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 1

PharmGenEd™: Bridging the Gap Between Science & Practice

Train-the-Trainer Session

for Diabetes

1st Webinar: Wednesday, May 23, 2012

2nd Webinar: Wednesday, September 19, 2012

UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY and PHARMACEUTICAL SCIENCES

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Disclaimer

This presentation was supported by Grant Number IU38GD000070 from Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.

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Presentation Outline

1. Introduction
   - Objective of PharmGenEd™ program
   - Shared curriculum and format
   - Introduction of author
2. Review of educational content for selected therapeutic area
3. Contact information
4. Survey to assess program materials

 4

Overall Objective of PharmGenEd™ Program

- The "Pharmacogenomics Education Program: Bridging the Gap between Science and Practice" (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals
- The overall objective of the PharmGenEd™ program is to increase awareness about the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests

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Shared Curriculum

Educational Materials (each 1 hour)

- Asthma
- Cardiology I (warfarin & statins)
- Cardiology II (clopidogrel & beta blockers)
- Concepts and clinical applications
- Economic issues
- HIV/AIDS
- Oncology I (solid tumors)
- Oncology II (hematologic malignancies)
- Psychiatry I (depression)
- Psychiatry II (antipsychotics)
- Toxicogenomics

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Authors

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and
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Learning Objectives:

- Briefly describe the correlation between diabetes and genetic risk
- Differentiate between classes of drugs used to treat type 2 diabetes for which there are known pharmacogenomic markers, and those for which there are not
- Practice some potential applications of genomics to patient care

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Diabetes Mellitus

- Affects 25.8 Million people in the USA (8.3% of the population) (ADA 2011)
- 6th leading cause of death (ADA 2011)
- Leading cause of blindness, renal failure, and nontraumatic lower extremity amputations (ADA 2011)
- Cost: $174 billion annually (ADA 2011)

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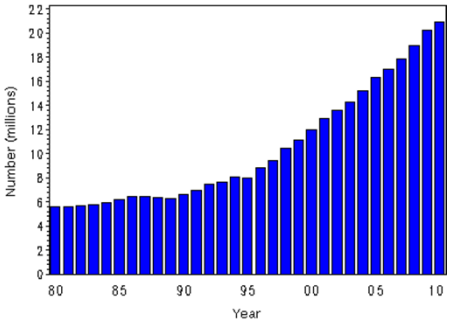
Prevalence of Diabetes



(The Centers for Disease Control and Prevention [CDC], 2011)

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Personalized Prevention

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Meet Mr. Smith

- 46 years old
- Male
- BMI = 30
- No family history of Diabetes Mellitus
- Not from higher-risk group

"I want screening for diabetes."

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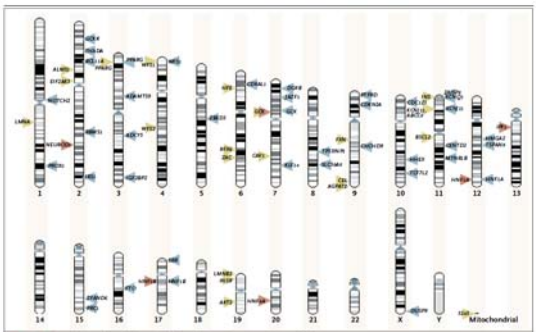


Figure 1. Genomic Locations of Proven Signals of Nonautoimmune Forms of Diabetes.
Signals are shown according to their location on each chromosome. Genes causing monogenic and selected syndromic forms of diabetes are shown to the left; genes implicated in maturity-onset diabetes of the young (red triangles) and those representing loci causal for other monogenic and syndromic forms of diabetes (green triangles). Common variants that have significant genomewide associations with multifactorial forms of diabetes are shown to the right (blue triangles); for these variants, the genes named within the triangles are indicative of signal position, but in most instances, formal proof that these are the specific genes responsible for the association is lacking.

McCarthy MI. NEJM 2010; 363(24):2339-50. Copyright © [2010] University of Oxford. All rights reserved.

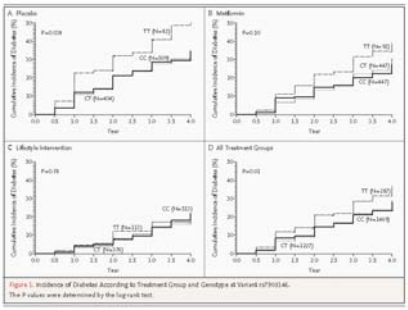
TCF7L2

- TCF7L2 is a transcription factor, part of the WNT signaling pathway and acts as a nuclear receptor for CTNNB1 (β-catenin)
- The specific genetic defect which causes the association of *TCF7L2* with Type 2 diabetes is still unclear
  - The single nucleotide polymorphism (SNP; rs7903146) showing the strongest association in the initial study remains the most likely candidate; however, it occurs in an intron (a non-coding, spacer, section of a gene) with no obvious mechanism by which it affects the activity of *TCF7L2*. As there are no coding polymorphisms correlated with rs7903146, it is likely that the causal variant acts by affecting expression of *TCF7L2*, rather than altering the structure of the expressed protein.

TCF7L2 & Diabetes Prevention Program

TT is the highest-risk genotype; associated w/ 50% risk of progress from prediabetes to diabetes over 4 yrs (vs. 25%)

Having 1 T allele carries incr lifetime odds for T2DM of **1.37**



Florez JC, et al. NEJM 2006;355:241-50. Copyright © [2006] George Washington University. All rights reserved.

Impact on patient/provider behavior?

- We know that **knowing is not enough**
- **Adherence** to healthy habits proven to reduce T2DM risk are poor
- **Family history** (FH) motivating for some
  - e.g., study of 1100 African Americans found those aware of +FH T2DM were more likely to make healthier food choices (Baptiste et al 2007)
- **REVEAL study**
  - finding of ApoE4+ led to increased AD-specific behavior change
  - patients also given ApoE info about heart disease risk reported more healthy behaviors (Grant et al 2009)
- **Survey of patients and physicians** re: their enthusiasm for the use of genetic information for T2DM risk
  - 71% of patients said this information would be motivating
  - 23% of providers said it would (Grant et al 2009)

How Does Pleiotropic Information Affect Health Behavior Changes? Initial Results from the REVEAL Study, a Randomized Trial of Genetic Testing for Alzheimer's Disease Risk

Kurt D. Christensen1, J. Scott Roberts1, Wendy R. Uhlmann2, Peter J. Whitehouse3,4, Thomas Obisesan5, Deepak L. Bhatt

Background: Des
about the impact
provides an oppo
cardiovascular di
pleiotropic infor

Methods: 257 sul
female; 16% Afr
During a risk dis
6%-70%). Subje
for CVD. Six we
that might reduc
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APOE genot

Results:
arm. Lo
differ
(OR=2.29), and
compared to the

- 62% of the pleiotropy arm reported making a health behavior change compared to 46% of the control arm.
- Logistic regression confirmed these findings (OR=2.01).
- Specific behaviors that the pleiotropy arm differed from the control arm included:
  - stress reduction (OR=2.46),
  - exercise (OR=2.40),
  - vitamin usage (OR=2.29), and
  - diet (OR=2.00)
- Distress levels at 6 weeks were not significantly different in the pleiotropy arm compared to the AD-only arm (mean IES scores 6.32 vs. 7.76)

Conclusions: Subjects receiving pleiotropic information were more likely to report changes in health behaviors, particularly those that would reduce CVD risk, but did not report higher levels of distress. The results suggest that incidental pleiotropic information may have incremental power to motivate health behavior changes for modifiable diseases. Future research using more sophisticated measures and larger samples will need to explore how people interpret pleiotropic information and what mechanisms motivate behavior changes

(Christensen et al 2010)

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deCODE T2™ test for T2DM risk in 1° care

- Panel of 4 SNPs associated w/ increased risk of developing T2DM

Table 1: Individual genotype results and their associate risks

Locus	SNP	Genotype	Risk	Population frequency of genotype	Number of cases/controls behind risk calculations	References
PPARG	rs1801282	CC	1.025	81%	14586/17968	11
CDKN2A	rs10811661	AG	0.88	28%	14586/17986	8-10
CDKAL1	rs7756992	GG	1.30	6.8%	3836/12562	7-10
TCF7L2	rs7903146	TT	1.54	7.8%	14586/17968	4,5,6
Combined	**Genetic**	**Risk**	**1.8**			

(Adapted from deCODE® 2012)

- Tests analyzed in a CLIA-certified lab

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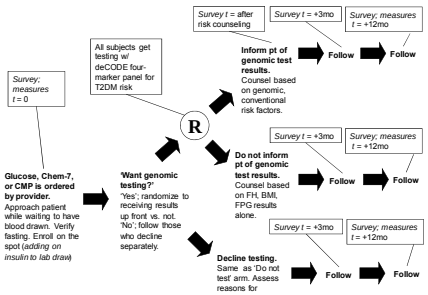
T2DM Genetic Risk Study



Outcomes

- HOMA-IR, weight loss
- Diet, physical activity
- Risk perception, other psychosocial

(Adapted from Cho et al 2012)

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Your Type 2 Diabetes Risk Profile

For Participant # clinic, ID #

Item	Result
Fasting Glucose ("Sugar")	Your fasting blood sugar (glucose) was **111** mg/dL. **This means that you are "pre-diabetic," which puts you at High Risk for diabetes.** You should probably see your doctor to follow up this test result. **1 out of 4** people with a blood sugar this high get diabetes in the next 3 to 5 years.
Family History	You have **0** first degree relatives with diabetes and **0** second degree relatives with diabetes.
Body Mass Index (BMI)	Your Body Mass Index (BMI) is **27.1**, which makes you **overweight**. Being overweight increases your risk of getting diabetes.
Age	Your age is **46**. Your chances of getting diabetes increase with age.
Genetic ("DNA") Testing	**Based on the genes tested, you are at increased genetic risk for diabetes.** • You have **6** of **8** possible higher-risk DNA changes tested for in four genes linked to higher diabetes risk.
Why Diabetes Prevention is Important	**Diabetes is a serious disease.** • Leading cause of blindness, kidney failure, and amputations in U.S. • Increases your risk of heart attack, nerve pain, digestive problems. **But diabetes can be delayed, or even prevented.**

Color Key: Yellow = average risk; Orange = increased risk; Red = highly increased risk

(Adapted from Cho et al 2012)

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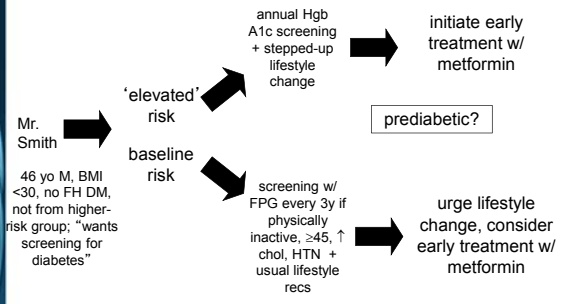
Mr. Smith (cont'd)

- **Chief complaint: "I want to be screened for diabetes."**
- Family history: Dad died of prostate cancer in his 50s
- Social history: Never smoked; has 3-5 drinks a week, usually beer
- Weight: 197 lbs (weight at last visit in 2004 was 191 lbs)
- BMI: 29.1 kg/m2
- BP: 158/82 mm Hg
- Fasting glucose: 111 mg/dl
- Hemoglobin A1C: 6.1%
- Total cholesterol: 189 mg/dl
- Triglycerides: 154 mg/dl
- HDL: 39 mg/dl
- LDL: 117 mg/dl
- PSA: 5.1
- Physical exam: Unremarkable
- **A/P: Next steps for personalized health plan?**

Role of DNA testing in managing DM risk?



Hgb A1c = hemoglobin A1c, FPG = fasting plasma glucose

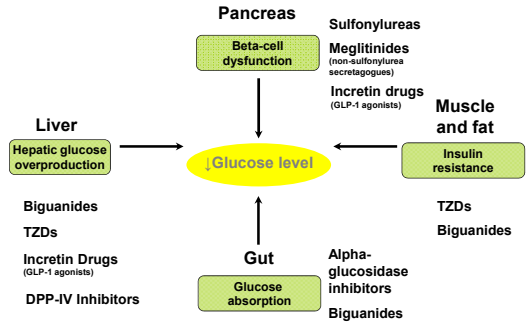
Mr. Smith is told he has a strong predisposition for diabetes. He is urged to make healthy lifestyle changes. He is also told that his blood pressure is elevated, and asked to return to clinic in a few weeks to have his blood pressure re-checked.

Glycemic Goals for Patients

	ADA (mg/dL)	AACE (mg/dL)
Fasting Glucose	70-130	<110
2 hours after eating	<180	<140
A1C (glycosylated hemoglobin)	<7%	<6.5%

(ADA 2012, CDA 2008)

Major Targeted Sites of Oral Drug Classes



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Current Drug Classes to Treat Type 2 Diabetes

- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Alpha-glucosidase inhibitors
- Nonsulfonylurea secretagogues
- DPP-IV inhibitors
- Insulins
- GLP-1 agonists
- Amylin derivative

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Biguanide

- Metformin
- Drops HbA1C levels by 1-3% (Franklin et al 2010)
- Adverse Effects: Diarrhea, nausea/vomiting, flatulence (Fortamet® Prescribing Information, Glucophage® XR Prescribing Information, Glumetza® Prescribing Information)
- Pgx: No known data available (Fortamet® Prescribing Information, Glucophage® XR Prescribing Information, Glumetza® Prescribing Information)
- Clinical Relevance: Usually first-line medication unless contraindicated or side effects not tolerated (Fortamet® Prescribing Information, Glucophage® XR Prescribing Information, Glumetza® Prescribing Information)

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Sulfonylureas

- Glipizide, glimepiride, and tolbutamide
- Drops HbA1C levels by 1-2% (Glucotrol XL® Prescribing Information, Amaryl® Prescribing Information, Orinase® Prescribing Information, Tol-Tab® Prescribing Information)
- Adverse Effects: hypoglycemia and weight gain upon initiation (Glucotrol XL® Prescribing Information, Amaryl® Prescribing Information, Orinase® Prescribing Information, Tol-Tab® Prescribing Information)
- Pgx: CYP2C9*2 and CYP2C9*3 (Holstein et al 2003, Nathan et al 2009, Zhou et al 2010)
- Clinical Relevance: Patient will be a poor metabolizer therefore excess drug will remain; may require lower doses (Holstein et al 2003, Nathan et al 2009, Zhou et al 2010)

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Tolbutamide (Sulfonylureas)

Other variants:

– CYP2C9 *1/*2 — 1.5 fold increased concentration, 29% greater reduction oral clearance (Lee et al 2002)

– CYP2C9 *1/*3 — 1.9 fold increase concentration, 48% greater reduction in oral clearance (Lee et al 2002)

Glipizide (Sulfonylureas)

Other variants:

- CYP2C9*1/*3—individuals had higher glipizide area under the curve (by 95.5%) and lower glipizide clearance (-51.1%) compared with CYP2C9*1/*1 (Tan et al 2010)

Thiazolidinedione

- Pioglitazone and rosiglitazone
- Drops HbA1C levels by 0.5-1.4% (Aquilante et al 2008, Kahn et al 2006, Kirchheiner et al 2006, Papanas et al 2009, Retnakaran et al 2009)
- Adverse Effects: edema, heart failure, upper respiratory tract infection (Actos® Prescribing Information, Avandia® Prescribing Information)
- Pgx: CYP2C8*3 (www.pharmgkb.org)
- Clinical Relevance: Patients may clear the drug faster, therefore a higher dose may be needed (Aquilante et al 2008, Kahn et al 2006, Kirchheiner et al 2006, Papanas et al 2009, Retnakaran et al 2009)

Rosiglitazone (Thiazolidinedione)

Other variants:

- Individuals with CYP2C8*3/*1 genotype had significantly lower rosiglitazone AUC and significantly higher rosiglitazone oral clearance compared with CYP2C8*1/*1 individuals (Aquilante et al 2008)

Alpha-glucosidase inhibitors

- Acarbose and miglitol
- Drops HbA1C levels by <1% (Precose® Prescribing Information, Glyset® Prescribing Information)
- Adverse Effects: Flatulence, diarrhea, abdominal pain (Precose® Prescribing Information, Glyset® Prescribing Information)
- Pgx: None known (www.pharmgkb.org)
- Clinical Relevance: Occasionally used as add-on therapy to achieve desired HbA1C goal. Often not tolerated due to adverse effects (www.pharmgkb.org)

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Nonsulfonylurea secretagogues

- Repaglinide
- Drops HbA1C levels by 1-1.5% (Black et al 2007)
- Adverse Effects: Upper respiratory infection (Prandin® Prescribing Information)
- Pgx: CYP2C8*3, KCNJ11 E23K, and SLCO1B1 (Niemi et al 2003, www.pharmgkb.org)
- Clinical Relevance:
  - Patients with CYP2C8*3 need higher doses due to having lower concentrations in AUC (Blickle 2006)
  - SLCO1B1 C>T patients will have higher AUC and respond better to a given dose (Kalliokoski et al 2008, Niemi et al 2005)
  - KCNJ11 E23K is associated with improved therapeutic effect (He et al 2008)

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Nonsulfonylurea secretagogues (cont'd)

- Nateglinide
- Drops HbA1C levels by 1-1.5%
- Adverse Effects: Upper respiratory infection (Starlix® Prescribing Information)
- Pgx: CYP2C9*2 and CYP2C9*3 and SLCO1B1 (Kirchheiner et al 2004, www.pharmgkb.org)
- Clinical Relevance: Patients with CYP2C9*2 and 3 need higher doses due to having lower concentrations in AUC (Sabia et al 2004)
- SLCO1B1C>T patients will have higher AUC and respond better to a given dose (Zhang et al 2006)

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DPP-IV inhibitors

- Sitagliptin
- Drops HbA1C levels by <1% (Januvia® Prescribing Information)
- Adverse Effects: URIs, nasopharyngitis, and headache (Januvia® Prescribing Information)
- Pgx: Minor impact on metabolism in CYP3A4 and CYP2C*8 (www.pharmgkb.org)
- Clinical Relevance: If co-administered with other drugs that go through CYP3A4 (e.g., statin), may increase side effect OF OTHER DRUG (i.e., rhabdomyolysis) (www.pharmgkb.org)

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GLP-1 agonists

- Exenatide and Liraglutide
- Drops HbA1C levels by <1% (Byetta® Prescribing Information, Bydureon® Prescribing Information, Victoza® Prescribing Information)
- Adverse Effects: nausea and hypoglycemia (Byetta® Prescribing Information, Bydureon® Prescribing Information, Victoza® Prescribing Information)
- Pgx: None known (www.pharmgkb.org)
- Clinical Relevance: Initiate as add on therapy to achieve desired HbA1C goal (www.pharmgkb.org)

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Amylin Derivative

- Pramlintide
- Drops HbA1C levels by <1% (Symline® Prescribing Information)
- Adverse Effects: Nausea, anorexia, vomiting, hypoglycemia (Symline® Prescribing Information)
- Pgx: None known (www.pharmgkb.org)
- Clinical Relevance: Initiate as add on therapy to achieve desired HbA1C goal (www.pharmgkb.org)

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Insulins

- Insulin regular, insulin glargine, insulin NPH, insulin aspart
- Adverse Effects: hypoglycemia
- Pgx: None known
- Clinical Relevance: Initiate as add on therapy to achieve glycemic control

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Return to Mr. Smith

 40

6 months later

Mr. Smith

- Mr. Smith misses his follow-up appt and returns to clinic for a cold
- Confesses he was unable to change lifestyle due to life demands
- He has gained 14 lbs; his BMI is now >30
- His blood pressure remains elevated at 162/78
- His A1C today is 7.3%

- Options for glycemic control are discussed
- Multi-marker Pgx testing is offered to help individualize care
- Mr. Smith agrees to take medications but wants to avoid giving himself multiple injections a day at all costs

Hgb A1c = hemoglobin A1c, BMI = body mass index

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Mr. Smith (cont'd)

- He is started on metformin 500 mg for 1 week and then increased to 500 mg twice a day
- Because biguanides are not reported to have associated Pgx variants, it is not necessary to wait for the results of Pgx testing
- He is also started on lisinopril for hypertension

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Pgx Test Results

- Mr. Smith has the following variants:
  - **CYP2C9*2**
  - **CYP2C9*3**
  - **KCNJ11 E23K**
  - **CYP3A4**

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Another 6 months later

- In the interim, Mr. Smith has been doing relatively well with improved glycemic control, but at this return visit complains of GI discomfort with the metformin
- His A1C remains improved at 6.9%, but his Scr is now 1.8 ml/min
- His blood pressure is 145/82
- Metformin is discontinued for concerns re:lactic acidosis

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Mr. Smith (cont'd)

Mr. Smith →

- Pgx test results:
  - **CYP2C9*2**
  - **CYP2C9*3**
  - **KCNJ11 E23K**
- These results suggest he will be a poor metabolizer of sulfonylureas, at greater risk of hypoglycemia
- They also suggest repaglinide may have enhanced effectiveness

→ Mr. Smith is started on repaglinide 0.5 mg before meals

Mr. Smith (cont'd)

- After increasing dose of repaglinide to 1 mg before meals, Mr. Smith's Hgb A1C drops to 6.5%
- Chlorthalidone is added at 25 mg daily to improve blood pressure control
- He remains above goal for LDL (cholesterol); atorvastatin 10 mg a day is started. Because he has the CYP3A4 variant, this may affect statin bioavailability
- This may also affect dosing of DPP-IV inhibitor

Takeaways

- There are ~40 common DNA variants that explain a small amount of risk for type 2 diabetes
- There are also DNA variants that affect the metabolism and action of drugs used to treat diabetes
- These pharmacogenomic markers have the potential to reduce the extent of trial and error medicine and improve outcomes for patients
- Patient preferences regarding interest in and comprehension of genetic risk information should be taken into account when considering using genetic risk and/or pharmacogenomic testing

END OF CONTENT SECTION

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Program Evaluation Survey

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Evaluate program implementation efficacy

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Question and Answer Session

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