Details of incidental finding-specific modeling

Familial Hypercholesterolemia (FH)

We based our estimates of the costs and effects for disclosing *FH*, an autosomal dominant hyperlipidemia most often caused by pathogenic variants in the *LDLR* gene, on a systematic review and technology appraisal conducted for the United Kingdom's Health Service that evaluated different approaches to screening for FH in England and Wales.(19, 20) The authors estimated that the gain in life years with treatment of FH would be highest when started early (approximately 7 and 9 years in men and women, respectively, who were 16-24 years of age), and decreased with increasing age (0.3 and 3.4 years at age 45-54). We assumed that there was no incremental benefits or costs associated with returning incidental findings related to familial hypercholesterolemia for individuals over the age of 55 as these individuals would be identified clinically through recommended lipid screening. The authors assumed that patients found to have FH would receive statins (70% simvastatin 40mg daily and 30% atorvastatin 20mg daily) and an annual general medical examination; the age-specific reduction in the risk of cardiac events with treatment was estimated directly from a UK cohort of 1185 patients with heterozygous FH followed prospectively since 1980.

We did not include estimates from another CEA of cascade genetic testing in *FH* (Nheara, 2011) in our model primarily because the results are presented for relatives who are assumed to be a combination of both children (age 18-25) and siblings (age 45-49) of the proband. The CEA by Marks el al. had shown that the age individuals were diagnosed with *FH* and subsequently started treatment had a substantial impact on the resulting gain in life expectancy; we therefore felt that extracting an estimate of benefit from a heterogeneous group of relatives of very different ages was not appropriate, particularly as we intended to report results across different ages.

Lynch Syndrome

Mvundura and colleagues conducted a cost-effectiveness analysis of cascade genetic testing strategies for Lynch syndrome(16), the autosomal dominant susceptibility of colon and other cancers due to pathogenic variants in several genes. The authors assumed that following identification of a pathogenic variant approximately 80% of asymptomatic relatives would undergo surveillance colonoscopy every two years. Increased surveillance was associated with a reduced risk of developing and dying from colorectal cancer (62% and 67% relative risk reduction, respectively), following results from a study of colonoscopy surveillance in patients with pathogenic variants in Lynch syndrome genes.(36) Incremental costs and QALYs for the return of Lynch syndrome results among relatives were not directly reported in the published paper, but were provided by the authors upon request (personal communication with Dr. Mercy Mvundura, February 2013). Dr. Mvundura also provided a copy of the original CEA model to facilitate sensitivity and scenario analyses (see below for details).

The projected incremental gain in life expectancy with disclosure of Lynch syndrome results from our model was similar to those from a previously published CEA evaluating population-based screening strategies for Lynch syndrome, but differed from another CEA of genetic testing in Lynch syndrome patients and their relatives. We estimated that 25 year-old mutation carriers would gain approximately 1.5 discounted QALYs (1.74 life years) by return of Lynch syndrome findings.

Dinh et al. (2011) evaluated several population-based screening strategies for Lynch syndrome and reported that 25-year-old mutation carriers would gain approximately 1.3 QALYs under a universal Lynch syndrome screening policy. Dinh et

al. assumed 81% adherence to Lynch syndrome screening recommendations among known mutation carriers.

Ladabaum et al. reported much lower estimates (0.485 and 0.506 discounted life years) using a strategy of IHC with BRAF testing compared to no active effort to diagnose Lynch syndrome; however, these estimates were (a) based on the assumption that only 52% of relatives would accept testing, (b) evaluated a less optimal testing strategy (IHC triage versus upfront genetic testing) than we did, and most importantly for our purposes (c) assumed that 50% of relatives who did not receive genetic testing for LS would adhere to Lynch syndrome screening recommendations (and 80% adherence for known mutation carriers). A subsequently published CEA by Wang et. al. incorporated quality-of-life adjustments into the Ladabaum et al. model and reported QALYs; however, they did not report estimates specifically for relatives and we therefore could not incorporate the estimates from this CEA into our model directly. Although it may be reasonable to assume 50% adherence to Lynch syndrome screening among untested relatives who learn of their increased risk from family history, such an assumption is not appropriate when considering Lynch syndrome mutations as a possible incidental finding and we therefore did not incorporate estimates from Ladabaum et al. (2011) in our model.

We were not able to compare the incremental costs of treatment and screening across the different studies given the difficulty in separating the costs of genetic testing from those of screening and treatment; however, we incorporated a similar level of uncertainty into our probabilistic sensitivity analyses regarding estimates for incremental costs as those for health benefits and conducted several extreme value scenarios to explore the robustness of our findings.

Breast and Ovarian Cancer

We derived estimates of incremental costs and QALYs saved by the return of results for breast and ovarian cancer risk due to pathogenic variants in *BRCA1 or BRCA2* from two sources: (1) a systematic review and economic evaluation conducted for the United Kingdom's Health Service that evaluated different genetic testing programs for women suspected of having *BRCA1 or BRCA2* mutations(22) and (2) a CEA by Holland *et al.* that evaluated testing women who were 35-years old for breast cancer susceptibility genes(21). The estimates of incremental costs and QALYs associated with returning test results were similar in both studies. We derived our base case estimates of costs and QALYs from the systematic review primarily because it presented results for different age categories; we used the results from Holland *et al.* in our sensitivity analyses of penetrance (see below for details). The model used in our base case assumed that prophylactic surgeries were utilized at the rate expected for women with a pathogenic variant, which depended on their current age. The overall rate of mastectomy use, with uptake modeled over 5 years following disclosure of positive genetic test results, was 42% for mastectomy and 54% for bilateral salpingo-oophrectomy.

Hypertrophic/dilated cardiomyopathy and Long QT Syndromes

Two recently published cost-effectiveness studies of genetic testing of asymptomatic family members were used for estimates of the incremental costs and life years saved with return of pathogenic variants associated with hypertrophic or dilated cardiomyopathy and Long QT syndromes (17) (23), both of which are autosomal dominant conditions caused by pathogenic variants in multiple genes which carry the risk of sudden death. These authors did not report the incremental costs and effectiveness for returning results to asymptomatic individuals. We therefore

reconstructed disease-specific decision models using Markov modeling techniques for these conditions, and in so doing, confirmed the key model inputs that were used in the original publications with several clinical genetics experts (GJ, CG, and WB; see Table S1). We made two important changes to the originally published models. First, we increased the cost of implanting cardiac defibrillators and yearly maintenance to account for the higher costs of this treatment in the US relative to other countries in which the models were originally developed(37). Second, we assumed in our base case that individuals would be 45 years old at the time they received the genetic test results as compared to 20 or 10 years old in the models of genetic testing for hypertrophic cardiomyopathy and Long QT syndromes, respectively. Both original decision models assumed that the increased annual risk of sudden cardiac death remained constant over the course of an individual's lifetime(38); the health benefits associated with returning a genetic test result for these conditions therefore decrease with age. As some evidence suggests that affected individuals with Long QT syndromes diagnosed after age 40(39) may not need to be treated, we also explored the impact of omitting this condition in sensitivity analyses. Treatment for both conditions involved a combination of surveillance, medications (antiarrhythmic medications or beta blockers) and implantable cardiac defibrillators (ICDs). The age of probands at the time of diagnosis varied from 44 to 48 years old in the CEA of genetic testing in cardiomyopathy.

Arrhythmogenic right ventricular cardiomyopathy (ARVD) and Malignant Hyperthermia Susceptibility

We did not identify any published cost-effectiveness analyses for the autosomal dominant disorders ARVD, which also increase risk of sudden death, or malignant hyperthermia, the genetic susceptibility to a potentially fatal anesthesia reaction. We therefore created decision models for each of these conditions using Markov modeling techniques. We obtained primary data about natural history progression, penetrance, and disease management for each condition from GeneReviews.(40, 41) We supplemented these data with expert opinion and additional literature sources for several key parameters. For ARVD we assumed that the increased annual risk of sudden cardiac death with a pathogenic variant was 0.6% (roughly a 30% lifetime risk) in our base case analysis for individuals who do not receive treatment. Importantly, ARVD is a rare cardiac condition for which there are no clear treatment guidelines, particularly the use or timing of ICD, or definitive data on the effectiveness of such interventions. We therefore evaluated a wide range of potential values for these uncertain parameters. For malignant hyperthermia, we conservatively assumed that 10% of individuals with an unknown pathogenic variant who underwent surgery would experience a malignant hyperthermia event, requiring the administration of dantrolene sodium and increasing the risk of death during surgery by 0.174%(42). We assumed that all individuals with a known malignant hyperthermia pathogenic variant would undergo surgery with a VaporClean charcoal filter and non-triggering agents, which would require additional costs in each surgery but also eliminate the increased risk of death.

Rare genetic conditions

We collected information from GeneReviews on natural history progression and recommended disease management for each of the 17 rare conditions that are expected to collectively account for ~5% of incidental findings from the ACMG list.(18) As these conditions are rare, there were often limited data to support recommended treatment guidelines or describe natural histories. We therefore conservatively assumed that disclosure of these incidental findings would not provide any benefit to patients, and that the additional costs associated with any screening or prophylactic management would

not offset future treatment costs. Furthermore, we selected from the list of rare conditions a single disease that was expected to be one of the most expensive to manage prophylactically (Peutz-Jeghers syndrome) based on the recommended treatment guidelines, and assumed all rare incidental findings would incur similar lifetime incremental costs. Following surveillance guidelines in GeneReviews, we assumed that individuals with an incidental finding for Peutz-Jeghers syndrome would receive an annual breast MRI, a colonoscopy every 18 months, and a small bowel screening using video capsule endoscopy every three years for the remainder of their expected lifetime.(39) We explored the impact of all of these assumptions through sensitivity analyses.

Patient populations evaluated in our model

The condition-specific models described above were used to estimate the incremental costs and QALYs associated with disclosure of an incidental finding related to that condition, and in the case of cardiomyopathy and Lynch syndrome, were used to model the actual patient population receiving genomic sequencing. The higher risk of death for these conditions meant that the incremental QALYs gained by disclosing an incidental finding were, on average, lower than for a healthy individual. We assumed that the management of patients would not differ across the patient populations (i.e., all patient groups would receive the same diagnostic workup and/or treatment); the incremental costs are lower in cardiomyopathy or colorectal cancer because of the higher rate of deaths was associated with a lower utilization of ongoing interventions. For the cardiac conditions, Lynch syndrome, and *MH* susceptibility we could model the increased risk of death and its consequences directly. For *FH* and hereditary breast and ovarian cancer conditions, we back-calculated the initial and ongoing costs from the inputs provided in the original publications, and approximated the difference in ongoing costs as proportional to the difference in life expectancy between otherwise healthy individuals and those with colorectal cancer or cardiomyopathy, respectively, separately for each 10-year age group. For health benefits, we assumed that disclosing *FH* or *BRCA1* and *BRCA2* variants to colorectal cancer or cardiomyopathy patients would correspond to the same relative gain in QALYs (as calculated for each 10-year age category); the reduced overall expected QALYs in these patient populations therefore translated into lower absolute gains. Lastly, we did not change the incremental costs associated with disclosure of incidental findings for rare conditions across different populations, but we explored the robustness of this assumption through scenario analyses.

Sensitivity and Scenario Analyses

Probabilistic Sensitivity Analyses

We simulated sampling distributions for each parameter in our model to perform probabilistic sensitivity analyses. We used distributions that reflected uncertainty regarding condition-specific model inputs (for hypertrophic or dilated cardiomyopathy, long QT syndrome, ARVD, and malignant hyperthermia) from the original CEAs or incremental costs and health outcomes directly (for *FH*, *BRCA 1* or *BRCA 2*, Lynch syndrome conditions, and all other rare conditions). We created distributions for estimates of prevalence in which the 95% confidence intervals corresponded approximately to the ranges reported in GeneReviews and the references cited therein. The full list of distributions and hyperparameters used in our probabilistic sensitivity analyses are given in Table S1.

Varying Age

We were able to vary the age of the cohort directly in our models of hypertrophic or dilated cardiomyopathy, long QT syndrome, ARVD, malignant hyperthermia, and all other rare conditions. The original CEAs for *FH* and *BRCA1/2* reported estimates of incremental costs and health outcomes separately by age groups, which we were able to incorporate into our model. We obtained estimates of incremental costs and health effects for different age groups for Lynch syndrome directly from the original CEA.

Reducing penetrance

For the cardiac conditions and malignant hyperthermia, we reduced the annual risk of sudden cardiac death or risk of death from anesthesia exposure directly in the relevant Markov model. We obtained from Holland *et al.* the incremental costs and QALYs gained among true and false positives of a *BRCA1* or *BRCA2* genetic test(21) and derived incremental costs and QALYs for lowered penetrance by increasing the relative proportion of women with a false positive result. We obtained estimates of incremental costs and QALYs for different estimates of penetrance for Lynch syndrome by modifying the original model directly. We could not vary penetrance directly for *FH*. Instead, we assumed that reduced penetrance would correspond to proportionally fewer health benefits gained from disclosure, but that there would be no difference in treatment patterns or lifetime costs. These assumptions are conservative for *FH* because the surveillance and early interventions are not associated with significant morbidity, and would likely be pursued even in the presence of reduced penetrance.

Table S1. Summary of distribution and hyperparameters policy model parameters.

Prevalence estimates	Distribution	Mean	SE	Alpha	Beta
Romano-Ward Long QT Syndromes Types 1, 2 and 3	Beta			20.00	99979
Malignant hyperthermia susceptibility	Beta			2.00	4997
Arrhythmogenic right ventricular cardiomyopathy	Beta			4.44	4995
Hypertrophic Cardiomyopathy; Dilated cardiomyopathy	Beta			10.00	4989
Lynch Syndrome	Beta			11.36	4988
Hereditary Breast and Ovarian Cancer	Beta			12.50	4987
Familial hypercholesterolemia	Beta			3.60	4995
Hypercholesterolemia					
Incremental cost given +IF returned	Normal	16748	4187		
Incremental life years gained per IF returned	Normal	0.78	0.19		
Malignant Hyperthermia					
Proportion IF+ individuals who have MH event | surgery	Beta			0.495	4.53
Total number of inpatient surgeries per year (in United States)	Normal	51,400,000	6556122		
Cost of Dantrolene (36 vials)	Normal	$2,340	334		
Costs for anesthesia prep given +IF (VaporClean charcoal filter)	Normal	$75	19		
Risk of death given MH susceptibility + surgery	Normal	0.00174	0.000783		
Lynch					
Incremental cost of surveillance and treatment given +IF returned	Normal	$3,500	875		
QALYs saved per IF returned	Normal	0.95	0.24		
BRCA 1/2					
Incremental costs of surveillance and treatment given +IF returned	Normal	-$5,300	1870		
Incremental QALYs saved per IF returned	Normal	0.189	0.047		
Hypertrophic Cardiomyopathy					
Additional annual risk of sudden cardiac death, given:					
High Risk	Beta			7.9	141
Low Risk	Beta			4.0	395
Transition from Low to High Risk	Beta			1.2	398
Annual probability of heart failure death	Beta			10.2	2538
Annual probability of stroke (age $\leq$40 years)	Beta			12.8	3984
Annual probability of stroke (age 41–60 years)	Beta			18.6	2375
Annual probability of stroke (age >60 years)	Beta			6.8	587
Probability of death given stroke	Beta			9.5	33

Proportion of mutation carrier at low (vs high) risk HCM at initial diagnosis	Beta			32	8
Risk of death with ICD implantation (HCM model only)	Beta			5	403
Relative Risk of SCD with ICD	Beta			4	96
Arrhymogenic Right Ventricular Cardiomyopathy					
Additional annual risk of sudden cardiac death	Beta			6.0	940.0
Relative Risk Reduction of SCD with ICD	Beta			7	7
Relative Risk Reduction of SCD with antiarrhythmic drugs	Normal	0%	0.025		
Proportion of patients receiving ICD	Beta			2	1
Long QT Syndromes					
Additional annual risk of sudden cardiac death	Beta			11.2	2788.8
Annual risk of developing symptoms	Beta			8.7	291.3
Relative Risk Reduction of SCD with ICD	Beta			4.99	494.01
Relative Risk Reduction of SCD with beta blockers	Beta			24.5	24.5
Proportion of patients receiving ICD	Beta			3	7
Utility with ICD (Long QT model only)	Beta			93	6
Cardiac Conditions Costs					
ICD implantation	Normal	$41,750	6760		
Low Risk HCM surveillance, annually	Normal	$939	251		
ICD maintenance, annually	Normal	$11,000	3061		
Stroke hospitalization	Normal	$13,936	1137		
Heart failure hospitalizations before death	Normal	$6,563	1674		
Beta blockers, annually	Normal	$300	128		
Statins, annually	Normal	$1,200	434		
Rare conditions, combined					
Incremental cost given +IF returned	Normal	$54,030	25000		
Incremental QALYs saved per IF returned	-	0	-		
Genetic testing and counseling					
Additional cost of pre-test genetic counseling (for potential of IFs)	Gamma			9	7
Cost of post-test genetic counseling (for individuals with +IFs)	Normal	$250	25		
Cost to review variants and determine pathogenicity	Normal	$95	20		

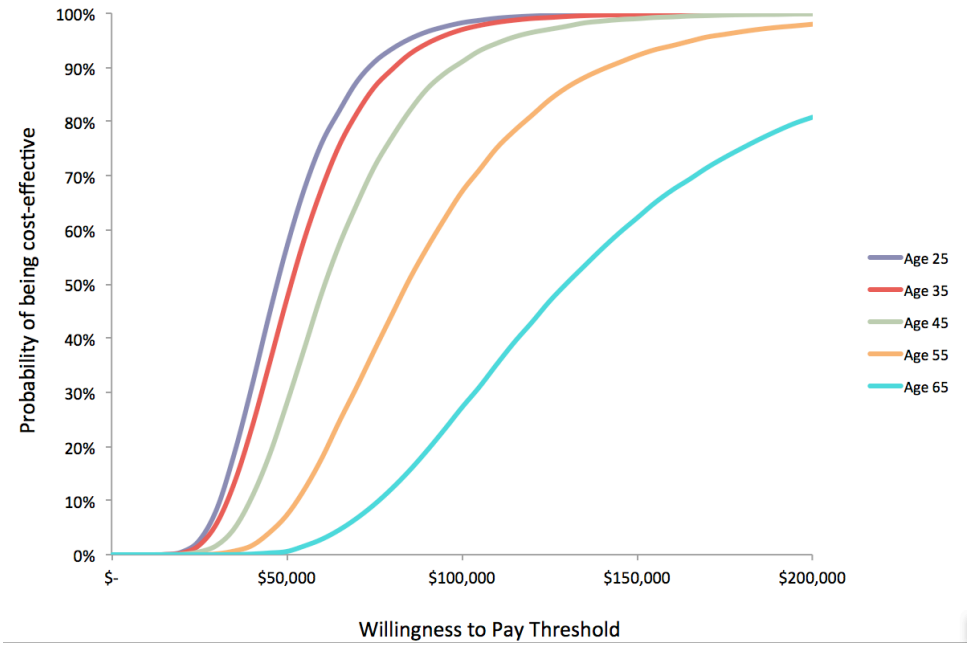
SE=Standard Error

Table S2. Incremental cost, QALYs gained, and ICERs of returning individual incidental findings to a cohort of 10,000 (a) generally healthy individuals, (b) patients with cardiomyopathy, or (c) patients with colorectal cancer across different age and assumptions about reduced penetrance.

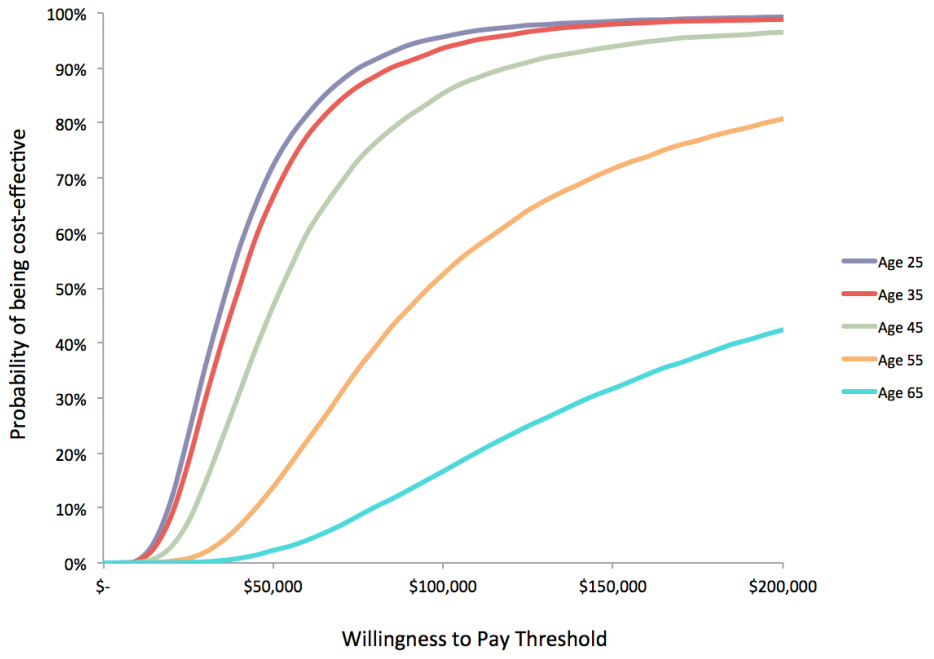
	Age at time of Genome Sequencing														
Reduced Penetrance	25			35			45			55			65		
	Costs	*QALYs*	*ICER*	*Costs*	*QALYs*	*ICER*	*Costs*	*QALYs*	*ICER*	*Costs*	*QALYs*	*ICER*	*Costs*	*QALYs*	*ICER*
	Generally healthy individuals														
0%	$4,569,000	100	$45,700	$4,278,200	86	$49,700	$3,918,600	67	$58,600	$3,500,000	44	$79,100	$3,006,200	25	$120,500
10%	$4,591,700	93	$49,500	$4,296,900	80	$53,800	$3,932,700	62	$63,600	$3,509,500	41	$85,800	$3,011,600	23	$130,800
20%	$4,614,200	85	$54,100	$4,315,300	73	$59,000	$3,946,600	57	$69,700	$3,518,800	37	$94,100	$3,016,900	21	$143,800
30%	$4,636,400	77	$59,900	$4,333,500	66	$65,400	$3,960,400	51	$77,500	$3,528,000	34	$104,700	$3,022,100	19	$160,400
	Cardiomyopathy Patients														
0%	$908,100	29	$31,100	$897,100	26	$34,100	$895,900	20	$44,800	$900,600	11	$81,500	$901,700	4.2	$214,600
10%	$909,200	27	$33,600	$897,900	24	$36,800	$896,500	19	$48,400	$901,100	10	$88,100	$902,100	3.9	$230,800
20%	$910,400	25	$36,700	$898,600	22	$40,100	$897,100	17	$52,700	$901,700	9.4	$96,000	$902,600	3.6	$250,100
30%	$911,500	22	$40,500	$899,400	20	$44,300	$897,700	15	$58,200	$902,300	8.5	$105,800	$903,000	3.3	$273,700
	Colorectal Cancer Patients														
0%	$3,952,100	52	$75,600	$3,666,600	43	$84,700	$3,253,700	32	$100,200	$2,767,000	21	$129,000	$2,271,300	12	$190,100
10%	$3,970,600	49	$80,700	$3,681,400	41	$90,700	$3,264,100	30	$107,600	$2,773,100	20	$139,100	$2,274,000	11	$206,100
20%	$3,989,000	46	$87,100	$3,696,000	38	$98,100	$3,274,300	28	$116,900	$2,779,000	18	$151,900	$2,276,600	10	$226,400
30%	$4,007,100	42	$95,300	$3,710,500	34	$107,800	$3,284,500	25	$129,000	$2,784,900	17	$168,400	$2,279,200	9.0	$252,800

Figure S1. Probability that returning incidental findings is cost effective at varying willingness to pay thresholds (dollars per QALY) in (a) generally healthy individuals, (b) patients with cardiomyopathy, and (c) patients with colorectal cancer.

(a)



(b)



(c)

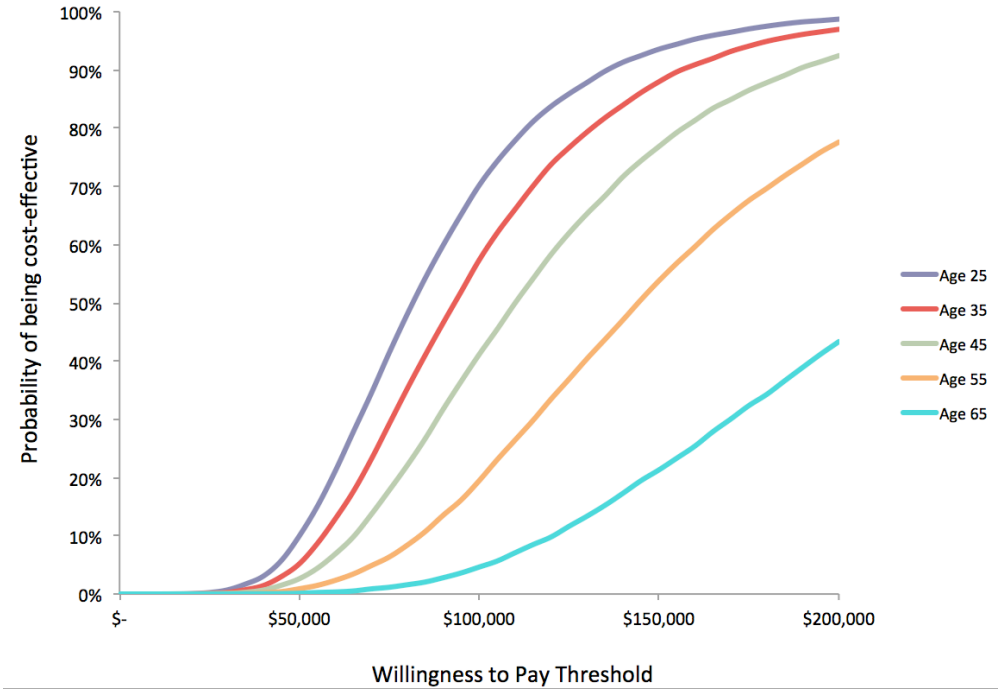

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability of being cost-effective
$-
$50,000
$100,000
$150,000
$200,000
Willingness to Pay Threshold
Age 25
Age 35
Age 45
Age 55
Age 65

Figure S2. Probability that returning incidental findings is cost effective at a $100,000 per QALY willingness to pay threshold across a range of sequencing costs and ages for primary screening.