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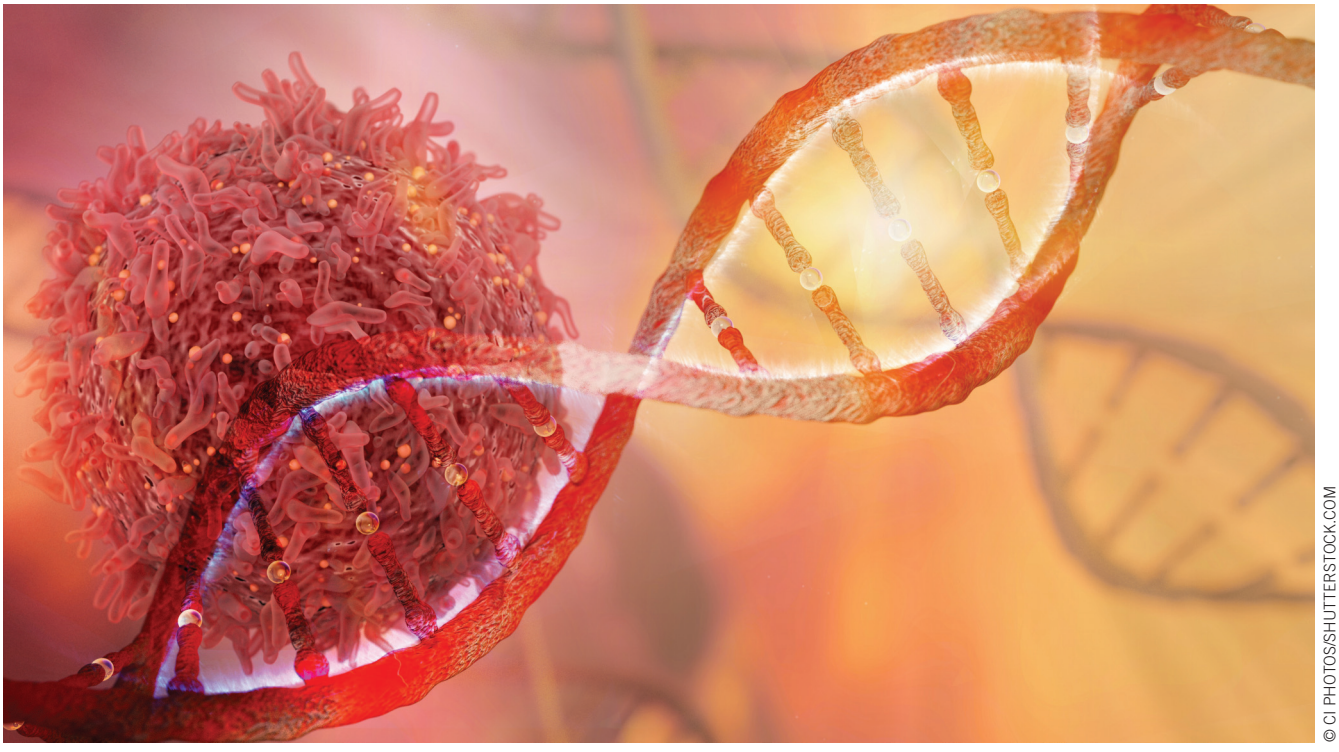

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A review of inherited cancer susceptibility syndromes

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ABSTRACT

Inherited cancer syndromes are caused by genetic mutations that place patients at an increased risk for developing cancer. Although most cancers are not caused by genetic inheritance, clinicians must understand these syndromes and be able to recognize their common characteristics. A thorough family history and identification of common patterns as well as specific clinical signs and symptoms can help with early recognition. This article describes symptoms of the more common cancer syndromes, including hereditary breast and ovarian cancer, Li-Fraumeni, Lynch, familial adenomatous polyposis, retinoblastoma, multiple endocrine neoplasia, and von Hippel-Lindau. Important patient education regarding genetic testing also is covered.

Keywords: cancer syndromes, genetics, family history, ICSS, genetic counseling, cancer screening, risk assessment

Learning objectives

- Identify patterns of an ICSS and know when further evaluation is indicated.
- Recognize the signs and symptoms of the more common ICSS and review their screening recommendations.
- Incorporate appropriate genetic education and referrals for ICSS.

Patients with inherited cancer susceptibility syndromes (ICSS) have a genetic mutation inherited from one or both parents. Many of these syndromes are autosomal dominant, with the patient having a 50% chance of passing it on to a child. Although ICSS (also known as familial cancer susceptibility syndromes and hereditary cancer syndromes) represent a small portion of all cancers, they often require proactive care of a patient's relatives and complex patient education for family members. Clinicians who are familiar with the patterns of these syndromes can help patients and their families understand why genetic testing is recommended for some patients and families and not for others. They also can explain genetic test results to families, helping

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Key points

- ICSS require extensive education for patients and their families.
- Genetic red flags help to alert providers to a likely ICSS.
- Early identification of an ICSS helps patients begin a targeted screening and prevention protocol to reduce morbidity and mortality.
- Hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, Lynch syndrome, familial adenomatous polyposis syndrome, retinoblastoma, multiple endocrine neoplasia, and von Hippel-Lindau disease are some of the more common ICSS.
- Recognizing signs and symptoms of these syndromes is key to prompt testing, patient education, and referrals.

them understand their actual risks for cancer and the benefits of individualized screening schedules and lifestyle changes.

In addition to general patterns that ICSS follow, specific syndromes have established clinical criteria that guide clinicians as to when testing is appropriate. More than 50 different syndromes have been identified, and most are rare.[1] Being familiar with the more-prevalent syndromes can help clinicians recognize different signs and symptoms in a patient as potentially having a common genetic source, allowing for appropriate diagnostic testing and referrals. This article focuses on:

- recognizing patterns of a hereditary cancer
- understanding principles of genetic education about ICSS testing
- reviewing the more common syndromes and their basic screening protocols.

GENERAL PATTERNS

Each ICSS carries its own clinical criteria, but most tend to have symptoms that appear in a unique yet consistent pattern, which serve as red flags. Prevalence of even the most common ICSS is rare (**Table 1**), making routine screening in the general population unnecessary. This is important education for patients who might be seeking testing due to media promotions or internet information. Genetic testing should be reserved for those with an increased risk, which is based on a patient's personal medical history and their family history. Findings that serve as genetic red flags include:

- Cancer diagnosed at an unusually young age.
- Multiple different cancer types occurring in the same person independently.
- Cancer that develops bilaterally in paired organs, such as the kidneys or breasts.
- Two or more first-degree relatives with the same cancer type or a known ICSS.
- Occurrence in the opposite-than-expected sex (for example, breast cancer in a man).
- Presence of certain genetic traits, such as congenital defects, skeletal abnormalities, benign skin growths, or rare diseases that are associated with a specific cancer syndrome.
- Being of a certain racial or ethnic group known to be associated with an ICSS, in addition to one or more of the above features.[2-5]

PATIENT EDUCATION

Advise patients that screening for ICSS is not indicated unless their history reveals a pattern consistent with anomalies characteristic of ICSS. Patients who have had genetic testing also may need advice about the interpretation of the results. ICSS are conditions with the potential for reduced penetrance: That is, although they are inherited in an autosomal-dominant fashion, patients may never show traits connected to a syndrome. Patients or family members who receive test results indicating that they have an ICSS have a predisposition for the syndrome, but may never develop cancer.[6] Different syndromes have different rates of reduced penetrance, which in turn influences their level of risk.[6] In addition, genetic test results that do not indicate an ICSS cannot be translated to mean that the patient will never get cancer. This is particularly true for direct-to-consumer tests available for familial breast, ovarian, prostate, and colon cancers. Although many genetic variants exist for these syndromes, the direct-to-consumer tests only detect a few of them, meaning that the patient may receive a negative report concerning a variant of breast cancer, but will not have been tested for the many hundreds of other variants that have been identified.[7]

Patients also should be prepared for results that reveal genetic variants of uncertain significance. These results are neither positive or negative and may require consultation or referral to determine if results should be managed as neutral or pathogenic.[8]

Explain the benefits of genetic testing for patients at increased risk. Ideally, patients with an ICSS will be identified early, preferably before cancer has occurred, or if not, in the earliest stages of disease. This allows for proper screenings, possible prophylactic treatment, or early treatment for the best chance of survival.[3,9] Refer patients to genetic counselors for further education and assessment when the nature of risk or appropriate genetic test remains unclear.[10]

Some of the more common cancer syndromes are reviewed below to help primary care providers (PCPs) identify these syndromes early and help patients obtain appropriate care.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Hereditary breast and ovarian cancer syndrome (HBOC) is the result of a mutation on one of the tumor-suppressor genes BRCA1 or BRCA2. Genetic mutations account for 5% to 10% of breast cancer cases and 10% to 15% of ovarian cancers.[11,12] BRCA1 and BRCA2 mutations carry

TABLE 1. Some common autosomal-dominant inherited cancer susceptibility syndromes[1,11,14,27,40,41,47-53]

Cancer syndrome	Prevalence	Associated cancer types and approximate risk (if known)
Basal cell nevus syndrome	1 in 40,000 to 57,000	• Basal cell carcinoma (unknown penetrance) • Medulloblastoma • Ovarian fibrosarcoma
Exostosis/enchondromatosis	1 in 50,000 (in white population)	Osteochondromas, 96%
FAP	1 in 6,000 to 13,000	• Colorectal, 100% • Gastric, 1% • Small intestine, 50%-90% • Thyroid, 2% • Pancreatic, 2% • Brain, hepatobiliary tract
Hereditary breast and ovarian cancer (BRCA1 and BRCA2)	1 in 300-500 (1 in 40 in Ashkenazi Jewish population)	• Breast cancer (female), 70% for BRCA1, 40% for BRCA2 • Ovarian cancer, 39% for BRCA1, 20% for BRCA2 • Fallopian tube, pancreatic, prostate
Hereditary multiple melanoma	5% of melanoma patients	• Melanoma, 67% • Pancreatic, 14%
Hereditary nonpolyposis colon cancer	1 in 400-500	• Colorectal, 25%-70% • Endometrial, 30%-70% • Gastric, 13% • Ovarian, 9% • Hepatobiliary tract, 13% • Small bowel, 7% • Renal pelvis, ureter, and bladder, 10% • Glioblastoma, 3% • Prostate, 20% • Breast, 12% • Sebaceous neoplasms, pancreas
Li-Fraumeni syndrome	1 in 5,000-20,000	• Breast (female), 54% • Soft tissue sarcoma, 19% • Brain, 16% • Osteosarcoma, 8%
MEN1	1 in 5,000-50,000 (in white population)	• Parathyroid, 95% • Pancreatic islet cell, 41% • Gastrinoma, anterior pituitary
MEN2	1 in 31,000	• Thyroid • Pheochromocytoma • Parathyroid
Neuroblastoma	1 in 7,500-10,000	Neuroblastoma, adrenal
Neurofibromatosis type 1	1 in 3,000	• Peripheral nerve sheaths and optic nerve glioma • Pheochromocytoma and nephroblastoma (Wilms tumor) • Neuroblastoma, leukemia
Retinoblastoma	1 in 17,000 births	Osteosarcoma
Tuberous sclerosis complex	1 in 5,800 births	• Brain • Renal
Von-Hippel Lindau disease	1 in 36,000	• CNS and retinal hemangioblastomas • Endolymphatic sac tumor • Pancreatic, 18% • Renal, 32%

up to a 60% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian cancer, compared with a 12.5% breast cancer risk in the general population of women.[11,13] For men, a BRCA mutation increases risk up to a 7% to 8% for breast cancer and up to a 20% for prostate cancer by age 80 years.[14]

HBOC is suspected with any diagnosis of premenopausal breast cancer or in a patient with a significant family history.[1] Guidelines for genetic testing for BRCA mutations were updated in 2019 by the US Preventive Services Task Force (USPSTF).[15] The USPSTF suggests that PCPs use a risk-assessment tool to screen women who have a family history of ovarian, breast, peritoneal, or tubal cancer, or a family history of the BRCA1 or BRCA2 mutation. The USPSTF has validated several assessment tools, one of which is available at www.breastcancergenescreen.org. A positive screen warrants referral for genetic counseling, followed potentially by BRCA testing. The USPSTF recommends against routinely performing BRCA testing or genetic counseling in women without a positive family history.[15] No recommendations are provided about screening for BRCA mutations in men.

Genetic testing for a BRCA mutation that reveals pathogenic (or "likely pathogenic") results requires early surveillance implemented by the PCP with the goal of reducing future cancer risk. Strategies for women include breast MRI, annual mammography starting at age 25 years, and semiannual clinical breast examinations.[15,16] Prophylactic options to reduce breast cancer risk include chemoprevention with selective estrogen receptor modulators or aromatase inhibitors.[16] Oral contraceptives have shown to be protective against ovarian cancers and can be considered if the patient is not ready for surgical options.[17] Risk-reducing surgeries include bilateral mastectomy and oophorectomy.[16,17]

Men with a BRCA mutation are encouraged to have an annual clinical breast examination beginning at age 35 years, and begin prostate cancer screening at age 45 years if they carry the BRCA2 variant, according to guidelines from the National Comprehensive Cancer Network (NCCN).[18]

LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome is characterized by four core cancers: sarcomas involving soft tissue and bone, breast cancer, central nervous system tumors, and adrenocortical cancer.[19] Characteristically, patients develop multiple cancers in multiple different organs, often beginning in childhood or adolescence, with the average age of onset about 25 years.[20] Leukemias, renal, and adrenocortical cancers are the most common cancers seen in children with this syndrome.[21] Although males and females equally inherit the mutation, females are more likely to develop cancer (100%) than males (73%).[21] Patients should be genetically tested if they have one of the following criteria: a family history of the pathogenic TP53 mutation, the patient fulfills the Chompret criteria, or the patient is diagnosed with hypodiploid acute lymphoblastic leukemia before age 21 years. The Chompret criteria encourages testing when a patient presents with a cancer within the Li-Fraumeni spectrum before age 46 years and also has a first- or second-degree relative with a Li-Fraumeni tumor at an early age.[22] Comprehensive criteria for testing can be found at www.ncbi.nlm.nih.gov/books/NBK1311/.

The American Society of Clinical Oncology and the American Society of Human Genetics recommend that patients and families who meet the criteria for Li-Fraumeni syndrome be referred to a genetic counseling center. Unless a specific pathologic variant has been identified in the family, TP53 testing should be comprehensive and test for all known variants. A lack of an identifiable TP53 mutation does not rule out clinical diagnosis of Li-Fraumeni syndrome, and about 5% of patients with the mutation do not meet clinical criteria.[19] This reinforces the necessity of genetic counseling before testing.

Once diagnosed, patients should undergo preventive measures such as bilateral mastectomy in women; screening is aggressive, with annual pelvic and abdominal ultrasounds, and whole-body MRI.[22] Women should begin annual mammograms combined with breast MRI at ages 20 to 25 years. Endoscopies and colonoscopies should be done at a minimum of every 5 years starting at age 25 years.[22]

LYNCH SYNDROME

Lynch syndrome, previously known as hereditary nonpolyposis colorectal cancer, is caused by a mutation in one of the mismatch repair (MMR) genes—MLH1, MSH2, MSH6, or PMS2.[23] Lynch syndrome is the most common cause of heritable colorectal cancer, accounting for about 3% of all colorectal cancer diagnoses.[24,25] This syndrome also increases the risk for endometrial cancer in women, as well as other cancers, depending on which gene is affected.[26] The risk of developing colorectal cancer varies based on the affected gene; the average risk for all mutation types is 38% of males and 31% of females by age 70 years.[27] For patients with Lynch syndrome, the mean age at diagnosis of colorectal cancer is 45 years compared with 67 years for all colorectal cancers combined.[27,28]

Findings that raise suspicion for Lynch syndrome follow the lines of the Amsterdam criteria, and include a family member with colorectal or endometrial cancer (or other Lynch syndrome cancer) diagnosed before age 50 years, along with additional relatives with cancer diagnoses and the exclusion of familial adenomatous polyposis.[24,25] These patients can be referred for genetic counseling.[25] Tumor testing is done on all patients with colorectal cancer to identify histologies consistent with Lynch syndrome. This identifies patients who should then proceed with genetic testing.[25] If pathogenic results occur on testing, at-risk family members also should be tested.[24]

A patient diagnosed with Lynch syndrome should have colonoscopy screenings beginning at ages 20 to 25 years and repeated every 1 to 2 years.[29] Women between the ages of 30 and 35 years should begin annual pelvic examinations, endometrial biopsies, and transvaginal ultrasound to screen for endometrial and ovarian cancer.[29] Prophylactic hysterectomy and bilateral salpingo-oophorectomy may be offered to women who are age 40 years or who have completed childbearing.[29]

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) occurs due to mutation of the adenomatous polyposis coli (APC) gene.[30] Usually, patients with this mutation will develop excessive numbers of colorectal adenomatous polyps (more than 100, and in severe cases, more than 1,000) in adolescence and early adulthood. Half develop adenomatous polyps by age 15 years, and 95% develop them by age 35 years.[30] The exact mutation on the APC gene determines the severity of the disease, allowing for an attenuated form of FAP in some patients; patients with this form tend to develop fewer than 100 polyps and develop them at an older age than patients with unattenuated FAP.[31]

> Referral to a genetic counselor can be helpful and often is recommended.

FAP is responsible for fewer than 1% of all cases of colorectal cancer but can have extracolonic complications, including polyps in the small intestines and stomach; thyroid, pancreatic, and brain malignancies; and nonmalignant complications such as desmoid tumors, epidermal cysts, dental abnormalities, and retinal hypertrophy.[1,32]

Patients are clinically diagnosed with FAP if they have multiple polyps and a first-degree relative diagnosed with FAP, or if they have 100 or more polyps and no family history.[30] Genetic testing in symptomatic patients confirms the diagnosis, but also serves as a diagnostic tool in presymptomatic patients with a significant family history.

As virtually all patients with FAP will develop colorectal cancer in their lifetime, surveillance and prophylactic measures are essential.[32] Encourage patients to enroll in genetic and clinical surveillance groups for detection of the extracolonic manifestations.[30] Unaffected family members should undergo colonoscopy or sigmoidoscopy annually starting at ages 10 to 15 years, and have upper endoscopies every 1 to 3 years, starting at ages 20 to 25 years.[30,32] Prophylactic colectomy is required with advancing polyposis.[32] Although celecoxib is not FDA-approved for treating FAP, it appears to reduce polyp formation in patients with FAP, and may slow progression.[33]

RETINOBLASTOMA

Retinoblastoma, the most common intraocular tumor in children, affects one in 13,500 to 25,000 births worldwide; however, fewer than 40% of these cases are inherited.[1,34] Inherited cases involve either deletions or mutations of the RB1 gene.[1] The most common initial signs are leukocoria (lack of red reflex), and strabismus, and may be unilateral or bilateral.[35] Patients with hereditary retinoblastoma carry significant risk of developing a secondary, extraocular malignancy, making genetic testing valuable in determining secondary risks.

Worldwide, most patients are diagnosed by age 5 years, and early detection is a key indicator of prognosis.[36] Detection begins in primary care, with regular fundoscopic examinations and vision screens at the appropriate intervals beginning at birth. Children with a positive family history should undergo genetic testing, and if an RB1 mutation is detected, fundus examinations under general anesthesia are indicated monthly. The frequency of these examinations may be reduced based on findings. These examinations, and any potential treatment are managed at specialized, interdisciplinary centers.[34,37] PCPs should be aware that patients with a history of hereditary retinoblastoma are at an increased risk of subsequent malignancy later in life, particularly malignancies of the soft tissues and bones of the head, in the form of osteosarcoma.[34,37,38]

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN) includes three syndromes, type 1, type 2, and type 4, that increase patient risk for cancer of the endocrine glands.[39] MEN types 1 and 2 (MEN1 and MEN2) have a similar prevalence and will be summarized here.[40]

Familial MEN1 involves a pathogenic variant of the MEN1 gene and most commonly presents with tumors of the parathyroid (about 95% of patients with MEN1) and pancreatic islet cells (about 41% of patients with MEN1, with many patients having both parathyroid and pancreatic tumors), usually in patients ages 20 to 30 years.[39,41] Cutaneous symptoms help in recognition of MEN1, with facial angiofibromas and collagenomas occurring in about 80% of patients.[42]

Patients who should receive MEN1 genetic testing include those with two or more MEN1-associated tumors; patients with a first-degree relative with a MEN1 mutation; patients with parathyroid tumors before age 30 years; and those with multigland parathyroid disease, gastrinoma, or multiple pancreatic neuroendocrine tumors at any age.[39] PCPs should collect an in-depth family history of patients diagnosed with parathyroid or islet cell tumors before age 30 years. This will aid in the diagnosis of MEN1 before surgery, allowing for referral to a surgeon who specializes in the treatment of MEN1 and who can weigh the individual risks of multiple surgeries and changes in endocrine function.[39]

MEN2 results from variants in the RET gene and is divided into MEN2A and MEN2B. Nearly all patients with MEN2 develop medullary thyroid carcinoma; of those with MEN2A, 50% develop pheochromocytoma and 25% develop adenomatosis of the parathyroid glands.[40] Patients may present with thyroid and lymph nodules, hoarseness, and dysphagia, typically before age 25 years.[40] MEN2B is very rare but aggressive, often leading to death before adulthood.[39,40] Screening for MEN2 is recommended in all patients with diagnosed medullary thyroid cancer and in patients who have a first-degree family member who is known to have MEN2.[39,43] Prophylactic thyroidectomies are the treatment of choice and are well tolerated in children with MEN2.[39,43]

VON HIPPEL-LINDAU DISEASE

von Hippel-Lindau disease is a syndrome of benign or malignant vascular tumors and cysts in various organs. Although this syndrome is autosomal dominant, the von Hippel-Lindau gene appears to require a somatic mutation within an organ or tissue for pathogenic proliferation to begin.[44] Potential tumors include central nervous system and retinal hemangioblastomas, pheochromocytomas, pancreatic tumors, endolymphatic sac tumors, cystadenomas of either the epididymis or the broad ligament, and renal tumors, with von Hippel-Lindau syndrome being the most common cause of clear-cell renal cell carcinoma.[44,45] Despite the potential for multiple tumor sites, von Hippel-Lindau syndrome is classified into four categories according to presence or absence and risk of both pheochromocytomas and renal cell carcinoma, making these the dominant symptoms for evaluation.[44]

For most patients, symptom onset occurs between ages 20 and 40 years, with 90% of patients having symptoms by age 65 years.[45] The most common symptoms include gait ataxia, weakness, hypesthesia, hyper-reflexia, headaches, visual changes, and hypertension, although symptoms ultimately depend on tumor location and size.[45,46] Bilateral epididymal cystadenomas are a pathognomonic finding that should alert clinicians to von Hippel-Lindau syndrome.[44] The criteria for genetic testing are complex and can be found at www.vhl.org, but include any first-degree family member of a diagnosed patient. Asymptomatic family members who test positive should participate in a complex screening program that can begin at age 1 year with eye examinations for retinal hemangioblastoma, and progress to various laboratory tests and imaging as the patient ages (full details at www.vhl.org).[44] Surgical interventions are standard care for patients with renal tumors and those with pheochromocytomas.

GENETIC REFERRALS

When a patient shows either specific signs or general patterns of an ICSS, referral to a genetic counselor or geneticist can be helpful and often is recommended. Patients living in rural areas are likely to find this referral challenging because many areas do not have this specialty. If referral is uncertain, a practical step in deciding if a referral is indicated is to have the patient complete a family health history via pedigree. The National Human Genome Research Institute and the office of the US Surgeon General created a downloadable tool that patients can use to chart their family health history (https://phgkb.cdc.gov/FHH/html/index.html). Locations of genetic services for referrals can be found on the American College of Medical Genetics website at www.acmg.net/GIS.

CONCLUSION

Although ICSS is relatively rare, patients require care that includes extensive education and includes the entire family. Recognizing when a patient is showing signs of a possible ICSS can enable PCPs to be proactive in collecting an in-depth family history, referring patients to an appropriate specialist, and initiating preventive care. This can reduce morbidity and mortality not only for patients, but for their extended families as well. **JAAPA**

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