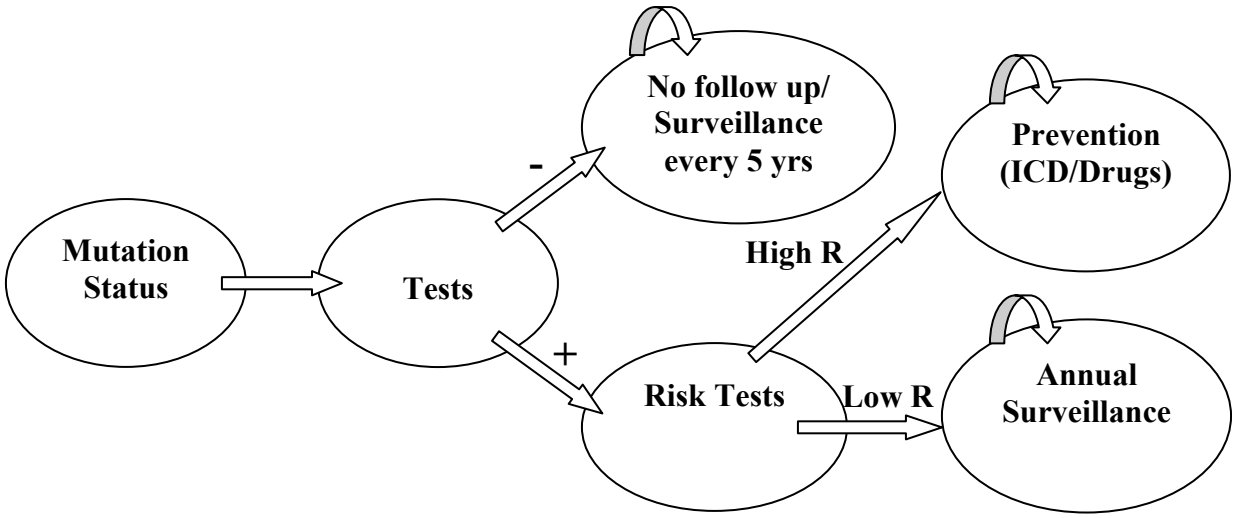
The economic evaluation aimed to compare the cost-effectiveness of clinical versus genetic approaches to (cascade) screening relatives of HCM patients in order to reduce the risk of SCD. The evaluation was based on the potential pathways that relatives of those diagnosed with HCM could take within a UK cardiology service and the Oxfordshire cardiology service was used as basis for the evaluation. Adopting a health service perspective a cost-effectiveness analysis was performed, with the primary outcome measure being a cost per life year gained.

3.1. METHODS

Model

A Markov model was built using Treeage Data software, to estimate the lifetime resource costs and health outcomes associated with the alternative screening strategies for HCM (Figure 1). The patient population was asymptomatic males aged 18, who were first degree relatives (brother) of those already identified as having HCM through a positive mutation using DNA testing. This age group was chosen because physical maturity is reached around 17 to 18 years of age, which means that HCM is usually detectable by ECHO and ECG(6). In addition, the genetic screening of younger age groups is of particular interest to clinicians, as teenagers are already at risk of SCD. The prevalence of the disease within this population is 50%(2;4-6) and the cohort was followed to 76 years of age (average life expectancy of men in England and Wales). Finally, a cycle length of one year was chosen for our model as HCM patients remain fairly stable over long time periods(5;6).

Fig.1. Basic Markov model for HCM screening strategies



3.2. Screening strategies

From the two alternative approaches for diagnosing HCM (clinical and genetic), a total of 10 screening strategies (A to J) were evaluated in the model (Table 1). The key difference between these strategies related to the combination of clinical and/or genetic tests used to identify those at risk from SCD. Other differences were the amount of cardiologist contact, follow-up of negative screening results and type of SCD prevention initiated.

The clinical screening comprised a 12-lead ECG, together with an ECHO. The genetic screening involved DNA testing (performed in the molecular genetics laboratory at the Churchill Hospital, Oxford) and genetic counselling. The clinical screening strategies are A, B, F and G, and the genetic screening strategies are C, D, E, H, I, and J. Strategies C and H involved clinical screening with posterior confirmation of all results by genetic screening. A genetic counsellor was involved in all the genetic screening strategies, but in strategies E and J the counsellor had a referring role, first to DNA testing (rather than a

cardiologist), and then to a cardiologist if a mutation was found. In the remaining strategies, the cardiologist made the decision about referral for DNA testing.

In the event of the initial screening result being positive (either clinical or genetic), this is followed by SCD risk stratification tests, including close examination of personal and family history, 24-h ambulatory (Holter) ECG and exercise stress test. Using the results of the risk stratification, patients considered at high risk of SCD were given SCD prevention measures, namely ICD implantation (Strategies F to J) or drug therapy using amiodarone (Strategies A to E). In contrast, those at low risk were kept under surveillance for continuous SCD risk assessment. This surveillance involved annual consultation with the cardiologist, two-dimensional ECHO and 12-lead ECG, together with a 24-h ambulatory (Holter) ECG every two years. In the event of a negative screening result, individuals did not receive further follow-up in eight of the strategies and in strategies B and G individuals were placed under clinical surveillance every five years (reflecting international guidelines)(6).

Table 1. Screening strategies evaluated

Strategy	Screening Tests	Risk stratification tests[1]	Cardiologist appointment	Follow up of negative results (clinical)	Follow up of negative results (genetic)	Prevention measure[2]
A	Clinical	Yes	Yes	No	-	Drug therapy
B	Clinical	Yes	Yes	Surveillance every 5 years	-	Drug therapy
C	Clinical , plus DNA test	Yes	Yes	Depends on genetic test	No	Drug therapy
D	Genetic	Yes, plus clinical tests	Yes	-	No	Drug therapy
E	Genetic[3]	Yes, plus clinical tests	Only if mutation found	-	No	Drug therapy
F	Clinical	Yes	Yes	No	-	ICD
G	Clinical	Yes	Yes	Surveillance every 5 years	-	ICD
H	Clinical , plus DNA test	Yes	Yes	Depends on genetic test	No	ICD
I	Genetic	Yes, plus clinical tests	Yes	-	No	ICD
J	Genetic[3]	Yes, plus clinical tests	Only if mutation found	-	No	ICD

1. If screening test is positive, 2. For positive high risk results, 3 Genetic counsellor has a referring role.

3.3. Baseline probabilities and effectiveness data

Information on the effectiveness data and baseline probabilities applied in the model are summarised below and more detailed information is presented in Table 2.

Clinical tests - The sensitivity and specificity of the clinical tests were calculated according to the diagnostic value of the clinical tests for familial HCM and rates were derived from the literature. (7)

Genetic tests - DNA testing is considered by some to be the 'gold standard' method for diagnosing HCM(6). Expert opinion suggested a very high specificity of 100% (enabling the discharge of non mutation carriers) and high sensitivity for the model.

Proportion of mutation carriers at high and low risk of SCD - For the risk stratification tests, McKenna and Behr (2002)(8) have identified six potential markers of increased risk of SCD in HCM patients. Patients are considered at high risk of SCD when they have two or more risk factors and at low risk with one or no risk factors. These risk factors include history of previous cardiac arrest, family history of premature sudden death, and unexplained syncope. This algorithm was employed in the model and expert opinion suggested that around 25-30% of cases would be high risk in our target population.

Mortality rates - A recent study has examined the annual probability of SCD for those (mean age 33) identified at low and high risk from the risk stratification tests(3). These estimates were used in our model and applied to all ages (18-75 years). This assumption is supported by findings of no statistically significant differences in SCD rates with respect to age(9). As well as death from SCD, death from other causes was modelled using age and sex specific life tables for England and Wales (10).

Treatment - There is limited information concerning the effectiveness of both the primary prevention treatments for use in healthy populations, as they are used largely for the secondary prevention of cardiac events. Expert opinion was therefore used to provide estimates of the reduction in SCD risk associated with each therapy. As expected, these estimates differed from studies assessing treatment effectiveness as a secondary

prevention.(11-14) It was assumed that the effectiveness measures would remain constant throughout the patient's lifetime. With respect specifically to ICD, the implant requires invasive surgery, with a small risk of death. Expert opinion provided an estimate for our target population since there is no published information for a young and healthy population. Finally, we assumed that replacing the ICD batteries every five years did not involve any immediate risk of death.

Table 2. Summary of parameters used in the model

	Baseline	Min	Max	Ref	Distribution
Age start screening	18				-
Age end screening	76				-
Yearly discount rate costs	3.5%	0%	6%	(15)	-
Yearly discount rate effects	3.5%	0%	6%	(15)	-
Characteristics of the target population					
Prevalence of mutation	50%			(2)	-
Proportion of mutation carriers at high risk	27.5%	25%	30%	*	Beta
Annual probability of dying of the general population	-			(10)	-
Incremental annual probability of dying if mutation carrier					
Mutation carriers at high risk	5.3%	2.1%	8.5%	(3)	Beta
Mutation carriers at low risk	1%	0.3%	1.7%	(3)	Beta
Effectiveness of screening					
Sensitivity of clinical tests	61%	50%	88%	(7)	Beta
Specificity of clinical tests	87%	82%	100%	(7)	Beta
Sensitivity of genetic tests	99%	90%	100%	*	Beta
Specificity of genetic tests	100%	90%	100%	*	Beta
Effectiveness of treatment				*	
Reduction in SD risk due to drug treatment	0.50	0.40	0.70	*	LogNorm
Reduction in SD risk due to ICD	0.90	0.80	0.99	*	LogNorm
Incremental mortality risk due to ICD surgery	0.5%	0%	1%	*	Beta

*Expert opinion.

3.4. Cost data

Table 3 presents a summary of the resources and unit costs used in the model. The categories of resource use included: contact with health care professionals, genetic and clinical tests, prevention (drugs or ICD implantation), surveillance and prevention follow-up. Estimates for staff resource use and clinical tests were derived largely from discussions with cardiologists, geneticists and genetic counsellors. Resource use

information for the genetic test was derived from primary data collection in the Molecular Genetics Laboratory (Churchill Hospital, Oxford)

Unit costs were largely derived from the published literature or primary data collection (genetic test). For ICDs the costs associated with battery replacement are still to be published for the UK, therefore we assumed them to be 50% of the ICD implantation costs, occurring every 5 years, based on a previous study(1). Costs and effects were discounted at 3.5% per annum as recommended by the HM Treasury(15). Finally, all costs are expressed in 2003 prices and earlier costs used were adjusted to 2003 using the hospital and community health services (HCHS) inflation index(16).

Table 3. Base case resource use and unit costs

Base case	Unit Cost	Resource Use	Mean cost per episode	Range of costs/resource use	Reference
Genetic screening test					
Genetic counselling sessions	£113	2	£226	1-4 consultations	(17)
Cardiologist consultations	£109	4	£436	1-5 consultations	(16)
Genetic test	£110	1	£110	£107-£154	*
Total cost per episode			**£756**		
Clinical screening test					
Cardiologist consultations	£109	4	£436	1-5 consultations	(16)
12-led ECG	£29	1	£29	£12-£42	(18)
ECHO	£65	1	£65	£31-£68	(18)
Total cost per episode			**£530**		
Risk Stratification tests					
24h Holter Monitoring	£136	1	£136	£136-£202	(19)
Exercise Stress test	£66	1	£66	£28-£74	(18)
Total cost per episode		-	**£202**	£164-£278	
Drug Treatment					
Amiodarone 200mg	£0.23	365 days	£84	-	(20)
Pharmaceutical services fee	£1.45	4	£6	45 -90 days	(21)
Outpatient visits annually	£109	3	£327	2-3 visits	(16)
Readmission 3 days	£255	1	£255	0-2 readmissions	(1)
Total cost per episode		-	**£672**	£308-£933	
ICD implantation	£20,370	1	£20,370	£16,501-£26,781	(1)
ICD follow up					
Outpatient visits	£109	3	£327	1 readmission of 3 days – 2visits	(16)
Adjunctive therapy	£207	1	£207	-	(1)
Total cost per episode		-	**£534**	£425-£789	
Battery replacement every 5 years	£10,185	1	£10,185	25%-75% of ICD implantation	#
Surveillance					
Cardiologist consultation	£109	1	£109	-	(16)
12-lead ECG	£29	1	£29	£12-£42	(18)
ECHO	£65	1	£65	£31-£68	(18)

24h Holter Monitoring every 2 years	£136	1 every 2 years		Annually	(18)
Total cost per episode		-	**£271**	£220-£361	

Gamma distributions were fitted to the cost data.
*NHS Molecular Laboratory
#50% of ICD implantation cost

3.5. Analysis

Recent guidelines for analysis from the National Institute for Clinical Excellence (NICE) were followed where appropriate and possible(22). The choices among the 10 strategies for HCM cascade-screening are mutually exclusive. The different strategies were ranked in terms of their increasing cost and incremental cost-effectiveness ratios (ICERs) were calculated between adjacent options. Dominated and extendedly dominated strategies were then removed and the ICERs recalculated. To examine the robustness of the model results, we performed a one-way sensitivity analysis, in which the best-case and worst-case scenarios for the parameters in Tables 2 and 3 were evaluated. Probabilistic sensitivity analysis (PSA) using a second-order Monte Carlo simulation employing 1000 iterations, was then performed to generate a distribution for the incremental cost-effectiveness estimates provided by the Markov Model. The distributions for model input parameters used for the PSA(23) are presented in Tables 2 and 3. Finally, a cost-effectiveness acceptability frontier (24) was built on the results of this stochastic analysis to illustrate the uncertainty associated with the optimal screening strategy over a range of willingness to pay thresholds.

4. RESULTS

The expected life years and costs for patients undergoing the different screening strategies (at baseline) are presented in Table 4. The table highlights that using clinical screening with drug therapy (Strategy A) is the least expensive option (£3,072). However, this strategy also provides the least amount of life years (20.77 LYs).

Table 4. Expected years of life and costs by strategy

Strategy		Discounted Lifetime Cost per patient (£)	Discounted Life Expectancy per patient (LY)	Incremental Cost per Life Year (£/LY)
Clinical	A	£3,072	20.77	
Clinical	B	£3,896	20.77	(Dominated)
Genetic	E	£4,023	21.18	£2,363
Genetic	D	£4,243	21.18	(Dominated)
Clinical followed by genetic test	C	£4,291	21.18	(Dominated)
Clinical	F	£8,137	21.28	(Extendedly dominated)
Clinical	G	£8,962	21.28	(Dominated)
Genetic	J	£12,245	21.99	£10,125
Genetic	I	£12,465	21.99	(Dominated)
Clinical followed by genetic test	H	£12,513	21.99	(Dominated)

Overall, screening for HCM using only clinical tests (A, B, F, and G), with the same follow up prevention measure, yields a lower health benefit than using genetic testing (C, D, E, H, I and J). Those strategies using ICD to prevent SCD (F to H), save more lives than those using drug therapy (Strategies A to E). However, the associated cost of using ICDs is consistently higher, ranging from £8,137 to £12,513.

In addition, strategies which included 5 year surveillance for patients with negative screening results (B and G), produced a higher cost, although this is not coupled with an increase in life expectancy when compared with similar strategies (A and F) that did not include surveillance.

There was no difference in life expectancy between the different strategies which used genetic testing and the same prevention therapy. However, the strategies that first screened using clinical tests and then used a genetic test (C and H) or that involved cardiologists before screening (Strategies D and I) were more expensive.

In terms of incremental costs and effects, after excluding dominated and extendedly dominated strategies, compared to clinical screening and drug therapy (Strategy A), the next most cost-effective strategy was genetic screening, with the genetic counsellor having a referring role (E), at £2,363 per additional life year saved. Moving from

strategy E, the next most cost-effective strategy uses ICD treatment (Strategy J) at £10,125 per additional life year saved.

The results of the one-way sensitivity analysis suggest that the model results are robust to the values of most parameters. However, the results are most sensitive to the discount rate, probability of SCD in high risk mutation carriers and effectiveness of drug treatment (Table 5). In addition, the incremental cost-effectiveness ratio for the genetic versus clinical strategy (E vs. A) is sensitive to the proportion of mutation carriers at high risk of SCD, sensitivity of the clinical tests and specificity of both the genetic and clinical tests. The ICER between the two genetic strategies, which used alternative treatments (E and J) is most sensitive to the cost of ICD battery replacement and the effectiveness of ICD in preventing SCD.

Table 5. Key parameters identified in one-way sensitivity analysis.

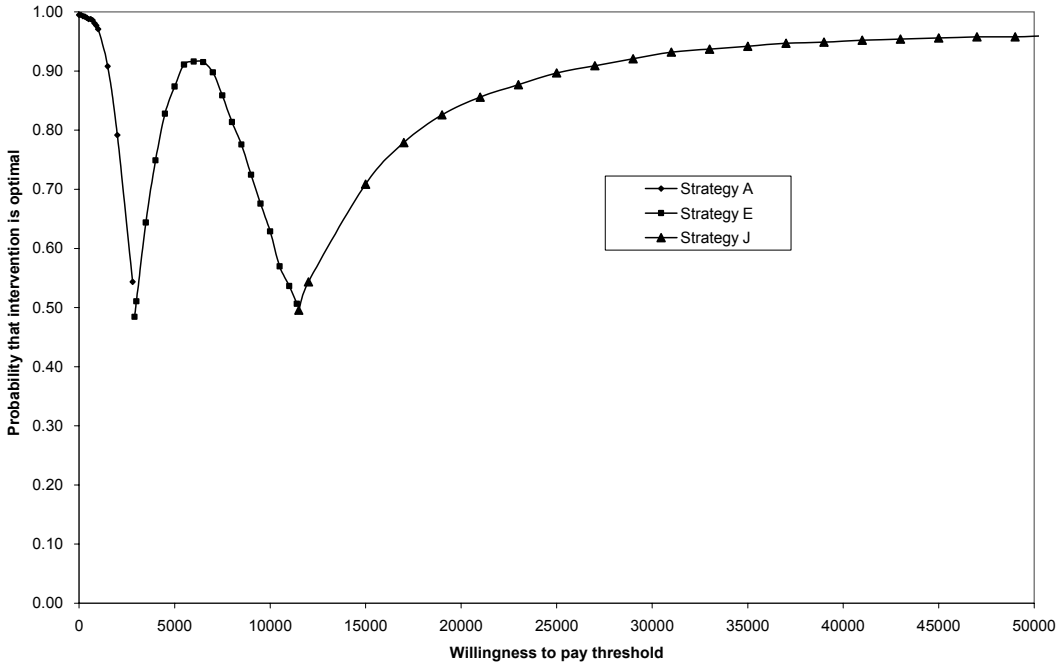
	Minimum parameter estimate*				Maximum parameter estimate*			
	Strategy#	**Disc. lifetime Cost**	**Disc. lifetime Effect**	**ICER**	**Strategy#**	**Disc. lifetime Cost**	**Disc. lifetime Effect**	**ICER**
SCD probability in high risk mut carriers	A E J	£3,318 £4,423 £12,734	21.61 21.78 22.19	 £6,359 £20,448	A E J	£2,905 £3,753 £11,790	20.15 20.77 21.81	 £1,384 £7,727
Effectiveness of Drug	A E J	£2,958 £3,840 £12,245	20.61 20.90 21.99	 £2,961 £7,745	A E J	£3,220 £4,265 £12,245	21.00 21.54 21.99	 £1,934 £17,600
Effectiveness of ICD	A E J	£3,072 £4,024 £11,602	20.78 21.18 21.75	 £2,365 £13,356	A E J	£3,072 £4,024 £12,988	20.78 21.18 22.27	 £2,363 £8,177
Cost of ICD battery replacement	A E J	£3,072 £4,024 £9,593	20.78 21.18 21.99	 £2,363 £6,859	A E J	£3,072 £4,024 £14,897	20.78 21.18 21.99	 £2,363 £13,390
Proportion of mutation carriers at high risk	A E J	£2,807 £3,544 £6,584	21.40 21.57 21.87	 £4,640 £10,125	A E J	£3,109 £4,085 £13,054	20.70 21.12 22.00	 £2,268 £10,125
Sensitivity of Clinical Tests	A E J	£2,691 £4,024 £12,245	20.66 21.18 21.99	 £2,567 £10,125	A E J	£4,006 £4,024 £12,245	21.06 21.18 21.99	 £155 £10,125
Specificity of Clinical Tests	A E J	£3,237 £4,024 £12,245	20.78 21.18 21.99	 £1,953 £10,125	A E J	£2,640 £4,024 £12,245	20.78 21.18 21.99	 £3,435 £10,125
Specificity of Genetic test	A E J	£3,072 £4,382 £12,603	20.78 21.18 21.99	 £3,254 £10,125				

ICER: Incremental cost-effectiveness ratio
*Minimum and maximum estimates as defined in Tables 2 and 3.
#Dominated and extended dominated options were excluded. In dominated options the next more effective strategy costs less, and with extended dominance, once dominated options have been excluded, if the next more effective strategy has a lower incremental cost-effectiveness ratio then this strategy is also excluded.

The results of the PSA illustrate that the 95% uncertainty intervals for genetic versus clinical strategies (E vs. A), vary from £905 to £8,161 per additional life year gained. These uncertainty intervals were much wider between the two genetic strategies when different treatments were used (E compared to J), ranging from £5,662 to £45,380 per additional life year gained. This finding reflects the lower level of certainty regarding the comparison of the effectiveness of ICD with drug therapy.

The cost-effectiveness acceptability frontier (Figure 2) shows that if the decision makers are willing to pay around £6,000 for an additional life year saved, genetic testing with amiodarone as the preventive measure (Strategy E), will be the most cost-effective strategy in this patient population 92% of the time. However, if decision makers are willing to pay £30,000 for an additional life year saved, genetic testing combined with ICD as the preventive measure (Strategy J) will be the most cost-effective strategy 93% of the time. No other strategies (besides A, E and J) were found to be optimal at any given threshold value. The discontinuities present in the frontier reflect the situation where the strategy with the highest expected net benefit (25;26) at a given threshold/ceiling ratio is not necessarily the one with the highest probability of being optimal. These discontinuities occur because the distributions of the incremental net benefit between the strategies under comparison are skewed. The information provided in Figure 2 may be important to decide whether more information should be required to aid the decision concerning the optimal screening approach for HCM. (24).

Figure 2. Cost-effectiveness acceptability frontier for additional life years saved. Strategy A, E, and J were compared with each other at different threshold values.



5. DISCUSSION

This paper has presented the preliminary results of a study designed to examine the cost-effectiveness of alternative screening options for those at risk of sudden cardiac death. The main results show that genetic screening is more likely to be cost-effective than clinical screening (standard approach) (Strategy A vs E). However, the choice between the alternative prevention (treatment) measures is less obvious. This is reflected by the wide 95% uncertainty limits of the incremental cost effectiveness ratio resulting from the comparison of ICD treatment with drug therapy (J vs E). In addition, assumptions such as the cardiologist managing all patients (negative and positive results) or performing the clinical tests first and then the DNA test failed to improve effectiveness, yet these scenarios were more expensive.

The results also illustrate that small pathway differences between strategies with the same screening (clinical or genetic) and prevention procedure (ICD or drug) did not lead to increases or reductions in effects. For example, the addition of surveillance for all negative results, cardiologist consultations before DNA testing results, or having clinical

followed by genetic screening only impacted upon the costs of strategies. In particular, clinical surveillance every 5 years for negative results did not produce any benefit in life years gained because it was assumed that clinically false results would remain so through the patient's lifetime. This is because uncertainty surrounds a hypothesis that HCM may appear or progress with age, and the heart characteristics that did not initially indicate HCM within a patient are unlikely to change over time (e.g. athlete's heart). Nevertheless, this assumption was changed and did not alter the results (data not shown).

In terms of the potential limitations arising from this study, there are several which need to be taken into account. First, the sensitivity and specificity of the DNA testing are set to high levels in our model, which the literature and expert opinion suggested as being appropriate. In order to address this issue research is being undertaken within the Oxford Genetics Knowledge Park to try and provide more empirical data on these rates. A further and similar concern relates to the estimates of sensitivity and specificity for the clinical tests. Our estimates were derived from a study with a relatively small sample size (155 adults), composed of men and women ranging from 18 to 80 years of age (7), rather than our target population of teenagers. However, these estimates are based on a study of fairly high quality (STARD guidelines), which is the only available evidence of genetic testing as the "gold standard", for a healthy population composed of first-degree relatives of HCM patients. Further, such concern over sensitivity and specificity is not unique to this clinical area and is common in screening models generally, such as cervical cancer screening models. Finally, whilst both these limitations are important, it is interesting to note that the uncertainty surrounding the accuracy of both clinical and genetic tests did not greatly influence our model predictions, as this was reflected in the relatively small uncertainty limit when genetic was compared to clinical screening (Strategy E vs A).

A potentially more concerning limitation is related to the effectiveness of the SCD prevention measures. Evidence suggests that ICD could be more effective in preventing SCD than amiodarone. However, there is no RCT with a population composed of first-degree relatives, nor an observational study which is compatible with our target

population. In our study, expert opinion provided estimates on what the mean efficacy for both prevention measures was likely to be. Nevertheless, ICD is more costly than amiodarone. If the evidence concerning the effectiveness is accurate, our model predicts that ICD is more cost-effective than amiodarone in this context. This uncertainty requires to be addressed more fully.

In addition to the above limitations, there are a number of issues which need to be considered before the introduction of DNA testing for SCD can be recommended for use in routine clinical practice. One such issue is the uptake of DNA testing and the demand from cardiologists (even clinical geneticists) and patients alike. With respect to cardiologists, potential reasons why they may not refer patients for DNA testing could be linked to questions of how to appropriately treat these patients, particularly if patients are asymptomatic. ICD implantation in particular is a highly invasive intervention. In addition, there is also a lack of a strong genotype-phenotype relationship with HCM. The expression of mutations is heterogeneous and HCM appears to be a complex inherited trait determined by other genetic and environmental factors.

In terms of the demand for DNA testing from patients, in our model we assumed that all patients would accept to undertake the DNA testing. However, this assumption could be unrealistic and lower patient numbers could influence the cost-effectiveness results and make the genetic screening less cost-effective. To address this question, a set of qualitative interviews and a discrete choice experiment are currently underway to elicit patient views and preferences for DNA testing for genetic linked SCD diseases, including HCM.

In conclusion, the results presented in this paper suggest that the use of genetic information in the diagnosis and management of CVD has the potential to provide a cost-effective approach to the primary prevention of sudden cardiac death. However, these results are very preliminary and more research is being undertaken to improve the HCM model. In particular, some of the concerns related to the sensitivity and specificity

parameters are being addressed. Research is also being undertaken to explore the expected value of perfect information (EVPI) associated with this study. Finally, we are examining more fully the implications of DNA testing creating the potential to discharge individuals with a negative mutation, who would previously have remained under clinical surveillance. This clinical surveillance involves costs to the NHS and dis-benefits to individuals in terms of anxiety associated with the uncertainty of whether they are likely to develop HCM and be at risk from SCD.

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