HARVARD MEDICAL SCHOOL | Executive Education

AI and Precision Medicine Around the World

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March 12, 2019

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Can AI and Precision Medicine Cure the Misdiagnosis Problem and Improve Clinical Outcomes?

How serious is the problem of diagnostic errors?

5% of U.S. adult outpatients experience diagnostic error each year

Autopsy data: dx errors contribute to about 10% of deaths

Medical record review: Dx errors cause 6-17% of hospital adverse effects

Dx errors affect about 12 million US adults annually.

National Academies of Sciences, Engineering, and Medicine. 2015. Improving diagnosis in health care. Washington, DC: The National Academies Pres
Singh H et al. BMJ Quality Safety 2014;23:727-731.

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Types of Dx errors

- Missed diagnosis
- Misdiagnosis, i.e, the wrong diagnosis
- Delayed diagnosis
- Overdiagnosis i.e., medicalization of everyday life

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What's causing these mistakes?

- Cognitive errors: Clinicians' inadequate reasoning skills, biases, prejudices
- Information overload
- Poor handoff procedures
- Delayed or misplaced lab results
- Ignoring patients' input
- "The complexity of medicine now exceeds the capacity of the human mind."

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Real-world examples of Personalized Medicine Solutions

geneticgenie

Profile: Methylation Profile
Generated: 4/23/2014

Gene & Variation	rsID	Alleles	Result
COMT V158M	rs4680	AG	+/-
COMT H62H	rs4633	CT	+/-
COMT P199P	rs769224	GG	-/-
VDR Bsm	rs1544410	CC	-/-
VDR Taq	rs731236	AA	+/+
MAO A R297R	rs6323	T	+/+
ACAT1-02	rs3741049	AG	+/-
MTHFR C677T	[illegible]1133	AG	+/-
MTHFR 03 P39P	rs2066470	GG	-/-
MTHFR A1298C	rs1801131	GT	+/-

- Jake needed 4 wisdom teeth pulled
- Talk about using Nitrous Oxide, laughing gas
- Forward thinking doc did gene sequencing years earlier

- MTHFR Methylenetetrahydrofolate reductase mutation
- 3 case reports of catastrophic neurologic complications when N2O given to patients with 2 MTHFR mutations

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ITGAM-P1147S	het unknown	0.141	Unknown not reviewed	Insufficiently evaluated	Prioritization score: 0 Polyphen 2: Unknown
CYP2C9-R144C	het unknown	0.027	Unknown pharmacogenetic	Moderate clinical importance, well-established	This variant, also called CYP2C9*2, is a pharmacogenetic variant that modulates sensitivity for Warfarin (due to reduced metabolism). This variant is associated with Caucasians. The FDA has approved reduced recommended Warfarin dosage based on the presence of this variant.

Excerpt from John Halamka's gene sequencing report

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- CYP2C9 gene → protein --> metabolizes warfarin.
- John's mutation SLOWS warfarin breakdown → lower dose requirement
- Normal dose → John bleeds out; w/o gene test: diagnostic error
- Pharmacogenomic testing individualizes care, reduces misdiagnoses.
- About 150 drugs now have FDA warning about possible genetic mutations that may influence drug metabolism.
- No national guidelines, almost no 3rd party reimbursement--despite good evidence that it reduces adverse effects.

JAMA. 2016;316(15):1533-1535. doi:10.1001/jama.2016.12103
Food and Drug Administration.Table of pharmacogenomic biomarkers in drug labeling. July 11, 2016.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ Pharmacogenetics/ucm083378.htm.

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- Most chronic diseases are polygenic.
- Big data analytics → Polygenic risk score →For example: data from 6.6 million SNPs/ 400,000 persons → detects person at FOUR times the average risk of heart disease.(1)
- BEWARE Marketing hype that gets ahead of the science.

"Precision medicine" is a marketing term; …. the overarching belief that precision medicine is the future of medicine has led to what has been called an "arms race" or "gold rush" among academic medical centers to develop precision medicine initiatives." (2)

1. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic score to identify a monogenic risk-equivalent for coronary disease. BioRxiv 2017. Available from: https://doi.org/10.1101/ 218388.

(2) David H. Gorski, MD, PhD, FACS, oncologist at the Barbara Ann Karmanos Cancer Institute

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The High Cost of Precision Medicine

- *Among 58 cancer drugs, many of which were precision med drugs*
  - 1995: additional year of life cost $54,000
  - 2005: $139,000
  - 2013: $207,000
  - ROI: Survival improved by only a few months
- Novartis CAR-T Gene Therapy, called Kymriah
  - The most precise form of cancer therapy yet
  - Price tag: $475,000 for one time treatment

Howard DH, Bach PB, Brendt ER et al. Pricing in the Market for Anticancer Drugs. J Economic Perspectives. 2015; 29(1):139-162.

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- Most cancer patients don't benefit from precision medicine.
- Checkpoint inhibitor drugs: Among all Americans who will die of cancer in one year, only 8% will benefit.(1)

Personalized nutrition services—not ready for prime time

- Habit.com and DNA Power claim gene variants dictate specific vitamin or mineral needs.
- Associations between mutations and nutritional dysfunction don't establish cause and effect relationship.
- Example: Variants of FTO gene linked to obesity; but clinical experiment found people lost weight just as well with and w/o the FTO mutation (2)

1. https://www.statnews.com/2017/03/08/immunotherapy-cancer-breakthrough/
2. Dow, D. *Nutrition Action Health Letter, May 2018, pg 3.*

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Role of machine learning in Medicine

IBM Deep Blue Supercomputer vs Google's AlphaZero (Old school vs new school AI).

- Old school example: Encyclopedia-like CDS tools vs machine-learning based algorithms for diabetic retinopathy, melanoma, sepsis
- Use of deep learning, neural networks, and back propagation—giant step forward in digital world

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Machine learning vs skin cancer

- Deep convolutional neural network
- Algorithm can distinguish melanoma from normal mole, initially trained using 129,000 clinical images
- As effective as trained dermatologists is accurately diagnosing skin cancer

Esteva A. Kuprel B, Novoa RA et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature.* 2017;542:115-118.

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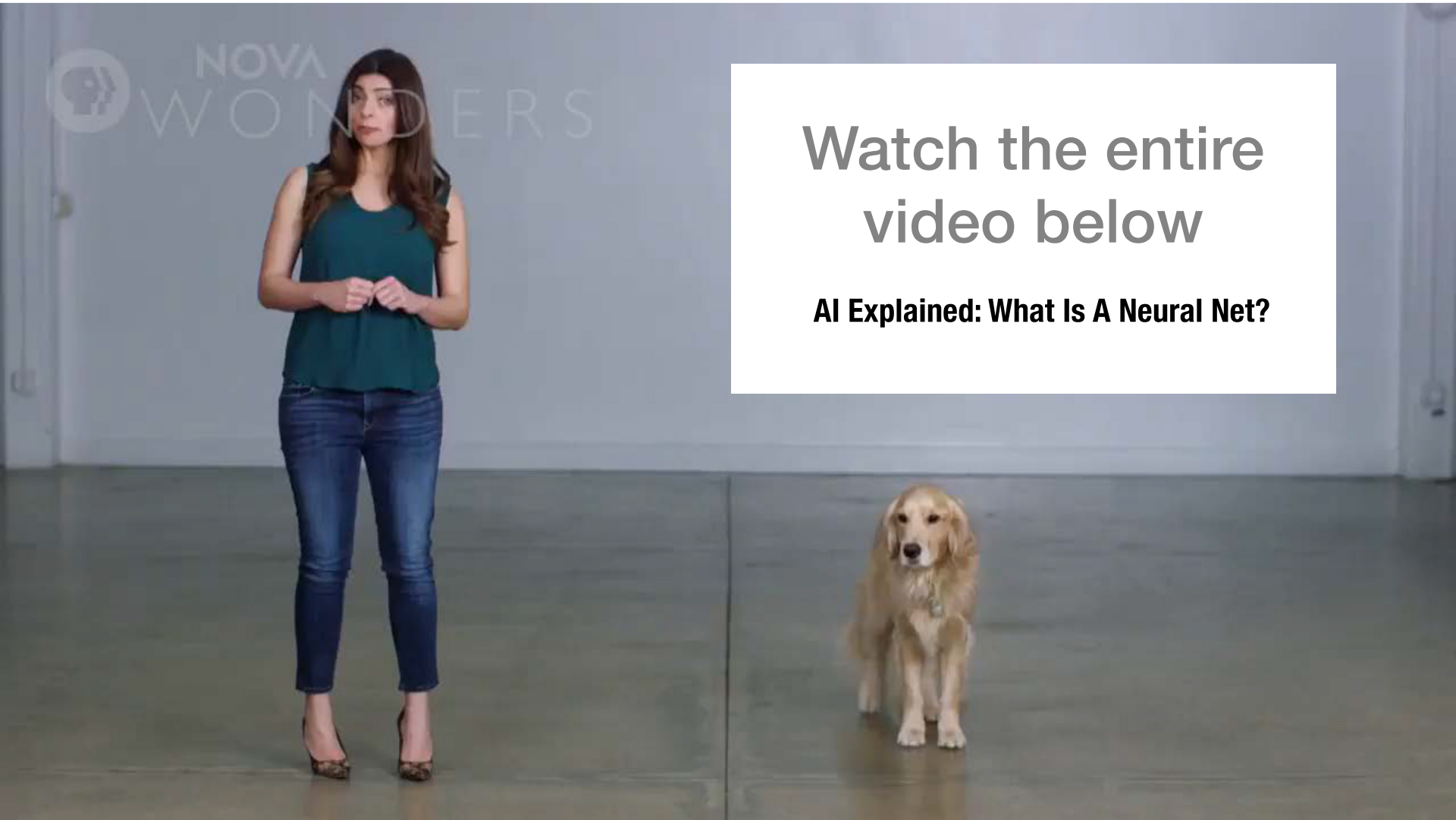
- IDx-DR is FDA cleared system that uses fundus camera and machine learning based algorithms to analyze retinal images and help detect diabetic retinopathy

- Google research:
  - Trained on 128,175 retinal images
  - Compared computer analysis to analysis by 54 ophthalmologists
  - Computer-based results: 87% to 90% sensitivity, 98% specificity
  - As good as or better than human counterparts

Gulshan et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. JAMA. 2016;316(22):2402-2410.



Watch the entire video below

AI Explained: What Is A Neural Net?

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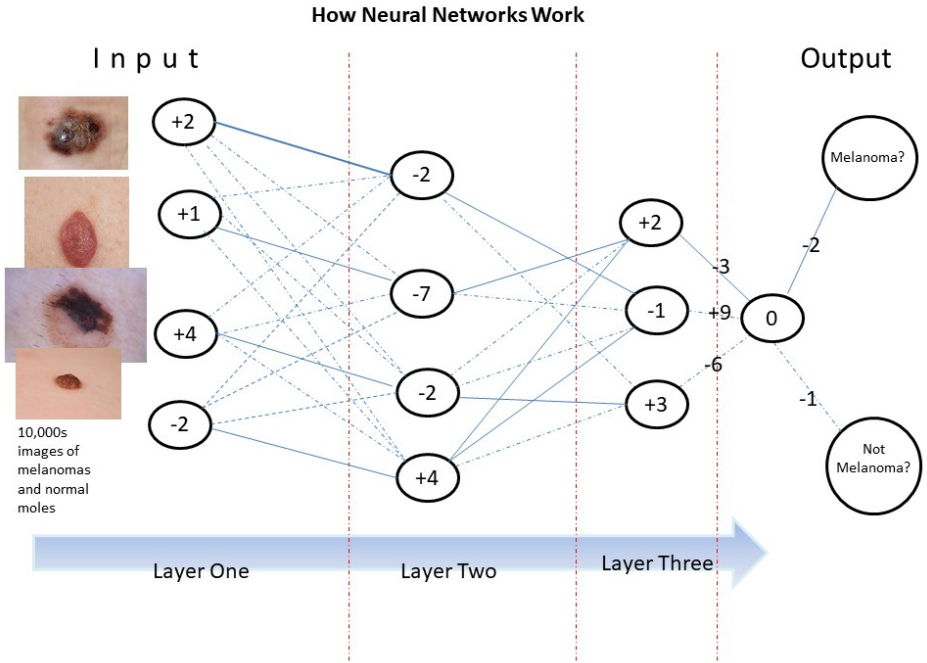

- Research project by Cerrato and Halamka
- A more in-depth look at mobile health, AI, machine learning, and clinical decision support tools.

- https://www.elsevier.com/books/the-transformative-power-of-mobile-medicine/cerrato/978-0-12-814923-2. Discount Code **HIMSS2019** valid until 3/31/2019

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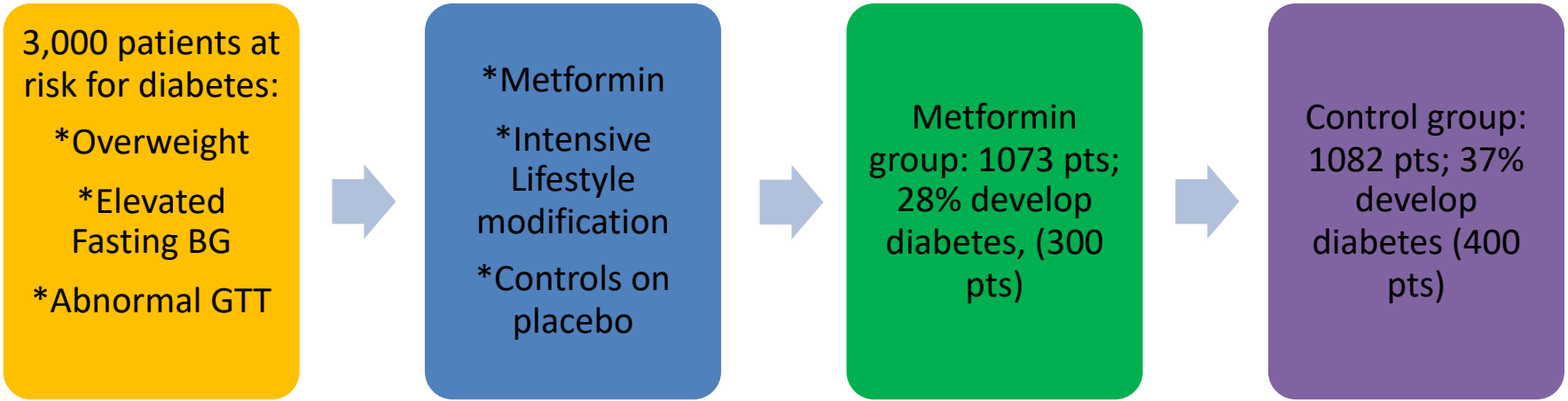
Big Data Analytics Applied to Type 2 Diabetes

Data from Diabetes Prevention Program (2002)



Diabetes Prevention Program Research Group; N Engl J Med 2002; 346:393-403

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- Flaw in Diabetes Prevention Trial: Couldn't predict who would respond to Tx and who would not.
- Jeremy Sussman University of Michigan et al.
  - Data analysis that looked at 17 risk factors for diabetes
  - Used proportional hazards regression to make predictions
  - SEVEN risk factors helped pinpoint individuals most likely to develop type 2 diabetes—This is Personalized/Precision Medicine!

Sussman et al. BMJ 2015; Feb 19;350:h454

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Sussman's Results: "Average reported benefit for metformin was distributed very unevenly across the study population, with the quarter of patients at the highest risk for developing diabetes receiving a dramatic benefit (21.5% absolute reduction in diabetes over three years of treatment) but the remainder of the study population receiving modest or no benefit."

Take home message**: Data Analytics informed more detailed set of risk factors, allowing clinicians identify individuals more likely to benefit from treatment and those who would not.**

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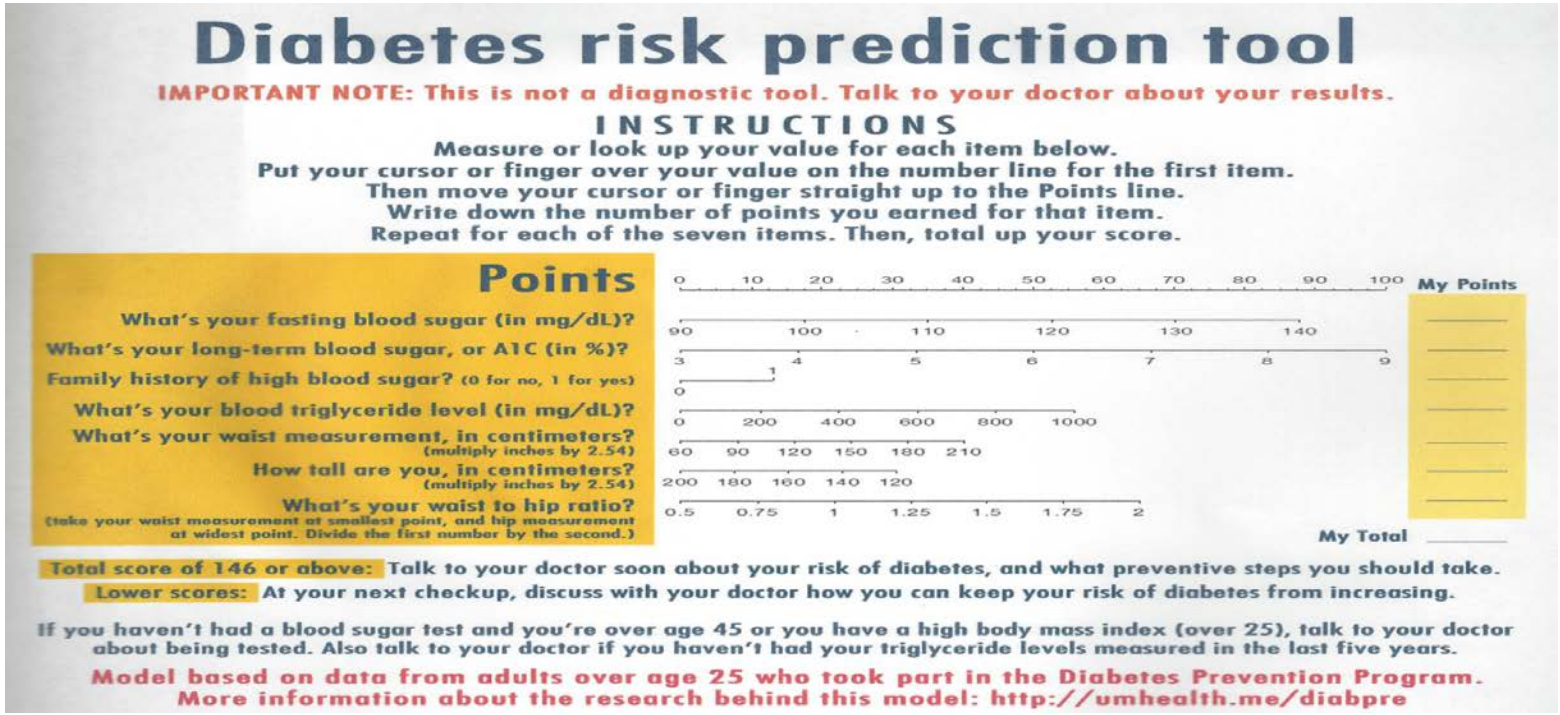


Diabetes risk prediction tool

IMPORTANT NOTE: This is not a diagnostic tool. Talk to your doctor about your results.

INSTRUCTIONS

Measure or look up your value for each item below.
Put your cursor or finger over your value on the number line for the first item.
Then move your cursor or finger straight up to the Points line.
Write down the number of points you earned for that item.
Repeat for each of the seven items. Then, total up your score.

Points

What's your fasting blood sugar (in mg/dL)?	0 10 20 30 40 50 60 70 80 90 100
What's your long-term blood sugar, or A1C (in %)?	90 100 110 120 130 140
Family history of high blood sugar? (0 for no, 1 for yes)	3 4 5 6 7 8 9
What's your blood triglyceride level (in mg/dL)?	0 1
What's your waist measurement, in centimeters? (multiply inches by 2.54)	0 200 400 600 800 1000
How tall are you, in centimeters? (multiply inches by 2.54)	60 90 120 150 180 210
What's your waist to hip ratio? (take your waist measurement at smallest point, and hip measurement at widest point. Divide the first number by the second.)	200 180 160 140 120
	0.5 0.75 1 1.25 1.5 1.75 2

My Points

My Total

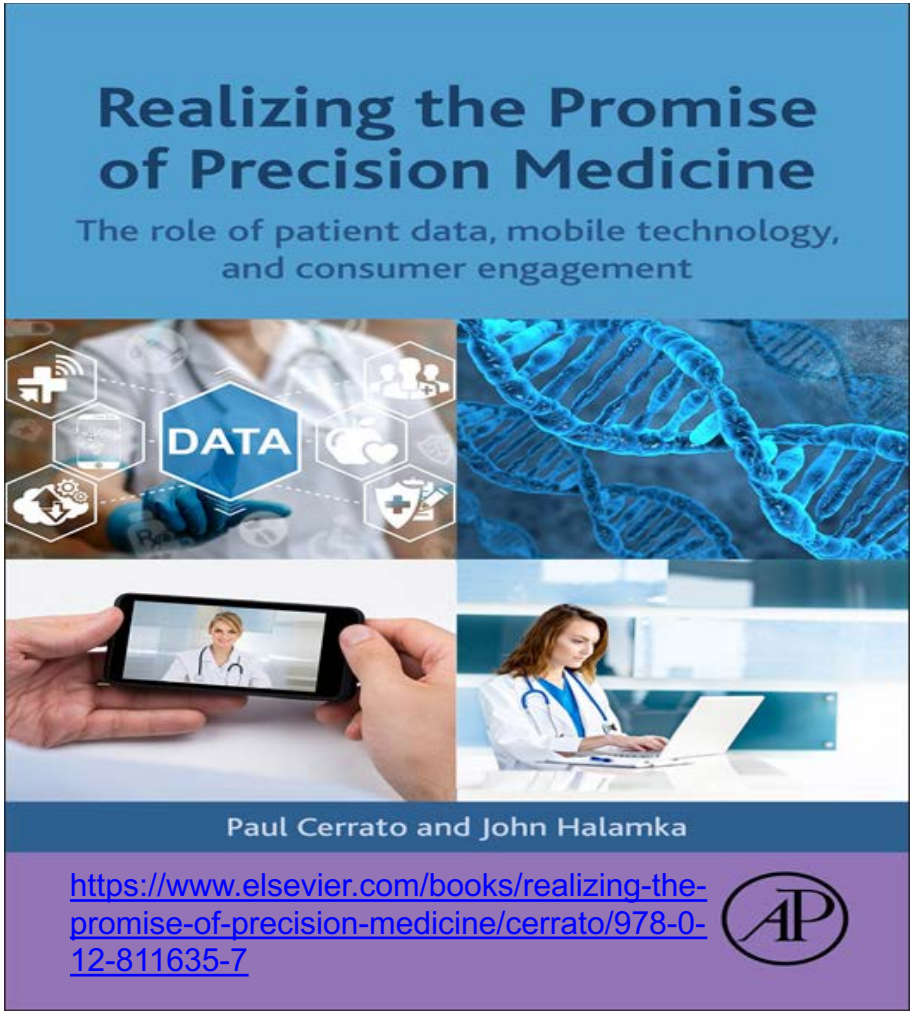
Total score of 146 or above: Talk to your doctor soon about your risk of diabetes, and what preventive steps you should take.

Lower scores: At your next checkup, discuss with your doctor how you can keep your risk of diabetes from increasing.

If you haven't had a blood sugar test and you're over age 45 or you have a high body mass index (over 25), talk to your doctor about being tested. Also talk to your doctor if you haven't had your triglyceride levels measured in the last five years.

Model based on data from adults over age 25 who took part in the Diabetes Prevention Program.
More information about the research behind this model: http://umhealth.me/diabpre

Used with permission, Univ of Michigan, Tufts University. Prediction tool is still undergoing clinical confirmation.


Realizing the Promise of Precision Medicine
The role of patient data, mobile technology, and consumer engagement
DATA
Paul Cerrato and John Halamka
https://www.elsevier.com/books/realizing-the-promise-of-precision-medicine/cerrato/978-0-12-811635-7

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What Big Data Analytics Can Do for Subgroup Analysis

Many clinical trials do subgroup analysis to look for smaller groups of patients who may respond to TX when main group didn't.

- Traditionally subgroup analyses consider *ONE* confounding variable or risk factor at a time.
  - Example: Clinical trial finds low fat diet for diabetic patients doesn't prevent heart disease, on average.
  - Factor in dietary intake of trans fats, which are atherogenic
  - Factor in extreme stress, e.g., death in family, divorce
- Many risk factors are synergistic, they only have effect on TX outcome in combination with others
- 10 risk factors can interact in 100s of ways not accounted for by single factor subgroup analysis
- Newer more sophisticated methods go beyond traditional subgroup analysis

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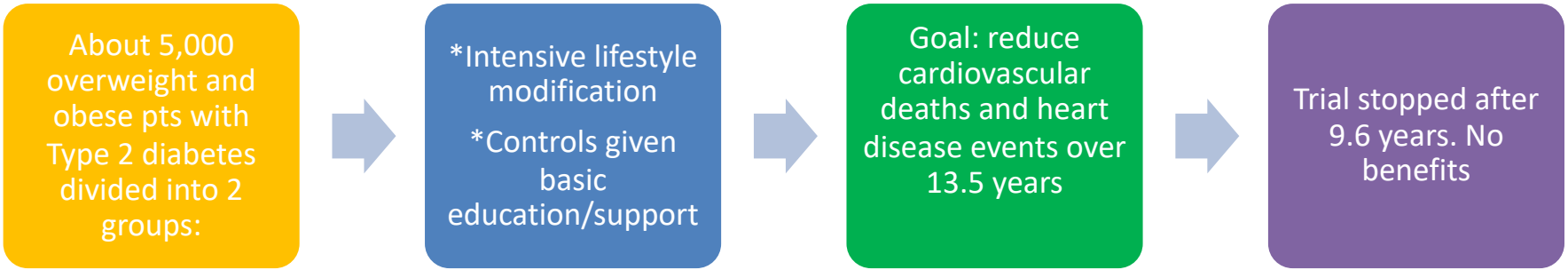
Clinical Trial: Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes.



N Engl J Med. 2013 Jul 11;369(2):145-54. Look AHEAD Research Group

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- Aaron Baum et al reanalysis: A machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial
  - Causal Forest modelling to detect subgroups that benefited from the lifestyle mod program
  - Causal forest analysis identifies subgroups by building numerous decision trees from pre-specified covariates in a random subsample of the data
- Didn't look at one factor at a time but MANY combinations of factors
- Analyzing combinations of A, B, C, D might detect interlocking risk factors.

Baum A, et al. Lancet Diabetes Endocrinol. 2017 Oct;5(10):808-815.

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Baum's results

- Intensive lifestyle modification averted cardiovascular events for these subgroups:
  - HbA1c 6.8% or higher (poorly managed diabetes)
  - Well controlled diabetes (Hba1c < 6.8%) and GOOD self reported health
- 85% of the study population benefitted
- 15% of population with controlled diabetes and POOR self-reported general health had NEGATIVE effects.
- One group cancelled out the other in original trial.

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Take home messages:

- HbA1c and a short questionnaire on general health might identify people with type 2 diabetes likely to derive benefit from an intensive lifestyle intervention aimed at weight loss.
- Big Data analytics needed to make Precision/Personalized Medicine a reality

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Advances in Clinical Decision Support Systems
Move from Static Enclycopedic CDS tools to AI enhanced tools

- Medial EarlySign ColonFlag to detect high risk of colorectal cancer https://earlysign.com
- UpToDateAdvanced and Pathways http://vid.uptodate.com/watch/scwKFikyHetLUoNLePokiH
- Via Oncology, Elsevier http://viaoncology.com
- VisualDx https://www.visualdx.com