A 54-year-old woman with an 11-year history of type 2 diabetes presents for care. She was first noted to have proteinuria 4 years earlier; her serum creatinine level then was 1.1 mg per deciliter (97 μmol per liter). Her urinary protein excretion has progressively increased to 2.8 g per 24 hours, and her serum creatinine level to 3.1 mg per deciliter (274 μmol per liter). The estimated glomerular filtration rate (GFR) is 26 ml per minute per 1.73 m$^2$ of body-surface area. Her blood pressure is 155/90 mm Hg, and the glycated hemoglobin level is 7.6 mg per deciliter. The medications she is currently taking include an oral hypoglycemic agent, an angiotensin-converting–enzyme (ACE) inhibitor, a statin, and a thiazide diuretic. How should her case be managed?

Chronic kidney disease is characterized by a progressive decline in the GFR; the diagnosis is made on the basis of a reduced GFR for a minimum of 3 months, often accompanied by albuminuria. The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation has proposed a classification scheme for chronic kidney disease that has been widely adopted (Table 1). Stage IV chronic kidney disease denotes a severe decline in the GFR to 15 to 29 ml per minute per 1.73 m$^2$. Table 2 shows the major causes of severe chronic kidney disease among people in the United States.

Several studies have examined the incidence of chronic kidney disease overall, although less is known about the incidence of stage IV disease specifically. Chronic kidney disease (defined in the Framingham Study as a GFR that is <60% of the normal level) developed in about 9% of the subjects in the Framingham Study cohort during an 18-year follow-up period. In the Atherosclerosis Risk in Communities study, chronic kidney disease (defined as a persistent rise in the serum creatinine level) developed in 4.4 of 1000 white subjects and 8.8 of 1000 black subjects during a 14-year follow-up period. Data from the National Health and Nutrition Examination Surveys of 1988 to 1994 and 1999 to 2004 suggest that the prevalence of chronic kidney disease increased from 10 to 13% over the 10-year period from 1994 to 2004. This rise is probably attributable to a progressively aging population and the increased prevalence of obesity, diabetes, and hypertension.

Chronic kidney disease is a well-known risk factor for cardiovascular disease (Fig. 1). Several conditions (e.g., diabetes and hypertension) may promote the development of chronic kidney disease and, together with proteinuria, are also risk factors for cardiovascular disease. Less than 2% of patients with chronic kidney disease ultimately require renal-replacement therapy. In part, this low rate is explained by the increased risk of death from cardiovascular causes before progression to end-stage renal disease can occur. Cardiovascular disease is the most frequent cause of death among patients...
with chronic kidney disease in longitudinal studies, but these studies involve primarily older patients and patients with diabetes and a history of cardiovascular disease.\(^7,8\) In a retrospective study of relatively young, well-nourished patients without diabetes and with a low prevalence of proteinuria, cardiovascular disease, and risk factors for cardiovascular disease, there was a higher incidence of kidney failure than of death during the course of the study.\(^9\)

Cardiovascular complications associated with chronic kidney disease include angina pectoris, myocardial infarction, heart failure, stroke, peripheral vascular disease, arrhythmias, and sudden death (Fig. 1).\(^10\) The risk of each of these conditions increases from early-stage to advanced chronic kidney disease.\(^10\) The increased risk of death and poor outcomes after myocardial infarction in patients with stage III or stage IV chronic kidney disease may be related to the frequent proximity of lesions to the coronary ostia.\(^11\) In laboratory animals, uremia is associated with cardiac fibrosis.\(^12\) In patients with advanced chronic kidney disease, uremic cardiomyopathy is characterized by diastolic dysfunction, heart failure, and left ventricular hypertrophy; these abnormalities, in combination with myocardial ischemia and electrolyte shifts, probably contribute to the high incidence of sudden death.\(^10\)

### Table 1. Stages of Chronic Kidney Disease and Prevalence in Adults.\(^9\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Estimated GFR†</th>
<th>Prevalence</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt;90</td>
<td>1.78</td>
<td>3.6</td>
</tr>
<tr>
<td>II</td>
<td>Kidney damage with small decrease in GFR</td>
<td>60–89</td>
<td>3.24</td>
<td>6.5</td>
</tr>
<tr>
<td>III</td>
<td>Kidney damage with moderate decrease in GFR</td>
<td>30–59</td>
<td>7.69</td>
<td>15.5</td>
</tr>
<tr>
<td>IV</td>
<td>Kidney damage with large decrease in GFR</td>
<td>15–29</td>
<td>0.35</td>
<td>0.7</td>
</tr>
<tr>
<td>V</td>
<td>Kidney failure with need for dialysis (end-stage renal disease)</td>
<td>&lt;15</td>
<td>0.25</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^9\) Data are from National Kidney Foundation guidelines,\(^1\) Coresh et al.,\(^2\) and the U.S. Renal Data System.\(^3\)

† The abbreviated Modification of Diet in Renal Disease (MDRD) formula was used to estimate the glomerular filtration rate (GFR).\(^1,2,4\)

General Management

Renal function should be followed closely (every 1 to 3 months, depending on the rate of progression), by periodic estimation of the GFR\(^4\) (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Although serum cystatin C has been proposed as a reliable marker for the estimation of the GFR, other factors besides the GFR may influence cystatin C levels, and this measurement is not used routinely in practice.\(^13\)

The guidelines of the Kidney Disease Outcomes

### Strategies and Evidence

**Evaluation**

An approach to the management of chronic kidney disease requires a correct diagnosis of the primary renal disease, attention to coexisting conditions, and an understanding of the systemic complications. Potentially reversible causes that may contribute to the decline in GFR in patients with chronic kidney disease should be identified. These include hypovolemia and hypotension; conditions associated with a decreased effective arterial-blood volume, such as cirrhosis and the nephrotic syndrome; obstructive uropathy, urinary tract infection, or occlusive renovascular disease; the use of nonsteroidal antiinflammatory drugs; and severe hypokalemia or hypercalcemia. A substantial loss of functioning nephrons is associated with functional, structural, and metabolic adaptations that contribute to the glomerular, vascular, and tubulointerstitial changes that are seen in patients with chronic kidney disease (Fig. 2). These maladaptive responses and associated complications are common mechanisms that are not specific to the primary cause of chronic kidney disease but that contribute to the progression of the disease. A comprehensive strategy to treat these complications is essential for slowing the progression to end-stage renal disease.
Quality Initiative recommend that patients with stage IV chronic kidney disease be referred to a nephrologist. However, this recommendation is not widely followed; in one study of U.S. veterans, less than 30% of the veterans with stage IV chronic kidney disease were seen by a nephrologist. Although there are no data from clinical trials to establish the optimal referral time, delayed referral of patients with late-stage chronic kidney disease is associated with suboptimal outcomes, including increased mortality. The practical challenges of providing adequate therapy for patients with chronic kidney disease include the large number of medicines that are often needed and the high rate of coexisting conditions that require meticulous follow-up at each visit. However, even among patients with chronic kidney disease who receive ongoing care from nephrologists, the management of the disease is not always optimal; the rates of use of ACE inhibitors, aspirin, statins, and beta-blockers that were reported in one study were only 41%, 65%, 24%, and 65%, respectively.

**Table 2. Major Causes of Severe Chronic Kidney Disease.**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percent of Cases (†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>44.9</td>
</tr>
<tr>
<td>Type 1</td>
<td>3.9</td>
</tr>
<tr>
<td>Type 2</td>
<td>41.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.2</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>8.2</td>
</tr>
<tr>
<td>Chronic interstitial nephritis or obstruction</td>
<td>3.6</td>
</tr>
<tr>
<td>Hereditary or cystic disease</td>
<td>3.1</td>
</tr>
<tr>
<td>Secondary glomerulonephritis or vasculitis</td>
<td>2.1</td>
</tr>
<tr>
<td>Neoplasms or plasma-cell dyscrasias</td>
<td>2.1</td>
</tr>
<tr>
<td>Miscellaneous conditions‡</td>
<td>4.6</td>
</tr>
<tr>
<td>Uncertain or unrecorded cause‡</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Data are from the U.S. Renal Data System. † The percentages are based on the incidence of reported end-stage renal disease according to the primary diagnosis. ‡ Examples of miscellaneous conditions are irreversible acute kidney injury and nephropathy associated with the acquired immunodeficiency syndrome.

**Reduction of Proteinuria**

Proteinuria is an independent risk factor for progressive renal structural damage. Prospective studies have shown that reducing albuminuria with the use of antihypertensive medications, in particular ACE inhibitors and ARBs, results in a reduced rate of decline in the GFR both in subjects who have diabetes and in those who do not. A reduction in urinary protein excretion to less than 300 to 500 mg per day is associated with a slowing of the progression of chronic kidney disease. An ACE inhibitor or an ic hypertension slows the rate of progression of chronic kidney disease both in subjects who have diabetes and in those who do not. ACE inhibitors or angiotensin-receptor blockers (ARBs) are considered to be the first line of antihypertensive therapy for patients with chronic kidney disease, including those with advanced chronic kidney disease, whether or not they have diabetes. It should be recognized that most randomized trials in which ACE inhibitors or ARBs were used involved relatively young adults who had well-defined causes of chronic kidney disease, and the applicability of the findings of those trials to adults older than 70 years of age who have chronic kidney disease is uncertain.

**Interventions to Slow the Rate of Progression of Chronic Kidney Disease**

**Treatment of Hypertension**

Randomized clinical trials and prospective observational studies have shown that control of systolic blood pressure slows the rate of decline in the GFR both in subjects who have diabetes and in those who do not. ACE inhibitors or ARBs, results in a reduced rate of decline in the GFR both in subjects who have diabetes and in those who do not. A reduction in urinary protein excretion to less than 300 to 500 mg per day is associated with a slowing of the progression of chronic kidney disease. An ACE inhibitor or an ARB, such as valsartan or losartan, is frequently required to control hypertension in patients with advanced chronic kidney disease; dihydropyridine calcium-channel blockers are acceptable treatments as long as patients are receiving ACE inhibitors or ARBs.

**Reduction of Proteinuria**

Proteinuria is an independent risk factor for progressive renal structural damage. Prospective studies have shown that reducing albuminuria with the use of antihypertensive medications, in particular ACE inhibitors and ARBs, results in a reduced rate of decline in the GFR both in subjects who have diabetes and in those who do not.
ARB should be the first line of therapy to reduce proteinuria. Dual therapy with an ACE inhibitor and an ARB may be more effective than either agent alone in reducing proteinuria, but data from long-term randomized trials are lacking to assess the effect of combined therapy in slowing the progression of chronic kidney disease. Short-term studies involving patients with type 1 or type 2 diabetes and proteinuria have shown that spironolactone has an additive effect in reducing proteinuria and blood pressure when it is combined with maximal doses of an ACE inhibitor or an ARB, although particular caution is needed when these agents are combined, because of the risk of hyperkalemia. On the basis of results from trials that showed that protein restriction reduces proteinuria and the progression of kidney disease, it is recommended that dietary protein be limited to approximately 0.8 to 1.0 g per kilogram of body weight per day.

**Glycemic Control**
Poorly controlled blood glucose levels are associated with an increased risk of nephropathy and cardiovascular complications. Although data from randomized trials suggest that strict control of blood glucose may prevent the development of diabetic nephropathy and retard the progression from microalbuminuria to proteinuria, no randomized trials have assessed the effect of glycemic control on disease progression in patients with advanced chronic kidney disease.

**Management of Associated Disorders**
**Mineral and Bone Disorders**
Disorders of mineral and bone metabolism are common in patients with stage IV chronic kidney disease and may be associated with increased cardiovascular calcification, potentially contributing to an increased risk of complications and death. Chronic kidney disease is characterized by decreased renal phosphate excretion, with resultant increases in serum phosphate levels; furthermore, there is decreased conversion of vitamin D to its active form, 1,25-dihydroxyvitamin D (1,25(OH)D₃), resulting in decreased levels of circulating 1,25(OH)D₃ and serum calcium and decreased intestinal calcium absorption. The hyperphosphatemia, hypocalcemia, and decreased levels of active vitamin D result in increased synthesis and...
secretion of parathyroid hormone. High phosphate levels may also increase the production by osteocytes of the phosphaturic hormone, fibroblast growth factor 23 (FGF-23). FGF-23 inhibits the synthesis of 1,25(OH)2D3 and may contribute to high levels of parathyroid hormone.

Hyperparathyroidism is present in more than half the patients who have a GFR of less than 60 ml per minute per 1.73 m2 and is independently associated with increased mortality and an increased prevalence of cardiovascular disease.34,35 Current guidelines recommend monitoring of serum calcium and phosphate levels (every 3 to 6 months), parathyroid hormone levels (every 6 to 12 months), and bone-specific alkaline phosphatase activity (every 6 to 12 months) in patients with stage IV chronic kidney disease,34 with the goal of normalizing these values.

Patients with persistently elevated parathyroid hormone levels (secondary hyperparathyroidism) should restrict their intake of dietary phosphate and be treated, in most cases, with a phosphate binder and an active vitamin D analogue if they have normal calcium levels.34 Serum levels of
25-hydroxyvitamin D (calcidiol) are also decreased in many patients with stage IV chronic kidney disease and end-stage renal disease, and supplementation is recommended if levels fall below 30 ng per milliliter.

**Cardiovascular Disease**

Given the high risk of cardiovascular disease in patients with chronic kidney disease, attention should be paid to preventing and treating cardiovascular risk factors in these patients. Table 3 lists the recommendations for the management of cardiovascular risk factors in patients with chronic kidney disease; these recommendations are based primarily on the results of trials that involved patients without chronic kidney disease.

Most patients with chronic kidney disease have dyslipidemia. The guidelines of the Kidney Disease Outcomes Quality Initiative recommend lowering low-density lipoprotein (LDL) cholesterol levels to less than 100 mg per deciliter (2.6 mmol per liter), although the benefit of this policy has not been documented in patients with advanced chronic kidney disease. A post hoc analysis of patients with a decreased estimated GFR who were enrolled in trials of statin therapy showed that treatment with statins reduced cardiovascular events in patients with stage II or stage III chronic kidney disease, but these trials did not include patients with stage IV disease.

A recent meta-analysis of randomized, placebo-controlled trials showed that statins reduced lipid levels, cardiovascular events, and proteinuria, but not all-cause mortality, in patients with chronic kidney disease, irrespective of the stage of the disease. In randomized trials of statin therapy for patients with end-stage renal disease — both those with diabetes and those without diabetes — statin therapy significantly reduced LDL cholesterol levels but did not result in a significant reduction in the rate of cardiovascular events.

**Anemia**

Anemia is common in patients with chronic kidney disease, especially in those with diabetes and in those with stage IV disease, more than half of whom have anemia. Deficient erythropoietin synthesis, iron deficiency, blood loss, and a decreased erythrocyte half-life are the major causes of anemia associated with chronic kidney disease.

The use of erythropoiesis-stimulating agents results in a reduced need for blood transfusions among patients with advanced chronic kidney disease and has also been associated with a reduction in left ventricular hypertrophy. However, there is increasing evidence that erythropoiesis-stimulating agents should be used cautiously.

In randomized trials involving patients with chronic kidney disease, in which target hemoglobin levels higher than 13 g per deciliter were compared with target levels of 10 to 12 g per deciliter, the higher hemoglobin levels led to an increased risk of death, cardiovascular events, and hospitalization for congestive heart failure. In the recent Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT; ClinicalTrials.gov number, NCT00093015), patients with chronic kidney disease and diabetes who were not undergoing dialysis were randomly assigned to receive darbepoetin to achieve a target hemoglobin level of 13 g per deciliter (the level actually achieved was 12.5 g per deciliter) or placebo (with rescue darbepoetin if the hemoglobin level was less than 9 g per deciliter). After an average 29-month follow-up period, there was no benefit with respect to cardiovascular or renal outcomes and there was a greater risk of stroke in the group with higher hemoglobin levels; this group needed fewer transfusions and had a modest reduction in fatigue but had no benefit in other quality-of-life measures. An important aspect of the management of anemia in patients with chronic kidney disease is a careful assessment of iron status to ensure that the transferrin saturation is between 20% and 50% and ferritin levels are between 100 and 800 ng per milliliter. Adequate iron supplementation can be achieved with either oral or parenteral iron.

**Electrolyte and Acid–Base Disturbances**

The kidney is generally able to compensate for a loss of functioning nephrons and maintain euolemia, electrolyte balance, and acid–base balance until the GFR falls below 30 ml per minute per 1.73 m². When the GFR is below that level, there is impairment in both sodium excretion in response to a sodium load and sodium conservation in response to an acute reduction in sodium intake; in most patients, sodium excretion does not fall below 20 to 30 mmol per day, at least initially.

A concomitant impairment in the physiological processes that allow for maximal concentration or dilution of the urine confers a predisposition to hyponatremia or hypernatremia in these patients.

Most patients with chronic kidney disease — with the exception of some patients who also have diabetes and hypoaldosteronism — have near-
normal serum potassium levels. However, hyperkalemia may develop in patients with chronic kidney disease after they receive treatment with aldosterone antagonists, ACE inhibitors, or ARBs. Non–anion-gap metabolic acidosis can develop in patients with chronic kidney disease, primarily owing to a reduction in renal ammonia synthesis and, among patients with advanced chronic kidney disease, a reduction in titratable acid (phosphate) excretion. An increased anion-gap metabolic acidosis due to the retention of organic acids is common in patients with uremia and stage IV kidney disease that is approaching the end stage. In a recent randomized trial, oral sodium bicarbonate supplementation slowed the progression of chronic kidney disease and improved nutritional status, finding that warrants confirmation in other trials.

### Areas of Uncertainty

Most randomized trials of cardiovascular disease have excluded patients with stage IV or stage V chronic kidney disease, and recommendations with respect to this population are therefore derived mainly from trials involving patients with less severe kidney disease or populations without chronic kidney disease. More data are needed to establish thresholds for the use of erythropoiesis-stimulating agents to treat anemia. Current recommendations that call for the use of erythropoiesis-stimulating agents to achieve a target hemoglobin level of 11 to 12 g per deciliter were developed before the results of the TREAT trial became available. The optimal treatment of abnormal divalent ion metabolism, the effect of glycemic control in patients with diabetes and advanced chronic kidney disease may differ from that seen in randomized trials.

### Table 3. Suggestions for the Management of Cardiovascular Risk Factors in Patients with Advanced Chronic Kidney Disease.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Recommend smoking cessation.</td>
</tr>
<tr>
<td>Diet</td>
<td>Recommend maintaining body-mass index at &lt;25 and waist circumference at &lt;102 cm for men and &lt;88 cm for women.†</td>
</tr>
<tr>
<td>Weight</td>
<td>For patients for whom it is feasible, recommend 30–60 min of moderate-intensity dynamic exercise (e.g., walking, jogging, cycling, or swimming) 4–7 days per week.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Target blood pressure should be &lt;130/80 mm Hg; patients with chronic kidney disease but without proteinuria (ratio of albumin [measured in milligrams per deciliter] to creatinine [measured in milligrams] of &lt;0.3) should be treated with an ACE inhibitor, an ARB, a loop diuretic, a beta-blocker (in patients younger than 60 years), a calcium-channel blocker, or some combination of these drugs.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Patients with chronic kidney disease and proteinuria (ratio of albumin [measured in milligrams per deciliter] to creatinine [measured in milligrams] of &gt;0.3) should be treated with an ACE inhibitor or an ARB.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Target glycated hemoglobin level should be &lt;7.0% and target fasting plasma glucose level, 90–160 mg/dl (5.0–8.9 mmol/liter); treatment with metformin is acceptable in patients with stable stage I, II, or III chronic kidney disease; short-acting sulfonylureas (e.g., gliclazide) are preferable to long-acting agents; sulfonylureas and insulin require dose adjustment; repaglinide can be used in patients with stage IV chronic kidney disease and needs no dose adjustment.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Targets for LDL cholesterol levels should follow guidelines for the general population; statin therapy is recommended; no dose adjustment is required for bile acid sequestrants, statins, niacin, or ezetimibe, but fibrates require dose adjustment according to their effect on kidney function.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Iron supplementation is recommended; erythropoiesis-stimulating agents have been used but caution is recommended because of cardiovascular risks associated with the use of these agents; target hemoglobin level should be no higher than 10 to 12 mg/dl if erythropoiesis-stimulating agents are being used.</td>
</tr>
<tr>
<td>Other</td>
<td>Aspirin, at a dose of 81 mg daily, is recommended if cardiovascular risk is high or cardiovascular disease is present and if there is no contraindication to aspirin.</td>
</tr>
</tbody>
</table>

* Data are from Rucker and Tonelli.† ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and LDL low-density lipoprotein.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.
ney disease, and the role of combined therapy consisting of an ACE inhibitor and an ARB or either drug with an aldosterone antagonist in slowing the progression of chronic kidney disease are unclear and require further investigation.

GUIDELINES

The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation and Kidney Disease: Improving Global Outcomes have published guidelines for the management of chronic kidney disease, including stage IV disease.1,2,6,34,38,44 Some recommendations (e.g., those regarding the use of inhibitors of the renin–angiotensin system to reduce blood pressure and proteinuria) are based on the results of randomized trials, whereas several other recommendations are based on expert opinion. The recommendations in this article are largely consistent with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has advanced diabetic kidney disease and proteinuria, and progression to end-stage renal disease can be expected to occur. Management of this case should be aimed at slowing the progression of the disease and reducing the risk of cardiovascular disease, preventing and treating coexisting conditions, and preparing the patient for renal-replacement therapy (see Table 1 in the Supplementary Appendix).53 Treatment with an ARB or an ACE inhibitor is warranted, with the medication adjusted to achieve a blood pressure below 130/80 mm Hg; reduction of blood pressure to this level slows the rate of decline of the GFR even in patients with advanced stages of chronic kidney disease.18-24 The thiazide diuretic that the patient is taking should be replaced by a loop diuretic; if the targetted blood pressure is not reached, a beta-blocker, a calcium-channel blocker, or both should be added. Dietary protein should be limited to approximately 0.8 to 1.0 g per kilogram per day.31 Treatment of hyperlipidemia with a statin and aspirin therapy are recommended to reduce the likelihood of cardiovascular disease,16 although data that support these interventions specifically in patients with advanced chronic kidney disease are lacking. Patients who smoke should be encouraged to stop smoking.

Whereas the current guidelines of the Kidney Disease Outcomes Quality Initiative recommend a target hemoglobin concentration of 11 to 12 g per deciliter, the appropriate hemoglobin target in patients with stage IV chronic kidney disease remains uncertain and requires further study. Iron deficiency should routinely be assessed and treated. Serum phosphate levels should be monitored, and if they are found to be higher than 4.6 mg per deciliter (1.5 mmol per liter), a phosphate binder should be prescribed.34,35 A low-dose active vitamin D analogue will help control secondary hyperparathyroidism. A bicarbonate concentration below 20 mmol per liter and systemic acidemia should be treated with sodium bicarbonate.52 Patients should be informed about methods of renal-replacement therapy, and efforts should be made to preserve the venous circulation in the upper extremities in order to maintain vascular access in those patients who opt for hemodialysis.

No potential conflict of interest relevant to this article was reported.

We thank Drs. Wajeh Qunibi and Biff Palmer for their review of an earlier version of the manuscript, and Ms. Tina Luther and Ms. Tapashya Ghosh for secretarial assistance.

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