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Hospitalist Edition

Featured Employer Profile

TEAMHealth
Physician Mentorship: Why It’s Important, and How to Find and Sustain Relationships

Mentorship is a key factor in promoting and maintaining fulfillment in medical practice. Senior colleagues who share your clinical, research, administrative, or community service interests should be approached early in your formal training. An open and honest dialogue can be instrumental in setting your professional goals, defining its trajectory, and learning how to overcome barriers by adopting successful strategies.

—John A. Fromson, MD

By Bonnie Darves

Most physicians who make their way into satisfying practice careers in a specialty they enjoy — and especially those who also end up in leadership roles — are usually quick to point out to their younger colleagues that they received some help, perhaps even a whole lot of assistance, along the way. Almost invariably, these physician success stories usually have a common thread: an important mentor, or possibly more than one key mentor, whose guidance proved invaluable.

In an era when it’s easy to network and seek guidance online in pretty much any area of one’s life, the notion of the traditional physician-mentor-mentee relationship carried out over a series of regularly scheduled formal in-person meetings and the occasional phone conversation might seem almost quaint. It isn’t, and such relationships might be more important now than in the past because the in-touch-and-constantly-connected online environment doesn’t necessarily foster or sustain the deep, candid exchanges that characterize good mentor-mentee interactions.

Anne Pereira, MD, MPH, assistant dean for curriculum at the University of Minnesota Medical School, thinks that some physicians in training fail to recognize the value of establishing and cultivating relationships with mentors. “Absolutely, in-person mentorship remains fundamentally important in medicine, because a lot of mentorship is about developing a relationship that’s close enough that your mentor wants to support you,” Dr. Pereira said. “Unfortunately, I think that the value of having mentors is probably underestimated by many trainees.”

One reason, she points out, is that many young people today who end up in residency have never worked because they have been on a fast track. They’re essentially high-achieving, highly driven professional students who
have been “on a fairly regimented pathway,” she explains, “and they haven’t reached a point where there are multiple pathways they could take.”

When physicians do get to that juncture, having an established mentor relationship might make the difference between a good, thoughtfully considered decision and a poor one later regretted, longtime physician mentors say. Ideally, that relationship — regardless of the logistics of how the parties meet and how frequently they connect — is a deep one predicated on two-way trust and defined objectives.

“In mentorship, I think anything that leads to a mutually beneficial relationship and the accomplishment of shared goals is fair game, but it’s definitely helpful to meet in person,” said Jennifer Best, MD, associate dean for graduate medical education at the University of Washington in Seattle. “Social media and the online universe can present a false sense of depth, and I think that we sometimes present different ‘selves’ in that environment.”

If there is one absolute prerequisite for a successful mentor-mentee relationship, it is a commitment to candor, according to Nathaniel Scott, MD, director of the combined emergency medicine/internal medicine residency program at Hennepin County Medical Center in Minneapolis. “There has to be some degree of personal connection, even in the most formal mentor mentee relationship, and that both parties must be invested in it and honest if it is going to provide a benefit,” he said. “I think what the local relationship offers over a remote or online one is that your mentor will be more aware of the circumstances you’re in and the issues you are confronting on a more intimate level.”

To look at how young physicians can identify mentors and ultimately thrive in those relationships, NEJM CareerCenter recently spoke with physicians who have served as mentors or benefitted from the guidance that mentors have given them — or both — to obtain their perspectives on key issues.

When should physicians start looking for a mentor, and what’s the best way to go about that?

“Ideally, people should start looking for a formal mentorship program when they’re looking for a residency program. Especially in a large program, having some help finding a mentor is important because it’s difficult to get your feet under you, and get to know the institution and individuals well enough to reach out on your own. I think that mentorship should be an important part of the culture in training programs.”

— Anne Pereira, MD, MPH, University of Minnesota Medical School

“The most important thing is to just start connecting with people in your institution, anyone — you can’t exist in a vacuum. You can do this without necessarily going out and looking for a mentor, by asking someone you admire for advice on a research project, for example, or guidance on how to publish a paper. Start with a specific request, and often, these exchanges will grow organically into a relationship. It’s also helpful to reach out to national physician organizations that provide mentor services on a group or individual level.”

— Chemen M. Neal, MD, assistant professor of clinical obstetrics and gynecology, Indiana University School of Medicine; mentor chair, American Medical Women’s Association

“All physicians should seek mentors as early as possible, and having a mentor when starting training is especially beneficial for international medical graduates [IMGs], because of the cultural challenges they might face. That initial mentor, ideally, should be a successful physician from the IMG physician’s country – whether the mentor is on the program faculty or not. It’s important for hospitals and health systems to help IMGs make those connections, but professional societies can also be helpful.”

— Thomas Norris, MD, board member, Educational Commission for Foreign Medical Graduates and former chair of the American Board of Medical Specialties; former vice dean for academic affairs, University of Washington
“I think the majority of mentor relationships today are informal. By that I mean that you don’t go ask someone, ‘Will you be my mentor?’ I don’t think I’ve ever said that out loud. Instead, look for someone you admire who is ahead of you in the field, or in a position that you might envision for yourself, and establish a relationship by asking a specific question. Then later, ask if that person will grab some coffee with you sometime.”

— Fatima Fahs, MD, dermatology resident, Wayne State University; budding mentor

**What qualities or traits should physicians look for in a mentor?**

“A good mentor is someone who says, ‘How can I help you succeed?’ and truly wants you to succeed. A lot of people still think that physician mentorship is hierarchical, but it isn’t — and shouldn’t be. When physician mentorship is done well, for the right reasons, the mentor-mentee relationship is a partnership.”

— Susan Reynolds, MD, PhD, president and CEO, The Institute for Medical Leadership

“It’s important to look for mentors who can connect with you on a one-to-one basis and who will inspire you and also give you a pat on the shoulder. It shouldn’t be about idolization; you want someone who will celebrate you as an individual, not intimidate you, and someone who will also help you figure out how to overcome roadblocks.

I’ve always found the best mentors to be people who fill up my tank a bit to give me more energy to meet the next milestone.”

— Joseph Vercellone, MD, internal medicine resident in Royal Oak, Michigan, who previously worked in the film and information technology industries

“Start by looking for physicians you admire for their expertise or their skills, who are willing to give you good advice. Also look for people who you see as good people, as models for how you would like to lead your life.”

— Janis Orlowski, MD, chief health care officer, Association of American Medical Colleges

“How many mentor relationships should young physicians try to establish?”

“Most of us benefit from having at least a few mentors — a clinical mentor, a research mentor, and an overall career mentor. They don’t all have to be in your field. I think it’s helpful to have a personal mentor, too, someone you bond with who’ll check in and ask you how you’re doing and whether you’re getting enough sleep.”

— Dominique Cosco, MD, associate internal medicine program director, Emory University, Atlanta

“Physicians absolutely need more than one mentor, maybe not in the beginning but definitely toward the end of residency as they start looking for their first job. There’s no perfect single mentor, so I think it’s helpful to create a quilt of mentors — a mentor who can help you procedurally, once who can help you with career planning, and another mentor for life planning.”

— Dr. Pereira
How should young physicians approach about the issue of expectations in a mentor-mentee relationship, and do they even need to address that formally?

“It’s important to make the expectations somewhat explicit from the start. For example, after a first meeting, you might ask the potential mentor if it’s OK to meet for coffee every few months. And if the person says, ‘sure,’ the mentee should reach out to set up the next meeting. After the relationship is established, there should be expectations set about what the mentor and the mentee will do, and by when, and what both are seeking from the meetings.”

— Nathaniel Scott, MD, director, combined emergency medicine/internal medicine residency, Hennepin County Medical Center, Minneapolis

“The physician who identifies a potential mentor should be direct, and say, ‘I’d like you to be one of my career advisors.’ If that person agrees, the two should set expectations about the kind of communication that will occur and how often, and when the mentor will check in to see how things are going. It’s important to set out the expectations of the exchange, because if one party has higher expectations than the other, that could be strain the relationship.”

— Jennifer Best, MD, associate dean for graduate medical education, University of Washington

“I think that expectations can be fluid at the start, but as the relationship develops, the parties should set goals and establish what the mentee wants to work on and what he or she will bring to the meeting. It’s important that there be a timeline for goals or projects.”

— Dr. Cosco

What should physicians be sure to do, or avoid doing, when they're seeking a mentor or working with one?

“Frame your request by telling the person the concrete thing(s) you are interested in, and be specific. One of my pet peeves is when I receive an email that reads ‘Hello, Dr. Fahs. I am interested in dermatology. What advice do you have?’ The right way would be: ‘Hello, Dr. Fahs. I am interested in dermatology. Do you have any advice on how I can obtain a research project in medical school when I don’t have a lot of clinical experience?’”

— Dr. Fahs

“It’s very important to be honest with yourself and with your mentor about the kind of help you’re seeking or what you’re struggling with. Be willing, once the relationship is established, to ask for feedback on what you could do better, and then try not to be defensive, because that could damage the relationship. That honesty should be on both sides. Mentors should be open in sharing the things they didn’t do right in their careers.”

— Joshua Corsa, MD, trauma surgeon who trained at Orlando Regional Medical Center and is doing a critical care fellowship at Harborview Medical Center in Seattle

“Do your homework before you approach your mentor with a question, and don’t use your mid-career mentors or senior faculty member to obtain information that you can get online. Go to your mentor with those more nuanced questions where their expertise and experience will enable you to understand things in a way that you couldn’t by just reading about it.”

— Dr. Pereira

“Prepare well for every meeting with your mentor, and remember that every good mentor is looking for a mentee who is passionate, devoted to the field, and diligent. Because unless the relationship is also gratifying to the mentor, that mentor won’t want to stay in it. Keep in mind that your mentor is very busy, and he or she needs to have a reason to devote that time to you.”

— Nitin Aggarwal, MD, neurosurgeon trainee-PGY 4, University of Pittsburgh; American Association of Neurological Surgeons resident advisor
What should physicians do if they’re in a mentor relationship that isn’t working out?

“During training, you only have so much bandwidth. If the relationship isn’t a good fit, let the mentor know that you're thinking about going in a different direction. Thank the person for the guidance so far, and say, ‘I hope you're willing to stay in my life in an advisory capacity.' It’s important to go out on a positive note.”

— Dr. Best

“Most of the time when mentor arrangements aren't working, things tend to fall off naturally. If it's a mismatch of expectations — one person wants to meet more frequently than the other — that should be addressed in a way that allows the two parties to just move on.”

— Dr. Scott

“If the chemistry [doesn’t] feel right when you start talking or meeting, find someone else. Working with a mentor is a little bit like dating; if you don’t connect early on, it's probably a relationship that's not going anywhere.”

— Dr. Norris

Did you find this article helpful? What other topics would you like to see covered? Please send us an email to let us know what you thought at resourcecenter@nejm.org.
Longtime recruiter Regina Levison, president of the national firm Levison Search Associates, agrees that the geographic preference statement is a vital piece of information that should appear early in the letter. “The geographic ‘connection’ to the opportunity’s location is the most important message you can include — whether it’s because you grew up there, have relatives in the region, or simply have always dreamed of living or working there,” Ms. Levison said. “Health care organizations today are not just recruiting to fill a specific opportunity; they are recruiting for retention.” As the health care delivery system changes to incorporate accountable care organizations and quality focused reimbursement, organizations are seeking physicians who will “stay around” to help meet long-term organizational objectives.

Craig Fowler, president of the National Association of Physician Recruiters (NAPR), and vice president of recruiting and training for Pinnacle Health Group in Atlanta, urges residents to include at least an introductory cover letter or note with their CV, even when it’s not requested. In his experience, 8 out of 10 physicians who express initial interest in a position don’t take the effort to write a letter unless asked.

“The cover letter really is a differentiator, and even though a recruiter will always look at your CV first, the letter is nice to have. I often feel that it gives me a sense of the physician — a good letter can make the physician come to life,” Mr. Fowler said. He enjoys, for example, learning about the physician’s personal interests and family, in addition to what he seeks in a practice opportunity.

Peter Cebulka, director of recruiting development for the national firm Merritt Hawkins, agrees that the cover letter can provide information that isn’t appropriate in a CV but could be important to a hiring organization. “The letter gives you a chance to talk about your professional goals, or why you’re committed to a particular area or practice setting,” Mr. Cebulka said. It can also highlight something compelling about the physician’s residency program that the recipient might not know.

If there are gaps in the CV that are not sensitive in nature, and therefore don’t require a phone conversation, that information should be included in the letter. “It’s important to briefly explain gaps because your application might be passed over if you don’t,” Mr. Fowler said.

Jim Stone, co-founder and president of The Medicus Firm, a national physician search company, offers helpful guidance on incorporating a career objective in the cover letter. “You may want to include a career objective or job search goals, but be careful not to be too specific or you may rule yourself out of consideration,” he advised. “Therefore, if there is one goal that really sums up your search, or some objective that is a must-have for you under any circumstances, it would be okay to include that.”

On another note, Mr. Stone urges physicians to include brief examples of any soft skills, such as communication, teamwork, technological aptitude, leadership, or problem solving.

Format and structure: short and targeted works

While there are no rules per se about a cover letter’s length or content, there are general guidelines for what works best and is likely to be well received. (See “Cover letters: What to do, what to avoid” section at the end of this article.) Dr. Tysinger, who counsels residents and practicing physicians on preparing CVs and cover letters, and frequently presents on the topic, recommends a single-page, three-paragraph format delivered in a professional, business letter layout, in simple language. Following is his basic guidance on the letter’s structure:

• First paragraph: Introduce yourself and state why you are writing — whether that is to be considered for a specific position, to express general interest in joining the organization, or the recommendation of a colleague.

• Second paragraph: Provide brief details about yourself and why you are interested in the opportunity and the location. Note any professional connections to the opportunity or organization, and any special skills or interests, such as management or teaching.

• Third paragraph: Thank the recipient for the opportunity to apply and for reviewing your CV, and end the letter with a statement indicating that you look forward to hearing from the recipient soon.

Other sources agreed that cover letters should not exceed one page, unless special circumstances dictate an extra paragraph or two. In that case, a two-page letter is acceptable. Ms. Levison advised briefly summarizing education and training in the second paragraph, and if it’s the physician’s first opportunity search, stating briefly why he became a physician.
It's best to avoid going into extensive detail about personal interests or extracurricular pursuits. That could give the recipient the impression that the physician is more concerned about lifestyle than medical practice.

**Professional tone, error-free content are musts**

It should go without saying that the cover letter must be professionally written and free of spelling or grammatical errors, but unfortunately, that's not always the case. All of the recruiters interviewed for this article have received cover letters that are poorly written or, in some cases, replete with misspellings; all agreed that an error-riddled letter could prevent its writer from being considered for an opportunity regardless of her or his qualifications.

Of course, word processing programs include spell-checkers and, usually, some grammar-checking functionality. That's helpful, but it isn't sufficient vetting to ensure the letter is in excellent shape. Because of the letter's potential importance, physicians should have several trusted individuals — on the professional and personal side — review the document, including a professional editor, if warranted. “If writing isn't your strong suit, or English isn't your first language, do get professional advice before you finalize the letter,” Mr. Cebulka recommends.

Ms. Levinson offers pointed advice regarding double-checking for errors. “Are there any typos or mistakes that would make the new organization question your ability to keep accurate records?” she said. It’s worth noting that some recruiting firms offer assistance with cover letter writing, but it’s best not to count on that service.

Striking the right tone in the cover letter can be somewhat challenging when the resident doesn’t have a good sense of the organization offering the opportunity. Some hospitals or groups are very formal, and therefore expect to receive formal communication. Others might be somewhat casual, from the standpoint of their culture, and therefore less inclined to bring in a physician who comes across as stiff, even if she isn’t. For these reasons, it’s smart to research the hiring entity to the extent possible before finishing the letter. The group’s website or the health system’s physician portal are good starting places to gauge the culture, but a discussion with a physician who practices there, happily, also can be helpful.

Ideally, the letter’s tone should be professional but friendly, and should sound like its writer, and not like a cookie-cutter form letter. “The letter should be professional and warm, and the tone should also reflect how you would communicate with patients and staff,” Ms. Levinson said.

“A little colloquialism is OK, if it shows your personality,” Mr. Fowler maintains, provided the overall tone remains professional.

The sources concurred that the cover letter is not the forum for including a laundry list of the physician’s position parameters, or for negotiating compensation or other potential contract terms. Physicians in a highly recruited specialty might mention required equipment or infrastructure, if the lack of those items would preclude further discussion. But for the most part, those specifics should be left for an on-site interview.

“If the parameter is a potential deal-breaker, you can mention it, but avoid sounding inflexible,” Mr. Cebulka advised. That means not setting limits on the amount of call, or number of night shifts or weekends, for example. Those details can be discussed and possibly negotiated later.

Very important parameters should, however, be provided to the recruiter outside the context of the cover letter if such detail is requested. That’s especially important if the recruiter will introduce the physician to multiple opportunities.

“If you’re in a highly recruited specialty, there will be plenty of opportunities. But it’s helpful for recruiters to know what you’re absolutely looking for, so that you don’t waste your time or theirs,” Mr. Cebulka said.
Cover letters: What to do, what to avoid

The sources who contributed to this article offered these additional tips on what physicians should do, or not do, when they craft their cover letters.

Do:

• Address the cover letter to an individual physician, practice administrator, recruiter, or other individual as the situation warrants, and not “to whom it may concern.”

• Be upbeat and positive. Ensure that the letter’s tone reflects your excitement about medicine, and that it reflects the way you would speak in an in-person interview.

• Include letters of reference with the cover letter if you’re looking for a fellowship or are formally applying for a specific position.

• Close the letter with a call to action if it’s an ideal opportunity (and likely a popular one). Let the recipient know that you will call in a few days to follow up, and indicate when you would be available to meet in person. It doesn’t hurt to state the best ways to reach you.

Avoid:

• Don’t sound desperate or beg for the job, even if it’s the perfect opportunity or you are worried about securing a position.

• Steer clear of “selling” yourself or making claims about why you would be the absolute best candidate. Instead, let your credentials and references make the case for you.

• Avoid sarcasm in any context, and generally steer clear of humor, unless you know the person to whom the letter is addressed very well.

• Don’t disparage individuals, programs, or institutions if you have had a negative experience somewhere — regardless of the reason.

From the Department of Rheumatology, Université Paris Sud, INSERM Unité 1184, Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique–Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre, France (M.J.), and the Rosalind Russell–Ephraim P. Engleman Rheumatology Research Center, Departments of Medicine and Orofacial Sciences, Université Paris Sud, Le Kremlin Bicêtre, France (L.A.C.). Address reprint requests to Dr. Criswell at the Rosalind Russell–Ephraim P. Engleman Rheumatology Research Center, 513 Parnassus Ave., Rm. 5B07, University of California at San Francisco, San Francisco, CA 94143, or at lindsey.criswell@ucsf.edu.

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Clinical Practice

Primary Sjögren’s Syndrome

Xavier Mariette, M.D., Ph.D., and Lindsey A. Criswell, M.D., M.P.H., D.Sc.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various stages is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

A 52-year-old woman presents with a 2-year history of an extremely dry mouth. She has difficulty swallowing dry food and has to drink water throughout the night. She also reports having episodes of fatigue and pain in her hands and wrists, particularly in the morning. Ten years before presentation, ocular discomfort and dryness caused her to discontinue the use of contact lenses. She has had several episodes of swelling of the parotid glands during the past 2 years. The physical examination reveals dry mouth, purpura purpuric on the legs, three swollen joints, and bilateral swelling of the parotid glands. Laboratory studies reveal lymphocytopenia (850 cells per cubic millimeter) without other abnormalities in the blood count, a serum creatinine level of 1.6 mg per deciliter (140 μmol per liter; as compared with 0.7 mg per deciliter [60 μmol per liter] 1 year earlier), polyclonal gammopathy, positive rheumatoid factor, the presence of antinuclear antibodies (including antibodies against Sjögren’s syndrome–related antigen A [anti-SSA antibodies]), and a low C4 level without cryoglobulinemia. How should this patient’s case be managed?

Primary Sjögren’s syndrome is a common systemic autoimmune disease, with a female-to-male predominance of 9:1 and peak incidence at approximately 50 years of age.1 The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain. These three symptoms are present in more than 80% of the patients with this disease and have a major effect on quality of life, primarily because of disabling fatigue, with associated loss of work productivity.2 This condition may occur in isolation or in association with organ-specific autoimmune diseases, such as thyroiditis or primary biliary cirrhosis or cholangitis, in which case the disease is referred to as primary Sjögren’s syndrome. In contrast, the term secondary, or associated, Sjögren’s syndrome has been used when the disease occurs in association with another systemic autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, or dermatomyositis.

On the basis of formal criteria for the diagnosis,3 which require the presence of immunologic abnormalities (the presence of serum anti-SSA antibodies or focal lymphocytic sialadenitis on biopsy of labial salivary glands), the estimated prevalence is 0.3 to 1 per 1000 persons.4 The major diagnostic challenge relates to the fact that mouth and eye dryness, limb pain, and fatigue are very common in the general population and may be associated with fibromyalgia or other pain syndromes, whereas primary Sjögren’s syndrome is relatively rare. Although the
recently validated American College of Rheumatology (ACR)-European League against Rheumatism (EULAR) criteria were designed for the purposes of classification,1 they may also be useful in establishing a diagnosis of primary Sjögren’s syndrome in the context of these common symptoms (Table 1).

SYSTEMIC COMPLICATIONS

Systemic manifestations occur in approximately 30 to 40% of the patients with primary Sjögren’s syndrome (Fig. 1).15 Lymphocytic infiltration of the epithelia of organs beyond the exocrine glands can cause interstitial nephritis, autoimmune primary biliary cholangitis, and obstructive bronchiolitis. Immune complex deposition as a result of the ongoing B-cell hyperactivity can result in extraepithelial manifestations, such as palpable purpura, cryoglobulinemia-associated glomerulonephritis, interstitial pneumonitis, and peripheral neuropathy. Renal involvement in primary Sjögren’s syndrome differs from that in SLE, since it is typically characterized by interstitial nephritis and associated with systemic acidosi, low levels of proteinuria, and progressive loss of renal function. Renal involvement in primary Sjögren’s syndrome is more rarely in primary Sjögren’s syndrome than in SLE and is most often associated with cryoglobulinemia.6

PATHOPHYSIOLOGICAL FEATURES

Current models of the pathophysiological features of this disease implicate the activation of mucosal epithelial cells, possibly from viral stimulation or from abnormal production of endogenous viral elements. This process leads to the activation of the innate and adaptive immune systems with the secretion of autoantibodies. These autoantibodies constitute immune complexes that maintain and amplify the production of interferon alpha, resulting in a cycle of immune-system activation that leads to tissue damage.

Data support such models are derived from studies of innate immunity, genetics, and B-cell activation in primary Sjögren’s syndrome. The increased expression of genes related to interferon (either type I or type II) can be detected in salivary glands and blood in more than half the patients with this disease.16 Consistent with this finding, multiple viral agents have been hypothesized to play a role in the disease, although none have been shown to be causally related.4 Genomewide association studies have shown associations between the syndrome and genes linked to interferon pathways.17,18 The presence of ectopic germinal centers in salivary glands highlights the B-cell activation that is characteristic of primary Sjögren’s syndrome. Recent studies have suggested the presence of plasma blasts in the blood and plasma cells in the salivary glands19 and of activated CD8 T cells in the blood and glands.20 The level of B-cell activating factor of the tumor necrosis factor family (BAFF), a cytokine that promotes B-cell maturation, proliferation, and survival, is increased in primary Sjögren’s syndrome, both in the serum and in salivary glands.11,12 BAFF, induced by interferon type I and type II, provides a link between innate immunity and autoimmunity in disease pathogenesis.12

Table 1. 2017 ACR–EULAR Classification Criteria for Primary Sjögren’s Syndrome.20

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Focus score of ≥1</td>
<td>A score determined by the number of mononuclear-cell infiltrates containing ≥5 inflammatory cells per mm² of minor labial salivary gland obtained on biopsy</td>
<td>3</td>
</tr>
<tr>
<td>Presence of anti-SSA antibodies†</td>
<td>Measured in serum; only anti-Ro60 antibodies have to be considered.</td>
<td>3</td>
</tr>
<tr>
<td>SICCA ocular staining score of ≥5</td>
<td>A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity</td>
<td>1</td>
</tr>
<tr>
<td>Schirmer test of ≤5 mm per min</td>
<td>An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper</td>
<td>1</td>
</tr>
<tr>
<td>Unstimulated whole salivary flow of ≤0.1 ml per min</td>
<td>An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed</td>
<td>1</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>9</td>
</tr>
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</table>

* On the basis of the listed classification criteria, a diagnosis of primary Sjögren’s syndrome is defined as a score of 4 or more. These criteria apply to patients who have at least one symptom of oral or dry eyes or the presence of systemic manifestations suggestive of primary Sjögren’s syndrome. Exclusion criteria include active hepatitis C virus infection on polymerase-chain-reaction assay, radiotherapy of the cervical spine, sarcoidosis, graft-versus-host disease, receipt of anticholinergic drugs, and IgG4-related disease. ACR denotes American College of Rheumatology, EULAR European League against Rheumatism, SICCA Sjögren’s International Collaborative Clinical Alliance, and SSA anti–Sjögren’s syndrome–related antigen A.
† Positive serologic results for anti-SSB/la antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

Clinical Practice

Strategies and Evidence

Diagnosis and Evaluation

A diagnosis of primary Sjögren’s syndrome is often considered on the basis of the classic symptoms of mouth and eye dryness, fatigue, and pain. However, systemic complications sometimes provide the first clues to the disease. Patients presenting with such complications should routinely be queried about manifestations of primary Sjögren’s syndrome and about the presence of other autoimmune diseases among family members.

Laboratory Testing

Anti-SSA antibodies (often associated with antibodies against Sjögren’s syndrome–related antigen B [anti-SSB antibodies]) are present in two thirds of patients and should be assessed when primary Sjögren’s syndrome is suspected. Rheumatoid factor is present in approximately half of the patients, whereas antibodies against double-stranded DNA (important in the diagnosis of SLE) are typically absent. Biopsy of minor salivary glands is typically recommended for establishing the diagnosis of primary Sjögren’s syndrome in the absence of anti-SSA antibodies. Such a biopsy procedure is usually performed by an oral medicine specialist or another clinician with specialized training.

Measures of oral and ocular dryness may also be useful. Among such measures, Schirmer’s test of oral dryness and determination of the unstimulated salivary flow rate to assess oral dryness can be performed by any clinician with appropriate training. Ultrasonography of the major salivary glands may reveal multiple hypoechoic or anechoic areas in the four main salivary glands (parotid and submandibular glands) and may be helpful in diagnosis or longitudinal assessment, although such evaluation is not formally included among the classification criteria (Fig. 1).14 Two indexes for the assessment of disease activity in primary Sjögren’s syndrome have been validated by EULAR. The EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI) is the mean of three visual-analogue scales that assess
The risk of B-cell lymphoma is 15 to 20 times as high among patients with primary Sjögren’s syndrome.23 A placebo-controlled trial evaluating two doses of pilocarpine (2.5 mg and 5 mg every 6 hours) in 373 patients showed that the 5-mg group had a higher frequency of improvement than the placebo group in dry mouth (61% vs. 31%, P<0.001) and dry eye (42% vs. 26%, P=0.009); there was no significant effect of the 2.5-mg dose on these outcomes.24 The main side effect of cholinergic agonists is sweating, which can be minimized by a gradual increase in the dose. (For example, pilocarpine could be started at 2 mg once or twice a day, with progressive dose escalation to 5 mg three or four times per day.) The use of topical cyclosporine eyedrops (0.05% or 0.1% concentration) has been shown to result in better tear production than placebo and in improvement in symptom scores among patients with moderate or severe ocular dryness and inflammation, although such findings have been mixed.21 Ocular glucocorticoid drops are not recommended in such patients, since they are not very effective23 and are associated with adverse effects, including cornea dam-
Table 2. Risk Factors for the Development of Lymphoma in Patients with Primary Sjögren’s Syndrome.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent swelling of parotid glands</td>
<td>1.94</td>
<td>1.17 to 3.62</td>
</tr>
<tr>
<td>Splanchnomagaly, lymphadenopathy, or both</td>
<td>2.57</td>
<td>0.99 to 6.48</td>
</tr>
<tr>
<td>Purpura</td>
<td>2.31</td>
<td>1.02 to 5.26</td>
</tr>
<tr>
<td>Score of S-ON on the ESSDAI</td>
<td>3.76</td>
<td>1.24 to 11.41</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>2.79</td>
<td>1.03 to 7.36</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>2.14</td>
<td>0.97 to 4.71</td>
</tr>
<tr>
<td>Low C4 level</td>
<td>2.54</td>
<td>1.01 to 6.25</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2.81</td>
<td>1.07 to 7.16</td>
</tr>
</tbody>
</table>

Guidelines and Recommendations

The woman described in the vignette has a classic case of primary Sjögren’s syndrome on the basis of clinical findings of dryness of the mouth and eyes, fatigue, and pain, along with the presence of anti-SSA antibodies and the similarity between Sjogren’s syndrome and SLE. The patient has some features predictive of an increased risk of lymphoma, including high disease activity, rheumatoid factor positivity, a low C4 level, recurrent parotid swelling, and purpura. We would generally recommend close follow-up in the present case such follow-up will definitely be needed, given the presence of purpura and renal dysfunction, which are among the recognized systemic complications of primary Sjögren’s syndrome. We would be especially concerned about

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interstitial nephritis associated with this disease; further evaluation is needed, including renal biopsies. If interstitial nephritis is present, we would initiate treatment with glucocorticoids. An immunosuppressive agent might also be useful in patients with inadequately controlled disease or to facilitate reduction of the prednisone dose. If the use of immunotherapy is considered, we would choose rituximab on the basis of the evidence of B-cell activation and the predominance of B cells in the lymphoid infiltrate. In addition, open-label studies of rituximab have shown benefit for the treatment of interstitial nephritis in patients with SLE and primary Sjögren’s syndrome, although data regarding its effectiveness have been inconsistent.

Dr. Mariette reports receiving grant support from Biogen and Pfizer, fees for serving on advisory boards from Pfizer, OCR, Beacor-sheds GlaxoSmithKline, MedImmune, Novartis, and Janssen, and fees for serving on a scientific council from Laboratoire Français des Biotechnologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Manuel Ramos Canals, Department of Systemic Autoimmune Diseases, Instituto de Medicina y Dermatologia, Hospital Clinic, Barcelona, for creating an earlier version of Figure 1.

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