Spring 5-18-2020

Precision Medicine and the Treatment of Type 2 Diabetes Mellitus

Emily Stunek
UND, emily.stunek@und.edu

Precision Medicine and the Treatment of Type 2 Diabetes Mellitus

An independent study submitted to the faculty of the College of Nursing and the University of North Dakota in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN NURSING

In

Family Nurse Practitioner

By

Emily Stunek BAN, RN, CDCES

Grand Forks, North Dakota

Permission

Precision Medicine and the Treatment of Type 2 Diabetes Mellitus

Department Nursing

Degree Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing & Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in his/her absence, by the chairperson of the department or the dean of the Graduate School. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use, which may be made of any material in my independent study.

Signature Emily Stunek

Date 04/18/2020

Precision Medicine and Type 2 Diabetes Mellitus

Abstract

This literature review was carried out based on the completed of an Objective Structured Clinical Examination (OSCE) and oral defense. After reviewing the case report, the topic of precision medicine and the treatment of type II diabetes was selected. Using CINAHL Complete and PubMed, a search was conducted using the controlled vocabulary terms precision medicine, pharmacogenetics, genetically guided therapy, type II diabetes, and diabetes mellitus type II. The search terms were connected using the Boolean connectors AND and OR. The search was further refined using the following criteria: published between 1/1/2015 and 12/31/2020, English language, peer-reviewed, and human. Guidelines from the American Association of Clinical Endocrinologists and the American Diabetes Association were reviewed for current recommendations on second-line treatment recommendations for type II diabetes.

The literature review shows precision medicine for the treatment of type II diabetes has started with monogenic diabetes and neonatal diabetes as well as specific genetic markers that may indicate patient response to second-line medications. The most impactful advancement of type II diabetes management through precision medicine is the sub stratification of diabetes into five subgroups and their associated genetic makeup and risk of complications. It also outlines that precision medicine also includes lifestyle intervention as well as machine learning. Further research is needed before implementation within healthcare regarding genomic markers, cost feasibility, and transferability across healthcare organizations.

Background

For many years there have been type I and type II diabetes. Over time, this has evolved to include gestational diabetes, latent autoimmune diabetes in adults, neonatal diabetes, and maturity-onset diabetes of youth. Of these, type 2 diabetes is the most common (American Diabetes Association, 2015). According to the American Diabetes Association (2018), in 2015, more than 30.3 million Americans were living with diabetes and of those, only 23.1 million were diagnosed. Currently, diabetes remains the seventh leading cause of death in the United States. However, it is widely accepted that these deaths are underreported as only 35 to 40% of people with diabetes who died had diabetes listed on their death certificate (American Diabetes Association, 2018). It is no surprise that with the rising incidence of type II diabetes, the cost of diabetes continues to rise as well. Recent statistics show that in 2017, type II diabetes cost the United States $327 billion due to both direct and indirect costs (American Diabetes Association, 2018). Compared to individuals living without diabetes, patients with diabetes have higher rates of all infections, including bone and joint infections, sepsis, and cellulitis (Carey et al., 2018). The risk of cellulitis for individuals living with type II diabetes increases with neuropathy, which is the loss of sensation, particularly in the hands and feet. Hyperglycemia also increases the risk of infections by providing infectious microorganisms nutrients to grow and thrive.

Organizations such as the American Diabetes Association (2019) and the American Association of Clinical Endocrinologists (2020) have created treatment algorithms that all agree first-line treatment, behind nutrition and lifestyle modification, should begin with metformin up to 2000 mg per day. In the case study outlined below, the individual was being treated with metformin at 1000 mg daily. However, her glucose remains elevated. Due to sustained hyperglycemia, it is recommended to increase metformin to the optimal dose of 2000 mg per day

as agreed upon by the American Diabetes Association (2019) and the American Association of Clinical Endocrinologists (2020). However, after the first-line treatment with metformin, the optimal second-line treatment becomes less clear. Options to select from include sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, SGLT2 inhibitors. A combination of these is often utilized before progressing to one or more of the various types of rapid, short, intermediate, and long-acting insulins.

In 2015, during the State of the Union Address, President Obama announced a Precision Medicine Initiative aimed at patient-powered research. This initiative was implemented to accelerate biomedical discoveries to help clinicians better select treatments that will work best for their patients (The White House, Office of the Press Secretary, 2015). With the implementation of precision medicine in the treatment of type II diabetes, the increased achievement of optimal glycemic control could reduce the risk of complications, including cellulitis and improve the diabetes outcomes.

In this literature review, a case report will be incorporated describing a woman in her late 50s who presented to the clinic with fever, chills, confusion, and forgetfulness for the past one day. She has a history of hypertension, dyslipidemia, as well as type 2 diabetes. Despite being on metformin, her glucose remained elevated. Hyperglycemia, as a result, was likely a contributing factor to her sepsis. Sepsis was identified to have resulted from cellulitis in her left lower extremity. The main emphasis of this literature review will be looking at the evidence-based recommendations utilizing precision medicine in the treatment of type II diabetes to help determine which secondary line of medication is optimal for individual patients with type II diabetes.

Case report

Chief Complaint: 58-year-old female who was brought to the clinic today by her sister with complaints of fever, chills, confusion, and forgetfulness for one day

HPI: Jessica Brown is a pleasant 58-year-old female who presents the clinic today brought in by her sister due to symptoms of fever, chills, confusion, and forgetfulness for the past day. She denies any recent exposure to illness. She denies any upper respiratory symptoms, including coughing, congestion, runny nose, sinus pressure, wheezing, or shortness of breath. Change and eyes any urinary symptoms, including urgency, frequency, or pain with urination. Her health history is positive for diabetes, hypertension, and dyslipidemia. She does not self-monitor glucose at home. She reports taking ibuprofen within the last two hours. Fever today in the clinic at 104.7°F. She denies any recent hospitalization or antibiotic use. She denies any chest pain shortness of breath palpitations dyspnea on exertion or lower extremity edema. She is not able to identify any aggravating factors. She denies any new rashes lesions or cuts on her skin. Her symptoms have progressively worsened over the past day. She states only presenting to the clinic today due to her sister's concerns regarding her confusion and forgetfulness. Her confusion and forgetfulness make her a poor historian.

Past Medical History

Medical:

1. Dyslipidemia
2. Hypertension
3. Type 2 diabetes mellitus

Surgical:

1. Tubal ligation

Medications:

1. Ezetimibe (ZETIA) 5 mg tablet
2. Lopressor 50 mg two times daily
3. Lisinopril 10 mg daily
4. Metformin 1000 mg daily
5. Fish oil 1000 mg daily
6. Zocor 80 mg daily
7. Aspirin 325mg daily

Allergies: No known allergies

Screening: Mammogram, colonoscopy, and pap smear up to date. All negative on most recent exams.

Immunizations: Up to date on all immunizations including influenza and pneumonia

Social History: She is retired and enjoys reading and watching television in her free time. She quit smoking in 2002. She denies any medical or recreational drug use or alcohol consumption. She exercises one to two times per week.

Family History: This is a positive history only for cardiovascular disease and type II diabetes in her father.

Review of Systems

General: Positive for fevers, chills, confusion, and forgetfulness. She denies weight loss, fatigue, or changes in sleep.

HEENT: Denies headache, hearing change, vision change, vertigo, congestion, rhinorrhea, or sore throat

Cardiovascular: Denies chest pain, palpitations, and edema. No history of heart murmurs

Respiratory: Denies cough, dyspnea, wheezing, or pain

Musculoskeletal: Denies muscle or joint pain/stiffness, back pain, or swelling of joints

Urinary: Denies urgency, frequency, pain, burning or hematuria

Gastrointestinal: Denies vomiting, diarrhea, constipation or appetite change

Skin: Denies rashes, itching, dryness or color change

Neurologic: Denies headaches, syncope, seizures, or difficulty with balance or coordination. Positive for numbness and tingling in bilateral toes and confusion.

Physical Examination

General: Healthy appearing, alert, oriented x3, well dressed, good hygiene, no acute distress. Poor historian.

Vitals: BP: 194/83, HR: 119, RR: 14, Temp: 104.7 F, O2: 93% RA, weight: 260 lb, height 5'5"

HEENT: Atraumatic, PERRL, EOMs intact, external ears normal, ear canals normal, tympanic membranes normal, no tenderness or discharge, normal lips, tongue, buccal mucosa and pharynx without lesions, mucus membranes moist, nares patent.

Neck: Full range of motion, supple, no palpable nodes, thyroid within normal limits

Respirations: Normal respirations, good expansion with good diaphragmatic excursion, clear to auscultation without wheezes or rhonchi.

Cardiovascular: Regular rhythm and rate, S1 and S2 normal; no murmurs. No peripheral edema.

Abdominal: Soft, non-distended, non-tender, normal bowel sounds in all quadrants, no masses

Musculoskeletal: Full range of motion to all extremities, strength, and sensation intact, capillary refill <2 seconds.

Skin: Area of erythema, edema, warmth, and pain with an indefinite border on the anterior aspect of the left lower limb. Negative for crepitus, vesicles, blisters, or necrosis. No apparent trauma.

Neurological: Cranial nerves II to XII intact, reflexes symmetric, sensation and gait normal

Differential diagnosis: cellulitis, deep vein thrombosis, contact dermatitis, thrombophlebitis, stasis dermatitis, hyperglycemia, hypertension, pneumonia, influenza, urinary tract infection, stroke, alcohol or drug ingestion, dehydration, hyperthermia, carbon monoxide poisoning, hypoxia

Labs/Imaging

1. CBC with differential – white blood count (12.5) and Seg Neut Absolute (10.1) elevated. All other counts within normal limits.
2. C-reactive protein – elevated (144.4 mg/dl)
3. CMP – glucose (266 mg/dl) and anion gap with K (22 meq/L) elevated, sodium (132 meq/L), chloride (94 meq/L), CO2 (20 meq/L) below normal limits. All other counts within normal limits
4. Lactic acid – elevated (4.4 mmol/L)
5. Erythrocyte sedimentation rate – elevated (57 mm/Hr)

Conclusion:

1. Sepsis due to cellulitis of the left lower leg
2. Systolic hypertension
3. Hyperglycemia

Recommendations:

1. Refer the patient to the emergency room for further evaluation and treatment

2. Follow up in the clinic within one week after hospital discharge
3. Continue to monitor hypertension
4. Consider increasing metformin and the addition of a second line antihyperglycemic medication

Plan

Send the patient to the emergency room for admission and treatment of sepsis due to cellulitis. Intravenous antibiotic therapy should be initiated within one hour of presentation after obtaining cultures. Empiric broad-spectrum antibiotics, such as carbapenem or piperacillin-tazobactam, should be selected to cover all likely pathogens, including gram-positive and gram-negative bacteria. Intravenous fluids should be initiated within the first three hours to treat and or prevent intravascular hypovolemia (Schmidt & Mandel, 2020). Follow up recommended within one week after hospitalization to evaluate hypertension as well as hyperglycemia.

Literature Review

In 2015, during the State of The Union Address, President Barack Obama announced the Precision Medicine Initiative with the hopes of fast-tracking biomedical discoveries and aiding clinicians in best-selecting treatments that would be optimal for their patients (The White House, Office of the Press Secretary, 2015). In modern medicine, a majority of precision medicine research has been geared toward cancer therapies and treatments. The Precision Medicine Initiative was aimed not only at cancer research and treatment but also genetic registries that can be used to further research and medicine for many acute and chronic medical conditions. To date, there has been little research on precision medicine and type 2 diabetes prevention and treatment. This literature review will focus on the utilization of precision medication to treat type 2 diabetes. The report will including how monogenic diabetes and neonatal diabetes have paved

the way for precision medicine, how precision medicine has allowed us to further stratify diabetes into subgroups, individual responses to specific medications, and the various type of precision medicine.

Monogenic Diabetes and Neonatal Diabetes

In the early phases of precision medicine and diabetes management, monogenic diabetes, as well as neonatal diabetes, have led the charge in the utilization of precision medicine in the management of diabetes. According to Gloyn and Drucker, up to 3% of diabetes cases diagnosed in children have a monogenic basis (2018). These patients typically present with a diabetes diagnosis under the age of 25 years old, a strong family history of diabetes, are thin, and have negative autoantibodies (Gylon & Drucker, 2018). They do, however, have positive C-peptide, a measure of their insulin production (Gylon & Drucker, 2018). They also typically have a mutation in the transcription gene HNF1A (Gylon & Drucker, 2018). Frequently these individuals are misdiagnosed as having type I diabetes. However, instead of requiring multiple daily insulin injections, many of these patients are sensitive to treatment with sulfonylureas (Gylon & Drucker, 2018). Through the use of precision medicine, genetic markers have been identified for individuals diagnosed with monogenic diabetes and recommend the best treatment options to provide the highest quality of life.

Along with monogenic diabetes, neonatal diabetes has also paved the way for precision medicine and diabetes management. Neonatal diabetes is diagnosed during the first six months of life. It has been shown to have mutations at several genes, including KCJN11, SUR1, GCK, and INS (Prasad & Groop, 2018). Neonatal diabetes can be either transient or permanent and optimal treatment is dependent on an appropriate genetic diagnosis (Prasad & Groop, 2018). Some forms of neonatal diabetes not only affect insulin production but can also cause developmental defects.

Similar to monogenic diabetes, individuals with neonatal diabetes can be sensitive to sulfonylureas and are often misdiagnosed as having type I diabetes (Prasad & Groop, 2018). In the clinical application of precision medicine and genetics, it remains limited to the rare genetic forms of diabetes, including monogenic diabetes and neonatal diabetes (Fitipaldi, McCarthy, Florez & Franks, 2018).

Stratification into Subgroups

As discussed earlier in this paper, to date, precision medicine has been focused on cancer research and treatment. It has allowed us to identify the increased risk of cancer, for example, in those with Ashkenazi Jewish heritage. It has also been recently identified as a common mutation in the Greenlandic Inuit of the TBC1D4 gene substantially increased the risk of type II diabetes (Manousaki et al., 2016). Manousaki et al. identify that this gene mutation is present in approximately 27% of Canadian and Alaskan Inuit (2018). The TBC1D4 gene mutation leads to increased postprandial glucose values and lower fasting glucose values and, as a result, in increased risk underdiagnosed this diabetes (Manousaki et al., 2016). Through the utilization of precision medicine, it would be recommended that those of Greenlandic Inuit heritage should undergo an oral glucose tolerance test to further assess for type II diabetes (Manousaki et al., 2016).

In modern medicine, type II diabetes is a diagnosis of exclusion. Hyperglycemia, in the absence of neonatal diabetes or monogenic diabetes, autoantibodies, trauma, illness, or medications, is given the diagnosis of type II diabetes (Prastad & Groop, 2018). However, with precision medicine, using the variable agents of diagnosis including body mass index, hemoglobin A1c, GAD autoantibodies, C-peptide, and glucose, diabetes is further stratified into five distinct subgroups (Fitipaldi et al., 2018; Prastad & Groop, 2018; Gloyn & Drucker, 2018).

1. Severe autoimmune diabetes with the presence of GAD autoantibodies, low insulin secretion, and poor metabolic control
2. Severe insulin-deficient diabetes with the presence of low insulin secretion, poor metabolic control and increased risk of retinopathy
3. Severe insulin-resistant diabetes with the presence of severe insulin resistance, obesity, late-onset, and increased risk of nephropathy
4. Mild obesity-related diabetes with the presence of obesity, early-onset and good metabolic control
5. Mild age-related diabetes with the presence of late-onset and good metabolic control

Similar to the sub stratification identified above, Dennis et al. similarly defines three subgroups based on clinical cut offs for obesity and high triglycerides (2018).

1. Group A – Nonobese and normal triglycerides
2. Group B – Nonobese or normal triglycerides
3. Group C – Obese and high triglycerides

These sub stratifications identified through new precision medicine allow providers and clinicians to begin to look at diabetes as more than type one and type II. By identifying the group that each patient falls into, the provider will better be able to recommend treatment options for improved management and quality of life.

Responses to specific medications

After the initiation of dietary and lifestyle changes, the most common treatment for type II diabetes is the addition of an oral hypoglycemic agent or a non-insulin in an injectable (Dawed, Zhou & Pearson, 2016). The classes of hypoglycemic agents to treat type II diabetes include biguanides, sulfonylureas (Sus), meglitinides (glinides), thiazolidinediones (TZDs),

alpha-glucosidase inhibitors, glucagon-like peptide (GLP)-1 receptors, dipeptidyl peptidase (DPP)-4 inhibitors, and sodium-glucose transporter (SGLT)-2 inhibitors. Increasing research is being done around each of these classes of medications and the specific biomarkers that may enhance or reduce their efficacy for individual patients.

Biguanides include the medication metformin, which is the first-line treatment for virtually all individuals with new-onset type II diabetes. The mechanism of action for metformin is the suppression of hepatic glucose production through gluconeogenesis. However, the exact mechanism of action is still unknown (Yang, Heredia, Beltramo & Soria, 2016). Despite being the first-line medication, many individuals treated with metformin are considered to have an inadequate response frequently due to gastrointestinal side effects (Mannino, Andreozzi & Sesti, (2018). It has been shown, nonetheless, that genetic factors can influence an individual's glucose response to metformin, including the organic cation transporter (OCT) family, ATM, and SLC 282 (Mannino, Andreozzi & Sesti, (2018). Those individuals with the OCT variant have been shown to have increased area under the curve compared to those without after metformin treatment as well as a more significant A1 C reduction during the initiation and maintenance (Dawed et al., 2016).

If metformin as a first-line medication is not sufficient to bring glucose values within the target range, a second-line medication must be selected. Through the utilization of precision medicine, we would anticipate being able to select a second line medication based on the patient's biomarkers to improve overall treatment, compliance, prevention of complications and quality-of-life. Markers of high insulin resistance and triglycerides were associated with a decreased response to DPP-4 inhibitors (Dennis et al., 2018). However, this response was not associated with GLP-1 receptor agonists (Dennis et al., 2018). SGLT-2 inhibitors, despite

showing promise for those individuals with established ASCVD, heart failure, or CKD the are relatively new, and evaluation of efficacy and safety of these medications has not yet fully been established (Heo & Choi, 2019). Each of the second line medications contains a different mechanism of action aimed at the improvement of glycemic control and has various gene associations that impact the efficacy for the individual patient. Pharmacogenetic biomarkers require further research specific to second-line medications for the treatment of type II diabetes; however, it is shaping up to be a promising tool implemented through the precision medicine initiative.

Types of Precision Medicine

Often when discussing precision medicine, we jump toward pharmacogenomics and the pharmaceutical options that can be utilized in the management and treatment of chronic diseases. However, the literature supports precision medicine beyond that of pharmaceuticals and also expands into lifestyle modification and machine learning (Mutie, Giordano & Franks, 2017; Kim et al., 2018). As discussed previously, genetics can impact how individual patients respond to specific medications, and this plays a significant role in the patient's ultimate success in treating their type II diabetes. However, as providers, we should also be aiming at preventing type II diabetes from occurring. It has been shown that even the successful lifestyle modifications only delay type II diabetes by approximately three years rather than preventing it from occurring (Mutie, Giordano & Franks, 2017). Of the research that has been completed, there have yet to be any biomarkers identified that will have a meaningful impact on recommendations for optimizing lifestyle modification (Mutie, Giordano & Franks, 2017). It is hopeful that with ongoing research, these biomarkers may provide useful information in the future for recommendations of individualized lifestyle modification for the prevention of type II diabetes.

Along with pharmacogenomics and lifestyle modification, another application for precision medicine is through machine learning. With type II diabetes being a multifactorial chronic disease, it is challenging to identify recommendations that can be transferred across populations and organizations. With the vast amount of information being gathered, our knowledge about the human genome continues to grow. Through the utilization of artificial intelligence in machine learning, we can enhance precision medicine by analyzing the data available to identify critical statistics to focus on the implementation of precision medicine within healthcare. Kim at all. (2018) created a model utilizing machine learning that would be transferable across healthcare systems for the implementation of precision and medicine. Pulling data from large national data sets, and multiple providers, allows healthcare models to be more transferable, as the models are not built on a single local healthcare system data (Kim et al., 2018). This utilization of machine learning can help precision medicine to become more accessible to the general healthcare community.

Summary and Recommendations

1. Maturity onset diabetes in youth (MODY) and neonatal diabetes have paved the way for the initiation of precision medicine in diabetes
2. Further stratification from type I and type II diabetes is required for further work in precision medicine and its impact on diabetes treatment
3. Specific medications have varying individual responses based on multiple genetic markers with mild to moderate effects.
4. Precision medicine is more than medicine but also includes lifestyle interventions and machine learning

5. Further research is needed as well as cost assessment for the implementation of precision medicine into practice

References

American Diabetes Association. (2015). Facts about Type 2. Retrieved March 3, 2019, from http://www.diabetes.org/diabetes-basics/type-2/facts-about-type-2.html

American Diabetes Association. (2019, January). Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2019. *Diabetes Care*, S90-S102. http://dx.doi.org/10.2337/dc19-S009

American Diabetes Association. (2018). Statistics about diabetes. Retrieved March 3, 2019, from http://www.diabetes.org/diabetes-basics/statistics/

Carey, I., Critchley, J., Dewilde, S., Harris, T., Hosking, F., & Cook, D. (2018). Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. Diabetes Care, 41(3), 513-521.

Dawed, A., Zhou, K., & Pearson, E. (2016). Pharmacogenetics in type 2 diabetes: Influence on response to oral hypoglycemic agents. Pharmacogenomics and Personalized Medicine, 9, 17-29.

Dennis, J., Shields, B., Hill, A., Knight, B., Mcdonald, T., Rodgers, L., . . . Jones, A. (2018). Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-term Glycemic Response to DPP-4 Inhibitor Therapy. Diabetes Care, 41(4), 705-712.

Fitipaldi, H., Mccarthy, M., Florez, J., & Franks, P. (2018). A Global Overview of Precision Medicine in Type 2 Diabetes. Diabetes, 67(10), 1911-1922.

Garber, A., Handelsman, Y., Grunberger, G., Einhorn, D., Abrahamson, M. J., Barzlay, J. I., ... Umpierrez, G. E. (2020, January). Consensus statement by the American Association of Clinical Endocrinologists and the American College of Endocrinology on the

Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocrine Practice*, *26*(1), 107-139. Retrieved from https://www.aace.com/pdfs/diabetes/algorithm-exec-summary.pdf

Gloyn, A., & Drucker, D. (2018). Precision medicine in the management of type 2 diabetes. The Lancet Diabetes & Endocrinology, 6(11), 891-900.

Heo, C., & Choi, C. (2019). Current Progress in Pharmacogenetics of Second-Line Antidiabetic Medications: Towards Precision Medicine for Type 2 Diabetes. Journal of Clinical Medicine, 8(3), Journal of Clinical Medicine, 2019, Vol.8(3).

Kim, E., Caraballo, P., Castro, J., Pieczkiewicz, M., & Simon, R. (2019). Towards more Accessible Precision Medicine: Building a more Transferable Machine Learning Model to Support Prognostic Decisions for Micro- and Macrovascular Complications of Type 2 Diabetes Mellitus. Journal of Medical Systems, 43(7), 1-12.

Mannino, G., Andreozzi, F., & Sesti, G. (2019). Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. Diabetes/Metabolism Research and Reviews, 35(3), N/a.

Manousaki, D., Kent, J., Haack, K., Zhou, S., Xie, P., Greenwood, C., . . . Richards, J. (2016). Toward Precision Medicine: TBC1D4 Disruption Is Common Among the Inuit and Leads to Underdiagnosis of Type 2 Diabetes. Diabetes Care, 39(11), 1889-1895.

Mutie, P., Giordano, G., & Franks, P. (2017). Lifestyle precision medicine: The next generation in type 2 diabetes prevention? BMC Medicine, 15(1), 171.

Prasad, R., & Groop, L. (2019). Precision medicine in type 2 diabetes. Journal of Internal Medicine, 285(1), 40-48.

Schmidt, G. A., & Mandel, J. (2020, March 6). Evaluation and management of suspected sepsis and septic shock in adults. *UpToDate*, 1-55. Retrieved from https://www.uptodate.com/contents/evaluation-and-management-of-sus?earch_result&selectedTitle=1~150&usage_type=default&display_rank=1

The White House, Office of the Press Secretary (2015). FACT SHEET: President Obama's Precision Medicine Initiative. Retrieved from https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

Yang, P., Heredia, V., Beltramo, O., & Soria, D. (2016). Pharmacogenetics and personalized treatment of type 2 diabetes mellitus. International Journal of Diabetes in Developing Countries, 36(4), 508-518.