MEDICAL POLICY – 12.04.54

Gene Expression-Based Assays for Cancers of Unknown Primary

BCBSA Ref. Policy: 2.04.54

RELATED MEDICAL POLICIES:
12.04.97 Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification
12.04.111 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

A primary site is the part of the body where cancer started. Cancers are named on this primary site, even when they spread to other parts of the body. For example, if cancer starts in the breast but spreads to the bones, lungs, or liver, it is still classified as breast cancer. Cancer treatment is often based on the primary cancer. In rare cases, a cancer may have already spread before the original cancer is found. This is known as cancer of unknown primary. Cancers of unknown primary happen in three to four percent of all cancers in the United States. Certain genetic tests are being studied as one way to try to find the original site of the cancer. There is not yet enough scientific evidence about how these genetic tests might affect overall health outcomes. These tests are considered unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression profiling</td>
<td>Gene expression profiling is considered investigational to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor.</td>
</tr>
</tbody>
</table>

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81504</td>
<td>Oncology (tissue of origin), microarray gene expression profiling of &gt; 2000 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as tissue similarity scores</td>
</tr>
<tr>
<td>81540</td>
<td>Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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Related Information

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.
The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce
inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

Description

Cancers of unknown primary represent 3% to 4% of cancers diagnosed in the United States. These cancers are heterogeneous and many accompanied by poor prognoses. A detailed history and physical combined with imaging and tissue pathology can identify some, but not all, primary sources of secondary tumors. It is suggested that identifying the likely primary source with gene expression profiling to direct treatment may improve health outcomes.

Background

Cancers of Unknown Primary

Cancers of unknown primary (CUPs), or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up about 3% to 4% of all cancers in the United States. Identifying the primary origin of a tumor can dictate cancer-specific treatment, expected outcome, and prognosis.¹

Most CUPs are adenocarcinomas or undifferentiated tumors; less commonly, they may be squamous carcinomas, melanoma, soft tissue sarcoma, or neuroendocrine tumors. Osteo- and chondrosarcomas rarely produce CUPs. The most common primary sites of CUPs are the lung and pancreas, followed by colon and stomach, then breast, ovary, prostate, and solid-organ carcinomas of the kidney, thyroid, and liver. Conventional methods used to aid in the identification of the origin of a CUP include a thorough history and physical examination; computed tomography scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.²
**Diagnosis and Classification**

Biopsy of a CUP with detailed pathology evaluation may include immunohistochemical (IHC) analysis of the tumor. IHC analysis identifies different antigens present in different types of tumors and can usually distinguish an epithelial tumor (ie, carcinoma) from melanoma or sarcoma. Detailed cytokeratin panels often allow further classification of carcinoma; however, tumors of different origins may show overlapping cytokeratin expression. Results of IHC may provide a narrow differential of possible sources of a tumor’s origin, but not necessarily a definitive answer.

Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification to improve the identification of the site of origin of a CUP. The molecular classification of cancers is based on the premise that, despite different degrees of differentiation, tumors retain sufficient gene expression “signatures” as to their cell of origin, even after metastasis. Theoretically, it is possible to build a gene expression database spanning many different tumor types to compare to the expression profile of very poorly differentiated tumors, or a CUP, to aid in the identification of the tumor type and organ of origin. The feasibility of using molecular classification schemes with gene expression profiling (GEP) to classify these tumors of uncertain origin has been demonstrated in several studies.3-6

**Tissue of Origin Testing, Treatment Selection, and Health Outcomes**

Patients with CUP have generally poor prognoses. For example, patients with disease limited to lymph nodes have a median survival of 6 to 9 months, and those with a disease that is extranodal 2 to 4 months.7 The premise of tissue of origin testing in CUPs is that identifying a likely primary tumor site will inform treatment selection leading to improved survival and other outcomes or as a predictive test. To evaluate whether treatment selection can be improved, the ability of a test to suggest a likely site of origin (clinical validity) must be first be shown. But demonstrating clinical validity may be problematic because patients with CUPs have no identified primary tumor for a reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, or comparisons IHC. A primary tumor diagnosed during follow-up might also be used as a reference standard, but its use would be subject to potential selection bias. Therefore, even substantial evidence supporting the ability of a test to suggest a likely site of origin will be insufficient to infer benefit. Convincing evidence for benefit requires demonstrating that using a test to select treatment will improve outcomes.
Tests Reviewed in This Report

Evidence on the clinical validity and clinical utility for 3 GEP tests is reviewed in this report (see Table 3).

Table 3. Gene Expression Profiling Tests for Cancers of Unknown Primary

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Platform</th>
<th>Genes Assayed, n</th>
<th>Tumor Types Assessed, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue of Origin</td>
<td>Cancer Genetics</td>
<td>Oligonucleotide microarray</td>
<td>2000</td>
<td>15</td>
</tr>
<tr>
<td>CancerTYPE ID</td>
<td>Biotheranostics</td>
<td>RT-qPCR</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>RosettaGX Cancer Origin</td>
<td>Rosetta Genomics</td>
<td>RT-qPCR (microRNA)</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>

Adapted from Agwa et al (2013)\(^8\)
RT-qPCR: real-time quantitative polymerase chain reaction
\(^a\) Formerly PathWork and ResponseDX: Tissue of Origin
\(^b\) Formerly miRview met\(^2\)

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX: Tissue of Origin; Cancer Genetics) measures the expression of 2000 genes and compares the similarity of the GEP of a CUP to a database of known profiles from 15 tissues with more than 60 histologic morphologies. The report generated for each tumor comprises a “similarity score,” which is a measure of similarity of GEP of the specimen to the profile of the 15 known tumors in the database. Scores range from 0 (very low similarity) to 100 (very high similarity), and sum to 100 across all 15 tissues on the panel. If a single similarity score is 30 or more, it indicates that this is likely the tissue of origin. If every similarity score is between 5 and 30, the test result is considered indeterminate, and a similarity score of less than 5 rules out that tissue type as the likely origin. PathWork Diagnostics developed the test, but the company filed for bankruptcy in early 2013; Response Genetics purchased its assets, and it, in turn, was acquired by Cancer Genetics in late 2015.

An alternative method to measure gene expression is real-time quantitative polymerase chain reaction (RT-qPCR). RT-qPCR can be used at the practice level; however, it can only measure, at most, a few hundred genes, limiting tumor categorization to 7 or fewer types. Tumor classification accuracy rates using real-time polymerase chain reaction have been reported to be as high as 87%, but lower (71%) for more undifferentiated tumors.\(^3\) One assay that uses RT-
qPCR is the CancerTYPE ID (Biotheranostics) assay, which measures the expression of messenger RNA in a CUP tissue sample. Samples for this are formalin-fixed, paraffin-embedded (FFPE) tissue sections or unstained 10 micron sections on glass slides. Expression levels of 92 genes (87 tumor-associated genes and 5 reference genes for normalization) are used to detect 27 tumor types in a known database of 578 tumors with a range of 5 to 49 tumors per type. The report generated is the probability for the main cancer type, possible subtypes, tumor types not able to be excluded, and those ruled out with 95% confidence calculated by K nearest neighbor analysis.

miRview mets is another RT-qPCR test that uses microRNAs (miRNA), small noncoding, single-stranded RNA molecules that regulate genes posttranscription, as a signature for tumor differentiation. Expression levels of these miRNAs have been shown to be a sensitive biomarker across various pathologic conditions. Samples for this test are formalin-fixed, paraffin-embedded tissue. The miRview test used 48 panel markers to detect 22 tumor types in a known database of 336 tumors, with a range of 1 to 49 tumors per type. Results from the test provide a tumor of origin but may list multiple possibilities calculated by a binary decision tree and K nearest neighbor algorithm. A second-generation test, the RosettaGX Cancer Origin Test (formerly miRview mets\(^2\) and ProOnc Tumor Source), has also been developed; this test expands the number of tumor types to 49 primary origins with a panel of 64 miRNAs.

**Summary of Evidence**

For individuals who have CUP who receive GEP, the evidence includes studies of clinical validity, and limited evidence on potential clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. Of the 3 commercially available tests reviewed, 1 has been cleared by the Food and Drug Administration (Tissue of Origin). For these tests, the clinical validity is the ability of a test to determine the site of origin. Using different reference standards (known tumor type, reference diagnosis, a primary tumor identified during follow-up, immunohistochemical analysis) for the tissue of origin, the tests have reported sensitivities or concordances generally high (eg, 80% to 90% or more). However, evidence for clinical validity does not support potential benefit. There is limited indirect evidence from nonrandomized studies on clinical utility, and all studies had significant limitations. Benefit would be most convincingly demonstrated through a marker strategy-designed trial randomizing patients who had CUP with treatment based on expression profiling results or to usual care. The evidence is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

One ongoing trial potentially influencing this review can be found in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03278600</td>
<td>The Value of Tissue-of-origin Profiling in Predicting Primary Site and Directing Therapy in Patients With Cancer of Unknown Primary: a Prospective Randomized Controlled Study</td>
<td>172</td>
<td>Sep 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01540058</td>
<td>A Randomised Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP)</td>
<td>223</td>
<td>Oct 2017 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

Practice Guidelines and Position Statements

*National Comprehensive Cancer Network*

Current National Comprehensive Cancer Network (NCCN) guidelines for the workup of an occult primary malignancy (v.2.2018) address the use of molecular methods to classify tumors.7 The guidelines state, “Tumor sequencing and Gene signature profiling for tissue of origin is not recommended for standard management at this time.” A footnote acknowledges that “there may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation [based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate].” The guidelines later note:

In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC). In addition, gene expression profiling (GEP) assays have been developed to attempt to identify the tissue of origin in patients with occult primary cancers. It is noteworthy that thus far the literature on this approach, as with the literature on IHC application in the workup of occult primary tumors, has focused far more on establishing a
tissue of origin than on establishing whether such identification leads to better outcomes in patients. Thus, while there is diagnostic benefit of GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend tumor sequencing and gene signature profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors. Overall, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately.

**National Institute for Health and Clinical Excellence**

A 2010 clinical guidance from the National Institute for Health and Clinical Excellence recommended against the use of gene expression profiling (GEP) to identify primary tumors in patients with CUPs. This recommendation is based on “limited evidence that gene-expression based profiling changes the management of patients with CUP and no evidence of improvement in outcome.” The guidance included a research recommendation for trials to assess the clinical utility of GEP.

**European Society of Medical Oncology**

The 2015 guideline from the European Society of Medical Oncology states that as relates to use of GEP assays to identify tissue of origin in patients with cancer of unknown primary, “their impact on patient outcome via administration of primary site specific therapy remains questionable and unproven in randomized trials” (level of evidence: IV based on “retrospective cohort studies or case–control studies”; grade of recommendation C: “insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages.”) Rather, “Immunohistochemistry should be applied meticulously in order to identify the tissue of origin and to exclude chemosensitive and potentially curable tumors (ie, lymphomas and germ cell tumors).”

**Medicare National Coverage**

A 2013 technology assessment was commission by Centers for Medicare & Medicaid for consideration by the MEDCAC panel. Studies identified evaluating CancerTYPE ID, miRview, and PathWorkDx through November 2012, were included. The report concluded that all tests had similar accuracies, ranging from 85% to 88% (9 studies of PathWorkDx, 6 of CancerTYPE ID, 4 of MiRview), but that evidence was insufficient to evaluate the effect on management and
outcomes. (Following review, the MEDCAC panel voted 2 [scale of 1 = low, 3 = intermediate, and 5 = high confidence] after considering the question: “How confident are you that there is sufficient evidence to determine whether genetic testing of tumor tissue affects health outcomes (including benefits and harms) for patients with cancer whose anticancer treatment strategy is guided by the results of each of the following?”)

There are no national Medicare coverage decisions for these tests, but local Medicare coverage decisions for all 3 tests have found them to be “reasonable and necessary.” In 2011, Palmetto GBA, issued positive coverage for the PathWork Tissue of Unknown Origin Test. Because all tests are processed out of the company laboratory in California, the test will be covered for Medicare patients in the United States. In 2012, Palmetto issued a similar statement for CancerTYPE ID, and, in 2013, Novitas issued a similar statement for miRview.

**Regulatory Status**

In 2008, the PathWork® Tissue of Origin Test™ (Response Genetics; now Cancer Genetics) was cleared for marketing with limitations (see below) by the U.S. Food and Drug Administration (FDA) through the 510(k) process (FDA product code: OIW), with subsequent clearances for expanded applications in 2010 and minor modifications in 2012. FDA determined that the test was substantially equivalent to existing tests for use in measuring the degree of similarity between the RNA expression pattern in a patient's fresh-frozen tumor and the RNA expression patterns in a database of tumor samples (poorly differentiated, undifferentiated, metastatic cases) that were diagnosed according to current clinical and histopathologic practice.

Limitations to the clearance were as follows:

- The PathWork® Tissue of Origin Test is not intended to establish the origin of tumors that cannot be diagnosed according to current clinical and pathologic practice (eg, a cancer of unknown primary)

- It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice, or to predict disease course, or survival or treatment efficacy, or to distinguish primary from metastatic tumor.

- Tumor types not in the PathWork® Tissue of Origin Test database may have RNA expression patterns similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

The test is now offered by Cancer Genetics, as the Tissue of Origin® test.
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. CancerTYPE ID® (Biotheranostics, San Diego, CA) are miRview® (or RosettaGX Cancer Origin™; Rosetta Genomics, Philadelphia, PA) are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/10/09</td>
<td>Add to Pathology/Laboratory section. - New Policy.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. References added.</td>
</tr>
<tr>
<td>01/11/11</td>
<td>Replace Policy - Policy updated with literature search; reference 12 added, reference 1 and 13 updated; new tests for formalin-fixed paraffin-embedded (FFPE) specimens added as investigational, no change to existing policy statement.</td>
</tr>
<tr>
<td>01/06/12</td>
<td>Replace Policy – Policy updated with literature search; references 11, 12 and 14 added. No change to policy statement. ICD-10 codes added.</td>
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<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.54 (previously 2.04.54) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>10/10/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>01/29/13</td>
<td>Replace policy. Policy statement revised to be general rather than test specific “Gene expression profiling is considered investigational to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor.” Policy rationale updated based on a literature review through September 2012 with info about clinical trials &amp; other new tests (CancerTypeID® and miReview®) commercially available. References 13, 15-22 added, others renumbered. Policy statement changed as noted. CPT codes 83890 – 83913 deleted as of 12/31/12; replaced with 81200 – 81479, effective 1/1/13 (added to policy); 81599, effective 1/1/13, also added.</td>
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<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<tr>
<td>01/13/14</td>
<td>Replace policy. Policy updated with literature search through September 2013; references 14, 15, 17, 25, and 29 added; references 1, 20, and 28 updated. No change to policy statement. Non-specific CPT codes 81200-81479, 88384-88386 removed from policy, along with deleted codes 83890-83913; ICD-9 Diagnosis and ICD-10-CM codes removed from the policy.</td>
</tr>
<tr>
<td>01/07/15</td>
<td>Update Related Policies. Change title to 12.04.111.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81540, effective 1/1/16, added to policy.</td>
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<tr>
<td>03/03/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
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<tr>
<td>06/01/17</td>
<td>Annual Review, approved May 2, 2017. Policy updated with literature review through January 25, 2017 and selected citations from publications submitted by Biotheranostics; references 21, 29, 33, and 37 added; some references deleted. Rationale reorganized and revised to reflect new literature and change of ResponseDX Tissue of Origin Test to Tissue of Origin. Policy statement unchanged.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 18, 2018. Policy updated with literature review through January 2018; no references added; note 1 updated. Policy statement unchanged.</td>
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</table>

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Trong thời gian tới, bạn có thể quan tâm đến việc đặt tên cho tổ chức y tế hoặc làm các điều gì đó để cải thiện tình trạng sức khỏe của mình.

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