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CME MOC

Cleveland Clinic Journal of Medicine

A cough that won't go away

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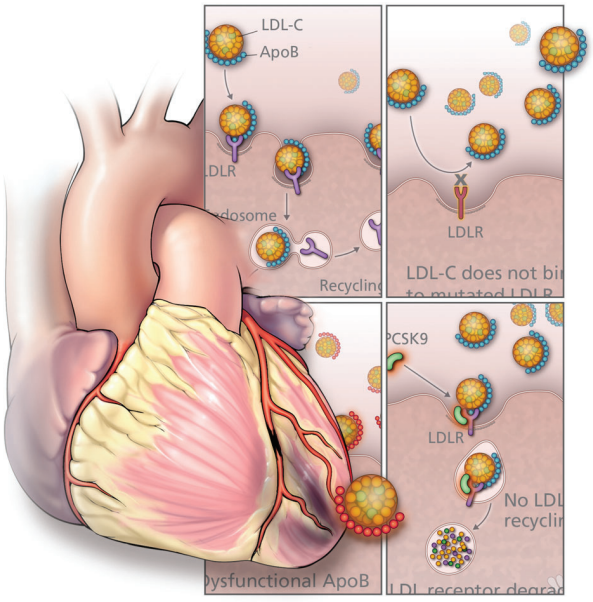

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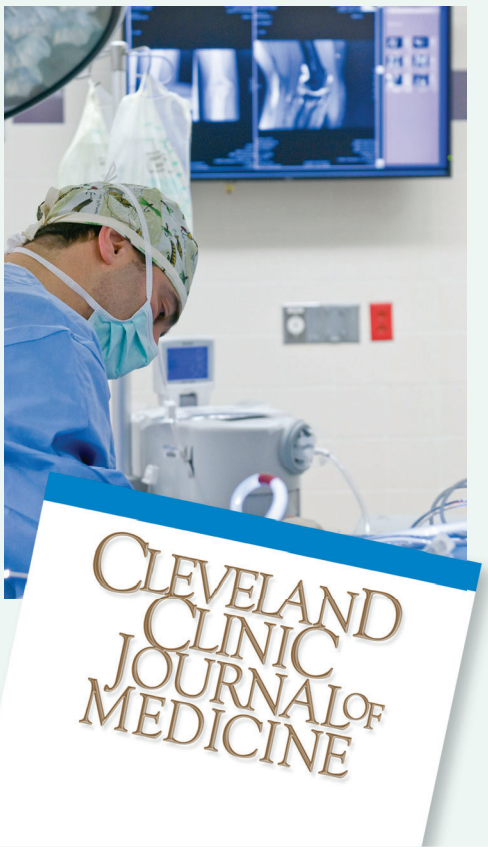


The search for precision

The concept of "precision medicine" includes the ability to prospectively determine how best to provide the right therapy to the right patient to treat the right disease. The goal of providing tailored treatment is not a new concept. It is the cornerstone of all therapies, especially antimicrobial and cancer chemotherapy, where we tailor therapeutic choice on the basis of host and target. What is new is the hope or expectation that we will be able to do this accurately in advance of gathering information from any empiric "n of 1" clinical trial in the individual patient. With our burgeoning understanding of the human genome and ever-advancing understanding of molecular pathophysiology linked to the parallel development of sophisticated molecular tests and targeted therapies, we are developing ways to predict with a degree of precision that was heretofore not attainable in the clinic.

It has been long recognized that some of the heterogeneity of responses to medications in terms of efficacy and side effects is due to genetic influences, even though we have not always been able to identify the exact factors responsible in advance of initiating therapy. Polymorphisms of genes responsible for enzymes, transmembrane transporters, and receptors can dictate interindividual heterogeneity of response to drugs in different ways. Some medications are given as prodrugs requiring enzymatic activation, others are metabolized through specific or competing enzymatic pathways, and yet others require specific transmembrane transporters or receptor binding to mediate their effects. These processes can be influenced by gene polymorphisms, which result in protein products with different functional activities. Molecular techniques allow us to identify these polymorphisms and their different biochemical consequences in advance and to use them prospectively to direct therapeutic choices and dosing—for example, to determine whether to prescribe prednisolone instead of prednisone for a patient with inflammatory disease.

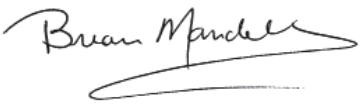
In this issue of the *Journal*, Hockings et al (page 91) discuss aspects of the growing field of pharmacogenomics, and Hoogwerf (page 100) describes clinical subsets of diabetes mellitus. Both approaches, one molecular and one clinical (supported by biochemical testing), can help predict successful initial therapeutic interventions. These molecular and clinical approaches (supported by specific testing) represent nascent examples of how precision medicine is evolving. But the clinical, genomic, and molecular approaches still have a way to go before they are uniformly accepted and widely applicable.

Further study is needed to understand how frequent a specific gene variant or clinical phenotype and associated event (altered efficacy or side effects) must be in the population to warrant testing. Issues surrounding insurance coverage remain a challenge, but testing is becoming less expensive, and gene-profiling panels will likely soon be routinely available and more affordable. The clinical impact of pharmacogenomic testing, as Hockings et al point out with several examples, has not been uniformly positive and in many situations cannot substitute for routine clinical and laboratory monitoring.

doi:10.3949/ccjm.87b.02020

Today, in 2020, we are not yet ready for general genetic screening, but I think we are off to an excellent conceptual start. In some instances, we can identify patients who are at greater or lesser genetic risk for a specific effect of a specific drug. Hockings et al offer examples of when the time is ripe for specific genetic tests; for linking that information to drug databases; and for uniformly incorporating the results into the patient's health record—just as is currently done for recognized drug allergies. I get an alert if I try to prescribe amoxicillin to a patient with a recorded allergy to penicillin. Someday, I should get an alert if I prescribe prednisone to a patient carrying the genes coding for an inefficient variant of the hepatic enzyme responsible for activating the prodrug prednisone to prednisolone, warning me that I should consider prescribing a higher dose of prednisone, or prescribing the active drug prednisolone.

That day may come soon.



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Barrett esophagus: Definition, treatment

SHIH-WEI LAI, MD
China Medical University
Taichung, Republic of China

To the Editor: In a well-written and informative article in the November 2019 issue, Singh et al reviewed the current management of Barrett esophagus and esophageal adenocarcinoma.[1] Here, I would like to discuss some concepts not addressed in their article.

First, the broad definition of Barrett esophagus is that metaplastic columnar epithelium replaces normal stratified squamous epithelium of the distal esophagus.[2] The broad definition is different from the traditional definition, which requires the presence of intestinal metaplasia and goblet cells. If we use the broad definition, more patients will match the diagnosis of Barrett esophagus and will have a chance to receive appropriate treatment and endoscopic surveillance to prevent esophageal dysplasia and adenocarcinoma.

Second, the American Gastroenterological Association[3] recommends that patients with Barrett esophagus receive a proton pump inhibitor once daily, but does not mention what duration of proton pump inhibitor therapy is needed. Based on the findings of available studies, continuous use of proton pump inhibitors for 1 year or longer is needed for patients with Barrett esophagus to prevent esophageal dysplasia and adenocarcinoma.[4]

Third, a cohort study revealed that statin use after the diagnosis of esophageal cancer was associated with a lower risk of esophageal cancer death than nonuse (hazard ratio for adenocarcinoma 0.79; 95% confidence interval 0.71–0.98).[5] Studies have shown that statins might have biologic effects on cancer and thus on outcomes, but the effects depend on the cancer cell type and on the statin used, with different agents having various antitumor potential.[6] These findings indicate a direction for research into chemoprevention of esophageal cancer. Well-designed randomized controlled trials are needed to clarify the association between statin use and the risk of esophageal cancer death.

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doi:10.3949/ccjm.87c.02001

In reply: Dr. Lai points out that the broader definition of Barrett esophagus can include the presence of metaplastic columnar epithelium that replaces the normal stratified squamous epithelium in the distal esophagus. Guidelines of both the American College of Gastroenterology[1] and the American Gastroenterological Association[2] require the presence of intestinal mucosa for the diagnosis of Barrett esophagus, as only intestinal metaplasia is associated with the risk of malignant transformation. Therefore, we recommend using the same standard definition.

The second point concerns the duration of therapy in Barrett esophagus. We recommend therapy with proton pump inhibitors indefinitely.

Lastly, we agree that use of statins has shown improved outcomes in patients with esophageal cancer,[3] but the existing data on this topic are limited, and a specific recommendation regarding use of statins for this

indication cannot be made with the available data. Randomized controlled trials are certainly needed to determine the association between statins and decreased mortality risk from esophageal cancer.

TAVANKIT SINGH, MD
Cleveland Clinic

VEDHA SANGHI, MD
Cleveland Clinic

PRASHANTHI N. THOTA, MD, FACG
Cleveland Clinic

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Flu vaccine and gout attacks

To the Editor: In the December 2019 issue, Dr. Sherif Mossad reported how to respond to 12 reasons people give for not wanting to receive the inactivated influenza vaccine.[1] His article provides much help to clinicians. I wish to add a question to support Dr. Mossad's article: Does the risk of gout attack increase after receiving a inactivated influenza vaccine?

A case-crossover study reported that people who received a nonzoster vaccine had a 2-fold increased odds of developing a gout attack within 2 days of vaccination (adjusted odds ratio 1.99, 95% confidence interval 1.01–3.89).[2] The authors commented that the benefits of vaccinations on individual persons and on public health are enormous, so rejecting vaccination out of fear of an increased risk of gout attacks is not advisable, as the benefit outweighs the risk.[2]

A preliminary analysis using the database of the Taiwan National Health Insurance Program reported that among people age 65 and older, the incidence rate of a gout attack within 30 days after vaccination was similar between the vaccination group and the nonvaccination group (0.05 vs 0.05 per 1,000 person-days, 95% confidence interval 0.73–1.57; $P = .735$).[3] The authors commented that at least older people were not at increased risk of a gout attack after influenza vaccination.

At present, no other systematic research has been conducted on the association between influenza vaccine and gout attack. Other real-world data are needed to clarify this issue.

SHIH-WEI LAI, MD
China Medical University
Taichung, Republic of China

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Zainah Chiko, BSHS
Cleveland State University, Cleveland, OH

Mohamad Hanouneh, MD
Instructor of Medicine, Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

C. John Sperati, MD, MHS
Associate Professor of Medicine, Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

A young man with hypertension and hypokalemia

A 20-year-old man with a 1-year history of untreated hypertension presented to the emergency department for evaluation and management of a hypertensive emergency. During the past 3 weeks, he had progressively worsening headaches, and on the day of presentation, his blood pressure was 184/154 mm Hg. Results of initial laboratory testing were as follows:

- Sodium 132 mmol/L (reference range 136–144)
- Potassium 3.1 mmol/L (3.7–5.1)
- Chloride 86 mmol/L (97–105)
- Bicarbonate 34 mmol/L (22–30)
- Blood urea nitrogen 14 mg/dL (9–24)
- Creatinine 1.2 mg/dL (0.73–1.22)
- Albumin 4.9 g/dL (3.4–4.9).

Urinalysis showed no hematuria or proteinuria. Plasma aldosterone was elevated at 49 ng/mL (reference range 3.0–35.4), as was plasma renin activity, at 115 ng/mL/hour. His 24-hour urine aldosterone secretion was quite elevated at 61.8 µg/24 hours (2.3–21). Thyroid-stimulating hormone, serum cortisol, and plasma catecholamine levels were normal. His urine normetanephrine level was mildly elevated at 399 µg/g creatinine (91–365), with a normal urine metanephrine level.

In light of the hypertension with elevated renin activity, hypokalemia, and metabolic alkalosis, the patient underwent computed tomographic angiography of the chest, abdomen, and pelvis with intravenous contrast. Aortic coarctation was ruled out, and the adrenal glands were unremarkable. The right kidney was small, measuring 9.6 cm (vs 11.1 cm for the left kidney), and the right renal artery had multiple midvessel stenoses (**Figure 1**). Subsequent renal artery duplex ultrasonography revealed a markedly elevated distal peak systolic velocity of 743 cm/second in the right renal artery (normal is < 150).

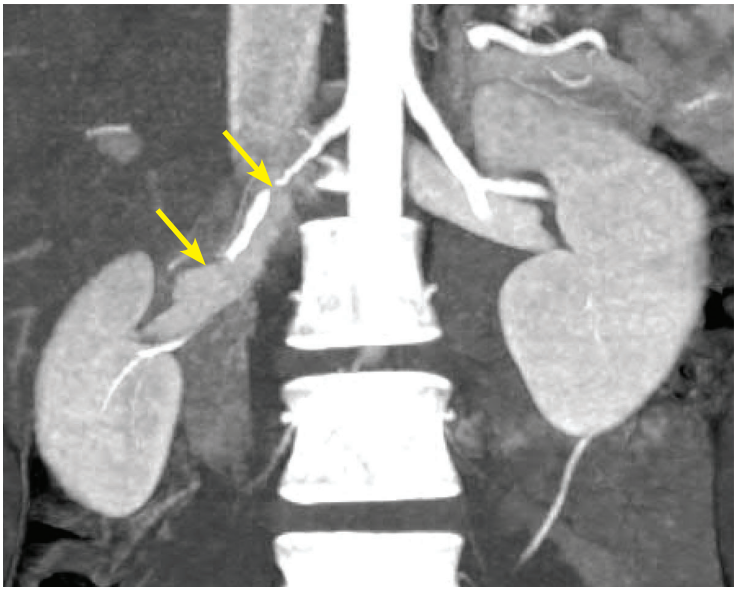

Figure 1. Coronal computed tomographic angiography demonstrated a small right kidney with multifocal fibromuscular dysplasia of the right renal artery (arrows).

The imaging characteristics were most consistent with multifocal fibromuscular dysplasia leading to secondary hyperreninemia with hyperaldosteronism. The patient underwent percutaneous transluminal angioplasty to 3 critical stenoses of the right renal artery, with less than 30% residual stenosis (**Figure 2**). Pressure wire measurements of the left renal artery did not demonstrate significant stenosis. Magnetic resonance angiography of the head and neck was normal, with no evidence of fibromuscular dysplasia in the cervical or intracranial circulation.

doi:10.3949/ccjm.87a.19111

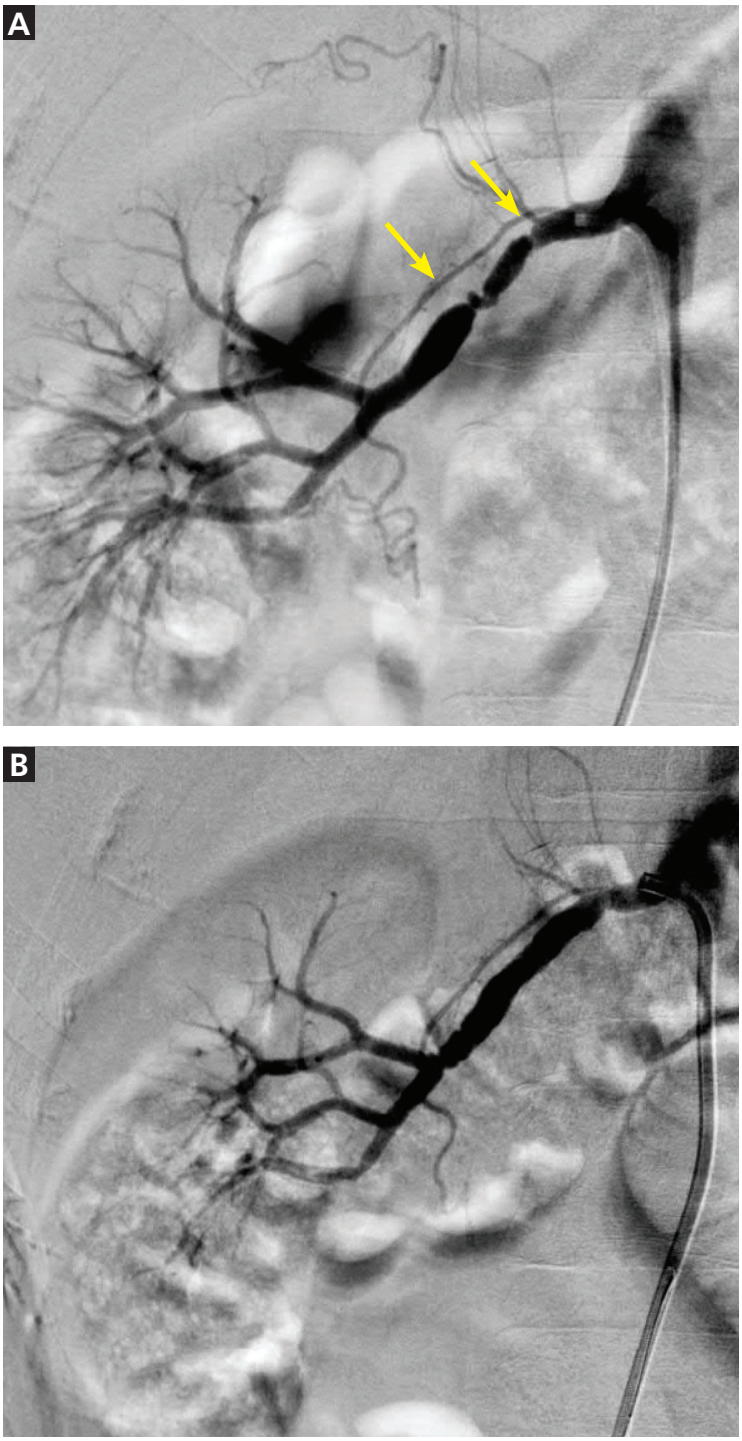

Figure 2. The right renal artery (arrows) before (A) and after (B) percutaneous transluminal angioplasty.

At follow-up 2 years later, his blood pressure was normal without medication; peak systolic velocity of the right renal artery was 203 cm/second.

RENAL ARTERY FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia, a noninflammatory vasculopathy of medium-sized arteries, is diagnosed primarily in women (80%–90% of cases), although it can occur in men.[1] The renal arteries are most frequently involved, followed by the extracranial internal carotid, vertebral, visceral, and iliac arteries.[1] Aneurysm or dissection or both occur in 40% of patients.[2] Renal artery fibromuscular dysplasia, when symptomatic, usually manifests with renovascular hypertension, dissection, infarction, and sometimes ischemic renal atrophy.

Diagnosis and treatment

Hypertensive disorders associated with elevated renin activity, hypokalemia, and metabolic alkalosis include renal artery disease and reninoma. Fibromuscular dysplasia is diagnosed radiographically and classified as multifocal (2 or more stenoses) or focal (single focal or tubular stenosis).[1,3]

Focal and multifocal fibromuscular dysplasia have different epidemiologies and histologies. The focal type is not well correlated with a specific histology, is more common in men, presents at a younger age, and is more often associated with both higher blood pressure and evidence of ischemic nephropathy.[3,4] Multifocal fibromuscular dysplasia is classically described as resembling a "string of beads" and correlating with medial fibroplasia on histology. Our patient's multiple, serial stenoses were clinically more similar to focal than to multifocal disease. Nevertheless, some investigators consider multiple focal, serial stenoses, as seen in this case, to be multifocal fibromuscular dysplasia.

Key to the diagnosis of fibromuscular dysplasia is to exclude vasculitis and other recognized vascular syndromes (eg, Ehlers-Danlos type IV, Loeys-Dietz syndrome) by history, laboratory evaluation, and imaging. Features of such diseases were not present in our patient.

Because disease is found in multiple arterial beds in as many as two-thirds of patients, it is recommended that all patients with fibromuscular dysplasia undergo baseline skull-to-pelvis cross-sectional imaging by computed tomographic angiography or magnetic resonance angiography.[1,5]

Although percutaneous transluminal angioplasty is not always curative, it is more likely to be successful when performed within 5 years of the onset of hypertension.[6] Assessment for restenosis every 6 to 12 months by duplex ultrasonography is common, although velocity data specific to fibromuscular dysplasia are not well established.

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***Address**: Mohamad Hanouneh, MD, 1830 East Monument Street, Room 416, Baltimore, MD 21287; mhanoun1@jhmi.edu*

CORRECTION

The article "Fever in a traveler returning from Ethiopia" by Ken Koon Wong, MD (Cleve Clin J Med 2020; 87(1):31–42, doi:10.3949/ccjm.87a.19017) contained an error. In Table 7, "Chemoprophylaxis for malaria" on page 40, the entry for doxycycline incorrectly carried a footnote that states this drug can be used in pregnancy. This footnote has been removed. According to the US Food and Drug Administration, "While there are no controlled studies of doxycycline use in pregnant women to show safety, an expert review of published data on experiences with doxycycline use during pregnancy by TERIS—the Teratogen Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = limited to fair), but the data are insufficient to state that there is no risk" (https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/doxycycline-use-pregnant-and-lactating-women).

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Sigmoid volvulus: Coffee bean sign, whirl sign

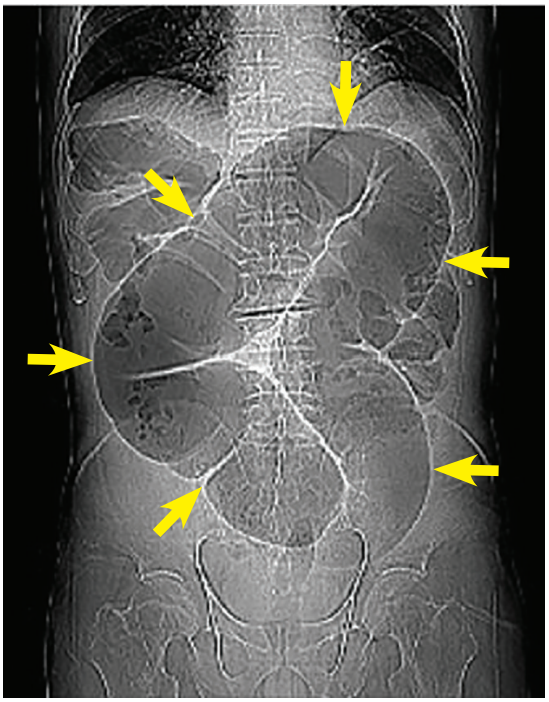

Figure 1. Computed tomography preliminary view showed a distended sigmoid loop with an inverted U-shape (arrows), also known as the coffee bean sign.

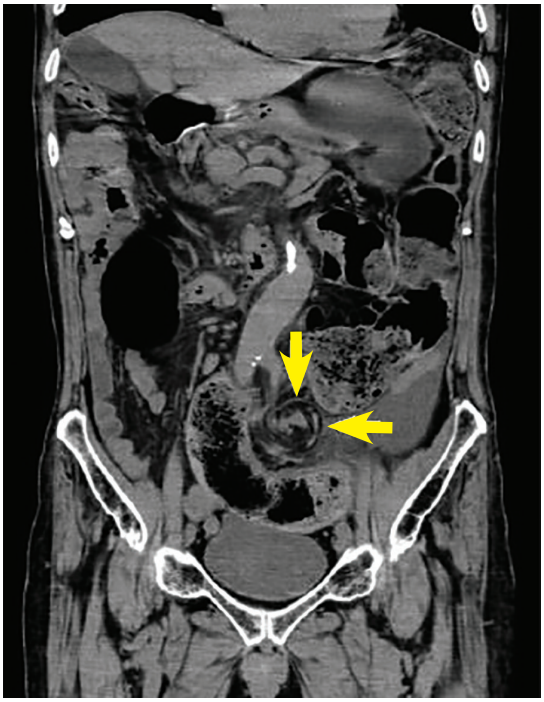

Figure 2. Computed tomography coronal view showed the whirl sign, representing twisted bowel and mesentery (arrows).

A 79-year-old man with cortical cerebellar atrophy presented with progressive abdominal distention and constipation

A 79-year-old man with cortical cerebellar atrophy presented to the gastroenterology department with a 7-day history of progressive abdominal distention and constipation. He had a history of chronic constipation due to neurogenic bowel dysfunction. The dysfunction had been managed with laxatives.

On physical examination, his abdomen was distended and tender, and bowel sounds were absent. There was no fever, abdominal rigidity, or guarding.

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'COFFEE BEAN' SIGN AND 'WHIRL' SIGN

The preliminary view on abdominal computed tomography (CT) showed a distended sigmoid loop with an inverted U-shape, also known as the coffee bean sign, bent innertube sign, or kidney bean sign (**Figure 1**). This feature was also seen on plain abdominal radiography. In addition, the CT coronal view revealed the whirl sign, representing twisted bowel and mesentery (**Figure 2**). These findings were consistent with sigmoid volvulus.

Emergency endoscopy confirmed torsion

of the sigmoid colon without mucosal ischemia or masses. The colonoscope was successfully passed through the volvulus and into the dilated colon, resulting in reduction of the volvulus.

SIGMOID VOLVULUS

Sigmoid volvulus is the third most common cause of bowel obstruction after cancer and diverticulitis.[1] Risk factors include chronic constipation, diabetes mellitus, neurologic disorders, and previous abdominal surgery.[2] The classic clinical presentation is a triad of abdominal pain, distention, and constipation.[3]

Sigmoid volvulus is potentially life-threatening, and early diagnosis and treatment are essential. Endoscopic procedures such as decompression and reduction are the emergency treatments of choice in uncomplicated acute sigmoid volvulus.[2] Flexible sigmoidoscopy or even rigid proctoscopy is usually used as nonoperative treatment; colonoscopy is not necessarily needed for decompression.

Emergency surgery is an option only when nonoperative treatment is unsuccessful, or in patients with perforation, bowel infarction, or peritonitis.[2,4]

Because of the high recurrence rate after endoscopic treatment, elective surgery is recommended to reduce morbidity and mortality risk.[4]

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Address: Yusaku Kajihara, MD, FACP, Department of Gastroenterology, Fuyoukai Murakami Hospital, 3-3-14 Hamada, Aomori 030-0843, Japan; y_kaji2012@yahoo.co.jp

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A cough that won't go away: Evaluation and treatment in 2 patients

A 65-YEAR-OLD MAN presents with a dry, nonproductive cough, which he has had for 10 months. He describes it as very intrusive, as it limits his effectiveness in his work. He says the cough is worse when he laughs, walks up stairs, or talks for more than 15 seconds at a time. He says he has mild postnasal drainage but feels this does not cause the cough. He denies heartburn or reflux. He does not cough when eating or drinking or at night.

His medical history is unremarkable. He has never smoked. He is on no medications. He takes a daily multivitamin. He has no known history of allergies.

A second patient, a 48-year-old woman, presents with a similar history of nonproductive cough for 8 months. She is embarrassed to attend social functions, as her cough often causes urinary incontinence. Her coughing sometimes wakes her up at night.

Her medical history is notable only for hypertension, which is well controlled with hydrochlorothiazide 25 mg once daily. She takes no other medications and has never smoked. She denies heartburn or other symptoms of reflux. She does not cough when eating or drinking. She has no known history of allergies.

Vital signs in both patients are within normal limits, and lung auscultation reveals no wheezing, crackles, or rales in either patient.

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FIRST STEP IN EVALUATION

1 Based on the available information, what is the most appropriate next step for these patients?

- ☐ An extensive history
- ☐ Chest radiography
- ☐ Nasal endoscopy
- ☐ A pulmonary workup

Two patients present with similar symptoms, but different causes and treatment

While all of the above are important in the diagnosis of chronic cough, collecting an extensive history is a crucial first step to rule out the most common causes of chronic cough and should always be done (**Table 1**). In particular, one should find out:

Is the patient taking an angiotensin-converting enzyme (ACE) inhibitor? These drugs are a common treatment for hypertension and are well known to cause a persistent dry cough.[1]

Does the patient have occupational exposure to allergens?

Does the patient smoke?

Are there symptoms of underlying disease? These can include:

- Wheezing and shortness of breath, indicating asthma
- Heartburn and regurgitation, indicating gastroesophageal reflux disease (GERD)
- Nasal discharge and phlegm, indicating postnasal drainage or untreated sinusitis
- Hemoptysis, chest pain, and weight loss, possibly indicating lung cancer.[2]

TABLE 1

Causes of chronic cough

Common causes
Angiotensin-converting enzyme inhibitor use
Asthma
Chronic obstructive pulmonary disease
Gastroesophageal reflux disease
Upper airway cough syndrome (eg, sinusitis, rhinitis)
Uncommon causes
Foreign body aspiration
Pneumonia
Lung cancer
Tuberculosis
Bronchitis
Sarcoidosis
Idiopathic pulmonary fibrosis

Diagnostic tests

Common diagnostic tests such as chest radiography, nasal endoscopy, laryngoscopy, spirometry with bronchodilator testing, and exhaled nitric oxide measurement can also be used to detect some of the less apparent causes of chronic cough.

Upper airway cough syndrome is the most common cause of chronic cough seen in respiratory clinics

Chest radiography will not reveal the most common causes of cough, but it is important in detecting foreign body aspiration and lung diseases such as pneumonia, lung cancer, and tuberculosis.

Nasal endoscopy is warranted in patients who report postnasal drip. Cough from postnasal drip, otherwise known as upper airway cough syndrome (UACS), is the most common cause of chronic cough seen in respiratory clinics, contributing to 26% to 87% of US cases.[2,3] UACS is characterized by a feeling of nasal secretions at the back of the throat, resulting in a persistent urge to clear the throat. Causes include allergic rhinitis, nonallergic rhinitis, bacterial sinusitis, and allergic fungal sinusitis. It is unknown how often the patient's description of symptoms correlates with actual confirmatory findings on endoscopy. Importantly, GERD can present with upper respiratory symptoms and can mimic UACS.[3]

Laryngoscopy can identify laryngeal irritation from chronic cough, evidence of reflux disease, and sinonasal pathology.

Spirometry can noninvasively uncover evidence of asthma and chronic obstructive pulmonary disease, both of which can cause chronic cough. Cough due to asthma can be classified as cough-variant asthma, in which cough is the sole symptom; cough-predominant asthma, which can include dyspnea and wheezing; and cough that persists despite therapy with corticosteroids and beta agonists.[4,5]

Of note, while variable airflow obstruction is classically detected in asthmatic patients, some patients exhibit no abnormal spirometry results.[6,7] Therefore, additional pulmonary tests are often needed, such as methacholine challenge and fraction of exhaled nitric oxide (FeNO) measurement.

Methacholine challenge is classically used to assess for bronchial hyperreactivity. However, it has been shown to be a poor diagnostic tool for chronic cough and is only recommended when no other obvious causes exist.[8,9]

FeNO measurement. Guidelines from the American Thoracic Society state that adult patients with low FeNO (< 25 ppb) likely have either noneosinophilic or no airway inflammation. In contrast, a high FeNO (> 50 ppb) implies uncontrolled or deteriorating eosinophilic airway inflammation.[10]

In a study by Yi et al,[11] a cutoff of 31.5 ppb or higher was found to have a sensitivity of 54%, a specificity of 91.4%, and a positive predictive value of 89.3% for corticosteroid-responsive cough. Possible causes in patients with high FeNO include atopic asthma, eosinophilic bronchitis, and COPD with a mixed inflammatory phenotype.[10] As a result, patients with a measurement of 31.5 ppb or higher are more likely to benefit from oral steroids, transitioning to inhaled corticosteroid treatment.[12,13]

CASES CONTINUED

Both patients undergo detailed questioning, chest radiography, nasal and laryngeal endoscopy, and pulmonary workup. In each patient, the history is unremarkable and chest radiographs are clear. Neither reports any sensation of nasal

drainage, nor does nasal endoscopy find remarkable results. Laryngeal examinations show no evidence of inflammation or pathology.

Although both patients have normal spirometry results, our female patient has an FeNO of 56 ppb, while our male patient has 10 ppb. As a result, our female patient is started on inhaled corticosteroid treatment. When she comes back for follow-up 1 month later, she reports that her cough is almost completely gone.

Does our male patient have GERD?

With all other common causes of chronic cough such as asthma, UACS, and lung disease ruled out, it may be useful to consider GERD as the underlying cause of our male patient's chronic cough, even though he has no gastrointestinal symptoms. Irwin et al[14] reported that 9 (75%) of 12 patients with GERD-related chronic cough had no gastrointestinal symptoms.

However, evidence supporting GERD treatments for chronic cough is controversial at best. A Cochrane review of 19 studies found insufficient evidence that GERD treatment was useful in the treatment of chronic cough.[15] Similarly, guidelines from the American College of Chest Physicians note that proton pump inhibitors lack efficacy when a workup of GERD is negative, and so they recommend against using these agents in this situation. However, they do recommend them for chronic cough caused by GERD, and they also state that drugs may be given to treat coexisting conditions, such as proton pump inhibitors to treat GERD, as long as they are used at a stable dose.[16]

Nevertheless, cough is common in GERD, we cannot rule out GERD even if 24-hour monitoring yields negative results,[17] and proton pump inhibitors pose a low level of risk. Therefore, we decide on a trial of a proton pump inhibitor for our patient.

Four months later, the patient returns, visibly agitated, and states that the proton pump inhibitor has not helped his cough at all. At this juncture, we make the diagnosis of unexplained chronic cough, also known as chronic refractory cough, as a diagnosis of exclusion.

Of note, although the most likely cause is neurogenic cough, this is not synonymous with unexplained chronic cough.

TREATMENT FOR UNEXPLAINED CHRONIC COUGH

2 What is the first-line treatment for the patient at this point?

- ☐ Neuromodulators
- ☐ Behavioral cough suppression therapy
- ☐ Superior laryngeal nerve block
- ☐ Codeine or another opioid
- ☐ Laryngeal botulinum toxin injection

Neuromodulators for chronic cough

Neuromodulators are most often the first-line treatment for unexplained chronic cough. Although this is an off-label use, these drugs are thought to lessen the increased neural sensitization that underlies many cases of chronic cough.[16] Currently, there is evidence that amitriptyline, gabapentin, pregabalin, tramadol, and baclofen may benefit chronic cough patients.[18,19]

In a randomized trial in 62 patients receiving gabapentin or placebo, Ryan et al[20] found that the gabapentin group demonstrated significantly improved cough-specific quality of life compared with the placebo group (number needed to treat 3.58; $P = .004$). On the other hand, 10 (31%) of the 32 patients receiving gabapentin experienced adverse effects vs 3 (10%) of the 30 in the placebo group. The most common adverse effects were, in order of frequency, nausea and stomach pain, dizziness, fatigue, dry mouth, and confusion.

Some patients with asthma have normal results on spirometry

As such, gabapentin is an effective and well-tolerated treatment in chronic cough, and several prospective case series and cohort studies support its efficacy.[21,22]

Similarly, the effectiveness of amitriptyline was assessed in a single randomized clinical trial[23] in 28 patients randomized to receive either amitriptyline or codeine-guaifenesin. Eleven (73%) of the 15 patients in the amitriptyline group achieved a complete response, compared with none of the patients in the codeine-guaifenesin group, indicating that amitriptyline may also be an effective treatment in chronic cough.

Lastly, a single randomized crossover study of baclofen in 2 patients,[24] a pilot case series of tramadol,[25] and a retrospective cohort study of pregabalin[26] demonstrated efficacy of these medicines.

As a result, neuromodulators are currently seen as an efficacious treatment for unex-

plained chronic cough and should be one of the first considerations for this patient, given his lack of benefit from a multispecialty workup.[21] A major limitation of this treatment approach is that we cannot predict the patient in front of us will respond to any particular medication at any given dose or frequency.

Behavioral therapy is also indicated

Consultation with a speech pathologist who has expertise in behavioral cough suppression therapy is also indicated. Behavioral therapy is usually done concurrently with drug treatment, though patients may respond to one or the other, or to both, to varying degrees.

Behavioral cough suppression therapy is a good option for patients with unexplained chronic cough and is recommended by current guidelines.[16] It is hypothesized that behavioral therapy, given by a speech-language pathologist, effectively reduces cough sensitivity, improves voluntary control over cough, and reduces laryngeal muscle tension. Additionally, there may be an element of placebo response. Behavioral cough suppression intervention involves education, strategies to control cough, vocal hygiene training, and psychoeducational counseling.[27]

Patients with FeNO ≥ 31.5 ppb are more likely to benefit from oral steroids

A single randomized controlled trial[28] in 87 patients with chronic cough found that those receiving a speech pathology intervention demonstrated greater reduction in cough, breathing, voice, and upper airway symptom scores compared with a placebo group ($P < .001$ for all scores). In total, 88% of participants in the treatment group achieved successful outcomes, compared with 14% in the placebo group ($P < .001$).

Behavioral cough suppression therapy by a speech pathologist would be an appropriate and likely effective intervention for our patient.

Superior laryngeal nerve block

Hypersensitivity of the superior laryngeal nerve has been implicated as a possible cause of neurogenic cough, also known as cough hypersensitivity syndrome.[29] Cough can be triggered by actions that stimulate the superior laryngeal nerve such as talking, laughing, and swallowing, and by exposure to strong smells.

Superior laryngeal nerve block is an emerging office-based treatment, but it is unknown how many injections are needed for cough suppression.[30] This is a good option for patients who develop diminished responses to neuromodulator therapy or who cannot tolerate adverse effects of this drug class.

In a retrospective study[30] of 18 patients treated with percutaneous blockade of the internal branch of the superior laryngeal nerve, cough severity index scores decreased significantly afterward, and 15 of the 18 patients reported cough improvement. Duration of benefit seems to be 2 to 3 months; however, it is unknown if patients are definitively "cured" after a series of injections or if they require extended long-term treatment. More data will provide more clarity. To our knowledge, there have been no blinded, randomized studies to assess the effectiveness of this treatment.

Superior laryngeal nerve block may be an effective, low-risk, low-cost treatment for neurogenic cough. However, because there is currently less evidence for this treatment vs other treatments such as neuromodulators or behavioral cough suppression therapy by a speech pathologist, we are hesitant to pursue this before trying the other treatments.

Botulinum toxin injections

Botulinum toxin type A is another agent thought to lessen laryngeal hypersensitivity and hyperactivity.[31]

A case series in 4 patients treated with botulinum toxin injection found that all patients experienced significant cough relief afterward, and that a median of 7 injections was sufficient to achieve complete resolution.[31] In a study of 22 patients,[32] 11 (50%) reported greater than 50% improvement in cough severity or symptoms after the first injection. No patients experienced adverse effects.

Small studies show that botulinum toxin injection has efficacy similar to that of superior laryngeal nerve block but with the undesirable effects of a weak voice and mild dysphagia. However, most studies have been observational, limiting the quality of evidence. Patient selection and long-term outcomes require further investigation.

Opioids

Morphine and codeine have a long history of use as centrally acting cough suppressants. Similarly, tramadol has been anecdotally successful in chronic cough and warrants further research. In the only published prospective case

series, all 16 patients reported improvement in cough symptoms, and validated assessment tools showed significant improvement in cough severity.[28] However, these medications have significant adverse effects such as constipation and drowsiness, and the risk of addiction.[33]

Yancy et al,[34] in a systematic review and meta-analysis comparing opioids and placebo, found that the standardized mean difference of cough severity with opioids was 0.55 (95% confidence interval [CI] 0.38–0.72; $P < .0001$) and the difference in frequency was 0.57 (95% CI 0.36–0.91; $P = .026$), indicating a medium effect size. However, while there have been more studies of opioids as cough suppressants than the other options listed, Yancy et al noted that the studies are generally of low quality and may not be accurate indicators of efficacy.[34]

CASE CONTINUED

After discussing treatment options with the patient, we decide to start a trial of gabapentin. This drug is typically started at a dose of 300 mg at bedtime, and then adding a dose every 5 to 7 days to a maximum dose of 300 mg 3 times daily.

We do not prescribe speech therapy for this patient, as he lives far from the nearest center and is unwilling to commit the necessary time.

At 1-month follow-up, he states that he is satisfied, as his cough has significantly improved.

IF GABAPENTIN DOES NOT WORK

3 During this visit, the patient asks what else might have been done if his trial of gabapentin had not worked.

- ☐ Try another neuromodulator
- ☐ Adjust the dose of gabapentin
- ☐ Try a different class of medications
- ☐ Enroll in a clinical trial of future therapies

Several studies have shown that it may be necessary to adjust the dose or type of neuromodulator multiple times to achieve maximal effect; adjustments and titration should be attempted before switching to another neuromodulator. But if no clinical response is seen after several weeks of gabapentin 300 mg 3 times a day, further escalation of the dose is unlikely to help.

Again, it is difficult to predict who will respond to what neuromodulator at what dose. In addition, a significant number of patients develop tachyphylaxis, ie, a diminished response to previously efficacious treatment. A recent retrospective review of amitriptyline in patients with idiopathic cough noted that it is necessary to titrate or restart the medication for cough control in many patients.[35] Moreover, a retrospective review found a 35% incidence rate of tachyphylaxis in patients treated with neuromodulators.[36] Increasing the neuromodulator dose may help these patients, but the clinician should periodically weigh the possible benefits.[16] Current guidelines recommend that physicians assess risks and benefits of gabapentin treatment and adjust accordingly every 6 months.[16]

Maximal therapeutic response is often achieved by 1 to 3 months, and patients undergoing subsequent trials of different neuromodulators show success rates less than 33%.[36] However, this does not mean that trying additional neuromodulators is futile: 40% of patients who ultimately experience success do so after the first neuromodulator trial. Importantly, successful treatment may take up to 5 trials in some patients; therefore, prescribing another neuromodulator should not be ruled out.[36]

Gabapentin is an effective, well-tolerated treatment in chronic cough

If the patient does not respond to neuromodulators or wishes to pursue other options, it may be beneficial to recommend a trial of an opioid, behavioral cough suppression therapy, laryngeal botulinum toxin injections, or superior laryngeal nerve block. Chlorpheniramine, a first-generation antihistamine that crosses the blood-brain barrier, may also have positive effects. These therapies all have evidence supporting their use and should not be ruled out before attempting more extreme interventions.

Experimental treatments

Research into novel treatments for refractory chronic cough is focused on blocking cough arising from various etiologies while minimizing adverse effects.

Recently, the class of P2X3 receptor antagonists has shown promise in achieving this goal. P2X3 receptors are ion channels located on vagal nerve fibers innervating the airways; blocking these receptors is thought to widely suppress neurogenic cough stimuli. P2X3 receptor antagonists have moved from preclinical studies to phase 2b clinical trials.

In the most recent phase 2b clinical trial,[37] in 253 patients, a P2X3 receptor inhibitor was found to significantly inhibit 24-hour cough frequency with an estimated change in awake cough frequency of –37% (95% CI –53.3% to 14.9%; *P* = .003). However, the most common side effect, taste disturbance, occurred in 81% of patients on the maximum dose of the P2X3 receptor inhibitor.[37]

Future trials will need to explore pharmacologic and dosing changes to minimize these adverse effects. As these trials continue to move forward, there is hope for new, better therapies for chronic cough patients like ours.

CASE CONCLUSION

At a 6-month follow-up visit, our male patient reports that his cough is completely resolved. He then begins tapering off his medications, and 18 months after starting his gabapentin regimen, he returns cough-free and successfully weaned off the medication.

TAKE-AWAY POINTS

Unexplained chronic cough (also known as chronic refractory cough) is common, imposes a large healthcare burden, and can adversely affect quality of life.

While the exact cause of chronic refractory cough is unknown, there are evidence-based treatment options.

A thorough and complete history may be able to uncover the underlying problem in a large number of patients.

The most common causes of chronic cough include asthma (and other lung diseases), UACS, and GERD. Testing for these underlying conditions should be pursued before establishing a diagnosis of unexplained chronic cough.

Neuromodulators have proved to be efficacious in the treatment of unexplained chronic cough and should be first-line therapy. Behavioral cough suppression therapy administered by a speech pathologist also shows efficacy and should be offered either in conjunction with other treatments or by itself.

Clinical response to neuromodulators and cough suppression therapy varies widely. Adjustments to the dose or type of neuromodulator may be required to achieve the desired effect.

Numerous alternative therapies have shown promise in treating unexplained chronic cough. More research is warranted toward developing the ideal treatment.

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***Address**: Paul C. Bryson, MD, Head and Neck Institute, A71, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; brysonp@ccf.org*

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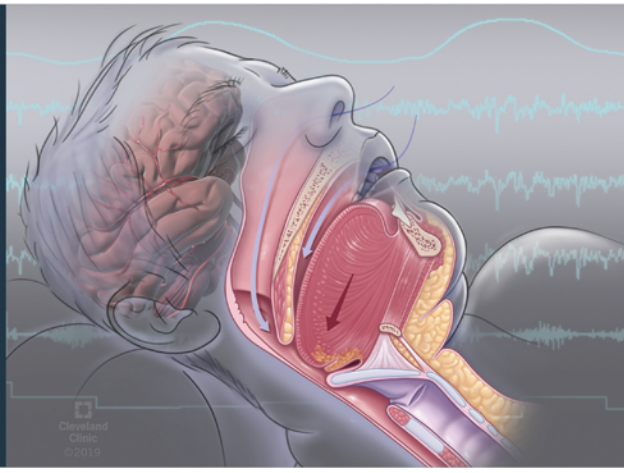

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REVIEW

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Jennifer K. Hockings, PharmD, PhD
Department of Pharmacy, Cleveland Clinic; Genomic Medicine Institute, Lerner Research Institute, and Center for Personalized Genetic Healthcare, Cleveland Clinic Community Care

Amy L. Pasternak, PharmD
Clinical Assistant Professor, Department of Clinical Pharmacy, College of Pharmacy, University of Michigan; Department of Pharmacy, Michigan Medicine, Ann Arbor, MI

Angelika L. Erwin, MD, PhD
Genomic Medicine Institute, Lerner Research Institute, and Center for Personalized Genetic Healthcare, Cleveland Clinic Community Care; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Neil T. Mason, MBA
Department of Individualized Cancer Management, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Charis Eng, MD, PhD
Genomic Medicine Institute, Lerner Research Institute, and Center for Personalized Genetic Healthcare, Cleveland Clinic Community Care; Professor, Department of Genetics and Genomic Sciences, Case Western Reserve University School of Medicine, Cleveland, OH

J. Kevin Hicks, PharmD, PhD
Genomic Medicine Institute, Lerner Research Institute, and Center for Personalized Genetic Healthcare, Cleveland Clinic Community Care; Department of Individualized Cancer Management, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Pharmacogenomics: An evolving clinical tool for precision medicine

ABSTRACT

Pharmacogenomics, ie, the study of how an individual's genomic profile influences his or her response to drugs, has emerged as a clinical tool to optimize drug therapy. Certain variants in some genes increase the risk of severe, life-threatening adverse effects from certain drugs. Integrating pharmacogenomics into clinical practice to assist in drug selection and dosing has the potential to improve the outcomes of treatment, reduce the risk of drug-induced morbidity and death, and be cost-effective.

KEY POINTS

Most people carry a genetic variant that causes an abnormal response to specific drugs, making many vulnerable to potentially life-threatening events.

Codeine is metabolized to morphine by an enzyme that has more than 100 genetic variants with a continuum of activity; children who were ultrarapid metabolizers have died after receiving codeine.

Challenges to using pharmacogenomics in prescribing drugs include developing the infrastructure to routinely store and report test results, educating physicians on the use of testing, and obtaining third-party payment.

Many variants are rare or are common only in certain ethnic groups, so that adequately powered studies are difficult to perform.

Dr. Hicks has disclosed membership on advisory committee or review panels for 23andMe, research or independent contracting for OneOme, and consulting for Quest Diagnostics.

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Pharmacogenomics can improve patient care by optimizing the choice and dosage of medications, thereby lessening the risk of adverse events and increasing patient and provider satisfaction through the practice of personalized medicine. Over the past decade, the technology for genetic testing has advanced, clinical evidence supporting integration of pharmacogenomics into clinical practice has gotten stronger, and the cost of testing has gone down. However, although rapidly advancing research and growing demand are bringing pharmacogenomic-guided therapy closer to reality, barriers remain.

This article reviews the clinical evidence supporting pharmacogenomics, the commonly prescribed drug classes influenced by known pharmacogenes, the costs of testing, research challenges, and what is needed for clinical implementation.

WHAT ARE PHARMACOGENES?

Genetic variants have been identified that affect the pharmacokinetics (ie, absorption, distribution, metabolism, elimination) or pharmacodynamics (ie, pharmacologic effects) of specific drugs. A patient who has a variant allele of one of these genes may experience severe and even life-threatening adverse events when exposed to certain drugs. Such events are a leading cause of morbidity and death in the United States and are costly to manage, and nearly half are estimated to be preventable.[1,2]

More than 90% of patients are thought to carry at least 1 genetic variant that should prompt a change in dosing or medication if certain drugs are prescribed.[3,4] Based on this estimate, a significant number are likely to be at

TABLE 1

Clinical Pharmacogenetics Implementation Consortium drug-gene pairs with evidence-based guidelines

Drugs	Genes
Abacavir[a]	*HLA-B*57:01*
Allopurinol	*HLA-B*58:01*
Amitriptyline[a]	*CYP2C19, CYP2D6*
Atazanavir	*UGT1A1*
Atomoxetine[a]	*CYP2D6*
Azathioprine[a]	*TPMT, NUDT15*
Capecitabine[a]	*DPYD*
Carbamazepine[a]	*HLA-A*31:01, HLA-B*15:02*
Citalopram[a]	*CYP2C19*
Clomipramine[a]	*CYP2C19, CYP2D6*
Clopidogrel[a]	*CYP2C19*
Codeine[a]	*CYP2D6*
Desipramine[a]	*CYP2D6*
Doxepin[a]	*CP2C19, CYP2D6*
Efavirenz	*CYP2B6*
Escitalopram	*CYP2C19*
Fluorouracil[a]	*DPYD*
Fluvoxamine	*CYP2D6*
Imipramine[a]	*CYP2C19, CYP2D6*
Ivacaftor	*CFTR*
Mercaptopurine[a]	*TPMT, NUDT15*
Nortriptyline[a]	*CYP2D6*
Ondansetron	*CYP2D6*
Oxcarbazepine[a]	*HLA-B*15:02*
Paroxetine	*CYP2D6*
Peg-interferon alfa-2a	*IFNL3 (IL28B)*
Peg-interferon alfa-2b	*IFNL3 (IL28B)*
Phenytoin[a]	*CYP2C9, HLA-B*15:02*
Rasburicase	*G6PD*
Ribavirin	*IFNL3 (IL28B)*
Sertraline	*CYP2C19*
Simvastatin	*SLCO1B1*
Succinylcholine	*RYR1, CACNA1S*
Tacrolimus	*CYP3A5*
Tamoxifen	*CYP2D6*
Tegafur	*DPYD*
Thioguanine[a]	*TPMT, NUDT15*
Trimipramine[a]	*CYP2C19, CYP2D6*
Tropisetron	*CYP2D6*
Volatile anesthetics	*RYR1, CACNA1S*
Voriconazole	*CYP2C19*
Warfarin[a]	*CYP2C9, CYP4F2, VKORC1*

[a]The drug also has US Food and Drug Administration-designated pharmacogenetic labeling as a boxed warning, a contraindication, a warning and precaution, or a dosing and administration recommendation.

From the Clinical Pharmacogenetics Implementation Consortium, https://cpicpgx.org/genes-drugs.

risk of poor treatment outcomes due to a gene-drug interaction. Using pharmacogenomics as a clinical tool to guide drug selection and dosage adjustments may be an effective and potentially cost-saving risk-mitigation strategy.

CLINICAL UTILITY OF PHARMACOGENOMICS

Strong evidence indicates that variants in about 20 genes affecting more than 60 drugs could affect one's response to these medications. Evidence-based, peer-reviewed guidelines are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (www.cpicpgx.org), an initiative funded by the US National Institutes of Health to help clinicians interpret the results of genomic tests and apply them to patient care.[5] **Table 1** lists the currently recognized gene-drug pairs for which clinical guidelines are available.

Numerous examples for implementing pharmacogenomic testing have been published, with strategies ranging from preemptively testing everyone with panels of genes to testing single genes before prescribing certain drugs.[6–9] But regardless of the implementation model, clinicians face challenges in deciphering the clinical evidence, and institutions face the challenge of creating the infrastructure to store genomic information that may be relevant throughout a patient's life.

OPIOIDS AND CYP2D6

Ultrarapid metabolizers can overdose on codeine

Codeine is a prodrug with weak affinity for the mu-opioid receptor. It exerts most of its

analgesic effect after it is activated to morphine, primarily by cytochrome P450 2D6 (CYP2D6). The *CYP2D6* gene has more than 100 variants that can result in a continuum of enzyme activity, ranging from ultrarapid to poor metabolism of CYP2D6 substrates.[10]

After taking codeine, people who are CYP2D6 ultrarapid metabolizers have higher concentrations of morphine in their blood, increasing the risk of severe opioid toxicity. Numerous cases of codeine-induced toxicity have been reported in children who were CYP2D6 ultrarapid metabolizers undergoing tonsillectomy or adenoidectomy; 10 children died and 3 experienced severe respiratory depression.[11] In addition, infant deaths from opioid toxicity have been attributed to breastfeeding mothers who were CYP2D6 ultrarapid metabolizers taking codeine for postpartum pain.[12]

After these case reports, the US Food and Drug Administration (FDA) amended codeine labeling to contraindicate its use in all children younger than 12 years old and in patients under 18 after tonsillectomy or adenoidectomy.

Children with sickle cell disease may be the most adversely affected by this contraindication, as codeine is recommended as an initial opioid to manage pain during crises.[13] This contraindication prohibits the use of acetaminophen with codeine, the only nonschedule II opioid (for which prescriptions can be refilled over the phone) as an option for managing pain in pediatric patients.

Other opioids pose similar problems

Although the current CPIC guideline focuses on codeine, several other opioids are also CYP2D6 substrates, including hydrocodone, oxycodone, and tramadol. The guideline specifically states that tramadol should not be used as an alternative to codeine[14]; it, like codeine, is activated through CYP2D6 to a more active metabolite and increases the risk of respiratory depression in CYP2D6 ultrarapid metabolizers. Tramadol carries the same US boxed warning as codeine, contraindicating its use in children.

Poor metabolizers may get little pain relief

Patients who are CYP2D6 intermediate or poor metabolizers are at risk of inadequate pain relief because of decreased metabolism. Testing could increase the judicious prescribing of opioids by preventing CYP2D6 poor metabolizers from receiving an opioid that would result in inadequate pain relief, and have the effect of reducing opioid prescriptions in circulation.[15,16]

Gammal et al[17] described a strategy of employing CYP2D6 pharmacogenomic clinical decision support alerts to identify pediatric patients who are at low risk for opioid toxicity or inadequate pain control with codeine administration. Such a system may serve as an alternative to the current broadly restrictive approach.[17]

A pragmatic study conducted by Smith et al[18] showed that better pain control was achieved with a strategy of guided prescribing of codeine, hydrocodone, and tramadol with *CYP2D6* genotype-guided prescribing. In more than 75% of those who were CYP2D6 intermediate metabolizers or poor metabolizers, an opioid was replaced with a nonopioid for pain management.

ANTIDEPRESSANTS AND CYP2D6, CYP2C19, SLC6A4, HTR2A, AND HTR2C

Antidepressants are one of the most commonly prescribed drug classes in the United States.[19] But in an estimated 30% to 50% of patients, initial antidepressant drug therapy fails because of ineffectiveness or drug-induced adverse effects.[20]

A patient with a genetic variant may be at increased risk for developing severe, life-threatening adverse effects

Most antidepressants are metabolized by CYP2D6 or CYP2C19, or both. Emerging data suggest that genomic variation in serotonin transporters (eg, SLC6A4) and receptors (eg, HTR2A, HTR2C) is also associated with antidepressant response. Guidelines are available to assist with selection and dosage of serotonin reuptake inhibitors and tricyclic antidepressants based on the *CYP2D6* and *CYP2C19* genotype.[21,22]

Pharmacogenomic guidance improves outcomes

Multicenter, randomized controlled trials have evaluated the impact of genotype-guided antidepressant drug prescribing using questionnaires to measure depressive symptoms. These studies employed combinatorial pharmacogenomic approaches consisting of panels that interrogate multiple genes (eg, *CYP2D6*,

CYP2C19, *SLC6A4*, *HTR2A*, and *HTR2C*), and recommend antidepressants based on patient genotypes. Patients randomized to genotype-guided treatment fared significantly better in standardized depression rating scores or response and remission rates compared with patients receiving usual clinical management.[23,24] In addition to improved clinical outcomes, pharmacogenomic-guided antidepressant drug selection may also reduce healthcare resource usage and lower medication-related costs of antidepressant therapy.[25]

CLOPIDOGREL AND CYP2C19

To inhibit platelets, clopidogrel must undergo activation by CYP2C19, and patients with decreased CYP2C19 activity have less active metabolite formation. Current evidence-based guidelines recommend using an alternative antiplatelet agent in patients who are intermediate or poor metabolizers of CYP2C19.[26]

CYP2C19-clopidogrel dosing guidelines have mostly focused on patients undergoing percutaneous coronary intervention, but recent evidence also indicates that the *CYP2C19* genotype affects the efficacy of clopidogrel when prescribed for other indications, such as ischemic stroke.[27]

Pharmacogenomics could increase the judicious prescribing of opioids

Multiple large observational studies have demonstrated the clinical impact of *CYP2C19* genotype-guided antiplatelet drug selection. These studies, which included thousands of patients, found that intermediate or poor metabolizers of CYP2C19 who received clopidogrel had significantly worse cardiovascular outcomes than patients who received antiplatelet therapy that matched genotype-guided recommendations, although the assessed composite outcomes differed among the studies.[28–30]

The Tailored Antiplatelet Therapy Following Percutaneous Coronary Intervention (TAILOR-PCI; NCT01742117) trial is currently accruing patients. This large, prospective, randomized controlled trial is designed to further evaluate the clinical utility of genotype-guided clopidogrel prescribing.

OTHER CLINICAL CONSIDERATIONS

Sometimes genotyping may not be useful

Although pharmacogenomics is an important consideration when prescribing many common drugs, other patient characteristics are also pertinent to prescribing decisions. For instance, interactions with other drugs can significantly alter enzymatic activity, which could reduce the reliability of pharmacogenomic-guided dosing.[31]

Medication decisions may also be influenced by specific practice formularies or insurance coverage, which can affect the relevance of pharmacogenomic testing. For example, the American College of Rheumatology recommends screening for carriers of *HLA-B*5801* before starting allopurinol in high-risk patients to reduce the risk of allopurinol-induced severe cutaneous adverse reactions.[32] But for patients with normal renal function who are receiving reduced doses of allopurinol, the risk of a cutaneous reaction is typically lower, and preemptive genotyping is arguably less warranted.[33] Third-party payers may not reimburse for preemptive testing, and the use of alternatives to allopurinol may be restricted or allocated to those in a higher copay group. These considerations may limit the clinical utility of *HLA-B*5801* testing in certain patients.

Other times, it can reduce morbidity and save money

In some circumstances, preemptive testing can prevent adverse effects that lead to expensive medical care.

In a case at our institution, a 76-year-old woman with rheumatoid arthritis inadequately controlled with steroids and methotrexate was subsequently switched to azathioprine 100 mg daily. About 6 weeks later, she was admitted to the hospital with pancytopenia, subdural hematoma, and cellulitis that resulted in more than a 2-week hospital stay, empiric use of antibiotics, multiple transfusions, and an evaluation for aplastic anemia vs azathioprine-induced pancytopenia.

Azathioprine-induced severe myelosuppression may be caused by genetic variants in thiopurine S-methyltransferase (TPMT), the enzyme that catabolizes azathioprine to less pharmacologically active compounds. Subsequent *TPMT* genotyping found that the patient was a TPMT-poor metabolizer, and the use of azathioprine should have been avoided.[34]

ADDRESSING CHALLENGES TO PHARMACOGENOMIC TESTING

Prospective, randomized clinical trials to assess the utility of pharmacogenomics can be difficult to carry out, particularly if testing for rare variants that would require a sample size of thousands to be sufficiently powered. Certain pharmacogenetic variants are more or less common in different ethnic groups; it would be difficult for any study population to adequately reflect all ethnic groups, making the large number needed to power a trial to demonstrate clinical utility a significant limitation.

Validity of clinical trial results may be limited by not testing for clinically important variants carried by the population being studied. Two randomized controlled trials for genotype-guided warfarin therapy illustrate this issue:

The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial[35] compared fixed warfarin dosing vs genotype-guided dosing and found better outcomes with genotype guidance. More than 90% of the study's participants identified as white.

The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial[36] compared patients who had warfarin dosage determined either by an algorithm based only on clinical variables or on clinical variables plus genotype data. In this trial, almost 30% of participants self-identified as black. Overall, no improvement in anticoagulation control was found, and in black patients, control was actually poorer in the genotype-guided group. A possible explanation for the poorer control in black patients is that *CYP2C9* genotyping did not include decreased-function alleles (eg, *CYP2C9*8*) that are commonly found in patients of African ancestry.

It is possible that the different dosing strategies between the 2 trials may have contributed to their opposite outcomes, suggesting that genotype-guided dosing may not be superior to algorithm-based dosing.[37]

The subsequent large Genetics Informatics Trial (GIFT)[38] randomized elderly patients to either an algorithm based on clinical variables alone to guide warfarin dosing or one based on clinical variables plus *CYP2C9*, *CYP4F2*, and *VKORC1* genetic data. Similar to the EU-PACT trial, this study's population was more than 90% white. The genotype-guided warfarin dosing arm had a reduction in the composite outcome of major bleeding, international normalized ratio greater than 4, venous thromboembolism, and death. These findings suggest that a genotype-guided algorithm is superior to a clinically guided algorithm when the appropriate genetic variants are included for the population being studied.

Alternatives to randomized trials

In most cases, pharmacogenomics can help guide selection between multiple medications that have similar efficacy and safety for the indication of interest. In such cases, it may not be necessary to conduct extensive, randomized clinical trials, but rather to rely on pragmatic trials focused on implementing pharmacogenomics to improve patient care.

Given the number of smaller studies including different racial and ethnic groups, meta-analyses of certain gene-drug pairs may be useful. In addition, identifying and validating pharmacogenetic associations by other methods, such as comparing prospective pharmacogenetic-guided therapy to matched historical controls, or evaluating results of well-designed retrospective studies, should be considered when determining the value of pharmacogenomics in practice.

In some situations, randomized controlled trials cannot be done because they would be considered unethical. When pharmacogenetic associations are known to predict life-threatening adverse events, prescribing a medication to a patient who carries the high-risk variant for the purpose of creating a control group would not be justifiable.

Genotype-based guidelines are available for selective serotonin reuptake inhibitors and tricyclic antidepressants

IS PHARMACOGENOMIC TESTING COST-EFFECTIVE?

The cost of pharmacogenomic testing may be an important barrier to implementation because of limited reimbursement. In a survey of 14 US payer organizations that cover 122 million patients, payers expressed concern about the initial costs and perceived uncertainty of benefits from preemptive pharmacogenomic testing. In particular, they pointed out that many low-cost generic drugs are often available that patients could be prescribed before

resorting to a new drug that would require panel genotyping before safely using it.[39]

But several studies have shown that preemptive pharmacogenomic testing could not only benefit patients, it may also be cost-effective over the long term. In a systematic review, Verbelen et al[40] assessed 44 economic evaluations that covered 10 of the known pharmacogenomic-associated drugs listed by the FDA. They found that 57% supported reactive pharmacogenomic testing, with 30% being cost-effective (ie, benefits are large compared with costs) and 27% estimated to be cost-saving (ie, costs are reduced). If genetic testing had negligible costs, 75% of the studies would support pharmacogenomic testing, with 25% rated as cost-effective and 50% as cost-saving. Although panel testing can be costly, depending on the platform and number of genes tested, prices would be expected to fall over time, and cost savings would be realized as patients require additional pharmacogenomic-associated treatments.

Analysis of the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program at Vanderbilt University Medical Center found that 91% of nearly 10,000 preemptively genotyped patients had at least 1 actionable variant, and 42% of these patients had been exposed to a risk-associated medication in the past.[3] If a separate test had been ordered before prescribing each of the drugs examined in this study, 14,656 tests would had to have been performed vs the 9,589 multiplex tests actually performed as part of this study, a rate 1.7 times higher.

Intermediate or poor metabolizers of CYP2C19 who received clopidogrel had worse cardiovascular outcomes

In a hypothetical cohort, Borse et al[41] compared 3 treatment strategies: universal clopidogrel, universal prasugrel, and CYP2C19-guided prescribing. They found that 658 major cardiovascular or bleeding events could be avoided over 30 days by guided therapy per 10,000 patients treated. Guided therapy also led to $50,308 saved over 1 year per patient compared with the other groups.

In a model of CYP2C19-guided voriconazole prophylaxis in patients diagnosed with acute myeloid leukemia, Mason et al[42] predicted a modest cost savings per patient, while reducing the incidence of invasive fungal infections and shortening average length of hospital stay.

A study by Sluiter et al[43] of *CYP2D6* genotyping for antidepressants was less conclusive. They found a wide incremental cost-effectiveness ratio ranging from $22,500 to $377,500, likely due to the many assumptions the model required. They did not include the effects of *CYP2C19* genotyping, which also has significant clinical impact on antidepressant medications.

The biggest obstacle to determining the cost-effectiveness of pharmacogenomic testing is a lack of real-world economic data. Most pharmacogenomic studies that try to assess cost-effectiveness are based on estimated costs and clinical parameters from the literature rather than direct reporting of costs before and after testing. As pragmatic studies are being designed, investigators should consider incorporating economic end points to generate more accurate estimates of costs and use of healthcare services. This would provide direct evidence of the financial impact of pharmacogenomic testing that may improve future economic models.

DIRECT-TO-CONSUMER TESTING

Increasing interest in pharmacogenomic testing may in part be due to decreasing costs of panel genotyping. However, genomic direct-to-consumer tests may also be a driving force.

Genomic direct-to-consumer testing has a tumultuous history starting about 15 years ago. Technologies quickly outpaced clinical evidence, regulations, and ethical considerations, resulting in concerns about what information consumers should be allowed to receive without guidance by medical professionals. The FDA sent warning letters to reference laboratories, telling them to discontinue direct-to-consumer health-related genetic tests.

In recent years, clinical evidence has strengthened, guidelines have emerged, and genomic medicine is becoming integrated into routine care for certain disease states, such as some cancers. Recently, the FDA approved direct-to-consumer tests for pharmacogenomics, cancer risk (eg, *BRCA1* and *BRCA2* testing), and propensity to develop certain conditions (eg, Parkinson and Alzheimer diseases). Because the recent FDA authorization has better

defined limits and costs have become lower, it is unlikely that these tests will be going away.

The FDA has stated that direct-to-consumer genomic test results should not be used to guide therapy, and an independent clinical test to confirm results is needed before making medical decisions. Clinicians should be prepared to discuss with patients direct-to-consumer pharmacogenomic testing, indications for confirmatory testing, and resources that are available when results arrive. Several educational resources are available, including those from the CPIC, the Pharmacogenomics Knowledgebase (PharmGKB), and the National Institutes of Health.

EDUCATION AND INFRASTRUCTURE NEEDED

Challenges to incorporating pharmacogenomics into clinical medicine include a lack of infrastructure to store and report test results and limited clinician confidence in interpreting, applying, and communicating results to patients.[6–9] A survey of 47 general practitioners and 375 specialist physicians also identified the paucity of guidelines surrounding pharmacogenomic testing and lack of provider familiarity with pharmacogenomics as major barriers to adoption.[44] As with other clinical guidelines, CPIC guidelines are updated regularly to incorporate growing evidence.[5] Despite this, it can be overwhelming to synthesize the recommendations, especially for patients prescribed multiple medications.

To overcome these challenges, interdisciplinary teams should be developed to incorporate the expertise of many healthcare professionals. Informatics experts can develop the infrastructure to enable adding pharmacogenomic test results to the medical record in a clinically meaningful way. They can also work with pharmacists and clinicians to develop clinical decision support rules to alert end users of significant drug-gene interactions at the point of prescribing, and provide alternative recommendations. Pharmacists and genetics counselors can train clinicians in the use of pharmacogenomic tests and communicate the meaning of test results directly to patients.

Implementation efforts often need to be customized to individual institutions, as recommendations may differ depending on available formulary agents and characteristics of the patient population.[8,9]

DEVELOPING PHARMACOGENOMIC SERVICES

A few institutions are making efforts to incorporate preemptive pharmacogenomics testing, which can serve as models for their use.

Hicks et al[8] described implementing clinical pharmacogenomic testing of 3 gene-drug pairs (*HLA-B*57:01*-abacavir, *HLA-B*15:02*-carbamazepine, and *TPMT*-thiopurines) in a large healthcare system. Custom rules and alerts were developed and integrated into the electronic health record to provide support for point-of-care decision-making. Such a system could be designed to also incorporate panel genotyping and triggering of clinical decision support alerts for those with an actionable genotype without further testing. A pharmacogenomics clinic was also established consisting of medical geneticists, genetic counselors, and a pharmacist with specialized training in pharmacogenomics, who assessed the need for pharmacogenomic testing in individual patients and provided results and interpretation and medication recommendations. Patients were educated on the benefits, risks, limitations, and financial costs of pharmacogenomics before testing.

Third-party payers may not reimburse for preemptive testing

Surgical services are conducting pilot studies to evaluate preemptive pharmacogenomic testing to better manage acute postoperative pain, reduce opioid consumption, and minimize recovery time after surgery. Senagore et al[45] compared overall benefit of analgesia scores and narcotic consumption in 2 groups: 50 patients who received pharmacogenomic-guided pain management after colorectal resection or major ventral hernia repair and a historical control group managed by an enhanced recovery protocol. The pharmacogenomic-guided group had significantly lower scores (indicating better pain control) and consumed 50% less narcotics compared with the control group.[45] Given that poor analgesia and adverse effects from medications may result in an unplanned admission to intensive care or lengthier hospital stays, preemptive pharmacogenomic testing could help minimize such events.

POISED TO IMPROVE CARE

As healthcare focuses on value-based care, pharmacogenomics is poised to improve patient care by optimizing pharmacotherapy, mitigating risk of adverse events, and increasing patient and provider satisfaction through the practice of personalized medicine. However, several barriers remain, including integration of pharmacogenomic results into existing electronic medical records to provide meaningful therapeutic recommendations at the appropriate time. With further research, education, and growing demand, the concept that an individual's therapy will be guided by pharmacogenomics will continue to become a reality.

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***Address**: Jennifer Hockings, PharmD, PhD, Department of Pharmacy, JJN1, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; hockinc@ccf.org*

CME MOC

Byron J. Hoogwerf, MD, FACP, FACE
Emeritus, Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Clinical Professor of Endocrinology, Medical Sciences Discipline, Central Michigan University College of Medicine, Mt. Pleasant

Type of diabetes mellitus: Does it matter to the clinician?

ABSTRACT

The classification of diabetes mellitus in 2020 still starts with 2 major types, ie, type 1 and type 2, but each of these now includes a few uncommon variants. Understanding the many faces of the diabetes syndrome can make a difference in how clinicians select glucose-lowering therapy.

KEY POINTS

Variants of type 2 diabetes include monogenic forms such as maturity-onset diabetes of youth (MODY) and ketosis-prone forms such as Flatbush diabetes. In addition, when diabetes occurs with lipodystrophy, it has many features of type 2.

If patients have a Flatbush phenotype, negative autoimmune testing may help confirm the diagnosis. Although these patients need insulin at the outset, treatment can often be changed to oral glucose-lowering agents.

Lipodystrophic variants of type 2 diabetes are likely to respond to insulin sensitizers, some specifically to metreleptin.

Although type 2 diabetes has many associated genes, genetic types do not yet consistently define the specific therapeutic approaches. The exception to this is that some MODY types respond quite specifically to sulfonylureas.

The most common variant of type 1 diabetes is latent autoimmune diabetes in adults, and when this diagnosis is established either by autoimmune testing or rapid failure of several glucose-lowering therapies in sequence, insulin therapy is appropriate.

Dr. Hoogwerf has disclosed formerly being an employee of and currently owning stock in Eli Lilly and consulting for Mannkind Corp.

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"…It is essential to realise that diabetes as commonly understood—namely the passage of sugar in the urine—is not a disease in itself. It is only a sign of disease*…In brief there are several kinds of diabetes, and their outcome varies from moderate personal inconvenience to invariable fatality."*

—Anonymous, 1923.[1]

THE STATEMENT ABOVE from nearly 100 years ago—just a few years after the discovery of insulin—is in many senses still true.[2] In 2020, diabetes mellitus is still likely a syndrome with many genetic, epigenetic, and pathophysiologic abnormalities, different complication profiles, and multiple environmental influences such as infections, nutrients, exercise regimens, and the gut microbiome.[3–10] The interplay among these factors is the topic of an ongoing process of discovery. Some of the discoveries help to inform the management of hyperglycemia, albeit still with many limitations.

The classification scheme in which there are 2 main types of diabetes, ie, type 1 and type 2, is still the starting point.[11] Although the American Diabetes Association's standards of care consider monogenic diabetes a separate entity,[11] I believe this distinction is premature, as monogenic diabetes does not show up in the clinic as an obvious distinct entity, but rather as type 2.

However, there are variations in these 2 major types of diabetes. Pathophysiologic and genetic approaches not only provide the basis for classification schemes, but also inform the use of glucose-lowering therapy.

This article summarizes information on type 1 and type 2 diabetes mellitus, their less common subtypes, approaches to diagnosis, and implications for selecting glucose-lower-

TABLE 1

Types of diabetes and their features

Type	Insulin level	Auto-immune	Genetic features	Glucose-lowering treatments
Type 2 diabetes mellitus[8,10,14,36,37]	High, but decreases over time	No	Multiple single nucleotide polymorphisms (SNPs), but no single SNP specifically associated with diabetes	Multiple Level of hyperglycemia and comorbid conditions guide decisions
MODY[14–19,25]	Variable	No	Autosomal-dominant and recessive	Sulfonylureas for 2 genotypes (*HNF4A, HNF1A)*; no medication for 1 genotype (*GCK*)
Flatbush[26–28]	Variable	No	Unknown	Insulin, followed by therapies for type 2 diabetes mellitus
Lipodystrophy[39–41]	High	No	Yes, for genetic types	Insulin, metformin, thiazolidinediones, metreleptin
Type 1 diabetes mellitus[11]	Low	Yes	Yes, human leukocyte antigen (HLA) system-related	Insulin
LADA[29–34]	Low	Yes	Yes, HLA system-related and some novel genes	Insulin
Secondary diabetes				
Cushing disease, acromegaly	Usually high secondary to counterregulatory hormones	No	No	See type 2 diabetes mellitus above
Medication-related	Variable; high with glucocorticoids	No	No	See type 2 diabetes mellitus above

LADA = latent autoimmune diabetes in adults; MODY = maturity-onset diabetes of youth

ing therapy. Understanding these issues does matter to the clinician.

TYPES AND BIOMARKERS OF DIABETES

Classification schemes for diabetes started to be devised more than a half century ago.[12] In the 1930s, Himsworth[13] infused both glucose and insulin into diabetes patients and observed 2 distinct glucose responses: either glucose levels declined, suggesting the patient was sensitive to insulin but did not make enough of it, or glucose increased, suggesting the patient was making insulin but was resistant to it. Himsworth speculated that the latter group must be missing a factor that sensitizes people to insulin. This distinction between insulin-deficient (but sensitive) and insulin-present

(but resistant) is still the framework for the current classification of diabetes mellitus.[11]

Assays for 2 types of soluble biomarkers helped to refine our understanding of type 1 diabetes:

Insulin and C-peptide to assess beta-cell function. Values can be low in type 1 diabetes, especially later in its course. In type 2 diabetes, insulin and C-peptide levels range from very high early in the disease process to low, but detectable, with long-standing disease.

Antibodies to islet cells and related proteins, especially glutamic acid decarboxylase. The presence of these antibodies also points to a diagnosis of type 1 diabetes.

These 2 groups of biomarkers help not only to characterize type 1 diabetes, but also to distinguish autoimmune from nonautoimmune types. They have also helped characterize subtypes of diabetes that occur in children and young adults, including:

- Maturity-onset diabetes of youth (MODY), also called maturity-onset *hyperglycemia* of youth (MOHY)[14–25]
- Flatbush diabetes[26–28]
- Latent autoimmune diabetes in adults (LADA).[29–34]

Each of these is discussed in more detail below (**Table 1**).[8,10,11,14–19,25–41]

Diabetes mellitus is a syndrome

The expectation that the results of the Human Genome Project[35,36] would provide greater refinement in classifying type 2 diabetes and guiding glucose-lowering regimens has not yet been fully realized.[37] Dozens of genetic markers are now associated with type 2 diabetes, and many are associated with phenotypic and mechanistic components of the pathophysiology of diabetes, including insulin secretion, insulin resistance, and obesity. However, none are sufficient to subdivide type 2 diabetes in a classification scheme that would help to guide glycemic therapy.[3,9,10,14,37,38]

The exception is the subgroup of patients with type 2 diabetes who have MODY, in which genetic markers help characterize the appropriate pharmacotherapy.[15–18] In patients who do not have genetic markers associated with response to sulfonylureas (*HFN1A, HFN4A*) or the risk for complications (*GCK*), glucose is managed with treatment regimens generally used in type 2 diabetes mellitus.

The discussion below will only briefly mention causes of secondary diabetes and diabetes associated with lipodystrophy[39–41] or hemochromatosis.[42,43] The rationale for including these diseases is that each time a clinician sees a patient with diabetes, the possibility of another entity such as Cushing syndrome, acromegaly, lipodystrophy, or hemochromatosis should be considered.

Disorders associated with pancreatic damage such as cystic fibrosis and pancreatitis do not consistently result in diabetes mellitus, but when they do, insulin therapy is the best option. Since the diagnosis and treatment of pancreatic disease-associated diabetes are generally straightforward for the clinician, they will not be discussed here in detail. Gestational diabetes and rare types of neonatal diabetes will also not be discussed.

TYPE 2 DIABETES MELLITUS

The most common type of diabetes mellitus, type 2, was formerly called adult-onset diabetes or non-insulin-dependent diabetes. However, it is now known to occur also in children, and it often requires insulin therapy for glycemic control.

Type 2 diabetes is characterized by several biochemical and pathophysiologic defects associated with hyperglycemia.[44] Concepts of declining insulin production not mediated by immune mechanisms and insulin resistance have been known for several decades. Additional mechanisms that have been elucidated are related to inflammation, increased hepatic glucose production, altered levels of gut hormones that regulate insulin and glucagon, and altered renal glucose thresholds. This topic has been summarized by DeFronzo.[44]

Many of these pathophysiologic mechanisms can now be targeted by drugs as an adjunct to diet and exercise. However, guidelines for glucose-lowering therapy take into account only general considerations of patient phenotype and comorbidities (**Table 2**) rather than actual pathophysiologic mechanisms.[45–52]

After studies of monozygotic twins and other evidence indicated that type 2 diabetes was a genetic disorder, there was hope that genetic information might be directly associated with specific pathophysiologic mechanisms

involved in the development of hyperglycemia. These relationships might use genetic profiles to guide pharmacotherapy. But in spite of intriguing data demonstrating clusters of genes associated with insulin processing and signaling, as well as markers of insulin resistance, clear patterns to guide therapy are still aspirational.[6,37,38]

The microbiome and epigenetics are current areas of research in type 2 diabetes. However, to date, genetic and mechanistic studies have not provided clear approaches to treatment. Rather, treatment of hyperglycemia in type 2 diabetes is guided by such things as level of glycemia and comorbid conditions such as coronary heart disease, heart failure, and renal disease (**Table 2**). When there are marked glucose elevations, early insulin therapy should be considered because of the ability to titrate to control glucose levels. The Holy Grail of precision medicine based on genetic markers is not yet a reality.

TABLE 2

Considerations for glucose-lowering medications in type 2 diabetes mellitus

Monotherapy is usually inadequate for glycemic control

Medications that work by different mechanisms have additive effects for glucose control

Insulin therapy can be broadly used as monotherapy or in combination with other agents

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have benefits in terms of renal failure, heart failure, and major adverse cardiovascular events (including death)

Some glucagon-like peptide 1 receptor agonists (liraglutide,[48] dulaglutide,[49] and semaglutide,[50] but not lixisenatide[51] or exenatide [weekly formulation])[52] reduce risk of major adverse cardiovascular events

Comorbidities of diabetes affect the selection of glucose-lowering medications

In renal compromise:

Metformin poses risk of lactic acidosis; do not initiate if estimated glomerular filtration rate (eGFR) is < 45 mL/min/1.73 m^2; but patients currently on metformin with eGFR ≥ 30 and < 45 mL/min/1.73m^2 may continue cautiously, considering a 50% reduction and frequent monitoring of renal function; discontinue if eGFR is < 30 mL/min/1.73 m^2

Adjust dose of dipeptidyl peptidase 4 (DPP4) inhibitors

SGLT2 inhibitors have reduced efficacy

In heart failure or risk of heart failure:

Discontinue peroxisome proliferator-activated receptor (PPAR) gamma agonists

Use DPP4 inhibitors (saxagliptin, alogliptin) with caution

In hypoglycemia:

Avoid sulfonylureas

Adjust dose of insulin

Based on information in references 45–52.

Maturity-onset diabetes of youth

MODY is a monogenic form of nonautoimmune diabetes mellitus that often manifests in adolescents or young adults, usually before age 30.[14–18] It is estimated to account for 1% to 2% of all patients with diabetes.[11,15,24] Whereas MODY is widely classified as a separate type of diabetes,[11] each time a clinician sees a patient with type 2 diabetes mellitus, MODY is a consideration.

Autosomal-dominant and autosomal-recessive genetic subsets of what looked like typical type 2 diabetes mellitus have been known for several decades. MODY was originally identified because of apparent autosomal-dominant patterns in families who had multiple members with non-ketosis-prone diabetes.[53,54]

MODY has now been characterized in several subtypes. Early genetic classifications used numbers such as MODY 1–9.[16,18] Specific genetic characterization is now the standard approach. The MODY genes are broadly associated with insulin deficiency or insulin resistance. Notably, genetic subtypes associated with abnormalities of insulin secretion such as *HNF1A* MODY and *HNF4A* MODY (in adolescents and young adults) and *KCNJ11* and *ABCC8* (both associated with permanent neonatal diabetes) are associated with very good glycemic responses to sulfonylureas.[11,19,20,22,25] The subtype associated with abnormalities of glucokinase (GCK) does not require glucose-lowering therapy because of absence of diabetic complications with this abnormality.[11,23,24] *GCK* mutations result in an altered glucose threshold for insulin response. Thus, patients with this abnormality usually have only mild elevations of glucose. Some patients with *GCK* abnormalities have normal glucose levels. Since the risk for compli-

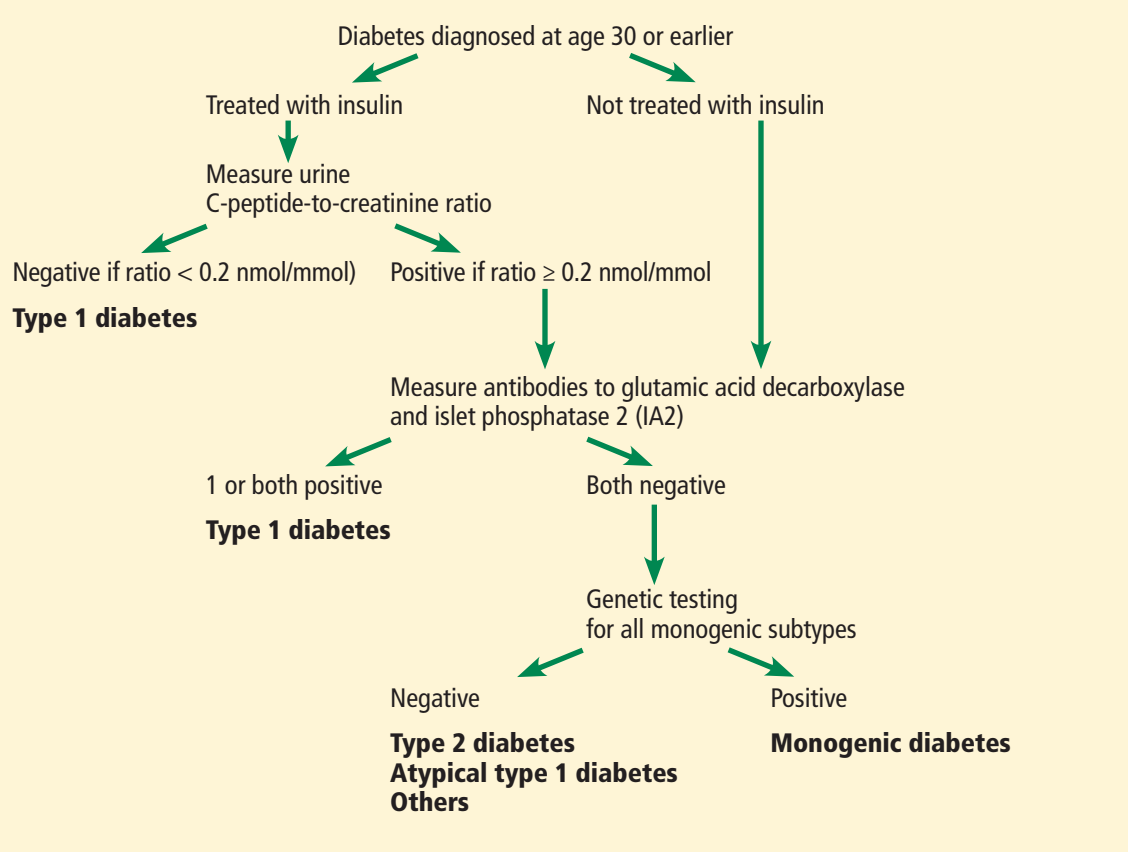

Figure 1. The Using Pharmacogenetics to Improve Treatment in Early-Onset Diabetes (UNITED) biomarker screening pathway to investigate the etiology of diabetes diagnosed in patients age 30 or younger. Genetic testing is carried out in all patients who have endogenous insulin (urinary C-peptide-to-creatinine ratio ≥ 0.2 nmol/mmol) and do not have either glutamic acid decarboxylase or IA2 autoantibodies. Patients without endogenous insulin or with these antibodies are classified as having type 1 diabetes.

Type 2 diabetes variants include maturity-onset diabetes of youth, Flatbush diabetes

cations is a function of the degree of hyperglycemia, and these patients have normal or only mildly elevated glucose levels, they are not at risk for microvascular complications. Thus, knowledge of these genetic subtypes helps the clinician select glucose-lowering therapy.

Because age of onset of MODY overlaps with that of type 1 diabetes, it is often important to distinguish MODY patients from those with type 1 diabetes to determine whether it is appropriate to treat them with drugs other than insulin. Rather than go directly to genetic testing for MODY, Shields et al[17] have devised an algorithm to use in patients under age 30 (**Figure 1**) to distinguish MODY from type 1 diabetes. Screening begins with assessment of beta-cell function with a urinary C-peptide level. Low levels of serum C-peptide could perhaps also be used with this algorithm. Low C-peptide levels confirm type 1 diabetes. In patients with a urine C-peptide-to-creatinine ratio greater than or equal to 0.2 mmol/mg creatinine, the next step is to measure glutamic acid decarboxylase and IA2 islet cell antibodies to determine if the diabetes is autoimmune. Positive antibody tests also confirm type 1 diabetes. Patients with negative antibodies should undergo testing for MODY genes. The purpose of genetic testing is to identify MODY subtypes for which either sulfonylurea therapy or no therapy is appropriate for glycemic control.

Flatbush diabetes

Flatbush diabetes was described in Afro-Caribbeans in 1994 by physicians at State University of New York Downstate based on observations in patients from the Flatbush neighborhood of Brooklyn, New York.[27] Flatbush diabetes is currently considered to be on the spectrum of type 2 diabetes, although this is an issue of ongoing discussion.

At presentation, Flatbush diabetes patients have hyperglycemia with ketoacidosis. When glucose is subsequently controlled, ketosis rarely recurs. Most patients are of African descent, although Asian and Hispanic patients have also been described. These patients were originally thought to have a form of MODY, but currently known MODY genotypes are absent. These patients do not have antibodies to glutamic acid decarboxylase or to islet cells, although a few studies do report associations with human leukocyte antigens.

In a review of several reports of this type of diabetes, Lebovitz and Banerji[28] note that many patients are black, male, middle-aged, overweight or moderately obese, and have a family history of type 2 diabetes.

After the ketosis at presentation has resolved, the disease looks more like type 2 diabetes. When patients present with ketoacidosis, insulin is the initial treatment of choice. When glycemic control is normal or near-normal (especially if antibody testing for glutamic acid decarboxylase or islet cell antibodies is negative), then the regimen can be changed to oral agents with approaches commonly used in type 2 diabetes.[45,46]

TYPE 1 DIABETES MELLITUS

Type 1 diabetes, formerly called juvenile-onset diabetes and ketosis-prone diabetes, is becoming increasingly well characterized. The pathophysiology of an autoimmune destruction of beta cells resulting in progressive insulin deficiency has been well studied over the past 40 years, and both genetic and soluble biomarker data are extensive.

Most of the time the clinical presentation is sufficient to make the diagnosis without needing measures of beta-cell function, measures of autoimmunity, or specific genetic testing. The diagnosis of type 1 diabetes clearly indicates a need for insulin replacement therapy. If there is uncertainty about the diagnosis and the corresponding need for insulin therapy, then measures of beta-cell function and islet cell antibody testing are indicated to guide treatment decisions.

The most commonly used measure of beta-cell function is the C-peptide test. Significant confounders in interpreting what may be a low C-peptide are the observations that earlier onset of type 1 diabetes is associated with lower C-peptide levels than later onset. In addition, early in the course of type 1 diabetes, C-peptide levels may still be detectable.[55,56] In fact, C-peptide may be detectable for many years in patients over age 20 at diagnosis. Glucose levels should be obtained simultaneously with a C-peptide measurement to show that low C-peptide is not the result of hypoglycemia.

Latent autoimmune diabetes in adults

LADA has elements of both type 1 and type 2 diabetes.[29–34] The prevalence of LADA is highly dependent on the cohort of patients under evaluation and on whether the diagnostic criteria are based on autoimmune antibodies associated with type 1 diabetes alone or on additional genetic testing in which overlap with type 2 diabetes genes is considered. Although LADA patients are often started on oral glucose-lowering agents, these agents usually do not control the glucose level for very long.

Type 1 diabetes variants include latent autoimmune diabetes of adults

LADA should be considered in any non-obese patient who has onset of diabetes as a young adult, especially if frequent addition of oral glucose-lowering agents is needed to maintain glycemic control. This medication use pattern suggests insulinopenia, the main pathophysiologic defect in LADA.

LADA has a close kinship with type 1 diabetes because LADA patients have autoantibodies commonly associated with type 1. When LADA is suspected, glutamic acid decarboxylase and islet cell antibody testing should be performed. If these tests are positive for autoimmunity, then these patients should be switched to a regimen that includes insulin. If antibody testing is not done, but the patients have clinical features consistent with LADA—including progressive loss of glycemic control that is more rapid than commonly

seen with type 2 diabetes—then insulin therapy should be initiated, even without testing for antibodies associated with type 1 diabetes.

OTHER HYPERGLYCEMIC STATES

Several other hyperglycemic states confound the classification of the diabetes syndrome. These include other endocrine disorders, medications that may increase glucose levels, and the lipodystrophies. These entities need to be considered by every physician who treats diabetes patients to avoid missing an important diagnosis. Specific therapies will not be addressed in detail except for lipodystrophy.

Endocrine disorders

Endocrine disorders including Cushing syndrome and acromegaly are often associated with hyperglycemia. If clinical features of either of these disorders are suggested by the history, physical examination, or diagnostic screens, these diagnoses should be pursued before assuming the patient has only type 2 diabetes. Hyperglycemic management follows the approach used in type 2 diabetes (**Table 2**).[45,46]

Diabetes is also associated with lipodystrophy, endocrine disorders, pancreatic disorders, hemochromatosis, and medications

Several nonimmune pancreatic disorders are associated with diabetes. These include chronic pancreatitis and chronic recurrent acute pancreatitis (from any of multiple causes including genetic, ethanol excess, hypertriglyceridemia), cystic fibrosis, and pancreatic cancer. Usually, the associated clinical history leads to this diagnosis. Historically, glucose management includes the use of insulin.

Hemochromatosis may present only with features of diabetes, but if a family history or associated liver and cardiac disorders suggest this diagnosis, appropriate screening for iron overload and in select cases for the *HFE* C282Y mutation is indicated.[42] Management of hemochromatosis-associated diabetes often requires insulin.

Medication-induced diabetes

Many medications can contribute to hyperglycemia, including glucocorticoids, statins, psychotropic agents, and immunomodulatory drugs.

Both glucocorticoids and immunomodulatory agents likely contribute to the entity now commonly called posttransplant diabetes. The benefits of these agents often outweigh the risks of discontinuing them simply to diminish the hyperglycemia. Tapering antirejection medications is common in posttransplant patients, and remission of diabetes may occur. However, even if there is remission of hyperglycemia, these patients should always be considered as being at increased risk for future recurrence of type 2 diabetes. Hyperglycemic management follows the approach used in type 2 diabetes (**Table 2**).[45,46]

Lipodystrophies

Lipodystrophies are uncommon, with a reported incidence of fewer than 5 cases per 1 million people.[57] Nevertheless, they are important to recognize because the diagnosis may affect the selection of glucose-lowering therapy.

Lipodystrophies are broadly classified as genetic (with associated leptin deficiency) or acquired. Both genetic and acquired forms may have a pattern of general or partial loss of fat. Typical patients with lipodystrophy are described by Araujo-Vilar and Santini[40] and Handelsman et al.[39] In addition to hyperglycemia, lipodystrophy is often associated with moderate to markedly elevated triglycerides. The genetic disorders[40] may be detected with a careful family history that suggests a genetic subtype.

Both genetic and acquired lipodystrophy require a careful physical examination to determine the extent and pattern of subcutaneous fat loss. Detecting some partial lipodystrophies may be more difficult in men than in women because men have greater muscle mass, which makes detection of loss of subcutaneous fat more difficult.

Two partial lipodystrophies deserve comment because they are commonly seen in internal medicine, endocrine, and lipid clinics. Familial partial lipodystrophy is a genetic lipodystrophy with clinical manifestations that may not occur until after puberty, so the diagnosis is often not made until adulthood.[39] Human immunodeficiency virus-associated lipodystrophy is acquired and partial[40] and is usually detected on examination, often in patients who have associated hypertriglyceridemia.

Treatment of hyperglycemia with lipodystrophies often parallels the treatment for

type 2 diabetes and the associated dyslipidemia. However, loss of subcutaneous fat is associated with significant insulin resistance, and an insulin-sensitizing agent such as thiazolidinediones should be considered in the therapeutic regimen.[39] High insulin doses may be required. The use of metreleptin is limited to patients who have the more severe lipodystrophies.[39–41] Thus, a diagnosis of lipodystrophy helps to guide the clinician in the therapeutic considerations for glucose control.

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***Address**: Byron J. Hoogwerf, MD, FACP, FACE, 8972 Huntington Pointe Drive, Sarasota, FL 34238; byronhoogwerf@gmail.com*

REVIEW

CME MOC

Nishant P. Shah, MD
Duke Heart Center; Assistant Professor of Medicine in Cardiology, Duke University School of Medicine, Durham, NC

Haitham M. Ahmed, MD, MPH
AdvantageCare Physicians, New York, NY

W. H. Wilson Tang, MD
Department of Cardiovascular Medicine, Department of Cellular and Molecular Medicine, Critical Care Center, and Transplantation Center, Heart and Vascular Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Familial hypercholesterolemia: Detect, treat, and ask about family

ABSTRACT

Familial hypercholesterolemia is an autosomal dominant disorder that affects the metabolism of low-density lipoprotein cholesterol (LDL-C) through mutations in the gene for LDL receptor (*LDLR*), and less commonly in those for apolipoprotein B (*APOB*), proprotein convertase subtilisin-kexin type 9 (*PCSK9*), and others. Patients with these mutations have elevated plasma levels of LDL-C and, as a result, an increased risk of atherosclerotic cardiovascular disease beginning in childhood, leading to significant risk of illness and death.

KEY POINTS

Indices are available to help practitioners estimate a patient's likelihood of having familial hypercholesterolemia based on lipid values, clinical presentation, and family history. Patients who likely have the disease should have further evaluation considered.

If a patient is found to have familial hypercholesterolemia, family members should be screened for it in a cascading process.

A statin is generally the first-line treatment, and a nonstatin therapy such as ezetimibe can be added. PCSK9 inhibitors should also be considered if adequate LDL-C lowering is not achieved by statins or if the patient is statin-intolerant. Patients with homozygous familial hypercholesterolemia may need LDL-C apheresis.

Dr. Tang has disclosed serving as a consultant for MyoKardia and Sequana Medical.

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FAMILIAL HYPERCHOLESTEROLEMIA is the result of mutations in genes for proteins involved in the metabolism of low-density lipoprotein cholesterol (LDL-C), and is inherited in an autosomal dominant fashion.[1,2] Patients born with it can develop elevated LDL-C and atherosclerotic cardiovascular disease at a young age,[3] which can often be detected in childhood.

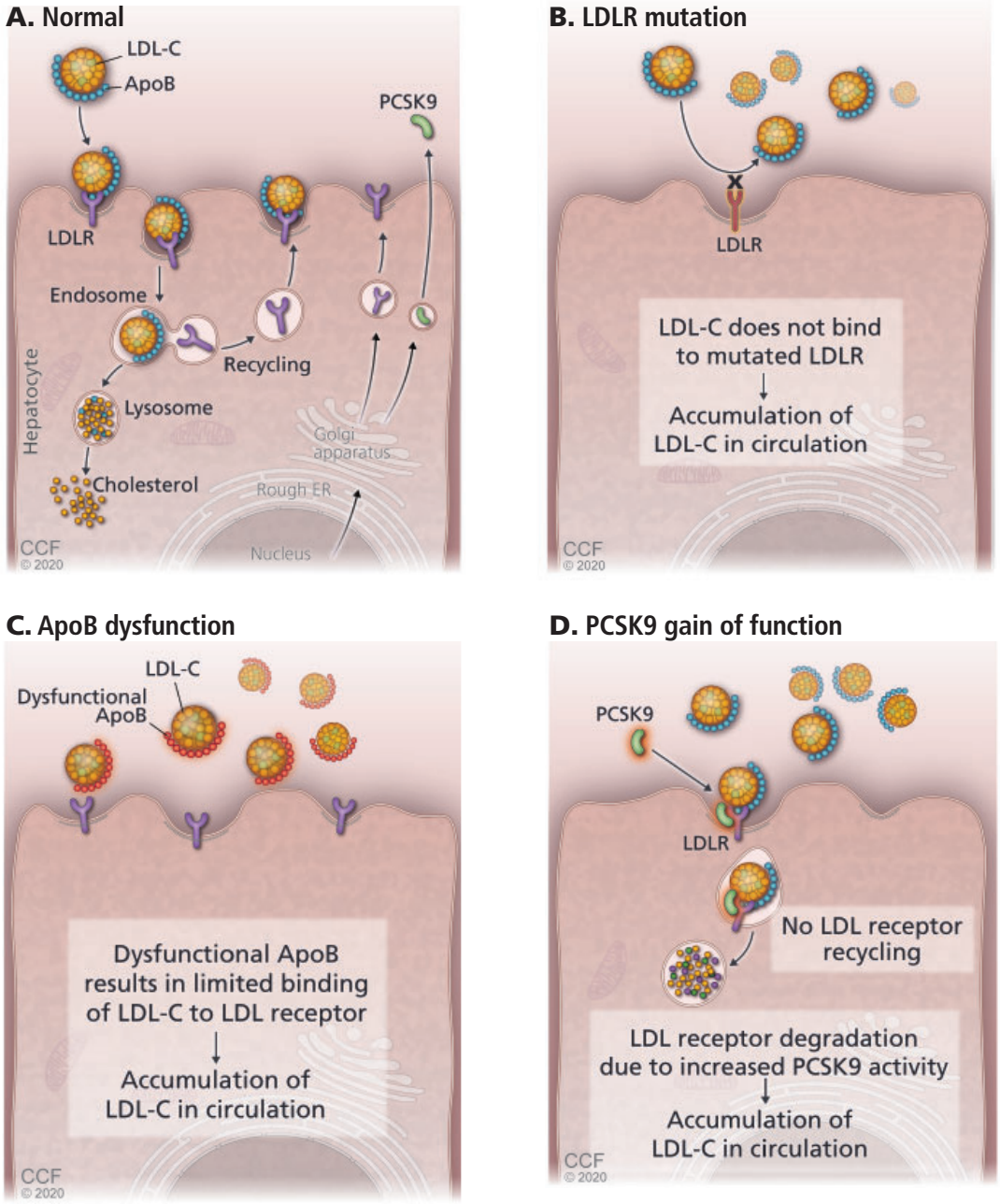
Strategies have been devised to detect the disease early for primary prevention, which is especially relevant now that novel lipid-lowering drugs are available.[4–8] Often, the first opportunity for detection is during a routine checkup with the primary care physician.

Here, we provide an overview of familial hypercholesterolemia for general practitioners, including current diagnostic strategies, treatments, guidelines for management, and avenues for future research.

MUTATIONS IN *LDLR* AND OTHER GENES

In more than 75% of cases of familial hypercholesterolemia, the LDL receptor is defective, owing to mutations in the *LDLR* gene.[9] Less often, the problem is a mutation in a gene for another molecule that interacts with the LDL receptor, such as apolipoprotein B (*APOB*), proprotein convertase subtilisin-kexin type 9 (*PCSK9*), or an unknown gene (**Figure 1**).[2,9]

Because familial hypercholesterolemia is inherited in an autosomal dominant fashion, most patients who have it are heterozygous, possessing 1 normal allele and 1 mutated allele.[10] The prevalence of heterozygous familial hypercholesterolemia is about 1 in 220, based on large genetic studies.[11] Homozygous familial hypercholesterolemia, in which the patient possesses 2 mutated alleles, is much less



Often, the first opportunity for detection is during a routine checkup with the primary care physician

Figure 1. (**A**) Low-density lipoprotein cholesterol (LDL-C) binds to its receptor (LDLR), using apolipoprotein B (ApoB) as its ligand. Defects in LDLR (**B**) or ApoB (**C**) result in less binding of LDL-C, raising LDL-C levels. (**D**) Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to LDLR and escorts it into the interior of the hepatocyte, where it is destroyed, resulting in fewer receptors and higher LDL-C concentrations. Gain-of-function mutations in *PCSK9* raise LDL-C levels.

prevalent, with a frequency estimated at 1 in 300,000.[10,12] Patients with homozygous disease face a worse prognosis.

The prevalence of familial hypercholesterolemia differs across ethnic groups, with higher frequencies of mutations in various parts of the world due to the founder effect. For instance, Finns, French-Canadians, Afrikaners, and Christian Lebanese populations have a higher prevalence of the disease.[13] Racial differences have been shown as well; blacks have a slightly higher prevalence than whites or Hispanics.[14]

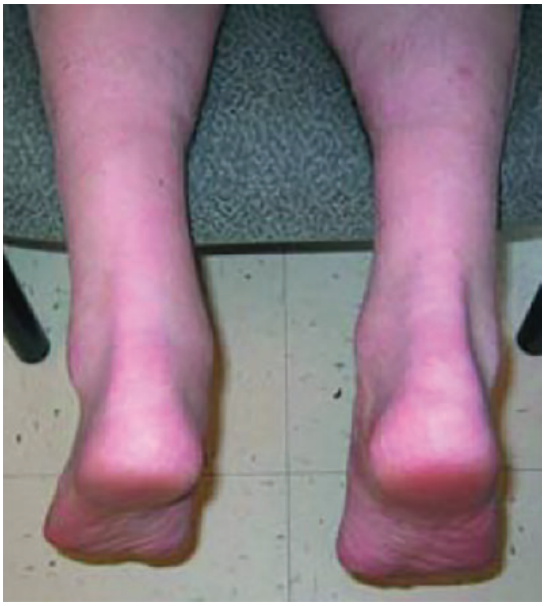


Figure 2. Xanthomas of the Achilles tendons. Note the position used for examination, with the patient kneeling on a chair.

From Sibley and Stone, reference 27.

Although cardiovascular events tend to occur at an earlier age in men than in women, the prevalence of familial hypercholesterolemia is similar between sexes.[4,14]

ELEVATED RISK FROM AN EARLY AGE

Because people with familial hypercholesterolemia have elevated LDL-C levels from an early age, they also begin to have manifestations of atherosclerotic cardiovascular disease early.[3,15–17] Children with familial hypercholesterolemia have greater carotid intimal thickness than unaffected children by age 8.[18] Coronary artery disease is evident in patients with familial hypercholesterolemia from age 17 in males and age 25 in females, and up to 25% of adolescents with familial hypercholesterolemia have coronary artery calcification.[19,20]

A study from Denmark showed an adjusted odds ratio for coronary artery disease of 3.3 in carriers of a familial hypercholesterolemia mutation.[21] Similarly, the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART) found the prevalence of atherosclerotic cardiovascular disease to be 3 times higher in people with familial hypercholesterolemia than in unaffected people.[22]

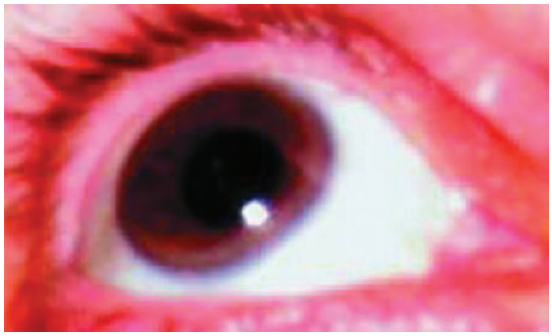


Figure 3. Corneal arcus.

From Sibley and Stone, reference 27.

Clinical atherosclerotic cardiovascular disease is even more accelerated in patients with homozygous familial hypercholesterolemia, in whom the first cardiovascular event usually occurs before age 30.[23] Thus, early diagnosis of familial hypercholesterolemia is essential for risk stratification.

WHEN TO SUSPECT IT

Three sets of clinical criteria have been devised to identify patients with heterozygous familial hypercholesterolemia.[24–26] Each is based on a combination of:

- **Lipid levels,** typically an LDL-C greater than 190 mg/dL
- **Family history** of premature coronary artery disease or familial hypercholesterolemia
- **Clinical history**
- **Physical signs** such as xanthelasma (cholesterol deposits in the skin of the eyelids); xanthoma (deposits in connective tissue in and around extensor tendons—pathognomonic for this disease) (**Figure 2**)[27] and arcus cornealis or corneal arcus (deposits along the corneal border) (**Figure 3**).[27]

The Dutch Lipid Network Criteria

The Dutch Lipid Network Criteria,[24] the most widely used of the 3 sets of criteria, yields a score based on LDL-C level, physical findings, premature cardiovascular disease in relatives, and positive genetic testing if available (**Table 1**). A score higher than 8 makes the diagnosis "definite," as 80% of people in that category were found to have a genetic mutation.[28] One purpose of developing this set of criteria was

Several mutations remain unknown, and not finding a mutation does not exclude the diagnosis

TABLE 1

The Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia

Criteria	Points
Family history	
First-degree relative with known premature atherosclerotic cardiovascular disease (age < 55 in men, age < 60 in women) or first-degree relative with LDL-C > 95th percentile	1
First-degree relative with tendon xanthomas or arcus cornealis, or child under age 18 with LDL-C > 95th percentile	2
Clinical history	
Premature coronary artery disease	2
Premature cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthomas	6
Arcus cornealis before age 45	4
LDL-C levels, mg/dL	
≥ 330	8
250–329	5
190–249	3
155–189	1
DNA analysis	
Functional mutation in the *LDLR*, *APOB*, or *PCSK9* gene	8

Interpretation	Total
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6–8
Possible familial hypercholesterolemia	3–5
Unlikely familial hypercholesterolemia	< 3

From the World Health Organization, reference 24.

to identify patients with familial hypercholesterolemia who did not have a family member with an established diagnosis.

The Simon Broome Registrar criteria

The Simon Broome Registrar criteria,[25] developed in the United Kingdom, also rely on a combination of clinical, physical, and biochemical data (**Table 2**).[13,16] Again, if certain clinical findings are met, a definite diagnosis can be made.

The MED-PED criteria

The Make Early Diagnosis and Prevent Early Deaths (MED-PED) criteria focus more on lipid levels and family history and less on clinical characteristics or genetic testing (**Table 3**).[26] They were developed to be broadly applicable and were found to achieve 54% sensitivity and 98% specificity in detecting heterozygous familial hypercholesterolemia in the general population.[26] The sensitivity improved to 88% when the criteria were used in patients with a first-degree relative with heterozygous familial hypercholesterolemia, 85% in those with an affected second-degree relative, and 81% in those with an affected third-degree relative. Thus, the authors suggested performing biochemical testing of relatives of patients found to have heterozygous familial hypercholesterolemia mutations, a process known as cascade screening.

Which set of criteria is best?

The 3 sets of clinical screening criteria were compared in a retrospective study[29] in 408 patients from 1995 through 2003. None outperformed the others, but when patients deemed to be in the "definite" diagnosis categories underwent genetic testing, the mutation detection rate was as low as 30% to 40%. The authors[29] acknowledged that perhaps not all mutations were tested for, and polygenetic factors may have been overlooked. Regardless, they emphasized that the phenotype (ie, elevated LDL-C value, physical findings, and clinical history) confers enough of a cardiovascular risk to justify treatment, and that negative genetic testing should not stratify patients to lower risk categories.

This notion is endorsed by the International Atherosclerosis Society, which has proposed criteria for severe familial hypercholesterolemia based on LDL-C levels and evidence of subclinical or clinical atherosclerotic cardiovascular disease.[30]

What about homozygous disease?

The clinical criteria do not apply to patients who may have homozygous familial hypercholesterolemia, which is much less common and more serious. However, the diagnosis can be suspected clinically if the patient has very high LDL-C levels (> 500 mg/dL if untreated, or > 300 mg/dL if on maximal lipid-lowering

treatment) and has cholesterol deposits in the first decade of life, especially if both parents have heterozygous familial hypercholesterolemia.[4]

WHAT IS THE PATIENT'S RISK?

The Montreal FH Score[31] predicts cardiovascular risk in patients with familial hypercholesterolemia. It was devised by Paquette et al, based on a study in which they identified age, hypertension, low levels of high-density lipoprotein cholesterol, male sex, and smoking as independent risk factors (**Table 4**).[31] A score higher than 20 points was associated with a cardiovascular risk 10 times greater than a score lower than 20 (odds ratio 10.3, 95% confidence interval 6.7–15.5, $P < .001$). The Montreal FH Score was validated in an independent cohort with familial hypercholesterolemia.[32]

GENETIC TESTING IS THE GOLD STANDARD

Genetic testing is the gold standard for diagnosing familial hypercholesterolemia. Most of the known mutations are in *LDLR*, but *APOB*, *PCSK9*, and potentially other genes involved in LDL-C catabolism can also have mutations. Several mutations remain unknown, and not finding a genetic mutation does not exclude the diagnosis, especially if there is strong phenotypic evidence.[9]

Finding a mutation also has prognostic value. At any LDL-C level, a gene-positive individual carries a higher risk of atherosclerotic cardiovascular disease than does a gene-negative one.[33] The type of *LDLR* mutation also carries its own risk.[34] Thus, if you strongly suspect that a patient has the disease based on clinical diagnostic criteria, then genetic testing can be considered, with appropriate genetic counseling.[35]

Genetic testing may be particularly helpful in younger patients, especially if they have relatives with confirmed familial hypercholesterolemia. Though familial hypercholesterolemia can be diagnosed clinically based on lipid profile, patients with it have a higher burden of lifelong LDL-C exposure, which is likely a reason that gene-positive patients have a higher risk of atherosclerotic cardiovascular disease.

TABLE 2

The Simon Broome diagnostic criteria for familial hypercholesterolemia

Criterion[a]	Description
A	Total cholesterol level > 290 mg/dL or LDL-C > 190 mg/dL in adults (age ≥ 16) Total cholesterol level > 260 mg/dL or LDL-C > 155 mg/dL in children (age < 16)
B	Tendon xanthomas in the patient or in a first- or second-degree relative
C	DNA-based evidence of a mutation in *LDLR, APOB,* or *PCSK9*
D	Family history of myocardial infarction before age 50 in a second-degree relative, or before age 60 in a first-degree relative
E	Total cholesterol > 290 mg/dL in a first- or second-degree relative

[a] "Definite" familial hypercholesterolemia requires criterion C by itself, or criterion A plus B; "probable" familial hypercholesterolemia requires either A plus D, or A plus E.

Information from the Simon Broome Register Group, reference 25.

Genetics may also explain some degree of phenotypic heterogeneity, as more deleterious mutations (*LDLR* null) are associated with higher LDL-C levels and higher cardiovascular risk.[30,36] Moreover, patients with severe heterozygous familial hypercholesterolemia can have LDL-C concentrations that overlap with those of patients who have homozygous familial hypercholesterolemia, and vice versa, leading to alternative therapeutic approaches.[30] Polygenetic factors, gene-environment interactions, and gene-gene interactions can also allow for variations in familial hypercholesterolemia without extreme elevations in LDL-C, making genetic testing even more important for risk stratification.[30]

At any LDL-C level, a gene-positive individual carries a higher risk than a gene-negative individual

Rarely, genetic testing can also help in guiding therapy, as particular mutations (eg, null mutations of *LDLR* in homozygous patients) can make certain therapies ineffective.

CASCADE SCREENING OF RELATIVES

Identifying affected relatives is important so that they can be treated and potentially avoid atherosclerotic cardiovascular disease. Unfor-

TABLE 3

MED-PED diagnostic criteria for probable heterozygous familial hypercholesterolemia

	Closest relative with familial hypercholesterolemia							
	First-degree		Second-degree		Third-degree		None	
	Threshold cholesterol level (mg/dL) in the patient							
Age	Total	LDL-C	Total	LDL-C	Total	LCL-C	Total	LDL-C
< 20	220	155	230	165	240	170	270	200
20–29	240	170	250	180	260	185	290	220
30–39	270	190	280	200	290	210	340	240
≥ 40	290	205	300	215	310	225	360	260

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tunately, many remain unaware of their risk.[37] Thus, screening strategies have been developed in the hope of rapid and cost-effective diagnosis.

Cascade screening in the United States can be challenging, given barriers in the healthcare system

This is primarily done through cascade screening, in which LDL-C measurement, genetic testing, or both are done in consenting relatives of patients (probands) identified with the disease. As more probands are identified, the process repeats itself by targeting more relatives. These strategies have been implemented in many European counties,[38] and data from the SAFEHEART registry have indicated that identifying 9,000 cases of familial hypercholesterolemia in 10 years could prevent 847 coronary events and 203 coronary deaths, and could add 767 quality-adjusted life years.[39]

Cascade screening can be implemented in several ways, with outreach cascade screening in relatives of patients who have:

- A worrisome lipid profile on a routine health screen but no symptoms
- Early-onset atherosclerotic cardiovascular disease and who meet clinical criteria for familial hypercholesterolemia
- Persistently elevated lipid levels despite treatment, and a family history that raises the suspicion of familial hypercholesterolemia.

Genetic testing, when positive, allows very accurate cascade testing. However, genetic testing must follow established recommendations[35] to maximize efficacy and minimize risk.[40] Privacy and ethical issues are also raised, including questions about appropriate informed consent.[40]

In the United States, cascade screening can be challenging due to barriers in our healthcare system.[41] Moreover, privacy policies mandate that the proband make first contact with family members, but the proband may have difficulty locating and getting in touch with them.[41]

Universal cholesterol screening of adults could help identify more people with familial hypercholesterolemia, but this strategy has not been fully implemented or recommended.[42] Further, universal cholesterol screening is more common in adults than in children, whereas we need to diagnose the disease as early in life as possible.

Other strategies are being implemented to identify patients who may have familial hypercholesterolemia. For example, artificial intelligence systems that use machine learning techniques can explore electronic health records, billing codes, and laboratory data.[43] Large-scale DNA sequencing may also help in finding cases that would not be detected.[44] Though these novel techniques are intriguing, whether they would be cost-effective remains unclear.

TREATMENT SHOULD START EARLY

Starting lipid-lowering therapy early is as important as early detection of disease. In untreated heterozygous patients, the first coronary event occurs about 20 years earlier than in the general population.[45] In untreated homozygous patients, the prognosis is even worse, with the first event often occurring in childhood.[46]

The type of mutation also affects treatment response. For instance, *LDLR* mutations can result in either a defective but somewhat functional LDL receptor or one with no functionality (null *LDLR*).[35] Thus, cases of null *LDLR* mutations are more likely to be medically refractory, as lipid-lowering therapy often relies on somewhat functional LDL receptors.[35]

Lipid-lowering therapy in familial hypercholesterolemia can be with statins, nonstatin drugs (eg, ezetimibe, PCSK9 inhibitors), and, rarely, LDL-C apheresis. Lifestyle modifications such as dietary changes and exercise should accompany any medical therapy, even though they reduce LDL-C only modestly in adults with this disease.[47]

Statins are the first-line treatment

Reducing LDL-C levels is the primary goal, and high-dose statins are the first-line treatment. Statins inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, resulting in decreased cholesterol production and increased LDL receptor expression on the surface of hepatocytes, which further reduces plasma LDL-C.[9]

Statin therapy should be started as soon as possible to help prevent cardiovascular events. In homozygous familial hypercholesterolemia patients, statin therapy is often started in the first decade of life.[23] Of note, however, homozygous patients are more likely to have null *LDLR* mutations, which make statin therapy less effective.

Thanks to statin therapy, the prognosis for patients with familial hypercholesterolemia has improved in the last 30 years.[48,49] In a randomized controlled trial in heterozygous patients, atorvastatin 80 mg lowered LDL-C levels by 50%.[49] In another study,[48] statin therapy reduced the 10-year risk of atherosclerotic cardiovascular disease from 60% at baseline to 10% (adjusted hazard ratio 0.18, 95% confidence interval 0.13–0.25). With statin therapy, the risk of atherosclerotic cardiovascular disease in heterozygous patients was only slightly higher than in the general population (6.7 vs

TABLE 4

The Montreal FH score to predict cardiovascular risk in familial hypercholesterolemia

Cutoff	Points
Age	
≤ 21	0
22–28	4
29–35	8
36–42	12
43–49	16
50–56	20
57–63	24
> 63	28
High-density lipoprotein cholesterol, mg/dL	
≤ 23	12
23–34	9
35–46	6
47–58	3
> 58	0
Hypertension	
Yes	2
No	0
Smoking	
Yes	1
Never	0
Sex	
Male	3
Female	0

A score > 20 is associated with a 10-fold higher cardiovascular risk.

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4.1 events per 1,000 patient-years).[48] Therefore, statin therapy has proven to be highly effective in terms of cost, morbidity, and mortality.[4,48,49]

Nonstatin therapies can be added

In cases in which statins do not effectively lower LDL-C, other lipid-lowering drugs can be considered as adjunctive therapy. The CASCADE, SAFEHEART, and other registries suggest that many patients with familial hypercholesterolemia cannot achieve their lipid goals with statins alone. Up to 50% require a second-line agent, and 20% require a PCSK9 inhibitor.[50]

Ezetimibe is a selective cholesterol absorption inhibitor that blocks uptake of cholesterol at both the enterocyte lumen and the hepatobiliary system.[9] This leads to depletion of cholesterol stores and increased expression of LDL receptor, which further reduces plasma LDL-C.[9] In patients already taking a statin, ezetimibe can further reduce LDL-C by 15% to 20% and is generally well tolerated in combination with statin therapy.[1,51] National and international guidelines suggest ezetimibe as a second-line agent when LDL-C goals are not met with statins alone.[50]

Thanks to statins, the prognosis in familial hypercholesterolemia has improved in the last 30 years

Combination therapy with ezetimibe and simvastatin was shown to significantly reduce the risk of atherosclerotic cardiovascular disease events after myocardial infarction.[52] Though this study did not specifically target familial hypercholesterolemia patients, it further supports the benefit of lowering LDL-C in general in all high-risk populations.

Nonstatin therapies such as bile acid sequestrants, niacin, and fibrates are not well studied in patients with familial hypercholesterolemia.

Bile acid sequestrants form insoluble complexes of bile acid and cholesterol molecules that avoid capture by enterocytes.[4,9] These complexes are then excreted. With less substrate for LDL-C, plasma levels can be decreased by 13% to 19%.[4] Unfortunately, these medications are not well tolerated, which limits their use.

Niacin, also known as vitamin B_3 or nicotinic acid, reduces free fatty acid mobilization from adipose tissue, which impairs the liver's ability to synthesize cholesterol and triglyceride-containing particles.[9] Unfortunately, the medication is not well tolerated and has not shown clinical efficacy in large randomized clinical trials in patients without familial hypercholesterolemia.[53,54]

Fibrates are typically used to lower triglyceride levels. Caution must be used when combining them with statins, as they can cause myopathies and other drug interactions.[1]

Newer agents have been developed that are currently reserved for homozygous familial hypercholesterolemia patients, who commonly have null *LDLR* mutations.

Lomitapide is a microsomal triglyceride transfer protein inhibitor that prevents assembly of lipids onto proteins.[9]

Mipomersen is an antisense oligonucleotide that binds *APOB* mRNA and further decreases LDL-C generation in the liver.[3]

Both of these medications are poorly tolerated due to adverse effects, and thus they are reserved for patients at very high risk of atherosclerotic cardiovascular disease, such as those with homozygous familial hypercholesterolemia.[9]

PCSK9 inhibitors

Perhaps the most effective therapies in reducing LDL-C independently and in combination with statins are PCSK9 inhibitors.[8] The US Food and Drug Administration and the European Medicines Agency have approved 2 of these medications—evolocumab and alirocumab.

PCSK9 inhibitors are monoclonal antibodies that target circulating PCSK9, which normally degrades LDL receptor. More LDL receptor is therefore recycled to the hepatocyte surface and is available to remove more LDL-C from circulation.[55]

These medications are recommended when traditional lipid-lowering therapy cannot effectively lower LDL-C.[55] They lower LDL-C levels by another 50% to 60% in addition to the reduction achieved by statins.[56,57] They have also been shown to decrease LDL-C levels modestly (up to 20%) in patients with homozygous familial hypercholesterolemia who have almost no LDL receptor activity.[58]

Overall, these agents reduce major cardiovascular events in patients at high risk of atherosclerotic cardiovascular disease, like

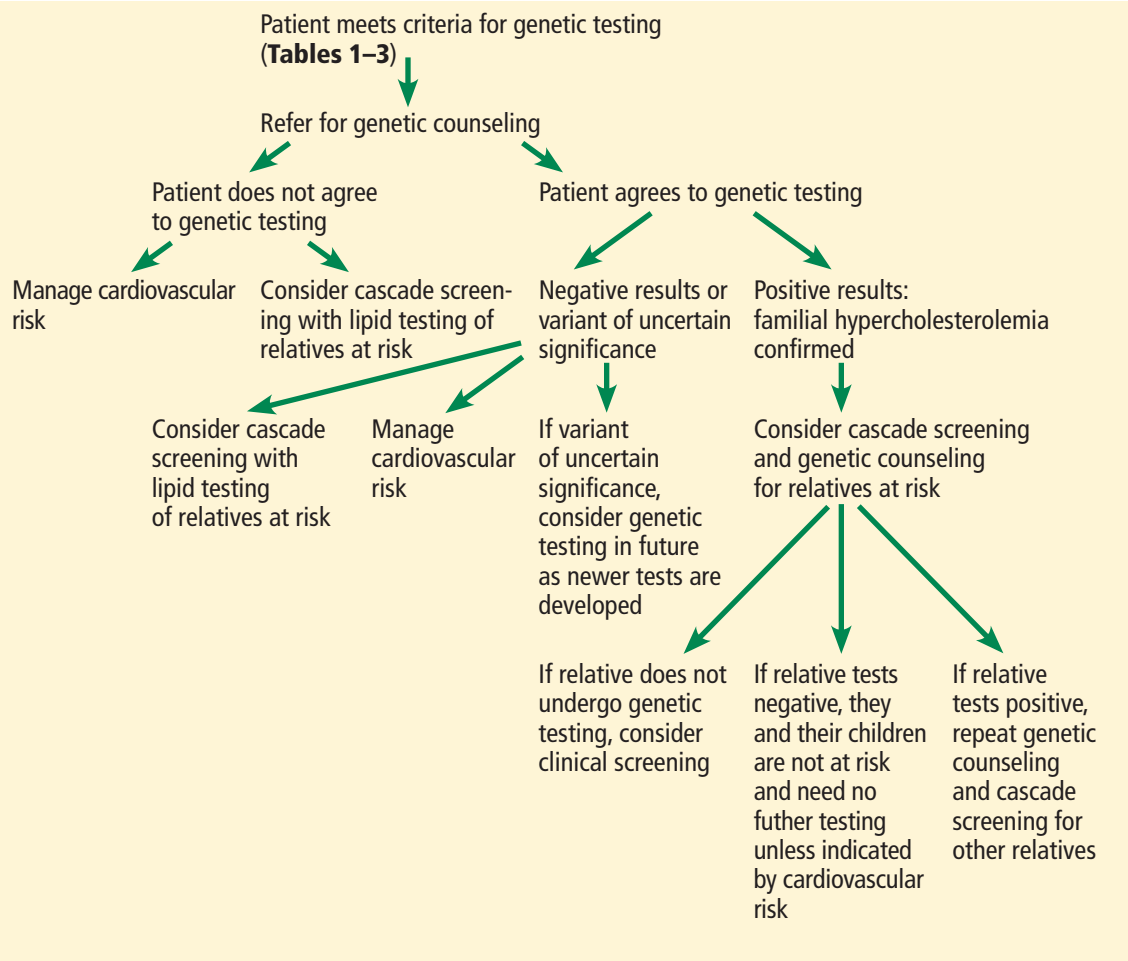

Figure 4. Algorithm for cascade screening.

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those with familial hypercholesterolemia.[59,60] Further, they are generally well tolerated, but unfortunately, their cost can pose a barrier to both patients and providers.[61] However, approvals from insurance companies are increasing, given the available evidence noted above.

LDL-C apheresis

LDL-C apheresis involves extracorporeal filtering of lipoproteins, using an indwelling venous catheter, either weekly or twice a week.[44] It is usually reserved for patients at extremely high risk in whom medical therapies have been ineffective, or in those with homozygous familial hypercholesterolemia who have a null *LDLR* mutation and no response to conventional lipid-lowering therapy.[44] In fact, it is one of the only therapies shown to prolong survival in this group of patients.[62]

Factors to consider before referring patients for apheresis are cost, problems with venous access, and time. Despite its benefit in homozygous familial hypercholesterolemia, there is still a scarcity of evidence on its use, precluding standardized guidelines and limiting its use to a case-by-case basis.[63]

WHAT DO THE GUIDELINES SAY?

Several professional societies have published guidelines to help providers diagnose and manage familial hypercholesterolemia.[6,35,64–66]

American professional societies generally agree on considering genetic testing for familial hypercholesterolemia in patients with elevated plasma LDL-C (usually > 190 mg/dL [> 4.9 mmol/L]), a family history of familial hypercholesterolemia, or who meet clinical

PCSK9 inhibitors lower LDL-C by another 50% to 60% in addition to the reduction achieved with statins

criteria.[35,65–67] The National Lipid Association[64] and International Familial Hypercholesterolemia Foundation[65] also recommend cascade screening when a mutation is identified (**Figure 4**).[35]

For management, the American guidelines recommend lifestyle modifications in addition to lipid-lowering therapy.[24,35,65,66] First-line drugs for patients with suspected familial hypercholesterolemia are high-intensity statins, which have class I recommendation (evidence or general agreement that the treatment is beneficial, useful, and effective) and a level of evidence of B-R (moderate, derived from 1 or more randomized controlled trials or meta-analyses of moderate-quality randomized controlled trials).[50, 65–67] The general consensus is that the initial LDL-C value should decrease by at least 50% in primary prevention settings. Alternative lipid-lowering therapies can be added if this goal is not reached, with the preferred second-line agent being ezetimibe, which has a class IIa recommendation (the weight of evidence or opinion is in favor of usefulness or efficacy), and a level of evidence of B-R.[50]

If patients strongly suspected of having familial hypercholesterolemia are on maximally tolerated statin therapy and ezetimibe and still have an LDL-C level of 100 mg/dL or higher or are statin-intolerant, then PCSK9 inhibitors can be considered (class IIb recommendation, level of evidence B-R).[50] In secondary prevention cases, LDL-C goals should be 70 mg/dL or less, according to the 2018 American College of Cardiology and American Heart Association cholesterol guidelines, and 55 mg/dL or less according to the American Association of Clinical Endocrinologists and American College of Endocrinology (recommendation grade A, best level of evidence 1 [strong evidence]).[66]

These recommendations were primarily aimed at those with heterozygous familial hypercholesterolemia. However, similar treatment algorithms exist for homozygous familial hypercholesterolemia. Childhood diagnosis is essential, and there are lower thresholds for LDL-C apheresis.[65,66] Referral to specialized centers for familial hypercholesterolemia should be strongly considered as soon as a diagnosis of heterozygous or homozygous familial hypercholesterolemia is established to aid in further screening, risk stratification, and treatment.

CALL FOR EARLIER DIAGNOSIS

Familial hypercholesterolemia is a genetic disease process that is associated with significant morbidity and mortality. The US Centers for Disease Control and Prevention has designated familial hypercholesterolemia as a tier 1 genomic application, indicating that it imposes a significant public health burden.[67] Thus, early diagnosis and treatment are essential to help reduce the burden of cardiovascular disease in these patients.

Unfortunately, a large percentage of people remain undiagnosed and at risk of cardiovascular events.[68,69] Efforts are being made to identify patients earlier, through cascade screening, genome-wide DNA sequencing, or screening algorithms in large electronic health records.[69] Earlier diagnosis should increase understanding of the disease and allow collaborations across specialties as we work to improve our care of familial hypercholesterolemia.

The Familial Hypercholesterolemia Foundation at www.thefhfoundation.org provides resources for patients and families.

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***Address**: Nishant P. Shah, MD, Duke Heart Center, 234 Crooked Creek Parkway, Suite 540, Durham, NC 27713-8507; nishant.shah@duke.edu*

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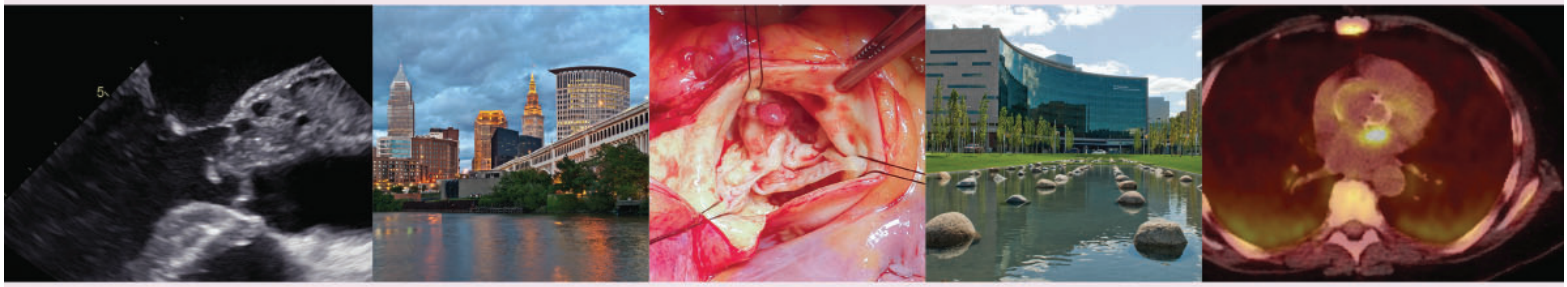

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