Supplementary Materials, Appendix 2

# Model Details

## Section 1. Simulation Population Data

The simulation population data specify the characteristics of individuals to be simulated in the model: demographic variables (age, sex, race/ethnicity, duration of diabetes at baseline); risk factors (HbA1c, systolic blood pressure [SBP], LDL and HDL cholesterol, triglycerides [in natural log format], BMI, serum creatinine, and smoking status); and history of complication variables. Users may submit complete data for a population of individuals; individuals are drawn from this population to reach the specified number of individuals in the population. Complete data for an individual will include demographics (age, sex, race, duration of diabetes, post-secondary education), risk factors (HbA1c, BMI, systolic blood pressure, HDL cholesterol, LDL cholesterol, ln[triglycerides], serum creatinine, and smoking status), and previous history of each of the complications in the model. If unavailable, users may set the previous history variables to 0.

Alternatively, users may submit summary statistics for a population of interest; percentages are entered for categorical variables and means and standard deviations are entered for continuous variables. Drawing from these statistics and appropriate distributions, the model generates the selected number of individuals to be simulated. For example, an individual could be generated as a 59-year-old Black woman who has had type 2 diabetes for 7 years and has HbA1c 7%, SBP 130 mm Hg, LDL cholesterol 100 mg/dl, HDL cholesterol 45 mg/dL, BMI 31 kg/m2, and serum creatinine 0.80 mg/dL; is non-smoking; has a previous myocardial infarction; and has no other previous complications. The default data source for characteristics is individuals with diabetes in the National Health and Nutrition Examination Survey (NHANES) in four waves from 2009–2010 through 2015–2016, but the user can supply population statistics from other data sources.

## Section 2. Risk Factor Progression

Changes in HbA1c, SBP, LDL and HDL cholesterol, triglycerides, BMI, and serum creatinine are modeled using risk factor equations that depend on the pooled ACCORD and Look AHEAD baseline and lagged values of the risk factor, time, and any interventions affecting the risk factor. For smoking status, we found that almost all participants in the ACCORD and Look AHEAD database who did not smoke at baseline remained nonsmokers; therefore, the model assumes that nonsmokers remain nonsmokers. For smokers, we include an annual quit probability equation based on ACCORD and Look AHEAD data.

Coefficients for the risk factor equations appear in Appendix 2, Table 1.

## Section 3. Costs

In the model, costs are calculated using an annual cost equation estimated for 608,237 individuals with type 2 diabetes using longitudinal data from the Optum de-identified Normative Health Information (dNHI) database.1 The estimate focused on privately insured individuals younger than 65. Costs are estimated for the year the complication occurred and, for selected complications, for people with a previous history of the event. The estimation is described in detail in Yang et al.1 Complication costs appear in Appendix 2, Table 2. Costs in the model are reported in 2016 U.S. dollars and are discounted at a default annual rate of 3%. Users can select alternative annual discount rates.

## Section 4. Patient Utility and Quality

Patient utility is estimated annually for each individual based on their age, BMI, and current and previous complications using a patient utility equation estimated from pooled ACCORD and Look AHEAD measurements of the Health Utility Index Mark 3 (HUI-3) 2. The HUI-3 measures eight health attributes and applies a validated scoring algorithm to convert the attribute values to a single health value on a scale from −0.36 (rare cases considered worse than death) to 0 (death) to 1 (perfect health).3 The patient utility equation was estimated as a function of current and previous complications. The negative coefficients for complications can be interpreted as decrements in patient utility. The estimation is described in detail in Neuwahl et al.,2 and the utility equation appears in Appendix 2, Table 3.

The model sums the patient utility estimates across individuals and years to calculate QALYs, which, in the model, are discounted at a default annual rate of 3%. Users can select alternative annual rates.

## Section 5. Interventions

The model allows users to define interventions that change risks or directly apply relative risk reductions to risk equations. The glycemic control, blood pressure control, cholesterol control, and smoking interventions each include a basic set-up screen, allowing users to set costs and effects of the intervention on risk factors or relative reductions for specific risk equations. For example, the basic glycemic control screen allows users to specify a change in HbA1c, but it also provides the flexibility to select relative reductions in risk equations. This approach may be useful for modeling new treatments that have a larger effect on CVD or renal complications than would be expected from the change in risk factors alone.4-8 The glycemic control, blood pressure control, and cholesterol control intervention include an advanced set-up screen that allows users to set additional parameters such as target levels for HbA1c9 or blood pressure control10 and a wider selection of intervention effects and costs by year. Users may also select a generic intervention that gives the user the flexibility to analyze a comprehensive intervention that affects multiple risk factors or relative risk reductions for risk equations. Users specify the effects of the intervention and its costs.

## Section 6. Probabilistic Sensitity Analysis

PSA conducts a number of simulation iterations as specified by the user, combined into a batch of simulations. Each iteration randomly draws key model parameters from appropriate distributions. Complications and mortality are calculated in the same manner as basic runs, applying the intervention values accordingly. At the end of the PSA, the batch of simulations are analyzed as a set. The user can specify the number of iterations. For example, a user may run 100 iterations, each with N=10,000. Incremental cost, incremental QALYs, and ICER will be estimated for each iteration. The incremental cost and incremental QALY pairs can be used to plot a cost-effectiveness acceptability curve (CEAC) that shows the probability that the net marginal benefit (NMB) of the intervention exceeds zero for different willingness-to-pay per QALY threshold. The NMB is given by

$$NMB=λΔQALY-ΔCost>0$$

where λ is the willingness-to-pay per QALY parameter.

The following variables can be varied in the PSA:

* Complication costs (varied in all PSA based on gamma distributions and input means and standard errors)
* Utility decrements (varied in all PSA based on beta distributions and input means and standard errors)
* Intervention costs (drawn from a uniform distribution with endpoints ±0% [no variation], ±10%, ±25%, or ±50% of the input cost)
* Intervention factor changes (varied across the confidence interval for the input change that is significant at the 1%, 5%, or 10% level based on a normal distribution; may also be set to “do not vary”)
* Intervention risk reductions (varied across the confidence interval for the input risk reduction that is significant at the 1%, 5%, or 10% level based on a lognormal distribution; may also be set to “do not vary”)
* Complication and mortality equations (varied based on normal distributions and input means and standard errors for each coefficient in the risk equation; complication and mortality equations can be independently set to “do not vary”)

PSAs typically take a long time to run because populations with N persons are simulated for multiple iterations.

## Section 7. Accessing and Improving Performance of the Model

The code for the model is available in a publicly accessible repository (<https://github.com/RTIInternational/diabetes-sim-backend-only>). The only software requirement to run the model is the presence of a Python installation (Python 3.8–3.10 have successfully been tested). Once a reader has cloned (or downloaded) the repository and installed all required software packages, all that is necessary to run the model is the execution of a run script. A readme file provides more details. Some scenario files are already included.

The speed and performance of the model may be improved by (1) parallelizing the model and( 2) minimizing IO (input/output) operations. The model currently updates individuals sequentially and generates output files for generated initial populations (each iteration outputs a single population) and for updated populations. Individuals in this microsimulation are updated independently from each other without any interactions between individuals. Splitting a population into chunks and updating each chunk on a different CPU core is the easiest way to parallelize the model. Keeping populations in memory between simulation stages (population generation, simulation, analysis) would not only lead to performance gains for single runs but would also guarantee correct output during parallelized runs.

## Section 8. Input Populations for Applications

To generate the simulation population for Application 1, we entered the mean and standard deviations for demographic variables, risk factors, and baseline history of complications for adult participants with diabetes in four NHANES waves (Appendix 2, Table 4). In Application 2, the intervention is applied to 10,000 individuals aged 61 with diabetes duration of 1 year who have an initial HbA1c of 9%. All other baseline variables are set equal to the mean values in the NHANES population with diagnosed diabetes.

Appendix 2, Table 1. Risk-Factor Equation Results Treatment Variables Included in Risk Equations for Adults with Diabetes

| Model Variable | Description | Risk Factors |
| --- | --- | --- |
| HBA1C | BMI | SBP | HDL | LDL | LN (Trig.) | Creatinine | Smoking (Weibull) |
| Mean(SE) | Mean(SE) | Mean(SE) | Mean(SE) | Mean(SE) | Mean(SE) | Mean(SE) | Mean(SE) |
| LAG\_X | Lagged value of risk factor | 0.743(0.004) | 0.902(0.004) | 0.551(0.004) | 0.748(0.004) | 0.632(0.004) | 0.670(0.003) | 0.961(0.013) |  |
| LN\_YEAR | Natural log of time (year of simulation) | 0.124(0.006) | −0.381(0.012) | 1.237(0.088) | 0.290(0.041) | −1.660(0.180) | −0.019(0.002) | 0.004(0.001) |  |
| BASE\_X | Baseline value of risk factor | 0.016(0.003) | 0.076(0.004) | 0.117(0.004) | 0.185(0.004) | 0.076(0.003) | 0.140(0.003) | 0.035(0.010) |  |
| OBSEXREC | Female | 0.002(0.006) | −0.063(0.011) | 0.486(0.096) | 0.675(0.046) | 2.714(0.182) | 0.005(0.002) | −0.005(0.001) | −0.002(0.081) |
| BLACK | Black race | 0.031(0.008) | −0.023(0.015) | 1.493(0.128) | 0.392(0.060) | 3.540(0.252) | −0.055(0.003) | 0.004(0.002) | −0.0411(0.099) |
| HISPANIC | Hispanic ethnicity | 0.056(0.011) | −0.050(0.019) | 0.320(0.166) | 0.090(0.071) | 1.512(0.306) | 0.004(0.004) | 0.000(0.002) | 0.341(0.134) |
| OTHER | Other race/ethnicity |  |  |  |  |  |  |  | 0.690(0.107) |
| AGE | Age at baseline | −0.008(0.000) | −0.012(0.001) | 0.038(0.007) | 0.011(0.003) | −0.075(0.013) | −0.002(0.000) | 0.000(0.000) | 0.021(0.006) |
| DUR\_YR00 | Duration of diabetes at baseline | 0.005(0.000) | 0.002(0.001) | 0.012(0.007) | −0.007(0.003) | −0.066(0.012) | −0.001(0.000) | 0.001(0.000) |  |
| EDUCOLL | College education or more | −0.028(0.006) | −0.051(0.011) | −0.379(0.101) | 0.168(0.044) | −0.533(0.181) | −0.014(0.003) | −0.003(0.001) |  |
| LA\_TRIAL | Dummy variable for Look AHEAD trial participant | −0.147(0.010) | −0.096(0.016) | −1.783(0.145) | 0.560(0.060) | −0.578(0.253) | −0.033(0.003) | −0.007(0.002) |  |
| FIRST\_YEAR\_OF\_TX | Dummy variable for period immediately after initiation of treatment | −0.392(0.016) | −0.029(0.022) | −0.807(0.164) | 0.551(0.097) | 1.162(0.442) | −0.004(0.006) | 0.011(0.003) |  |
| INTENSIVE\_LA\_TX | Dummy variable for Look AHEAD trial participant in the intensive intervention | 0.012(0.011) | 0.109(0.019) | −0.305(0.176) | 0.183(0.069) | 0.636(0.280) | 0.008(0.004) | 0.009(0.002) |  |
| LA\_TRIAL\_FIRST\_YEAR | Interaction of LA\_TRIAL and FIRST\_YEAR\_OF\_TX | 0.403(0.025) | −0.484(0.046) | 1.038(0.340) | 0.044(0.160) | −0.304(0.692) | −0.013(0.009) | −0.017(0.004) |  |
| INTENSIVE\_LA\_TX\_ FIRST\_YEAR | Interaction of INTENSIVE\_LA\_TX and FIRST\_YEAR\_OF\_TX | −0.536(0.029) | −3.056(0.071) | −4.176(0.444) | 1.951(0.201) | −0.060(0.800) | −0.125(0.011) | −0.081(0.006) |  |
| HBA1C\_TX | Receiving HbA1c treatment (ACCORD Only) | −0.104(0.008) |  |  |  |  |  |  |  |
| SBP\_TX | Receiving SBP treatment (ACCORD Only) |  |  | −3.288(0.124) |  |  |  |  |  |
| HDL\_TX | Receiving cholesterol treatment (ACCORD Only) | .. | .. | .. | −0.010(0.054) | .. | .. | .. | .. |
| LDL\_TX | Receiving cholesterol treatment (ACCORD Only) | .. | .. | .. | .. | −1.747(0.220) | .. | .. | .. |
| LN\_TRG\_TX (Triglycerides treatment) | Receiving cholesterol treatment (ACCORD Only) | .. | .. | .. | .. | .. | −0.027(0.003) | .. | .. |
| CREAT\_TX | Receiving any intensive intervention from LA or ACCORD (potential effect on creatinine) | .. | .. | .. | .. | .. | .. | −0.010(0.002) | .. |
| SMOKES\_TX | Receiving any intensive intervention from LA or ACCORD (potential effect on smoking) | .. | .. | .. | .. | .. | .. | .. | .. |
| HBA1C\_TX\_FIRST\_YEAR | Interaction of HBA1C\_TX and FIRST\_YEAR\_OF\_TX | −0.927(0.020) | .. | .. | .. | .. | .. | .. | .. |
| BPS\_TX\_ FIRST\_YEAR | Interaction of BPS\_TX and FIRST\_YEAR\_OF\_TX | .. | .. | −3.254(0.239) | .. | .. | .. | .. | .. |
| HDL\_TX\_FIRST\_YEAR | Interaction of HDL\_TX and FIRST\_YEAR\_OF\_TX | .. | .. | .. | 1.576(0.162) | .. | .. | .. | .. |
| LDL\_TX\_FIRST\_YEAR | Interaction of LDL\_TX and FIRST\_YEAR\_OF\_TX | .. | .. | .. | .. | −5.786(0.641) | .. | .. | .. |
| TRG\_TX\_FIRST\_YEAR | Interaction of TRG\_TX and FIRST\_YEAR\_OF\_TX | .. | .. | .. | .. | .. | −0.215(0.009) | .. | .. |
| CREAT\_TX\_FIRST\_YEAR | Interaction of CREAT\_TX and FIRST\_YEAR\_OF\_TX | .. | .. | .. | .. | .. | .. | 0.078(0.004) | .. |
| Intercept | Intercept value | 2.147(0.046) | 2.197(0.073) | 38.155(0.683) | 1.691(0.227) | 30.596(1.050) | 1.079(0.020) | 0.003(0.007) | −4.550(0.402) |
| Shape | Weibull shape parameter (smoking only) |  |  |  |  |  |  |  | 1.369 |
|  |  |  |  |  |  |  |  |  | (0.43) |

Appendix 2, Table 2. Type 2 Diabetes Complication Cost Estimated from the Panel Fixed-Effects Model (2016 $)

|   | Coefficient | Standard Error |
| --- | --- | --- |
| Age (in years) | −64\*\*\* | 9 |
| Nephropathy | 11,509\*\*\* | 315 |
| Nephropathy history | 3,057\*\*\* | 291 |
| ESRD | 94,231\*\*\* | 4,336 |
| ESRD history | 98,981\*\*\* | 5,066 |
| Neuropathy | 4,323\*\*\* | 160 |
| Neuropathy history | 2,012\*\*\* | 186 |
| Lower-extremity amputation | 25,008\*\*\* | 3,767 |
| Retinopathy | 1,684\*\*\* | 226 |
| Retinopathy history | 2,202\*\*\* | 276 |
| Blindness and vision loss | 12,995\*\*\* | 1,733 |
| Blindness and vision loss history | 2,378 | 1,813 |
| Congestive heart failure (CHF) | 31,202\*\*\* | 920 |
| CHF history | 7,062\*\*\* | 883 |
| Foot ulcer | 11,045\*\*\* | 704 |
| Foot ulcer history | 2,147\*\*\* | 684 |
| Myocardial infarction (MI) | 45,251\*\*\* | 1,203 |
| MI history | 8,572\*\*\* | 1,107 |
| Stroke | 23,780\*\*\* | 850 |
| Stroke history | 4,729\*\*\* | 876 |
| Angina | 8,907\*\*\* | 331 |
| Revascularization | 20,328\*\*\* | 560 |
| Photocoagulation | 4,393\*\*\* | 995 |
| Hypoglycemia | 7,656\*\*\* | 296 |
| Ketoacidosis | 13,457\*\*\* | 808 |
| Constant | 9,311\*\*\* | 445 |

Note: \*\*\*: P<0.01; \*\*: P<0.05; \*: P<0.10.

Appendix 2, Table 3. Health Utility Decrements for Complications of Diabetes: Fixed-Effects Model Results

| Covariate | Coefficient | SE |
| --- | --- | --- |
| Current Smoker | −0.006 | 0.005 |
| BMI (one-unit increase) | −0.003\*\*\* | 0.000 |
| Duration of diabetes in years (time-varying) | −0.008\*\*\* | 0.000 |
| Stroke event | −0.109\*\*\* | 0.015 |
| History of stroke | −0.051\*\*\* | 0.014 |
| Amputation event | −0.092\*\*\* | 0.027 |
| History of amputation | −0.150\*\*\* | 0.034 |
| Dialysis event † | −0.039\*\*\* | 0.015 |
| History of dialysis † | −0.015 | 0.013 |
| MI event | −0.028\*\*\* | 0.009 |
| History of MI | −0.006 | 0.008 |
| CHF event ¶ | −0.051\*\*\* | 0.014 |
| History of CHF | −0.041\*\*\* | 0.014 |
| angina event ¶ | −0.015 | 0.009 |
| history of angina  | −0.028\*\*\* | 0.008 |
| eGFR < 30 mL/min/1.73 m2 event § | −0.043\*\*\* | 0.010 |
| History of eGFR < 30 mL/min/1.73 m2 § | −0.025\*\*\* | 0.010 |
| eGFR < 60 mL/min/1.73 m2 event § | −0.014\*\*\* | 0.003 |
| History of eGFR < 60 mL/min/1.73 m2 § | −0.015\*\*\* | 0.003 |
| Revascularization event | −0.005 | 0.006 |
| History of revascularization | −0.001 | 0.007 |
| Laser photocoagulation event | −0.011\* | 0.007 |
| History of laser photocoagulation | −0.014\*\* | 0.006 |
| Hypoglycemia (any assistance) | −0.001 | 0.006 |
| Constant ‡ | 0.935\*\*\* | 0.012 |
| N (total person-visit observations) | 128,873 |  |
| N (total persons) | 15,252 |  |

Note: \*\*\*: P<0.01; \*\*: P<0.05; \*: P<0.10. All observations (128,873) from the estimation sample had a BMI and duration-of-diabetes variable present. Coefficients are shown for a one-unit change in these variables.

† Typically, someone with dialysis or a history of dialysis also has a history of eGFR < 30 mL/min/1.73 m2 and a history of eGFR < 60 mL/min/1.73 m2. Thus, these coefficients should be added together for someone with a dialysis event or a history of dialysis. For example, someone who started dialysis in the past year has a decline in utility of about 0.079 relative to someone with eGFR ≥ 60 mL/min/1.73 m2. Someone who started dialysis more than 1 year ago has a decline in utility of about 0.055 relative to someone with eGFR ≥ 60 mL/min/1.73 m2.

¶ Angina and CHF events represent hospitalization events for these two complications.

§ By definition, someone with eGFR < 30 mL/min/1.73 m2 also has history of eGFR < 60 mL/min/1.73 m2, so these two coefficients should be combined for someone with eGFR < 30 mL/min/1.73 m2. Similarly, someone with a history of eGFR < 30 mL/min/1.73 m2 also has history of eGFR < 60 mL/min/1.73 m2. Again, the coefficients should be combined.

Appendix 2, Table 4. Population Characteristics for Adult U.S. Diabetes Patients

| Population Characteristics Variables | Mean | Standard Deviation |
| --- | --- | --- |
| Demographic variables |  |  |
| Age | 61.28 | 12.85 |
| Diabetes duration | 11.00 | 10.45 |
| Female | 50.2% |  |
| Non-Hispanic White | 33.0% |  |
| Non-Hispanic Black | 24.4% |  |
| Hispanic | 31.3% |  |
| Non-Hispanic other race | 11.3% |  |
| Some college education | 44.0% |  |
| Risk factors |  |  |
| HbA1c | 7.35 | 1.77 |
| SBP | 129.57 | 17.86 |
| LDL cholesterol | 105.71 | 39.67 |
| HDL cholesterol | 48.42 | 14.52 |
| ln(triglycerides) | 4.81 | 0.49 |
| BMI | 32.55 | 7.42 |
| Serum creatine | 0.94 | 0.38 |
| Current smoker | 17.5% |  |
| History of previous complications |  |  |
| History of microalbuminuria | 23.1% |  |
| History of macroalbuminuria | 0.0% |  |
| History of eGFR<60 mL/min/1.73 m2 event | 20.5% |  |
| History of eGFR<30 mL/min/1.73 m2 event | 1.7% |  |
| History of dialysis | 0.2% |  |
| History of neuropathy\* | 0.9% |  |
| History of foot ulcer\* | 0.0% |  |
| History of amputation\* | 0.0% |  |
| History of laser retinopathy | 0.0% |  |
| History of blindness\* | 0.0% |  |
| History of myocardial infarction | 9.9% |  |
| History of stroke | 8.0% |  |
| History of CHF | 8.2% |  |
| History of angina | 6.5% |  |
| History of revascularization\* | 0.0\* |  |

Source: Analysis of four waves of National Health and Nutrition Examination Survey data for adults with diagnosed diabetes.

CHF=congestive heart failure, eGFR=estimated glomerular filtration

\*Not reported, assumed 0%

## Section 9. Look AHEAD Research Group at End of Continuation

**Clinical Sites**

The Johns Hopkins University Frederick L. Brancati, MD, MHS1\*; Jeanne M. Clark, MD, MPH1 (Co-Principal Investigators); Lee Swartz2; Jeanne Charleston, RN3; Lawrence Cheskin, MD3; Richard Rubin, PhD3\*; Jean Arceci, RN; David Bolen; Danielle Diggins; Mia Johnson; Joyce Lambert; Sarah Longenecker; Kathy Michalski, RD; Dawn Jiggetts; Chanchai Sapun; Maria Sowers; Kathy Tyler
\*deceased

Pennington Biomedical Research Center George A. Bray, MD1; Allison Strate, RN2; Frank L. Greenway, MD3; Donna H. Ryan, MD3; Donald Williamson, PhD3; Timothy Church, MD3 ; Catherine Champagne, PhD, RD; Valerie Myers, PhD; Jennifer Arceneaux, RN; Kristi Rau; Michelle Begnaud, LDN, RD, CDE; Barbara Cerniauskas, LDN, RD, CDE; Crystal Duncan, LPN; Helen Guay, LDN, LPC, RD; Carolyn Johnson, LPN, Lisa Jones; Kim Landry; Missy Lingle; Jennifer Perault; Cindy Puckett; Marisa Smith; Lauren Cox; Monica Lockett, LPN

The University of Alabama at Birmingham Cora E. Lewis, MD, MSPH1; Sheikilya Thomas, PhD,MPH2; Monika Safford, MD3; Stephen Glasser, MD3; Vicki DiLillo, PhD3; Gareth Dutton, PhD, Charlotte Bragg, MS, RD, LD; Amy Dobelstein; Sara Hannum; Anne Hubbell, MS; Jane King, MLT; DeLavallade Lee; Andre Morgan; L. Christie Oden; Janet Wallace, MS; Cathy Roche, PhD, RN, BSN; Jackie Roche; Janet Turman

Harvard Center
*Massachusetts General Hospital*. David M. Nathan, MD1; Enrico Cagliero, MD3; Heather Turgeon, RN, BS, CDE2; Barbara Steiner, EdM; Valerie Goldman, MS, RDN2; Linda Delahanty, MS, RDN3; Ellen Anderson, MS, RDN3; Laurie Bissett, MS, RDN; Christine Stevens, RN; Mary Larkin, RN; Kristen Dalton, BS, Roshni Singh, BS

*Joslin Diabetes Center*: Edward S. Horton, MD1; Sharon D. Jackson, MS, RD, CDE2; Osama Hamdy, MD, PhD3; A. Enrique Caballero, MD3; Sarah Bain, BS; Elizabeth McKinney, BSN, RN; Barbara Fargnoli, MS,RD; Jeanne Spellman, BS, RD; Kari Galuski, RN; Ann Goebel-Fabbri, PhD; Lori Lambert, MS, RD; Sarah Ledbury, MEd, RD; Maureen Malloy, BS; Kerry Ovalle, MS, RCEP, CDE

*Beth Israel Deaconess Medical Center*: George Blackburn, MD, PhD1\* Christos Mantzoros, MD, DSc3; Ann McNamara, RN
\*deceased

University of Colorado Anschutz Medical Campus James O. Hill, PhD1; Marsha Miller, MS RD2; Holly Wyatt, MD3,Brent Van Dorsten, PhD3; Judith Regensteiner, PhD3; Debbie Bochert; Gina Claxton-Malloy RD Ligia Coelho, BS; Paulette Cohrs, RN, BSN; Susan Green; April Hamilton, BS, CCRC; Jere Hamilton, BA; Eugene Leshchinskiy; Loretta Rome, TRS; Terra Thompson, BA, Kirstie Craul, RD, CDE; Cecilia Wang, MD

Baylor College of Medicine John P. Foreyt, PhD1; Rebecca S. Reeves, DrPH, RD2; Molly Gee, MEd, RD2; Henry Pownall, PhD3; Ashok Balasubramanyam, MBBS3; Chu-Huang Chen, MD, PhD3; Peter Jones, MD3; Michele Burrington, RD, RN; Allyson Clark Gardner, MS, RD; Sharon Griggs; Michelle Hamilton; Veronica Holley; Sarah Lee; Sarah Lane Liscum, RN, MPH; Susan Cantu-Lumbreras; Julieta Palencia, RN; Jennifer Schmidt; Jayne Thomas, RD; Carolyn White; Charlyne Wright, RN; Monica Alvarez, PCT

The University of Tennessee Health Science Center
*University of Tennessee East.* Karen C. Johnson, MD, MPH; Karen L. Wilson, BSN; Mace Coday, PhD3; Beate Griffin, RN, BS; Donna Valenski; Polly Edwards; Brenda Fonda; Kim Ward

*University of Tennessee Downtown.* Helmut Steinburg, MD3; Carolyn Gresham, BSN; Moana Mosby, RN; Debra Clark, LPN; Donna Green RN; Abbas E. Kitabchi, PhD, MD (retired)

University of Minnesota Robert W. Jeffery, PhD1; Tricia Skarphol, MA2; John P. Bantle, MD3; J. Bruce Redmon, MD3; Richard S. Crow, MD3; Scott J. Crow, MD3; Manami Bhattacharya, BS; Cindy Bjerk, MS, RD; Kerrin Brelje, MPH, RD; Carolyne Campbell; Mary Ann Forseth, BA; Melanie Jaeb, MPH, RD; Philip Lacher, BBA; Patti Laqua, BS, RD; Birgitta I. Rice, MS, RPh, CHES; Ann D. Tucker, BA; Mary Susan Voeller, BA

St. Luke’s Roosevelt Hospital Center Xavier Pi-Sunyer, MD1; Jennifer Patricio, MS2; Carmen Pal, MD3; Lynn Allen, MD; Janet Crane, MA, RD, CDN; Lolline Chong, BS, RD; Diane Hirsch, RNC, MS, CDE; Mary Anne Holowaty, MS, CN; Michelle Horowitz, MS, RD; Les James; Raashi Mamtani, MS

University of Pennsylvania Thomas A. Wadden, PhD1; Barbara J. Maschak-Carey, MSN, CDE2 ; Robert I. Berkowitz, MD3; Gary Foster, PhD3; Henry Glick, PhD3; Shiriki Kumanyika, PhD RD, MPH3; Yuliis Bell, BA ; Raymond Carvajal, PsyD; Helen Chomentowski; Renee Davenport; Lucy Faulconbridge, PhD; Louise Hesson, MSN, CRNP; Sharon Leonard, RD; Monica Mullen, RD, MPH

University of Pittsburgh John M. Jakicic, PhD1; David E. Kelley, MD1; Jacqueline Wesche-Thobaben, RN, BSN, CDE2; Daniel Edmundowicz, MD3; Lin Ewing, PhD, RN3; Andrea Hergenroeder, PhD, PT, CCS3; Mary L. Klem, PhD, MLIS3; Mary Korytkowski, MD3; Andrea Kriska, PhD3; Lewis H. Kuller, MD, DrPH3; Amy D. Rickman, PhD, RD, LDN3; Rose Salata, MD3; Monica E. Yamamoto, DrPH, RD, FADA3; Janet Bonk, RN, MPH; Susan Copelli, BS, CTR; Rebecca Danchenko, BS; Tammy DeBruce, BA; Barbara Elnyczky; David O. Garcia, PhD; George A. Grove, MS; Patricia H. Harper, MS, RD, LDN; Susan Harrier, BS; Diane Heidingsfelder, MS, RD, CDE, LDN; Nicole L. Helbling, MS, RN; Diane Ives, MPH; Janet Krulia, RN, BSN, CDE; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, PhD, RD, LDN; Lisa Martich, BS, RD, LDN; Meghan McGuire, MS; Tracey Y. Murray, BS; Anna Peluso, MS; Karen Quirin; Jennifer Rush, MPH; Joan R. Ritchea; Linda Semler, MS, RD, LDN; Karen Vujevich, RN-BC, MSN, CRNP; Kathy Williams, RN, MHA; Donna L. Wolf, PhD

The Miriam Hospital/Brown Medical School Rena R. Wing, PhD1; Renee Bright, MS2; Vincent Pera, MD3; Deborah Tate, PhD3; Amy Gorin, PhD3; Kara Gallagher, PhD3; Amy Bach, PhD; Barbara Bancroft, RN, MS; Anna Bertorelli, MBA, RD; Richard Carey, BS; Tatum Charron, BS; Heather Chenot, MS; Kimberley Chula-Maguire, MS; Pamela Coward, MS, RD; Lisa Cronkite, BS; Julie Currin, MD; Maureen Daly, RN; Caitlin Egan, MS; Erica Ferguson, BS, RD; Linda Foss, MPH; Jennifer Gauvin, BS; Don Kieffer, PhD; Lauren Lessard, BS; Deborah Maier, MS; JP Massaro, BS; Tammy Monk, MS; Rob Nicholson, PhD; Erin Patterson, BS; Suzanne Phelan, PhD; Hollie Raynor, PhD, RD; Douglas Raynor, PhD; Natalie Robinson, MS, RD; Deborah Robles; Jane Tavares, BS

The University of Texas Health Science Center at San Antonio Helen P. Hazuda, PhD1; Maria G. Montez, RN, MSHP, CDE2; Carlos Lorenzo, MD3; Charles F. Coleman, MS, RD; Domingo Granado, RN; Kathy Hathaway, MS, RD; Juan Carlos Isaac, RC, BSN; Nora Ramirez, RN, BSN

VA Puget Sound Health Care System / University of Washington Steven E. Kahn, MB, ChB1; Anne Kure, BS2; Edward J. Boyko, MD, MPH3; Edward Lipkin, MD, PhD3; Dace Trence, MD3; Subbulaxmi Trikudanathan, MD, MRCP, MMSc3; Elaine Tsai, MD3; Brenda Montgomery, RN, MS, CDE; Ivy Morgan-Taggart; Jolanta Socha, BS; Lonnese Taylor, RN, BS; Alan Wesley, BA

Southwestern American Indian Center, Phoenix, Arizona and Shiprock, New Mexico William C. Knowler, MD, DrPH1; Paula Bolin, RN, MC2; Tina Killean, BS2; Maria Cassidy-Begay, BSND, RND 2; Katie Toledo, MS, LPC2; Cathy Manus, LPN3; Jonathan Krakoff, MD3; Jeffrey M. Curtis, MD, MPH3; Sara Michaels, MD3; Paul Bloomquist, MD3; Peter H. Bennett, MB, FRCP3; Bernadita Fallis, RN, RHIT, CCS; Diane F. Hollowbreast; Ruby Johnson; Maria Meacham, BSN, RN, CDE; Christina Morris, BA; Julie Nelson, RD; Carol Percy, RN, MS; Patricia Poorthunder; Sandra Sangster; Leigh A. Shovestull, RD, CDE; Miranda Smart; Janelia Smiley; Teddy Thomas, BS

University of Southern California Anne Peters, MD1; Siran Ghazarian, MD2; Elizabeth Beale, MD3; Kati Konersman, RD, CDE; Brenda Quintero-Varela; Edgar Ramirez; Gabriela Rios, RD; Gabriela Rodriguez, MA; Valerie Ruelas MSW, LCSW; Sara Serafin-Dokhan; Martha Walker, RD

**Coordinating Center**

Wake Forest University Mark A. Espeland, PhD1; Judy L. Bahnson, BA, CCRP3; Lynne E. Wagenknecht, DrPH1; David Reboussin, PhD3; W. Jack Rejeski, PhD3; Alain G. Bertoni, MD, MPH3; Wei Lang, PhD3; David Lefkowitz, MD3\* Patrick S. Reynolds, MD3; Denise Houston, PhD3; Mike E. Miller, PhD3; Laura D. Baker, PhD3; Nicholas Pajewski, PhD3; Stephen R. Rapp, PhD3; Stephen Kritchevsky, PhD3; Haiying Chen, PhD, MM3; Valerie Wilson, MD3; Delia S. West, PhD3; Ron Prineas, MD3; Tandaw Samdarshi, MD3; Amelia Hodges, BS, CCRP2; Karen Wall2; Carrie C. Williams, MA, CCRP2; Andrea Anderson, MS; Jerry M. Barnes, MA; Tara D. Beckner; Delilah R. Cook; Valery S. Effoe, MD, MS; Melanie Franks, BBA; Katie Garcia, MS; Sarah A. Gaussoin, MS; Candace Goode; Michelle Gordon, MS; Lea Harvin, BS; Mary A. Hontz, BA; Don G. Hire, BS; Patricia Hogan, MS; Mark King, BS; Kathy Lane, BS; Rebecca H. Neiberg, MS; Julia T. Rushing, MS; Debbie Steinberg, BS; Jennifer Walker, MS; Michael P. Walkup, MS
\*deceased

**Central Resources Centers**

Central Laboratory, Northwest Lipid Metabolism and Diabetes Research Laboratories Santica M. Marcovina, PhD, ScD1; Jessica Hurting2; John J. Albers, PhD3, Vinod Gaur, PhD4

ECG Reading Center, EPICARE, Wake Forest University School of Medicine
Elsayed Z. Soliman MD, MSc, MS1; Charles Campbell 2; Zhu-Ming Zhang, MD3; Mary Barr; Susan Hensley; Julie Hu; Lisa Keasler; Yabing Li, MD

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1 Principal Investigator

2 Program Coordinator

3 Co-Investigator

All other Look AHEAD staffs are listed alphabetically by site.

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