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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

Disclaimer
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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

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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.

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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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
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)

Prevalence of Diabetes

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.”
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

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)
Background: Despite the growing number of genes associated with risk for multiple diseases, little is known about the impact of disclosing pleiotropic information to patient populations. Apolipoprotein E (APOE) ε4 carriers were at increased risk of developing cardiovascular disease (CVD) and its 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 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.

Methods: 257 subjects seeking AD risk assessments were enrolled across four study sites (mean age 58; 55% female; 16% African American; 71% with affected FDR) and randomized into one of two disclosure arms.

During a risk disclosure session, all subjects received their APOE genotypes and an AD risk estimate (range: 6%-70%). Subjects randomized to a pleiotropy arm were also told that APOE ε4 risk allele is common. In a randomized clinical trial, we explored how pleiotropic information affected health behavior changes. 

Results: 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=2.09)

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). 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, compared to the AD-only arm (mean IES scores 6.32 vs. 7.76).
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.
Glucose absorption

Hepatic glucose overproduction

Beta-cell dysfunction

Insulin resistance

Major Targeted Sites of Oral Drug Classes

Pancreas

Sulfonylureas
Meglitinides
Gut

Insulin

Muscle and fat

Liver

Gluco- absorption

Thiazolidinediones
Alpha-glucosidase inhibitors
Nonsulfonylurea secretagogues
DPP-4 inhibitors
Insulins
GLP-1 agonists
Amylin derivative

Current Drug Classes to Treat Type 2 Diabetes

• Biguanides
• Sulfonylureas
• Thiazolidinediones
• Alpha-glucosidase inhibitors
• Nonsulfonylurea secretagogues
• DPP-4 inhibitors
• Insulins
• GLP-1 agonists
• Amylin derivative

• 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)

• 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)
• 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)
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
- 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)

Nonsulfonylurea secretagogues

- Repaglinide
- Drops HbA1C levels by 1-1.5% (Black et al 2007)
- Adverse Effects: Upper respiratory infection (Prandin® Prescribing Information)
- 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)

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)

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)
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)

Amylin Derivative

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

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

Return to Mr. Smith
6 months later

- Mr. Smith misses his follow-up appointment 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%

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

Pgx Test Results

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

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
Mr. Smith (cont’d)

- 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

https://kuooffice.wufoo.com/forms/pharmgeda-diabetes/

Evaluate program implementation efficacy

Question and Answer Session