A Dangerous Pairing
COVID-19 & OBESITY
Heightened risk for COVID-19 severity
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Publisher’s Note

Venn diagrams of COVID-19

We are now two years into the COVID-19 pandemic. In early 2020, few of us foresaw just how significant this novel respiratory disease would be. Experts were caught off guard. The CDC says close to a million people in the United States have died from COVID-19. The disease also leaves behind a trail of morbidity with many people — exactly how large a proportion is difficult to say — experiencing lingering symptoms known as long COVID-19. Fortunately, vaccines and treatments were developed at record speed. Healthcare innovation of many kinds sprang to life in remarkable ways, with telehealth and remote care gaining a new and more significant foothold in how healthcare is delivered.

COVID-19 did not write its myriad effects on a blank slate. The disease intersected and combined with other diseases and health conditions. Before COVID-19, the opioid epidemic was widely seen as the most pressing public health issue in the U.S. COVID-19 pushed opioid-related content further down the pageview rankings. But data released by the National Center for Health Statistics last year suggest that COVID-19 may have been an accelerant of the opioid pandemic. Between December 2019 and December 2020, more than 93,000 Americans died from drug overdoses, an increase of almost 30% over the previous 12 months.

Our cover story is about another intersection in COVID-19’s Venn diagram. The prevalence of obesity (defined as a body mass index of 30 or more) in the U.S. has been increasing for decades. Now about 40% of the people in the country have obesity and its attendant health risks. With COVID-19’s arrival, obesity became even riskier. Research published in the Morbidity and Mortality Weekly Report last year showed that in the U.S. a little more than half (51%) of those who were hospitalized because of COVID-19 had obesity and that just under half (46%) of those who died from the disease had obesity.

Researchers are still figuring out the whys and wherefores of the interaction between COVID-19 and obesity. One possible explanation is people with obesity are in a chronic state of inflammation, resulting in dysregulated immune systems that make severe COVID-19 more likely.

We seem to be headed for a time when COVID-19 will be endemic — a new normal of boosters, variants of varying significance, and metrics that will help us decide which precautions need to be taken when and for how long. Still, everyone involved in healthcare will need to keep a close eye on COVID-19 and other healthcare conditions. Even if COVID-19 calms down and becomes part of everyday life, many people will be at heightened risk for severe illness and mortality from the disease because of overlapping health conditions.

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President and CEO
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MARCH 2022

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A Fixed-Ratio Option for Adult Patients With T2DM Uncontrolled on Oral Anti-diabetic (OAD) Treatment, as an Adjunct to Diet and Exercise

Indications and Usage for SOLIQUA® 100/33
SOLIQUA 100/33 is a combination of a long-acting human insulin analog with a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not recommended for use in combination with any other product containing a GLP-1 RA.
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Not recommended for use in patients with gastroparesis.
- Has not been studied in combination with prandial insulin.

Important Safety Information for SOLIQUA® 100/33
Contraindications
- During episodes of hypoglycemia.
- In patients with known hypersensitivity to insuline glargine, lixisenatide, or to any of the product components.

Real-world evidence retrospective data: Interpret with caution.
Two authors (Terry Dex and Xuan Li) are Sanofi employees, and this study was sponsored by Sanofi.

Intended for use with payers, formulary committees, or other similar entities for purposes of population-based drug selection, coverage, and/or reimbursement decision making, pursuant to FD&C Act Section 502(a).

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
Higher Persistence and Adherence at 12 Months Seen With SOLIQUA 100/33 vs Free Ratio

A retrospective, observational study to evaluate persistence, adherence, healthcare resource utilization (HRU), and costs for SOLIQUA 100/33 compared to free-dose combinations of basal insulin (BI) and GLP-1 RA. Adult patients with type 2 diabetes mellitus (T2DM), mean age 62 years, and A1C ≥8% were included from US Optum Clinformatics® database (N=5839). Propensity score matching was conducted to form 2 cohorts: newly initiated SOLIQUA 100/33 (N=1357) and newly initiated free-ratio combinations (N=1357). Eligible patients were followed from index date (treatment initiation) for 360 days, or plan disenrollment, death, or last day of available data. Patients received SOLIQUA 100/33 or free-dose combinations of either (1) BI followed by GLP-1 RA, (2) GLP-1 RA followed by BI, or (3) both prescribed on the same day. The primary outcome was persistence at 12 months. Adherence, HRU, and costs outcomes at 12 months were secondary outcomes.

Study Design

A retrospective, observational study to evaluate persistence, adherence, healthcare resource utilization (HRU), and costs for SOLIQUA 100/33 compared to free-dose combinations of basal insulin (BI) and GLP-1 RA. Adult patients with type 2 diabetes mellitus (T2DM), mean age 62 years, and A1C ≥8% were included from US Optum Clinformatics® database (N=5839). Propensity score matching was conducted to form 2 cohorts: newly initiated SOLIQUA 100/33 (N=1357) and newly initiated free-ratio combinations (N=1357). Eligible patients were followed from index date (treatment initiation) for 360 days, or plan disenrollment, death, or last day of available data. Patients received SOLIQUA 100/33 or free-dose combinations of either (1) BI followed by GLP-1 RA, (2) GLP-1 RA followed by BI, or (3) both prescribed on the same day. The primary outcome was persistence at 12 months. Adherence, HRU, and costs outcomes at 12 months were secondary outcomes.

Important Safety Information for SOLIQUA® 100/33 (cont’d)

Warnings and Precautions

- Anaphylaxis and Serious Hypersensitivity Reactions: In clinical trials of lixisenatide, there have been cases of anaphylaxis and other serious hypersensitivity reactions including angioedema. Severe, life-threatening, generalized allergic reactions, including anaphylaxis and angioedema, can occur with insulin, including insulin glargine. There have been reports of serious hypersensitivity reactions, including anaphylactic reactions and angioedema, in patients treated with SOLIQUA 100/33. If hypersensitivity reactions occur, discontinue SOLIQUA 100/33. Use caution in patients with a history of anaphylaxis or angioedema with another GLP-1 RA because it is unknown whether such patients will be predisposed to anaphylaxis.

Intended for use with payers, formulary committees, or other similar entities for purposes of population-based drug selection, coverage, and/or reimbursement decision making, pursuant to FD&C Act Section 502(a).

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
Fixed-ratio SOLIQUA 100/33 Treatment Is Associated With Lower Diabetes-related HRU and Costs vs Free Ratio

**Diabetes-related HRU (Secondary Endpoint)**

<table>
<thead>
<tr>
<th></th>
<th>SOLIQUA 100/33 (n=1357)</th>
<th>FREE RATIO (n=1357)</th>
<th>SOLIQUA 100/33 (n=1357)</th>
<th>FREE RATIO (n=1357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visits*</td>
<td>990</td>
<td>1050</td>
<td>1240</td>
<td>1460</td>
</tr>
</tbody>
</table>

*Statistically significant difference in favor of SOLIQUA 100/33; P<0.001.

**Pharmacy visits**

<table>
<thead>
<tr>
<th>Pharmacy visits*</th>
<th>SOLIQUA 100/33 (n=1357)</th>
<th>FREE RATIO (n=1357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy visits</td>
<td>4239</td>
<td>5865</td>
</tr>
</tbody>
</table>

*Statistically significant difference in favor of SOLIQUA 100/33; P<0.001.

**Real-world Evidence (RWE) Study Limitations**

- Hypothesis generating and has inherent limitations as it was not prespecified
- Observational study design evaluates association as it is not powered to determine causal relationships between variables and endpoints
- Retrospective chart review can have the potential for selection bias, including reason for switching
- Based on claims data using diagnostic/procedural codes, which may be driven by reimbursement concerns and may not represent a complete medical record for individual patients
- Limited in generalizability of the results to a larger population of patients with T2DM
- RWE retrospective data should be interpreted with caution. Two authors (Terry Dex and Xuan Li) are Sanofi employees, and this study was sponsored by Sanofi

**Important Safety Information for SOLIQUA® 100/33 (cont’d)**

**Warnings and Precautions (cont’d)**

- **Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 RAs. Cases of pancreatitis were reported in clinical trials of lixisenatide. After initiation of SOLIQUA 100/33, observe patients for signs and symptoms of pancreatitis (e.g., persistent severe abdominal pain, sometimes radiating to the back and which may be accompanied by vomiting). If pancreatitis is suspected, SOLIQUA 100/33 should promptly be discontinued. If pancreatitis is confirmed, restarting SOLIQUA 100/33 is not recommended and other antidiabetic therapies should be considered.

Intended for use with payers, formulary committees, or other similar entities for purposes of population-based drug selection, coverage, and/or reimbursement decision making, pursuant to FD&C Act Section 502(a).

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
Important Safety Information for SOLIQUA 100/33

Contraindications

- During episodes of hypoglycemia.
- In patients with known hypersensitivity to insulin glargine, lixisenatide, or to any of the product components.

Warnings and Precautions

- Anaphylaxis and Serious Hypersensitivity Reactions: In clinical trials of lixisenatide, there have been cases of anaphylaxis and other serious hypersensitivity reactions including angioedema. Severe, life-threatening, generalized allergic reactions, including anaphylaxis and angioedema, can occur with insulins, including insulin glargine. There have been reports of serious hypersensitivity reactions, including anaphylactic reactions and angioedema, in patients treated with SOLIQUA 100/33. If hypersensitivity reactions occur, discontinue SOLIQUA 100/33. Use caution in patients with a history of anaphylaxis or angioedema with another GLP-1 RA because it is unknown whether such patients will be predisposed to anaphylaxis.
- Pancreatitis: Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 RAs. Cases of pancreatitis were reported in clinical trials of lixisenatide. After initiation of SOLIQUA 100/33, observe patients for signs and symptoms of pancreatitis (e.g., persistent severe abdominal pain, sometimes radiating to the back and which may be accompanied by vomiting). If pancreatitis is suspected, SOLIQUA 100/33 should promptly be discontinued. If pancreatitis is confirmed, restarting SOLIQUA 100/33 is not recommended and other antidiabetic therapies should be considered.
- Never Share a SOLIQUA 100/33 SoloStar® Pen between Patients: Pen-sharing poses a risk for transmission of blood-borne pathogens, even if the needle is changed.
- Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen: Changes in insulin regimen including, strength, manufacturer, type, injection site or method of administration may affect glycemic control and predispose to hyperglycemia or hypoglycemia. Changes should be made cautiously and the frequency of blood glucose monitoring should be increased. Adjustments in concomitant oral antidiabetic treatment may be needed. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis may result in hyperglycemia; sudden change in the injection site (to unaffected area) has been reported to result in hypoglycemia. Advise patients to rotate injection site to unaffected areas and closely monitor for hypoglycemia.
- Medication Errors: SOLIQUA 100/33 contains two drugs. Do not administer more than 60 units of SOLIQUA 100/33, which may result in overdose of the lixisenatide component. Do not use other GLP-1 RAs. Accidental mix-ups between insulin products have been reported. Instruct patients to always check the label before administration. Do not withdraw SOLIQUA 100/33 from the pen with a syringe.
- Hypoglycemia: Hypoglycemia is the most common adverse reaction associated with insulin-containing therapy, which may be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity, and in patients with renal or hepatic impairment and hypoglycemia unawareness.
- Acute Kidney Injury: There have been reports of acute renal failure and worsening of chronic failure, which may sometimes require hemodialysis in patients treated with GLP-1 RAs, such as lixisenatide. Some of these events were reported in patients without known underlying renal disease. Most reports occurred in patients who experienced nausea, vomiting, diarrhea, or dehydration; advise patients to take precautions to avoid fluid depletion. Monitor blood glucose and renal function in patients with renal impairment. SOLIQUA 100/33 is not recommended in patients with end-stage renal disease.
- Immunogenicity: Patients may develop antibodies to insulin and lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, then other antidiabetic therapy should be considered.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
Important Safety Information for SOLIQUA 100/33 (cont’d)

Warnings and Precautions (cont’d)

- **Hypokalemia**: All insulin containing products can cause hypokalemia, which may be life-threatening. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated.

- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists**: Fluid retention, which may lead to or exacerbate heart failure, can occur with concomitant use of thiazolidinediones (TZDs) and insulin. These patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of TZD must be considered.

**Most Common Adverse Reactions**

The most common adverse reactions reported in ≥5% of patients treated with SOLIQUA 100/33 include hypoglycemia, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache.

**Drug Interactions**

- Certain drugs may affect glucose metabolism, requiring dose adjustment of SOLIQUA 100/33 and close monitoring of blood glucose.

- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine).

- The lixisenatide in SOLIQUA 100/33 delays gastric emptying, which may reduce the rate of absorption of orally administered medication with a narrow therapeutic ratio or that require careful clinical monitoring. If such medications are to be administered with food, do not co-administer with SOLIQUA 100/33.

- Antibiotics, acetaminophen, or other medications that are dependent on threshold concentrations for efficacy, or where a delay in effect is undesirable, should be administered at least 1 hour before SOLIQUA 100/33 injection.

- Oral contraceptives should be taken at least 1 hour before SOLIQUA 100/33 administration or 11 hours after.

Please see Brief Summary of the Prescribing Information on the following pages.

**References**

1. SOLIQUA 100/33. Prescribing Information.
SOLIQUA® 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**5.5 Overdose Due to Medication Errors**

SOLIQUA 100/33 contains two drugs: insulin glargine and lixisenatide. Administration of more than 60 units of SOLIQUA 100/33 daily can result in overdose of the lixisenatide component. Do not exceed the 20-mcg maximum recommended dose of lixisenatide or use with other glucagon-like peptide-1 receptor agonists. Accidental mix-ups between insulin products have been reported. To avoid medication errors between SOLIQUA 100/33 and other insulins, instruct patients to always check the insulin label before each injection.

**5.6 Hypoglycemia**

Hypoglycemia is the most common adverse reaction associated with insulin-containing products, including SOLIQUA 100/33 (see Adverse Reactions [6.1]). Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time. This may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). SOLIQUA 100/33 (an insulin-containing product), or any insulin, should not be used during episodes of hypoglycemia (see Contraindications [4]).

Hypoglycemia can happen suddenly, and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions [7.1]] or in patients who experience recurrent hypoglycemia.

**Risk Factors for Hypoglycemia**

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of the action of the insulin. In general, highest glucose lowering effect of the insulin is maximal. As with all insulin-containing preparations, the glucose lowering effect of course of SOLIQUA 100/33 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection-site blood supply and temperature [see Clinical Pharmacology (12.2) in the full prescribing information].

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to coadministered medication [see Drug Interactions [7.1]].

Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.5, 8.6)].

**Risk Mitigation Strategies for Hypoglycemia**

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. At the start of therapy, dose reduction, discontinuation of therapy, or switching to another antidiabetic therapy may be necessary. In these situations, hypoglycemia may be more likely to occur, particularly in situations where there is a change in the amount and distribution of carbohydrate in the diet, or there is an increase in physical activity. If hypoglycemia is controlled and the patient or caregiver can identify the warning signs of hypoglycemia, use of glucose-related intervention strategies may be effective in preventing further episodes of hypoglycemia. Monitor patterns of blood glucose and share these patterns with health professionals to ensure the effectiveness of these strategies.

**5.7 Acute Kidney Injury**

Acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, has been reported postmarketing in patients treated with SOLIQUA 100/33. Some of these events were reported in patients without a known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

Monitor renal function when initiating or escalating doses of SOLIQUA 100/33 in patients with renal impairment. In patients reporting severe gastrointestinal reactions, advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. SOLIQUA 100/33 is recommended in patients with end-stage renal disease [see Use in Specific Populations (8.6)].

**5.8 Immune reactivity**

Patients may develop antibodies to insulin and lixisenatide following treatment. A pooled analysis of studies of lixisenatide-treated patients showed that 70% were antibody positive at Week 24. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection-site reactions occurred in antibody-positive patients [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].

If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection-site reactions or allergic reactions, alternative antidiabetic therapy should be considered.

**5.9 Hyperkalemia**

All insulin-containing products, including SOLIQUA 100/33, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hyperkalemia. Untreated hyperkalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hyperkalemia if indicated (e.g., patients using potassium-sparing diuretics, patients taking medications sensitive to serum potassium concentrations).

**5.10 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists**

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, cause dose-related fluid retention, particularly when used in combination with insulin-containing products, including SOLIQUA 100/33. Fluid retention may lead to or exacerbate heart failure. Patients treated with SOLIQUA 100/33 and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, discontinuation or dose reduction of the PPAR-gamma agonist must be considered.
6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Anaphylaxis and Serious Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
- Pancreatitis [see Warnings and Precautions (5.2)]
- Hypoglycemia [see Warnings and Precautions (5.6)]
- Acute Kidney Injury [see Warnings and Precautions (5.7)]
- Hypokalemia [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The safety of SOLIQUA 100/33 (n=854, with a mean treatment duration of 203 days) has been evaluated in two clinical studies (30 weeks duration) in type 2 diabetes patients. The studies, Study A and B [see Clinical Studies (14) in the full prescribing information] had the following characteristics: mean age was approximately six years; approximately 50% were male, 90% were Caucasian, 6% were Black or African American, and 18% were Hispanic. The mean duration of diabetes was 10.3 years. mean HbA1c at screening for Study A was 8.2 and Study B was 8.5. The mean BMI at baseline was 32 kg/m². Baseline eGFR was ≤60 mL/min in 87.2% of the pooled study population and mean baseline eGFR was 83.0 mL/min/1.73 m².

Nausea, vomiting, constipation, diarrhea, flatulence, abdominal pain, and abdominal distension

Nasopharyngitis

Upper respiratory tract infection

Headache

Table 3: Adverse Reactions Occurring in ≥5% of SOLIQUA 100/33–Treated Patients with Type 2 Diabetes Mellitus from Two Pooled Clinical Trials

<table>
<thead>
<tr>
<th>SOLIQUA 100/33, % (n=854)</th>
<th>N=469</th>
<th>N=385</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Headache</td>
<td>6.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, and insulin-containing products including SOLIQUA 100/33 [see Warnings and Precautions (5.6)]. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, severity of insulin treatment, intensity of glucose control, use of glucose-lowering medication, and use of background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for SOLIQUA 100/33 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the SOLIQUA 100/33 program, severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 70 mg/dL (see Table 4). No clinically important differences in risk of severe hypoglycemia between SOLIQUA 100/33 and comparators were observed in clinical trials.

Table 4: Hypoglycemic Episodes in SOLIQUA–Treated Patients with T2DM

<table>
<thead>
<tr>
<th>SOLIQUA 100/33</th>
<th>SOLIQUA 100/33</th>
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<tbody>
<tr>
<td>Study A N=469</td>
<td>Study B N=385</td>
</tr>
</tbody>
</table>

Severe symptomatic hypoglycemia* (%)

0.0

1.1

Hypoglycemia (self-monitored plasma glucose ≤54 mg/dL) (%)

8.1

17.8

*Defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions are the most commonly observed adverse reaction in patients using lixisenatide. Gastrointestinal adverse reactions occur more frequently at the beginning of SOLIQUA 100/33 therapy. Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gastric distress, abdominal pain, flatulence, gastrointestinal reflex disease, abdominal distension, and decreased appetite have been reported in patients treated with SOLIQUA 100/33.

In Study A, vomiting was 6.4% in the lixisenatide-treated patients versus 3.2% in the SOLIQUA 100/33–treated patients and 1.5% in the insulin glargine–treated patients; nausea was 24% in the lixisenatide-treated patients versus 9.6% in the SOLIQUA 100/33–treated patients, and 3.6% in the insulin glargine–treated patients.

7 DRUG INTERACTIONS

7.1 Medications That Can Affect Glucose Metabolism

As is the case with medications affecting glucose metabolism and may require dose adjustment of SOLIQUA 100/33 and particularly close monitoring.

Lipodyrophy

Administration of insulin subcutaneously, including SOLIQUA 100/33, has resulted in lipodyrophy (depression in the skin) or lipo hypertrophy (enlargement or thickening of tissue) in some patients [see Dosage and Administration (2.5)]

Anaphylaxis and Hypersensitivity

Lixisenatide

In the lixisenatide development program anaphylaxis cases were adjudicated. Anaphylaxis was defined as a skin or mucosal lesion of acute onset associated with at least 1 other organ system involvement. Symptoms such as hypotension, laryngeal edema or severe bronchospasm could be present but were not required for the case definition. More cases adjudicated as meeting the definition for anaphylaxis occurred in lixisenatide–treated patients (incidence rate of 0.2% or 16 cases per 10,000 patient years) than placebo–treated patient (incidence rate of 0.1% or 7 cases per 10,000 patient years).

Allergic reactions (such as anaphylactic reaction, angioedema, and urticaria) adjudicated as possibly related to the study medication were observed more frequently in lixisenatide–treated patients (0.4%) than placebo–treated patients (0.2%) [see Warnings and Precautions (5.1)].

Insulin glargine

Severe, life–threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including SOLIQUA 100/33, and may be life–threatening.

Injection–Site Reactions

As with any insulin or GLP-1 receptor agonist–containing product, patients taking SOLIQUA 100/33 may experience injection–site reactions, including injection–site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection–site mass. In the clinical program the proportion of injection–site reactions occurring in patients treated with SOLIQUA 100/33 was 1.7%.

Insulin Initiation and Intensification of Glucose Control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic reflex disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long–term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Some patients taking insulin glargine, a component of SOLIQUA 100/33 have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Weight Gain

Weight gain can occur with insulin–containing products, including SOLIQUA 100/33, and has been attributed to the anabolic effects of insulin.

6.2 Immunogenicity

SOLIQUA 100/33

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLIQUA 100/33 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

After 30 weeks of treatment with SOLIQUA 100/33 in two phase 3 trials, the incidence of formation of anti-insulin glargine antibodies was 21.0% and 26.2%. In primarily anti-insulin glargine antibodies showed cross-reactivity to human insulin. The incidence of formation of anti-lixisenatide antibodies was approximately 43%.

Lixisenatide

In the pool of 9 placebo–controlled studies, 70% of patients exposed to lixisenatide tasted positive for anti-lixisenatide antibodies during the trials. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection–site reactions occurred in antibody positive patients [see Warnings and Precautions (5.6)]. Anti-lixisenatide antibody characterization studies have demonstrated the potential for development of antibodies cross–reactive with endogenous GLP-1 and glucagon, but their incidence has not been fully determined and the clinical significance of these antibodies is not currently known.

No information regarding the presence of neutralizing antibodies is currently available.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal: Acute kidney injury

Skin: Localized cutaneous amyloidosis at the injection site has occurred with insolus. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a change to an unaffected injection site.

SOLIQUA® 100/33

(insulin glargine and lixisenatide) injection, for subcutaneous use
7.2 Effects of Delayed Gastric Emptying on Oral Medications

Lixisenatide-containing products, including SOLIQUA 100/33, delay gastric emptying which may reduce the rate of absorption of orally administered medications. Use caution when coadministering oral medications that have a narrow therapeutic ratio or that require careful clinical monitoring. These medications should be adequately monitored when concomitantly administered with lixisenatide. If such medications are to be administered with food, patients should be advised to take them with a meal or snack when lixisenatide is not administered. • Antibiotics, acetylsalicylic acid, corticosteroids, danazol, diuretics, estrogen, glucagon, iron dextran, niacin, oral contraceptives, progestins, and thyroid hormones.

Intervention: Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

Drugs That May Increase the Risk of Hypoglycemia

Drugs: Antidiabetic agents, ACE inhibitors, angiotensin II receptor blockers, angiotensin II receptor antagonists, blood glucose lowering drugs, guanethidine, and sulfonylurea.

Intervention: Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

Drugs That May Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33

Drugs: Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogen, glucagon, iron dextran, niacin, oral contraceptives, progestins (e.g., in oral contraceptives), propranolol, reserpine, somatostatin analogs (e.g., octreotide), and thyroid hormones.

Intervention: Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33

Drugs: Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Intervention: Dose adjustment and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

Drugs That May Blunt Signs and Symptoms of Hypoglycemia

Drugs: Blockers, clonidine, guanethidine, and reserpine.

Intervention: Increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide, a component of SOLIQUA 100/33, during pregnancy. SOLIQUA 100/33 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The limited available data with SOLIQUA 100/33 and lixisenatide in pregnant women is not sufficient to inform a drug-associated risk of major birth defects and miscarriage. Published studies with insulin glargine use during pregnancy have not reported a clear association with insulin glargine and major birth defect or miscarriage risk (see Uta). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations).

Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral and skeletal malformations, including closure defects, at doses up to 0.36 mg/kg/day, which is approximately 2-times the recommended human subcutaneous high dose of 60 units/day (0.0364 mg/kg/day), based on mg/m². In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg/day during organogenesis (gestation day 6 to 18), fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥2.5 mg/kg/day, resulting in systemic exposure that is 1-time the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of ≤0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg/day during organogenesis (gestation day 6 to 18), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at ≥2.5 mcg/kg/day or systemic exposures that are 6-times the 20 mcg/day highest clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of ≤0.3%. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 1.5, 10, and 2.5 mg/kg/day administered during organogenesis, resulting in systemic exposures up to 6-times the clinical exposure at 20 mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, and motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at 400 mcg/kg/day, which is approximately 200-times the 20 mcg/day clinical dose based on mg/m².

Insulin glargine

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 2-times the recommended human subcutaneous high dose of 60 units/day (0.0364 mg/kg/day), based on mg/m². In pregnant rabbits, doses up to 0.072 mg/kg/day, which is approximately 1-times the maximum recommended human subcutaneous dose of 60 units/day (0.0364 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lixisenatide and insulin glargine in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. Lixisenatide is present in rat milk (see Uta).

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SOLIQUA 100/33 and any potential adverse effects on the breastfed child from SOLIQUA 100/33 or from the underlying maternal condition.

Data

Lixisenatide

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.001%) levels of unchanged lixisenatide protein in the gastric contents of weaning offspring.

8.4 Pediatric Use

Safety and effectiveness of SOLIQUA 100/33 have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects (n=834) in controlled clinical studies of patients with type 2 diabetes, who were treated with SOLIQUA 100/33, 25.2% (n=210) were ≥65 years of age and 4% (n=33) were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.
Nevertheless, caution should be exercised when SOLIQUA 100/33 is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

8.6 Renal Impairment

Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with renal impairment [see Warnings and Precautions (5.7)].

Insulin Glargine

Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure.

Lixisenatide

In patients with mild and moderate renal impairment no dose adjustment is required but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because of higher incidences of hypoglycemia, nausea and vomiting that were observed in these patients. Increased gastrointestinal adverse reactions may lead to dehydration and acute renal failure and worsening of chronic failure in these patients.

Clinical experience in patients with severe renal impairment is limited as there were only 5 patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m²) exposed to lixisenatide in all controlled studies. Lixisenatide exposure was higher in these patients [see Clinical Pharmacology (12.3) in the full prescribing information] Patients with severe renal impairment exposed to lixisenatide should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes in renal function.

There is no therapeutic experience in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m²). There is no therapeutic experience in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m²), and it is not recommended to use SOLIQUA 100/33 in this population.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of SOLIQUA 100/33 has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with hepatic impairment [see Warnings and Precautions (5.6)].

8.8 Patients with Gastroparesis

Lixisenatide slows gastric emptying. Patients with preexisting gastroparesis were excluded from clinical trials of SOLIQUA 100/33. SOLIQUA 100/33 is not recommended in patients with severe gastroparesis.

10 OVERDOSAGE

Insulin Glargine

Excess insulin administration may cause hypoglycemia and hypokalemia [see Warnings and Precautions (5.6, 5.9)]. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

Lixisenatide

During clinical studies, doses up to 30 mcg of lixisenatide twice daily (3 times the daily recommended dose) were administered to type 2 diabetic patients in a 13-week study. An increased incidence of gastrointestinal disorders was observed. In case of overdose, appropriate supportive treatment should be initiated according to the patient’s clinical signs and symptoms and the SOLIQUA 100/33 dose should be reduced to the prescribed dose.
When managed care got started in the early ’80s, the focus was on physician and hospital services. Primary care doctors were positioned as gatekeepers, controlling referrals to specialists. Insurers came under a lot of criticism for shortening hospital stays. Now much of the managed care energy is trained on drug costs, and a recent report on prescription spending from the Congressional Budget Office (CBO) offers some clues as to why.

In 1980, nationwide spending on prescription was about $30 billion and accounted for about 5% of total U.S. spending on healthcare. By 2018, the spending had increased more than tenfold to $335 billion and accounted for 10% of all healthcare spending. On a per capita basis, spending (with rebates and other discounts factored in) on prescription drugs increased from $140 per year in 1980 to $1,073 in 2018.

The CBO report, which came out in January, delves into some of the reasons for the rise in prescription spending. Starting in the mid-1990s, it was fueled in part by the advent of blockbuster drugs — drugs with over $1 billion in annual sales — for common conditions: statins for high LDL cholesterol, ACE inhibitors for high blood pressure, antidepressants for depression and other mental health conditions.

When those drugs hit the “patent cliff” and lost patent protection, generics hit the market and put some downward pressure on price spending. The steep upward pitch of prescription drug spending plateaued in the mid-2000s, and there were decreases for several years. In 2006, spending on prescription drugs accounted for 10.5% of total healthcare spending. By 2013, it slipped to a 9.2% slice of the pie.

In late 2013, there was an inflection point. Spending on prescription drugs started to go up again when Sovaldi (sofosbuvir), the hepatitis C drug, came on the market. It was priced at $84,000 for a 12-week course. Other hepatitis C drugs followed. After that jolt, the CBO report shows another plateau in spending from 2015 to 2018, despite the growing number of prescriptions being written.

One important proviso about these figures: As the CBO report points out, they do not include expenditures on drugs in nonretail settings such as physician offices, clinics and hospitals. Expensive specialty drugs — medications for rare conditions — have proliferated recently and are bought and sold in nonretail settings.

— Peter Wehrwein

In Brief

Per capita spending on prescription drugs purchased from pharmacies

Conrad@Stock.Adobe.com

Congressional Budget Office, Prescription Drugs: Spending, Use and Prices, January 2022
Mixed verdict on ESRD ACOs

How successful accountable care organizations (ACOs) have been in bringing about value-based care hinges, of course, on how success is defined. CMS’ comprehensive end-stage renal disease (ESRD) care model is a good example.

It was launched in October 2015 to improve quality of care for people with ESRD and to cut CMS spending on that care in the process. Initially, 13 ESRD seamless care organizations (ESCOs) participated. The ESCOs consisted of dialysis centers, nephrologists and other providers. They operated much like the ACOs anchored in primary care but were exclusively for people with ESRD and the specialists who provide their care. Large dialysis companies such as Fresenius, DaVita and Dialysis Clinic participated in some of the ESCOs. They brought scale to the program. In the program’s fifth and final year, each ESCO had, on average, 35 dialysis centers and approximately 62,500 people with ESRD were being taken care of by ESCO providers.

A CMS two-page summary of the lengthy evaluation report prepared by the Lewin Group highlights some positive results. From October 2015 through December 2020, the Medicare beneficiaries in the ESCOs experienced 5% fewer hospitalizations from ESRD complication than those not in the ESCOs. Care in an ESCO was associated with 9% improvement in adherence to taking phosphate binders, drugs that people on dialysis are prescribed to control phosphorous levels in the blood because high phosphorus levels cause kidney damage. Care in the ESCOs was also associated with a modest improvement in patient survival. The summary also says the ESCOs reduced Medicare spending by $88 per beneficiary per month.

However, those cost savings do not include the shared savings payments CMS made to the ESCOs for meeting quality and financial benchmarks. Information about the shared savings payments for all five years is not available, but according to the evaluation report done after the fourth year, the shared savings payments to the ESCOs swung a $151 million reduction in Medicare spending to a $46 million increase in spending (“aggregate net losses”). Those losses are seen by some as a worthwhile investment that results in improved patient care. But if the goal was to save the Medicare program money overall, it was not met.

The evaluations suggest that the ESCOs did produce better outcomes for people with ESRD, and CMS has launched a new kidney care program called Kidney Care Choices that builds on some elements of the ESCOs. The new program is broader program and includes people in early stages of kidney disease.

— Peter Wehrwein

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The emergence of the SARS-CoV-2 virus in late 2019 prompted drug manufacturers, biotechnology companies and laboratories to swing into action to develop agents that would neutralize the virus and prevent death, hospitalization and symptomatic disease from COVID-19. Much was riding on developing a safe and effective vaccine, and by the summer of 2020, 28 companies had candidates in clinical trials, and 13 of those had advanced to phase 3 studies. The companies with early contenders included major pharmaceutical companies — Pfizer and BioNTech, Johnson & Johnson, Sanofi, Merck, AstraZeneca — and smaller biotech companies such as Moderna and Novavax. Several of these candidates have since gained full approval or emergency use authorization in various parts of the world.

By the end of 2020, the Pfizer and Moderna vaccines had emerged as the strongest candidates; if the initial vaccine development were a race, they were the gold and silver medalists. They were the first to gain emergency use authorization from the FDA for the prevention of COVID-19 disease in adults. Comirnaty, the brand name of Pfizer-BioNTech’s vaccine, was authorized for emergency use by the FDA on Dec. 11, 2020, and received full approval on Aug. 23, 2021, for use in people 16 years and older. It is also authorized for emergency use in children 5 to 15 years old and is awaiting emergency use authorization by the FDA for children 6 months through 4 years old. Spikevax, the brand name of the vaccine developed by Moderna, was authorized for emergency use on Dec. 18, 2020, and gained full FDA approval for use in adults 18 years and older on Jan. 31, 2022. The Johnson & Johnson vaccine followed the Pfizer and Moderna vaccines out of the pipeline and into use. The FDA granted the Johnson & Johnson vaccine emergency use authorization on Feb. 27, 2021. It has not yet received full FDA approval.

With the availability of various types of vaccines throughout the world and the emergence of new variants, the COVID-19 vaccine pipeline looks quite different today than it did in 2020. According to The New York Times’ Coronavirus Vaccine Tracker, there are 114 COVID-19 vaccine candidates in clinical studies. Of those, 48 are in phase 3 or combined phase 2 and 3 trials. The up-and-comers include messenger RNA (mRNA), protein-based, viral vector and inactivated coronavirus vaccines.

**mRNA Vaccines**

The Pfizer and Moderna vaccines are mRNA vaccines that carry the RNA instruction for making the spike protein that provokes an immune response. Arcturus Therapeutics in San Diego and Duke-NUS Medical School in Singapore have partnered to develop three self-amplifying mRNA vaccine candidates — ARCT-021, ARCT-154 and ARCT-165. The vaccines are in various stages of phase 1 through phase 3 trials. Preliminary data recently released by Arcturus suggest that ARCT-154 and ARCT-165 may produce an antibody response to effectively neutralize SARS-CoV-2 and several variants, including omicron. Arcturus intends to apply for emergency use authorization in the United States and Singapore.

In Asia, the Academy of Military Medical Sciences, Abogen Biosciences and Walvax Biotechnologies have joined efforts to develop what may potentially be China’s...
first mRNA vaccine. The vaccine candidate ARCoV is in phase 3 trials. The companies are also testing a potential booster vaccine in a separate phase 3 trial.

**Protein-based vaccines**

Protein-based vaccines use part of the virus to prime the immune system. In the case of the protein-based COVID-19 vaccines, the vaccines use the spike protein that juts out from the surface of the SARS-CoV-2 virus. A protein-based COVID-19 vaccine would offer an alternative for people who are worried about the new mRNA vaccine technology. They would be made using the same methods as some widely used vaccines, such as the one that protects against hepatitis B and pneumococcal infections.

Novavax developed a protein-based vaccine containing nanoparticles studded with genetically engineered coronavirus spike proteins that the immune system recognizes. The vaccine, known as NVX-CoV2373, Covovax and Nuvaxovid, is stable for three months at refrigerated temperatures and is given by intramuscular injection as a two-dose series, three weeks apart.

In phase 3 trials, NVX-CoV2373 demonstrated 90.4% efficacy in preventing COVID-19 symptoms and 100% efficacy in preventing severe disease. It has received emergency use authorization from the World Health Organization, the European Union and other countries.

On Jan. 31, 2022, Novavax applied for an emergency use authorization in the United States. The company will continue to extend its phase 3 trials to test for vaccine boosters.

**Viral vector vaccines**

Viral vector vaccines use a modified version of a virus other than SARS-CoV-2 to ferry DNA instructions for making the SARS-CoV-2 telltale spike protein. Vaxzevria, the brand name of the vaccine developed by researchers at the University of Oxford in England and produced by AstraZeneca, contains coronavirus spike-producing instructions in DNA carried inside an adenovirus. Although this vaccine was among the early contenders, it has not gained authorization for use in the United States. It is fully approved for use in adults in Brazil and India and authorized for emergency use in the European Union. Problems with data reporting have impeded the vaccine from authorization for use in the United States.

Another viral vector vaccine of interest is an oral vaccine developed by Vaxart, a San Francisco biotech company. The Vaxart candidate is currently in a phase 2 trial. The company is testing its vaccine in unvaccinated volunteers and also in vaccinated adults to see if it might be used as a booster.

Other noninjectable COVID-19 vaccines in the pipeline include a repurposed oral polio vaccine, several intranasal vaccine candidates and a vaccine with a transdermal delivery mechanism. These agents are primarily in phase 1 and phase 2 trials. If they succeed in moving through the pipeline, they will be a welcome alternative for people with an aversion to needles.

**Inactivated coronavirus vaccine**

Inactivated vaccines are made using viruses or bacteria that have been killed by heat, radiation or chemicals. Although they cannot cause disease, the body can recognize the antigens and mount an immune response. Valneva, a French company, has created the only inactivated coronavirus vaccine developed in Europe. The vaccine candidate, called VLA2001 for now, can be stored at refrigerated temperatures, and it is given as two intramuscular injections separated by four weeks. In a phase 3 trial conducted in the United Kingdom, VLA2001 produced an immune response 40% higher than that produced by Vaxzevria. However, more recent laboratory results suggest that VLA2001 is not as effective against the omicron variant as it is against other variants. If those results hold up, that limitation may cloud the future of the Valneva vaccine.

**Variant-specific vaccines**

As variants continue to emerge, several companies have expanded research on the efficacy of their current vaccines against circulating variants, especially omicron. On Jan. 25, 2022, Pfizer-BioNTech enrolled the first participants in a trial comparing the safety and efficacy of a new omicron-specific vaccine with its current one. The trial is meant to determine if a variant-specific vaccine can produce an immune response at least as strong as the currently available vaccine and perhaps with a longer duration.

The next day, Moderna started a phase 2 study of an omicron-specific booster. Moderna said the trial is designed to compare the safety and efficacy of its omicron-specific booster candidate with two doses of its current vaccine and a three-shot series that also includes the current booster. Moderna is also evaluating a multivalent booster that would be...
designed to combat more than one variant at a time.

Who dropped out?
As numerous companies set forth unprecedented efforts to develop safe and effective vaccines quickly, a few emerged as front-runners while others abandoned their projects. Sanofi and Merck had initially received federal support for the development of their vaccines but have since discontinued their research. Sanofi and Translate Bio collaborated in 2020 in the development of a mRNA vaccine. However, by the time they had results from trials, the Pfizer and Moderna vaccines were widely available. Sanofi decided to cease efforts on the mRNA vaccine production but is continuing phase 3 trials on a protein-based vaccine that may be used as a booster.

Merck worked with two organizations, Themis Bioscience, an Austrian company, and IAVI, a nonprofit group devoted to developing vaccines, in 2020 on separate projects to develop an injectable and an oral vaccine against COVID-19. Merck abandoned the development of both vaccines because neither produced a more robust immune response than that produced by natural infection. Instead, the company partnered with Johnson & Johnson to help produce their vaccine.

Rosanna Sutherby, Pharm.D., is a medical writer and community pharmacist in High Point, North Carolina.

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For years, clinicians have considered multiple daily injections of insulin to be the best treatment for patients with Type 2 diabetes (T2D), but the outcomes of newer agents have shown this might not be true anymore.

The American Diabetes Association’s standards of care guidelines for patients with T2D are sophisticated and make recommendations on how to choose treatments based on the patient’s level of risk for cardiovascular and kidney events or complications, explained Jennifer Brigitte Green, M.D., professor of medicine in the Division of Endocrinology, Metabolism, and Nutrition at Duke University School of Medicine in Durham, North Carolina.

In addition to choosing medications based on the patient’s risk factors, individual priorities such as reducing the risk of hypoglycemia, promoting weight loss and cost must be considered. Patients with T2D often have overlapping concerns, Green noted.

Keep it simple

Managing T2D can become more difficult because patients who have had diabetes for years are on multiple medications to control blood sugar as well as to address related comorbidities such as obesity, hypertension and hyperlipidemia.

“The medication burden for the individual patient can become very significant,” Green said. “I like to look for opportunities to choose a pharmacotherapy or intervention that can address multiple aspects of care at the same time.”

Fixed-ratio combinations such as iGlarLixi — a combination of insulin glargine, a basal insulin, and lixisenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist — simplify the burden of care for patients. Rodolfo Javier Galindo, M.D., assistant professor of medicine in the Division of Endocrinology, Diabetes and Lipids at Emory University School of Medicine in Atlanta, Georgia, noted that reducing the burden of care for patients with diabetes is important. “We know that the simpler the regimen, the better (patient) adherence and persistence on the therapy,” he said.

When patients on an oral therapy aren’t meeting their glycemic goals or responding to oral medications, Green said she investigates. Are they taking the medications? If they aren’t filling and taking the medications, why aren’t they? Is there a regimen better suited to the patient’s lifestyle?

Lifestyle changes aren’t enough

Many patients with T2D progress to insulin therapy but adding insulin to the treatment regimen does not mean they will easily achieve adequate glycemic control, Green said. Although insulin is a “powerful tool,” it only addresses inadequate insulin secretion and not the other aspects of metabolism that are present in T2D. “Thus (insulin) alone can often be inadequate to control blood sugars.”

According to Galindo, many patients are being treated with premixed insulin, which is a combination of an intermediate-acting and short-acting insulin. This regimen was first introduced in the 1990s. Although it produced good results, it also had undesirable side effects such as hypoglycemia, he said.

For reasons of cost and access, many patients are still treated with this option. Insurance coverage “is very friendly” for premix insulin and “less friendly with the newer agents,” Galindo said.

Green added that there is a clinical inertia, or a failure to start therapy, in the management of T2D because of the desire to use lifestyle changes to improve glycemic control. Although lifestyle management is important, it is not an adequate way to manage T2D, she said.

“There are many studies of early Type 2 diabetes management that have been published that have shown that combination therapy implemented right from the start of a diagnosis of Type 2 diabetes is a much more effective approach ... in achieving glycemic goals and maintaining good glycemic control for extended periods,” Green said.

Fixed-ratio combinations

Prescribing a combination of basal insulin with a GLP-1 receptor agonist can help address multiple issues for patients with T2D. Basal insulin reduces fasting plasma glucose, which is high in patients with uncontrolled diabetes. GLP-1 receptor agonists address postprandial glucose spike that happens after a meal. The two agents together can address hemoglobin A1c, explained Galindo.

Both iGlarLixi and IDegLira, which consists of insulin degludec and liraglutide, are fixed-ratio combinations delivered in single injection. In addition to addressing high hemoglobin A1c levels, iGlarLixi and IDegLira delay gastric
emptying, an effect that results in feeling full earlier and suppressing cravings and hunger. As a result, these agents can lead to patients losing weight. Weight loss is important in the management of T2D because 80% to 90% of patients with the condition have obesity or are overweight. “If we think about the patients for whom that kind of combination therapy might be appropriate, I have to say that those could be considered appropriate interventions for just about anyone with type 2 diabetes,” Green said.

Research findings
Research has shown the benefits of basal insulin combined with GLP-1 receptor agonists. In the LixiLan-O study, iGlarLixi was compared with insulin glargine alone and lixisenatide alone. Patients in the study were insulin naïve, had uncontrolled diabetes with hemoglobin A1c between 7.5% and 10%, and had been taking metformin alone or with another oral agent.

“This is a common population that we see in our practices, as many of our patients are struggling to get their A1c controlled on metformin or metformin and a second oral therapy,” Galindo said. “And insulin can do that. But what we learned over the years is that it will do that at the expense of weight gain and expense of increasing hypoglycemia, a complication of insulin therapy.”

The study found the patients in the iGlarLixi group had a greater reduction in hemoglobin A1c and more patients in that arm reached the target hemoglobin A1c of 7% or less. The patients treated with iGlarLixi and lixisenatide also had a decrease in body weight compared with patients on insulin glargine. “When you treat a patient, they know they’re going to be losing weight and they see the weight loss; they actually feel much better,” Galindo commented.

The DUAL-1 study, similar in design to LixiLan-O, evaluated IDegLira. The outcomes of the two studies were similar: Patients in the IDegLira group had a greater reduction in hemoglobin A1c with more patients achieving the target of less than 7%. The patients in the IDegLira group also had less weight gain compared with those in the degludec group.

A third trial, SoliMix, compared iGlarLixi with a premix insulin regimen in patients with hemoglobin A1c between 7.5% and 10%. iGlarLixi is taken once a day but the premix insulin is taken twice a day. Similar to DUAL-1 and LixiLan-O, patients in the iGlarLixi group had a greater reduction in hemoglobin A1c. They also lost more weight — almost 5 pounds, on average.

More importantly in Galindo’s view is that patients on iGlarLixi had less hypoglycemia than patients on the premix insulin. If hemoglobin A1c is controlled but patients tend to experience hypoglycemia, “you’re not really helping your patient,” he said. “You’re putting them into treatment-related complications that don’t need to happen because there are newer agents with a safer profile.”

When insurers cover premix insulin because it’s less expensive, they’re only considering the short term, he added. Costs may be lower month to month, but in the long-term patients may have more complications, gain weight and become less adherent.

The advantage of treatments like iGlarLixi and IDegLira is that they are delivered as a single injection. However, it’s not uncommon for clinicians to prescribe the individual components, sometimes referred to as free-dose combinations. Clinicians will prescribe insulin glargine followed by lixisenatide, lixisenatide followed by insulin glargine, or both simultaneously.

Galindo discussed findings presented at the Academy of Managed Care Pharmacy (AMCP) Nexus 2021 meeting that compared iGlarLixi with free-dose combinations. The results showed that patients in the iGlarLixi group were more likely to be persistent and adherent to their treatment than patients in the free-dose combination. In addition to iGlarLixi being more convenient for patients because it is a single injection, the results shown at AMCP Nexus showed that the patients in the iGlarLixi group had lower pharmacy costs.

“The reality is that the pharmacy costs of this combination when you compare that to the individual components were lower,” Galindo observed. “I think it’s important data for the payers.” iGlarLixi also resulted in fewer hospitalizations and fewer emergency department visits compared with patients on the free-dose combination.

“I will encourage clinicians … (and) our colleagues from pharmacy and health care systems and at insurers to use this evidence to support their coverage decisions,” Galindo said.
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RESULTS REVEALED IN RECORD TIME BECAUSE TIME MATTERS advanced cancer patients in 3-5 business days* 

*Data on File. †Turnaround time is based on qualified sample receipt. ‡QNS = quantity not sufficient.

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Comparative turnaround time data on file.

Low QNS ‡ rate* means more patients get tested and treated.
People with obesity are already at heightened risk for a number of serious illnesses: diabetes, heart disease, some cancers. Severe COVID-19 can now be added to that list. Especially concerning is research that shows the risk is high among young adults, ages 20 to 39.

“I would daresay that almost all of the patients that we have seen who were young and did very poorly were all significantly obese,” says Aaron Eli Glatt, M.D., chief of infectious diseases and the hospital epidemiologist at Mount Sinai South Nassau in Oceanside, New York. “I can’t say it was 100%. But there were medically significant risk factors in terms of having bad COVID(-19) in the hospital in your 30s. And we see this literally almost every day of the pandemic.” Glatt notes the difficulty of teasing out whether it is obesity itself that increases the risk of severe COVID-19 or the web of cardiovascular and metabolic disorders associated with being overweight or obese.

“I don’t know if we will ever have an absolute, definitive answer,” Glatt says. “But the overwhelming evidence certainly suggests that people who have obesity, whether that is the risk or not ... are far, far worse off if they have COVID-19. I don’t know how anybody can argue with that.”

The epidemiologic evidence of an association between obesity and severe COVID-19 and death is strong and not in dispute, at least during the early phase of the pandemic. A study published in March 2021 in the CDC’s Morbidity and Mortality Weekly Report that...
included more than 148,000 U.S. adults who received a COVID-19 diagnosis in 2020 showed that just over half (50.8%) of those who were hospitalized had obesity (a body mass index, or BMI, of 30 or more) and that just under half (46.0%) of those who died had obesity.

Possible explanations

It is not entirely understood why obesity would worsen COVID-19, but researchers have proposed a number of explanations. Several theories trace the risk to the properties of adipose tissue in people with obesity. In a patient with obesity, the proinflammatory cytokines normally released by adipose tissue become amplified, and that amplification may lead to dysregulated immune function and greater difficulty fending off infections.

Leptin is one of those cytokines, and people with obesity can develop leptin resistance that is similar to insulin resistance that induces chronic inflammation. Adipose tissue in obesity is also a source of interleukin 6, a cytokine that may contribute to the runaway inflammation of the "cytokine storm" that characterizes many severe cases of COVID-19.

There’s also a theory that adipose tissue acts as a kind of reservoir for the SARS-CoV-2 virus and therefore plays a role in viral shedding. The extra adipose tissue in a person who is obese may mean a bigger SARS-CoV-2 reservoir and even more shedding.

Other explanations about the association between obesity and severe COVID-19 center on obesity’s effect on lung function. Central adiposity — the accumulation of adipose tissue in the abdomen — can limit expansion of the lungs. As a result, the lungs do not take in as much air, and that, in turn, means less oxygen reaches the blood.

“We are still learning about COVID-19 and its interaction with adipose tissue,” says Katherine H. Saunders, M.D., an obesity specialist and an assistant professor of clinical medicine at Weill Cornell Medicine in New York. “There will likely be several mechanisms identified that explain the greater prevalence of severe disease among people with obesity.” Saunders mentions that the chronic inflammation associated with excess weight may make it harder for the immune
system to protect the body against the SARS-CoV-2 virus and that individuals with obesity can have impaired lung function.

**Obesity as a disease**

One way to view obesity and COVID-19 is as two epidemics combining and accentuating one other. Obesity is a risk factor for severe COVID-19, and the pandemic has led to weight gain.

A Harris Poll last year found that 42% of Americans said they had gotten heavier since the pandemic started in early 2020 and that the average weight gains was 29 pounds (the median was 15). Almost certainly that means many people in the U.S. went from being overweight to obese. With that change may have come a higher risk for developing diabetes, hypertension and, possibly, severe COVID-19.

Of course obesity has been a problem in the U.S. long before the pandemic. According to a February 2020 report from the National Center for Health Statistics (NCHS), the prevalence of obesity among adults in the U.S. increased from 30.5% in 1990-2000 to 42.4% in 2017-2018. During that same span, the prevalence of severe obesity increased from 4.7% to 9.2%. Health researchers define severe obesity as a BMI of 40 or higher. Some data suggest, though, that the rate at which the prevalence of obesity has been growing is slowing down some.

The figures in that NCHS report foreshadow to some extent that that COVID-19 might be bad news for 20- to 39-year-olds. The prevalence of obesity in that age group was 40%, which was not that much lower than the prevalence of 44.8% among middle-aged adults, ages 40 to 59, and the prevalence of 42.8% among older people, ages 60 or more.

Obesity has been typically viewed through the lens of personal responsibility and individual choice. Attitudes are changing, but people with obesity are still viewed inaccurately as being lazy or undisciplined. For quite some time, public health officials and others have seen obesity differently. In 1948, the World Health Organization weighed in by classifying obesity as a disease. U.S. health officials were decades behind; 50 years later, the National Institutes of Health declared obesity a disease, followed in 2013 by the American Medical Association.

“Obesity is much more complex than most people realize,” says Saunders. “There are so many different pathways involved. We have learned so much in the last few decades,” says Saunders, the first physician to complete a fellowship in obesity medicine at the Comprehensive Weight Control Center at Weill Cornell Medicine. “There is exciting research happening right now. We have several very effective medications and there are even more in the pipeline.” The obesity subspecialty is growing, with more than 5,200 board-certified obesity physicians, according to Saunders.

Still, too many healthcare providers, not trained in obesity medicine, continue to rely on the traditional diet and exercise regimens. Diet and exercise are the cornerstones of every weight loss program, Saunders says. But by themselves, they don’t work for everyone.

“When people with obesity try to lose weight with dietary strategies and they are not successful … they can and should seek medical treatment, because this is more than a lifestyle problem for most people and medical treatment is warranted,” says Saunders, a co-founder of Intellihealth, a company that provides a medical approach to obesity. “The most important thing is that obesity is not a lifestyle problem. It’s not about willpower. It is a complex disease.”

Obesity is associated with more than many comorbidities. It’s one reason why, prior to the pandemic, it was, by some accounts, the second-leading cause of preventable deaths in America, killing between 280,000 and 300,000 Americans each year.

**More evidence**

Meanwhile, the evidence for the danger of the COVID-19/obesity combination continues to pile up, although comorbidities are also involved. For example, a study published in the September 2021
Percentage of hospitalized patients with COVID-19 by body mass index

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>Percentage</th>
</tr>
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<tr>
<td>Under 18.5</td>
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<tr>
<td>18.5-24.9</td>
<td>19.7%</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>27.8%</td>
</tr>
<tr>
<td>30.0-39.9</td>
<td>36.2%</td>
</tr>
<tr>
<td>40 and above</td>
<td>14%</td>
</tr>
</tbody>
</table>


Source: Morbidity and Mortality Weekly Report, March 12, 2021

issue of Clinical Microbiology and Infection looked at 134,209 French adults admitted to hospitals with COVID-19. The authors concluded that "mortality was more frequent among patients with obesity and diabetes." They also noted that intubation was three times more frequent among patients with obesity than among patients without.

Three months later, a retrospective cohort study published in the journal Clinical Infectious Diseases echoed some of the French findings. The researchers combed through data on 66,000 patients with a COVID-19 diagnosis seen at 613 U.S. hospitals, 18.6% of whom died. Diabetes without chronic complications was not a risk factor for mortality, and hypertension without complications was only a risk factor in 20- to 39-year-olds. But diabetes with chronic complications, hypertension with chronic complications and obesity were risk factors at most ages and posed the greatest risk in the 20- to 39-year-old age group.

**Weight loss**

To avoid COVID-19 danger, Glatt tells patients — regardless of weight — to get vaccinated and boosted. But the recommendation is even stronger for people with obesity. "Obese people can have difficulty breathing because of the physical dynamics of their obesity," says Glatt, referencing some of the current thinking about why severe COVID-19 is greater threat for people who are heavy. "They may not be in good shape and they don’t take deep breaths. Obesity can impair their immune function. There are so many complicating factors. It is extremely unusual that a patient is just obese and has no other medical problems."

People with obesity may want to consider steps to lose the adiposity. "Begin to assess whether or not this is the weight you want to be at," Glatt advises.

If one can think of a pandemic that is on its way to claiming a million American lives as having a silver lining, Saunders and her colleagues say that lining might be all the attention that obesity is getting as a bona fide health problem. "Our mission is to make it clear to the medical community and beyond that obesity is something that is treatable and it is something that requires medical attention," she says. "In terms of COVID-19, we do have evidence that treating obesity can reduce the risk of morbidity and mortality."

Robert Calandra is an independent journalist in the Philadelphia area.
Comprehensive Genomic Profiling: Advancing Cancer Care

In this Managed Healthcare Executive® KCast, David R. Gandara, M.D., discusses comprehensive genomic profiling and some issues related to tissue- or plasma-based tests. Gandara is professor emeritus and director of the thoracic oncology program at the UC Davis Comprehensive Cancer Center in Sacramento, California, and senior adviser to the center’s director. This transcript of his remarks has been edited for clarity and length.

**Summary**
The value of comprehensive genomic profiling can’t be overstated. Non-small cell lung cancer is a poster child for such testing, but it is coming on rapidly for several other tumor types. The test results inform decisions that match the treatment to a tumor’s genetic makeup. Comprehensive genomic profiling can lead to better outcomes for patients and savings from more cost-effective care.

**Evolution of genomic testing**
The term “comprehensive genomic profiling” has come about as we have transitioned from research tools like whole-exome sequencing to commercially available platforms. There are quite a few available entities in the United States that do broad-based testing for genomic abnormalities in a variety of cancer types. Particularly pertinent is non-small cell lung cancer because of the large number of oncogenes. These platforms will assess from 70 to over 500 gene targets. They’re constructed in such a way that they use minimal amounts of DNA. Some incorporate RNA. They’re also designed to have a turnaround time of between 10 and 21 days.

We used to test sequentially. We tested for EGFR or KRAS. If that was negative, then we would test for other oncogenes. Then there was so-called multiplexing or “hot spot” testing. We would test for a limited number of oncogenes.

Now we have next-generation sequencing and comprehensive genomic profiling. In the example of non-small cell lung cancer, studies have shown it is more cost-effective to test up front for all the genes at once with next-generation sequencing than it is to first use sequential or exclusion testing, which leaves out certain abnormalities.

The need for comprehensive genomic profiling today is greatest in advanced-stage non-small cell lung cancer because of eight guideline-recommended oncogenes that should be tested for in all patients with advanced-stage disease, particularly those with nonsquamous histology. When one of these oncogenes is found, the treatment is a targeted tyrosine kinase inhibitor. It’s important that oncologists employ a test that has a fast turnaround time because, in addition to specificity and sensitivity, you don’t want to start treatment until you get the results.

**Who should get tested**
Our thinking about who should get next-generation sequencing done by a comprehensive genomic profiling platform has changed over the years. I’m confining these remarks to non-small cell lung cancer because this is the clearest example. Initially, we said, “Maybe this should be done only in never-smokers, in adenocarcinoma, or in young patients in the United States who are Asian American because of a higher prevalence of EGFR-mutated disease.”

Our thinking has changed because if you find an abnormality, it’s like hitting a grand slam. Even if that patient has a prior smoking history, there’s still a significant chance you’ll find one of the oncogenes.

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**Firsthand experience**
I’ve had many examples in my clinic. Within the last week, a patient was referred to me with rapid disease; the patient had a remote history of smoking. I recommended, instead of starting chemotherapy and immunotherapy, to get next-generation sequencing in blood, because of the faster turnaround time. Within 1 week, an ALK translocation was found. The patient was started on appropriate therapy within 3 days of starting that therapy. The patient reported to me — we have a chart; that’s how you communicate — that his shortness of breath, his chest pain had almost completely gone away within 72 hours. This is like turning off a light switch. If you don’t find that target, this same patient has been proven in studies to do poorly with immunotherapy.

Typically, we exclude patients with EGFR mutation: the other nonsmoker-related oncogenes from initial treatment with immunotherapy. This is a practical example of why this is important, and insurers understand that. It used to be that we would get disapprovals left and right when we order next-generation sequencing. Where I practice in California, that essentially never happens anymore.
Tissue versus blood

Comprehensive genomic profiling can be accomplished in two ways. One is a classic tissue-based test that has been available in the United States for close to 10 years. The same genomic information can be obtained through plasma circulating tumor DNA.

When to choose which is complicated. In 2021, the International Association for the Study of Lung Cancer published updated guidelines on the emerging role of plasma-based liquid biopsy and described the differences between tissue and blood tests. In some cases, you want to order both at the same time.

But in up to one-third of patients with newly diagnosed, advanced-stage non-small cell lung cancer, there may not be adequate tissue from the biopsy upon which to perform next-generation sequencing. The tissue may have been used up for immunohistochemistry or for other purposes. In those patients, rather than doing another biopsy, we're using a plasma-first approach. We obtain the blood and look for actionable oncogenes. If you find one in blood, then you can treat on that basis.

There are no false positives with the available tests. On the other hand, if the blood is not informative, then you would proceed with, in this case, a rebiopsy if there were not adequate tissue.

The NILE, or Noninvasive versus Invasive Lung Evaluation, study was a prospective, multicenter study of 282 patients newly diagnosed with non-small cell lung cancer. It showed that if you use a plasma-based test along with some tissue assessment, the tests are complementary, so you gain even more information. You're able to find a higher percentage of actionable oncogenes.

The turnaround time for all the plasma-based assays is shorter than that for tissue-based ones. No matter where the test is sent around the world, the turnaround time is seven days. For a tissue-based assay, you must have adequate tissue. If you don't, it will take about a week to do the rebiopsy, process it and start the tissue analysis. If you do have adequate tissue and you're going to send it out compared with doing it in some in-house fashion, the turnaround time is 14 days. Depending on the company of institution doing the testing, it can take a month.

Avoid this mistake

Let's say you're a practicing oncologist. You're seeing a new patient with stage 4 adenocarcinoma of the lung. Your choices are to treat empirically or to wait until the results of the next-generation sequencing come back. Having a rapid turnaround time facilitates that.

The mistake that's made is the patient is started on immunotherapy and chemotherapy before the results of the molecular testing come back. When it does come back, it shows an oncogene favorable to targeted therapy. The problem then is stopping the immunotherapy component and starting the patient on the tyrosine kinase inhibitor.

Evidence is accumulating that the efficacy of the tyrosine kinase inhibitors is diminished by prior exposure, even briefly, to checkpoint immunotherapy and that the (side effect) profile of the tyrosine kinase inhibitor is increased.

If it's a true emergency — such as rapidly progressive disease or falling performance status — an oncologist needs to start treatment emergently. This happens less than 10% of the time in advanced stage non-small cell lung cancer. The recommendation is to start with chemotherapy alone, so you avoid that subsequent negative interaction if you have to switch to a tyrosine kinase inhibitor.

Economic value

Several studies have shown that it's more cost-effective to test for all the genes up front simultaneously with next-generation sequencing than it is using sequential or exclusion testing, when you exclude certain abnormalities, before you go to next-generation sequencing. This has been shown to be the same in plasma-based testing — that it's more cost-effective in plasma-based testing to do next-generation sequencing.

Insurers understand that they're not just paying for the testing. They're paying for a result that is practice changing. The decision-making process for patients will turn on its heel if one of the actionable oncogenes is found.

Benefits of commercially available tests

With a few exceptions, it's better to use the commercial tests from a good, reliable company, with good sensitivity and specificity in their assay, because not only can you get the results in a timely fashion, but all the annotation in the report is important and difficult to keep up.

Let's say a patient is found to have a ROS1 fusion in their cancer. A good next-generation sequencing comprehensive genomic profiling report tells you what the allele frequency is and how much is there. It tells you if it's functional or not. If it's not, it tells you that it's a variant of unknown significance. It tells you what drugs the abnormality is sensitive to. It tells you what clinical trials are available for that patient against this target, and it gives all the references.

New drugs come on board, new clinical trials open or close. Although you can do this in your own institution, it's quite laborious. At the UC Davis Comprehensive Cancer Center, we have our own next-generation sequencing platform. We use it only for research.
In January, CMS proposed rules that would, among other changes, require health insurers to be more transparent, to lower out-of-pocket costs for prescription drugs and to improve patient outcomes.

In an extensive proposal taking up more than 115 pages in the Federal Register, CMS proposed changes in 14 areas, including new regulations on how Medicare Advantage (MA) and Medicare Part D plans establish networks, report medical-loss ratio (MLR) data, assess members’ risks for social determinants of health, and conduct appeals, marketing and communications.

If approved as proposed, the rule — CY 2023 Medicare Advantage and Part D Proposed Rule (CMS-4192-P) — would require MA, Part D plans and special needs plans (SNPs) to be more transparent in how they calculate MLR and set up networks, says Monisha Machado-Pereira, a senior partner in McKinsey’s Healthcare Systems and Services Practice. SNPs are a type of MA plan for beneficiaries with specific diseases or conditions.

The rules also are focused on improving health outcomes for Medicare members, particularly those in SNPs and who require more care at home, she added. Comments on the proposal were due to CMS by March 7. The rules must be finalized by CMS no later than April 4.

For Medicare members, some of the most significant parts of the proposal zero in on reducing what beneficiaries pay as their share of costs for prescription drugs and limits on the the maximum out-of-pocket amounts for dual-eligible beneficiaries, who are people who qualify for Medicare and Medicaid.

**Lowering drug costs**

To reduce what Medicare members pay in copayments or deductibles for prescription drugs, CMS has proposed eliminating direct and indirect remuneration (DIR) fees to pharmacists. Under DIR-fee provisions in pharmacy contracts, health plans and pharmacy benefit managers (PBMs) “claw back” payments weeks or months after paying pharmacies for the medications they dispense to health plan members. Under some Part D contracts, the plans claw back payments they’ve made to pharmacists if they do not meet certain criteria when dispensing drugs, according to CMS. When Part D plans claw back payments, they report the previously negotiated price for the drug, which is higher than the final price after claw backs. CMS uses that price to set beneficiary cost-sharing amounts and to adjudicate Part D claims. The effect of reclaiming some of what the PBMs and Part D plans have already paid to pharmacies, the PBMs and Part D plans have caused Medicare members and CMS itself to pay more than they should, the agency said. In this extensive new rule, CMS has proposed redefining the negotiated price as the baseline, or lowest possible, payment to a pharmacy by requiring Part D plans to apply all price concessions at the point of sale so that beneficiaries can share in the savings.

Although the proposal on DIR fees could cut what beneficiaries pay for prescription drugs, it is unclear whether or how much the proposal would increase transparency in the pharmacy supply chain, says Julie Carter, senior federal policy associate at the Medicare Rights Center, a nonprofit organization in New York that helps consumers navigate the Medicare program.

“We don’t necessarily know exactly how much money we might be talking about or whether it would reduce beneficiaries’ overall costs,” adds Carter. “It may reduce costs at the pharmacy counter, but also it may increase premiums. Either way, we don’t know by how much.”

**Out of pocket limits**

Also in the CMS proposed rules is a plan to limit the maximum out-of-pocket amounts for dual-eligible members in MA plans. CMS projects that over 10 years the new limits would save state Medicaid agencies about $2 billion and increase payments to providers who care for dual-eligible beneficiaries by about $8 billion.
The proposed rules call for more oversight of third-party brokers and marketing organizations. Brokers would need to explain clearly which benefits are or are not included, Machado-Pereira explains. They would also need to disclose whether they get paid more to steer consumers to one plan over another.

CMS is also proposing tighter rules for fully integrated dual-eligible special needs plans (D-SNPs). Certain states with integrated care programs could require that MA plans establish a contract including one or more D-SNPs. The idea is to make a health plan's star ratings more accurately reflect the D-SNPs local performance, according to Machado-Pereira.

**More MLR details**

Insurers also would be required to provide more data on how they calculate MLR under the proposed rules. In effect, CMS is reinstituting the MLR rules it used from 2014 to 2017. Under the previous administration, those rules were relaxed, notes Machado-Pereira.

“For four years, ending in 2017, CMS asked for a full breakdown of what insurers spent on medical care, but since 2017 they didn’t have to report the underlying cost and revenue numbers for providing medical care for members,” Machado-Pereira explains. Starting next year, MA and Part D plans would need to report the underlying cost and revenue information used to calculate the MLR percentage and what they would need to pay CMS for failing to reach the 85% goal under the MLR rules. In addition, CMS proposes requiring MA plans to report what they spend on such supplemental benefits as dental, vision, hearing or transportation.

More data on medical care spending would allow CMS to see how much health insurers are putting into the supplemental benefits that the MA plans use to differentiate themselves among the growing number of zero-premium offerings, Machado-Pereira says. “This information will help CMS know whether plans are stretching the definition of which supplemental benefits are primarily improving health or not,” she adds.

Another advantage of ensuring that supplemental benefits are related to health is that such benefits could help improve member outcomes, notes Machado-Pereira. Improving outcomes is a goal CMS proposed for all Medicare plans and particularly for SNPs. Recognizing that these members often have food insecurity, may be homeless, or lack transportation and have low health literacy, CMS will require all SNPs to complete health risk assessments for all members at enrollment and annually thereafter.

**Ensuring adequate networks**

Just as the proposed rules on the MLR and health risk assessment aim to increase transparency, so too does the CMS proposal regarding network adequacy. Under the proposal, CMS would require plans to show they have networks of providers under contract who can care for all beneficiaries before CMS will approve an application for a new or expanded MA plan. The Medicare Rights Center favors this proposal because it has encouraged CMS to provide more oversight of how MA plans structure their networks, as well as accurate and up-to-date information to members about those networks, Carter said.

Flaviu Simihaian, CEO of Troy Medicare, a small MA plan in North Carolina, sees merit in the network adequacy proposal, but also a drawback. For Simihaian, the proposal is unfair to small plans and to those just entering the market because hospitals, physicians and other providers have no requirement to join networks that small and newly established plans set up even when those plans pay fair rates.

“If there’s a rule for providers to accept a fair rate, there’s no competition because the only plans that have the leverage to negotiate are the big ones that already contract with most or all of the providers in their service area,” Simihaian says.

**Health equity**

CMS under the Biden administration has announced that it will be incorporating efforts to address healthcare equity in all of its programs. A request for feedback on several healthcare equity measurements and methodologic adjustments was part of these proposed MA and Part D plan rules. For example, CMS might add a “health equity index” to its star ratings of MA plans. □

Joseph Burns is an independent journalist in Brewster, Massachusetts, who writes about healthcare.

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“...and revenue numbers used to...”

–MONISHA MACHADO-PEREIRA, A SENIOR PARTNER IN MCKINSEY’S HEALTHCARE SYSTEMS AND SERVICES PRACTICE
The Biden administration had a good plan. But giving health insurers five days to execute that plan has led to problems for payers, pharmacies and consumers.

On Jan. 10, the administration instructed health insurers to cover the costs for every plan member to obtain eight FDA-approved at-home COVID-19 tests at retail pharmacies or online each month.

Insurers were told to implement the plan by Jan. 15. For insurers, five days was not enough time, says Eileen Wood, chief pharmacy officer for CDPHP, a nonprofit health plan in Albany, New York.

“The HHS rule calls for health plans to allow members to get those tests for free or the insurers need to set up systems to reimburse members as much as $12 per test for eight tests per member per month. When buying the tests, members do not need a physician’s prescription, nor do they need to have symptoms.

Some pharmacies have not had the tests in stock. Even those that do have not always followed the protocols that insurers set up. “We have to do more communications with our retail pharmacy partners, but so far it’s not been easy,” says Wood.

For CDPHP members to get the tests without cost at pharmacies, the pharmacies have told CDPHP that their systems require store staff to enter a prescriber’s name and National Provider Identification number, Wood explains. Without a prescription, some pharmacies have required CDPHP members to pay at the point of sale or the pharmacies need to enter the pharmacist’s name as the prescribing provider, she adds. Communicating the details that the tests should be free to health plan members to each pharmacy in 29 counties is a challenge, she notes. In addition to the start-up frustrations, the cost of providing eight tests per month at $12 apiece for each of the health plan’s 400,000 members for an entire year could total more than $460 million, an amount equal to about 25% of the plan’s annual premium revenue, she notes.

Chris Kastman, M.D., the chief medical officer at Group Health Cooperative of South Central Wisconsin in Madison, also was worries about how much the new rule could boost premiums next year. “Even the most modest estimates call for what probably will be a 2% increase in premiums next year,” he says. “But those costs could be much, much higher depending on how it goes this year.”

Kastman and Wood say that establishing the payment systems has been a struggle. “Most health plans will piggyback off of their existing pharmacy network, which sounds easy,” Kastman explains. “But then you realize that our pharmacy benefit manager and the company that manages our pharmacy claims need to set up new workflows for all of their health plan clients all at once.” Kastman adds: “We set up everything we could and then watched with dismay how the people we work with, even with the best of intentions, just couldn’t quite get all the pieces in place in such a short time.”

Kaiser Family Foundation (KFF) researchers reviewed the COVID-19 test policies that 13 large U.S. health insurers had posted online in January. Six had established a direct-coverage option in which members can get rapid at-home tests without paying up front or having to file a claim if the member buys the test at a preferred network of pharmacies or from a mail-order pharmacy, KFF said. By allowing the direct-coverage option, HHS provided an incentive for insurers to simplify coverage for consumers and to contain insurers’ costs somewhat by putting a limit of $12 on what they must pay for the tests. After the KFF report came out in January, Blue Cross Blue Shield of Minnesota established a direct-coverage option and other insurers may follow suit.

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New TEFCA framework brings some clarity to interoperability push

Voluntary guidelines passed in January show a way to making interoperability work on a practical level. by JARED KALTWASSER

When the 21st Century Cures Act was signed into law in the waning days of the Obama administration, it was promoted as a revolutionary revision that would help healthcare innovation to flow through the regulatory process. Yet, five years on, one of the most-watched components of the law is still in its early stages. Those provisions called for new interoperability standards to ensure that patient healthcare data could easily and securely be shared across a wide range of healthcare entities.

The law’s implementation was delayed in part by the COVID-19 pandemic. In 2020, HHS’ Office of the National Coordinator for Health Information Technology (ONC) published rules designed to govern interoperability, although those rules raised concerns from some about whether the agency went far enough to protect patients’ privacy.

In January, ONC went a step further, publishing a new set of principles for the exchange of healthcare information. The principles — known as the Trusted Exchange Framework — are a set of voluntary guidelines designed to facilitate secure interoperability. In addition, ONC published a Common Agreement (CA), a contract that health entities can join that sets forth the technical structure and governance for health information exchanges. A portmanteau of their initials, TEFCA (pronounced tef-ka), has been coined.

“Simplified nationwide connectivity for providers, health plans, individuals and public health is finally within reach,” said Micky Tripathi, Ph.D., the national coordinator for health information technology, in a news release.

Now that the framework has been published, ONC said entities will “soon” be able to apply for designation as “qualified health information networks” (QHINs), which will facilitate connections and information exchange between healthcare industry players.

The Sequoia Project, which is implementing TEFCA under ONC’s authority, describes the QHINs as networks that will abide by the common agreement and governance structure outlined in TEFCA. Covered entities can choose which QHIN to join based on factors such as services provided and costs. ONC said the design is meant to be flexible enough to work for stakeholders from hospitals to health information networks to patients.

In a joint news release announcing TEFCA, ONC and the Sequoia Project said they expect to evaluate QHIN applications and launch information sharing on accepted networks by the end of the year.

Nilesh Chandra, MBA, partner in healthcare strategy at PA Consulting, says TEFCA is a “significant development” because until now there has been no national framework for data sharing. “While the immediate impact may not be obvious, in the long term these frameworks will eventually help drive us to a future where patients’ health data are shared appropriately across care settings, across provider networks, to help every provider get access to all relevant information at the point of care,” comments Chandra.

The TEFCA framework lays out six permitted uses for healthcare data exchange within the networks: treatment, payment, healthcare operations, public health, government benefits determinations and “individual access services,” an umbrella category that includes patient-facing applications.

Along with the TEFCA framework, ONC also published a TEFCA Health Level Seven Fast Healthcare Interoperability Resource (FHIR) Roadmap, which it said is designed to show how TEFCA will accelerate the adoption of FHIR across the industry. FHIR standards are designed, in part, to make it easier to access individual data points within medical records.

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This may be the cause of MS

Harvard researchers say their findings prove that Epstein-Barr virus is the leading cause of multiple sclerosis. Other factors, including genetic predisposition, likely also play a role. by SUSAN KREIMER

Epstein-Barr virus (EBV) may be the leading cause of multiple sclerosis (MS), a progressive and incurable neurological disease afflicting 2.8 million people worldwide, a new study shows.

The study, led by researchers at the Harvard T.H. Chan School of Public Health in Boston, used blood samples stored by the Department of Defense that came from 10 million young adults on active duty (the samples were collected to test for HIV). The researchers identified 955 service members who had received an MS diagnosis. Their case-control analysis included 801 MS cases matched with 1,566 controls. Only one of the blood samples of the 801 MS cases showed no antibody evidence of EBV infection.

The researchers calculated that EBV infection was associated with a 32-fold greater risk of developing MS. They reported their findings in Science in January.

As a chronic inflammatory disease of the central nervous system, MS wreaks havoc on the myelin sheaths, insulating layers of fatty tissue and protein that safeguard neurons in the brain and spinal cord. EBV is a herpes virus, transmitted most commonly through saliva. EBV is typically contracted in early childhood or adolescence. Although young children usually don’t develop symptoms, adolescents and young adults can get infectious mononucleosis from EBV. The mechanism by which it could cause MS remains unclear.

Substantiating EBV’s causal role in MS has been fraught with challenges, partly because EBV infections are so common. About 95% of adults get infected with the virus, yet only a tiny fraction ever develops MS. Moreover, the onset of MS symptoms occurs, on average, a decade after EBV infection, and some studies have found that MS develops 30 years after the infection caused mononucleosis, says Kassandra Munger, Sc.D., one of the study’s two senior co-authors.

“We can consider EBV necessary to developing MS, but there need to be other mitigating factors.”

— KASSANDRA MUNGER, SC.D., HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

The researchers suspect the delay between EBV infection and MS onset might be explained by MS symptoms occurring only relatively late in the pathophysiology. Another factor may be the interaction between the viral infection and the immune system, with the latent infection reactivating due to persistent stimulation.

There are antiviral medications for EBV infections but no drugs for MS that target EBV. The researchers expressed hope for development of an EBV vaccine or EBV-specific antiviral drugs. An EBV vaccine may be in the works. In early January, Moderna announced that it was starting early-stage clinical trials of a messenger RNA (mRNA) vaccine against EBV. The phase 1 randomized, observer-blind, placebo-controlled study will be conducted at about 15 sites in the United States. If the experimental vaccine proves to be safe and efficacious, the same mRNA technology underpinning Moderna’s COVID-19 vaccine could be used to produce this EBV vaccine.

Susan Kreimer is a freelance healthcare journalist in New York.
Reducing Readmissions for Complex Pulmonary Patients

By Sean R. Muldoon, MD, MPH, FCCP CMO and Audra Early, SVP Strategy and Network Development, Kindred Hospitals

Recent research shows that the need for expertise in pulmonary care is increasing as the population of medically complex patients grows. Studies also reveal that long-term acute care hospitals (LTACHs) are playing a significant role in reducing readmissions for these patients.

Acute Respiratory Distress Syndrome (ARDS) and Its Impact
Despite advances in care, the unplanned 30-day readmission rate for ARDS patients is 18%. Studies have found that sepsis and pneumonia cause 40-60% of all ARDS diagnoses and that patients with chronic illnesses and comorbidities are more susceptible to developing ARDS.2,3

There is currently no cure for ARDS. Rather, treatment involves addressing the immediate hypoxia, often through ventilation, thus allowing time to treat underlying conditions.4

The Increasing Demand for Respiratory Care
There are two key factors that are contributing to the rise in serious pulmonary diseases such as ARDS.

• **COVID-19**: COVID-19, and its variants, is a virus that can cause serious lung injury. Observational studies conducted in Wuhan, China, found that 42-67% of COVID patients developed ADRs.5
• **Chronic Illnesses**: Currently, 64% of the population age 65 and older have at least two chronic conditions, which increase the likelihood of developing severe respiratory diseases such as ARDS.6

As the COVID-19 virus mutates and surges, and as the population ages and becomes more chronic, America’s health systems can expect a greater demand for pulmonology expertise.

LTACH Expertise in Pulmonary Care and Recovery
Patients with acute lung conditions, including those with COVID-19, often require long-term respiratory support and weaning from mechanical ventilation. At an LTACH, patients receive care from a team of pulmonologists and respiratory therapists. When respiratory therapists at an LTACH use ventilator weaning protocols, time on ventilator, mortality, and cost of care can all significantly decrease.7

LTACHs also treat underlying conditions. Their interdisciplinary care teams are trained to treat patients with chronic illnesses and multiple comorbidities and specialize in conditions such as pneumonia and sepsis which are significant causes of severe lung complications like ARDS.

How Kindred Can Help Your Respiratory Patients
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Cancer mortality is decreasing in the U.S.

The American Cancer Society’s 2022 statistical report shows that the 30-year trend is continuing. 

Cancer is a major killer. In its annual report on cancer incidence and deaths released earlier this year, the American Cancer Society projects that 609,360 people in the United States will die from cancer this year — an average of about 1,700 deaths per day — and close to 2 million cases of cancer will be diagnosed, which works out to about 5,250 cases per day. As has been true for many years, the greatest number of deaths stems from cancers of the lung, prostate, and the colon and rectum in men and of the lung, breast, and the colon and rectum in women.

But as sobering as those statistics may be, they are, in another way, heartening because they show the continuing decline in cancer mortality in the U.S., which peaked in 1991 and has been on a steady, downward trajectory ever since. Incidence (the detection of new cases) also peaked in the early ‘90s, although there are more ups and downs to cancer incidence because it is affected by screening and changes in screening guidelines.

Prostate cancer is a prime example. As explained by the paper elucidating the cancer society’s statistics that was published in the January/February 2022 issue of CA: A Cancer Journal for Clinicians, incidence dropped from 2007 through 2014 following changes to guidelines from the U.S. Preventive Services Task Force that curbed the use of PSA screening tests. Recently, though, the incidence of regional- and distant-stage prostate cancer have been increasing, noted lead author Rebecca Siegel, M.P.H., senior scientific director of surveillance research at the American Cancer Society, and her co-authors. One important proviso to this year’s report is that it is based on incidence and mortality data from 2018 and 2019 and therefore doesn’t reflect the effect of the COVID-19 pandemic, which resulted in fewer screenings and some delays in care.

Credit goes to less smoking
Cancer mortality in the U.S. has been declining for the past three decades for many reasons. Adjuvant chemotherapy — chemotherapy after surgery or radiation — for colon and breast cancers and combination therapies for other cancers deserve some credit, noted Siegel and her colleagues. They also mention advances in early detection, surgical techniques and making treatments more targeted. But they say the decline is largely because of reductions in smoking. Cigarette smoking remains the main cause of lung cancer deaths. About 80% of the projected number of lung cancer deaths this year (105,840 out of 130,180) will be caused by cigarette smoking, according to calculations by Siegel and her team. The researchers estimate that another 3,650 lung cancer deaths will be caused by secondhand smoke. But the toll from lung cancer that is not caused by smoking is considerable. According to the cancer society’s estimates, those 21,700 deaths make lung cancer not associated with smoking the eighth-leading cause of cancer mortality in the U.S.

Lung cancer incidence has also been decreasing as fewer people smoke. Among men the decrease started in the mid-1980s and among women, in the mid-2000s. “Declines in mortality began shortly thereafter but have accelerated in recent years because of earlier-stage diagnosis and improved treatment, which is reflected in longer survival,” notes Siegel. About 2 in 10 people who received diagnoses of lung cancer in 2004 were alive three years later. Now it is 3 in 10. Moreover, because lung cancer accounts for about 20% of cancer deaths in the U.S. each year, reducing lung cancer mortality has a major effect on cancer mortality overall. “We’re talking about large
numbers of people," Siegel says. More people die from lung cancer every year than from prostate, breast and pancreatic cancers combined.

The report notes the rising incidence of breast cancer and of prostate cancer discovered at a later stage. Even more concerning, says Siegel, are the persistent racial, socioeconomic and geographic disparities for highly preventable cancers that may be worsened by uneven access to interventions such as HPV vaccination and expanded health care. The researchers trace cancer disparities by race and ethnicity to wealth disparities that are the result of structural racism and point to redlining — discriminatory home financing practices — as a manifestation of structural racism.

Gerold Bepler, M.D., Ph.D., thoracic oncologist and president and CEO at the Barbara Ann Karmanos Cancer Institute in Detroit, notes that it is perhaps surprising that overall cancer incidence rates are declining in the U.S. because of the shift in the country’s demographic profile to an older population as the baby boomers age into their 60s and 70s. “However,” notes Bepler, “given that lung cancer is among the most frequently diagnosed cancers and much has been done over the past several decades to reduce risk factors associated with this disease, most notably cigarette smoking, this is the most likely explanation for the overall trend,” he says. “We should be proud as healthcare providers in this country that lung cancer is significantly on the decline.” Bepler says bans on cigarette advertising, increases in cigarette taxes and restrictions on indoor smoking have helped.

Following are other noteworthy developments mentioned by Siegel and her colleagues.

Liver cancer deaths are leveling off. Liver cancer mortality was increasing faster than mortality from any other type of cancer for decades. But the rate has leveled in the past five years. The big surge reflected steep increases in hepatitis C infections as a result of injection drug use during the 1960s and 1970s, Siegel says. Hepatitis C infection is the strongest risk factor for liver cancer and accounts for about a quarter of cases in the U.S. Effective antiviral treatment for hepatitis C infection may also be contributing to liver cancer declines in recent years, she adds.

Cervical cancer deaths, largely preventable, continue to happen. Cervical cancer is almost completely preventable, Siegel and her colleagues say, yet every year it’s the second-leading cause of cancer death among women in their 20s and 30s. “This is so frustrating because these are needless deaths; most of these women have either never been screened or haven’t been screened in decades,” Siegel says. “Pap tests detect precancers that can be easily removed before they progress to cancer, and also detect disease at an early stage when it can be treated successfully. And now we have HPV tests, which are even better, and HPV vaccination, which is better still. This is one cancer that really could be 100% eradicated, but even in one of the wealthiest countries in the world, we have a long way to go.”

People diagnosed with cancer are living longer. The survival gains have been especially large for people with the hematopoietic and lymphoid malignancies, according to Siegel and her colleagues. They cited the five-year survival rate for people diagnosed with chronic myeloid leukemia as an example. In the mid-1970s, the five-year survival rate was 22%. Now people treated with tyrosine kinase inhibitors — Gleevec (imatinib) was the first one developed — have a near-normal life expectancy, they said.

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Frequent and feared.
But can dementia be avoided?

There’s no guarantee, but physical activity and corralling cardiovascular risk factors and diabetes improve the odds. Health insurers can assist by helping members address the “upstream” social determinants of health. 

by KAREN APPOLD

Dementia is one of the most common and dreaded conditions in the United States. According to the CDC, about 5 million Americans have Alzheimer’s disease, the most common dementia diagnosis among older adults. Others estimate the prevalence at 6.1 million. By 2060, this number is expected to climb to 13 million. “These numbers are projected to increase because elderly individuals are the fastest-growing segment in the United States,” says Claudia H. Kawas, M.D., a professor in the Department of Neurology at the University of California, Irvine, School of Medicine. Alzheimer’s is the fifth-leading cause of death among Americans 65 and older and the sixth-leading cause of death in the U.S.

Dementia — especially Alzheimer’s as the best known cause of dementia — is also one of the most feared conditions in the U.S. “People are afraid of the uncertainty surrounding risks and developments, and the thought of losing their independence,” says Mateo P. Farina, Ph.D., a scientist at the Leonard D. Schaeffer Center for Health Policy & Economics at the University of Southern California. With heart disease or diabetes, there are proven ways to treat and manage the conditions, notes Farina. Dementia, though, “feels out of someone’s control,” he says.

“People also fear losing themselves and becoming a burden on their loved ones,” Farina continues. Someone with dementia will have personality changes, may need to alter their living circumstances and will require an immense amount of care from loved ones as well as medical doctors.

Risk factors
Dementia is influenced by many factors, including genetics, age, living situation, lifestyle and various medical conditions. “When a patient presents with multiple components, there is a compounding effect that can negatively impact the body and lead to an earlier onset,” says Elizabeth Marshall, M.D., MBA, director of clinical analytics at Linguamatics, an IQVIA Company. Although dementia is often equated with Alzheimer’s, there are other forms with well-characterized underlying pathologies. Frontotemporal dementia, for example, is associated with abnormal accumulations or forms of the tau and TDP-43 proteins in the brain. Lewy body dementia is caused by namesake Lewy bodies, deposits of a protein called alpha-synuclein. Vascular dementia is caused by brain damage that is the result of impaired blood flow.

Poor and disadvantaged individuals are at much higher risk of developing dementia for many reasons. In those who are genetically susceptible, limited access to healthy food and healthcare is a factor. Some research has linked vitamin deficiencies to the development of Alzheimer’s disease. Healthy foods are often good sources of the B vitamins and other nutrients that can reduce the risk of developing dementia.
vitamins D and E, as well as omega fatty acids needed for proper brain health, notes Marshall.

Workplace and home environments are another thread in the web of factors affecting dementia risk. Someone who works in a factory with potential exposure to toxic chemicals might be at increased risk of dementia, depending on the chemical. Disadvantaged people are more likely to live in places that are near sources of pollution and toxic chemicals.

Research has consistently shown an association between high blood pressure and Alzheimer’s disease. Observational studies suggest that treating high blood pressure counteracts the risk, although the evidence from randomized trials is less certain. There’s also a large body of research suggesting that physical activity may help keep the brain healthier, especially when coupled with avoiding risk factors for cardiovascular disease (obesity and smoking) and managing conditions such as diabetes.

Education level also plays a significant role in dementia risk. Studies have shown an association between education levels and brain function, with high levels linked to better brain function and low levels to worse function, points out Dennis B. Liotta, M.D., MBA, chief medical officer at Florida Community Care in Miami. Studies have shown that among adults 45 or older, the proportion experiencing subjective cognitive decline was lowest for college graduates and nearly three times greater for those without a high school diploma. Although researchers don’t have a definitive cause, one theory is that lower education levels and the risk of developing dementia are related.

THE COST BURDEN OF ALZHEIMER’S

The toll that Alzheimer’s disease takes on the health of those affected by the disease is enormous. And so is the associated expense.

According to the Alzheimer’s Association 2021 Alzheimer’s Disease Facts and Figures report, the healthcare and long-term care costs for all individuals with Alzheimer’s and other forms of dementia totaled $305 billion in 2020, with Medicare footing just over half of the bill.

The Alzheimer’s Association report puts the cost in perspective by comparing the per-person costs for someone with Alzheimer’s to someone without the disease. In 2019, the annual per-person payments from all payers for Medicare patients with Alzheimer’s and other forms of dementia was $50,201. For people without the disease, they were $14,326, or less than a third of that amount. The report cites research calculating that the lifetime cost of care for someone with Alzheimer’s to be just shy of $360,000 (in 2019 dollars), double the lifetime costs for people without the disease. These cost differences are explained, in part, by much greater utilization of healthcare and long-term care services by people with Alzheimer’s. For example, people with Alzheimer’s have seven times as many skilled nursing facilities stays on a per 1,000 beneficiaries per year basis as those without the disease.

The care that family and loved ones provide often goes unaccounted for in the cost figure for Alzheimer’s. The Alzheimer’s Association report calculated that caregivers provide an average of 21.9 hours of care a week, which adds up to 1,139 hours per year. If the 16.3 million estimated caregivers were paid $13.11 an hour, the cost of the care they provide without pay would come to nearly $244 billion in 2019, the report says.

—Peter Wehrwein
to ‘cognitive reserve,’” explains Liotta. The cognitive reserve hypothesis is that some people may experience little or no dementia despite pathological changes in their brain that in people with less cognitive reserve would result in dementia and that, furthermore, this cognitive reserve tends to be associated with education level.

**Reducing the chances** Although many of the risks for dementia occur in adulthood, researchers have also traced them back to childhood exposures and experiences. “A child’s socioeconomic conditions can help shape risk at an important early developmental period that is then carried forward,” says Hyungmin Cha, M.A., a doctoral student at the Population Research Center at The University of Texas at Austin. Although a disadvantaged childhood cannot be fully overcome, upward mobility as evidenced through greater education levels and wealth can significantly reduce both dementia risk and years of life spent in that dependent state, Cha says. This finding suggests that although socioeconomic circumstances are additive, the magnitude of their effect on cognitive health risk may differ.

The things known about dementia risk that are potentially modifiable are all related to general health and maintenance of health, says Kawas, noting the as-

**More than doubling** Projections show the number of people with Alzheimer’s in the U.S. increasing from 6.1 million to 13.8 million by 2060.

Ages 85+
Ages 75-84
Ages 65-74

2020 2030 2040 2050 2060

**Ages 85+**
**Ages 75-84**
**Ages 65-74**

6.1 8.5 11.2 12.7 13.8

Alzheimer’s Association 2021 Alzheimer’s Disease Facts and Figures, Figure 5

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sociation between control of high blood pressure and cholesterol levels and a lower risk of dementia. Marshall says keeping the brain active is a way to reduce dementia. Socializing can stimulate the brain with conversation and debate. Education is also good “brain exercise” and can include simple tasks such as learning a new word each day, doing puzzles such as Wordle or reading about current events.

Access to healthcare can also modify the risk of Alzheimer’s. “Providing access to care through health insurance coverage will increase the number of people who receive screening and early treatment of chronic diseases such as hypertension, diabetes and heart disease,” notes Michael Dulin, M.D., Ph.D., chief medical officer at Gray Matter Analytics. “These preventative actions can, in turn, result in lower rates (of dementia) or delay in onset of dementia.”

The treatment options for Alzheimer’s disease are limited. Cholinesterase inhibitors such as Aricept (donepezil) are modestly effective in slowing the worsening of dementia. Last year, the FDA approved Aduhelm (aducanumab), a treatment targeting beta-amyloid protein deposits that many experts believe are an underlying cause of Alzheimer’s. But the approval of Aduhelm is the most controversial FDA decision in recent memory because it’s not clear from the clinical trials done so far whether the drug improves the clinical manifestations of the disease — in other words, the dementia. CMS has proposed limiting Medicare coverage of the drug to patients who are enrolled in clinical trials.

How insurers might help
Health insurers have started to move “upstream” to address the social determinants of health (SDOH). They are tackling food insecurities by providing healthy meals, encouraging people with conditions, such as diabetes to join support groups, and launching efforts to combat loneliness. Social isolation, which is related to loneliness, has been linked to dementia.

Kawas says health insurers should offer incentives that support behaviors known to result in better health outcomes. “Enough studies have been done to show that exercise is good for body health, heart health and brain health,” she says. “What we need to do is to figure out how to modify behaviors so that people will actually do that exercise and live a healthy lifestyle. Health insurers should take care of us as healthy people, not just pay the medical bills, and anything they can do to encourage healthy lifestyle throughout the life span.”

Providing incentives for their members to get regular checkups and maintain a primary care home would be another step insurers could take, Dulin says. In addition, identifying members with adverse SDOH, such as inadequate housing or poor access to healthy food, can be an important step for insurance companies looking to reduce the burden of dementia. Once this information is available, insurers can advocate for policy changes that provide better food access or assist their members by sharing this information directly with them and their healthcare providers.

Karen Appold is a medical writer who lives in the Lehigh Valley region of Pennsylvania.

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