

***Technical Appendix for Age at Initiation and Frequency of Screening to Detect Type 2 Diabetes: A Cost-Effectiveness Analysis***

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This appendix provides information and results that were not included in the published paper because of space limitations. For consistency, all repeated references have kept the same reference numbers as those in the print version of the paper.

**Description of the Archimedes model**

The Archimedes model is a trial-validated, clinically detailed simulation model of human physiology, disease progression, and healthcare delivery. The core of the model is a set of algebraic and differential equations representing the physiological pathways pertinent to diseases and their complications. Currently the model includes coronary artery disease, diabetes and its complications, congestive heart failure, stroke, hypertension, and more, in a single integrated model. Use of a single model enables Archimedes to compare a wide range of treatments, guidelines and performance measures using a consistent methodology that represents the relationships between different conditions in a physiologically realistic way. It also enables the model to address co-morbidities, syndromes that span multiple organ systems, drugs that have multiple effects, and combinations of treatments. The use of differential equations preserves the continuous nature of biological variables and the interactions between them, as well as the continuous nature of time. Diseases and clinical outcomes are defined in terms of the underlying variables, enabling diseases to occur and progress in the same continuous fashion as in reality, without the need for artificial “states” or annual time-steps.

Interventions, both to prevent diseases and to manage them when they occur, are modeled at the level of the underlying biology. The model also includes signs and symptoms; patient and provider behaviors; office visits and hospital admissions; tests and treatments;

care delivery protocols; performance and compliance; utilization; and costs. The accuracy of the model is checked using a variety of techniques, most importantly the simulation of epidemiological studies and clinical trials, comparing the model's results with the observed results. To date, the model has been validated against more than 50 major clinical trials. To conduct simulations we use person-specific data to create simulated people that match real people with respect to factors such as demographics (e.g. age, sex), risk factors and behaviors (e.g. smoking), physiological variables (e.g. blood pressure), past medical history, current signs and symptoms, and current medications. For this particular analysis, a simulated population was created to match the US population not yet diagnosed with diabetes and approximately age 30. The baseline demographic and biomarker values of patients in the simulation are shown in **Table A1**.

### **Validation of the model for the population being screened for diabetes**

The accuracy of the Archimedes model has been validated by simulating a large number of epidemiological, basic science, clinical and health service research studies, as well as controlled clinical trials (14). There are no clinical trials of screening for diabetes against which to validate the model. However, the model has been validated for aspects of physiology that determine the effectiveness of screening, specifically the incidence rates at which people develop diabetes as a function of age, sex, and race/ethnicity; and the rates at which hyperglycemia progresses in those who are at risk for diabetes, as well as those who are newly diagnosed with the condition.

Specifically, the model has been validated against epidemiological studies of the incidence of diabetes in several different populations (e.g. White males/females, Hispanic males/ females, Black males/females, Asian-Americans, etc.). An example is shown in **Figure A1** which compares the predicted and actual incidence rates of diabetes in White

males. The figure does not show error bars, but the model's calculated results are well within the confidence intervals of the actual incidence rates. Subsequently, the incidence of diabetes has been updated with data from NHANES III and validated against NHANES 1999-2004 (23). In addition, we have tested the accuracy of the model in calculating the progression of hyperglycemia and the development of diabetes in people who have elevated glucose levels but do not yet have diabetes – a group that is very pertinent to an analysis of screening. We did this by simulating the Diabetes Prevention Program (DPP). This was a prospective, blinded validation, performed and reported before the DPP's results were made public. The results for the progression of hyperglycemia and development of diabetes, as well as the effects of lifestyle modification and Metformin, are shown in **Figures A2 and A3**. The predicted results are well within the confidence limits of the real results. We have also validated the model's accuracy in calculating the progression of hyperglycemia in people with newly diagnosed diabetes (the control group in the UKPDS). This validation is shown in **Figure A4**. These validations against epidemiological studies, the DPP, and the UKPDS indicate that the model is accurately calculating the biomarkers screening is intended to measure. **Figures A3 and A4** were not published in Eddy et al. (14) because that paper focused on clinical trials and their primary endpoints, not biomarkers.

A blinded validation of the CARDS trial showed the model to be accurate in predicting the rates of heart attacks and strokes in people with diabetes (16). More detail is shown in **Table A2**. Of note, while this validation exercise showed the model to be very accurate in calculating the natural history and incidence of coronary artery disease and cerebral vascular disease, as well as the effect of atorvastatin on coronary artery disease, it underestimated the effect of atorvastatin on reducing strokes (16% vs. 56% relative

reductions). At the time of the validation there was no information available about the drug-specific effect of atorvastatin on strokes, and the model's representation of atorvastatin on coronary artery plaque was based on the effect seen for other statins. The effect of atorvastatin in the model has subsequently changed to reflect what appears to be a drug-specific effect of atorvastatin on cerebral vascular disease.

### **How the Archimedes model addresses uncertainty**

The Archimedes model captures uncertainty and randomness in a variety of ways. They include:

- The chance that any particular individual will get a condition (subject to their risk factors, etc.), when they will get the condition, how rapidly the condition will progress, what symptoms will occur and when, what outcomes will occur and when, how patient's physiologies will respond to treatments, etc.
- The accuracy of tests (e.g. what the reported FPG level will be, as a function of the patient's true FPG when the test is performed).
- The behaviors of practitioners (e.g. the chances they will follow a particular guideline, what treatment they will choose as the first-line treatment, what further tests will be performed, etc). These parts of the model represent variations in practice patterns and imperfect performance.
- The behaviors of patients (e.g. whether they will change a behavior such as smoking, whether they will follow a provider's recommended treatment). These parts of the model capture variations in compliance.

All of these types of uncertainty and chance are represented in the model by random variables. When a particular individual is simulated, values are assigned to each random

variable using standard methods. The outcomes for that individual are then calculated for that set of values. This means that if a particular person were “re-run”, their outcomes would be different. In order to reduce sample variability between arms we used the same cohort of people in each arm of the simulation. We calculated the health outcomes, quality-of-life outcomes, cost outcomes, and cost/QALY for each person or groups of people. From these we calculated a distribution and summary statistics for each of those outcomes for the population as a whole.

### **How the baseline rates of hypertension and lipid screening were determined**

All subjects in the nine screening strategies were screened for hyperlipidemia and hypertension at frequencies derived from the National Ambulatory Medical Care Survey (25) and the Medicare Expenditure Panel Survey (<http://www.meps.ahrq.gov/mepsweb>). Specifically, people were screened for hypertension every 2 years from age 30 to 44, every 1.5 years from age 45 to 64, and every year from age 65 to 75. People were screened for elevated low density lipoprotein cholesterol (LDL-C) every 5 years from age 45 to 75. People determined to have diabetes were screened for hypertension at each office visit for diabetes, and were screened for hyperlipidemia annually.

To determine these hypertension and cholesterol screening frequencies used during the trial, but prior to a diagnosis of diabetes (described above), we performed the following analysis: We first looked at the distribution of number of visits per person. For each visit, we assumed an independent probability of blood pressure (BP) screening (approximately 66%, although this value depended on age). Then, for a given number of visits for a person, the probability of at least one blood pressure screening during the year is:

$$1 - (1 - \text{probability of BP screening per visit})^{(\text{number of visits})}$$

Next, we calculated the probability of being screened during the year as:

$$\sum_0^n (\text{Probability of } n \text{ visits})(\text{conditional probability of being screened, given } n \text{ visits})$$

Finally, assuming independence from year to year, we estimated the average time between blood pressure screenings as:

$$1/(\text{probability of blood pressure screening per year})$$

### **Treatment of patients in the simulation**

Anyone diagnosed with diabetes was treated according the 2009 consensus algorithm from the American Diabetes Association (28). Specifically, patients with diabetes were started on metformin and lifestyle modification at the time of diagnosis, regardless of initial HbA1c levels. Treatment was intensified with a sulfonylurea then insulin, as needed, to maintain an HbA1c < 7%. Thiazolidinediones were not included in the treatment protocol. Hyperlipidemia and hypertension were treated according to ATP-III (27) and JNC-7 (29) guidelines, respectively.

### **Additional results**

In the published paper, the effect of screening is shown only for the sum of the diabetic complications of blindness, ESRD, and lower extremity amputation (figure 2c in the paper). The constituents of this aggregate outcome are shown in **Figures A5a-c**: the effects of the screening strategies over 50 years of follow-up on cases of blindness (A5a), cases of ESRD (A5b), and cases of lower extremity amputation (A5c).

## Calculation of the lead time of diagnosing diabetes

To calculate the lead time of diagnosing diabetes we performed the following analysis: The same virtual people were used as the initial population in all simulations. For each screening strategy (i.e., a particular age to begin screening and a particular frequency for re-screening) we performed two calculations, in one of which the simulated people were screened according to the designated strategy (screening arm), and in the other of which there was no screening (control arm). Then, for each virtual individual who was diagnosed with diabetes in both of those simulations, we calculated the age at which the diagnosis of diabetes was made. The difference in the age of diagnosis of diabetes *without screening* (control arm) minus *with screening* (screening arm) is the lead time of diagnosing diabetes as a result of screening for that individual. The mean of the individual lead times is shown for each of the screening strategies in Table 2 of the paper.

**Table A1**

Baseline demographics, and mean laboratory and biomarkers values for the simulated study population

age (yrs.)	29.5
Female (%)	49.5
Caucasian (%)	65.2
Black (%)	11.9
Hispanic (%)	7.2
Diastolic Blood Pressure (mm/Hg)	69
Systolic Blood Pressure (mmHg)	114
BMI (kg/m <sup>2</sup> )	27.4
HDL Cholesterol (%)	50
LDL Cholesterol (mg/dL)	115
Total Cholesterol (mg/dL)	190
Triglycerides (mg/dL)	126
Fasting Plasma Glucose (mg/dL)	91
Smokers (%)	31.5

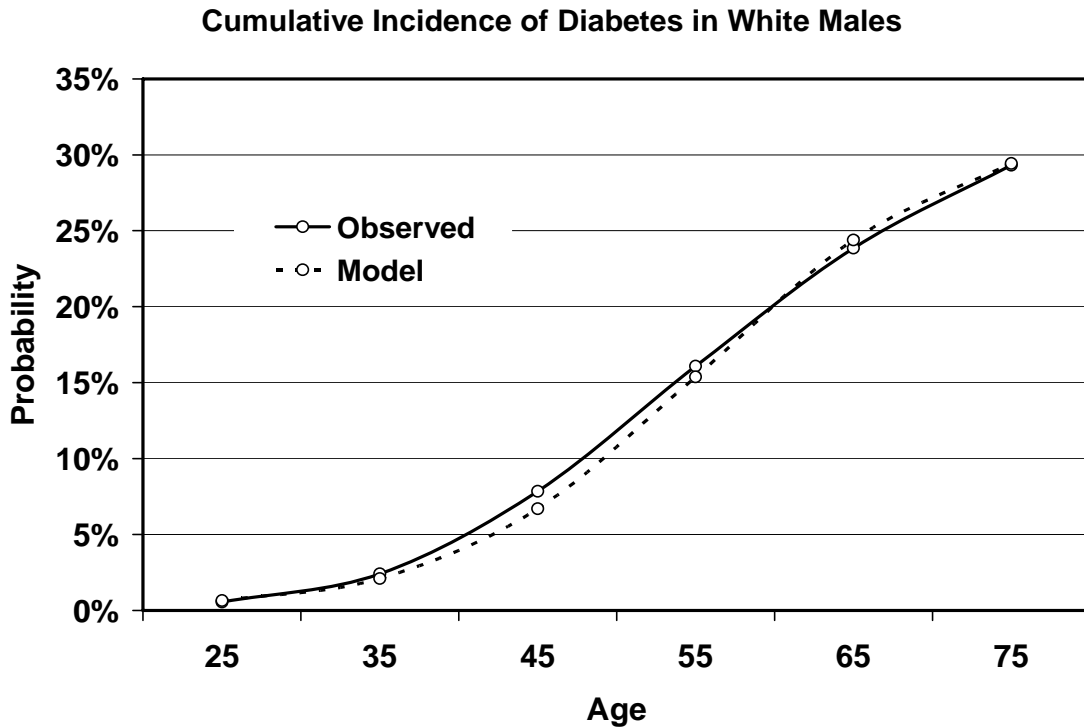
**Table A2**

Results of Mount Hood Challenge for CARDS Trial

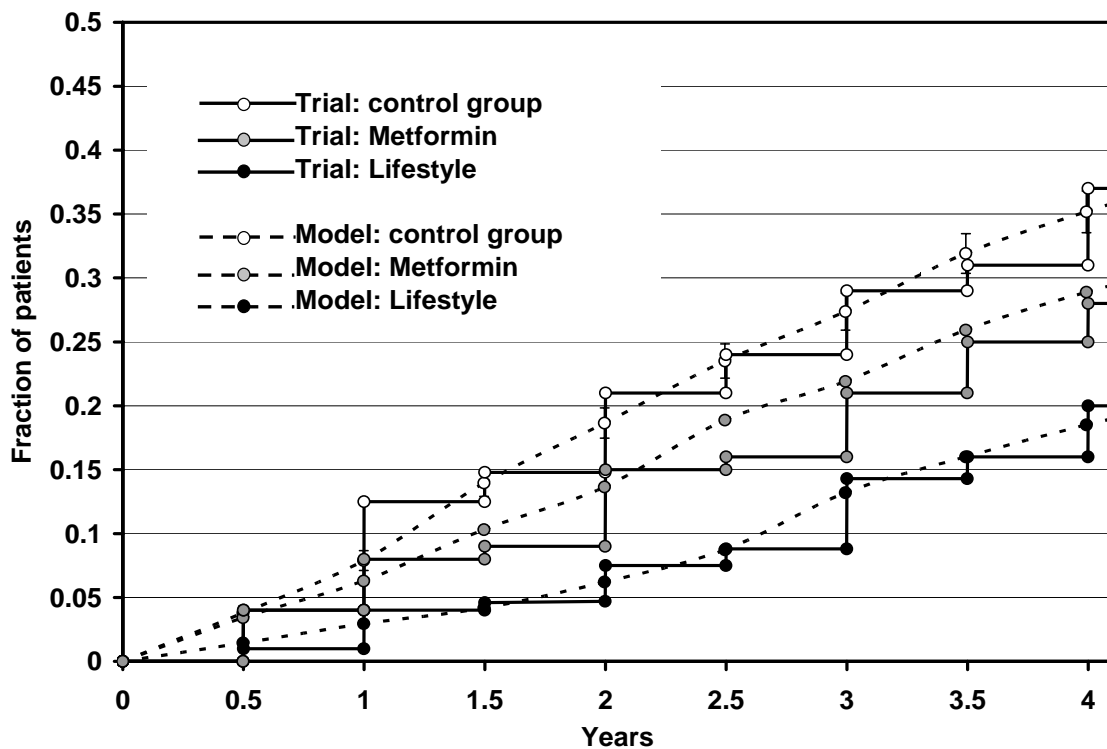
Archimedes	4 year cumulative incidence rates of outcomes <sup>‡</sup>	
	Archimedes prediction	Actual results <sup>§</sup>
Acute coronary events in control group <sup>Δ</sup>	5.4%	5.1% (4.0-6.2)
Acute coronary events in treated group <sup>◇</sup>	3.4%	3.2% (2.3-4.1)
Strokes in control group	3.2%	3.2% (2.3-4.1)
Strokes in treated group	2.7%	1.4% (0.8-2.0)

Data are % (95% CI) where available. <sup>Δ</sup> Control was placebo <sup>◇</sup> Intervention was atorvastatin <sup>§</sup> In CARDS trial Acute Coronary Events include: MI, silent MI, unstable angina, acute CHD, death, and unresuscitated cardiac arrest, all hospital verified. <sup>‡</sup> Unpublished correspondence from Prof. Helen Calhoun on behalf of the CARDS group. Cumulative hazard at 4 years estimated by Nelson-Aalen method. Best possible comparison for model-calculated results.

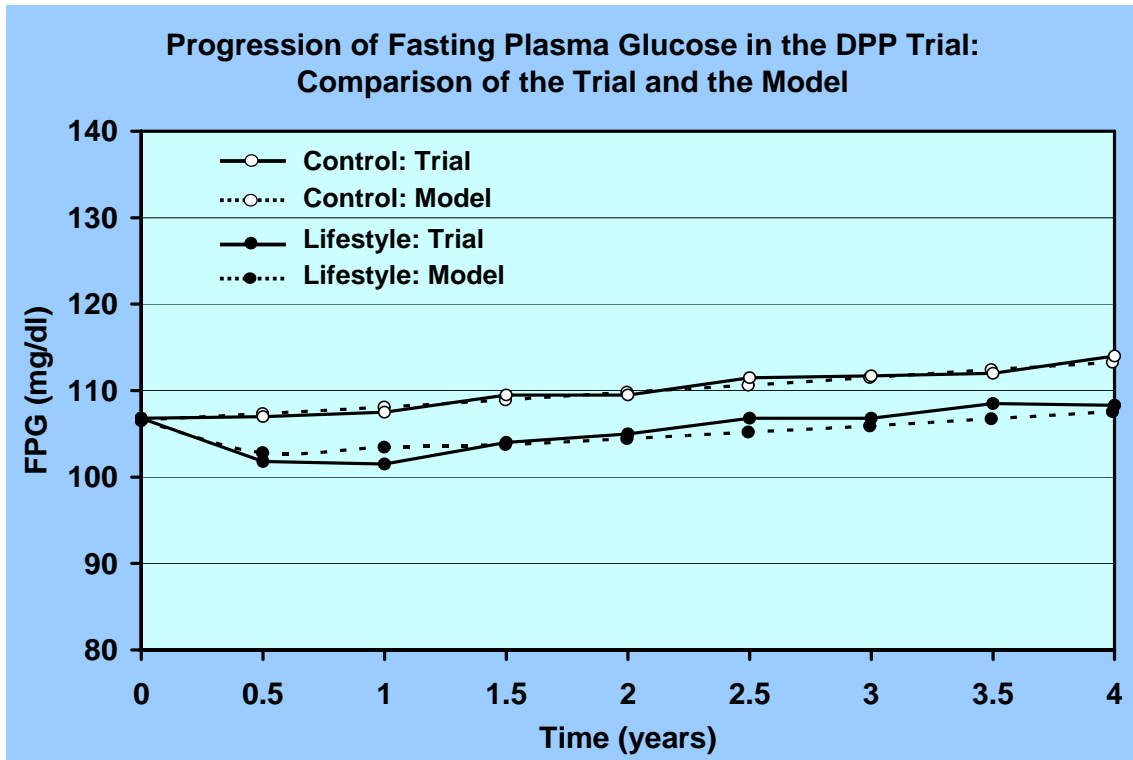
**Figure A1** Comparison of model and observational data: Cumulative Incidence of diabetes in white males over 50 years as reported in Diabetes in America, 2<sup>nd</sup> edition, 1995.



**Figure A2** Comparison of model and trial: Fraction of patients developing diabetes in the Diabetes Prevention Program

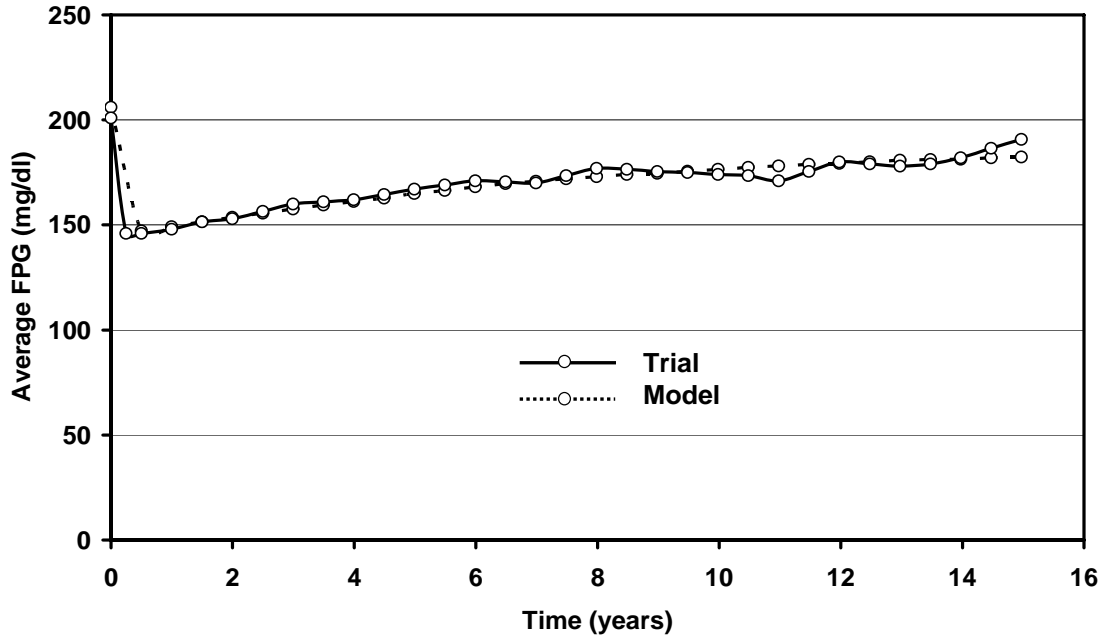


**Figure A3** Comparison of model and trial: Progression of average fasting plasma glucose of individuals in the Diabetes Prevention Program



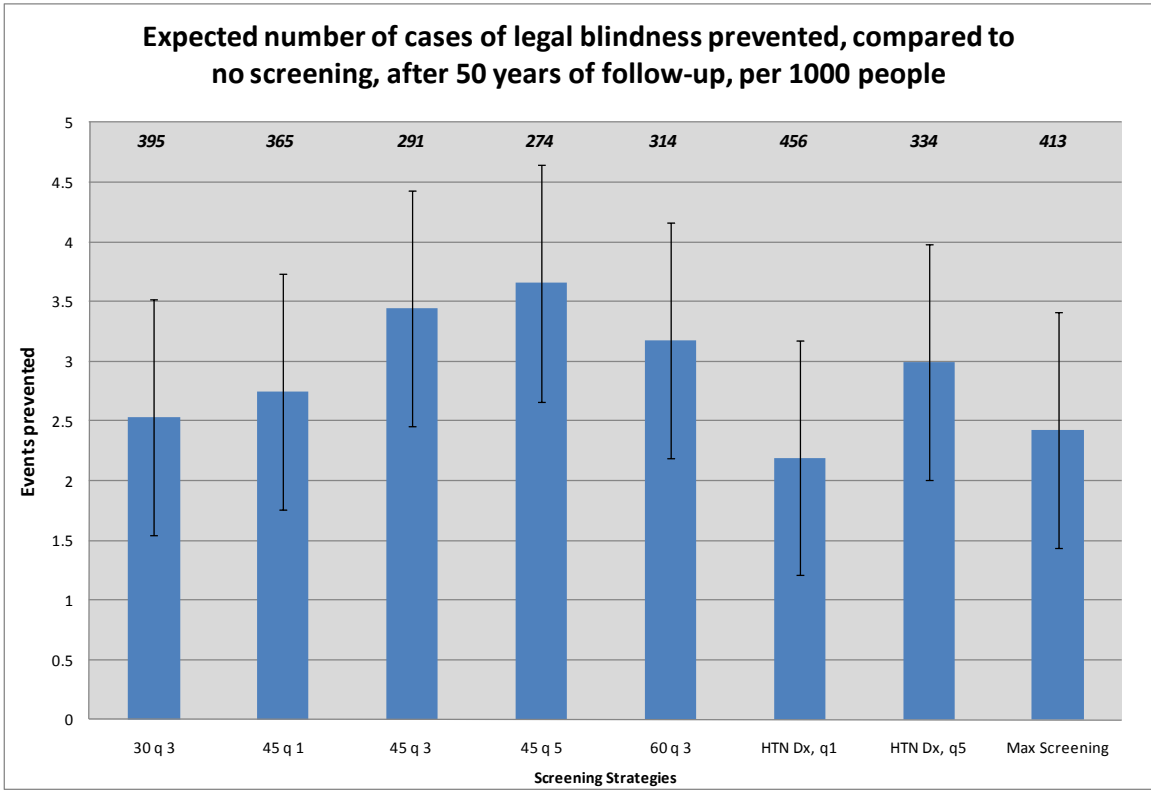
**Figure A4** Comparison of model and trial: Average fasting plasma glucose of individuals in the UKPDS trial

**Fasting Plasma Glucose in the Control Group of UKPDS:  
Comparison of Trial and Model**

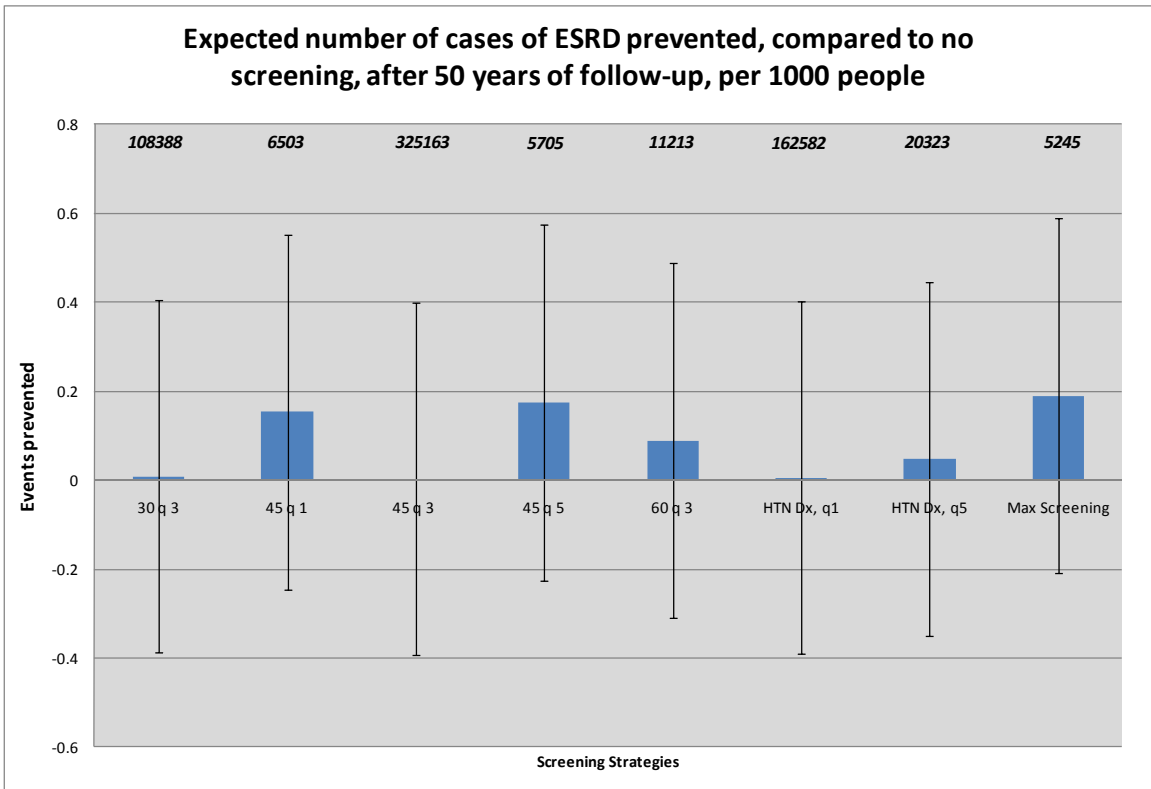


**Figure A5.** Effect of screening on the prevention of a) cases of legal blindness, b) cases of ESRD, and c) cases of LE amputation, after 50 years of follow-up, per 1000 people. Error bars represent  $\pm 2$  standard errors of the mean. In the control arm, after 50 years of follow-up, there were 42 cases of blindness, 7 cases of ESRD, and 89 cases of LE amputation per 1000 people. Number needed to treat (NNT) to prevent one event, over 50 years, is listed in italics above each column in the figures.

**Figure A5a.**



**Figure A5b.**



**Figure A5c.**

