Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

• Benefits are available in the member’s contract/certificate, and
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider once per lifetime testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment choice in individuals with certain types of cancer to be eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for once per lifetime testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment choice in individuals with certain types of cancer when ALL of the following criteria are met:

• Individual has cancer of stomach, colon, pancreas, or breast; AND
• Treating clinician is considering treatment with 5-FU or capecitabine; AND
• The results of the test will be used in drug management decisions.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers My5-FU™‡ testing or other types of assays for determining 5-fluorouracil (5-FU) area under the curve (AUC) in order to adjust 5-FU dose for colorectal cancer (CRC) patients or other cancer patients to be investigational.*

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

Based on review of available data, the Company considers testing for genetic variants in thymidylate synthase (TYMS) genes to guide 5-FU dosing and/or treatment choice in individuals with cancer to be investigational.*

Based on review of available data, the Company considers testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment in all other situations to be investigational.*

**Background/Overview**

**5-fluorouracil**

The agent 5-fluorouracil is a widely used antineoplastic chemotherapy drug that targets the thymidylate synthase (TYMS) enzyme, which is involved in DNA production. 5-fluorouracil has been used for many years to treat solid tumors (eg, colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 4 toxicity (ie, mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-fluorouracil. Several studies also have reported statistically significant positive associations between 5-fluorouracil exposure and tumor response. In current practice, however, 5-fluorouracil dose is reduced when symptoms of severe toxicity appear but is seldom increased to promote efficacy.

Based on known 5-fluorouracil pharmacology, it is possible to determine a sampling scheme for the area under the curve determination and to optimize an area under the curve target and dose-adjustment algorithm for a particular 5-fluorouracil chemotherapy regimen and patient population. For each area under the curve value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target area under the curve without overshooting and causing severe toxicity.

In clinical research studies, 5-fluorouracil blood plasma levels most recently have been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass spectrometry. Both methods require expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings.
FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 (CLIA). Assay testing for 5-fluorouracil blood plasma concentrations and genetic testing for variants in DPYD and TYMS for predicting the risk of 5-fluorouracil toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test. The My5-FU assay is no longer marketed by Saladax Biomedical or Myriad Genetics in the United States. It is possible that therapeutic drug monitoring for 5-FU is available at a given institution as an in-house assay.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Variability in systemic exposure to 5-fluorouracil chemotherapy is thought to directly impact 5-fluorouracil tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-fluorouracil: (1) dosing based on the determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-fluorouracil metabolism. For genetic testing, currently available polymerase chain reaction tests assess specific variants in genes encoding dihydروpyrimidine reductase (DPYD) and thymidylate synthase (TYMS) in the catabolic and anabolic pathways of 5-fluorouracil metabolism, respectively.

Summary of Evidence

For individuals who have cancer for whom treatment with 5-fluorouracil is indicated who receive laboratory assays to determine 5-fluorouracil area under the curve, the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes are
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. Several analyses of patients with colorectal cancer have evaluated clinical validity. Two studies found that the rate of severe toxicity was significantly lower in patients with metastatic colorectal cancer who received dosing using pharmacokinetic monitoring versus body surface area (BSA); however, progression-free survival was not significantly different between groups. Most RCTs and nonrandomized studies comparing health outcomes were either single-center or did not use chemotherapy regimens used in current clinical practice. A systematic review of the available literature found a significantly higher response rate with body surface area based monitoring and no significant difference in toxicity. Most observational data were derived from studies conducted in the 1980s when different chemotherapy protocols were used. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer for whom treatment with 5-fluorouracil is indicated who receive genetic testing for variants (eg, in DPYD and TYMS) affecting 5-fluorouracil metabolism, the evidence includes observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A TEC Assessment (2010) concluded that DPYD and TYMS variant testing had poor prognostic capacity to identify patients likely to experience severe 5-fluorouracil toxicity. Since the publication of that assessment, no prospective trials comparing the efficacy and toxicity outcomes in patients who did and did not undergo pretreatment DPYD and/or TYMS testing have been published. Three prospective observational studies used a historical control group and 1 also used a matched-pairs analysis to compare outcomes in patients who received genotype-based dosing to those who received standard dosing. No differences in overall survival, progression-free survival, or tumor progression were observed. Risk of serious toxicity was higher in DPYD allele carriers who received genotype-based dosing compared to wild-type patients but lower when compared to historical controls who were carriers but received standard dosing. The evidence is limited by retrospective data collection, use of historical control groups, small sample sizes, and missing data. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Clinical Pharmacogenetics Implementation Consortium
In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB, an internet research tool developed by Stanford University, and the Pharmacogenomics Research Network of the National Institutes of Health. In 2013, the Clinical Pharmacogenetics Implementation Consortium published evidence-based guidelines for DPYD genotype and fluoropyrimidine dosing. The guidelines did not address testing.

An update to the Clinical Pharmacogenetics Implementation Consortium (2017) guidelines was published by Amstutz et al (2018). As in 2013, the primary focus of the guidelines was on the DPYD genotype and implications for dosing of fluoropyrimidine. In the 2017 update, the Clinical Pharmacogenetics Implementation Consortium noted that genetic testing for DPYD may include “resequencing of the complete coding regions” or may be confined to analysis of particular risk variants, among which Clinical Pharmacogenetics Implementation Consortium listed the c.1905+1G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-fluorouracil toxicity. Additional alleles potentially associated with 5-fluorouracil toxicity were added in online updates to the guideline's tables in 2020. The guideline further noted that, while other genes (TYMS, MTHFR) may be tested for variants, the clinical utility of such tests is yet unproven. In patients who have undergone genetic testing and who are known carriers of a DPYD risk variant, the guidelines recommended that caregivers strongly reduce the dosage of 5-fluorouracil-based treatments, or exclude them, depending on the patient’s level of DPYD activity. The CPIC advised follow-up therapeutic drug monitoring to guard against underdosing and cautioned that genetic tests could be limited to known risk variants and, therefore, not identify other DPYD variants.

International Association of Therapeutic Drug Monitoring and Clinical Toxicology
In 2019, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology published recommendations for therapeutic drug monitoring of 5-fluorouracil therapy. The work was supported in part by grants from the National Institutes of Health National Cancer Institute. Several authors reported relationships with Saladax, the manufacturer of the My5-FU assay available in Europe. The committee concluded that there was sufficient evidence to strongly recommend therapeutic drug monitoring for the management of 5-fluorouracil therapy in patients with early or
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

advanced colorectal cancer and patients with squamous cell carcinoma of head-and-neck cancer receiving common 5-fluorouracil dosing regimens.

National Comprehensive Cancer Network Guidelines
National Comprehensive Cancer Network (NCCN) guidelines do not recommend use of area under the curve guidance for 5-fluorouracil dosing or genetic testing for DPYD and/or TYMS variants in patients with colon, rectal, breast, gastric, pancreatic, or head and neck cancers.

The colon cancer guideline discusses the use of genetic testing for DPYD and the risk of severe toxicity after a standard dose of a fluoropyrimidine. Although the guideline discusses evidence for genetic testing for DPYD, it states: "However, because fluoropyrimidines are a pillar of therapy in colorectal cancer (CRC) and it is not known with certainty that given DYPD variants are necessarily associated with this risk, universal pretreatment DYPD genotyping remains controversial and the NCCN Panel does not support it at this time."

National Institute for Health and Care Excellence
In 2014, the NICE published evidence-based diagnostics guidance on the My5-FU assay for 5-fluorouracil chemotherapy dose adjustment. The evidence for the guidance was reviewed in February 2018. The guidance stated: “The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
There are currently no relevant ongoing trials. Some unpublished trials that might influence this review are listed in Table 1.
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291  
Original Effective Date: 03/16/2011  
Current Effective Date: 06/12/2023

Table 1. 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>Unpublished</td>
<td><strong>Area under the curve-guided dosing of 5-fluorouracil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00943137</td>
<td>The Optimisation of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer</td>
<td>55</td>
<td>June 2017</td>
</tr>
<tr>
<td>NCT02055560&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-fluorouracil Exposure Optimization Testing</td>
<td>350</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>Unpublished</td>
<td><strong>Testing for genetic variants affecting 5-fluorouracil dosing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00131599</td>
<td>Thymidylate Synthase Polymorphisms as a Predictor of Toxicity to 5-Fluorouracil Based Chemotherapy in Stage III Colon Cancer</td>
<td>104</td>
<td>July 2017</td>
</tr>
<tr>
<td>NCT04269369</td>
<td>Implementation of Pre-emptive Geno- and Phenotyping in 5-Fluorouracil- or Capecitabine-treated Patients</td>
<td>250</td>
<td>Sep 2021</td>
</tr>
<tr>
<td>NCT05266300</td>
<td>Implementation and Quality Assurance of DPYD- genotyping in Patients Treated with Fluoropyrimidines</td>
<td>722</td>
<td>Oct 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.  
<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

References

Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023


Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023


Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023


Policy History
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023
03/03/2011 Medical Policy Committee review
03/16/2011 Medical Policy Implementation Committee approval. New Policy.
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy #  00291
Original Effective Date:  03/16/2011
Current Effective Date:  06/12/2023

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2012</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>03/21/2012</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>05/02/2013</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>05/22/2013</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>06/05/2014</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>06/18/2014</td>
<td>Medical Policy Implementation Committee approval. Investigational OnDose statement modified to reflect new test name, My5-FU. Investigational statement for TheraGuide testing for genetic mutations in <em>DPYD</em> or <em>TYMS</em> added. Title changed from “Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Patients Administered 5-FU for Cancer” to “Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer” to reflect incorporation of new test.</td>
</tr>
<tr>
<td>08/06/2015</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>08/19/2015</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>08/04/2016</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>08/17/2016</td>
<td>Medical Policy Implementation Committee approval. Removed TheraGuide test from policy statement as it is no longer available.</td>
</tr>
<tr>
<td>01/01/2017</td>
<td>Coding update: Removing ICD-9 Diagnosis Codes</td>
</tr>
<tr>
<td>08/03/2017</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>08/09/2018</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>08/15/2018</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>03/01/2019</td>
<td>Coding update</td>
</tr>
<tr>
<td>08/01/2019</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>08/14/2019</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>08/06/2020</td>
<td>Medical Policy Committee review</td>
</tr>
</tbody>
</table>
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021 Medical Policy Committee review
08/04/2022 Medical Policy Committee review
08/10/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023 Medical Policy Implementation Committee approval. Added that once per lifetime testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment choice in individuals with certain types of cancer to be eligible for coverage with criteria. Added an investigational statement testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment in all other situations.

Next Scheduled Review Date: 05/2024

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

©2023 Blue Cross and Blue Shield of Louisiana
Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81232, 81346, 81400, 81401, 84999</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S3722</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 06/12/2023

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.