Cystic Fibrosis

Care Guidelines for CF-Related Diabetes

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This document is based on a consensus of evidence and/or clinical expert opinion.

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General Age Range Guide

Infant	Preschool	Child	Adolescent	Adult
0 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years	≥ 18 years

Abbreviation Guide

BS . . . . . Blood Sugar
CF . . . . . Cystic Fibrosis
CFRD . . . . Cystic Fibrosis-Related Diabetes
CF-IGT . . . Cystic Fibrosis-Impaired Glucose Tolerance
CFTR . . . . Cystic Fibrosis Transmembrane Regulator
CGM . . . . Continuous Glucose Monitoring
DKA . . . . Diabetic Ketoacidosis
FH . . . . . Fasting Hyperglycemia
FBS . . . . . Fasting Blood Sugar
FPG. . . . . Fasting Plasma Glucose
OGTT . . . . Oral Glucose Tolerance Test
PCTL . . . . Percentile
PFT . . . . . Pulmonary Function Test
PICC . . . . Peripherally inserted central catheter
SMBG . . . Self-Monitoring Blood Glucose

Introduction

Cystic Fibrosis-related diabetes (CFRD) is a type of diabetes unique to Cystic Fibrosis and is the end point of a spectrum of glucose abnormalities which begins with early insulin deficiency causing glucose tolerance abnormalities. CFRD is a common complication of cystic fibrosis, occurring in approximately 20% of adolescents and up to 40-50% of adults. It is most commonly seen in those individuals with severe CF mutations associated with exocrine pancreatic insufficiency.

The pathophysiology of CFRD is complex. It is thought to be primarily due to insulin deficiency occurring as a result of pancreatic destruction. More recent data suggests that additionally, the cystic fibrosis transmembrane regulator (CFTR) plays a direct role in insulin secretion, and that the defect plays an as yet not fully understood role in the development of CFRD. Insulin resistance also occurs in CFRD, usually worsening with acute pulmonary exacerbation and corticosteroid therapy.

While it shares characteristics of Type 1 and Type 2 Diabetes, CFRD is a distinct disorder. CFRD is the end-point of a spectrum of glucose abnormalities which begins with early insulin deficiency. Glucose abnormalities in CF are known to be variable – an individual might fluctuate between CFRD, CF-Impaired Glucose Tolerance (CF-IGT) indeterminate glucose tolerance, and normal glucose tolerance - but ultimately these abnormalities will progress. Refer to Diagnosis section for CFRD diagnostic criteria.

Cystic Fibrosis-Impaired Glucose Tolerance (CF-IGT)

Cystic Fibrosis-Impaired Glucose Tolerance (CF-IGT) is characterized by an abnormally raised glucose but under the CFRD threshold using a 2-hour plasma glucose level on an OGTT.

CF-IGT can last for many years and precedes a CFRD diagnosis. It is frequently found in individuals with CF, and becoming recognized as an important diagnosis in its own right. Data shows that the years preceding a CFRD diagnosis are associated with an increased number of respiratory exacerbations and poorer lung function and nutritional status. As such, there is increasing evidence to suggest that CF-IGT might be just as important in CF as CFRD.

Small studies have described a clinical, nutritional, and respiratory benefit of insulin therapy in patients with CF-IGT. It has also been suggested that early institution of insulin therapy could prolong the lifespan of remaining insulin-secreting beta cells. At this time however, there is insufficient outcome-based data available to support a recommendation of insulin therapy for CF-IGT. Randomized controlled trials evaluating the benefit of insulin therapy in CF patients with early glucose abnormalities are underway and we can anticipate further recommendations on this soon.

It is important to note that the reproducibility of the Oral Glucose Tolerance Test (OGTT) is generally poor. Thus, if a prior OGTT result is abnormal but the repeat result falls within a normal range, and if the patient has symptoms that could be attributed to glucose abnormalities (such as unexplained decreased pulmonary function values and/or recent unexplained weight loss.) despite a normal OGTT result, consider:

- endocrine referral and/or
- 2-hour postprandial home glucose monitoring using a glucometer

Other Glucose Abnormalities

a. **Impaired Fasting Glucose** (in the presence of a normal 2-hr plasma glucose level)

b. **Indeterminate Glycemia** - when a mid-OGTT level (example - a 1-hr sample) is high, in an otherwise normal OGTT. (Note: most OGTTs do not include a 1-hr sample.)

- Currently, there is insufficient information to describe the significance or make recommendations on therapy for these two forms of glucose abnormalities.
- If either of these abnormalities are present, consider endocrine referral and/or 2-hour post prandial monitoring (see CF-IGT above).

Diabetic ketoacidosis (DKA) is so rare in CFRD that any individual with CF and DKA should be screened for diabetes autoantibodies to rule out Type 1 Diabetes.

c. **Reactive hypoglycemia**

- The incidence of reactive hypoglycemia on an OGTT in CF individuals does not appear to be higher than in individuals without CF.
- The presence of reactive hypoglycemia does not seem to predict development of CF-IGT or CFRD.

Table 1: Incidence of CFRD and CF-IGT in British Columbia

CF Clinic	# CF Pts ≥10 Yrs	# with CFRD	# with CF-IGT	# CFRD Post-transplant
BC Children's Hospital (Pediatrics)	62	10 (16.1%)	17 (27.4%)	N/A
Victoria General Hospital (Pediatrics)	10	2 (20%)	3 (30%)	0
St. Paul's Hospital (Adults)	253	81 (32%)	16 (6.3%)	3
Royal Jubilee Hospital (Adults)	51	10 (19.6%)	15 (29.4%)	5

(April 2017)

Screening

The diagnosis of CFRD is associated with worse health outcomes (accelerated nutritional decline, loss of lung function, and earlier mortality). Appropriate and timely intervention might help to prevent significant morbidity and even mortality. Furthermore, early CFRD can be clinically silent, and therefore regular screening is imperative.

When to screen

- Begin annual screening starting at aged 10 years for all those not previously diagnosed with diabetes.[1,2]
- In particular, screen those ≥ 10 years at increased risk for developing CRFD:
  - Those on I.V. antibiotics or corticosteroids (once in stable health, see below)
  - Those on enteral feeding
  - Those planning or confirmed pregnant
  - Those who are pre-transplant
- Screen those ≤ 10 years of age if risk factors or clinical concerns are present.

Studies have shown a higher prevalence and incidence of CFRD after age 10 years in both pancreatic sufficient and insufficient patients, therefore it is recommended for all individuals with cystic fibrosis to start screening by age 10 years.

Recommended Screening Method

- Screen using a 2-hour 75 g (1.75 g/kg to max 75 g) Oral Glucose Tolerance Test (OGTT).[1]
  - Always do an OGTT while in stable baseline health *(not, for example, during an acute pulmonary exacerbation)*.
  - Patients should fast for at least 8 hours prior to the start of testing.
  - If applicable, enteral continuous drip feedings should be held for at least 8 hours.
  - When an OGTT cannot be done, a 2-hour postprandial reading might provide valuable information.

The OGTT was designed to estimate the risk of microvascular complications in Type 2 Diabetes and not the nutritional and respiratory complications seen in CFRD. It may be that the OGTT is not sensitive enough to predict these secondary complications in CFRD and that new treatment strategies will be considered in the near future, such as Continuous Glucose Monitoring (CGM).

Note: HbA1C not recommended as a screening test.[1, 2]
HbA1C has been shown to not be sensitive enough to identify CFRD in children. In certain situations, A1C could be used to confirm a diagnosis – see 'Diagnosis of Cystic Fibrosis-Related Diabetes'.

Screening those at risk

a. Acute illness (such as PEx) requiring intravenous antibiotics and/or systemic glucocorticoids:[1]

- Monitor fasting and 2-hour postprandial plasma glucose levels for the first 48 hours.
- Repeat fasting and 2-hour postprandial plasma glucose levels on day 8 for those receiving glucocorticoids.
- Confirm elevated blood glucose levels found with self-monitoring blood glucose (SMBG) by a certified laboratory.

b. Continuous enteral feedings:[1]

- Measure mid- and immediate post-feeding plasma glucose levels:
  - at the time of initiating gastrostomy feeding
  - monthly by SMBG
- Confirm elevated blood glucose levels found with SMBG by a certified laboratory.

c. Planning or confirmed pregnant[1]

- For women planning a pregnancy or confirmed pregnant, screen for pre-existing CFRD if they have not had a normal CFRD screen in the last 6 months.
- For pregnant women not known to have CFRD, screen for gestational diabetes mellitus with blood glucose measures at 0 hour, 1 hour, and 2 hours:
  - at 12 to 16 weeks gestation and
  - at 24 to 28 weeks gestation
- For postnatal women with gestational diabetes mellitus (diabetes first diagnosed during pregnancy), screen for CFRD 6 to12 weeks after the end of the pregnancy.

Note: CF patients with gestational diabetes are not considered to have CFRD.

d. Pre-transplant[1]

- For those who are not known to have diabetes, screen preoperatively if they have not had CFRD screening in the last 6 months.
- Monitor plasma glucose levels closely in the perioperative critical care period and until hospital discharge.
- Screen those who do not meet diagnostic criteria for CFRD at the time of hospital discharge, as recommended for all patients with CF.

Diagnosis

The onset of CFRD is defined as the date a person first meets diagnostic criteria, even if hyperglycemia subsequently abates.[1]

It is not necessary to distinguish between CFRD with and without Fasting Hyperglycemia (FH).[1, 2]

During a period of stable baseline health[1, 2]

- Diagnose with CFRD according to standard ADA criteria of any of the following:
  - 2-hour OGTT plasma glucose ≥11.1 mmol/L (200 mg/dL)
  - Fasting Plasma Glucose (FPG) ≥7 mmol/L (126 mg/dL)
  - A1C ≥ 6.5%
  - Classical symptoms of diabetes (polyuria and polydipsia) in the presence of a casual glucose level ≥11.1 mmol/L (200 mg/dL)
- Do an OGTT on 2 separate days to rule out laboratory error unless there are unequivocal symptoms of hyperglycemia (polyuria and polydipsia).
- A positive FPG or A1C can be used as a confirmatory test, but if it is normal the OGTT should be performed or repeated.
- If the diagnosis of diabetes is not confirmed, resume routine annual testing.

A1C <6.5% does not rule out CFRD because this value is often spuriously low in CF.

During acute illness[1]

- Diagnose with CFRD when FPG levels ≥7 mmoL/L (126 mg/dL) or 2-hour postprandial plasma glucose levels ≥11.1 mmol/L (200 mg/dL) persist for more than 48 hours.

On continuous enteral feedings[1]

- Diagnose with CFRD when mid- or post-feeding plasma glucose levels ≥11.1 mmol/L (200 mg/dL) on 2 separate days.

During pregnancy

Diagnose with gestational diabetes mellitus where any one of the following are present (based on recommendations from the International Association of Diabetes and Pregnancy Study Group - IADPSG)[3]:

- FPG ≥5.1 mmol/L (92 mg/dL)
- 1-h plasma glucose >10.0 mmol/L (180 mg/dL)
- 2-h plasma glucose ≥8.5 mmol/L (153 mg/dL)

Ongoing Monitoring and Interventions

Ongoing monitoring

a. Monitoring CFRD

- If on insulin, direct patient to perform SMBG at least 3 times a day.[1]
  Strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes, bearing in mind that higher or lower goals may be indicated for some patients and that individualization is important.[1]
  Ideally, arrange for patients to be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF.[1]
- Monitor A1C quarterly.[1]
  A1C treatment goal is ≤7%, bearing in mind that higher or lower goals may be indicated for some patients and that individualization is important.[1, 2]

b. Monitoring for complications

Hypoglycemia:[1]

- Educate patients and their care partners about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon.

Hypertension:[1]

- Measure blood pressure at every routine diabetes visit as per ADA guidelines.
- Repeat blood pressure measurement on a separate day to confirm diagnosis of hypertension when:
  - systolic blood pressure is >130 mmHg, or
  - diastolic blood pressure is >80 mmHg, or
  - for children and adolescents, blood pressure is >90th percentile for age and sex

Microvascular complications:[1]

- Monitor annually using ADA guidelines.
- Begin 5 years after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that FH is first diagnosed.

Exocrine Pancreatic Sufficiency (PS)[1]

- Do an annual lipid profile for patients with exocrine PS.

- Do an annual lipid profile if any of the following risk factors are present:
  - obesity
  - family history of coronary artery disease
  - immunosuppressive therapy following transplantation

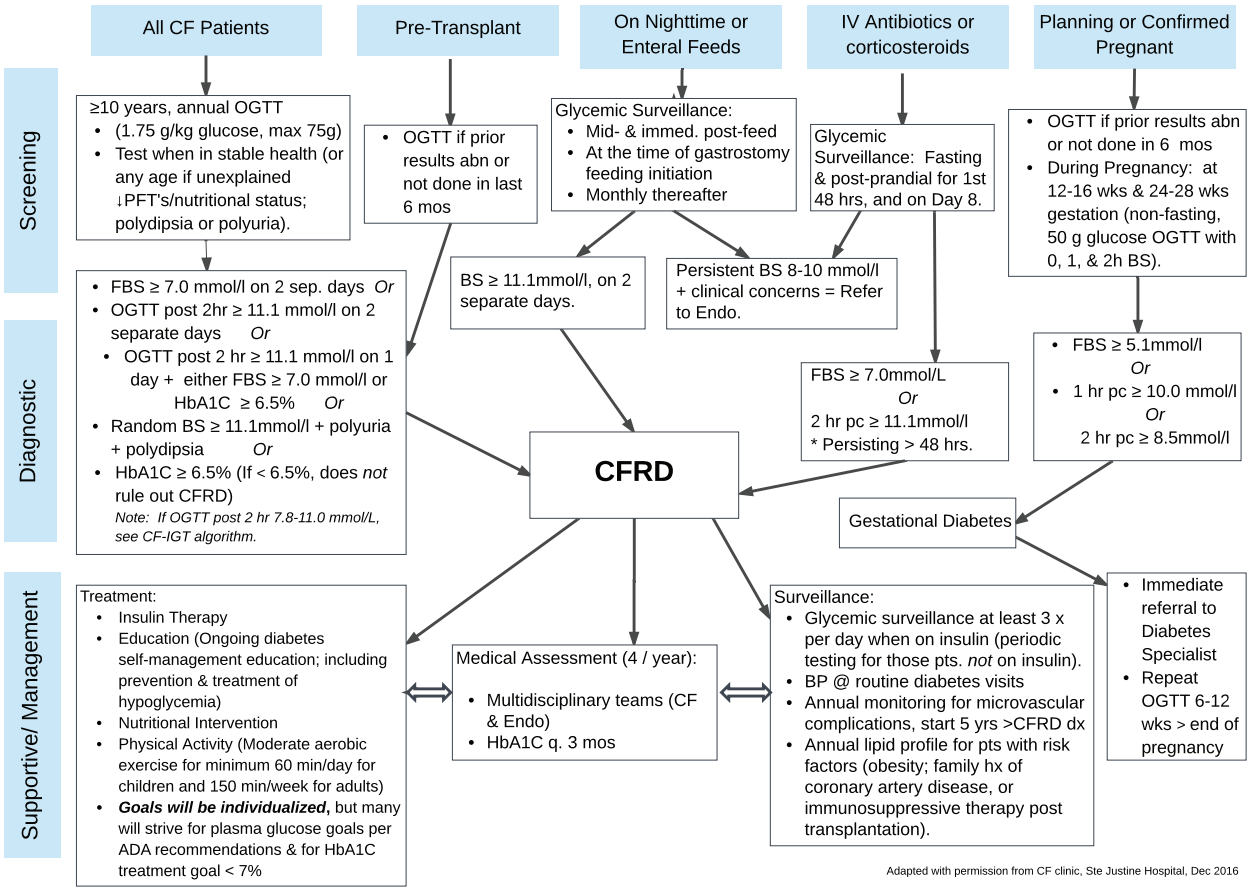
Interventions

- Provide ongoing diabetes self-management education from diabetes education programs that meet national standards for Diabetes Self-Management Education (DSME).[1]
- Treat with insulin therapy.[1, 2]
- Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes and are not recommended outside the context of clinical research trials.[1, 2]
- Follow CF Care Guidelines for nutritional management.[1]
- Advise patients to do moderate aerobic exercise for at least 150 minutes per week.[1] For children, this should be a minimum of 60 minutes per day.[4]
- For those patients diagnosed with hypertension or microvascular complications, follow treatment guidelines recommended by ADA for all people with diabetes.

Exception: There is no restriction of sodium and, in general, no protein restriction.

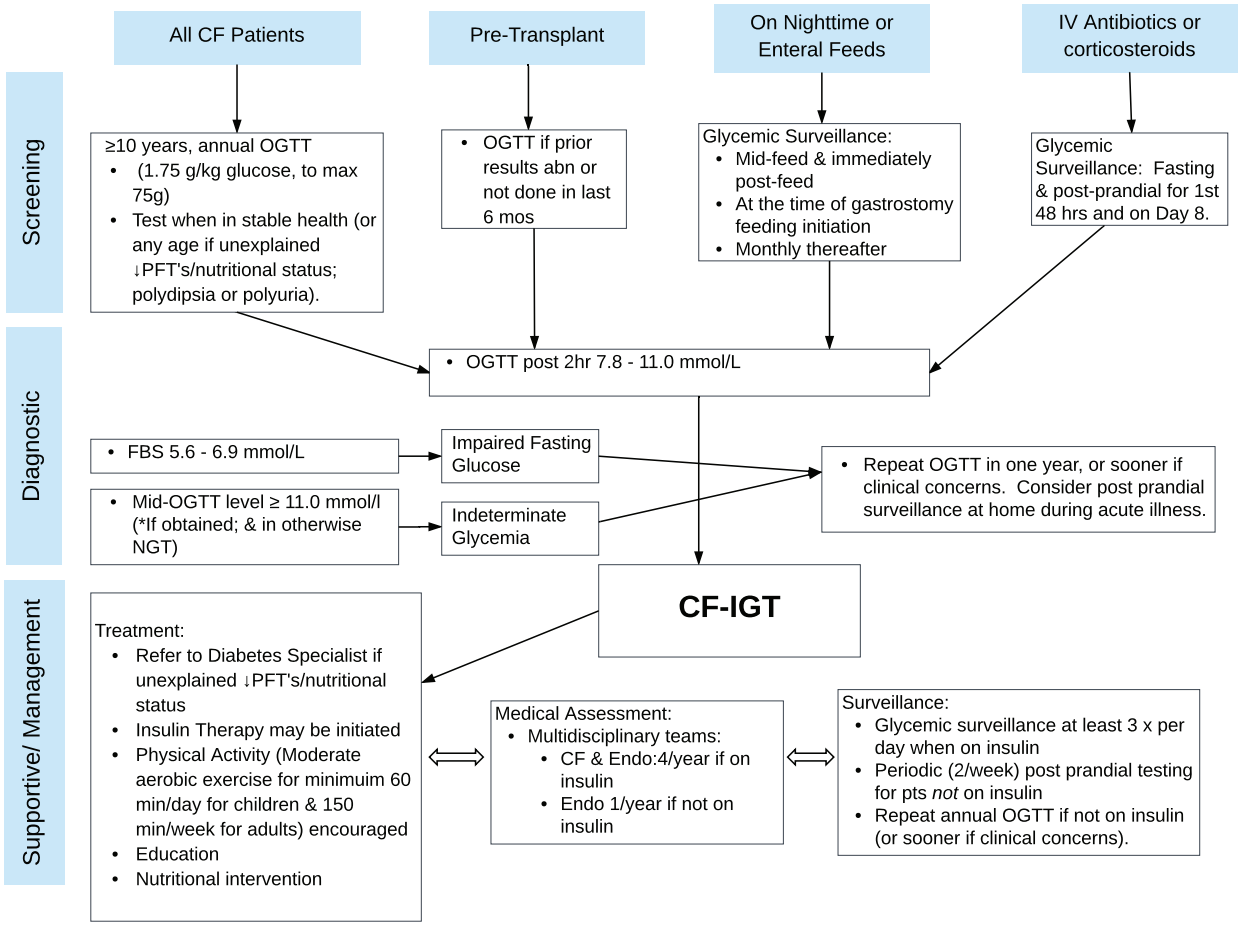
Appendix

Figure 1: CFRD Screening, Diagnosis & Management Algorithm for British Columbia



Adapted with permission from CF clinic, Ste Justine Hospital, Dec 2016

Figure 2: CF-Impaired Glucose Tolerance (IGT) Screening, Diagnosis & Management Algorithm for British Columbia



References

American Diabetes Association. (2016). *ADA 2016 Recommendations for Individuals with Cystic Fibrosis.* Retrieved from http://www.ndei.org/ADA-diabetes-management-guidelines-recommendations-for-patients-with-cystic-fibrosis-related-diabetes.aspx.html on October 3, 2016.

Canadian Society for Exercise Physiology. (2011). *Canadian Physical Activity Guidelines.* Retrieved from http://www.csep.ca/CMFiles/Guidelines/PAGuidelinesBackgrounder_E.pdf on November 13, 2017.

Cystic Fibrosis Foundation, USA. (n.d.).*Cystic Fibrosis-Related Diabetes Care Guidelines.* Retrieved from https://www.cff.org/Care/Clinical-Care-Guidelines/Other-CF-Related-Conditions-Clinical-Care-Guidelines/Cystic-Fibrosis-related-Diabetes-Clinical-Care-Guidelines/ on November 13, 2017.

Gosmanov, A. R., & Umpierrez, G. E. (2013). Management of hyperglycemia during enteral and parenteral nutrition therapy. *Current Diabetes Reports, 13*(1), 155-162.

Hadjiliadis, D., Madill, J., Chaparro, C., Tsang, A., Waddell, T. K., Singer, L. G., Hutcheon, M.A., Keshavjee, S. & Elizabeth Tullis, D. (2005). Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. *Clinical Transplantation, 19*(6), 773-778.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care, 33*(3), 676-682.

Kelly, A., & Moran, A. (2013). Update on cystic fibrosis-related diabetes. *Journal of Cystic Fibrosis, 12*(4), 318-331.

Lee, K. M., Miller, R. J., Rosenberg, F. M., & Kreisman, S. H. (2007). Evaluation of glucose tolerance in cystic fibrosis: comparison of 50-g and 75-g tests. *Journal of Cystic Fibrosis, 6*(4), 274-276.

Miller, R. J., Tildesley, H. D., Wilcox, P. G., Zhang, H., & Kreisman, S. H. (2008). Sex disparities in effects of cystic fibrosis-related diabetes on clinical outcomes: a matched study. *Canadian Respiratory Journal, 15*(6), 291-294.

Moran, A., Dunitz, J., Nathan, B., Saeed, A., Holme, B., & Thomas, W. (2009). Cystic fibrosis–related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care, 32*(9), 1626-1631.

Moran, A., Brunzell, C., Cohen, R. C., Katz, M., Marshall, B. C., Onady, G., Robinson, K.A., Sabadosa, K.A., Stecenko, A., Slovis, B. & CFRD Guidelines Committee. (2010). *Clinical care guidelines for cystic fibrosis–related diabetes. Diabetes Care, 33*(12), 2697-2708.

Prentice, B., Hameed, S., Verge, C. F., Ooi, C. Y., Jaffe, A., & Widger, J. (2016). Diagnosing cystic fibrosis-related diabetes: current methods and challenges. *Expert review of respiratory medicine, 10*(7), 799-811.

Smyth, A.R., Bell, S.C., Bojcin, S., Bryon, M., Duff, A., Flume, P., Kashirskaya, N., Munck, A., Ratjen, F., Schwarzenberg, S.J., Sermet-Gaudelus, I., Southern, K.W., Taccetti, G., Ullrich, G., Wolfe, S., European Cystic Fibrosis Society (2014). European Cystic Fibrosis Society Standards of Care: Best Practice Guidelines. *Journal of Cystic Fibrosis, 13*, S23-S42.

U.S. Preventive Services Task Force. (September 2017.) *Recommendations for Primary Care Practice.* Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Name/recommendations

Endnotes

1 American Diabetes Association. (2016). *ADA 2016 Recommendations for Individuals with Cystic Fibrosis.* Retrieved from http://www.ndei.org/ADA-diabetes-management-guidelines-recommendations-for-patients-with-cystic-fibrosis-related-diabetes.aspx.html on October 3, 2016.

2 U.S. Preventive Services Task Force. (September 2017.) *Recommendations for Primary Care Practice.* Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Name/recommendations

3 Association of Diabetes and Pregnancy Study Groups Consensus Panel. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care, 33*(3), 676-682.

4 Society for Exercise Physiology. (2011). *Canadian Physical Activity Guidelines.* Retrieved from http://www.csep.ca/CMFiles/Guidelines/PAGuidelinesBackgrounder_E.pdf on November 13, 2017.